DFT Based Pharmacokinetic, Molecular Docking, and ADMET Studies of Some Glucopyranoside Esters

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Abstract

*Monosaccharide esters (MEs) are getting more attention from bioorganic chemists due to their biodegradable and drug-likeness properties. As a consequence, carbohydrate derivatives (sugar-based esters, SEs) are an essential part of medicinal chemistry. In this context, density functional theory (DFT) with B3LYP/ 3-21G has been employed to optimize the methyl 4,6-O-benzylidene-α-D-glucopyranoside (**3**) of methyl α-D-glucopyranoside (**2**) and its protected acyl esters **4**-6. The prediction of activity spectra for substances (PASS) of these compounds showed better antifungal functionalities than the antibacterial potentiality. Thermodynamic properties and molecular electrostatic potential (MEP) of these MEs indicated their stability and both the electrophilic and nucleophilic attack sites. Due to their better antifungal potentiality, molecular docking was conducted against fungal protein lanosterol 14α-demethylase (3JUS), and SARS-CoV-2 main protease (6LU7) along with absorption, distribution, metabolism, excretion, and toxicity (ADMET) studies. The study indicated a better binding affinity of some esters compared to the standard antifungal and COVID-19 related drug hydroxychloroquine (HCQ).*

Keywords: COVID-19, *Glucopyranoside ester, DFT calculation, Molecular docking, Pharmacokinetic study.*

1. Introduction

Carbohydrates (sugars or saccharides) are very abundant in nature and they participate in numerous biological roles. Sugar can exist in nature as single entities or as a forming part of glycoconjugates, essentially glycolipids and glycoproteins [1]. They represent an important element in our diet and a fundamental source of metabolic energy. These molecules play different roles in the cells such as anticoagulant, antigen, and hormones due to their highly specific interaction with the physiological receptors [2-3]. In most cases, glycosylation is the process that links glycans with proteins and lipids which is strictly dependant on the activity-specific enzymes (glycosyl transferases and glycosidases). Therefore, glycan has become a major topic and interest to develop therapeutic drugs [4-5]. Glycans are involved in physiological and pathological events. Hence, the significance of glycan–protein interactions is getting comprehensive attention in the field of structure-based drug design and molecular engineering. Based on the development and application of the above research, several carbohydrate-based drugs are currently being used as antibiotics and antivirals agents [6].

Nowadays, carbohydrate esters have attracted great interest due to their wide range of

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applications in industry and medicine [7]. Investigations found that glycan-based drugs such as streptomycin [8], framycetin, paromomycin, kanamycin [9], and amphotericin B [10] were synthesized and applied. Considering the diverse biological events, several classes of monosaccharide-based sugar esters (SEs) [11-13], amino-sugars [14], and halogenated sugars [15] were applied successfully. Of them, SEs are composed of a carbohydrate moiety and one or more fatty acid parts and widely used in food additives, pharmaceutical, cosmetics, and personal care products [16]. Inspired by the novel molecular architectures and important biological properties of monosaccharide, Matin et al. [17-21] also synthesized and evaluated the antimicrobial potentiality of several monosaccharide esters (MEs). It was also found that methyl 4,6-*O*-benzylidene-2-*O*-(4-*t*-butylbenzoyl)-3-*O*-palmitoyl-α-D-glucopyranoside **1** (Figure 1) was highly active against *Macrophomina phaseolina* [22]. However, it has been notoriously difficult to predict and characterize their conformational and structural properties in a systematic manner. For these reasons, computational aided molecular modelling/engineering techniques offer an attractive alternative method for the study to develop an active site and novel pharmacophore for drugs [23].

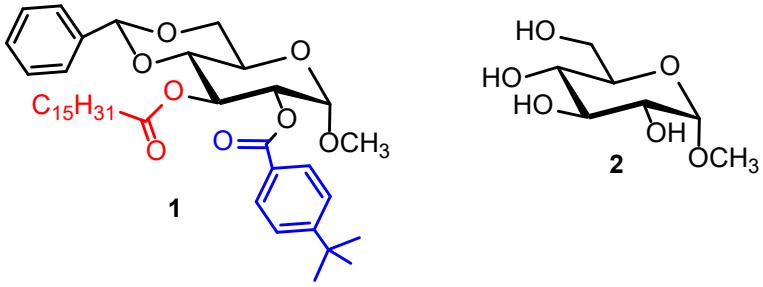

Figure 1. Structure of compound **1** and **2**.

Since the novel coronavirus (COVID-19) outbreak in Wuhan, the disease has become a major public health issue in the world [24]. Many researchers are trying to overcome it [25-26] by searching for novel and effective compounds [27-29] through analyzing their potentiality with computational tools. Computer-aided drug design (CADD) is frequently used to estimate the probable inhibitors that could prevent the activity of an enzyme. So, molecular docking studies were carried out to establish the binding mode with the target protein [30]. In chemical or molecular engineering, many drugs relied on targeting to inhibit or act against specific protein or enzyme. In the current study we have chosen a quantum mechanical approach especially density functional theory (DFT) for our glucopyranoside based compounds against lanosterol 14α-demethylase (3JUS), and SARS-CoV-2 main protease (Mpro; 6LU7).

As a continuous effort of our group in carbohydrate related bioactive molecules [31-41] here we presented *in silico* biological properties including binding affinity with SARS-CoV-2 proteases of several benzylidene protected esters of methyl α-D-glucopyranoside (**2**, Figure 1). A detailed investigation of pharmacokinetic enumeration (ADME/T, drug-likeness) has been performed to compare their absorption, metabolism, and toxicity of these glucopyranosides.

2. Materials and methods

2.1. Materials: glucopyranosides 2-6

In the current study, we have employed a total of five glucopyranosides such as methyl α-D-glucopyranoside (**2**), benzylidene protected glucopyranoside **3**, and benzylidene protected 2-*O*- and 2,3-di-*O*- acyl esters **4**-**6** (Figure 2). These compounds were already prepared and characterized well by spectroscopic techniques [22, 42]. These compounds were prepared from the glucopyranoside **2** by 4,6-*O*-benzylidine protection, selective 2-*O*-(4-*t*-bytylbenzoylation) and finally 3-*O*-acylation [22, 42].

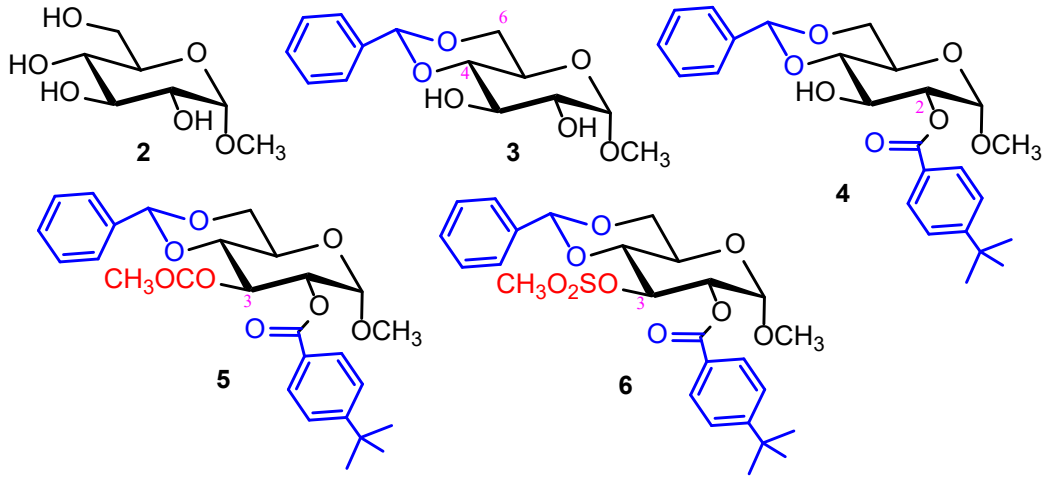

Figure 2. Structure of compound **2** - **6**.

2.2. PASS predication

Online web-based PASS (prediction of activity spectra for substances) programme was established by the successful application and confirmation in the pharmacological research experiments [43]. This program was designed to anticipate more than 4000 forms of biological activity with 90% accuracy [44]. Initially, structures of the monosaccharide esters (MEs) were drawn with ChemDraw 18.0 and then converted into their standard data (SD) file formats which were then used to predict biological spectrum using the PASS online software (http://www.way2drug.com/passonline/). The PASS result is designated as Pa (probability for active compound) and Pi (probability for inactive compound). Only the activities with Pa>Pi are considered as possible for a particular drug and in general, Pa+Pi≠1. Also, the predicted activity of the spectrum of a drug is known as its intrinsic property [45].

2.3. Computational details: DFT

Recently greater attention in quantum mechanical (QM) approaches were observed for the thermodynamic properties, molecular orbital features, dipole moment and as well as interpretation of different types of interactions. In this regard, molecular geometry optimization and all the designed compounds (MEs) were modified by using the Gaussian 09 program. After optimization, density functional theory (DFT) employing Becke's (B) three-parameter hybrid model, Lee, Yang and Parr's (LYP) correlation functional under 3-21G basis set [46]. Dipole moment, electronic energy, enthalpy and free energy are calculated for the synthesized compounds **3**-**6**. Frontier molecular orbital features HOMO (highest occupied molecular orbital), LUMO (lowest unoccupied molecular orbital) were calculated at the same level of theory. For each of the structure HOMO-LUMO gap, hardness (η), softness (S) and chemical potential (μ) were calculated. Considering Parr and Pearson interpretation of DFT and Koopmans theorem, hardness (η), softness (S) and chemical potential (μ), HOMO and LUMO energy (ε), are calculated using the reported methods [47].

2.3.1. Preparation of protein and molecular docking

Molecular docking is the most common method applied in structure-based design. As the protein target of the molecular docking was lanosterol 14α-demethylase (CYP51) (PDB ID: 3JUS; organism: *Homo sapiens*), and COVID-19 main protease (PDB ID: 6LU7) its crystal structure was

retrieved in pdb format from the protein data bank [48]. Further, the protein crystal structure 3JUS and 6LU7 were prepared using PyMol (version 1.3) software packages. SwissPdb viewer software (version 4.1.0) was employed for energy minimization of the protein. The optimized structures were subjected for docking analysis against lanosterol 14α-demethylase (CYP51), and COVID-19 main protease (6LU7) considering the protein as a macromolecule and all Monosaccharide esters (MEs) as ligands. Virtual screening of all MEs was executed through PyRx software by AutoDock wizard. The size of the grid box in AutoDockVina was kept at 54.4875, 63.0738, 70.2701 Å for 3JUS; and 34.6057, 43.3679, 36.2915 Å for 6LU7 along x, y and z directions, respectively. Accelrys Discovery Studio (version 4.1) to explore and visualize the molecular docking results and macromolecule and ligand structures were saved in pdbqt format. Finally, finding the nonbonding interactions between ligands and amino acid residues of receptor protein and binding affinities of ligand-protease was observed by kcal/mole unit for a negative score [49].

2.3.2. Prediction of ADMET

Online computational approaches ADMET (absorption, distribution, metabolism, excretion, and toxicity) analyses were conducted for monosaccharide esters (MEs) [50]. In the present study, we utilized *in silico* screening approaches employing pkCSM server (http://biosig.unimelb.edu.au). The pkCSM signatures were successfully used across five main different pharmacokinetic property classes to develop predictive regression and classification models. All the structures of monosaccharide esters (MEs) in ChemDraw 16.0 were then 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 (http://biosig.unimelb.edu.au) and admetSAR server to evaluate drug-likeness properties [51].

3. Results and discussion

3.1. PASS predicted biological activities

PASS predicted biological profiles of the monosaccharide compounds (**2**-**6**) are designated as Pa and Pi form (Table 1).

Table 1. PASS predicted the biological activities of the monosaccharides by PASS software.

Drug	Biological activity							
	Antibacterial		Antifungal		Anti-carcinogenic		Antioxidant	
	Pa	Pi	Pa	Pi	Pa	Pi	Pa	Pi
2	0.541	0.013	0.628	0.016	0.731	0.008	0.667	0.004
3	0.377	0.036	0.610	0.017	0.444	0.025	0.470	0.008
4	0.354	0.042	0.622	0.016	0.400	0.031	0.414	0.011
5	0.349	0.044	0.588	0.020	0.364	0.038	0.413	0.011
6	0.281	0.067	0.408	0.048	0.287	0.064	0.320	0.020
AMP	0.750	0.003	-	-	-	-	-	-
NST	0.967	0.00	0.986	0.00	0.416	0.028	0.145	0.108

Pa = Probability 'to be active'; Pi = Probability 'to be inactive'; AMP = ampicillin; NST = nystatin.

The PASS results showed 0.28<Pa<0.54 for antibacterial and 0.40<Pa<0.62 for antifungal which depicted that these compounds were relatively more potent against phytopathogenic fungi compared to bacterial pathogens. Prediction of the anti-carcinogenic and antioxidant property was also

conducted. These compounds showed 0.28<Pa<0.73 for anti-carcinogenic and 0.32<Pa<0.66 for antioxidant (Table 1), which indicated that the monosaccharide esters were more potent as anti-carcinogenic agents than that of antioxidant properties.

3.2. Optimization of the designed glucopyranosides

In this study, the mode of different properties of the designated glucopyranosides **2**-**6** (Figure 3) was calculated by computational study. Gaussian09 software was used to perform this work. The density functional theory (DFT) and B3LYP/3-21G basis set) were used to optimize their structures, as shown in Figure 3.

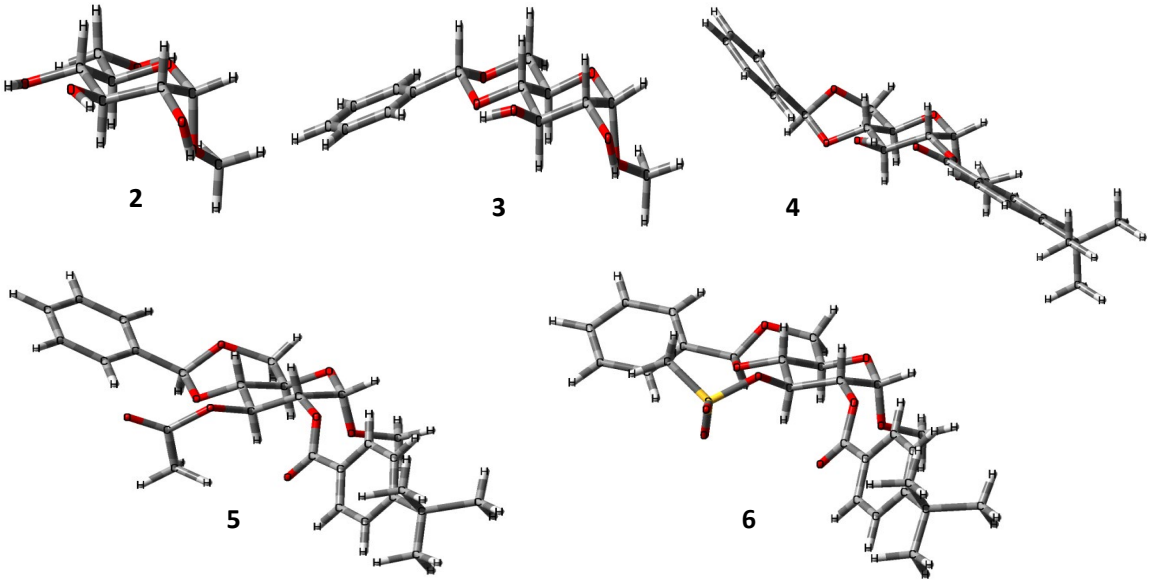

Figure 3. Optimized structures of **2**-**6** (DFT-B3LYP/3-21G) in tube model.

3.3. Thermodynamic analysis of the glucopyranosides 2-6

Thermodynamic properties of these monosaccharide esters (MEs) such as electronic energy (E), enthalpy (ΔH), Gibbs free energy (G) and dipole moment (μ) are presented in Table 2. Greater negative values can predict better the thermodynamic properties. In these studies, the ME compounds **4**-**6** had greater negative electronic energy (-1489.9021 to -2085.1565 Hartree, RB3LYP/3-21G) than the starting compound **2** (-722.4733 Hartree). It means that the addition of the acyl and sulfonyl group increased their stability. Also, the MEs showed the highest enthalpy (-2084.5633 Hartree) as compared to non-ester **2** (Table 2). Again, spontaneously of a reaction when G < 0, and stability of a product can be elucidated from the free energy and enthalpy values. It is also evident that with the attachment of acyl group(s) and bulkiness, the G (negative) values increased.

The dipole moment of **2** is 2.6827 Debye, whereas MEs **4** has the highest dipole moment 6.9214 Debye. The addition of the alkyl group containing esters **4**-**5** has a higher dipole moment (~7 debye) than the sulfonyl ester **6** (4.44 debye). This analysis reveals that with the increase of molecular weight of MEs, their stability gradually increased.

Table 2. Various thermodynamic parameters of MEs 2-6.

Compound	MF	MW	E (Hartree)	ΔH (Hartree)	G (Hartree)	μ (Debye)
2	$C_7H_{14}O_6$	194.18	-722.4733	-722.2348	-722.2887	2.6827
3	$C_{14}H_{18}O_6$	282.29	-990.1603	-989.8282	-989.8930	3.4706
4	$C_{25}H_{30}O_7$	442.50	-1489.9021	-1488.5342	-1488.6270	6.9214
5	$C_{27}H_{32}O_8$	484.54	-1640.3109	-1640.3099	-1640.4088	6.7998
6	$C_{26}H_{32}O_9S$	520.59	-2085.1565	-2084.5633	-2084.6685	4.4402

3.4. Frontier Molecular orbital (FMO) analysis

The frontier molecular orbital (FMO) theory plays an important role in chemical reactivity as well as kinetic stability. FMO related HOMO (highest occupied molecular orbital) and LUMO (lowest unoccupied molecular orbital) gap, hardness (η) and softness (S) of the glucopyranosides are shown in Table 3 and Figure 4.

Table 3. Energy (eV) of HOMO, LUMO, Gap, η and S of compound **2**-**6**.

Compound	εHOMO	εLUMO	Gap	η	S
2	-6.7073	1.5367	8.244	4.122	0.2426
3	-6.5558	-0.1167	6.4391	3.2196	0.3106
4	-6.3277	-1.5859	4.7418	2.3709	0.4218
5	-6.5767	-1.2596	5.3171	2.6586	0.3761
6	-6.6164	-1.0368	5.5796	2.7898	0.3584

Kinetic stability increases with the increase of the HOMO-LUMO gap and chemical reactivity stability depends on the small HOMO-LUMO gap. It is evident from Table 3 that the incorporation of an acetyl group (**5**) decreases the HOMO-LUMO gap (5.3171 eV). So, its hardness decreased and inversely softness increased. On the other hand, among the esters **4**-**6**, sulfonyl ester **6** showed the highest HOMO-LUMO gap (5.5796 eV, Figure 4) as compared to acetyl ester **5** (0.1954 eV), and consequently slightly increased its hardness and decreased softness.

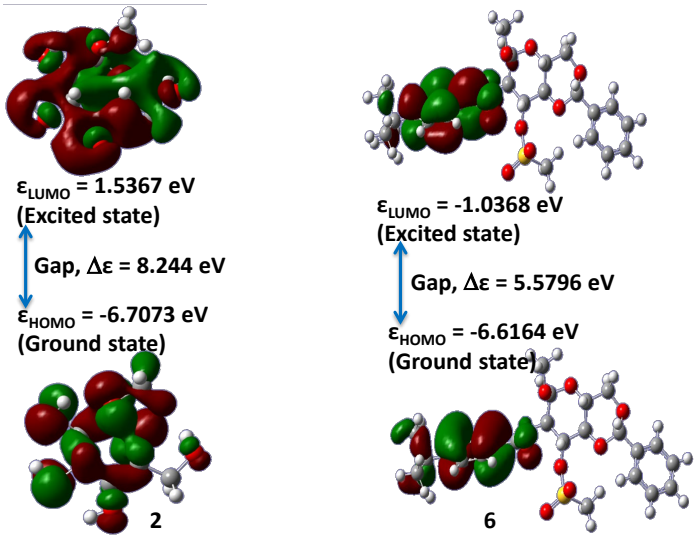

Figure 4. HOMO-LUMO gap of compound **2** and **6**.

3.5. Molecular electrostatic potential (MEP) analysis

Molecular electrostatic potential (MEP) is a map representing the possible reactive site of any compound. It helps to interpret the biological recognition process and hydrogen bonding interaction [50]. The optimized structures of **2-6** were checked for their reactive sites for the electrophilic and nucleophilic attack which was calculated by MEP. The different colours of electrostatic potential indicate different values. The potentiality of the attacking zone like the area in red represents the maximum negative area which is a favourable site for the electrophilic attack, blue indicates the maximum positive area which is a favourable site for the nucleophilic attack, and green represents zero potential areas. Excess electronegative atom (oxygen atoms) is present in the negative potential region, and over hydrogen atoms are present in the positive potential region. The MEP results (Figure 5) indicated that the incorporation of the ester group(s) gradually increased the negative red area and thus imposed the maximum possible for the electrophilic attack. In addition, the positive blue area increased for the sulfonyl (**6**) esters indicating that only these MEs possess maximum nucleophilic attack site.

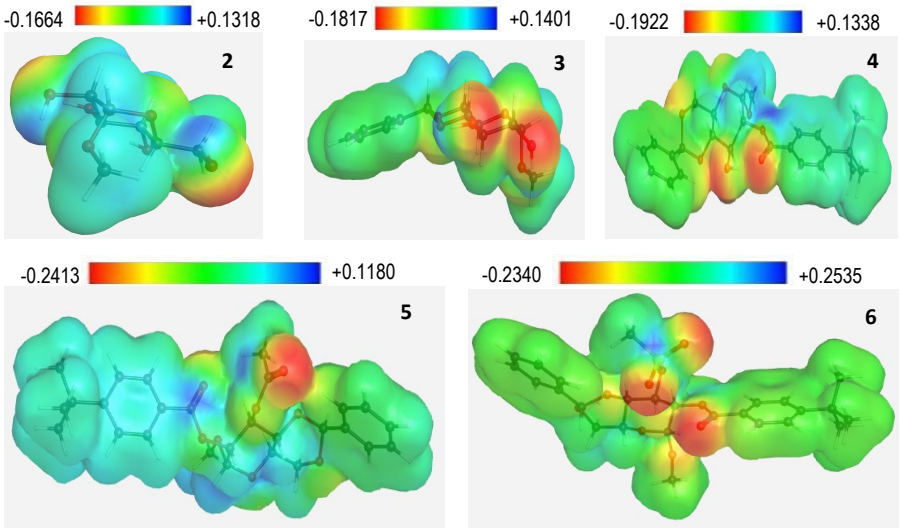

Figure 5. Molecular electrostatic potential map of **2- 6**.

3.6. Molecular docking studies against lanosterol demthylase and COVID-19 protease

The excellent *in vitro* experimental antimicrobial and molecular docking scores of various monosaccharide esters (MEs) were reported [6, 47, 50-51]. Thus, molecular biding affinity of **2-6** with lanosterol 14α-demethylase and SARS-CoV-2 main protease were carried out (Table 4).

Table 4. Molecular docking score of 2-6.

Compound	3JUS (kcal/mol)	6LU7 (kcal/mol)
2	-5.2	-4.4
3	-7.6	-6.5
4	-9.8	-8.0
5	-9.8	-7.5
6	-9.8	-7.5
AMP	-7.9	-
HCQ	-	-6.1

Ampicillin (AMP) and hydroxychloroquine (HCQ) were standard drugs; Discovery

Studio (version 4.1) was performed for analysis and view of docking results.

For CYP51 enzyme 3JUS and for main protease enzyme 6LU7 were used with the known reference ligands Ampicillin (AMP) and hydroxychloroquine (HCQ) for rigorous validation. The calculated docking score (binding affinity) of **4-6** (-9.8 kcal/mol) against lanosterol 14α-demethylase (3JUS), and SARS-CoV-2 main protease (6LU7; -7.5 to -8.0 kcal/mol) proteins, which were higher than the standard antibiotic ampicillin (-7.9 kcal/mol) and hydroxychloroquine (-6.1 kcal/mol) (Figure 6).

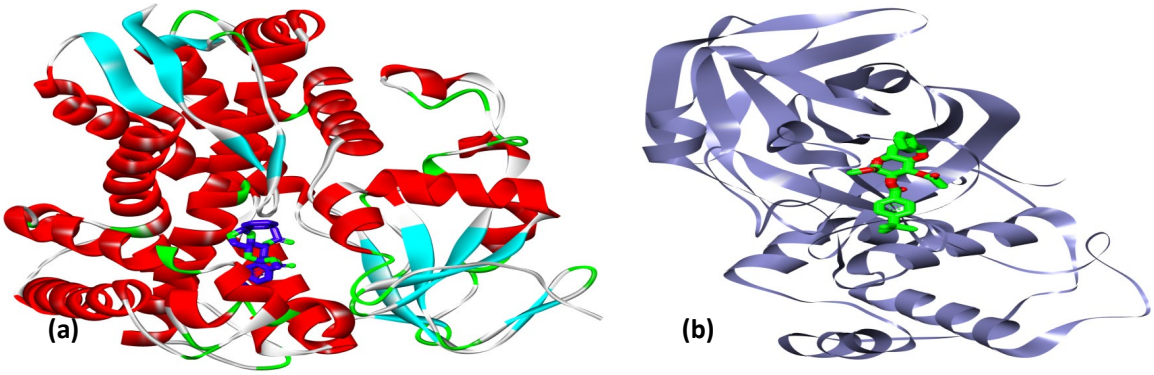

Figure 6. The figure illustrates binding modes of **5** with (a) 3JUS, & (b) 6LU7.

To our surprise, the addition of multiple ester groups in monosaccharide ring (increasing hydrophobicity), binding affinity with lanosterol 14α-demethylase (3JUS), and SARS-CoV-2 main protease (6LU7) increases. Detailed investigation of non-bond interaction of compound **5**, with lanosterol 14α-demethylase (3JUS), and SARS-CoV-2 main protease (6LU7) showed different patterns of bonds (Figure 7). These observations promoted us to calculate their ADMET properties.

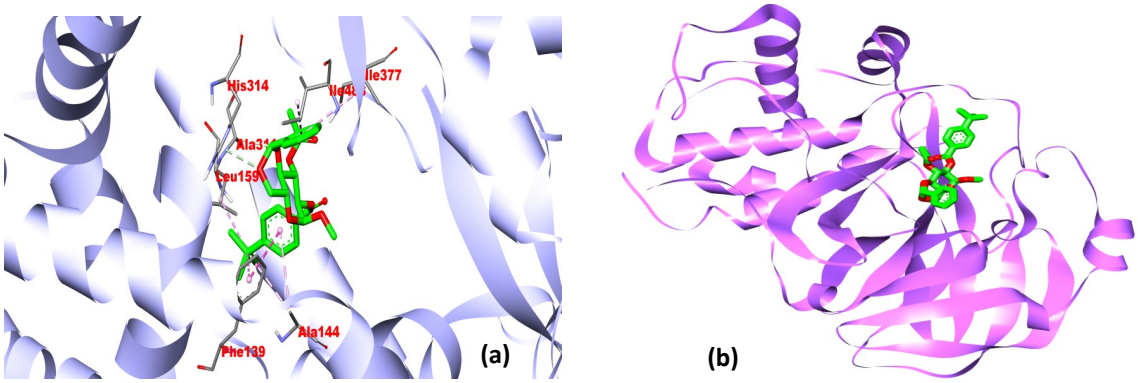

Figure 7. The best non-bonding interaction of **5** in the active site of (a) 3JUS and (b) 6LU7 in 3D style.

3.7. ADMET properties of glucopyranoside 2-6

The different ADMET (absorption, distribution, metabolism, excretion, and toxicity) properties of the monosaccharide esters are depicted in Table 5. In this study, we analyzed the ADMET properties of selected compounds employing the ADMET analysis server (http://biosig.unimelb.edu.au). The study indicated that these monosaccharide derivatives possess better absorption value than standard antibiotics (ampicillin and nystatin). All these esters drugs are P-glycoprotein inhibitor (except **2** and **3**). In addition, CNS (>-2) permeability and blood-brain barrier (BBB) (>-1) permeability showing are comparable to standard drugs. Compounds **4-6** are CYP3A4

enzyme substrate while **2**, **3**, ampicillin, and nystatin are non-substrate for this enzyme. However, all the monosaccharide esters have shown negative values inhibitory characteristics for human ether–a go-go-Related Gene (hERG). Here, most of the esters LD_{50} values (values <3 mol/kg) are consistent with the value of nystatin (2.52 mol/kg).

Table 5. ADMET properties of **2**-**6**.

Drugs	Absorption			Distribution		Metabolism	Excretion	Toxicity	
	C2P	HIA (%)	P-gpI	BBB (permeability)	CNS (permeability)	CYP3A4 Substrate	Total clearance	hERG	Acute LD_{50}
2	-0.211	32.87	No	-0.881	-4.67	No	0.686	No	1.533
3	1.215	69.53	No	0.096	-3.36	No	0.313	No	2.510
4	1.552	93.79	Yes	-0.092	-2.99	Yes	0.743	No	2.587
5	1.721	96.58	Yes	-0.981	-3.08	Yes	0.632	No	3.016
6	1.391	100	Yes	-1.384	-3.34	Yes	0.556	No	2.762
AMP	0.395	43.03	No	-0.767	-3.17	No	0.337	No	1.637
NYS	-0.609	0.00	No	-2.09	-3.70	No	-1.357	No	2.518

C2P = Caco-2 permeability; HIA = Human intestinal absorption; P-gpI = P-glycoprotein inhibitor; BBB (blood brain barrier); CNS (central nervous system) is expressed as logPS; Total clearance is expressed in log mL/min/kg; hERG = human ether-à-go-go-related gene; Toxicity is calculated in oral rat acute toxicity (mol/kg); AMP = ampicillin; NYS = nystatin.

Additionally, the SwissADME properties of these compounds were also checked for drug-likeness properties and presented in Table 6. It was found that all the monosaccharide esters (MEs) had good hydrogen bonds donor and acceptor which were consistent with the Lipinski's rule of five (Table 6). The more the value of the topological polar surface area (TPSA), the more the polarity of the esters and should be less than 140 $Å^2$ [52-53]. The TPSA in these molecules was in excellent agreement (<115 $Å^2$) with the most important rules of drug-likeness.

Table 6. SwissADME properties of **2**-**6**.

Drug	HB acceptors	HB donors	TPSA ($Å^2$)	CYP1A2 inhibitor	CYP2C19 inhibitor	PAINS alerts
2	6	4	99.38	No	No	0
3	6	2	77.38	No	No	0
4	7	1	83.45	No	No	0
5	8	0	89.52	No	No	0
6	9	0	114.97	No	Yes	0
AMP	5	3	138.03	No	No	0
NYS	18	12	319.61	No	No	0

*HB = Hydrogen bond, TPSA = Topological polar surface area, PAINS = Pan-assay interference compounds, AMP = ampicillin, NYS = nystatin.

We have also checked the CYP enzymes (isoforms 1A2, 2C19) inhibitory activities which are responsible for about 90% of oxidative metabolic reactions. Inhibition of CYP enzymes inhibitory will lead to inductive or failure of drug metabolism (**4**-**6**). In addition, Pan-assay interference compounds (PAINS) revealed no violation with these monosaccharide esters. PAINS are chemical compounds that often give false-positive results in high-throughput screens. PAINS tend to react nonspecifically with numerous biological targets rather than specifically affecting one desired target.

4. Conclusion

Considering the present pandemic situation, several glucopyranoside esters were investigated for their biological profiles. Initially, PASS predication indicated that the glucopyranosides were more potential against fungal pathogens. Hence, their thermodynamic properties along with molecular binding affinity with the fungal protein lanosterol 14α-demethylase (3JUS), and SARS-CoV-2 main protease (6LU7) were calculated and discussed. Encouraged by the better binding affinity of some glucopyranoside esters their ADMET and drug-likeness properties were predicted and rationalized with standard drugs.

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