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SYNTHESIS, CHARACTERIZATION AND ANTIMICROBIAL ACTIVITY OF RUTHENIUM(III) (*E*)-2-((6-METHYLBENZO[d]THIAZOL-2-YLIMINO)METHYL)PHENOLCOMPLEXES

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ABSTRACT
Ruthenium(III) complexes of the type $[RuX_2(PPh_3)(L)]$ (where X = Cl/Br; L = Benzothiazolyl-Salal Schiff base ligand) has been synthesized. The synthesized complexes were characterized by various physicochemical and spectral techniques. An octahedral geometry has been tentatively proposed for all the complexes. The cytotoxic activity of the synthesized ruthenium(III) complexes has shown significant activity against a panel of microbes.
Keywords: Ruthenium(III) complexes, Schiff's base, Benzothiazole, Bacteria, Fungi.

INTRODUCTION

In General, the transition metal Schiff base complexes have invited considerable interest for numerous reasons like catalytic properties, structural diversity, and Biological properties.[1] More often ruthenium complexes with Schiff base and non Schiff base ligands are one of the most studied areas due to favorable properties *viz.* kinetic ligand-exchange, variable oxidation states of ruthenium may be used to fine-tune the properties of the complexes.[2] In addition, low toxicity of ruthenium complexes towards the normal cells is advantages of using these in medicinal applications. Also, the entrance of two ruthenium(III) based drugs into the clinical trials is increased interest on this metal.[3] Microbial infections often produce pain and inflammation, Chemotherapeutic, analgesic, and anti inflammatory drugs are prescribed simultaneously in normal practice.[4] The compound possessing all three activities is not common. It has been known that thiazole possesses anticancer, analgesic, antiviral, anti inflammatory, and antimicrobial activities.[5,6] Moreover, heterocyclic molecules constitute a class of bioactive drugs that attracted the attention of medicinal chemists. Several structurally simple benzothiazoles are reported to possess excellent in vitro and in vivo cytotoxicity at low nanomolar concentrations.[7,8] Phortress, a prodrug is one of the best examples of such drug candidates presently undergoing phase I clinical trials.[9] With this forefront investigations, we have synthesized thiazole-based ruthenium(III) complexes and explored their antimicrobial activity.

EXPERIMENTAL

Material and Methods

All the chemicals used are AR grade and the solvents were purified and dried according to the standard procedure.[10] The metal starting complexes, $[RuCl_3(PPh_3)_3]$, $[RuBr_3(PPh_3)_3]$ and Schiff base ligands were prepared by reported literature methods.[11-13] Elemental analyses (C, H, N& S) were carried out on a Vario EL III CHNS analyzer at STIC, Cochin University of Science and Technology, Kerala, India. IR spectra were recorded as KBr pellets in the 400-4000 cm^{-1} region using a Perkin Elmer FT-IR 8000

spectrophotometer. Electronic spectra were recorded in DMSO solution with a Systronics double beam UV-vis spectrophotometer 2202 in the range 200-800 nm. Magnetic susceptibility measurements of the complexes were recorded using Guoy balance. EPR spectra were recorded on a Varian E-112 ESR spectrophotometer at X- band microwave frequencies for powdered samples at room temperature. EI mass spectrum of the complex was recorded on a JEOL GCMATE II mass spectrometer. Melting points were recorded with Veego VMP-DS heating table and are uncorrected.

Synthesis of Ruthenium(III) complexes

The Schiff base ligands (0.5 mmol) in methanol is added with the metal precursors, $[RuX_3(PPh_3)_3]$ (X=Cl/Br) (0.5 mmol) in benzene and refluxed for 8 h. The resulting solution was then cooled to room temperature, which results in the formation of a precipitate. It was then filtered and purified. The solid was recrystallized from CH_2Cl_2 and Hexane mixture.Our sincere effort to obtain a single crystal of the complexes went unsuccessful.

Antibacterial and Antifungal Assays

The antibacterial and antifungal activity tests were performed by agar diffusion method. Petri plates were prepared by pouring 10 mL of Mueller Hinton Agar for bacteria, and allowed to solidify and inoculated with 0.1 mL of a standardized bacterial suspension (2x106 cells/mL). A 6 mm well was cut at the center of the agar plate and the well was filled with a solution of the complexes. The each bacterium was incubated for about 24 h at 37 ^oC and then the diameter of the inhibition zone was observed. Sterile distilled water was used to serve as a control. For fungus, the complexes were amended with Sabouraud Dextrose Agar medium at the warm condition and poured into Petri plates. After 48 h of incubation, the diameter of the inhibition zone for each fungus at 28 ^oC was measured.

RESULTS AND DISCUSSION

Structure of the Complexes

The synthesized monobasic tridentate ligand, (*E*)-2-((6-methylbenzo[d]thiazol-2-ylimino)methyl)phenol forms stable and nonhygroscopic ruthenium(III) complexes with metal precursors. The complexes are soluble in most common solvents. The analytical data (Table-1) of the complexes are in good agreement with the proposed structure of the complexes.

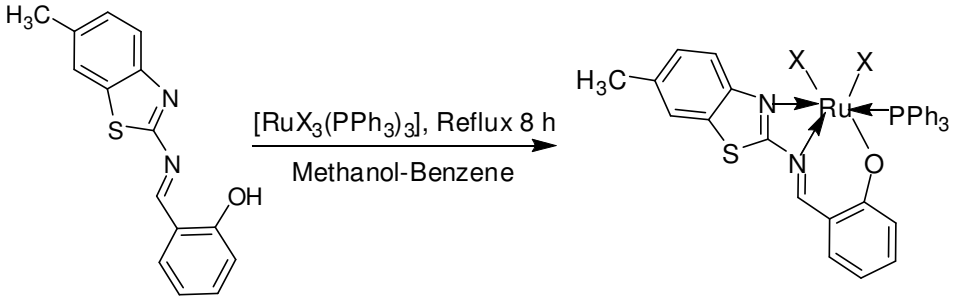
Table-1: Analytical data, Magnetic moment and EPR data of ruthenium(III) complexes

Complexes	Color	Yield %	M.P. °C	Elemental analysis calculated (Found)				μ_{eff} (μ_B)	EPR
				C%	H%	N%	S%		'g' value
$[RuCl_2(PPh_3)(L)]$	Dark Brown	58	263	56.49 (56.82)	3.74 (4.19)	3.99 (3.28)	4.57 (4.93)	1.45	2.58
$[RuBr_2(PPh_3)(L)]$	Brown	55	271	50.14 (50.99)	3.32 (2.99)	3.54 (3.01)	4.06 (4.78)	1.48	2.25

IR Spectra

The most important IR spectral frequencies of the complexes (Table-2) were compared with the ligand in order to confirm the binding mode of the Schiff base ligand in the complexes. The complexes showed azomethine C=N stretching frequency at 1597-1599 cm^{-1} which is lower when compared to free ligand (1621 cm^{-1})[14]. This confirms one of the binding modes of the Schiff base ligand with the ruthenium metal is azomethine N. The phenolic CO band of the complexes shifts towards higher frequencies at 1251-1252 cm^{-1} compared to free ligand (1240 cm^{-1}) reveals the another coordination mode through C–O–M. The thiazole C=N stretching frequency of the complexes shifts to lower frequency at 1572-1574 cm^{-1} than ligand suggest the coordination of thiazole C=N to ruthenium atom[15]. Further, the stretching frequency at

586-589 cm^{-1} attributed to M–N. Overall, the Schiff base ligand act as monobasic tridentate to the complexes studied.



Scheme-1: Synthetic route of the ruthenium(III) Schiff base complexes, where X=Cl/Br

Electronic Spectra

The DMSO solvent was used to record the electronic spectra of the complexes (Table-2). The complexes showed four bands in the region 312-523 nm. The ligand centered transitions were shifted at 312-406 nm confirms the coordination of Schiff base ligand (308-420 nm) to the ruthenium atom[15]. The ground state of ruthenium(III) ($t^5{}_{2g}$ configuration) is ^2T_2g, while the first excited doublet levels in the order of increasing energy are ^2A_2g and ^2T_1g, which arise from the $t_{2g}{}^4$ $e_g{}^1$ configuration. In a d^5ruthenium(III) system has relatively high oxidizing properties and hence, the bands of the type $L_{\pi y} \rightarrow t_{2g}$ are prominent in the low energy region obscuring the weaker bands due to d-d transition. Therefore, it is difficult to assign the bands appearing in the visible region. Therefore, the bands at 516-523 nm have been assigned to charge transfer transitions, which are in good agreement with the similarly reported ruthenium(III) complexes[16].

Table-2: IR, Electronic spectral data, and EI-mass of ruthenium(III) complexes.

Complexes	FT-IR, cm^{-1}			UV-Vis	EI-mass, *m/z*
	ν(C=N)	ν(Ph–CO)	ν(C=N) thiazole	λ_{max} (nm)	Calculated (found) (M^+)
$[RuCl_2(PPh_3)(L)]$	1599	1252	1572	312, 369, 406, 523	701.45 (701)
$[RuBr_2(PPh_3)(L)]$	1597	1251	1574	316, 361, 399, 516	790.85 (790)

Magnetic moment measurements

Both the ruthenium(III) complexes showed magnetic moment value μ_B= 1.45-1.48 (Table-1) at room temperature reveals that they are paramagnetic. This corresponds to an unpaired electron in a low-spin $4d^5$ configuration and confirms that ruthenium is in +3 oxidation state.

EPR Spectra

The EPR spectra (X-band) of the powdered complexes were recorded at room temperature (Table-1) and the spectrum of the complex, $[RuCl_2(PPh_3)(L)]$ is given in Fig-1. Due to the interactions of other nuclei present in the complexes, the nature of the spectra does not any hyperfine splitting. The observed *g* values for a single isotropic resonance are in the range 2.25-2.58. Although the complexes have some distortion in their octahedral geometries, the observation of isotropic lines in the EPR spectra may be due to the occupancy of the unpaired electron in a degenerate orbital.[15] The obtained EPR spectra are in good agreement with the reported ruthenium(III) complexes.[17]

Mass Spectral Analysis

The EI-mass spectrum of the complexes (Table-2) is in good agreement with the proposed molecular structure. The molecular ion peak, $[M^+]$ appears at *m/z* = 701.45 and 790.85 confirms the stoichiometry of the complexes, $[RuCl_2(PPh_3)(L)]$ and $[RuBr_2(PPh_3)(L)]$, respectively.

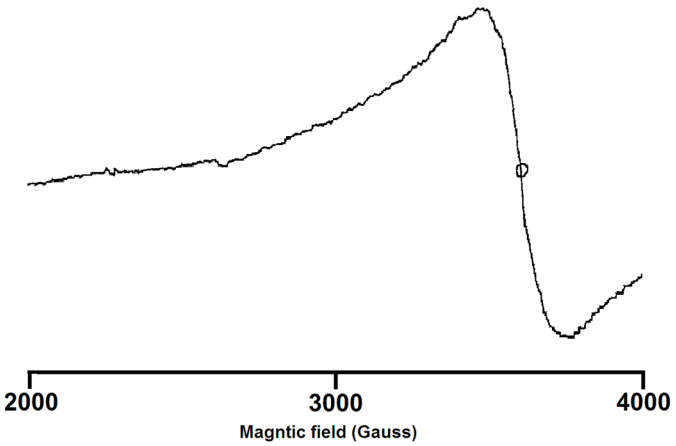


Fig-1: EPR spectrum of the complex,[$RuCl_2(PPh_3)(L)$]

Antimicrobial Activity

The antimicrobial activity of the ligand and complexes were screened (Table-3) against a panel of microbes. From these data, it is to be noted that the ruthenium(III) complexes showed significant growth inhibition activity against the selected bacteria and fungi. Even though, the ligand shows considerable cytotoxic activity against the bacteria, it does not show any insight against a panel of fungi. It is suggested that coordination facilitates the significant cytotoxic activity of the complexes. Moreover, the presence of C=N group may involve hydrogen bond with the active centers of cell constituent which subsequently influence the cytotoxic activity of the complexes.[18] Both the complexes showed significant activity against microbes but they could not reach the effectiveness of the standard drug. The higher activity of the complex, [$RuCl_2(PPh_3)(L)$] may be due to the higher electronegativity of the chlorine atom.

Table-3: Antimicrobial activity of the complexes

Complexes	Diameter of inhibition zone (mm)[a]			
	Bacteria		Fungi	
	E. coli	*S.* aureus	*A.* ochraceous	*P.* variotii
Ligand	13	14	5	10
[$RuCl_2(PPh_3)(L)$]	19	22	13	17
[$RuBr_2(PPh_3)(L)$]	18	19	10	14
Ciprofloxacin	23	26	-	-
Cotrimazole	-	-	19	24
DMSO	No activity			

[a]Values are an average of triplicate runs.

CONCLUSION

Ruthenium(III)(*E*)-2-((6-methylbenzo[d]thiazol-2-ylimino)methyl)phenol complexes have been synthesized and characterized by various physio-chemical methods. The ligand acts as a monobasic tridentate in both the complexes studied. An octahedral geometry has been tentatively proposed for the ruthenium(III) Schiff base complexes. The growth inhibition activity of the complexes containing chlorine as a co-ligand shows better cytotoxicity than bromine against a panel of bacteria and fungi.

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