

MOLECULAR DOCKING AND EVALUATION OF ANTIBACTERIAL POTENTIAL OF TRANSITION METAL(II) COMPLEXES OBTAINED FROM MACROCYCLIC SCHIFF BASE LIGAND

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ABSTRACT

The antibacterial activity of ligand L1 and their corresponding Cu(II), Co(II), Ni(II) and Zn(II) metal complexes were evaluated by in silico molecular docking analysis. In the docking analysis, fluconazole was used as a standard drug for antibacterial activity. The molecular docking analysis for antibacterial activity of the metal complexes revealed that the L₁-Ni and L₁-Cu metal complexes have good binding interaction with antibacterial receptors compared to the standard fluconazole drug. In this analysis, L₁-Ni and L₁-Cu metal complexes formed several bonded and non-bonded interactions with the active site of the residues.

Keywords: Docking Studies, Macrocyclic Ligand, Metal Complex, Antibacterial Activity, Fluconazole

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INTRODUCTION

Docking is a technique for predicting drug candidate affinity and activity by anticipating their binding orientation to protein targets. Docking is therefore crucial in the drug design and development process.¹⁻⁴ Molecular docking methods are used to determine Schiff Base ligand and its metal (II) complexes - binding and linking affinity scores. Abdur *et al.* reported their findings on the docking of a Schiff base with metal(II) complexes. The antibacterial activity of a 1-((3-nitrophenylimino)methyl)naphthalen-2-olate (Schiff base) and its complexes with Zn(II) and Co(II) metals was examined by docking analysis. Docking tests were used to establish their topoisomerase II binding capacity.⁵ Elena *et al.* developed and synthesized a range of Fe(III), Co(II), Pd(II), Cu(II), Pt(II), Cd(II) and Zn(II) complexes using 1-phenyl-2,3-dimethyl-4-(N-3-formyl-6-methylchromone)-3-pyrazolin-5-one (Schiff base).⁶ The biological activity of ligand as well as the Zn and Pd metal-complexes, was investigated using molecular docking experiments. Najlaa *et al.* used a triazole chelating ligand to perform docking and assessed the anti-bacterial potential of metal ligand-complexes. By molecular docking, the triazole ligand in this work has different peptide(aminoacid) receptors from the host: *E.coli*, *B.subtilis*, *P. vulgaris* (PDB ID: 3t88, PDB ID: 5h67 and PDB ID: 5i39).⁷ Vijayakrishnan *et al.* presented their docking analysis of dihydropyrimidinone metal complexes.⁸ The ligand with these metal complexes exhibits higher antibacterial action in the docking studies.

Herein we report the Molecular Docking and Evaluation of Antibacterial Potential of Transition Metal (II) Complexes obtained from Macrocyclic Schiff Base Ligand

EXPERIMENTAL

Methods

In this study, we used BIOVIA Discovery Studio (DS) 2017 software to perform in silico molecular docking.

Preparation of Protein, Ligand and its metal (II) Complexes

The X-ray crystal structure of *E. coli* (PDB ID: 3T88) was selected from the database. The Force field algorithm was used to add hydrogen to all of the proteins, and then the energy of the protein was

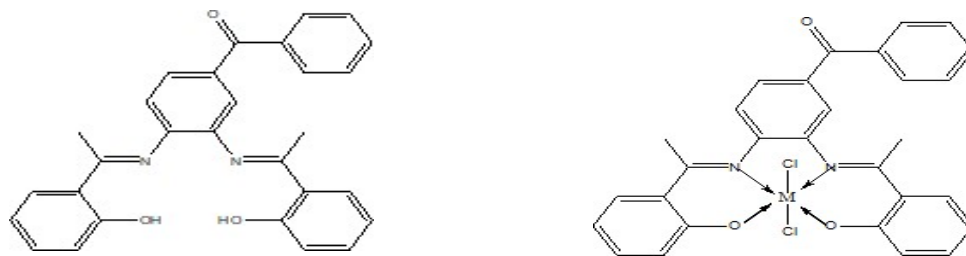
minimized using the CHARM forcefield in DS. In ChemDraw software, the ligands with their metal complexes and reference compound (fluconazole) were drawn, then energy reduced and saved in mol format for molecular docking experiments.

Molecular Docking Studies

A molecular binding docking study was carried out with the goal of determining the most favored protein-metal complex architecture. To better understand the antibacterial activity, molecular docking was subjected to analyze structural complexes of E. coli protein (PDB ID: 3T88), Secreted as particulate protease in complex with ritonavir. The CDOCKER (CHARMm-based DOCKER) methodology included in DS was used to investigate mechanisms between the metal complexes and proteins. The CHARMm force fields are used in the algorithm, which provides for complete ligand flexibility. The CDOCKER energy was calculated by the ligand-binding affinity. The -CDOCKER binding energy is indicated in negative score values. A more (-) value energy indicates better obligatory like-mindedness of the ligands with the receptor.

RESULTS AND DISCUSSION

The following ligand and their metal complexes are used in this molecular docking study (Fig.-1).



Ligand (L₁) Ligand with Metal (II) Complex (M=Co, Ni, Cu, Zn)
Fig.-1

Antibacterial Activity of the Metal Complexes

Molecular docking is an in-silico method used for the analysis of the interaction of ligands with the receptor. The docking analysis was achieved for all the metal complexes and ligands on the target enzyme 3T88 to identify the binding affinity. In this *in silico* antibacterial study, the fluconazole drug was used as a standard drug for assessment of the metal complexes binding activity. The secondary structure of the E. coli protein with active site sphere and surface morphology are shown in Fig.-2. The metal complexes binding energy in target protein (CDOCKER energy) are listed out in Table-1.

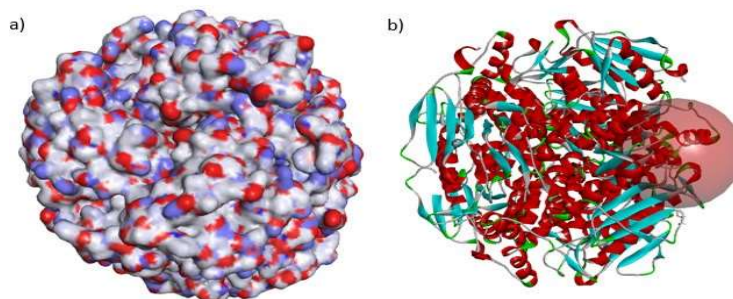


Fig.-2:(a) Surface Morphology and (b) Secondary Structure of *Escherichia coli* MenB Protein with Active Site Sphere

The CDOCKER energy for the L₁ - Ni with an active site of 3T88 is -459.829 Kcal/mol. In the docked complexes, the L₁ -Ni complex forms higher binding interaction with the active site of 3T88 receptor compared to other metal complexes and standard Fluconazole drugs. The benzene group of the L₁ -Ni complex forms Pi-Pi T-shaped and Pi-alkyl interaction with Val159 and Phe 270 amino acids. The keto group forms one strong Hydrogen bond with Ala 47 amino acid with 2.1 Å bond length. The other

hydrophobic group of the L₁-Ni complex forms Vander Waals Interaction with major active amino acids (Fig.-3).

Table-1: Molecular Docking Energy of the Schiff Base ligand and its Metal (II) Complexes in Antibacterial Activity

S. No.	Metal Complex Name	CDOCKER Energy(Kcal/mol)
1	L ₁ -Ni	-459.829
2	L ₁ -Cu	-308.356
3	L ₁ -Zn	-27.1855
4	L ₁ -Co	-23.2779
5	L ₁	-20.813
6	Fluconazole	-7.5120

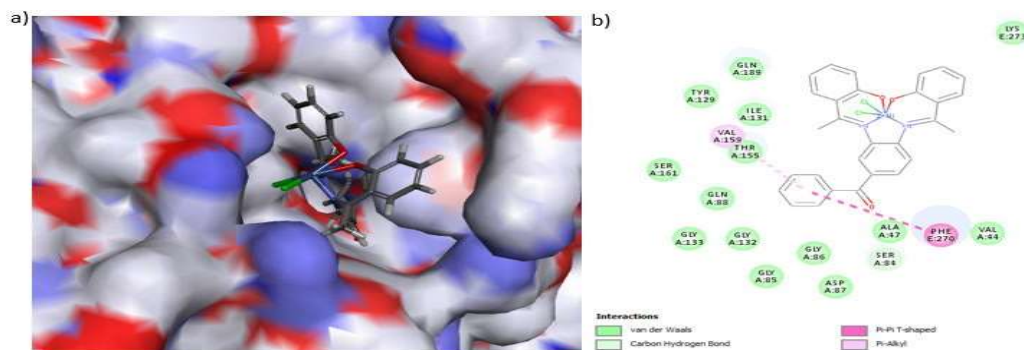


Fig.-3: (a) Three-dimensional and (b) Two-dimensional Binding Interactions of L₁ -Ni Complex with Active Site Amino Acids of the 3T88 Receptor

The L₁-Cu metal complex forms one Pi-sigma and one Pi-Pi T-Shaped interaction with aromatic benzene groups with -308.356 Kcal/mol CDOCKER energy. The other active site amino acids form Van der Waals interactions (Fig.-4). In this docking analysis, the Pi electrons of the benzene group of metal L₁-Cu complex forms a Pi-sigma interaction with the sigma bond of the Phe270 residue. Similarly, the other benzene group of this complex forms a Pi-Pi T-shaped interaction with the benzene side chain of the Phe 270 residue. The above interactions were involved in increasing the stability of the L₁-Cu complex in the active site of the 3T88 receptor.

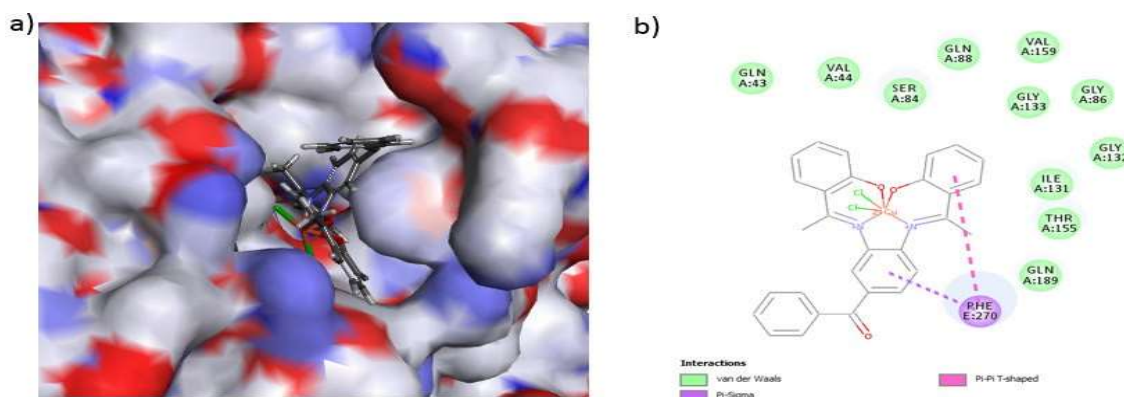


Fig.-4:(a)Three-dimensional and (b) Two-dimensional binding interactions of L₁-Cu Complex with Active Site Amino Acids of the 3T88 Receptor

Similarly, L₁ -Zn complex forms only Vander Waals interactions with most of the active site amino acids. Nearly 22 amino acids are involved in these interactions and show -27.1855 Kcal/mol CDOCKER energy (Fig.-5). Here, the L₁-Zn complex had mostly aromatic hydrophobic nature groups. These groups generally form a stable Vander Waals interaction with hydrophobic nature amino acids. So that, in this L₁-Zn complex docking in 3T88 receptor shows only Vander Waals interactions.

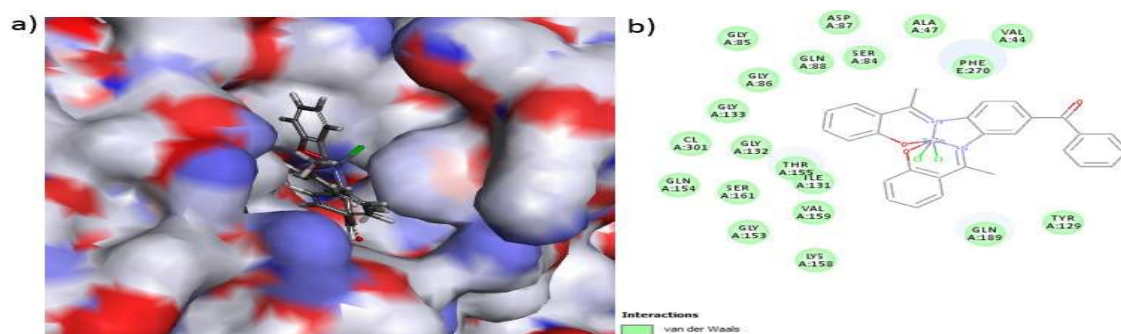


Fig.-5: (a)Three-dimensional and (b)Two-dimensional binding interactions of L_1 -Zn complex with Active Site Amino Acids of the 3T88 Receptor.

Additionally, the benzene group of L_1 -Co complex forms strong Pi-Alkyl interaction with Arg45 amino acid. Further, the keto group of this metal complex forms strong hydrogen (1.9 Å) bond interaction with the primary amine group ($-NH_2$) of Arg45 with -20.813 Kcal/mol CDOCKER energy (Fig.-6). In this L_1 -Co metal complex, the Co metal complex restricts the possible rotations of the aromatic group in this complex. So that, the single-bonded aromatic groups could not for many other interaction except conventional hydrogen bond.

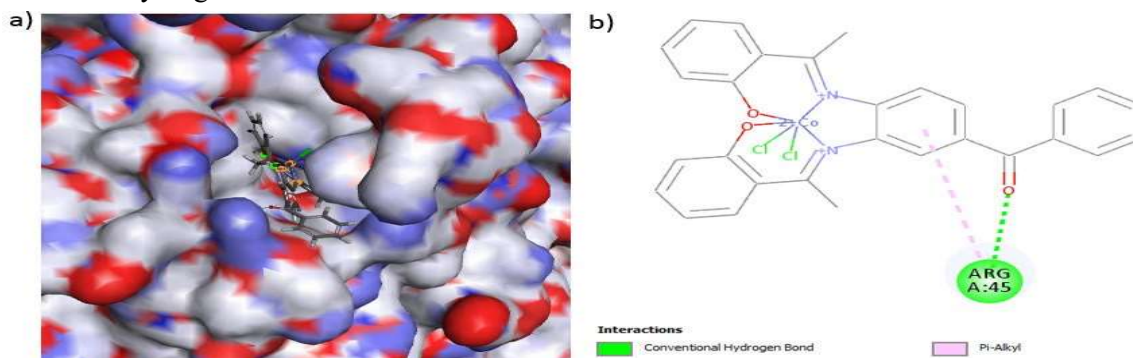


Fig.-6: (a)Three-dimensional and (b)Two-dimensional binding interactions of L_1 -CoComplex with Active Site Amino Acids of the 3T88 Receptor.

The L_1 ligand had more binding energy with -20.813 Kcal/mol. The side chain $-NH_2$ group of the Gln88 forms a strong hydrogen bond (2.0 Å) with keto group of the L_1 ligand. Also, Tyr129 and Phe 270 amino acid show Pi-PI- T-T-shaped interaction to the Pi-electrons of the aromatic benzene group. Similarly, Arg 45, Val 44 and Ala 47 show Alkyl and Pi-Alkyl interaction with the L_1 ligand. Moreover, the Phe270 and Arg 45 form Pi-Sigma and Pi-cation interaction with the L_1 ligand, respectively. The Asp87 shows only carbon-hydrogen bond (2.0 Å) interaction with keto group of the L_1 ligand (Fig.-7).

The standard drug fluconazole shows -7.5120 Kcal/mol CDOCKER energy. In this docking analysis, the lone pair electrons on the fluorine atom of fluconazole form one strong hydrogen interaction with $-NH_2$ group of the Gln 88 amino acid. The side chain alkyl group of the Val159 and Ala 47 amino acids forms Pi-Alkyl interaction with Pi- electrons of the fluconazole drug (Fig.-8). Mainly, the other fluorine atom of the fluconazole drug shows halogen interaction with aliphatic Val47 amino acid.

CONCLUSION

The molecular docking analysis for antibacterial activity of the metal complexes revealed that the L_1 -Ni and L_1 -Cu metal complexes have good binding interaction with antibacterial receptors compared to the standard fluconazole drug. In this analysis, L_1 -Ni and L_1 -Cu metal complexes formed several bonded and non-bonded interactions with the active site of the residues.

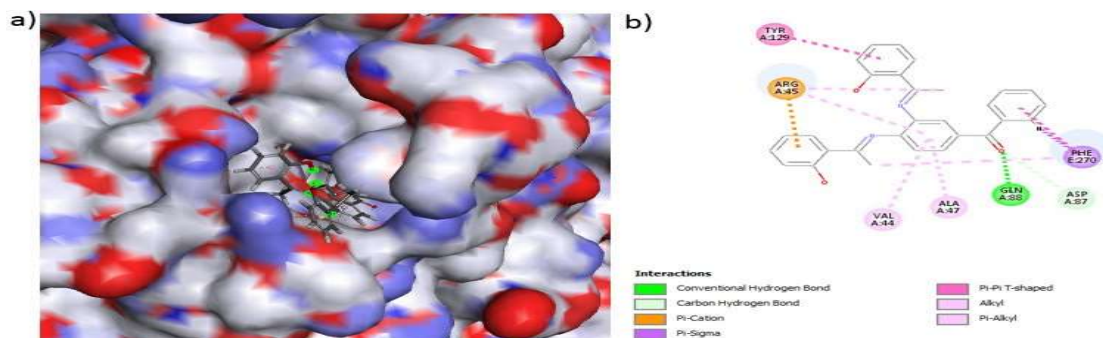


Fig.-7: (a) Three-dimensional and (b) Two-dimensional binding interactions of L₁ ligand with Active Site Amino Acids of the 3T88 Receptor.

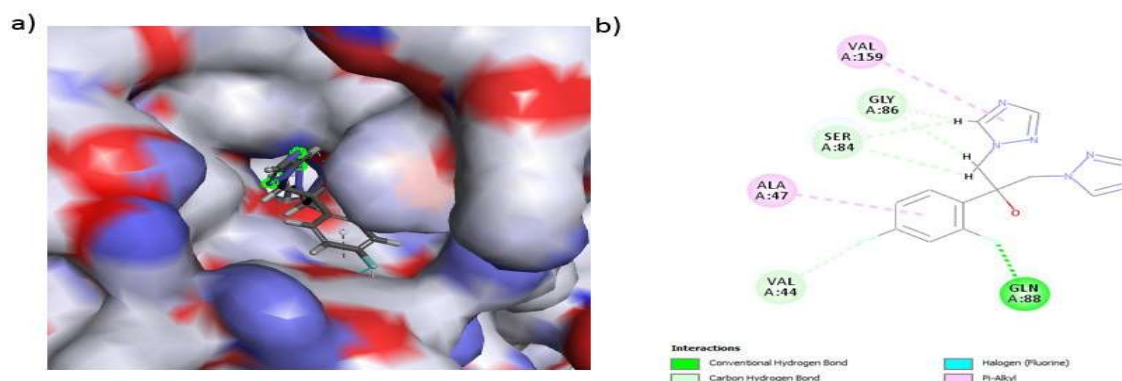


Fig.-8: (a) Three-dimensional and (b) Two-dimensional binding interactions of Fluconazole Ligand with Active Site Amino Acids of the 3T88 Receptor.

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