Efficient Synthetic Technique, PASS Predication, and ADMET Studies of Acylated *n*-Octyl Glucopyranosides

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Abstract

Direct dimolar pentanoylation of octyl β-D-glucopyranoside (OBG) in pyridine-chloroform solvent system furnished the corresponding 3,6-di-O-pentanoate in improved yield. The pentanoate was further converted into three 2,4-di-O-acyl esters to get novel octyl glucopyranosides. To explore the medicinal probability of OBG-based esters, all the synthesized compounds were subjected to in silico PASS (prediction of activity spectra for substances) predication and ADMET (absorption, distribution, metabolism, excretion, and toxicity) studies. Both the studies indicated that OBG derived carbohydrate fatty acid (CFA) esters are a potential alternative for multidrug-resistant (MDR) pathogens, especially for fungal infections.

Keywords: *n-Octyl β-D-glucopyranoside (OBG), Carbohydrate Fatty Acid (CFA) Esters (SEs), PASS Predication, ADMET, SwissADME.*

1. Introduction

The numerous biological properties of carbohydrate derivatives have garnered special attention from researchers [1-2]. Among them, carbohydrate fatty acid (CFA) esters are important due to them being amphiphilic, non-toxic, biodegradable, non-irritating and environment-friendly [3-6]. In addition to their uses as detergent and cosmetic products, some CFA esters are used in pharmaceutical industries considering their suitable insecticidal and antimicrobial activities [7-9]. Recently, it was observed that sugar ester part(s) of uridine (**1**, Figure 1) is more potent against SARS-CoV-2 main protease (Mpro; 7BQY) than the traditional hydroxychloroquine (HCQ, **2**) drug [10]. Therefore, the CFA esters have always been an important component(s) of drugs, and their design and synthesis play an important role in the diagnosis, prevention and treatment of diseases.

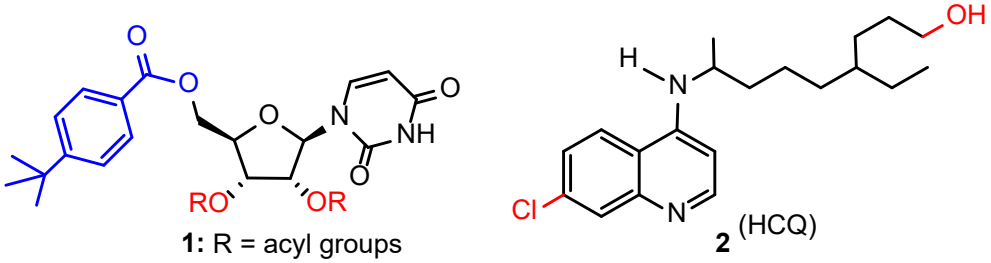

Figure 1. Structure of compound **1** and **2**.

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CFA esters are also used as significant intermediates in the syntheses of various natural products due to the presence of multifunctional groups, [11-13] in addition to their extensive use for the design and development of new drugs [14-15]. They can be synthesized by an esterification reaction between sugars (sugar alcohols) and non-polar fatty acids or acyl halides in basic solvent(s) [16]. Also, these can be achieved by using catalytic and enzymatic methods. However, industrial sugar esters are currently being manufactured by chemical syntheses. The major challenges with CFA ester syntheses are: (i) the presence of several 2° hydroxyl groups of almost similar reactivity, mostly affecting functionalization (esterification) step which form a mixture of mono-, di-, and polyesters [16], and (ii) the many variations of carbohydrate structures. The separation of the different esterification mixtures into individual sugar esters is practically challenging and imposes high process cost. Hence, several methods have been attempted and reported in the last couple of decades for selective esterification (acylation) [17-26]. There are advantages and shortcomings in all the methods and/or strategies. Some of the shortcomings reported were the complex processes involving multiple steps, and they were tedious, expensive, had low selectivity and gave extremely low yield [27-28]. Hence, in most cases, a direct acylation technique maintaining proper reaction conditions is preferred for the monosaccharide based CFA ester synthesis to increase the final yield(s) [29-32].

From the structure-activity relationship (SAR) of several CFA esters, it was found that several acylated methyl 4,6-*O*-benzylidene-α-D-glucopyranosides **3a,b** (Figure 2) exhibited promising antimicrobial activities especially antifungal activities at a very low concentration [33-34]. The activities generally increased with the increase of hydrophobic character, and also depend on the nature and length of the lipophilic side chain(s) [3-4, 16].

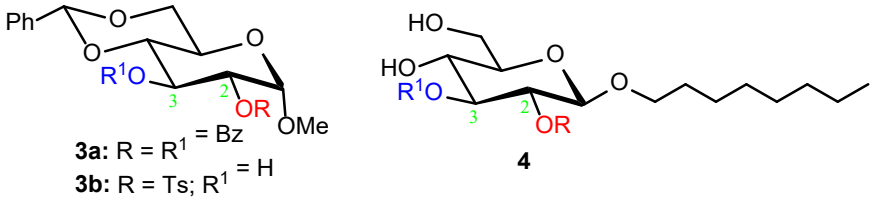


Figure 2. Structure of glucopyranosides **3** and **4**.

Thus, the nature and mode of action of the CFA compounds are still open for future scientific and applied studies although these esters have been known for many years with a variety of applications. Octyl β-D-glucopyranoside (OBG, **4**), a bio-surfactant, was found to be nontoxic and to inhibit carbohydrate hydrolyzing enzymes (like α-amylase). In this context, and our continuous effort in this field [35-37] led us to design and synthesize some esters of octyl β-D-glucopyranoside (OBG, **4**) for *in silico* biological spectrum and drug-likeness studies.

2. Materials and methods

2.1. Instrumentation and general methods

The melting point (mp) was determined on an electro-thermal melting point apparatus (England) and was uncorrected. Evaporations were carried out under diminished pressure using a Buchi rotary evaporator (R-100, Switzerland) with a bath temperature of below 40 °C. Thin-layer chromatography (TLC) was performed on Kieselgel GF_{254} and the spots were detected by spraying the plates with 1% H_2SO_4 and heating it at 150–200 °C till a blackish colouration appeared. For work-up, a few pieces of ice were added to the reaction mixture to decompose the excess acyl halide and extracted with dichloromethane (DCM, 5×3 mL). The DCM layer was washed successively with 5% hydrochloric acid, saturated aqueous sodium hydrogen carbonate solution and brine. The DCM layer was dried and

concentrated under reduced pressure. The residue obtained on column chromatography gave the corresponding pure compound(s). Column chromatography (CC) was performed with silica gel G_{60}. The solvent system employed for the TLC analyses was *n*-hexane/ethyl acetate (EA) in different ratios. FT-IR spectra were recorded on an FT-IR spectrophotometer (Shimadzu, IR Prestige-21) in the KBr disc. ^{1}H (400 MHz, Bruker DPX-400 spectrometer, Switzerland) and ^{13}C (100 MHz) NMR spectra were recorded in $CDCl_3$ solution using tunable multinuclear probe at Wazed Miah Science Research Centre (WMSRC), Jahangirnagar University, Bangladesh Chemical shifts were reported in δ scale (ppm) with reference to TMS (tetramethylsilane) as an internal standard and coupling constant (*J*) values are shown in Hz.

2.2. Synthesis

2.2.1. Octyl 3,6-di-*O*-pentanoyl-β-D-glucopyranoside (5)

A mixture of octyl β-D-glucopyranoside (**4**, 500 mg, 1.71 mmol) in pyridine (2 mL) and chloroform (2 mL) was cooled to 10 °C whereupon pentanoyl chloride (0.434 g, 3.59 mmol) was added to this mixture slowly. The mixture was warmed to 30 °C and stirred for 10 h when TLC (*n*-hexane/EA, 1/2, v/v) indicated the formation of one faster-moving major product. Work-up as mentioned in the previous section 2.1, followed by chromatography gave the 3,6-di-*O*-pentanoate **5** (528 mg, 67%) as a clear solid, mp 62-65 °C [3].

R_f = 0.48 (*n*-hexane/EA = 2/1); FT-IR (KBr): ν 3250-3540 (OH), 1741, 1733 cm^{-1} (CO); ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 5.07 (t, 1H, *J* = 9.6 Hz, H-3), 4.48 (dd, 1H, *J* = 12.1 and 4.5 Hz, H-6a), 4.42 (dd, 1H, *J* = 2.0 Hz, H-6b), 4.34 (d, 1H, *J* = 8.2 Hz, H-1), 3.83-3.93 [m, 2H, H-2 and $CH_3(CH_2)_6CH_AH_BO$], 3.46-3.59 [m, 3H, H-4, H-5 and $CH_3(CH_2)_6CH_AH_BO$], 2.46 [t, 2H, *J* = 7.7 Hz, $CH_3(CH_2)_2CH_2CO$], 2.38 [t, 2H, *J* = 7.6 Hz, $CH_3(CH_2)_2CH_2CO$], 1.55-1.70 [m, 6H, $CH_3(CH_2)_5CH_2CH_2O$ and 2×$CH_3CH_2CH_2CH_2CO$], 1.31-1.44 [m, 14H, $CH_3(CH_2)_5CH_2CH_2O$ and 2×$CH_3CH_2(CH_2)_2CO$], 1.21-1.28 (br s, 2H, 2×OH), 0.95 [t, 6H, *J* = 7.6 Hz, 2×$CH_3(CH_2)_3CO$], 0.89 [t, 3H, *J* = 7.2 Hz, $CH_3(CH_2)_7O$]; ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 174.4, 174.2 (CO), 101.0 (C-1), 74.3 (C-3), 74.2 (C-5), 71.1 (C-2), 70.4 [$CH_3(CH_2)_6CH_2O$), 69.4 (C-4), 63.0 (C-6), 34.1, 33.9 [2×$CH_3(CH_2)_2CH_2CO$], 31.8, 29.6, 29.3, 29.2, 27.0, 26.9, 25.9, 22.6, 22.2, 22.1 [$CH_3(CH_2)_6CH_2O$ and 2×$CH_3(CH_2)_2CH_2CO$], 14.0 [$CH_3(CH_2)_7O$], 13.6, 13.5 [2×$CH_3(CH_2)_3CO$].

2.2.2. Octyl 2,4-di-*O*-mesyl-3,6-di-*O*-pentanoyl-β-D-glucopyranoside (6)

Mesylation of diol **5** (50 mg, 0.109 mmol) in anhydrous pyridine followed by workup and CC furnished the title compound **6** (60 mg, 89%) as an oil.

R_f = 0.48 (*n*-hexane/EA = 4/1); FT-IR (KBr): ν 1748, 1738 (CO), 1365, 1362 cm^{-1} (SO_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 5.25 (t, 1H, *J* = 9.8 Hz, H-3), 5.10 (t, 1H, *J* = 9.6 Hz, H-4), 4.99 (dd, 1H, *J* = 9.6 Hz, H-2), 4.47 (d, 1H, *J* = 8.2 Hz, H-1), 4.23 (dd, 1H, *J* = 12.2 and 4.8 Hz, H-6a), 4.43 (dd, 1H, *J* = 2.4 Hz, H-6b), 3.89 [dt, 1H, *J* = 9.5 and 6.4 Hz, $CH_3(CH_2)_6CH_AH_BO$], 3.67-3.74 (m, 1H, H-5), 3.47 [dt, 1H, *J* = 9.5 and 6.9 Hz, $CH_3(CH_2)6CH_AH_BO$], 3.29 (s, 3H, SO_2CH_3), 3.15 (s, 3H, SO_2CH_3), 2.36 [t, 2H, *J* = 7.6 Hz, $CH_3(CH_2)_2CH_2CO$], 2.27 [t, 2H, *J* = 7.4 Hz, $CH_3(CH_2)_2CH_2CO$], 1.51-1.68 [m, 6H, $CH_3(CH_2)_5CH_2CH_2O$ and 2×$CH_3CH_2CH_2CH_2CO$], 1.27-1.42 [m, 14H, $CH_3(CH_2)_5CH_2CH_2O$ and 2×$CH_3CH_2(CH_2)_2CO$], 0.94 [t, 3H, *J* = 7.6 Hz, $CH_3(CH_2)_3CO$], 0.91 [t, 3H, *J* = 7.6 Hz, $CH_3(CH_2)_3CO$], 0.88 [t, 3H, *J* = 7.0 Hz, $CH_3(CH_2)_7O$].

2.2.3. Octyl 2,4-di-*O*-hexanoyl-3,6-di-*O*-pentanoyl-β-D-glucopyranoside (7)

Diol **5** (50 mg, 0.109 mmol) on treatment with hexanoyl chloride (32 mg, 0.253 mmol) in dry pyridine (1 mL) for 12 h and CC purification gave compound **7** (66 mg) as a thick syrup in 92%.

R_f = 0.52 (*n*-hexane/EA = 4/1); FT-IR (KBr): ν 1755, 1749, 1742, 1738 cm^{-1} (CO); ^1H NMR (400 MHz, $CDCl_3$): δ_H 5.21 (t, 1H, *J* = 9.6 Hz, H-3), 5.04 (t, 1H, *J* = 9.6 Hz, H-4), 5.02 (dd, 1H, *J* = 9.6 Hz, H-2), 4.45 (d, 1H, *J* = 8.0 Hz, H-1), 4.22 (dd, 1H, *J* = 12.2 and 4.6 Hz, H-6a), 4.13 (dd, 1H, *J* = 12.2 and 2.0 Hz, H-6b), 3.85 [dt, 1H, *J* = 9.6 and 6.4 Hz, $CH_3(CH_2)_6CH_AH_BO$], 3.66-3.72 (m, 1H, H-5), 3.46 [dt, 1H, *J* = 9.6 and 6.8 Hz, $CH_3(CH_2)_6CH_AH_BO$], 2.24-2.39 [m, 8H, 2×$CH_3(CH_2)_2CH_2CO$ and 2×$CH_3(CH_2)_3CH_2CO$], 1.48-1.65 [m, 10H, $CH_3(CH_2)_5CH_2CH_2O$, 2×$CH_3CH_2CH_2CH_2CO$ and 2×$CH_3(CH_2)_2CH_2CH_2CO$], 1.20-1.35 [br m, 22H, $CH_3(CH_2)_5(CH_2)2O$, 2×$CH_3CH_2(CH_2)_2CO$ and 2×$CH_3(CH_2)_2(CH_2)_2CO$], 0.88-0.95 [m, 15H, $CH_3(CH_2)_7O$, 2×$CH_3(CH_2)_3CO$ and 2×$CH_3(CH_2)_4CO$].

2.2.4. Octyl 2,4-di-*O*-octanoyl-3,6-di-*O*-pentanoyl-β-D-glucopyranoside (8)

Reaction of the diol **5** (50 mg, 0.109 mmol) and octanoyl chloride (39 mg, 0.24 mmol) followed by work-up and CC gave compound **8** (67 mg, 87%) as a semi-solid which resisted crystallization.

R_f = 0.56 (*n*-hexane/EA = 4/1); FT-IR (KBr): ν 1754(2), 1742, 1738 cm^{-1} (CO); ^1H NMR (400 MHz, $CDCl_3$): δ_H 5.19 (t, 1H, *J* = 9.8 Hz, H-3), 5.05 (t, 1H, *J* = 9.8 Hz, H-4), 5.00 (dd, 1H, *J* = 9.6 Hz, H-2), 4.48 (d, 1H, *J* = 8.2 Hz, H-1), 4.20 (dd, 1H, *J* = 12.0 and 4.8 Hz, H-6a), 4.12 (dd, 1H, *J* =12.0 and 2.0 Hz, H-6b), 3.85 [dt, 1H, *J* = 9.6 and 6.4 Hz, $CH_3(CH_2)_6CH_AH_BO$], 3.68-3.72 (m, 1H, H-5), 3.44 [dt, 1H, *J* = 9.6 and 6.8 Hz, $CH_3(CH_2)_6CH_AH_BO$], 2.40 [t, 2H, *J* = 7.6 Hz, $CH_3(CH_2)_2CH_2CO$], 2.23-2.37 [m, 6H, $CH_3(CH_2)_2CH_2CO$ and 2×$CH_3(CH_2)_5CH_2CO$], 1.46-1.66 [m, 10H, $CH_3(CH_2)_5CH_2CH_2O$, 2×$CH_3CH_2CH_2CH_2CO$ and 2×$CH_3(CH_2)_4CH_2CH_2CO$], 1.18-1.38 [br m, 30H, $CH_3(CH_2)_5(CH_2)_2O$, 2×$CH_3CH_2(CH_2)_2CO$ and 2×$CH_3(CH_2)_4(CH_2)_2CO$], 0.88-0.96 [m, 15H, $CH_3(CH_2)_7O$, 2×$CH_3(CH_2)_3CO$ and 2×$CH_3(CH_2)_6CO$].

2.3. PASS predication

Nowadays, several freely available computational programs are available online, which predict multi-target profiles of drug-like compounds [38]. Prediction of drug bio-profiles provides a non-laborious and less expensive way for finding new human medicines. Computational assessment of bioactivity profiles shed light on the hidden pharmacological potential of the launched drugs. In this respect, we used web-based PASS (Prediction of Activity Spectra for Substances; http://www.way2drug.com/passonline/) for the prediction of a plethora of biological activities [39-41] which can predict or calculate a plethora of biological activities with 90% accuracy. The structures of the OBGs were drawn with ChemDraw 16.0, and then converted into their SD file format and used to calculate or predict biological spectrum using PASS online version (http://www.way2drug.com/passonline/). The calculated results are presented as Pa (probability for active compound) and Pi (probability for inactive compound). Here, Pa>Pi is considered on the scale of 0.000 to 1.000 and in general, Pa+Pi≠1.

2.4. Prediction of ADMET

Pharmacokinetic (PK) properties such as ADMET (absorption, distribution, metabolism, excretion, and toxicity) analyses of the synthesized CFA esters were determined using the pkCSM ADMET descriptors algorithm protocol (http://biosig.unimelb.edu.au) [42]. This could avoid the tremendous cost and time associated with the *in vivo* experiments for drug discovery. First of all, appropriate OBG esters were converted to InChI Key, isomeric SMILES (simplified molecular-input line-entry system), and SD file formats. These formats were used to predict ADMET from online pkCSM-pharmacokinetics [43]. In addition, these data were compared with standard antibiotic (drug) fluconazole.

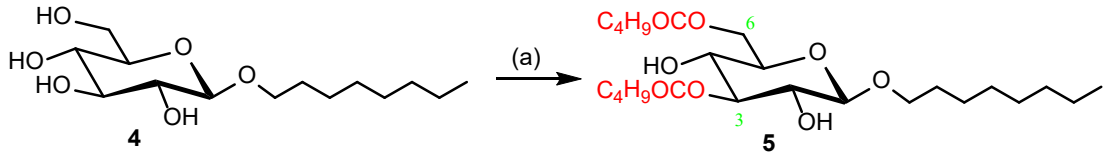
Nowadays, during the design of drug molecules, more attention is given to the molecules which fit into the rule of drug-likeness. For drug-likeness calculations, and medicinal chemistry friendliness,

the same SMILES of the compounds were used. We employed SwissADME free web tools (http://www.swissadme.ch) to calculate various related parameters [44]. As one of the most important chemical descriptors which correlate well with PK properties, the topological polar surface area (TPSA) was calculated and explained with other drug-likeness parameters.

3. Results and discussion

3.1. Synthesis of 3,6-di-*O*-pentanoate 5

Octyl β-D-glucoside **4**, a nonionic detergent, has been widely used for membrane protein solubilization. It is also useful for solubilizing enzymes, receptors, and phosphatidylcholine. It is non-toxic in cell lines, and inhibited the starch hydrolyzing enzyme α-amylase to a good extent [45]. Furthermore, it was observed that the dimolar acylation of **4** in only pyridine solution gave 3,6-di-*O*-pentanoate in lower yield (56%) [3]. To improve the yield, we conducted the reaction in different solvent systems. Even the use of DMAP catalyst also did not improve the yield. However, the use of a pyridine-chloroform (1:1) solvent system at 30 °C was found to produce a comparatively higher yield. Accordingly, OBG **3** was treated with dimolar pentanoyl chloride in pyridine-chloroform solution for 10 h at 30 °C. Usual workup and purification gave a solid (mp 62-65 °C) with a higher yield (67%) (Scheme 1).

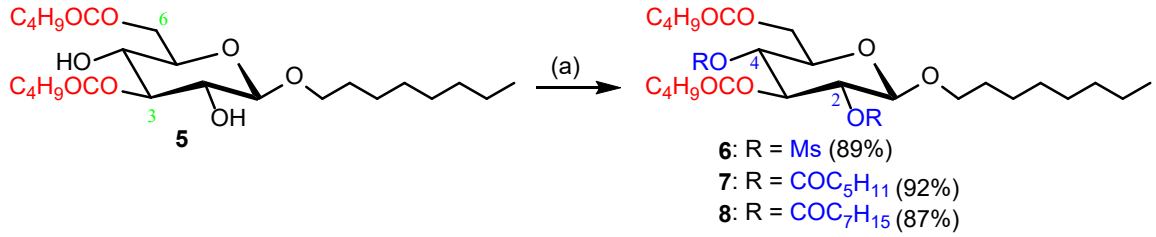


Scheme 1. Reagents and conditions: (a) Py-chloroform, C_4H_9COCl, 10-30 °C, 10 h, 67%.

The presence of hydroxyl stretching at 3250-3540 cm^{-1} and characteristic carbonyl bands at 1741 and 1733 cm^{-1} indicated the partial pentanoylation of the molecule. The fact was further confirmed by analyzing its ^1H NMR spectrum, where two-proton broad singlet corresponding to two hydroxyl protons appeared at δ 1.21-1.28. In addition to the glycosidic octyl group, extra eighteen protons appeared at the aliphatic region indicating the attachment of two pentanoyl groups in the molecule. The attachment of pentanoyl groups at C-3 and C-6 position was confirmed by the downfield shift of H-3 and H-6 protons compared to its precursor compound **4**. Finally, its ^{13}C NMR spectrum showed two carbonyl signals at δ 174.4 and 174.2, and thus, confirming the attachment of two pentanoyl groups in the molecule. Hence, the compound was assigned the structure as octyl 3,6-di-*O*-pentanoyl-β-D-glucopyranoside (**5**). The formation of 3,6-di-*O*-pentanoate **5** clearly indicated that the reactivity order of hydroxyl groups in OBG **4** follows 6-OH, 3-OH > 2-OH, 4-OH.

3.2. Synthesis of 2,4-di-*O*-acyl esters 6-8

Initially, pentanote **5** was treated with mesyl chloride at low temperature for 5 h, which upon purification, gave an oil an 89% yield (Scheme 2).



Scheme 2. Reagents and conditions: (*a*) dry Py, MsCl/$C_5H_{11}COCl$/ $C_7H_{15}COCl$, 0 °C-rt, 5-12 h.

Its FT-IR spectrum showed characteristic sulphonyl bands at 1365 and 1362 cm^{-1} in addition to two carbonyl bands. Also, the absence of hydroxyl stretching bands clearly demonstrated the mesylation of the molecule. In its ^1H NMR spectrum, two three-proton singlets at δ 3.29 and 3.15 ppm were assigned for the two mesyl (CH_3SO_2-) groups. The spectrum indicated considerable downfield shift of H-2 (δ 4.99) and H-4 (δ 5.10) protons as compared to its precursor compound **5** (δ 3.83-3.93 and 3.46-3.59, respectively). These observations are in agreement with the attachment of mesyl groups at C-2 and C-4 positions. Complete analysis of the rest of the NMR spectrum led us to assign the structure of the compound as octyl 2,4-di-*O*-mesyl-3,6-di-*O*-pentanoyl-β-D-glucopyranoside (**6**).

In the next step, dimolar hexanoylation of 5 for 14 h followed by chromatography furnished a thick syrup in 92% yield (Scheme 2). Its FT-IR spectrum showed the absence of hydroxyl bands and exhibited four carbonyl bands at 1755, 1749, 1742 and 1738 cm^{-1} indicating the attachment of hexanoyl group in the molecule. In the ^1H NMR spectrum, glycosidic octyl group protons appeared in the aliphatic region. In addition, extra twenty-two protons appeared at δ 2.24-2.39, 1.48-1.65, 1.20-1.35, 0.88-0.95 along with the protons of two pentanoyl groups (which were already present at C-3 and C-6 positions). Thus, in correlation with compound **6**, the structure of the compound was assigned as octyl 2,4-di-*O*-hexanoyl-3,6-di-*O*-pentanoyl-β-D-glucopyranoside (**7**).

Finally, the reaction of **5** with octanoyl chloride in dry pyridine for 12 h followed by usual work-up and purification provided a semi-solid in good yield which resisted crystallization. Its FT-IR spectrum showed absence of hydroxyl band and shoed characteristic stretchings at 1754(2), 1742, 1738 cm^{-1} (CO). In its ^1H NMR spectrum, total of sixty-five protons resonated in the aliphatic region in addition to the glucopyanoside protons (7H). The appearance of extra thirty protons (30H) represented the incorporation of two octanoyl groups in the molecule. Also, H-2 and H-4 resonated considerable down fields. Based on spectral evidence the structure of the compound was unambiguously assigned as octyl 2,4-di-*O*-octanoyl-3,6-di-*O*-pentanoyl-β-D-glucopyranoside (**8**).

3.2. PASS predicted biological activities

In recent years, some freely available via the internet computational tools for the prediction of biological activity profiles of drug-like compounds have appeared and used to search for new targets which lead to new drugs. We used the prediction of activity spectra for substances (PASS) programme (http://www.way2drug.com/passonline/) for our synthesized compounds [38-41].

Having characterized CFA esters **5-8** in hand, their biological profile was predicted by PASS [38]. PASS biological results in its designated Pa and Pi form is presented in Table 1.

Table 1. PASS predicted biological activities of the compound **4**-**8**.

Drug	Biological activity							
	Antibacterial		Antifungal		Anti-carcinogenic		Antioxidant	
	Pa	Pi	Pa	Pi	Pa	Pi	Pa	Pi
4	0.529	0.014	0.685	0.010	0.751	0.007	0.600	0.005
5	0.563	0.011	0.738	0.008	0.798	0.005	0.560	0.005
6	0.500	0.016	0.541	0.024	0.551	0.015	0.372	0.015
7	0.544	0.013	0.705	0.009	0.646	0.011	0.508	0.006
8	0.544	0.013	0.705	0.009	0.646	0.011	0.508	0.006
TTC	0.694	0.005	0.523	0.023	-	-	-	-
FCZ	-	-	0.726	0.008	-	-	-	-

Pa = Probability 'to be active'; Pi = Probability 'to be inactive'; TTC = tetracycline; FCZ = fluconazole.

As shown in Table 1, PASS predication indicated that di-*O*-pentanoate **5** possess the highest antifungal activities (Pa = 0.738) which is higher than that of the antifungal drug fluconazole (Pa = 0.726). Like other sugar-based mesyl esters [36], the addition of mesyl group(s), as in compound **6**, decreased antifungal potentiality (Pa = 0.541). While addition aliphatic ester group(s), as in **7** and **8**, increased antifungal activities (Pa = 0.705). Thus, esterification of OBG (**4**) with fatty acyl groups increased its antifungal potentiality than the sulphonyl ester. Similarly, esterification of OBG (**3**) with fatty acyl groups raised its antibacterial activity than the sulphonyl ester (**6**) although lower than the standard antibacterial drug tetracycline.

Notably, the addition of fatty acyl groups like pentanoyl increased the anti-carcinogenic properties of OBG (**4**). However, these CFA esters **5**-**8** have a lower antioxidant profile. In all respect, mesyl ester **6** showed a poor biological spectrum compared to aliphatic esters. Overall, the PASS predication indicated $0.50<Pa<0.56$ for antibacterial and $0.54<Pa<0.74$ for antifungal. Thus, the synthesized CFA esters **5**-**8** should be more potent against fungi than that of bacterial pathogens.

3.5. ADMET properties

Pharmacokinetic (PK) descriptors ADMET (absorption, distribution, metabolism, excretion, and toxicity) analyses of the synthesized compounds were determined using the pkCSM protocol (http://biosig.unimelb.edu.au) [42-43] and mentioned in Table 2. The absorption of drugs depends on factors including membrane permeability [indicated by colon cancer cell line (Caco-2)], human intestinal absorption (HIA), and P-glycoprotein substrate or inhibitor (P-gpI). Several CFA esters (**7**-**8**) were found 100% HIA which were better than that of the fluconazole (87.82%). These compounds are not P-glycoprotein inhibitor. Their distribution as indicated by the blood-brain barrier (BBB), and central nervous system (CNS) permeability are also comparable to fluconazole. The CFA esters **5**-**8** including OBG (**4**) have better renal clearance concerning the standard drug. The prediction of toxicity, as indicated by the human ether-a-go-go-gene (hERG) inhibitor and oral rat acute toxicity (LD_{50}), indicated that these CFA esters are safe to use.

Table 2. ADMET calculation of glucopyaranosides **4**-**8**.

Drug	Absorption			Distribution		Metabolism	Excretion	Toxicity	
	C2P	HIA (%)	P-gpI	BBB (permeability)	CNS (permeability)	CYP3A4 substrate	Total clearance	hERG inhibitor	LD_{50} (rat)
4	-0.191	39.392	No	-1.212	-3.431	No	1.671	No	2.18
5	0.803	74.46	Yes	-0.929	-0.929	Yes	1.879	No	2.527
6	-0.229	100	Yes	-2.623	-3.741	Yes	1.468	No	2.041
7	0.818	100	Yes	-1.979	-2.794	Yes	1.774	No	1.758
8	0.776	100	Yes	-2.067	-2.688	Yes	1.845	No	2.113
FZ	1.191	87.82	No	-1.200	-3.221	No	0.386	No	2.21

C2P = Caco-2 permeability (log Papp in 10^{-6} cm/s, >0.90 indicates high permeability); HIA = Human intestinal absorption (% absorbed, >30% is better absorbed); P-gpI = P-glycoprotein inhibitor; BBB (blood brain barrier) is expressed in logBB (logBB >-1.0 is moderately cross blood brain barrier); CNS is expressed as logPS (logPS>-2.0 can easily penetrate the CNS); Total clearance is expressed in log mL/min/kg; Toxicity is calculated in oral rat acute toxicity (mol/kg); FZ = fluconazole.

Drug-likeness calculation was conducted by the SwissADME program [44] and summarized in Table 3. According to the Lipinski rule, one of the most important chemical descriptors that correlate well with PK properties is the topological polar surface area (TPSA), and the TPSA of a good drug should be less than 140 $Å^2$. In the present study, all the CFA esters (except sulphonyl ester **6**) have TPSA less than 124 $Å^2$ (Figure 3) and this satisfies the Lipinski rule. Metabolism is predicted based on the CYP models for substrate or inhibition (CYP1A2, CYP2C19, CYP2C9, CYP2D6, and CYP3A4) indicated an acceptable range (Table 3). Pan-assay interference compounds (PAINS) are chemical compounds that often give false-positive results in high-throughput screens. It is clear from Table 3 that these synthesized compounds have not violated PAINS. Also, the CFA esters do not have any toxic functional group(s). Based on both ADME and SwissADME along with PASS results, it can be expected that the OBG based CFA esters, especially **7** and **8**, could be better dug candidates. Encouraged by these results *in vivo* and *in vitro* ADMET related other applied studies will be conducted for further confirmation of such compounds [45-49].

Table 3. Calculation of drug-likeness using SwissADME descriptors.

Drug	HB acceptors	HB donors	TPSA $Å^2$	CYP1A2 inhibitor	CYP2C19 inhibitor	CYP2C9 inhibitor	CYP2D6 inhibitor	CYP3A4 inhibitor	PAINS alerts
4	6	4	99.38	No	No	No	No	No	0
5	8	2	111.52	No	Yes	N o	No	Yes	0
6	12	0	174.56	No	Yes	No	No	No	0
7	10	0	123.66	No	No	No	No	No	0
8	10	0	123.66	No	No	No	No	No	0

*HB = Hydrogen bond, TPSA = Topological polar surface area, PAINS = Pan-assay interference compounds

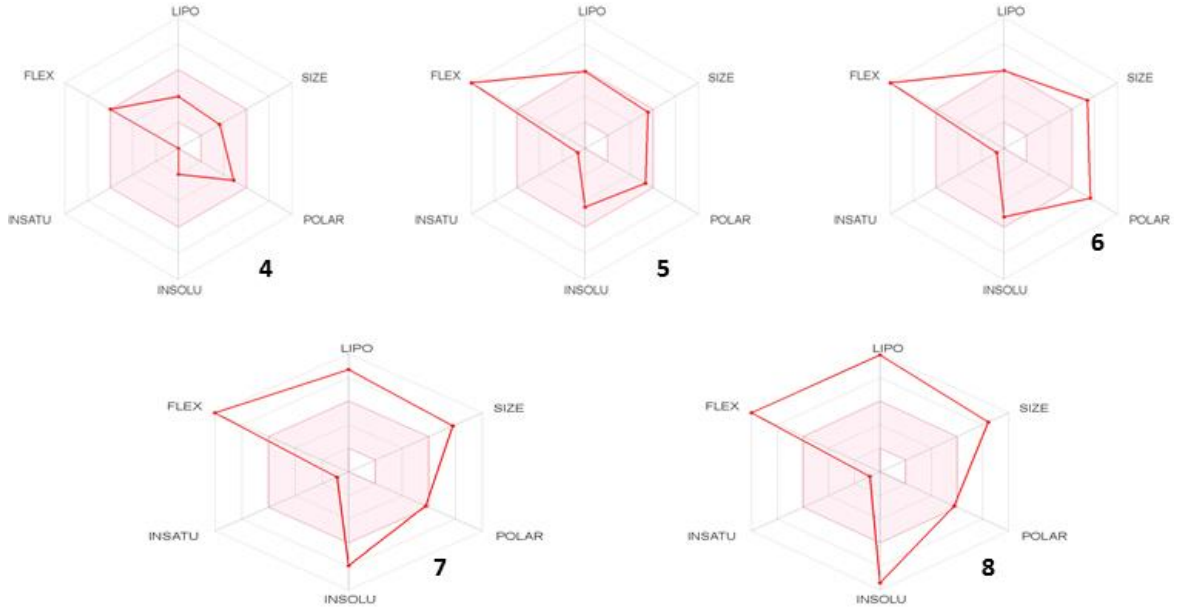


Figure 3. Topological polar surface area (TPSA) of glucopyranoside **4-8**.

4. Conclusion

An efficient method for di-*O*-pentanoylation of octyl β-D-glucopyranoside (**4**) with improved yield is discussed. Easy reaction conditions and convenient work-up procedure will make the technique favourable for further application in other sugars. For structural elucidation as well as to get newer CFA esters, dipentanoate **5** was further converted into three 2,4-di-*O*-acylates **6-8** in good yields. All the CFA esters (**5-8**) were characterized well by spectroscopic techniques. PASS predication profile indicated that esterification of OBG (**4**) with fatty acyl groups increased its antifungal potentiality more than the sulphonyl ester. Pharmacokinetic (PK) descriptors ADMET showed safer nature of these CFA esters concerning human intestinal absorption (HIA), human ether-a-go-go-gene (hERG) inhibition and rat acute oral toxicity (LD_{50}). Also, drug-likeness calculation as conducted by the SwissADME programme was in support of the ADMET and PASS predication results. Especially, the CFA esters topological polar surface area (TPSA) was found below 124 $Å^2$. Based on these encouraging results, further biological studies are in progress to establish them as potential antifungal agents.

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