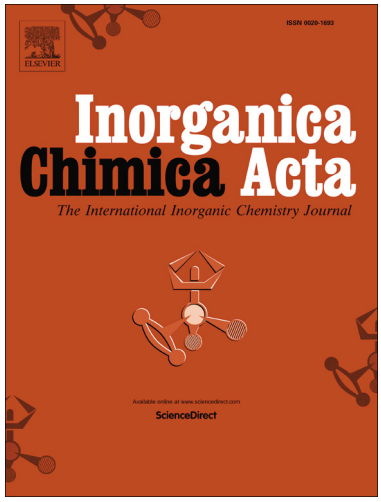


Synthesis, characterization and biological studies of S-4-Methylbenzyl-β-N-(2-furylmethylene)dithiocarbazate (S4MFuH) its Zn^{2+}, Cu^{2+}, Cd^{2+} and Ni^{2+} complexes

Enis Nadia Md Yusof, Thahira B.S.A. Ravoof, Junita Jamsari, Edward R.T. Tiekink, Abhimanyu Veerakumarasivam, K.A. Crouse, M.Ibrahim M. Tahir, Haslina Ahmad

PII: S0020-1693(15)00435-1
DOI: http://dx.doi.org/10.1016/j.ica.2015.08.029
Reference: ICA 16672

To appear in: *Inorganica Chimica Acta*

Received Date: 1 April 2015
Revised Date: 3 June 2015
Accepted Date: 24 August 2015

Please cite this article as: E.N. Md Yusof, T.B.S. Ravoof, J. Jamsari, E.R.T. Tiekink, A. Veerakumarasivam, K.A. Crouse, M.Ibrahim M. Tahir, H. Ahmad, Synthesis, characterization and biological studies of S-4-Methylbenzyl-β-N-(2-furylmethylene)dithiocarbazate (S4MFuH) its Zn^{2+}, Cu^{2+}, Cd^{2+} and Ni^{2+} complexes, *Inorganica Chimica Acta* (2015), doi: http://dx.doi.org/10.1016/j.ica.2015.08.029

Synthesis, characterization and biological studies of S-4-Methylbenzyl-β-N-(2-furylmethylene)dithiocarbazate (S4MFuH) its Zn^{2+}, Cu^{2+}, Cd^{2+} and Ni^{2+} complexes

Enis Nadia Md Yusof[a], Thahira B.S.A. Ravoof[a]*, Junita Jamsari[a], Edward R. T. Tiekink[b], Abhimanyu Veerakumarasivam[a], K. A Crouse[a,c], M. Ibrahim M. Tahir[a] and Haslina Ahmad[a]

[a]*Department of Chemistry, Faculty of Science, Universiti Putra Malaysia, 43400 UPM Serdang, Selangor*

[b]*Department of Chemistry, University of Malaya, 50603 Kuala Lumpur, Malaysia*

[c]*Department of Chemistry, Cape Breton University, Sydney, Nova Scotia, Canada B1P 6L2*

corresponding author: thahira@upm.edu.my*

S-4-methylbenzyl-β-N-(2-furylmethylene)dithiocarbazate (S4MFuH, **1**) derived from the condensation reaction of furaldehyde (Fu) with S-4-methylbenzyldithiocarbazate (S4MBDTC) has been complexed with transition metal acetates to give $Zn(S4MFu)_2$ (**2**), $Cd(S4MFu)_2$ (**3**), $Cu(S4MFu)_2$ (**4**) and $Ni(S4MFu)_2$ (**5**). It is evident from the shift in ν(C=N) and ν(N-N) in the IR spectra of the complexes that deprotonated **1** acts as a bidentate ligand coordinating through the azomethine nitrogen and thiolato sulphur atoms. This was confirmed by single crystal X-ray diffractometry. The U-shaped dithiocarbazate **1** exists in the E configuration with the thione bond anti to the azo bond. A change in conformation is noted in the transition metal complexes resulting from deprotonation and N-S-chelation. **2** and **3** display a distorted tetrahedral geometry with the major cause of the distortion being two close intramolecular M…O interactions. Binding interaction studies with calf thymus DNA demonstrated that **4** also had the strongest DNA binding affinity (K_b = 2.85 x 10^4 M^{-1})

among all compounds prepared in this work. The Cu(II) complex, **4,** was also moderately active against estrogen receptor-positive breast cancer cells, MCF-7 (IC_{50} = 3.02 μM) while the remainder were inactive against MCF-7 and all showed no activity towards receptor negative breast cancer cells, MDA-MB-231.

Keywords: S-4-methylbenzyldithiocarbazate; furaldehyde; transition metal complexes; NS bidentate Schiff base; Single crystal X-ray diffraction; cytotoxic activity.

1. Introduction

Since the early investigations on substituted derivatives of dithiocarbazate, NH_2NHCS_2, and their metal complexes in the 1970's [1], these compounds have continued to be of interest to researchers because of the wide variation in their structures and properties, and especially because of their bioactivity [1-3]. S-benzyl-β-N-(5-methyl-2-furylmethylene)dithiocarbazate, which differs from the ligand in this study only in the para substituent in the benzyl ring, was reported to be inactive against human T-lymphoblastic leukemia (CEM-SS), but chelation with metal ions produced cytotoxic complexes which also showed inhibition of *Aspergillus ochraceous* (398) [4].

Carcinostatic and fungitoxic activities in some related Schiff bases and metal complexes have been reported previously [5]. The Schiff bases derived from 2-acetyl- and 2-benzoylpyridine with S-methyl- and S-benzoyldithiocarbazate were [6] shown to be toxic towards *A. solani, F. equisetti and M. phaseolina*. Cu(II), Ni(II), Zn(II) and Cd(II) octahedral complexes of two 2-(6-methylpyridin-2-ylmethylene) hydrazine carbodithioate ligands were active against estrogen receptor positive MCF-7 and estrogen receptor negative MDA-MB-231 breast cancer cell lines. However, only the Cu(II) and Cd(II) complexes inhibited methicillin-

resistant *staphylococcus* (MRSA), *Bacillus subtilis* wild type (B29), *Pseudomonas aeruginosa* (60690), *Salmonella choleraesuis* (S.C.), *Candida albicans* (C.A.), *Aspergillusochraceous* (398) and *Saccaromycesceciricaee* (20341) [7].

The activity of some compounds can be enhanced when they are complexed to metals. Sigman and co-workers reported the first copper(II) complexes containing 1, 10-phenantroline ligands that showed good DNA cleavage activity. They were developed as therapeutic agents [8]. Binuclear copper(II) complexes have been found to have better DNA interaction than mononuclear complexes [9]. It has been reported that interaction of DNA with metal complexes may be the result of electrostatic interactions with the negatively charged nucleic sugar-phosphate, or through grooves of the DNA double helix, or by intercalation between the stacked base pairs of native DNA [10]. Howe-Grant *et al.,* in an early study of the intercalation of DNA, reported that square planar Pt(II) complexes of aromatic ligands, 2,2',2"-terpyridine, *o*-phenanthroline and 2,2'-bipyridine intercalated into DNA sequences producing strong interactions [11]. It was determined that increasing the concentration of calf thymus DNA increased the intensity of the $\pi \rightarrow \pi^*$ and LMCT absorption bands, but did not affect *d-d* transitions in the metal complexes reflecting the stacking interaction of the planar aromatic rings of the complexed ligand with double-helix strand of DNA base pairs [12]. The significant hypochromism and red shift were due to the strong $\pi \rightarrow \pi^*$ stacking interaction between the aromatic chromophore of the ligand in the copper(II) complexes and the base pair of DNA [13, 14].

As part of our ongoing study of dithiocarbazate compounds that exhibit specific biological profiles, we report herein the synthesis, characterization, DNA binding affinity studies and

cytotoxicity of a Schiff base, S-4-methylbenzyl-β-N-(2-furylmethylene) dithiocarbazate (S4MFuH, **1**) and its copper, nickel, zinc and cadmium complexes.

2. Experimental

2.1. Materials and reagents

All chemicals and solvents were of analytical grade and were used as received

Chemicals: 4-methylbenzyl chloride (ACROS), potassium hydroxide (HmbG), hydrazine hydrate (Fluka), carbon disulphide (BDH), furaldehyde (Fluka), nickel(II) acetate tetrahydrate (Fluka), zinc(II) acetate dihydrate(Fluka), cadmium(II) acetate dihydrate (Fluka), copper(II) acetate (Univar) and nitric acid (65%) (Fisher).

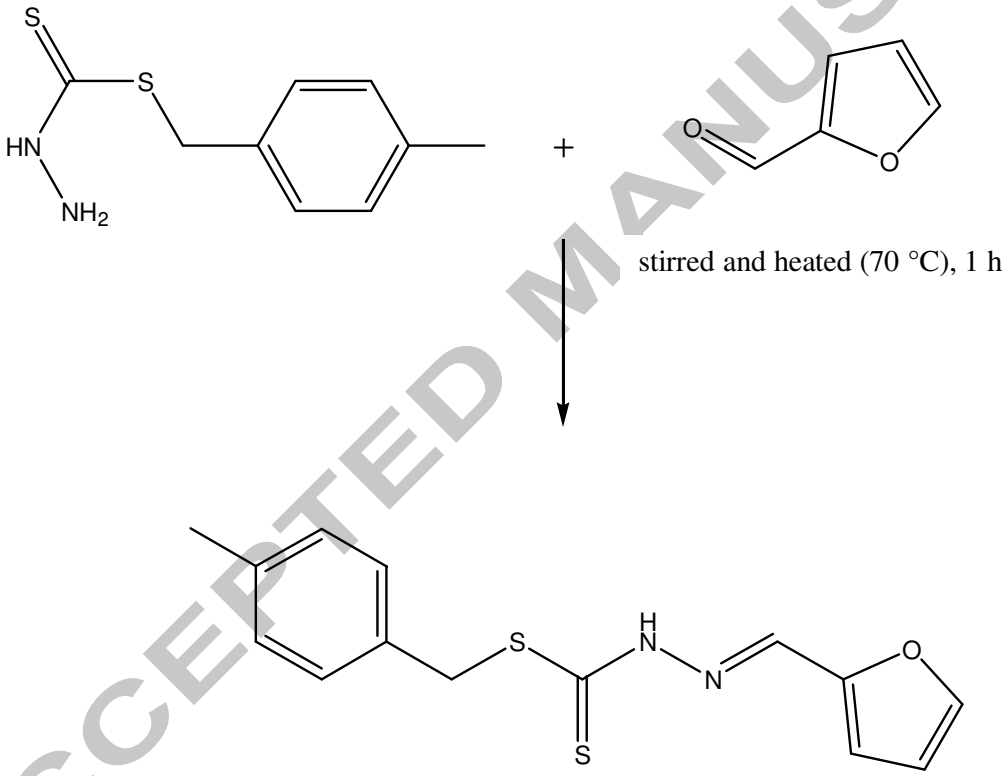
Solvents: acetonitrile (Baker), absolute ethanol (99.8%, Scharlau), ethanol (95%, J. Kollin Chemical), methanol (Fisher Scientific) and dimethylsulphoxide (Scharlau).

2.2. Synthesis of S-4-methylbenzyldithiocarbazate (S4MBDTC)

Following a procedure adapted from Ravoof *et al.* [15], potassium hydroxide (11.4 g, 0.2 mol) was dissolved in ethanol (70 ml, 90%). To this solution, hydrazine hydrate (10 g, 0.2 mol) was added and the mixture was maintained at 0°C in an ice-salt bath. Carbon disulphide (15.2 g, 0.2 mol) was added drop-wise with vigorous stirring (750 rpm) over a period of 1 h. The two layers that formed were separated using a separating funnel. The light-brown lower layer was dissolved in 40% ethanol (60 mL) below 5°C. The mixture was kept in an ice-bath and 4-methylbenzyl chloride (26.5 mL, 0.2 mol) was added drop-wise with vigorous stirring. The sticky white product, S4MBDTC, was filtered and left to dry overnight in a desiccator over anhydrous silica gel. Yield: 77%. m.p. 90-92 °C (lit. 86-89 °C).

*2.3. Synthesis of S-4-methylbenzyl-β-N-(2-furylmethylene) dithiocarbazate, S4MFuH (**1**)*

S-4-Methylbenzyldithiocarbazate (S4MBDTC) (2.12 g, 0.01 mol) was dissolved in hot acetonitrile (150 mL) and added to an equimolar amount of furaldehyde (0.96g) in ethanol (20 mL). The mixture was maintained at 70°C while stirring for 30 min. The product was recrystallised from CH_3CN:EtOH (1:1).Yield, 85%.m.p. 165-166 °C.



Scheme 1. Synthesis of S4MFuH (**1**) [4]

2.4. Synthesis of $M(S4MFu)_2$ where M = Zn(II), Cd(II), Cu(II) and Ni(II)

Acetate salts of Zn(II), Cd(II), Cu(II) and Ni(II) (1 mmol) were dissolved in hot 95% ethanol (10 ml) and added to a solution of S4MFuH (0.5 mmol) in hot acetonitrile (80 ml) and heated for 30 min. Yield for each complex: ~80%.

2.5. Instrumentation

IR spectra were recorded using PerkinElmer Spectrum 100 with Universal ATR Polarization in the range of 4000-280 cm^{-1}. C, H, N and S elemental analyses were carried out using a LECO CHNS-932 instrument. Metal determinations were carried out using a Perkin-Elmer Plasma 1000 Emission Spectrometer. Molar conductivities of 10^{-3} M solutions of the metal complexes in DMSO were measured at 27 °C using a Jenway 4310 conductivity meter fitted with a dip-type cell with a platinised electrode. Electronic spectra were recorded on a Shimadzu UV-1650 PC recording spectrophotometer (1000-200 nm). Magnetic susceptibilities were measured with a Sherwood Scientific MSB-AUTO magnetic susceptibility balance at 25 °C. Melting points were determined using an Electrothermal digital melting point apparatus.

2.5.1. X-ray crystallography

X-ray diffraction measurements for **1**–**3** were performed at 100 K on an Oxford Diffraction Gemini CCD diffractometer [16]. The structures were solved by direct methods (SHELXS97 [17] through the WinGX Interface [18]) and refined (anisotropic displacement parameters, C-bound H atoms in the riding model approximation and a weighting scheme of the form $w = 1/[\sigma^2(F_o^2) + aP^2 + bP]$ where $P = (F_o^2 + 2F_c^2)/3)$ with SHELXL97 on F^2 [17]. The N-bound hydrogen atoms in **1** were refined with N–H = 0.88±0.01 Å. For **3**, the maximum and minimum residual electron density peaks of 1.29 and 1.60 e $Å^{-3}$, were located 0.98 and 0.84 Å, respectively, from the Cd atom. The molecular structures shown in Figs 1 and 2, were drawn with 50% displacement ellipsoids for **1** and 70% for **2** and **3** [18]. The overlay diagram, Fig. 1c, was drawn with QMol [19] and the crystal packing diagrams with DIAMOND [20].

2.6. DNA binding studies

The DNA binding experiments were carried out at 25°C. DNA concentration per nucleotide (4.21×10^{-5}M) was determined using the molar absorption coefficient (6.6×10^{3} M^{-1} cm^{-1}) at 260 nm [21]. Absorption titration experiments were performed maintaining the concentration of the metal complex solution at 50 µM and gradually increasing the concentration of CT-DNA. The compounds were dissolved in DMSO and Tris-HCI buffer (50:50) containing 5 mM Tris, pH 7.1 and 25 mM NaCl [22] at room temperature (25°C). The solutions were scanned over the range 250-800 nm. Absorbance values were recorded 10 min after the addition of DNA solution. The binding constant, K_b was determined, using the equation :

$$[DNA] / (\varepsilon_a - \varepsilon_f) = [DNA] / (\varepsilon_b - \varepsilon_f) + 1/K_b(\varepsilon_a - \varepsilon_f)$$

where [DNA] is the concentration of DNA in the base pairs, ε_a corresponds to the apparent molar extinction coefficient $A_{abs}/[M]$, ε_f is the extinction coefficient for the free metal [M] complex and ε_b is the extinction coefficient for the fully bound metal complex [21-24].

2.7. Cytotoxic Assay

The MCF-7 (estrogen receptor positive human breast cancer) and MDA-MB-231 (estrogen receptor negative human breast cancer) cell lines used in this study (ATCC, Virginia, USA) were cultured in RPMI-1640 (High glucose) medium supplemented with 10% fetal calf serum (Sigma). The cytotoxic activity was determined using the microtitration of 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay (Sigma, USA) as previously reported [25]. Untreated cells were included for each compound as negative control. The standard breast cancer chemotherapeutic, Tamoxifen was used as the standard

positive control. Cytotoxicity levels were expressed as IC_{50} values, i.e., the concentration of compound that results in 50% cell death as compared to the negative controls *in vitro*.

3. Results and discussion

Table 1

Analytical and physical data for the Schiff base (**1**) and its metal complexes, (**2**-**5**).

Compound	Formula	Color	Melting point (°C)	Analytical (%) calculated (found)				Molar conductance (S cm^2 mol^{-1})
				C	H	N	M	
1	$C_{14}H_{14}N_2OS_2$	Yellow	165-166	57.90 (58.34)	4.86 (4.78)	9.65 (10.03)	-	-
2	$C_{28}H_{26}N_4O_2S_4Zn$	Light brown	182-183	52.21 (50.71)	4.07 (4.12)	8.70 (9.28)	10.15 (10.00)	0.14
3	$C_{28}H_{26}CdN_4O_2S_4$	Yellow	189-191	48.56 (47.96)	3.79 (3.72)	8.11 (7.15)	16.17 (15.60)	0.17
4	$C_{28}H_{26}CuN_4O_2S_4$	Dark-brown	171-172	52.36 (50.48)	4.08 (4.03)	8.72 (8.75)	9.89 (9.59)	1.05
5	$C_{28}H_{26}N_4NiO_2S_4$	Brown	217-218	52.75 (51.73)	4.11 (3.87)	8.79 (8.03)	9.15 (9.25)	0.42

All compounds are non-hygroscopic and stable at room temperature. Whereas **1** is soluble in common organic solvents, its metal complexes are insoluble in water and many organic solvents other than DMSO and DMF. Analytical data for the synthesized compounds are detailed in Table 1. The low molar conductance values show that the metal complexes are non-electrolytes [15]. The Zn(II) and Cd(II) complexes, are diamagnetic and are expected to have tetrahedral geometry. The magnetic moment of 1.88 B.M for the Cu(II) complex **4** indicates the presence of one unpaired electron, suggesting a square planar environment [4]. The Ni(II) complex is also diamagnetic, evidence of a square planar geometry.

2.1. IR spectral studies

Table 2

Important IR spectral bands (cm^{-1}) of the Schiff base and its metal complexes

Compound	*v*(N–H)	*v*(C=N)	*v*(N–N)	*v*(CSS)	*v*(COC)
1	2956 (w)	1611 (m)	1016 (s)	762(s)	1095 (m)
2	-	1592 (m)	1033 (s)	755 (s)	1088 (m)
3	-	1587 (m)	1031 (s)	760 (s)	1087 (m)
4	-	1610 (m)	1019 (s)	754 (s)	1100 (m)
5	-	1610 (m)	1015 (s)	751 (s)	1151 (m)

Important characteristic absorptions are given in Table 2. Compound **1** contains a thioamide group (-NH–C(=S)SR-) which is known to undergo thione-thiol tautomerism [1]. The medium intensity peak at 2955 cm^{-1}. consistent with *v*(N–H) shows that **1** exists predominantly in the thione form in the solid-state. This assignment is further supported by the absence of *v*(S-H) at ~2570 cm^{-1}. *v*(N–H) band is absent in the spectra of the metal complexes (**2-5)** indicating deprotonation of the N–H group on binding to the metal ion. A sharp band at 1611 cm^{-1} in the spectrum of the free ligand (1) is attributed to the *v* (C=N) stretch of the azomethine group. This band shifted to lower wavenumbers in all the complexes confirming the involvement of nitrogen in coordination to the metal ions. The shift in *v*(CSS) stretching to lower wavenumbers is expected on complexation [4]. The stretching vibration, *v*(COC) of the furan ring shifted upon complexation (**2-5**) as a result of interaction of the furanic oxygen atom with the central metal ion [26, 27].

3.2. NMR spectral studies

In the ^{1}H NMR spectrum of S4MFuH (**1**), recorded in DMSO-d_6,, the resonance for N–H appears at 13.22 ppm. The absence of a signal at ~4 ppm (thiol H) indicates that **1** exists

predominantly in the thione form in DMSO-d_6 solution as well as in the solid-state. The remaining resonances observed were those expected for the molecular formula proposed.

The signals at 200.04 and 114.56 ppm in the ^{13}C NMR spectrum are attributed to C=S and C=N functionalities, respectively, in line with the greater electronegativity of the sulphur atom.

3.3. Mass spectral studies

The mass spectrum for **1** is consistent with the proposed formula (molecular ion m/z 290). The base peak observed at m/z 105 for **1** is assigned to the $C_8H_9^{\bullet}$ fragment and peaks observed at m/z 138, 91 and 77 correspond to fragments $C_8H_9S^{\bullet}$, $C_7H_7^{\bullet}$ and $C_6H_4^{\bullet\bullet}$, respectively.

3.4. Electronic spectral studies

Table 3

Electronic Spectral Data for S4MFuH (**1**) and its metal complexes, (**2-5**).

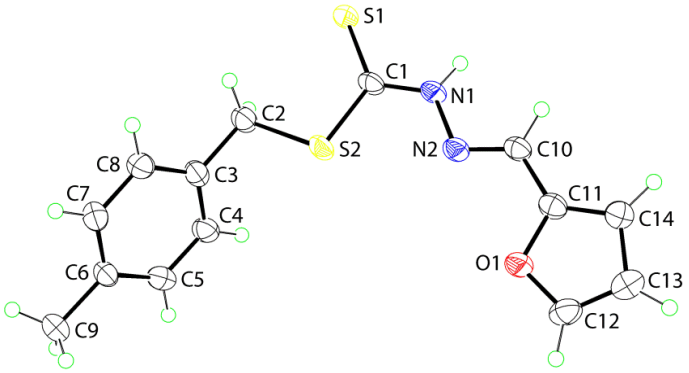
Compound	Electronic spectra (in DMSO) $^{a}\lambda_{max}(^{b}\log \varepsilon_{max})$
1	348 (4.80)
2	351 (5.09)
3	348 (3.60)
4	351 (4.98), 383 (4.46), 779 (2.36)
5	348 (4.93), 458 (3.68), 592 (2.19)

[a] λ_{max} in nm
[b] $\log \varepsilon_{max}$ = L mol^{-1} cm^{-1}

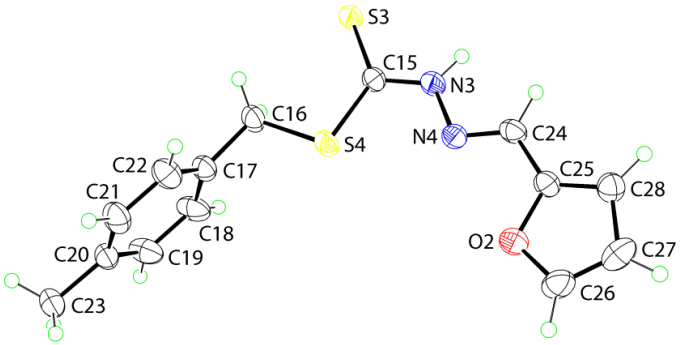
The electronic spectral data for compounds **1-5** are tabulated (Table 3). Compounds **1-5** were dissolved in DMSO at room temperature at three concentrations, i.e. 10^{-3}, 10^{-4} and 10^{-5} M. The π-π* transition associated with non-bonding electrons of the azomethine chromophore [28] in the spectrum of **1** was recorded at 348 nm. The dark-brown copper complex (**4**) showed a broad *d-d* absorption at 592-779 nm. A strong S→Cu(II) charge-transfer band at ca 383 nm and an intraligand band (n→π*) at 256 nm were also observed. The occurrence of an S→Cu LMCT band is common in square planar Cu(II) complexes of thiosemicarbazones and dithiocarbazates [29, 30]. The diamagnetic Ni(II) complex (**5**) showed an absorption band at 592 nm consistent with the $^1A_{1g} \rightarrow {}^1E_g$ transition of a square planar d^8 metal complex. The other two bands observed corresponded to the transitions $^1A_{1g} \rightarrow {}^1A_{2g}$ (348 nm) and $^1A_{1g} \rightarrow {}^1B_{1g}$ (458 nm) expected for a square planar complex. The absorption observed for the Zn complex (**2**) at 407 nm is due to LMCT [10]. Absorptions consistent with ligand π → π* and L → M charge transfer bands appeared in the spectrum of the cadmium complex (**3**).

3.5. Structural commentary

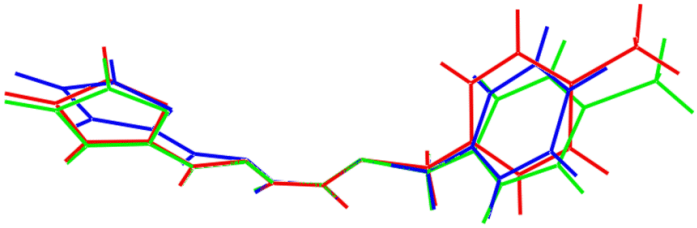
The crystallographic asymmetric unit of **1** comprises two independent molecules as illustrated in Fig. 1; selected bond lengths (Å) and angles (°) are collected in Table 4 and crystallographic and refinement details for 1–3 are given in Table 5.



(a)



(b)



(c)

Figure 1: (a) and (b) The molecular structures of the two independent molecules comprising the asymmetric unit of **1**, showing atom-labeling scheme. (c) Overlay diagram of the two independent molecules of **1**, S1 (red image) and S2 (green), and of a closely related literature precedent, benzyl 3-((E)-furfurylidene)dithiocarbazate [30] (blue). The molecules have been superimposed so that the central CS_2 residues are coincident.

The configuration about the imine bond is *E* and the overall shape of the molecule is that of a flattened "U" with the aromatic residues being *syn*, the furanyl-O orientated toward the

concave region of the molecule, and with the thione-S directed to the outside of the molecule and anti to the azo bond. The seven atoms comprising the central residue, i.e.,CSC(=S)NNC, are coplanar with a r.m.s. deviation 0.0326 Å (the equivalent value for the second independent molecule is 0.0405 Å). While to a first approximation the two independent molecules have similar conformations, as highlighted in the overlay diagram in Fig. 1(c), some differences are noted in the orientations of the terminal residues. While the difference in the dihedral angles between the central residual and furanyl ring are not great, i.e., 8.55(16) and 6.80 (17)º, for the two independent molecules, respectively, greater differences are seen in the dihedral angles between the central residue and the tolyl rings, 62.53(6) and 80.69(7)º, respectively, and between the furanyl and tolyl rings of 61.83(8) and 79.97(9)º. The relevant structure in the literature most appropriate for comparison is that of benzyl 3-((E)-furfurylidene)dithiocarbazate [30], i.e., the unsubstituted benzyl derivative of **1**. A comparable overall conformation is found along with similar geometric parameters, but the relative disposition of the terminal rings is almost orthogonal with a dihedral angle of 87.82(6)º, Fig. 1(c). The most significant intermolecular interactions in the crystal structure of **1** are N–H…S(thione) hydrogen bonds [31] whereby the two independent molecules associate via an eight-membered $\{\ldots HNCS\}_2$synthon to form dimeric aggregates. These assemble into columns along the *a*-axis with no specific interactions between them. See Fig. 2 below for a view of unit cell contents.

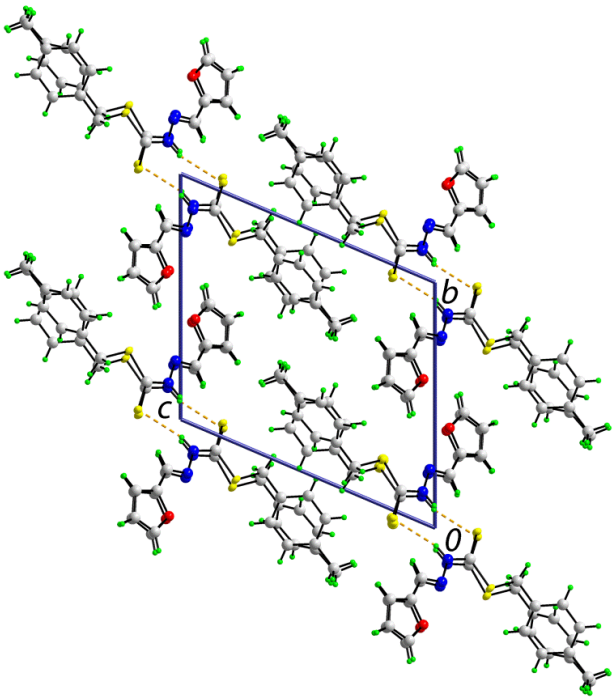
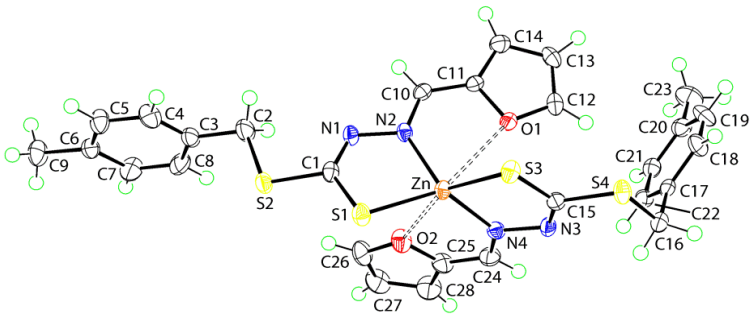


Figure 2. A view in projection down the *a*-axis of the unit cell contents of **1**. The N–H…S hydrogen bonds are shown as orange dashed lines.

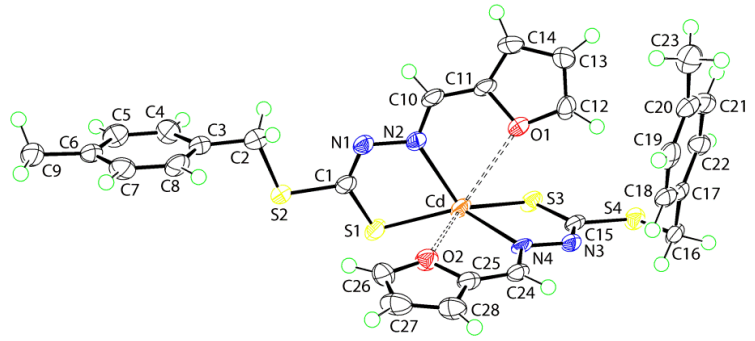
In the structure of **3** (Fig. 2(a) and Table 4), the zinc atom is N-,S-chelated by two dithiocarbazate anions forming an N_2S_2 donor set. The resulting five-membered chelate rings have different configurations with that containing the S1 atom being twisted about the Zn–S1 bond, and the second ring being an envelope with the Zn atom being the flap. The dihedral angle between the two chelate rings of 83.13(5)ºis consistent with a tetrahedral geometry. However, the range of tetrahedral angles is relatively wide, i.e., from an acute 86.10(5)º for the S1–Zn–N2 chelate angle, consistent with the restricted bite angle of the ligand, to a wide 129.78(5)º for S1–Zn–N4. These deviations are ascribed to the close approach of the furanyl-O atoms, Table 4. If the latter interactions were considered significant, the coordination geometry might be considered as comprising two N-,O-,S-coordinating anions each occupying *mer*-positions in a heavily distorted octahedral coordination geometry. The key difference in geometric parameters as a result of deprotonation and coordination of **1** in **2** is

the elongation of the formally thione bond by 0.06-0.07 Å and the contraction of the quaternary-C–N bond, by 0.03-0.04 Å, consistent with the formation of a thiolate-S and an adjacent imine bond; the other bond lengths are remarkably similar, Table 4. The major conformational change associated with coordination of **1** is the *syn* disposition of the thiolate-C−S and azo-N−N bonds which arises owing to chelation and accompanying change in conformation. As a result, some significant changes in bond angles ensue. Referring to Table 4, the most notable changes are seen about the quaternary-C atoms where the S–C–S angle has contracted by over 10° with a concomitant increase in the coordinated-S–C–N angles by nearly the same amount in **2** compared with **1**. The other significant change is found in the narrower angles, i.e., by 6-7°, subtended at the non-coordinating-N1, N3 atoms compared to **1**.

In the structure of **3**, Fig. 3(b) and Table 4, the cadmium atom exhibits essentially the same features as just described for **2**. The five-membered chelate rings have the comparable configurations as for **2**, i.e., that containing the S1 atom being twisted about the Cd–S1 bond and the second ring being an envelope with the flap atom being Cd. The dihedral angle between the two chelate rings is 81.74(7)º. Reflecting the larger size of the cadmium atom and its propensity to expand its coordination number, the intramolecular Cd…O interactions are shorter and therefore stronger than the comparable interactions in **2**. As a consequence of the close approach of the furyl-O atoms, the range of tetrahedral angles is wider in **3** than for **2**, i.e., 78.49(8)º, for the S1–Zn–N2 chelate angle, to 134.40(8)º for S1–Zn–N4. If the Cd…O interactions were considered significant, the resulting $N_2O_2S_2$ donor set defines a polyhedron best described as being based on a twisted trigonal prism in which each triangular face is occupied by a single oxygen, nitrogen and sulphur atom. (See the caption to Fig. 3(b) below for more details.)



(a)



(b)

Figure 3: The molecular structures of (a) **2** and (b) **3**. The intramolecular M…O interactions are highlighted as dashed lines. If these interactions were considered significant, the coordination geometry for the zinc atom is distorted octahedral with one triangular face being defined by the S1, S3 and N4 atoms. In the case of cadmium, where the coordination geometry would be considered twisted trigonal prismatic, one triangular face is occupied by the S1, O2 and N2 atoms.

The most closely related structure in the literature available for comparison with **1** and **2** is a cadmium complex with an unsubstituted benzyl group and with the furanyl ring bearing a methyl group adjacent to the oxygen atom, i.e., bis[*S*-benzyl-β-*N*-(5-methyl-2-furylmethylene) dithiocarbazato]cadmium(II) [2]. This structure adopts an arrangement very similar to **3**. Other structures worth mentioning are thienyl analogues of **1** but with unsubstituted benzyl residues [32]. When complexed to nickel(II) and copper(II), the thienyl-S atoms do not form intramolecular M…S interactions owing to the steric constraints imposed by the square planar geometry about each metal center.

In the crystal packing of **2**, the molecules self-assemble into double layers in the *ac*-plane via π…π interactions between O2-furanyl and C3-tolyl rings. Layers are connected along the *b*-axis by O1-furanyl-C-H…S3 interactions which by themselves assemble molecules into helical chains. A view of the crystal packing is given as Fig. 4, and geometric details given below, ref. [33].

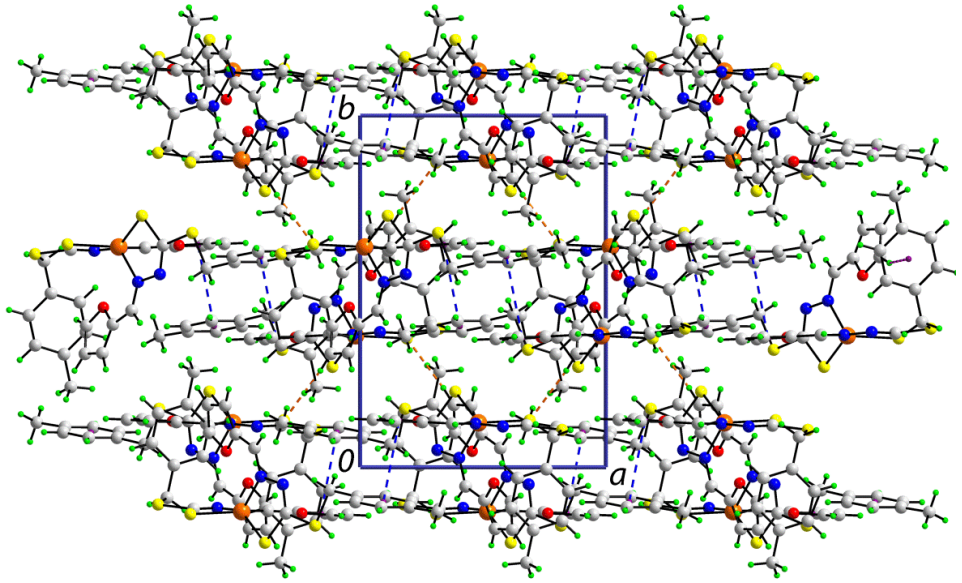


Figure 4. A view in projection down the *c*-axis of the unit cell contents of **2**. The C–H…S and π…π interactions are shown as orange and blue dashed lines, respectively.

For **3**, double layers are formed parallel to (101), see Fig. 5, and the only recognisable interactions are of the type π…π again occurring between O2-furanyl and C3-tolyl rings [34].

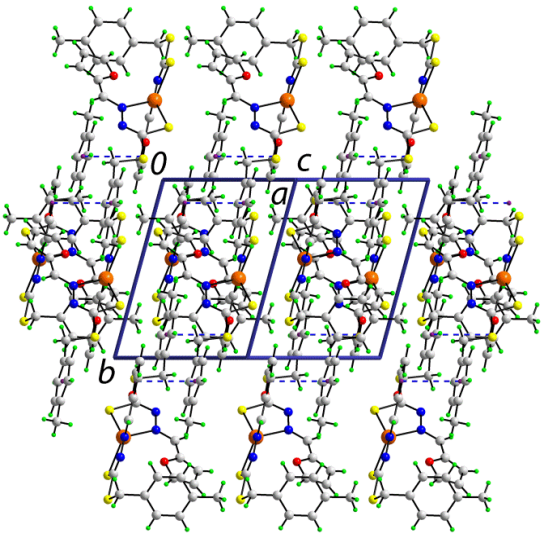


Figure 5.A view of the unit cell contents of **3**. The π…π interactions are shown as blue dashed lines.

Table 4

Selected bond lengths and angles (Å, º) for **1**–**3**.

Compound	**1**	**2** (M = Zn)	**3** (M = Cd)
Parameter			
M–S1	–	2.2896(6)	2.4825(11)
M–S3	–	2.2949(6)	2.4923(10)
M–N2	–	2.0627(18)	2.314(3)
M–N4	–	2.052(2)	2.269(3)
M…O1	–	2.9313(15)	2.932(3)
M…O2	–	2.8454(16)	2.793(3)
C1–S1	1.672(2)	1.742(2)	1.737(4)
C1–S2	1.746(2)	1.749(2)	1.753(4)
C2–S2	1.828(3)	1.826(2)	1.823(4)
C15–S3	1.682(2)	1.743(3)	1.746(4)

C15–S4	1.751(2)	1.756(2)	1.762(4)
C16–S4	1.816(3)	1.821(3)	1.820(4)
N1–N2	1.384(3)	1.398(2)	1.406(4)
N3–N4	1.385(3)	1.404(3)	1.396(4)
C1–N1	1.334(3)	1.304(3)	1.306(5)
C10–N2	1.285(3)	1.297(3)	1.294(5)
C15–N3	1.327(3)	1.301(3)	1.292(5)
C24–N4	1.280(3)	1.297(3)	1.296(5)
S1–C1–S2	124.04(15)	113.09(12)	111.8(2)
S1–C1–N1	121.30(16)	128.84(17)	131.0(3)
S2–C1–N1	114.66(17)	118.08(17)	117.3(3)
S3–C15–S4	125.41(14)	111.78(13)	112.2(2)
S3–C15–N3	120.24(17)	130.25(18)	131.4(3)
S4–C15–N3	114.35(17)	117.96(18)	116.3(3)
C1–N1–N2	121.33(18)	114.33(18)	114.8(3)
C15–N3–N4	121.12(19)	113.85(19)	115.3(3)

Table 5

Crystallographic and refinement details for **1**–**3**.

Compound	**1**	**2**	**3**
Formula	$C_{14}H_{14}N_2OS_2$	$C_{28}H_{26}N_4O_2S_4Zn$	$C_{28}H_{26}CdN_4O_2S_4$
Formula weight	290.39	644.14	691.17
Crystal color/habit	Yellow prism	Light-brown prism	Yellow prism
Crystal dimensions/mm	0.06 x 0.12 x 0.33	0.05 x 0.15 x 0.25	0.05 x 0.13 x 0.25
Crystal system	triclinic	monoclinic	triclinic
Space group	$P\bar{1}$	$P2_1/n$	$P\bar{1}$

a/Å	9.4658(8)	11.0684(4)	10.7805(7)
b/Å	12.4477(7)	15.5959(5)	11.0505(6)
c/Å	13.8832(9)	17.1770(6)	12.8127(7)
α/°	64.342(6)	90	91.758(4)
β/°	76.011(6)	99.864(3)	95.217(5)
γ/°	74.180(6)	90	107.662(6)
V/Å^3	1404.17(17)	2921.29(17)	1445.67(15)
Z	4	4	2
D_c/g cm^{-3}	1.374	1.465	1.588
F(000)	608	1328	700
Radiation, λ/Å	CuKα, 1.54180	MoKα, 0.71073	MoKα, 0.71073
μ/mm^{-1}	3.378	1.160	1.078
Measured data	18488	12834	11904
θ range/°	3.6–71.6	2.3–26.5	2.3–26.5
Unique data	5403	6040	5988
Observed data ($I \geq 2.0\sigma(I)$)	4589	4906	4936
R, obs. data; all data	0.058; 0.066	0.035; 0.049	0.048; 0.063
a, *b* in weighting scheme	0.114, 0.514	0.034, 0.987	0.060, 0
R_w, obs. data; all data	0.156; 0.166	0.077; 0.084	0.111; 0.123
Residual electron density peaks/e Å^3	0.95, -0.31	0.46, -0.53	1.29, -1.60

3.6. DNA binding studies

Electronic absorption titrations are usually used to determine the binding affinity of complexes to the calf-thymus DNA (CT-DNA) helix. The absorption spectra are recorded in

the absence and presence of CT-DNA (at a constant concentration of complexes, with increasing concentration of CT-DNA). Hypochromism and red-shifts indicate strong stacking interactions between the DNA double helix strand and an aromatic chromophore [35-37].

The electronic absorption spectra for the titrations of complexes (**2**-**5**) are reproduced in Fig. 6. Each spectrum displays two intense absorption bands attributed to the LMCT and intra-ligand ($\pi \rightarrow \pi^*$) transitions of the aromatic chromophore in the regions 322-392 nm and 263-282 nm, respectively. The decreasing energies of $\pi \rightarrow \pi^*$ indicate that the π^* orbital of the ligands on the complexes are coupled with a π orbital of the DNA base pairs. This interaction is manifested by hypochromism and red-shifts [22]. The hypochromism observed were 22%, 23%, 52%, and 25%, for complexes **2**–**5** respectively. In order to compare the binding strengths of the complexes to CT-DNA, the binding constants were quantitatively determined. The K_b obtained for complexes **2-5** are 1.42 x 10^4, 1.71 x 10^3, 2.85 x 10^4 and 3.42 x 10^3 M^{-1}, evidence of good binding affinity due to $\pi \rightarrow \pi^*$ stacking interactions between the respective complex and the DNA base pairs for all complexes [22, 37-39]. The copper complex (**4**) has the highest binding constant consistent with it having the lowest IC_{50} value among the compounds assayed. The greater potency of **4** is expected to relate to its ability to block the enzymatic binding to the nitrogen bases of DNA or RNA [40]. The data obtained was comparable to *N,N′*-bis{5-[(triphenylphosphonium chloride)-methyl] salicylidine}-*o*-phenylenediamine) Schiff base, which was revealed to have intercalative binding modes with the value of intrinsic binding constant being 8.5×10^5 M^{-1} which was greater that its cobalt(II) complex ($K_b = 5 \times 10^4$ M^{-1}). The cobalt(II) complex most likely interacted with DNA in an electrostatic binding mode [41]. However, the values obtained were much lower than the potential intercalators like ethidium bromide ($k_b = 7 \times 10^7$ M^{-1}) [42]. The data in this work was also comparable to $[Co(phen)_3]^{3+}$ (1.6×10^4 M^{-1}) [42]; Co(III) complexes with

asymmetric ligand, $[Co(phen)_2(pdta)]^{3+}$ ($k_b = 2.8 \times 10^4$) [43]; $[Co(bpy)_2(CNOIP)]^{3+}$ ($k_b = 5 \times 10^4\ M^{-1}$) [44].

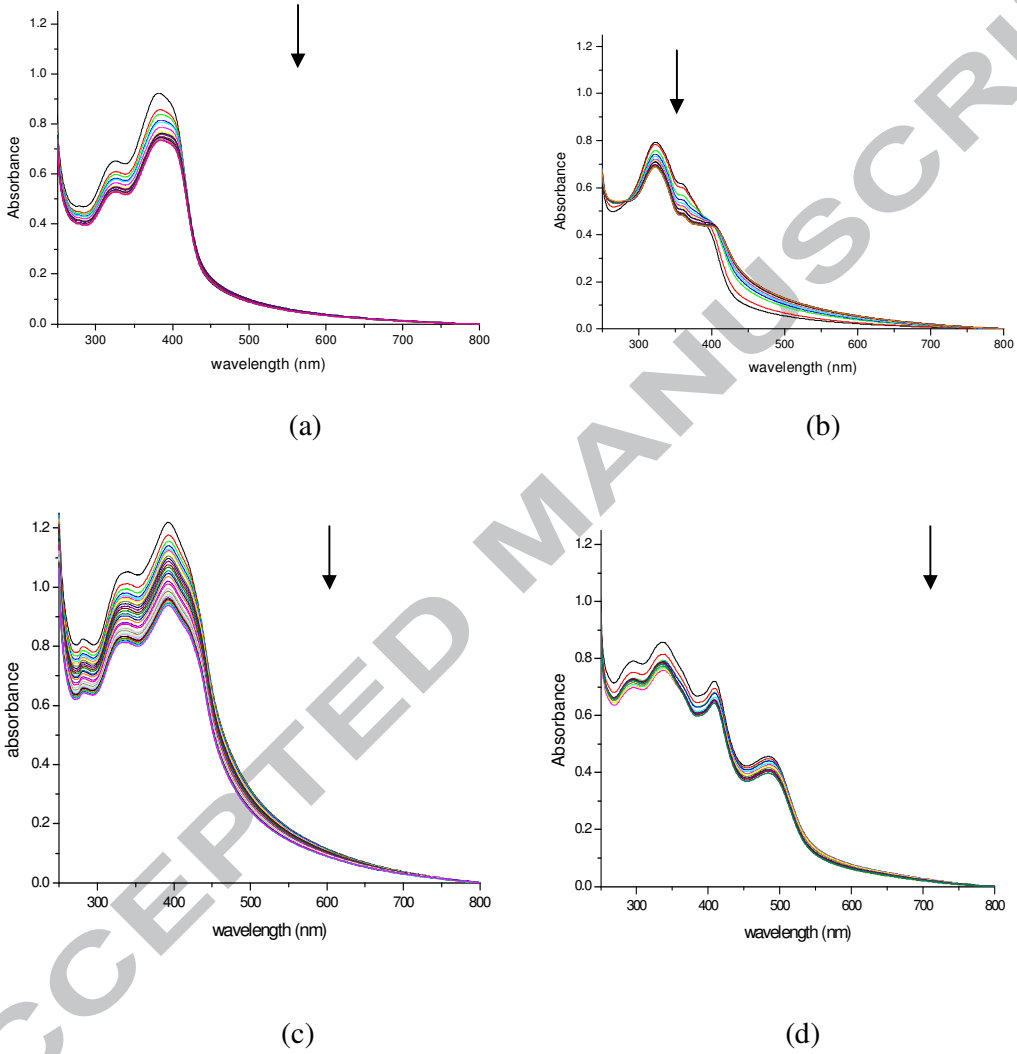


Figure 6. Electronic absorption spectra of (a) **2**, (b) **3**, (c) **4** and (d) **5**, (50 µM) recorded in the absence and presence of increasing amounts of CT-DNA. Arrows show the absorption changes upon increasing the concentration of CT-DNA.

3.7. Cytotoxicity Assay

Several factors are known to affect the biological activity of a given molecule. These factors include lipophilicity, chemical structure, resonance, and thermodynamic stability [1,

45]. Many dithiocarbazate Schiff bases and their metal complexes have been shown to exhibit a wide range of cytotoxic activities, with small changes in the chemical composition often leading to vast differences in selectivity and activity [45-49]. The complexation of Schiff bases with metal ions reduces the polarity of the metal ions through the partial sharing of positive charge with the donor atoms and π-electron delocalization upon chelation [50]. This results in the enhancement of the lipophilic characteristics of the central metal atom allowing the blocking of cellular enzymatic activity [51].

Compound **1** was inactive against the two breast cancer cell lines assayed, [MCF-7 (estrogen receptor positive human breast cancer) and MDA-MB-231 (estrogen receptor negative human breast cancer)]. Consistent with previously published findings, the cytotoxicity of **1** improved with the complexation to a metal[1]. The Cu(II) complex, **4**, showed moderate cytotoxic activity against the MCF-7 cell line (IC_{50}= 3.02μM) but was inactive against MDA-MB-231, however. complexes **2**, **3** and **5** were inactive against both. This order of potency is consistent with an earlier investigation [11] and is related to both the ionic radii and the ligand field stabilization energies. The Cu(II) ion has the smallest radius of the first-row transition metals. This results in the strongest binding of the ligand that plays an important role in ligation and transport upon complexation. In addition, the activity of the Cu(II) complex could be due to other factors such as redox activity, ligand exchange reactions, the existence of metabolic pathways for transport and excretion, and activation of metal-dependent enzymes all of which, could play vital roles in determining the most cytotoxic metal [52, 53]. The cytotoxic data were also comparable to the copper complexes of quinoline-2-carboxaldehyde, which showed dose-dependent cell growth inhibition in LNCaP and PC-3 cell (prostate cancer cell lines) at IC_{50} of 5 μM and 7 μM after 72 h of treatment.

These complexes were expected to be used for targeting the ubiquitin-proteasome pathway for the treatment of prostate cancer [54].

Copper complexes with a CH_3 moiety, an electron donating group, at the *para* position of the benzene ring have been shown to have higher cytotoxic activity than those with a methyl group at the *ortho* position [15]. A methyl group in the *ortho* position is affected by steric interference and interactions with the lone pair from the neighbouring sulphur atom. In addition, the presence of methyl groups prevents metabolic hydroxylation and subsequently makes the copper complexes less cytotoxic towards cancer cells [55].

4. Conclusion

The synthesis of S-4-methylbenzyl-β-N-(2-furylmethylene)dithiocarbazate (S4MFuH), a new Schiff base and its Zn^{2+}, Cu^{2+}, Cd^{2+} and Ni^{2+} complexes is reported. S4MFuH, **1,** has an *E* configuration, features the thione *anti* to the azo bond and has a U-shape overall. When deprotonated, it chelates through nitrogen and sulfur to Zn^{2+} (**2**) and Cd^{2+} (**3**), resulting in a change in conformation (*syn*) as revealed by X-ray crystallography. A distorted tetrahedral geometry with two bidentate NS ligands was found for complexes **2** and **3**, with two close intramolecular M…O interactions being largely responsible for the distortions. The Cu^{2+} complex (**4**) is paramagnetic indicating that it has tetrahedral geometry while the diamagnetic character of **5** shows that it is likely to be square planar. The biological activity of the Schiff base and its metal complexes was evaluated against MCF-7 (estrogen receptor positive human breast cancer) and MDA-MB-231 (estrogen receptor negative human breast cancer) cell lines. Complex **4** was found to be moderately active against MCF-7 cells but inactive towards MDA-MB-231 while all other compounds were inactive against both cell lines. All complexes bound to CT-DNA with a moderate binding affinity, K_b, = 10^4-10^3 M^{-1}. As

expected, the most cytotoxic compound, complex **4,** showed the strongest CT-DNA binding affinity among them.

Acknowledgements

We thank the Department of Chemistry, the Molecular Genetics Laboratory and the Department of Obstetrics and Gynaecology, Universiti Putra Malaysia, and the Malaysian Genome Institute for the use of their facilities. This research was funded by Universiti Putra Malaysia (UPM) and the Malaysian Government under the Research University Grant Scheme (RUGS No. 9419400), the Malaysian Fundamental Research Grant Scheme (FRGS No. 01–02-13-1344FR) and the Science Fund under the Ministry of Science, Technology and Innovation (MOSTI) (06-01-04-SF1810). E.N.M.Y and J.J. wish to thank UPM for the award of Graduate Research Fellowships. Support from the High Impact Research Ministry of Education Grant UM.C/625/1/HIR/MoE/SC/12 from the Ministry of Higher Education Malaysia and the University of Malaya is also gratefully acknowledged.

Supplementary Material

The crystallographic data for the structural analysis of compounds $C_{14}H_{14}N_2OS_2$, $C_{28}H_{26}N_4O_2S_4Zn$ and $C_{28}H_{26}CdN_4O_2S_4$, **1–3,** have been deposited with the Cambridge Crystallographic Data Centre, CCDC No. for **1** is 1004617, for **2** is1004618 and for **3** is 1004619. A copy of this information may be obtained free of charge from the Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (Tel.: +44 (0) 1223 762911; E-mail: deposit@ccdc.cam.ac.uk).

References

[1] M. A. Ali, S. E. Livingstone, Metal complexes of sulphur-nitrogen chelating agents, Coord. Chem. Rev. 13 (1974) 101-132.

[2] M.T.H. Tarafder, T.-J.Khoo, K.A. Crouse, A.M. Ali, B.M. Yamin, H.-K. Fun, Coordination chemistry and bioactivity of Ni^{2+}, Cu^{2+}, Cd^{2+} and Zn^{2+} complexes containing bidentateNS Schiff bases derived from S-benzyldithiocarbazate and the X-ray crystal structure of bis[S-benzyl-β-N-(5-methyl-2-furylmethylene)dithiocarbazato] cadmium(II), Polyhedron 21 (2002) 2547-2554.

[3] M. B. Halli, R. B. Sumathi, Synthesis, physico-chemical investigations and biological screening of metal (II) complexes with Schiff base derived from naphthofuran-2-carbohydrazide and citral, Arabian J. Chem. (2013) In Press, Corrected Proof DOI : 10.1016/j.arabjc.2013.06.025.

[4] M. T. H. Tarafder, T.-J. Khoo, K. A. Crouse, M. A. Ali, B. M. Yamin, H. K. Fun, Coordination chemistry and bioactivity of some metal complexes containing two isomeric bidentate NS Schiff bases derived from S-benzyldithiocarbazate and the X-ray crystal structures of S-benzyl-β-N-(5-methyl-2-furylmethylene)dithiocarbazate and bis[S-benzyl-β-N-(2-furylmethylketone)dithiocarbazato]cadmium(II),Polyhedron. 21 (2002) 2691-2698.

[5] K. B. Chew, M. T. H. Tarafder, K. A. Crouse, M. A. Ali, B. M. Yamin, H. -K. Fun, Synthesis, characterization and bio-activity of metal complexes of bidentate N–S

isomeric Schiff bases derived from S-methyldithiocarbazate (SMDTC) and the X-ray structure of the bis[S-methyl-β-N-(2-furylmethylketone)dithiocarbazato]cadmium(II) complex, Polyhedron 23 (2004) 1385–1392.

[6] M. E. Hossain, J. Begum, M. N. Alam, M. Nazimuddin, M. A. Ali, Synthesis, characterization and biological activities of some nickel (II) complexes of tridentate NNS ligands formed by condensation of 2-acetyl-and 2-benzoylpyridines with S-alkyldithiocarbazates, Transition Met. Chem, 18(5) (1993) 497-500.

[7] T. B. S. A. Ravoof, K. A. Crouse, M. I. M. Tahir, F. N. F. How, R. Rosli, D. J. Watkins, Synthesis, characterization and biological activities of 3-methylbenzyl 2-(6-methyl pyridin-2-ylmethylene)hydrazine carbodithioate and its transition metal complexes, Transition Met. Chem, 35 (2010) 871-876.

[8] D. S. Sigman, D. R. Graham, V. D. Aurora, A. M. Stern, Oxygen dependent cleavage of DNA by 1, 10 phenthroline cuprous complex, J. Biol Chem, 254 (1979) 12269–12272.

[9] M. C. B. Oliveira, M. S. R. Couto, P. C. Severino, T. Foppa, G. T. S. Martins, B. Szpoganicz, R. A. Peralta, A. Neves, H. Terenzi, H., 2005. Nucleic acid cleavage by Cu (II) polyaza macrocylic complex, Polyhedron 24 (2005) 495-499.

[10] H.-P. Zhou, D.-M. Li, P. Wang, L.-H. Cheng, Y.-H. Gao, Y.-M. Zhu, J.-Y. Wu, Y.-P. Tian, X.-T. Tao, M.-H. Jiang, H.-K. Fun, Synthesis, crystal structures, and two-photon

absorption properties of dithiocarbazate Zn(II) and Pd(II) complexes, J. Mol. Struc. 826 (2007) 205-210.

[11] M. Howe-Grant, K. C. Wu , W. R. Bauer, S. J. Lippard. Binding of platinum and palladium metallointercalation reagents and antitumor drugs to closed and open DNAs, Biochemistry 1976 15 (19) 4339–4346.

[12] T. Hirohama, Y. Kuranuki, E. Ebina, T. Sugizaki, H.Arii, M. Chikira, P. T. Selvi, M.Palaniandavar, Copper(II) complexes of 1,10-phenanthroline-derived ligands: Studies on DNA binding properties and nuclease activity, J. Inorg. Biochem. 99 (2005) 1205-1219.

[13] P. Jayaseelan, E. Akila, M. U. Rani, R. Rajavel, Synthesis, spectral characterization, electrochemical, anti-microbial, DNA binding and cleavage studies of new binuclear Schiff base metal (II) complexes derived from o-hydroxyacetophenone, Journal of Saudi Chemical Society. (2013) In Press, Corrected Proof. DOI:10.1016/j.jscs.2013.07.001

[14] P. Nagababu, J. N. L. Latha, Y. Prashanthi, S. Satyanarayana, DNA-Binding and Photocleavage Studies of Cobalt (III) Ethylenediamine Complexes:$[Co\ (en)_2phen]^{3+}$ and $[Co\ (en)_2bpy]^{3+}$, *J. Chem. Pharm. Res*, *1* (2009) 238-249.

[15] T. B. S. A. Ravoof , K. A. Crouse, M. I. M. Tahir, R. Rosli, D. J. Watkins, F. N. F. How, Synthesis, Characterisation and Biological Activities of 2-Methylbenzyl 2-

(dipyridin-2-yl methylene)hydrazinecarbodithioate, J. Chem Crystallogr. 41 (2010) 491-495.

[16] CrysAlis PRO, Agilent Technologies, Yarnton, Oxfordshire, England, 2011.

[17] G.M. Sheldrick, "A short history of SHELX.", Acta Crystallogr. Sect. A 64 (2008) 112-122.

[18] L.J. Farrugia, WinGX and ORTEP for Windows: an update, J. Appl. Crystallogr. 45 (2012) 849-854.

[19] J. Gans, D. Shalloway, Qmol: a program for molecular visualization on Windows-based PCs, J. Mol. Graphics Modell. 19 (2001) 557-559.

[20] K. Brandenburg, DIAMOND. Crystal Impact GbR, Bonn, Germany, 2006.

[21] D.S. Badiger, R.S. Hunoor, B. R. Patil, R.S. Vadavi, C.V. Mangannavar, I.S. Muchchandi, K.B. Gudasi, Synthesis. spectroscopic properties and biological evaluation of transition metal complexes of salicylhydrazone of anthranilhydrazide: X-ray crystal structure of copper complex, Inorg. Chim.Acta. 384 (2012) 197–203.

[22] K.R. Sangeetha Gowda, H.S. BhojyaNaik, B. Vinay Kumar, C.N. Sudhamani, H.V. Sudeep, T.R. RavikumarNaik, G. Krishnamurthy, Synthesis, antimicrobial, DNA-binding and photonuclease studies of cobalt(III) and nickel(II) Schiff base complexes, Spectrochim. Acta Mol. Biomol.Spectros. 105 (2013) 229–237.

[23] M.E. Reichmann, S.A. Rice, C.A. Thomas, P. Doty, A Further Examination of the Molecular Weight and Size of Desoxypentose Nucleic Acid, J. Am. Chem. Soc. 76 (1954) 3047-3053.

[24] J.B. Chaires, N. Dattagupta, D.M. Crothers, Studies on interaction of anthracycline antibiotics and deoxyribonucleic acid: equilibrium binding studies on the interaction of daunomycin with deoxyribonucleic acid, Biochem**.** 21(1982) 3933–3940.

[25] T. Mosmann, Rapid colorimetric assay for cellular growth and survival: application to proliferation and cytotoxicity assays, J. Immunol Methods. 65 (1983) 55–63.

[26] Shahidhar, K. Shivakumar, P.V. Reddy, M.B. Halli, Synthesis and spectroscopic characterization of metal complexes with naphthofuran-2-carbohydrazide Schiff's base, J. Coord. Chem. 60 (2007) 243-256.

[27] M.B. Halli, R. Malipatil, Synthesis, characterization and spectral studies of metal (II) complexes derived from benzofuran-2-carbohydrazide and 2-acetylthiophene Schiff's base, Der Pharma Chemica. 3 (2011) 146-157.

[28] R. Selwin Joseyphus, M. Sivasankaran Nair, Synthesis, characterization and biological studies of some Co(II), Ni(II) and Cu(II) complexes derived from indole-3-carboxaldehyde and glycylglycine as Schiff base ligand, Arabian J. Chem. 3 (2010) 195-204.

[29] M.A. Ali, A.H. Mirza, R.J. Fereday, R.J. Butcher, J.M. Fuller, S.C. Drew, L.R. Gahan, G.R. Hanson, B. Moubaraki, K.S. Murray, Synthetic, EPR spectroscopic, magnetic, and X-ray crystallographic structural studies on copper(II) complexes of the tridentate N_2S donor ligand formed from 6-methyl-2-formylpyridine and S-methyldithiocarbazate (Hmpsme), Inorg. Chim.Acta.358 (2005) 3937-3948.

[30] S. Shan, Y.-L. Tian, S.-H. Wang, W.-L. Wang, Y.-L. Xu, Benzyl 3-[(E)-furfurylidene]dithiocarbazate, ActaCrystallogr. Sect. E, 64 (2008) o1024 - o1024..

[31] Parameters characterising the hydrogen bonding in the crystal structure of **1**: N1–H1n...S3^{i} = 2.55(2) Å, N1...S3^{i} = 3.398(2) Å, with angle at H1n = 163(2)°; N3–H3n...S1^{i} = 2.49(2) Å, N3...S1^{i} = 3.319(2) Å, with angle at H3n = 158(2)°. Symmetry operation i: 1-x, -y, -z.

[32] M.A. Ali, A.H. Mirza, R.J. Bucher, M. Rahman, Nickel (II), copper (II), palladium (II) and platinum (II) complexes of bidentate SN ligands derived from S-alkyldithiocarbazates and the X-ray crystal of the [Ni(tasbz)$_2$] and [Cu(tasbz)$_2$].$CHCl_3$ complexes, Transition Met. Chem. 25 (2000) 430-436.

[33] Parameters characterising the intermolecular interactions in the crystal structure of **2**: C13–H13...S3^{i} = 2.82 Å, C13...S3^{i} = 3.757(2) Å, with angle at H13 = 171°; π(O2,C25-C28)…π(C3-C8)^{ii} = 3.7079(14) Å with an angle of inclination = 8.72(13)°. Symmetry operations i: -½-x, -½+y, ½-z; ii: 1-x, 1-y, 1-z.

[34] Parameters characterising the intermolecular interactions in the crystal structure of **3**: π(O2,C25-C28)…π(C3-C8)^{i} = 3.513(3) Å with an angle of inclination = 9.5(2)°. Symmetry operations i: -x, -y, 1-z.

[35] J.K. Barton, A. Danishefsky, J. Goldberg, Tris(phenanthroline)ruthenium(11): stereoselectivity in binding to DNA, J. Am. Chem. Soc. 106 (1984) 2172–2176.

[36] S.A. Tysoe, R.J. Morgan, A.D. Baker, T.C. Strekas, Spectroscopic Investigation of Differential Binding Modes of Δ and Δ-$Ru(bpy)_2(ppz)^{2+}$ with Calf Thymus DNA, J. Phys. Chem. 97 (1993) 1707–1711.

[37] J.M. Kelly, A.B. Tossi, D.J. McConnell, C. OhUigin, A study of the interactions of some polypyridylruthenium (II) complexes with DNA using fluorescence spectroscopy, topoisomerisation and thermal denaturation, Nucl. Acids Res. 13 (1985) 6017–6034.

[38] B.Y. Wu, L.H. Gao, Z.M. Duan, K.Z. Wang, Syntheses and DNA-binding studies of two ruthenium(II) complexes containing one ancillary ligand of bpy or phen: $[Ru(bpy)(pp[2,3]p)_2](ClO_4)_2$ and $[Ru(phen)(pp[2,3]p)_2](ClO_4)_2$, J. Inorg. Biochem. 99 (2005) 1685–1691.

[39] E.C. Long, J.K. Barton, On Demonstrating DNA Intercalation, Acc. Chem. Res. 23 (1990) 271–273.

[40] D. Kovala-Demertzi, J.R. Miller, N. Kourkoumelis, S.K. Hadjikakou, M.A. Demertzis, Palladium(II) and platinum(II) complexes of pyridine-2-carbaldehyde thiosemicarbazone with potential biological activity. Synthesis, structure and spectral properties. Extended network via hydrogen bond linkages of [Pd(PyTsc)Cl], Polyhedron. 18 (1999) 1005-1013.

[41] N. Shahabadi, S. Kashanian, F. Darabi. DNA binding and DNA cleavage studies of a water soluble cobalt (II) complex containing dinitrogen Schiff base ligand: The effect of metal on the mode of binding. Eur. J. Med. Chem. 45 (2010) 4239-4245.

[42] M. J. Waring. Complex formation between ethidium bromide and nucleic acids. J. Mol. Biol. 13 (1965), 269-282.

[43] X.L. Wang, H. Chao, H. Li, X.L. Hong, Y.J. Liu, L.F. Tan, L.N. Ji, L. N. DNA interactions of cobalt (III) mixed-polypyridyl complexes containing asymmetric ligands. J. Inorg. Biochem., 98 (2004), 1143-1150.

[44] Q.L. Zhang, J.G. Liu, J. Liu, G.Q. Xue, H. Li, J.Z. Liu, H. Zhou, L.H. Qu, L.N. Ji. DNA-binding and photocleavage studies of cobalt(III) mixed-polypyridyl complexes containing 2-(2-chloro-5-nitrophenyl)imidazo [4,5-f][1,10]phenanthroline. J. Inorg. Biochem., 85 (2001), pp. 291–296.

[45] G. Thomas, Medicinal chemistry: an introduction, second ed., John Wiley & Sons, England, 2008, pp. 504-518.

[46] M. Nazimuddin, M. Rahman, K.M. Rahman, M.A. Ali, M.A. Mridha, Rearrangement and complexation of 5-substituted-1,3,4-thiadiazolidine-2-thiones with divalent transition metals, Transition Met. Chem. 17 (1992) 404-408.

[47] M.A. Ali, K.R. Fernando, D. Palit, M. Nazimuddin, The preparation and characterization of some new nickel(lI), copper(II), zinc(II) and cadmium(II) complexes of the pyrrole-2-carboxaldehyde Schiff bases of S-alkyl esters of dithiocarbazic acid, Transition Met. Chem. 20 (1995) 19-22.

[48] S. Ianelli, P. Mazza, M. Orcesi, C. Pelizzi, G. Pelizzi, F. Zani, Synthesis, structure, and biological activity of organotin compounds with Di-2-pyridylketone and phenyl(2-pyridyl) ketone 2-aminobenzoylhydrazones, J. Inorg. Biochem. 60 (1995) 89-108.

[49] G.L. Patrick, An introduction to medicinal chemistry, fifth ed., Oxford university press, United Kingdom, 2013, pp. 514-577.

[50] N. Bharti, F. Athar, M. R. Maurya, A. Azam, Synthesis, characterization and in vitro anti-amoebic activity of new palladium(II) complexeswith 5-nitrothiophene-2-carboxaldehyde N(4)-substituted thiosemicarbazones, Bioorg. & Med. Chem. 12 (2004) 4679-4684.

[51] B. K. Singh, U. K. Jetley, R. K. Sharma, B. S. Garg, Synthesis, characterization and biological activity of complexes of 2-hydroxy-3,5-dimethylacetophenoneoxime

(HDMAOX) with copper(II), cobalt(II), nickel(II) and palladium(II), Spectrochim. Acta Part A. 68 (2007) 63-73.

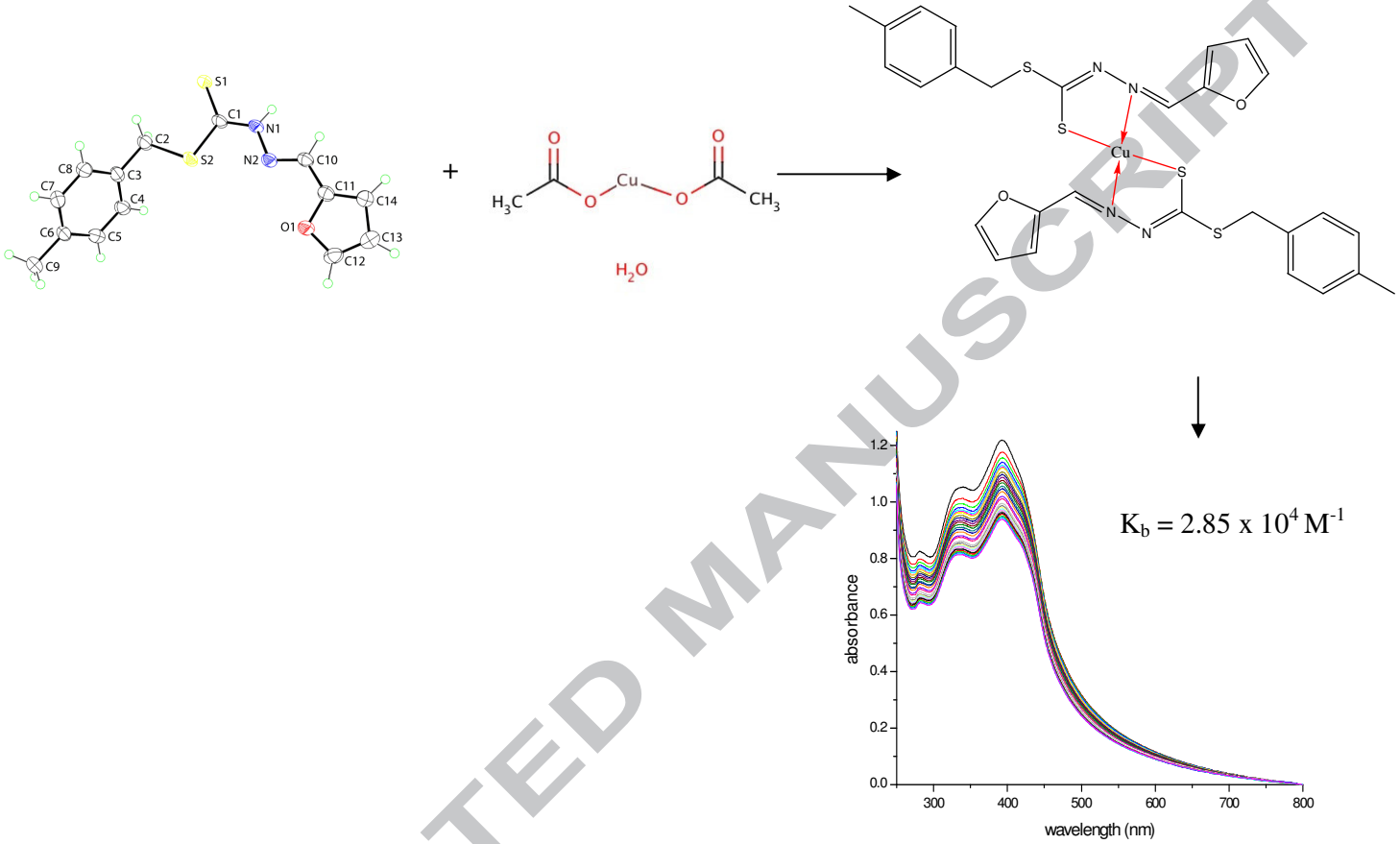
[52] M. Gerloch, E. C. Constable, Transition Metal Chemistry: The Valence Shell in *d*-Block Chemistry, VCH, Weinheim, 1994, pp 161-165.

[53] E. W. Ainscough, A. M. Brodie, W. A. Denny, G. J. Finlay, S. A. Gothe, J. D. Ranford, Cytotoxic of salicylaldehydebenzoylhydrazoneanalogs and their transition metal complexes: quantitative structure-activity relationships, J. Inorg. Biochem. 77 (1999) 125-133.

[54] S. Adsule, V. Barve, D. Chen, F. Ahmed, Q.P. Dou, S. Padhye, F.H. Sarkar. Novel Schiff base copper complexes of quinoline-2 carboxaldehyde as proteasome inhibitors in human prostate cancer cells. J. Med. Chem. 49 (2006) 7242-7246.

[55] G. Thomas, Medicinal chemistry: an introduction, J. Wiley & Sons, New York. 2000, pp. 279.

A new bidentate dithiocarbazate Schiff base and its metal complexes have been synthesized and characterized. The Cu(II)-Schiff base complex shows moderate activity against MCF-7 breast cancer cells and has the strongest binding affinity.



Graphical abstract

A new bidentate dithiocarbazate Schiff base derived from furaldehyde and its metal complexes have been synthesized and characterized by various spectroscopic and physicochemical analysis. Some of the metal complexes have been characterised by single crystal X-ray diffraction analysis. The Cu(II)-Schiff base complex showed moderate activity against MCF-7 breast cancer cells and has the strongest DNA binding affinity.

Highlights

- A new bidentate dithiocarbazate Schiff base and its metal complexes are reported.
- The complexes have been characterised by physical and spectroscopic techniques.
- The U-shaped dithiocarbazate and its Zn(II) and Cd(II) have been structurally confirmed.
- Only the Cu(II) complex shows moderate activity against MCF-7 breast cancer cells.
- DNA binding studies prove that the Cu(II) complex had the strongest binding affinity.

.