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Synthesis of Protected D-Glucopyranosides as Mucormycosis Inhibitors: DFT, Docking, ADMET, and SAR Studies

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Abstract

Fungal infections especially mucormycosis cause devastating health problems worldwide and the recent invasion of mucormycosis (*Mucorales*) after SARS-CoV-2 infection worsens the severity of patient conditions leading to increased deaths. Non-ionic sugar esters (SEs) with amphiphilic properties show antimicrobial activities and have potential applications in medicines, foods, agriculture, and pharmaceutical industries. Several benzylidene-protected glucopyranoside esters were synthesized and their*in vitro* antifungal potentialities were assessed. With encouraging results against *Alternaria alternata* their potentialities were checked by molecular docking with three black fungus-related proteins (PDB ID: 4BFN, 4BFO, and 2WTP) which indicated that the presence of hexanoyl group at the C-2 position of glucopyranoside skeleton highly increased its binding affinities. Hence, it can be an alternative to azole drugs for the treatment of mucormycosis infections. Molecular orbital, global reactivity descriptors, drug-likeness, and structure-activity relationship are used to rationalize these binding results and to ensure that the compounds are safe for humans.

Keywords: Antifungal; Black fungus; Methyl α-D-glucopyranoside; Molecular docking; Glucose esters.

1. Introduction

Among the biomolecules, sugars are important resources for the synthesis of novel biodegradable and biocompatible products [1,2]. Depending on the degree and nature of ester group(s) these SEs can be exploited for their potential applications in surfactant, cosmetic, pharmaceutical, and food industries [3-6]. In pharmaceutical industries, hydrophilic-lipophilic balance (HLB) controlled SEs (e.g. sucrose stearate) are used to get desired drug release rate and to improve the tablet qualities with compaction [7]. In food-related industries, several suitable biochemical and physical properties of SEs (such as shelf life, antimicrobial activities, tasteless, odorless, non-toxic, biodegradable, etc.) lead to their extensive applications [8-13]. Besides, these modified sugars showed noteworthy interactions with target enzymes, which is different from the original sugar molecules [14].

However, site-selective mono-acyl SEs preparation has long been faced with numerous inherent challenges [15-17]. This is due to the existence of several secondary hydroxyl groups with almost similar reactivity and generally producing a mixture of esters [18]. Hence, many methods for site-selective acylation of sugars are developed [19-23]. Of the sugar-based products, acyl sugars or sugar esters (SEs) have both hydrophilic and lipophilic moieties [7]. By controlling hydrophobic alkyl chains, synthetic SEs-protected glucose esters are

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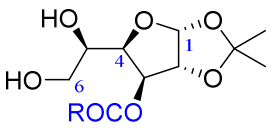
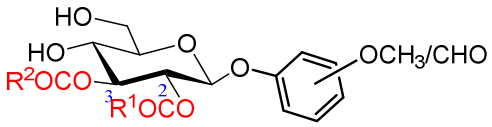
found suitable to increase drug properties in hyper-proliferative and inflammatory agents and pave the way to synthesize newer bioactive products [24-27]. For example, 3-*O*-acyl glucofuranoses (**1a-c**; Figure 1) were found significant to regularize uncontrolled cell growth in erythroid tumor cells [28]. The ester moiety, especially the palmitoyl group as in glucopyranoside **2** related to papulacandin D (a standard antifungal drug) showed antifungal properties against *Candida albicans* and *C. tropicalis* [29].



1a: R = $CH_2CH_2CH_3$
1b: R = $CH_2CH(CH_3)_2$
1c: R = $C(CH_3)_3$

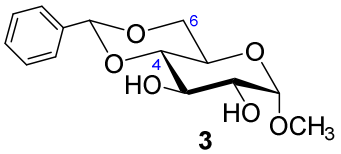


2a: R^1 = H, R^2 = $CH_2(CH_2)_{13}CH_3$
2b: R^1 = $CH_2(CH_2)_{13}CH_3$, R^2 = H
2c: R^1 = R^2 = $CH_2(CH_2)_{13}CH_3$

Fig. 1. Structure of glucose ester **1** and **2**

Mucormycosisalso called black fungus (soil fungus) [30], is a deadly fungal infection causing a higher mortality rate for immune-compromised patients [31]. During the massive second wave of SARS-CoV-2, the death toll increased in India due to black fungal infection along with COVID infection [32-33]. Steroidal drugs (used to treat COVID-19 patients) were found to increase the severity of mucormycosis. In search for alternative medicine to the commonly prescribed drugs (amphotericin B, posaconazole, or isavuconazole) some D-glucose esters are investigated as many SEs are reported to possess antifungal efficacy [34-35]. Recently, it was observed that protected D-glucose esters in the furanose form exhibited excellent binding affinity (approximately -8.00 kcal/mol) with the soil fungal protein [36].

The significant antimicrobial results of SEs along with biodegradability, non-toxicity, hydrophilic-lipophilic balance (HLB), lower irritation to eyes and skin, and emulsifying stability [37] encourage the synthesis and study of protected glucopyranosides **3-5** (Figure 2) for antifungal properties, especially to check their binding energy with mucormycosis's pathogens (black fungus; PDB ID: 4BFN, 4BFO and 2WTP). Besides, density functional theory (DFT) based on molecular orbital, thermodynamic properties, and drug-likeness properties are discussed here.



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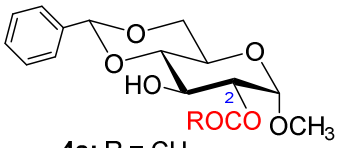
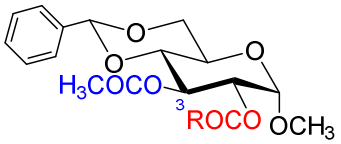


4a: R = CH_3
4b: R = $(CH_2)_4CH_3$
4c: R = $(CH_2)_6CH_3$
4d: R = $(CH_2)_8CH_3$



5a: R = CH_3; **5b:** R = $(CH_2)_4CH_3$
5c: R = $(CH_2)_6CH_3$; **5d:** R = $(CH_2)_8CH_3$

Fig. 2. Protected glucopyranoside **3** derived esters **4a-d** and **5a-d**

2. Experimental

2.1. Preparation of protected glucopyranosides

The protected methyl 4,6-*O*-benzylidene-α-D-glucopyranoside (**3**) was successfully prepared from methyl α-D-glucopyranoside in 75% yield using

literature procedure [15], mp 162-163 °C (lit. mp 166-167 °C).

*General procedure for selective 2-O-acylation of glucopyranoside **3** using dibutyltin oxide method*: In this method, a solution of dibutyltin oxide (0.485 g, 1.948 mmol) in dry methanol (15 mL) was added to**3** (0.5 g, 1.772 mmol) and the mixture was heated under gentle reflux under nitrogen atmosphere until the mixture became homogeneous and transparent (~4 h). The solution was then refluxed for an additional hour and the solvent was removed under reduced pressure. The white tin complex suspension in 1,4-dioxane was treated with an unimolar amount of acetic anhydride/ hexanoyl chloride/ octanoyl chloride/ decanoyl chloride and was stirred at room temperature overnight. Evaporation of the solvent under reduced pressure left a solid residue, which was passed through packed silica gel columns eluting with petroleum ether to remove the contaminating tin compounds. Further elution with petroleum ether: ethyl acetate (5:1) gave the corresponding 2-*O*-acylated product (**4a-d**).

Methyl 2-*O*-acetyl-4,6-*O*-benzylidene-α-D-glucopyranoside (4a): R_f = 0.47 (*n*-hexane/ethyl acetate (EA) = 3/1). Needles, mp 131-133 °C; yield = 82%. FT-IR (neat): 1714 (CO), 3220-3490 cm^{-1} (OH).^{1}H NMR ($CDCI_3$, 400 MHz): δ_H 7.43-7.49, 7.32-7.37 (2×m, 5H, Ar-*H*), 5.56 (s, 1H, PhC*H*), 4.92 (dd, *J* = 3.5 and 10.0 Hz, 1H, H-2), 4.82 (d, *J* = 3.6 Hz, 1H, H-1), 4.70 (t, *J* = 9.8 Hz, 1H, H-3), 4.28-4.32 (m, 1H, H-5), 4.15 (t, *J* = 9.8 Hz, 1H, H-4), 3.84-3.87 (m, 1H, H-6a), 3.60-3.64 (m, 1H, H-6b), 3.36 (s, 3H, OCH_3), 2.16 (s, 3H, $COCH_3$).

Methyl 4,6-*O*-benzylidene-2-*O*-hexanoyl-α-D-glucopyranoside (4b): R_f = 0.49 (*n*-hexane/EA = 3/1). Colorless syrup, yield = 67% [38].FT-IR (neat): 3350-3560 (OH), 1712 cm^{-1} (CO);^{1}H NMR ($CDCI_3$, 400 MHz): δ_H 7.46-7.52, 7.33-7.38 (2×m, 5H, Ar-*H*), 5.56 (s, 1H, PhC*H*), 4.92 (dd, *J* = 9.5 and 3.7 Hz, 1H, H-2),4.82 (d, *J* = 3.7 Hz, 1H, H-1),4.70 (t, *J* = 9.7 Hz, 1H, H-3),4.30-4.34 (m, 1H, H-5),4.15 (t, *J* = 9.7 Hz, 1H, H-4),3.83-3.87 (m, 1H, H-6a), 3.60-3.65 (m, 1H, H-6b),3.35 (s, 3H, OCH_3),2.38-2.43 [m, 2H, $CH_3(CH_2)_3CH_2CO$],1.66-1.72 [m, 4H, $CH_3CH_2(CH_2)_2CH_2CO$],1.27-1.36 [m, 2H, $CH_3CH_2(CH_2)_3CO$], 0.95 [t, *J* = 6.8 Hz, 3H, $CH_3(CH_2)_4CO$].Anal. Calcd. for $C_{20}H_{28}O_7$: C 63.14, H 7.41; found: C 63.21, H 7.45%.

Methyl 4,6-*O*-benzylidene-2-*O*-octanoyl-α-D-glucopyranoside (4c): R_f = 0.50 (*n*-hexane/EA = 3/1). Syrup, yield = 81% [38]. FT-IR (neat): 3340-3520 (OH), 1710 cm^{-1} (CO); ^{1}H NMR ($CDCI_3$, 400 MHz): δ_H 7.48-7.53, 7.35-7.42 (2×m, 5H, Ar-*H*), 5.55 (s, 1H, PhC*H*), 4.94 (dd, *J* = 9.6 and 3.7 Hz, 1H, H-2),4.84 (d, *J* = 3.7 Hz, 1H, H-1),4.71 (t, *J* = 9.6 Hz, 1H, H-3),4.33-4.37 (m, 1H, H-5),4.15 (t, *J* = 9.8 Hz, 1H, H-4),3.81-3.84 (m, 1H, H-6a), 3.60-3.64 (m, 1H, H-6b),3.36 (s, 3H, OCH_3),2.35-2.41 [m, 2H, $CH_3(CH_2)_5CH_2CO$],1.64-1.69 [m, 4H, $CH_3(CH_2)_3(CH_2)_2CH_2CO$],1.27-1.38 [m, 6H, $CH_3(CH_2)_3(CH_2)_3CO$], 0.94 [t, *J* = 7.0 Hz, 3H, $CH_3(CH_2)_6CO$].

Methyl 4,6-*O*-benzylidene-2-*O*-decanoyl-α-D-glucopyranoside (4d): R_f = 0.52 (*n*-hexane/EA = 3/1). Clear syrup, yield = 78% [38]. FT-IR (neat): 3320-3510 (OH), 1710 cm^{-1} (CO); ^{1}H NMR ($CDCI_3$, 400 MHz): δ_H 7.50-7.54, 7.33-7.37 (2×m, 5H, Ar-*H*), 5.56 (s, 1H, PhC*H*), 4.98 (dd, *J* = 9.7 and 3.7 Hz, 1H, H-2),4.88 (d, *J* = 3.7 Hz, 1H, H-1),4.75 (t, *J* = 9.7 Hz, 1H, H-3),4.35-4.39 (m, 1H, H-5),4.16 (t, *J* = 9.7 Hz, 1H, H-4),3.83-3.88 (m, 1H, H-6a), 3.60-3.64 (m, 1H, H-6b),3.35 (s, 3H, OCH_3), 2.29-2.34 [m, 2H, $CH_3(CH_2)_7CH_2CO$],1.69-1.73 [m, 2H, $CH_3(CH_2)_6CH_2CH_2CO$], 1.23-1.38 [m, 12H, $CH_3(CH_2)_6(CH_2)_2CO$], 0.96 [t, *J* = 7.2 Hz, 3H, $CH_3(CH_2)_8CO$].

*General procedure for 3-O-acylation of glucopyranoside **4a-d** using direct method*: Compound **4a-d** (0.1 g) was separately dissolved in dry pyridine (1 mL). The solution was cooled with ice water and little excess of acetic anhydride was added slowly followed by stirring at room temperature for 8-10 h. Excess acetic anhydride was decomposed by adding 0.5 mL water and extracted with dichloromethane. The organic layer was washed with 5% HCl (3×3mL), dried over anhydrous $MgSO_4$, concentrated, and purified by silica gel column chromatography (*n*-hexane/EA), which gave corresponding 3-*O*-acetates **5a-d** in good yields.

Methyl 2,3-di-*O*-acetyl-4,6-*O*-benzylidene-α-D-glucopyranoside (5a): R_f = 0.52 (*n*-hexane/ethyl acetate (EA) = 4/1). Clear solid, mp 108-110 °C; yield = 93%. FT-IR (neat): 1716, 1712 cm^{-1} (CO); ^{1}H NMR ($CDCI_3$, 400 MHz): δ_H 7.47-7.52, 7.33-7.39 (2×m, 5H, Ar-*H*), 5.61 (t, *J* = 9.7 Hz, 1H, H-3), 5.55 (s, 1H, PhC*H*), 5.10 (dd, *J* = 3.7 and 9.7 Hz, 1H, H-2), 4.92 (d, *J* = 3.8 Hz, 1H, H-1), 4.29-4.33 (m, 1H, H-5), 4.15 (t, *J* = 9.7 Hz, 1H, H-4), 3.77-3.81 (m, 1H, H-6a), 3.64-3.68 (m, 1H, H-6b), 3.41 (s, 3H, OCH_3),

2.14, 2.19 (2×s, 6H, 2×COCH_3).

Methyl 3-*O*-acetyl-4,6-*O*-benzylidene-2-*O*-hexanoyl-α-D-glucopyranoside (5b): R_f = 0.56 (*n*-hexane/EA = 4/1). Homogeneous syrup, yield = 83% [38].FT-IR (neat): 1710, 1690 cm^{-1} (CO);^{1}H NMR ($CDCI_3$, 400 MHz): δ_H 7.45-7.52, 7.33-7.38 (2×m, 5H, Ar-*H*), 5.61 (t, *J* = 9.7 Hz, 1H, H-3), 5.55 (s, 1H, PhC*H*), 5.10 (dd, *J* = 3.7 and 9.6 Hz, 1H, H-2), 4.92 (d, *J* = 3.8 Hz, 1H, H-1),4.28-4.33 (m, 1H, H-5),4.15 (t, *J* = 9.7 Hz, 1H, H-4),3.77-3.81 (m, 1H, H-6a),3.64-3.69 (m, 1H, H-6b),3.40 (s, 3H, OCH_3),2.35-2.39 [m, 2H, $CH_3(CH_2)_3CH_2CO$],2.10 (s, 3H, CH_3CO),2.02-2.08 [m, 2H, $CH_3(CH_2)_3CH_2CH_2CO$],1.35-1.43 [m, 4H, $CH_3(CH_2)_2(CH_2)_2CO$], 0.95 [t, *J* = 7.2 Hz, 3H, $CH_3(CH_2)_6CO$].

Methyl 3-*O*-acetyl-4,6-*O*-benzylidene-2-*O*-octanoyl-α-D-glucopyranoside (5c): R_f = 0.57 (*n*-hexane/EA = 4/1). Syrup, yield = 80% [38].FT-IR (neat): 1712, 1698 cm^{-1} (CO);^{1}H NMR ($CDCI_3$, 400 MHz): δ_H 7.51-7.57, 7.33-7.38 (2×m, 5H, Ar-*H*), 5.62 (t, *J* = 9.6 Hz, 1H, H-3), 5.56 (s, 1H, PhC*H*), 4.96 (dd, *J* = 3.7 and 9.6 Hz, 1H, H-2), 4.86 (d, *J* = 3.7 Hz, 1H, H-1),4.29-4.34 (m, 1H, H-5),4.14 (t, *J* = 9.6 Hz, 1H, H-4),3.82-3.86 (m, 1H, H-6a), 3.68-3.71 (m, 1H, H-6b),3.33 (s, 3H, OCH_3),2.38-2.43 [m, 2H, $CH_3(CH_2)_5CH_2CO$],2.05 (s, 3H, CH_3CO),1.64-1.72 [m, 4H, $CH_3(CH_2)_3(CH_2)_2CH_2CO$], 1.27-1.38 [m, 6H, $CH_3(CH_2)_3(CH_2)_3CO$], 0.92-0.97 [m, 3H, $CH_3(CH_2)_6CO$].

Methyl 3-*O*-acetyl-4,6-*O*-benzylidene-2-*O*-decanoyl-α-D-glucopyranoside (5d): R_f = 0.61 (*n*-hexane/EA = 4/1). Needles, mp 60-61 °C; yield = 77% [38]. FT-IR (neat): 1710, 1695 cm^{-1} (CO); ^{1}H NMR ($CDCI_3$, 400 MHz): δ_H 7.52-7.57, 7.30-7.36 (2×m, 5H, Ar-*H*), 5.64 (t, *J* = 9.7 Hz, 1H, H-3), 5.55 (s, 1H, PhC*H*), 4.98 (dd, *J* = 3.7 and 9.7 Hz, 1H, H-2), 4.85 (d, *J* = 3.7 Hz, 1H, H-1), 4.32-4.37 (m, 1H, H-5), 4.15 (t, *J* = 9.7 Hz, 1H, H-4), 3.80-3.84 (m, 1H, H-6a), 3.63-3.67 (m, 1H, H-6b), 3.35 (s, 3H, OCH_3), 2.30-2.34 [m, 2H, $CH_3(CH_2)_7CH_2CO$], 2.01 (s, 3H, CH_3CO), 1.62-1.66 [m, 2H, $CH_3(CH_2)_6CH_2CH_2CO$], 1.26-1.38 [m, 12H, $CH_3(CH_2)_6(CH_2)_2CO$], 0.94 [t, *J* = 6.8 Hz, 3H, $CH_3(CH_2)_8CO$]. Anal. Calcd. for $C_{26}H_{38}O_8$: C 65.2, H 8.00; found: C 65.32, H 8.10%.

2.2. Ligand (SEs) optimization and calculation of chemical reactivity and descriptors

First, the appropriate geometry of methyl α-D-glucopyranoside was collected from the Chemspider. All the necessary structures were then drawn in ChemDraw followed by the preliminary minimization with MM2 which is attached to ChemDraw 3D. Compounds **3**-**5** were finally optimized using the Gaussian 09 program [39]. B3LYP functional and 3-21G* basis sets were used throughout the DFT process [40] in a Core i7 processor. Various chemical reactivity descriptors and frontier MOs (molecular orbitals) are calculated from their optimized structures. The equations used in this regard are- energy gap, $\Delta\varepsilon = \varepsilon_{LUMO} - \varepsilon_{HOMO}$; ionization potential, $I = -\varepsilon_{HOMO}$; electron affinity, $A = -\varepsilon_{LUMO}$; electronegativity, $\chi = (I+A)/2$; chemical potential, $\mu = -(I+A)/2$; hardness, $\eta = (I-A)/2$; electrophilicity, $\omega = \mu^2/2\eta$; softness, $S = 1/\eta$.

2.3. In vitro antifungal evaluation

Antifungal activities of the protected glucopyranoside esters **4**-**5** were assessed *in vitro* against two fungi viz. *Macrophominaphaseolina* (Tassi) Goid and *Alternaria alternata* (Fr.) Kedissler. The poisoned food technique [41] in Sabouraud (agar and broth, PDA) medium was used for the assessment [42]. A mycelial disc of 6 mm diameter was cut out from 5 to 7 day old fungal culture. It was aseptically positioned onto the center of the potato dextrose agar (PDA) plates. The plates contain the test compound (100 µg/mL). Positive and negative control plates were prepared for each fungus. The inoculated plates were incubated at 37 °C and colony diameter was measured and recorded for five days (24 h intervals) of incubation. For validity, the results were compared with the standard antifungal drugfluconazole (100 µg/mL medium, brand name Omastin, Beximco Pharmaceuticals Ltd., Bangladesh). Three replications were prepared for each treatment. The percentage of mycelial growth inhibition was calculated as [43]:

$$\%\,inhibition = \frac{mean\ diameter\ \ fungal\ colony\,(control) - mean\ diameter\ fungal\ colony\,(compd.)}{mean\ diameter\ \ fungal\ colony\,(control)} \times 100$$

2.4. Molecular docking procedure

Mucormycosis proteins such as 2WTP, 4BFO and 4BFN were collected from PDB (Protein Data Bank) in their 3D structures [44]. These were then opened in software named PyMOL V2.3 (https://pymol.org/2/). These were purified by removing H_2O and unnecessary ligands present there followed by saving them as PDB files. Molecular docking of the optimized compounds **3**-**5** was then performed in AutoDock Vina (PyRx software) using these purified proteins. Discovery Studio (Release 4.0, 2013) was thoroughly used to view docked complex and necessary calculations and analysis.

2.5. ADMET data calculation and Lipinski rule

Considering the importance of AMDET (absorption, distribution, metabolism, excretion, and toxicity) parameters this prediction was performed before molecular docking of **3**-**5**. SwissADME online database (http://www.swissadme.ch) and amdetSAR (http://lmmd.ecust.edu.cn/admetsar2) database were used as the most acceptable predictor for ADMET calculations [45].

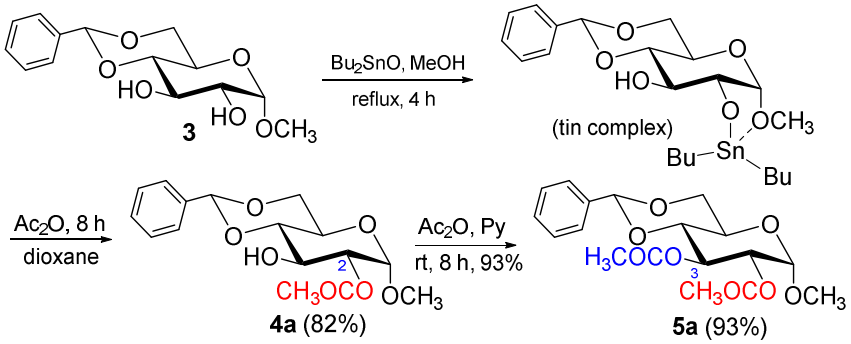
3. Results and discussion

3.3.1. Synthesis of protected glucopyranoside esters and their optimized structures

Considering a variety of significant biological properties of carbohydrate derivatives, protected glucopyranose **3** was selected for the present study. Upon preparation of compound **3** as per the literature procedure (Demchenko et al. 2006), **3** was subjected to selective acetylation using the dibutyltin oxide (DBTO) method and furnished a solid (Scheme 1). The solid showed both CO (1714 cm^{-1}) and OH (3220-3490 cm^{-1}) stretchings in its FT-IR spectrum. In the ^1H NMR spectrum, the appearance of a three-proton singlet at δ 2.16 indicated the attachment of only one acetyl group in the molecule. In addition, the downfield shift of H-2 at δ 4.92 as compared to precursor **3** confirmed the attachment of the acetyl group at the C-2 position.

This observation is already explained for the acylation of glucosides by the DBTO method that a tin-complex is formed between *cis*-vicinal glycol systems of the molecule [46]. In the absence of such systems tin complex is formed with a hydroxyl group and coordinated with the anomeric oxygen (close to the *cis*-vicinal system). In the present study, substrate compound **3** doesn't have any *cis*-vicinal system. Thus, the tin complex must form between the C-2 OH and anomeric alpha oxygen as presented in Scheme 1. In such a tin complex, equatorial OH (C-2 OH) is more activated by the intermediate tin-complex. Thus, the compound was named methyl 2-*O*-acetyl-4,6-*O*-benzylidene-α-D-glucopyranoside (**4a**).

Further direct acetylation of **4a** in dry pyridine with acetic anhydride gave **5a** in good yield (Scheme 1) and was characterized by spectroscopic techniques.



Scheme 1. Synthesis of **4a** and **5a** starting from **3**

Following a similar strategy, compound **4b-d** and their 3-*O*-acetyl derivatives **5b-d** were prepared as reported earlier [38].

In the last decade, molecular geometry study and energy minimization by computational programs have been used for a variety of experimental and theoretical investigations. In our study, DFT optimization was used to check the conformation of a protected glucopyranose ring. The obtained structures of **3-5** are presented in Figure 3, which clearly indicated that these molecules retained their $^4C_1$ conformation (although bond angles slightly varied).

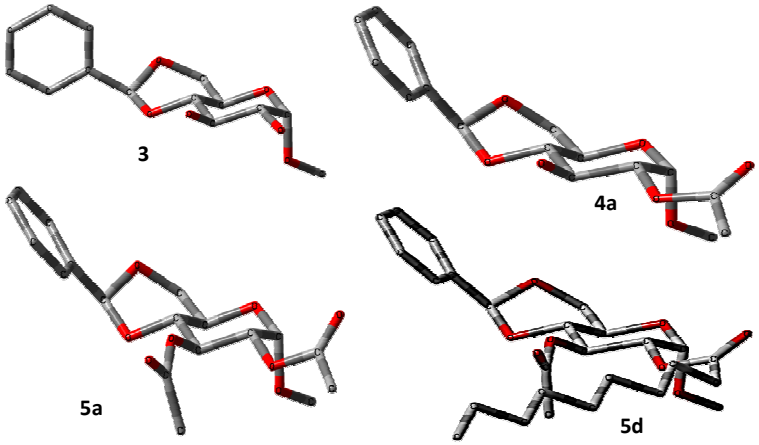


Fig. 3. DFT optimized structures of **3-5** (H atoms are omitted)

3.2. Molecular orbitals and chemical reactivity descriptors

Molecular orbitals of the glucopyranosides in the HOMO and LUMO forms (known as *frontier orbitals*) are computed from their DFT-optimized structures using GaussView 5.0. It is observed that the pi-bonds of the phenyl group and the oxygen atom(s) of pyranose and benzylidene rings contributed to the HOMO (Figure 4). This part is responsible for the electrophilic attack. Whereas, the alkyl chain(s) mostly contributed to the LUMO part and is responsible for the attack of any nucleophile. In the biological context, more stabilized LUMO (lower value) contributed to excellent activities [47]. Thus, the theoretical biological activities of the glucopyranoside esters are also related to their MOs, especially LUMO (Figure 4).

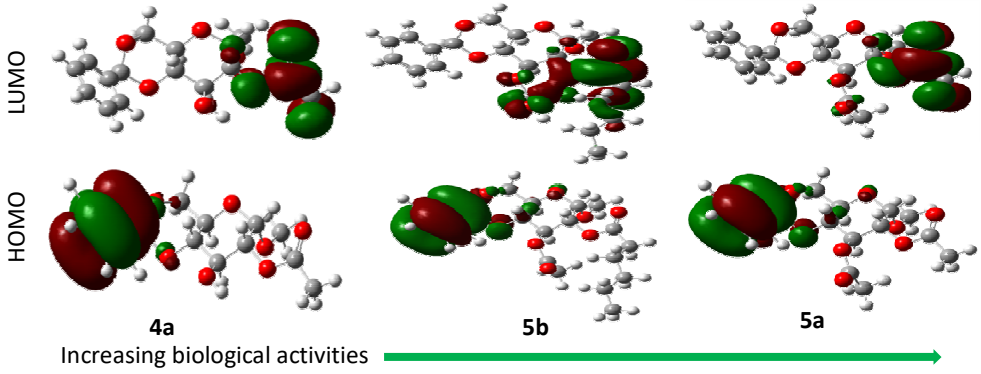


Fig. 4. The HOMO and LUMO isosurfaces of some glucopyranoside esters

The global reactivity parameters are of great importance in determining the behavior of compounds. The magnitude of theoretical reactivity parameters is summarized in Table 1, which iscalculated by applying the equations mentioned in the experimental section.

The LUMO-HOMO (**Δε**) energy gap parameters indicate the chemical activity and stability of any molecule. All the esters have almost similar **Δε** (6.5-7.1 eV) indicating their almost similar reactivity and stability. The electrophilicity index (ω) indicates the stabilization energy of any molecules and is considered a powerful tool for the study of the reactivity of organic compounds. Table 1 indicates that all the glucopyranosides have a strong electrophilicity index (ω > 1.5 eV). However, hexanoate **5b** (2.538 eV) and acetate **4a** (2.595 eV) have excellent electrophilicity and can act as strong electrophiles in polar reactions. With the addition of ester moiety in **3**, the hardness of the molecules slightly increased and softness slightly decreased as compared to non-ester **3**. Hence, the biological activity of SEs **4**-**5** should be better and more stable than **3** as per the maximum hardness principle (MHP) [48].

Table 1.

Frontier molecular orbitals (FMO) and reactivity descriptor analysis of **3**-**5**

Mol	εLUMO (eV)	εHOMO (eV)	Δε (eV)	I (eV)	A (eV)	μ (eV)	χ (eV)	η (eV)	ω (eV)	S (eV)
3	-0.844	-7.176	6.332	7.176	0.844	-4.010	4.010	3.166	2.539	0.316
4a	-0.950	-6.923	5.973	6.923	0.950	-3.937	3.937	2.987	2.595	0.335
4b	-0.046	-6.508	6.462	6.508	0.046	-3.277	3.277	3.231	1.662	0.310
4c	-0.040	-6.507	6.467	6.507	0.040	-3.274	3.274	3.234	1.657	0.309
4d	-0.037	-6.510	6.473	6.510	0.037	-3.274	3.274	3.237	1.654	0.309
5a	-0.210	-6.628	6.418	6.628	0.210	-3.419	3.419	3.209	1.821	0.312
5b	-0.845	-7.165	6.320	7.165	0.845	-4.005	4.005	3.160	2.538	0.316
5c	-0.177	-6.683	6.506	6.683	0.177	-3.430	3.430	3.253	1.808	0.307
5d	-0.174	-6.686	6.512	6.686	0.174	-3.430	3.430	3.256	1.807	0.307

Mol = molecule (compound); LUMO = lowest unoccupied molecular orbital; HOMO = highest occupied molecular orbital.

3.3. Antifungal activities of the protected glucopyranoside esters

The *in vitro* results of % inhibition of mycelial growth in mm are listed in Table 2. It is observed that the hexanoyl derivative, **4b** showed the highest inhibition (71.4%) against *A. alternate*, which was higher than that of standard fluconazole (*69.4 %). However, its 3-*O*-acetate **5b** showed comparatively lower inhibition against both fungi. In addition, **4c**, **4d**, and **5c** showed very good potentiality against*A. alternate*. More importantly, the acylated derivatives were found more active against the fungal pathogen *A. alternata* than the *M. phaseolina.*

Black fungus is borne by life-threatening mucormycosis that mainly affects immunocompromised hosts like COVID-19 patients. Black fungus is borne by life-threatening mucormycosis that mainly affects immunocompromised hosts like COVID-19 patients.

Table 2.

In vitro antifungal screening of glucopyranosides **3**-**5**

Compound	% inhibition of fungal mycelial growth (100 µg dw/mL PDA)	
	M. phaseolina	*A. alternata*
3	40.6±0.33	10.9±0.29
4a	42.8±0.67	38.3±0.48
4b	-	*71.4±0.50
4c	10.3±0.33	*64.0±0.64
4d	15.6±0.38	*65.6±0.50
5a	33.7±0.33	42.1±0.44
5b	20.2±0.36	26.1±0.48
5c	40.8±0.64	*61.5±0.32
5d	47.5±0.72	55.6±0.81
Fluconazole	*65.2±0.54	*69.4±0.64
*Good inhibition; dw = dry weight; PDA = potato dextrose agar; standard deviation is shown with±.		

3.4. Molecular docking studies

The most common proteins responsible for humanmucormycosis are related to *Rhizopus* (family) of *Mucorales* (order) [49] and are called black fungi. Hence, related three proteins (PDB ID: 4BFN, 4BFO, and 2WTP) and two standard drugs were selected for molecular docking and rigorous validation (Table 3).

Table 3 indicates that attachment of acyl ester group(s) in glucopyranoside **3** increases the binding affinity for 4BFO, in some compounds (**4b**) for 2WTP, and decreases the binding affinity for 4BFN. In all the cases, the binding affinities are comparable to the standard drugs fluconazole and amphotericin B. 2-*O*-Hexanoate **4b** showed good binding affinities with 4BFN (-6.0 kcal/mol, Figure 5a), 4BFO (-6.2 kcal/mol, Figure 5b) and 2WTP (-7.6 kcal/mol, Figure 5c). These results are also discussed in the SAR section.

Table 3.

Docking binding energy of **3-5** with the fungal proteases

Compound	Binding affinity(kcal/mol)		
	4BFN (*R. oryzae*)	4BFO (*R. oryzae*)	2WTP (*C. metallidurans*)
3	-7.1	-5.8	-7.3
4a	-6.4	-5.3	-6.4
4b	-6.0	-6.2	-7.6
4c	-6.3	-6.2	-6.9
4d	-5.8	-5.8	-7.1
5a	-5.5	-6.1	-6.4
5b	-6.2	-5.8	-6.3
5c	-4.7	-5.8	-6.8
5d	-5.2	-6.4	-6.9
Fluconazole	-6.0	-5.0	-7.6
Amphotericin B	-4.0	-6.9	-8.7

*Standard binding affinity = <-6.0 kacl/mol.

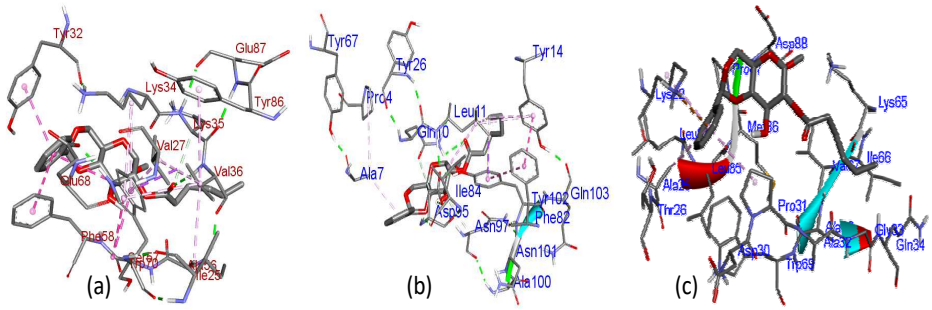


Fig. 5.3D Docking poses of **4b** with: (a) 4BFN, (b) 4BFO and (c) 2WTP indicating protein-ligand interaction

3.5. Pharmacokinetics: drug-likeness and ADMET study

With the adequate therapeutic index (*in vitro* antifungal and docking scores) glucopyranosides, **3-5** are considered for drug-likeness and ADMET study. Initially, drug-likeness properties are predicted by SwissADME (which predicts easily and rapidly with reliability) and are shown in Table 4. It is clear from the Table that all the glucopyranosides follow the most important drug-likeness rule named 'Lipinski rule of five'. Their topological polar surface area (TPSA) is found between 77-90 Å^2 (should be ≤140

Å^2). However, compounds **4d**, **5c,** and **5d** violated the Veber rule (NRB≤10) [50]. Considering all the related parameters, the glucopyranoside esters **4**-**5** possess good drug-likeness characteristics.

Table 4.
Calculation of drug-likeness parameters using SwissADME

Drug	MW	HBA	HBD	NRB	TPSA (Å^2)	LogP	Lipinski's rule violations	Bio-availability score	PAINS alert
3	282.29	6	2	2	77.38	2.49	0	0.55	0
4a	324.33	7	1	4	83.45	2.58	0	0.55	0
4b	380.43	7	1	8	83.45	3.38	0	0.55	0
4c	408.49	7	1	10	83.45	4.15	0	0.55	0
4d	436.54	7	1	12	83.45	4.43	0, (Veber 1)	0.55	0
5a	366.36	8	0	6	89.52	2.94	0	0.55	0
5b	422.47	8	0	10	89.52	3.97	0	0.55	0
5c	450.52	8	0	12	89.52	3.69	0, (Veber 1)	0.55	0
5d	478.58	8	0	14	89.52	5.09	0, (Veber 1)	0.55	0
FCZ	306.27	7	1	5	81.65	0.45	0	0.55	0

FCZ = fluconazole; HBA = Hydrogen bond acceptor; HBD = Hydrogen bond donor; TPSA = Topological polar surface area; PAINS = Pan-assay interference compounds; According to Lipinski's 'Rule of 5' LogPo/w ≤5; According to Veber, number of rotatable bonds (NRB) should be less than 10 [50].

In the drug development process, early prediction/assessment of absorption, distribution, metabolism, excretion (ADME), and toxicity (T) are highly appreciated to avoid late-stage failures of drugs due to ADMET and to minimize cost. *In silico*prediction and modelling are significantly appearing essential for the relevant pharmacokinetic, metabolic, and toxicity endpoints. Table 5 shows the data of ADMET parameters of compounds **3**-**5** by *in silico* filtering from admetSAR.

Table 5.
ADMET properties of the protected glucopyranoside **3**-**5**

Drug	C2P	HIA	P-gpI	BBB	CYP3A4 inhibitor	PPB (%)	hERG inhibitor	Carcino-genicity	AOT
3	+(0.56)	-(0.79)	-(0.92)	-(0.50)	-(0.78)	1.03	-(0.48)	-	III
4a	+(0.65)	+(0.65)	-(0.69)	-(0.44)	-(0.74)	0.97	+(0.68)	-	III
4b	+(0.53)	-(0.37)	-(0.46)	+(0.87)	-(0.68)	1.09	-(0.36)	-	III
4c	-(0.58)	-(0.37)	+(0.60)	+(0.87)	-(0.63)	1.07	+(0.76)	-	III
4d	-(0.57)	-(0.37)	+(0.67)	+(0.87)	-(0.63)	1.08	+(0.81)	-	III
5a	+(0.75)	+(0.83)	-(0.49)	+(0.78)	-(0.73)	0.84	+(0.73)	-	III
5b	+(0.56)	+(0.79)	+(0.78)	+(0.92)	-(0.66)	0.95	+(0.78)	-	III
5c	-(0.55)	+(0.79)	+(0.80)	+(0.92)	-(0.66)	0.94	+(0.88)	-	III
5d	-(0.56)	+(0.79)	+(0.84)	+(0.92)	-(0.66)	0.94	+(0.88)	-	III
FCZ	+(0.93)	+(0.99)	-(0.92)	+(0.99)	-(0.82)	0.94	-(0.48)	-	III

The sign '+' and '-' indicate positive and negative activity, respectively; The values in the parenthesis indicate probabilities; FCZ = fluconazole; C2P = Caco-2 permeability; HIA = human intestinal absorption; P-gpI = P-glycoprotein inhibitor; PPB = plasma protein binding; AOT = acute oral toxicity

Initial screening indicated that compounds with lower acyl chain(s) (e.g. **4a,b**, **5a,b**) can pass through Caco-2 membrane. However, with the increase in molecular size (e.g. **4c,d**, **5c,d**) they lose their permeability. Most of them can be absorbed in the human intestine. Some of the SEs are found to be P-gp inhibitors. Like standard drugs, **4b,c,d**, and **5a-d** can pass through the blood-brain barrier (BBB) and are non-inhibitor of CYP3A4. The compounds' plasma protein binding (PPB) nature is almost similar to fluconazole. Since compounds, **4a-d**, and **5a-c** have good HBA, HBD, and TPSA (Table 4) they have suitable ADMET properties, such as membrane permeability and phase 2 metabolisms. Finally, toxicity parameters like carcinogenicity and acute oral toxicity of the compounds indicated their safer application that will lead to good clinical outcomes.

3.6. Structure-activity relationship (SAR)

In drug discovery, structure-activity relationships (SAR) are used to predict biological activity from molecular structure change(s) and help to conclude any new synthetic molecules. Considering the structural change(s) of the compound **4**-**5** in the form of the addition of acyl group(s) at C-2 and C-3 positions, it was observed that activity increased for the attachment of acetyl (2C) to hexanoyl (6C) and

further increment of chain length (8C, 10C, etc.) decreased the antifungal activity (Table 2). In addition, further addition of the acyl group at the C-3 position mostly decreased its antifungal activity (except compound **5c**).

Secondly, molecular docking against life-threatening mucormycosis three proteins (Table 3) indicated that the overall hexanoyl (6C) chain at the C-2 position showed better potentiality, which is comparable to the standard antifungal drugs.

Finally, the biggest influence was observed for their HBA, HBD, TPSA, and PAINS alert, which indicated their good drug-likeness. The incorporation of acyl chains increased lipophilicity in the molecule and contributed to the ADMET properties.

4. Conclusions

Easy structural modification of glucopyranosideled to the successful formation of SEs **4**-**5**. The incorporation of acyl ester chain(s) added more lipophilicity to the SEs **4**-**5** and influenced their antifungal and binding with mucormycosis (black fungus) related proteins. Hexanoate **4b** was found the most effective against black fungal proteins and is comparable to the standard drugs. In short, several *in vitro* and *in silico* features of protected glucopyranoside esters are discussed that might have a profound impact on future design and applications of SEs as safer, biodegradable, and potential antifungals instead of azoles which have several side effects.

5. Conflicts of interest

There are no conflicts to declare.

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