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-enolic 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 studied 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.

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-5 inhibitor 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 complexation 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)amino)but-2-enolic 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 (Italy) the metals were determined volumetrically by Vogel’s method [22].

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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, NH₂), 3430, 1680 (COOH),1620-1680(C=O). ¹H- 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, NH₂). ¹³C 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](image)

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 Cu²⁺, Co²⁺, Zn²⁺, Mn²⁺, and Ni²⁺ 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.

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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 °C, 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)phenylamino)butenoic 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 2850cm⁻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

<table>
<thead>
<tr>
<th>Metal Complexes</th>
<th>( B_{\text{eff}} ) (BM)</th>
<th>Electronic spectral data (cm(^{-1}))</th>
<th>Transition</th>
</tr>
</thead>
<tbody>
<tr>
<td>OTSPAB-Cu(^{2+})</td>
<td>2.54</td>
<td>23445 13208</td>
<td>Charge transfer ( ^2B_g \rightarrow ^1A_g )</td>
</tr>
<tr>
<td>OTSPAB-Ni(^{2+})</td>
<td>3.67</td>
<td>22590 15387</td>
<td>(^3A_{2g} \rightarrow ^3T_{2g}(P)), (^3A_{2g} \rightarrow ^3T_{2g}(F))</td>
</tr>
<tr>
<td>OTSPAB-Co(^{2+})</td>
<td>4.72</td>
<td>23735 19099 8920</td>
<td>(^4T_{2g}(F) \rightarrow ^4T_{2g}(F)), (^4T_{2g}(F) \rightarrow ^4T_{2g}(P))</td>
</tr>
<tr>
<td>OTSPAB-Mn(^{2+})</td>
<td>5.55</td>
<td>23230 19032 16902</td>
<td>(^6A_{1g} \rightarrow ^4A_{2g}), (^6A_{1g} \rightarrow ^4T_{2g}(4G)), (^6A_{1g} \rightarrow ^4T_{2g}(PG))</td>
</tr>
<tr>
<td>OTSPAB-Zn(^{2+})</td>
<td>Diamag</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Sample</th>
<th>Zone of inhibition at 1000 ppm (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Escherichia coli</td>
</tr>
<tr>
<td>OTSPAB</td>
<td>52</td>
</tr>
<tr>
<td>OTSPAB-Cu(^{2+})</td>
<td>73</td>
</tr>
<tr>
<td>OTSPAB-Co(^{2+})</td>
<td>61</td>
</tr>
<tr>
<td>OTSPAB-Ni(^{2+})</td>
<td>57</td>
</tr>
<tr>
<td>OTSPAB-Mn(^{2+})</td>
<td>59</td>
</tr>
<tr>
<td>OTSPAB-Zn(^{2+})</td>
<td>74</td>
</tr>
<tr>
<td>Ampicillin</td>
<td>84</td>
</tr>
</tbody>
</table>

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 \(^2B_g \rightarrow ^1A_g\) 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 \(^4T_{2g}(F) \rightarrow ^4T_{2g}(F)\), \(^4T_{2g}(F) \rightarrow ^4T_{2g}(P)\) transitions, respectively. These absorption bands and the \( B_{\text{eff}} \) value indicate an octahedral configuration of the Co\(^{2+}\) metal chelate [23]. The spectrum of Mn\(^{2+}\) polymeric chelate comprised two bands at 19032cm\(^{-1}\) and 23230cm\(^{-1}\). 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 \( B_{\text{eff}} \) values in the range 2.54-5.55 BM 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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REFERENCES