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Molecular docking study, and ADMET analysis for the synthesized novel Zn(II) complexes as potential SARS-CoV-2 inhibitors

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Abstract: A new SARS-CoV-2 virus and its variants including omicron created a pandemic situation and caused more deaths in worldwide prompted many researchers to explore potential drug candidates. In this connection, we explored the first-of-its-kind report on computational studies such as molecular docking, and ADMET properties of Zn(II) complexes. The studies revealed the novel zinc complexes have high binding affinities with the SARS-CoV-2 spike glycoprotein (6vxx) alpha variant (7EKF), beta variant (7ekg), gamma variant (7EKC), delta variant (7V8B), and the omicron variant (7T9J). Molecular docking results of RMSD for SARS-CoV-2 beta variant (7ekg) and gamma variant (7EKC) are within excellent chemical stability in their protein-ligand complex state and should be effective in the biological system. ADME studies provided the better results with no adverse effect of toxicity related AMES along with absence of hepatotoxicity and skin sensitization when compared to Molnupiravir drug and it has a greater hepatotoxicity. This study could open further exploration of these novel zinc complexes for SARS-CoV-2 inhibition.

Keywords: Molecular docking; ADMET; Zinc complexes; SARS coronavirus; synthesis

1. Introduction

During the last decade, benzimidazole is considered as one of the vital scaffolds and its analogues with adducts of thiazolyl, ester, carboxyl, alkyl, amine groups, and beta-lactam scaffolds, etc. It has drawn the attention of researchers for its wide range of biological activities such as antimicrobial [1-7], anti-cancer [8,9], anti-viral [10], and radiation protector [10], etc, including their strong coordinating abilities as multidentate ligands. The inclusion of the various substituents on the benzimidazole ring, tunes its complex's structure, photo physical, photochemical, antimicrobial properties and enhances their efficiency with transition metal complexation due to tunable redox properties [11]. Lewis's acid nature evolves them as a potential tool in medicinal applications like inhibit HCV RNA replication, anti-viral behavior against HIV influenza, ebola, as well SARS viruses [12]; the transition metals like Zn, Cu, etc are

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significant in the biological system of the human being. Malnutrition of Zn(II) causes diseases suffering from hypogonadism, emotional disturbance, dermatitis, alopecia, and delayed wound healing which also reduces immunity [13]. The stereochemistry of Zn(II) complexes is determined by the size, electrostatic, and covalent bonding forces since the spherically symmetric d10 configuration has no ligand field stabilization [14]. The pandemic situation arisen worldwide over the last three years due to a new virus protein which is related to SARS-CoV. The SARS-CoV-2, a new virus enters in the host cell via receptor-mediator interaction with host cell membrane which is similar mechanism of SARS-CoV-2 [15, 16]. This prompted us to develop quickly a drug discovery model. In fact, virus enters in the host cell with spike and protease proteins, therefore, it is necessary to inhibit of these proteins as to control spreading of pandemic diseases. This inhibition occurs through a different mechanism that are i) interfering with the primary viral pathogenetic processes, ii) inhibition of the viral entry into the host cells by inhibiting the RNA replication process or virus budding processes [17]. DFT studies account for electronic energies of ligands, metal complexes, bonding in the molecules and band gap to find the chemical stability and reactivity in the reactions [18, 19].

The field of drug designed, and molecular pharmacology has a long and distinguished history, spanning over a century, with researchers capable of drawing qualitative or semi-quantitative connections between in silico and experimental work. In the recent decade, we witnessed an increase in the use of in silico approaches for evaluating hypotheses in pharmacology. Databases, quantitative structure-activity correlations, pharmacophores, homology models, other molecular modeling techniques, as well as machine learning, data mining, and network analysis tools, are all examples of what are known as "in silico" methodologies [20]. The model is developed and validated using in silico techniques, which are increasingly employed alongside in vitro data production. Such models have been widely used for purposes including the identification and optimization of new target-affinity compounds; the elucidation of absorption, distribution, metabolism, excretion, and toxicity features; and the assessment of a drug's physicochemical qualities [21].

In view of our earlier interest of our reported studies [22-24] of biological moelcules, we disclose the molecular docking, and ADMET properties of the novel dichlorobis[2-(4-methoxyphenyl)-[(1,4-methoxyphenyl)methyl]-1H-1,3-benzodiazol-3ium-3yl]zinc and dibromobis[2-(4-methoxyphenyl)-[(1,4-methoxyphenyl)methyl]-1H-1,3-benzodiazol-3ium-3yl]zinc complexes. Molecular docking studies of zinc complexes with respect to the pandemic SARS-CoV-2 protein, two spike glyco protein and its variants including omicron were analyzed.

2. Computational Method

2.1. Synthesis of molecules

o-phenylenediamine of 0.1 mol and p-methoxy-benzaldehyde of 0.2 mol in benzene was refluxed for 2 h on a steam bath and left throughout the night to get a solid which was separated by a filter, washed many times with aq. hexane and after dried it. Recrystallization of mbmpbi was achieved with ethanol and dried it in vacuo over P2O5 to get yellow crystals with 90% yield. [Zn-mbmpbi] complexes were prepared by refluxing of zinc chloride or bromides (1mmol) and mbmpbi (2 mmol) in ethanol for 3 h. The resulting solid was filtered, washed thoroughly with cold ethanol and dried in vacuo over P2O5 (yields: 85-90%) [25]. Synthesis and characterization were reported by our group. Synthesized structures are given in Fig.1.

2.2. Determination of the data of ADMET and Lipinski rule

The reported chemical complexes were uploaded on SwissADME online database (http://www.swissadme.ch) for assessment of their Lipinski rule satisfaction. After that, the data has been listed and analyzed based on the guideline of the Lipinski rule. The primary value was taken Water solubility, Caco-2 Permeability, BBB permeability, CYP 3A4 substrate, CYP450 1A2 inhibitor, etc.

2.3. Method for molecular docking

The non-purify three-dimensional (3D) tertiary structure of SARS CoV-2 and its different variants SARS-CoV-2 spike glycoprotein (6vxx) , SARS-CoV-2 alpha variant (7EKF), SARS-CoV-2 beta

variant (7ekg), SARS-CoV-2 gamma variant 7EKC, SARS-CoV-2 delta variant (7V8B), and SARS-CoV-2 omicron variant (7T9J) which have inherent ability to enter the host. The proteome of SARS CoV-2 for various virulence factors were collected from protein databank (https://www.rcsb.org/) [25].

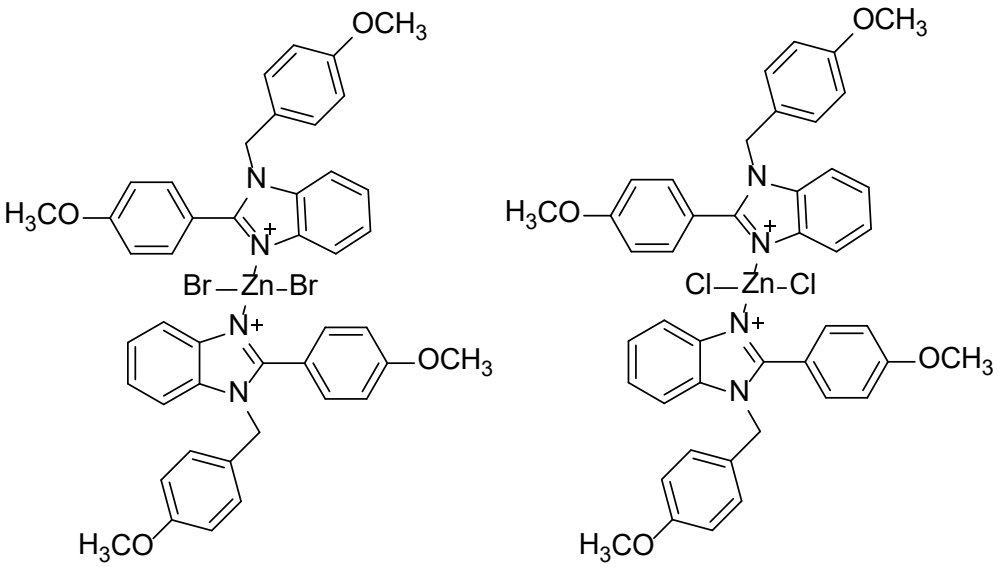


Figure 1. 2D chemical structures of the studied molecules

Table 1. Grid box parameters used for docking analysis in this study	
Protein Name with the PDB ID	
	GRIDBOX SIZE
	Center
SARS-CoV-2 spike glycoprotein (6vxx)	X = 204.456
	Y = 186.645
	Z = 251.644
SARS-CoV-2 Alpha variant (7EKF)	X = -44.345
	Y = 2.645
	Z = -27.644
SARS-CoV-2 Beta variant (7ekg)	X = -44.345
	Y = 2.645
	Z = -27.644
SARS-CoV-2 Gamma variant (7V84)	X= 190.456
	Y= 192.645
	Z= 190.644
*SARS-CoV-2 Delta variant (7**V8B**)*	X = 189.456
	Y = 243.645
	Z = 273.644
SARS-CoV-2 Omicron variant (7T9J)	X = 195.456
	Y = 243.645
	Z = 283.644

After that, the excess heteroatom and drug molecules were removed from the tertiary structure of SARS CoV-2 protein and saved as PDB file format. In this performed purification, Discovery studio (BIOVIA) software version V2.3 was used and visualized. The 2D structure of chemical structure was prepared using Marvin sketch. The generated 2D structure was saved as .mol2 file and

the same was to generate 3D coordinates and hydrogens were added and saved it in mol2 format. The macromolecules were uploaded to Maestro software for protein preparation by removing water residues, and further refined by merging non polar hydrogens. Then, the AutoDock Vina program is applied for molecular docking and Discovery Studio version 2017 has been conducted for active site analysis. The dimensions (A0) for Autodock Vina was set to standard size [26,27].

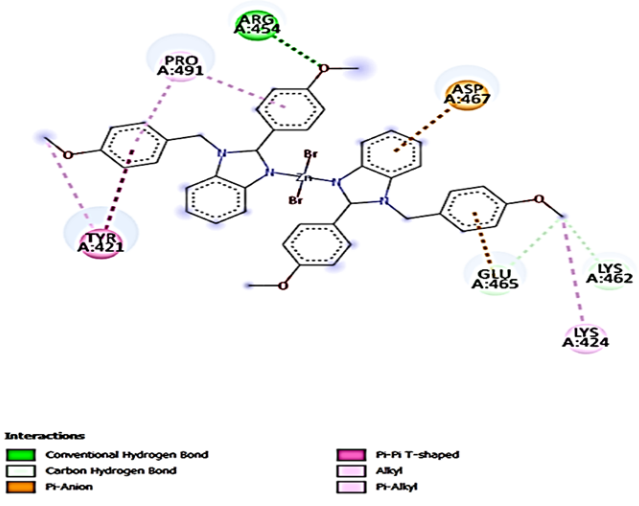
3. Results and discussion

3.1. Molecular docking analysis

The binding site of crystalline structure of SARS-CoV-2 was found to be LYS 417, TYR 453, GLY 485 and ASN 510. Hence, the above mentioned residues were considered as active site. The molecular docking has been represented by the binding affinity of a chemical, with the active site of the targeted pathogen and during this complex formation different types of active sites are generated. In general, the binding affinity is greater than -4 kcal/mol are considered as good modulator. The binding energy was reported against targeted SARS-CoV-2 protein are -5.3 kcal/mol to -7.2 kcal/mol for SARS-Co-V-2 main protein, -5.3 kcal/mol to -5.8 kcal/mol for spike glycoprotein (6vxx), -6.1 kcal/mol to -6.4 kcal/mol for alpha variant(7ekf), -6.3 kcal/mol to -6.0 kcal/mol for *beta variant (7ekg), -6.4* kcal/mol *to -6.0* kcal/mol *for* gamma variant (7v84), -7.2 kcal/mol to -6.8 kcal/mol for *delta variant (7v8b), and for the* omicron variant (7T9J) was reported as -6.1 kcal/mol to -5.7 kcal/mol. It was understood that the molecules have better affinities against the alpha, beta, gamma, delta and omicron variants in Table 2.

Table 2. Docking scores, and binding affinities (kcal/mol)

	SARS-CoV-2 spike glycoprotein (6vxx)	**Structure of SARS-CoV-2 Alpha variant (7EKF)**	**SARS-CoV-2 Beta variant (7ekg)**	**SARS-CoV-2 Gamma variant 7EKC**	**SARS-CoV-2 Delta variant (7V8B)**	**SARS-CoV-2 Omicron variant (7T9J)**
[Zn-mbmpbi]Cl_2	-5.3	-6.4	-6.3	-6.1	-7.2	-6.4
[Zn-mbmpbi]Br_2	-5.8	-6.4	-6.4	-5.7	-7.2	-6.4



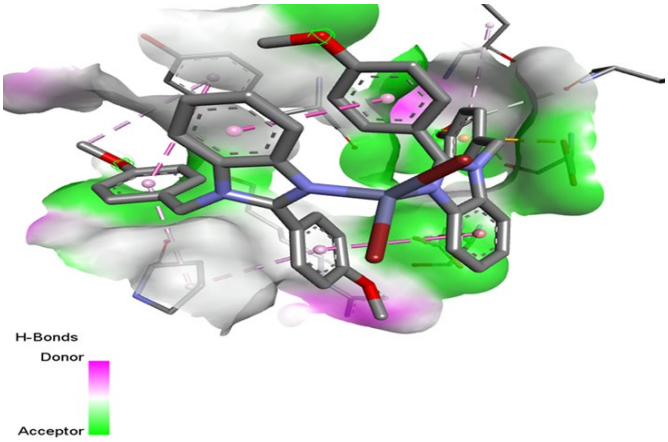


Figure 4. Various docking poses for ligand-protein interaction in hydrophobicity surface preset with chemical structure depicted in cylinder model.

3.2. Different poses of ligand-protein interactions

During the formation of drug protein complexes, a dingiest bond has been found such as covalent hydrogen bonds, carbon hydrogen bonds, hydrophobic bonds, polar and non-polar which are linked together shown in figure 4. Studies have been found that the polar bonding occurs with a ligand partially charged atom and a protein molecule. The chemical structure was found to bind to SARS-CoV-2 spike glycoprotein by interacting with PRO 491, ARG 454, ASP 467, TY2 421, GLU 465, LYS 462 and LYS 424.

4. Conclusions

In conclusion, we disclose a first report on molecular docking, and ADMET properties of two Zn(II) complexes. In addition, the novel zinc complexes have high binding affinities with the SARS-CoV-2 spike glycoprotein (6vxx) alpha variant (7EKF), beta variant (7ekg), gamma variant (7EKC), delta variant (7V8B), and the omicron variant (7T9J). ADME studies provided the better results with no adverse effect of toxicity related Salmonella typhimurium reverse mutation assay (AMES) along with absence of hepatotoxicity and skin sensitization when compared to Molnupiravir drug and it has a greater hepatotoxicity. This study could open that these novel zinc complexes have a further drug discovery for SARS-CoV-2 inhibition.

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Conflict of interest

The authors declare no conflict of interest.

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