



Synthesis, Characterization, and Antimicrobial Activity Studies of New Schiff Base Tetradentate Ligands and Their Manganese (II) Complexes

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Authors' contributions

This work was carried out in collaboration by all authors. Author MHAD designed, managed the study, wrote the introduction and experimental sections in the manuscript. Author EABS wrote the chemistry in the results and discussion section in the manuscript. Author DSAN managed the chemistry and microbial experimental parts of the study in the manuscript. Authors WMAH and KSS managed and wrote the microbial experimental part of the study in the manuscript. Authors EABS and MHAD wrote the first draft. All authors read and approved the final manuscript.

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ABSTRACT

Two Schiff base tetradentate ligands **4** and **5** were synthesized by condensation reactions of 4-hydroxy-3-methoxy-5-((2-nitrophenyl)diazenyl) benzaldehyde **1** with 1,2-diaminoethane **2** and 1,2-diaminobenzene **3**, respectively. Treatment of synthesized ligands with the manganese (II) chloride $MnCl_2$ **6** gave two complexes **7** and **8** of general formula ML . The synthesized ligands and their complexes were characterized by FTIR, UV-Vis, Mass spectroscopy, and elemental analysis. The biological activity of the synthesized compounds were tested. It was found that ligand **5** and the complexes **7** and **8** possess antibacterial activity against the gram -ve *Proteus mirabilis*.

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1. INTRODUCTION

In September 1862, Hugo Joseph Schiff was discovered the new double bond between carbon atom and nitrogen atom as C=N linkage imine functional group from the condensation reaction between aldehydes or ketones with primary amines or amino acids in the presence of an acid catalyst [1,2]. Organic compounds containing the substituted imine are called azomethines, aldimines, anils, benzanils, ketimines or Schiff's bases [1,3,4]. The condensation of two equivalent aldehydes or ketones with a diamine produced the bis-Schiff base compounds, which have symmetric or unsymmetric/asymmetric structures [5,6].

Both unsymmetrical and symmetrical bis-Schiff bases can be coordinated as ligands with the central transition metal ion to form complexes. The complexes of unsymmetrical bis-Schiff base ligands are used as irregular binding model with peptides [7], while the intercalation of some symmetrical bis-Schiff bases with DNA and UV-Vis spectroscopy has been studied [8,9]. However, some symmetrical bis-Schiff base structures are studied and characterized by 1D and 2D NMR spectroscopy and X-Ray Crystallography analysis [10-12].

Recently, we have been reported the synthesis and characterize of the diazo dye **1** [13]. The aim of this paper is to synthesize and characterize the new bis-Schiff base tetradentate ligands **4** and **5** derived from condensation reactions of compound **1** with 1,2-diaminoethane **2** and 1,2-diaminobenzene **3**, respectively. The Mn(II) complexes of these ligands **7** and **8** have also been studied. All the synthesized compounds were characterized by melting points, FTIR, UV-Vis, Mass spectroscopy, and elemental analysis. Additionally, the microbial inhibitory of these derivatives **4**, **5**, **7** and **8** against some pathogenic bacteria such as *Staphylococcus aureus* as gram +ve, *Escherichia coli* and *Proteus mirabilis* as gram -ve were evaluated.

2. EXPERIMENTAL DETAILS

2.1 General

The melting points were determined with Electrothermal Melting Point Apparatus. FTIR spectra were recorded with JASCO FTIR 4600,

Single beam, Path Laser, by KBr disk technique in the frequency range of 4000–400 cm⁻¹. UV-Vis spectra were recorded with JASCO V-750 Spectrophotometer in ethanol at the wavelength range of 900–200 nm. All experiments were done at PCB Research Laboratory, Faculty of Science, Hadhramout University, Mukalla, Hadhramout, Yemen. Mass spectra were carried out on Direct Inlet part to mass analyzer in Thermo Scientific GCMS model ISQ, and Elemental analyses were carried out using FLASH 2000 CHNS/O analyzer, Thermo Scientific at the Regional Center for Mycology and Biotechnology RCMB, Al-Azhar University, Nasr City, Cairo, Egypt. All microbial experiments were done at Alsalam Medical Center, Mukalla, Hadhramout, Yemen.

2.2 Synthesis

2.2.1 Preparation of 4-Hydroxy-3-methoxy-5-((2-nitrophenyl)diazenyl)benzaldehyde **1**

Compound 4-hydroxy-3-methoxy-5-((2-nitrophenyl)diazenyl)benzaldehyde **1** was prepared as described previously [13].

2.2.2 Synthesis of bis-Schiff bases **4** and **5**

Both bis-Schiff bases **4** and **5** were synthesized from **1** by the method described earlier, with some modification [14-16]. In 100 mL dried round bottom flask equipped with a reflux condenser, a 6.03 g of compound **1** (0.02 mol) was dissolved in 15 mL of absolute ethanol containing a drop of glacial acetic acid and refluxed for about 10 min on an oil bath. The solution was mixed dropwise for 10 min with 1,2-diaminoethane **2** (0.60 g, 0.01 mol) in 15 mL hot absolute ethanol or 1,2-diaminobenzene **3** (1.08 g, 0.01 mol) in 15 mL hot absolute ethanol. The resulting mixture was stirred for 5 hr, and then amount of crashed ice was added with stirring for 30 min. The separated solid was filtered by vacuum filtration, washed with cooled water and then with distilled water, and finally recrystallized from ethanol to yield colored crystals of bis-Schiff base **4** or **5**.

2.2.3 Synthesis of complexes **7** and **8**

The complexes **7** and **8** were synthesized from **4** and **5**, respectively, as the method reported previously, with some modification [17]. In 100 mL dried round bottom flask equipped with a reflux condenser, a 6.27 g of **4** (0.01 mol) or 6.75

g of **5** (0.01 mol) was added to a solution of the manganese(II) chloride **6** $\text{MnCl}_2 \cdot 4\text{H}_2\text{O}$ (1.98 g, 0.01 mol) in 20 mL of absolute ethanol. The solution was refluxed for 3 hr on an oil bath. The obtained mixture was cooled with stirring by adding a crashed ice for 30 min. The resulting solid was filtered by vacuum filtration, washed with cooled water and then with distilled water, and recrystallized from ethanol to yield colored crystals of the complex **7** or **8**.

2.3 Methodology of Antimicrobial Activity

2.3.1 Bacterial strains

The bacteria strains that used in this study are most commonly involved in causing gastroenteritis, wound and burn exudates, urinary tract infection and ear secretions. Three bacteria strains *Staphylococcus aureus*, *Escherichia coli* and *Proteus mirabilis* were isolated from different patients attending Alsalam Medical Center laboratory in Mukalla, Hadhramout – Yemen, and used throughout this study. The isolated bacteria were subcultured on Nutrient agar Difco and incubated aerobically at 37°C for 24 hr. Organisms were maintained in the laboratory on nutrient agar slopes at 4°C [18].

2.3.2 Determination the minimal inhibitory concentration of **4**, **5**, **7** and **8**

The minimum inhibitory concentration MIC of **4**, **5**, **7** and **8** was determined by using a different dilution for that compounds, which diluted with sterile ethanol 75%. It was weighed amount of **4**, **5**, **7** and **8**, separately, and dissolved in ethanol 75%. The following concentration was prepared 1:2, 1:4, 1:8, 1:16 and 1:32 from the stock of each solutions [18,19].

2.3.3 Antimicrobial activity

The antibiotic susceptibility tests were carried out by the Kirby–Bauer disk diffusion technique according to Clinical Laboratory Standard Institute guidelines [20,21]. About 20 mL of the sterilized medium was poured into each sterile 9 cm diameter of Petri-dish and allowed to solidify. Bacterial suspension for each strain tested was adjusted at 3×10^8 CFU/mL by McFarland scale which prepared by mixing 0.1 mL of 1.0% dehydrate barium chloride with 9.9 mL of 1.0% sulfuric acid H_2SO_4 as described by [22].

About 0.1 mL of the prepared bacterial suspension was spread evenly onto the agar

surface using a cotton swab and kept in a refrigerator for 2 hr. The compound diffuses into the agar resulting in a concentration gradient that is inversely proportional to the distance from the disc. The test medium was Mueller–Hinton agar [23]. Thereafter, all prepared plates were incubated at 37°C for 24 hr [24]. After that, the size of the inhibition zone around the disc is a measure in mm of the degree of inhibition [20,21].

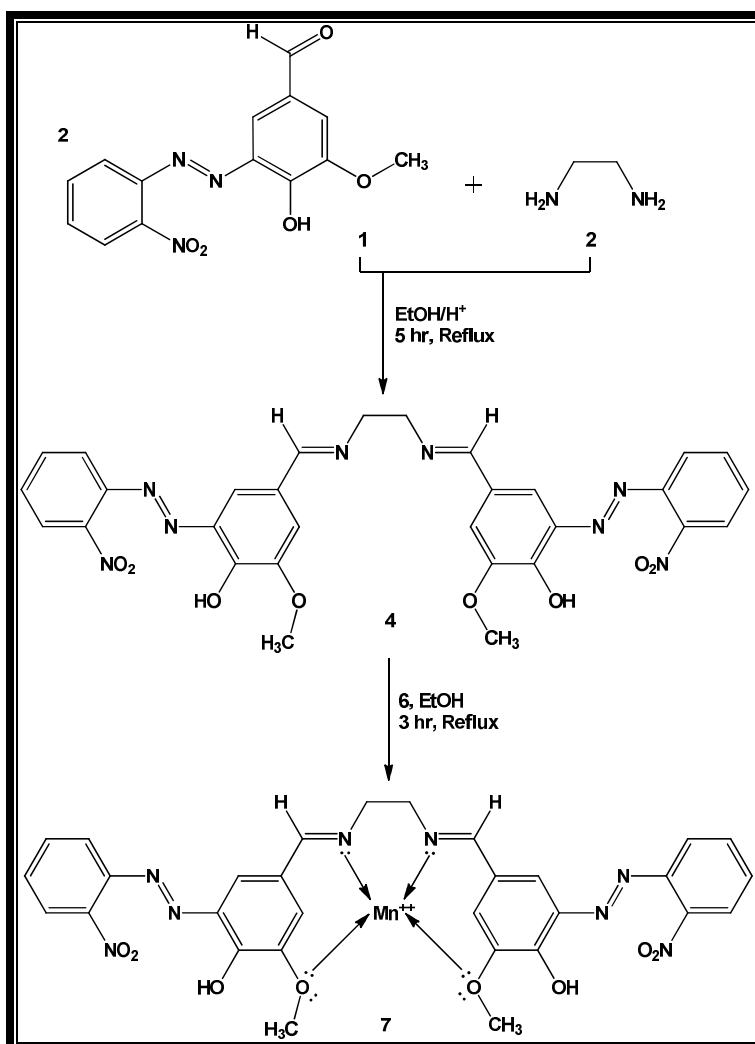
Seven of different antibiotics disks were used as a reference for evaluation of antibacterial: Ciprofloxacin, Amikaci, Clarithromycin, Cefaclor, Cefepime, Azithromycin and Co-trimoxazole [25]. The antibiotics were compared to the effect of synthesized compounds to antimicrobial activity of these pathogenic bacteria.

3. RESULTS AND DISCUSSION

3.1 Ligands and Complexes

4-Hydroxy-3-methoxy-5-((2-nitrophenyl) diazenyl) benzaldehyde **1** was synthesized and characterized previously [13]. Ligand **4** was obtained as a reddish orange solid by condensation reaction of compound **1** with 1,2-diaminoethane **2**. It has a melting point about 124°C. The interaction of **4** with a manganese dichloride MnCl_2 **6** gave a complex **7** which is a reddish brown solid, Scheme 1. It has a melting point > 400°C. It is soluble in ethanol, stable toward air and moisture. Table 1 described the physical properties and elemental analyses of synthesized compounds.

The FTIR spectrum of **4** exhibited absorption frequency at 1631 cm^{-1} which was a characteristic of the stretching vibration of imine functional group $\text{C}=\text{N}$. Two bands at 1170 cm^{-1} and 1283 cm^{-1} indicated the stretching vibrations of the methoxy functional group $-\text{OCH}_3$. The FTIR spectrum of **4** also showed a broad band at 3349 cm^{-1} due to the ν $-\text{OH}$ of phenol, two absorption bands around 3173 and 3109 cm^{-1} due to the ν C-H unsaturated, and two bands at 1429 cm^{-1} and 1469 cm^{-1} for the symmetric and asymmetric stretching vibrations of the azo functional group $-\text{N}=\text{N}-$ [13], respectively. Additional peaks around 1345 cm^{-1} and 1484 cm^{-1} were observed that were assigned to the symmetric and asymmetric stretching vibrations of the nitro functional group $-\text{NO}_2$, respectively. On the other hand, the C-H aldehydic and $\text{C}=\text{O}$ bands disappeared in the FTIR spectrum of **4** as compared to the FTIR spectrum of compound **1**.



Scheme 1. Synthetic route towards ligand 4 and complex 7

Table 1. Physical properties and elemental analysis of ligands and their complexes

Cpd.	Mol. Formula	Mol. Wt.	m.p. °C	Yield %	Elemental Analysis		
					Calc. (Found) %		
					C	H	N
4	C ₃₀ H ₂₆ N ₈ O ₈	626.594	124	86	57.51 (57.78)	4.18 (4.31)	17.88 (17.62)
5	C ₃₄ H ₂₆ N ₈ O ₈	674.638	199	70	60.53 (60.41)	3.89 (4.06)	16.61 (16.89)
7	C ₃₀ H ₂₆ N ₈ O ₈ MnCl ₂	752.438	> 400	60	47.89 (48.07)	3.48 (3.71)	14.89 (14.97)
8	C ₃₄ H ₂₆ N ₈ O ₈ MnCl ₂	800.482	220	85	51.02 (51.26)	3.27 (3.58)	14.00 (13.86)

A comparison of the FTIR spectra of complex 7 and 4 displayed a significant change in the intensities and positions of some bands. The absorption band of the C=N group in complex 7

was shifted to a lower frequency 1598 cm⁻¹, indicating the involvement of this group in coordination with a manganese ion [17,26]. This was supported by the appearance of a new band

around $449\text{-}480\text{ cm}^{-1}$ which was a characteristic absorption frequency of manganese nitrogen bond Mn-N [17,26]. Also, the band of methoxy functional group -OCH_3 changed in shape, and also there was a new band around $504\text{-}518\text{ cm}^{-1}$ that was assigned to the stretching vibration of manganese oxygen bond Mn-O [17,26], indicating that coordination also take place through the oxygen of methoxy functional group. However, the absorption bands of both azo -N=N- and phenolic hydroxyl -OH functional groups were not significantly affected, suggesting these groups were not participating in coordination, Fig. 1.

The UV-Vis spectrum of **4** in ethanol exhibited three bands, the first and second bands were observed at 274.4 nm and $321.6\text{-}335.2\text{ nm}$ which were indicated the $\pi\rightarrow\pi^*$ transitions of the aromatic rings and imine functional group, respectively [14-16,27]. The third band was located at $445.6\text{-}444.8\text{ nm}$ which was assigned to the intramolecular charge-transfer and resulted from $\pi\rightarrow\pi^*$ transition between benzene rings through the azo functional group -N=N- as a bridged [13]. While the UV-Vis spectrum of an ethanolic solution of the complex **7** referred to the bathochromic shift of the λ_{max} of the imine functional group C=N as compared to its value in UV-Vis of **4**. It is observed at $342\text{-}344\text{ nm}$

suggesting the participation in the bond formation with manganese ion in complex **7** [26,28,29]. The spectrum also showed the absorption at 273.2 nm due to the $\pi\rightarrow\pi^*$ transitions of the aromatic rings, and the absorption band of the azo functional group remained unaffected, suggesting the nonparticipation of this functional group in the coordination with manganese ion.

From both FTIR and UV-Vis studies, it can be suggested that **4** binds to the manganese ion through the imine functional group and oxygen of the methoxy functional group. Elemental analysis CHN of **4** was in a good agreement with the calculated value, Table 1. Also, the mass spectrum of **4** exhibited a molecular ion peak at $m/z\ 626.86$, which was equivalent to its molecular weight, Fig. 2. This confirmed the structure of **4**. Elemental analysis of complex **7** indicated that the metal:ligand ratio is 1:1 in the complex **7**, Table 1. Moreover, the mass spectrum of complex **7** showed a molecular ion peak at $m/z\ 752.34$ which was the same as the molecular weight of the complex **7**, Fig. 2. This confirmed the proposed ratio of M:L is 1:1. So, according to the results obtained from FTIR, UV-Vis, Mass spectra and CHN analysis, it can be concluded that the **4** interacts with manganese ion and a tetradentate structure can be suggested for the complex **7**, as shown in Fig. 3.

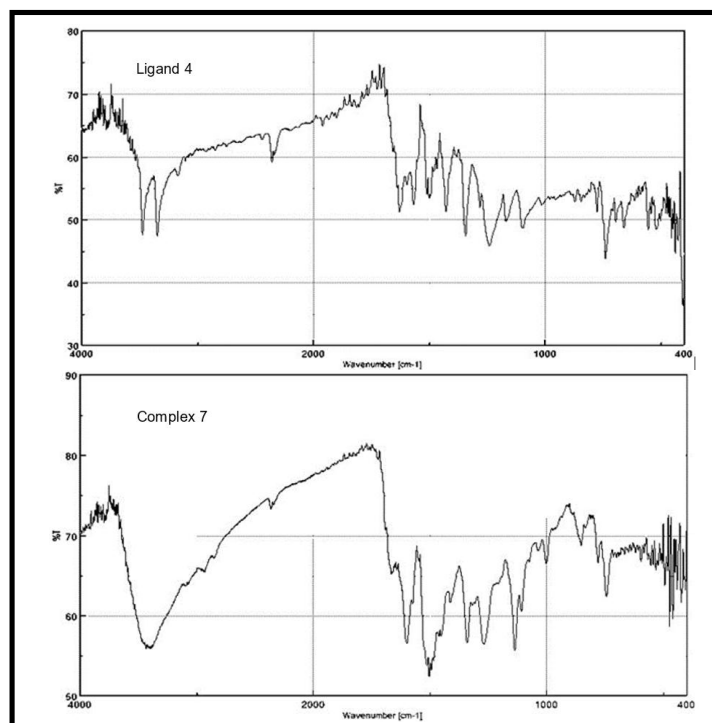


Fig. 1. FTIR Spectra of synthesized ligand **4** and complex **7**

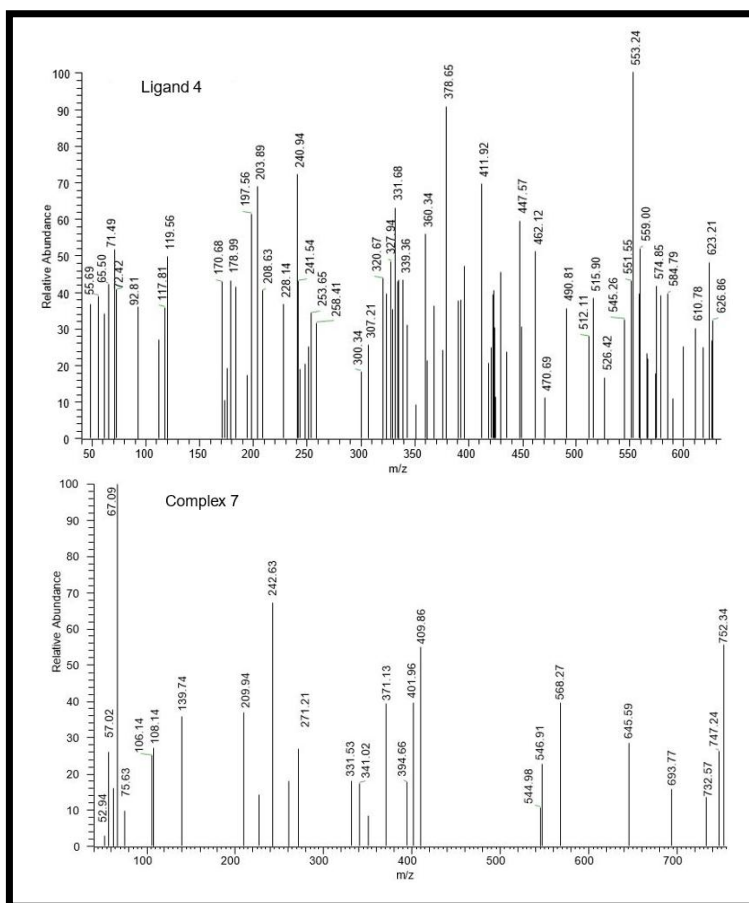


Fig. 2. Mass Spectra of synthesized ligand 4 and complex 7

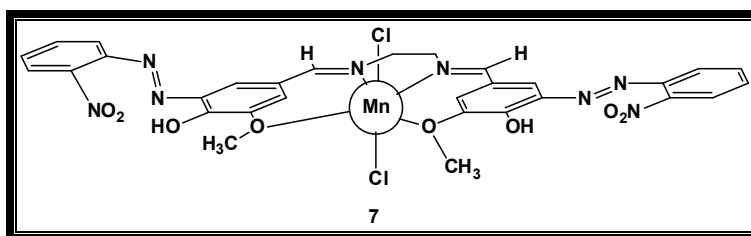


Fig. 3. Suggested structure of tetradentate complex 7 of ligand 4

Ligand **5** was obtained as a reddish brown solid by condensation reaction between compound **1** and 1,2-diaminobenzene **3**. It has a melting point about 199°C. Complex **8** has been synthesized by the interaction of **5** and manganese dichloride $MnCl_2$ **6**, Scheme 2. It is a reddish brown solid, soluble in ethanol. It is thermally stable and has a melting point about 220°C. Physical properties and elemental analysis were tabulated in Table 1.

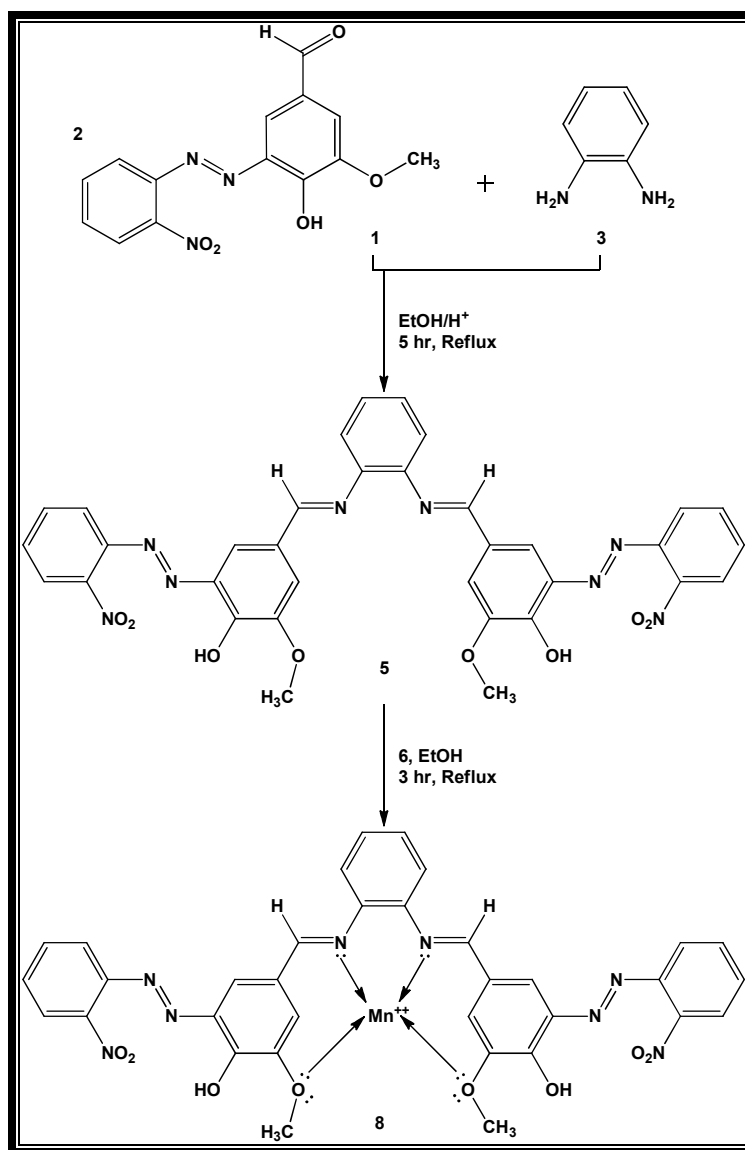
The FTIR spectrum of **5** showed a band at 1628 cm^{-1} due to the ν C=N stretching vibration

frequency. Two bands at 1139 and 1283 cm^{-1} were assigned to ν =C-OCH₃ of the methoxy functional group. However, the FTIR spectrum of **5** also showed a broad band centered at 3349 cm^{-1} indicated ν -OH of phenol, two bands around 3173 and 3109 cm^{-1} due to the ν C-H unsaturated, and other two bands appeared at 1414 cm^{-1} and 1573 cm^{-1} that assigned to the symmetric and asymmetric stretching vibrations of the azo functional group -N=N- of the **5**, respectively [13]. Both bands observed around 1345 cm^{-1} and 1484 cm^{-1} were attributed to the symmetric and asymmetric stretching vibration

frequencies of the nitro functional group $-\text{NO}_2$, respectively. On the other hand, there were no the characteristic absorption frequencies of the aldehydic functional group in the FTIR spectrum of **5** as compared to the FTIR spectrum of compound **1**.

A comparative study of the FTIR spectra of **5** and complex **8** exhibited that the band of $\nu \text{C}=\text{N}$ in the complex **8** observed to be lowered at 1598 cm^{-1} due to the participation of imine functional group in coordination with the manganese ion [17,26]. This confirmed by the appearing of new

band around $503\text{-}517 \text{ cm}^{-1}$ which was attributed to the manganese nitrogen bond Mn-N [17,26]. There was a change in the shape of methoxy band, in addition of a new band appeared around 540 cm^{-1} which was a characteristic band of manganese oxygen bond Mn-O [17,26], indicating the participation of methoxy functional group in the coordination with the manganese ion. The absorption bands of both the azo functional group $\nu -\text{N}=\text{N}-$ and phenolic functional group $\nu -\text{OH}$ were unaffected in the complex **8** indicating that these groups remain uncoordinated, as shown in Fig. 4.



Scheme 2. Synthetic route towards ligand **5** and complex **8**

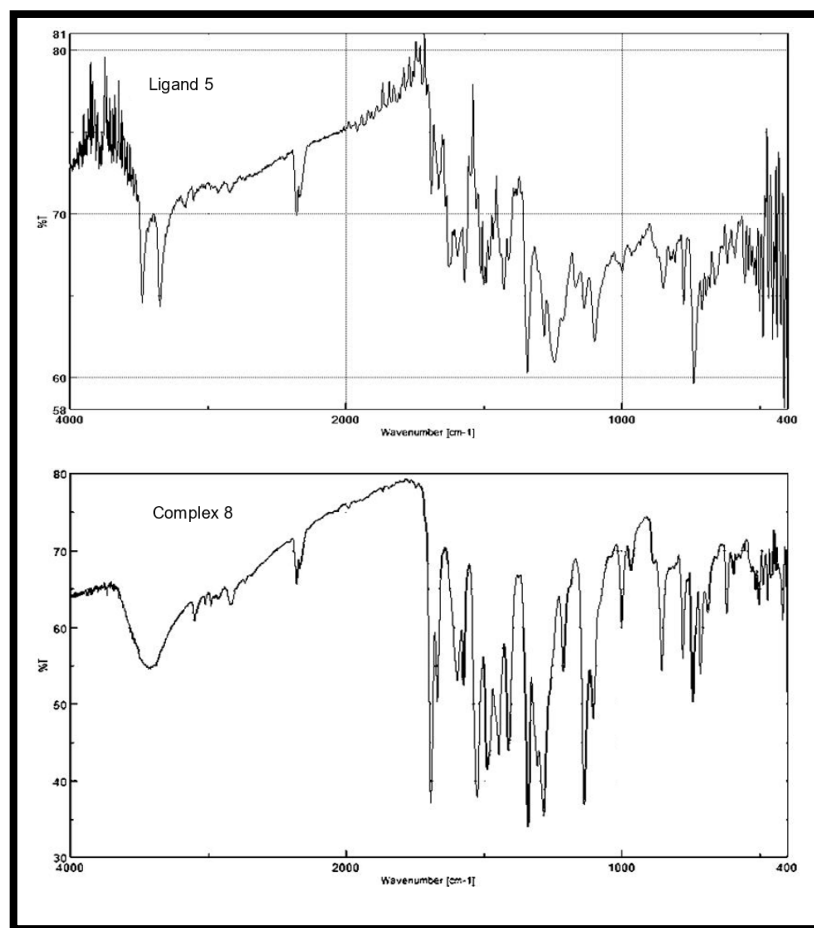


Fig. 4. FTIR Spectra of synthesized ligand 5 and complex 8

The UV-Vis spectrum of **5** displayed three bands in an ethanolic solution. The first band observed at 273.2 nm due to the $\pi \rightarrow \pi^*$ transition of benzene rings. The second band located at 321.6-337.2 nm for $\pi \rightarrow \pi^*$ transition of imine functional group C=N [14-16,27], while the third band observed at 480.4-506 nm that was attributed to azo functional group -N=N- [13]. Additionally, the UV-Vis spectrum of the complex **8** in ethanol solvent showed a band a 273.2 nm for $\pi \rightarrow \pi^*$ transition of benzene rings. The second band is observed at 340.4-345.6 nm due to the $\pi \rightarrow \pi^*$ transition of imine functional group C=N. This band showed a red shift due to the coordination with a manganese ion in the complex **8** [26,28-29]. However, the spectrum exhibited that the absorption of the azo functional group remained unchanged, indicated this group was not involved in coordination in complex **8**.

From FTIR and UV-Vis observation, it can be suggested that the **5** coordinates with the

manganese ion through the nitrogen of imine functional group and oxygen of methoxy functional group. Elemental analysis CHN of **5** revealed a good agreement with the calculated value, Table 1. Moreover, the mass spectrum of **5** exhibited a molecular ion peak at m/z 674.45, which was equivalent to its molecular weight, Fig. 5. These analyses confirmed the structure of ligand **5**.

Elemental analysis of complex **8** indicated that general composition a M:L ratio of 1:1, Table 1. This supported by the mass spectrum of complex **8** in that a molecular ion peak located at m/z 800.15 which was the same as the molecular weight of the complex **8**, Fig. 5. Both elemental analysis and mass spectrum were confirmed the proposed composition a M:L ratio of 1:1. According to the FTIR, UV-Vis, Mass spectra, and CHN analysis studies, the tetradentate structure has been suggested of the complex **8**, as shown in Fig. 6.

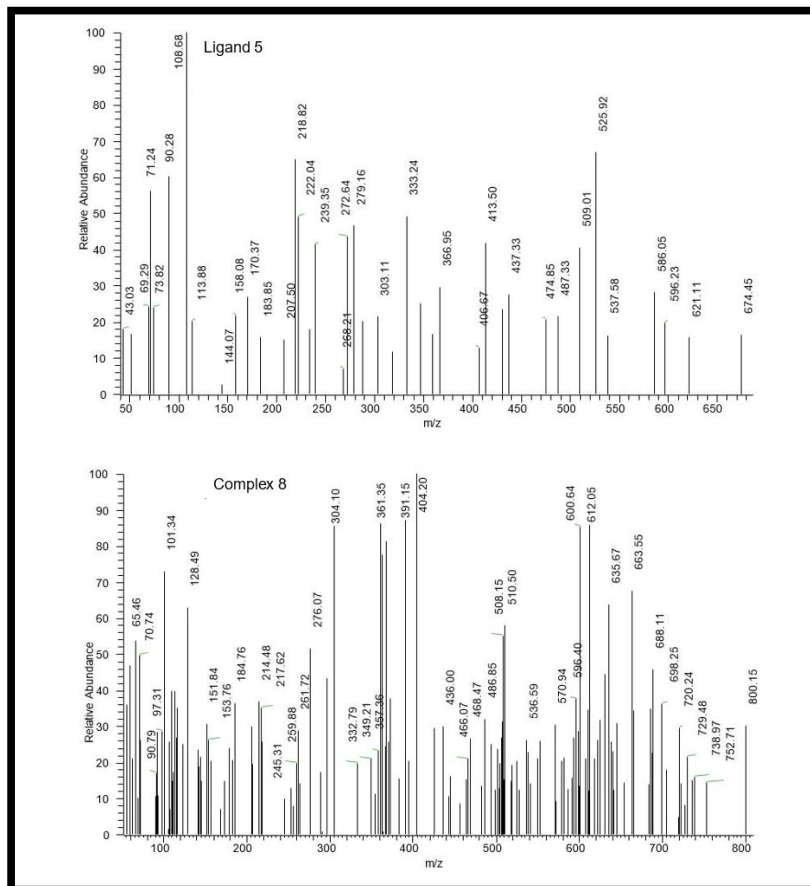


Fig. 5. Mass Spectra of synthesized ligand 5 and complex 8

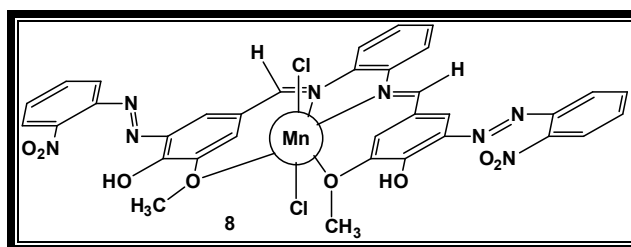


Fig. 6. Suggested structure of tetradentate complex 8 of ligand 5

3.2 Microbiology Activity

The ligands **4**, **5** and their Schiff base complexes **7** and **8** were screened against *Staphylococcus aureus*, *Escherichia coli* and *Proteus mirabilis*. The results are tabulated in Table 2. It was found that ligand **5**, complex **7** and complex **8** have antibacterial activities against the gram –ve *Proteus mirabilis*, and they have not antibiological activity against both *Staphylococcus aureus* and *Escherichia coli* at

room temperature. The concentration 0.125 mM of complex **8** showed inactive of all pathogenic bacteria *Staphylococcus aureus*, *Escherichia coli* and *Proteus mirabilis*. By the way, the ligand **5** has a high anti-bacterial effect against *Proteus mirabilis* at the concentrations 0.125 and 0.25 mM with [++=IZ 13-19 mm] as compared to the complexes **7** and **8**. However, ethanol 75% was tested of all pathogenic bacteria used in this study, and the obtained results were without inhibition zone.

Table 2. Inhibitory growth activity of both ligands 4, 5 and their complexes 7 and 8 against pathogenic bacteria (diameter of inhibition zone = IZ)

Compound	Conc. mM	Microorganisms		
		Mean diameter of inhibition zone IZ (mm)		
		gram +ve	gram -ve	
		<i>S. aureus</i>	<i>E. coli</i>	<i>P. mirabilis</i>
4	2.0	–	–	–
	1.0	–	–	–
	0.5	–	–	–
	0.25	–	–	–
	0.125	–	–	–
	0.0625	–	–	–
5	2.0	–	–	+
	1.0	–	–	+
	0.5	–	–	+
	0.25	–	–	++
	0.125	–	–	++
	0.0625	–	–	+
7	2.0	–	–	+
	1.0	–	–	+
	0.5	–	–	+
	0.25	–	–	+
	0.125	–	–	+
	0.0625	–	–	+
8	2.0	–	–	+
	1.0	–	–	+
	0.5	–	–	+
	0.25	–	–	+
	0.125	–	–	–
	0.0625	–	–	+
ethanol 75%	–	–	–	–
Cf	5*	+++	–	–
Am	30*	+++	–	–
Ct	15*	+++	–	–
Ca	30*	–	++	+++
Ce	30*	–	++	++
Az	15*	–	+	–
Cm	25*	–	+++	+++

* Key to symbols: *: ug, Cf: Ciprofloxacin, Am: Amikaci, Ct: Clarithromycin, Ca: Cefaclor, Ce: Cefepime, Az: Azithromycin and Cm: Co-trimoxazole as antibacterial, Disc diameter = 6 mm, Highly active: +++ [IZ > 19 mm], Moderately active: ++ [IZ 13-19 mm], Slightly active: + [IZ 7-13 mm], Inactive: – [IZ < 7 mm]

4. CONCLUSION

In this study, two Schiff base ligands **4**, **5** and their manganese complexes **7** and **8** have been synthesized. According to the UV-Vis and FTIR spectra, the ligands **4** and **5** coordinate to the manganese ion (II) through the imine nitrogen and the methoxy oxygen. The physico-chemical methods, FTIR, UV-Vis, Mass spectroscopy, and elemental analysis, suggest that the ligands **4** and **5** behave as the tetradentate and the metal:ligand ratio is 1:1. The microbiological activity study of these compounds shows that **5** and the complexes **7** and **8** have antibacterial

activity against the gram –ve *P. mirabilis*, and **5** has a high antibacterial effect at the concentrations 0.125 and 0.25 mM with [++=IZ 13-19 mm] as compared to the complexes **7** and **8**.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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