Synthesis and Pharmacological Evaluation of Molybdenum Complex with Biologically active Ligand

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Abstract

Molybdenum Complex with organic ligand is compound of great theoretical and practical interest especially valuable as model systems for biochemical process. Moreover, dithiocarbamate ligand is known to form stable Complex with many Transition metals. Interest in Complex arises because of its versatile structure of Biological activity. The Mo (V) Complex was optimized and a description of the structural parameters is given. Finally the complex was examined as potential antimicrobial agents.

Keywords: Synthesis, spectra, antibacterial, cytotoxic studies, dithiocarbamate.

INTRODUCTION

The Molybdenum is Ubiquitous and plays a Complex role in the environment. The interactions of Molybdenum with organic compounds have been the object of many studies. The preparation and characterization of Molybdenum Complexes based on different carriers with appropriate functional groups is one of the promising and interesting research fields in Polymer and Pharmaceutical Chemistry that significantly broadens the Prospective practical application of these materials. In the present investigation Complexes of Molybdenum with α-, m-, β- Ammonium toludinyl dithiocarbamates have been proposed as models of Molybdenum Coordination in enzymes. In molybdoenzymes eg. Xanthine oxidase, the active site species monomeric molybdenum (V) Coordinated by sulphur. Molybdenum (V), Sulphur complexes Prepared by reduction of molybdate (vi) in aqueous solution, usually contain dimeric, diamagnetic molybdenum species. In this paper the synthesis, characterization and Biological studies of Molybdenum (V) Complex with Containing dithiocarbamate group have been discussed. Most of the chemicals used were of AR grade. Laboratory grade chemicals, whenever used were purified by standard methods, while the solvents were purified and double distilled before use. C, H, N and S Contents were determined by Perkin Elmer 2400 elemental analyser, IR spectra were recorded in the range 4000 cm⁻¹ – 100 cm⁻¹ with a Bruker IFS 66V in KBr and polyethylene medium for compound. The Molar Conductance of the complex in DMF (10⁻³ M) solution was measured at 27 ±3°C with an Elico Model Conductivity meter. UV-visible Spectra were recorded in DMF with Perkin - Elmer Lambda 35 spectrophotometer NMR spectra on Bruker Advance III 400 MHz spectrometer. Ligand and metal Complex were investigated for antibacterial and antifungal against Staphylococcus aureus and Bacillus species as gram positive bacteria and Escherichia Coli and Proteus mirabilis as Gram negative and The Fungi Candida albicans and Aspergillus fumigatus by using disc - agar diffusion method was followed to determine the activity of the synthesized Compounds against the Bacterial and Fungal species. The antibiotic chloramphenicol, tetracycline and clotrimazole were used as standard reference for in the case of Gram negative, Gram positive and antifungal species. The tested Compounds were dissolved in DMF (which have no inhibition activity) to get a Concentration of 100 µg/mL incubation period for bacterial species 36h at 27°C and for Fungal species 48h at 24°C inhibition of the organism which evidenced by clear zone surround each disk was measured and used to calculate mean of inhibition Zone. The anticancer activities of the ligand and its metal Complex against the human liver Carcinoma (HEPG 2) and Colon Carcinoma (HCT 116) cell lines were screened using MTT assay. The results were analysed by cell viability curves and expressed as IC₅₀ values.

The ligand Ammonium Toluidinyl dithiocarbamate and metal salts Ammonium dithiolumolybdate were prepared by standard reported procedure. Synthesis of metal complex: 6.67 g (10.25 mmol) of o-, m-, p- toluidinyl dithiocarbamate and 2.05 g (10.25 m mol) of Ammonium dithiolumolybdate were dissolved separately in minimum Quantity of double distilled water. Now both the solution mixed together the mixture solutions kept for 45-60 minutes on water bath at 80-90°C. The precipitate was filtered off washed with 1:1 ethanol:water mixture followed by ether and desiccated under vacuum. A Yellow Colored complex was obtained with 69.2% Yield metal Complex is insoluble in common solvents such as water, benzene, chloroform, dichloromethane etc. but it is soluble in DMF and DMSO. The result of elemental analysis is in good agreement with the calculated values. The metal Contents of the complexes were determined according to literature methods.

Elemental analysis: Calc Mo 29.33, C = 29.40, H = 2, 45 N = 4.30, S = 29.49 Found Mo, 29.40, C 28.9, H= 2.50, N=4.62, S= 30.10. The electrolytic nature of the complex is measured in DMF, at to 10⁻³M the Conductivity value was found to be 13.4 Ω⁻¹ cm⁻¹ mol⁻¹. Thus the prepared Complex is non electrolytic in nature and there is no ion present in the out of the Coordination sphere Spectral studies: There is no Coordination through nitrogen atom because there is almost no shifting of the band position of nitrogen centres in the IR spectra of metal Complex. The complex shows additional bands in the region of 925 cm⁻¹ indicating the presence of two terminal oxygen. Due to the reaction of molybdate with the dithiocarbamate group there arises Mo-s vibration band which is present of at 340 cm⁻¹ The additional important band is also present are at 480 cm⁻¹ and other 510 cm⁻¹ suggesting the presence of bridging Sulfur atom. The Electronic absorption of metal complex in the visible region shows two transition bands in the region around 24900 and 13000 cm⁻¹ respectively. The diffuse reflectance spectrum of the Molybdenum Complex shows the d-d transition bands around 16800 and 19200 cm⁻¹ which are assigned to Transitions 3T₁g (F) → 1A₂g (F) (ν₂) and 3T₁g(F) → 3T₁g (F) (P) (ν₃) respectively as ν₁ band occurs at lower energy it is not observed in complex. Mentioned bands are probably a combination of the Sulfur to metal Transition and S→ Mo charge Transfer band. The NMR spectra of the Complex were recorded in DMSO-d₆. The absence of S-H protons and a slight downfield Shift of the Protons in The NMR spectra of Complex, with respect to corresponding ligand were observed. This indicates that the ligand is coordinated to Molybdenum through sulfur atom in the ¹H NMR spectra signals of all protons belong to Ammonium Toluidinyl dithiocarbamate ligand was found for a Complex. In the ¹³C NMR spectrum for complex there are signals at 50.35, 21.12, 25.90 and 23.70 ppm that belong to the dithiocarbamate ligand only one signal that corresponds to the CS₂ moieties of dithiocarbamate ligand was observed in the spectrum of Molybdenum Complex indicating that the Chemical environments of the CS₂ moieties of the two dithiocarbamate ligands bound to the Mo₂ centre. Further A singlet observed at δ3.50 in the parent dithiocarboxylic acid and assigned for SH Proton is found to be absent in the spectra of Corresponding complex indicating the deprotonation of SH group and the formation of Mo-S bond [13-16].

Antimicrobial Studies: The results show that the metal Complex is more active than the Parent ligand dithiocarbamate. The enhanced activity of the metal complex Compared to free ligand can be ascribed to increased lipophilic nature of the molybdenum Complex arising due to chelation. Solubility of the compound also plays an important role in ascertaining the degree of inhibition. Metal Complex of the ligand having sulfur as a donor atom was found to be more potent than those without sulfur it has been proposed that the ultimate action of structurally non-specific toxicants is the denaturation of one or more proteins of the cell. Chelating agents are often powerful inhibitors of metalloenzymes, so it is evident from data Table I that activity significantly increases on Coordination [21, 22].
Table-1: Antibacterial activity of ligand and metal complex

<table>
<thead>
<tr>
<th>Sample</th>
<th>Gram +ve</th>
<th>Gram -ve</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>S.aureus</td>
<td>Bacillus Sp.</td>
</tr>
<tr>
<td>1. Tetracycline</td>
<td>25</td>
<td>27</td>
</tr>
<tr>
<td>2. Chloramphenicol</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>3. Clotrimazole</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>4. C_{8}H_{12}N_{2}S_{2}</td>
<td>14</td>
<td>12</td>
</tr>
<tr>
<td>5. Mo_{2}C_{16}H_{16}N_{2}O_{2}S_{6}</td>
<td>20</td>
<td>21</td>
</tr>
</tbody>
</table>

Inhibition Zone in mm Concentration 100 µg/mL

The anticancer activities of the ligand and its metal complex against the human liver (HEPG2) and Human colon (HCT116) cell lines were screened using MTT assay. The results were analysed by cell viability curves and expressed as IC_{50} values. The maximal inhibition concentration given in table 2 showed that the cytotoxicity efficiencies of the compounds under the investigation follow the order Mo(V) complex > dithiocarbamate ligand from the result it is evident that the Molybdenum Complex exhibited higher Invitro cytotoxicity against both the selected cell lines when compared to the ligand compared with that of the standard drug cisplatin. Th cytotoxicity of Molybdenum Complex is depending on their ability to bind DNA and damage its structure resulting in the impairment of its function which is followed by the replication and Transcription processes inhibition and eventually cell death. Thus the relatively higher toxicity exhibited by the Mo(V) complex as compared to the ligand may be due to the stronger binding ability of the complex with DNA.

Table-2: Anticancer Studies of the dithiocarbamate ligand and its Molybdenum Complex

<table>
<thead>
<tr>
<th>S.No.</th>
<th>Compound</th>
<th>HEPG 2</th>
<th>HCT 116</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>C_{8}H_{12}N_{2}S_{2}</td>
<td>25 ± 1.2</td>
<td>28 ± 1.4</td>
</tr>
<tr>
<td>2.</td>
<td>Mo_{2}C_{16}H_{16}N_{2}O_{2}S_{6}</td>
<td>18 ± 1.5</td>
<td>21 ± 1.7</td>
</tr>
<tr>
<td>3.</td>
<td>Cisplatin</td>
<td>13 ± 0.5</td>
<td>12 ± 0.9</td>
</tr>
</tbody>
</table>

*IC_{50} Concentration of the drug required to inhibit growth of 50% of the cancer cells (µM) the data are mean ± SD of three replicants each.

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REFERENCES


