

## Bromobenzal thiosemicarbazones of ruthenium(II) complexes: Synthesis and bio applications

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### ABSTRACT

Ru(II)BT have been synthesized by the reaction between substituted bromobenzal thiosemicarbazones and precursors of ruthenium metal complexes, [RuHCl(CO)(EPh<sub>3</sub>)<sub>3</sub>] (where E = P/As). The bromobenzal thiosemicarbazones and Ru(II)BT was characterized by analytical and spectroscopic techniques. It confirms the coordination of the thiosemicarbazone ligands and suggest the octahedral geometry of the complexes. The Ru(II)BT is comprised of a metal centre with bidentate ligands. The stabilization of free radicals with Ru(II)BT was studied. The ligand and Ru(II)BT have significant anticancer activity on MCF-7 cancer cells.

**Keywords:** Ru(II), Anticancer, Antioxidant, Bromobenzal thiosemicarbazones.

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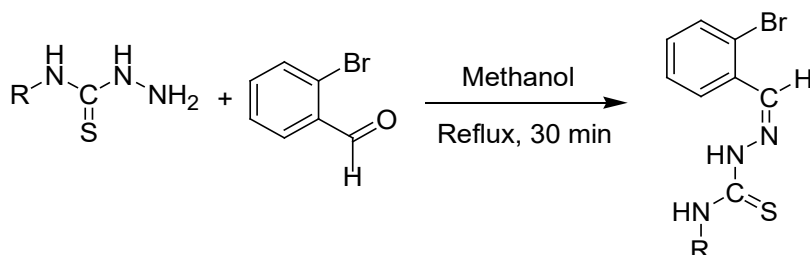
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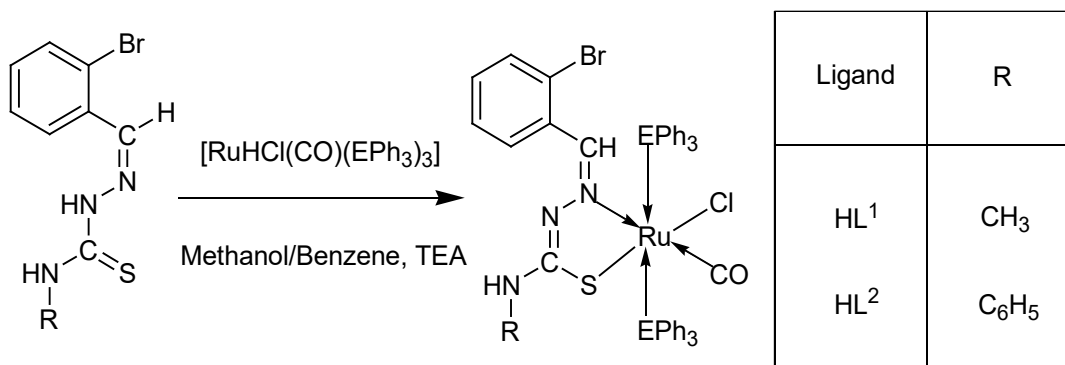
### 1. INTRODUCTION

In the living kingdoms, metals offer an unprecedented versatility in terms of potent drugs (Barolli et al., 2017). Exploring metallodrugs with fascinating chemical and pharmacological properties remains a challenge in the recent years. In addition, to overcome the destructive effects of platinum based drugs like tumor resistance, dose dependent toxic effects, etc., alternative metal drugs with mimic toxicity have been discovered by Arjmand et al. (2012). The complexes of ruthenium metal offers promising innovative alternatives to platinum compounds. In addition, ruthenium compounds are known to be stable in solid states as well as in solutions shown in Gilewska et al. (2018). Complexes of ruthenium possesses high activity against a series of diseases like cancer, malaria, etc. Moreover, the inhibition power of organic drugs is increases by the substitution to a ruthenium atom implies (Sampath and Jayabalakrishnan, 2017).

The derivatives of thiosemicarbazones have attracted special interest because of their significant superior actions in various directions (Chowdhury et al., 2011). The thiosemicarbazones containing sulphur and nitrogen atoms which shown significant applications in the pharmacology, viz., antituberculous, also Anitha et al. (2013) point out antiviral infection, antimalarial as well as analgesic drugs. The integration of benzal thiosemicarbazone ligand with ruthenium atom may increase their properties and activities indicated by Khan and Asiri (2017). In this research work, we have synthesized bromobenzal thiosemicarbazone ligands and the ligand substituted ruthenium(II) complexes. All the compounds were characterized using various analytical and spectroscopic techniques. Further, the compounds were tested their anticancer using MCF-7 cell lines and antioxidant activities.



**Scheme 1.** Synthesis of thiosemicarbazone ligands where R = CH<sub>3</sub>/C<sub>6</sub>H<sub>5</sub>



**Scheme 2.** Synthesis scheme of the ruthenium(II) complexes, where E = P/As

## 2. EXPERIMENTAL

### 2.1 Materials and Methods

The chemicals or substances were used in this research are of AR grade. The ruthenium metal precursors were synthesized by the report given by Natarajan and Agarwala (1978); Sanchez-Delgado et al. (1991). IR spectra were recorded by means of KBr pellets between 400 and 4000 cm<sup>-1</sup> region in Perkin Elmer spectrophotometer. In DMSO solvent, electronic spectra were recorded using a Systronics UV-Vis spectrophotometer in between 200-800 nm. <sup>1</sup>H, <sup>13</sup>C and <sup>31</sup>P NMR spectra in DMSO-d<sub>6</sub> were recorded on a Bruker 500 MHz instrument using TMS and ortho phosphoric acid as references. Anticancer analysis were carried out at KMCH Pharmacy College. Melting points were recorded using Veego heating table and were uncorrected.

### 2.2 Synthesis of Thiosemicarbazone Ligands

A 20 mL methanol solution of respective thiosemicarbazide (0.01 mol) was added with stirring to a methanolic solution (20 mL) of 2-bromobenzaldehyde (0.01 mol). Then the mixture was refluxed for about 30 mins. A white colored precipitate was formed, filtered and the yield is 88 %. It is washed with methanol and recrystallized using methanol.

### 2.3 Synthesis of Ruthenium(II)thiosemicarbazone Complexes

A 20 mL methanol solution of respective thiosemicarbazone ligands (0.5 mmol) is mixed with 0.5

mmol, triethylamine and were added with stirring to ruthenium metal precursors (0.5 mmol) [RuHCl(CO)(EPh<sub>3</sub>)<sub>3</sub>], E = P/As, in 20 mL of benzene. The red colored reaction mixture was refluxed for about 8h. The resulted solution was cooled and the formed precipitate was filtered. The TLC was used to check the purity and recrystallized from the solvent mixture of CH<sub>2</sub>Cl<sub>2</sub>/n-Hexane.

### 2.4 Biological Properties

#### 2.4.1 *In Vitro* Anticancer Activity

Anticancer activity as *in vitro* conditions on MCF-7 i.e. breast cancer cells of human was tested by cell viability using the MTT assay method proposed by Mossman (1983). The cells were loaded onto 96-well plates and incubated at 35°C with 5 % CO<sub>2</sub>, 95 % air for about 24 h. After this, the test compounds in DMSO with 1 % fetal bovine serum medium at various concentrations were added. Triplicate run was carried out and the medium alone acts as a control. After 48 h, 15 μL in phosphate buffered saline of MTT was added to all the wells and incubated at 37°C for 4 h. The absorbance was measured at 570 nm and then IC<sub>50</sub> value was calculated.

#### 2.4.2 Antioxidant Activity

The antioxidant activity of the compounds against the DPPH radical was analyzed by the modified reported procedure exhibit by Elizabeth and Rao (1990). The experimental test solution concentration, 100 μL, was added to methanol solution of DPPH, 0.3 mM, 1 mL. The solution was made up to 4 mL and the methanol solvent used as a

**Table 1.** Physico-chemical analysis data of the ligands and complexes

Ligands and complexes	Color	M.P (°C)	Elemental analysis calculated (Found) %			
			C	H	N	S
HL <sup>1</sup>	White	170	39.72 (39.11)	3.70 (3.99)	15.44 (15.47)	11.78 (11.75)
HL <sup>2</sup>	White	180	50.31 (50.21)	3.62 (3.52)	12.57 (12.58)	9.59 (9.72)
[RuCl(CO)(PPh <sub>3</sub> ) <sub>2</sub> (L <sup>1</sup> )]	Yellow	215	55.85 (55.95)	4.06 (4.16)	4.34 (4.46)	3.31 (3.65)
[RuCl(CO)(AsPh <sub>3</sub> ) <sub>2</sub> (L <sup>1</sup> )]	Orange	223	51.20 (51.01)	3.72 (3.99)	3.98 (4.25)	3.04 (3.04)
[RuCl(CO)(PPh <sub>3</sub> ) <sub>2</sub> (L <sup>2</sup> )]	Yellow	248	58.32 (58.60)	4.01 (3.88)	4.08 (3.86)	3.11 (3.17)
[RuCl(CO)(AsPh <sub>3</sub> ) <sub>2</sub> (L <sup>2</sup> )]	Red	236	53.73 (53.35)	3.70 (3.80)	3.76 (3.99)	2.87 (2.74)

**Table 2.** FT-IR (cm<sup>-1</sup>) and electronic (nm) spectral data of the ligands and complexes

Ligands and complexes	$\nu(\text{C}=\text{N})$	$\nu(\text{C}=\text{S})$	$\nu(\text{C}-\text{S})$	$\nu(\text{C}\equiv\text{O})$	$\nu(\text{Ru}-\text{N})$	UV-Vis, $\lambda_{\text{max}}$
HL <sup>1</sup>	1592	881	-	-	-	302, 358
HL <sup>2</sup>	1594	859	-	-	-	304, 361
[RuCl(CO)(PPh <sub>3</sub> ) <sub>2</sub> (L <sup>1</sup> )]	1557	-	743	1902	519	307, 369, 406
[RuCl(CO)(AsPh <sub>3</sub> ) <sub>2</sub> (L <sup>1</sup> )]	1559	-	735	1927	589	306, 365, 405
[RuCl(CO)(PPh <sub>3</sub> ) <sub>2</sub> (L <sup>2</sup> )]	1522	-	753	1917	541	315, 362, 410
[RuCl(CO)(AsPh <sub>3</sub> ) <sub>2</sub> (L <sup>2</sup> )]	1522	-	736	1911	539	312, 366, 407

blank with DPPH in methanol as positive control. The absorbance of DPPH solution with test compounds (20-100  $\mu\text{g}/\text{mL}$ ) run in triplicate which was measured at 517 nm. The IC<sub>50</sub> value can be calculated using the percentage of activity.

### 3. RESULTS AND DISCUSSION

All the complexes are stable in air and soluble in most common solvents. The micro analyses (C, H, N&S) of the ligand and the ruthenium(II) bromobenzal thiosemicarbazone complexes, Ru(II)BT, are shown in Table 1 which are agree well with proposed molecular formula.

#### 3.1 Infrared Spectra

The FT-IR spectra of Ru(II)BT have shown some changes in comparison with bromobenzal thiosemicarbazones, which shows the coordination of bromobenzal ligand to ruthenium. The significant spectral bands were tabulated in Table 2. A strong sharp band for azomethine C = N stretching frequency shown at 1592-1594 cm<sup>-1</sup> for bromobenzal ligands. According to Selvamurugan et al. (2017), this was lowered at 1522-1559 cm<sup>-1</sup> in the Ru(II)BT indicates the coordination of ligand centered C = N nitrogen to ruthenium. A band at 881-859 cm<sup>-1</sup> is confirmed by the existence C = S group. Sampath et al. (2013) proposed disappearance of this band and new band of C-S is appeared at 735-753 cm<sup>-1</sup> confirms the next coordination mode is thiolateS. In all the Ru(II)BT, the medium intensity bands at 519-589 cm<sup>-1</sup> and 1902-1927 cm<sup>-1</sup> were attributed to Ru-N

and terminal carbonyl group respectively. Overall, the bromobenzal thiosemicarbazones coordinated to Ru(II)BT via NS coordination.

#### 3.2 Electronic Spectra

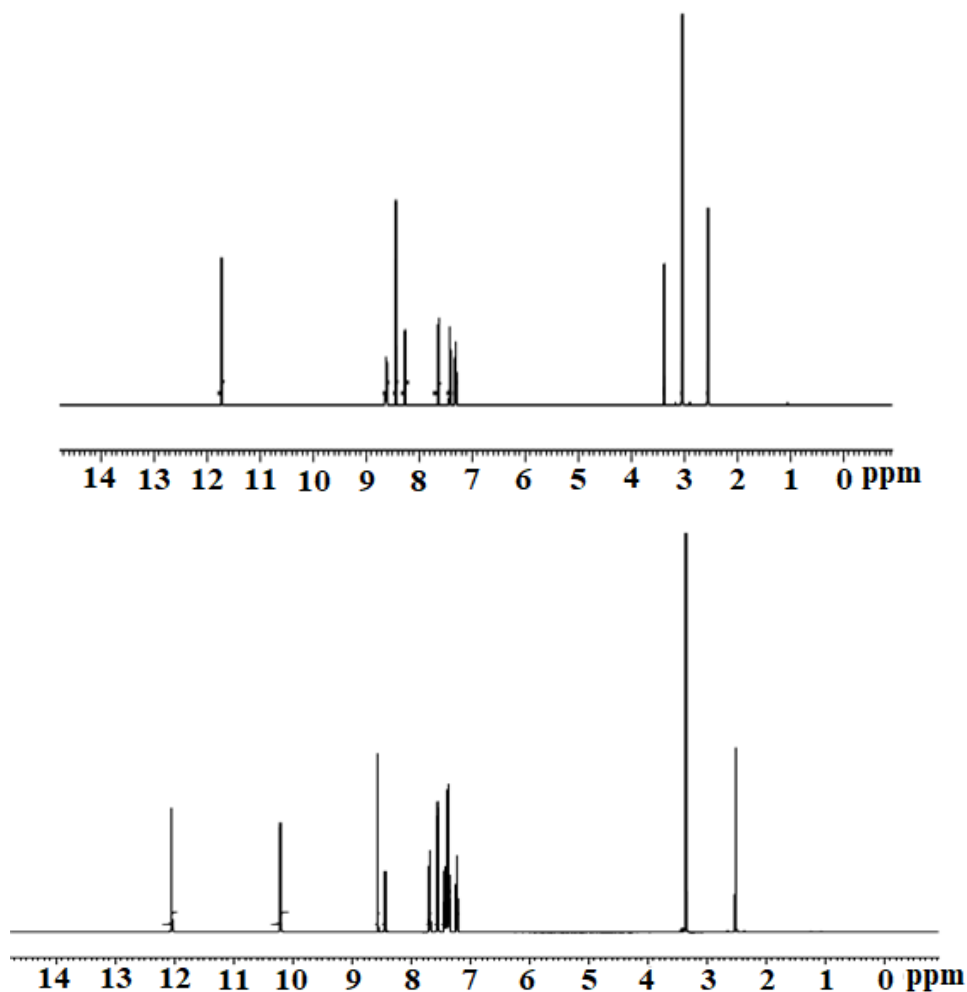
The absorption spectrum of all the bromobenzal thiosemicarbazones and Ru(II)BT complexes in DMSO solvent is tabulated (Table 2). The bromobenzal thiosemicarbazone ligands showed two ligand centric bands in the range 302- 410 nm regions associated with  $\pi \rightarrow \pi^*$  and  $n \rightarrow \pi^*$  transitions. In Ru(II)BT, the ligand bands were shifted at 306-369 nm, indicates the involvement of the bromobenzal thiosemicarbazone ligand in coordination to ruthenium proven by White et al. (2017). Rodrigues et al. (2008) suggested new bands appeared at 405-410 nm due to charge transfer transitions of molecular orbital from the ruthenium to bromobenzal thiosemicarbazones. The pattern of the electronic spectra obtained indicates the octahedral environment around the Ru(II) and these patterns are similar to the other Ru(II) complexes manifest by Nagaraju and Pal (2014); Manikandan et al. (2015).

#### 3.3 NMR Spectra

The NMR spectra for bromobenzal thiosemicarbazone ligands and Ru(II)BT were recorded and the chemical shift values are shown (Table 3, Fig. 1 and Fig. 2) to confirm the mode of coordination of bromobenzal thiosemicarbazones to ruthenium. The proton NMR spectrum of the bromobenzal thiosemicarbazones showed a singlet for the presence of NH proton of hydrazine moiety in the region  $\delta$  8.62-10.21. It is absent in the spectra of Ru(II)BT indicates the enolization of hydrazine NH moiety and deprotonation.

**Table 3.** <sup>1</sup>H NMR data of the ligands and complexes

Ligands and complexes	<sup>1</sup> H NMR data, δ				
	HC = N	Hydrazine NH	Terminal NH	Aromatic	CH <sub>3</sub>
HL <sup>1</sup>	11.72	8.62	8.43	7.29-8.28	3.01
HL <sup>2</sup>	12.04	10.21	8.56	7.21-8.45	-
[RuCl(CO)(PPh <sub>3</sub> ) <sub>2</sub> (L <sup>1</sup> )]	11.84	-	8.46	7.11-7.93	3.14
[RuCl(CO)(AsPh <sub>3</sub> ) <sub>2</sub> (L <sup>1</sup> )]	11.87	-	8.47	7.00-8.01	3.15
[RuCl(CO)(PPh <sub>3</sub> ) <sub>2</sub> (L <sup>2</sup> )]	12.10	-	8.61	6.80-7.95	-
[RuCl(CO)(AsPh <sub>3</sub> ) <sub>2</sub> (L <sup>2</sup> )]	12.19	-	8.64	6.85-7.92	-



**Fig. 1.** <sup>1</sup>H NMR spectra of the ligands (top: HL<sup>1</sup>, bottom: HL<sup>2</sup>)

Hence, the coordination is through thiolate sulphur reveal by Mir et al. (2019).

A peak observed at δ 11.72-12.04 due to the -CH = N proton which is downfield in the Ru(II)BT at δ 11.84-12.19, supports the -C = N group in coordination as suggested by Mishra et al. (2005). The bromobenzal thiosemicarbazone ligands and Ru(II)BT showed a multiplets in the region of

δ 6.80-8.45 for the aromatic protons which is due to the electron delocalization in the compounds and these signals cannot be differentiated with the aromatic signals of PPh<sub>3</sub>/AsPh<sub>3</sub> because of their extensive electron density overlap designated by Sampath et al. (2013). The bromobenzal thiosemicarbazone and its Ru(II)BT showed a chemical shift for CH<sub>3</sub> group at δ 3.01-3.15 for its methyl proton.

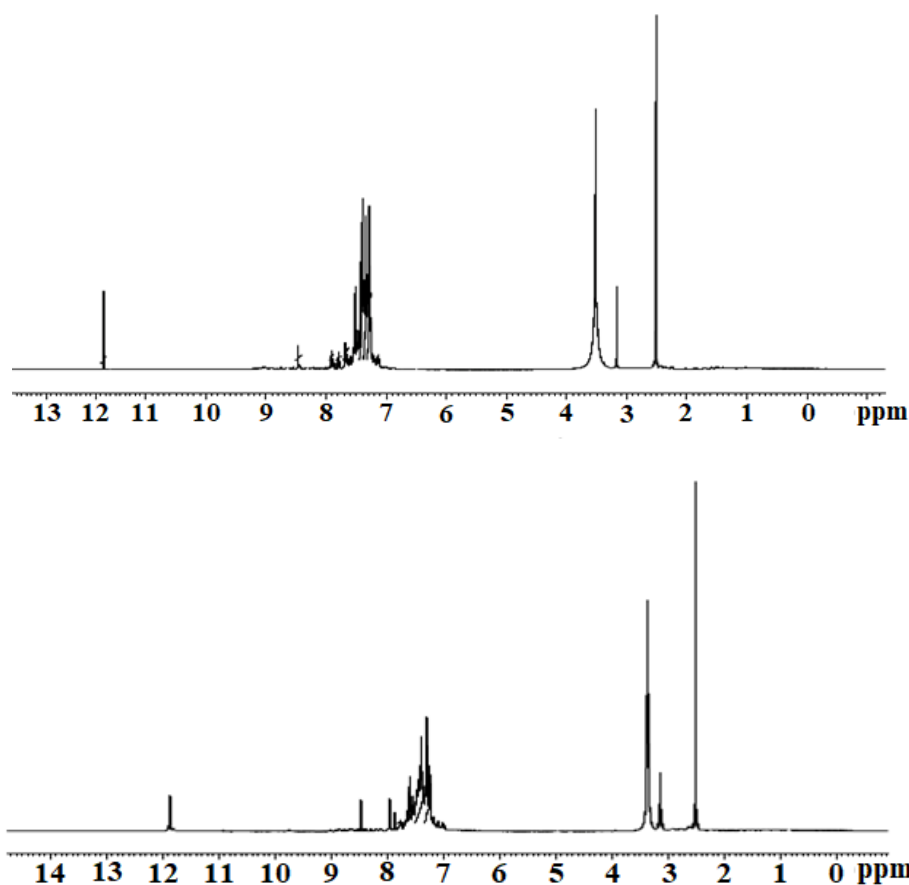


Fig. 2.  $^1\text{H}$  NMR spectra of the complexes (top:  $[\text{RuCl}(\text{CO})(\text{PPh}_3)_2(\text{L}^1)]$ , bottom:  $[\text{RuCl}(\text{CO})(\text{AsPh}_3)_2(\text{L}^1)]$ )

Table 4.  $^{13}\text{C}$  and  $^{31}\text{P}$  NMR data of the ligands and ruthenium (II) thiosemicarbazone complexes

Ligands and complexes	$^{13}\text{C}$ NMR data, $\delta$						$^{31}\text{P}$ NMR data, $\delta$ PPh <sub>3</sub>
	C = N imine	C = S	C - S	Aromatic Carbon	CH <sub>3</sub>	C $\equiv$ O	
HL <sup>1</sup>	178	140	-	123-133	31	-	-
HL <sup>2</sup>	176	141	-	124-139	-	-	-
$[\text{RuCl}(\text{CO})(\text{PPh}_3)_2(\text{L}^1)]$	185	-	136	128-132	32	194	36.21
$[\text{RuCl}(\text{CO})(\text{AsPh}_3)_2(\text{L}^1)]$	186	-	134	128-133	33	196	-
$[\text{RuCl}(\text{CO})(\text{PPh}_3)_2(\text{L}^2)]$	183	-	135	123-133	-	197	36.46
$[\text{RuCl}(\text{CO})(\text{AsPh}_3)_2(\text{L}^2)]$	182	-	133	123-131	-	192	-

The  $^{13}\text{C}$  NMR spectral data of the bromobenzal thiosemicarbazones and the Ru(II)BT were given in Table 4. The thioamide carbon (C = S) signal observed for the bromobenzal thiosemicarbazone ligands at  $\delta$  140-141, which disappears in the Ru(II)BT spectra and appearance of (C - S) signal showed at  $\delta$  133-136 suggests the deprotonation of sulphur were shown. Therefore ruthenium is coordinated with sulphur as proposed by White et al. (2017).

The azomethine carbon signal of the bromobenzal thiosemicarbazone ligands showed at  $\delta$  176-178 which shifts to downfield in Ru(II)BT at  $\delta$  182-186 indicates by Thota et al. (2015), that the coordination of azomethine group to ruthenium. In all the bromobenzal

thiosemicarbazone ligands and its Ru(II)BT show the aromatic signal in the region  $\delta$  123-139. The peak for CH<sub>3</sub>, and terminal C  $\equiv$  O, carbon is observed at  $\delta$  31-33 and  $\delta$  192-197 respectively shown by Manikandan et al. (2015).

The presence of PPh<sub>3</sub> group was confirmed by  $^{31}\text{P}$  NMR. This NMR were recorded only to Ru(II)BT containing PPh<sub>3</sub> (given in Table 4). At  $\delta$  36, a singlet peak was observed because of the magnetically equivalent PPh<sub>3</sub> groups. The two PPh<sub>3</sub> groups in Ru(II)BT are trans to each other which are in accordance to Sampath et al. (2013).

### 3.4 Biological Studies

### 3.4.1 *In Vitro* Anticancer Evaluation

The anticancer activity of the bromobenzal thiosemicarbazones and their Ru(II)BT were evaluated on MCF-7 cell line by MTT assay. The results were shown by IC<sub>50</sub> value and the compounds concentration in the range from 0.1 to 100 μM and are shown in Table 5. The cell viability curve with respect to the ligands and complexes were shown in Fig. 3. The results reveal that, when the concentration of compounds increases, it shows significant activity against the cancer cells. As noted by Thota et al. (2016) that, the Ru(II)BT showed higher activity than the respective bromobenzal thiosemicarbazone ligands which confirms the coordination of these thiosemicarbazones to ruthenium atom is the only reason for their observed significant cytotoxic activity. Compare to triphenylarsine complexes, triphenylphosphine complexes have shown better results due to the lipophilic nature of triphenylphosphine. Among the Ru(II)BT studied, the Ru(II)BT with methyl thiosemicarbazone have shown higher activity than the Ru(II)BT with phenyl thiosemicarbazone ligands. Though, the Ru(II)BT complexes have shown significant activity but it does not reach to the standard, cisplatin (Krishnamorthy et al. 2011).

### 3.4.2 Antioxidant Studies

From the anticancer studies, it reveals the significance of Ru(II)BT in the development of potent anticancer drugs, it is valuable to analyze the scavenging activity of antioxidants by bromobenzal ligands and the complexes (Table 5). Bal-Demirci et al. (2020) mentioned antioxidants which exhibits considerable radical scavenging activity receives great attention because they present significant anti-inflammatory and antiaging activities. The activity of the Ru(II)BT was found to be higher than that of bromobenzal thiosemicarbazone ligands. The complexes containing methyl thiosemicarbazones ligands showed higher activity than the complexes containing phenyl group. Among these methyl thiosemicarbazone substituted complexes, the complexes containing PPh<sub>3</sub> as co-ligands showed higher activity than AsPh<sub>3</sub> complexes.

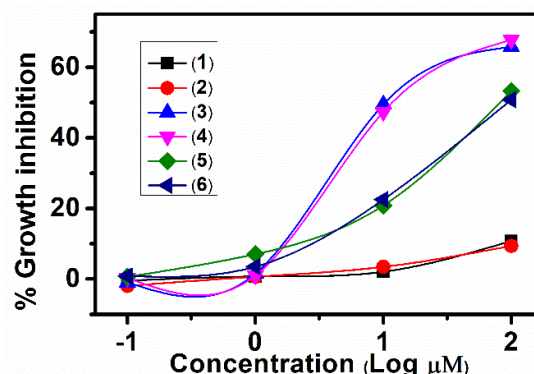


Fig. 3. Cell viability curve of the ligands and complexes

## 4. CONCLUSION

The research work focuses on the synthesis and various characterization of bromobenzal thiosemicarbazone ligands and Ru(II)BT with PPh<sub>3</sub>/AsPh<sub>3</sub> as co-ligands. The bromobenzal thiosemicarbazone ligands and its Ru(II)BT characterized by analytical and spectroscopic techniques. An octahedral geometry has been tentatively proposed for all the complexes. The synthesized ligands and complexes were analyzed against tumor cells and antioxidants by *in vitro*. The anticancer and antioxidant activity reveals that the complex containing methyl thiosemicarbazone ligands along with PPh<sub>3</sub> as co-ligands showed higher activity than the other complexes and the free bromobenzal thiosemicarbazone ligands.

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Table 5. *In vitro* anticancer and antioxidant activity of the ligands and complexes

Ligands and Complexes	IC <sub>50</sub> value	
	MCF-7 Cancer cell line	DPPH radicals
HL <sup>1</sup> (1)	>100	118
HL <sup>2</sup> (2)	>100	137
[RuCl(CO)(PPh <sub>3</sub> ) <sub>2</sub> (L <sup>1</sup> )] (3)	57.45	54
[RuCl(CO)(AsPh <sub>3</sub> ) <sub>2</sub> (L <sup>1</sup> )] (4)	58.04	63
[RuCl(CO)(PPh <sub>3</sub> ) <sub>2</sub> (L <sup>2</sup> )] (5)	81.56	75
[RuCl(CO)(AsPh <sub>3</sub> ) <sub>2</sub> (L <sup>2</sup> )] (6)	98.82	81



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