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**Research Article**

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# Sulfonamide derivative and maleic anhydride based transition metal complexes: As potent antimicrobial agents

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**ABSTRACT**

*In the present study a novel 4-oxo-4-((4-N-(thiazol-2-yl)sulfamoyl)phenyl)amino)but-2-enoic acid (OTSPAB) was prepared by reaction of maleic anhydride with Sulphathiazol. The prepared ligand was characterized by elemental analysis and spectral studies. The transition metal complexes viz. $Cu^{2+}$, $Ni^{2+}$, $Co^{2+}$, $Mn^{2+}$ and $Zn^{2+}$ of OTSPAB were prepared and characterized by metal-ligand (M:L) ratio, IR, reflectance spectroscopies and magnetic properties. All the prepared metal complexes and ligand were studies as antimicrobial agent. Among all the metal complexes, $Zn^{2+}$ and $Cu^{2+}$ metal complexes have shown significant activity.*

**Keywords:** maleic anhydride, Sulphathiazol, Magnetic moment, Spectroscopic study and Antifungal properties.

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## INTRODUCTION

In inorganic chemistry most active research area is coordination chemistry. Recently, numbers of coordination metal complexes have been synthesized and investigated, which exhibit various biological activities [1-5]. Sulfonamides (sulfa drugs) were the first drugs largely employed and systematically used as preventive and chemotherapeutic agents against various diseases [6]. Over 30 drugs containing this functionality are in clinical use, including antihypertensive agent bosentan [7], antibacterial [8], antiprotozoal [9], antifungal [10], antiinflammatory[11], nonpeptidic vasopressin receptor antagonists [12] and translation initiation inhibitors [13]. Some important sulfonamide derivatives used as carbonic anhydrase inhibitors of commercial importance[14]. They are also effective for the treatment of urinary, intestine, and ophthalmic infections, scalds, ulcerative colitis [15], rheumatoid arthritis [16], male erectile dysfunction as the phosphodiesterase-5inhibitor sildenafil – better known under its commercial name, Viagra [17], and obesity [18]. More recently, sulfonamides are used as an anticancer agent [19], as the antiviral HIV protease inhibitor amprenavir [20] and in Alzheimer's disease [21]. The reaction of maleic anhydride derivatives with Sulphathiazol has not been reported for metal complaxation so far. Hence, it was thought that maleic anhydride and Sulphathiazol moieties can put into one molecule frame may afford good biological active compound. The present article discuss about synthesizes, characterization and biological studies of 4-oxo-4-((4-N-(thiazol-2-yl)sulfamoyl)phenyl)amino)but-2-enoic acid (OTSPAB). Also its metal complexes based on literature serve regarding importance of complexes, it was thought to synthesis transition metal complexes of prepared ligand in order to improve in biological activity.

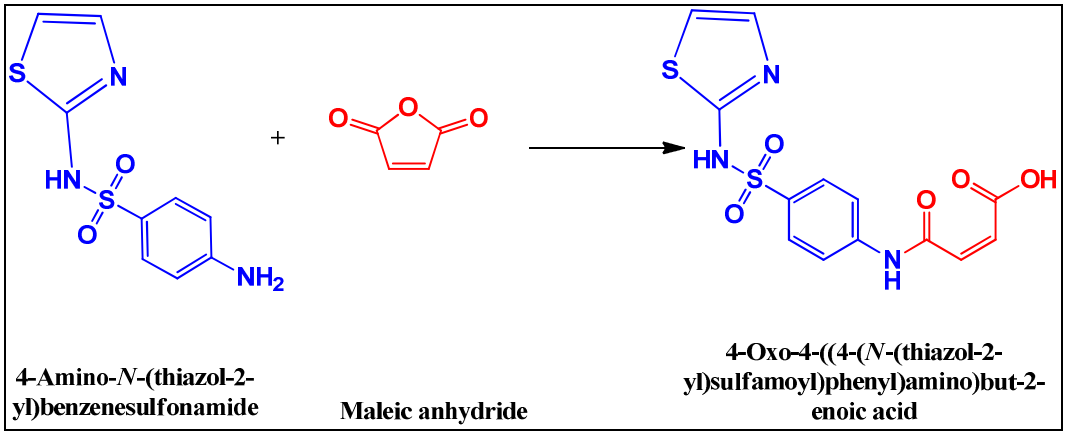
## EXPERIMENTAL SECTION

All the chemicals used were of laboratory grade received from Sigma–Aldrich. Sulphathiazol was taken direct purchase to Sigma–Aldrich . $^{1}H$, $^{13}C$ and DEPT-135 NMR spectra were recorded in $CDCl_3$ at room temperature

using a Bruker AVANCE III 500 MHz (AV 500) multi nuclei solution NMR Spectrometer, TMS was used as internal reference. IR spectra were recorded neat by ATR on a Thermo Nicolet iS50 FT–IR spectrometer and are reported in $cm^{-1}$. HR–MS data were obtained in methanol, with Thermo Scientific Orbitrap Elite Mass spectrometer. The elemental contents were determined by Thermo Finigen Flash1101 EA (Itally) the metals were determined volumetrically by Vogel's method [22]. To a 100 mg chelate sample, each 1 ml of HCl, $H_2SO_4$ and $HClO_4$ were added and then 1 g of $NaClO_4$ was added. The mixture was evaporated to dryness and the resulting salt was dissolved in double distilled water and diluted to the mark. From this solution the metal content was determined by titration with standard EDTA solution. Magnetic susceptibility measurement of the synthesized complexes were carried out on Gouy Balance at room temperature. Mercury tetrathiocynatocobalate (II) $Hg[Co(NCS)_4]$ was used as a calibrant. The electronic spectra of complexes in solid were recorded on at room temperature. MgO was used as reference. Melting point is measured by open capillary method using Sigma Melting Point Apparatus.

**2.2. Synthesis of 4-oxo-4-((4-N-(thiazol-2-yl)sulfamoyl)phenyl)amino)but-2-enoic acid (OTSPAB)**

The reaction mixture of maleic anhydride (0.01 mole) in ethanol and (0.01 mole) Sulphathiazol in ethanol was refluxed for 2-3 hrs. The resulting solid was washed with water, dried and recrystallized from MeOH. Yield: 73.24 %, M.P. (193-194°C) was measurement with open capillary method and it is uncorrected. IR ($cm^{-1}$): 2950-2850 (Ar C-C), 3450-3360 (CONH, $NH_2$), 3430, 1680 (COOH),1620-1680(C=C). $^1$H- NMR(δ ppm, 500 MHz, CDCl3): 11.80 (s, 1H, COOH), 8.32 (s, 1H, NH), 7.71-7.98 (m, 4H, Ar-H), 6.51-6.92 (d, 2H, CH=CH), 3.14 (s, 2H, $NH_2$). $^{13}$C MNR (δ ppm, 125 MHz, CDCl3): 182.23, 172.62, 152.12, 148.07, 138.20, 129.38, 127.98. DEPT-135 (δ ppm, 125 MHz, CDCl3): 138.20, 129.38, 127.98.




**Scheme 1 Synthesis of OTSPAB**

**2.3. Synthesis of metal complexes of 4-oxo-4-((4-N-(thiazol-2-yl)sulfamoyl)phenyl)amino)but-2-enoic acid (OTSPAB)**

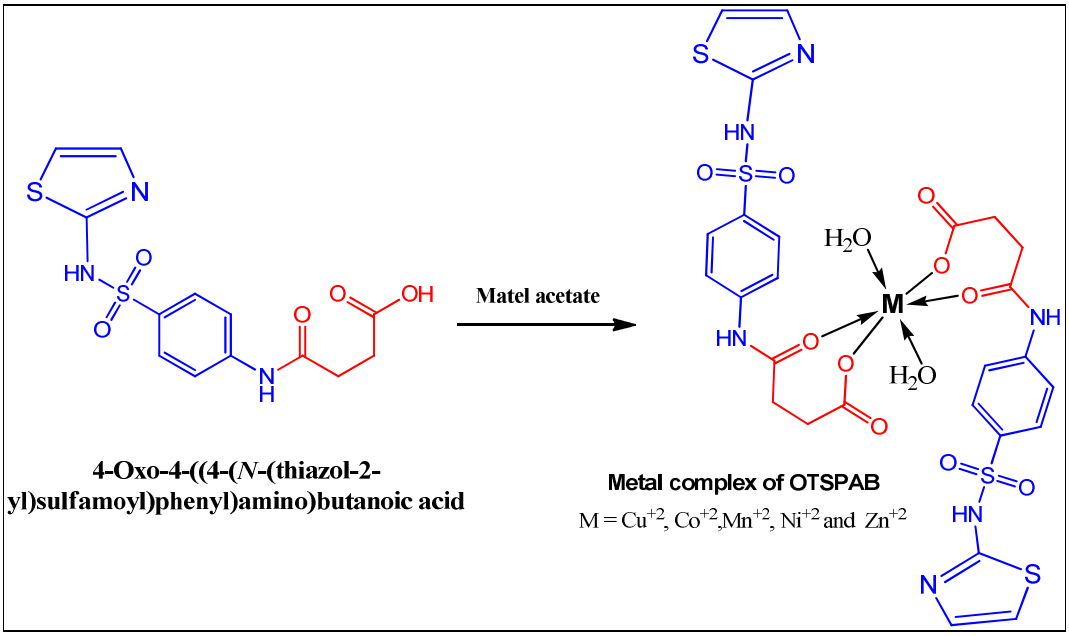
The metal complexes of OTSPAB with $Cu^{2+}$, $Co^{2+}$, $Zn^{2+}$, $Mn^{2+}$, and $Ni^{2+}$ metal ions were prepared in two steps. All the metal complexes were prepared in an identical procedure.

***Preparation of OTSPAB solution***

The OTSPAB (0.05 mol) was taken in 100 ml beaker and formic acid (85% v/v) was added up to slurry formation. To this slurry water was added till the complete dissolution of OTSPAB. It was diluted to 20 ml.

***Synthesis of OTSPAB-metal-complexes***

In a solution of metal acetate (0.025 mol) in acetone: water (50:50 v/v) mixture (40 ml) the 20 ml of above mentioned OTSPAB solution (i.e. containing 0.05 M OTSPAB) was added with vigorous stirring at room temperature. The appropriate pH was adjusted by addition of sodium acetate for complete precipitation of metal chelate. The precipitates were digested on a boiling water bath and filtered off, washed by water and air-dried.




**Scheme - 2 Synthesis of metal complexes of OTSPAB**

**Table 1. Analysis of OTSAPB ligand and its metal complexes**

| Empirical Formula | Yield (%) | Elemental Analysis | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | C% | | H% | | N% | | S% | | M% | |
| | | Cald | Found | Cald | Found | Cald | Found | Cald | Found | Cald | Found |
| OTSPAB | 75 | 43.93 | 43.91 | 3.69 | 3.68 | 11.82 | 11.81 | 18.04 | 18.02 | - | - |
| $(OTSPAB)_2Cu^{2+}$ | 63 | 38.63 | 38.62 | 3.49 | 3.48 | 10.40 | 10.39 | 15.87 | 15.88 | 7.86 | 7.87 |
| $(OTSPAB)_2Co^{2+}$ | 62 | 38.85 | 38.86 | 3.51 | 3.50 | 10.46 | 10.45 | 15.96 | 15.95 | 7.33 | 7.32 |
| $(OTSPAB)_2Ni^{2+}$ | 64 | 38.87 | 38.85 | 3.51 | 3.50 | 10.46 | 10.47 | 15.96 | 15.95 | 7.30 | 7.31 |
| $(OTSPAB)_2Mn^{2+}$ | 67 | 39.05 | 39.03 | 3.53 | 3.52 | 10.51 | 10.50 | 16.04 | 16.05 | 6.87 | 6.86 |
| $(OTSPAB)_2Zn^{2+}$ | 63 | 38.54 | 38.56 | 3.48 | 3.47 | 10.37 | 10.36 | 15.83 | 15.82 | 8.07 | 8.06 |

### 2.4. Antibacterial activity

The synthesized compounds were screened for their antibacterial activities against *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus vulgaris*, *Staphylococcus aureus*, and *Pseudomonas aeruginosa* at a concentration of 200 µg $ml^{-1}$ in dimethylsulphoxide by agar diffusion method using streptomycin as standard. The minimum inhibitory concentrations (MIC) were detected by serial dilution method. The lowest concentration (µg $ml^{-1}$) of the compound, which inhibits the growth of bacteria maximum after 24 h inhibition at 37 ºC, was taken as MIC. The stock solution ($10^{-2}$ M) was prepared by dissolving the complex in dimethylsulphoxide and the solutions were diluted to different concentrations in the same solvent in order to find the MIC values.

## RESULTS AND DISCUSSION

The synthesis of 4-oxo-4-((4-N-(thiazol-2-yl)sulfamoyl)phenyl)amino)but-2-enoic acid (OTSPAB) was performed by a simple reaction of maleic anhydride and Sulphathiazol. The resulted OTSPAB ligand was an amorphous brown powder. The C,H,N contents of OTSPAB (Table-1) are consistent with the structure predicted (**Scheme-1**). The IR spectrum of OTSPAB comprises the important bands of structure.

The broad band due to –OH group appeared at 3430 $cm^{-1}$. In this band the inflections are observed at 2970, 2930 and 2850$cm^{-1}$. The NMR spectrum of OTSPAB in DMSO indicates that the singlet of 1H at 11.8 δ ppm due to –COOH group. The aromatic protons are appeared in multiplicity at 7.7-7.9 δ. Thus the structure of OTSPAB is confirmed as shown in **Scheme - 1**.

The metal and C, H, N contents of metal complexes of OTSPAB (Table - 1) are also consistent with the predicted structure. The results show that the metal: ligand (M:L) ratio for all divalent metal chelate is 1:2.

**Table 2. Spectral features and magnetic moment of OTSPAB metal complexes**

| Metal Complexes | $\mu_{eff}$ (BM) | Electronic spectral data ($cm^{-1}$) | Transition |
|---|---|---|---|
| OTSPAB-$Cu^{2+}$ | 2.54 | 23445<br>13208 | Charge transfer<br>$^2B_{1g}\rightarrow{}^2A_{1g}$ |
| OTSPAB-$Ni^{2+}$ | 3.67 | 22590<br>15367 | $^3A_{1g}\rightarrow{}^3T_{1g}(P)$<br>$^3A_{1g}\rightarrow{}^3T_{1g}(F)$ |
| OTSPAB-$Co^{2+}$ | 4.72 | 23735<br>19099<br>8920 | $^4T_{1g}(F)\rightarrow{}^4T_{2g}(F)$<br>$^4T_{1g}(F)\rightarrow{}^4T_{2g}$<br>$^4T_{1g}(F)\rightarrow{}^4T_{2g}(P)$ |
| OTSPAB-$Mn^{2+}$ | 5.55 | 23230<br>19032<br>16902 | $^6A_{1g}\rightarrow{}^6A_{2g}\ {}^4E_g$<br>$^6A_{1g}\rightarrow{}^4T_{2g}$ (4G)<br>$^6A_{1g}\rightarrow{}^4T_{1g}$(PG) |
| OTSPAB-$Zn^{2+}$ | Diamag. | -------- | --------- |

**Table 3. Antibacterial activity of OTSPAB ligand and its metal complexes**

| Sample | Zone of inhibition at 1000 ppm (%) | | | |
|---|---|---|---|---|
| | *Escherichia coli* | *Klebsiella pneumonia* | *Proteus vulgaris* | *Staphylococcus aureus* |
| OTSPAB | 52 | 59 | 48 | 59 |
| OTSPAB-$Cu^{2+}$ | 73 | 73 | 69 | 72 |
| OTSPAB-$Co^{2+}$ | 61 | 69 | 70 | 65 |
| OTSPAB-$Ni^{2+}$ | 57 | 66 | 62 | 63 |
| OTSPAB-$Mn^{2+}$ | 59 | 58 | 63 | 61 |
| OTSPAB-$Zn^{2+}$ | 74 | 70 | 57 | 73 |
| Ampicillin | 84 | 88 | 76 | 86 |

The infrared spectra of all the complexes are identical and suggest the formation of all the metalocyclic compound by the absence of band characteristic of free –OH group of parent OTSPAB. The other bands are almost at their respectable positions as appeared in the spectrum of parent-OTSPAB ligand. However, the band due to (M-O) band could not be detected as it may appear below the range of instrument used. The important IR Spectral data are shown in Table - 2.

Magnetic moments of metal complexes are given in Table - 2. The diffuse electronic spectrum of $Cu^{2+}$ complexes shows two broad bands around 13208 and 23445 $cm^{-1}$. The first band may be due to a $^2B_{1g}\rightarrow{}^1A_{1g}$ transition. While the second band may be due to charge transfer. The first band shows structures suggesting a distorted octahedral structure for the $Cu^{2+}$ metal complexes. The higher value of the magnetic moment of the $Cu^{2+}$ chelate supports the same. The $Co^{2+}$ metal chelate gives rise to two absorption bands at 23735 and 19099 $cm^{-1}$, which can be assigned $^4T_{1g}\rightarrow{}^2T_{2g}$, $^4T_{1g}\rightarrow{}^4T_{1g}(P)$transitions, respectively. These absorption bands and the µeff value indicate an octahedral configuration of the $Co^{2+}$ metal chelate [23]. The spectrum of $Mn^{2+}$ polymeric chelate comprised two bands at 19032$cm^{-1}$ and 23230$cm^{-1}$. The latter does not have a very long tail. These bands may be assigned to $^6A_{1g}\rightarrow{}^4T_{2g(G)}$ and $^6A_{1g}\rightarrow{}^4A_{2g(G)}$ transitions, respectively. The high intensity of the bands suggests that they may have some charge transfer character. The magnetic moment is found to be lower than normal range. In the absence of low temperature measurement of magnetic moment it is difficult to attach any significance to this. The observed µeff values in the range 2.54-5.55 B.M are consistent with the above moiety[24].

The examination of antibacterial activity of ligand and its all complexes (Table-3) reveals that the ligand is moderately toxic against bacteria, while all the complexes are more toxic than ligand. Among all the complexes the $Cu^{2+}$ chelate is more toxic against tested bacteria.

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