Research Article

Preparation and characterization of Ruthenium(III), Iron(III), Chromium(III) Tetrachloride, 1,10- phenanthrolinium salts [PhenHMCl$_4$]; M=Ru(III), Fe(III), Cr(III): Contribution to the study of the mechanism of action of the gold therapeutic complexes

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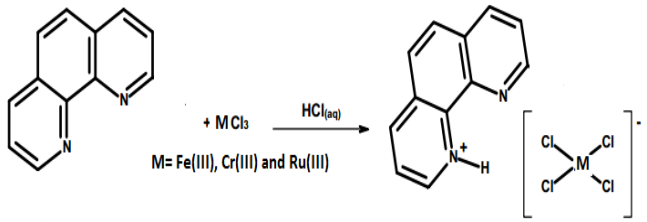
Abstract

Ruthenium III, Chromium III, and Iron III tetrachloride 1,10-phenanthrolinium salts [phenHMCl$_4$] M=Ru(III), Fe(III), Cr(III) are synthesized by direct reaction with 1,10-phenanthroline in HCl, or 1,10-phenanthrolinium chloride with trivalent metal chloride at room temperature**.** In order to characterize 1,10-phenanthroline, 1,10phenanthrolinium chloride and 1,10-phenanthrolinium salts by infrared, ^{1}H ; ^{13}C NMR, DEPT, UV-Visible and molar conductivity, suggest that 1,10-phenanthroline is protonated by one nitrogen atom and form 1,10-phenanthrolinium metal tetrachloride salts with the type of electrolyte 1:1.



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Introduction

Cisplatin is an anticancer agent used [1], for the treatment of testicular, ovarian, head, neck and germ cell tumors. However, the optimal use of this drug is limited due to its dose limiting nephrotoxicity. The new platinum compounds likes carboplatin and oxaliplatin are found to possess comparatively very arrow therapeutic index, and also it has limited clinical utility due to drug resistance and side effects. Hence it is necessary to look for more effective and less toxic than other metal-based anticancer agents.

In an effort to discover potential alternatives to the anticancer drug cis-platinum(II) the synthesis of gold(III) [2, 9] disubstituted phenanthroline complexes (1,10-phen)AuCl$_3$ was pursued, phenanthroline complexes with metals other then gold(III) exhibit cytotoxic proprieties and a range of phenanthroline complexes are significantly more active anti-cancer drugs then cisplatinium against selected cancer lines through inhibition of DNA synthesis, both intercalatrively and non-intercalatively.

The phenanthroline bipyridine are important ligands which form stable complexes to formula (MLn X$_2$), n= 1, 2, 3 ; L= phenanthroline or bipyridine; X=Cl, With transition metal ions. In recent years, considerable attention has been paid to studying the phenanthroline complexes through their role in catalysis, antitumor activities, solar energy and nanotechnology [2-4].

It has recently been found that gold drugs can have a different mechanism leading to cytotoxity in cancer cells with DNA binding. Cis-platinium [1, 5] typically binds to the DNA, which inhibits DNA repair, where as DNA binding of (1,10-phen)AuCl$_3$ complexes have been found to be variable and less frequent. In an effort to help assess the mechanism by which these ligands may cause tumor cell death, iron binding and removal experiments have been considered. The close linkage between all proliferation and intracellular iron concentrations suggest that iron deprivation strategies [6-8]. May be a mechanism involved in inhibiting tumor cell growth. Therefore, iron(III) complexes possessing (1,10-phen) [9,10]. The proton and/or metal occupies one the dominant positions in inorganic

and bioinorganic chemistry playing an important role in ubiquitous proton and/or metal transfer reactions in coordination in charge and mass transport processes in membranes, in intracellular, in catalysis and biocatalysts. Protonation reactions of 1,10-phenanthroline in aqueous solutions have been studied, and it has reported that $phenH^+$ were formed in pH =2-7. The solubility of the neutral species is low in water, but remarkably increases in inorganic solvents and also in aqueous organic mixtures [11].

[1,10-phen.HX.H_2O] X=Cl^-,Br^- is isostructural crystallizes in the monoclinic system, space group $P_{2.1}$/b, the crystal structure analysis of compounds [1,10-phen.HX.H_2O]X=Cl^-,Br^- indicate that is stable to bind proton and form protonated cation, which is stable by hydrogen bond interactions by OH---X and N-H---O in the solid state [12, 13]. Other studies demonstrate that coordination phenanthroline complexes is obtained by reacting of 1,10-phenanthroline and iron(III) chloride in equimolar quantities in methanol or by refluxing $[FeCl_4]^-$ $[RphenH]^+$ in DMSO solvent it's noted a similar protocol [10] for synthesis of $[FeCl_4]$ [phenH]. We obtained a minor product where the phenanthroline was chelating to the iron III metal center.

Experimental

Materials and Reagents

All the chemicals used were of E. Merck, DMF or Fluka $FeCl_3,6H_2O$; $CrCl_3,6H_2O$ $RuCl_3,3H_2O$, 1,10-phenanthroline, HCl 10M.

The molar conductance values of the metal salts in DMSO (10^{-3} M solution) were measured at room temperature. Conductivity measurements were performed at 25 °C in DMSO using Hach HQ 430d flex. The infrared spectra were recorded on Shimadzu 470, UV-Visible spectra were measured in DMSO using Shimadzu UV-1800.^1H ; ^{13}C NMR were recorded on Bucker 300MHz in D_2O at room temperature.

General procedure for synthesis

The phenanthrolinium salts were obtained by reaction of the 1,10-phenanthroline with $FeCl_3,6H_2O$, $CrCl_3,6H_2O$ and $RuCl_3,3H_2O$, in the presence of 10M aqueous hydrochloric acid in hot aqueous solution in 1/1/1molar ratio, or the 1,10-phenanthroline in HCl,10M and trivalent metal chloride in equimolar ratio1/1/1.The some salts were filtered, washed with water, alcohol and finally with ether and dried in vacuum.

Results and Discussion

The molar conductance of these salts M=Fe(III),Cr(III),Ru(III), values is 70, 78 and 86 $\Omega^{-1}cm^2mol^{-1}$ respectively which indicates the ionic nature of the complexes and the type of electrolyte being 1 : 1. [14]

Infrared spectra

Infrared spectra data of 1,10-phenanthroline, 1,10-phenanthrolinium chloride and 1,10-phenanthrolinium metal salts (phenHMCl_4), M= Ru(III), Cr(III), Fe(III) was obtained from Shimadzu 470 in KBr, in the range (4000-400)cm^{-1}. The infrared spectrum of the 1,10-phenanthroline free was compared with that of 1,10-phenanthrolinium chloride, 1,10-phenanthrolinium metal salts. The 1,10-phenanthroline free is C_{2v} symmetry point group [16]. The 1,10-phenanthrolinium chloride molecule, where the infrared characteristics are explained by the Cs symmetry. The molecule is absently flat with a deviation from planarity less than 1,10-phenanthroline. The infrared data for the compounds, are summarized in **Table 1**.

A broad band at (3465-3450) cm^{-1} may be assigned to υOH stretching vibration of water molecule upon protonation of 1,10-phenanthroline leads to the appearance of the new broad band at (3360-3300) cm^{-1} corresponding to the NH stretching vibration of the protonated nitrogen. The 1,10-phenanthrolinium chloride participate in interaction of NH----OH type, where the water hydrate molecule form weak hydrogen bonds in the region (2100-1900) cm^{-1}. Shifting of bands in the region (1640-1300) cm^{-1} of free (1,10-phen) is observed in the spectra. Undergo shifting to lower frequencies indicate the protonation of the 1,10-phenanthroline.

Shifting of bands in the region (1600-1300) cm^{-1} is observed in the spectra of the salts [1,10-phen $HMCl_4$] H_2O; M= Ru(III), Cr(III), Fe(III). The three relatively strong bands in the range of (1620-1585) cm^{-1} (**Figure 1** and **2**)

appeared and assigned as δNH, υC=C stretching. These bands were combined with the bending vibration of the conjugated system.

Table 1 vibrations of the salts [MCl_4][phenH]; M=Cr(III), Fe(III), Ru(III) in KBr

Phen,H_2O	**phenHFeCl_4**	**PhenHCrCl_4**	**phenHRuCl_4**	**Assignment**
3456 m	3456 m	3450 m	3450 m	υ OH (H_2O)
	3360	3350-3320	3300 m	υ NH
3058 br	3056 w	3055 m	3045 w	υ CH
1640m	1648m	1650m	1640m	δ OH (H_2O)
1616m	1620m	1618s	1620s	δ NH
1586m	1594m	1595vs	1600e	υ C=C
1560m	1540m	1542s	1530m	υ C=C
1502s	1480m	1470w	1480w	υ C=C
	1453w	1450m	1456m	δ CH
1425s	1424s	1424s	1420m	δ CH
1400w	1370w	1370w	1376w	δ CH
1346m	1338m	1340w	1340w	δ CH
	1226m			
1218w	1210w	1190w	1170w	δ CH
1137m	1149	1140w	1140w	δ CH
1035	1110m	1040w	1038w	δ CH
988m	950w			δ CH
854 vs	845vs	850vs	850m	δ CH
780m	770m	780m	800 w	δ CH
740vs	726 vs	720s	718m	δ CH
724 m	726vs	720s	718m	δ CH
710m	643w	650w	660w	δ CH
695m				
625m	620w	620w	620w	δ (CCC)
610	557w	556w	560w	δ (CCC)
	525w	535w	540w	δ (CNC)
	500w	535w	510w	δ (CNC)
	480w	480 w	490w 480w	γ(CCC)
	464w	460w	460w	γ(CCC)
	444w	442w	445w 430w	γ(CCC)
	413m	410w	410w	γ(CCC)

A comparison with the spectral data of 1,10-phenanthroline free, indicates that the band at the (1620-1618) cm^{-1} (figure 2) is attributed to the δNH bending and two bands at the (1600-1530) cm^{-1} range corresponding of the υC=C, are shifted to lower frequencies which indicate the involvement of both one of the nitrogen atoms to protonation [16].

The bands at 854 cm^{-1}, 740 cm^{-1} and 625 cm^{-1} attributed to out of plane hydrogen bending modes of the free 1,10 phenanthroline were shifted to the (850-845) cm^{-1}, (726-718) cm^{-1} regions and at 620 cm^{-1} for phenanthrolinium metal complexes [1,10 phenHMCl_4] H_2O; M= Fe(III), Cr(III), Ru(III) (Table 1). The change in the intensity of the peak at 780 cm^{-1} is observed in all complexes and it is shifted to the lower frequency at 760 cm^{-1} [16].

More information about the low frequency part in the spectra of the neutral 1,10-phenanthroline and phenanthrolinium salts in the (600-400) cm^{-1} range corresponds to in plane and out of plane of CH deformation vibrations [17] (Table 1). All these bands are very weak in the spectra of 1,10-phenanthroline monohydrate and phenanthrolinum metal chloride. The changes of the relative intensities of the bands of the out-of-plane δ(CNC) introduced by the strong interaction of the phenanthrolinium with the tetragonal species MCl_4 M = Fe(III), Cr(III), Ru(III).

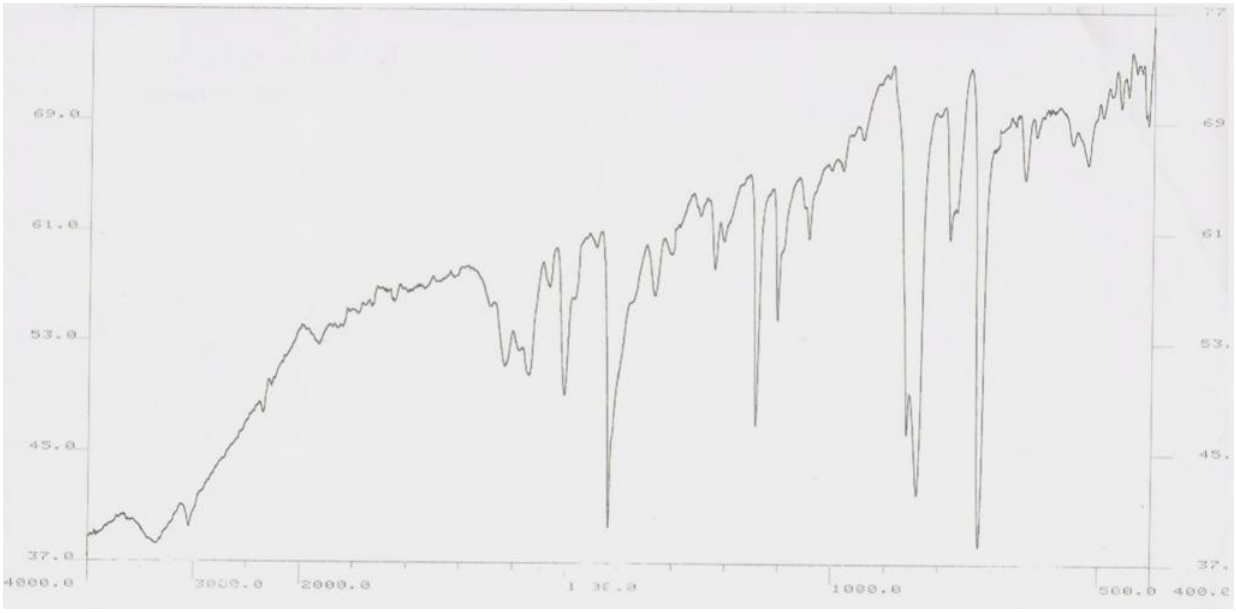

Figure 1 Infrared spectrum of the salt $[FeCl_4][PhenH]$ in KBr

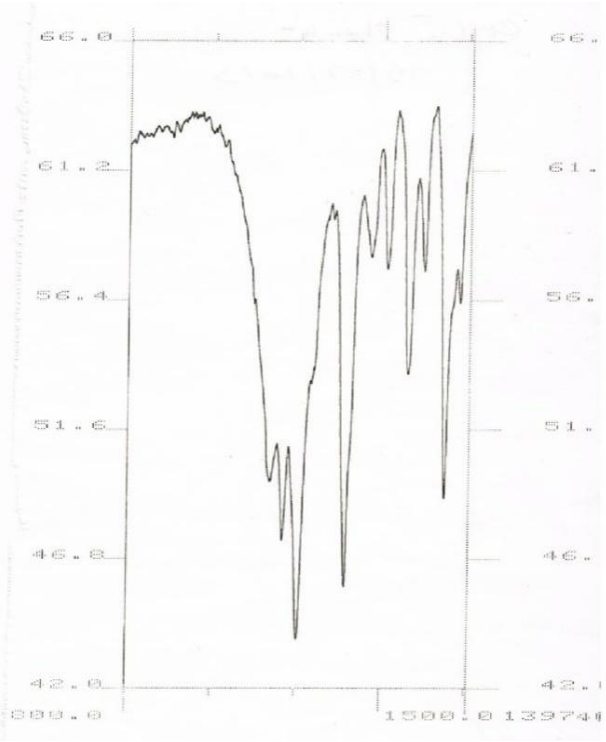

Figure 2 Infrared spectrum of the salt $[CrCl_4][PhenH]$ in KBr

NMR spectra

The ^1H NMR spectrum (300 MHz, D_2O) of phenanthrolinium iron tetrachloride showed new signal at 4,72 ppm (S,1H, NH^+) which was confirmed by comparison with δNH^+ (4,69 ppm) of the phenanthrolinium chloride in D_2O. The ^1H NMR spectrum of 1,10-phenanthroline in deuterated acetone showed eight doublets around the (9,14-9,71) ppm range with typical C_{2v} symmetry for the molecule.

These signals of proton Hd split into a doublet, in accordance with Cs symmetry (**Figure 3**). In comparison with the proton signal of the salts, the chemical shift differences are less than (0,07-0,45) ppm. These data are in accordance with dept spectral data of the salt (**Table 2**).

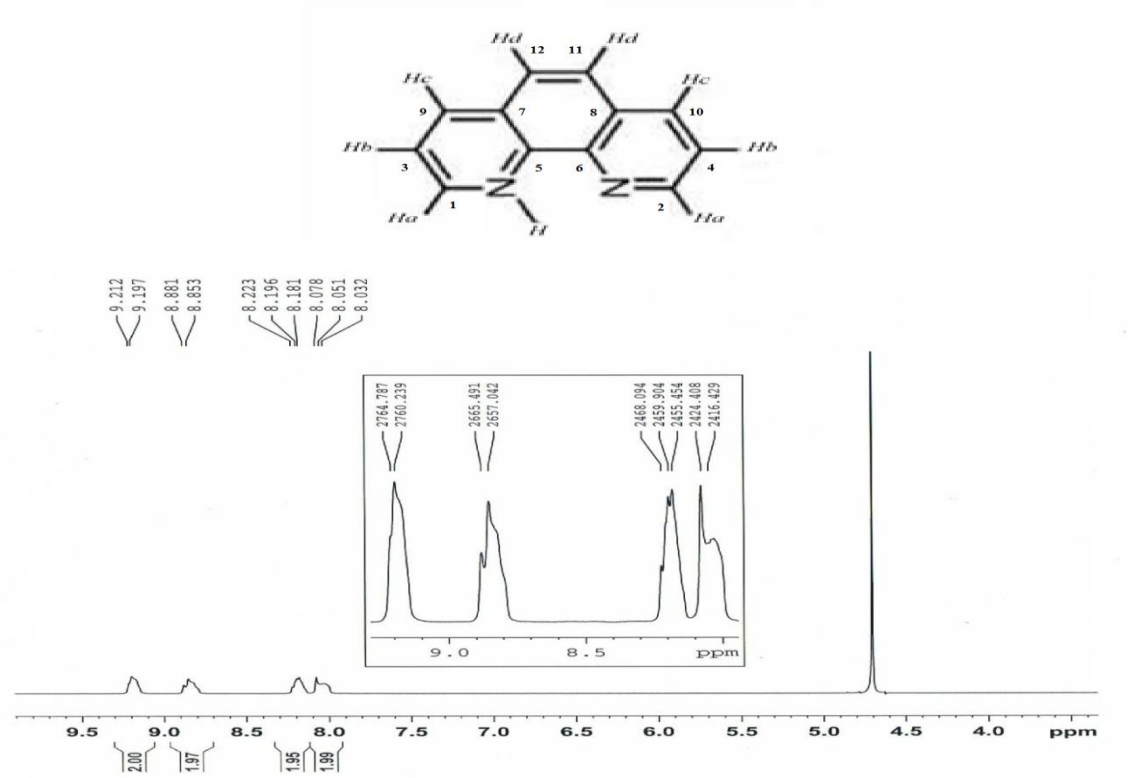

Figure 3 [1]HNMR spectrum of the salt $[FeCl_4][PhenH]$ in DMSO

Table 2 [1]H, [13]C Data of 1,10- phenanthroline and salt $[FeCl_4][PhenH]$ in DMSO

	Ha	**Hb**	**Hc**		**Hd**		**Hd**	**NH^+**	
1,10phen	9,14	9,125	8,45	8,42	7,75	7,74	7,73	7,71	
1,10phenHFeCl$_4$	9,21	9,20	8,88	8,85	8,2		8,1		4,72
	$C_{1,2}$	**$C_{3,4}$**	**C_{56}**	**$C_{7,8}$**	**$C_{9,10}$**	**$C_{11,12}$**			
1,10phen	149,9	146,4	136	128,8	126,7	123,1			
1,10phenHFeCl$_4$	147,1	142,15	136,7	129,6	127,5	125,7			

In the [13]C NMR spectrum of phenanthrolinium iron tetrachloride (**Figure 4**), six signals are clustered around the (125-147) ppm and (123-149) ppm regions for 1,10 phenanthrolinium salts and 1,10-phenanthrolinium chloride respectively, with typical downfield shifts for carbons according to their positions and proximity to the electronegative nitrogen atoms, carbon nuclei ortho and para to the electronegative nitrogen being more deshielded [16]. Dept spectrum of phenanthrolinium iron tetrachloride has further supported the proposal indicating the exact position of the carbon chains.

Electronic Spectra

The UV-Visible spectra of the 1,10-phenanthroline, 1,10-phenanthrolinium chloride, and phenanthrolinium salts have been recorded in the (200-600) nm range. Upon protonation, the absorption bands attributed to $\pi - \pi^*$ transitions were found to be shifted to higher energy regions compared to free 1,10-phenanthroline, in addition to apparance of new bands at longer wavelength (310-354) nm range may be assigned to charge transfer transitions (**Figure 5**), (**Table 3**). The similarity betwen UV-Visible absorption spectra iron(III) and gold(III) possessing protonated disubstitued methyl, sec butyl 1,10-phenanthrolinium was observed [5,14]. This generally confirms that the phenanthrolinium interacts with tetra chloride metal ion charge cotranfert.

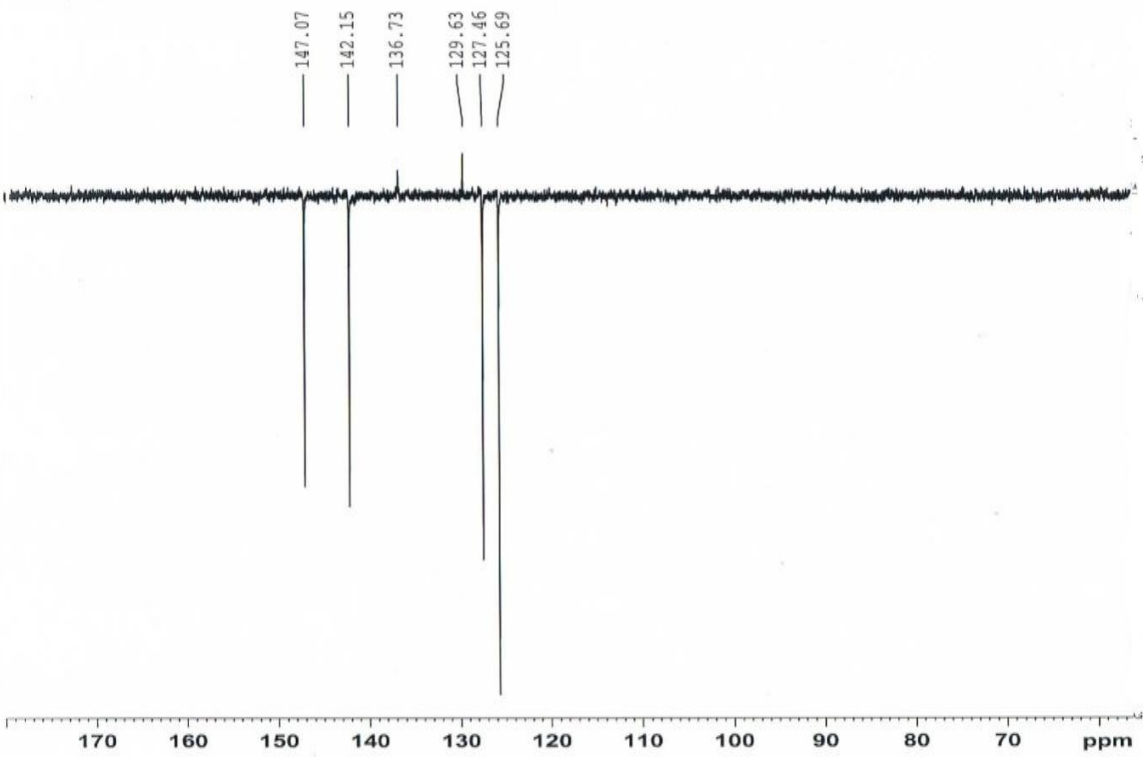

Figure 4 ^{13}C NMR spectrum of salt $[FeCl_4][PhenH]$ in DMSO.

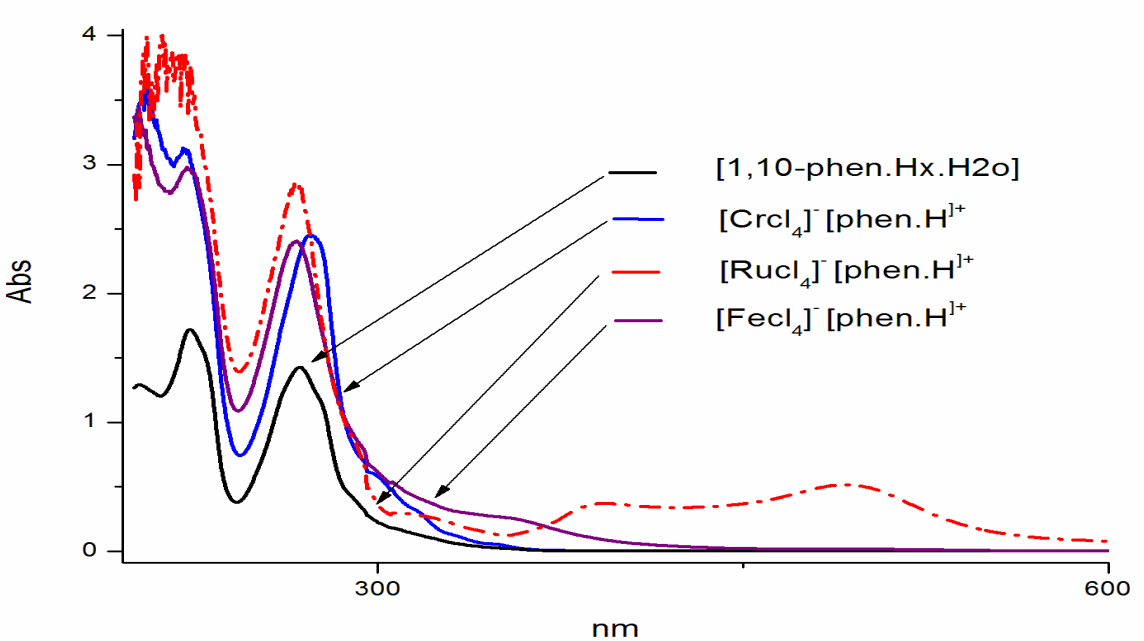

Figure 5 Electronic spectrum of the salts$[MCl_4][PhenH]$ M= Cr(III),Fe(III),Ru(III) and free ligand in DMSO

Conclusion

Three phenanthrolinium salts [phen $HMCl_4$] M=Ru(III), Fe(III), Cr(III) were synthesized and characterized by molar conductivity, infrared, ^1H ; ^{13}C NMR, DEPT and UV-Visible. According to all as the prepared salts, we can suggest that the phenanthrolinium cation and the metal tetrachloride anion are bonded by strong interaction hydrogen N…H…Cl and N…H…N. Finally, the cytotoxicity of the 1,10-phenanthroline was prevented by phenanthrolinium salt formation and stability of $[FeCl_4][phenH]$.

Table 3 UV-Visible data of the salts [MCl_4][PhenH] where M= Cr(III),Fe(III), Ru(III) in DMSO

Compound	λmax (nm)	Assignment
1,10-phenanthroline	223	π→π*
	266	π→π*
	291	π→π*
[$FeCl_4$][PhenH]	223	π→π*
	266	π→π*
	296	π→π*
	356	M→L
	524	
[$CrCl_4$][PhenH]	221	π→π*
	273	π→π*
	295	π→π*
	318	M→L
	350	M→L
	450	
[$RuCl_4$][PhenH]	224	π→π*
	266	π→π*
	294	π→π*
	313	M→L
	354	M→L
	480	

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