

STUDIES ON TRANSITION METAL CHELATES OF HETEROCYCLIC LIGANDS CONTAINING FURAN RING

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ARTICLE INFO

Article History:

Received 7th November, 2017

Received in revised form 13th

December, 2017

Accepted 3rd January, 2018

Published online 28th February, 2018

Key words:

5-((dipropylamino)methyl)furan-2-yl propionate, 4-amino salicylic acid, Reflectance spectroscopy, Spectral studies and Antifungal activity.

ABSTRACT

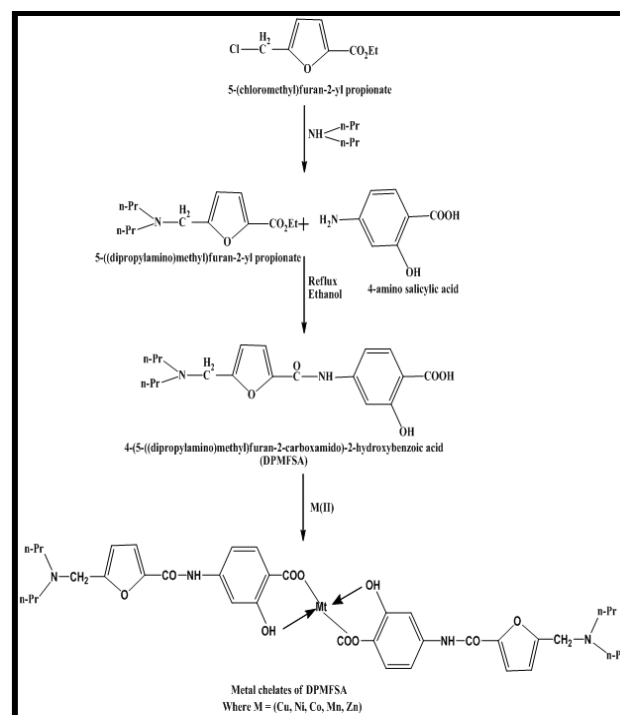
4-(5-((dipropylamino)methyl)furan-2-carboxamido)-2-hydroxybenzoic acid(DPMFSA) was prepared by reaction between 5-((dipropylamino)methyl)furan-2-yl propionate and 4-amino salicylic acid. The synthesized ligand was further characterized on the basis of their elemental as well as spectral analyses. Further the transition metal chelates of newly synthesized ligand (DPMFSA) were synthesized according to reported method. The characterization of all metal chelates (i.e. Cu, Ni, Co, Mn and Zn) were carried out by elemental analyses, metal-ligand (M:L) ratio, spectral analyses, reflectance spectroscopies and magnetic properties. The antifungal screening of synthesized ligand and its metal chelates against various fungal strains shows the higher antifungal activity of all metal chelates than its parent ligand.

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INTRODUCTION

Now a day, the research on synthesis and chelating properties of metal-containing heterocyclic compounds become an interesting field of chemistry. Heterocyclic ligands and their coordinated compound play a vital role in the development of coordination chemistry as they shows a broad range of applications including biological field [1-4]. Salicylic acid derivatives are proven as an important class of pharmaceutical compounds. Metal chelates of one of the important derivatives named 4-amino salicylic acid shows significant biological activities such as antibacterial, antifungal, antitumor, antipyretic and anti-inflammatory activities [5-9].

Furan derivatives can be synthesized easily and studied extensively for their biological features. Some of the transition metal chelates of these derivatives were reported with good biological potentiality [10-12]. In recent past the metal chelates of furan derivatives were synthesized by us exhibits significant biological activities. Hence, in continuation of our previous work [13], the present work comprises synthesis, characterization and antifungal activity of transition metal chelates containing 4-amino salicylic acid and furan moieties. The synthetic route of synthesized metal chelates are shown in Scheme-1.



Scheme 1 The synthetic route of synthesized metal chelates

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MATERIALS AND METHODS

All the raw materials such as Ethyl furan-2-carboxylate and 4-Amino salicylic acid was obtained from local market. All

solvents used were of analytical grade. 5-(chloromethyl)furan-2-yl propionate synthesized according method reported [14].

Measurements

On elemental analyzer TF-EA.1101 (Italy) the elemental analysis of C, H and N were carried out. IR spectra of MENFSA and its metal complexes were scanned on a Nicolet 760 FTIR spectrophotometer in KBr. The NMR spectrum of DPMFSA 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 [14]. Magnetic susceptibility measurement of the entire metal complex was carried out at room temperature by the Gouy method. Mercury tetrathiocyanatocobalate (II) Hg [Co(NCS)₄] was used as a calibrant. The diffused reflectance spectra of solid metal complex were recorded on a Backman DK Spectrophotometer with a solid reflectance attachment, MgO was employed as the reflectance compound. The electrical conductivity of all the complexes was measure in acetonitrile at 10⁻³ M concentration.

Synthesis of 5-((dipropylamino)methyl)furan-2-ylpropionate

5-((dipropylamino)methyl)furan-2-yl propionate and K₂CO₃ were taken in the round bottom flask following the addition of small amount of KI powder. The above mixture was stirred at room temperature in 20 ml DMF for 2 hrs. Then the ethyl methyl amine (0.01 mole) was added to above reaction mixture which was refluxed for 4-5 hrs. 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 obtained compound in pure form. Yield: 75%, m.p. 147-148°C, Anal. Calcd for C₁₄H₂₃NO₃ (253): C, 66.37; H, 9.15; N, 5.53; Found: C, 66.30; H, 9.11; N, 5.47. IR (cm⁻¹) (KBr): 3415 (Amine), 3062 (Ar.C-H), 2925 (aliphatic C-H), 1342 (CN), 1712 (CO), 1271 (C-O). ¹H NMR δppm: δ 0.95 (6H, t, N-CH₂CH₂CH₃), 1.21 (3H, t, -CH₃), 1.70 (4H, sext, N-CH₂CH₂CH₃), 4.15 (4H, sext, N-CH₂CH₂CH₃), 4.22 (2H, q, -CH₂), 4.98 (2H, d, N-CH₂), 6.38-6.57 (2H, d, furan CH).

Synthesis of 4-(5-((dipropylamino)methyl)furan-2-carboxamido)-2-hydroxybenzoic acid (DPMFSA)

A equimolar mixture of 5-((dipropylamino)methyl)furan-2-yl propionate and 4-amino salicylic acid in 60 ml ethanol was refluxed for 4-5 hrs. Furthermore ethyl alcohol was distilled off and the solid mass obtained. The solid DPMFSA was isolated and dried in air. Yield was 72%. It's m.p. was 252-254°C (uncorrected).

Elemental Analysis: C₁₉H₂₄N₂O₅ (360)

	C%	H%	N%
Calculated:	63.32	6.71	7.77
Found :	63.28	6.65	7.70

IR Features:

3440 cm ⁻¹	Sec.NH
3382 cm ⁻¹	-OH
2886, 2950 cm ⁻¹	CH ₂ , CH ₃
1625 cm ⁻¹	CO

¹H NMR (DMSO, δ ppm)

11.32 (1H)	Singlet	-COOH
8.54 (1H)	Singlet	CO-NH
7.42 - 8.25 (3H)	Multiplet	Aromatic
6.61, 7.24 (2H)	Doublet	Furan CH

5.21 (1H)	Singlet	-OH
3.92 (2H)	Quartet	N-CH ₂
4.11 (4H)	Sextet	N-CH ₂ CH ₂ CH ₃
1.71 (4H)	Sextet	N-CH ₂ CH ₂ CH ₃
0.92 (6H)	Triplet	N-CH ₂ CH ₂ CH ₃

Synthesis of metal chelates of DPMFSA

The transition metal chelates of DPMFSA of Cu²⁺, Ni²⁺, Co²⁺, Mn²⁺ and Zn²⁺ metals have been prepared using following method

To a solution of DPMFSA (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 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. The final product obtained in form of amorphous powder with good yield. The analysis details are given in **Table-1**.

Table 1 Analytical results of the DPMFSA-M(II) metal chelates

Empirical Formula	Yield (%)	Elemental Analysis							
		C%		H%		N%		M%	
		Calcd	Found	Calcd	Found	Calcd	Found	Calcd	Found
DPMFSA	72	63.32	63.28	6.71	5.65	7.77	7.70	--	--
(DPMFSA) ₂ Cu ²⁺ ·2H ₂ O	70	59.21	59.18	6.34	6.31	6.90	6.85	7.83	7.79
(DPMFSA) ₂ Ni ²⁺ ·2H ₂ O	66	59.57	59.52	6.37	6.39	6.95	6.92	7.28	7.26
(DPMFSA) ₂ Co ²⁺ ·2H ₂ O	68	59.55	59.53	6.37	6.34	6.94	6.90	7.30	7.27
(DPMFSA) ₂ Mn ²⁺ ·2H ₂ O	69	59.84	59.80	6.40	6.36	6.98	7.96	6.84	6.81
(DPMFSA) ₂ Zn ²⁺ ·2H ₂ O	62	59.07	59.03	6.32	6.29	6.89	6.86	8.04	8.00

Antifungal activity

The antifungal evaluation of ligand and their metal chelates were carried out at 1000 ppm concentration using different fungal strains listed in **Table-3**. The agar cup method (**Figure-2**) reported in literature [15] was employed to evaluate antifungal activities of all the samples as follows

Each of the antifungal 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 novel ligand DPMFSA was an amorphous yellowish white powder, soluble in most organic solvents and insoluble in water. The CHN analysis results are found (Table-1) are consistent with the predicted structure as shown in Scheme-1. The transition metal chelate of DPMFSA with Cu, Co, Ni, Mn and Zn are differ in colours. The empirical formula of the DPMFSA ligand is $C_{14}H_{23}NO_3$ while the complexation coordinates with one central metal atom at four coordination sites and with two water molecules shows the general molecular formula of the resulting metal chelate is $[DPMFSA]_2M(II).2H_2O$. The general formula is further supported by the element analysis results given in Table-1. The results are in agreement with the calculated values.

The FTIR spectrum of DPMFSA (Figure-1) shows the broad band of -OH stretching frequency observed at 3382 cm^{-1} . The bands observed at 3440 cm^{-1} due to amine group stretching. The strong bands at 1625 cm^{-1} due to C=O. Also other bands for CN stretching, C-O stretching, aromatic stretching and aliphatic stretching are found at their respective positions. However, examination of the FTIR Spectra of metal chelates reveals that all the spectra are identical in all respects. The comparison of IR spectrum of the parent ligand DPMFSA with each metal chelates has revealed certain characteristics differences. The most significant difference is found between the FTIR spectrum of the ligand and its metal chelates is the presence of more broadened bands in the region of $3200\text{-}3400\text{ cm}^{-1}$ for the metal chelates as the oxygen of the O-H group of the ligands forms a coordination bond with the metal ions [16,17] which confirmed by the fact that water molecule might have strongly absorbed to the metal chelates samples during their formation. Another important difference is the formation of CO shows important band at around $\sim 1735\text{ cm}^{-1}$ in the IR spectrum of the each metal chelates. The chelate formation is supported by the band value of OH plane determination shifted at higher frequency than its parent ligand [16-18]. Also the each metal chelates was confirmed by the M-L band found at their respective position for particular metal chelate. Thus all of these characteristics features of the FTIR studies confirm the structure of the metal chelates as shown in Scheme-1.

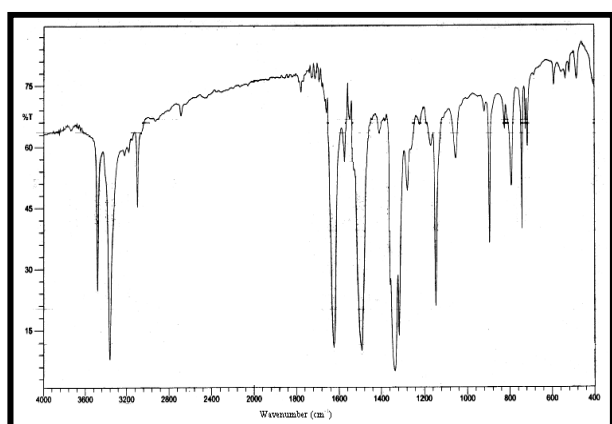


Figure 1 IR spectrum of ligand DPMFSA

The NMR spectrum of DPMFSA in DMSO shows that the singlet of 1H at $5.21\text{ }\delta$ ppm, due to -OH group. The bands at 8.54 and 11.32 ppm attributed to -NH and -COOH group, respectively. The furan ring protons were shows doublet of 2H at $6.61\text{-}7.24$ ppm. The aromatic protons are appeared in multiplicity at $7.42\text{-}8.25\text{ }\delta$ ppm. Also the important protons of

substituted n-propyl group found at their respective positions as describe in experimental part which confirms the predicted structure of ligand as shown in Scheme-1.

The metal content analysis carried out by EDTA titration method for each metal chelate revealed a metal:ligand (1:2) stoichiometry. The reflectance spectral analysis along with magnetic moment (μ_{eff}) of each metal chelate is given in Table-2 which suggests the para magnetic nature for all metal chelates except Zn(II) which is diamagnetic in nature.

The diffuse electronic spectrum of the Cu(II) metal chelate shows two broad bands at 16125 and 22852 cm^{-1} attributed to the ${}^2T \rightarrow {}^2T_{2g}$ transition and charge transfer, respectively suggest a distorted octahedral geometry [19], which is further confirmed by the higher value of μ_{eff} . The Ni(II) and Co(II) complexes shows two absorption bands at 15110 , 23145 and 15574 , 22920 cm^{-1} corresponding to ${}^3A_{2g} \rightarrow {}^3T_{1g}(p)$, ${}^3A_{1g} \rightarrow {}^3T_{1g}(F)$ and ${}^4T_{1g}(F) \rightarrow {}^4T_{2g}(F)$, ${}^4T_{1g}(F) \rightarrow {}^3A_{2g}$ transitions [20,21]. Thus absorption bands and the value of the magnetic moments indicate octahedral configuration for both metal chelates. The reflectance spectra of Mn(II) shows weak bands at 15402 , 17874 and 23107 cm^{-1} assigned to the transitions ${}^6A_{1g} \rightarrow {}^4T_{1g}(4G)$, ${}^6A_{1g} \rightarrow {}^4T_{2g}(4G)$ and ${}^6A_{1g}(F) \rightarrow {}^4T_{1g}$, respectively suggests an octahedral structure [21]. 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 Zn(II) chelate is not well resolved, it is not interpreted but it is μ_{eff} value shows that it is diamagnetic as expected.

The antifungal activity of all the compounds measured against four plant pathogens and was displayed in Table-3 which indicates that all compounds are good to moderately toxic for fungi. Among them Cu(II) chelate is found more toxic than other. Also all chelates found more toxic than its parent ligand.

Table 2 Reflectance Spectral and Magnetic measurement data of all compounds

M(II) Chelate	μ_{eff} (B.M.)	Absorption band (cm^{-1})	Transitions
Cu-DPMFSA	2.45	22852 16125	C.T. ${}^2T \rightarrow {}^2T_{2g}$
Ni- DPMFSA	3.82	15110 23145	${}^3A_{1g} \rightarrow {}^3T_{1g}(P)$, ${}^3A_{1g} \rightarrow {}^3T_{1g}(F)$
Co-DPMFSA	4.58	15574 22920	${}^4T_{1g}(F) \rightarrow {}^4T_{2g}(F)$ ${}^4T_{1g}(F) \rightarrow {}^3A_{2g}$
Mn-DPMFSA	5.21	15402 17874 23107	${}^6A_{1g} \rightarrow {}^4T_{1g}(4Eg)$ ${}^6A_{1g} \rightarrow {}^4T_{2g}(4G)$ ${}^6A_{1g} \rightarrow {}^4T_{1g}(4G)$

*Zn(II) is Diamagnetic in Nature.

Table 3 Antifungal activity results of all compounds

Sample	Zone of inhibition of fungus at 1000ppm (%)			
	Botrydepladia thiobromine	Nigrospra sp.	Rhizopus nigricans	Aspergillus niger.
DPMFSA	65	58	60	50
Cu-DPMFSA	78	74	71	66
Ni- DPMFSA	72	69	70	65
Co-DPMFSA	66	66	68	60
Mn-DPMFSA	70	71	73	67
Zn-DPMFSA	66	61	55	50



Figure2 Antifungal activity of DPMFSA and its metal chelates

Acknowledgement

I am greatly thankful to Dr. Asha D. Patel M.L.A. of Gujarat, Former Assistant Professor Chemistry Department, M. N. College, Visnagar, Gujarat, India for providing necessary research guidance.

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How to cite this article:

Harshadkumar P. Patel (2018) 'Studies on Transition Metal Chelates of Heterocyclic Ligands Containing Furan Ring ', *International Journal of Current Advanced Research*, 07(2), pp. 10216-10219.
DOI: <http://dx.doi.org/10.24327/ijcar.2018.10219.1720>
