European Journal of Medicinal Chemistry 62 (2013) 139–147

Contents lists available at SciVerse ScienceDirect

European Journal of Medicinal Chemistry

journal homepage: http://www.elsevier.com/locate/ejmech

Original article

Synthesis, characterization, cytotoxicity and antimicrobial studies on bis(*N*-furfuryl-*N*-(2-phenylethyl)dithiocarbamato-*S*,*S*′)zinc(II) and its nitrogen donor adducts

Palanisamy Jamuna Rani, Subbiah Thirumaran*

Department of Chemistry, Annamalai University, Annamalainagar 608 002, Tamil Nadu, India

ARTICLE INFO

Article history:
Received 28 July 2012
Received in revised form
2 December 2012
Accepted 31 December 2012
Available online 7 January 2013

Keywords:
Dithiocarbamate
Nitrogen donor ligands
Zinc(II)
X-ray structure
HeLa cell line
Antimicrobial studies

ABSTRACT

$[Zn(fpedtc)_2]$ (**1**), $[Zn(fpedtc)_2(py)]$ (**2**), $[Zn(fpedtc)_2(1,10\text{-phen})]$ (**3**) and $[Zn(fpedtc)_2(2,2'\text{-bipy})]$ (**4**) (where fpedtc = *N*-furfuryl-*N*-(2-phenylethyl)dithiocarbamate, py = pyridine, 1,10-phen = 1,10-phenanthroline and 2,2′-bipy = 2,2′-bipyridine) were synthesized. Characterization of the complexes were achieved by IR and NMR (^1H and ^{13}C) spectra and in addition, for **2** and **3**, by X-ray crystallography. Single crystal X-ray structural analysis of **2** and **3** showed that complex **2** is almost half way between trigonal bipyramidal and square pyramidal and complex **3** has a distorted octahedral geometry. Zn–N distances in **2** is shorter than that found in a six coordinate complex **3** due to the change in coordination number. These complexes were also screened for *in vitro* antibacterial and antifungal activities and significant activities have been found. *In vitro* cytotoxic activity of all the synthesized complexes was evaluated on HeLa cell line. Complex **1** exhibits maximum inhibitory effect at a concentration of 40 μg mL^{-1} on HeLa cell line.

1. Introduction

Dithiocarbamates have a wide range of applications in medicine, industry and rubber vulcanization [1–4], and can serve as antioxidants for increasing the longevity and photo-stability of a variety of polymers, oils and other materials [5]. Metal dithiocarbamate complexes and their nitrogen donor adducts are useful precursors for the synthesis metal sulfide nanoparticles [6,7].

Several dithiocarbamate salts and metal complexes of dithiocarbamates have been used as agrochemicals, mainly due to their high efficiency in controlling plant fungal diseases and their relatively low toxicity [8–13]. Cervical carcinoma significantly affects women world wide, especially in developing countries [14]. Approximately, 500,000 cases of cervical cancer diagnosed per year with nearly 40% of those resulting in death [15]. Although cancer has existed as a disease since prehistoric time, it is still one of the major causes of death in the world. To date, the most reliable way to reduce or cure cancer is to remove and/or to block the fast proliferating malignant tissues. The discovery of cisplatin (cis-$[Pt(NH_3)_2Cl_2]$), the first inorganic compound to block DNA replication and cell division, has demonstrated that metal complexes can play an important role in the treatment of cancer opening up new perspectives in anticancer research based on metallopharmaceuticals [16]. Despite high nephrotoxicity, neurotoxicity and acquired drug resistance as major drawbacks, cisplatin and its two analogs (carboplatin and oxaliplatin), are among the most effective chemotherapeutic agents in clinical use to date [17]. Dithiocarbamates have been evaluated for their efficiency as inhibitors of cisplatin-induced nephrotoxicity [18]. In particular, dithiocarbamates selectively protects normal tissue without inhibiting the antitumor effect [19,20]. The majority of the dithiocarbamate $[M(S_2CNR^1R^2)_n]$ complexes studied have simple R^1 and R^2 groups such as methyl, ethyl and phenyl [21]. Only one structural report has been made on furfuryl based dithiocarbamate complex from our laboratory [22].

To understand the influence of furfuryl based dithiocarbamate and nitrogen donor ligands (py, 1,10-phen, 2,2-bipy) on biological properties, we report results on cytotoxicity, antifungal and antibacterial properties of complexes **1**–**4**, as well as their IR and NMR spectra. In addition, the crystal structures of **2** and **3** are described.

2. Results and discussion

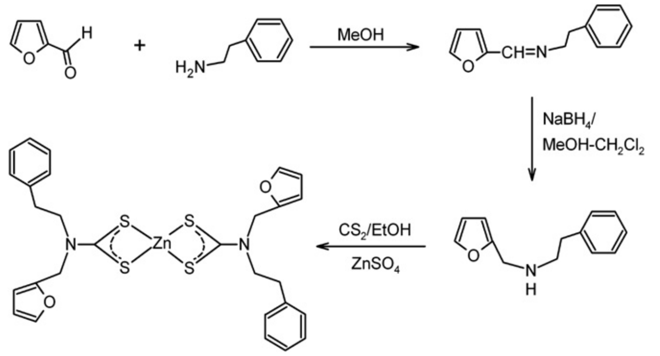
2.1. Synthesis of complexes 1–4 and their characterization

Complexes **1**–**4** were prepared according to the synthetic procedure shown in Schemes 1 and 2. Furfuraldehyde was condensed

---

* Corresponding author. Tel.: +91 9842897597.
E-mail address: sthirumaran@yahoo.com (S. Thirumaran).

0223-5234/$ – see front matter © 2013 Elsevier Masson SAS. All rights reserved.
http://dx.doi.org/10.1016/j.ejmech.2012.12.047

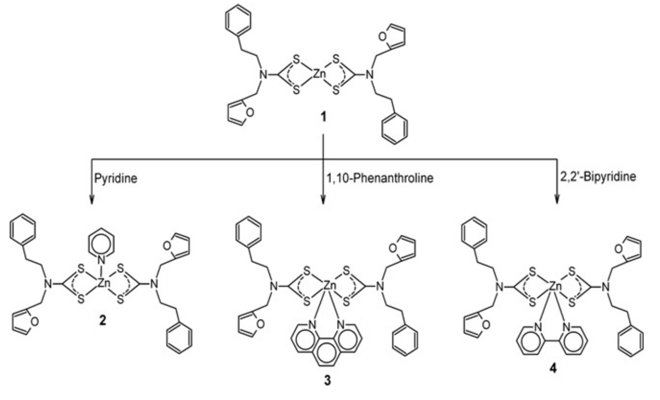


Scheme 1. Preparation of complex **1**.

with 2-phenylethylamine to form the imine. Sodium borohydride reduction of imine in methanol–dichloromethane afforded *N*-furfuryl-*N*-(2-phenylethyl)amine as yellow oil. Complex **1** was prepared from amine in EtOH by reaction with carbon disulfide and ZnSO$_4$ in water. The reaction of complex **1** with nitrogen donor ligands (py, 1,10-phen, 2,2′-bipy) yielded **2**, **3** and **4**. The complexes are quite stable at ambient conditions. They are soluble in chloroform, dichloromethane and acetonitrile and insoluble in ethanol, methanol and water.

IR spectroscopy has been used to understand the nature of coordination mode (monodentate or bidentate) of dithiocarbamate moiety. IR spectra of complexes **1** and **2** are given in Fig. 1. Based on Bonati et al. criterion, the presence of only one characteristic band in the region 1050–900 cm^{-1}, the $\nu_{\text{C–S}}$ mode, is due to bidentate coordination of the dithiocarbamate group while a split band within narrow range of 20 cm^{-1} is indicative of the monodentate nature of the dithiocarbamate group [23]. In the present study, the C–S stretching vibrations are observed in the region 1017–1014 cm^{-1} without any splitting, supporting the bidentate coordination of the dithiocarbamate ligand. The dithiocarbamate compounds exhibit another characteristic band in the region 1550–1450 cm^{-1} assignable to the $\nu_{\text{C–N}}$ (thioureide) [24]. The infrared spectra of **1**–**4** show $\nu_{\text{C–N}}$ (thioureide) bands in the region 1487–1462 cm^{-1}, indicating the partial double bond character.

The thioureide $\nu_{\text{C–N}}$ bands of complexes follow the order **1** > **2** > **3** ≈ **4**. This indicates that the $\text{N}^{\delta+}\cdots\text{C}^{\delta-}$ double bond character decreases with increasing coordination number [25]. The characteristic band due to pyridine appears at 1604 cm^{-1} in **2**. The ring frequencies associated with 1,10-phenanthroline and 2,2′-bipyridine are 1600–1000 cm^{-1} [26]. In this study 1,10-phenanthroline adduct **3** shows bands at 1584 and 1507 cm^{-1} whereas 2,2′-bipyridine adduct **4** reveals bands at 1600 and 1567 cm^{-1}. Other bands due to nitrogen ligands are masked by those due to dithiocarbamate.



Scheme 2. Preparation of complexes **2**, **3** and **4**.

^{1}H NMR spectrum of *N*-furfuryl-*N*-(2-phenylethyl)amine shows a singlet at 3.68 ppm and two triplets at 2.72 and 2.79 ppm due to methylene protons of furfuryl group and the ethylene unit of 2-phenylethyl group, respectively; that shifted to lower field being nitrogen bound. The signal of methylene protons (singlet) of N–CH$_2$ (furfuryl) appears in the region 4.95–5.12 ppm in all the complexes **1**–**4**. All the complexes showed two equal intensity triplets in the aliphatic region 3.00–4.10 ppm associated with the ethylene unit of 2-phenylethyl group; that shifted to lower field being nitrogen bound. The nitrogen bound methylene proton signals of complexes **1**–**4** are strongly deshielded compared to those of free *N*-furfuryl-*N*-(2-phenylethyl)amine, which confirms the formation of dithiocarbamate.

Complexes **1**–**4** show N^{13}CS$_2$ signals in the region 205.2–207.1 ppm, indicating contribution of double bond character to a formally single N–C bond in the dithiocarbamate. The N^{13}CS$_2$ chemical shift of dithiocarbamate is also affected by coordination of nitrogen donor to metal. Additional coordination of nitrogen donors to metal dithiocarbamates yields a decrease of nitrogen–carbon partial double bond character and, as a result of that, the N^{13}CS$_2$ carbon of nitrogen donor adducts **2**–**4** are additionally deshielded compared to parent complex **1**.

2.2. Structural studies on complexes **2** and **3**

An ORTEP diagram of complex **2** is shown in Fig. 2. Complex **2** contains four discrete molecules per unit cell. The zinc atom in complex **2** is five coordinated to four sulfur atoms from the dithiocarbamates and to one nitrogen atom from pyridine. The coordination group around zinc is distorted trigonal bipyramid with coplanar atoms Zn, N(pyridine), S(1) and S(1^i) lying in the equatorial plane and S(2) and S(2^i) occupying the axial positions. In this complex, dithiocarbamate ligands are bound in a chelating fashion that bridge equatorial and axial sites. The two dithiocarbamate ligands in **2** coordinate in an anisobidentate fashion [Zn–S1 = 2.3600(7) and Zn–S2 = 2.5621(6) Å]. The C–S distances are slightly asymmetric and the shorter Zn–S1 bond is associated with longer C–S distance. The structure of complex **2** is intermediate between the tetragonal pyramid (TP) and trigonal bipyramidal. For accurate description of the geometry, this complex is characterized by using the τ descriptor for five coordination suggested by Addison et al. [27]. From the τ values, the coordination geometry is described as being 56% along the pathway of distortion from square pyramid toward trigonal bipyramid. The short thioureide C–N distance [1.339(3) Å], indicates that the π-electron density is delocalized over the S$_2$CN moiety and this bond has a significant double bond character. All the C–S bonds in the present structure are of partial double bond character as observed in other dithiocarbamate complexes [28].

The ORTEP diagram of complex **3** is shown in Fig. 3. Zinc is hexacoordinated by two nitrogen atoms from 1,10-phenanthroline and four sulfur from the chelating dithiocarbamate groups. In this complex, the zinc atom is situated at the center of a distorted tetragonal bipyramidal arrangement with two sulfur atoms from dithiocarbamate groups [S1, S3] and two nitrogen atoms from the 1,10-phenanthroline ligand [N3, N4] on the basal plane and the two remaining sulfur atoms as vertices. The two bonds Zn–S2 and Zn–S4 are relatively longer than others due to the steric influence of the 1,10-phenanthroline ligand. The two S–Zn–S angles [S2–Zn–S4 = 170.54(2) and S1–Zn–S3 = 101.93(2)°] correspond to *trans* and *cis* octahedral values, respectively. The N4–Zn–N3 angle observed in the adduct is 75.18(7)°. The short thioureide C–N distance [1.373(3) Å] indicates that the π-electron density is delocalized over the S$_2$CN