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Short communication

New Pd(II) complexes of the synthesized 1-*N*-substituted thiosemicarbazones of 3-indole carboxaldehyde: Characterization and antiamoebic assessment against *E. histolytica*

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Abstract

Reaction of 3-indole carboxaldehyde with aminothiocarbonyl hydrazines resulted in the formation of 3-indole carboxaldehyde thiosemicarbazones (TSCs) **1**–**13**. The synthesized thiosemicarbazones were used as ligands in the formation of $[Pd(TSC)Cl_2]$ complexes with palladium(II) metal ion precursor, $[Pd(DMSO)_2Cl_2]$. The chemical structures of all the compounds were established by electronic, IR, ^{1}H NMR and ^{13}C NMR spectral data. The structure of the complexes was further established by FABMS and DTA. It is concluded that the thione sulphur and the azomethine nitrogen atom of the ligands are bonded to the metal ion. The testing of the antiamoebic activity of these compounds against the protozoan parasite *Entamoeba histolytica* suggests that compounds **5**, **3a**, **5a** and **8a**–**13a** might be endowed with important antiamoebic properties since they showed less IC_{50} values than metronidazole. Moreover, compound **12a** displays remarkable antiamoebic activity than metronidazole (IC_{50} values of **0.29** vs **1.81** μM, respectively). MTT assay showed that the compounds are non-toxic to human kidney epithelial cell line.

Keywords: Palladium(II) complexes; Indole-3-carboxaldehyde; Thiosemicarbazones; *Entamoeba histolytica*

1. Introduction

Amoebiasis is the second leading cause of death among parasitic diseases worldwide. The causative protozoan parasite, *Entamoeba histolytica*, is a potent pathogen. Secreting proteinases that dissolve host tissues, killing host cells on contact, and engulfing red blood cells, *E. histolytica* trophozoites invade the intestinal mucosa, causing amoebic colitis [1]. Metronidazole (MTZ, 1-[2-hydroxyethyl]-2-methyl-5-nitroimidazole) is an antibacterial and antiprotozoal drug that has been in use for over 35 years. In an event of overt clinical resistance to metronidazole in the anaerobic protozoa, there is no alternative treatment for invasive amoebiasis, keeping in mind the documented cross-resistance between currently used nitroimidazole drugs [2] and worldwide availability. Treatment with metronidazole has several side effects that include nausea, vomiting, dry mouth, metallic taste, abdominal pain and headache. In some cases additional side effects viz. dizziness, vertigo, paresthesias and rarely encephalopathy or convulsions have been reported leading to even discontinuation of the drug [3]. Due to long-term treatment toxicity and clinical resistance to drugs commonly used, new effective agents are urgently needed. On the positive side, a great deal of flexibility is offered by the replacement of the imidazole ring structure by the heterocyclic moiety.

Of the various heterocyclic systems, the indole nucleus has been reported as a common dominator of psychotropism and is of great value in the field of medicine and biochemistry [4,5]. This nitrogen heterocycle and its derivatives have occupied a unique place in the chemistry because of its varied biodynamic properties such as anticancer [6–9], antidepressant [10], antihypertensive [11], psychomimetic [12], antimicrobial [13,14], antidiabetic [15], antimalarial [16] and anti-inflammatory [17,18]. Moreover, thiosemicarbazones are a class of

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compounds very promising in the treatment of many diseases and their development is still in progress [19–21]. In addition, metal ions are known to accelerate drug action, and the efficacy of a therapeutic agent may be enhanced upon coordination with a metal ion [22]. In particular, neutral palladium(II) and (IV) complexes exhibit potential antitumour activity and apoptosis [23,24]. The literature reports that palladium(II) and platinum(II) complexes of phenylacetaldehyde thiosemicarbazone are able to *in vitro* bind to DNA, and present enhanced capacity to form inter-strand crosslinks by comparison with cisplatinum [22,25].

We have previously reported the structural and spectral studies of several transition metal complexes of *N*4-substituted thiosemicarbazones with the aim to correlate the structural features and chelating ability to the antiprotozoal properties [26,27]. Here the synthesis of 3-indole carboxaldehyde thiosemicarbazones **1–13** and their subsequent bidentate Pd(II) complexes **1a–13a** were screened for their antiamoebic activities against *HM1:IMSS* strain of *E. histolytica in vitro* experiments and it was found that the coordination of palladium to thiosemicarbazone enhances the activity. The toxicity study of these compounds was performed against KB cell lines.

2. Results and discussion

The synthesis of indole-3-carboxaldehyde thiosemicarbazones and their Pd(II) complexes is represented in Scheme 1. All the thioglycolic acids were prepared by the reported O'Sullivan method [28]. Thiocarbonylhydrazines were prepared by refluxing the alkaline solution of thioglycolic acid with hydrazine hydrate and their thiosemicarbazones were synthesized by refluxing aqueous solution of thiocarbonylhydrazines and ethanolic solution of 3-indole-carboxaldehyde in equimolar ratio at 8 °C for 3 h with continuous stirring. After cooling at ca. 10 °C for 24 h, the precipitated compound was filtered and recrystallized from appropriate solvent. The precursor $[Pd(DMSO)_2Cl_2]$ used for the synthesis of Pd(II) complexes was synthesized by the literature procedure [29,30]. The complexes were prepared by mixing 1:1 ratio of the appropriate ligand and $[Pd(DMSO)_2Cl_2]$ and the reaction mixture was heated under reflux for 1–3 h. After keeping the solution at 0 °C overnight the colored solid separated out. This was filtered off and washed with hot water followed by small quantity of methanol, and dried *in vacuo* over silica gel to give amorphous solids. The complexes gave high yields around 80%, while the yields for thiosemicarbazones showed variable results. The chemical structures of all the compounds were confirmed by means of elemental analysis and electronic, IR, ^{1}H NMR and ^{13}C NMR spectral studies. The structures of complexes were further established by thermogravimetric analysis and FABMS. The analytical data of these compounds are in good agreement with their composition (Table 1).

Selected significant IR bands revealed the structural characteristics of the compounds. All the thiosemicarbazones **1–13** may exhibit in thione–thiol tautomerization since they contain thione group (C=S) and a proton adjacent to thione group. The absence of ν (S–H) stretch at 2500–2600 cm^{-1} and the presence of ν (N–H) stretch at 3100–3300 cm^{-1} in the spectra of the ligands suggest that all the ligands remain in the thione form in the solid state. The band appearing at 790–820 cm^{-1} ascribed to ν (C=S) [31] of ligands is shifted to lower wave number by ca. 15–30 cm^{-1}, indicating that the thione sulphur participates as a coordinating site. This coordination is confirmed by the presence of two new bands at around 550 and 440 ν (Pd–N, Pd–S) [32]. Thione form reveals preferential coordination of thionic sulphur over nitrogen of indole is due to more nucleophilic character of the former. The band due to ν (C–N–C) (ring) of indole moiety remains unaltered in **1a–13a**, indicating non-participation of ring nitrogen in coordination. The negative shift of 25–57 cm^{-1} of ν (C=N) stretch in the complexes indicates the involvement of azomethine nitrogen in complexation [33]. The broad band observed in region 3300 cm^{-1} due to ν (N–H) stretch is slightly shifted in complex probably due to the adjustment of current arising due to coordination of thionic sulphur, thus, confirming the fact that ligands behave as neutral NS donor bidentate in these complexes.

The electronic spectra of these complexes exhibited bands at expected position as cited in the literature for the similar system [34]. A perusal of these spectra revealed that they were dominated by intense intra-ligand and charge transfer bands. Thus a band appearing at 47 500–49 000 cm^{-1} in the spectra of complexes was assigned to π–π^* transition of indole ring. Another band at 38 000–40 000 cm^{-1} was attributed to n–π^* transitions of indole ring. This band, followed by a shoulder band at 29 000–31 000 cm^{-1}, appears due to the thiosemicarbazones' moiety. A comparison of these three bands with free ligands revealed that there is increase in intensity and decrease in the frequency that is attributed to extended conjugation in the ligand moieties after complexation. The complexes show absorption peaks in the visible region due to the d–d transition of the single d electron of the palladium(II) ion.

Further evidence for the formation of compounds was obtained from the ^{1}H NMR spectra, which provide diagnostic tools for the positional elucidation of the protons. Assignments of the signals are based on the chemical shifts and intensity patterns. The ligands **1–13** do not show any resonance at ca. 4.0 ppm, attributed to –SH proton resonance, while the appearance of a broad peak at 11.51–11.69 ppm due to the –NH proton of thioamide group indicates that even in a polar solvent such as DMSO they remain in the thione form. The –NH proton signal of the thiosemicarbazones usually shifts 0.86–2.83 ppm upfield in their respective complexes. However, in complexes, we are unable to calculate the coupling constant values for aromatic region. This might be assumed due to the merging of peaks upon coordination. This information suggests the adjustment of electronic current upon coordination of >C=S group to the metal ion. The protons belonging to the aromatic ring and the other cyclic groups were observed with the expected chemical shift and integral values in the same region as those of free ligands.

Moreover, the ^{13}C NMR spectra of all the ligands taken in DMSO gave the spectral signals in good agreement with the