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Synthesis, Characterisation and Biological Activities of Ru(III), Mo(V), Cd(II), Zn(II) and Cu(II) Complexes Containing a Novel Nitrogen-Sulphur Macrocyclic Schiff Base Derived from Glyoxal

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ABSTRACT

A novel nitrogen-sulphur macrocyclic Schiff base, 4,11,20,27-tetrathioxo-3,12,19,28-tetrathia-5,6,9,10,21,22,25,26-octaazatricyclo[28.2.2.2^{14,17}]hexatriaconta 1(33),6,8,14(36),15,17(35),22,24,30(34),31-decaene-2,13,18,29-tetraone (TGSB) derived from terephthaloyl-bis-dithiocarbazate (TDTC) and glyoxal (ethane-1,2-dione) is synthesised via condensation. Metal complexes are formed by reacting the Schiff base with various metal salts such as Ru(III), Mo(V), Cd(II), Zn(II) and Cu(II). The complexes are expected to have a general formula of M_2L or M_3L with a square planar or square pyramidal geometry. These compounds were characterised by various physico-chemical and spectroscopic techniques. From the data, it is concluded that the azomethine nitrogen atom and the thiolate sulphur atom from the ligand are bonded to the metal ion. In the IR spectra of the complexes, the presence of the C=N band in the region of 1600 cm^{-1} indicates the successful formation of the Schiff base. The structures of the Schiff base and metal complexes are confirmed via FT-IR, GC-MS and NMR spectroscopic analysis. The magnetic susceptibility measurements, electronic spectral data and molar conductivity analysis support the desired geometry of the complexes. The Schiff base and its metal complexes are evaluated for their biological activities against the invasive human bladder carcinoma cell line (EJ-28) and the minimum-invasive human bladder carcinoma cell line (RT-112). The RuTGSB and CdTGSB complexes showed selective activity against RT-112.

Keywords: Biological activities, bladder cancer, complexes, dithiocarbazate, glyoxal, macrocyclic Schiff base

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INTRODUCTION

Ligands are very promising compounds from the view point of coordination due to their ability for complexation (Singh et al., 2009). Hence, they can react with metals to produce metal complexes that often have better biological properties and applications such as anticancer agents and antimicrobial agents (Azarkish et al., 2012; Mewis et al., 2010; Hossain et al., 1996; Chandra et al., 2008; Mohamed et al., 2009). Dithiocarbazate, $NH_2NHCS_2^-$ and its substituted derivatives, especially ligands with nitrogen and sulphur as donor atoms, have been of great interest to researchers over the past few decades. Schiff bases are prepared through condensation of dithiocarbazate derivatives with various aldehydes and ketones.

The term 'macrocycle' is defined as a cyclic macromolecule or a cyclic compound with nine or more members (Constable, 1999). Macrocyclic Schiff bases act as ligands that are formed by reacting dithiocarbazate with various dicarbonyl compounds. Macrocyclic ligands are of interest because of their unique coordination chemistry (Aqra, 1999). The cytotoxicity of the complexes is higher than that of the ligand; this implies an increase in antitumor activity with coordination. The macrocycle ring enables a molecule to achieve a degree of structural pre-organisation, such that key functional groups can interact across extended binding sites in proteins without a major entropic loss on binding (Driggers et al., 2008). Macrocyclic structures appear as promising polydentate ligands, complexones and ionophores for obtaining magneto-contrast compounds, extragents and analytical reagents as well as compounds with potentially high pharmacological and biological activities.

The macrocyclic Schiff base in this work was synthesised by reacting dithiocarbazate with glyoxal via condensation. In coordination chemistry, the functionally substituted Schiff bases bearing additional donor groups represent the most important class of heteropolydentate ligands capable of forming polynuclear complexes with transition metals (Borisova et al., 2007). The synthesis of macrocyclic ligands still remains challenging for coordination chemists due to unexpected complexations (Xie et al., 2008).

Recently, researchers have been interested in the synthesis of new metal-based anticancer drugs with minimal side effects. This is because several serious side effects from the treatment will decrease the efficacy of the commercial drugs used for anticancer treatment. Hence, a novel macrocylic Schiff base and metal complexes are reported in this research to evaluate their structural properties and their potential as anticancer drugs. The geometry of the synthesised compounds is proposed to have a planar structure so that they can easily interact with deoxyribonucleic acid (DNA) in the DNA binding studies.

MATERIALS AND METHOD

All the chemicals and solvents were of analytical reagent grade, purchased from Merck, Sigma Aldrich, BDH or Fluka and used without further purification. The melting points of the ligand and metal complexes were determined by the electrothermal IA9100 digital melting point apparatus. Infrared spectra were obtained with a Perkin-Elmer 100 Series FT-IR spectrophotometer (4000-280 cm^{-1}) using KBr pellets. ^{1}H and ^{13}C NMR spectra of the ligand were recorded via a JOEL JNM 500 MHz spectrometer using deuterated chloroform as the

solvent and TMS as the internal reference. The ^{1}H spectrum was measured from $\delta_H = 0$ to 14 ppm, while the ^{13}C spectrum was from $\delta_C = 0$ to 250 ppm. The mass spectrum (GC-MS) of the ligand was recorded by a Shimadzu GC-MS QP5050A spectrometer using an electron ioniser with the voltage of 70 eV. Carbon, hydrogen and nitrogen elemental analysis was carried out using the LECO CHNS-932 analyser with a temperature of 1000 K. Metal content in the complexes was obtained by a Perkin Elmer emission plasma 1000, inductively coupled plasma optical emission spectrometer. Three different concentrations were prepared according to the absorption range. Magnetic susceptibilities of the complexes were measured by the Gouy method at room temperature using the Sherwood scientific magnetic susceptibility balance and distilled water as calibrant. The molar conductance of 10^{-3} M solutions of the complexes in dimethyl sulfoxide (DMSO) was measured at room temperature. A Jenway 4310 conductivity meter and a dip-type cell with platinised electrode were used in these measurements. The electronic spectra were obtained using the Shimadzu UV-Vis 160A Spectrophotometer over a range of 200-1000 nm. Complex solutions of molar conductance 10^{-3} M, 10^{-4} M and 10^{-5} M were prepared by dissolving the substances in DMSO and then measuring the solutions using a quartz cuvette.

Synthesis of Terephthaloyl-bis-dithiocarbazate (TDTC)

Hydrazine hydrate (6.3 mL, 0.2 mol) was added dropwise into a solution of KOH (11.2 g, 0.2 mol) in ethanol (70 mL) followed by carbon disulphide (12.1 mL, 0.2 mol) and terephthaloyl dichloride (20.3 g, 0.1 mol) in warm ethanol (200 mL). The mixture was stirred to reduce the volume to half and the white precipitate that was formed was filtered and then recrystallised from absolute ethanol (Figure 1). The yield was 87%, m.p. 128-129°C.

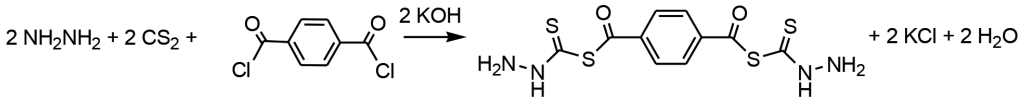

Figure 1. Synthesis of terephthaloyl-bis-dithiocarbazate (TDTC)

Synthesis of the Schiff Base, 4,11,20,27-tetrathioxo-3,12,19,28-tetrathia-5,6,9,10,21,22,25,26-octaazatricyclo[28.2.2.2^{14,17}]hexatriaconta-1(33),6,8,14(36),15,17(35),22,24,30(34),31-decaene-2,13,18,29-tetraone (TGSB)

Glyoxal (0.9 mL, 0.02 mol) was added to a solution of TDTC (6.9 g, 0.02 mol) in warm absolute ethanol (120 mL). The mixture was refluxed for 8 h and the yellow precipitate that formed was recrystallised from absolute ethanol (Figure 2). The yield was 52%, m.p. 137-138°C.

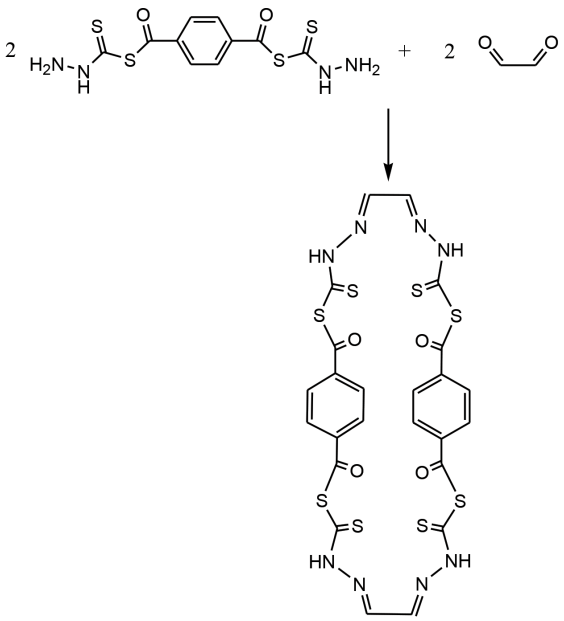

Figure 2. Synthesis of Schiff base,4,11,20,27-tetrathioxo-3,12,19,28-tetrathia-5,6,9,10,21,22,25,26-octaazatricyclo[28.2.2.2^{14,17}]hexatriaconta 1(33),6,8,14(36),15,17(35),22,24,30(34),31-decaene-2,13,18,29-tetraone (TGSB)

Synthesis of Macrocyclic Schiff Base Complexes

Macrocyclic complexes, M_2L or M_3L, were synthesised via the reaction between TGSB and metal acetates [Cu(II), Zn(II) and Cd(II)] or metal chlorides [Mo(V) and Ru(III)] in a molar ratio of 1:2. A solution of metal acetate or metal chloride (2 mmol) in ethanol (20 mL) was added to a solution of ligand (1 mmol) in absolute ethanol (40 mL). The mixture was refluxed for 16 h. The precipitate that formed was filtered off, washed with cold ethanol and then diethyl ether and finally air-dried.

Cytotoxicity Studies

Two bladder cancer cell lines, EJ-28 and RT-112, were used to study the anticancer properties of the compounds and were obtained from the National Cancer Institute, U.S.A. The cells were cultured in an RPMI-1640 medium supplemented with 10% fetal bovine serum. During plating, phosphate buffered saline was used to remove dead cells. Trypsin was used for cell detachment. A haemacytometer and trypan blue were used during cell counting. One hundred microlitres of mixture of medium and cells were titrated into 96 well plates using a multichannel pipette and incubated for 24 h with 5% CO_2 and 37°C. For treatment, six different concentrations (1 µM, 0.5 µM, 0.4 µM, 0.3 µM, 0.2 µM and 0.1 µM for active compounds; 5 µM, 4 µM, 3 µM, 2 µM, 1 µM and 0.5 µM for moderately active compounds) of compounds were used to determine the IC_{50} values that were the minimum concentration of the drug to kill the cancer cells by 50%. DMSO was used as the control. Anticancer activity or cytotoxicity was

determined using the microtitration of 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay (Mosmann, 1983). MTT was reduced to purple formazan in living cells caused by mitochondrial reductase. Enzyme-linked immunosorbent assay (ELISA) was used to determine the anticancer activity of the compounds.

RESULTS AND DISCUSSION

A macrocyclic Schiff base, TGSB, and five of its metal complexes [Ru(III), Mo(V), Cd(II), Zn(II), and Cu(II)] were synthesised and fully characterised by physico-chemical and spectroscopic techniques. The macrocyclic Schiff base, TGSB, was synthesised by a [2+2] template condensation reaction of terephthaloyl-bis-dithiocarbazate and glyoxal in a ratio of 2:2 (Figure 2). All the synthesised compounds were stable in air and at room temperature. TGSB was soluble in DMSO, chloroform and absolute ethanol but insoluble in water. All the synthesised complexes were soluble in DMSO, DMF and chloroform but insoluble in water, absolute ethanol and methanol. The complexes were only slightly soluble in acetonitrile and ethyl acetate.

The melting point obtained for the TGSB was 137-138ºC and the melting point obtained for all the complexes was greater than 300ºC except for CdTGSB, which had a melting point of 262-263ºC. The synthesised metal complexes had higher melting points compared with the corresponding ligand (Ali et al., 2006); hence, the complexes were more stable compared with the ligand. The melting points for all the compounds were sharp (over a 1 or 2ºC range), indicating that the compounds were relatively pure and free from impurities. Unfortunately, repeated recrystallisation only produced crystals that were unsuitable for single-crystal X-ray structure determination. The differences between the experimental and calculated values for the elemental analysis were within the experimental errors (Table 1). RuTGSB, MoTGSB and CuTGSB were expected to be dinuclear while ZnTGSB and CdTGSB were expected to be trinuclear.

Table 1
Physical data, elemental analyses, magnetic moment and molar conductance of the compounds

Compound	Colour	Melting Point (ºC)	Yield (%)	μ_{eff}	Λ_m	Found (Calculated %)			
				(B.M.)	($\Omega^{-1}cm^2mol^{-1}$)	C	H	N	M
TDTC	White	128-130	77	-	-	35.1 (34.7)	2.9 (2.9)	16.4 (16.3)	-
TGSB	Yellow	137-138	52	-	-	39.6 (39.1)	2.3 (2.2)	15.7 (15.2)	-
RuTGSB	Black	>300	71	Dia	46.3	25.6 (25.1)	1.0 (1.1)	9.3 (9.8)	17.1 (17.6)
MoTGSB	Dark Blue	>300	56	Dia	6.96	25.0 (25.3)	1.2 (1.1)	9.8 (9.9)	16.0 (16.9)
CdTGSB	Brown	262-263	58	Dia	14.5	27.7 (28.3)	1.7 (1.7)	10.0 (9.4)	27.9 (28.3)
ZnTGSB	Dark Brown	>300	65	Dia	16.3	32.7 (32.1)	1.7 (1.9)	11.2 (10.7)	19.4 (18.7)
CuTGSB	Grey	>300	69	2.07	36.9	35.8 (35.1)	2.0 (2.2)	10.7 (10.2)	10.9 (11.6)

Dia - Diamagnetic

From physico-chemical and spectroscopy data, the atoms bound to the central metal in RuTGSB were two azomethine nitrogen atoms, two thiolate sulphur atoms and a Cl^- ion. For MoTGSB, the donor atoms involved in the complexation were two azomethine nitrogen atoms, two thiolate sulphur atoms, and three Cl^- ions, whereas for the ZnTGSB and CdTGSB complexes, the binding modes towards the central metal were two azomethine nitrogen atoms, two thiolate sulphur atoms and an oxygen atom from the CH_3COO^- ion. For CuTGSB, the donor atoms involved in the complexation were two azomethine nitrogen atoms and two thiolate sulphur atoms.

Hence, the proposed geometry for the RuTGSB, CdTGSB and ZnTGSB complexes was square pyramidal, while MoTGSB was expected to be pentagonal bipyramidal and CuTGSB had a square planar geometry. Long-distance binding is favoured for central large metal ions but not for smaller metal ions like Cu(II), Ni(II), Zn(II) ions generally (Temel et al., 2006; Morales et al., 2001). Hence, the structure of CuTGSB and ZnTGSB were kinetically and thermodynamically stable compared with that of MoTGSB, RuTGSB and CdTGSB.

FT-IR spectral analysis

The IR absorption bands of the macrocyclic Schiff base and its metal complexes are summarised in Table 2. The presence of the ν(C=N) band at 1542 cm^{-1} for TGSB indicated the successful formation of the Schiff base. During the complexation with metal salts, shifting of the ν(C=N) band to higher wavenumbers was observed (West et al., 1998). This was due to the coordination of the azomethine nitrogen atom with the central metal ion when complexation occurred (Mohan et al., 1985). The ν(N-H) stretching of the primary amine was found around 3432 cm^{-1} in TGSB. On complexation, disappearance of the ν(N-H) bands in the IR spectra of the metal complexes suggested deprotonation of the N-H because of bonding (Prasad et al., 2007). A proton was lost through complexation, leading to the formation of a covalent bond between the nitrogen donor atom of the ligand and the metal complex. The ν(N-N) stretching for the Schiff base was observed at 1110 cm^{-1}. The ν(N-N) stretching shifted to the right in the IR spectra of the metal complexes (Hossain et al., 1996). The IR spectrum also exhibited the presence of ν(CSS) bands, which were observed at 877 cm^{-1}. The ν(CSS) stretching shifted to higher wavenumbers in the IR spectra of the metal complexes. This was due to the reduction in the repulsion between the lone pairs of electrons on the sulphur atoms as a result of the coordination through the thiolate sulphur atom (Crouse et al., 2004).

Table 2
IR and electronic spectra data of the compounds

Compound	IR (cm^{-1})				λ_{max} (nm)
	N-H	C=N	N-N	CSS	
TDTC	3422 w	-	1104 s	875 m	-
TGSB	3432 w	1542 w	1110 s	877 m	263, 298
RuTGSB	-	1569 m	1084 s	894 m	252, 303
MoTGSB	-	1563 w	1084 s	892 m	262, 294, 418
CdTGSB	-	1567 s	1079 m	887 m	264, 310, 420
ZnTGSB	-	1571 m	1079 s	897 m	248, 267, 304
CuTGSB	-	1564 m	1073 s	894 m	260, 291, 418, 578

w– weak intensity
m– medium intensity
s – strong intensity

NMR and GC-MS spectral analysis

The structure of the macrocyclic Schiff base, TGSB, was confirmed using ^{1}H NMR. The NMR spectrum data of TGSB are summarised in Table 3. TGSB contains a benzyl group para-substituted, which exhibited bands at δ_H = 8.24 to 8.05 ppm, and this chemical shift was assigned as the aromatic hydrogen bands. The resonance at δ_H = 7.27 ppm was attributed to the solvent, $CDCl_3$ (Gottlieb et al., 1997). Lastly, the band at δ_H = 4.07 ppm was assigned to =C-H, found at higher fields with the most highly shielded type of proton. The structure was further supported by ^{13}C NMR, where the spectrum showed a weak singlet signal at δ_H = 166.35 ppm, which was ascribed to the azomethine carbon, C=N (Keypour et al., 2007). The doubly substituted benzyl showed bands at δ_H = 133.99 to 129.62 ppm. These bands appeared at the aromatic carbon region as expected (Keypour et al., 2008). Another significant signal was observed at δ_H = 77.37 ppm, which was assigned to the solvent $CDCl_3$.

Table 3
NMR spectral data of TGSB

Compound	^{1}H (ppm)			^{13}C (ppm)	
	C-H Ar.	$CDCl_3$	=C-H	C=N	C=C Ar.
TGSB	8.05-8.24	7.27	4.07	166.35	129.62-133.99

Ar. - Aromatic

The mass spectra showed a molecular ion peak at *m/z* 346 for TDTC and this matched the molecular formula and molecular weight expected for TDTC, $C_{10}H_{10}N_4O_2S_4$. For TGSB, the molecular ion peak at *m/z* 736 matched the molecular formula and molecular weight expected,

$C_{24}H_{16}N_8O_4S_8$. The tallest peak in the mass spectrum had the most abundant ion formed in the ionisation chamber (Pavia et al., 2001). From the mass spectra, the base peak occurred at *m/z* 163, which was the most stable ion fragment, and corresponding to $C_8H_3O_2S^+$. The possible fragments of TGSB are shown in Figure 4.

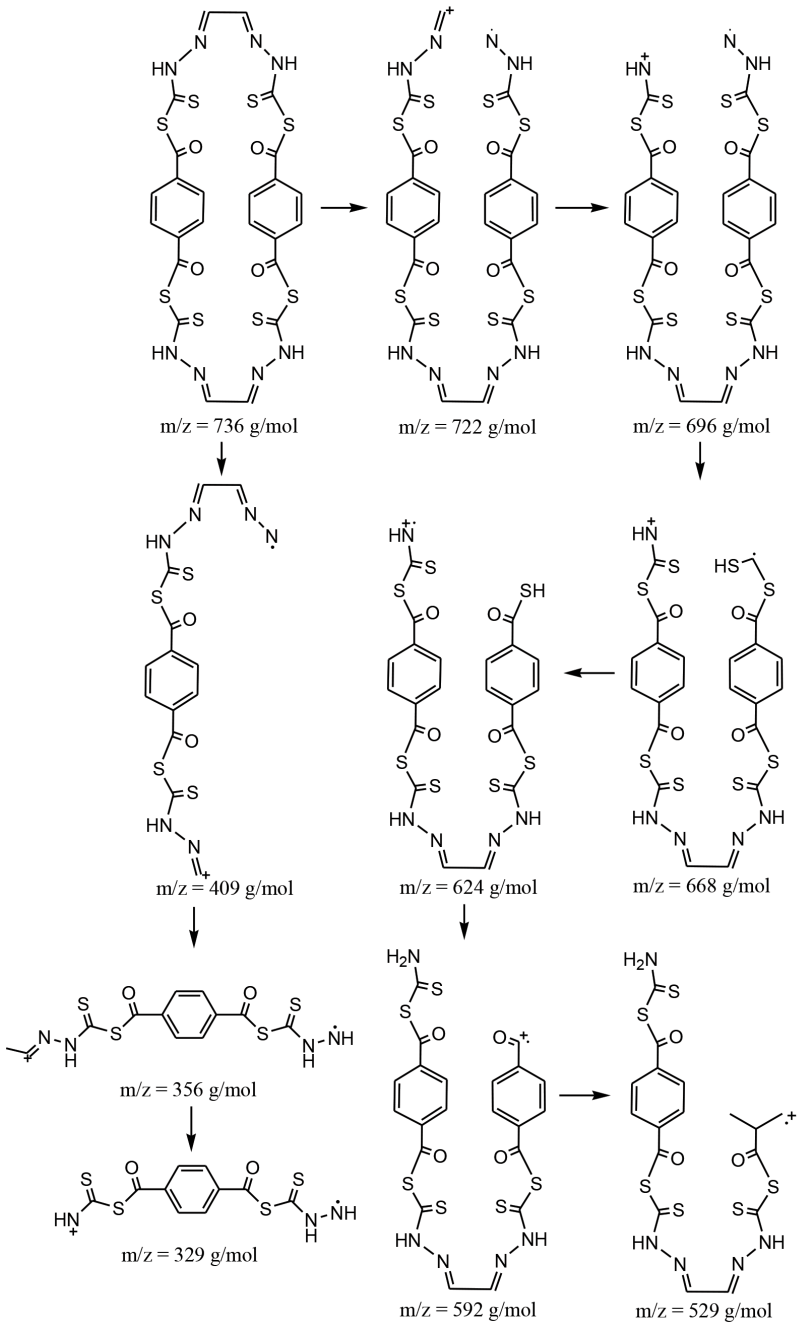

Figure 4. Fragmentation pattern of TGSB

Magnetic Susceptibility, Molar Conductivity and Electronic Spectral Analysis

The magnetic moment and molar conductance are shown in Table 1 and the electronic spectra data are shown in Table 2. In the magnetic susceptibility analysis, metal complexes are subjected to an external magnetic field and only the paramagnetic compounds are susceptible to this field due to the presence of unpaired electrons. At room temperature, the magnetic susceptibility analysis showed that all the complexes obtained except CuTGSB had diamagnetic properties. CuTGSB exhibited paramagnetism with magnetic moments of 2.07 B.M., indicating the presence of one unpaired electron (Geary, 1971). The slightly higher magnetic moment obtained was due to the distorted structure of the complex. A planar complex should have magnetic moments of 1.73 B.M. for Cu(II) ion (Ali et al., 1977).

From molar conductivity measurements, MoTGSB, CdTGSB and ZnTGSB were covalently bonded in the inner sphere and were non-electrolytes as the molar conductance values obtained were lower than 30 $\Omega^{-1}cm^2mol^{-1}$ in DMSO (Ilhan et al., 2008; Temel et al., 2008). RuTGSB and CuTGSB had higher conductance values, indicating their electrolytic nature. These high conductance values were due to the presence of other anions such as $CH3COO^-$ and Cl^- in the outer sphere. The presence of the Cl^- anion could be supported by a Cl^- test with $AgNO_3$ solution via halide abstraction (Abou-Hussein et al., 2012). Formation of the white precipitate, AgCl, happened when $AgNO_3$ reacted with RuTGSB, indicating the presence of the Cl^- anion on the outer sphere lattice. For MoTGSB, the Cl^- anion was only coordinated with the metal ion due to the absence of the white precipitate, AgCl.

In the electronic spectral analysis, four different transitions were observed in the complexes, namely $\pi \rightarrow \pi^*$, $n \rightarrow \pi^*$ intra-ligand transitions, ligand to metal charge transfer (LMCT) transition and d→d transitions. All the metal complexes showed an intense absorption band in the far UV region from 248 to 264 nm, which was assigned to the $\pi \rightarrow \pi^*$ transition (Ilhan, 2008). A moderately intense band in the region of 291 and 310 nm was assigned to the $n \rightarrow \pi^*$ transition. Bands between 418 and 420 nm were assigned as LMCT transition (Kalia et al., 2011) due to the sulphur donor atom to metal centre charge transfer transitions. Presence of this band further proved that the metal complexes were coordinated to sulphur through the thiolo sulphur atom (Crouse et al., 2004). Lastly, the lowest energy band at 578 nm was assigned to a d→d transition or $^1B_{1g}$ - ^1A_g transition for CuTGSB due to the presence of one unpaired electron consistent with a square-planar geometry (Raman et al., 2011). The proposed geometries for RuTGSB, CdTGSB and ZnTGSB were hence, square pyramidal and MoTGSB was expected to be pentagonal bipyramidal (Sayin, 2014). The proposed structures for all the synthesised complexes are shown in Figure 3 (a-e).

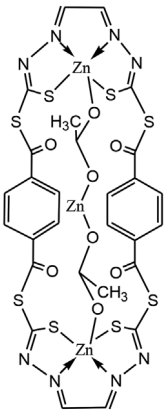

Figure 3(a). Proposed structure of the Zn(II) complex of 4,11,20,27-tetrathioxo-3,12,19,28-tetrathia-5,6,9,10,21,22,25,26-octaazatricyclo[28.2.2.2^{14,17}]hexatriaconta 1(33),6,8,14(36),15,17(35),22,24,30(34),31-decaene-2,13,18,29-tetraone (ZnTGSB)

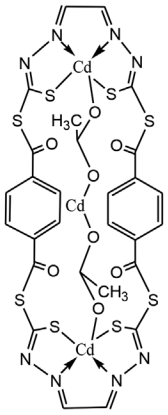

Figure 3(b). Proposed structure of the Cd(II) complex of 4,11,20,27-tetrathioxo-3,12,19,28-tetrathia-5,6,9,10,21,22,25,26-octaazatricyclo[28.2.2.2^{14,17}]hexatriaconta 1(33),6,8,14(36),15,17(35),22,24,30(34),31-decaene-2,13,18,29-tetraone (CdTGSB)

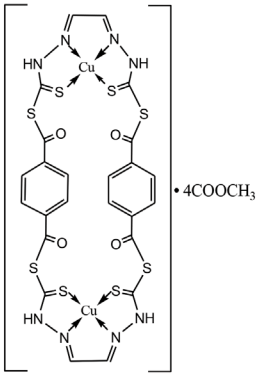

Figure 3(c). Proposed structure of the Cu(II) complex of 4,11,20,27-tetrathioxo-3,12,19,28-tetrathia-5,6,9,10,21,22,25,26-octaazatricyclo[28.2.2.2^{14,17}]hexatriaconta 1(33),6,8,14(36),15,17(35),22,24,30(34),31-decaene-2,13,18,29-tetraone (CuTGSB)

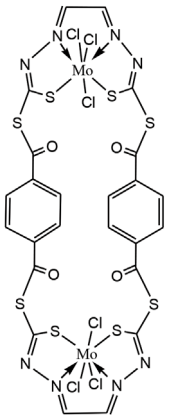

Figure 3(d). Proposed structure of the Mo(V) complex of 4,11,20,27-tetrathioxo-3,12,19,28-tetrathia-5,6,9,10,21,22,25,26-octaazatricyclo[28.2.2.2^{14,17}]hexatriaconta 1(33),6,8,14(36),15,17(35),22,24,30(34),31-decaene-2,13,18,29-tetraone (MoTGSB)

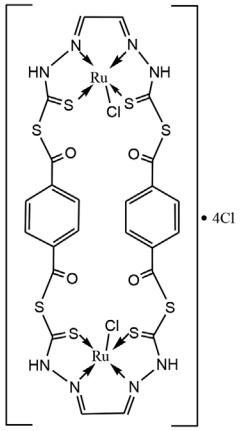

Figure 3(e). Proposed structure of the Ru(III) complex of 4,11,20,27-tetrathioxo-3,12,19,28-tetrathia-5,6,9,10,21,22,25,26-octaazatricyclo[28.2.2.2^{14,17}]hexatriaconta 1(33),6,8,14(36),15,17(35),22,24,30(34),31-decaene-2,13,18,29-tetraone (RuTGSB)

Cytotoxicity Studies

All the synthesised complexes were tested for their cytotoxic properties *in vitro* against two different bladder cancer cell lines, RT-112 and EJ-28. An invasive cell line is not native or fixed to a specific location and has a tendency to spread uncontrollably to a degree believed to cause damage to the environment. It has been found in previous studies that metal complexes of nitrogen-sulphur donor atoms were active against different cancer cell lines such as leukemic and breast cancer cell lines (Ali et al., 1974; Tarafder et al., 2001a; Tarafder et al., 2001b).

IC_{50} values were determined using the MTT method (Mosmann, 1983) and the results are shown in Table 4. IC_{50} is the inhibitory concentration at 50% i.e. the concentration of drug that inhibited the growth of cancer cells by 50%. IC_{50} values less than 0.5 µM

indicated that the complex was strongly active, whereas IC_{50} values of 0.5-5.0 μM and more than 5.0 μM indicated that the complex was moderately active and inactive, respectively.

Table 4
IC_{50} data for the compounds against RT-112 and EJ-28 cell lines

Compound	IC_{50} (μM)	
	RT-112	EJ-28
TGSB	>5	>5
RuTGSB	0.47	>5
MoTGSB	>5	>5
CdTGSB	3.99	>5
ZnTGSB	>5	>5
CuTGSB	>5	>5

EJ-28 - Invasive human bladder carcinoma cell line
RT-112 - Minimum-invasive human bladder carcinoma cell line

TGSB was inactive (IC_{50}>5 μM) against both the RT-112 and EJ-28 cell lines. All the complexes were inactive (IC_{50}>5 μM) against EJ-28. This may be due to the huge and non-planar macrocyclic structure of the complexes. Interestingly, for RT-112, RuTGSB was strongly active with an IC_{50} value of 0.47 μM and CdTGSB was moderately active at an IC_{50} of 3.99 μM. MoTGSB, ZnTGSB and CuTGSB were inactive against RT-112 cells. The relative effectiveness of the anti-cancer activities showed that the different complexes with different metal ions acted against the same cell with different mechanisms, while a complex such as RuTGSB acted against different cells with a different mechanism of action. These results suggested that complexes can act as selective and specific agents for antitumor activities (Du et al., 2011). It has been suggested that chelation or coordination on complexation will reduce the polarity of the metal ion (Raman et al., 2009); thus, it can increase the lipophilic behaviour of the complexes, and this will enhance the permeation through the lipid layer of the membrane in the cells.

CONCLUSION

A new macrocyclic Schiff base and five new metal complexes containing the Schiff base were synthesised and characterised via various physico-chemical and spectroscopic techniques. The proposed geometries for RuTGSB, CdTGSB and ZnTGSB were hence, square pyramidal, while MoTGSB was expected to be pentagonal bipyramidal. CuTGSB obeyed square planar geometry. None of the complexes were active against EJ-28 bladder cell lines but RuTGSB was strongly active and CdTGSB was moderately active against RT-112 bladder cell lines, indicating that the complexes were selective and specific in action.

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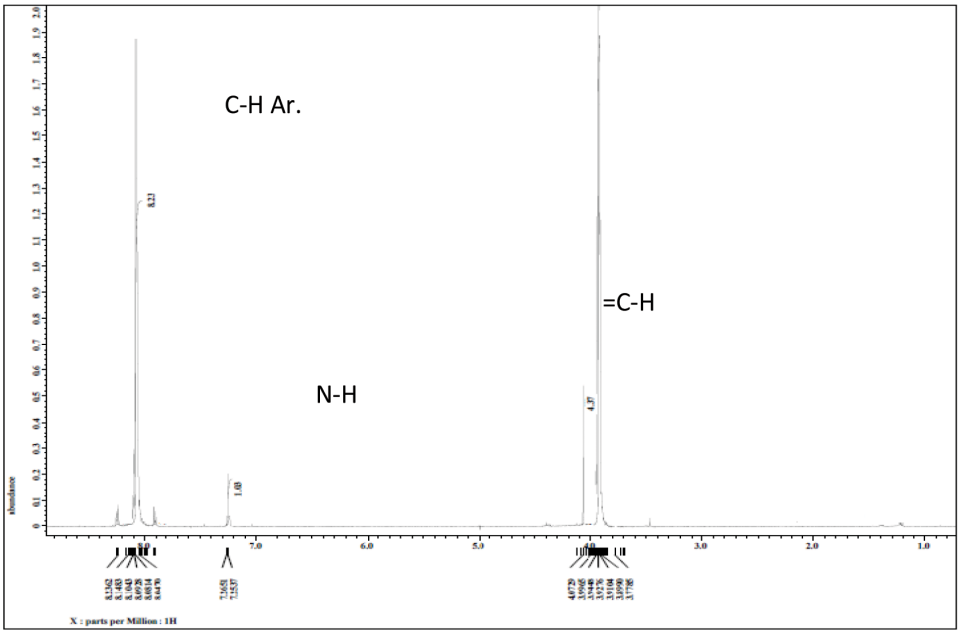
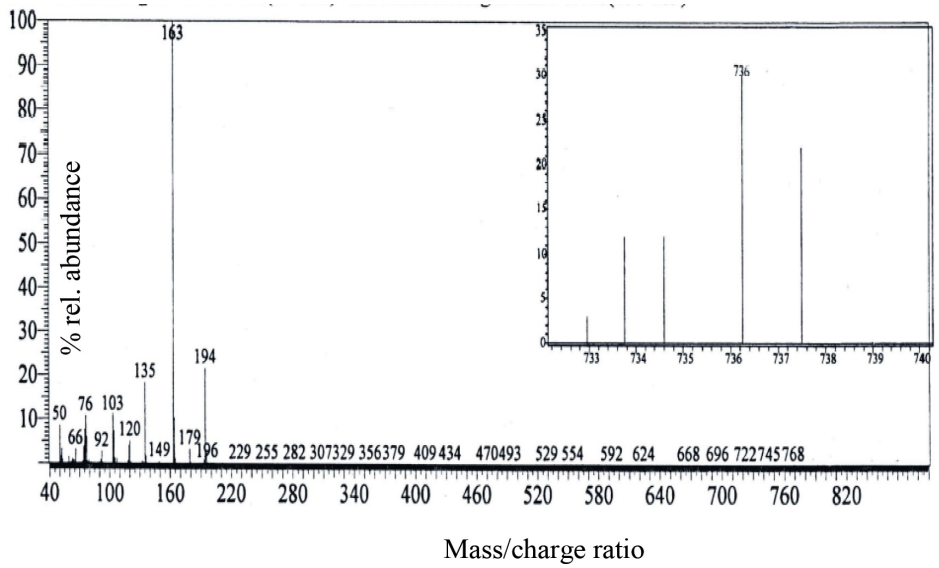
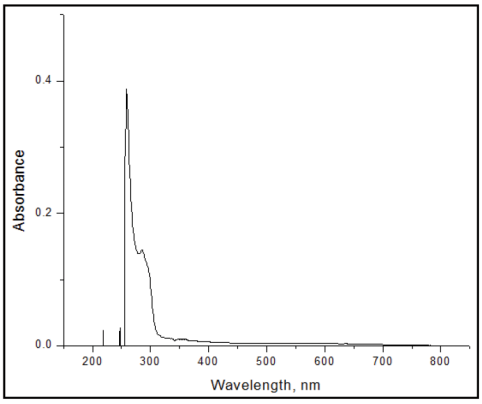
SUPPLEMENTARY DATA



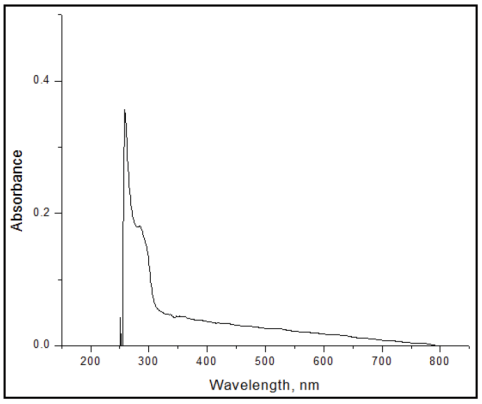
Supplement 1. ^{1}H NMR spectrum of TGSB



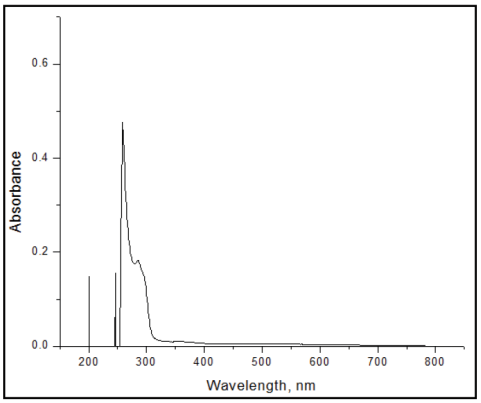
Supplement 2. Mass spectrum of TGSB



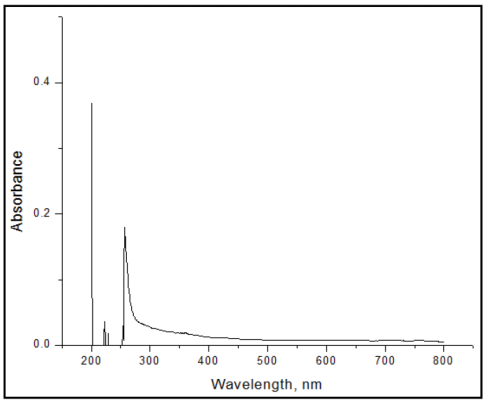
S 3a. UV/Vis spectrum of TGSB.



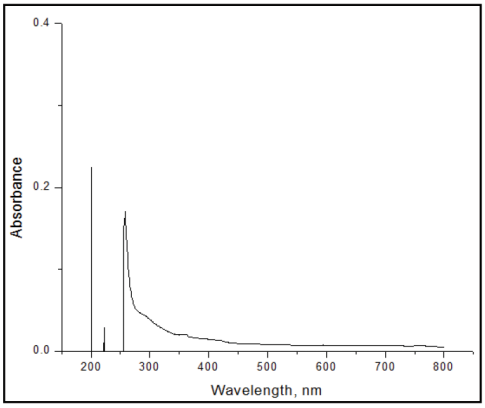
S 3b. UV/Vis spectrum of RuTGSB.



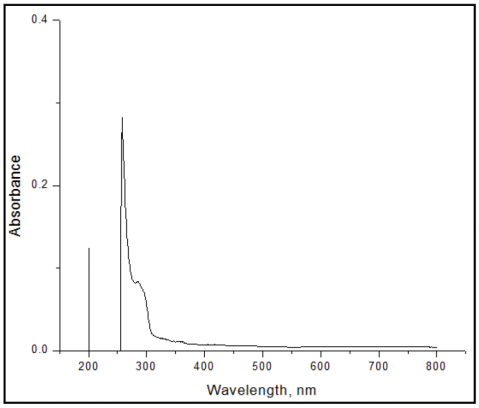
S 3c. UV/Vis spectrum of MoTGSB.



S 3d. UV/Vis spectrum of CdTGSB.



S 3e. UV/Vis spectrum of ZnTGSB.



S 3f. UV/Vis spectrum of CuTGSB.