

SYNTHESIS, CHARACTERIZATION AND ANTIMICROBIAL STUDIES OF SOME METAL NITRATO COMPLEXES WITH A NEW MANNICH BASE *N*-(3-(FURAN-2-YL)-3-OXO-1- PHENYLPROPYL) ACETAMIDE

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ABSTRACT

The complexes of Mn(II), Co(II), Ni(II) and Zn(II) *N*-(3-(furan-2-yl)-3-oxo-1-phenylpropyl)acetamide (FBA) have been synthesized and characterized. The resulting complexes were characterized by elemental analysis, conductivity measurements, IR and ¹H NMR spectral studies. The Mannich base ligand acts as a neutral bidentate, coordinating through the 2-FMK carbonyl oxygen and amide nitrogen atoms. The complexes are non-electrolytic in DMSO. The presence of the coordinated water molecules in all the complexes was indicated by IR spectra of the complexes. From the analytical and spectral data, the three complexes exhibit octahedral geometry and Co(II) complex exhibit tetrahedral geometry. The antimicrobial activities of ligand and their complexes were screened by disc diffusion method. It is found that the metal complexes have higher antimicrobial activity than the free ligand.

Key words: Mannich base, Condensation, Metal complexes, physicochemical techniques.

INTRODUCTION

Mannich base complexes have remained an important and popular area of research due to their simple synthesis, adaptability, and diverse range of applications. From the survey of existing literature, it appears that metal complexes of Mannich bases played a vital role in the development of coordination chemistry^[1-3]. Many potent antibacterial and antifungal compounds synthesized by the condensation of aldehyde, amine and amide have been reported. Organic chelating ligands containing amide moiety as a functional group have a strong ability to form metal complexes and exhibit a wide range of biological activities^[4-7]. Literature studies revealed that during the past decades, there has been a great deal of interest in the synthesis and structural elucidation of transition metal complexes containing amide moiety^[8]. However, there is no study on any metal nitrate complexes of *N*-(3-(furan-2-yl)-3-oxo-1-phenylpropyl) acetamide(FBA)

In the present work, Mannich base derived from the condensation of 2-furyl methyl ketone benzaldehyde, and acetamide and its metal nitrate complexes with Mn(II), Co(II), Ni(II) and ligand and its metal complexes have biological activity against various microbes were tested *in vitro* against four bacterial species and two fungal species by disc diffusion method.

MATERIALS AND METHODS

Chemicals

Reagents such as 2-Furyl methyl ketone, benzaldehyde, acetamide and various Metal (II) nitrates were of Merck product. Spectroscopic grade solvents were used for the spectral measurements. The carbon, hydrogen and nitrogen contents in each samples were done at the Regional Sophisticated Instrumentation Centre, Central Drug Research Institute, Lucknow. The ^1H NMR and ^{13}C NMR spectra of the samples were measured in Bruker 300 MHz Instrument using DMSO as solvent. Mass spectra were recorded on a JEOL-8X102. The IR spectra were recorded with KBr pellets using FT-IR Shimadzu Instrument. Molar conductivity was measured using 10^{-3} M solution of complexes in DMSO on Systronic Conductivity Bridge. UV-Visible spectra of the complexes were recorded on Perkin Elmer Lambda EZ 301 spectrometer in DMSO solutions. Magnetic susceptibility was measured with Gouy balance at room temperature. $\text{Hg}[\text{Co}(\text{SCN})_4]$ was used as a standard. Nutrient agar was used for testing the susceptibility of microorganisms to antimicrobial agents using the *Disc-diffusion* technique. *Ciprofloxacin* was used as standard for antibacterial activity and *Nystatin* for antifungal activity.

In vitro antibacterial and antifungal assay

The biological activities of synthesized Mannich base and its Mn(II), Co(II), Ni(II) and Zn(II) complexes have been studied for their antibacterial and antifungal activities by *Disc diffusion* test using Nutrient agar (NA) and Sabouraud Dextrose Agar (SDA). The antibacterial and antifungal activities were done at $10\ \mu\text{g/mL}$ concentrations in DMSO solvent using bacteria (*S. aureus*, *B. subtilis*, *E. coli* and *P. aeruginosa*) and fungi (*C. albicans*, *A. niger*) at the minimum inhibitory concentration (MIC) method. These bacterial strains were incubated for 24 h at $37\ ^\circ\text{C}$ and fungi strains were incubated for 48 h at $37\ ^\circ\text{C}$. Standard antibacterial (*ciprofloxacin*) and antifungal drug (*Nystatin*) were used for comparison under similar conditions. Activity was determined by measuring the diameter of the zone showing complete inhibition (mm).

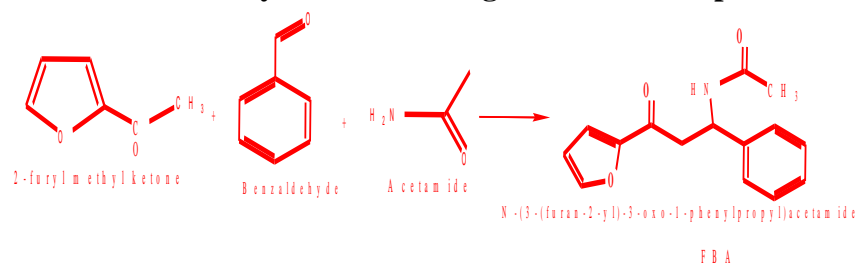
Synthesis of Mannich base

In the preparation of the acetamide derivative, acetamide, benzaldehyde and 2-furyl methyl ketone were taken in 1:1:1 mol ratio. Acetamide (2.95 g, 0.05 mol) dissolved in DMSO was mixed with 2-furylmethylketone (5.5 ml, 0.05 mol) and stirred to get a clear solution. Benzaldehyde (4.3 ml, 0.05 mol) was then added dropwise and the mixture was stirred for 1 h in an ice bath at $10\ ^\circ\text{C}$. The colorless solid separated was washed with water followed by methanol and recrystallized from petroleum ether. N-(3-(furan-2-yl)-3-oxo-1-phenylpropyl)acetamide is a colorless solid and its melting point is $240\ ^\circ\text{C}$. Purity of the compound was checked by TLC and the melting point of the compound was determined in an open capillary tube and was uncorrected. Yield: 79%

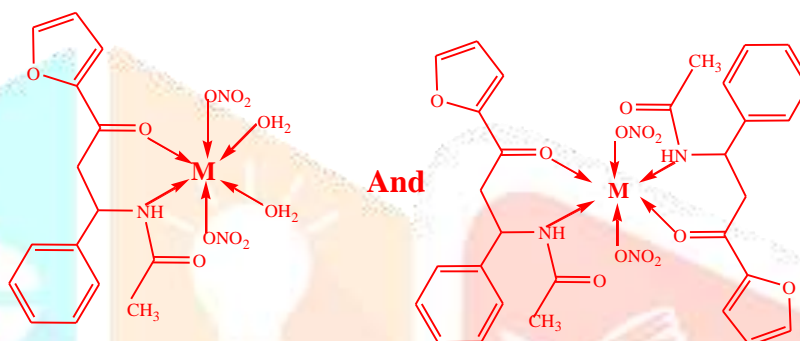
Synthesis of metal complexes

Metal(II) nitrate complex was prepared by mixing methanolic solution of Metal(II) nitrate to the ligand dissolved in DMSO with constant stirring (1:1 mol ratio). The reaction mixture was warmed on a hot water bath for about 15 min. On cooling a pale green precipitate separated from the solution and it was washed with methanol.

Scheme - 1: Synthesis of the ligand and its complexes



$MNO_3 \cdot x H_2O$



RESULTS AND DISCUSSION

Molar conductance

The complexes prepared are various colored, powder like, air stable, soluble in dimethylformamide (DMF) and dimethylsulfoxide (DMSO). The analytical data and some physical properties of the metal complexes were listed in Table-1 and synthetic scheme of complex is given in scheme -1. The molar conductivities values showed that all the complexes are non-electrolytes nature with $\Lambda_m = 35-45 \Omega^{-1} \text{cm}^2 \text{mol}^{-1}$ in 10^{-3} in DMSO solutions at room temperature.

Table-1: Physical characterization, Analytical, Molar conductance
Magnetic susceptibility data

| Compoun | Colour | Found/Calculated | | | | Yield % | $\Lambda\text{-m}$ Mho | $\mu\text{-eff}$ |
|------------------|------------|------------------|------------------|----------------|----------------|---------|------------------------|------------------|
| | | M% | C% | H% | N% | | | |
| FBA | Colourless | - | 70.02 | 5.88 | 5.44 | 78 | - | - |
| $C_{15}H_{15}NO$ | | | (70.03) | (5.83) | (5.45) | | | |
| Mn(II) Complex | pink | 7.77 (7.78) | 50.91 (50.94) | 4.24 (4.26) | 9.90 (9.92) | 68 | 15.63 | 5.72 |
| Co(II) | pink | 13.40 (13.40) | 40.90 (40.93) | 3.40 (3.44) | 9.54 (9.57) | 68 | | 4.38 |

| Complex | | | | | | | 12.2 | |
|----------------|------------|------------------|------------------|----------------|----------------|----|-----------|------|
| Ni(II) Complex | green | 13.44 (13.45) | 41.00 (41.03) | 3.41 (3.44) | 9.56 (9.58) | 68 | 14.4 0 | 3.52 |
| Zn(II) Complex | Colourless | 9.65 (9.67) | 50.20 (50.24) | 4.18 (4.20) | 9.76 (2.86) | 61 | 14.2 1 | -- |

IR spectra

IR spectra of ligand (Fig.-1) and metal (II) nitrate (Fig -2) complexes are recorded in KBr medium. For the free FBA, characteristic vibrational absorption bands at 1683 and 1657 cm^{-1} are due to FMK carbonyl stretching vibration and amide I band. Co^{II} nitrate complex of FBA exhibits ν_3 , ν_1 and ν_2 bands at 1465 , 1394 and 1052 cm^{-1} respectively due to the coordinated nitrate group. The separation between ν_5 and ν_1 bands is 69 cm^{-1} suggesting the unidentate coordination of the nitrate group to the metal ion. The Mn^{II} nitrate complex of FBA exhibits bands in the far IR region at 534 cm^{-1} which is assigned to ν_{MO} mode and at 440 cm^{-1} which is due to ν_{MN} vibration.^[9-11] The IR band at 1444 , 1371 and 1010 cm^{-1} in the spectrum of the manganese (II) nitrate complex is due to nitrate group and is shown in Fig -2. The difference in frequencies between the higher energy bands is within 100 cm^{-1} . It suggests unidentate coordination of the nitrate group. Normally, the difference is in the range of $120\text{-}180\text{ cm}^{-1}$ for a bidentate nitrate group.^[12, 13]

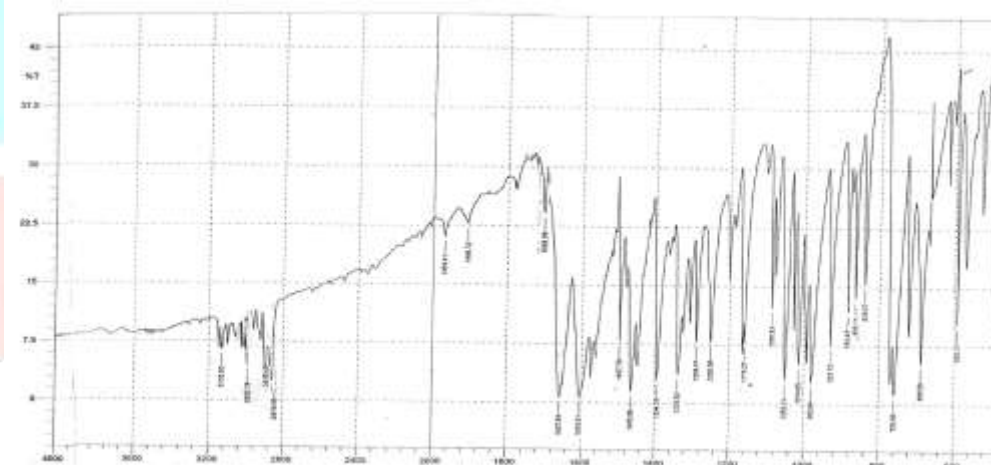


Fig. 1: IR Spectra of ligand using KBr pellet

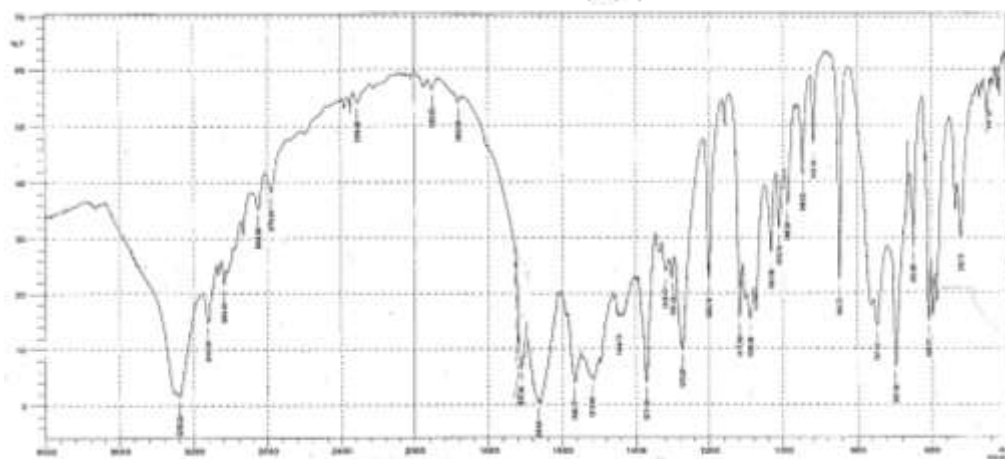


Fig. 2: IR Spectra of complex using KBr pellet

Magnetic moment and UV-Visible spectra

Electronic spectra and magnetic measurements were recorded in order to obtain information about the geometry of the complexes. The μ_{eff} (5.84) value of the Mn (II) representing an octahedral geometry of the ligand around the central metal ion. The four coordinated Co(II) and Ni(II) complexes shows μ_{eff} values of 4.72 and 3.70 which supports tetrahedral and octahedral geometry. The Zn (II) complex is found to be diamagnetic as expected for d^{10} configuration.

The Mn (II) complex under the present study exhibit a broad band in the region 21,590- 25,464 cm^{-1} due to transition between ${}^6A_{1g} \rightarrow {}^4T_{2g}$ which indicated octahedral geometry. The Ni (II) nitato complex showed broad signal at 8,740 cm^{-1} which is assigned to $3A_{2g} \rightarrow 3T_{2g}$ transition. which further confirmed the octahedral geometry of the complex. The spectra of Zn (II) complex exhibited band assigned to $L \rightarrow M$ charge transfer. It is diamagnetic as expected.

${}^1\text{H}$ NMR and ${}^{13}\text{C}$ NMR spectra

The ${}^1\text{H}$ NMR spectrum of N-(3-(furan-2-yl)-3-oxo-1-phenylpropyl) acetamide recorded in dimethyl sulphoxide-deuterated (DMSO- d_6) medium is shown in (Fig. 3). It shows resonance signals of protons at five regions from the TMS internal standard. Signals due to aromatic protons appear at δ 7.7-7.8 ppm. A sharp signal appearing at δ 2.34 ppm is assigned to free CH_3 proton. The multiplet between δ 7.3-7.4 ppm is due to the protons of furan. A weak doublet at δ 4.5 ppm is attributed to methylene protons. A broad band at δ 6.78 ppm is assigned to N-H proton. The aliphatic methine proton signals appear at δ 6.80-6.83 ppm (according to Shooley rules).

The ${}^{13}\text{C}$ NMR spectrum of N-(3-(furan-2-yl)-3-oxo-1-phenylpropyl)acetamide in DMSO solvent was recorded by proton off-resonance decoupling and proton noise decoupled techniques (Fig. 4.). The off-resonance decoupled spectrum exhibits chemical shifts of individual ${}^{13}\text{C}$ atoms at δ 27.30, 38.61, 39.16, 40.28, 112.7, 121.88, 130.43, 152.86 and 176.61 ppm along with some other weak peaks which may due to residual ${}^{13}\text{C}$ -H coupling. The noise decoupled spectrum is the simplified spectrum exhibiting signals of ${}^{13}\text{C}$ resonance only. The spectrum exhibits the resonance of ketonic carbonyl carbon at 176.61 ppm and amide carbonyl carbon at δ 152 ppm. The chemical shifts of aromatic carbons appear at δ 128.35, 130.43 and 134.37 ppm. The substituted aromatic carbon can be distinguished from other carbons by its decreased peak height. The peak at δ 143.14 ppm may be assigned to the substituted carbons in benzene and furyl rings. The methine carbon which is directly bonded to benzene ring exhibits signal at δ 27.30 ppm. The methylene carbon exhibits δ 65.04. The peak at δ 40.28 ppm is assigned to C-O-C of furan.

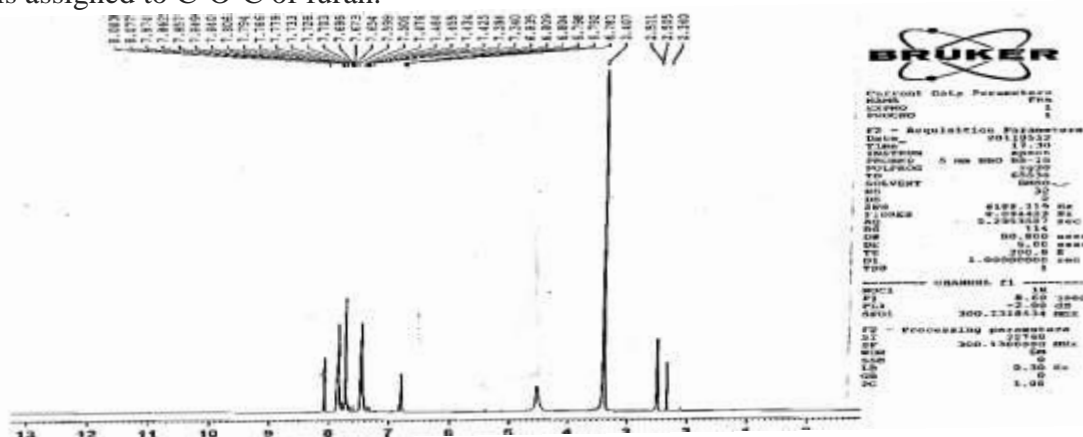
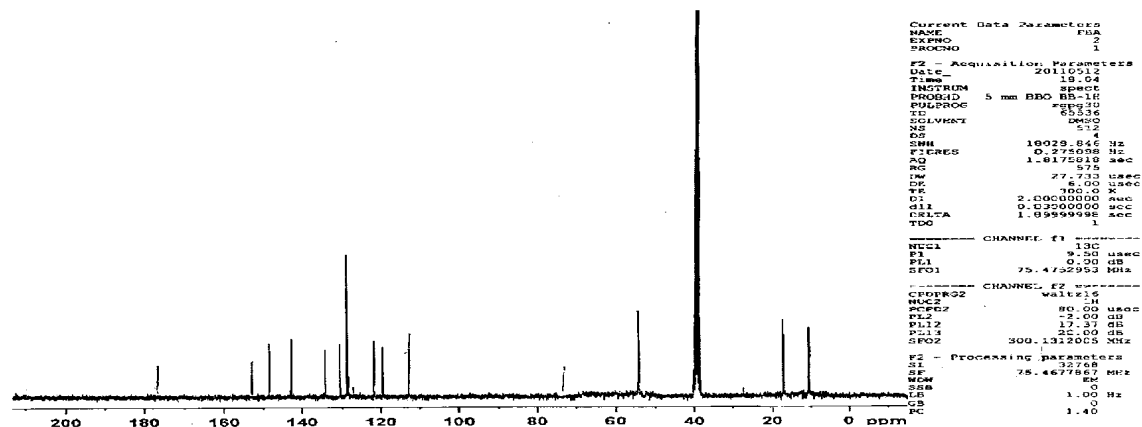


Fig. 3: ${}^1\text{H}$ -NMR Spectra of ligand in DMSO- D_6 solvent



In vitro antibacterial assay

For in vitro antimicrobial activity, the synthesized compounds were tested against the bacteria *Bacillus Subtilis*, *Staphylococcus aureus*, *Escherichia coli* and *Pseudomonas aeruginosa* and fungi *Candidaalbicans* and *Aspergillus niger*. The minimum inhibitory concentration (MIC) values of the investigated compounds with the standard drugs are presented in Table 2. Antimicrobial activity of metal chelates can be explained on the basis of coordination theory^[12]. On chelation, the polarity of the metal ion will be reduced to a greater extent due to the overlap of the ligand orbital and partial sharing of the positive charge of the metal ion with donor groups. Further, it increases the delocalization of π electrons over the whole chelate ring and enhances the presentation of the complexes into lipid membranes and blocking of the metal binding sites in the enzymes of microorganism. These complexes also disturb the respiration process of the cell and thus block the synthesis of proteins, which restricts further growth of the organism.

Table:2 Antimicrobial Activities of Metal Complexes of FBA

| Compound | <i>Bacillus</i> | <i>Staphylococcus</i> | <i>Escherichia Coli</i> | <i>Pseudomonas</i> | <i>Candida</i> | <i>Aspergillus</i> |
|--------------|-----------------|-----------------------|-------------------------|--------------------|----------------|--------------------|
| FBA | 2 | 1 | 20 | | 1 | 23 |
| Mn(II) | 2 | 1 | 32 | 19 | 1 | 17 |
| Co(II) | 32 | 2 | 20 | 2 | 15 | 30 |
| Ni(II) | 1 | 2 | 19 | 2 | 1 | 19 |
| Zn(II) | 2 | 1 | | 1 | 1 | 20 |
| Standard | 3 | 23* | 31* | 30* | 33 | 32 |
| Solvent(DMS) | NI | NI | NI | NI | NI | NI |

NI=No Inhibition, *Ciprofloxacin, **Nystatin

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