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In silico Molecular Docking, ADMET Property, Molecular Dynamic Simulation Evaluation of *N,N′-bis*(2-Hydroxybenzylidene)-1,2-diaminobenzene and its Metal Complexes against SARS-CoV-2

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In search of potent inhibitors of SARS-CoV-2, well familiar *N,N′-bis*(2-hydroxybenzylidene)-1,2-diaminobenzene [HBDB]/salophen ligand and its corresponding metal complexes such as [VO(HBDB)], [$Mo(O)_2$(HBDB)], [$W(O)_2$(HBDB)], [$Fe(H_2O)_2$(HBDB)], [$Pb(H_2O)_2$(HBDB)], [$Sn(Cl)_2$(HBDB)] have been accompanied with standard drug hydroxychloroquine employing CADD tools such as the molecular docking, ADMET toxicity assessment and molecular dynamics of the coronavirus main protease (PDB id: 6LZG) enzyme. The synthesized salophen metal complexes exhibited the greater binding energy than corresponding salophen Schiff base ligand and standard hydroxychloroquine drug. Consequently, salophen metal complexes could serve as potential lead molecules against COVID-19 for further optimization and drug development to combat the virulent SARS-CoV-2 syndrome. The molecular dynamic simulation studies for [$Mo(O_2)$(HBDB)] complex shows an excellent binding free energy about -170.833 Kcal/mol. Subsequently, it is confirmed that salophen metal complexes could serve as potential drugs against COVID-19 for further optimization and drug development to combat the virulent SARS-CoV-2 syndrome.

Keywords: SARS-CoV-2, Salophen Schiff base complexes, Molecular Docking, Molecular dynamic simulation, ADMET property.

INTRODUCTION

Globallly all the countries are suffering with the unprecedented pandemic due to the outbreak of largest category of RNA virus known as "COVID-19". Still now, the transmission of this causative agent to humans remains unclear [1]. However, it is reported that deadly SARS-CoV-2 viral pathogen was identified earlier at 2002-2003 with particular strain, which may be disseminated into human life through various animals hosts such as bats, pangolins, civets, camels, *etc.* [2,3]. The M^{pro} or 3-chymotrypsin like protease ($3CL^{pro}$) a proteolytic enzyme is a basis for viral proliferation. Therefore, to eradicate SARS-CoV-2, its necessary to hamper M^{pro} [4,5]. Owing to this global pandemic, the whole world were paralyzed with lack of essential necessities like health, education, social, economic, medical amenities, *etc*. The worldwide economy was totally imbalanced and fallen during the pandemic [6,7]. To overcome, scientists/researchers from the worldwide are craving for the detection of potential drugs to combat this deadly virus and to cure the severe corollary of COVID-19, which is prevailing continuously [8-12].

In year 2020, azithromycin (AZM) was functionalized as better potent ability against deadly SARS-CoV-2 disease, but due to its multifaceted biological applications, AZM is not found effective [13]. However, the strategy of employing several antiviral agents leads to prove themselves as inefficient against this catastrophic virus, SARS-CoV-19. Many repurposed drugs exhibits its inefficacy against the demand of potential inhibitors [14,15]. Keeping all these targets, several attenuated vaccines, using the host of RNA and DNA, viral vectored, protein incorporated and inactivated vaccines of different kinds with different mechanistic approach have been developed to combat the replication of this viral pathogen at the initial stage [16]. Instead of inhibition action towards deadly pathogen, the vaccines pose several side effects during phase III trials such as fatigue, headache, lowering body temperature, diarrhoea, swelling, myalgia, arthralgia, becomes red while itching, *etc*. [17]. For instance,

United States Food and Drug Administration (USFDA) authorized remdesivir, as a nucleotide analog for emergency owing to its inhibition action against the viral replication of infected host body [18]. However, the potential function of this remdesivir drug is susceptible for COVID-19 patients whom suffer with heart failure and lower immune system, hypotension, respiratory problems and also renal failure [19]. The recent report evidenced that one of the immunoprotection strategy as proved clinically is that consuming the trace elements during the treatment has a potential to dimunition of COVID-19 viral disease effectively [20].

Therefore, the development of inorganic and organic Schiff base ligand shows potent pharmacological properties due to its absorption and biomimetic actions [21]. Metal coordinated salophen type Schiff base complexes attracts researchers widely due to their broad characteristics applications such as viable preparation methodology, biological functions in medicinal field, extraordinary stability owing to their different stable oxidation states and catalytic property. In coordination chemistry field, tetradentate ligand with N_2O_2 chelating modes makes the complex excells in fields of coordination chemistry [22]. Despite following the cost burden, ineffeicient pedestrian mode to drug design and evolution, the computer assisted drug design (CADD), a tool preferrably followed due to its traditional approach, cost effectiveness, better results and removed the lapse between biological science and chemistry [23,24].

In view of this fact, well characterized, structurally proved, potential biological active effects of salophen Schiff base ligand and some of its metal complexes [25] selected from literature are intended to examine the resistant towards SARS COV-2 viral protein main protease (M^{pro}) with the assistance of molecular docking to investigate the binding affinity followed by ADMET assay to prove their druggability and protein complex stability was confirmed with molecular dynamic simulation (MD) in search of a possible candidate drug for screening the virulent SARS COV-2 *via in silico* approach.

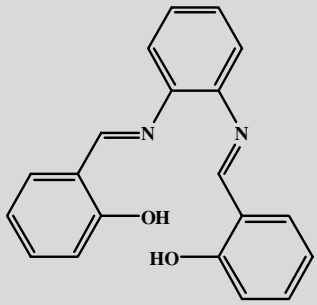
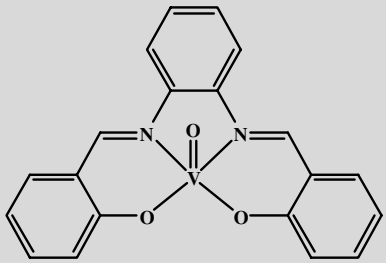
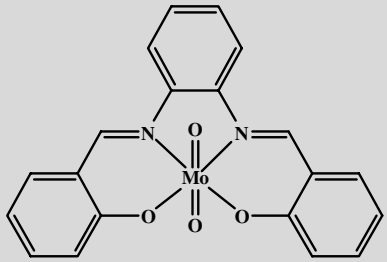
EXPERIMENTAL

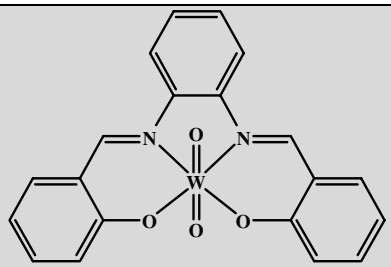
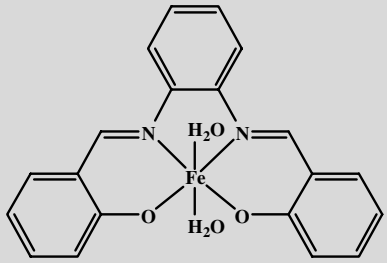
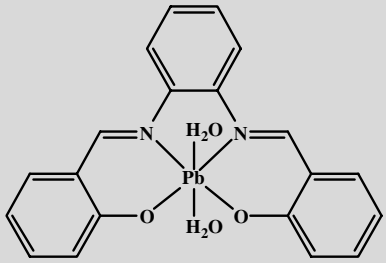
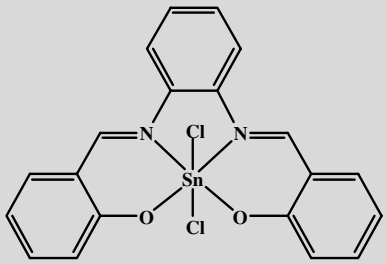
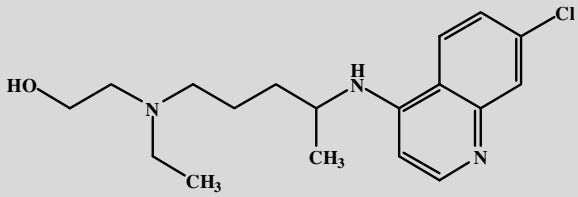
The fundamental *in silico* molecular docking, physicochemical properties evaluation and molecular docking (MD) simulation analysis were accomplished utilizing BIOVIA Discovery Studio (DS) 2017 software.

Protein preparation: The COVID-19 M^{pro} crystal structure with 2.5 Å fetched from the protein data bank(pdb) [26]. The protein 6LZG enzyme was build on hydrogen with a support of force field algorithm. Eventually, the protein energy was diminished applying CHARM forcefield in Discovery studio.

Ligand construction: Salophen Schiff base ligand (HBDB) and its metal complexes converted to 3D coordinate using chemdraw software. The designed [HBDB] and its metal complexes are shown in Table-1. Adequate non-polar hydrogen bonds were fused, rotatable bonds and torsion tree was generated and

TABLE-1
CDOCKER ENERGY FOR SALOPHEN LIGAND AND ITS SELECTED METAL COMPLEXES

Selected	Structure	CDOCKER energy (Kcal/mol)
N,N′-Bis(2-hydroxybenzylidene)-1,2-diaminobenzene (HBDB)		-22.254
[VO(HBDB)]		-82.240
[Mo(O_2)(HBDB)]		-170.833

$[W(O)_2(HBDB)]$		-133.961
$[Fe(H_2O)_2(HBDB)]$		-128.4676
$[Pb(H_2O)_2(HBDB)]$		-153.595
$[Sn(Cl)_2(HBDB)]$		-145.302
Hydroxychloroquine		-20.357

made all the ligand and its complexes as perfect modules. Later energy was deduced and saved in .sdf file layout for the docking work. Salophen Schiff base ligand and its metal complexes were compared with standard hydroxychloroquine drug. The selected salophen Schiff base metal complexes are (i) [HBDB], (ii) [VO(HBDB)], (iii) $[Mo(O)_2(HBDB)]$, (iv) $[W(O)_2(HBDB)]$, (v) $[Fe(H_2O)_2(HBDB)]$, (vi) $[Pb(H_2O)_2(HBDB)]$ and (vii) $[Sn(Cl)_2(HBDB)]$.

Molecular docking analysis: Molecular docking is a sensible drug designing analysis for efficient drug development through biomolecular interactions [27,28]. It is an helping hand to achieve the most favourable geometry of the protein-ligand complex. The inclusion of CHARMM-based DOCKER (CDOCKER) within Discovery studio was availed to perform molecular docking against the selected protein (PDB id: 6LZG) to assess the possible binding modes of Schiff base ligand and its complexes with the target protein. The suitable parameter were laydown to run the CDOCKER. Those parameters provide ligand to complete flexibility. Ligand binding empathy was determined make use of CDOCKER energy, hydrogen bonds, binding energies, CDOCKER interaction energy, protein energy and ligand-protein complex energy. All the complexes produced docking energy with highest negative values. The lowest CDOCKER energy emphasized that greater binding attraction with Schiff base ligand and its metal complexes with the target protein.

ADMET studies: Optimistic report of ADMET property helps the researchers as cake walk to achieve drug designing work and saves economically rather than proceeding with costly experimental test that ends with negative result. The ADMET descriptors with discovery studio (Accelrys, San Diego, CA, USA) software were aided to procure the druglikeness property

or absorption, distribution, metabolism, elimination and toxicity (ADMET) examination. The human intestinal absorption (HIA) and blood brain barrier (BBB) property with the help of suitable parameter set Alog P and 2D polar surface area (PSA 2D) were also predicted. The HIA reports were further agreed with 95% and 99% confidence spheroid model. The solubility assessment task based on a genetic partial least squares method.

Molecular dynamic simulation: To authenticate the molecular docking evaluation, an alluring tool molecular dynamic simulation analysis were performed utilizing BIOVIA Discovery studio version 2017 [29,30]. The synchronization of the protocol set were defined [31]. The potent biological [$Mo(O)_2$(HBDB)] complex and the protein was MD simulation to about 300 ps.

RESULTS AND DISCUSSION

Molecular docking studies: The molecular docking study was evaluated against the suitable protein crystal structure (PDB id: 6LZG) [26] to identify the best docking pose with salpohen Schiff base ligand and its metal complexes in the active site suitably using CDOCKER within Discovery Studio. The ligand and its metal complexes were selected from literature are very easy to prepare in a compatible way. The well processed protein and selected compounds were designed and saved in a PDB format to assess the molecular docking work. The CDOCKER energy of salpohen Schiff base ligand and its metal complexes were compared with standard drug hydroxychloroquine (Table-1). The overall binding pose of [HBDB] and its metal complexes with main protease 6LZG enzyme depicts secondary structure and the exact binding site are shown in Fig. 1a-b.

Salpohen Schiff base ligand [HBDB] and all the selected metal complexes binding interaction were explicitly reveals from the 2D and 3D representation (Fig. 2). The ligand HBDB and protein receptor binding interactions with a formation of strong three conventional hydrogen bonds with different amino acids such as Asn 397, Gly 395 and Phe 390 was shown clearly in 2D and 3D view in Fig. 2a. Additionally, carbon-hydrogen bond with Leu 391 amino acid, π-lone pair and π-alkyl interactions further enhance the interactions. These molecular interaction exhibits identified CDOCKER energy is -22.254 Kcal/mol. Similarly, the [VO(HBDB)] complex forms one hydrogen bond with Asn394 amino acid and π-π stacked cation interaction with Phe 40 and 390 amino acids. In addition with π-alkyl interaction with Arg 393 amino acid is also predicted (Fig. 2b). The binding energy for the [VO(HBDB)] complex with receptor 6LZG is -82.240 -Kcal/mol.

In consent with [$Mo(O_2)$(HBDB)] complex, 6LZG protein receptor visualizes excellent binding energy is about -170.833 Kcal/mol amongst the selected salophen complexes, which encompasses the two oxygen atoms form strong two conventional hydrogen bond interaction with Asn 394 residue. Moreover, a type of T-shaped π-π interactions with Phe 390, His 378 and also π-alkyl attractions involved in Arg 393 amino acid observed in [$Mo(O_2)$(HBDB)]. Subsequently, the C-H bond binding interaction with Asp 350 with this one more interesting interaction is that attractive nuclear charge mapped between N^+ and Asp 382 amino acid.

Similarly, the complex [$W(O)_2$(HBDB)] with binding energy is about -133.961 Kcal/mol, reveals the binding interactions pertains one hydrogen bond with Asn 394 and also both π-carbon and C-H bonds involved in same Phe 390 amino acid. Further, complex formed strong carbon-hydrogen π-alkyl interactions with Arg 393 amino acid.

Considering [$Fe(H_2O)_2$(HBDB)] complex, a π-π T- shaped interaction with His 378 and His 401 amino acid of COVID-19 6LZG receptor. The Schiff base group of the complex forms an attractive charge with the Asp382 receptor as similar as tungsten salophen complex and shows that binding CDocker energy is -128.4676 Kcal/mol. The complex [$Pb(H_2O)_2$(HBDB)] and 6LZG protein receptor docking elucidates various interactions ability with residues such as conventional H-bond with Asn 394, two π-C interaction were mapped with Phe 40 and Phe390. It also formed C-H bond interaction with Asp 350 and π-alkyl interaction with Arg 393 amino acid having the binding energy exclusively about -153.595 Kcal/mol. In [$Sn(Cl)_2$(HBDB)] complex, the observed interactions were conventional H-bond,

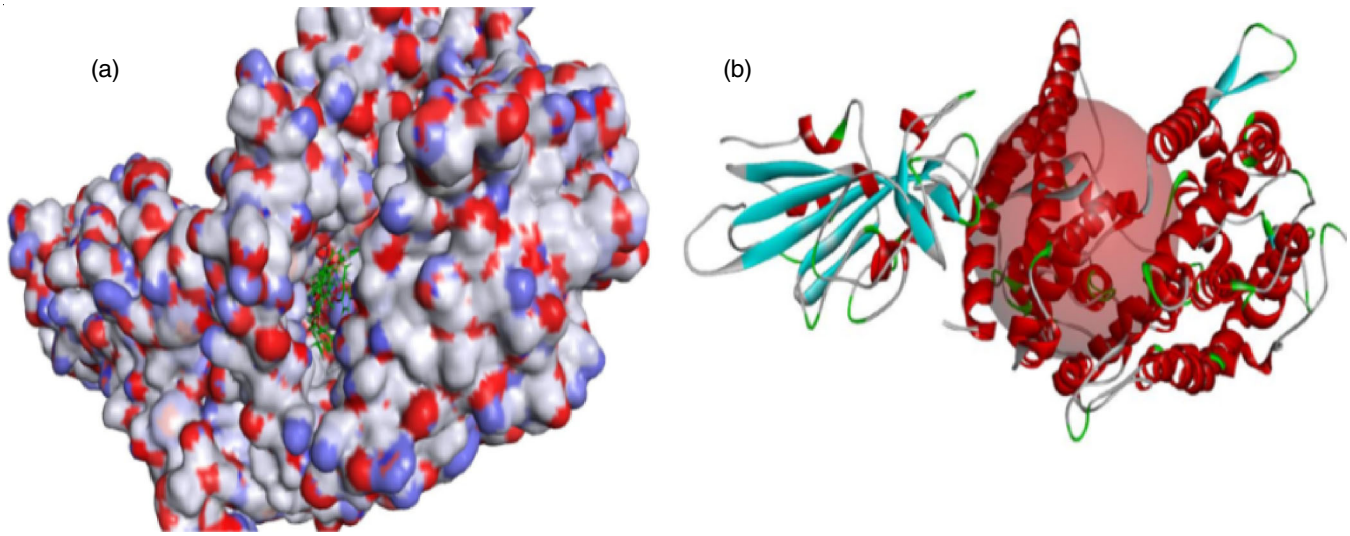
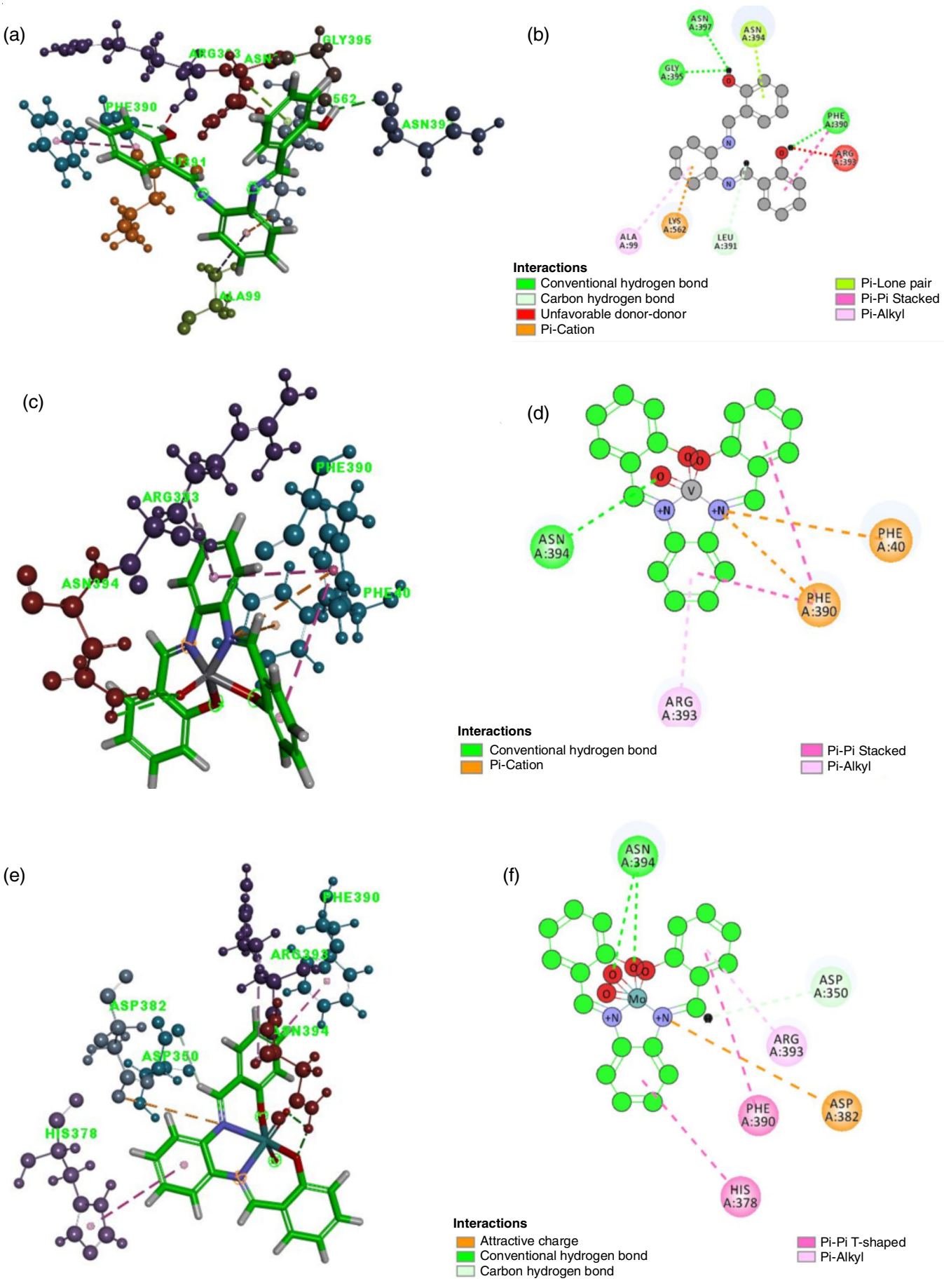
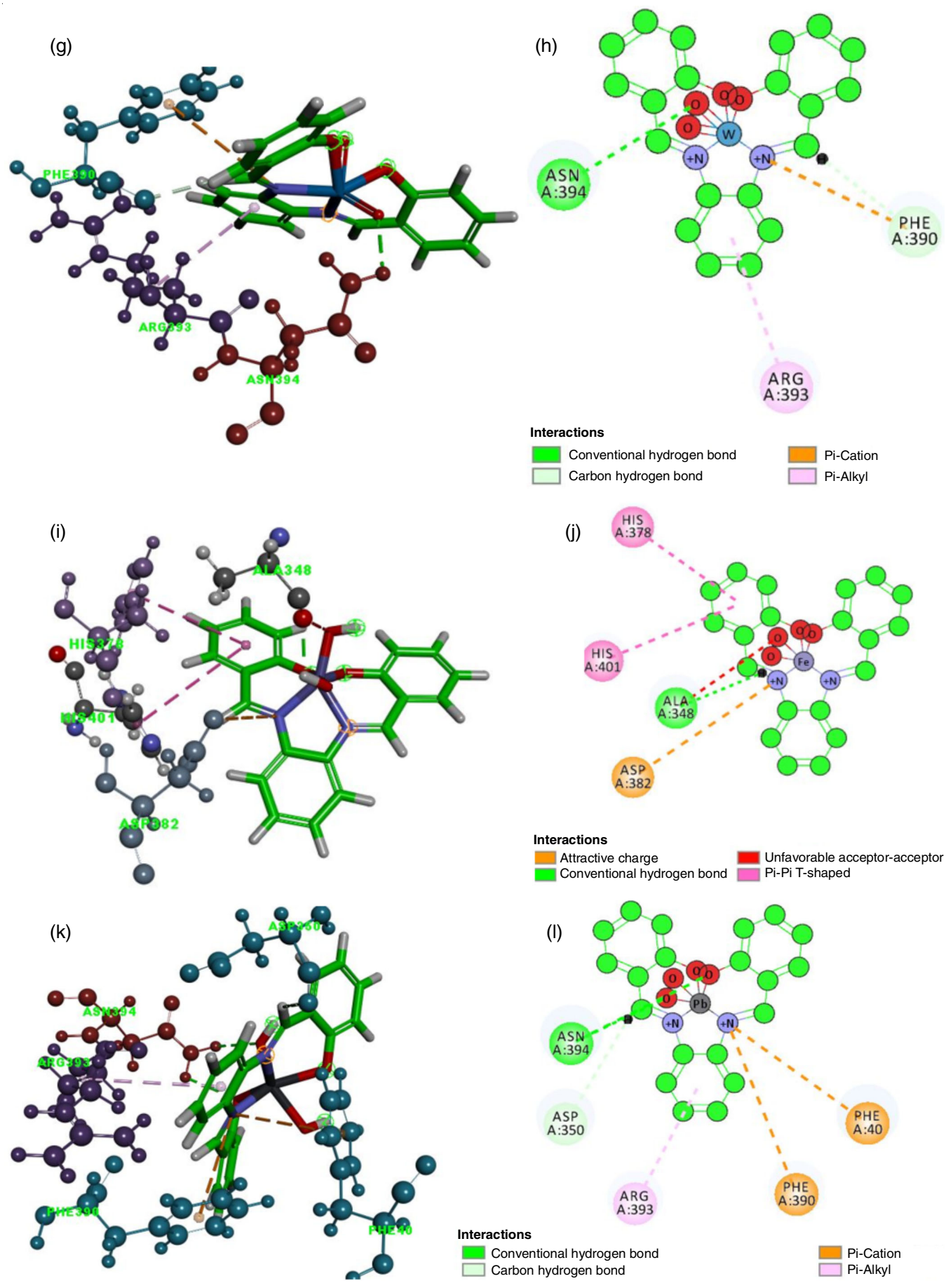


Fig 1. (a) Docked pose of [HBDB] ligand and its complexes with protein, (b) Exact binding site of protein-ligand interactions


(a)
GLY395
PHE390
ASN39
ALA99
(b)
ASN A:397
ASN A:394
GLY A:395
PHE A:390
ARG A:393
LYS A:562
ALA A:99
LEU A:391
Interactions
Conventional hydrogen bond
Carbon hydrogen bond
Unfavorable donor-donor
Pi-Cation
Pi-Lone pair
Pi-Pi Stacked
Pi-Alkyl
(c)
PHE390
ARG393
ASN394
(d)
ASN A:394
PHE A:40
PHE A:390
ARG A:393
Interactions
Conventional hydrogen bond
Pi-Cation
Pi-Pi Stacked
Pi-Alkyl
(e)
PHE390
ASP382
ASP350
HIS378
(f)
ASN A:394
ASP A:350
ARG A:393
PHE A:390
ASP A:382
HIS A:378
Interactions
Attractive charge
Conventional hydrogen bond
Carbon hydrogen bond
Pi-Pi T-shaped
Pi-Alkyl


(g)
PHE390
ARG393
ASN394
(h)
ASN A:394
PHE A:390
ARG A:393
Interactions
Conventional hydrogen bond
Carbon hydrogen bond
Pi-Cation
Pi-Alkyl
(i)
ALA348
HIS378
HIS401
ASP382
(j)
HIS A:378
HIS A:401
ALA A:348
ASP A:382
Interactions
Attractive charge
Conventional hydrogen bond
Unfavorable acceptor-acceptor
Pi-Pi T-shaped
(k)
ASP350
ASN394
ARG393
PHE390
PHE40
(l)
ASN A:394
ASP A:350
ARG A:393
PHE A:40
PHE A:390
Interactions
Conventional hydrogen bond
Carbon hydrogen bond
Pi-Cation
Pi-Alkyl

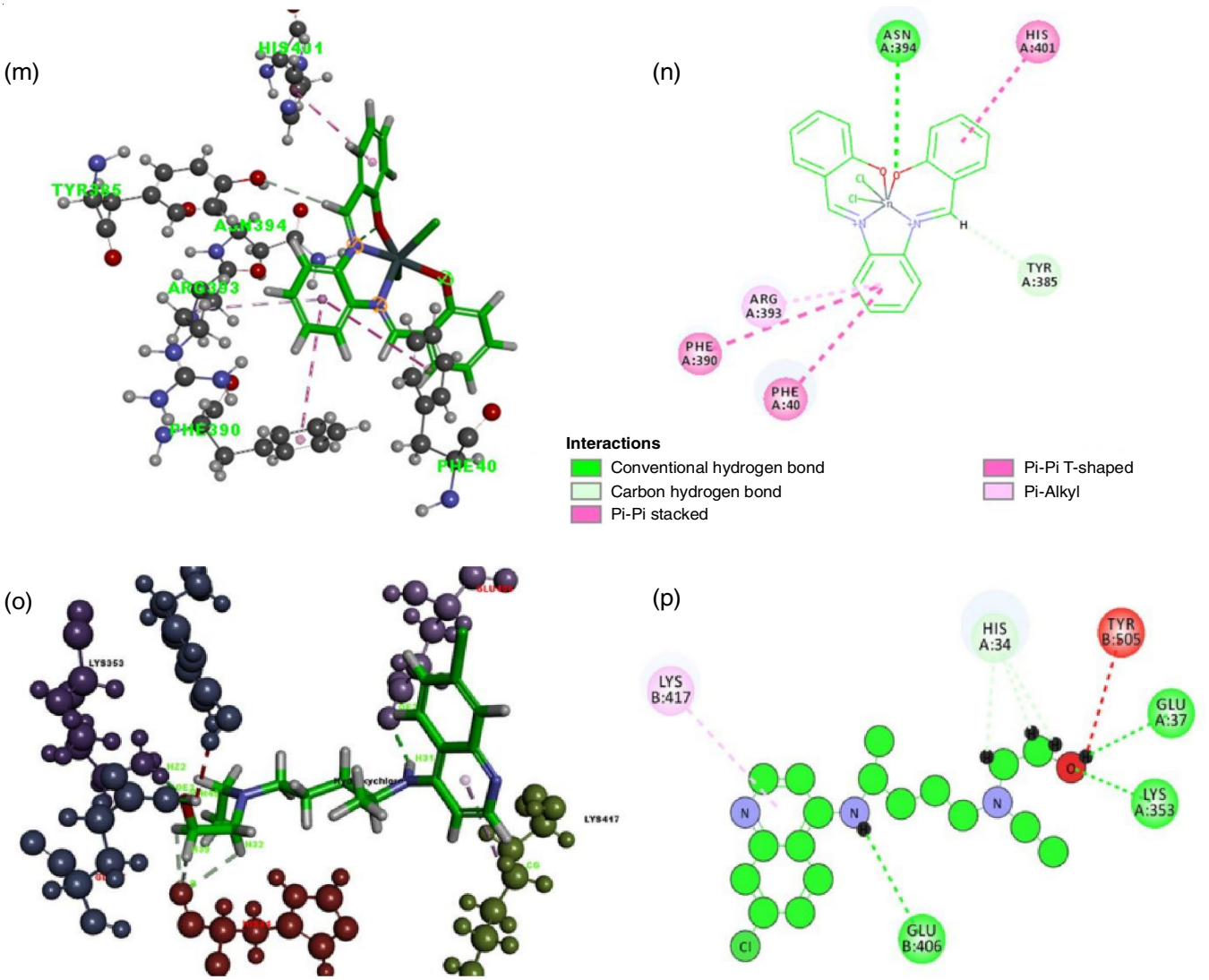


Fig. 2. 2D and 3D view of (a,b) [HBDB], (c,d) [VO(HBDB)], (e,f) [Mo(O_2)(HBDB)], (g,h) [W(O)$_2$(HBDB)], (i,j) [Fe(H_2O)$_2$(HBDB)], (k,l) [Pb(H_2O)$_2$(HBDB)], (m,n) [Sn(Cl)$_2$(HBDB)] and (o,p) HCQ (standard) drug interactions with the receptor 6LZG protein

C-H bond, π-π T-shaped, π-π stacked, π-alkyl with Asn 394, Tyr 385, PHe 390 and Phe 40, His 401, Arg 393 amino acid respectively, and the CDocker binding energy was found to be -145.302 Kcal/mol.

In this docking study, hydroxychloroquine drug used as standard for comparison analysis and its binding CDocker energy was -20.357 Kcal/mol, which was very less while compared to CDOCKER binding energies of the salophen Schiff base ligand [HBDB] and the selected metal complexes. Especially, molybdenum complex encompasses extraordinary binding energy, which is highest among the selected complexes with target 6LZG protein receptor. Moreover, the other salophen metal complexes also shows an extraordinary binding affinity, greater CDOCKER energy towards the protein receptor. Subsequently in general, these interactions gave authenticity to the hypotheses based on the binding energy value.

ADME toxicity studies: The ADMET properties of the selected HBDB and its metal complexes are shown in Table-2.

TABLE-2
ADMET PROPERTIES OF THE HBDB AND ITS METAL COMPLEXES

Name	Level of absorption	Level of solubility	Level of BBB	Level of PPB	Hepatotoxic limit	CYP 2D6	PSA 2D	AlogP98
HBDB	Good	Yes, optimal	Too low	0	< 90%	No inhibition	63.27	4.560
[VO(HBDB)]	Appreciable	Yes, good	Too low	0	< 90%	No inhibition	35.16	4.000
[Mo(HBDB)]	Appreciable	Yes, good	Too low	0	< 90%	No inhibition	52.46	4.000
[W(HBDB)]	Appreciable	Yes, good	Too low	0	< 90%	No inhibition	52.46	4.760
[Fe(HBDB)]	Moderate	Yes, good	Too low	1	< 90%	No inhibition	59.49	5.580
[Pb(HBDB)]	Moderate	Yes, good	Too low	0	< 90%	No inhibition	59.49	4.539
[Sn(HBDB)]	Appreciable	Yes, good	Too low	1	< 90%	No inhibition	58.21	4.492

On plotting the obtained values of 2D PSA *vs.* Alog P for the selected metal complexes for the purpose of identifying the penetration of designed drug in human intestinal absorption and BBB with 95% and 99% confidence spheroid shape [31]. The expected absorption regions were in acceptable zone that was elucidated by the spheroid. The maximum absorption limit of PSA 2D spheroid of 95% confidence limit shows 131.62 whereas the minimum limit of the PSA 2D spheroid reveals that 148.19 (Fig. 3). The ADMET value reports that the probability of absorption and solubility of the selected salophen Schiff base ligand and its metal complexes are in considerable limit [32]. Therefore, these salophen ligand and its metal complexes agreed with the better suitable pharmacokinetic properties and non-toxic capability. From the result of ADMET, it is found that metal complexes will obey drug-likeness properties and future promising potential drug for COVID-19.

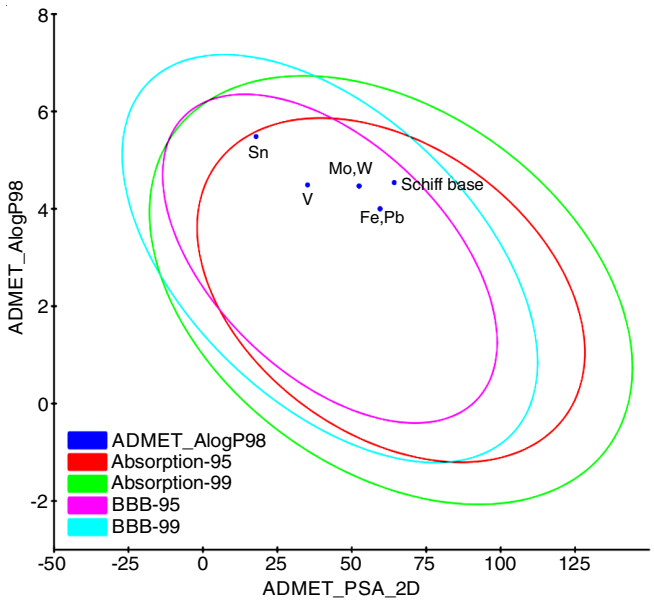


Fig. 3. Spheroid shows druglikeness property for [HBDB] and its metal complexes

Molecular dynamic simulation: Molecular dynamic simulation study fulfills the crucial need of the drug designing mode by predicting protein-complex stability even in atomic form at different temperature [29,30]. From the evaluation report of molecular docking study and ADMET assessment, the [Mo(O_2)(HBDB)] complex hits greater binding affinity with the COVID-19 6LZG receptor. Thus, this complex is suggested for further MD simulation analysis to identify the stability changes. The solvation process is proceeded by added 1247 water molecules, 67 sodium and 55 chloride ions. Fig. 4 shows the conformation of molecules at active site, property of electron and energy of the binding affinity towards 6LZG protein with [Mo(O_2)(HBDB)]complex.

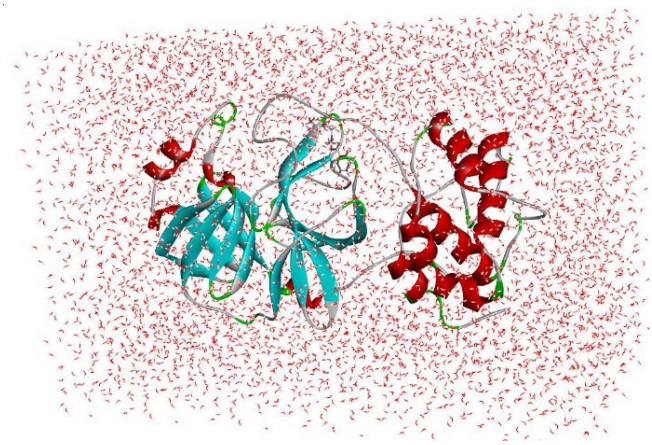


Fig. 4. Solvation process of 6LZG with [Mo(O_2)(HBDB)]

It is confirmed that the stability of each conformation of 6LZG protein and 6LZG with [Mo(O_2)(HBDB)] by manipulating the root mean square deviation (RMSD) and root mean square fluctuation (RMSF). Fig. 5a expressed the various conformer of protein residues produced during the RMSF and Fig. 5b a RMSD plot for the stability confirmation is very much satisfactory for 6LZG protein and 6LZG with [Mo(O_2)(HBDB)]

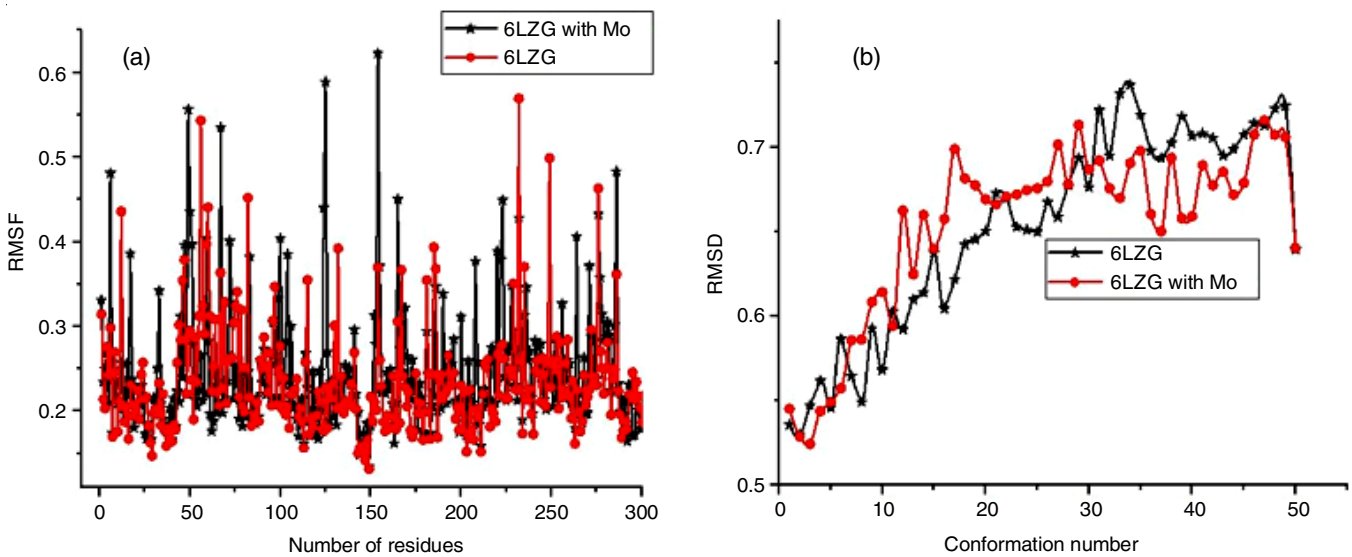


Fig. 5. (a) Production of different residues of 6LZG and 6LZG with [Mo(O_2)(HBDB)] during RMSquare fluctuation and (b) The maximum RMSD limit for the residues

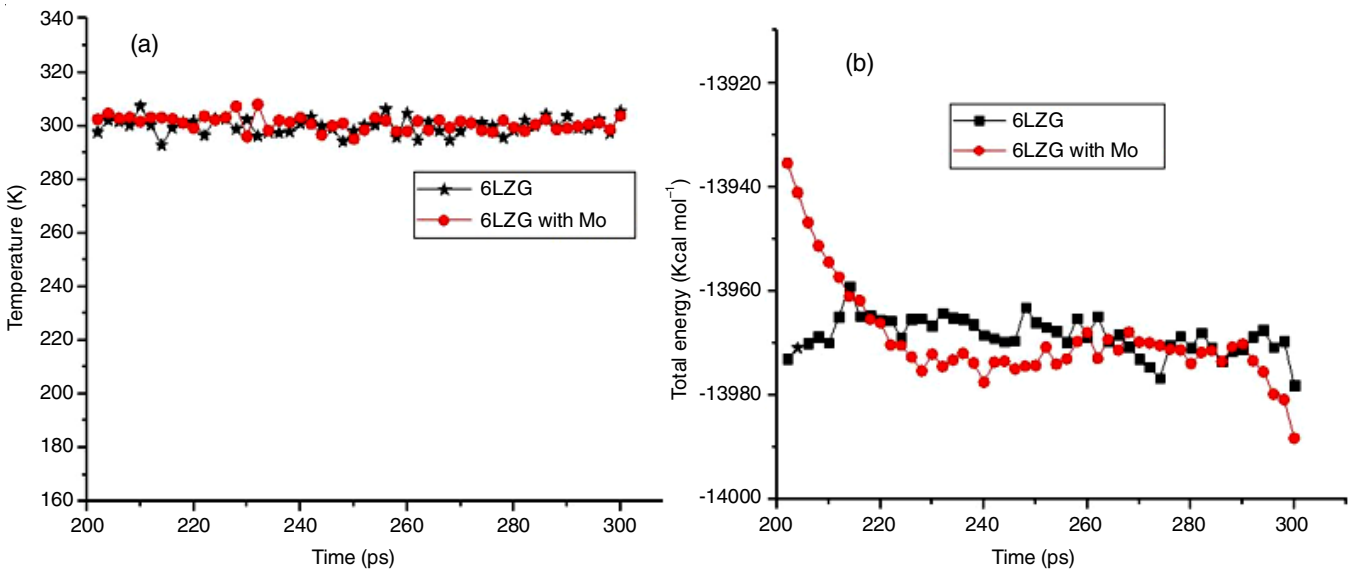


Fig. 6. (a) Formation of stable residues depends on time and temperature and (b) Prediction of stable energy for the unique receptor 6LZG with Mo

complex at 0.75 Å and 0.72 Å, respectively. These range 0.75-0.72 Å possess an average of 0.735 Å represents that protein and ligand are with the compactness.

Fig. 6a-b shows the results of RMSD and RMSF, the complex [Mo(O_2)(HBDB)] does not change the conformation of 6LZG structure and residues by means of varying the total energy and also at stable temperature of the protein complex. The obtained stable protein and protein-complex receptors were constant at 210 ps time range at 300-304 K and the receptor energy was stabilized exactly at -13965 Kcal/mol. Moreover, the [Mo(O_2)(HBDB)] complex does not influence the RMSD and stability of the 6LZG protein at various temperatures and energy values based on the above MD findings. However, these complexes may be stabilized due to hydrophobic interactions essentially above the electrostatic attractions.

Conclusion

The molecular docking results found that all the selected salophen metal complexes exhibited important binding affinity with the COVID-19 protein. Moreover, the ADMET findings proved the drug-likeness properties and druggability for better availability and safety. It is thought that these metal complexes could help in the discovery of COVID-19 drugs based on the observation of the docking score and ADMET results. Furthermore, the molecular docking results suggested that [Mo(O_2)-(HBDB)] does not change the 6LZG protein nature as well as its stability. Thus, the selected salophen complexes will be the future promising drug capability to overcome SARS-CoV-2. The current results need to be validated for further medicinal use in corona virus treatment by *in vitro* and *in vivo* antiviral activities.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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