# Chemical Reactivity Descriptors and Molecular Docking Studies of Octyl 6-*O*-hexanoyl-β-D-glucopyranosides

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***Abstract***

*The present study describes different chemical reactivity predictions of 6-O-hexanoylation of octyl β-D-glucopyranosides prepared from octyl β-D-glucopyranoside (OBG). Also, molecular docking of the OBGs was conducted against SARS-CoV-2 main protease (6LU7), urate oxidase (Aspergillus flavus; 1R51) and glucoamylase (Aspergillus niger; 1KUL). DFT optimization indicated that glucoside **1** and its ester derivatives **2-7** exist in $^4C_1$ conformation with C1 symmetry. Interestingly, the addition of ester group(s) decreased the HOMO-LUMO gap (Δε) of glucosides indicating their good chemical reactivities, whereas the other chemical reactivity descriptors indicated their moderate reactive nature. This fact of moderate reactivity was confirmed by their molecular docking with 6LU7, 1R51 and 1KUL. All the esters showed a moderate binding affinity with these three proteins. More importantly, incorporation of the ester group(s) increased binding affinity with 6LU7 and 1R51, whereas decreased with 1KUL as compared to non-ester OBG **1**.*

***Keywords:*** *COVID-19, DFT, Docking, n-Octyl β-D-glucopyranoside (OBG), Potential drugs, Urate oxidase*.

## 1. Introduction

To date, researchers have made huge efforts in investigating the roles of carbohydrates and their derivatives in different essential biological processes [1-2]. Efforts are continuing to make and establish them as safe therapeutic drugs [3-5]. Many esters, known as sugar esters (SEs), are known for their multiple surfactants [6,7], and biological properties [8-11]. These are mainly used as non-ionic type surfactants [6,7]. Different biological properties and applications are reported by many researchers [10,11]. The most common structural features of SEs are the combination of hydrophilic and hydrophobic parts [12,13]. Hydroxyl group(s) of sugar are contributing to the hydrophilic part and aglycon alkyl chain(s) of ester part(s) are contributing as hydrophobic portion [13]. This is the reason these SEs bear better stability, and aerobic or anaerobic degradation [14]. Also, the combination of hydrophilicity and lipophilicity with reasonable molecular weight are responsible for their low stimulatory effects [15]. Most of them are colourless syrup and have no taste in general [10,11]. In addition, this hydrophilicity and lipophilicity ratio can be manipulated via changing their hydrophobic

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chains [16]. Thus, these SEs are important targets for structure-activity relationships related to the bioactivities [17] by changing hydrophilicity and lipophilicity ratio. A plethora of effective biological activities of SEs supported the above observations [18-23].

Despite heavy investments into basic and applied pharmaceutical research and steadily increasing public and private efforts the unmet medical need is still considered [24]. In this regard, to accelerate drug targets and development of new medicines High Throughput Screening (HTS) has been considered [25]. The recent outbreak of a pandemic situation due to COVID-19 (severe acute respiratory syndrome coronavirus-2, its different variants) has further created a necessity for related potential drugs [26-28]. The outbreak of coronavirus disease (COVID-19) emerged at the end of 2019 and was caused by a novel enveloped single-strand positive-sense RNA virus. This disease creates mild to moderate influenza symptoms and pneumonia with acute respiratory distress syndrome (ARDS) and is responsible for multi-organ failure [29]. Four major types of coronaviruses such as alpha (α), beta (β), gamma (γ) and delta (δ) are so far reported [30]. Although α- and β-coronaviruses are considered pathogenic strains for humans, the other types are found more deadly and responsible for the upraise of the death toll [30]. The unavailability of appropriate medicine and vaccine is taking a dangerous turn due to this virus. It has been reported that carbohydrate-based several molecules are active against SARS-CoV-2 main proteases [31]. Additionally, carbohydrate molecules are very important biomolecules used to indicate position, place, or route in the realization of immune systems. Some selective polysaccharides and SEs found on the surface of microorganisms and malignant cells have defence functions [32]. These polysaccharides can be specifically recognized by the host immune system [33] and are thus termed antigens (produce antibodies and boost up the immune system). These are the basic strategies behind the design and development of carbohydrate derived vaccines [32,33]. Glycochemists and glycobiologists are contributing to the development and evaluation of carbohydrate derived vaccines to treat a wide variety of human infections.

Carbohydrate-based therapeutic replacements could be promising to overcome COVID-19 creating favourable circumstances [34-37]. In the devising combat strategies, the morphology of COVID-19 and its relevance has been discussed. In this respect, many reviews emphasized the importance and advantages of carbohydrate-based strategies for diagnosis, treatment, and tackling infectious diseases [38]. Tetra-*O*-acetyl Auranofin (Figure 1) is a glucose-derived metal salt. The World Health Organization (WHO) has classified it as an antirheumatic agent. It is applied and sold under the brand name Ridaura and is a safer therapeutic compared to the most common related drugs [39]. In addition, it is under extended research for the reduction of the HIV viral reservoir present in the body's T-cells [40]. Encouragingly, the glucoside ester (Ridaura) may inhibit replication of SARS-CoV-2 as observed in cell culture with reduced inflammation [41].

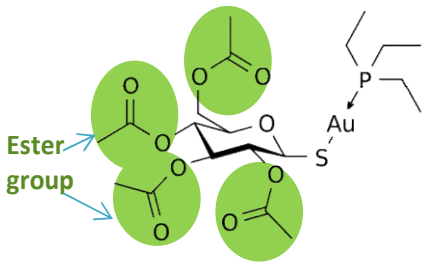


Figure 1. Structure of auranofin (Ridaura).

There is highly convincing evidence that proper molecular modifications of natural carbohydrate molecules resulted in the generation of novel bioactivities of the compounds with enhanced solubility and pharmacokinetic properties [42-44]. The increasing interest towards the process of developing new drug(s) from carbohydrate compounds has been observed currently as these compounds display remarkable pharmacological activities and low toxicity [45-50]. Considering the prospect of glucopyranoside based esters and the necessity of anti-COVID drugs several

hexanoylated octyl β-D-glucopyranosides were subjected for molecular docking with COVID-19 proteases and the results are discussed here.

## 2. Materials and methods

### 2.1. Materials: Octyl glucosides 1-7

Hexanoyl glucosides **2-7** of *n*-octyl β-D-glucopyranoside (**1**) were selected for the present study (Figure 2). These compounds were synthesized and duly characterized previously by our group [51] using the direct acylation technique [52-56].

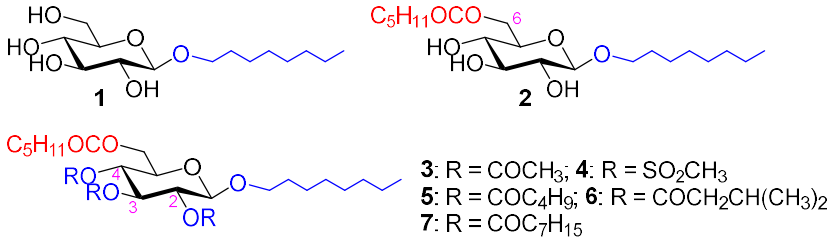


Figure 2. Structure of glucopyranosides **1** - **7**.

### 2.2. DFT optimization

Initially, an accurate geometrical structure of *n*-octyl glucoside **1** was taken from Chemspider. The rest of the molecules **2-7** were drawn before optimization in the GaussView (5.0) program [57]. All the structures **1-7** were optimized by density function theory (DFT) [56]. B3LYP (Becke, 3-parameter, Lee-Yang–Parr) method and 6-31G+ basis set were used in the Gaussian 09 program [56]. These optimized structures were used for the calculation of their chemical reactivity descriptors and molecular docking.

### 2.3. Calculation of chemical reactivity descriptor

To know the values of chemical reactivity and related descriptors several calculation equations were applied in acceptable forms. For example energy gap, Δε was calculated as εLUMO – εHOMO. Similarly, ionization potential, I = -εHOMO; electron affinity, A = -εLUMO; and electronegativity, χ = (I+A)/2. Additionally, chemical potential, μ from -(I+A)/2, hardness, η = (I-A)/2, and electrophilicity, $\omega = \mu^2/2\eta$. Finally, softness, S was calculated as 1/η.

### 2.4. Method for molecular docking

In an aim to build good data sets, the SDF format of these synthetic compounds (**1-7**) was saved separately after drawing in ChemDraw 18.0. Also, similar formats of ampicillin and hydroxychloroquine (HCQ) were saved from PubChem online database. Further, all the SDF files of ligands were prepared from DFT optimized structures.

As the basic target protein of the molecular docking was SARS-CoV-2 main protease and fungal organisms, their crystal structures were downloaded from the RCSB protein data bank (PDB id: 6LU7, 1R51; and 1KUL). Further, these proteins' crystal structures were arranged by using the protein preparation wizard of Discovery Studio, in which the crystal structure is initially assigned proper hydrogen, charges, bond orders, dehydrated and heteroatoms were deleted followed by saved as PDB. The proteins were then subjected for energy minimization in Swiss PDB viewer in the steepest way.

In the PyRx the proteins (macromolecules) and ligands were opened. The ligands after energy minimization were converted into PDBQT format. Both the protein and ligands were then forwarded for docking with maximum box size in vina wizard. The size of the grid box in AutoDockVina was kept at 43.6053, 48.3679, 38.2546 Å for 6LU7; 74.4435, 73.0731, 70.2754 Å for 1r51 and 56.4565, 44.1349, 52.2576 Å for 1kul along x, y and z directions, respectively. The resulting file was saved and further analyzed with the Discovery Studio.

## 3. Results and discussion

### 3.1. Optimized structures of 1-7

*n*-Octyl β-D-glucoside (**1**) and its hexanoyl derivatives **2**-**7** are found to exist in the $^4C_1$ chair conformation (Figure 3). The symmetry of these compounds was found C1.

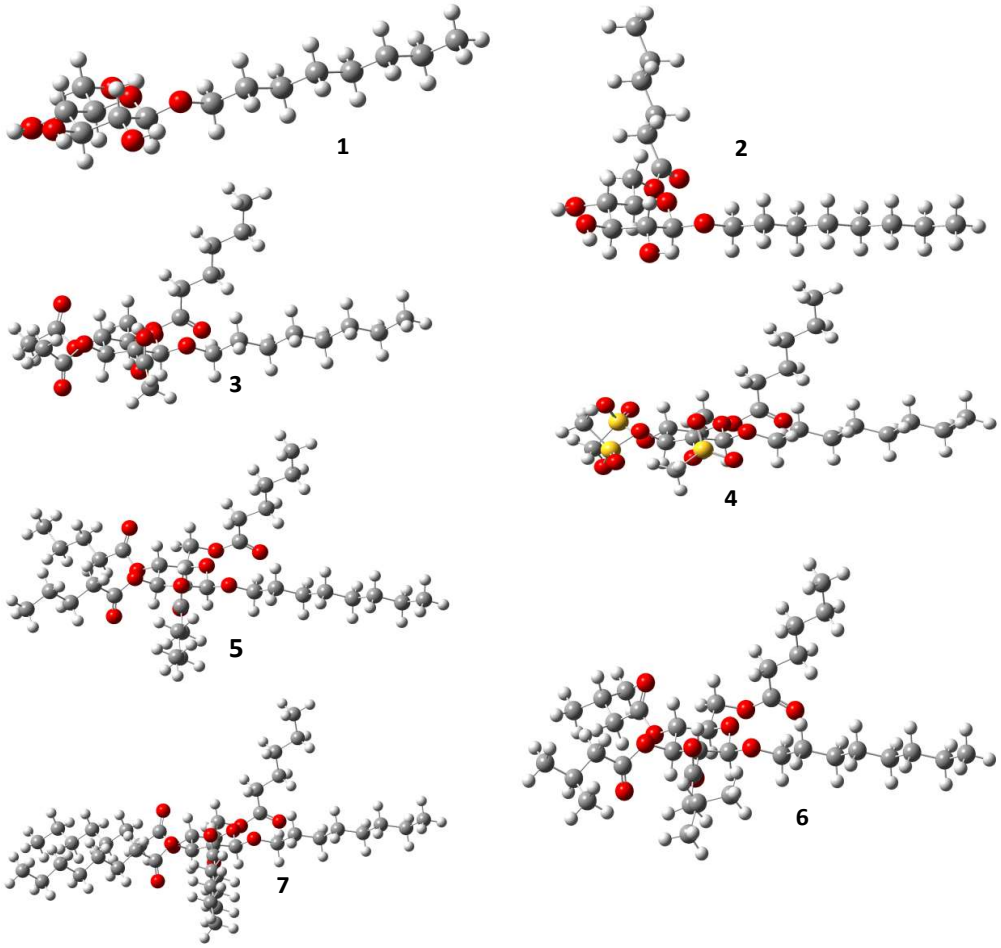


Figure 3. Optimized structures of glucopyranosides **1**–**7** (B3LYP method and 6-31G+).

### 3.2. Chemical reactivity descriptors

Octyl β-D-glucoside (**1**) and its esters, as non-toxic in cell-lines, have been widely used for membrane protein solubilization. It is also useful for solubilizing enzymes, receptors, and

phosphatidylcholine. The chemical descriptors are the general indicators and representations of the molecules. The numerical values of these physical and chemical descriptors have a significant relationship with their activities, especially biological behaviours. The numerical values of εHOMO, εLUMO, and their energy gap (Δε), electron affinity (A), ionization potential (I), chemical potential (μ), electronegativity (χ), hardness (η), electrophilicity (ω) and softness (S) of glucosides **1**-**7** are presented in Table 1. These data were calculated from their DFT optimized structures.

It is evident from Table 1 that the addition of ester groups, as in **2**-**7**, had lower HOMO-LUMO gap (Δε) values as compared to the non-ester glucoside **1**. This indicated their better chemical reactivities as it is well known that the smaller the energy gap Δε the greater the reactivity of a molecule. Among the esters, sulfonyl ester **4** showed a maximum HOMO-LUMO gap (7.433 eV). The HOMO-LUMO gaps of compounds **4** and **7** are shown in Figure 4 in the form of a DOS plot. Again, monohexanoate **2** and sulphonyl ester **4** had a lower electrophilicity index ω than the glucoside **1** and fully esterified glucosides (**3**, **5**-**7**). All the esters (**2**-**7**) hardness (η) values are found to be higher than the non-ester glucoside **1**, and inversely for softness (S). These results indicated the moderate reactive nature of esterified glucosides **2**-**7** (according to the maximum hardness principle).

**Table 1.** Molecular orbitals (MOs) and reactivity descriptor values of **1**-**7**.

| Mol | εLUMO | εHOMO | Δε | I | A | μ | η | χ | ω | S |
|---|---|---|---|---|---|---|---|---|---|---|
| **1** | 1.0250 | -7.1239 | 8.149 | 7.124 | 1.025 | -4.075 | 3.050 | 4.075 | 2.722 | 0.328 |
| **2** | 0.07537 | -7.1658 | 7.241 | 7.166 | 0.075 | -3.621 | 3.546 | 3.621 | 1.849 | 0.282 |
| **3** | -0.7371 | -7.2382 | 6.501 | 7.238 | 0.737 | -3.988 | 3.251 | 3.988 | 2.446 | 0.308 |
| **4** | 0.25442 | -7.1783 | 7.433 | 7.178 | 0.254 | -3.717 | 3.462 | 3.717 | 1.995 | 0.289 |
| **5** | -0.6400 | -7.1974 | 6.557 | 7.197 | 0.640 | -3.919 | 3.279 | 3.919 | 2.342 | 0.305 |
| **6** | -0.6898 | -7.2028 | 6.513 | 7.203 | 0.690 | -3.947 | 3.257 | 3.947 | 2.392 | 0.307 |
| **7** | -0.6351 | -7.1865 | 6.551 | 7.187 | 0.635 | -3.911 | 3.276 | 3.911 | 2.335 | 0.305 |

*Mol = molecule; LUMO = lowest unoccupied molecular orbital; HOMO = highest occupied molecular orbital; all numerical values are in eV.

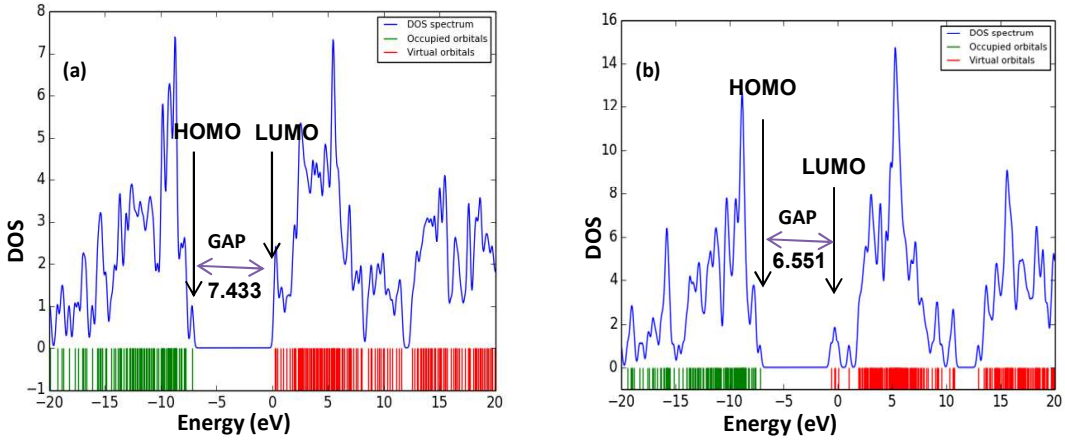


**Figure 4.** DOS plot representing HOMO-LUMO gap of the compound- (a) **4**, and (b) **7**.

### 3.3. Molecular docking: Anti-COVID and antifungal activities

Molecular docking of the OBGs (**1**-**7**) was conducted against SARS-CoV-2 main protease (6LU7), urate oxidase (*Aspergillus flavus*; 1R51), and glucoamylase (*Aspergillus niger*; 1KUL). The docking scores are shown in Table 2.

Initially, molecular docking was conducted with 6LU7 which is a 2 chain structure with a sequence from SARS-CoV-2. It was found that only acetate **3** showed a better binding affinity (-5.8 kcal/mol) than OBG (-5.5 kcal/mol). However, the binding affinities are almost similar to that of

hydroxychloroquine (HCQ, Table 1). It should be noted that the antimalarial drug HCQ was initially used to treat COVID-19.

**Table 2.** Molecular docking score (binding energy) of **1**-**7**.

| Drugs | 6LU7 (kcal/mol) | 1R51 (kcal/mol) | 1KUL (kcal/mol) |
|---|---|---|---|
| **1** | -5.5 | -5.8 | -5.3 |
| **2** | -5.2 | -5.8 | -4.6 |
| **3** | -5.8 | -6.4 | -4.6 |
| **4** | -5.5 | -5.7 | -4.7 |
| **5** | -5.1 | -5.9 | -4.3 |
| **6** | -5.4 | -6.1 | -4.6 |
| **7** | -5.0 | -5.2 | -4.3 |
| ***AMP** | -7.9 | -7.5 | -6.2 |
| ***HCQ** | -5.4 | -6.0 | -6.1 |

AMP = ampicillin; HCQ = hydroxychloroquine; *Standard drug.

In the next step, 1R51 was used for molecular docking which is a 1 chain structure with a sequence from a common fungal strain named *Aspergillus flavus*. Acetate **3** (-6.4 kcal/mol) and isovaleroate **6** (-6.1 kcal/mol) showed good binding affinities as compared to the other compounds. Their different interactions are shown in Figure 4. The docking score also indicated that these octyl glucoside esters are more potent against *Aspergillus flavus* than the SARS-CoV-2 main protease (Table 2).

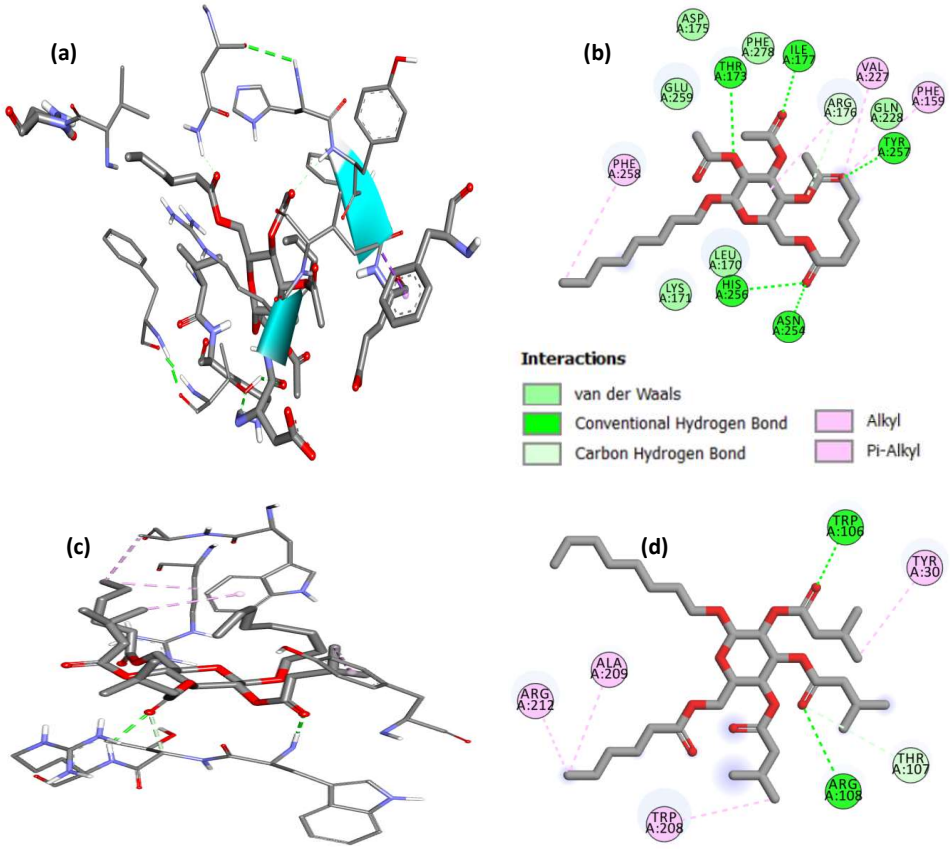


**Figure 5.** Docking interactions of 1R51 with compounds- (a) **3** (3D); (b) **3** (3D); (c) **6** (3D); (d) **6** (2D).

Finally, molecular docking was conducted with another fungal protein originating from

*Aspergillus niger* (1KUL). It has 1 chain structure and shows a well-defined beta-sheet structure consisting of one parallel and six antiparallel pairs of beta-strands which form an open-sided beta-barrel. As shown in Table 2, the OBG esters **2-7** are moderate inhibitors (4.2-4.7 kcal/mol) of this *Aspergillus niger* protein 1KUL. Also, the addition of the ester group(s) decreased binding affinities of OBG (**1**) with 1KUL, hence these molecules might be less active against *Aspergillus niger* fungus. All these docking results are in conformity with their chemical reactivity descriptors as mentioned earlier.

## 4. Conclusion

Octyl β-D-glucoside, a membrane protein solubilization agent and nonionic detergent, and its six hexanoyl esters were investigated for their chemical reactivities and molecular docking computationally. Different reactivity parameters like energy gap (Δε), ionization potential (I), electron affinity (A), electronegativity (χ), hardness (η), chemical potential (μ), electrophilicity (ω) and softness (S) indicated that these OBG esters have moderate reactivities. Interestingly, molecular docking against SARS-CoV-2 main protease (6LU7), and two fungal proteins also supported this observation where lower to moderate binding affinities were observed. Overall, a higher HOMO-LUMO gap may be responsible for moderate predicted biological potentiality.

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