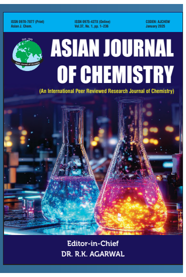
Asian Journal of Chemistry; Vol. 37, No. 5 (2025), 1060-1068

ASIAN JOURNAL OF CHEMISTRY

https://doi.org/10.14233/ajchem.2025.32495



Newly Fabricated Thiobarbiturate Mannich Base Derived Metal Complexes and its Larvicidal, Antifeedant and Molecular Docking Studies

Devaraj Kavitha[1,2], Velayutham Gurunathan[3], Karumalaiyan Palanisamy[4] and Sangilimuthu Aruna Devi[1,*]

[1]PG & Research Department of Chemistry, Urumu Dhanalakshmi College (Affiliated to Bharathidasan University), Tiruchirappalli-620019, India
[2]PG and Research Department of Chemistry, Government Arts College (Affiliated to Bharathidasan University), Ariyalur-621713, India
[3]Department of Chemistry, Bishop Heber College (Affiliated to Bharathidasan University), Tiruchirappalli-620017, India
[4]Department of Chemistry, School of Science and Technology, Dhanalakshmi Srinivasan University, Perambalur-621212, India

*Corresponding author: E-mail: aruna07ravi@gmail.com; karupalani106@gmail.com

Received: 13 October 2024; *Accepted*: 20 March 2025; *Published online*: 30 April 2025; AJC-21970

Inorganic elements are essential in ecological therapies and it is clear that numerous organic substances utilized in healthcare do not operate only through organic mechanisms; a few are triggered or biotransformed by the metabolism of metal ions. The chemistry of Mannich bases and its metal complex counterparts has garnered considerable attention owing to its diverse uses. The primary aim of this article is to report the synthesis of Mannich-base and its chelating properties with various metal chlorides including Cu(II), Ni(II), Co(II), Fe(II) and Mn(II). The novel Mannich base ligand, 5-(hydrazinyl(2-hydroxyphenyl)methyl)-2-thioxodihydropyrimidine-4,6(1*H*,5*H*)-dione, was synthesized through the reaction of thiobarbituric acid, salicylaldehyde and hydrazine hydrate. The ligand and its metal(II) complexes were characterized through analytical and spectral techniques including nuclear magnetic resonance spectroscopy (^{1}H NMR and ^{13}C NMR), electron paramagnetic resonance spectroscopy (EPR), ultraviolet and visible spectroscopy (UV-Vis) and Fourier transform infrared spectroscopy (FT-IR). The ligand and its metal(II) complexes were screened for their larvicidal efficacy towards the south-urban mosquito larvae *Culex quinquefasciatus* and assessed for toxicity towards non-target aquatic organisms. The copper(II) complex demonstrated significant larvicidal activity (LC_{50} = 20.83 μg/mL) than free ligand and control permethrin.

Keywords: Antifeedant, *Culex quinquefasciatus*, Larvicidal activity, Mannich base, Metal complexes, Molecular docking.

INTRODUCTION

Mosquitoes, responsible for transmitting several illnesses including dengue (*Aedes aegypti*), filariasis (*Culex*, *Mansonia*) and malaria (*Anopheles*), result in millions of fatalities annually and are the most significant category of invertebrates concerning the well-being of humanity [1]. *Anopheles stephensi* serves as a principal vector for malaria in India. Approximately 40% of the global population resides in regions where malaria is common [2,3]. *Culex quinquesfasciatus* is a possible vector for *Wuchereria bancrofti*, the causing organism of filariasis, which infects about 130 million individuals globally [4]. The strategy to tackle these diseases mostly depended on disrupting the process of transmission through either treating mosquito larvae with the application of pesticides to stagnant water locations or by exterminating adult mosquitoes with insecticide. In past few years, mosquito control programs have experienced setbacks due to heightened pesticide resistance [5]. In addition to insect repellent resistance, the repetitive application of synthetic pesticides for controlling mosquitoes has damaged native ecosystems. It has also produced adverse impacts on non-target creatures. Consequently, it is essential to explore alternate vector-control strategies that may be more environmentally benign and targeted in their efficacy [6].

Mannich base synthesis involves the condensation reaction that involves a compound containing at least one active hydrogen atom, ammonia and formaldehyde. Secondary amines are employed as synthetic substances in the synthesis of numerous medicinal compounds including trihexylphenidyl hydrochloride as an antispasmodic, ranitidine, triprolidine as an H-receptor antagonist, benzoquinamide as a high psychotic drugs, ethacrynic acid as a high-ceiling loop diuretic and fluoxetine as an anti-depressant [7]. Mannich bases exhibit physiological reactivity due to their basic functionality, which enhances solubility in aqueous solvents upon conversion to salts of ammonium [8]. In recent years, Mannich base analogues of heterocyclic compounds have attracted the interest of researchers due to its extensive range of biotic uses, including antimalarial, anti-Parkinson, anti-HIV, analgesic, anticonvulsant, antispasmodic, anticancer, antibacterial properties, as well as serving as intermediates in drugs synthesis [9-11]. The Mannich base metal complexes enhance the efficacy of its ligands in therapeutic uses, including antitumor, antioxidants, antimalarial, antiviral, anticonvulsant, anticancer, antimicrobial, anti-inflammatory, anti-HIV activities as well as in industrial uses that include polymer production, detergents, resins and surfactants [12-20].

The present study focused on the complexation of a novel Mannich base synthesized from thiobarbituric acid, salicylaldehyde and hydrazine hydrate with various metal(II) chlorides. The larvicidal efficacy of Mannich base ligand and their corresponding metal complexes was assessed towards 4th instar mosquito larvae, along with toxicity evaluations on non-target aquatic organisms. Molecular docking experiments were also performed to elucidate the mechanism of action of the synthesized larvicides.

EXPERIMENTAL

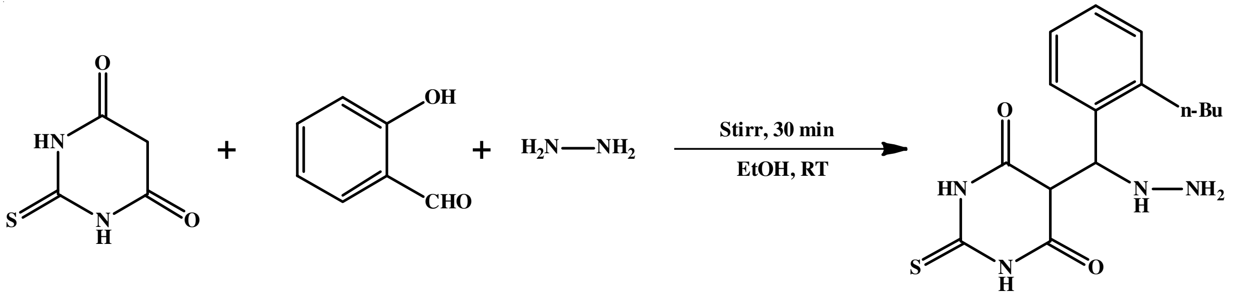
All the chemicals were obtained from the commercial suppliers and used without further purification. The melting points were evaluated through an electrothermal Stuart apparatus, type SMP40 and are uncorrected. The NMR spectra (^{1}H and ^{13}C) of Mannich base ligand were acquired in $CDCl_3$ utilizing a Bruker spectrometer (400 MHz for ^{1}H and 75 MHz for ^{13}C), with tetramethylsilane (TMS) as the reference substance. The FT-IR spectra were acquired *via* KBr and CsI discs within a 4000-400 cm^{-1} region on a Shimadzu FT-IR spectroscopy (FTIR-600). The mass spectra of Mannich base ligand was examined with a Sciex ESI mass spectrometer. The UV-Vis spectra were acquired utilizing a Shimadzu UV-160 across the wavelength range of 800-200 nm, with concentrations of the samples of 10^{-3} to 10^{-5} mol L^{-1} in DMSO solution. Molar conductivity of the metal(II) complexes were performed at ambient temperature for 10^{-3} M concentrations in DMSO using a digital conductivity meter, Eutech Device Cyber Scan Con 510. The magnetic moments at 306 K were evaluated with a magnetic susceptibility balance from Johnson Matthey India Pvt. Ltd., India.

Synthesis of Mannich base ligand (L1): A clear solution was prepared in a round-bottom flask through the combination of thiobarbituric acid (2.24 g, 0.02 mol), hydrazine hydrate (0.6 mL, 0.02 mol) and salicylaldehyde (2.4 mL, 0.02 mol) in ethanol. At ambient temperature, the round bottom flask was positioned in a magnetic stirrer and agitated at 1000 rpm for approximately 30 min. The progression of the reaction was assessed utilizing thin-layer chromatography (TLC). The resulting mixture was immersed in crushed ice, followed by the filtration and drying of the obtained yellow solid (**Scheme-I**). The crude product underwent purification *via* recrystallization with hot ethanol.

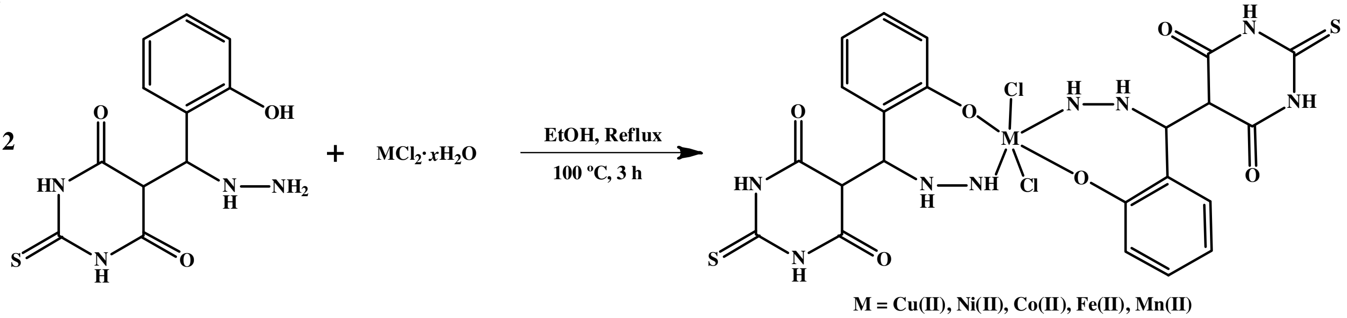
5-(Hydrazinyl(2-hydroxyphenyl)methyl)-2-thioxodihydropyrimidine-4,6-(1*H*,5*H*)-dione (L1): Red solid; *m.w.*: 280.30; m.p.: 220 ºC; IR (KBr, ν_{max}, cm^{-1}): 3436 (OH), 3076 (NH), 2950 ($Ph_{str.}$), 1641 (C=O), 1373 (C=S); ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm: 10.84 (s, 1H, OH), 9.86 (s, 1H, NH), 8.20 (s, 2H, NH), 7.35-6.72 (m, 4H, Ph-OH), 5.34 (s, 2H, NH_2), 4.58 (s, 1H, -CH-Ph), 3.82 (s, 1H, CH-CH-NH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm: 183.0 (1C, C=S), 176.0 (2C, C=O), 152.0, 138.2, 127.4, 120.0, 116.2 (6C, Ph ring), 56.0 (1C, CH-CH-Ph), 47.2 (1C, CH-Ph); EI-MS: *m/z* 281.06 (M^+, 16%); Elemental analysis: Anal. calcd. (found) % for $C_{11}H_{12}N_4O_3S$: C, 47.13 (47.10); H, 4.32 (4.34); N, 19.99 (19.96).

Synthesis of metal(II) complexes: Mannich based metal(II) complexes having formula $[M(L1)_2Cl_2]$ (M = Ni^{2+}, Cu^{2+}, Mn^{2+}, Fe^{2+} and Co^{2+}] were synthesized by mixing a solution of metal precursor $MCl_2{\cdot}H_2O$ (1 mmol, 1 equiv.) in 10 mL of ethanol to an ethanolic solution of **L1** (2.0 mmol). The reaction mixture was agitated and subjected to reflux in an oil bath for a period of 3 h. The resulting suspension, which produced a solid precipitate, underwent filtering, was rinsed with ethanol and dried under vacuum to separate the metal(II) complex (**Scheme-II**). The metal(II) complexes were purified using column chromatography employing an eluent consisting of DCM: CH_3CN:CH_3OH (2:3:5 v/v/v) over silica gel.

Mosquito larvicidal effect: The larvicidal effects were assessed using a binary alive/dead approach. Inspections were done on a scale from 0 to 100, with 0 indicating no action and 100 denoting total mortality. The larvicidal effectiveness of Mannich base ligand and its metal(II) complexes was evaluated at dosages of 100, 75, 50 and 25 µg/mL towards 4th instar *C. quinquefasciatus* utilising the water immersion technique, under settings of relative humidity ranging from 50-70%, a photoperiod of 14:10 (dark:light) and at room temperature [21]. All test vessels containing 20 *C. quinquefasciatus* larvae were



Scheme-I: Synthesis of Mannich base ligand (L1)



Scheme-II: Synthesis of metal complexes

assessed 24 h post-administration and the results were documented as mean percentage mortality. The larvicidal assessment was performed three times and the bioactivity outcome was the average among these duplicates. The commercial pesticide permethrin was assessed as a control component under uniform settings. The LC_{50} values for particular active compounds were evaluated through the statistical package SPSS version 16.0.

Antifeedant activity: The harmful effects of Mannich base ligand and its metal(II) complexes was evaluated through antifeedant testing by following the reported method with slight changes [22]. Aquatic-adapted *Oreochromis mossambicus*, measuring 1.5-2.0 cm, were employed to evaluate antifeedant activity. Ten fishes were placed in testing and normal glassware vessels each containing 1 L of saltwater and a sufficient quantity of compound. Changes in responses and mortality were observed promptly. After a 24 h exposure period, changes in responses and mortality were observed promptly.

Molecular docking methods

Ligand and protein preparation: The Mannich base ligand, its metal(II) complexes and control permethrin were constructed using ChemDraw Ultra 12.0 and their energy was minimized with Chem3D Pro 12.0 software. The resultant structures were preserved in PDB format for docking assessment. The Mannich base and its metal(II) complexes are referred to as ligands in the setting of docking procedure. The protein databank of the Research Collaboratory for Structural Bioinformatics (RCSB) at https://www.rcsb.org/ to acquire the crystal structures of proteins linked to the specific experimental biological studies. The mosquito OBP structure (PDB ID: 3OGN) was employed for the larvicidal experiment. In the crystal structure, one protein chain was selected and retained as a candidate for docking, while water molecules, heteroatoms, separate ligands and further chains were eliminated. Simultaneously, the co-crystallized ligand within the target protein was allocated for a reserve of under 5 Å. The arrangement of amino acids inside this region was documented and regarded as the extent of the binding cavity for an inhibitory action.

Docking procedure: The docking trials were conducted utilizing the Autodock Vina simulation screening program [23]. The protein structure (receptor) was first input into Vina and then converted into a macromolecule by translating it into a PDB format with partial charge (q) and atom type (t) (pdbqt) for docking purposes. The grid box for the 3OGN receptor was established at centre coordinates (x,y,z): 18.681, 49.66 and 11.409, alongside the following dimensions: size_x: 22, size_y: 20 and size_z: 22. The grid has a consistent spacing of 1.0 Å between each point. A numeric value of 8 has been assi-gned to the exhaustiveness score. The additional constraints were established to their default configurations and were not specifically delineated. The compound with the lowest binding score is considered to possess the greatest activity. The docking results were visually evaluated using the Discovery Studio Visualiser.

RESULTS AND DISCUSSION

The solubility and physico-chemical results of the Mannich base ligand and its corresponding complexes are presented in Table-1. The solubility investigations demonstrate that both the metal(II) complexes and Mannich base ligand the display enhanced solubility in aprotic solvents compared to protic solvents.

NMR spectral studies of Mannich base ligand: The peak at δ 9.88 ppm belongs to the -NH protons of the thiobarbituric acid moiety. The protons of the phenyl ring exhibit a multiplet at δ 7.12-6.90 ppm. The $-CH_2$ protons linked to the amine hydrogen atoms of hydrazine and salicylaldehyde are observed as a signal at 4.58 ppm, while the aromatic –OH resonated at δ 10.84 ppm. The absence of a peak for the proton of secondary amine $–NH_2$, which was eliminated during the Mannich base

TABLE-1
PHYSICAL DATA AND SOLUBILITY OF THE METAL COMPLEXES MANNICH BASE AND LIGAND (L1)

Compound	Colour	m.p. (°C)	Solubility			
			Water	Ethanol	Chloroform	DMSO
Ligand (L1)	Red	220	Insoluble	Soluble	Sparingly soluble	Soluble
Copper(II) complex	Purple	184	Insoluble	Soluble	Insoluble	Soluble
Nickel(II) complex	Red	162	Insoluble	Soluble	Insoluble	Soluble
Cobalt(II) complex	Pink	203	Insoluble	Soluble	Insoluble	Soluble
Iron(II) complex	Brown	172	Insoluble	Soluble	Insoluble	Soluble
Manganese(II) complex	Black	238	Insoluble	Soluble	Insoluble	Soluble

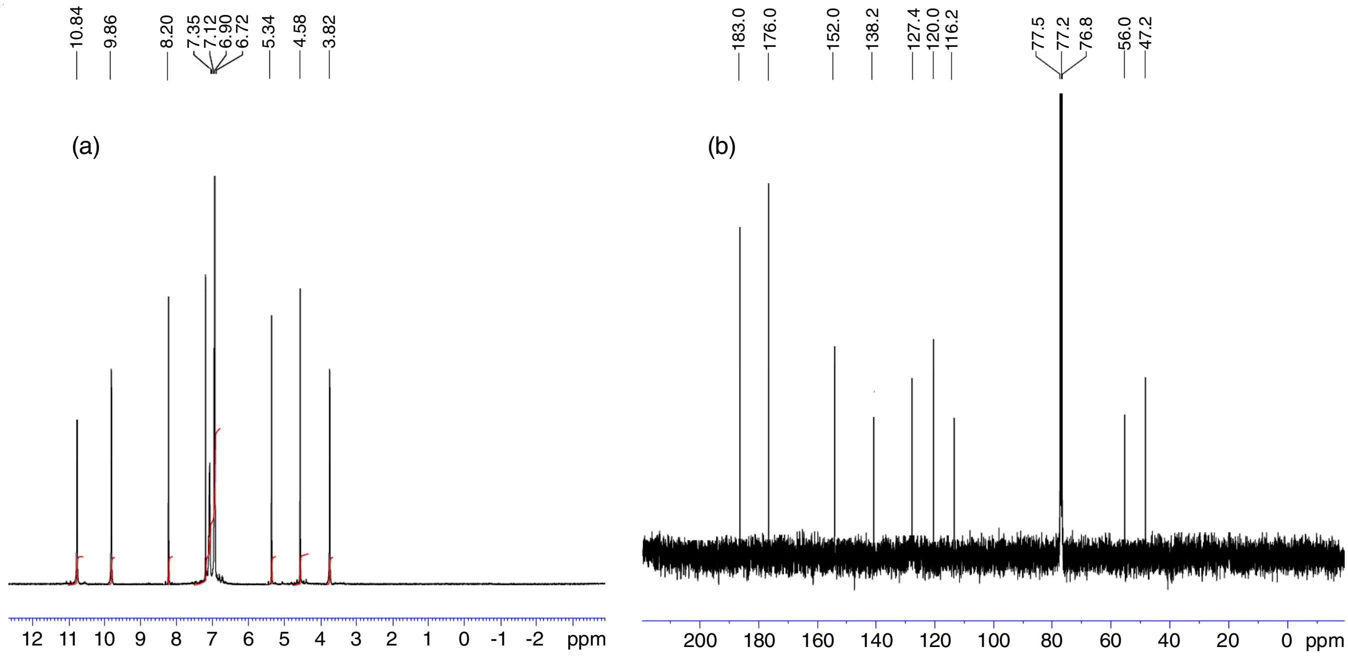


Fig. 1. (a) ^{1}H NMR and (b) ^{13}C NMR spectra of ligand (L1)

synthesis, further confirmed the synthesis of the ligand. The carbon atoms of the phenyl ring exhibited signals around δ 153.0-116.2 ppm. The presence of a peak at δ 47.2 ppm indicates that the -CH$_2$ group is attached to the amine hydrogens of hydrazine and salicylaldehyde. The peaks at δ 183.0 and 176.0 ppm responsible to the thiocarbonyl and carbonyl carbons of the thiobarbituric acid moiety, respectively. The ^{1}H and ^{13}C NMR spectra of the Mannich base ligand (**L1**) are obtainable in Fig. 1.

Mass spectral studies of Mannich base ligand: The mass spectrum of Mannich base ligand exhibited distinct peaks at molecular weights that corresponded closely with the theoretically predicted values. The molecular weight of ligand was empirically ascertained to be 280.30, a finding validated by mass spectrum analysis revealing a mass-to-charge ratio (*m/z*) of 281.06 (Fig. 2). The molecular ion peak was detected at a *m/z* value of 243.03.

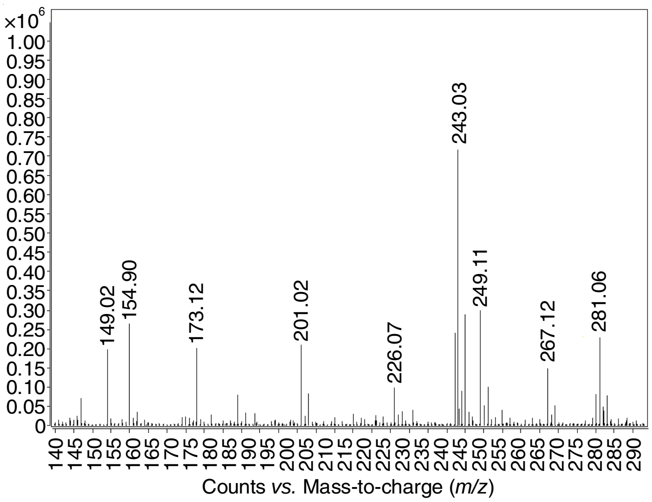


Fig. 2. Mass spectra of ligand (L1)

Conductivity and magnetic susceptibility measurements: The non-electrolytic nature of the metal(II) complexes were verified by evaluating the conductivity in 10^{-3} M DMSO solvent. The metal(II) complexes demonstrated a molar conductance ranging from 13 to 25 Ω^{-1} mol^{-1} cm^{2}. The conductivity results indicated that chloride ions exhibit a tendency to combine with metal ions, implying they function as ligand instead of as independent ions. The configuration of the synthesized complexes may be affected by the metal-ligand ratio (1:2) and the types of electrolytes utilized in the conductance assessment. The magnetic moment of the complexes of Fe(II), Ni(II), Mn(II) and Co(II) exhibits a high-spin octahedral configuration. The lower magnetic moment of the Cu(II) complex signifies a low-spin distorted octahedral geometry. Table-2 presents the electrical conductivity and magnetic characteristics of the metal(II) complexes.

TABLE-2
CONDUCTANCE AND MAGNETIC PROPERTIES
OF METAL COMPLEXES WITH LIGAND (L1)

Compounds	Conductance (Ω^{-1} mol^{-1} cm^{2})	Magnetic susceptibility (μ_{eff}, B.M.)
Copper(II) complex	13	2.18
Nickel(II) complex	24	3.23
Cobalt(II) complex	22	5.42
Iron(II) complex	25	4.65
Manganese(II) complex	21	5.30

IR spectra: A significant observation in the FT-IR spectrum of Mannich base ligand confirmed the presence of the distinct bands at 3435 and 3163 cm^{-1}, which signifies to the νOH and NH amine moieties, respectively. A shift in frequencies was observed in the N-H and O-H bands in all the metal(II) complexes, indicating the involvement of hydroxyl oxygen and amine nitrogen in coordination with the metal ions. The bands at 1638 and 1240 cm^{-1} in the FT-IR spectrum of ligand demonstrated the presence of carbonyl and thiocarbonyl moieties. The absence of alterations in the carbonyl and thiocarbonyl regions in the FT-IR spectra of metal(II) complexes indicates that the carbonyl and thiocarbonyl moieties do not coordinate with metal ions. The existence of peaks at 783-753 cm^{-1} confirmed the existence of M-N bonds. The presence of discrete peaks at 640-598 cm^{-1} linked to the M-O bond, indicates the production of metal(II) complexes. The M-Cl bond is characterized by a prominent peak within the spectral range of 488-468 cm^{-1}. Table-3 displays the key FT-IR spectral data of the Mannich base ligand and its metal(II) complexes.

UV-visible spectra: The UV-Vis spectrum of Mannich base ligand exhibited two distinct peaks at 275 and 237 nm, attributed to n→π* and π→π* shifts, respectively (Fig. 3a). The spectra of the metal(II) complexes in DMSO exhibited three distinct peaks. Intra-ligand alterations were identified by two distinct bands observed at 218-261 nm and 310-331 nm. The molecule was confirmed by the peak observed at 424-459 nm, consistent with ligand-to-metal charge transfer (LMCT) transformations (Fig. 3b-f).

EPR spectra: The presence of an unpaired electron in the $d_{x^2-y^2}$ orbital of copper(II) complex is confirmed by the observation that the parallel g-value ($g_{\parallel}$) exceeds the perpendicular g-value ($g_{\perp}$), which is greater than 2.0023. The $g_{\parallel}$ and $g_{\perp}$ values for the copper complex have been reported as 2.2836 and 2.0735, respectively. An ionic character is denoted by a $g_{\parallel}$ value over 2.3, while a covalent character is represented by a $g_{\parallel}$ value below 2.3. The $g_{\parallel}$ value (2.2836) is definitely below 2.3, indicating that the copper(II) complex is covalent. Hathaway [24] suggests that G values below four indicate considerable interaction between metal centers, whereas G values exceeding four imply minimal charge transfer. In this case, the G value is 3.43, indicating that the exchange contact is substantial. The Cu(II) complex exhibits a deformed octahedral geometry, as indicated by its EPR characteristics (Fig. 4).

Larvicidal activity: The Mannich base ligand and its metal(II) complexes were assessed for larvicidal effectiveness towards 4th instar *C. quinquefasciatus* larvae. The Mannich base ligand demonstrated significant larvicidal effectiveness, with an LC_{50} value of 45.80 µg/mL, compared to the control permethrin, which had an LC_{50} value of 38.73 µg/mL. While

TABLE-3
FT-IR SPECTRAL INFORMATION OF THE LIGAND (L1) AND THE COMPLEXES

Compound	IR stretching frequency (cm^{-1})						
	ν(-OH)	ν(-NH)	ν(>C=O)	ν(>C=S)	ν(M-N)	ν(M-O)	ν(M-Cl)
Ligand (L1)	3436	3076	1641	1373	–	–	–
Copper(II) complex	3450	3080	1641	1374	758	642	493
Nickel(II) complex	3449	3084	1641	1375	760	640	490
Cobalt(II) complex	3442	3082	1641	1375	759	645	493
Iron(II) complex	3440	3087	1641	1374	774	643	494
Manganese(II) complex	3429	3064	1641	1375	759	648	498

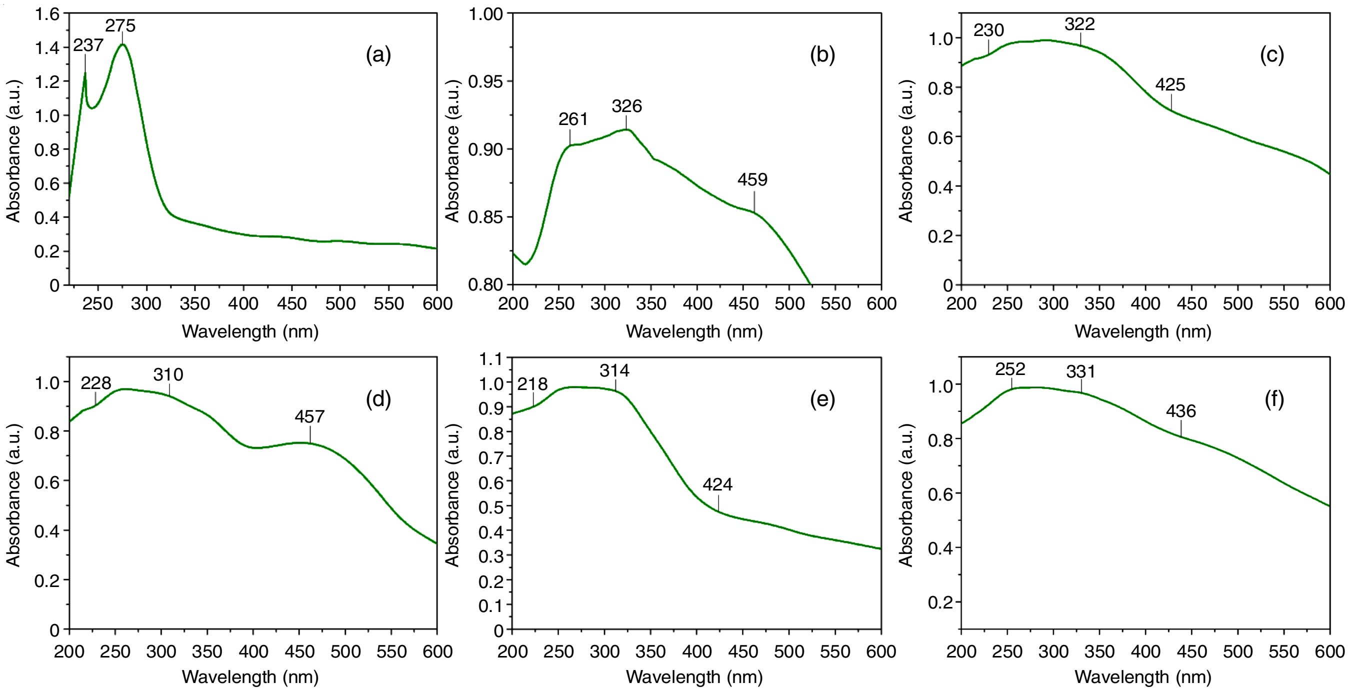


Fig. 3. UV-Visible spectrum of (a) ligand L1, (b) copper(II) complex, (c) nickel(II) complex, (d) cobalt(II) complex, (e) iron(II) complex and (f) manganese(II) complex

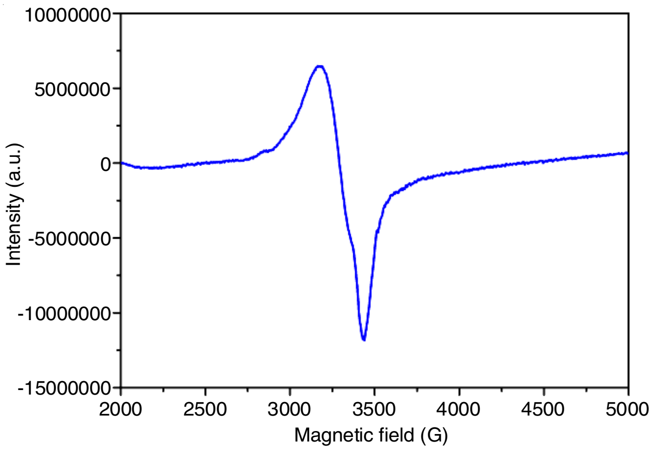


Fig. 4. EPR spectra copper(II) complex

the metal(II) complexes shown enhanced larvicidal efficacy in comparison to Mannich base ligand (Table-4). The reason is due to the fact that the larvicidal effectiveness of the unbound ligand was improved by complexation with metal ions. Amongst the synthesized complexes, the copper complex demonstrated enhanced larvicidal activity (LC_{50} = 20.83 µg/mL) relative to the Mannich base ligand (LC_{50} = 45.80 µg/mL) and the standard permethrin (LC_{50} = 38.73 µg/mL). Whereas the cobalt(II) and manganese(II) complexes had significant larvicidal efficacy, with LC_{50} values of 27.77 and 33.70 µg/mL than control permethrin (LC_{50} = 38.73 µg/mL). The nickel(II) and iron(II) complexes demonstrated moderate larvicidal efficacy, having LC_{50} values of 55.35 and 38.33 µg/mL, respectively, in comparison to the control permethrin (LC_{50} = 38.73 µg/mL).

Antifeedant activity (Ichthyotoxicity activity): The harmful impacts of the Mannich base ligand and its metal(II) complexes were assessed utilizing the marine fish, *O. mossambicus*. The synthesized Mannich base ligand demonstrated more toxicity over its metal(II) complexes. The adverse impacts of the uncoordinated ligand was minimized upon complexation with metal ions. The significant larvicidal activity of metal(II) complexes (**1**, **3**, **5**) demonstrated lower toxicities in non-target aquatic organisms (*O. mossambicus*) and each had an LC_{50} value over 100 µg/mL. The moderate larvicidal activity of metal(II) complexes (**2** & **4**) displayed higher toxicities (LC_{50} = 57.83 and 61.22 µg/mL) to non-target aquatic organisms, while exhibiting reduced toxicity compared to the free ligand (LC_{50} = 45.79 µg/mL). The findings are presented in Table-5.

Docking studies: The docking studies of the Mannich base ligand, metal(II) complexes and the control permethrin were analyzed using the 3OGN protein and the AutoDock Vina modelling tool. The Mannich base ligand showed lower larvicidal effectiveness, possessing a binding score of -4.6 kcal/mol, in contrast to its respective metal(II) complexes and the conventional permethrin, which exhibited a binding score of -7.6 kcal/mol. The Mannich base ligand coordinates two hydrogen bonds with the protein 3OGN. The two amino acid residues Ser79 (bond length: 3.03 Å) and Phe123 (bond length: 2.85 Å) engaged in hydrogen bonding interactions. The amino acid residues Leu76, Met91 and Trp114 engaged in hydrophobic contacts. The copper(II) complex demonstrated greater larvicidal activity, with a binding score of -9.4 kcal/mol, exceeding the scores of the other complexes and the control permethrin, which recorded a binding score of -7.6 kcal/mol. The copper(II) complex created a hydrogen bond interaction with the 3OGN protein. The amino acid residue Ala62 (bond length: 2.50 Å) engaged in hydrogen bonding interactions. The amino acid residues Ala18, Leu22 and Ser79 engaged in hydrophobic contacts. The conventional permethrin had significant larvicidal activity, with a binding score of -7.6 kcal/mol, above that of Mannich base ligand at -4.6 kcal/mol, the nickel(II) complex at -6.2 kcal/mol and the iron(II) complex at -6.3 kcal/mol. The standard permethrin

TABLE-4
LARVICIDAL EFFECT OF MANNICH BASE LIGAND (L1) AND METAL COMPLEXES

Compounds	Concentration (µg/mL)/Mortality (%)				LC_{50} (µg/mL)
	100	75	50	25	
Ligand (L1)	83 ± 1.23	70 ± 0.63	56 ± 1.21	34 ± 0.32	45.80
Copper(II) complex	90 ± 1.36	74 ± 0.52	62 ± 1.36	54 ± 0.74	20.83
Nickel(II) complex	74 ± 1.35	60 ± 0.62	52 ± 1.45	30 ± 0.45	55.35
Cobalt(II) complex	80 ± 0.40	72 ± 1.34	60 ± 0.63	48 ± 1.26	27.77
Iron(II) complex	86 ± 0.34	72 ± 1.40	60 ± 0.32	40 ± 1.12	38.33
Manganese(II) complex	100 ± 0.00	78 ± 1.28	56 ± 0.74	48 ± 1.62	33.70
Permethrin	100 ± 0.00	82 ± 0.65	64 ± 1.28	32 ± 0.38	38.73

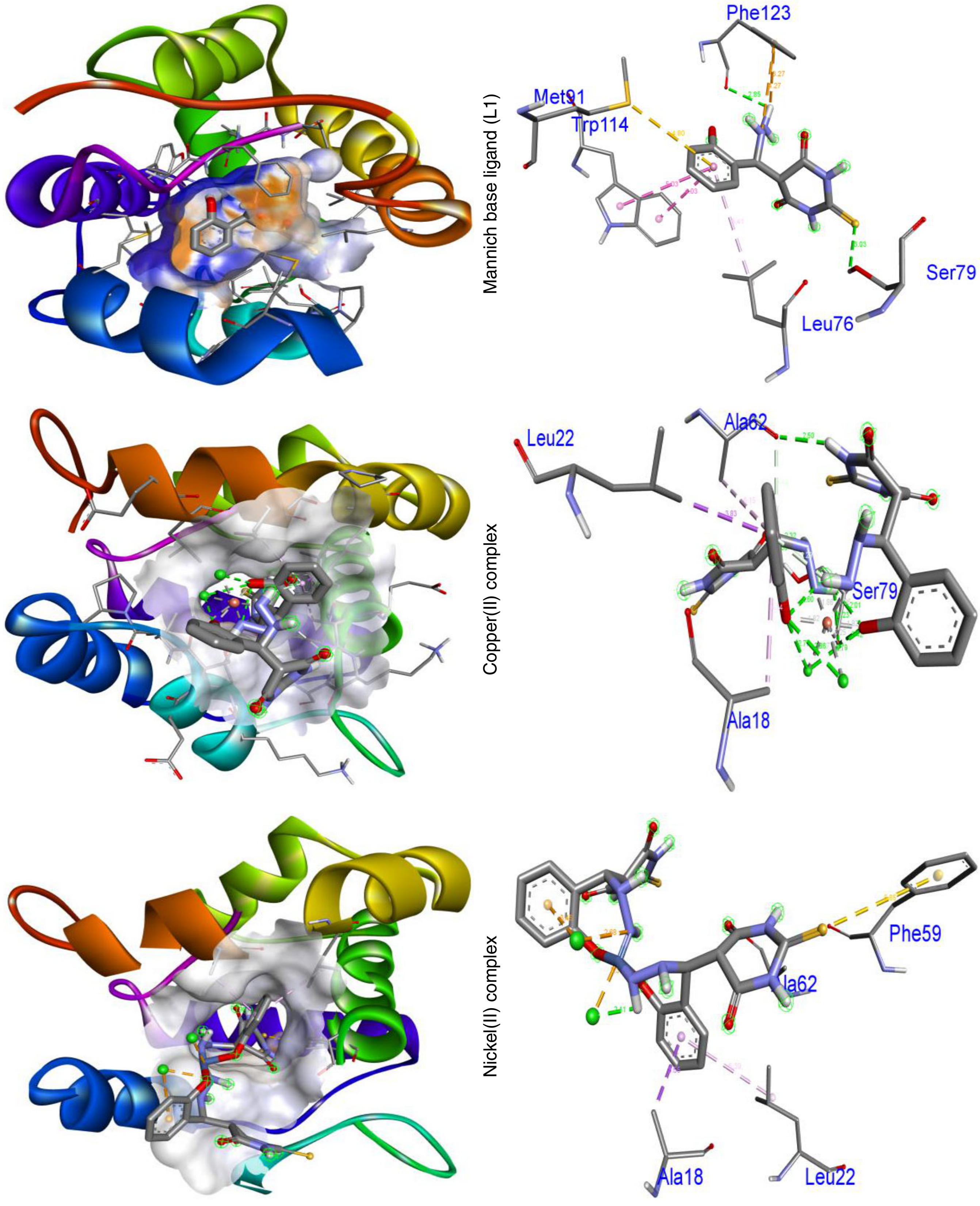
[a]Values are the means of three replicates ± SD.

TABLE-5
ANTIFEEDANT EFFECT OF MANNICH BASE LIGAND (L1) AND METAL COMPLEXES

Compounds	Concentration (µg/mL)/Mortality (%)				LC_{50} (µg/mL)
	100	75	50	25	
Ligand (L1)	92 ± 1.32	74 ± 0.46	58 ± 1.23	30 ± 0.56	45.79
Copper(II) complex	42 ± 0.42	26 ± 1.25	12 ± 0.34	0 ± 0.00	>100
Nickel(II) complex	86 ± 1.36	60 ± 0.74	45 ± 1.26	24 ± 1.36	57.83
Cobalt(II) complex	46 ± 0.72	30 ± 1.58	20 ± 0.64	10 ± 0.28	>100
Iron(II) complex	80 ± 1.62	64 ± 0.48	36 ± 1.52	24 ± 1.73	61.22
Manganese(II) complex	48 ± 0.16	32 ± 1.83	16 ± 0.48	10 ± 0.65	>100

[a]Values are the means of three replicates ± SD.

failed to create any hydrogen bond connections with the 3OGN receptor; however, the amino acid residues Leu124, Leu19, Phe123, Leu73, Leu80, Leu76, Met89, His77, His111, Ala88, Gly92, Trp114, Phe59 and Leu15 engaged in the hydrophobic interactions (Table-6). Fig. 5 exhibits the interactions of the Mannich base ligand, metal(II) complexes and the control permethrin with the 3OGN receptor. The results demonstrated that copper(II) complex inhibited the activity of odorant-binding protein 3OGN in *C. quinquefasciatus* more effectively than the other complexes, free ligand and control permethrin.



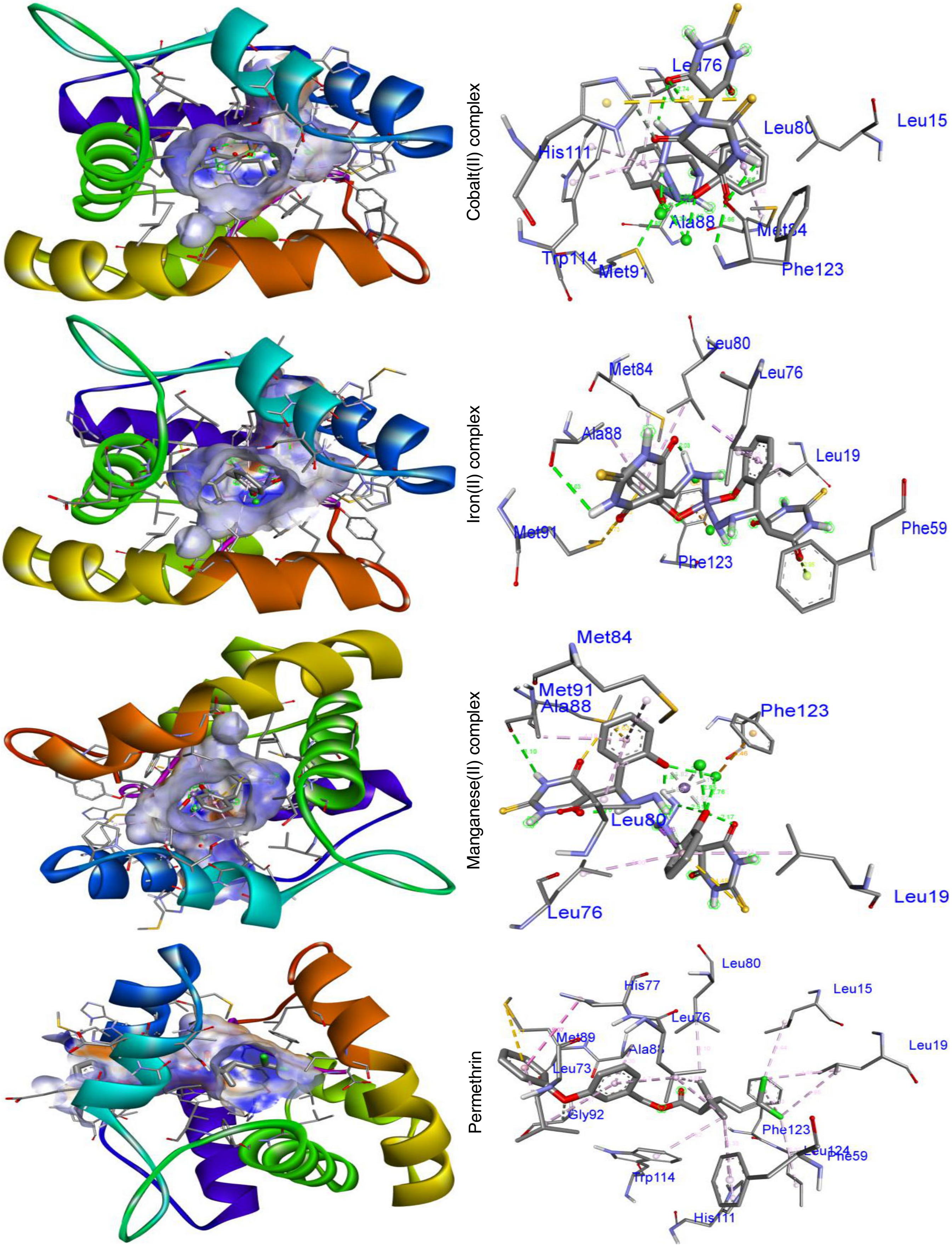


Fig. 5. Interaction modes of Mannich base ligand (L1), copper(II) complex, nickel(II) complex, cobalt(II) complex, iron(II) complex, manganese(II) complex and standard permethrin inside the binding cavity of 3OGN receptor

TABLE-6
MOLECULAR DOCKING INTERACTION OF LIGAND (L1), METAL COMPLEXES AND CONTROL PERMETHRIN TOWARDS OBP OF 3OGN

Compounds	Mosquito OBP of 3OGN		
	Binding score (kcal/mol)	Number of H-bonds	H-bonding residues (bond length)
Mannich base ligand (L1)	-4.6	2	Ser79 (3.03 Å), Phe123 (2.85 Å)
Copper(II) complex	-9.4	1	Ala62 (2.50 Å)
Nickel(II) complex	-6.2	-	–
Cobalt(II) complex	-7.8	1	Phe123 (2.58 & 2.66 Å)
Iron(II) complex	-6.3	1	Ala88 (3.03 Å)
Manganese(II) complex	-8.5	1	Ala88 (3.10 Å)
Permethrin	-7.6	-	–

Conclusion

The Mannich base ligand was synthesized by condensing thiobarbituric acid with salicylaldehyde and hydrazine hydrate and its complexation properties with the metals Cu(II), Ni(II), Co(II), Fe(II) and Mn(II) were evaluated. The synthesized ligand and its corresponding metal(II) complexes have been examined using spectroscopic, analytical and magnetic data. The ligand coordinates to the metal ion *via* the nitrogen atom of hydrazine hydrate and the oxygen of salicylaldehyde, acting as a neutral bidentate ligand. All the synthesized metal(II) complexes exhibited octahedral geometry. The biological effects of Mannich base and their metal(II) complexes on *Culex quinquefasciatus* mosquito larvae and their toxicity to non-target aquatic organisms. The data indicated that the metal(II) complexes of Mannich base exert advantageous effects on the larval stage of *Culex quinquefasciatus*. The most efficacious substances were Cu(II) complex, followed by Co(II) and Mn(II) complexes. The Cu(II) complex displayed potent larvicidal efficacy while showing less toxicity to non-target aquatic species, particularly marine fish. The complexes mode of action and the prediction of their efficient receptor binding were established by molecular docking techniques. These findings may inspire researchers to seek novel active compounds that could serve as viable alternatives to current insecticides.

ACKNOWLEDGEMENTS

The authors acknowledge their respective managments for providing the opportunity to accomplish this research work.

CONFLICT OF INTEREST

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

REFERENCES

1. O. Dutta, A. Prasanth, A. Kumari, K. Akanksha, F. Deeba and N. Salam, *PLoS One*, **18**, e0292723 (2023); https://doi.org/10.1371/journal.pone.0292723
2. S. Singh, R. Marwal, S. Lata, P. Saroha, S.K. Gupta and H. Singh, *PLoS One*, **20**, e0313227 (2025); https://doi.org/10.1371/journal.pone.0313227
3. Q. Liu, M. Wang, Y.-T. Du, J.-W. Xie, Z.-G. Yin, J.-H. Cai, T.-Y. Zhao and H.-D. Zhang, *BMC Infect. Dis.*, **24**, 333 (2024); https://doi.org/10.1186/s12879-024-09213-3
4. A. Sinha, S. Kumar, D. Dayal, V. Yadav, A. Pramanik, K.K. Chaubey, and S. Kumar, *Asian Pacific J. Trop. Med.*, **16**, 385 (2023); https://doi.org/10.4103/1995-7645.380729
5. G.P. Georghiou, *Phytoprotection*, **75**, 51 (1994); https://doi.org/10.7202/706071ar
6. J.R. Coats, *Annu. Rev. Entomol.*, **39**, 489 (1994); https://doi.org/10.1146/annurev.en.39.010194.002421
7. K.L. Hanson, B.M. VandenBrink, K.N. Babu, K.E. Allen, W.L. Nelson and K.L. Kunze, *Drug Metab. Dispos.*, **38**, 963 (2010); https://doi.org/10.1124/dmd.110.032391
8. K.C. Achar, K.M. Hosamani and H.R. Seetharamareddy, *Eur. J. Med. Chem.*, **45**, 2048 (2010); https://doi.org/10.1016/j.ejmech.2010.01.029
9. G. Roman, *Eur. J. Med. Chem.*, **89**, 743 (2014); https://doi.org/10.1016/j.ejmech.2014.10.076
10. B. Biersack,K. Ahmed, S. Padhye and R. Schobert, *Expert Opin. Drug Discov.*, **13**, 39 (2017); https://doi.org/10.1080/17460441.2018.1403420
11. D. Quiroga and E. Coy-Barrera, *Organics*, **4**, 503 (2023); https://doi.org/10.3390/org4040035
12. R. Ganjoo, C. Verma, A. Thakur, A. AlFantazi, H. Assad, S. Sharma, S. Dubey and A. Kumar, *J. Ind. Eng. Chem.*, **131**, 136 (2024); https://doi.org/10.1016/j.jiec.2023.10.056
13. A.A. Al-Amiery and W.K. Al-Azzawi, *J. Mol. Struct.*, **1294**, 136421 (2023); https://doi.org/10.1016/j.molstruc.2023.136421
14. G. Giorgioni, F. Claudi, S. Ruggieri, M. Ricciutelli, G.F. Palmieri, A.D. Stefano, P. Sozio, L.S. Cerasa, A. Chiavaroli, C. Ferrante, G. Orlando and R.A. Glennon, *Bioorg. Med. Chem.*, **18**, 1834 (2010); https://doi.org/10.1016/j.bmc.2010.01.041
15. S. Kannan and M.S. Padusha, *World J. Pharm. Res.*, **6**, 1138 (2017); https://doi.org/10.20959/wjpr201710-9462
16. S.N. Pandeya, D. Sriram, G. Nath and E. DeClercq, *Eur. J. Pharm. Sci.*, **9**, 25 (1999); https://doi.org/10.1016/S0928-0987(99)00038-X
17. S. Joshi, D. Khosla and P. Tiwari, *Bioorg. Med. Chem.*, **12**, 571 (2004); https://doi.org/10.1016/j.bmc.2003.11.001
18. L.A. Chodosh, A. Fire, M. Samuels and P.A. Sharp, *J. Biol. Chem.*, **264**, 2250 (1989); https://doi.org/10.1016/S0021-9258(18)94169-4
19. L. Welage and R.R. Berardi, *J. Am. Pharm. Assoc.*, **40**, 52 (2000); https://doi.org/10.1016/S1086-5802(16)31036-1
20. S.J. Billups and B.L. Carter, *Ann. Pharmacother.*, **32**, 659 (1998); https://doi.org/10.1345/aph.17323
21. X. Li, X. Yang, Z. Cui, Y. Li, H. He and Y. Ling, *Chin. J. Chem.*, **28**, 1233 (2010); https://doi.org/10.1002/cjoc.201090214
22. A.A.-Fattah Mostafa, C.S. Kumar, A.A. Al-Askar, S.R.M. Sayed, R.S. Kumar and A. Idhayadhulla, *RSC Advances*, **9**, 25533 (2019); https://doi.org/10.1039/C9RA04496E
23. O. Trott and A.J. Olson, *J. Comput. Chem.*, **31**, 455 (2010); https://doi.org/10.1002/jcc.21334
24. B.J. Hathaway, *Struct. Bond.*, **57**, 55 (1984).