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Original Article

SYNTHESIS, CHARACTERIZATION, *IN VITRO* ANTIMICROBIAL, ANTHELMINTIC AND DOCKING STUDIES OF NEW 2-[(*E*)-{[4-(1*H*-1,2,4-TRIAZOL-1 YLMETHYL)PHENYL]IMINO} METHYL]PHENOL, AND THEIR COMPLEXES WITH 3D METAL IONS

JITHENDRA KUMARA K. S.[a], KRISHNAMURTHY G.[a*], SUNIL KUMAR N.[a]

[a]**Department of Chemistry, Sahyadri Science College, Shivamogga, Karnataka, India**
Email: gkmnaiksahyadri@gmail.com

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ABSTRACT

Objective: The main objectives of this research work is the synthesis and characterization of biologically potential triazole ring containing the Schiff base legend and their transition metal complexes, followed by screenings of their antimicrobial and anthelmintic activity the results of antimicrobial activity were compared with docking scores.

Methods: The coordination complexes of Co(II), Cu(II), Fe(III) and Zn(II) with Schiff base derived ligand 4-(1*H*-1,2,4-triazol-1-ylmethyl) aniline and substituted aldehydes have been synthesized. The complexes are characterized by elemental analysis, conductivity measurements, electronic, IR, and ^{1}H NMR spectral data. The synthesized compounds were also screened *In vitro* antimicrobial activity was carried out according to diffusion method by using agar and potato dextrose agar at 100, 500 and 700 mg/ml concentrations in DMF. HEX 8.0 programmers were used to perform the docking experiments on *nucleotide* of *S. typhi at* as ligand [PDB: 3B6O].

Results: Schiff base ligand and their transition metal complexes were studied for antimicrobial activity as well as docking. The results of both studies concluded that 4a, 4c and 4d compounds are more active in minimum inhibition concentration (30µg/ml) against *Staphylococcus aureus* (*S. aureus), Salmonella typhi (S. typlei)* bacteria and *Penicillium chrysogenum* (*P. Crysogenum)* fungi. The compounds showed highest docking score (-257.47,-275.61 and-280.17 respectively) with the secondary structure of the alpha-amylase with a nucleotide from *s. typhi* in the solid model. In the study of anthelmintic activity among these three compounds, 4d compound exhibits more activity compared with the standard.

Conclusion: The compounds 4a, 4c and 4d were found to be more promising pharmacological activity this observation may promote a further development of this triazole group of compounds which may lead to better pharmacological profile than standard drugs.

Keywords: Schiff bases, Triazoles, Metal complexes, Antimicrobial activity, Docking study

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INTRODUCTION

Inorganic elements play a crucial role in biological, medical processes, and it is evident that many organic compounds used in medicine are not purely organic; most of them are activated or biotransformed by the metal ions. [1-3]. The first Schiff base compounds were reported by Hugo Schiff in 1864. In recent years, the chemistry of Schiff bases contains N-donor atom has been extensively studied and has acquired a great interest because of the azomethine C=N linkage essential for biological activity, nowadays, cases of microbial resistance pose a major concern to the scientific community and have become a threat to human life worldwide. Moreover, invasive microbial infections caused by multi-drug-resistant Gram-positive bacteria and microbes are difficult to diagnose. To overcome these problems, the development of new and safe antimicrobial agents with better effectiveness is urgently required. To concern this end, one of the best ways to design new antimicrobial agents is to generate hybrid molecules by combining two bioactive heterocyclic moieties in a single molecular scaffold.

Among this pharmacologically important heterocyclic compounds, 1,2,4-tiazole with azomethine linkage and derivatives have been known to possess a wide range of biological properties, in our literature survey showed several triazol with azomethines were reported to possess remarkable antibacterial, antifungal, anticancer and diuretic activities [4-6] and it is having remarkable applications in many areas including organic synthesis, catalysis, designing of new metallomesogens, therapeutic drugs, asymmetric synthesis, resolution of racemic ligands, intermolecular aromatic C-H bond activation [7-12], crystal engineering [13-15] and anti-corrosion agent, etc. [16,17]. In this paper, we are presenting the synthesis, characterization and potential biological activity of the new triazole containing Schiff base complexes with transition metal elements.

MATERIALS AND METHODS

Triazole amine, aldehyde and all other chemicals were procured from the Sigma-Aldrich (INDIA), Himedia (INDIA), Lobo Chemicals (INDIA) (Commercially available from local sources) and were used as received without further purification. Freshly distilled solvents were employed for all synthetic purposes. Spectroscopic grade solvents were employed in spectral works.

All other chemicals were of AR grade. The progress of every reaction was monitored by TLC. Yield refers to the isolated yields after crystallization of the compounds that have a purity of ≥95%.^{1}H NMR spectra were recorded on a JNM-ECS-400 NMR spectrometer at 399.78 and Bruker avance III, 400 MHz, 9.4-tesla magnet with chemical shifts reported in ppm relative to the residual deuterated solvent or the internal standard tetramethylsilane. Elemental analyses were carried out with a Perkin-Elmer 2400 Series-II H, C and N analyzer. UV-Vis spectra recorded on varian, cary 5000. Melting points were determined in an electrically heated apparatus by taking the sample in a glass capillary sealed at one end.

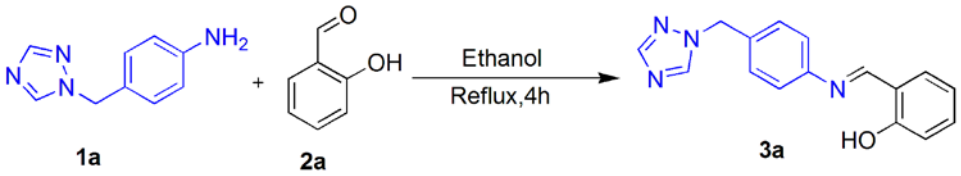
Preparation of the Schiff base ligand

The Schiff base ligand was prepared by condensation of 4-(1*H*-1,2,4-triazol-1-ylmethyl)aniline(0.01 mol) with 2-hydroxybenzaldehyde (0.01 mol) in a 15 ml ethanol solvent the resulting mixtures was refluxed on a water bath for about 3-4 h; reaction was monitored by TLC. After completion of reaction reacting mixture was cooled to room temperature, the yellow color crystals were separated out, which was filtered and washed with cold ethanol, dried and recrystallized in ethanol. M. P. 108±1ºC (Yield 75%), IR (KBr, cm^{-1}) 3407 (br), 3093.6 (w), 1620.9 (s), 1571.88 (s), 1512.09 (s), 1456.16 (m), 1269 (s), 1174.5 (s), 1018.3 (s), ^{1}H NMR (DMSO-d_6, 400 MHz) 11.61 (1H, s, OH), 8.95 (1H, s, CH-Triazole), 8.74 (1H, s, CH-Triazole),

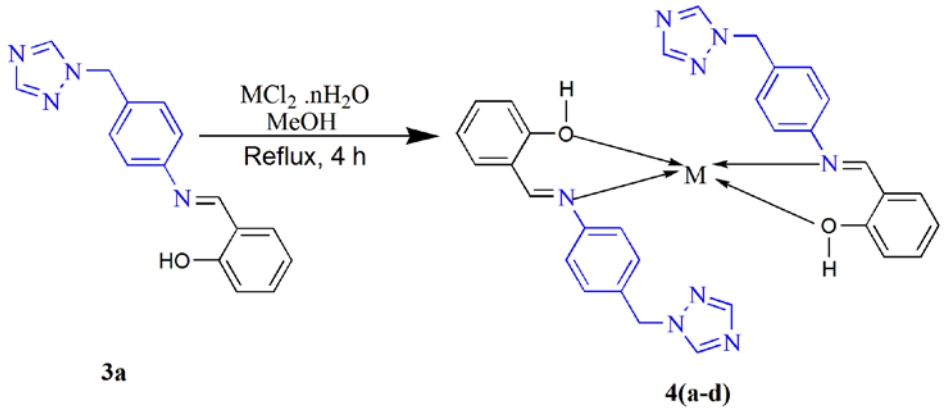
8.04 (1H, m, Ar-Aldehyde), 7.47 (1H, m, Ar-Aldehyde), 7.29-7.27 (5H, d,), 6.82 (2H, d, Ar-Aldehyde) and 5.29 (2H, s, Methaylene-H).

Preparation of the complexes

An alcoholic solution of Schiff base (45 ml, 0.002 mol) was added to the alcoholic solution of $CoCl_2.6H_2O$, $CuCl_2.2H_2O$, $FeCl_3$ and $ZnCl_2$ (5 ml of 0.001 mol) metal salt, one at a time, the resultant mixture colour change instantly and it was refluxed on a water bath for about 3 h. Then, the reaction mixture was cooled to room temperature; the solid separated was collected by filtration, washed thoroughly with water, then ethanol followed by either, finally dried in vacuum over fused $CaCl_2$.



Scheme 1: Synthesis of 2-[(*E*)-{[4-(1*H*-1,2,4-triazol-1-ylmethyl)phenyl]imino}methyl]phenol



Scheme 2: synthesis of metal complexes with ligand, M=Co, Cu, Zn and Fe

***In vitro* antibacterial and antifungal assay**

The antibacterial and antifungal activities at different concentration of newly synthesized trazole Schiff base ligand and their Fe(III), Co(II), Cu(II) and Zn(II) complexes have been studied by using agar and potato dextrose agar on the basis of the previously reported diffusion method [16-18]. The antibacterial and antifungal activities were done at 100, 500 and 700 mg/ml concentrations in DMF using three bacteria (*S. aureus, Bacillus subtilis (B. subtilis), s. typi*) and two fungi (*Aspergillus niger (A. Niger) P. Crysogenum*). The bacterial strains were incubated for 24 h at 37 °C and fungal stains were incubated for 48 h at 37 °C. Standard for antibacterial (Chloramphenicol, Fluconazole) and antifungal drugs (Kanamycin) were used for comparison under similar condition.

Anthelmintic activity (*in vitro*)

The anthelmintic assay was evaluated by the method given in the literature [18] with minor modifications. The assay was performed on adult Indian earthworms, Pheretima posthuma, due to its anatomical and physiological resemblance with the intestinal roundworm parasite of human beings [18]. Earthworms (P. posthuma) collected from moist soil and washed with normal saline to remove all fecal matter were used for the anthelmintic study. The earthworms of 3 to 4 cm in length and 0.1 to 0.2 cm in width were used for the experimental protocol. The compounds were subjected to anthelmintic studies against earthworms at 2 and 10 mg/ml by using Albendazole as a standard drug. The paralyzing and death time was noted, and their mean was calculated for triplicate sets. The death time was ascertained by placing the earthworms in warm water (50 °C) which stimulated the movement if the worm was alive. The results of anthelmintic studies are tabulated in table 5.

RESULTS AND DISCUSSION

All the metal complexes were stable at room temperature and non-hygroscopic in nature. On heating, they decompose at high temperatures. The complexes were insoluble in water but are soluble in organic solvent. The elemental analysis, physical properties, and analytical data of the ligand and complexes were summarized below.

IR spectra

The FT-IR spectrums of all the complexes are similar but strikingly different from the spectrum of the free ligand. In the spectrum (table 2) of ligand (L) Showed a sharp band at 3093 cm^{-1}, attributed to υ (N-H) and weak brad band at 3400 cm^{-1} for υ (O-H) stretching frequency of the aldehyde group of the ligand. The other strong bands belong to the υ (C=N stretching), υ (N-H bending) were absorbed in 1620 and 1571 cm^{-1} respectively. The positions of the absorption band in IR spectra of the complexes are almost similar to that of uncoordinated ligand except the slight shift in the position of υ_{O-H} and $\upsilon_{C=N}$ bands. The band in the range 3100–3128 $cm^{-1}$is assigned to υ_{O-H} of the ligand in the complexes. Thus the IR spectral results provide strong evidence for the complexation of Schiff base with metal ions with bidentate mode.

^{1}H-NMR spectral study of ligand

The ^{1}H NMR spectrum of triazole ligand, showed signal at 11.6 ppm for OH proton; while a singlet at 8.95 ppm and 8.74 ppm are due to triazole ring protons; two aromatic aldehydic protons with multiplets appear at 8.04 and 7.47 ppm another five protons of aromatic ring resonated in the range of 7.29 to 7.27 ppm. As multiples, remaining aldehyde proton showed at 6.82 p. m. and the methylene group protons resonances at 5.29 ppm. The results are in good agreement with the earlier elsewhere reported similar type of ligand [19].

Electronic spectral studies

The electronic spectra of the ligand and all the complexes were recorded in DMF at room temperature. The absorption band of the

ligand appeared at 39215 cm^{-1} is attributed to $\pi \rightarrow \pi^*$ transition. The band around 25575 $cm^{-1}$is due to then $\rightarrow\pi^*$ transition of the non-bonding electrons present on the nitrogen of the azomethine group in the ligand. The $[CoL_2Cl_2]$ showed a less intense band with a shoulder at 16666 and 14925 cm^{-1} assigned as d-d transitions of the Co(II) ions. The former band is probably due to the $^4T_{1g}$ (F) $\rightarrow$ $^4T_{2g}$ (F) (υ_1); $^4T_{1g}$ (F) $\rightarrow$ $^4T_{1g}$ (P) (υ_3). These assignments are in good agreement with the reported value [17]. The $[CoL_2Cl_2]$ is assigned as a tetrahedral geometry; the molar conductivity measurement showed that the complex was non-ionic.

Table 1: IR data of the L and its metal complexes

		FT-IR spectral data(cm^{-1})					
Entry	**Compounds**	**N-H**	**C=N**	**C=N(Ar)**	**O-H**	**C-N**	**Others**
3a	Ligand	3093	1512	1620	3400	1269	
4a	$[CoCl_2L_2]$	3109	1523	1618	3407	1285	M-N = 452 M-O = 512
4b	$[CuCl_2L_2]$	3128	1521	1618	3421	1282	M-N = 480 M-O = 526
4c	$[ZnCl_2L_2]$	3110	1527	1618	3421	1284	M-N = 497 M-O = 522
4d	$[FeCl_3L_2]$	3107	1515	1602	3396	1278	M-N = 464 M-O = 530

Table 2: Physical properties and analytical data of the ligand and their complexes

Entry	**Compounds**	**Mol. wt**	**yield**	**CHN and metal (%) Analysis found (calculated)**				**Ohm/Cm^2/mol**	**D. T (°C)**
				M	**C**	**N**	**H**		
3a	L Dark yellow	278.30	80%	-	69.05	20.13	5.07		135
4a	$[CoCl_2L_2]$ Dark green	686.45	79%	8.59	55.99	16.32	4.11	0.028	220
4b	$[CuCl_2L_2]$ Light green	691.06	84%	9.20	55.62	16.21	4.08	0.011	215
4c	$[ZnCl_2L_2]$ yellow	692.93	87%	9.44	55.47	16.17	4.07	0.012	206
4d	$[FeCl_3L_2]$ black	683.36	79%	8.17	56.24	16.40	4.13	0.043	212

DT= Decomposition temperature

The electronic spectra of the Cu (II) complex showed the broadband at 12820 cm^{-1}due to $^2T_{2g} \rightarrow {}^2E_g$ for Cu(II) complex, On the basis of electronic spectra tetrahedron geometry around Cu(II) ion is suggested. The conductivity measurement showed that the complex was non-electrolytic in nature.

The electronic spectra of the Fe (III) complex showed a strong absorption band at 22471 cm^{-1} and It was not possible to identify the type of the d–d transition, this is due to a strong charge-transfer (CT) band appeared from the UV-region to the visible region. Generally, a tentative interpretation expects the structure of Fe (III) complex is to be tetrahedron geometry; the conductivity measurement showed that the complex was non-ionic, table 2.

In Zn (II) complex do not possess any d-d transitions due to d[10] configuration, the conductivity measurement showed that the complex was non-ionic, and possible geometry of the complex was predicted as a square planar.

Antimicrobial activity

Antibacterial activity carried out by a well diffusion method using the nutrient agar medium, DMSO as control and chloramphenicol is used as a standard bactericide. Antifungal activity was carried out by a well diffusion method using potato dextrose agar (PDA) medium, DMSO as control and fluconazole is used as a standard fungicide [20, 21]. The results of the biological properties of the synthesized compounds are screened for bacterial and fungal strains (tables 3 and 4 respectively).

Table 3: Results of the antibacterial activity–zone of inhibition

Compounds	**Growth Inhibition against bacteria in mm**			**Growth inhibition against fungi in mm**	
	S. aureus	***B. subtilis***	***S. typhi***	***A. niger***	***P. crysogenum***
3a 100 µg/ml	4.0±0.1	1.0±0.0	1.0±0.0	7.0±0.0	3.0±0.0
3a 500 µg/ml	4.1±0.1	1.0±0.0	1.0±0.0	10.0±0.05	4.0±0.1
3a 700 µg/ml	5.0±0.1	2.0±0.0	1.9±0.05	12.9±0.1	6.0±0.05
4a 100 µg/ml	4.0±0.0	8.0±0.05	3.1±0.1	1.0±0.0	7.0±0.0
4a 500 µg/ml	3.9±0.1	10.9±0.05	7.0±0.05	3.9±0.1	9.0±0.0
4a 700 µg/ml	4.1±0.1	13.0±0.0	7.1±0.1	4.0±0.05	10.0±0.05
4b 100 µg/ml	1.0±0.0	8.9±0.05	1.0±0.0	1.0±0.0	8.0±0.05
4b 500 µg/ml	1.9±0.05	11.0±0.05	1.0±0.0	3.0±0.0	9.0±0.0
4b 700 µg/ml	3.9±0.07	11.9±0.05	3.9±0.05	4.9±0.05	10.9±0.05
4c 100 µg/ml	11.9±0.1	1.0±0.0	13.0±0.05	2.0±0.0	3.0±0.05
4c 500 µg/ml	14.0±0.0	3.0±.0.05	10.9±0.05	3.0±0.05	5.0±0.0
4c 700 µg/ml	11.9±0.05	5.0±0.0	10.0±0.0	4.0±0.05	6.0±0.05
4d 100 µg/ml	3.0±0.1	11.0±0.05	1.0±0.0	6.0±0.05	5.0±0.0
4d 500 µg/ml	4.9±0.05	12.9±0.05	2.9±0.05	9.0±0.05	7.0±0.05
4d 700 µg/ml	6.9±0.1	13.9±0.05	5.0±0.0	12.0±0.05	8.0±0.0
Std1.* 100 µg/ml	4.9±0.05	3.9±0.05	3.9±0.05	6.0±0.0	7.0±0.0
Std1.* 500 µg/ml	7.0±0.0	7.0±0.0	6.9±0.05	9.0±0.0	8.0±0.0
Std1.* 700 µg/ml	8.0±0.0	8.0±.0.0	8.0±0.05	10.0±0.0	9.0±0.0
Std2.* 100 µg/ml				7±0.0	7±0.0
Std2.* 500 µg/ml				8±0.0	8±0.0
Std2.* 700 µg/ml				9±0.0	9±0.0

Less than 8 mm-inactive; 10–12 mm-moderately active; above 12 mm-highly active, *#Chloramphenicol,*Fluconazole,* (sample size n-3)

Most of the synthesized compounds showed inhibition property against the strains used. Among the test samples, Co(II), Zn(II) and Fe(III) complexes showed more activity when compared to the standards used. After comparing the zone of inhibition, the selected compounds were checked for their MIC (minimum inhibition concentration) values. The MIC values of less than 30 µg/ml are shown in table 3. It is observed that 4a, 4c, and 4d compounds showed most promising activity. The compounds Co(II) and Fe(III) complexes have been considered as good inhibitors and also shows over inhibition relative to the previously reported compounds [18].

Table 4: Results of the antifungal activity–minimum inhibition concentration

Compound	Conc. (µg ml^{-1})	Growth inhibition against bacteria in mm			Growth inhibition against fungi in mm	
		S. aureus	*B. subtilis*	*S. typlei*	*A. Niger*	*P. Crysogenum*
4a	30 µg/ml	1±0.1	15±0.2	8±0.1	12±0.0	15±0.1
4c	30 µg/ml	14±0.2	08±0.2	13±0.0	08±0.1	11±0.0
4d	30 µg/ml	13±0.1	1±0.2	14±0.1	13±0.0	10±0.1

Less than 8 mm-inactive; 10–12 mm-moderately active; above 12 mm-highly active, (n-3)

Anthelmintic activity

The results of anthelmintic activity of synthesized compounds are collected in table 5. It is clear that all the newly synthesized triazole compounds exhibited more activity than the standard, against the earthworms used. The concentration of test samples and the standard used were 10 mg/ml in DMF. The impact of most of the compounds was more than that of the standard. The results are concluded that the activity of the complex is more potential is may be due to the presence triazole ring.

Table 5: Anthelmintic activity of the legend and their complexes

Compounds	Time in min		
	Pin pinch	Paralysis	Death
3a	24.07±0.1	28.45±0.1	37.26±0.1
4a	12.45±0.2	15.00±0.1	28.34±0.2
4b	17.34±0.0	25.49±0.0	29.05±0.0
4c	21.50±0.1	27.03±0.2	36.00±0.1
4d	11.42±0.1	16.13±0.1	24.05±0.2
Albendazole (Stan.)	18.00±0.2	25.00±0.1	28.20±0.0
DMF	18.30±0.0	32.47±0.0	46.08±0.1

Less than 18 min–highly active; 18–25 min-moderately active; above, 25 mm-inactive, (n-3)

Molecular docking studies

Molecular docking studies were conducted in order to validate the obtained pharmacological data and to provide understandable evidence for the observed antimicrobial activity of all synthesized compounds. Molecular docking study is a well-established technique to determine the interaction of two molecules and find the best orientation of ligand would form a complex with minimum overall energy. All the synthesized compounds were docked Structure of TREX1 in complex with a nucleotide of *S. typhi* at ten different orientations. The structure of the protein mentioned above [PDB: 3B6O] was retrieved from the Protein Data Bank [www. rcsb. org (DOI: 10.2210/pdb3b6o/pdb)] and further modified for docking calculations. The ligand molecules were drawn and analysed using Chem Draw Ultra 8.0. 3D, coordinates were prepared using dock server. It was observed that the most active compound of the series, i.e., Co(II) and Fe(III) was predicted to be a most significant antibacterial activity are also found to have good docking scores as shown in the fig. 1 The acting force of this binding mode mainly depends on hydrogen bonding, electrostatic forces, van der Waals forces and hydrophobic interaction due to non-polar residue interaction and water structure effect alteration. For the receptor, all compounds exhibited more binding interaction energy with a least docking score expect legend compare to the standard and hence compounds may be considered as potential inhibitors of the receptor. Among all compounds docked, the ligand showed comparatively least *E-total value*-177.18 kjmol^{-1} Form the table 5; it can be concluded that all compounds potentially inhibits the receptor.

Table 6: Parameters used for docking study

Correlation type	Shape only
Grid Dimension	0.6
Receptor range	180
Ligand Range	180
Twist range	360
Distance Range	40

Table 7: Docking scores of the synthesized compounds; E-total values in kjmol^{-1}

Compounds	Tyrosine kinase (RTK)
3a	-177.58
4a	-257.47
4b	-250.47
4c	-275.61
4d	-280.17
Standard	-205.28

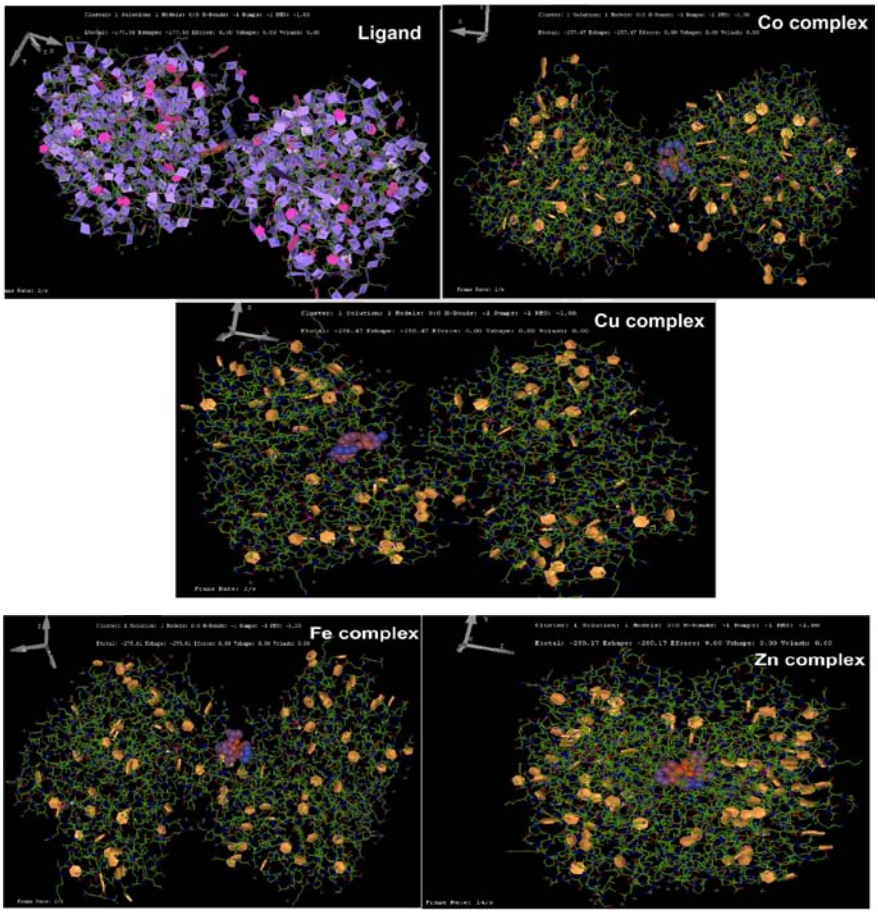


Fig. 1: Docked ligand molecule with secondary structure of the alpha-amylase with a nucleotide from salmonella typhi (PDB ID: 1B6O) in solid model

CONCLUSION

Based on the reported results, it is concluded that the ligand act as bidentate, coordinating through one of the nitrogen atom and the oxygen atom. In the present investigations, all the complexes are found to be mononuclear, based on spectral evidence possible geometry of the synthesized compounds are predicted. The antimicrobial activity results indicated that some of the tested compounds showed the most promising antibacterial and antifungal activities. These observations may promote a further development of our research in this field. Further development of this group of compounds may lead to better pharmacological profile than standard drugs and serve as templates for the construction of better drugs to combat bacterial and fungal infection. After studying the docking poses and binding modes of the docked compounds, the necessity of hydrogen bond formation for enhancing the activity of this class of compounds can be highly advocated.

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CONFLICT OF INTERESTS

Declared none

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