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Synthesis and cytotoxic activity of some mononuclear Ru(II) Complexes

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ABSTRACT

A series of mononuclear Ru(II) complexes of the type $[Ru(T)_2(S)]^{2+}$, where T=2,2'-bipyridine/1,10-phenanthroline and S= 4-N-$(CH_3)_2$-btsz, 4-OH-btsz, 4-N-$(CH_3)_2$-binh have been prepared and characterized by UV-Vis, IR, ^{1}H-NMR, FAB-Mass spectroscopy, and elemental analysis. The title complexes were subjected to in vitro cytotoxic activity against human cancer cell line Molt 4/C_8, CEM and murine tumor cell line L 1210. Invitro evaluation of these ruthenium complexes revealed cytotoxic activity from 1.30 to 50µM against Molt 4/C_8, 0.30 to 24 µM aginst CEM, 0.87 to 41 µM against L1210 cell proliferation, depending on the nature of the compound.

Keywords: Ruthenium complexes, cytotoxic activity, proliferation

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INTRODUCTION

Various Ru(II) complexes of the type $[Ru(M)_2(U)]^{2+}$, where M=2,2'-bipyridine/1,10-phenanthroline and U= tpl, 4-Cl-tpl, 4-CH_3-tpl, 4-OCH_3-tpl, 4-NO_2-tpl, pai [1]. The objectives of the present investigations were to develop analogs of $Ru(T)_2(S)]$ principally as candidate cytotoxins. The literature survey reveled that the discovery of the antitumor properties of cisplatin in 1965 marked the development of metallo pharmaceuticals in cancer chemotherapy [2]. Platinum drugs are believed to induce cytotoxicity by cross-linking DNA, causing changes to the DNA structure resulting in inhibition of replication and protein synthesis. However, the application of platinum drugs suffers from their high general toxicity leading to severe toxic side effects. In comparison, ruthenium complexes have attracted largr attention in the last 20 years as potential antitumor agents. Some of them exhibit very encouraging pharmacological profiles [3].

Ruthenium compounds are regarded as promising alternatives to platinum compounds and offer many approaches to innovative metallopharmaceuticals, the compounds are known to be stable and to have predictable structures both in the solid state and in solution: tuning of ligand affinities and accompanied by a steadily increasing knowledge of the biological effects of ruthenium compounds [4]. The first systematic investigation of ruthenium compounds and their antitumor property was done in beginning of 1980s with the compounds fac-$[RuCl_3(NH_3)_3]$and cis-$[RuCl_2(NH_3)_4]Cl$ [5] preceded by the discovery that ruthenium red possesses antitumor properties made in the 1970s [6-7]. Since then compounds such as trans-(IndH)$[Ru(ind)_2Cl_4]$ (Ind = indazole),mer-$[Ru(terpy)Cl_3$(ter=2,2'-terpyridine),[8-10]$[Ru(dmso)_4Cl_2]$ [11], (DMSO = dimethylsulfoxide) ,ImH$[Ru(im)Cl_5]$[12], ImH$[Ru(im)_2$-$Cl_4]$ [13], and ImH$[Ru(im)(dmso)Cl_4]$ [14], NAMI-A (im =imidazole) are also well-known antitumor agents.

Ruthenium (II) arene complexes show remarkable cytotoxic properties in vitro as well as in vivo [15-16]. A series of complexes with the general formula $[Ru(\eta^6$-arene)Cl(en)$][PF_6]$ (en=ethylene diamine, arene= benzene, p-cymene, tetrahydroanthracene etc) have been studied for their in vitro anticancer activity [17].

The ruthenium compounds with bidentate ligands show intercalation properties with DNA.[18] The Ru(II) compounds are kinetically more reactive than Ru(III) [19]. So, we have reported that Ru(II) compounds bearing thiosemicarbazides, 8-hydroxy quinolines, have in vivo anticancer and in vitro antibacterial activity [20-21]. So recently we have reported Ru(II) compounds bearing isatin thiosemicarbazones, chloro-fluoro-phenyl imno methyl phenol have in vivo anticancer and invitro cytotoxic activity [22]. In this work, we describe the synthesis and characterization of some ruthenium complexes, there in vitro cytotoxic activity against human cancer cell line Molt $4/C_8$, CEM and murine tumor cell line L 1210, and their in vivo anticancer activity against transplantable murine tumor cell line EAC. Our research has been focused on complexes of the general formula $[Ru(T)_2(S)]Cl_2$, where T=2,2'-bipyridine/1,10-phenanthroline and S= 4-$N(CH_3)_2$-bitsz, 3-$OCH_3$4-OH-btsz, 4-$N(CH_3)_2$-binh.

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MATERIAL AND METHODS

The solvents AR grades were obtained from Sd Fine Chem., Mumbai, and E.Merck, Mumbai. The reagents (puriss grade) were obtained from Fluka and E.Merck. Hydrated ruthenium trichloride was purchased from Loba Chemie, Mumbai, and used as received.

Experimental

All the melting points were determined in open capillary and are uncorrected. UV-visible spectra were on a Jasco spectrophotometer. FTIR spectra were recorded in KBr powder on a Jasco V410 FTIR spectrometer by diffuse reflectance technique. ^{1}H-NMR spectra were measured in $CDCl_3$ and DMSO-d_6 on a Bruker Ultraspec 500 MHz/AMX 400 MHz/300 MHz spectrometer. The reported chemical shifts were against that of TMS. FAB mass spectra were recorded on a JEOL JMS600 spectrum with mNBA matrix.

General procedure for preparing substituted benzyl thiosemicarbazones (r-btsz).

A mixture of substituted benzaldehyde (1 mmol) and thiosemicarbazide (1mmol) in 100 ml of ethanol was refluxed for 3h and left overnight. The solid that separated was filtered and dried. The crude solid was purified by recrystallization from alcohol to give crystals.

4-N-$(CH_3)_2$-btsz.

Yield 91%, m.p. 198-199ºC. IR (KBr) cm^{-1}: 3417-3380(NH_2 and NH), 3136 (C-H), 1370 (C==S). Calcd. For $C_{10}H_{14}N_4S$: C, 54.03; H, 6.35; N, 25.20. Found C, 54.00; H, 6.29; N, 25.28%. λ_{max} nm (MeOH): 236, 299,370. ^{1}H NMR (DMSO-d_6): δ= 11.18 -6.88 (8H, Ar-H), 2.81 (3H, CH_3), 2.75 (3H, CH_3).

3-$OCH_3$4-OH-btsz.

Yield 78%, m.p. 186-188ºC. IR (KBr) cm^{-1}: 3529 (O-H), 3438-3281(NH_2 and NH), 3136 (C-H), 1374 (C==S). Calcd. For $C_9H_{11}N_3O_2S$: C, 47.99; H, 4.92; N,18.65. Found C, 47.87; H, 4.90; N, 18.62%. λ_{max} nm (MeOH): 229, 301,383. ^{1}H NMR (DMSO-d_6): δ= 11.41 -6.72 (8H, Ar-H), 3.81 (3H, OCH_3).

General procedure for preparing substituted benzyl isonicotinylhydrazones (r-binh).

A mixture of substituted benzaldehyde (1mmol) and Isoniazid (1mmol) in 100 ml of ethanol was refluxed for 3h and left overnight. The solid that separated was filtered and dried. The crude solid was purified by recrystallization from alcohol to give crystals.

4-N-$(CH_3)_2$-binh.

Yield 65%, m.p. 185-187ºC. IR (KBr) cm^{-1}: 3406(NH), 3189 (C-H),1665 (C=O), Calcd. For $C_{15}H_{16}N_4O$: C, 67.15; H, 6.01; N,20.88. Found C, 67.10; H, 5.99; N, 20.78%. λ_{max} nm (MeOH): 253,

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296,350. ^{1}H NMR (DMSO-d_6): δ= 10.97 -6.79 (10H, Ar-H), 2.81 (3H, CH_3), 2.80 (3H, CH_3).

Preparation of cis-[bis (S)dichlororuthenium(II)] cis-[Ru(T)$_2$Cl$_2$] [21] **(where T=2,2'-bipyridne/ 1,10-phenanthroline).** $RuCl_3.H_2O$, 1g (2.5mmol) and Ligand S (5mmol) was refluxed in 50 ml DMF for 3h under nitrogen atmosphere. The reddish brown solution slowly turned purple and the product precipitated in the reaction mixture. The solution was cooled overnight at 0^{o}C. A fine microcrystalline mass was filtered off. The residue was repeatedly washed with 30% LiCl solution and finally recrystallised from the same. The product was dried and stored in a vacuum desiccator over P_2O_5 for further use (yield 75%).

General procedure for preparing-[Ru(T)$_2$(S)Cl$_2$] (where T=1,10-phenanthroline/ 2,2'-bipyridne; where S = 4-N-$(CH_3)_2$-btsz,3-$OCH_3$4-OH-btsz, 4-N-$(CH_3)_2$-binh To the black microcrystalline cis-bis(S)dichloro ruthenium(II){cis-$Ru(S)_2Cl_2$}(2 mmol) excess of ligand (2.5 mmol) was added and refluxed in ethanol under nitrogen atmosphere. The initial coloured solution slowly changed to brownish orange at the end of the reaction, which was verified by TLC on silica plates. Then the excess of ethanol distilled off and to this solution add silica gel (60-120 mesh). The product was purified by column chromatography by using silica gel as stationary phase and chloroform-methanol as mobile phase.

[Ru(phen)$_2$(4-N-(CH$_3$)$_2$-btsz)]Cl$_2$: 45%, black crystals, IR (KBr) cm^{-1}: 3403-3357 (NH_2&N-H), 3066 (C-H) 2915 (C-H), 1383 (C==S). Calcd. For $C_{34}H_{30}Cl_2N_8Ru_1S_1$: C, 54.11; H, 3.97; N, 14.85. Found C, 54.08; H, 3.99; N, 14.79%. ^{1}H NMR (DMSO-d_6): δ ppm: δ= 12.22 -6.42 (24H, Ar-H), 2.81 (3H, CH_3), 2.82 (3H, CH_3). FAB-MS (mNBA): 754 [Ru(phen)$_2$ (4-N-$(CH_3)_2$-btsz)]$^{2+}$$(Cl_2)^-$; 683 [Ru(phen)$_2$ (4-N-$(CH_3)_2$-btsz)]$^{2+}$; 503 [Ru(phen) (4-N-$(CH_3)_2$-btsz))]$^{2+}$; 461 [Ru(phen)$_2$].

[Ru(bpy)$_2$(4-N-(CH$_3$)$_2$-btsz)]Cl$_2$:

43%, black crystals, IR (KBr) cm^{-1}: 3432-3302 (NH_2&N-H), 3098 (C-H) 2909 (C-H), 1328 (C==S). Calcd. For $C_{30}H_{30}Cl_2N_8Ru_1S_1$: C, 50.99; H, 4.25; N, 15.86. Found C, 50.88; H, 4.22; N, 15.77%. ^{1}H NMR (DMSO-d_6): δ ppm: δ= 11.99 -6.86 (24H, Ar-H), 2.82 (3H, CH_3), 2.80 (3H, CH_3). FAB-MS (mNBA): 706 [Ru(bpy)$_2$ (4-N-$(CH_3)_2$-btsz)]$^{2+}$$(Cl_2)^-$; 635 [Ru(bpy)$_2$ (4-N-$(CH_3)_2$-btsz)]$^{2+}$; 479 [Ru(bpy) (4-N-$(CH_3)_2$-btsz))]$^{2+}$; 413 [Ru(bpy)$_2$].

[Ru(phen)$_2$(3-OCH$_3$ 4-OH-btsz)]Cl$_2$:

45%, black crystals, IR (KBr) cm^{-1}: 3510 (O-H), 3423-3301 (NH_2&N-H), 3011 (C-H) 1381 (C==S). Calcd. For $C_{33}H_{27}Cl_2N_7O_2Ru_1S_1$: C, 52.31; H, 3.56; N, 12.95. Found C, 52.27; H, 3.49; N, 12.89%. ^{1}H NMR (DMSO-d_6): δ ppm: δ= 12.09 -6.01 (24H, Ar-H), 3.81 (3H, OCH_3), FAB-MS (mNBA): 757 [Ru(phen)$_2$ (3-$OCH_3$4-OH-btsz)]$^{2+}$$(Cl_2)^-$; 686 [Ru(phen)$_2$ (3-$OCH_3$4-OH-btsz)]$^{2+}$; 506 [Ru(phen) (3-$OCH_3$4-OH-btsz))]$^{2+}$; 461 [Ru(phen)$_2$

[Ru(bpy)$_2$(3-OCH$_3$ 4-OH-btsz)]Cl$_2$:

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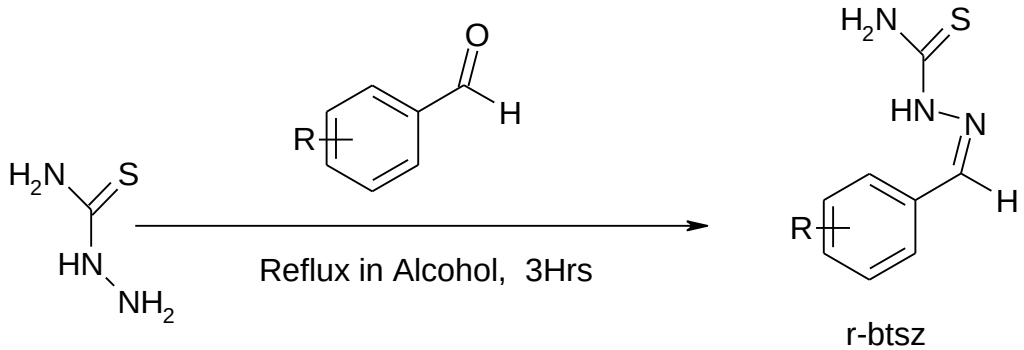
45%, black crystals, IR (KBr) cm^{-1}: 3490 (O-H), 3410-3324 (NH_2&N-H), 3088 (C-H) 1381 (C==S). Calcd. For $C_{29}H_{27}Cl_2N_7O_2Ru_1S_1$: C, 49.08; H, 3.81; N, 13.82. Found C, 49.07; H, 3.79; N, 13.76%. ^1H NMR (DMSO-d_6): δ ppm: δ= 12.42 -6.13 (24H, Ar-H), 3.78 (3H, OCH_3), FAB-MS (mNBA): 709 $[Ru(bpy)_2$ (3-$OCH_3$4-OH-btsz)$]^{2+}(Cl_2)^-$; 638 $[Ru(bpy)_2$ (3-$OCH_3$4-OH-btsz)$]^{2+}$; 482 [Ru(bpy) (3-$OCH_3$4-OH-btsz))$]^{2+}$; 413 $[Ru(bpy)_2$.

$[Ru(phen)_2$(4-N-$(CH_3)_2$-binh)$]Cl_2$:

45%, black crystals, IR (KBr) cm^{-1}: 3321 (N-H), 3069 (C-H) 1683 (C==O). Calcd. For $C_{39}H_{32}Cl_2N_8O_1Ru_1$: C, 58.50; H, 4.00; N, 14.00. Found C, 58.42; H, 3.98; N, 13.95%. ^1H NMR (DMSO-d_6): δ ppm: δ= 10.52 -6.77 (26H, Ar-H), 2.81 (3H, CH_3), 2.80 (3H, CH_3). FAB-MS (mNBA): 800 $[Ru(phen)_2$ (4-N-$(CH_3)_2$-binh)$]^{2+}(Cl_2)^-$; 729 $[Ru(phen)_2$ (4-N-$(CH_3)_2$-binh)$]^{2+}$; 549 [Ru(phen) (4-N-$(CH_3)_2$-binh))$]^{2+}$; 461 $[Ru(phen)_2]$.

2.4.6. $[Ru(bpy)_2$(4-N-$(CH_3)_2$-binh)$]Cl_2$:

43%, black crystals, IR (KBr) cm^{-1}: 3319 (N-H), 3090 (C-H) 1681 (C==O). Calcd. For $C_{35}H_{32}Cl_2N_8O_1Ru_1$: C, 55.85; H, 4.25; N, 14.89. Found C, 55.77; H, 4.21; N, 14.78%. ^1H NMR (DMSO-d_6): δ ppm: δ= 10.02 -6.24 (26H, Ar-H), 2.75 (3H, CH_3), 2.73 (3H, CH_3). FAB-MS (mNBA): 752 $[Ru(bpy)_2$ (4-N-$(CH_3)_2$-binh)$]^{2+}(Cl_2)^-$; 681 $[Ru(bpy)_2$ (4-N-$(CH_3)_2$-binh)$]^{2+}$; 525 [Ru(bpy) (4-N-$(CH_3)_2$-binh))$]^{2+}$; 413 $[Ru(bpy)_2]$



thiosemicarbazide

r-btsz

R = (4-N-$(CH_3)_2$), (3-OCH_3 4-OH)

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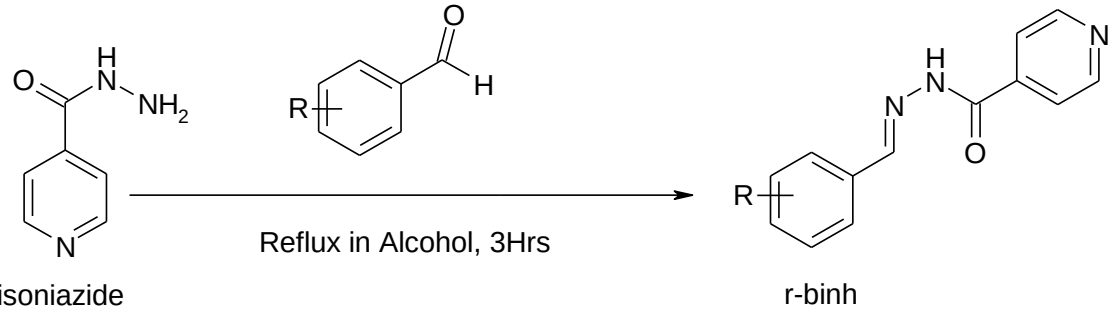
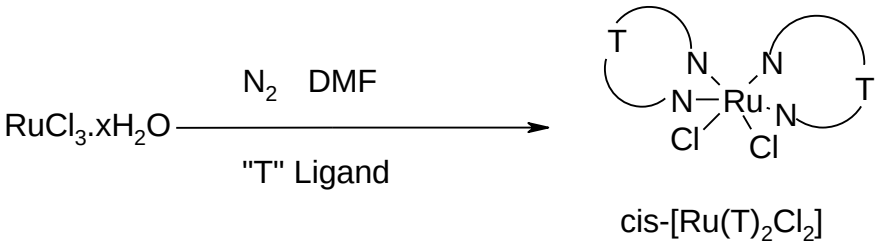


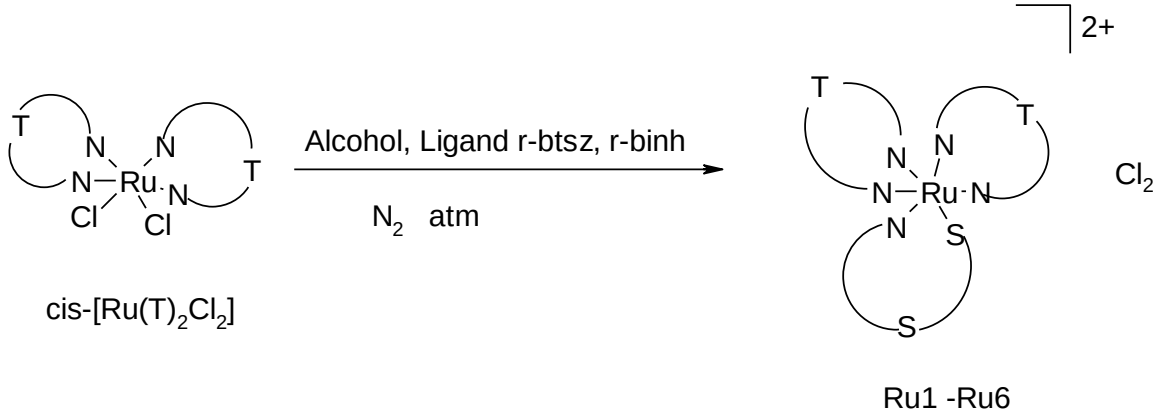
R = 4-N-$(CH_3)_2$

Scheme 1. Preparation of ligands r-btsz, r-binh).



Where T=2,2'-bipyridine/ 1,10-phenanthroline

Scheme 2. Preparation of cis-$[Ru(T)_2Cl_2]$



Scheme 3. Preparation of tris chelates from cis-$[Ru(T)_2Cl_2]$

Biological assays

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The antiviral assays were based on inhibition of virus induced cytopathicity in confluent cell cultures, and the cytostatic assays on inhibition of tumor cell proliferation in exponentially growing tumor cell cultures.

Cytotoxic evaluation

The compounds prepared in laboratory were evaluated against Molt 4/C_8, CEM, and L1210 cells by a literature procedure [23].

Table 1. Cytotoxic studies of ligands and ruthenium complexes

Compound	IC_{50}[a] (µM)		
	L1210	Molt 4/C8	CEM
4-N-$(CH_3)_2$-btsz	188 ± 12	82 ± 5	127 ± 11
3-$OCH_3$4-OH-btsz	133 ± 24	104 ± 21	76 ± 12
4-N-$(CH_3)_2$-binh	216 ± 02	174 ± 19	252 ± 5
$Ru(phen)_2$ (4-N-$(CH_3)_2$-btsz)Cl_2	0.90 ± 0.09	2.5 ± 0.8	0.3 ± 0.07
$Ru(bpy)_2$ (4-N-$(CH_3)_2$-bitsz)Cl_2	0.87 ± 0.1	1.3 ± 0.4	0.69 ± 0.01
$Ru(phen)_2$ (3-$OCH_3$4-OH -btsz)Cl_2	7.8 ± 0.2	31 ± 7	3.6 ± 0.8
$Ru(bpy)_2$ (3-$OCH_3$4-OH-btsz)Cl_2	14 ± 0.8	27 ± 1.7	9.9 ± 1.1
$Ru(phen)_2$ (4-N-$(CH_3)_2$-binh)Cl_2	14 ± 3	9.4 ± 0.6	8.1 ± 1.3
$Ru(bpy)_2$ (4-N-$(CH_3)_2$-binh)Cl_2	41 ± 5	>50	24 ± 1.8
Cisplatin	1.2 ± 0.02	0.87 ± 0.06	0.51 ± 0.1

[a]50% inhibitory concentration, required to inhibit tumor cell proliferation by 50%

RESULTS AND DISCUSSION

Chemistry

The ligands like r-binh (r-binh = substituted benzyl thiosemicarbazones) were prepared by reacting substituted benzaldehydes with Isonizid in alcohol at 1:1 molar ratio (Scheme 1). r-btsz (r-btsz = substituted benzyl thiosemicarbazones) were prepared by reacting substituted benzaldehydes with thiosemicarbazide in alcohol at 1:1 molar ratio (Scheme 1)..All ligands were confirmed for their purity by their melting point, elemental analysis, and other spectral studies. The details of the synthetic strategy adopted for the synthesis of these ruthenium homoleptic compounds was as follows. The starting material for the synthesis of the compounds are cis-bis(1,10-phenanthroline) dichlororuthenium(II)/cis-bis(2,2'-bipyridine)dichlororuthenium(II).

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Ruthenium trichloride was refluxed in DMF in the presence of 1,10-phenanthroline/2,2'-bipyridine and in excess of the stoichiometric amount. Which afforded the final product cis-bis(1,10-phenanthroline)dichlororuthenium(II)/cis-bis(2,2'-bipyridine) dichlororuthenium (II) [21] (Scheme 2). The third ligand was introduced in alcohol in the presence of nitrogen atmosphere (Scheme 3).

The structures of the ligands especially r-binh, and r-btsz were capable of exhibiting bidentate behavior. There were very few cases in which the thiosemicarbazide acts as monodentate ligand binding to the metal center through the sulfur atom.[24-25] In case of ligands (r-btsz) the chelating mode was via sulfur atom and imine nitrogen by coordination covalent bond. In case of ligands (r-binh) the covalent bond formed between metal ion and oxygen atom and coordinate covalent bond with imine nitrogen.

The infrared spectra of all the ligands and their ruthenium (II) compounds were recorded in KBr powder by diffuse reflectance technique and are reported in their respective titles by tentative assignments. The r-btsz ligands showed vibrational frequency from 3550 to 3200 cm^1 for $NH_2$and N–H stretching and from 1380 to 1370 $cm^1$for C=S stretching. In r-binh ligands showed vibrational frequency from 3410 to 3200 cm^1 for N–H stretching and from 1690-1670 $cm^1$for C=O stretching.

A comparison of IR spectra of ligands r-btsz with ruthenium complexes indicates this was coordinated to the metal center by sulfur atom and imine nitrogen, which was confirmed by the IR spectra.In case of IR spectra of ligands r-binh with ruthenium
compound indicates this was coordinated to the metal center by oxygen atom and imine nitrogen. In the complexess such as Ru1–Ru2, Ru3-Ru4 the coordination had occurred via sulfur and imine nitrogen but not with terminal amine group, which was confirmed by the spectra, which indicates no change in vibrational frequency of NH_2group between 3400 and 3300 cm^1. A comparison of IR spectra of ligand r-binh with ruthenium complexes indicates this was coordinated to the metal center by oxygen atom and imine nitrogen, which was confirmed by the IR spectra.

Coordination of ligands (K = r-binh, r-btsz,) to ruthenium results in compounds such as $[Ru(T)_2(S)]^{2+}Cl_2$(Ru1–Ru6) , respectively. All these compounds do not possess any C2 axes of symmetry.

In the 1H-NMR spectra of the complexe, **Ru 1**there were 30 resonance peaks (δ 12.22-2.81), and 30 well resolved peaks (δ 11.99-2.80) for **Ru 2**.The mass spectra of the complexes confirmed the suggested formula by their molecular ion peaks. The spectrum showed numerous peaks representing successive degradation of the molecule. FAB mass spectroscopic data clearly suggested that mononuclear complexes had been formed in each case, the first fragment being due to $[Ru(T)_2(S)]^{2+}$ Cl_2^- ion pair. The complex also showed a peak due to the complex cation $[Ru(T)_2(S)]^{2+}$and others due to $[Ru(T)(S)]^{2+}$, $[Ru(T)_2]^{2+}$ respectively [Where T= 1,10-phenanthroline/2,2'-bipyridine and S= r-binh,r-btsz]. This type of fragmentation reported

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for $[Ru(phen)_2(nmit)]Cl_2$ and $Ru(bpy)_2$ (ihqs)] Cl_2, where phen=1,10-phenanthroline, bpy=2,2'-bipyridine, nmit= N-methyl isatin thio semicarbazone, ihqs= 7-iodo-8-hydroxy quinoline-5-sulfonicacid. In all the cases, the loss of chlorine ions was detected where S = 2,2'-bipyridine/1,10-phenanthroline and K = r-binh, r-btsz. Thus, based on the above observations, it is tentatively suggested that Ru(II) complexess showed an octahedral geometry.

Biological activity and discussion

Results are summarized in Table1. The in vitro cytotoxic activity was evaluated for all the synthesized ligands and its ruthenium complexes against human 4/C8, CEM, T-Lymphocytes as well murine L1210 cells, and its results were summarized in table. The relative potencies between ligands and their ruthenium complexes revealed the importance of ruthenium metal using the $4/C_8$, CEM, assays and murine L1210 assays. These determinations showed that in comparison to ligands , the ruthenium complexes were more potent.

The cytotoxicity data in table revealed that most ruthenium complexes have significant cytotoxic potencies (IC_{50} figures in the 1.3-50 for Molt 4/C8, 0.87-41 µM for L1210 and 0.30-24 µM for CEM). While for ligands, the IC_{50} values were in excess (76-252 µM against CEM, 76-174 µM for Molt 4/C8, and 133-216 µM for L1210). Of the tested ligands and ruthenium complexes $Ru(phen)_2$ (4-N-$(CH_3)_2$-btsz)Cl_2 showed cytotoxicity against all three cell lines tested in range of 2.5, 0.90, and 0.30 µM for Molt 4/C8, CEM, and L1210, respectively. Whereas another complex $Ru(bpy)_2$ (4-N-$(CH_3)_2$-btsz)Cl_2 did show cytotoxicity against cell lines tested 1.3 µM for Molt 4/C8, 0.87 for CEM and 0.69 for L1210. While remaining other ruthenium complexes for Molt 4/C8 and CEM (low) µM and L1210 (higher) µM. On comparison to ruthenium complexes the ligands displayed the cytotoxicty at higher µM concentration.

From the results presented in Table-2, it is clear that several ruthenium complexes exhibited a marked inhibitory effect on the proliferation of tumor cells: IC_{50} from as low as 1.3 µM for Molt 4/C8, 0.87 µM CEM, and 0.30 µM for L1210. Thus the ruthenium complexes proved inhibitory to tumor growth at submicromolar concentration. Their ligands however were not antitumorally active.

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