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Studies on chelating properties of furan ring containing organic ligands

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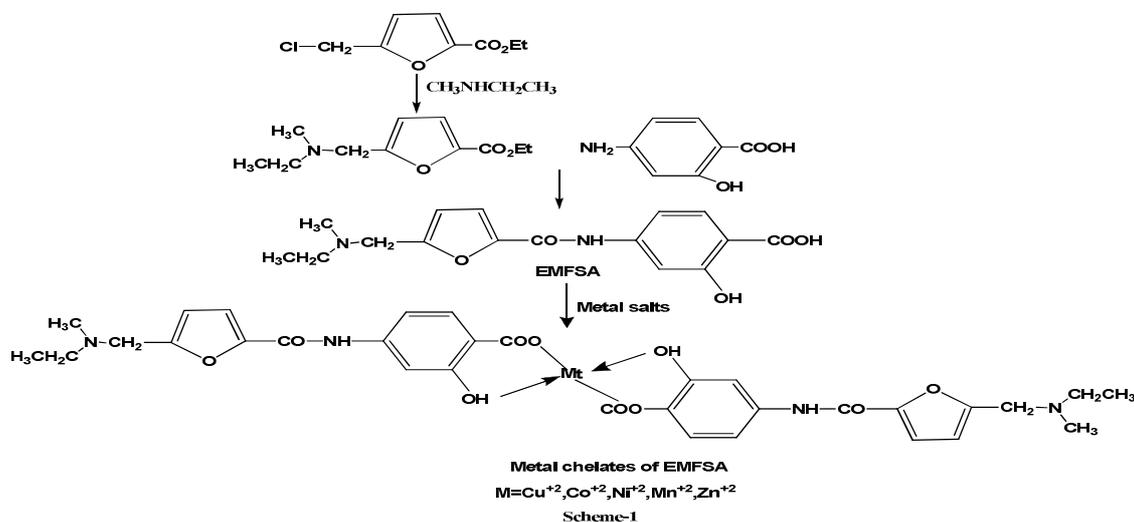
ABSTRACT

The novel ligand namely, 4-(5-((ethyl(methyl)amino)methyl)furan-2-carboxamido)-2-hydroxybenzoic acid (EMFSA) was synthesized by reaction between 5-((ethyl(methyl) amino) methyl)furan-2-yl propionate and 4-amino salicylic acid. The transition metal complexes like Cu^{2+} , Co^{2+} , Ni^{2+} , Mn^{2+} and Zn^{2+} of EMFSA have been prepared and characterized by elemental analyses, spectral studies, magnetic moment determination, molar conductivity measurement and antimicrobial activity.

Keywords: 5-((ethyl(methyl)amino)methyl)furan-2-yl propionate, 4-amino salicylic acid, spectral studies and Antimicrobial activity.

INTRODUCTION

Literature survey indicates that Metal complexes are widely used in various fields, such as biological processes, pharmaceuticals, separation techniques, analytical processes etc [1-3]. In recent years, there has been significant research done in the coordination chemistry [4-6]. Salicylic acid plays a important role in plant growth, as anti-pyretic, as anti-septic and as anti-inflammatory agent [7-10]. 4-amino salicylic acid was an excellent anti T.B agent. The reaction between furan derivative with 4-amino salicylic acid has not been reported so far. They all are act as a chelating ligand with improved microbicidal activity. Hence it was thought interesting to prepare the ligand having furan-salicylic acid moieties [11]. Thus the present communication comprises the studies on furan-salicylic acid combined molecule and its metal chelates. The research work is illustrated in **scheme-1**.



MATERIALS AND METHODS

Ethyl furan-2-carboxylate and 4-Amino salicylic acid was obtained from local dealer. All other chemicals used were of analytical grade. 5-(chloromethyl)furan-2-yl propionate prepared according to literature [12].

Synthesis of 5-((ethyl(methyl)amino)methyl)furan-2-yl propionate:

The 5-(chloromethyl)furan-2-yl propionate (0.01mole) and K_2CO_3 (0.02mole) were stirred at room temperature in DMF(20 ml) for 1.5-2 hrs and pinch of KI was added. After that ethyl methyl amine (0.01mole) was added to reaction mixture which was refluxed for 4-5hrs. The reaction mixture was poured into water (20 ml) and the mixture was extracted. The organic extracts were washed with water, dried over anhydrous sodium sulphate and concentrated to obtain crude product. The residue was recrystallized aq. ethyl acetate from to give pure compound. Yield: 78%, m.p. 132-131°C, IR ν cm⁻¹(KBr): 3338(amine), 3075(Ar.C-H), 2920 (aliphatic C-H), 1335(CN), 1720(CO).¹H NMR δ ppm: 6.52-6.34 (2H,d,furanCH), 3.85 (2H,s,CH₂), 2.67, 2.32 (4H, q, CH₂), 1.11-1.04 (6H,t,CH₃), 2.28 (3H,s,CH₃). Anal. Calcd for C₁₁H₁₇NO₃ (211): C, 62.54; H, 8.11; N, 6.63; Found: C, 62.53; H, 8.09; N, 6.62.

Synthesis of 4-(5-((ethyl(methyl)amino)methyl)furan-2-carboxamido)-2-hydroxybenzoic acid (EMFSA)

A mixture of 5-((ethyl(methyl)amino)methyl)furan-2-yl propionate and (0.01 mole) and 4-amino salicylic acid (0.01 mole) in ethanol (60 ml) was refluxed for 4-5 hrs. Afterward ethyl alcohol was distilled off and the solid mass obtained. The solid EMFSA was isolated and dried in air. Yield was 76%. It's m.p. was 236-237°C (uncorrected).

Elemental Analysis: C₁₆H₁₈O₅N₂(318)

	C%	H%	N%
Calculated:	60.37	5.70	8.80
Found :	60.36	5.68	8.78

Acid Value **Theoretical:** 153.8mg KOH/1g. Sample.
Found: 156 KOH/1g Sample.

IR Features	Wavenumber (cm ⁻¹)	Assignment
	3035, 1540, 1660	Aromatic
	1680	CO
	3400-3355	OH
	3420	Sec.NH
	2850, 2920	CH ₂ , CH ₃

NMR (DMSO)	δ ppm	Multiplicity	Assignment
	7.46 – 8.32 (3H)	Multiplet	Aromatic
	6.60, 7.38 (2H)	Doublet	Furan CH
	3.79 (2H)	Singlet	CH ₂
	6.83 (1H)	Singlet	CO-NH
	4.26 (1H)	Singlet	OH
	10.96 (1H)	Singlet	COOH
	1.22 (3H)	Triplet	CH ₃
	2.95 (2H)	Quartate	CH ₂
	2.33 (3H)	Singlet	CH ₃

Synthesis of metal chelates of EMFSA

The metal chelates of EMFSA of Cu²⁺, Co²⁺, Ni²⁺, Mn²⁺ and Zn²⁺ metal have been prepared in a similar manner. The general process is:

To a solution of EMFSA (33.2g, 0.1 mole) in ethanol-acetone (1:1v/v) mixture (150 ml), 0.1N KOH solution was added dropwise with stirring. The pasty precipitates were acquired at neutral pH. These were dissolved by addition of water to make clear solution. It was diluted to 250 ml. by water and was known as stock solution. 25 ml of the stock solution (which contains 0.01 mole EMFSA) was added drop wise to the solution of metal salt (0.005 mole for divalent metal ions) in water at room temperature. Sodium acetate or ammonia was added up for complete precipitation. The precipitates were digested on water bath at 80° C for 2hrs. The digested precipitates of chelates were filtered washed with water and air dried. It was amorphous powder. Yield was almost quantitative. The details are given in **Table-1**.

Table-1. Analytical Data of the Metal Chelates of EMFSA

Empirical Formula	Yield (%)	Elemental Analysis							
		C%		H%		N%		M%	
		Calcd	Found	Calcd	Found	Calcd	Found	Calcd	Found
EMFSA	76	60.37	60.36	5.70	5.68	8.80	8.78	--	--
(EMFSA) ₂ Cu ²⁺ ·2H ₂ O	69	52.35	52.33	5.18	5.16	7.63	7.61	8.66	8.64
(EMFSA) ₂ Co ²⁺ ·2H ₂ O	64	52.68	52.67	5.21	5.20	7.68	7.66	8.09	8.07
(EMFSA) ₂ Mn ²⁺ ·2H ₂ O	66	52.97	52.96	5.24	5.22	7.72	7.70	7.58	7.56
(EMFSA) ₂ Ni ²⁺ ·2H ₂ O	67	52.70	52.68	5.21	5.19	7.68	7.66	8.06	8.05
(EMFSA) ₂ Zn ²⁺ ·2H ₂ O	70	52.22	52.21	5.17	5.15	7.62	7.60	8.89	8.87

Measurements

On elemental analyzer TF-EA.1101 (Italy) the elemental analysis of C, H and N were carried out. IR spectra of EMFSA and its metal complexes were scanned on a Nicolet 760 FTIR spectrophotometer in KBr. The NMR spectrum of EMFSA was scanned on Bruker NMR spectrophotometer using DMSO solvent. The metal content of the metal chelate were performed by decomposing a weighed amount of each metal complexes followed by EDTA titration as reported in literature [13]. Magnetic susceptibility measurement of the entire metal complex was carried out at room temperature by the Gouy method. Mercury tetrathiocyanatocobaltate (II) Hg [Co(NCS)₄] was used as a calibrant. The diffused reflectance spectra of solid metal complex were recorded on a Beckman DK Spectrophotometer with a solid reflectance attachment, MgO was employed as the reflectance compound. The electrical conductivity of all the complexes was measured in acetonitrile at 10⁻³ M concentration.

Antifungal activity

The fungicidal activity of all the compounds was studied at 1000 ppm concentration in vitro plant pathogenic organisms listed in **Table-3**. The antifungal activities of all the samples were measured by cup plate method [14]. Each of the plant pathogenic strains on potato dextrose agar (PDA) medium. Such a PDA medium contained potato 200 gms, dextrose 20gms, agar 20gms and water 1 litre. 5 days old cultures were employed. The compounds to be tested were suspended (1000ppm) in a PDA medium and autoclaved at 120° C for 15 min. at 15 atm pressure. These medium were poured into sterile Petri plate and the organisms were inoculated after cooling the Petri plate. The percentage inhibition for fungi was calculated after 5 days using the formula given below.

$$\text{Percentage of inhibition} = \frac{100(X-Y)}{X}$$

Where, X: Area of colony in control plate

Y: Area of colony in test plate

The fungicidal activity all compounds are shown in **Table-3**.

RESULTS AND DISCUSSION

The parent ligand EMFSA was an amorphous yellowish white brown powder, soluble in various solvents like dioxane, DMSO and DMF. The results of elemental analysis of the ligand are reported in experimental part. They are consistent with the predicted structure as shown in **Scheme-1**.

Examination of IR spectrum (not shown) of EMFSA reveals that broad band of phenolic hydroxyl stretching is observed at 3400-3355 cm⁻¹ as well as additional absorption bands at 3035, 1540, 1680 are characteristics of the salicylic acid [12,14]. The strong bands at 1680 for C=O and band at 3420 for sec. NH. The NMR data (shown in experimental part) also confirm the structure of EMFSA.

The Metal chelate of EMFSA with ions Cu²⁺, Co²⁺, Ni²⁺, Mn²⁺ and Zn²⁺ vary in colours. On the basis of the proposed structure as shown in **Scheme-1**, the molecular formula of the EMFSA ligand is C₁₆H₁₈O₅N₂. This upon complexation coordinates with one central metal atom at four coordination sites and with two water molecules. Therefore the general molecular formula of the resulting metal chelate is [C₁₆H₁₇O₅N₂]₂ M₂·2H₂O for divalent metal ions. This has been confirmed by results of elemental analysis reported in **Table-1**. The data are in agreement with the calculated values.

Inspection of the IR Spectra (not shown) of metal chelates reveals that all the spectra are identical in all respects. The comparison of IR spectrum of the parent ligand EMFSA with that of its each metal chelates has revealed certain characteristics differences.

One of the significant differences to be expected between the IR spectrum of the parent ligand and its metal chelates is the presence of more broadened bands in the region of 3200-3400 cm^{-1} for the metal chelates as the oxygen of the O-H group of the ligands forms a coordination bond with the metal ions [15,16]. This is explained by the fact that water molecule might have strongly absorbed to the metal chelates samples during their formation. Another noticeable difference is that the bands due to the CO at 1730 cm^{-1} in the IR spectrum of the each metal chelates. The band at 1400 cm^{-1} in the IR Spectrum of EMFSA ligand assigned to in plane OH determination [15,16] is shifted towards higher frequency in the spectra of confirmed by a weak bands at 1095 cm^{-1} corresponding to C-O-M stretching [13-15]. Thus all of these characteristics features of the IR studies suggested the structure of the metal chelates as shown in **scheme**.

Table -2 Magnetic Moment and Reflectance Spectral data of Metal Chelates of EMFSA ligand

Metal chelate	Magnetic Moment μ_{eff} (B.M.)	Molar Conductivity $\Omega\text{m ohm}^{-1}\text{ cm}^2\text{ mol}^{-1}$	Absorption band (cm^{-1})	Transitions
Cu-EMFSA	1.95	32.4	22788 15964	C.T ${}^2\text{T} \rightarrow {}^2\text{T}_{2g}$
Ni-EMFSA	3.87	35.7	14786 23083	$3\text{A}_{2g} \rightarrow 3\text{T}_{1g}(\text{p})$ $3\text{A}_{1g} \rightarrow 3\text{T}_{1g}(\text{F})$
Co-EMFSA	4.53	34.3	15481 22822	$4\text{T}_{1g}(\text{F}) \rightarrow 4\text{T}_{2g}(\text{F})$ $4\text{T}_{1g}(\text{F}) \rightarrow 3\text{A}_{2g}$
Mn-EMFSA	5.13	36.6	15484 17753 23071	$6\text{A}_{1g} \rightarrow 4\text{T}_{1g}(4\text{Eg})$ $6\text{A}_{1g} \rightarrow 4\text{T}_{2g}(4\text{G})$ $6\text{A}_{1g} \rightarrow 4\text{T}_{1g}(4\text{G})$

Zn^{2+} Diamagnetic in Nature.

Examination of data of the metal content in each compound revealed a 1:2 metal: ligand (M: L) stoichiometry in all of the chelate of divalent metal ions. Magnetic moment (μ_{eff}) of each of the metal chelates is given in **Table-2**. Examination of these data reveals that all chelates other than that of Zn^{2+} , are Para magnetic while those of Zn^{2+} are diamagnetic.

The diffuse electronic spectrum of the $[\text{CuEMFSA}(\text{H}_2\text{O})_2]$ metal complex shows broad bands at 15964 and 22788 cm^{-1} due to the ${}^2\text{T} \rightarrow {}^2\text{T}_{2g}$ transition and charge transfer, respectively suggesting a distorted octahedral structure [17-19] for the $[\text{CuEMFSA}(\text{H}_2\text{O})_2]$ complex. Which is further confirmed by the higher value of μ_{eff} of the $[\text{CuEMFSA}(\text{H}_2\text{O})_2]$ complex. The $[\text{NiEMFSA}(\text{H}_2\text{O})_2]$ and $[\text{CuEMFSA}(\text{H}_2\text{O})_2]$ complex gave two absorption bands respectively at 14786, 23083 and 15964, 22788 cm^{-1} corresponding to ${}^4\text{T}_{1g} \rightarrow {}^2\text{T}_{1g}$ and ${}^4\text{T}_{1g}(\text{p})$ transitions. Thus absorption bands at the diffuse, reflectance spectra and the value of the magnetic moments μ_{eff} indicate an octahedral configuration for the $[\text{NiEMFSA}(\text{H}_2\text{O})_2]$ and $[\text{CuEMFSA}(\text{H}_2\text{O})_2]$ complex. The spectra of $[\text{MnEMFSA}(\text{H}_2\text{O})_2]$ shows weak bands at 15484, 17753 and 23071 cm^{-1} assigned to the transitions ${}^6\text{A}_{1g} \rightarrow {}^4\text{T}_{1g}(4\text{G})$, ${}^6\text{A}_{1g} \rightarrow {}^4\text{T}_{2g}(4\text{G})$ and ${}^6\text{A}_{1g}(\text{F}) \rightarrow {}^4\text{T}_{1g}$, respectively suggesting an octahedral structure for the $[\text{MnEMFSA}(\text{H}_2\text{O})_2]$ chelate. The high intensities of the bands suggests that they might be charge transfer in origin μ_{eff} is found to be lower than normal range. In the absence of low temperature moments it is difficult to give any significance. As the spectrum of the $[\text{ZnEMFSA}(\text{H}_2\text{O})_2]$ polymer is not well resolved, it is not interpreted but its μ_{eff} value shows that it is diamagnetic as expected.

Conductivities of all the complexes were measured in acetonitrile solvent and all the complexes were found to be electrolytic [20] in nature of 1:2 type and molar conductivity values are in the range of 32.4-36.6 $\text{Ohm}^{-1}\text{ cm}^{-1}$.

The antifungal activity of all the compounds measured for various plant pathogens. Inspection of the result shown in **Table-3** indicates that all compounds are good toxic for fungi. Out of all the compounds copper chelates is more toxic than other. These compounds almost inhibit the fungi about 70%. Hence produced metal chelates can be employed as garden fungicides. Further work in the direction is in progress.

Table 3. Antifungal Activity of Ligand MENFS and its metal chelates.

Sample	Zone of inhibition of fungus at 1000ppm (%)			
	<i>Botrydepladia thiobromine</i>	<i>Nigrospra sp.</i>	<i>Rhizopus nigricans</i>	<i>Aspergillus niger.</i>
EMFSA	63	60	62	51
Cu-EMFSA	76	75	72	68
Ni-EMFSA	75	74	70	65
Co-EMFSA	68	68	68	65
Mn-EMFSA	74	73	75	67
Zn-EMFSA	65	60	54	54

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REFERENCES

- [1] K. C. Ravindra, H. M. Vagdevi, V. P. Vaidya, *Ind. J. Chem.*, **2003**, 47B, 1271.
- [2] H. M. Vagdevi, K. P. Latha, V. P. Vaidya, *Ind. J. Pharm. Sci.*, **2001**, 63, 286.
- [3] K. M. Mahadevan, V. P. Vaidya, H. M. Vagdevi, *Ind. J. Chem.*, **2003**, 42B, 1931.
- [4] J. C. Patel, H. R. Dholariya, K. S. Patel, J. Bhatt, K. D. Patel, *Med. Chem. Res.*, **2014**, 23, 3714.
- [5] R. S. Joseyphus, C. Shiju, J. Joseph, C. J. Dhanaraj, K. C. Bright, *Der Pharma Chem.*, **2015**, 7, 265.
- [6] S. Saini, R. Pal, A. K. Gupta, V. Beniwal, *Der Pharma Chem.*, **2014**, 6, 330.
- [7] O. Rahn, J. E. Conn, *Ind. Eng. Chem.*, **1944**, 36, 185.
- [8] T. Zhang, L. Sun, R. Liu, D. Zhang, X. Lan, C. Huang, W. Xin, C. Wang, D. Zhang, G. Du, *Mol. Pharmaceutics*, **2012**, 9, 671.
- [9] M. R. S. Vicente, J. Plasencia, *J. Exp. Botany.*, **2011**, 62, 3321.
- [10] S. V. Lisina, A. K. Brel, L. S. Mazanova, A. A. Spasov, *Pharm. Chem. J.*, **2008**, 42, 574.
- [11] H. P. Patel, S. S. Patel, A. D. Patel, *Jour. of. Chem. and Pharm. Res. J.*, **2015**, 7(9):690-694.
- [12] H. Su, A. Nebbioso, V. Carafa, Y. Chen, B. Yang, L. Altucci, Q. You, *Bioorg. Med. Chem.*, **2008**, 16, 7992.
- [13] W. R. Baily, E. G. Scott, **1966**, *Diagnostic Microbiology*, The C.V.Moshy Co.St. Lovis, 257.
- [14] A. K. Bhatt, P. K. Shah, H. G. Karadia, H. D. Patel, *Orient. J. Chem*, **2003**, 19, 643.
- [15] W. Kemp, *Organic Spectroscopy*ELBS.(Macmillan' UK), **1998**.
- [16] K. Nakamoto, *Infrared Spectra of Inorganic and Co-Ordination Compound*, Wiley, NY,**1970**.
- [17] B. N. Figgis, *Introduction to Ligands Field*, Wiley Eastern Ltd. NY, **1976**.
- [18] J. C. Patel, H. R. Dholariya, K. S. Patel, K.D. Patel, *Appl. Organometal. Chem.*, **2012**, 26, 604.
- [19] R. N. Carlin, A. J. Van Dryneveldt, *Magnetic properties of Transition Metal Compound*, Springe-Berlag,NY, **1997**.
- [20] F. A. Kettle, *Coordination Compounds*, Thomas Nelson & Sons, **1975**.