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The computational screening of inhibitor for black fungus and white fungus by D-glucofuranose derivatives using in silico and SAR study

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Abstract: Black fungus is the foremost life-threatening disease during the SARS-CoV-2 affected patients and spreading quickly in the region of the subcontinent of India although there was no prescribed proper medication. As the Dglucofuranose and its derivatives are reported to show strong antifungal activity, this study has been designed with them for their computational investigation. Firstly, the overall prediction of activity spectra for substances (PASS) value illustrates a goodprobability to be active(Pa) and probability to be inactive (Pi) value. Next, pharmacokinetics parameters including drug-likeness and Lipinski's rules, absorption, distribution, metabolism, excretion, and toxicity (ADMET) parameters, and overall quantum calculation of computational approaches by Density Functional Theory (DFT) have graduallybeen performed to analyze quantum calculations. After the analysis of docking score, it is found at -9.4 kcal/mol, -7.5 kcal/mol, -7.8 kcal/mol, -8.5 kcal/mol against the strain of black fungus protein strains Mycolicibacterium smegmatis, Mucor lusitanicus, Rhizomucor mieh, and white fungus protein Candida Auris, Aspergillus luchuensis and Candida albicans. Next, the molecular dynamics of docked complexes have been performed to check their stability in biological systems with water ranging 100 ns calculating the Root Mean Square Deviation (RMSD) and Root Mean Square Fluctuation (RMSF)where the minimum RMSD and RMSF value indicated the higher stable configuration of docked complexes. These compounds have perfectly matched all the pharmacokinetics criteria to be a good drug candidate against both black and white fungus, and they are non-carcinogenic, low solubility, low toxic for both aquatic and non-aquatic. In addition, the quantum calculation using DFT conveys the strongest support and information about their chemical stability and biological significance. Finally, it could be concluded that the carboxylic group and methyl group in the benzene ring causes higher binding affinity against black and white fungus protein strain through the formation of hydrogen and hydrophobic bonds.

Keywords: DFT; PASS predication; docking; molecular dynamics; ADMET. © 2021 ACG Publications All rights reserved.

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1. Introduction

In the last two decades, there have been complaints that the patients with fungal infection have been considered as the life-threatening problems,¹ such as crucial phase in surgical place,²zygomycotic,³Alzheimer'sdisease,⁴ epidemiologic surveillance,⁵ lung,⁶epidemiology,⁷ immunocompromised patients,⁸ acute leukemia,⁹ lung transplantation,¹⁰ liver transplantation,¹¹ hospital renovation,¹² mucormycosis.^{13,14}It is estimated that fungal infections caused 25.0–73.7 percent of all SARS-related deaths.¹⁵⁻¹⁷People with COVID-19, who have had trauma or uncontrolled diabetes mellitus, are more susceptible to cause mucormycosis infection¹⁸⁻²⁰, which is commonly known as black fungus ²¹and frequently affects the sinuses lungs, skin, and the brain ^{22,23}. A study reported that mucormycosis (black fungus) was the third most aggressive fungal infection observed in haematological and organ transplantation patients ^{19,24}, and the most fungal strains such as *Mycolicibacterium smegmatis*, *Mucor lusitanicus*, *Rhizomucor mieh* are responsible for the black fungal infection.^{25,26} Another concern occurred during the COVID-19 pandemic due to white fungus infection caused by *Candida* and *Aspergillus* species of fungi.²⁷ White fungus are often more life-threatening pathogens for COVID-19 patients compared to black fungus infections due to its immediate effects on the lungs and other body organs and spreads and damages key organs, like kidney, brain, private parts, and mouth.²⁸⁻³¹ *Candida auris, Aspergillus luchuensis*, and *Candida albicans* considered to cause the white fungal infection.³²

A common group of antifungal drugs isazoles, and theyare globally used against both black and white fungus. But studies have found that azole is already-resistant against black and white fungus strains in India.³³ Researchers have also found that white fungus (Candida) is also resistant to multiple drugs.³⁴Several pre-existing antifungal medications (Amphotericin B) are used to treat black and white fungus diseases. However, it is a matter of sorrow that this Amphotericin B is also found resistant against *Aspergillus fumigatus*.³⁵ Still, it is not possible to find an effective medication against white and black fungus.^{36,37} It is estimated that the D-glucofuranose and its derivatives had to convey a study onantifungal potential,³⁸ antibacterial and antiviral activities.³⁹⁻⁴² Regarding this fact, this study has been designed against black and white fungus protein strains through computational tools such as molecular optimization by DFT, molecular docking, PASS prediction, molecular docking, molecular docking, and ADMET properties.

Since this deadly black and white fungus disease are spreading very fast, there is no effective drug.⁴³ Therefore, effective medicine is critical to prevent these diseases. So, to design an effective drug against black fungus and white fungus, the computational method is followed, the most persuasive approach with low cost and less time consumption. This new technology (Computational Chemistry) creates a new era to build effective medication and design the new biological substance in a short period that reduces costs and time.⁴⁴⁻⁴⁸

2. Experimental

2.1. PASS Predication

The pass prediction data has been collected (Pa>Pi value) from the PASS online website"<u>http://way2drug.com/PassOnline/predict.php</u>". After opening the PASS online software, the Pa>Pi value was collected from selected molecules with their SMILES which showed all the values in a Table. This value of PASS predication means it investigates and evaluates the biological potential of a drug candidate molecule.⁴⁹

2.2. Optimization and Ligand Preparation

Molecular optimization was performed with the help of a technique called DFT functional by utilizing vibrational frequency from the DMol3 code of Material Studio 08.^{50.51} The functional, B3LYP, and basis set, DNP+,were utilized for the setup of functions in DMol3 code to obtain extremely precise results, as an electronegative atom, oxygen, seemed to be present. The analytical techniques were utilized after optimizing to build the frontier molecular orbitals (HOMO and LUMO), and the magnitude of HOMO, LUMO. The optimized chemical molecules were exported as a pdb file for future computational work including molecular docking, molecular dynamics, and ADMET.

2.3. Preparation of the Protein

The black fungus strains, such as *Mycolicibacterium smegmatis* (7D6X, Resolution: 2.88 Å),⁵²*Mucor lusitanicus* (6ZDW, Resolution: 1.65 Å),⁵³*Rhizomucor mieh* (4WTP, Resolution: 1.30 Å),⁵⁴and white fungus strains -*Candida auris* (6U8J, Resolution: 2.49 Å),⁵⁵ *Aspergillus luchuensis* (1BK1, Resolution: 2.00 Å)⁵⁶and *Candida albicans*(5HW7, Resolution: 2.29 Å)⁵⁷- crystal structure was downloaded from the Protein Data bank (PDB) of RCSB Protein web portal. Using PyMOL software version V2.3 (<u>https://pymol.org/2/</u>) ⁵⁸, protein purification was completed carefully elimination of ligand and water. Once the excess water and Ligand are cleaned, the crystal structure of the cleaned protein file is loaded into AutoDock Tools and followed the instruction to obtain the pdbqt file format.

2.4. Molecular Docking

Molecular docking mainly investigated the binding affinity of biologically active compounds against pathogenic protein stains. The docking procedure was performed with the help of AutoDock Vina incorporated with PyRx Virtual Screening Tools.⁵⁹ The grid center points were set to X = -36.6352, Y = -22.1218, Z = 55.6026, and the dimension (Å) X = 57.40, Y = 55.69, Z = 41.11. The grid box dimensions were selected and set up to wrap the protein's substrate-binding region. The BIOVIA Discovery Studio Visualizer 2017 was used to analyze the non-covalent interaction between the ligands and the pathogenic protein.⁶⁰

2.5. ADMET Properties

ADMET parameters are mainly obtained to analyze the pharmacokinetic properties of medicinal compounds. Absorption, Distribution, Metabolism, Excretion, and Toxicity (ADMET) parameters of our reported 10 biological active compounds were collected from an online Database is called admetSAR (<u>http://lmmd.ecust.edu.cn/admetsar2</u>), which is the most trusted database for predicting the AMDET parameters Substrate.⁶¹⁻⁶³ We have focused on the ADMET parameters such as Plasma Protein Binding, Human Intestinal Absorption, Caco-2 Permeability, Blood-Brain Barrier, Renal Organic Cation Transporter, CYP450 2C9.

2.6. Calculation of QSAR and pIC₅₀

QSAR and pIC₅₀ values were calculated with the help of the Chemdesk website and a standard equation of multiple linear regression (MLR) for QSAR and pIC₅₀. From this online database, eight most acceptable biochemical descriptors, such as Chiv5, bcutm1, MRVSA9, MRVSA6, PEOEVSA5, GATSv4, J and Diametert.⁶⁴

3. Results and Discussions

3.1. Chemistry

D-Glucofuranose and its derivatives are considered very common compounds of carbohydrates as glucose group and have antibacterial and antifungal properties. Therefore,glucofuranose (1,2-*O*-isopropylidene protected) has been taken to this study. The most conceivable goal of this study is to examine the effect of changing the D-glucofuranose side chain at the C-6 position on their antimicrobial activity. As it can be seen from Figure 1 below, an -OH is converted to phenyl ether at the C-6 position of the parent D-glucofuranose (01) forming6-*O*-phenyl-D-glucofuranose derivative (02). This benzene was later combined with eight different functional groups to form compounds 03-10. With the help of molecular modelling, the computational chemistry tools of these compounds have been executed through specific studies of specific pathogens(black and white fungus) with proteins using molecular docking, and molecular dynamics tools. From the molecular docking study, it is illustrated how theseD-glucofuranose derivatives combine with the protein of black and white fungus that is the main goal of this study. It has also been shown that bonds are formed for a functional group ofD-glucofuranose and its derivatives to help neutralize protein pathogens, resulting in more pending affinity results for multiple bonds.

3.2. PASS Predication

Our reported molecules have shown the most potent antifungal activity, which is above Pa value 0.550+. Ligand no 03 and 10 showed the highest Pa value (Pa>0.618 & Pa>0.652) although the main focus is on the

prediction of antifungal activity, considering some other prediction parameters, including antiviral, antibacterial, antibiotic, and cytotoxic activity, indicated that antibacterial and antifungal Pa value is much better. For antivirals, the highest Pa value is reported 0.452 in Ligand no **01**, whereas antibacterial has shown 0.563 is the highest the Pa> value in ligand no **07&09**. Among them, the PASS prediction value is much higher against fungi compared to antiviral, antibacterial, antibiotic, and cytotoxic activity. So, these values indicate that the drugs candidate molecules will show strongactivity against the black and white fungus.



Figure 1. Molecular structure of the tested compounds

Ligands	Antiviral		Antibac	terial	Antifur	ngal	Antibiotic		Cytotox	oxic		
	Pa	Pi	Pa	Pi	Pa	Pi	Pa	Pi	Pa	Pi		
01	0.452	0.018	0.537	0.013	0.599	0.019	0.352	0.010	0.158	0.094		
02	0.198	0.190	0.510	0.015	0.587	0.020	0.283	0.016	0.153.	0.098		
03	0.354	0.154	0.474	0.019	0.618	0.017	0.224	0.015	0.127	0.126		
04	0.360	0.054	0.501	0.016	0.532	0.026	0.255	0.019	0.127	0.126		
05	0.434	0.023	0.529	0.014	0.597	0.019	0.293	0.015	0.381	0.078		
06	0.296	0.234	0.523	0.014	0.579	0.021	0.275	0.017	0.173	0.084		
07	0.081	0.072	0.563	0.011	0.587	0.020	0.323	0.012	0.131	0.121		
08	0.403	0.034	0.500	0.016	0.585	0.020	0.006	0.004	0.140	0.110		
09	0.363	0.053	0.563	0.011	0.587	0.020	0.323	0.012	0.131	0.121		
10	0.406	0.033	0.510	0.015	0.652	0.013	0.276	0.017	0.155	0.096		

3.3. Lipinski Rule, Pharmacokinetics and Drug Likeness

The typical assumption for the drug-likeness obtained from Lipinski's five-rule is commonly investigated.⁶⁵ In this section, all the drug candidate compounds have fulfilled the expected criteria and this section also investigated that the drug candidate has overall good bioavailability with high human intestinal absorption (HIA) (Table 2). The molecular value ranges of reported compounds are 220-342 g/mol and the lower molecular weight is reported 220.22 g/mol, where the higher molecular value is 342.31 g/mol. The topological surface area (TPSA) range was found between 77–123 (Å²). Overall these findings fully obeyed the Lipinski rule. As these reported compounds have high bioavailability, high GI absorption rate as well as followed Lipinski rule, so we reached a decision that these all compounds are human usable.

ligands	NBR	HBA	HBD	TPSA, Ų	Consensu s Log Po/w	Log Kp (skin permeatio n), cm/s	Lipinski Result	i rule Viol.	MW	Bioavaila bility Score	GI absorptio n
01	2	6	3	88.38	-0.54	-7.84	Yes	0	220.22	0.55	High
02	4	6	3	77.38	1.07	-7.17	Yes	0	296.32	0.55	High
03	4	6	2	77.38	1.60	-6.93	Yes	0	330.76	0.55	High
04	4	7	2	77.38	1.34	-7.21	Yes	0	314.31	0.55	High
05	4	7	3	97.61	0.74	-7.52	Yes	0	312.32	0.55	High
06	5	8	2	123.20	0.25	-7.57	Yes	0	341.31	0.55	High
07	5	8	3	114.68	0.58	-7.77	Yes	0	340.33	0.56	High
08	4	6	2	77.38	1.50	-6.99	Yes	0	310.44	0.55	High
09	5	8	3	114.68	0.58	-7.77	Yes	0	340.33	0.56	High
10	5	7	2	94.45	0.79	-7.72	Yes	0	324.34	0.55	High

Table 2. Data of Lipinski rule, pharmacokinetics and drug likeness

Viol: Violation

3.4. Optimized structure of D-glucofuranose and its derivatives

Figure 2 represents the optimized chemical structures of D-glucofuranose and its derivatives which have been simulated by computational techniques using the DFT method. It is well revealed that the optimized structure carries the symmetry and asymmetry point through the molecules, which has to contribute to the forming of chemical properties as well as biological significance with perfect configuration.



Figure 2. Optimized structure of molecules

3.5. Chemical Descriptors

The word HOMO belongs to the highest occupied molecular orbital, whereas LUMO illustrates the lowest unoccupied molecular orbital. With the help of the DFT method, the energies of HOMO and LUMO have been measured. Energy gaps of frontier molecular orbitals are used to assess atomic electrical transport characteristics. For good chemical stability, it is necessary to have a broad HOMO-LUMO distance, and a narrow HOMO-LUMO gap represents the higher atomic system, and lower chemical stability because they are the closest to each other. From Table 3, the energy gap is about -8.00 kcal/mol which indicates the lower atomic system and higher chemical stability for each molecule but it slightly changes with respect to changing the functional groups.

Bioactivity can be described by the chemical potential (m), hardness (h), softness (S), and electrophilicity coefficient.^{66,67} The positive chemical potential discloses the stability of the systems. The general magnitude of hardness is greater than the softness of the compound, which indicates that the molecules convey high biochemical stability. It is recorded that the hardness isabout -4.00 kcal/mol All the values of chemical potentials havebeen obtained positively, which indicates reinforcement to the stability. The results are summarized below (Table 3). This evidence can play a crucial role in the bioactivity of the compound.

In this study, compound **8** has the HOMO-LUMO largest gap of 8.667 eV whereas compound **6** shows the lowest energy gap (7.38 eV) and the lowest chemical potential (-3.7252 eV) with the highest chemical softness (0.9986 eV) values which may contribute to the higher chemical reactivity than others.

Ligands	A=-		EG	Che pote	Ele ity:	Han	Sof	Eleo y:
	-LUMO	номо	AP=I-A	emical ential μ) = $-\frac{I+A}{2}$	ctronegati (χ) = $\frac{I+A}{2}$	rdness: $(\eta) = \frac{I-A}{2}$	thess $(\sigma) = \frac{1}{\eta}$	ctrophilici $(\boldsymbol{\omega}) = \frac{\mu^2}{2\eta}$
01	-2.492	-10.08	7.590	6.287	-6.287	-3.795	-0.2635	-5.2077
02	-0.103	-8.121	8.018	4.112	-4.112	- 4.009	- 0.2494	- 2.1088
03	-0.126	-8.736	8.610	4.431	-4.431	-4.305	-0.2323	-2.2803
04	-0.176	-8.803	8.627	4.489	-4.489	-4.313	-0.2318	-2.3363
05	-0.51	-9.173	8.663	4.841	-4.841	-4.331	-0.2309	-2.7058
06	-2.286	-9.672	7.386	5.979	-5.979	-3.693	-0.2708	-4.8400
07	-1.513	-9.439	7.926	5.476	-5.476	-3.963	-0.2523	-3.7833
08	-0.030	-8.697	8.667	4.363	-4.363	-4.333	-0.2308	-2.1969
09	-2.181	-9.729	7.926	5.955	-5.955	-3.774	-0.2649	-4.6982
10	-1.149	-8.989	7.840	5.069	-5.069	-3.920	-0.2551	-3.2774
11	-9.052	-1.238	7.814	5.145	-5.145	-3.907	-0.2560	-3.3876
12	-0.778	-6.781	6.003	3.779	-3.779	-3.001	-0.3332	-2.3796

Table 3. Data of chemical descriptors

3.6. Frontier Molecular Orbitals (HOMO and LUMO)

HOMO and LUMO are superior catalysts regulating the chemical properties of any chemical compound by which all their chemical properties are determined and controlled. In this context, the chemical properties of designed derivatives have been predicted. Since these compounds contain oxygen atoms in addition to the aromatic ring and heterocyclic ring, it is still difficult to find an alternative to the HOMO and LUMO diagram to clearly understand whether the aromatic chain or heterocyclic ring controls the chemical properties.⁶⁸⁻⁷³ As it can be seen from the picture shown in Figure 3 (the deep maroon and yellow of LUMO are positive and negative ends of the orbital node, respectively, and lime and orange color are for positive and negative ends of the orbital node, respectively), there is a very subtle difference between HOMO and LUMO. HOMO, on the other hand, is similarly extended just above the benzene ring, although this extent is less than that of HOMO, and no effect can be observed on the benzene ring and chain. But the LUMO is illustrated through the benzene ring as well as the side chain. Not to mention that after adding benzene, their orbitals (HOMO and LUMO) are not found in any part of the furanose

ring as acting the functional group, so it is clear that benzene and the associated site chain control the chemical behavior of these compounds.



Figure 2. HOMO-LUMO diagram of teh reported compounds

3.7. Map of Electrostatic Potential (MEP) Charge Distribution

The MEP map is a helpful tool for determining how a molecule's total charges (positive and negative) are dispersed across the molecule. In addition, it can determine the presence of ligands or protein binding regions, as well as suitable sites for an electrophilic attack site or nucleophilic attack site. The nucleophilic and electrophilic sites of the compounds can be obtained by the molecular electrostatic potential MEP. Below Figure 4, the positive electrostatic potential regions have been highlighted in blue color (electrophilic site), whereas the red color represents the nucleophilic attack region. The positive charges areas are observed to be significantly greater compared to the negative charge region, which indicated that, the electrophilic groups in these molecules are more attracted to nucleophilic.



Figure 4. Map of Electrostatic Potential (ESP)charge distribution of the reported compounds

3.8. Molecular Docking Against Black Fungus

As the recognized binding energy is about -6.0 kcal/mol for standard drugs ⁷⁴⁻⁷⁸ and the selected drug candidate molecules against black fungus proteins of *Mycolicibacterium smegmatis* (7D6X), *Mucor lusitanicus*(6ZDW), and *Rhizomucor miehei*(6ZDW) have shown a good and strongest binding affinity. When the overall binding affinity was investigated, it is seen that D-glucofuranose and its derivatives have much more effectiveness including better binding affinity against these three fungal proteins. Among them, the largest binding affinity was recorded -9.4 kcal/mol against 7D6X in ligand no **07**, -7.5 kcal/mol was recorded against

6ZDW in Ligand no **06** and **07**, and -7.8 kcal/mol was recorded against *Rhizomucor miehei* in ligand no **07** (Table 4).

Mycolicibacterium smegmatis (7D6X)				Mu	icor lusita (6ZDW	nicus)	Rhizomucor miehei (4WTP)			
L/N	Binding Affinity (kcal/mol)	No of H bond	No of Hydrophobic bond	Binding Affinity (kcal/mol	No of H bond	No of Hydrophobic bond	Binding Affinity (kcal/mol	No of H bond	No of Hydrophobic bond	
01	-7.0	03	02	-5.4	01	01	-6.4	04	01	
02	-7.6	05	05	-7.0	01	02	-7.4	03	07	
03	-7.5	02	07	-6.6	01	02	-7.7	02	08	
04	-7.5	09	02	-6.7	03	01	-7.6	01	07	
05	-7.4	06	03	-6.9	01	01	-7.5	02	07	
06	-8.0	05	06	-7.5	03	01	-73	03	07	
07	-9.4	03	04	-7.5	02	01	-7.8	02	07	
08	-8.8	02	04	-6.7	01	02	-7.7	04	10	
09	-8.3	02	03	-7.0	03	01	-7.7	05	08	
10	-8.7	03	03	-7.1	03	01	-7.4	01	07	
11	-7.2	05	03	-7.2	02	02	-7.0	03	03	
12	-8.4	02	01	-8.3	03	00	-10.5	04	04	

Table 4. Data of molecular docking against black fungus pathogens

3.9. Molecular Docking Against White Fungus

The excellent binding affinity against black fungus has been illustrated in Table 5. The selected three white fungus proteins such as *Candida Auris*(6U8J), *Aspergillus luchuensis* (1BK1), and *Candida albicans* (5HW7) have performed the docking to complete this research work more broadly and to see if the designed drugs would work against white fungus or what kind of binding affinity was available against white fungus. The most acceptable outcome from designing drugs also has a better binding affinity against white fungus than black fungus from Table 4 and Table 5. Our finding has obtained the highest binding affinity -8.5 kcal/mol against *Aspergillus luchuensis*. Since the standard value or binding energy of a potential drug is almost -6.0 kcal/mol⁷⁴ and all the designing compounds cross this standard value excluding ligand no **01** against *Candida albicans* (5HW7).

Table 5. Data of molecular docking against white fungus pathogens

	Candid (6U	a Auris [8J]		Asperg	gillus luchu (1BK1)	ensis	Candida albicans (5HW7)			
L/N	Binding Affinity (kcal/mol)	No of H bond	No of Hydrophobic bond	Binding Affinity (kcal/mol	No of H bond	No of Hydrophobic bond	Binding Affinity (kcal/mol	No of H bond	No of Hydrophobic bond	
01	-6.4	06	04	-6.4	03	05	-5.6	04	01	
02	-6.7	05	03	-8.5	01	07	-6.9	01	05	
03	-7.4	04	02	-8.4	01	07	-6.6	00	05	
04	-7.1	04	03	-8.4	02	08	-7.0	02	04	
05	-8.1	05	05	-8.0	03	06	-7.3	02	07	
06	-6.6	06	03	-8.1	03	06	-7.0	05	04	
07	-7.0	05	03	-8.4	03	06	-6.8	03	03	
08	-6.8	01	07	-8.5	02	09	-7.1	01	10	
09	-7.2	06	02	-8.1	06	07	-6.6	03	05	
10	-6.7	05	03	-8.3	05	01	-7.0	03	04	
11	-7.0	05	05	-7.6	05	06	-6.3	02	01	
12	-7.5	05	00	-8.3	05	00	-8.2	01	04	

3.10. Protein-Ligands Interaction and Active Sites Binding by Docking

There are two types of bonds, such as hydrophobic bonds and hydrogen bonds which occur between ligands and protein. As it is observed that compound **07** (Figure 5) conveys the highest binding score in protein by docking. For compound **07** against *Mycolicibacterium smegmatis*, the binding sites are at LYS-39(1.95298), SER-40 (2.62951), GLY-15 (3.74059) as hydrogen bonds and LEU-432 (4.07746), HIS-46 (4.85362), LYS-39(5.26593) as the hydrophobic bond and other interaction shown in Table S01, S02, and S03.



Figure 5. Different docking poses of 07 sample against Mycolicibacterium smegmatis and Aspergillus luchuensis

3.11. Molecular Dynamics

The molecular dynamics is a boulevard for trying the accuracy docking procedure in the prospect of the rootmean-square deviation (RMSD) and root-mean-square fluctuation (RMSF) which provide in rank about their binding pose ligand-protein complex after docking. It is divulged that the RMSD of the docking complex is less than 2 Å for becoming a good fitting pose of Ligand in drug pocket and software can accurately dock the ligandprotein complex.⁷⁹Molecular docking score showed docked complexes that the compound **07** and **08** with the highest binding score against black fungus protein. Besides the standard **12** showed the top binding score as standard for black fungal infection. That is why in this study molecular dynamics was performed for only **07**, **08**, and **12**. The molecular dynamics were analyzed for time versus protein chain where there is no interaction with the protein shown in Figure 6. It is observed that the RMSD is below 1.1 Å. After interacting with the backbone, it is similar to the previous picture.



Figure 6. Various picture of RMSD and RMSF for protein (7d6x)

On the other hand, the RMSF is observed that there is a use fluctuation after time period 50 ns which are higher for **07** and the low fluctuation is observed for **08** and **12** in case of time vs protein skeleton as shown in Figure 7.



3.12. ADMET Properties and Aquatic and Non-aquatic Toxicity

The characteristics of a new drug candidate or any therapeutic agent like absorption, distribution, metabolism, elimination, or toxicity (ADMET) are the most important parameters or factors. The chemical ADMET parameter has been obtained from admetSAR including; human intestinal absorption (HIA), blood-brain barrier (BBB), Caco-2 Permeability, etc. attached in Table 6. Our designed all drugs have provided excellent GI absorption, positive of BBB+ except **06**, positive to P-I glycoprotein inhibitor, negative response in Renal Organic Cation Transport, CYP4502C9 Substrate, and CYP4501A2 Inhibitor. In addition, all of the compounds have to stay in Mitochondria, as well as the values of Human Intestinal Absorption and Caco-2 Permeability are slightly higher than moderate.

S/N	Human Intestinal Absorption	Caco-2 Permeability	Blood Brain Barrier	P-I glycoprotein inhibitor	Р-П glycoprotein substrate	Renal Organic Cation Transporter	Sub-cellular localization	CYP450 2C9 Substrate	CYP450 1A2 Inhibitor
01	0.5952	0.7302	BBB+	No	Yes	No	Mitochondria	No	No
02	0.8026	0.6128	BBB+	No	Yes	No	Mitochondria	No	No
03	0.7840	0.5500	BBB+	No	Yes	No	Mitochondria	No	No
04	0.7847	0.5540	BBB+	No	Yes	No	Mitochondria	No	No
05	0.9482	0.6025	BBB+	No	Yes	No	Mitochondria	No	No
06	0.5567	0.5899	BBB-	No	No	No	Mitochondria	No	Yes
07	0.8371	0.6397	BBB+	No	Yes	No	Mitochondria	No	No
08	0.6765	0.6020	BBB+	No	Yes	No	Mitochondria	No	No
09	0.8371	0.6397	BBB+	No	Yes	No	Mitochondria	No	No
10	0.8371	0.6397	BBB+	No	Yes	No	Mitochondria	No	No

Table 6. Data for ADME parameters

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On the other hand, aquatic and non-aquatic toxicity has been reported for all drugs shown in Table 7. It is found that all drugs are non-carcinogenic, non-responder to AMES toxicity without **06**, intermediate watersoluble which is found the highest in **03**, indicating the functional groups can be acted to reduce the water solubility, as a result, lead the low toxicity for both the aquatic and non-aquatic environment and its composition after use or extracted from human body after doses. The different compounds have shown different acute oral toxicity and their value range is recorded 2.168 kg/mol to 2.850 kg/mol. *T. Pyriformis* toxicity is also reported positive and only Ligand no **01** has shown negative value.

S/N	AMES toxicity	Carcinogenicit y	Water solubility, Log S	Plasma protein binding	Acute Oral Toxicity, kg/mol	Oral Rat Acute Toxicity (LD50) (mol/kg)	Fish Toxicity pLC50 mg/L	<i>T.</i> <i>Pyriformis</i> toxi city (log ug/L)
01	No	No	-0.801	0.179	2.464	1.9593	2.4984	-0.6809
02	No	No	-2.064	0.951	2.168	2.5058	1.061	0.1795
03	No	No	-3.097	1.231	2.850	2.7886	0.4593	0.5871
04	No	No	-2.86	1.191	2.582	2.8900	0.5698	0.5359
05	No	No	-2.143	0.993	2.347	2.5309	0.8951	0.3867
06	Yes	No	-2.949	1.012	2.569	2.6449	1.0354	0.7324
07	No	No	-2.029	0.986	2.559	2.6974	0.6775	0.4923
08	No	No	-2.710	1.166	2.238	2.7747	0.9953	0.5980
09	No	No	-2.029	0.986	2.559	2.6974	0.6775	0.4923
10	No	No	-2.090	0.926	2.209	2.6974	0.6775	0.4923

Table 7. Aquatic and non-aquatic toxicity

3.13. Calculation of QSAR and pIC₅₀

Quantitative structure activities relationship (QSAR) calculation has been performed to determine the relationship between biological activities and structural activities of chemical compounds using computational methods.utilizing the multiple linear regression (MLR) equation, the QSAR model has been carried out. The overall value of QSAR and pIC₅₀ investigation meets all the criteria and it is observed that different compounds have differentQSAR and pIC₅₀. It is found the range of QSAR and pIC_{50 is} between 4.77 and 4.33 where the higher value of QSAR and pIC₅₀ is at 4.77 and the lower value is found at 4.33. The estimated pIC₅₀ (Table 8) suggests that these reported compounds might be biologically useful against fungi.

Here, pIC50 (Activity) = $-2.768483965 + 0.133928895 \times$ (Chiv5) + 1.59986423 × (bcutm1) + (-0.02309681) × (MRVSA9) + (-0.002946101) × (MRVSA6) + (0.00671218) × (PEOEVSA5) + (-0.15963415) × (GATSv4) + (0.207949857) × (J) + (0.082568569) × (Diametert)

Table 8.	Data of	QSAR	parameters
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SL. No.	Chiv5	(bcutm1)	(MRVSA9)	(MRVSA6)	(PEOEVSA5)	GATSv4	J	Diametert	PIC50
01	1.231	3.828	0.000	0.000	0.000	1.029	2.046	8.0	4.33
02	1.718	3.844	0.000	30.332	18.199	1.069	1.485	12	4.77
03	1.84	3.941	11.601	29.288	23.734	1.018	1.501	12	4.73
04	1.73	3.851	0.000	30.083	12.133	1.103	1.501	12	4.74
05	1,74	3.852	0.000	24.265	12.133	1.100	1.501	12	4.76
06	0.336	3.874	5.687	34.38	12.133	1.072	1.516	12	4.46
07	1.856	3.868	5.969	29.829	12.133	1.011	1.516	12	4.67
08	1.823	3.856	0.000	29.829	18.199	1.018	1.501	12	4.82
09	1.856	3.868	5.969	29.829	12.133	1.011	1.516	12	4.67
10	1.819	3.862	6.286	29.829	12.133	1.013	1.503	12	4.64

3.14. Comparative Study of Docking Score Between Ketal and Non-ketal Form of Molecules

Glucofuranoses **01-10** are in ketal form (with 1,2-*O*-isopropylidene group) and are moderately stable as the anomeric position is involved in the acetonide group. However, under the acidic condition, the acetonide group undergo ring-opening as shown below (Scheme 1).



Scheme 1.Interconversion between acetonide and non-acetonide forms of D-glycofuranose

In the present investigation, molecular docking has been performed for **01-10** having acid-sensitive acetonide group, which may open under biological condition(s). Thus, for comparison and validation, three non-acetonide glucofuranoses (NK01, NK02, and NK03; Figure 8) corresponding to **01-03** are also performed for molecular docking.



Figure 3. Molecular structure of NK01-NK03 (non-ketal form).

For comparison, **NK01-NK03** have been docked with both the black and white fungal strain to evaluate the binding affinity. The results are compared with the results of the ketal form attached in Figure 9 through the bar diagram. In the case of black fungus, the binding affinity of non-ketal compounds is higher than non-ketal form, and it is obtained a similar result for white fungus protease.

4. Conclusion

The computational investigations have been performed against both black and white fungus using the D-glucofuranose and its derivatives, where the molecular modeling from computational tools has been executed to design new functionalized molecules. The PASS prediction proposed their slightly antifungal activity rather than other pathogens. To get more authentic exploration, molecular docking has been performed against both black and white fungus, calculating the binding affinity. Regarding that scale, the highest docking score is recorded at -9.4 kcal/mol against *Mycolicibacterium smegmatis*(7D6X), a black fungus pathogen strain, whereas the binding affinity -8.5 kcal/mol is obtained as the highest binding energy against *Aspergillus luchuensis* (1BK1), a white fungus. It must be noted that the used standard drugs, **11**, **12**, convey -7.2 and -8.4 against *Mycolicibacterium smegmatis*, and -7.6 and -8.3 binding affinity against *Aspergillus luchuensis* (1BK1).



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Figure 9. Comparative study of docking score between ketal and non-ketal form

However, it could be concluded that the tested drugs would be able to show a higher binding affinity rather than standard and a similar case for molecular dynamic accounting for RMSD and RMSF. Into the bargain, the potential drug candidates are also shown overall a better pharmacokinetics parameter, non-carcinogenic, low solubility in water, satisfied the Lipinski rule and drug-likeness properties. Finally, it might be said that the D-glucofuranose and its derivatives are more effective in black fungus than white fungus protein, and the

carboxylate group (07) and methyl group (08) are highly responsible for conveying the higher binding affinity (-9.4 and -8.8, respectively) against black fungus. At the same time, compounds 02 and 08 showed the highest binding affinity against white fungus, and 03, 04, and 07 are in the second position. They have been proved that the carboxylic group proliferates the binding affinity for both black and white fungus protein.

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