

SYNTHESIS, STRUCTURAL INVESTIGATION AND ANTIMICROBIAL ACTIVITIES OF A NOVEL SCHIFF BASE-2-METHOXY-6-PHENYLIMINOMETHYLPHENOL AND ITS TRANSITION METALS

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ABSTRACT

Schiff bases are considered to be excellent ligands. Their instantaneous and enduring reputation undeniably stem from the ease of their synthesis, incomprehensible flexibility and wide ranging complexing capacity once formed. This research paper deals with synthesis and structural elucidation of potentially active Schiff base ligand and its corresponding metal complexes and their biological implications. In this paper, synthesis of 2-methoxy-6-phenyliminomethylphenol (MSA) from 3-methoxysalicylaldehyde with aniline is carried out which has not been previously accounted. Starting from this ligand, different complexes using Mn(II) and Ni(II) metal ions, were prepared. They have been synthesized and characterized with the help of analytical as well as physico-chemical methods. All the synthesized compounds were placed under the biological evaluation.

Keywords: MSA, Metal Complexes, Spectral Characterizations, Antimicrobial Activities.

1. INTRODUCTION

Schiff base complexes are considered to be among the most significant stereo chemical model in the main group and transition metal coordination chemistry due to their perspective accessibility and structural variety. Schiff bases have been widely employed as ligands because of high stability of the co-ordination compounds and their good solubility in common solvents.¹ In the preparation of Schiff base, an aromatic amine reacts with carbonyl compound by nucleophile addition. Dehydration of the resultant hemiaminal produces an imine carbon-nitrogen double bond which provides a significant contribution in various development of chemical sciences.² The general structural feature of these compounds is the azomethine group with a general formula $RHC=N-R'$. Schiff bases are accounted to have biological activities like antibacterial, antifungal, antitumors, antiviral, anti-HIV and anti-influenza-A virus activities.³⁻⁶ Additionally they have extensive relevance in the field such as homogenous and heterogeneous catalysis. Schiff bases find greater role in bioinorganic chemistry and redox enzymes systems.⁷ Schiff bases are potential anticancer drugs and when administered as their metal complexes, the anticancer activity of the complexes is enhanced compared to the free ligand. In recent times, hydroxy substituted Schiff bases have received substantial attention due to good anticancer activity.⁸ Considering the numerous applications of Schiff bases in various fields of chemistry, there has been tremendous interest in evolving proficient methods for their synthesis. Many methods and procedures have been brought in for the preparation of imines in the literature since the pioneering work of Hugo Schiff. Based on the above facts and its applications, the primary aim of our present work is to synthesize Schiff base transition metal complexes derived from 3-methoxysalicylaldehyde and aniline and its various metal chlorides.

The analytical and spectral characterizations of synthesized metal complexes are examined and their biological activities are explored.

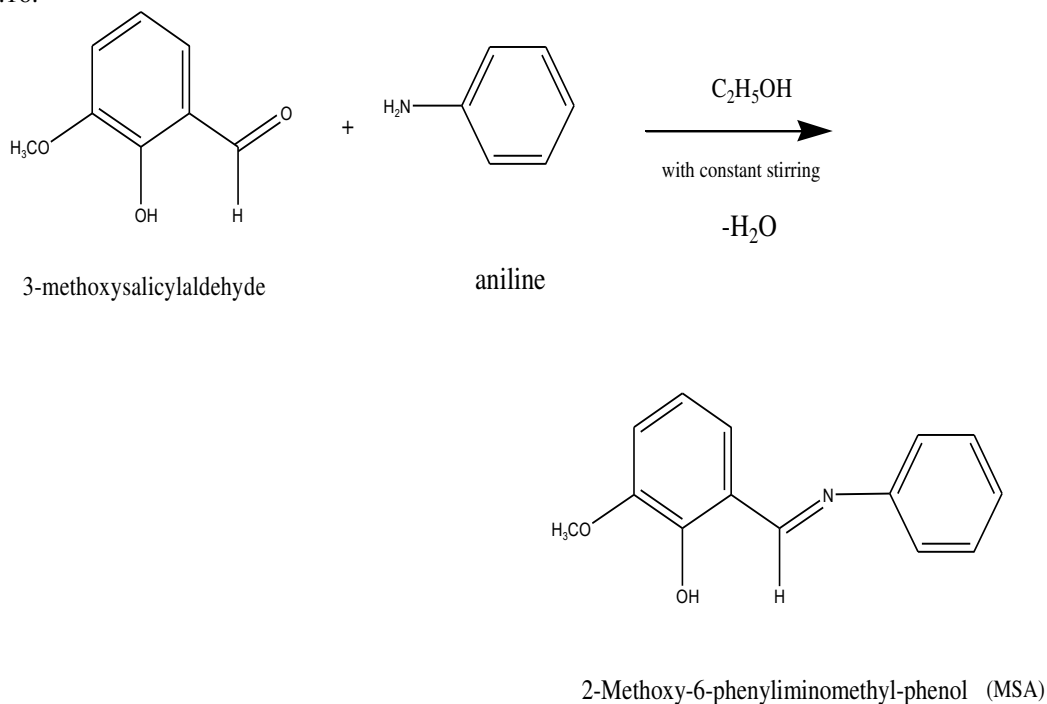
2. EXPERIMENTAL

2.1. Materials and methods

All the reagents and chemicals were purchased from Sigma Aldrich and used for our work without further purification. AR grade solvents were utilized for synthesis and recrystallization. The elemental analysis (C,H,N) was performed using elemental analyzer namely Elemental Model Ratio EL(111),CECRI-Karaikudi. Melting points of newly synthesized compounds were noted by Electro Thermal 9100 apparatus using open capillaries and are uncorrected. IR spectra of ligand and its metal complexes were recorded as KBr pellets on a Perkin Elmer RX⁻¹ spectrophotometer in the conventional range of 4000-400 cm⁻¹. UV-Visible spectra were recorded using Perkin Elmer Lambda 35 spectrophotometer in the range of 200-800 nm. Magnetic susceptibility measurements on powder samples were carried out by the Goy method. Mass spectra were determined by JEOL D-300(EI) Mass spectrometer. ¹H and ¹³C NMR spectra of ligand and its Mn(II) and Ni(II) complexes were recorded on the FT-NMR spectrometer model BrukerAvance II,400MHz using d₆-DMSO as solvent. Thermogravimetric analysis (TGA) was done on STA6000 PerkinElmer instrument under inert H₂ atmosphere.

2.2. Synthesis of Schiff base (MSA)

2-methoxy-6-phenyliminomethylphenol (MSA) was synthesized according to the literature method. The solution containing 3-methoxy salicylaldehyde (1.521g) dissolved in ethanol was mixed with aniline (0.913ml) in an equimolar (1:1) ratio (Scheme 1).The resulting solution was continuously stirred for one hour using magnetic stirrer and then mother liquor was left to slow evaporation at room temperature. The solid product was washed in ethanol, filtered and dried in open air. Recrystallization from hot ethanol gave analytically pure reddish orange solid. Yield is 78%.m/z: 228.2 (Fig. 1); Melting point is 80°C. Anal. (%): found C-70.44; H-5.61; N-5.75. calculated C-70.99; H-5.77; N-6.16.



Scheme 1:- Formation of Schiff base (MSA)

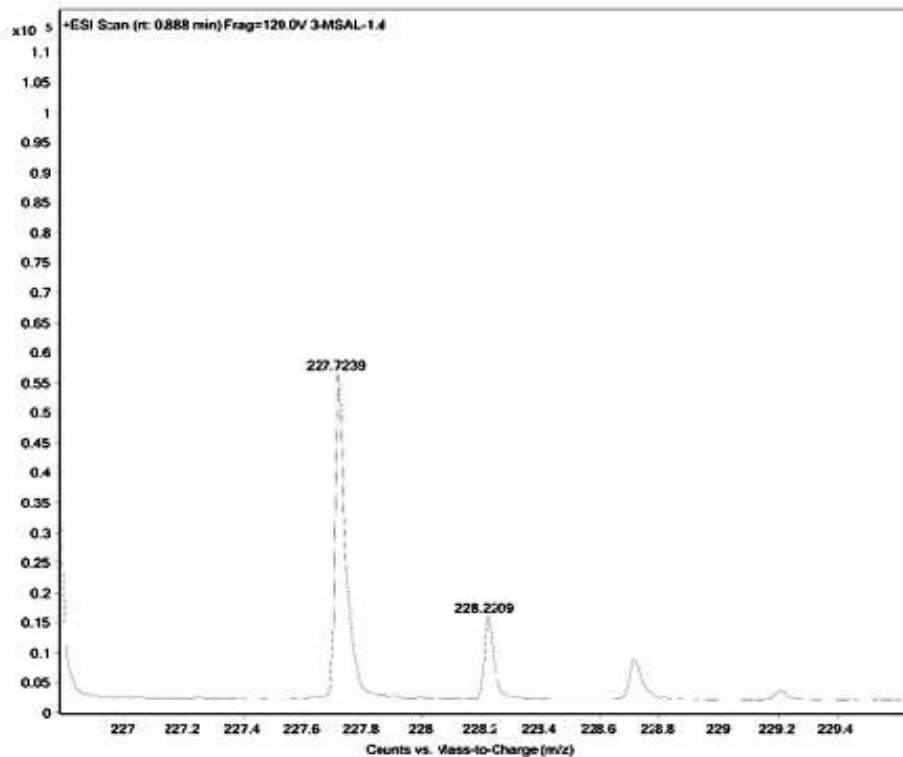
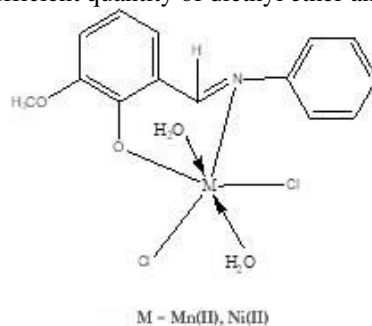


Fig. 1:- Mass spectrum of MSA

2.3. Synthesis of Mn(II) and Ni(II) complexes

To the hot solution corresponding Schiff base (0.005mol) in ethanol (20ml) was added the hot ethanolic solution (20ml) of respective metal chloride (0.005mol) and the reaction mixture was then refluxed for about 5 hours on mantle with water condenser and then cooled with ice bath. The coloured solid precipitates were obtained and collected by filtration, washed with sufficient quantity of diethyl ether and dried in a hot air oven (Scheme 2).



Scheme 2:- Structure of Mn(II) and Ni(II) metal complexes

2.4. Study of Antibacterial activity

Petri plates containing 20 ml nutrient agar medium were seeded with the 24 hours culture of bacterial strains (*Escherichia coli* and *Staphylococcus aureus*). Wells were cut and different concentration of compounds, MSA, Mn(II) and Ni(II) metal complexes (1000 µg/ml, 500 µg/ml, 200 µg/ml, and 100 µg/ml) were added. The plates were then incubated at 37 °C for 24 hours. The antibacterial activity was assayed by measuring the diameter of the inhibition zone formed around the wells. Gentamicin antibiotic was used as a positive control. The values were calculated using Graph Pad Prism 6.0 software (USA).

2.5. Study of Antifungal activity

Petri plates containing 20 ml potato dextrose agar medium were seeded with 72 hours culture of fungal strain (*Aspergillusniger*). Wells were cut and different concentration of compounds, MSA, Mn(II) and Ni(II) metal complexes (1000 µg/ml, 500 µg/ml, 200 µg/ml and 100 µg/ml) were added. The plates were then incubated at 27°C for 72 hours. The anti-fungal activity was assayed by measuring the diameter of the inhibition zone formed around the wells. Amphotericin B was used as a positive control. The values were calculated using Graph Pad Prism 6.0 software (USA).

3. RESULT AND DISCUSSION

3.1. FT-IR spectra

The Schiff base ligand showed absence of carbonyl bond (C=O) at 1643cm⁻¹ and (NH₂) amine bond (3432, 3356cm⁻¹) due to stretching vibrations and instead appearance of a strong new bond at the range of 1485 cm⁻¹ is assigned to azo-methine (HC=N) linkage.⁹ It is suggested that amine and aldehyde moieties of the starting reagent are absent and they have been converted into the azomethine moiety. The comparison of the IR spectra of Schiff base was coordinated to the metal ions in three ways, representing the ligand acting bi-dentative manner. The bond appearing at 1485cm⁻¹ due to the azomethine was shifted to lower frequency by 10-35cm⁻¹ indicating partition of the azomethine nitrogen in the complexation of bond at 1450 cm⁻¹. This shift to lower wave number (1485-1450cm⁻¹) in Mn(II), Ni(II) complexes suggests that co-ordination of the azomethine nitrogen to the metal centers. This is further substantiated by the presence of new bond around 410-440cm⁻¹ assignable to ν(M-N). A bond at 1256cm⁻¹ due to ν(C-O) phenolic group was also observed in the ligand. The disappearance of phenolic ν(OH) bond at 3394cm⁻¹ in Mn(II), Ni(II) complexes suggests the co-ordination by the phenolic oxygen after deprotonation with the metal ion.^{10-12,16} This is further supported by the shifting of ν(C-O) phenolic bond at 1256cm⁻¹ to lower wave number 1248 cm⁻¹ in the metal complexes. The appearance of the new bond around 630-650 cm⁻¹ in Mn(II), Ni(II) complexes is due to ν(M-O). (Fig. 2-4)

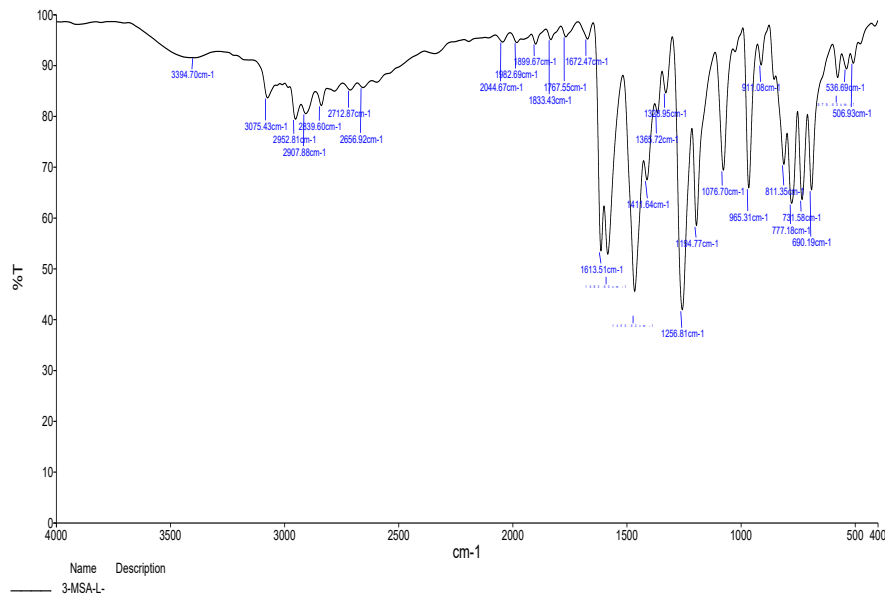


Fig. 2:- FT-IR spectrum of MSA

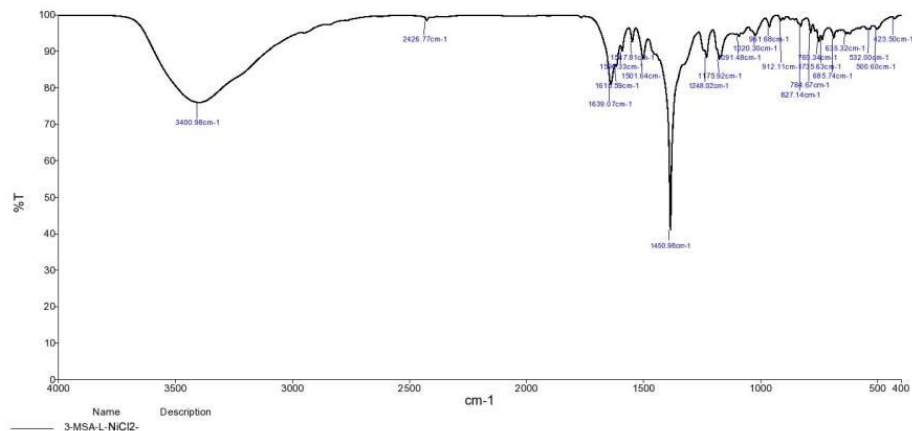


Fig. 3:- FT-IR spectrum of Mn(II) complex

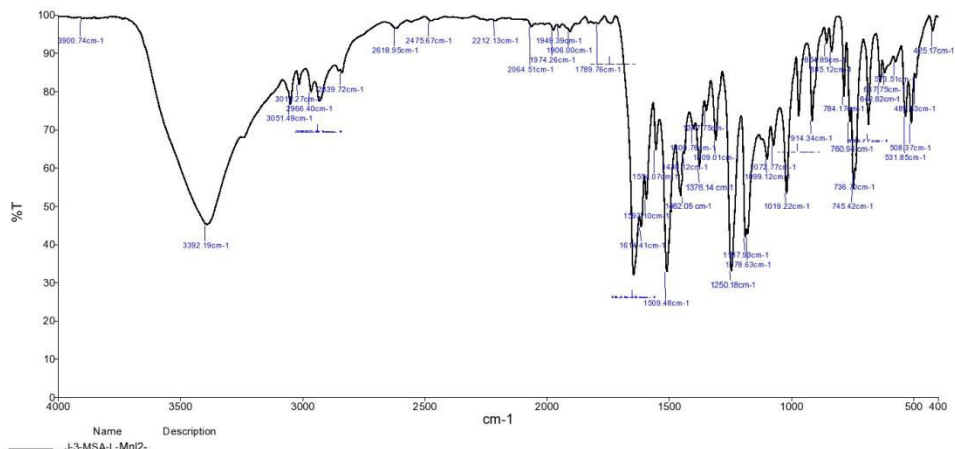


Fig. 4:- FT-IR spectrum of Ni(II) complex

3.2. ¹H & ¹³C NMR spectra

¹H NMR spectra of free ligand and its Mn(II) and Ni(II) complexes were recorded in DMSO-d₆. The signal due to the azomethine proton resonated at δ 8.62(1s, ¹H, CH=N)¹³ and the multiplet which extends from δ6.86-7.44 correspond to the 8 protons of the aromatic ring(m,8H,Ar-C-H). The peak at δ 13.71 confirms the presence of OH proton in the Schiff base ligand.^{13,14} The Schiff base ligand upon complexation with Mn(II), Ni(II) ions showed the disappearance of signal due to proton of phenolic group OH which confirms the involvement of bonding of oxygen atom with metal ion via deprotonation. The signals appeared at δ 8.91, 8.88 and multiplet in the regions of δ 6.22-8.52, 5.01-6.83 are due to azomethine proton and aromatic protons respectively. When compared to the ¹H NMR spectra of ligand and its Mn(II), Ni(II) complexes, all the signals due to proton have been shifted towards down field strengths confirming the complexation of Mn(II), Ni(II) ions with the ligand.¹⁵ Thus the ¹H-NMR spectral data support the IR spectral inference and complexation of Mn(II), Ni(II) ions with Schiff base ligand (MSA). In ¹³C NMR spectra of the ligand, the aromatic and imine carbon atoms appear in the region of (δ163.77-121.33), which is in agreement with various values reported in the literature.¹⁶ The carbon atom conjugated to the OH group produced a signal down field from the other carbon atom, whereas the aromatic carbon atoms were shifted down field, as expected due to the nitrogen atom. In ¹³C NMR spectra of the Mn(II), Ni(II) complexes, the signals appeared at δ151.02, 152.01 (ph-CH=N, 1C) were assigned to azomethine carbon atoms (CH=N) and the signals at δ 161.01, 160.11 (ph-C-O, 1C) were assigned to phenolic carbons. The phenyl rings of ligand showed signals between δ116.08-126.77, 116.08-128.02 (Ar-C, 7C). (Fig. 5-10)

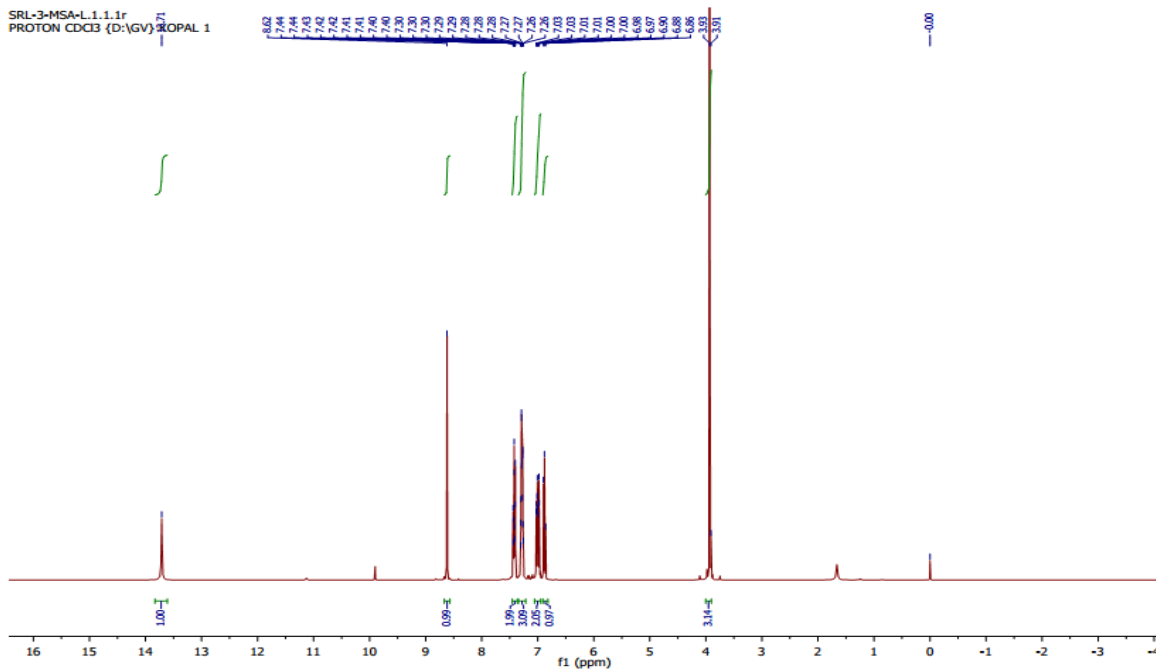


Fig. 5:- ¹H NMR spectrum of MSA

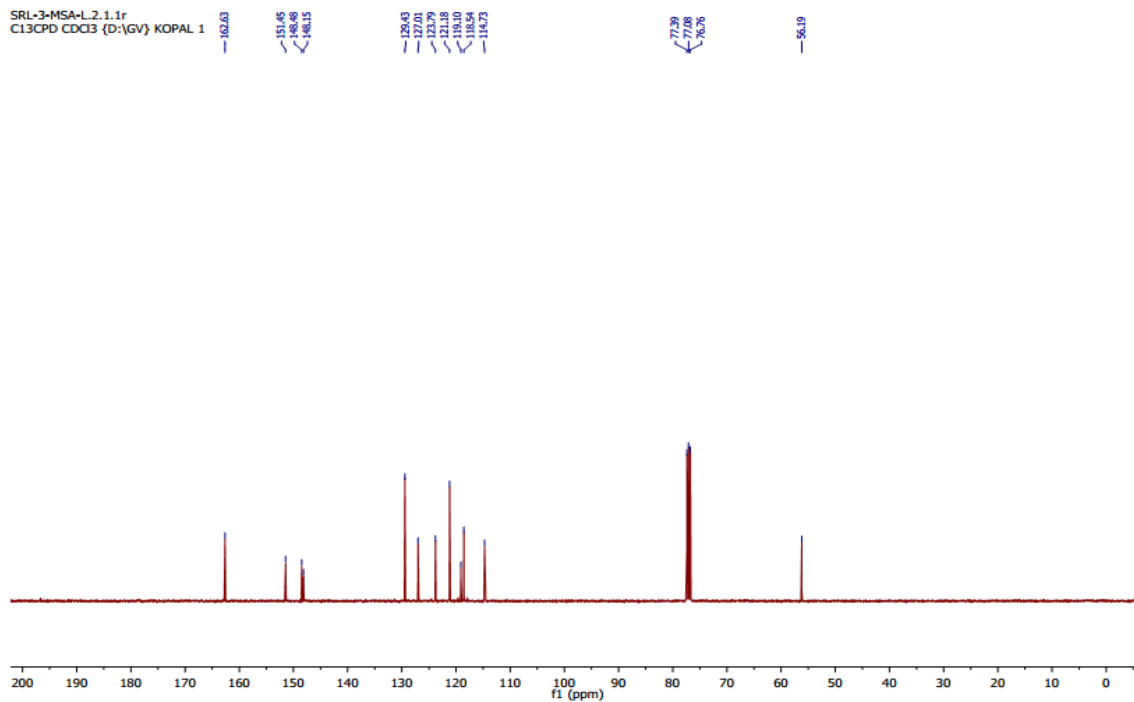


Fig. 6:- ¹³C NMR spectrum of MSA

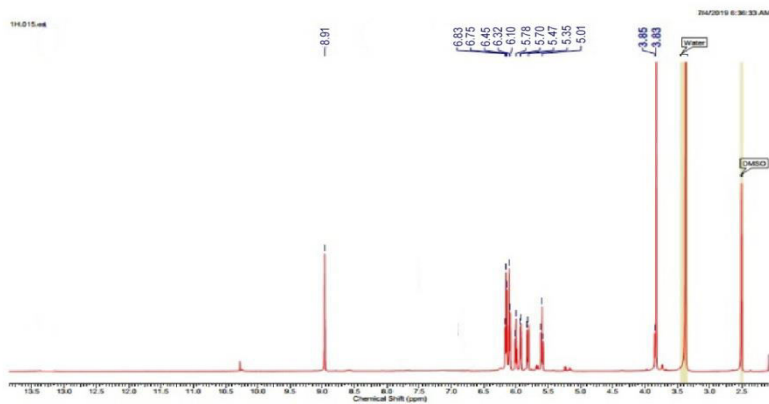


Fig. 7:- ¹H NMR spectrum of Mn(II) complex

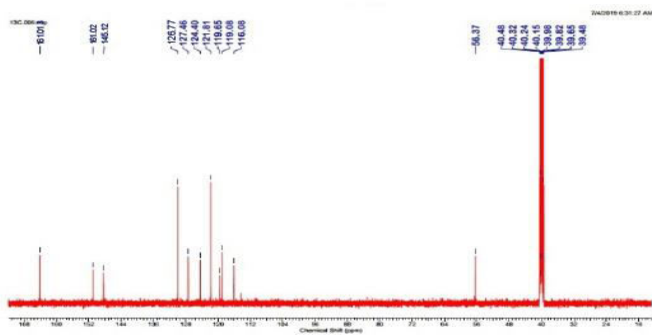


Fig. 8:- ¹³C NMR spectrum of Mn(II) complex

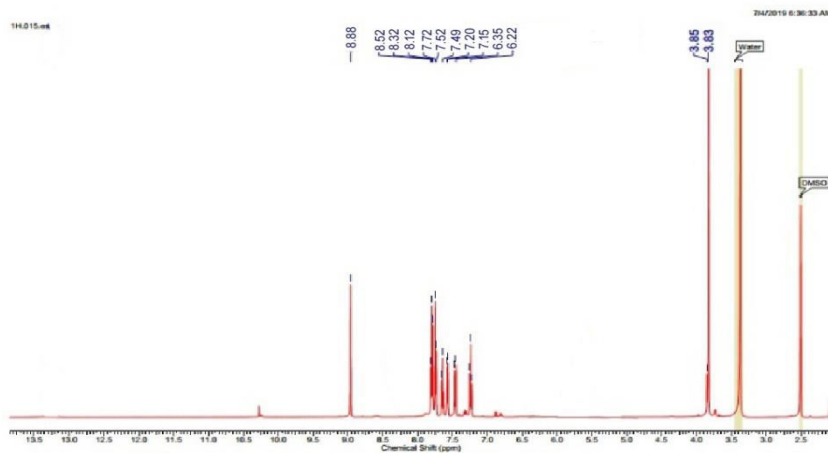


Fig. 9:- ¹H NMR spectrum of Ni(II) complex

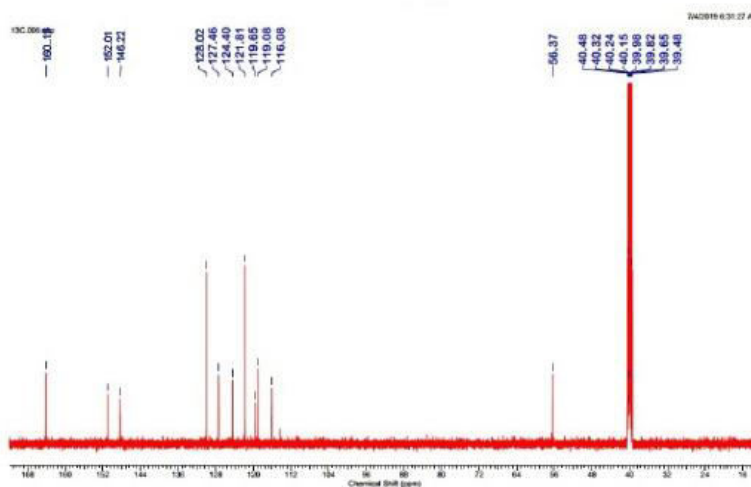


Fig. 10:-¹³C NMR spectrum of Ni(II) complex

3.3. UV-Visible spectra

The electronic spectra of MSA and Mn(II), Ni(II) metal complexes have been measured in DMSO solution between 200-800 nm at room temperature. The spectral data of MSA and Mn(II), Ni(II) metal complexes are observed. In the spectra of Mn(II), Ni(II) complexes, the bands in range 550-700 nm in metal complexes are assigned to LMCT and d-d transition respectively. The absence of these charge transfer bands in spectra of ligand confirms the coordination of metal complexes.¹⁷ The colored complexes with metal ions have a series of overlapping absorption band in the UV part of the spectrum as well as in visible part. The metal complexes of Mn(II) and Ni(II) show a distorted octahedral geometries.^{18,19}(Fig. 11-13)

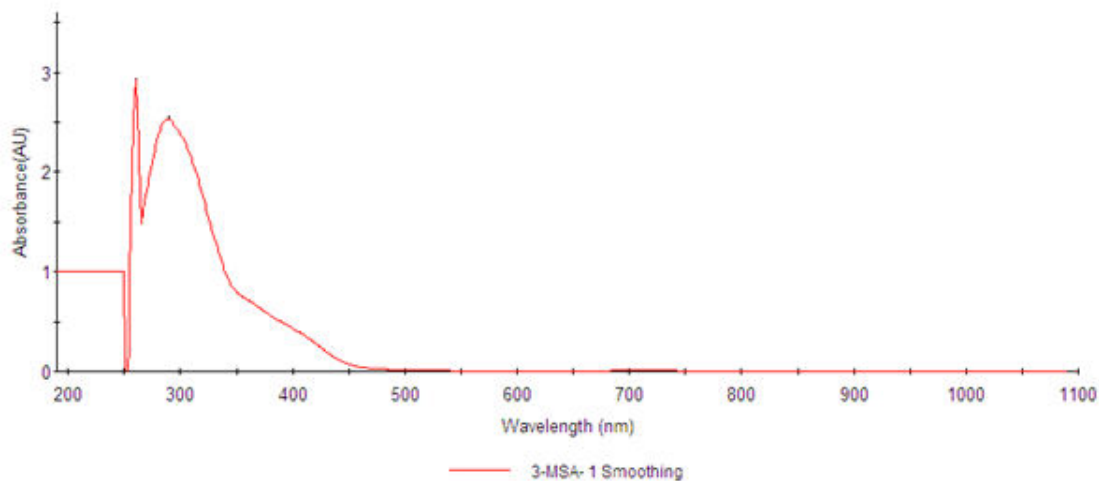


Fig. 11:- UV visible spectrum of MSA

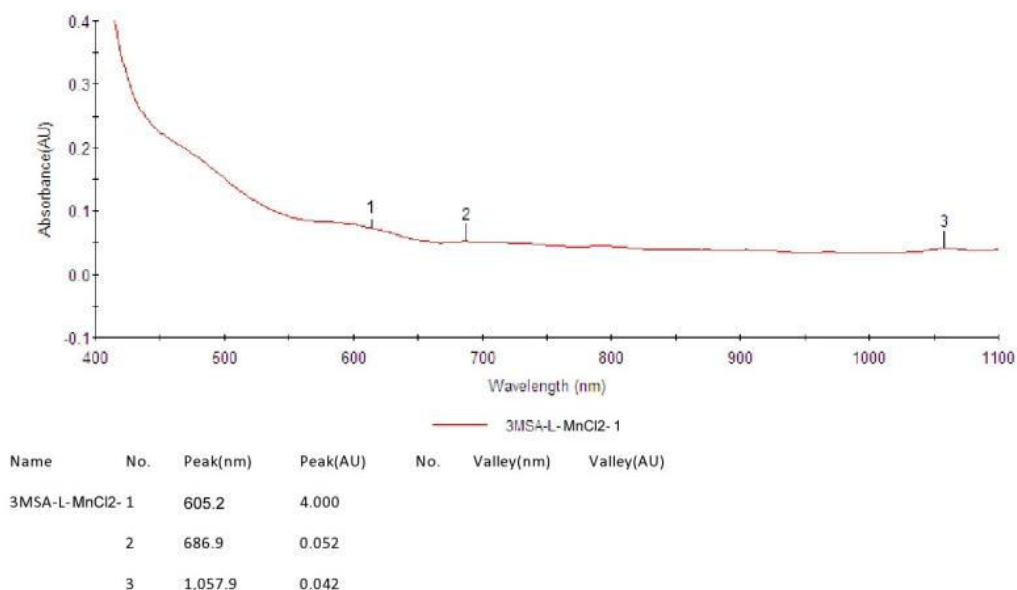


Fig. 12:- UV visible spectrum of Mn(II) complex

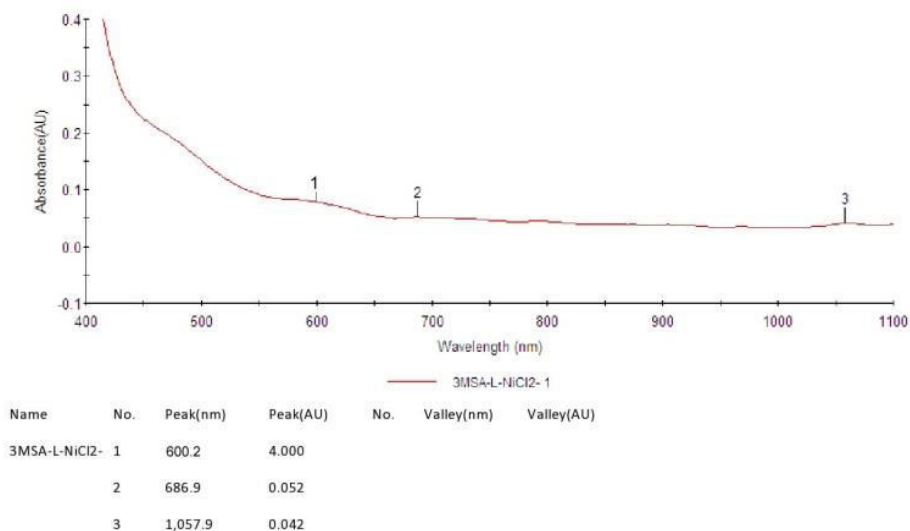


Fig. 13:- UV visible spectrum of Ni(II) complex

3.4. Thermal analysis

TGA of Mn(II) and Ni(II) complexes was studied under nitrogen gas at a heating range 25-600°C and heating rate (10°C/min). The thermal analysis is performed to prove the suggested structures and to study the thermal stability of the complexes. The first step decomposition occurs in the temperature range of 100-250°C with the mass loss of 38% which indicates the presence of water molecule. The second step decomposition pattern occurs in the temperature range of 260-600°C, due to the decomposition of organic moiety. The final products formed are stable Manganese oxide and Nickel oxide. (Fig.14-15)

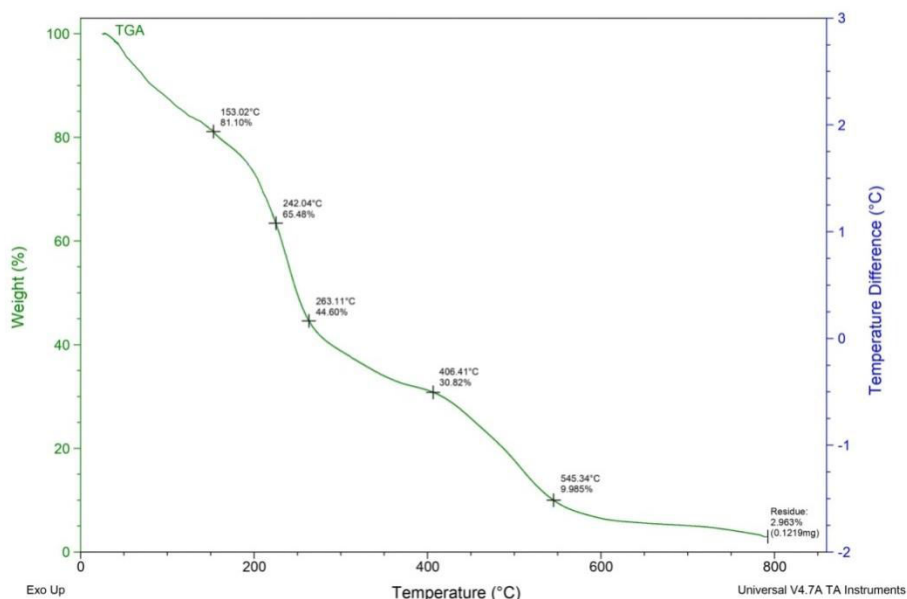


Fig. 14:- TGA analysis of Mn(II) complex

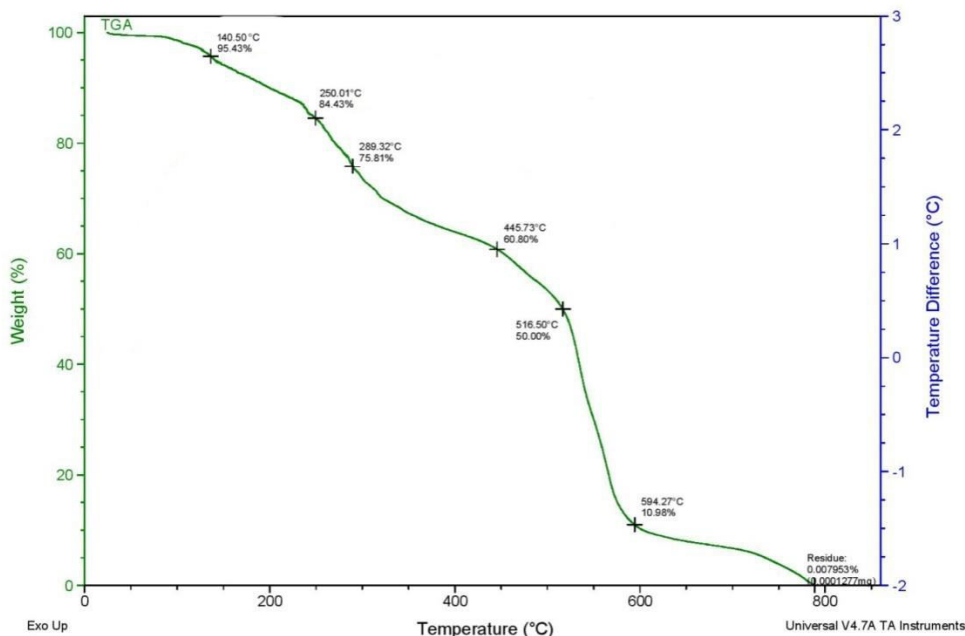


Fig. 15:- TGA analysis of Ni(II) complex

4. ANTIMICROBIAL ACTIVITY

The MSA and Mn(II) and Ni(II) complexes were tested for antimicrobial activities against the bacteria(Staphylococcus aureus, Escherichia coli)and fungi (Aspergillusniger). The data of the antifungal and antibacterial activities of MSA and metal complexes and standard are given in Table 1. From the data, it is evident that the Mn(II) and Ni(II) complexes are more active than the MSA ligand. On comparing the biological activity of the MSA and Mn(II) and Ni(II) complexes, it was found that some complexes are more effective against the bacteria and fungi. The higher activity of the some complexes, as compared to the free ligand (MSA), can be understood in terms of the chelation theory. This theory explains that a decrease in the polarizability of the metal could enhance the lipophilicity of the complexes.(Fig.16)

Table 1:- Antimicrobial activities of MSA, Mn(II) and Ni(II) metal complexes

Compounds	Zone of inhibition in (mm) (µg/ml)											
	Bacteria								Fungi			
	Staphylococcus aureus				Escherichia coli				Aspergillusniger			
	1000	500	200	100	1000	500	200	100	1000	500	200	100
MSA	15	13.5	9	9	12	12	5.5	4.5	10.5	9	7.5	7.5
Mn(II) Complex	20	19.1	12	9.7	15	12.9	9.1	9.2	13.3	8.8	8.7	7.2
Ni(II) Complex	19.5	18.8	11.3	9.1	14	11.8	8.9	8.8	12.8	7.8	8.2	6.7
Standard	18				22.5				15			
Negative control	0	0	0	0	0	0	0	0	0	0	0	0

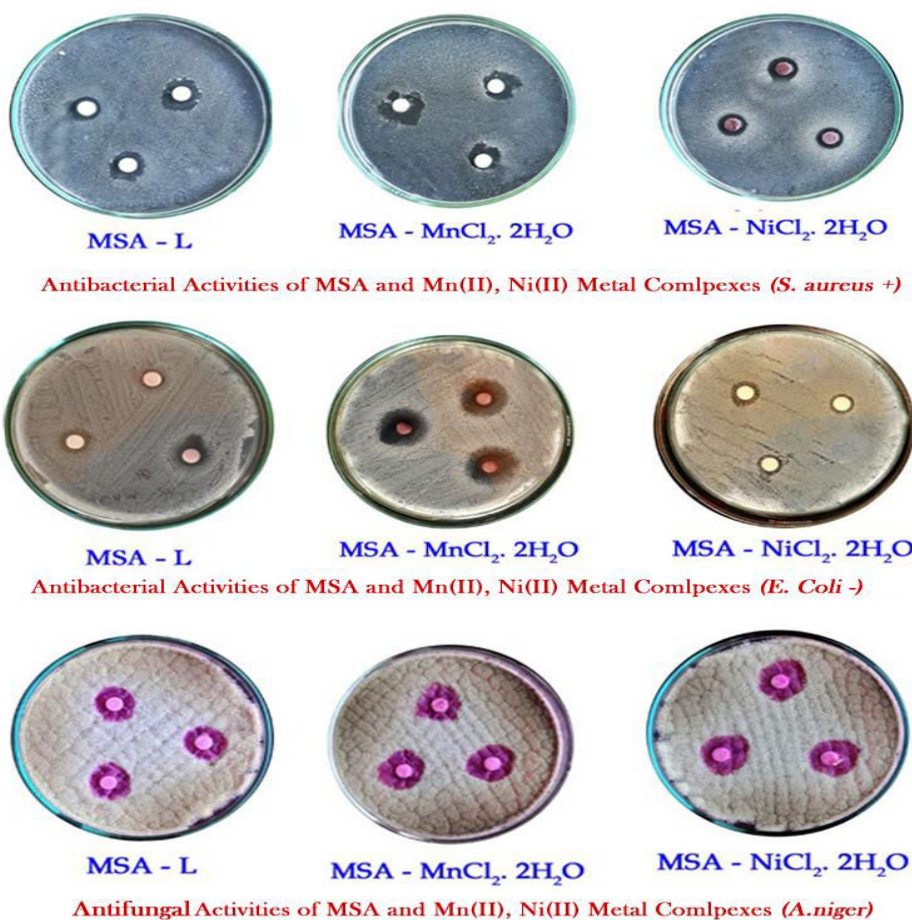


Fig. 16:- Antimicrobial activities of MSA and Mn(II), Ni(II) metal complexes

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