

# Computational Investigation of Mannopyranoside Derivatives as Potential Dopamine D2 Inhibitors Using DFT and Molecular Docking Approaches

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## Abstract

Methyl  $\alpha$ -D-mannopyranoside derivatives were investigated to overcome the limited stability and weak receptor-binding affinity of native mannopyranosides. Previously synthesized derivatives were computationally evaluated for their stability, pharmacokinetic properties, and dopamine D2 receptor-binding potential using DFT optimization, ADMET prediction, and molecular docking studies. Density Functional Theory (DFT) geometry optimization provided important molecular descriptors, including HOMO, LUMO, ionization potential, electron affinity, hardness, softness, electronegativity, and electrophilicity indices. Among the studied compounds, derivative 7 exhibited the lowest energy gap (5.3042 eV), indicating higher chemical reactivity, whereas the parent compound (1) showed the highest energy gap (7.4074 eV). Thermodynamic parameters and molecular electrostatic potential (MEP) analyses further explained their chemical stability and reactive behavior. Molecular docking studies demonstrated that compound 7 possessed the strongest binding affinity (−9.7 kcal/mol) toward the dopamine D2 receptor, forming hydrogen bonds and several hydrophobic interactions within the active binding pocket. ADMET predictions suggested favorable pharmacokinetic characteristics for the synthesized derivatives, while PASS analysis indicated several potential biological activities. Overall, this study provides valuable insights into the stability, reactivity, pharmacokinetic behavior, and potential dopamine D2 inhibitory activity of methyl  $\alpha$ -D-mannopyranoside derivatives.

## Keywords

DFT, Methyl  $\alpha$ -D-Mannopyranoside, Dopamine, Molecular Docking,

## 1. Introduction

The use of carbohydrate-based chemicals, whether synthetic, semisynthetic, or derived from natural sources, that are used to treat diseases such as diabetes, cancer, and bacterial and viral infections, among others, is evidence of the therapeutic potential of carbs. Interdisciplinary research spanning chemistry, biology, and pharmaceutical/medical sciences, including carbohydrate chemistry, biochemistry, glycobiology, drug design, microbiology, and oncology, is necessary for the discovery of bioactive carbohydrates and their advancement toward additional pharmaceutical applications [1]. Rat adjuvant arthritis was treated with methyl- $\alpha$ -D-mannopyranoside, mannooligosaccharides made from acetolyzing yeast mannan, and pure mannans extracted from the cell walls of pathogenic (*Candida albicans*) and nonpathogenic (*Saccharomyces cerevisiae*) yeasts. Injection of Freund's full adjuvant into the tail region of rats can cause arthritis [2] [3]. Antibacterial therapy is used to concentrate on selective toxicity with the explicit goal of direct bactericidal or bacteriostatic action. However, antiadhesion therapy is a new tactic to combat bacterial infections. Since the adherence of bacteria to a particular tissue determines their capacity to infect host tissues, inhibiting this process is thought to be an effective means of preventing infection and the formation of biofilms [4]. The neurotransmitter dopamine has been linked to a wide range of functions, including reward, addiction, metabolism, hormone release, and the regulation of coordinated movement. Accordingly, disorders such as schizophrenia, Parkinson's disease, depression, attention deficit hyperactivity disorder, nausea, and vomiting have been linked to the dysregulation of the dopaminergic system. A family of five G-protein-coupled receptors mediates the effects of dopamine. Drugs used to treat Parkinson's disease and both conventional and atypical antipsychotics mostly target the D2 dopamine receptor [5]. Carbohydrates [6]-[8] and nucleosides [9]-[11] have garnered significant attention because of their therapeutic qualities in addition to their fundamental biological roles, with new research emphasizing their potential in medication development.

Methyl  $\alpha$ -D-mannopyranoside and its derivatives, which share structural similarities with natural sugars, present potential choices for a range of biological uses [12]. We created three isoenergetic maps by B3LYP/6-31G in the gas phase. This allowed us to determine the influence of the orientation of the hydroxyl group on the energy landscape [13]. Molecular docking analysis of the 6CM4 dopamine receptor with several mannopyranoside derivatives was the main focus of this investigation. The docking results revealed that the derivatives had different binding affinities, which shed light on their possible effectiveness [14]. To compare their thermal and chemical properties, the following metrics were computed: free energy, enthalpy, entropy, heat capacity, dipole moment, HOMO-LUMO gap, DOS

plot, polarizability, molar refractivity, atomic partial charge, and molecular electrostatic potential. All the compounds were subjected to antimicrobial screening, and their PASS characteristics were predicted [15] [16]. Drug-receptor interactions are inversely correlated with the distance between the HOMO and LUMO energies, meaning that a greater distance results in less stability and vice versa [17]. Numerous biological effects, such as anti-inflammatory, anticancer, antifungal, antiviral, antidiabetic, and antibacterial activities, were predicted *via* the PASS web-based program [18]. *In vitro* studies of bacteria and fungi with PASS (activity spectra for substances) prediction revealed the excellent antimicrobial activity of some analogs [19]. The industries in which these compounds can be employed now depend heavily on ADME and molecular target prediction. Both ligand-based and structure-based drug design approaches are crucial drug discovery instruments in the logical drug discovery process. In structure-based drug design, docking studies are sophisticated computational techniques that use a reduced-energy-free system to examine the relative orientation of the ligand-receptor interaction and produce an optimal shape.

The dopamine D2 receptor (DRD2) is part of the G protein-coupled receptor (GPCR) superfamily and is classified within the D2-like subfamily, which also encompasses the D3 and D4 receptors [20]. Two primary isoforms of dopamine D2, D2 long (D2L) and D2 short (D2S), result from alternative splicing. Although both isoforms share similar ligand-binding characteristics, they differ in their intracellular signaling properties and tissue distributions [21]. From a functional standpoint, DRD2 is crucial for regulating neuroendocrine signaling, reward systems, motor control, and intelligence [22]. Computer-aided drug design is a quick and affordable modern method that makes it possible to synthesize new ideas for molecular structures and analyze experimental results in a meaningful, accurate, and thorough way [23]. This study involved adding acyl substituents to methyl  $\alpha$ -D-mannopyranoside, optimizing it via quantum mechanical approaches, and then evaluating its electrical and thermal stability as well as its biological properties.

The main reasons for the selection of mannopyranoside derivatives as potential dopamine D2 receptor (DRD2) inhibitors were their unique combination of structural chirality, high biocompatibility, and favorable pharmacokinetic properties. The versatility of the carbohydrate scaffold lies in the presence of several hydroxyl groups that can be selectively modified to improve the binding affinity to the receptor by specific hydrogen bonding and hydrophobic interactions within the binding site of the receptor, which in turn can be enhanced [24] [25]. Specifically, mannopyranosides are used because they promote enhanced ADMET properties, including increased solubility and decreased systemic toxicity, which are essential for therapeutics that target the central nervous system [26]. Moreover, the identification of naturally occurring glycosides such as salidroside, which is known to directly affect DRD2, offers a biologically derived model for exploring the use of carbohydrate-based scaffolds to control dopaminergic

pathways effectively [27].

To assess the compounds' stability, antibacterial qualities, and pharmacokinetics, a variety of computational tools, such as density functional theory (DFT) analysis and molecular docking, were used [28]. In this work, derivatives were synthesized and optimized by DFT to explore their structural and electronic properties. AD-MET predictions were performed to assess pharmacokinetic behavior, while molecular docking against the dopamine D2 receptor provided insights into the receptor-binding affinity of these proteins. These findings highlight the potential of these derivatives as promising candidates for drug development.

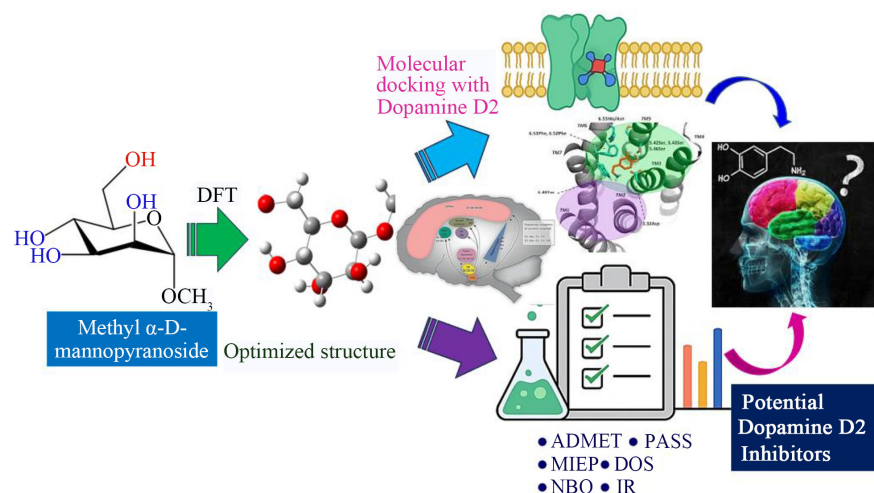
## 2. Computational Details

The derivatives were displayed by the Gauss view (6.0) program. Each compound was optimized separately using Gaussian software and density functional theory (DFT) [29]. The basis set 6-31G was utilized on a Core i5 laptop. The LUMO and HOMO energies and electrostatic potentials of the molecules and MEP were computed. The finite field approach was used to calculate the first-order molecules, polarizability, and hyperpolarizability by DFT methods with 6-31G as the basis set. The frequency at which the optimized structure was yielded was represented as the infrared spectrum. The geometries reached true structural minima confirmed by frequency calculations, yielding zero imaginary frequencies. The mean dipole moment, first-order hyperpolarizability (nonlinear) and polarizability optical characteristics were calculated with the application Gaussian 09 W [30]. Virtual screening of carbohydrate derivatives is accomplished by docking with PyRx, an open-source program that runs on all major operating systems (Linux, Windows, and Mac OS) and has an easy-to-use interface. In addition to considerations for data preparation, docking, and data analysis, specific steps for using PyRx are also explained [31]. The energy of the protein compounds was minimized by using Swiss PDB Viewer 4.1.0 software [32]. Biovia Discovery Studio was used to visualize the molecular interactions [33]. PyMol software was used to eliminate heteroatoms and water molecules, visualize 3D structures, and perform computational drug design by PyMOL [34]. Polar hydrogen was added to the protein mixture, and AutoDock Tools was used to extract the cocrystallized ligands. The docking simulations were performed in AutoDock Vina. Small compounds can be computationally docked to macromolecular receptors and virtually screened by the AutoDock suite of free open-source tools [35]. The gridbox parameters were centered: X = 10.0809, Y = 7.5055, and Z = 7.6650, while the dimensions (angstroms) were X = 27.5362, Y = 27.5362, and Z = 27.5362, with an exhaustiveness = 8. Rat acute toxicity, human intestinal absorption, blood-brain barrier, cytochrome P450 inhibition, and human ether-go-go-related gene inhibition are among the pharmacokinetic and pharmacodynamic parameters associated with pkCSM. pkCSM builds predictive models of key ADMET features for drug development via graph-based signatures [36]. Dopamine D2 (6CM4) protein crystal structures are available from the Protein Data Bank (<https://www.rcsb.org/>).

Better predictability is obtained by docking the pose with the real pose [37].

### 3. Results and Discussion

Prior synthesis of methyl- $\alpha$ -D-mannopyranoside (1) and its derivatives (2-7) was carried out using a direct technique [38]. The overall experimental design, computational workflow, and outline of the current study are illustrated in **Figure 1**.

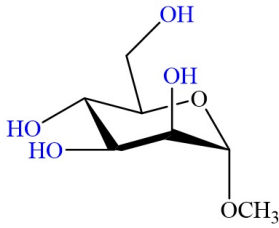
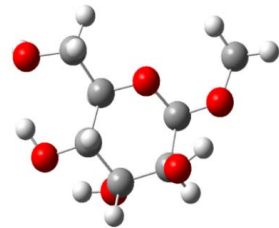
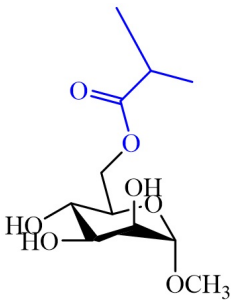
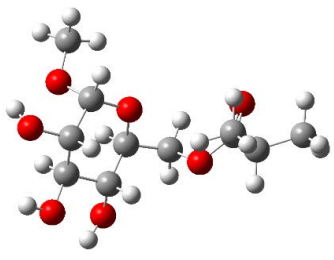
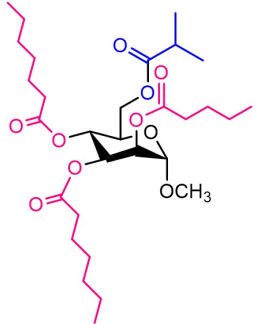
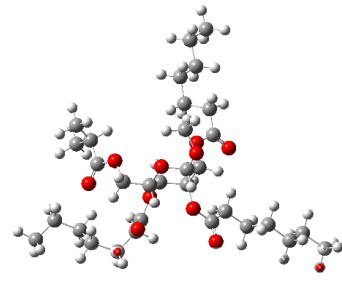
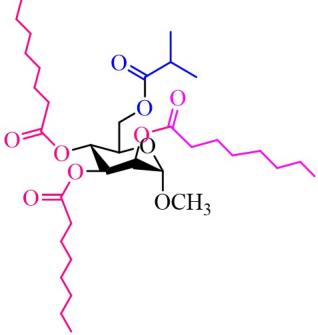
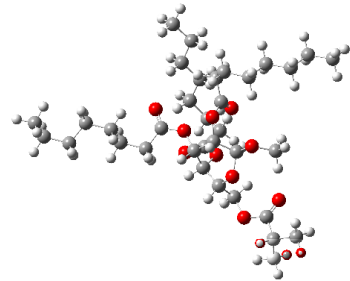
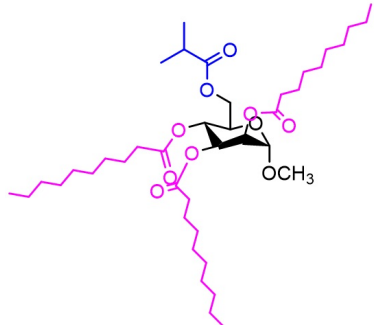
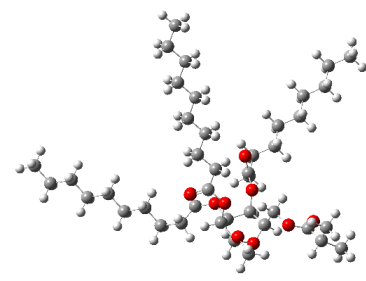


**Figure 1.** Overall workflow and outline of the current study.

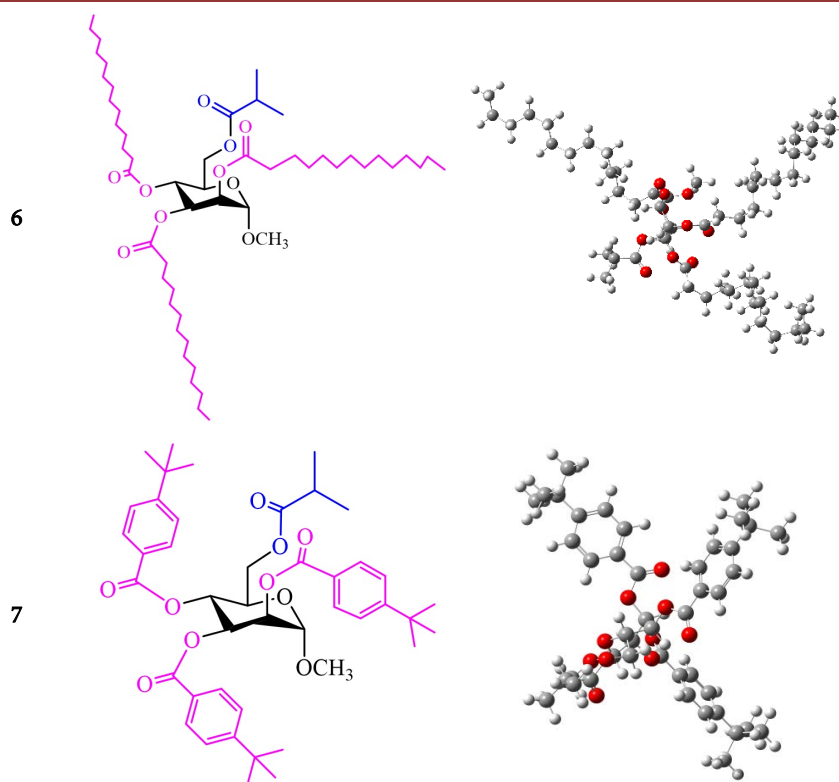
#### 3.1. Optimized Structure

The geometry, rotational barrier, vibrational frequency, and electrical characteristics of the compounds are precisely and reliably determined via density functional theory (DFT) [39] [40]. **Table 1** displays the optimized structure for each of the six distinct compounds. The computations were performed via the 6-31G basis set and the hybrid B3LYP functional technique. One of the most widely used and effective functionals for drug design is B3LYP, which can balance calculation efficiency and accuracy. The geometry, vibrational frequencies, dipole moments, and reaction energies of many pharmacological compounds can be replicated by B3LYP. Ionization potentials, electron affinities, spin densities, and NMR chemical shifts are only a few of the electrical and magnetic characteristics of pharmacological compounds that B3LYP can record. In quantum chemistry, B3LYP is regarded as a workhorse functional and has been frequently used. Because it strikes a compromise between accuracy and computing expense, it is very popular. Its ability to strike a compromise between computing cost and precision accounts for its appeal. Because it yields reasonable results over a wide range of systems, including organic and inorganic molecules, researchers frequently choose it. Frontier molecular orbitals (FMOs) provide accurate qualitative evidence of electron susceptibility and control how drugs interact with their receptors. An electron acceptor is the LUMO, which is the lowest energy orbital with an opening for electrons [41].

**Table 1.** Optimization of mannopyranoside (1) and its derivatives (2-7).

| Entry | Structure                                                                            | Optimized                                                                             |
|-------|--------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------|
| 1     |     |    |
| 2     |     |    |
| 3     |    |   |
| 4     |  |  |
| 5     |  |  |

Continued



### 3.2. Thermodynamic Analysis

**Table 2.** Thermodynamic properties of methyl  $\alpha$ -D-mannopyranoside (1) and its derivatives (2-7).

| Compound | Stoichiometry                                   | Electronic Energy (Hartree) | Enthalpy (Hartree) | Gibbs free energy (Hartree) | Dipole moment (Debye) | Polarizability (a.u.) |
|----------|-------------------------------------------------|-----------------------------|--------------------|-----------------------------|-----------------------|-----------------------|
| 1        | C <sub>7</sub> H <sub>14</sub> O <sub>6</sub>   | -722.461                    | -722.222           | -722.276                    | 4.556                 | 86.188                |
| 2        | C <sub>15</sub> H <sub>20</sub> O <sub>7</sub>  | -957.461                    | -957.120           | -957.191                    | 2.476                 | 133.710               |
| 3        | C <sub>32</sub> H <sub>56</sub> O <sub>10</sub> | -2004.827                   | -2003.909          | -2004.056                   | 7.574                 | 364.654               |
| 4        | C <sub>35</sub> H <sub>62</sub> O <sub>10</sub> | -2122.736                   | -2121.728          | -2121.883                   | 4.419                 | 395.215               |
| 5        | C <sub>41</sub> H <sub>74</sub> O <sub>10</sub> | -2358.556                   | -2357.368          | -2357.545                   | 5.728                 | 466.152               |
| 6        | C <sub>53</sub> H <sub>98</sub> O <sub>10</sub> | -2830.171                   | -2828.621          | -2828.835                   | 3.716                 | 589.445               |
| 7        | C <sub>44</sub> H <sub>56</sub> O <sub>10</sub> | -2462.035                   | -2461.042          | -2461.198                   | 2.721                 | 504.609               |

Normal changes in molecular structure substantially affect structural features such as thermal and molecular orbital parameters. Free energy and enthalpy data can be used to deduce the spontaneous nature of a reaction and the stability of a product [42]. For thermal stability, values that are extremely negative are better. The dipole moment also affects the development of hydrogen bonds and non-bonded interactions in drug design. The binding property may improve with increasing dipole moment. The free energy of methyl  $\alpha$ -D-mannopyranoside is -722.276 hartrees, where the Gibbs free energies of derivatives 6 and 7 are

−2828.835 and −2461.198 hartrees, respectively. The highest electronic energy was observed for 6 (−2830.171 Hartree), and the highest dipole moment was observed for 3 (7.574 Debye); these values are listed in **Table 2**. The presence of a bulky acylating group suggests that the possible improvement in the polarizability of derivative 6 results in the highest polarizability value of 589.445 a.u.

### 3.3. Quantum Chemical Parameters

The quantum chemical characteristics of molecules can be reliably predicted *via* density functional theory (DFT) [43]. Quantum chemical parameters are essential descriptors that shed light on the electronic structure, stability, and reactivity of chemical compounds. They are obtained from density functional theory (DFT) and molecular orbital theory. While their energy gap indicates chemical stability, frontier molecular orbital energies, such as the lowest unoccupied molecular orbital (LUMO) and the highest occupied molecular orbital (HOMO), indicate a molecule's capacity to accept and donate electrons, respectively. To predict the reactive nature of molecules in a variety of chemical and biological environments, global reactivity descriptors such as ionization potential, electron affinity, chemical hardness, softness, electronegativity, chemical potential, and electrophilicity indices can be computed from these orbital values [44] [45]. Furthermore, characteristics such as the atomic charge distribution, dipole moment, polarizability, and MEP reveal details about potential sites for electrophilic and nucleophilic attack as well as intermolecular interactions. To further understand thermodynamic stability, one might consider energetic quantities such as total energy, free energy, and binding energy. Researchers can describe and predict molecular behavior at the atomic level by combining these quantum chemical characteristics, which makes them effective tools in computational chemistry, drug design, and materials science [46].

### 3.4. HOMO-LUMO Properties

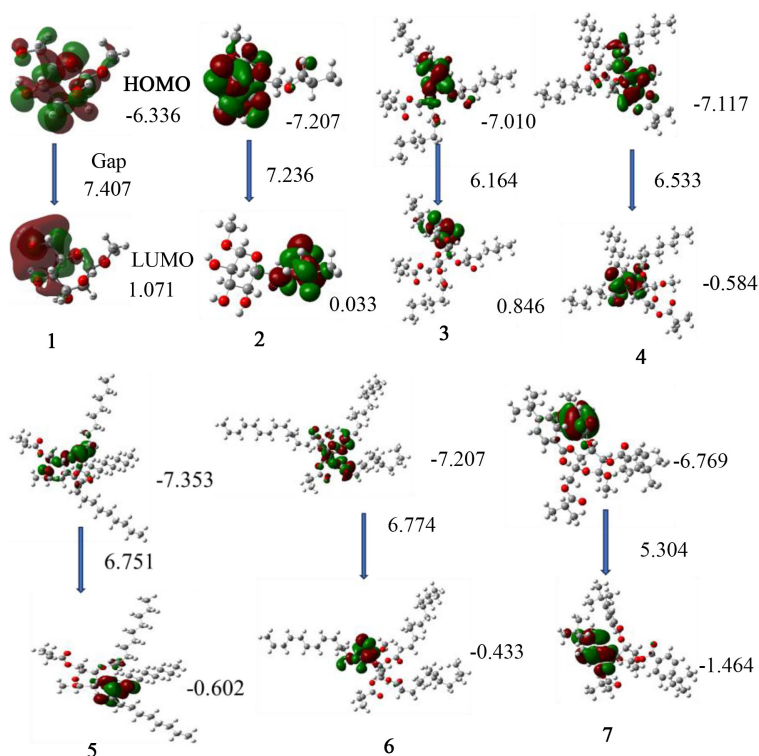
The electron density of the lowest energy orbital that is unoccupied is represented by the LUMO, and the electron density of the highest energy orbital that is fully occupied is represented by the HOMO. A crucial factor in determining a molecule's stability and reactivity is the HOMO-LUMO gap, which is the energy differential between the HOMO and LUMO. Some new descriptors based on quantum chemistry have been computed because of the capacity of HF and DFT approaches to characterize the chemical and physical characteristics of molecules [47]. Several quantum chemical characteristics, including electronegativity ( $\chi$ ), chemical hardness ( $\eta$ ), global softness ( $S$ ), chemical potential ( $\mu$ ), and global electrophilicity ( $\omega$ ), were computed from the values derived from  $E_{\text{LUMO}}$  (IP) and  $E_{\text{HOMO}}$  (EA) [48] [49]. Gaussian09 was thus used to generate the molecular HOMOs and LUMOs. The HOMO-LUMO gap ( $\Delta E = E_{\text{LUMO}} - E_{\text{HOMO}}$ ), HOMO energy ( $E_{\text{HOMO}}$ ), and LUMO energy ( $E_{\text{LUMO}}$ ) values of methyl  $\alpha$ -D-mannopyranoside (1) and its derivatives (2-7) are listed in **Table 3**.

**Table 3.** Data on the chemical reactivity descriptor of methyl  $\alpha$ -D-mannopyranoside (1) and its derivatives (2-7).

| Entry | $\epsilon$ HOMO | $\epsilon$ LUMO | Gap   | Hardness | Softness | chemical potential | electronegativity | electrophilicity |
|-------|-----------------|-----------------|-------|----------|----------|--------------------|-------------------|------------------|
| 1     | -6.336          | 1.071           | 7.407 | 3.703    | 0.270    | -2.632             | 2.632             | 0.935            |
| 2     | -7.207          | 0.033           | 7.236 | 3.620    | 0.276    | -3.587             | 3.587             | 1.777            |
| 3     | -7.010          | -0.846          | 6.164 | 3.082    | 0.324    | -3.928             | 3.928             | 2.503            |
| 4     | -7.117          | -0.584          | 6.533 | 3.266    | 0.306    | -3.851             | 3.851             | 2.268            |
| 5     | -7.353          | -0.602          | 6.751 | 3.375    | 0.296    | -3.977             | 3.977             | 2.343            |
| 6     | -7.207          | -0.433          | 6.774 | 3.387    | 0.295    | -3.820             | 3.820             | 2.156            |
| 7     | -6.769          | -1.464          | 5.304 | 2.652    | 0.377    | -4.117             | 4.117             | 3.196            |

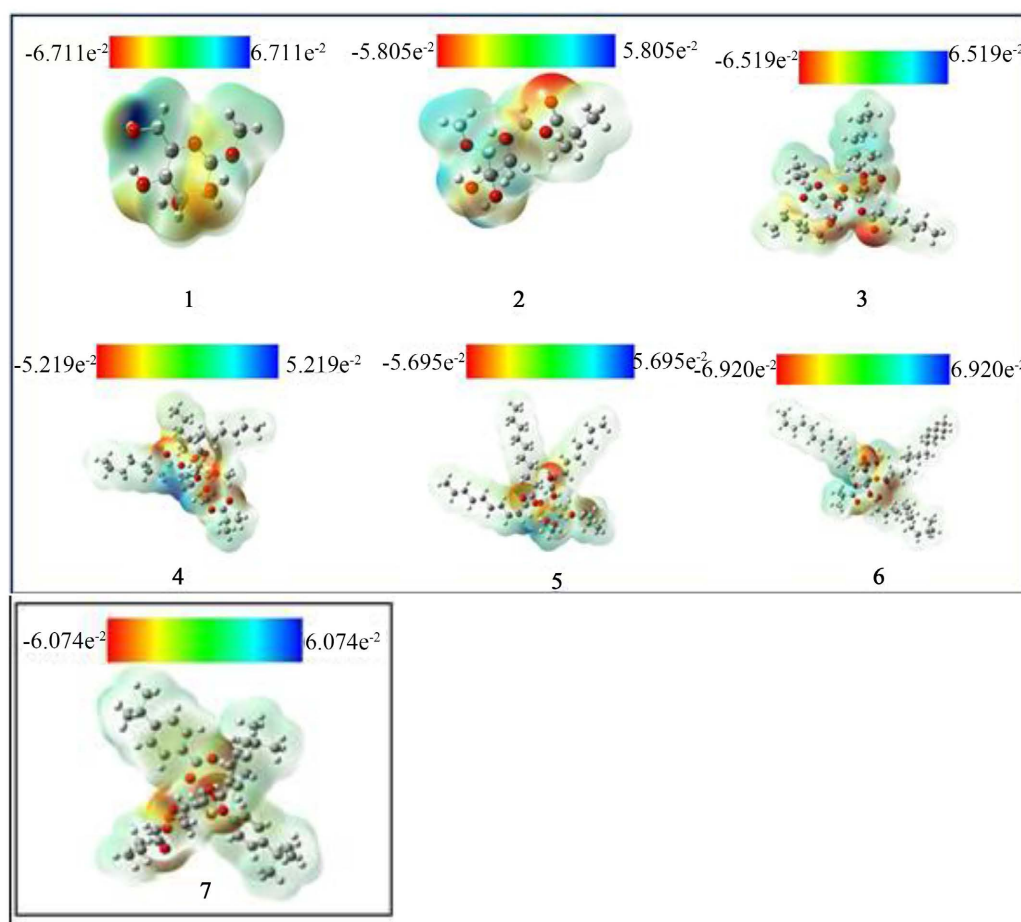
**Table 3** presents the values of orbital energies, along with the two global chemical descriptors, hardness and softness, which are also calculated for all the compounds. The highest softness was observed for compound 7. Compound 7 also had the lowest HOMO-LUMO gap and hardness, indicating that the molecule is more reactive than the other compounds, according to [50] (**Figure 2**).

With an energy gap of 7.407 eV, compound 1 had the highest chemical hardness (3.703 eV) and the lowest softness (0.270 eV). The lowest energy gap, 5.304 eV, is found in compound 7 (4-*t*-butylbenzoyl), which also has the highest softness (0.377 eV) and the lowest hardness (2.652 eV) (**Table 3** and **Figure 2**) [51]. These results clarify the relative stability and reactivity of these chemicals, which will facilitate further research and design.

**Figure 2.** Molecular orbital distribution plots of the HOMO and LUMO.

### 3.5. Molecular Electrostatic Potential (MEP)

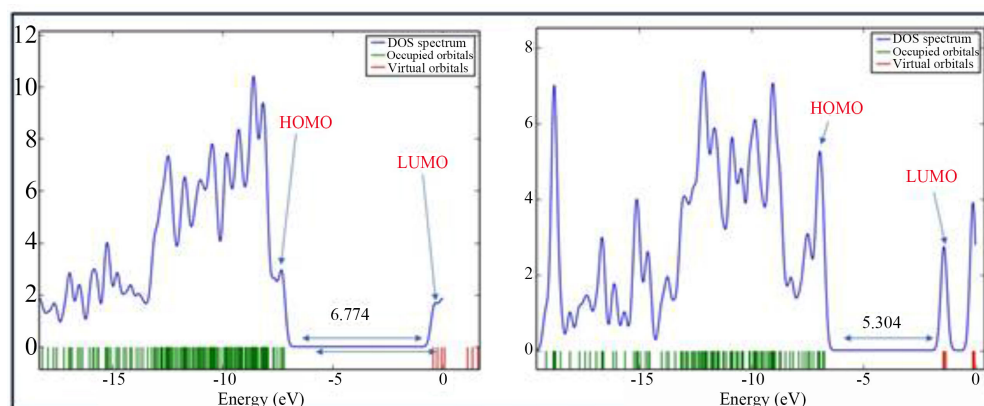
The molecular electrostatic potential (MEP) is widely used as a reactivity map to display the most likely region for the electrophilic and nucleophilic attack of charged points, such as reagents, on organic molecules [52]. This method helps to interpret the biological recognition process and hydrogen bonding interactions. The MEP counter map provides a simple way to predict how different geometries could interact. The MEPs of methyl  $\alpha$ -D-mannopyranoside and its derivatives (2 to 7) were obtained on the basis of the DFT model with the basis set 6-31G optimized result, as shown in **Figure 3**. The importance of the MEP lies in the fact that it simultaneously displays molecular size and shape, as well as positive, negative, and neutral electrostatic potential regions in terms of color grading, and is very useful in research on the relationships between molecular structure and physicochemical properties. The molecular electrostatic potential (MEP) was calculated to predict the reactive sites for electrophilic and nucleophilic attack of the optimized structure of methyl  $\alpha$ -D-mannopyranoside and its derivatives (2 to 7). The different values of the electrostatic potential are represented by different colors.



**Figure 3.** Molecular electrostatic potential map of methyl  $\alpha$ -D-mannopyranoside (1) and its derivatives (2 to 7).

### 3.6. Density of States (DOS) Analysis

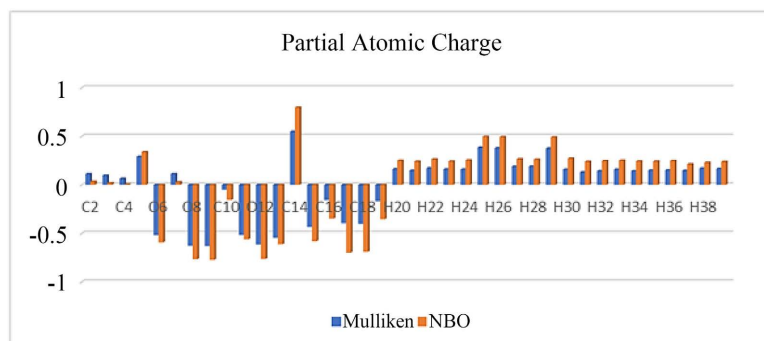
The density of states (DOS), which offers a straightforward method for characterizing intricate electronic structures, is arguably the most crucial idea for comprehending the physical characteristics of materials. The DOS provides important visible features that underpin a material's electrical and optical characteristics, such as the band gap and carrier effective masses [53]. The HOMO of compound **6** is located between  $-6$  and  $-7$  eV. The LUMO can be observed close to  $0$  eV, and the HOMO of compound **7** is the same as that of compound **6**, but the LUMO is close to  $-2$  eV (**Figure 4**). Nevertheless, the density of states profiles of the derivatives exhibits minor variations because of their distinct structural attributes [54].



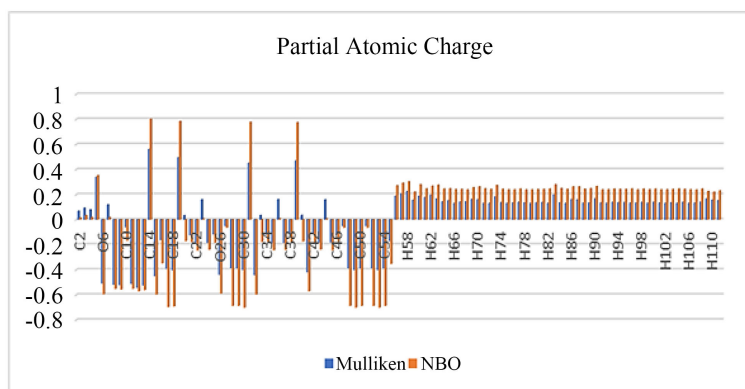
**Figure 4.** DOS plot representing the HOMO-LUMO gap of compounds **6** and **7**.

### 3.7. NBO Analysis

NBO analysis is a quantum chemical tool that helps us understand molecules in terms of localized orbitals that are close to classical chemical concepts such as bonds, lone pairs, and hybridization. The investigation of the influences of covalence and hybridization in polyatomic wave functions resulted in the creation of the natural bond orbital (NBO) analysis technique. The work of Foster and Winhold [55] was expanded upon by Reed *et al.* [56], who utilized NBO analysis, which revealed mainly H-bonded and other strongly bound van der Waals complexes. The results for compounds **2** and **7** are presented in **Figure 5** and **Figure 6**, respectively.



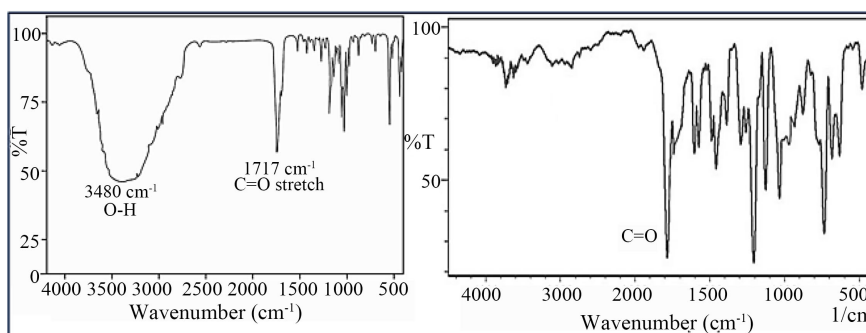
**Figure 5.** Comparison of the NBO charge and Mulliken charge of compound **2**.



**Figure 6.** Comparison of the NBO charge and the Mulliken charge of compound 7.

### 3.8. IR Spectrum

A popular spectroscopic method for analyzing the structure of carbohydrates is infrared (IR) spectroscopy, which is quick, nondestructive, and easily accessible [57]. The FTIR spectrum of compound 2 exhibited strong ester carbonyl absorption at  $1740\text{ cm}^{-1}$  along with a broad  $\text{--OH}$  stretching band at  $3400\text{ cm}^{-1}$ , indicating partial esterification at the C-6 position, whereas characteristic C–O stretching vibrations were observed in the  $1050 - 1150\text{ cm}^{-1}$  region. The FTIR spectrum of 7 displayed multiple strong ester carbonyl absorptions between  $1710$  and  $1740\text{ cm}^{-1}$ , along with aromatic C=C stretching bands at  $1600$  and  $1500\text{ cm}^{-1}$ , para-substituted aromatic out-of-plane bending near  $830\text{ cm}^{-1}$ , and intense C–O stretching in the  $1100 - 1200\text{ cm}^{-1}$  region, confirming complete esterification at positions C-2, C-3, C-4, and C-6. In **Figure 7**, compound 2 shows a broad  $\text{--OH}$  peak at  $3480\text{ cm}^{-1}$  and a sharp peak at  $1717\text{ cm}^{-1}$ . However, after acylation, the  $\text{--OH}$  group should disappear because the acylating agent blocks it, but the  $\text{C=O}$  peak should remain.



**Figure 7.** IR spectra of compounds 2 (right) and 7 (left).

### 3.9. ADMET Analysis

The PreADMET server was used to examine whether the modified chemicals resulted in any toxicity or changed the pharmacokinetic profile. pkCSM is an online tool for in silico drug-like library construction and ADME data prediction. A number of pharmacokinetic and pharmacodynamic factors, including acute toxicity in rats, human intestinal absorption, the blood-brain barrier, cytochrome

P450 inhibition, and human ether-a-go-go-related gene inhibition, have been considered. **Table 4** provides a summary of the findings. The pharmacokinetic and toxicological characteristics of the synthesized carbohydrate derivatives were assessed utilizing the pkCSM predictive model, which revealed that structural modifications throughout the series systematically influence absorption, distribution, metabolism, excretion, and toxicity (ADMET) properties. The values associated with human intestinal absorption (HIA) exhibited significant structural dependence, increasing dramatically from a modest 38.567% in compound 1 and 43.201% in compound 2 to an exceptional peak of 95.804% in compound 7, indicating that the sequential incorporation of lipophilic acyl protecting groups enhances membrane permeability. Moreover, all the compounds exhibited negative blood-brain barrier (BBB) permeability values ( $\log_{BB} = -0.851$  to  $-2.318$ ), thereby meeting the essential safety criteria for the mitigation of central nervous system (CNS) side effects. Although the more hydrophilic, low-absorption structures (Entries 1 and 2) do not function as P-glycoprotein inhibitors, the highly permeable lipid-rich variants (compounds 3-7) act as P-glycoprotein inhibitors, suggesting their potential to modulate efflux pump kinetics. The solubility in pure water ( $\log S$ , mol/L) progressively decreased from  $-0.645$  (compound 1) to  $-3.325$  (compound 7) concomitant with increases in molecular weight and lipophilicity, aligning with the trends observed in membrane tracking studies. From a metabolic and safety perspective, none of the investigated derivatives serve as inhibitors of the cytochrome P450 isoform CYP2C19, nor do they possess cardiotoxic effects, as corroborated by a consistent “No” for hERG channel inhibition [58]. Ultimately, toxicity profiling indicated moderate threshold doses for rat carcinogenicity (1.474 to 2.653 mg/kg/day) accompanied by a highly favorable safety outlook, thereby reinforcing the therapeutic potential of these mannopyranoside derivatives as non-CNS-active candidate scaffolds. These findings suggest that the compounds are excellent peripherally selective D2 inhibitors. By preferentially targeting peripheral dopaminergic sites—such as the gastrointestinal tract or systemic vasculature—without crossing the blood–brain barrier, these mannopyranoside derivatives offer a highly promising therapeutic avenue for treating peripheral dopaminergic disorders (e.g., gastroparesis or severe emesis) while completely avoiding central extrapyramidal or neurological side effects. Alternatively, these profiles establish a clear baseline for future lead optimization, serving as structural blueprints for introducing targeted prodrug linkages or specific de-esterification strategies designed to systematically bypass efflux pumps and tune central bioavailability.

**Table 4.** ADMET analysis of mannopyranoside (1) and its derivatives (1-7).

| Entry | BBB    | CYP2C19 inhibitor | Human Intestinal absorption | P-glycogen inhibitor | Pure water solubility | Carcinogenicity (Rat) | hERG |
|-------|--------|-------------------|-----------------------------|----------------------|-----------------------|-----------------------|------|
| 1     | −0.907 | No                | 38.567                      | No                   | −0.645                | 1.474                 | No   |
| 2     | −0.851 | No                | 43.201                      | No                   | −0.817                | 1.856                 | No   |
| 3     | −1.865 | No                | 71.954                      | Yes                  | −3.144                | 2.357                 | No   |

## Continued

|   |        |    |        |     |        |       |    |
|---|--------|----|--------|-----|--------|-------|----|
| 4 | -1.926 | No | 74.283 | Yes | -3.048 | 2.389 | No |
| 5 | -2.059 | No | 78.787 | Yes | -2.933 | 2.439 | No |
| 6 | -2.318 | No | 87.49  | Yes | -2.892 | 2.477 | No |
| 7 | -1.43  | No | 95.804 | Yes | -3.325 | 2.653 | No |

## 3.10. PASS Prediction

**Table 5.** Prediction of the biological activities of mannopyranoside (1) and its derivatives (2-7) via PASS.

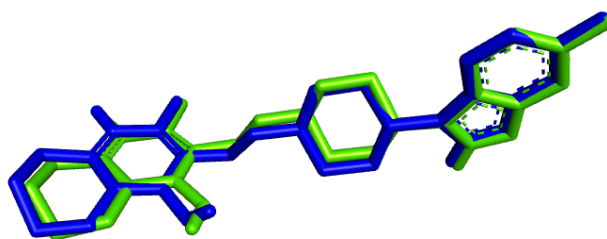
| Entry | Antibacterial |       | Anti-carcinogenic |       | Antifungal |       | Anti-inflammatory |       |
|-------|---------------|-------|-------------------|-------|------------|-------|-------------------|-------|
|       | Pa            | Pi    | Pa                | Pi    | Pa         | Pi    | Pa                | Pi    |
| 1     | 0.541         | 0.013 | 0.731             | 0.008 | 0.628      | 0.016 | 0.650             | 0.023 |
| 2     | 0.552         | 0.012 | 0.656             | 0.010 | 0.686      | 0.010 | 0.608             | 0.030 |
| 3     | 0.569         | 0.011 | 0.497             | 0.020 | 0.721      | 0.009 | 0.596             | 0.033 |
| 4     | 0.569         | 0.011 | 0.497             | 0.020 | 0.721      | 0.009 | 0.596             | 0.033 |
| 5     | 0.569         | 0.011 | 0.497             | 0.020 | 0.721      | 0.009 | 0.596             | 0.033 |
| 6     | 0.569         | 0.011 | 0.497             | 0.020 | 0.721      | 0.009 | 0.596             | 0.033 |
| 7     | 0.498         | 0.017 | 0.497             | 0.021 | 0.665      | 0.012 | 0.634             | 0.025 |

A software program called PASS (Prediction of Activity Spectra for Substances) was created as a means of assessing an organic drug-like molecule's overall biological potential. PASS uses the structure of organic molecules to predict multiple biological activity categories simultaneously. Therefore, before virtual compounds undergo chemical production and biological testing, PASS can be used to assess their biological activity profiles. Pa (probability "to be active") calculates the likelihood that the compound under study is a member of the active compound subclass (similar to the most common molecular structures in a subset of "actives" in the PASS training set). In the leave-one-out cross-validation process, the average prediction error for the whole PASS training set is called the invariant error of prediction (IEP). The Way2Drug primary web server made the PASS predictions. PASS Online uses structural formulas to predict the biological activity of organic compounds with a 95% accuracy rate and over 4000 different categories of activity [59]. **Table 5** presents the predicted biological activities of the mannopyranoside derivatives (1-7), including antibacterial, anticarcinogenic, antifungal, and anti-inflammatory effects. The table lists Pa (probability of activity) and Pi (probability of inactivity) for each derivative. Higher Pa values indicate a greater likelihood that the compound exhibits the specified activity. Most derivatives (2-7) show moderate activity (Pa  $\approx$  0.552 - 0.569). Compound 1 has the highest predicted anticarcinogenic potential (Pa = 0.731), whereas those of the other compounds range from 0.477 - 0.656. These findings suggest that these derivatives may help prevent carcinogenesis rather than directly treat existing cancer. Compounds 3-6 show

strong antifungal potential ( $P_a = 0.721$ ). The  $P_a$  values ranged from 0.596 - 0.634, indicating moderate activity across the derivatives. Overall, these derivatives possess multitargeted biological potential, with antiviral, antimicrobial, and anticarcinogenic effects, which supports their suitability for further drug development and molecular docking studies.

### 3.11. Molecular Docking Validation

To ensure the accuracy, reliability, and predictive validity of the molecular docking simulations carried out in this study, a native ligand redocking protocol was executed prior to screening the synthesized methyl D-mannopyranoside derivatives. The cocrystallized antagonist, risperidone, was computationally extracted from the active binding pocket of the human dopamine receptor D2 (PDB ID: 6CM4) and subjected to an identical, unbiased redocking sequence within the designated grid coordinates. The structural reliability of the docking protocol was assessed by calculating the root-mean-square deviation (RMSD) between the experimentally determined crystal structure conformation of risperidone and its best-scoring, redocked computational pose. As illustrated by the alignment profiles, the redocked ligand configuration strongly mirrored the native spatial geometry within the binding pocket (**Figure 8**). The calculated RMSD was 0.0402 Å, which falls well below the generally accepted threshold of 2.0 Å for highly successful docking validation.



**Figure 8.** Superimposition of the co-crystallized ligand (blue) and the docked ligand (green).

### 3.12. Molecular Docking and Protein-Ligand Interactions

A computational method for predicting ligand binding affinities to receptor proteins is called molecular docking. It can be used in nutraceutical research, but it has become a powerful tool for medication development [60]. Molecular docking has emerged as a crucial component of *in silico* drug development in recent years. This technique involves predicting the interaction between a small molecule and a protein at the atomic level [61]. Numerous computational tools and algorithms for molecular docking approaches are accessible, both commercially and at no cost. These programs and tools have been developed and are currently being used in drug research and academic fields [62]-[65]. The efficacy of the docking algorithms in determining the conformation of the protein-bound ligand was evaluated through redocking of the cocrystallized ligand to validate the precision of the

docking methodology [66]. Protein–ligand complex docking investigations were conducted via the Lamarckian genetic algorithm (LGA) [67]. Molecular docking is a technique commonly used in molecular modeling to examine in detail the interactions between a ligand and a receptor and identify the ligand's preferred orientation with respect to a target receptor. Comprehensive in silico molecular docking simulations were meticulously executed on the synthesized methyl  $\alpha$ -D-mannopyranoside derivatives in relation to the high-resolution structural conformation of the human dopamine D2 receptor (DRD2, PDB ID: 6CM4). The crystal structure was taken from the Protein Data Bank. All of the molecules were successfully docked within the receptor active site, as confirmed by the common interacting residues [68] [69]. The studied receptor was prepared by removing any nonprotein components or water molecules prior to starting the molecular docking calculation. The binding affinities of the derivatives (1-7) for 6CM4 ranged from approximately  $-5.2$  to  $-9.7$  kcal mol $^{-1}$  (Table 6 and Figure 9).

**Table 6.** The binding affinity (kcal/mol) and nonbonding interactions of methyl  $\alpha$ -D-mannopyranoside (1) and its derivatives (2-7) and native 8NU with 6CM4 were evaluated.

| Entry | Binding Affinity | Residues contacts | Distance (Å) | Interaction Types          |
|-------|------------------|-------------------|--------------|----------------------------|
| 1     | -5.2             | SER193            | 3.0317       | Conventional Hydrogen Bond |
|       |                  | SER193            | 3.3320       | Carbon Hydrogen Bond       |
|       |                  | SER197            | 3.4092       | Carbon Hydrogen Bond       |
|       |                  | TRP386            | 3.6132       | Pi-Sigma                   |
| 2     | -6.5             | VAL115            | 3.0559       | Conventional Hydrogen Bond |
|       |                  | THR119            | 2.5001       | Conventional Hydrogen Bond |
| 3     | -7.1             | TRP100            | 2.8882       | Conventional Hydrogen Bond |
|       |                  | THR412            | 2.7989       | Conventional Hydrogen Bond |
|       |                  | TRP413            | 2.7047       | Conventional Hydrogen Bond |
|       |                  | VAL91             | 4.7866       | Alkyl                      |
|       |                  | VAL115            | 4.7786       | Alkyl                      |
|       |                  | TRP100            | 5.2787       | Pi-Alkyl                   |
|       |                  | PHE110            | 5.2550       | Pi-Alkyl                   |
|       |                  | PHE189            | 5.2916       | Pi-Alkyl                   |
|       |                  | PHE189            | 4.9111       | Pi-Alkyl                   |
|       |                  | PHE389            | 4.9923       | Pi-Alkyl                   |
|       |                  | HIS393            | 5.4973       | Pi-Alkyl                   |
|       |                  | TYR408            | 5.0617       | Pi-Alkyl                   |
| 4     | -6.1             | TYR416            | 5.4825       | Pi-Alkyl                   |
|       |                  | TRP100            | 2.2962       | Conventional Hydrogen Bond |
|       |                  | SER409            | 2.7371       | Conventional Hydrogen Bond |
|       |                  | THR412            | 2.3806       | Conventional Hydrogen Bond |
|       |                  | TYR408            | 3.6509       | Pi-Sigma                   |
|       |                  | VAL91             | 4.1623       | Alkyl                      |

## Continued

|   |      |        |        |                            |
|---|------|--------|--------|----------------------------|
| 5 | -6.3 | LEU94  | 4.6549 | Alkyl                      |
|   |      | ILE184 | 4.3187 | Alkyl                      |
|   |      | TRP100 | 5.2575 | Pi-Alkyl                   |
|   |      | TRP413 | 4.5789 | Pi-Alkyl                   |
|   |      | CYS118 | 2.5927 | Conventional Hydrogen Bond |
|   |      | THR412 | 1.9957 | Conventional Hydrogen Bond |
|   |      | HIS393 | 3.2911 | Carbon Hydrogen Bond       |
|   |      | ASP114 | 3.1287 | Carbon Hydrogen Bond       |
|   |      | HIS393 | 3.1922 | Carbon Hydrogen Bond       |
|   |      | TRP386 | 3.7076 | Pi-Sigma                   |
|   |      | VAL91  | 4.1038 | Alkyl                      |
|   |      | VAL91  | 5.2432 | Alkyl                      |
|   |      | LEU94  | 5.1705 | Alkyl                      |
|   |      | PRO405 | 5.3033 | Alkyl                      |
|   |      | LEU94  | 4.3438 | Alkyl                      |
|   |      | TRP100 | 5.3122 | Pi-Alkyl                   |
|   |      | TYR408 | 5.3977 | Pi-Alkyl                   |
|   |      | TYR408 | 5.3160 | Pi-Alkyl                   |
|   |      | TRP413 | 4.7792 | Pi-Alkyl                   |
|   |      | TRP413 | 5.4004 | Pi-Alkyl                   |
| 6 | -6.7 | TRP100 | 2.4213 | Conventional Hydrogen Bond |
|   |      | SER409 | 3.0732 | Carbon Hydrogen Bond       |
|   |      | VAL91  | 4.7252 | Alkyl                      |
|   |      | LEU94  | 5.0346 | Alkyl                      |
|   |      | VAL115 | 5.4728 | Alkyl                      |
|   |      | ILE184 | 4.9003 | Alkyl                      |
|   |      | VAL190 | 4.2634 | Alkyl                      |
|   |      | LEU94  | 3.9130 | Alkyl                      |
|   |      | VAL111 | 3.6436 | Alkyl                      |
|   |      | ILE184 | 4.8962 | Alkyl                      |
|   |      | TRP100 | 5.4741 | Pi-Alkyl                   |
|   |      | PHE110 | 4.0805 | Pi-Alkyl                   |
|   |      | PHE189 | 5.4589 | Pi-Alkyl                   |
|   |      | PHE389 | 4.8667 | Pi-Alkyl                   |
|   |      | PHE389 | 5.1551 | Pi-Alkyl                   |
|   |      | HIS393 | 5.1047 | Pi-Alkyl                   |
|   |      | TRP413 | 5.3339 | Pi-Alkyl                   |
| 7 | -9.7 | CYS118 | 2.4087 | Conventional Hydrogen Bond |
|   |      | ASP114 | 3.1288 | Carbon Hydrogen Bond       |
|   |      | HIS393 | 3.1884 | Carbon Hydrogen Bond       |
|   |      | LEU94  | 3.6894 | Pi-Sigma                   |

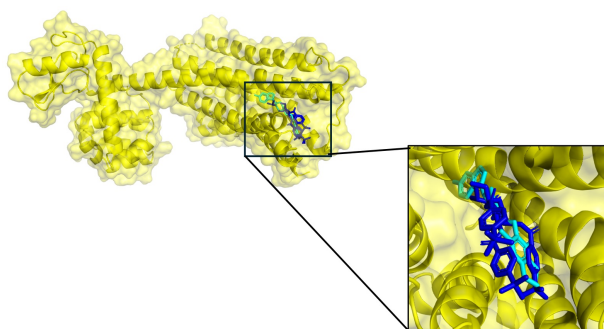
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|     |       |        |        |                            |
|-----|-------|--------|--------|----------------------------|
|     |       | THR412 | 3.9789 | Pi-Sigma                   |
|     |       | TRP386 | 3.6608 | Pi-Pi Stacked              |
|     |       | TYR408 | 4.8927 | Pi-Pi T-shaped             |
|     |       | LEU94  | 4.5423 | Pi-Pi T-shaped             |
|     |       | TRP413 | 5.0089 | Pi-Alkyl                   |
|     |       | VAL91  | 4.7367 | Pi-Alkyl                   |
|     |       | TYR416 | 2.0379 | Conventional Hydrogen Bond |
|     |       | SER197 | 3.4224 | Carbon Hydrogen Bond       |
|     |       | CYS118 | 3.3037 | Halogen (Fluorine)         |
|     |       | THR412 | 3.6192 | Pi-Sigma                   |
|     |       | TRP100 | 5.2435 | Pi-Pi T-shaped             |
|     |       | TRP386 | 4.9949 | Pi-Pi T-shaped             |
|     |       | TRP386 | 4.8412 | Pi-Pi T-shaped             |
|     |       | PHE390 | 5.1913 | Pi-Pi T-shaped             |
| 8NU | -11.9 | VAL91  | 5.2001 | Alkyl                      |
|     |       | LEU94  | 4.5941 | Alkyl                      |
|     |       | TRP386 | 5.4003 | Pi-Alkyl                   |
|     |       | PHE389 | 4.9049 | Pi-Alkyl                   |
|     |       | TRP413 | 5.3787 | Pi-Alkyl                   |
|     |       | VAL115 | 4.7674 | Pi-Alkyl                   |
|     |       | CYS118 | 4.4400 | Pi-Alkyl                   |
|     |       | CYS118 | 4.1973 | Pi-Alkyl                   |

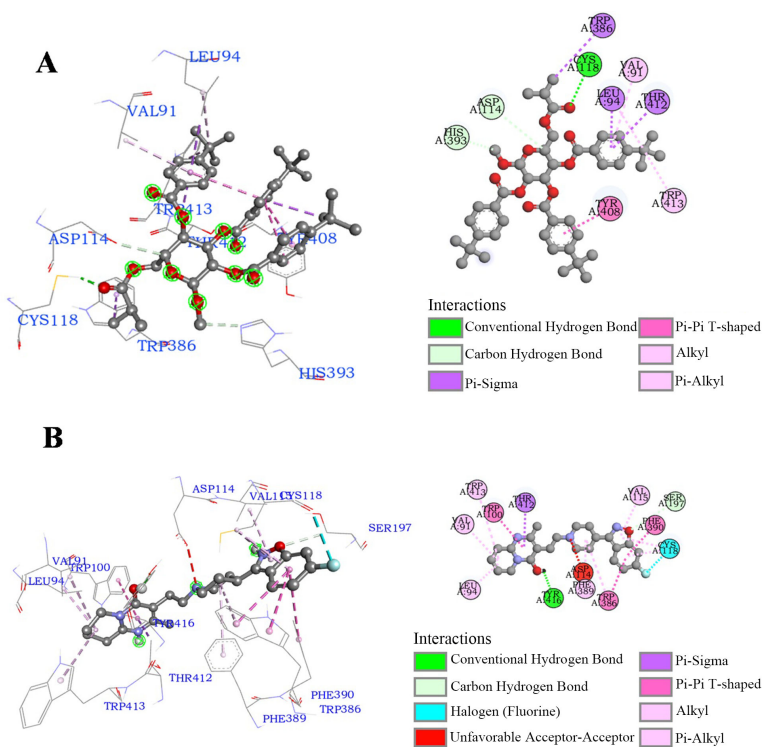
H = Conventional hydrogen bond; C = Carbon-hydrogen bond; A = alkyl; PA = Pi-alkyl; PPS = Pi-Pi stacked; PS = Pi-Sigma; PPT = Pi-Pi T-shaped.

The docking methodology was effectively validated through the redocking of the co-crystallized atypical antipsychotic ligand 8NU2 (Risperidone), which successfully reproduced its native binding conformation with a remarkable affinity of -11.9 kcal/mol. This validation procedure accurately mirrored the experimental structural fingerprint, securing anchorage via a pivotal fluorine-mediated halogen interaction with CYS118 (3.30 Å), a robust conventional hydrogen bond with TYR416 (2.04 Å), and a four-way T-shaped  $\pi$ - $\pi$  stacking nesting matrix involving TRP100, TRP386, and PHE390. After the protocol was validated, the binding scores of the screened carbohydrate derivatives ranged from -5.2 kcal/mol to -9.7 kcal/mol. The configuration with the lowest energy was identified in compound 1 (-5.2 kcal/mol), which adopted a shallow, polar orientation primarily interacting with SER193 and SER197. In contrast, the intermediate conformations (compounds 3, 4, and 6) adapted to the receptor cavity by embedding deeply into the lipophilic and aromatic ceiling of the pocket, thereby establishing extensive non-polar contact networks across the residues TRP100, VAL91, LEU94, PHE110, PHE189, and TRP413. Notably, the structural assessment addressed significant peer-review inquiries pertaining to target validation by capturing the canonical aminergic anchoring linkage across multiple poses. Compounds 5 (-6.3 kcal/mol)

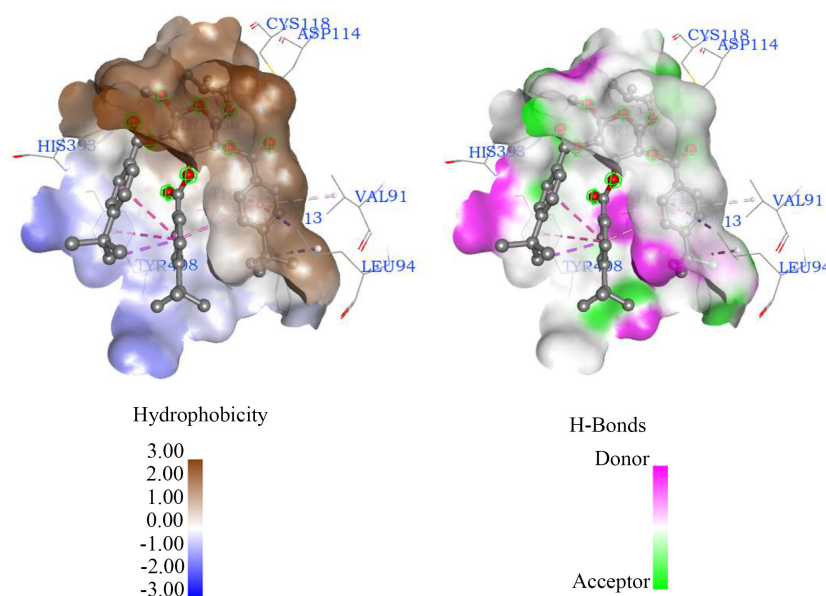
and 7 (−9.7 kcal/mol) both successfully formed a direct carbon–hydrogen bond with the carboxylate oxygen of the highly conserved ASP114 (3.32 Å) residue. In addition, nonbonding 3D interactions and 2D interactions of (A) compound 7 with 6CM4 and (B) 8NU with 6CM4 are shown in **Figure 10**. Compound 7 emerged as the most energetically favorable lead compound throughout the entire docking series and was uniquely stabilized by a compact network of hydrogen and hydrophobic interactions (**Table 6** and **Figure 11**). These findings furnish compelling thermodynamic and structural evidence that the stereochemically rich hydroxyl core of the mannopyranoside scaffold, in conjunction with hydrophobic acyl groups, fulfills the essential pharmacophoric criteria required to serve as a viable lead series for novel dopamine D2 receptor inhibitors.



**Figure 9.** Docked poses of compound 7 (blue) and the native ligand (cyan) at the inhibition binding site of 6CM4.



**Figure 10.** Nonbonding 3D interactions and 2D interactions of (A) compound 7 with 6CM4 and (B) 8NU with 6CM4.



**Figure 11.** Hydrogen bonds and hydrophobicity of compound **7** with 6CM4.

#### 4. Conclusions

In this work, the stability and electrical distribution of methyl- $\alpha$ -D-mannopyranoside derivatives were investigated by designing and structurally optimizing them *via* density functional theory. Favorable electronic characteristics were found using quantum chemical parameters, suggesting possible stability and reactivity. The appropriateness of these compounds as drug-like candidates was supported by ADMET and PASS predictions, which indicated good pharmacokinetic behavior, drug-likeness, and low toxicity. Strong binding affinities and persistent interactions with important active site residues were demonstrated by molecular docking against the dopamine D2 receptor (6CM4), suggesting potential neuroprotective and anticancer properties. The combined computational findings offer a solid theoretical basis for understanding the pharmacological potential of derivatives of mannopyranosides. Overall, these findings indicate that these substances could be potential leads in drug discovery, and further experimental research is advised to confirm their therapeutic efficacy.

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#### Conflicts of Interest

The authors declare that there are no conflicts of interest.

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