

Pharmacokinetic Profiling, Molecular Docking, and Thermochemical Properties of Methyl α -D-Glucopyranoside Derivatives Through ADMET and DFT Approaches

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Abstract

Carbohydrate derivatives, particularly monosaccharide derivatives, are of significant interest in carbohydrate chemistry due to their role in synthesizing biologically active compounds. Consequently, the chemistry, biochemistry, and microbiology of carbohydrate derivatives are essential in drug development and pharmaceutical research. Modification of hydroxyl (-OH) groups through acylation enhances their biological activity. In this research, we optimized methyl α -D-glucopyranoside (M α GP, **1**), a monosaccharide molecule, and several of its acylated derivatives via density functional theory (DFT). All synthesized derivatives are optimized at the B3LYP/3-21G level of theory. The electronic energies, enthalpies, free energies, heat capacities, entropies, molar refractivity, polarizability, dipole moments, HOMO–LUMO gaps, and molecular electrostatic potentials (MEPs) of these modified compounds were also investigated in the subsequent analysis. Most of the synthesized derivatives inhibited the gram-positive bacteria *Bacillus subtilis* and the fungus *Fusarium equisetis* more strongly. In this study, we used a blinded molecular docking approach to identify potential inhibitors of the *Bacillus subtilis* Opg protein (PDB: 1LNZ) and *Fusarium equisetis* (PDB: 5AJH). Compound **4** had the highest binding affinity for the 1LNZ protein (-7.0 kcal/mol), and compounds **5** and **6** had the highest binding affinity for the 5AJH protein (-7.2 and -7.1 kcal/mol, respectively). Some of the compounds investigated here could bind near crucial catalytic residues, Arg236 and Arg238, of the main protease, and the molecules were surrounded by other active site residues, such as Lys156, Pro91, and Glu333. Finally, ADMET analysis revealed that modified derivatives of methyl α -D-glucopyranoside are less toxic, as the oral rat acute toxicity (LD₅₀) values of compounds **4** and **6** were 2.170 mg/kg and 2.080 mg/kg, the oral rat chronic toxicity (LOAEL) values of compounds **3**, **4**, and **5** were 1.524 mg/kg, 1.421 mg/kg, and 1.293 mg/kg, whereas the BBB permeability values of compounds **2** and **4** were -0.367 cm/s and -0.542 cm/s, respectively. Thus, these derivatives have improved pharmacokinetic features compared with those of the mother drug.

Keywords: Methyl α -D-glucopyranoside; Molecular docking; DFT; MEP; ADMET

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সারমর্ম: কার্বোহাইড্রেট জাতকসমূহ, বিশেষত মনোস্যাকারাইড জাতকগুলো, জৈব সক্রিয় যৌগের সংশ্লেষণে তাদের কার্যকারিতার কারণে কার্বোহাইড্রেট রসায়নের ক্ষেত্রে অত্যন্ত গুরুত্বপূর্ণ। এর ফলে, কার্বোহাইড্রেট জাতকের রসায়ন, জৈবরসায়ন এবং অণুজীববিজ্ঞান ওষুধ সংশ্লেষণ, জৈবরসায়ন এবং ফার্মাসিউটিক্যাল গবেষণার অপরিহার্য অংশ। মনোস্যাকারাইডের হাইড্রোক্সিল (-OH) গ্রুপসমূহের অ্যাসাইলেশনের মাধ্যমে পরিবর্তন তাদের জৈবিক ক্রিয়াশীলতা বৃদ্ধি করে। এ গবেষণায়, ডেনসিটি ফাংশনাল থিওরি (DFT) ব্যবহার করে মিথাইল α -D-গ্লুকোপাইরানোসাইড (MaGP, 1), একটি মনোস্যাকারাইড অণু, এবং তার একাধিক অ্যাসাইলেটেড জাতককে অপটিমাইজ করা হয়েছে। সকল সংশ্লেষিত জাতককে B3LYP/3-21G ভরের তত্ত্বে অপটিমাইজ করা হয়েছে। অপটিমাইজেশনের পর এসব পরিবর্তিত যৌগের ইলেকট্রনিক শক্তি, এনথ্যালপি, মুক্ত শক্তি, তাপ ধারকতা, এন্ট্রপি, মোলার রিফ্র্যাকটিভিটি, পোলারাইজেবিলিটি ডাইপোল মোমেন্ট, HOMO–LUMO গ্যাপ এবং মলিকিউলার ইলেক্ট্রোস্ট্যাটিক পোটেনশিয়াল (MEP) বিশ্লেষণ করা হয়েছে। সংশ্লেষিত বেশিরভাগ ডেরিভেটিভ গ্রাম-পজিটিভ ব্যাকটেরিয়া *Bacillus subtilis* এবং ছত্রাক *Fusarium equiseti*-এর বিরুদ্ধে অধিকতর শক্তিশালী প্রতিবন্ধকতা প্রদর্শন করেছে। এই গবেষণায়, অন্ধ পদ্ধতিতে মলিকিউলার ডকিং বিশ্লেষণ করা হয়েছে *Bacillus subtilis* Olg প্রোটিন (PDB: 1LNZ) এবং *Fusarium equiseti* (PDB: 5AJH)-এর সম্ভাব্য ইনহিবিটর সনাক্ত করার জন্য। জাতক ৪-এর 1LNZ প্রোটিনের সাথে সর্বোচ্চ বন্ধন শক্তি (-7.0 kcal/mol), এবং জাতক ৫ ও ৬-এর 5AJH প্রোটিনের সাথে সর্বোচ্চ বন্ধন শক্তি যথাক্রমে (-7.2 Ges -7.1 kcal/mol) পাওয়া গেছে। এ গবেষণায় অন্তর্ভুক্ত কয়েকটি জাতক মূল প্রোটিনের গুরুত্বপূর্ণ প্রভাবকীয় অ্যামাইনো অ্যাসিড অবশিষ্টাংশ Arg236 এবং Arg238-এর নিকটে আবদ্ধ হতে সক্ষম হয়েছে, এবং অণুগুলোকে ঘিরে রেখেছিল অন্যান্য সক্রিয় সাইট অবশিষ্টাংশ যেমন Lys156, Pro91, এবং Glu333। শেষ পর্যন্ত, ADMET বিশ্লেষণ নির্দেশ করে যে, মিথাইল α -D-গ্লুকোপাইরানোসাইডের সংশোধিত জাতকসমূহ কম বিষাক্ত। জাতক ৪ এবং ৬-এর LD50-এর মান যথাক্রমে 2.170 mg/kg এবং 2.080 mg/kg ছিল। জাতক ৩, ৪, এবং ৫-এর LOAEL-এর মান যথাক্রমে 1.524 mg/kg, 1.421 mg/kg, এবং 1.293 mg/kg। অন্যদিকে, জাতক ২ এবং ৪-এর BBB-এর মান যথাক্রমে -0.367 cm/s এবং -0.542 cm/s ছিল। অতএব, এই জাতকসমূহ মূল ঔষধের তুলনায় উন্নত ফার্মাকোকাইনেটিক বৈশিষ্ট্য প্রদর্শন করে।

Abbreviation:

ADMET: Absorption, distribution, metabolism, excretion, and toxicity

DFT: Density functional theory

HOMO: Highest occupied molecular orbital

LUMO: Lowest unoccupied molecular orbital

MEP: Molecular electrostatic potential

MaGP: Methyl α -D-glucopyranoside

1. Introduction

Carbohydrates are the most prevalent macromolecules in nature and are frequently coupled with lipids to form glycolipids or proteins to form glycoproteins. Recent research has focused on carbohydrates as selective mediators in molecular recognition processes, as these molecules play numerous roles in cells. They

participate in a range of intracellular and extracellular processes as well as physiological and pathological processes. The majority of saccharides initially interact with cells at the levels of the cell-matrix and cell-cell interactions [1,2]. However, under pathological conditions, such as inflammation and cancer development, changes to the normal cell glycosylation pattern are frequently observed. As a result, glycans are now of great interest for the development of therapeutic medications or diagnostic instruments [3,4]. Currently, several carbohydrate-based medications are used to treat various illnesses; antibiotics and antivirals are the best examples [5]. Aminoglycosides, which inhibit bacterial protein synthesis, have been used as antibiotics for many years, particularly for infections caused by aerobic, gram-negative bacteria [6]. Metabolic medications are also associated with glycans. Glycan-lectin interactions have advanced vaccine, antiviral, and immunotherapy development [7,8]. Modern extraction methods have also revealed numerous carbohydrate-containing natural products with cytotoxic activity [9,10]. To date, several sugar-based medications have been created and are being used for vaccinations, treatments, and diagnostics; many more are anticipated in the coming years. Our synthesized monosaccharide derivatives were more stable, less toxic, and biologically active. These compounds could be potential antibacterial and antifungal drugs. The intramolecular hydrogen bonding between neighboring -OH groups [11], anomeric effects, orientation of all torsional angles [12,13], and linkages that join monosaccharides (the fundamental units of saccharides) all contribute to glycan diversity. Predicting and systematically characterizing their conformational and structural features is therefore crucial. In this context, computational methods play a key role in analysis and prediction [14].

The hydroxyl (-OH) groups of carbohydrates [15,16], especially methyl α -D-glucopyranoside (MaGP, **1**) (Figure 1) and nucleosides [17], are modified by acyl substituents, including aromatic and heteroaromatic groups [18]. These modified MaGP (**1**) derivatives were optimized *via* quantum mechanical techniques to achieve their thermal and electrical stability and their biochemical behavior. To compare their thermal and chemical characteristics, the following quantities were computed: free energy, enthalpy, entropy, heat capacity, dipole moment, HOMO-LUMO gap, DOS plot, polarizability, molar refractivity, and molecular electrostatic potential. To determine the nonbonding interactions, binding affinities, and binding manners of the receptor proteins (*Bacillus subtilis* (PDB: ILNZ) and *Fusarium equisati* (PDB: 5AJH) (Figure 2), compounds **4**, **5**, and **6**, which have shown remarkable antibacterial and antifungal activities, were subjected to molecular docking. Finally, pharmacokinetic enumeration has been used to compare their toxicity, metabolism, and absorption. Understanding the thermodynamic, molecular orbital, binding mode, molecular electrostatic potential, physicochemical, and ADMET characteristics (MaGP, **1**) and its derivatives was the

main goal of our work. Computational methods have proven to be needed in this respect [19]. In this study, we found that our synthesized compounds were capable of binding to pathogenic protein residues and acting as effective bacterial and fungal inhibitors. As these compounds are non-toxic and exhibit good ADMET profiles, they show strong potential as drug or antibiotic candidates.

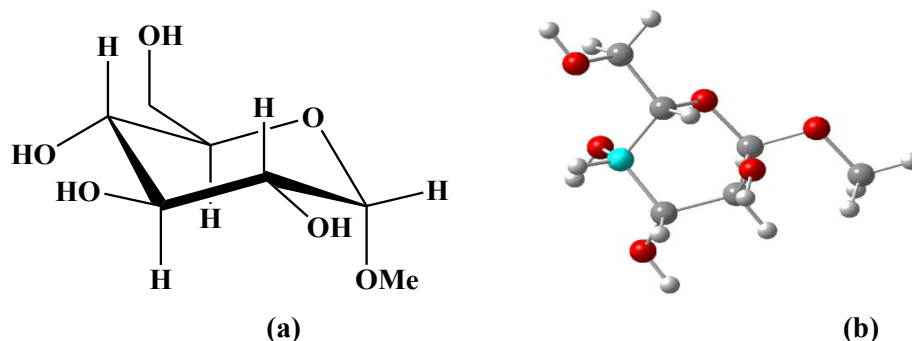


Figure 1. Chemical (a) and optimized (b) structures of methyl α -D-glucopyranoside (MaGP 1).

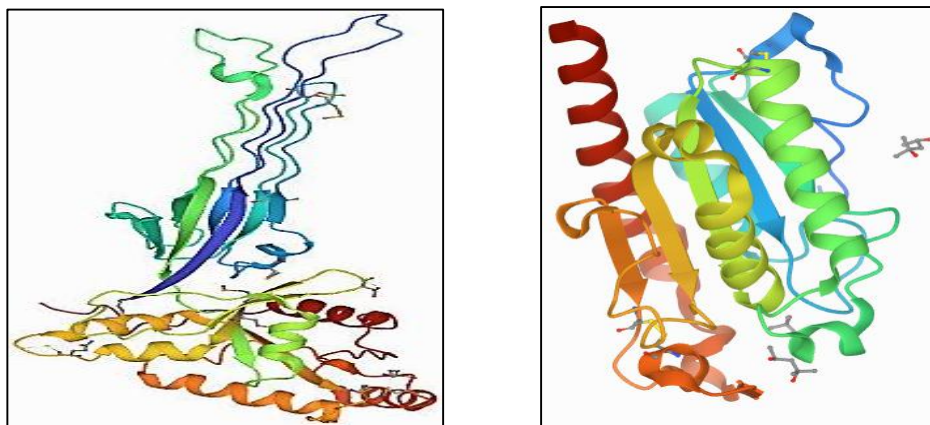


Figure 2. Crystal structures of *Bacillus subtilis* (PDB: ILNZ) (left) and *Fusarium equisati* (PDB: 5AJH) (right).

2. Computational methods

2.1 Designing and optimization of MaGP derivatives

Quantum mechanical techniques are often employed in computational chemistry to compute molecular electrostatic characteristics and thermal and molecular orbitals [20]. Gaussian 09 software was used to optimize the geometry and subsequently

modify all synthesized derivatives [21]. The thermal and molecular orbital characteristics of the materials were optimized and predicted using density functional theory (DFT) with Beck's (B) [22] three-parameter hybrid model and Lee, Yang, and Parr's (LYP) [23] correlation functional under the 3–21G basis set. For each compound, the dipole moment, enthalpy, free energy, and entropy were calculated. The HOMO (highest occupied molecular orbital) and LUMO (lowest unoccupied molecular orbital), which are key frontier molecular orbital characteristics, were also analyzed at the same theoretical level. Following Parr and Pearson's interpretation of DFT and Koopmans' theorem [24] on the relationship between ionization potential (I) and electron affinity (E) with HOMO and LUMO energies (ϵ), the HOMO–LUMO energy gap, hardness (η), and softness (S) of each methyl α -D-glucopyranoside derivative were determined from the frontier orbital energies. Hardness (η) and softness (S) were calculated using the following formulas.

$$\eta = \frac{[\epsilon_{\text{LUMO}} - \epsilon_{\text{HOMO}}]}{2}; \quad S = \frac{1}{\eta}$$

2.2 Protein design and molecular docking

The three-dimensional structure of *Bacillus subtilis* Obg. (PDB ID. 1LNZ) was retrieved in pdb format from the protein data bank [25]. All heteroatoms and water molecules were removed via PyMol (version 1.3) software packages [26]. Swiss-Pdb viewer software (version 4.1.0) was employed for energy minimization of the protein [27]. The optimized drugs were subsequently subjected to a molecular docking study against the bacterial protein *Bacillus subtilis* Obg. (PDB ID. 1LNZ) target proteins [28]. The results of the molecular docking simulation were generated via PyRx software (version 0.8) [29], which considers the protein as a macromolecule and the drug as a ligand. AutodockVina was employed for docking analysis, and AutoDock Tools (ADT) of the MGL software package was used to convert pdb into a pdbqt format to input protein and ligands. The size of the grid box in AutoDockVina was kept at 57.9266, 113.4821, and 47.0085 Å for the X, Y, and Z directions, respectively. After docking, the macromolecule and ligand structures were saved in pdbqt format, as required by Accelrys Discovery Studio (version 4.1), to visualize the docking results and examine nonbonding interactions between the ligands and receptor protein residues [30].

2.3 ADMET study

The pkCSM server was employed to evaluate the pharmacokinetic properties and toxicity of the modified methyl α -D-glucopyranoside derivatives and the parent compound. Using this online tool, pharmacokinetic parameters related to drug absorption, metabolism, and toxicity were calculated [31]. pkCSM predicts ADMET profiles by comparing chemical structures with a manually curated database of

diverse compounds. Drug-likeness was assessed according to Lipinski's rule of five [32]. To validate the predictions for the glucopyranoside derivatives, well-known metal-based drugs, including Pt-based cisplatin and carboplatin, as well as FDA-approved and clinical trial compounds, were used as test references.

2.4 Stratigraphy and optimization of synthesized M α GP derivatives

The M α GP derivatives in this study were designated and optimized using a quantum mechanical method (Table 1). In computational chemistry, energy minimization identifies an atomic arrangement where the net interatomic forces are near zero, corresponding to a stationary point on the potential energy surface (PES). Geometry optimization provides the physically meaningful structure; optimized geometries (Figure 3) often reflect the molecule's natural conformation and can be used in studies of chemical structure, thermodynamics, kinetics, spectroscopy, and more. The lowest-energy conformation is determined from bond lengths and angles that minimize steric energy, allowing the identification of stable molecular conformations.

3. Results and Discussion

3.1. Optimization of the compounds

To determine the mode of their various characteristics, we adjust a set of M α GP (1) derivatives (Figure 3) and attempt to conduct computer research. Gaussian 09 is a molecular modeling tool that permits the development and analysis of various molecular structures as well as the determination of their molecular electrostatic potential, frontier orbital, thermophysical, and thermochemical properties. Gaussian 09 software and a Core i7 machine were used to complete this task; the optimized structures are shown in Figure 3. Molecular symmetry is an extremely powerful tool for setting up reactivity computations on the basis of Gaussian 09. According to molecular optimization, every modified derivative has many symmetry axes. The molecules are nonplanar, are asymmetric, and have two or more symmetry elements in addition to their plane.

Table 1. Chemical structures of the M α GP (1) derivatives 2-7.

Entry	Name	Structure	SMILES
2	Methyl 4,6- <i>O</i> -(4-methoxybenzylidene)- α -D-glucopyranoside (2)		<chem>[H][C@]1(O)[C@@](O[C@@](C2=CC=C(OC)C=C2)([H])OC3)([H])[C@]3([H])O[C@]([H])(OC)[C@](O)1[H]</chem>
3	Methyl 2,3-di- <i>O</i> -acetyl-4,6- <i>O</i> -(4-methoxybenzylidene)- α -D-glucopyranoside (3)		<chem>[H][C@]1(OC(C)=O)[C@@](O[C@@](C2=CC=C(OC)C=C2)([H])OC3)([H])[C@]3([H])O[C@]([H])(OC)[C@](OC(C)=O)1[H]</chem>
4	Methyl 2,3-di- <i>O</i> -methanesulphonyl-4,6- <i>O</i> -(4-methoxybenzylidene)- α -D-glucopyranoside (4)		<chem>[H][C@]1(OS(=O)(C)=O)[C@@](O[C@@](C2=CC=C(OC)C=C2)([H])OC3)([H])[C@]3([H])O[C@]([H])(OC)[C@](OS(=O)(C)=O)1[H]</chem>
5	Methyl 2,3-di- <i>O</i> -benzenesulphonyl-4,6- <i>O</i> -(4-methoxybenzylidene)- α -D-glucopyranoside (5)		<chem>[H][C@]1(OS(=O)(C2=CC=C(C=C2)=O)[C@@](O[C@@](C3=CC=C(OC)C=C3)([H])OC4)([H])[C@]4([H])O[C@]([H])(OC)[C@](OS(=O)(C5=CC=C(C=C5)=O)1[H]</chem>
6	Methyl 4,6- <i>O</i> -(4-methoxybenzylidene)-3- <i>O</i> -pentanoyl- α -D-glucopyranoside (6)		<chem>[H][C@]1(OC(CCCC)=O)[C@@](O[C@@](C2=CC=C(OC)C=C2)([H])OC3)([H])[C@]3([H])O[C@]([H])(OC)[C@](O)1[H]</chem>
7	Methyl 2- <i>O</i> -acetyl-4,6- <i>O</i> -(4-methoxybenzylidene)-3- <i>O</i> -pentanoyl- α -D-glucopyranoside (7)		<chem>[H][C@]1(OC(CCCC)=O)[C@@](O[C@@](C2=CC=C(OC)C=C2)([H])OC3)([H])[C@]3([H])O[C@]([H])(OC)[C@](OC(C)=O)1[H]</chem>

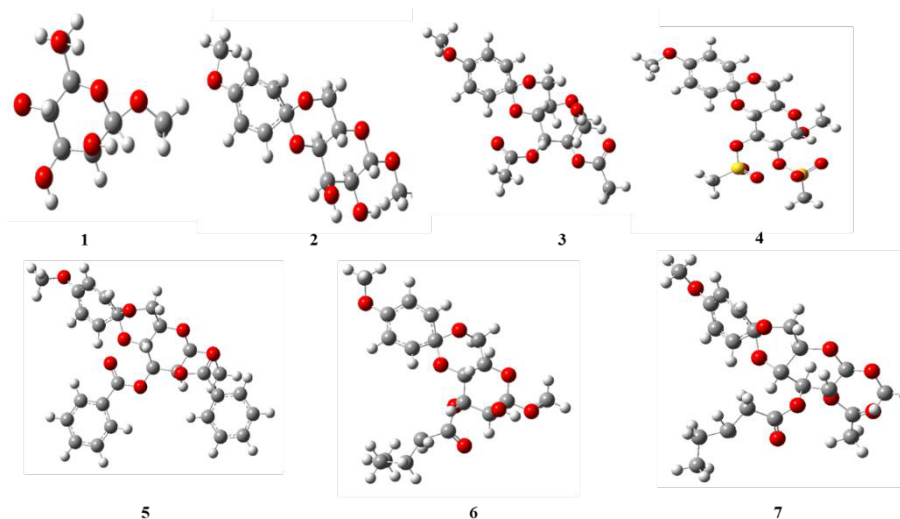


Figure 3. Optimized structures of the M α GP (**1**) derivatives **2-7**.

3.2. Thermochemical analysis

Thermal and molecular orbital parameters are significantly influenced by changes in molecular structure. Free energy and enthalpy values can indicate the spontaneity of a reaction and the stability of the product [33], with more negative values reflecting greater thermal stability. The dipole moment affects hydrogen-bond formation in nonbonded interactions, and an increased dipole moment can enhance binding properties [34]. Table 2 and Table 3 present the thermochemical properties of M α GP and its synthesized derivatives. The highest free energy is (-2234.7196 Hartree) for derivative **4**, which also has the highest enthalpy (-2235.0544 Hartree), highest electronic energy (-2235.0544 Hartree), and dipole moment (4.0758 Debye).

Table 2. Molecular formula, molecular weight (g/mol), electronic energy, enthalpy, Gibbs free energy (Hartree), and dipole moment (Debye) of M α GP (**1**) derivatives.

Entry	Molecular formula	Molecular Weight (g/mol)	Electronic energy (Hartree)	Enthalpy (Hartree)	Gibbs free energy (Hartree)	Dipole moment (Debye)
1	C ₇ H ₁₄ O ₇	194.183	-722.4431	-722.206	-722.261	3.0471
2	C ₁₅ H ₂₀ O ₇	312.320	-1065.1610	-1065.1398	-1065.2119	5.2389
3	C ₁₉ H ₂₄ O ₉	396.392	-1368.7292	-1368.7022	-1368.7905	3.0589
4	C ₁₇ H ₂₄ O ₁₁ S ₂	468.502	-2235.0544	-2234.6240	-2234.7196	4.0758
5	C ₂₇ H ₂₈ O ₁₁	502.644	-1750.5009	-1749.9575	-1750.5009	5.2582
6	C ₂₀ H ₂₈ O ₈	369.436	-1334.2239	-1334.1433	-1334.2329	5.3925
7	C ₂₂ H ₃₀ O ₉	438.473	-1485.969	-1485.0372	-1486.0366	5.9996

Table 3. Polarizability (a.u.), heat capacity (cal/mol-kelvin), entropy (cal/mol-kelvin), and total energy (Hartree).

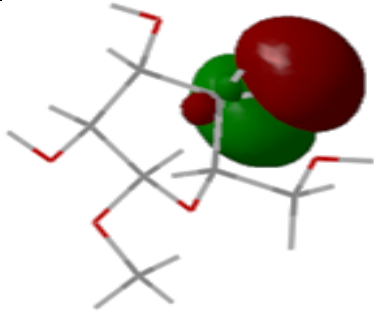
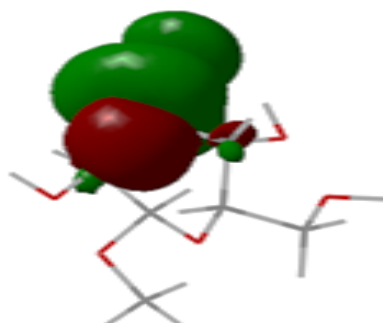
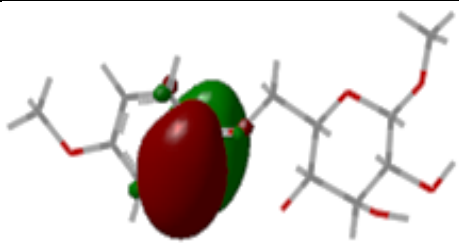
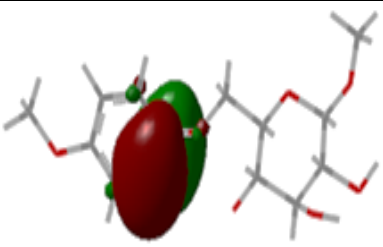
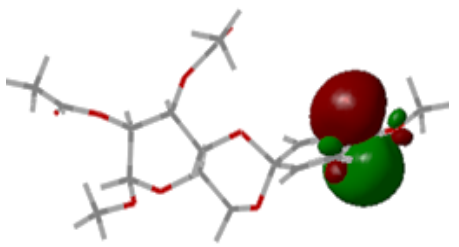
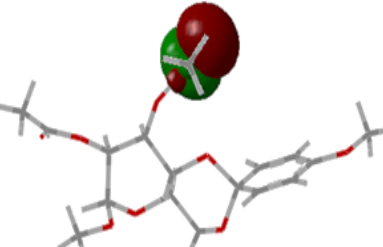
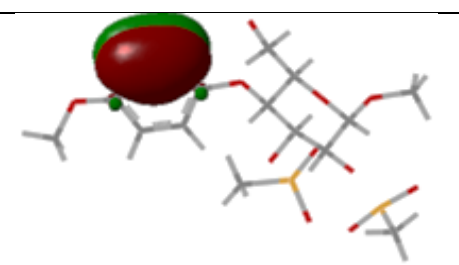
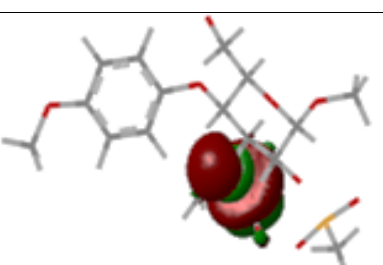
Entry	Polarizability (a.u.)	Heat capacity (Cv) (cal/mol- kelvin)	Entropy(S) (cal/mol- kelvin)	Total Energy (E) (Hartee)
1	86.9283	52.871	116.376	-722.2073
2	166.1113	77.304	151.908	-1065.488
3	207.6066	100.423	187.727	-1369.1305
4	240.3530	113.844	201.178	-2234.6249
5	303.9993	125.906	220.602	-1749.9584
6	210.0400	103.031	188.445	-1334.223
7	237.7753	115.916	209.308	-1485.4578

Table 3 lists additional thermophysical properties, with compound **4** exhibiting the highest polarizability, while compound **5** shows the highest heat capacity and entropy. The presence of bulky acylating groups also suggests a possible improvement in polarizability. In Table 2 and Table 3, the values of all the properties increase with increasing molecular weight from compounds **2** to **7**, and these derivatives contain long-chain pentanoyl acetyl, methanesulphonyl, and benzenesulfonyl substituents. The analysis indicated that increasing the molecular weight of MaGP (**1**) derivatives generally enhances their stability. However, for compound **4**, the heteroaromatic ring exhibited higher energy than the long-chain acyl substituents. Overall, all derivatives showed notable characteristics compared with the parent molecule (**1**).

3.3. Frontier molecular orbital analysis

The frontier molecular orbitals are the most vital in a molecule, and they are considered to characterize the chemical reactivity and kinetic stability. These frontier molecular orbitals are known as the highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO) (Table 4). The electronic absorption is related to the transition from the ground state to the first excited state and is described mainly by one electron excitation from the HOMO to the LUMO [35]. The kinetic stability increases with increasing HOMO–LUMO gap. As a result, the removal of electrons from the ground-state HOMO to the excited-state LUMO requires more energy.

Table 4. Molecular orbital diagrams of the HOMOs and LUMOs of M α GP (1) derivatives 2-7.

Entry	HOMO	LUMO
1		
2		
3		
4		

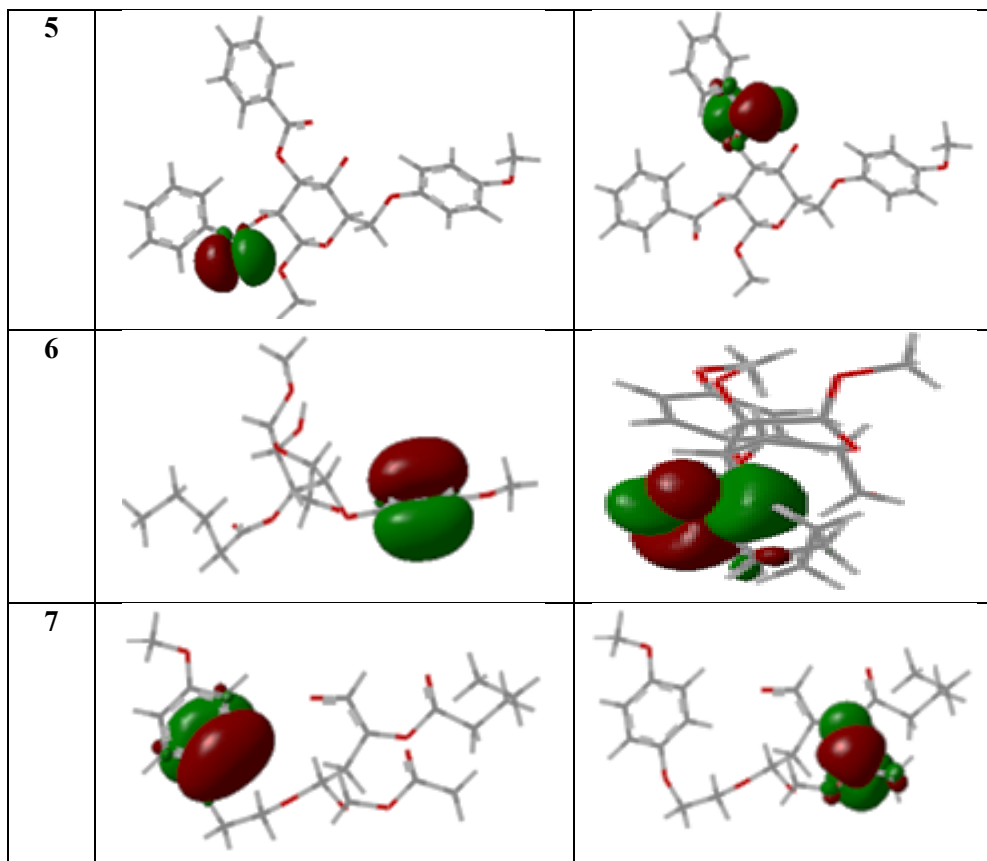
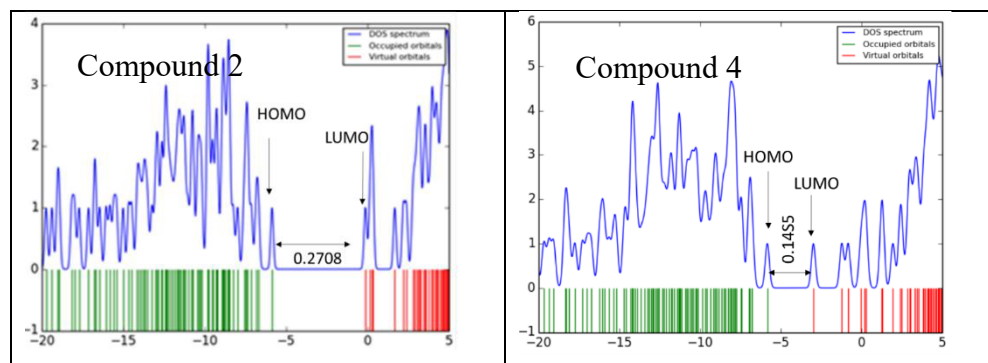


Table 5 presents the values of orbital energies, along with the two global chemical descriptors, hardness and softness, which were calculated for all the compounds. The highest softness (13.7551) was observed for compound **4**, which also presented the lowest HOMO-LUMO gap (0.1455) and hardness (0.0727), indicating that the molecule is more reactive than other compounds according to Haque *et al.* and Parr and Zhou [36,37]. Compound **2** exhibited the highest HOMO-LUMO gap (0.2708), slightly lower than that of the parent compound **1** (0.2812), indicating a stability comparable to MaGP (**1**). LUMO plots showed electron localization primarily at the modified acyl groups, while HOMO plots indicated electron density on the upper part of the pyranose ring.

Table 5. Energy (eV) of the HOMO, LUMO, energy gap, hardness, and softness of MaGP(1) and its derivatives.

Entry	ϵ HOMO	ϵ LUMO	Gap	Hardness (η)	Softness (S)
1	-0.2245	0.0567	0.2812	0.1406	7.1123
2	-0.2475	0.0233	0.2708	0.1354	3.6927
3	-0.2412	-0.0870	0.1542	0.0771	12.9701
4	-0.2488	-0.1033	0.1455	0.0727	13.7551
5	-0.2457	-0.0248	0.2209	0.1104	9.0579
6	-0.2433	-0.0144	0.2289	0.1144	8.7412
7	-0.2355	-0.0360	0.1995	0.9975	1.0025

Figure 4 presents the DOS plot for the highest and lowest energy gaps of the modified derivatives.

**Figure 4.** DOS plot and HOMO–LUMO energy gap of compounds 2 and 4.

3.4. Molecular electrostatic potential (MEP)

In computational studies, atomic charges are used to explore the relationship between molecular structure and biological activity. The molecular electrostatic potential (MEP) serves as a reactivity map, highlighting regions most susceptible to electrophilic and nucleophilic attacks by charged species [38]. This approach also aids in understanding biological recognition processes and hydrogen-bonding interactions [39]. The MEP contour map offers a straightforward way to predict interactions based on molecular geometry. The MEP of the title compound, calculated using B3LYP/3-21G optimized geometry, is shown in Figure 5. The MEP

is valuable because it simultaneously depicts molecular size, shape, and regions of positive, negative, and neutral electrostatic potential through color grading, aiding studies of structure–property relationships [40]. The molecular electrostatic potential (MEP) of M α GP (**1**) and its derivatives **2–7** was calculated to predict reactive sites for electrophilic and nucleophilic attacks. In Table 6 and Figure 5, electrostatic potential values are color-coded: red < orange < yellow < green < blue, with red indicating maximum negative potential (favorable for electrophilic attack), blue indicating maximum positive potential (favorable for nucleophilic attack), and green representing near-zero potential.

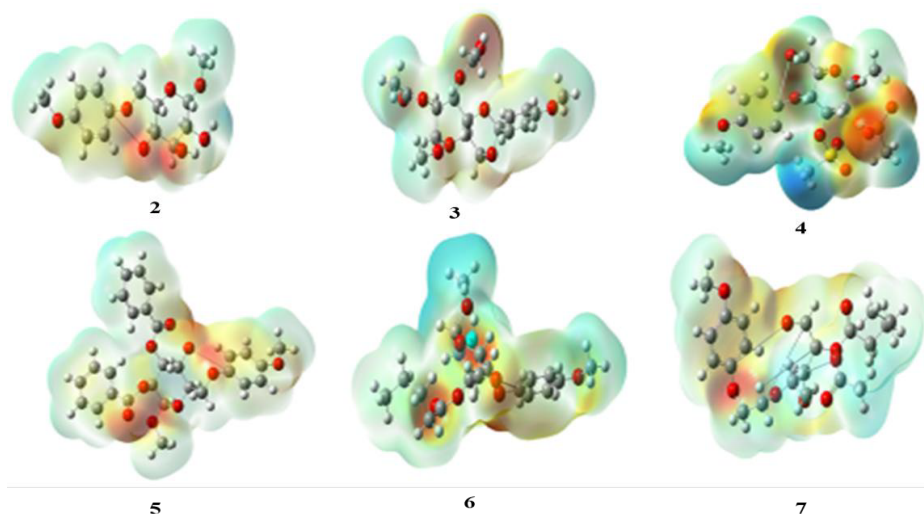


Figure 5. Surface of the molecular electrostatic potential of M α GP derivatives (**2–7**).

Table 6. Electrostatic potential charge of M α GP, **1** and its derivatives (**2-7**).

Entry	ESP (electrostatic potential charge in e^{-2})
1	± 8.318
2	± 7.570
3	± 6.850
4	± 5.636
5	± 6.479
6	± 6.055
7	± 6.724

In this study, all the derivatives presented an electrostatic potential charge lower than that of the parent molecule. Among the derivatives, compound **4** displayed the lowest EPS ($\pm 5.636 e^{-2}$). Thus, the reactivity and bioactivity of compound **4** are relatively high.

3.5. Molecular docking analysis

Molecular docking is a bioinformatics technique that models interactions between molecules to form stable complexes. Its primary goal is to predict the potential binding geometries of a ligand with a known three-dimensional target protein. In this study, a series of methyl α -D-glucopyranoside derivatives (**2-7**) were analyzed in silico to evaluate their binding energies and interaction modes with the active sites of *Bacillus subtilis* (PDB ID: 1LNZ) and *Fusarium equiseti* (PDB ID: 5AJH) using AutoDock Vina. Based on docking results, three analogs (**4**, **5**, and **6**) with the strongest binding energies were selected to illustrate the binding mode of potential M α GP derivatives. The docking analysis showed that all compounds, including the parent, exhibited binding affinities ranging from -5.3 to -7.2 kcal/mol. Modifications of the -OH group with a long carbon chain or aromatic ring enhanced binding affinity, whereas the introduction of hetero groups, such as sulfonyl groups, caused minor fluctuations. The inhibitor interactions with neighboring residues of ILNZ and 5AJH are depicted in 2D schematics generated using Discovery Studio Visualizer (Figure 6).

Tables 7 and 8 show that the binding affinities of all the designed derivatives were greater than those of the parent compound, with values of parent compound **1** for both the protein ILNZ (-5.3 kcal/mol) and 5AJH (-4.9 kcal/mol). Compound **1** binds confidently through the hydrogen bonds Asp160, Arg53, Arg236, Glu50, and Glu329. The binding affinities of compound **2** with ILNZ and 5AJH are -6.4 and -

6.2 kcal/mol, respectively. Thus, the compound exhibits similar interactions with both bacterial and fungal proteins. Compound **2** forms hydrogen bonds with ILNZ residues Glu50, Leu52, Arg53, Arg236, and Ars238, and with 5AJH residues Gln93 and Ser53. For compound **3**, the binding affinity with ILNZ is -6.5 kcal/mol, involving conventional hydrogen bonding with Leu249 and carbon–hydrogen bonding with Asp245, Ser168, and Gly251. Its binding affinity with the fungal protein 5AJH decreases to -5.9 kcal/mol, with no notable interactions.

Compound **4** binds strongly to ILNZ residues via conventional hydrogen bonds with Arg238, Arg53, Glu50, and Glu329, along with hydrophobic interactions with Pro91 (alkyl). The shortest distance was observed for Arg53 (2.08 Å), corresponding to the highest binding affinity of -7.0 kcal/mol. For 5AJH, the binding affinity is -6.3 kcal/mol, with hydrogen bonds to Asn67 and Trp70 and a carbon–hydrogen bond with Asn26 (Figures 6, 7A, and 7B). The sulfonated derivative **5**, with a binding affinity of -6.7 kcal/mol, shares some binding sites, such as Arg236 (carbon–hydrogen bond) and Lys156 (pi-alkyl hydrophobic interaction), while also showing new interactions with Arg232 (2.11 Å) and Leu158. The binding affinity of the same compound with 5AJH reached -7.2 kcal/mol, reflecting entirely different binding sites due to the sulfur atom's structural influence. The interactions included hydrogen bonds, carbon–hydrogen bonds, π -sigma, and π -alkyl interactions with Arg167, Lys207, Val114, Lys141, Ala211, and Ala215 (Figures 7B, 8A, and 8B). Compound **6**, with a binding affinity of -7.1 kcal/mol, interacted with both ILNZ and 5AJH residues, exhibiting hydrogen bonds, carbon–hydrogen bonds, and π -alkyl interactions with Arg53, Arg236 (2.12 Å), Leu328, Lys156, and Leu158. Compound **7** exhibited a binding affinity of -6.4 kcal/mol, with entirely different binding sites. It formed π -alkyl interactions with Lys40 and Arg121 and conventional hydrogen bonds with His78 and Arg128 (2.55 Å). Structural modifications in compounds **4**, **5**, and **6**, including methanesulfonyl, aromatic (benzenesulfonyl), and long-chain (pentanoyl) substituents, increased electron density and resulted in comparatively higher binding affinities (Figures 7C and 8C).

Table 7. Binding affinity (kcal/mol) and nonbonding interactions of M α GP (**1**) and its derivatives (**2-7**) with 1LNZ.

Entry	Protein	Binding affinity	Bond category	Residues in contact	Interaction types	Distance (Å)
1	1LNZ	-5.3	Hydrogen	ASP160	H	2.37238
			Hydrogen	GLU333	H	2.77488
			Hydrogen	ARG53	H	3.09558
			Hydrogen	ARG53	H	2.11152
			Hydrogen	ARG238	H	2.82182
			Hydrogen	ARG238	H	2.63917
			Hydrogen	ARG238	H	2.66959
			Hydrogen	GLU50	H	3.56626
			Hydrogen	GLU329	H	3.78156
2	1LNZ	-6.4	Hydrogen	GLU50	H	2.52744
			Hydrogen	LEU52	H	2.00736
			Hydrogen	ARG53	H	2.68675
			Hydrogen	ARG236	H	2.83051
			Hydrogen	ARG238	H	2.80145
3	1LNZ	-6.5	Hydrogen	LUE249	H	2.38278
			Hydrogen	ASP245	C	3.31557
			Hydrogen	SER168	C	3.16937
			Hydrogen	ASP257	C	3.54732
			Hydrogen	GLY251	C	3.26068
4	1LNZ	-7.0	Hydrogen	ARG53	H	2.08347
			Hydrogen	ARG53	H	2.52826
			Hydrogen	ARG236	H	2.74286
			Hydrogen	ARG238	H	2.58744
			Hydrogen	ARG238	H	2.21188
			Hydrogen	ARG238	H	2.36376
			Hydrogen	ARG238	H	2.61723
			Hydrophobic	PRO91	A	4.50968
5	1LNZ	-6.7	Hydrogen	ARG236	C	2.11825
			Hydrophobic	LYS156	PA	5.40113
			Hydrophobic	LEU158	PA	5.33484
6	1LNZ	-6.8	Hydrogen	ARG53	H	2.86388
			Hydrogen	ARG53	H	2.54204
			Hydrogen	ARG236	H	2.12185

7	1LNZ	-6.4	Hydrogen	LEU328	C	3.50014
			Hydrophobic	LYS156	PA	5.29106
			Hydrophobic	LEU158	PA	5.29709
			Hydrogen	LYS11	H	2.32279
			Hydrogen	LYS11	H	2.21675
			Hydrogen	LYS40	H	2.40261
			Hydrogen	ARG50	H	2.27473
			Hydrogen	LYS101	H	2.55524
			Hydrogen	ARG11	H	2.76904

H = conventional hydrogen bond; C = carbon hydrogen bond; A= alkyl; PA = Pi-alkyl; PCa = Pi-cation; PDH = Pi-donor hydrogen bond; PS = Pi-sigma.

Table 8. Binding affinity (kcal/mol) and nonbonding interactions of MaGP (1) and its derivatives (2-7) with 5AJH.

Entry	Protein	Binding affinity	Bond category	Residues in contact	Interaction types	Distance (Å)
1	5AJH	-4.9	Hydrogen	ASP23	H	1.95739
			Hydrogen	LYS66	H	1.96187
			Hydrogen	ASP23	H	2.26121
			Hydrogen	ARG21	H	2.58759
2	5AJH	-6.2	Hydrogen	GLN193	H	2.30138
			Hydrogen	SER43	C	3.27991
3	5AJH	-5.9	-	-	No Interaction	-
4	5AJH	-6.3	Hydrogen	ASN67	H	2.35935
			Hydrogen	TRP70	H	2.70617
			Hydrogen	TRP70	H	2.21792
			Hydrogen	ASN26	C	3.78758
			Hydrogen	ASN26	C	3.49399
5	5AJH	-7.2	Hydrogen	ARG167	H	2.8311
			Hydrogen	LYS207	C	3.75586
			Hydrophobic	VAL114	PS	3.69066
			Hydrophobic	LYS141	PA	5.15907
			Hydrophobic	ALA211	PA	4.72961
			Hydrophobic	ALA215	PA	4.65601
			Hydrophobic	LYS141	PA	5.26724

6	5AJH	-7.1	Hydrophobic	VAL178	PA	5.43711
			Hydrophobic	VAL185	PA	4.96169
			Hydrophobic	LEU82	PA	4.14988
7	5AJH	-6.4	Hydrogen	GLU50	H	2.82279
			Hydrogen	LEU52	H	2.23675
			Hydrogen	ARG53	H	2.31261
			Hydrogen	ARG53	H	2.67473
			Hydrogen	ARG53	H	2.52524
			Hydrogen	ARG236	H	2.80904

H = conventional hydrogen bond; C = carbon hydrogen bond; A= alkyl; PA = Pi-alkyl; PCa = Pi-cation; PDH = Pi-donor hydrogen bond; PS = Pi-sigma.

The binding affinity and specificity increased in the order **4** < **6** < **5** due to stronger hydrogen bonding. Modifying the –OH group enhanced π – π and hydrogen-bonding interactions, and all derivatives (**2**–**7**) formed the highest number of H-bonds.

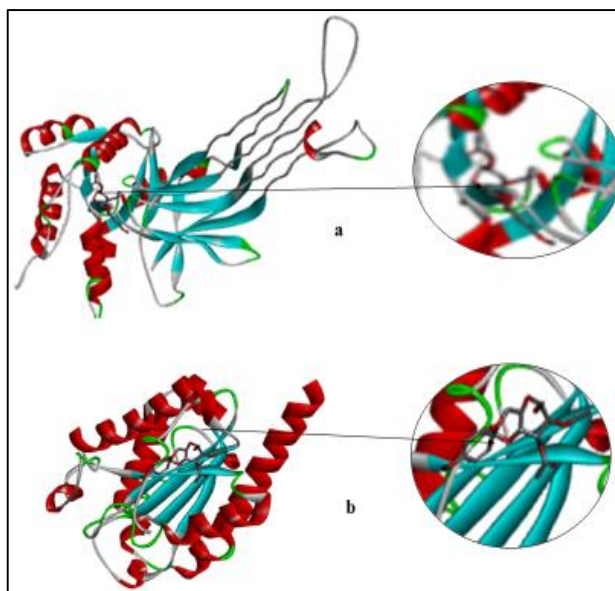


Figure 6. Binding interactions of compound **4** with (a) ILNZ and (b) 5AJH.

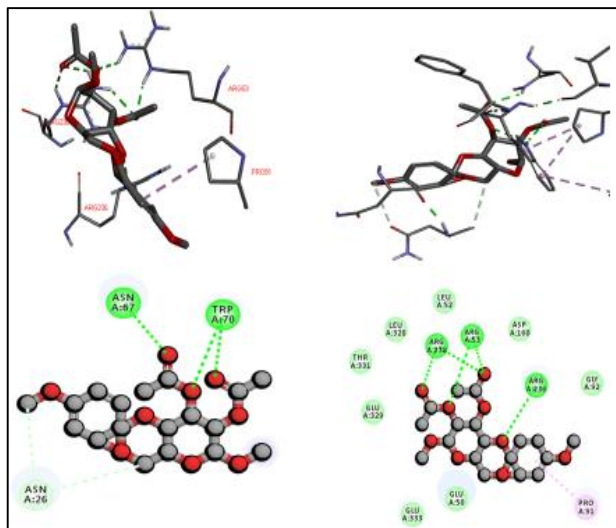


Figure 7(A). Ligand interaction and 2D nonbonding interactions of **4-ILNZ** (top) and **4-5AJH** (bottom) generated by Discovery Studio.

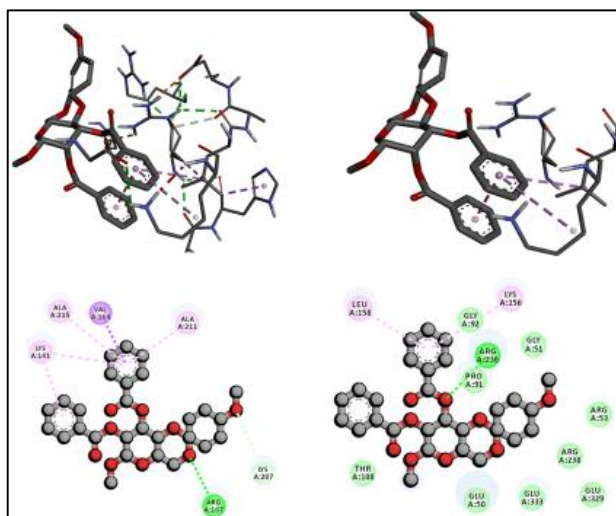


Figure 7(B). Ligand interaction and 2D nonbonding interactions of **5-ILNZ** (top) and **5-5AJH** (bottom) generated by Discovery Studio.

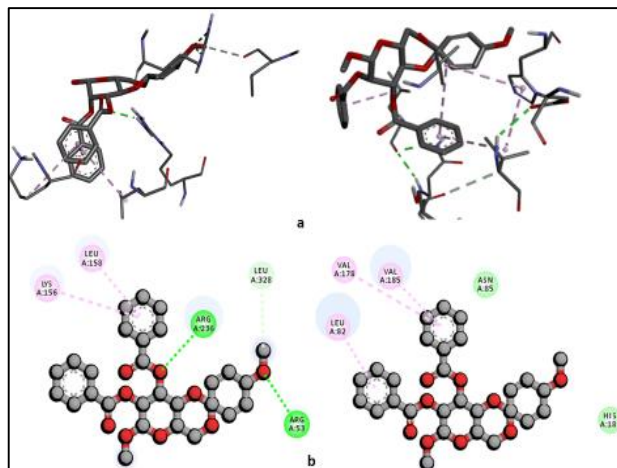


Figure 7(C). Ligand interaction (a) and 2D nonbonding interactions (b) of **6-ILNZ** and **6-5AJH** generated by Discovery Studio.

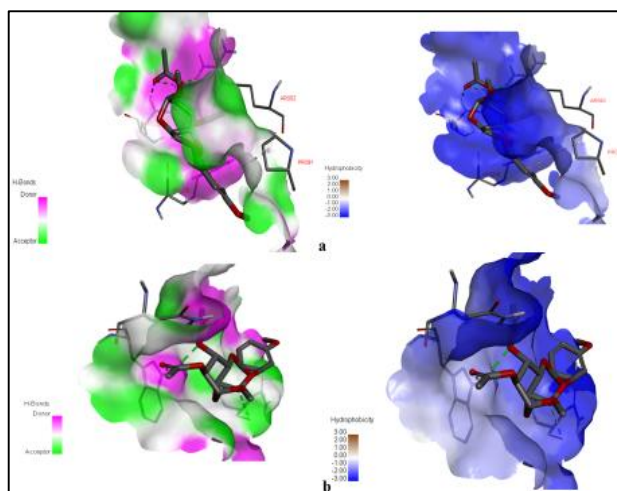


Figure 8(A). (a): Hydrogen and hydrophobic bond surfaces of **4-ILNZ**; (b): Hydrogen and hydrophobic bond surfaces of **4-5AJH**.

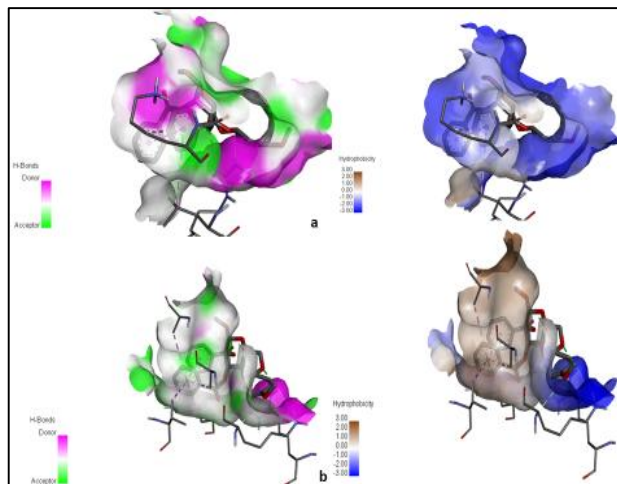


Figure 8(B). (a): Hydrogen and hydrophobic bond surfaces of **5-ILNZ**; (b): Hydrogen and hydrophobic bond surfaces of **5-5AJH**.

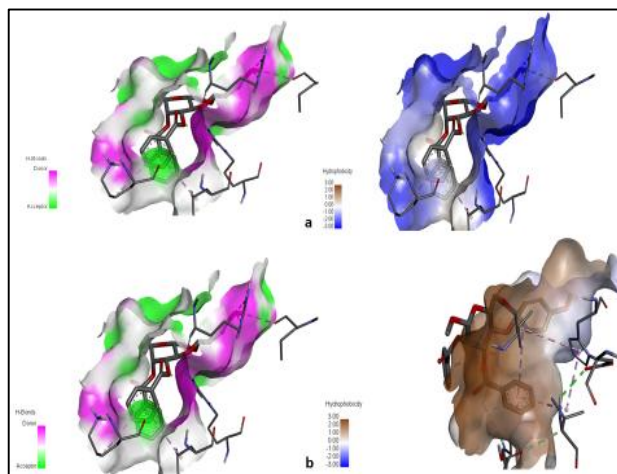


Figure 8(C). (a): Hydrogen and hydrophobic bond surfaces of **6-ILNZ**; (b): Hydrogen and hydrophobic bond surfaces of **6-5AJH**.

3.6. Pharmacokinetic and drug-likeness prediction

The pharmacokinetic properties were computed to compare the absorption, metabolism, distribution, metabolism and toxicity of all the designed derivatives [41]. Water solubility (log mol/L), log PAPP (caco-2 cell permeability), skin

permeability, human intestinal absorption, blood–brain barrier permeation, *p*-glycoprotein substrate, *p*-glycoprotein I-inhibitor, *p*-glycoprotein II- inhibitor, oral rat acute toxicity (LD₅₀), oral Rat chronic toxicity (LOAEL), AMES toxicity, hERG II- inhibitor, hERG II- inhibitor, volume of distribution, central nervous system (CNS) permeability, renal OCT2 substrate, total clearance, CYP450 1A2 inhibitor, CYP450 3A4 inhibitor, CYP450 2C9 inhibitor, CYP450 2D6 inhibitor, hERG1 inhibition, human hepatotoxicity, and skin sensitivity of all the synthesized compounds were determined via pkCSM [42,43]. Some properties are presented in Tables 9 and 10. From the above pharmacokinetic data, we concluded that, compared with the parent compounds, most of the compounds are less toxic and have probable drug characteristics.

Table 9. Pharmacokinetic properties of M α GP (1) and its derivatives (2-7).

Entry	Log p	RB	HBA	HBD	TPSA (Å ²)
1	-2.5673	2	6	4	75.327
2	0.2023	3	7	2	127.860
3	1.3439	5	9	0	162.282
4	0.1701	7	11	0	174.898
5	3.0287	9	11	0	232.282
6	1.9434	7	8	1	164.166
7	2.5142	8	9	10	181.377

RB = number of rotatory bonds, HBA = hydrogen bond acceptor. HBD = hydrogen bond donor, TPSA = topological surface area.

Table 10. Pharmacokinetic properties of M α GP (1) and its derivatives (2-7).

Properties	Compounds						
	1	2	3	4	5	6	7
Water solubility	-0.152	-2.453	-4.123	-3.949	-3.649	-4.244	-4.770
Caco permeability	-0.168	0.306	1.009	1.108	1.256	1.06	0.979
Intestinal absorption (human)	38.005	71.801	73.240	53.892	83.036	75.605	79.178
Skin permeability	-3.395	-2.935	-2.723	-2.735	-2.735	-2.865	-2.738

p-glycoprotein substrate	No	No	No	No	No	No	No
p-glycoprotein I- inhibitor	No	No	No	Yes	Yes	No	Yes
p-glycoprotein II- inhibitor	No	No	No	No	Yes	No	No
BBB permeability	-0.901	-0.367	-1.276	-2.082	-2.100	-0.542	-1.341
Oral Rat acute toxicity (LD ₅₀)	1.366	2.372	2.894	2.170	2.822	2.080	2.622
Oral Rat chronic toxicity	3.712	2.952	1.524	1.421	1.293	3.353	3.456
AMES toxicity	No	No	No	No	No	No	No
hERG I- inhibitor	No	No	No	No	No	No	No
hERG II- inhibitor	No	No	No	No	Yes	No	No
Skin sensation	No	No	No	No	No	No	No

4. Conclusion and Future Perspectives

In this study, the stability and biochemical behavior of M α GP (**1**) and its derivatives (**2–7**) were examined using a DFT-based quantum-mechanical approach. Key properties related to biological activity and chemical reactivity—such as HOMO, LUMO, the HOMO–LUMO gap, and MEP—were optimized, indicating their potential as promising therapeutic agents. Compared with the parent molecule, all designed derivatives exhibited lower HOMO–LUMO gaps and improved pharmacokinetic profiles. Thus, the modified compounds are generally more reactive than M α GP (**1**), although some derivatives may retain comparable stability. Molecular docking analysis showed that derivatives **4**, **5**, and **6** achieved higher binding affinities and stronger nonbonding interactions with 1LNZ and 5AJH than the parent compound. These findings suggest that the designed derivatives may serve as potential antibacterial and antifungal agents, possibly inhibiting *Bacillus subtilis* and *Fusarium equiseti*. MEP analysis further identified the most negative and positive surface regions, highlighting likely sites for hydrogen bonding. Pharmacokinetic evaluation indicated reduced toxicity and enhanced ADMET characteristics for the modified derivatives relative to the parent drug. Overall, this

work provides important insights into the chemical, thermal, physicochemical, biological, and pharmacokinetic properties of M α GP (**1**) and its derivatives (**2–7**), supporting their potential use in future pharmaceutical and medicinal applications.

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