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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Design, synthesis, structural characterization and in vitro cytotoxic activity of mononuclear Ru(II)complexes

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Abstract The synthesis and characterization of ruthenium complexes (**Ru-1–Ru-6**) of the type $[Ru(R)_2(K)]^{2+}$ (where R = 1,10-phenanthroline/2,2′-bipyridyl and K = acetyl coumarin-inh, pyrazole-tch, acetyl coumarin-tsz, are described. These ligands form bidentate octahedral ruthenium complexes. The in vitro cytotoxic activities of the complexes measurement against the human cancer T-lymphocyte cell lines. In vitro evaluation of these title complexes revealed cytotoxicity from 0.34 to 1.4 µg/mL against CEM, 0.28 to 1.8 µg/mL against L1210, 0.44 to 2.5 µg/mL against Molt4/C_8, 0.98 to 1.6 µg/mL against HL60, and 0.66 to 1.4 µg/mL against BEL7402. Ruthenium complexes **Ru-5** & **Ru-6** showed that quite significant anticancer activities over standard drugs.

Keywords Acetyl coumarin · Ruthenium complexes · Cytotoxicity

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Introduction

Research on drugs based on ruthenium complexes is a fast developing field in medicine, especially in development of chemotherapeutic agents with less side effects and immunity to acquisition of drug resistance. (Muggia, 2009) The synthesis of ruthenium complexes with thiosemicarbazone ligands has been receiving considerable attention due to the pharmacological properties of both complexes & ligands. (Beckford et al., 2009; Mazumder et al., 2005; Thota et al., 2012) Thiosemicarbazone ligands exhibit a wide variety of biological activities such as antiviral (Finkielsztein et al., 2008), antitumor (Patel and Divatia, 2013), antibacterial (Agarwal et al., 2006), and antifungal properties (Costa et al., 2005). The thiosemicarbazone ligands usually coordinate to ruthenium through Nitrogen & Sulfur donor atoms in their (N, S) bidentate form. (Thota et al., 2013; El-shazly et al., 2006) Recently, two Ru(III) compounds, namely, KP1019 (indazolium trans-[tetrachloro bis (*1H*-indazole) ruthenate(III)] (Hartinger et al., 2008) and NAMI-A (imidazolium trans-[tetrachloro(dimethylsulfoxide)(*1H*-imidazole)-ruthenate(III)] entered phase II clinical trials as antimetastatic compounds.

A series of ruthenium complexes having the general formula $[Ru(S)_2(K)]$, where S = 2,2′-bipyridine/ 1,10-phenanthroline and K = hfc, itsz, Meo-btsz, 4-Cl-btsz etc., reported (Karki et al., 2007). Complex $[Ru(Phen)_2(p\text{-}MOPIP)]^{2+}$ can effectively inhibit the proliferation of Hep G-2 cell line with low IC_{50} value (7.2–1.3 µM) (Schatzschneider *et al.*, 2008), $[Ru(Phen)_2(DBHIP)]^{2+}$ can effectively induce apoptosis of BEL-7402 cell lines (Liu et al., 2010). In recent year, several ruthenium-based complexes have been investigated such as chiral ruthenium complex [(1s, 2s)-DEPN]–$RuCl_2(PPh_3)_2$ (Liu et al., 2010), new chiral—bridged diamine/diphosphine Ru(II)

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complexes (Cui et al., 2010) $RuCl_2$ (PPh_3)*N*-b-bis(2-(di-o-tolylphosphino)–benzyl] cyclohexane -1,2-diamine, (1,4,7,10,13–penta thio cyclo pentadecane) chloro ruthenium (II) hexa fluoro phosphate (Janzen et al., 2010), pyridyl-based liquid supported ruthenium complex (Mei-Ran et al., 2009), $[Ru(bpy)Br)_2$ (acac)] (PF6) (Viala and Bonvoisin, 2010), antiviral activity of ruthenium(II) arene complexes (Allardyce et al., 2003). Recently we reported Ru(II) complexes with pyrazoline ligands as anticancer activity (Thota et al., 2012). In this report, we evaluated the complexes type $[Ru(R)_2(K)]^2$+, (where R = 1,10-phenanthroline/2,2′-bipyridyl and K = acetyl coumarin-inh, pyrazole-tch, acetyl coumarin-tsz, for anticancer activities. The in vitro cytotoxic and activitiy of the complexes measurement against the human cancer T-lymphocyte cell lines.

Experimental

Materials for synthesis

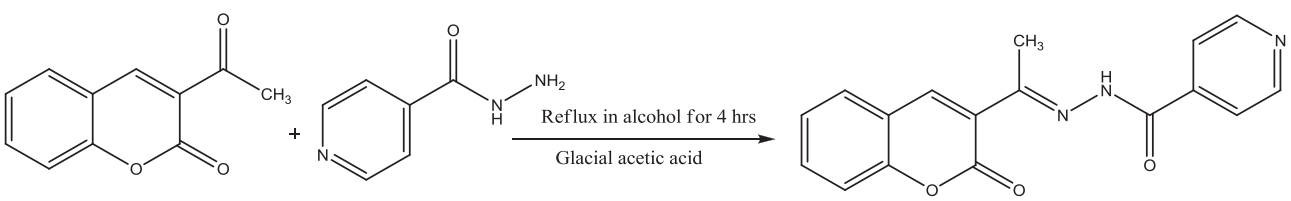
All reagents and solvents were purchased from Sigma-Aldrich and used as received. The $RuCl_3.3H_2O$ was purchased from Sigma-Aldrich. All the melting points were determined in open capillary and are uncorrected. ultra violet–visible (UV-Vis) spectra were on a Jasco spectrophotometer. Fourier transform infrared (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 AMX 400 MHz/300 MHz spectrometer. The reported chemical shifts were against that of tetramethylsilane. FAB-mass spectra were recorded on a JEOL JMS600 spectrometer with 3-nitro benzyl alcohol as matrix. Microanalyses were carried out on an Elementar Vario elemental analyzer.

The ruthenium compounds Ru-1–Ru-6 were prepared using the synthetic strategy describes (Schemes 4 and 5). The synthesis began by preparation of thiosemicabzone, isonicotinyl hydrazones, and pyrazole thiocarbohydrazide ligands (Schemes 1–3). The ligands were prepared according to the published procedures. (de Oliveira et al., 2008). The next step was performed by commercially available ruthenium trichloride with 1,10–phenanthrolene/2,2′-bipyridyl. The final ruthenium complexes were synthesized by treating $[Ru(phen)_2Cl_2]$ with phenyl thiosemicarbazone ligands to offered the corresponded complex.

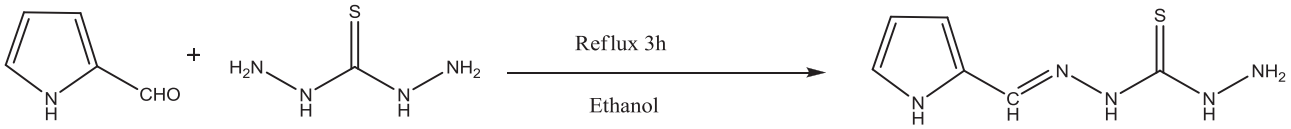
Synthesis

General procedure for preparing $[Ru(R)_2(K)Cl_2]$ (where R = 2,2′-bipyridine/ 1,10-phenanthroline; K = acetyl coumarin-inh, pyrazole-tch, acetyl coumarin-tsz To the black microcrystalline *cis*-bis(R)dichlororuthenium(II){*cis*-$Ru(R)_2Cl_2$}(2 mmol) excess of ligand **B** (2.5 mmol) was added and refluxed in anhydrous ethanol under nitrogen. The initial colored solution slowly changed to brownish orange at the end of the reaction, which was verified by thin layer chromatography on silica plates. Then excess ethanol was distilled off and silicagel (60–120 mesh) added to this solution. The final complex was purified by column chromatography by using silica gel as stationary phase and chloroform–methanol as mobile phase.

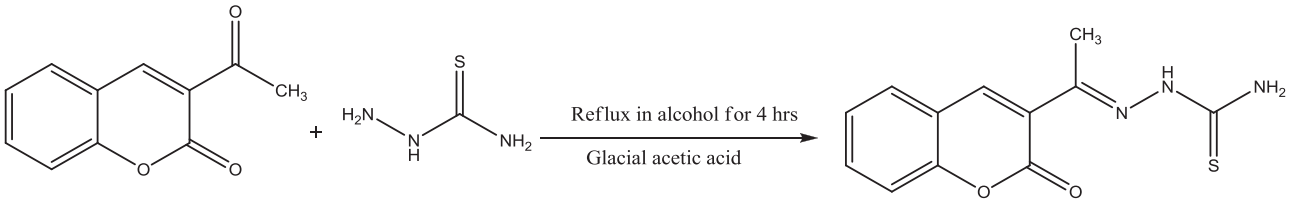
Characterization of synthesized Ru(II) complexes Ru-1: $[Ru(phen)_2(ACINH)]Cl_2$, 52 %, black crystals; IR (KBr) νmax: 3336 (N–H), 3014 (C–H), 2913 (C–H), 1680 (C=O) cm^{-1}. ^{1}H-NMR (DMSO-d_6, 400 MHz): $\delta = 9.26$ (1H, s), 8.94 (1H, s), 8.89 (1H, s), 8.70 (2H, d), 8.58 (2H, d, $J = 4.9$ Hz), 8.42–8.31(2H, d, $J = 5.0$ Hz), 8.23 (1H, s), 8.11 (1H, s), 7.98 (1H, s, NH), 7.83 (4H, m), 7.68–7.58 (4H, m) 7.54 (2H, dd) 7.42 (1H, s), 6.94 (2H, d), 6.52 (1H, s), 2.22 (3H, CH_3). ^{13}C-NMR (DMSO-d_6): 159.2 (s, 1C, C=O), 153.8 (s, 1C, C=O), 152.1(s, 1C), 149.4 (s, 1C), 149.0 (s, 1C), 148.8 (s, 1C), 148.4 (s, 1C), 148.0 (s, 1C), 147.4 (s, 1C), 147.2 (s, 1C), 146.8 (s, 1C), 146.4 (s, 1C), 143.6 (s, 1C), 138.4 (s, 1C), 137.8 (s, 1C), 137.6 (s, 1C), 137.2 (s, 1C), 136.4 (s, 1C), 133.8 (s, 1C), 129.8 (s, 1C), 129.4 (s, 1C), 129.2 (s, 1C), 129.0 (s, 1C), 127.8 (s, 1C), 127.6 (s, 1C), 127.2 (s, 1C), 127.0 (s, 1C), 126.4 (s, 1C), 125.8 (s, 1C), 125.2 (s, 1C), 125.0 (s, 1C), 124.6 (s, 1C), 124.2 (s, 1C), 123.8 (s, 1C), 123.2 (s, 1C), 122.4 (s, 1C), 122.0 (s, 1C), 120.8 (s, 1C), 119.4 (s, 1C), 119.0 (s, 1C) 4.9 (s, 1C, CH_3). FAB-MS (mNBA): 768 $[Ru(phen)_2$ $(ACINH)]^{2+}$, 461 $[Ru(phen)_2]$, 307 [ACINH]. Anal. Calcd. for $C_{41}H_{29}Cl_2N_7O_3Ru_1$: C, 58.64; H, 3.45; N, 11.68. Found: C, 58.52;



Scheme 1 Synthesis of acetyl coumarin isonicotinyl hydrazone (ACINH)



Scheme 2 Synthesis of pyrazole thicarbohydrazides (PTCH)



Scheme 3 Synthesis of acetyl coumarin thiosemicarbazone (ACTSZ)

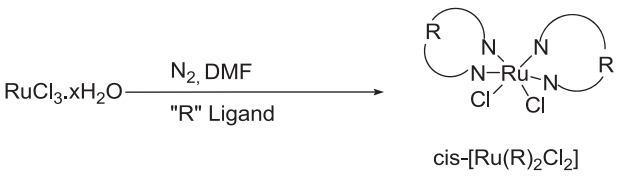
H, 3.44; N, 11.56. Ru-2: $[Ru(bpy)_2(ACINH)]Cl_2$, 48 %, black crystals; IR (KBr) νmax: 3298 (N–H), 3094 (C–H) 2936 (C–H), 1680 (C=O) cm^{-1}. ^{1}H-NMR (DMSO-d_6, 400 MHz): δ ppm: 9.18 (1H, s), 9.12 (1H, s), 9.08 (1H, s), 8.98 (1H, s), 8.86 (1H, s), 8.68 (2H, d), 8.54 (2H, d), 8.38–8.32 (2H, d, $J = 5.0$ Hz), 8.24–8.22 (2H, dd), 8.02 (1H, s, NH), 7.92 (3H, t), 7.66 (2H, d, $J = 14.2$ Hz), 7.54–7.48 (3H, m) 7.36 (2H, dd) 7.14 (2H, d), 2.24 (3H, CH_3). ^{13}C-NMR (DMSO-d6): 159.2 (s, 1C, C=O), 153.8 (s, 1C, C=O), 152.1(s, 1C), 149.4 (s, 1C), 149.0 (s, 1C), 148.8 (s, 1C), 148.4 (s, 1C), 148.0 (s, 1C), 147.4 (s, 1C), 147.2 (s, 1C), 146.8 (s, 1C), 146.4 (s, 1C), 143.6 (s, 1C), 138.4 (s, 1C), 137.8 (s, 1C), 137.6 (s, 1C), 137.2 (s, 1C), 136.4 (s, 1C), 133.8 (s, 1C), 129.8 (s, 1C), 129.4 (s, 1C), 129.2 (s, 1C), 129.0 (s, 1C), 127.8 (s, 1C), 126.6 (s, 1C), 125.8 (s, 1C), 125.2 (s, 1C), 124.0 (s, 1C), 123.6 (s, 1C), 123.4 (s, 1C), 123.0 (s, 1C), 121.6 (s, 1C), 121.4 (s, 1C), 120.2 (s, 1C), 118.8 (s, 1C), 118.6 (s, 1C) 4.9 (s, 1C, CH_3). FAB-MS (mNBA): 791 $[Ru(bpy)_2(ACINH)]^{2+}(Cl_2)^-$; 720 $[Ru(bpy)_2(ACINH)]^{2+}$; 413 $[Ru(bpy)_2]$; 307 [ACINH]. Anal. Calcd. for $C_{37}H_{29}Cl_2N_7O_3Ru_1$: C, 56.14; H, 3.67; N, 12.39. Found: C, 56.08; H, 3.62; N, 12.28. Ru-3: $[Ru(phen)_2(PTCH)]Cl_2$, 44 %, black crystals; IR (KBr) νmax: 3462 (NH_2), 3268 (N–H) 2982 (C–H), 1328 (C=S) cm^{-1}. ^{1}H NMR (DMSO-d_6, 400 MHz): $\delta = 9.28$ (1H, s), 8.96 (1H, s), 8.88 (1H, s), 8.80 (1H, s, $J = 4.9$ Hz), 8.62 (2H, d, $J =$ 8.4 Hz), 8.48 (2H, d), 8.36 (2H, d), 7.94 (2H, d, $J = 5.0$ Hz), 7.86 (3H, m), 7.58 (2H, d), 7.32 (1H, s), 7.28 (2H, d, $J =$ 14.6 Hz), 7.15 (1H, s), 6.95 (1H, s), 6.51–6.44 (2H, d) 6.25 (1H, s). FAB-MS (mNBA): 715 $[Ru(phen)_2(PTCH)]^{2+}(Cl_2)^-$; 644 $[Ru(phen)_2(PTCH)]^{2+}$; 461 $[Ru(phen)_2]$; 183 [PTCH]. Anal. Calcd. for $C_{30}H_{25}Cl_2N_9Ru_1S_1$: C, 50.35; H, 3.49; N, 17.62. Found: C, 50.26; H, 3.42; N, 17.64. Ru-4: $[Ru(bpy)_2(PTCH)]Cl_2$, 54 %, black crystals; IR (KBr) νmax: 3480 (NH_2), 3294 (N–H) 2976 (C–H), 1332 (C=S) cm^{-1}. ^{1}H NMR (DMSO-d_6, 400 MHz): $\delta = 9.04$ (1H, s), 8.92 (1H, s), 8.82 (1H, s), 8.76 (1H, s, $J = 4.9$ Hz,), 8.64–8.44 (2H, d, $J = 8.4$ Hz), 8.40–8.28 (2H, d), 8.12 (3H, d), 7.82 (2H, d, $J = 4.9$ Hz), 7.82–7.64 (4H, m), 7.46 (1H, s), 7.34 (2H, d, $J = 14.8$ Hz), 7.08 (1H, s), 6.98 (1H, s), 6.76–6.52 (2H, d) 6.18 (1H, s). FAB-MS (mNBA): 667 $[Ru(bpy)_2(PTCH)]^{2+}(Cl_2)^-$; 596 $[Ru(bpy)_2(PTCH)]^{2+}$; 413 $[Ru(bpy)_2]$; 183 [PTCH]. Anal. Calcd. for $C_{26}H_{25}Cl_2N_9Ru_1S_1$: C, 46.77; H, 3.75; N, 18.89. Found: C, 46.68; H, 3.66; N, 18.78. Ru-5: $[Ru(phen)_2(ACTSZ)]Cl_2$, 46 %, black crystals; IR (KBr) νmax: 3421 (NH_2), 3255 (N–H) 2986 (C–H), 1678 (C=O), 1334 (C=S) cm^{-1}. ^{1}H NMR (DMSO-d_6, 400 MHz): δ ppm = 9.32 (1H, s), 9.18 (1H, s), 9.02 (1H, s), 8.94 (1H, s, $J = 4.9$ Hz), 8.72 (2H, d, J = 8.4 Hz), 8.64 (2H, d), 8.44 (2H, d), 8.32 (2H, d, $J = 5.0$ Hz), 8.16 (2H, d), 8.04 (2H, d), 7.98-7.68 (4H, m), 7.36 (2H, d), 7.22 (2H, d, $J = 14.6$ Hz) 2.24 (3H, s). ^{13}C-NMR (DMSO-d6): 179.6 (s, 1C, C=S), 165.42 (s, 1C, C=O), 149.8 (s, 1C), 149.6 (s, 1C), 149.2 (s, 1C), 149.0 (s, 1C), 148.6 (s, 1C), 148.4 (s, 1C), 147.8 (s, 1C), 147.2 (s, 1C), 142.4 (s, 1C), 137.2 (s, 1C), 136.8 (s, 1C), 136.6 (s, 1C), 136.2 (s, 1C), 135.6 (s, 1C), 134.8 (s, 1C), 129.4 (s, 1C), 128.8 (s, 1C), 128.2 (s, 1C), 128.0 (s, 1C), 127.4 (s, 1C), 127.0 (s, 1C), 126.8 (s, 1C), 126.4 (s, 1C), 125.2 (s, 1C), 125.0 (s, 1C), 124.8 (s, 1C), 124.4 (s, 1C), 124.2 (s, 1C), 123.0 (s, 1C), 122.8 (s, 1C), 122.6 (s, 1C), 121.6 (s, 1C), 119.8 (s, 1C) 4.9 (s, 1C, CH_3). FAB-MS (mNBA): 793 $[Ru(phen)_2(ACTSZ)]^{2+}(Cl_2)^-$; 722 $[Ru(phen)_2(ACTSZ)]^{2+}$; 461 $[Ru(phen)_2]$; 261 [ACTSZ]. Anal. Calcd. for $C_{36}H_{27}Cl_2N_7O_2Ru_1S_1$: C, 54.47; H, 3.41; N, 12.36. Found: C, 54.42; H, 3.29; N, 12.24. Ru-6: $[Ru(bpy)_2(ACTSZ)]Cl_2$, 61 %, black crystals; IR (KBr) νmax: 3442 (NH_2), 3288 (N–H) 2924 (C–H), 1678 (C=O), 1334 (C=S) cm^{-1}.. ^{1}H NMR (DMSO-d_6, 400 MHz): δ ppm: 9.14 (1H, s), 9.06 (1H, s), 8.92 (1H, s), 8.88 (1H, s, $J = 5.0$ Hz), 8.82 (2H, d, J = 8.4 Hz), 8.58 (2H, d), 8.46 (2H, d), 8.28 (2H, d, $J = 5.0$ Hz), 8.12 (2H, d), 8.01–7.98 (3H, m), 7.90–7.66 (4H, m), 7.24 (1H, s), 7.18 (2H, d, $J = 14.6$ Hz) 2.16 (3H, s). ^{13}C-NMR (DMSO-d6): 180.2 (s, 1C, C=S), 164.8 (s, 1C, C=O),

150.6 (s, 1C), 150.4 (s, 1C), 149.8 (s, 1C), 149.6 (s, 1C), 149.4 (s, 1C), 148.8 (s, 1C), 148.6 (s, 1C), 148.4 (s, 1C), 142.6 (s, 1C), 137.4 (s, 1C), 137.2 (s, 1C), 136.6 (s, 1C), 136.0 (s, 1C), 129.8 (s, 1C), 129.4 (s, 1C), 128.8 (s, 1C), 128.6 (s, 1C), 127.0 (s, 1C), 126.6 (s, 1C), 126.2 (s, 1C), 125.4 (s, 1C), 124.6 (s, 1C), 124.0 (s, 1C), 123.8 (s, 1C), 122.4 (s, 1C), 121.8 (s, 1C), 119.0 (s, 1C) 5.2 (s, 1C, CH_3). FAB-MS (mNBA): 745 $[Ru(bpy)_2\ (ACTSZ)]^{2+}(Cl_2)^-$; 674 $[Ru(bpy)_2\ (ACTSZ)]^{2+}$; 413 $[Ru(bpy)_2]$; 261 [ACTSZ]. Anal. Calcd. for $C_{32}H_{27}Cl_2N_7Ru_1S_1$: C, 51.54; H, 3.63; N, 13.15. Found: C, 51.48; H, 3.57; N, 13.08.

Results and discussion

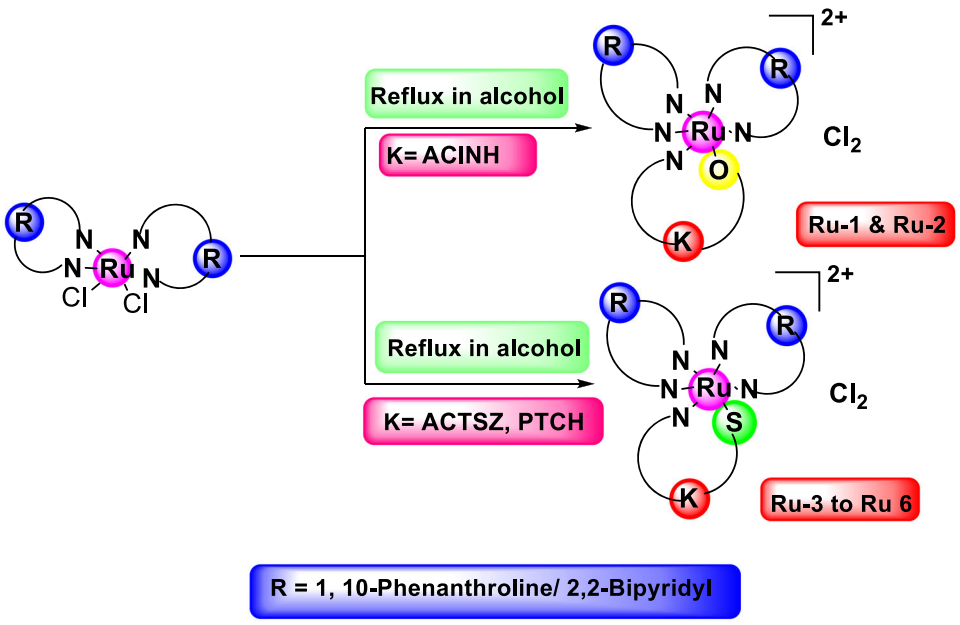
Chemistry

Ruthenium trichloride undergoes reduction when refluxed in dimethyl formamide (DMF). So when refluxed along with two-fold molar ratios of the bidentate ligand (1, 10-phenanthroline/2,2′-bipyridine), a homoleptic complex is formed. The product *cis*-bis(1,10-phenanthroline/2,2′-bipyridine)dichlororuthenate(II) is the starting material for the synthesis of complexes. The product *cis*-bis(1,10-phenanthroline/2,2′-bipyridine)dichlororuthenate(II) was then refluxed in ethanol in presence of nitrogen with various ligands to yield the final octahedral ruthenium complexes. In this homoleptic chelate the first two ligands to enter the complex in a stepwise assembly were 1,10-phenanthroline/2,2′-bipyridine molecule, respectively. Since both the ligands are same, so a single step method was adopted for its synthesis. Ruthenium trichloride was refluxed in DMF in the presence of 1,10-phenanthroline/2,2′-bipyridine, 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) (Scheme 4). The introduction of the third ligand was carried out in the presence of alcohol in the presence of nitrogen atmosphere (Scheme 5). The final chelate formed had ionic chloride in the molecule.



Scheme 4 Synthesis of *cis*-$[Ru(R)_2Cl_2]$ where R = 1, 10-Phenanthroline/ 2,2′-bipyridyl

The compounds of the newly synthesized ruthenium compounds were confirmed by UV-Vis, FTIR, ^{1}H-NMR, ^{13}C-NMR, mass spectroscopy and elemental analysis. In the UV-Vis spectra, all the ruthenium compounds showed broad and intense visible bands between 320 and 520 nm due to metal to ligand charge transfer transition. In the UV region, the bands at 280 and 320 nm were assigned to 1,10-phenanthroline ligand π–π^*charge transfer transitions. The IR spectras contained the absorption bands revealing the existence of the NH_2, NH, C=S, and C=O gps. The ^{1}H-NMR spectra of the complex, $[Ru(phen)_2(ACINH]Cl_2$ shown 29 resonance peaks (δ 9.34–2.12). The mass spectra of the Complex Ru-1 gave the anticipated molecular ion peak and main fragmentation peaks, which were in accordance with the title complexes. The in vitro antineoplastic



Scheme 5 Synthesis of tris chelates from *cis*-$[Ru(R)_2Cl_2]$

Table 1 Cytotoxic studies of ruthenium complexes

Comp. code	IC_{50}[a] (μmol/L)				
	CEM	L1210	Molt 4/C8	HL60	BEL7402
ACINH	110 ± 8	224 ± 28	230 ± 72	192 ± 48	154 ± 46
PTCH	96 ± 34	140 ± 65	158 ± 46	116 ± 25	98 ± 40
ACTSZ	108 ± 12	148 ± 52	126 ± 24	228 ± 14	116 ± 12
Ru-1	0.98 ± 0.04	1.2 ± 0.4	0.92 ± 0.6	1.6 ± 0.02	0.92 ± 0.8
Ru-2	1.4 ± 0.6	1.8 ± 0.2	2.5 ± 0.25	0.98 ± 0.04	1.26 ± 0.4
Ru-3	0.64 ± 0.06	0.82 ± 0.02	0.96 ± 0.04	0.68 ± 0.04	0.92 ± 0.06
Ru-4	0.76 ± 0.08	0.49 ± 0.25	1.2 ± 0.02	0.76 ± 0.08	1.4 ± 0.6
Ru-5	0.34 ± 0.04	0.28 ± 0.2	0.44 ± 0.04	0.84 ± 0.6	0.66 ± 0.24
Ru-6	0.48 ± 0.06	0.45 ± 0.25	0.64 ± 0.6	0.92 ± 0.04	0.84 ± 0.06
Cisplatin	0.51 ± 0.1	1.2 ± 0.02	0.87 ± 0.06	0.98 ± 0.02	0.78 ± 0.04

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

activities of the synthesized complexes against the human cancer T-lymphocyte cell lines molt $4/C_8$ and CEM and the murine tumor leukemia cell lines L1210, human oral epidermoid carcinoma KB cells, human promyelocytic leukemia cells (HL60), and Bel-7402 liver cancer cells were evaluated by the standard MTT assay. (Thota et al., 2009). As described in Table 1, complexes Ru-3, Ru-4, Ru-5 & Ru-6 exhibit very potent antineoplastic activity against all the cell lines, especially Ru-5 & Ru-6 shown very potent antitumor activity than cisplatin and shows good selectivity. On comparison to ruthenium compounds, the ligands displayed the cytotoxicity at higher concentration. Thus, the ruthenium compounds proved inhibitory to tumor growth at submicromolar concentration.

Conclusion

In summary, we described the synthesis of novel Ru(II) complexes bearing ACINH, PTCH, and ACTSZ derivatives. From the results presented in Table 1, it is clear that several ruthenium compounds exhibited a marked inhibitory effect on the proliferation of tumor cells. Thus, the ruthenium compounds proved inhibitory to tumor growth at submicromolar concentration. Their ligands, however, were not antitumorally active. Nevertheless, further translational development of low molecular weight bifunctional Ru(II) −arene complexes are worthwhile as their low toxicity is attractive for development of future anticancer therapies.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interests.

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