Synthesis, Characterization, Biological Activity and Use of Thiourea Derivative (PhTTU) Studies of dinitrate-1-phenyl-3-(thiazol-2-yl)-2-thioureato Cd(II) ion Complex

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Abstract: In this study a complex of the general formula Cd(PhTTU)₂(NO₃)₃, (PhTTU is 1-phenyl-3-(thiazole-2-yl)-2-thiourea), was synthesized in two steps starting with the reaction of 2-amino thiazol with phenyl isothiocyanate then followed by the addition of PhTTU ligand. Initial characterization based on the elemental analysis has suggested one possible structure (scheme 1). This ligand as one of the thiourea derivatives was successfully synthesized. The ligand was characterized by IR, NMR and CHN elemental analysis. The complex was characterized by elemental analysis and melting point. Although, both PhTTU ligand and the cadmium complex showed antimicrobial activities, the complex inhibition to the studied microorganisms was higher.

Keywords: Thiourea Derivatives and Cadmium Extraction

1. Introduction

Urea is the first organic compound that was synthesized in lab in 1982, which became the important step in the history of synthetic organic chemistry and played important physiological and biological roles in animal kingdom [1-3]. Interest has grown rapidly in the preparation and the study of the critical effects of compounds containing systems N-N-S or O-N-S with three claws of these compounds that have energetic effects against cancers as well as its objection vital role for the synthesis of amino acids have been prepared and the study of many derivatives of thiourea compounds that have effects against the types of microbes and viruses [4-10]. Thiourea and its derivatives represent a well-known important group of organic compound due to their diverse application in fields such as medicine, agriculture, coordination, and analytical chemistry [11]. They moreover can be used as selective analytical reagents, especially for the determination of metals in complex interfering materials [12-14]. Thiourea derivatives and their transition metal complexes have been known since the beginning of the 20th century [15]. Also these complexes display a wide range of biological activity including antibacterial, antifungal properties [16,17]. One of the important thiourea derivatives is thayazol thiourea which is known to have a wide range of biological activities including antiviral [18], antibacterial [19,20], antifungal [21], antitubercular [22,23], herbicidal [24], insecticidal [25]. In addition, thayazol thiourea derivatives were often used in analytical and biological applications[15]. Metal complexes of ligands containing sulfur as donor atoms are known to possess antifungal and antibacterial activities. The complex with thiourea derivatives which has biological activity has been successfully screened for various biological activities: antidepressant, anticonvulsant, antihelminthic, antithistaminic, anesthetic, antitussive, analgesic etc. [26]. Cisplaten is successfully used in chemotherapy, but is effective only against a narrow range of tumors [27]. The development of analogues has resulted in a few clinically useful complexes, most of which, however, are cross-resistant to Cisplaten [28]. Next to platinum, ruthenium is also used for the construction of anticancer agents [29]. Many ruthenium complexes have been evaluated for the treatment of cancer, in part because ruthenium(II) and ruthenium(III) complexes exhibit relatively low ligand exchange rates, which are comparable to those of platinum(II) complexes [29]. Recently researchers working on the developments of poly nuclear metals complexes are focusing on their anticancer activity. The compounds presented are often supposed to exert their anticancer activity by different modes of action as compared to established drugs, including newly proposed mechanisms such as enzyme inhibition, cross linking of biomacromolecules or through photo-activation, though many of the examples are also capable of binding to DNA nucleon bases [30].

2. Experimental

Cadmium dinitrate Cd(NO₃)₂, ammonia conc., toluene and all chemical were used as purchased from Sigma–Aldrich Chemical Co. Inc. The following compounds were synthesized according to the scheme 1 given below. The phenyl thiourea derivative was prepared by a similar procedure that was reported in the literature [15]. All Solvents used were dried according to standard procedures. Elemental analyses were performed using a Perkin-Elmer 2400 CHN elemental analyzer. ¹H NMR spectra were performed on a JEOL-270 MHz, NMR spectrometer in DMSO-d₆ solvent and TMS was used as an internal reference. Infrared spectra (4000-400 cm⁻¹) were recorded as KBr pellets on a Unicam Mattson 1000 FTIR spectrometer. The electronic absorption spectra were recorded by using Unicam UV2–300 UV–Vis spectrometer. Samples of 2.6×10⁻³ mol dm⁻³ concentrations in DMSO were measured against the solvent in the reference cell. Antimicrobial activity of the tested samples for the ligand and the complex was determined using a modified Kirby-Bauer disc diffusion method [31].
Synthesis of phenyl isothiocyanate

90 ml of ammonia concentrated placed in a flask circular bottom with three slots and cooled in a mixture of ice and salt, added to 54 g (43 ml, 0.71 ml) of carbon disulfide [32]. Stir and then add the 56 g (55 ml, 0.6 ml) of aniline suppression distillery during the period of 20 minutes. Extracted sludge four times with water (200 ml x 4) and transferred to the flask size of 5 liters and add to it with constant stirring solution of (200 g, 0.605 ml) of lead nitrate dissolved in 400 ml of water. Deposit consists of lead sulfide, distills the mixture steam to receiving flask containing 10 ml of 0.5 M sulfuric acid until the end of the organic matter (2-3 liters of distilled water.) separates the oil in separating funnel and dried over calcium chloride or magnesium sulfate and then distilled under reduced pressure. Product 62 g (76%).

Synthesis of 1-phenyl-3-(thiazol-2-yl)-2-thiourea (PhTTU)

A solution 2-amino thiazol 10 g (0.1 mol) was added drops wise with stirring to the of phenyl isothiocyanate 13.5 g (0.1 mol). The mixture was heated to reflux in air for 2 h and then cooled in ice bath and the solvent was evaporated on a vacuum line. The obtained residue was washed several times by dry toluene and then recrystallized from a mixture of ethyl alcohol. The complex was left to dry on vacuum line for a few hours (yield 70%). Anal. Calc. For $C_{26}H_{23}N_8Cd$ (MW = 635.95): C, 33.97; H, 2.55; N, 15.85%. Found: C, 33.75; H, 2.32; N, 15.66%.

3. Results and Discussion

Phenyl isothiocyanate was produced by the reaction of ammonia concentrated, carbon disulfide and aniline. 1-phenyl-3-(thiazole-2-yl)-2-thiourea was synthesized from phenyl isothiocyanate and 2-amino thiazol in toluene (scheme 1) outline the synthesis of thiourea derivatives. The ligand (PhTTU) were purified by recrystallization from hot ethyl alcohol and obtained in 65% yield. The synthesized compound structure was confirmed by melting point, elemental analysis, IR spectra and 1HNMR. The thiazol group in this thiourea derivative permits the coordination of cadmium ions to form stable neutral complex. The extraction of cadmium ions from its solution was done using -phenyl-3-(thiazole-2-yl)-2-thiourea (PHTTU). During the extraction at neutral pH, the ligand (PhTTU) will react with cadmium ions in ratio of 1:2 form a orange complex. Complex structure was showed in figure 1.

4. The effects of PhTTU and complex on alkaline phosphates (ALP) Activity

The enzyme alkaline phosphates functions to generate $PO_4^{3-}$ ions from organic phosphates during bone mineralization in humans [33] the effects of the ligand PhTTU and the complex. On the ALP were tasted in blood samples of a human. The ligand and complex showed an equal inhibitory effect on the enzyme in concern, as illustrated in the table below.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Concentration of compounds $10^{-4}$ mol/l</th>
<th>The concentration of compounds $10^{-4}$ mol/l</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Concentration of the enzyme (U/L)</td>
<td>Discouragement %</td>
</tr>
<tr>
<td>*human blood sample</td>
<td>539.5</td>
<td>34.96</td>
</tr>
<tr>
<td>PhTTU (ligand)</td>
<td>367.6</td>
<td>31.86</td>
</tr>
<tr>
<td>Cd(PhTTU)$_2$(NO$_3$)$_2$</td>
<td>409.5</td>
<td>24.76</td>
</tr>
</tbody>
</table>

* Reference: human blood sample before compounds adding

**Scheme 1:** synthesizes of phenyl isothiocyanate and 1-phenyl-3-(thiazol-2-yl)-2-thiourea (PhTTU)
5. Conclusions

Biological importance of thiourea is well known as mentioned earlier under the review of literature. This prompted us to synthesize thiourea derivatives. The synthesis of the proposed thiourea was successfully done. From the extraction data it can be conclude that, the ligand 1-phenyl-3-(thiazole-2-yl)-2-thiourea (PhTTU), has high ability to bond and extract cadmium ions from its solution, that mean it can be used in precipitate, determine, separate and extract the cadmium ions from low concentration solutions and can be used for concentrated cadmium solutions by repeating the extraction process.

References