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In Silico Biological Profile Prediction of Some Selectively Synthesized Acyl Rhamnopyranosides

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Abstract

Over the past several decades significant biological activities including brains protective and antimicrobial activities have made sugar esters (SEs) as a topic of great interest. In this context, unimolar 3-chlorobenzoylation of methyl α-L-rhamnopyranoside (**4**) using dibutyltin oxide method regioselectively furnished only the 3-*O*-substitution product **5** in excellent yield. The reaction proceeded *via* the formation of a cyclic 2,3-*O*-dibutylstannylene intermediate where equatorial hydroxyl group is activated by the tin atom leading to the formation of product **5** only. To get biologically important rhamnopyranoside esters chlorobenzoate **5** was further converted into three newer 2,4-di-*O*-acyl products **6**-**9** with other acylating agents using direct acylation method. Prediction of activity spectra for substances (PASS) indicated that these rhamnopyranoside esters have many promising biological profiles including CYP2H substrate, membrane permeability inhibitor and better antifungal activities. Additionally, ADMET and drug likeness properties of SEs **5**-**8** were predicted and discussed.

Keywords: Acylation; Dibutyltin oxide (DBTO) method; Methyl α-L-rhamnopyranoside; PASS predication; Regioselectivity.

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1. Introduction

A plethora of biological properties of carbohydrate derivatives like good stabilizing and conditioning properties, non-ionic and biodegradable surfactants, and antimicrobial properties made them special attention towards researchers [1,2]. Among the carbohydrate derivatives monosaccharide-based sugar esters (SEs) are important due to their amphiphilic, biodegradable, nonirritating, nontoxic, and environment friendly nature [3-6]. In addition to their uses as detergent and cosmetic products, some SEs are used in the food, pharmaceutical, detergent, agricultural, fine chemical, and personal care industries considering their suitable insecticidal and antimicrobial activities [7-9]. Recently, Matin *et*

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al. [10] reported the synthesis of several uridine-based SEs and observed that the sugar ester part(s) of uridines (**1**, Fig. 1) is more potent against SARS-CoV-2 main protease (Mpro; 7BQY) as compared to the traditional drug hydroxychloroquine (HCQ). Various SEs were found to active against *E. coli*, *L. monocytogenes*, methicillin resistant *S. aureus* (MRSA), and psychrotrophic spoilage microorganisms [11]. Therefore, the SEs have been important component(s) of drug targets, and their design, development and synthesis play a significant value in the medicinal applications.

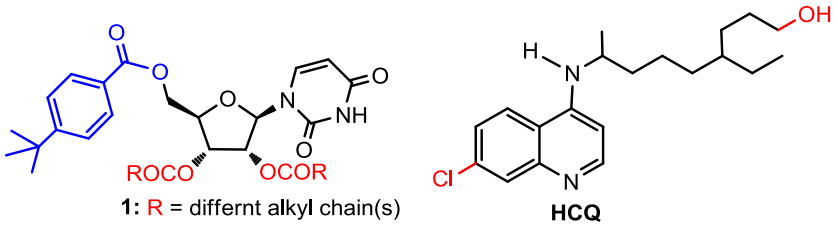


Fig. 1. Structure of uridine ester **1** and HCQ.

SEs can be prepared by an esterification reaction between sugar/sugar alcohols (e.g., mannose, fructose, glucose, sorbitol, xylitol, rhamnose, sucrose) and nonpolar fatty acids [12,13]. The higher substitution esters like hexa (C6) to laura (C12) have application in fat replacers. The lower substitution esters such as mono-, di-, and tri-esters are reported to have use in oil-in-water (O/W) as well as water-in-oil (W/O) emulsifiers [14]. SEs are also used as synthetic intermediates of various natural products synthesis due to the presence of multifunctional groups, [15-17], and hence, they contribute in the design and development of new drugs [18,19]. Although various methods were reported for SEs synthesis [20-25] the presence of several similar reactive 2° hydroxyl groups with tremendous structural variation made selective acylation (esterification) challenging [26]. Most of the synthetic methods have both advantages and shortcomings like complex processes of multiple steps, tedious, expensive, low selectivity and gave extremely low yield [27-28]. Thus, direct acylation method [29-31] and dibutyltin oxide (DBTO) method [32-35] are preferred for the SEs synthesis.

From the structure activity relationship (SAR) it was observed that the rhamnopyranoside-based esters (**2**, Fig. 2) showed cytotoxic activity against several different cancers causing cell lines [36]. In 2020, four novel rhamnopyranose esters (**3a-d**, Fig. 2) were isolated from the *P. odorata* which demonstrated triple-negative breast cancer suppressive activities and antioxidant properties [37]. Our group also reported the synthesis of various SEs that incorporated ester group(s) at different position of rhamnose which enhanced its antimicrobial functionality [38-41] like other SEs [42-43]. Considering all these promising results, several 3-*O*-(3-chlorobenzoyl)rhamnopyranosides (**5-8**) were synthesized starting from the commercially available methyl α-L-rhamnopyranoside (**4**). Their spectroscopic characterization, PASS predicted antimicrobial activities, ADMET (absorption, distribution, metabolism, excretion, and toxicity) and drug-likeness properties are discussed here.

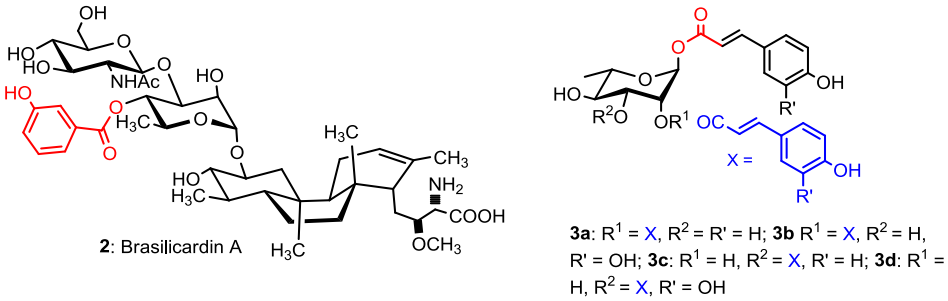


Fig. 2. Structure of bioactive rhamnopyranosides **2-3**.

2. Experimental

2.1. *Materials and general methods*

Methyl α-L-rhamnopyranoside (starting sugar), acylating agents, and related reagents/solvents were commercially available (Merck, Germany) and were used as received, unless otherwise mentioned. Melting point (mp) was determined on an electro-thermal melting point apparatus (England) and is uncorrected. Evaporations were carried out under low pressure using a Buchi rotary evaporator (R-100, Switzerland) with a bath temperature below 40 °C. Thin layer chromatography (TLC) was conducted on Kieselgel GF_{254} and the spots were detected by spraying the plates with 1% methanolic H_2SO_4 and heating at 150–200 °C until coloration appeared. For work-up the reaction(s) was stopped by adding a few pieces of ice to the reaction mixture to decompose excess acyl halide. The product was then 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 over Na_2SO_4 and concentrated. The residue thus obtained on column chromatographic purification gave the corresponding pure compound(s). For column chromatography (CC) silica gel G_{60} was used. The solvent system employed for the TLC analyses was different ratios of *n*-hexane/ethyl acetate (EA). In all the cases distilled solvents were used. FT-IR spectra were scanned on a FT-IR spectrophotometer (Shimadzu, IR Prestige-21) in $CHCl_3$. ^1H NMR (400 MHz, Bruker DPX-400 spectrometer, Switzerland) spectra were recorded in $CDCl_3$ solution using tunable multinuclear probe at Wazed Miah Science Research Centre (WMSRC), Jahangirnagar University, Bangladesh. For the chemical shift measurements tetramethylsilane (TMS) was used as an internal standard and reported in δ scale (ppm). Coupling constant (*J*) values are shown in Hertz (Hz).

2.2. *Synthesis*

2.2.1. *Methyl 3-O-(3-chlorobenzoyl)-α-L-rhamnopyranoside (**5**)*

Methyl α-L-rhamnopyranoside (**4**) (0.5 g, 2.806 mmol) and dibutyltin oxide (0.768 g, 3.085 mmol) were dissolved in anhydrous methanol (20 mL). The mixture was heated under reflux condition in nitrogen atmosphere until a clear solution was obtained (~5 h). Removal of the solvent under reduced pressure gave intermediate tin complex (**4a**), as a white solid. The tin complex was dissolved in dry 1,4-dioxane (20 mL) and treated with 3-chlorobenzoyl chloride (0.540 g, 3.086 mmol) and stirring was continued at room temperature for 12 h when TLC indicated the formation of faster moving single product. Removal of the solvent gave a thick liquid which was subjected for silica gel column chromatography. Initial *n*-hexane (50 mL) was eluted to remove excess tin compound. Further elution with *n*-hexane-ethyl acetate (1:5) furnished the title compound **5** (0.791 g, 89%) as needles, mp 140-l42 °C (ethyl acetate-hexane) [44].

R_f = 0.45 (with *n*-hexane/EA = 1/2); FT-IR ($CHCl_3$) υ_{max} (cm^{-1}): 3360-3560 (OH), 1695 (CO); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H ppm: 8.15 (s, 1H, Ar-*H*) 8.05 (d, *J* = 7.9 Hz, 1H, Ar-*H*), 7.65 (d, *J* = 8.0 Hz, 1H, Ar-*H*), 7.52 (t, *J* = 4.6 Hz, 1H, Ar-*H*), 5.15 (dd, *J* = 9.4 and 3.3 Hz, 1H, H-3), 4.65 (d, *J* = 1.5 Hz, 1H, H-l) 3.72-3.76 (m, 3H, H-2, H-4 and H-5), 3.40 (s, 3H, 1-OCH_3), 1.33 (d, 3H, *J* = 5.7 Hz, 6- CH_3).

2.2.2. *Methyl 3-O-(3-chlorobenzoyl)-2,4-di-O-octanoyl-α-L-rhamnopyranoside (**6**)*

Octanoylation of the diol **5** (0.100 g, 0.316 mmol) in anhydrous pyridine for 12 h followed by usual work-up (mentioned in the Section 2.1) and CC furnished the title compound **6** (0.155 g, 86%) as a clear oil.

R_f = 0.52 (*n*-hexane/EA = 5/1); FT-IR ($CHCl_3$) υ_{max} (cm^{-1}): 1752, 1748, 1698 (CO); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H ppm: 7.92 (s, 1H, Ar-*H*), 7.84 (d, *J*=8.0 Hz, 1H, Ar-*H*), 7.46 (d, *J*=8.0 Hz, 1H, Ar-*H*), 7.37 (t, *J*=5.6 Hz, 1H, Ar-*H*), 5.40 (dd, *J*=10.0 and 3.3 Hz, 1H, H-3), 5.33 (d, *J*=3.3 Hz, 1H, H-2), 5.28 (t, *J*=10.0 Hz, 1H, H-4), 4.62 (s, 1H, H-1), 3.82-3.88 (m, 1H, H-5), 3.40 (s, 3H, 1-OCH_3), 2.26-2.38 [m, 4H, 2×$CH_3(CH_2)_5CH_2$CO], 1.53-1.62 [m, 4H, 2×$CH_3(CH_2)_4CH_2CH_2$CO], 1.27 (d, *J*=6.2 Hz, 3H, 6-CH_3), 1.18-1.36 [br m, 16H, 2×$CH_3(CH_2)_4(CH_2)_2$CO], 0.89-0.94 [m, 6H, 2×$CH_3(CH_2)_6$CO].

2.2.3. *Methyl 3-O-(3-chlorobenzoyl)-2,4-di-O-decanoyl-α-L-rhamnopyranoside (**7**)*

Reaction of the diol **5** (0.100 g, 0.316 mmol) with decanoyl chloride (0.133 g, 0.697 mmol) for 13 h followed by usual work-up and CC gave compound **7** (0.171 g, 87%) as a semi-solid which resisted crystallization.

R_f = 0.54 (*n*-hexane/EA = 5/1); FT-IR ($CHCl_3$) υ_{max} (cm^{-1}): 1755, 1747, 1696 (CO); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H ppm: 7.94 (s, 1H, Ar-*H*), 7.88 (d, *J*=7.8 Hz, 1H, Ar-*H*), 7.46 (d, *J*=7.8 Hz, 1H, Ar-*H*), 7.37 (t, *J*=5.2 Hz, 1H, Ar-*H*), 5.43 (dd, *J*=9.8 and 3.2 Hz, 1H, H-3), 5.36 (d, *J*=3.2 Hz, 1H, H-2), 5.29 (t, *J*=9.8 Hz, 1H, H-4), 4.63 (s, 1H, H-1), 3.80-3.85 (m, 1H, H-5), 3.42 (s, 3H, 1-OCH_3), 2.276-2.41 [m, 4H, 2×$CH_3(CH_2)_7CH_2$CO], 1.51-1.61 [m, 4H, 2×$CH_3(CH_2)_6CH_2CH_2$CO], 1.29 (d, *J*=6.4 Hz, 3H, 6-CH_3), 1.18-1.39 [br m, 24H, 2×$CH_3(CH_2)_6(CH_2)_2$CO], 0.87-0.94 [m, 6H, 2×$CH_3(CH_2)_8$CO].

2.2.4. *Methyl 3-O-(3-chlorobenzoyl)-2,4-di-O-lauroyl-α-L-rhamnopyranoside (**8**)*

Diol **5** (0.100 g, 0.316 mmol) on treatment with lauroyl chloride (0.152 g, 0.694 mmol) in anhydrous pyridine (1 mL) for 12 h and CC purification gave compound **8** (0.197 g) as a thick syrup in 92%.

R_f = 0.55 (*n*-hexane/EA = 5/1); FT-IR ($CHCl_3$) υ_{max} (cm^{-1}): 1756, 1748, 1698 (CO); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H ppm: 7.95 (s, 1H, Ar-*H*), 7.78 (d, *J*=8.2 Hz, 1H, Ar-*H*), 7.38-7.44 (m, 2H, Ar-*H*), 5.41 (dd, *J*=10.0 and 3.4 Hz, 1H, H-3), 5.36 (d, *J*=3.4 Hz, 1H, H-2), 5.31 (t, *J*=10.0 Hz, 1H, H-4), 4.60 (s, 1H, H-1), 3.85-3.89 (m, 1H, H-5), 3.42 (s, 3H, 1-OCH_3), 2.28-2.42 [m, 4H, 2×$CH_3(CH_2)_9CH_2CO$], 1.52-1.61 [m, 4H, 2×$CH_3(CH_2)_8CH_2CH_2CO$], 1.26 (d, *J*=6.2 Hz, 3H, 6-CH_3), 1.18-1.43 [br m, 32H, 2×$CH_3(CH_2)_8(CH_2)_2CO$], 0.88-0.94 [m, 6H, 2×$CH_3(CH_2)_{10}CO$].

2.3. *PASS Predication*

In silico prediction of drug bio-profiles provides a non-laborious and less expensive way to find novel drug candidates, and also shed light on the hidden pharmacological potential of the launched drugs [45]. Considering these aspects, we have used web-based PASS (Prediction of Activity Spectra for Substances; http://www.way2drug.com/passonline/) for the prediction of biological activities of the synthesized SEs [45-47]. It is well known program which can predict/calculate a plethora of biological activities with 90% accuracy. In this program, calculated results are shown as Pa (probability for active compound) and Pi (probability for inactive compound) in the scale 0.000 to 1.000 where Pa+Pi≠1. First of all, appropriate geometry of the rhamnopyranoside esters were drawn and converted to InChI Key, isomeric SMILES (simplified molecular-input line-entry system), and SD file formats which were used for the prediction.

2.4. *ADME/T analysis*

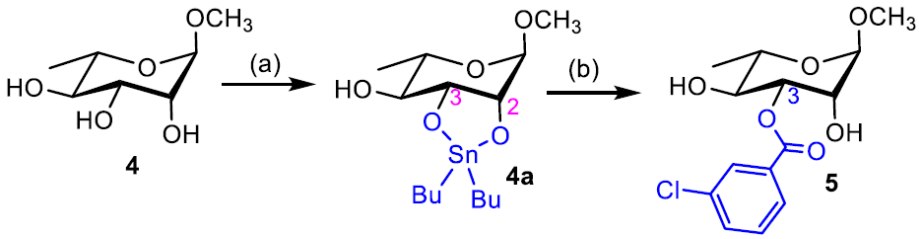
Pharmacokinetic (PK) properties such as absorption, distribution, metabolism, excretion, and toxicity (ADMET) calculations of the synthesized SEs were determined using the pkCSM ADMET protocol (http://biosig.unimelb.edu.au) [48]. In all the calculations, SMILES and SD file formats of the SEs were used. In addition, SwissADME based free web tools (http://www.swissadme.ch) was employed to calculate various drug-likeness related parameters [49-50].

3. Results and Discussion

3.1. *Regioselective monobenzoylation at C-3 position of rhamnopyranoside 4*

Our first aim was to check the regioselectivity of three 2° hydroxyl groups present in the methyl α-L-rhamnopyranoside (**4**) by the dibutyltin oxide (DBTO) method. Thus, initial treatment of **4** with the dibutyltin oxide in anhydrous methanol under reflux condition

afforded corresponding intermediate tin complex **4a** (Scheme 1). Tin complex **4a**, on unimolecular reaction with 3-chlorobenzoyl chloride furnished a solid (mp 140-142 °C) in good yield (Scheme 1).



Scheme 1. Reagents and conditions: (*a*) Bu_2SnO, MeOH, reflux, 5 h; (*b*) 3-Cl.C_6H_4COCl, 1,4-dioxane, rt, 12 h, 88 %.

In its FT-IR spectrum, appearance of absorption bands at 3360-3560 and 1695 cm^{-1} suggested the presence of carbonyl and hydroxyl groups in the molecule i.e., partial chlorobenzoylation of the molecule. In its ^1H NMR spectrum, a doublet at δ 4.65 with small coupling constant (1.5 Hz) was assigned for equatorially oriented H-1. Again, additional four aromatic protons resonated at δ 8.15 (s, 1H), 8.05 (d, 1H), 7.65 (d, 1H) and 7.52 (t, 1H) which clearly indicated the incorporation of one chlorobenzoyl group in the molecule. The huge downfield shift of H-3 to δ 5.15 from its usual value (~δ 4.00) [34-35] suggested the incorporation of 3-chlorobenzoyl group at C-3 position. Complete analysis of its spectrum led us to assign its structure as methyl 3-*O*-(3-chlorobenzoyl)-α-L-rhamnopyranoside (**5**).

Mechanism: The formation of regioselective 3-*O*-(3-chlorobenzoyl) ester **5** may be rationalized by assuming that initially a highly stable five-membered stannylene ring **4a** was formed between the *cis*-vicinal glycol system which is present only between the C-2 OH (axial) and C-3 OH (equatorial) groups of the rhamnopyranoside **4** (Fig. 3). Such type of tin complex formation (such as **4b**) mechanism was also proposed and explained by Tsuda *et al*. [51] wherein tin atom selectively activates the equatorial oxygen atom than the axial one. Thus, acyl halide selectively attacks equatorial C-3 position leading to the formation of only C-3 substituted mono-ester **5** [52].

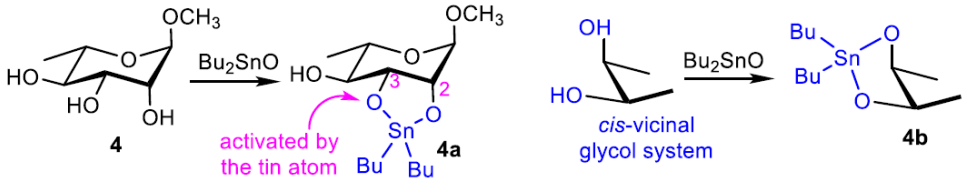
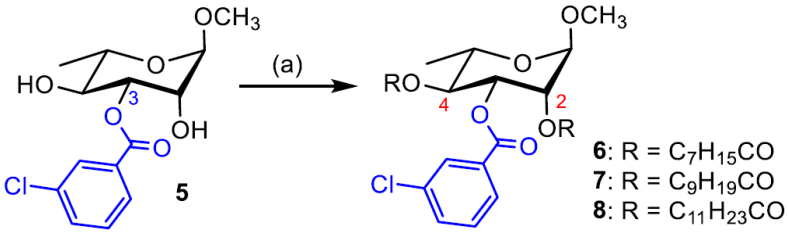


Fig. 3. Activation of *cis*-vicinal glycol system by DBTO method.

3.2. *Synthesis of 2,4-di-O-acyl esters 6-8 from chlorobenzoate 5*

Having successful preparation of 3-*O*-chlorobenzoate **5**, some 2,4-di-*O*-acyl esters were prepared with three acylating agents of different chain length (C8-C12) to get biological potential SEs (Scheme 2). Thus, direct reaction of diol **5** with dimolar octanoyl chloride in pyridine for 12 h furnished oily compound in 86 % (Scheme 2).



Scheme 2. Reagents and conditions: (*a*) dry Py, $C_7H_{15}COCl/C_9H_{19}COCl/ C_{11}H_{237}COCl$, 0 °C-rt, 12-13 h; **6** = 86 %; **7** = 87 %; **8** = 92%.

Its FT-IR showed disappearance of hydroxyl stretching and exhibited υ_{max} 1752, 1748 and 1698 cm^{-1} corresponding to three carbonyl groups. In addition, its ^1H NMR spectrum showed new appearance of thirty aliphatic protons at δ_H 2.26-2.38 (m, 4H), 1.53-1.62 (m, 4H), 1.18-1.36 (br m, 16H) and 0.89-0.94 (m, 6H) which clearly indicated the attachment of two octanoyloxy groups in the compound. Due to the addition of octanoyl oxy groups at C-2 and C-4 positions H-2 and H-4 resonated considerable down fields (Table 1). Thus, the structure of the compound was established as methyl 3-*O*-(3-chlorobenzoyl)-2,4-di-*O*-octanoyl-α-L-rhamnopyranoside (**6**)

Table 1. ^1H NMR shift values of protons (δ ppm, *J* in Hz).

SEs	H-1	H-2	H-3	H-4	H-5	H-6
5	4.65	3.72-3.76	5.15	3.72-3.76	3.72-3.76	1.33
6	4.62	5.33	5.40	5.28	3.82-3.88	1.27
7	4.63	5.36	5.43	5.29	3.80-3.85	1.29
8	4.60	5.36	5.41	5.31	3.85-3.89	1.26

Similarly, reaction of the diol **5** with di-molar decanoyl chloride in anhydrous pyridine followed by usual work-up and CC gave a faster moving semi-solid in good yield (Scheme 2). Its FT-IR spectrum showed carbonyl characteristic stretching at 1755, 1747 and 1696 cm^{-1} indicating decanoylation of the molecule. This was further supported by its ^1H NMR spectrum where extra thirty-eight aliphatic protons resonated at δ_H 2.276-2.41 (m, 4H), 1.51-1.61 (m, 4H), 1.18-1.39 (br m, 24H) and 0.87-0.94 (m, 6H) which corresponded to two decanoyl groups. Also, H-2 and H-4 shifted down fields as compared to its precursor compound **5** (Table 1). Thus, the structure of the compound was established as methyl 3-*O*-(3-chlorobenzoyl)-2,4-di-*O*-decanoyl-α-L-rhamnopyranoside (**7**).

Encouraged by the formation of **6** and **7**, lauroyl chloride is used as potential fatty acid halide for esterification (acylation) of chlorobenzoate **5**. Di-molar lauroylation of the diol **5** furnished a thick syrupy compound (Scheme 2). Its FT-IR spectrum exhibited characteristic bands at 1756, 1748 and 1698 cm^{-1}. ^{1}H NMR also indicated the presence of two lauroyloxy groups in the molecule as it showed extra forty-six aliphatic protons. Considering the down field shift H-2 and H-4 protons (Table 1), and complete analysis of its spectra the structure of the compound was assigned as methyl 3-*O*-(3-chlorobenzoyl)-2,4-di-*O*-lauroyl-α-L-rhamnopyranoside (**8**).

3.3. *PASS predicted biological activities*

Web based PASS (Prediction of Activity Spectra for Substances; http://www.way2drug.com/passonline/) [45-47] predication selective results are presented in Table 2. The data indicated that these rhamnopyranoside esters **5**-**8** could be more active against fungal pathogens (0.66 < Pa < 0.70) as compared to bacterial organisms (0.53 < Pa < 0.54). However, the PASS study revealed that these compounds have lower anticarcinogenic (Pa < 0.57) and antioxidant (Pa < 0.40) properties than the rhamnopyranoside **4** (Pa 0.662 and 0.65, respectively). Encouragingly, all the SEs (**5**-**8**) showed excellent Pa value (> 0.90) for CYP2H substrate and membrane permeability inhibitors. It should be noted that inhibition of mitochondrial membrane permeability is a putative pharmacological target for cardio-protection, and hence, these SEs could have potentiality for the treatment of acute myocardial infarction (AMI).

Table 2. Predicted biological activities of **4**-**8** using PASS software.

Drug	Biological Activity							
	Antibacterial		Antifungal		Anticarcinogenic		Antioxidant	
	Pa	Pi	Pa	Pi	Pa	Pi	Pa	Pi
4	0.574	0.010	0.650	0.013	0.662	0.010	0.650	0.004
5	0.537	0.013	0.665	0.012	0.571	0.014	0.400	0.012
6	0.545	0.013	0.700	0.010	0.449	0.024	0.315	0.021
7	0.545	0.013	0.700	0.010	0.449	0.024	0.315	0.021
8	0.545	0.013	0.700	0.010	0.449	0.024	0.315	0.021

Pa = Probability 'to be active'; Pi = Probability 'to be inactive'

3.4. *In silico ADME/T studies*

In the present study ADMET (absorption, distribution, metabolism, excretion, and toxicity) properties of the SEs was calculated from pkCSM online server (http://biosig.unimelb.edu.au) [48]. It should be noted that ADMET are the most important properties of pharmacokinetic (PK) profiles. As shown in Table 3, the SEs have good absorption especially human intestinal absorption and comparable to the standard drug fluconazole. SEs **5** and **6** aren't P-glycoprotein inhibitor while higher molecular weight compounds **7** and **8** are P-glycoprotein inhibitor. P-glycoprotein inhibition can interrupt the absorption, permeability and retention of the chemical species. Their

distribution through blood brain barrier (BBB) and central nervous system (CNS) are almost similar to that of fluconazole.

However, these compounds can't metabolize easily as they aren't CYP3A4 enzyme substrate (except **5**). Their excretion through renal system is excellent and better than the fluconazole. They aren't human ether-a-go-go-related gene (hERG) inhibitor, and hence, they can be used as safe drug as hERG inhibitor causes fatal long QT syndrome to human. Their safer use is further supported by their low rat acute toxicity value (expressed as LD_{50}, Table 3).

Table 3. ADMET calculation of rhamnopyranoside derived SEs **5**-**8**.

Drug	Absorption			Distribution		Metabolism	Excretion	Toxicity	
	C2P	HIA (%)	P-gpI	BBB (permeability)	CNS	CYP3A4 substrate	Total clearance	hERG inhibitor	LD_{50} (rat)
4	0.648	75.31	No	-0.67	-3.162	No	0.628	No	1.403
5	0.635	72.84	No	-0.679	-3.041	No	0.35	No	2.562
6	0.896	84.92	No	-1.505	-2.565	Yes	0.546	No	1.819
7	0.848	87.82	Yes	-1.593	-2.489	Yes	0.669	No	1.695
8	0.800	90.72	Yes	-1.679	-2.442	Yes	0.792	No	1.696
FCZ	1.191	87.82	No	-1.200	-3.221	No	0.386	No	2.210

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); FCZ = fluconazole.

Considering the medicinal importance of the rhamnopyranoside esters [53] additional drug likeness properties are mentioned in Table 4 as calculated from the SwissADME [49]. SwissADME calculation indicated that all the SEs have good hydrogen bonds donor or acceptor.

Table 4. Calculation drug likeliness using SwissADME programme.

Dr-ug	HBA	HBD	TPSA Å²	Rotatable bonds	Water Solubility (class)	GI absorption	PAINS alerts	Drug likeness score
4	5	3	79.15	1	Highly soluble	High	0	-0.48
5	6	2	85.22	4	Soluble	High	0	-0.19
6	8	0	97.36	20	Poorly soluble	Low	0	-0.51
7	8	0	97.36	24	Poorly soluble	Low	0	-0.51
8	8	0	97.36	28	Insoluble	Low	0	-0.51

*HBA = Hydrogen bond acceptor, HBD = Hydrogen bond donor, TPSA = Topological polar surface area, GI = Gastrointestinal; PAINS = Pan-assay interference compounds.

Topological polar surface area (TPSA) data showed the good agreement with the acceptable values (below 86 $Å^2$) where the TPSA value should be less than 140 $Å^2$ (Fig.

4). With the increase of the chain length of the acyl group(s) their water solubility decreased. Gastrointestinal absorption of **5** is high whereas **6**-**8** are low. More importantly, none of the SEs violates Pan-assay interference compounds (PAINS) whereas positive PAINS value indicates false results in high-throughput screens with numerous biological targets. Overall, drug likeness scores of rhamnopyranosides **4**-**8** using Molsoft's chemical fingerprints are found to be moderate (Table 4 and Fig. 5).

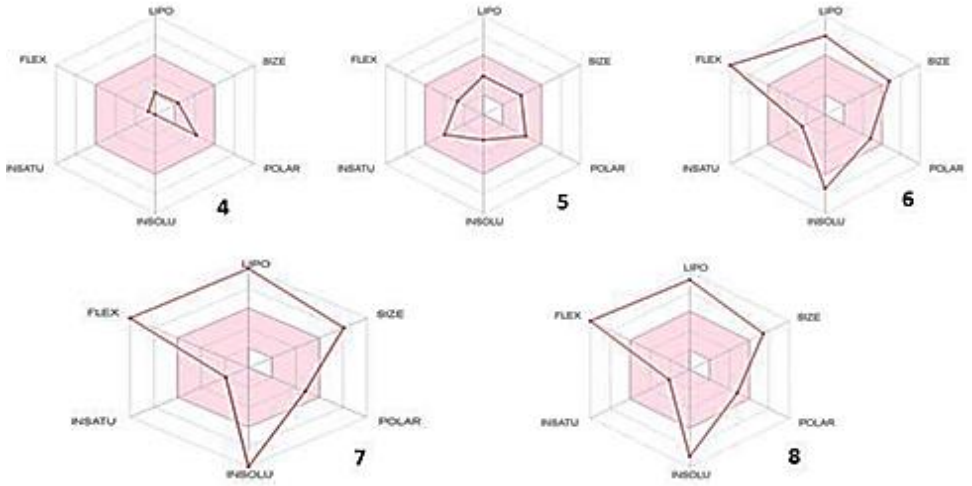


Fig. 4. TPSA of synthesized rhamnopyranosides.

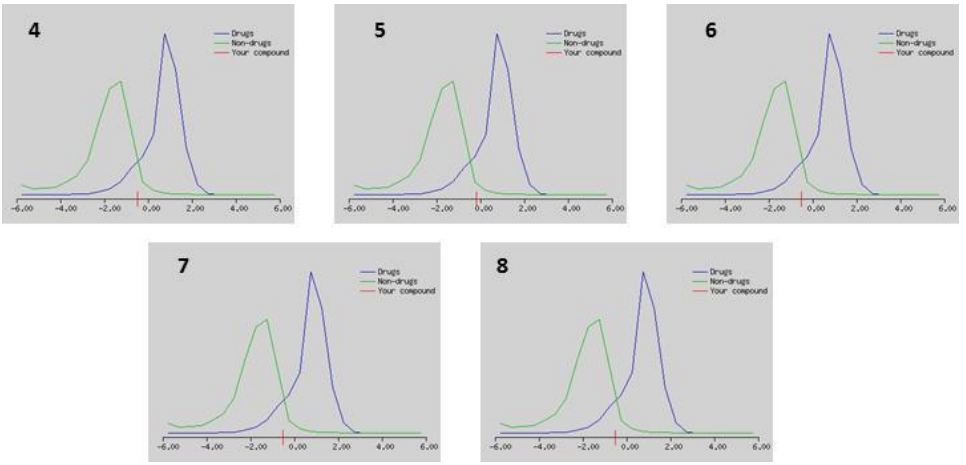


Fig. 5. Drug likeness score of synthesized rhamnopyranosides.

4. Conclusion

Dibutyltin oxide mediated 3-chlorobenzoylation of methyl α-L-rhamnopyranoside (**4**) furnished 3-*O*-substitution product **5** only indicating regioselectivity at C-3 position. Three 2,4-di-*O*-acyl esters **6**-**8** of chlorobenzoate **5** were also prepared by direct method. PASS predication indicated that their better effectiveness as antifungal agents than as antibacterial with other promising biological profiles. In this context their pharmacokinetic profile like ADMET and drug likeness properties are predicted and discussed.

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