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PASS Prediction, ADMET and Molecular Docking Studies of Some Mannopyranoside Derivatives Against HCV NS 5B Polymerase

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Abstract. Several carbohydrate-based medications are now being used to treat a variety of human ailments all around the world. Therefore, we concentrated on computational investigations of previously synthesized methyl α-D-mannopyranoside (MDM) derivatives. To determine the structural and thermodynamical properties of the modified derivatives, a quantum chemical research was conducted using Gaussian09 employing density functional theory (DFT). Molecular electrostatic potential (MEP) calculation has performed to calculate their possible electrophilic and nucleophilic attack. The binding energy and binding strategies of certain viral proteins from the Hepatitis C virus (2IJN, 3MWV, and 3FKQ) were investigated using molecular docking simulations, and adequate binding affinity was discovered. ADMET calculations predict the improved pharmacokinetic properties with better drug-likeness profile of all MDM derivatives. Finally, these compounds can be described as molecules with high antiviral/antimicrobial potential that have been modified in terms of their structural side chains in α-D-mannopyranoside sequence.

Keywords: methyl α-D-mannopyranoside, PASS, ADMET, molecular docking and molecular electrostatic potential.

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Исследования по прогнозированию проходимости, ADMET и молекулярному докингу некоторых производных маннопиранозида против полимеразы NS 5B HCV

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Аннотация. Несколько препаратов на основе углеводов в настоящее время используются для лечения различных заболеваний человека по всему миру. Поэтому мы сосредоточились на вычислительных исследованиях ранее синтезированных производных метил-α-D-маннопиранозида (MDM). Чтобы определить структурные и термодинамические свойства модифицированных производных, было проведено квантово-химическое исследование с применением Gaussian 09 и с использованием теории функционала плотности (DFT). Был проведен расчет молекулярного электростатического потенциала (MEP) для расчета их возможной электрофильной и нуклеофильной атаки. Энергия связывания и стратегии связывания определенных вирусных белков вируса гепатита С (2IJN, 3MWV и 3FKQ) были исследованы с использованием моделирования молекулярного докинга, и была обнаружена адекватная аффинность связывания. Расчеты ADMET предсказывают улучшенные фармакокинетические свойства с лучшим профилем лекарственного подобия всех производных MDM. Наконец, эти соединения могут быть описаны как молекулы с высоким противовирусным/антимикробным потенциалом, которые были модифицированы с точки зрения их структурных боковых цепей в последовательности α-D-маннопиранозида.

Ключевые слова: метил α-D-маннопиранозид, PASS, ADMET, молекулярный докинг и молекулярный электростатический потенциал.

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Introduction

Carbohydrates are important substances in nature, playing a variety of roles in biological processes. Carbohydrates have long been a popular research topic among scientists due to their role in biological systems such as viral and bacterial infections, cell growth and proliferation, cell-cell communication, and immunological response [1, 2]. They are a source of metabolic energy, but they are also used to fine-tune cell-cell connections and other critical functions. They are a source of metabolic energy, but they are also used to fine-tune cell-cell connections and other critical functions [3, 4]. According to a review of the literature, a high number of biologically active chemicals have aromatic, heteroaromatic, and acyl substituents [5–8]. Hepatitis C virus (HCV) infection causes liver diseases such as cirrhosis, hepatocellular carcinoma, chronic hepatitis, and others; it is one of the biggest health problems that infects around 200 million people worldwide, and the majority of HCV-infected individuals become gradually unwell [1–4, 9]. At the moment, neither an HCV vaccination nor an effective therapeutic with an appropriate broad spectrum of activity against all HCV genotypes is available [5, 10]. As a result, the best strategy to discover effective antiviral medications is to synthesize novel compounds and investigate their antiviral activity. Carbohydrates have the potential to be effective antiviral medicines. Furthermore, selective acylation of carbohydrates and microbiological activity evaluation show that, in many circumstances, the combination of two or more heteroaromatic nuclei and acyl groups significantly increases biological activity when compared to the parent nucleus [11–15]. ADMET is a computer program that calculates the pharmacokinetic parameters/properties of drug-like compounds based on their molecular structures [16–22]. SwissADME web tool is free software that is used to forecast the physicochemical qualities, absorption, distribution, metabolism, elimination, and pharmacokinetic features of molecules, all of which are important factors in future clinical studies. It takes into account six physico-chemical properties, which are very vital, like lipophilicity, flexibility, saturation, polarity, solubility, and size [23–27].

In this research, we have focused on the computational studies of previously synthesized methyl α-D-mannopyranoside and it's derivatives to investigate their biochemical behavior on the basis of the quantum mechanical methods.

Experimental

Methods and materials

The following softwares systems were used in the present study: i) Gaussian 09, ii) AutoDock 4.2.6, iii) Swiss-Pdb 4.1.0, iv) Discovery Studio 3.5, v) PyMOL 2.3, vi) LigPlot^{+} v.1.4.5, vii) Hyperchem and ix) Webmo.

Optimization and ligand preparation

This study was carried out on a series of molecules using the Gaussian 09 program. The structures were drawn in GaussView 6. The initial step in getting the leading characteristic parameters of the compounds is to optimize the molecular structure to attain a configuration characterized by a minimum free energy through DFT with B 3LYP using basis set 6–311G (d, p).

PASS (prediction of activity spectra for substances) prediction

Web based PASS (http://www.pharmaexpert.ru/ PASSonline/index.php) was used for the prediction of a plethora of biological activities. This tool was created to predict a wide range of biological processes with 90 % accuracy. ChemDraw 16.0 was used to construct the structures, which were then converted into Smiles format and utilized to predict the biological spectrum using the PASS online version [28]. The result was presented as Pa (probability for active compound) and Pi (probability for inactive compound). Here, Pa>Pi is considered in the scale 0.000 to 1.000 and in general, Pa+Pi≠1.

Protein preparation and visualization

The crystal 3D format of some Hepatitis C virus protein (pdb ID: 2IJN, 3MWV and 3FKQ) was recuperated in the pdb from the protein data bank. The molecules of water and excess ligand, which was previously attached with protein, have been cleaned using Pymol software 3 and obtained the raw protein strain for molecular docking. The proteins were then subjected to energy minimization by using Swiss-Pdb Viewer (version 4.1.0).

In silico pharmacokinetics ADMET and drug-like parameters analysis

Computational chemistry use computer simulation to aid in the resolution of chemical problems. It employs theoretical chemistry methodologies embedded in efficient computer programs to compute the physicochemical properties of the produced molecules [29]. It can predict many properties of molecules and reactions, such as molecular energies and structures, transition state structures, bond and reaction energies, molecular orbitals in different solvent phases, vibrational frequencies, thermochemical properties, reaction pathways, spectroscopic quantities, and many other molecular properties for systems in the solid, gas, or solution phase [30]. ADMET is a computer tool designed to estimate pharmacokinetic parameters/properties of drug-like substances based on their molecular structures. SwissADME web tool (http://www.swissadme.ch) is freely available software utilized to predict the physicochemical properties and pharmacokinetic properties of molecules [31].

Molecular docking studies

In the PyRx the proteins and ligands were opened. The ligands after energy minimization were converted into PDBQT format. Both the protein and ligands were then forwarded for docking with maximum box size in vina wizard. The size of the grid box in AutoDockVina was kept at 76.0819, 71.6840, 144.4157 Å for 2IJN; 114.3841, 82.5353, 80.1561 Å for 3FQK and 85.1214, 114.3757, 113.3500 Å for 3MWV along x, y and z directions, respectively. The resulting file was saved and further analyzed with the BIOVIA Discovery Studio Visualizer.

Results and discussion

Optimized structures of the tested ligands

The produced ligands' chemical characteristics were further examined using DFT method for their quantum calculation and their geometry optimization.

Molecular electrostatic potential map

Molecular electrostatic potential (MEP) is widely preferred as a map of reactivity that reveals the most suitable region for organic molecules to perform electrophilic and nucleophilic reactions of charged point-like reagents [32]. It aids to explore the biological recognition process and hydrogen bonding interaction [33]. The primary significance of MEP is that it concurrently displays positive, negative, and neutral electrostatic potential regions, as well as molecule size, shape by color grading, and is extremely valuable in the study of molecular structure with physicochemical properties related [34]. The potentiality of the attacking zone decreases in the sequence of blue > green > yellow > orange > red. The maximum negative area is indicated by red color, where electrophiles can readily attack, while the maximum positive area is indicated by blue color, where nucleophilic assault is possible. Furthermore, the green color indicated that there were no potential zones. Webmo, a free program, was used to visualize the MEP images.

Biological activities using PASS

In the modern age, it is possible to predict more than 3678 pharmacological effects, modes of action, carcinogenicity, teratogenicity and other biological properties of compounds using an easy online server named PASS Online [28]. PASS predication of the compounds **1–6** were found 0.21<Pa<0.50 in antiviral, 0.39<Pa<0.51 in antibacterial and 0.50<Pa<0.73 in antifungal [35–37]. This clearly indicated that the compounds were more potent against fungi as compared to that of bacterial and viral pathogens. We have extended our studies for anti-carcinogenic and antibiotic evaluation. Thus, PASS predication indicated 0.69<Pa<0.90 for anti-carcinogenic and 0.22<Pa<0.34 for antibiotic, which refers that the mannopyranoside derivatives were more potent as anti-carcinogenic agents than that of antibiotic properties.

Pharmacokinetic prediction

A drug/drug-like compound has to satisfy the "Rule of Five" [38] which is a well known parameter to examine whether it can be taken as a drug or not. Hence, ADMET properties of the synthesized compounds were evaluated using SwissADME web tool [39, 40]. The physicochemical properties of the synthesized (MDM) derivatives can be revealed from ADMET analysis which includes the rules of five (MW, iLOGP, HBAs and HBDs) and several other properties like molecular polar surface area (TPSA), number of rotatable bonds (ROTBs), number of aromatic heavy atoms, and number of alerts for undesirable substructures (PAINS and Brenk). All the compounds were in accordance with the rules That means MW, RB, HBD, HBA, TPSA, iLOGP, nAH and MR of the all compounds are within the acceptable range. So we assume that all the compounds possess a good pharmacokinetic profile.

Molecular docking studies
and ligand-protein interactions

Molecular docking of the compounds (**1–6**) was conducted against HCV NS 5B polymerase (PDB ID: 2IJN, 3MWV and 3FQK). Initially, molecular docking was conducted with 2IJN which is a 2 chain structure. It was found that compounds **2**, **3**, **4** and **6** showed a better binding affinity –5.9 kcal/mol, –6.0 kcal/mol, –6.0 kcal/mol and –7.6 kcal/mol. Then, 3MWV was used for molecular docking which is also a 2 chain structure. Compounds **2** (–5.9 kcal/mol), **3** (–6.0 kcal/mol) and **6** (–8.8 kcal/mol) showed

good binding affinities as compared to the other compounds. Finally molecular docking was conducted against 3FQK protein which is also a two chain stucture. Compounds **2**, **3** and **6** showed satisfactory results (–6.2 kcal/mol, –6.3 kcal/mol and –7.8 kcal/mol) here also.

Non-bonding interactions of the compounds **2**, **3** and **6** are generated by Discovery studio and two dimensional image was generated by) LigPlot^{+} v.1.4.5. Non-bonding interactions and two dimensional images are shown in Fig. 1.

However, Fig. 2 represents the hydrogen bonds and hydrophobic surface of the compound **2** with 3FQK (a, b), compound **3** with 2IJN (c, d) and 3FQK (e, f) and compound **6** with 3MWV (g, h). These pictures are generated by Discovery studio. Hydrogen-bonds execute a vital function in shaping the specificity of ligand binding with the receptor, drug design in chemical and biological processes, molecular recognition, and biological activity. Fig. 2 reveals that all the compounds contain hydrogen bonds and hydrophobic bonds. But it has been found that the number of hydrogen bond is less than hydrophobic bonds against all proteins but the hydrogen bonds is stronger than hydrophobic bonds with respect to bond distance. Due to hydrogen bond forming characteristics the compounds can work as potential drugs.

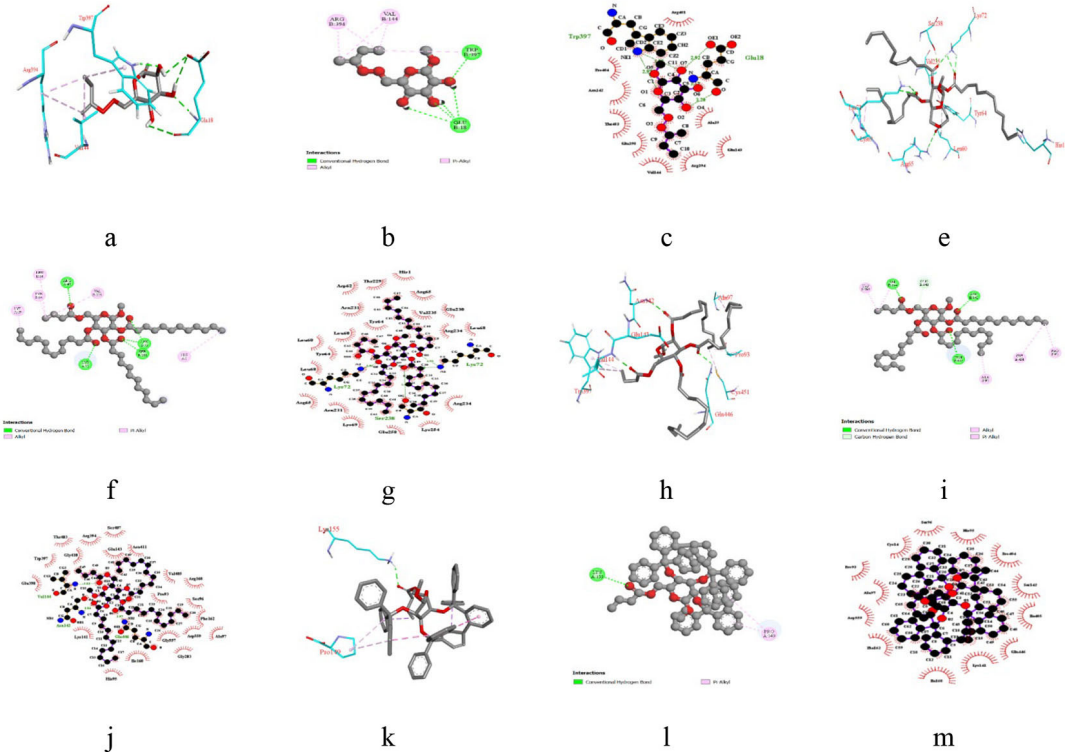

Fig. 1. Docking interactions of compound **2** with 3FQK (a, b, c), compound **3** with 2IJN (e, f, g) and 3FQK (h, I, J) and compound **6** with 3MWV (k, l, m)

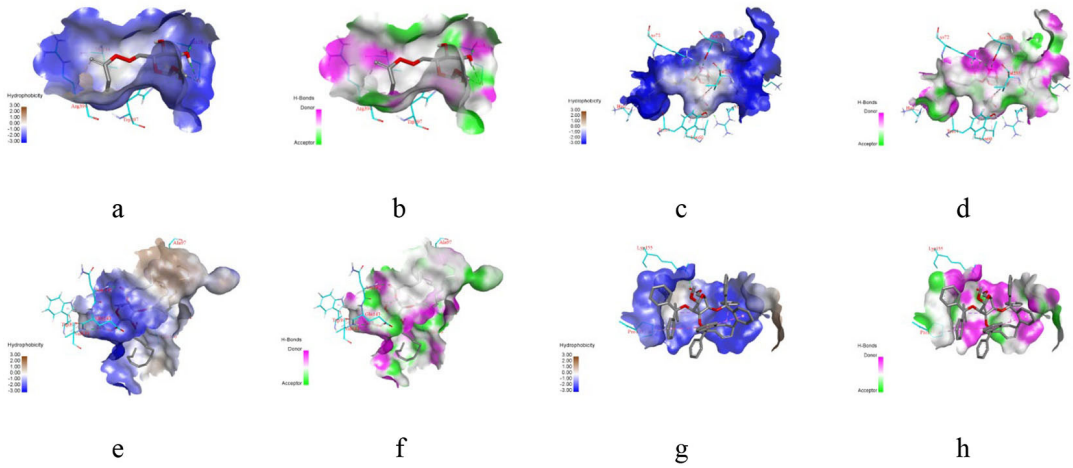

Fig. 2. Hydrogen bond and Hydrophobic surface of compound **2** with 3FQK (a, b), compound **3** with 2IJN (c, d) and 3FQK (e, f) and compound **6** with 3MWV (g, h)

Conclusion

In this study, in silico six mannopyranoside derivatives were investigated for their chemical reactivities and molecular docking. PASS predication indicated that these compounds have antiviral, antibacterial, antibiotics and anticarcinogenic characteristics. ADMET properties indicated that these compounds have drug-likeliness characteristics and there are biologically active compounds. Molecular docking against HCV NS 5B polymerase (2IJN, 3MWV and 3FQK). All the compounds showed lower to moderate binding affinities. This investigation can be helpful in the development of new compounds derived from structural modifications of methyl α-D-mannopyranoside (MDM). The addition of various functional groups in the MDM derivatives improved its physicochemical, biological, and pharmacological properties. Thus, the present study might be helpful for designing mannopyranoside-based antiviral drugs.

Author contributions

IIA performed the computational study and wrote the draft manuscript. S.M.A.K. supervised, designed, edited and improved the manuscript. All authors have read and approved the final version of this paper.

Declaration of interest

The authors declare no conflict of interest.

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