Ultra Chemistry Vol. 9(2), 279-286 (2013).

Synthesis and Biological Screening of Some Mixed-Ligand Phosphine and Arsine Complexes of Ruthenium(III) Ligated by Heterocyclic Thioamide

R.N. PANDEY*, PRAMILA SHARMA[a] and MANOJ KUMAR[b](II)

*P.G. Centre of Chemistry (M.U.),
College of Commerce, Patna- 800020 (INDIA)
email : rameshwarnath.pandey@yahoo.com
[a]Department of Chemistry,
Ganga Devi Mahila Mahavidyalaya, Patna- 800020 (INDIA)
email : reachpramilaji@gmail.com
[b]Department of Biotechnology
College of Commerce, Patna- 20 (INDIA)

(Acceptance Date 20th August, 2013)

Abstract

The synthesis, characterization and biological screening of six coordinated ruthenium(III) chelates of the type $[RuClL_2E\phi_3]$ (E = P/As; L = monobasic bidentate 1-substituted tetrazoline-5-thione anion) are reported. Antifungal activity of ligands and complexes against A. Flavus, A. Parasiticus and C. Albicans using Carbendazin as standard and antibacterial activity against S. Aureus, B. Subtilis and E. Coli are examined. All complexes are characterized using various physico-chemical, IR, electronic and 'H NMR Spectral data.

Key words : Heterocyclic thioamide, ruthenium (III) chelates, bio-activities.

Introduction

The relationship between structural and biological properties of metal complexes with thioamide ligands has been reviewed by West *et al.*[1]. Several ruthenium complexes are reported to be potential medicinal properties[2-3], activity against viruses, tumours, fungi[4-5] and anti-bacterial activity[6-7]. In continuation of our previous efforts[8-10] aiming to locate thioamides exhibiting antimicrobial agent(s) with enhanced potency, the present work is under taken. The tetrazoline ring having thioamide group was selected and substituted at various location in phenyl ring with methyl, methoxy & chloro groups to correlate the electronic effect of such substituents on the magnitude of the antimicrobial activity and antifungal activity. The evaluation

of anti microbial activity against E. Coli, S. Enteritidis, S. Aureus and S. Epidermitis and antifungal activity against A. Niger, A. Flavus and C. Albicans with synthesized ruthenium complexes are reported.

Experimental

All the chemicals used were of AR or CP-grade. The 1-substituted tetrazoline-5-thione[11] and percursor complexes $[RuCl_3(E\phi_3)_3]$[12-13] (X = Cl, E = P/As) were prepared by the method reported in literature and $RuCl_3.xH_2O$, $P\phi_3$, $As\phi_3$, CS_2 and NaN_3 were commercial products. All complexes were prepared using our previous methods[14].

Analysis :

Sl. No. 1 :

[RuCl(O-CH_3-L)$_2$($P\phi_3$)]: Calculated (%) for **$RuClC_{34}H_{29}N_8S_2P$:** C = 52.26; H = 3.71; N = 14.34; Cl = 4.54; Ru = 12.95; Found (%) : C = 52.01; H = 3.72; N = 14.20; Cl = 4.50; Ru = 13.01;

Sl. No. 2 :

[RuCl(O-CH_3-L)$_2$($As\phi_3$)]: Calculated (%) for **$RuClC_{34}H_{29}N_8S_2As$**: C = 49.47; H = 3.51; N = 13.58; Cl = 4.30; Ru = 12.26; Found (%) : C = 49.62; H = 3.54; N = 13.62; Cl = 4.38; Ru = 12.36;

Sl. No. 3 :

[RuCl(m-CH_3-L)$_2$($P\phi_3$)]: Calculated (%) for **$RuClC_{34}H_{29}N_8S_2P$**: C = 52.26; H = 3.71; N = 14.34; Cl = 4.54; Ru = 12.95; Found (%) : C = 52.46; H = 3.76; N = 14.52; Cl = 4.62; Ru = 13. 12;

Sl. No. 4 :

[RuCl(m-CH_3-L)$_2$($As\phi_3$)]: Calculated (%) for **$RuClC_{34}H_{29}N_8S_2As$**: C = 49.47; H = 3.51; N = 13.58; Cl = 4.30; Ru = 12.26; Found (%) : C = 49.48; H = 3.48; N = 13.62; Cl = 4.36; Ru = 12.36;

Sl. No. 5 :

[RuCl(P-CH_3-L)$_2$($P\phi_3$)]: Calculated (%) for **$RuClC_{34}H_{29}N_8S_2P$**: C = 52.26; H = 3.71; N = 14.34; Cl = 4.54; Ru = 12.95; Found (%) : C = 52.558; H = 3.70; N = 14.24; Cl = 4.55; Ru = 12.89;

Sl. No. 6 :

[RuCl(O-MeO-L)$_2$($P\phi_3$)]: Calculated (%) for **$RuClC_{34}H_{29}N_8O_2S_2P$**: C = 50.20; H = 3.56; N = 13.78; Cl = 4.36; Ru = 12.44; Found (%) : C = 50.30; H = 3.58; N = 13.50; Cl = 4.38; Ru = 12.50;

Sl. No. 7 :

[RuCl(O-MeO-L)$_2$($As\phi_3$)]: Calculated (%) for **$RuClC_{34}H_{29}N_8O_2S_2As$**: C = 47.63; H = 3.38; N = 13.07; Cl = 4.14; Ru = 11.80; Found (%) : C = 47.70; H = 3.82; N = 13.17; Cl = 4.41; Ru = 12.01;

Sl. No. 8 :

[RuCl(O-Cl-L)$_2$($P\phi_3$)]: Calculated (%) for **$RuClC_{32}H_{26}N_8S_2Cl_2P$**: C = 46.73; H = 3.04; N = 13.63; Cl = 12.96; Ru = 12.30; Found (%) : C = 14.80; H = 3.12; N = 13.66; Cl = 13.01; Ru = 12.35;

Sl. No. 9 :

[RuCl(O-Cl-L)$_2$($As\phi_3$)]: Calculated (%) for **$RuClC_{32}H_{26}N_8S_2Cl_2As$**: C = 44.36; H = 3.00; N = 12.94; Cl = 12.96; Ru = 11.68; Found (%) : C = 44.40; H = 3.11; N = 13.01; Cl = 12.88; Ru = 11.72;

Sl. No. 10 :

[RuCl(P-Cl-L)$_2$(Pϕ_3)]: Calculated (%) for **RuClC$_{32}$H$_{26}$N$_8$S$_2$Cl$_2$P**: C = 46.73; H = 3.04; N = 13.63; Cl = 12.96; Ru = 12.30; Found (%) : C = 46.80; H = 3.14; N = 13.73; Cl = 13.01; Ru = 12.11;

Sl. No. 11 :

[RuCl(L)$_2$(Pϕ_3)]: Calculated (%) for **RuClC$_{32}$H$_{25}$N$_8$S$_2$P**: C = 51.02; H= 3.32; N = 14.88; Ru = 13.420; Found (%) : C = 51.15; H = 3.38; N = 14.90; Ru = 13.421;

The elemental analysis, spectral conductance and Magnetic data were obtained as reported in our previous paper[14].

Results and Discussion

The analytical data of the complexes correspond to the composition [RuCl(Eϕ_3)L$_2$] (E=P/As; L=monobasic bidentate anionic ligand). These complexes are prepared by the reaction between precusor complexes [RuCl$_3$(Eϕ_3)$_3$] and 1-substituted tetrazoline-5-thione ligands in molar ratio 1:2 in benzene.

$$[RuCl_3(E\phi_3)_3] + 2LH \xrightarrow[\text{reflux.5h.}]{C_6H_6} [RuCl(E\phi_3)L_2] + 2HCl + 2E\phi_3$$

(E = P/ As)

The molar conductance values indicate their non-electrolytic nature and magnetic moment value of the complexes fall in the range of 1.91- 2.01 BM corresponding to a single unpaired in low spin 4d^5 configuration consistent with reported value reported in literature[19] for octahedral six coordinated complexes (str. I).

The electronic spectra of complexes showed two to three bands in the 250-675 nm region. The band in the 540-490 nm are assigned to $^2T_{2g} \rightarrow {}^2A_{2g}$ transition for similar to octahedral Ru(III) complexes[20]. The bands in the 350-350 nm region are probably due to charge transfer and the other bands at 670 nm and 470 nm are spin forbidden transitions[21].

The IR spectra of free ligands were compared with those of ruthenium(III) complexes which confirms the formation of simultaneous Ru-N and Ru-S bonds. The υN-H(3145cm^{-1}) of ligands disappear in complexes indicating deprotonation of N-H group and formation of Ru-N bond. Further evidence in support of formation of simultaneous Ru-N and Ru-S bond comes from systematic shift of thioamide bands on complexation considering our previous results[22-23]. New bands at 425 cm^{-1} and 350cm^{-1} in far- IR spectra of complexes assigned to Ru-N and Ru-S stretching mode respectively.

The ligand to metal bonding is further supported by 'H NMR spectra. The resonances due to imino proton in the ligands observed at δ1.25 PPM is absent in the spectra of the complexes suggesting formation of Ru-N bond and deprotonation of N-H group on complexation. The aromatic protons of Pϕ_3 and Asϕ_3 ligands resonated as broad multiplet in the region δ7.32- 7.15 PPM and δ8.0 – 8.76 PPM respectively[24]. The phenyl protons of 1-substituted phenyl tetra zoline-5-thione appeared at δ7.45-7.75 PPM as broad multiplet. The broad nature of peak may be due to large quadruple resonances broadening effect of tetrazole nitrogen atoms[25]. The methoxy

Table 1. Major IR, electronic and 'HNMR Spectral data of ligands and Ruthenium(III) Complexes

Comds	IR(cm^{-1}), Thioamide Bands					λmax (nm)				'H NMR (PPM)			
	Band I	Band II	Band III	Band IV	(υRu-N/ (υRu-S)					Imino proton	Methyl proton (Meth-oxy Proton)	Phenyl Protons	Phenyl Protons of Pϕ3/ Asϕ3
LH (ligand)	1520	1290	980	740	-(-)	305	265			1.25 (-)	- (-)	7.40-7.70 (multiplet)	(-)
Complex (Sl. No. 11)	1500	1300	1000	800	430 (325)	670	480	345	260				
O-CH_3-L (ligand)	1505	1290	1025	810	- (-)	305	260			1.25	2.40	7.34	8.12
Complex (Sl. No. 1)	1480	1295	1010	785	430 (330)	672	485	350	255	-	2.42	7.44	8.00
Complex (Sl. No. 2)	1480	1290	1005	780	435 (325)	670	480	355	250	-	2.40	7.45	8.10
m-CH_3-L (ligand)	1500	1280	1060	790	- (-)	303	260			1.20	2.42	7.55	8.02
Complex (Sl. No. 3)	1480	1275	995	770	440 (325)	670	480	350	255	-	2.25	7.40	8.11
Complex (Sl. No. 4)	1482	1270	1005	775	445 (335)	660	480	355	255	-	3.80	7.34	8.22
P-CH_3-L (ligand)	1500	1280	1044	810	- (-)	305	262			1.25	2.40	7.30-7.82	8.32
Complex (Sl. No. 5)	1475	1275	990	785	440 (340)	660	485	355	255	-	2.38	7.42-7.52	8.11
O-CH_3O-L (ligand)	1500	1290	1025	810	- (-)	305	270			1.25	- (-)	7.34-7.45	(-)
Complex (Sl. No. 6)	1485	1285	1000	790	445 (355)	662	485	355	265	-	-	7.35-7.44 (multiplet)	8.10
Complex (Sl. No. 7)	1485	1280	1010	790	450 (345)	630	480	350	262	-	-	7.36-7.50 (multiplet)	8.12
O-Cl-L (ligand)	1500	1285	1020	805	- (-)	305	265			1.25	-	7.30-7.46 (multiplet)	8.11
Complex (Sl. No. 8)	1475	1280	990	745	445 (350)	660	485	355	260	-	-	7.32-7.45 (multiplet)	8.10
Complex (Sl. No. 9)	1475	1280	985	745	440 (340)	670	480	350	260	-	-	7.46	8.20
P-Cl-L (ligand)	1498	1280	1055	785	- (-)	305	265			1.28	-	7.42-7.66	-
Complex (Sl. No. 10)	1480	1270	1020	745	445 (340)	660	480	350	265	-	-	7.50-7.55	8.02

LH = 1-phenyl tetrazoline-5-thione; Band I = δNH + δCH + υC = N;
Band II = υC-N + δNH + δCH + υC=S; Band III = υC ... N + υC ... S;
Band IV = υC ... S

Table 2. Antibacterial activity of ligands and ruthenium(III) complexes at different concentration (PPM)

Compd.	Diameter of inhibition (mm)								
	S. Aureus			B. Subtilis			E. Coli		
	25	50	100	25	50	100	25	50	100
O-CH_3-L (ligand)	-	-	+	-	+	+	-	-	+
Sl. No. 1 (Complex)	-	+	+	+	++	++	-	-	++
Sl. No.2 (complex)	-	+	++	++	++	+++	-	+	+++
m-CH_3-L (ligand)	-	-	-	-	-	+	-	-	-
Sl. No. 3 (Complex)	-	-	+	-	-	+	-	-	+
Sl. No. 4 (Complex)	-	+	+	+	+	++	-	+	++
P-CH_3-L (Ligand)	-	+	++	+	+	++	-	+	++
Sl. No. 5 (Complex)	+	++	+++	+	++	+++	+	++	+++
O-CH_3O-L (ligand)	-	+	++	NT	NT	NT	-	-	+
Sl. No. 6 (Complex)	+	++	+++	NT	NT	NT	+	+	++
Sl. No. 7 (Complex)	++	+++	+++	NT	NT	NT	+	++	+++
O-Cl-L (ligand)	+	++	++	+	++	++	NT	NT	NT
Sl. No. 8 (Complex)	++	++	+++	++	++	+++	NT	NT	NT
Sl. No. 9 (Complex)	+++	+++	+++	++	+++	+++	NT	NT	NT
P-Cl-L (ligand)	+	++	++	+	+	++	-	-	+
Sl. No. 10 (Complex)	++	+++	+++	++	++	+++	+	+	++
Stretomycin (Stand)	++	+++	++++	++	+++	++++	NT	NT	NT

Inhibition diameter in mm : (+) 15-20 mm; (++) 20-25 mm; (+++) 25-30 nm; (++++) 30-35 nm; (-) Inactive Zone < 10 nm; NT = not tested.

Table 3. Antifungal(%) inhibition of ligands and ruthenium (III) complexes at different concentration (μgml^{-1})

Compd.	A. Flavus			a. Parasiticus			c. Albicans		
	25	50	100	25	50	100	25	50	100
O-CH_3-L (ligand)	-	-	-	-	-	+	NT	NT	NT
Sl. No. 1 (Complex)	-	-	-	-	-	+	-	+	+
Sl. No.2 (complex)	-	-	-	-	-	+	-	+	+
m-CH_3-L (ligand)	-	-	-	-	-	-	-	-	-
Sl. No. 3 (Complex)	-	-	-	-	-	-	-	-	-
Sl. No. 4 (Complex)	-	-	+	-	-	+	-	-	+
P-CH_3-L (Ligand)	-	-	-	-	-	-	-	-	-
Sl. No. 5 (Complex)	-	-	-	-	-	-	-	-	-
O-Cl-L (ligand)	-	+	++	+	++	+++	+	+	++
Sl. No. 8 (Complex)	+	+	++	+	++	+++	+	++	+++
Sl. No. 9 (Complex)	+	+	++	+	+	++	+	+	++
P-Cl-L (ligand)	+	++	++	+	++	+++	NT	NT	NT
Sl. No. 10 (Complex)	++	++	+++	++	++	+++	NT	NT	NT
Griscofulvin (stand)	++	+++	++++	++	+++	++++	NT	NT	NT

Inhibition diameter in mm : (+) 15-20 mm; (++) 20-25 mm; (+++) 25-30 nm; (++++) 30-35 nm; (-) Inactive Zone < 10 nm; NT = not tested.

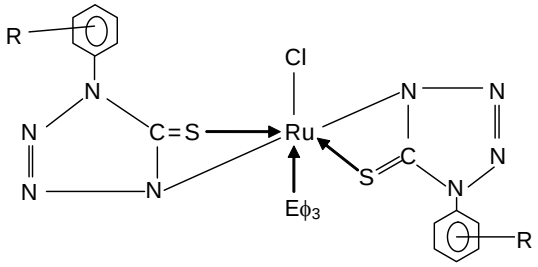
protons and methyl protons of ligands observed at δ3.74 PPM and δ2.4 PPM remain almost unchanged in position on coordination.

Antifungal activity :

All ligands and their corresponding ruthenium(III) chelates were screened against A. Flavus, A. Parasiticus and C. Albicans using cup-plate method reported in literature[15] using DMSO solvent. The inhibition zone formed around each filter paper was measured[16]. The standard fungicide carbendazim was used for comparison. The results are given in table 3. A close examination of the structure of the active compound reveal that antifungal activity was more confined mainly to chlorosubstituted phenyl derivatives of 1-substituted tetrazoline-5-thione and their metal chelates. The methyl substituted phenyl derivatives of 1-substituted tetrazoline-5-thiones have almost negligible activity against these organism.

Antibacterial activity :

The in vitro antibacterial screening of ligands and their ruthenium complexes have been carried out against S. Aureus, Bacillus Subtilis and E. Coli using a nutrient agar medium by disc diffusion method[17-18]. The complexes to be tested were dissolved in DMSO to a final concentration of 0.25%, 0.5% and 1% and 50 asked in filter paper disc of 5 mm diameter and of 1 mm thickness. The discs were placed on the previously seeded plated and incubated at room temperature for 24 h. The diameter of inhibitory zone around each disc was measured. Streptomycin was used as standard. The results (Table 2) showed that the complexes exhibit moderate activity and the toxicity of ruthenium chelates increases on increasing the concentration[26]. The increase in the antibacterial activity of the metal chelates may be due to the effect of the metal ion on the normal cell process. A possible mode of the toxicity increase may be explained in light of Tweedys chelation theory[27]. Moreover, metal chelates are more active than ligands. Bonding of thioamide ligands reduces the polarity of ruthenium(III) ion and increases lipophilic character of central metal atom which subsequently favours its permeation through the lipid layers of cell membrane[28,8-9].



Str. - I

(E= P/As; R = H, CH_3^-, CH_3O^-, Cl^-)

Acknowledgements

The authors thank Dr. P.K. Verma, Principal, College of Commerce, Patna for providing facilities and C.D.R.I. Lucknow for recording spectral data.

References

1. D. X. West, A.E. Liberta, S.B. Padhye, R.C. Chikate P.B. Sonawane, A.S. Kumbhar and R.G. Yarande, *Coord. Chem, Rev. 123*, 49 (1993).
2. K. Karidi, A. Caroufic, A. Tsipis, N.

Hadjiliadis H. Den Dulk and J. Reedijik, *J. Chem. Soc. Dalton trans*, 1176 (2005).
3. P.I. Anderbeg, M.M. Harding, I.J. luck and P. Turner, *Inorg. Chem. 41*, 1365 (2001).
4. Patterring and J.A. Grim, *Cancer Res. 27*, 1278 (1967).
5. F.A. Farach, E.J. Bianz, S.C. Dadix and N. Brackjman, *J. Med. Chem. 17*, 172 (1974).
6. K.P. Balasubramaniam, S. Manivannam and V. Chinnusamy *J. Ultra Chem.* Vol. *4*, 15 (2008).
7. K.P. Bala Subramaniam and V. V. Raju, *Asian J. Chem.* Vol. *22*, (No 2), 978 (2010).
8. R. N. Pandey, Pramila Sharma and Renu Kumari, *J. Ultra Chem*. Vol. *9(1)*, 49 (2013).
9. R.N. Pandey, Sheo Shankar Kumar, Pramila Sharma and Renu Kumari, *Int. J. Chem. Sci.*, Vol. *11(1)*, 665 (2013).
10. R.N. Pandey, Sheo Shankar Kumar, Kalpna Shahi and Renu Kumari, *Oriental J. Chem.* Vol. *29(2)*, 691 (2013).
11. E. Liber and J. Ramchandran *Can. J. Chem. 37*, 101 (1959).
12. J. Chatt, G.J. Leigh, D.M.P. Mingos and R.J. Pask, *J. Chem. Soc.* A, 2636 (1968).
13. R.K. Poddar, I.P. Khullar and U. Agarwala, *Nucl. Chem. Lett. 10*, 221 (1974).
14. R.N. Pandey, A.K. Nag and D.K. Sharma, *Oriental J. Chem.* Vol. *28(4)*, 1809 (2012).
15. W.G. Hanna and M.M. Manwad, trans. Met. Chem. *26*, 644 (2001).
16. B. Hesse and Hiopka, *Pesticides, 8*, 37 (1974).
17. N. Dharmaraj, P. Vishwanathamurthi and K. Natrajan, *Trans. Met. Chem. 26*, 105 (2001).
18. B.G. Tweedy, Phytopathology, *55*, 910 (1964).
19. N. Prasanna, S. Srinivasan, G. Rajagopal and P.R. Athappan, *Indian J. Chem. 40A*, 426 (2001).
20. L.R. Ramirez, T.A. Stephenson and E.S. Switkes, *J. Chem. Soc. A*, 1770 (1973).
21. K.P. Balasubramaniam, K. Parameshwari, V. Chinnusamy R. Prabhakaran and K. Natarajan, *Spectrochim, Acta 65A*, 678 (2006).
22. R.N. Pandey, Renu bala and A.K. Sinha, *Oriental J. Chem. 27(1)*, 293 (2011).
23. R.N. Pandey, A. Aanand, R.K. Singh and A. Kumar, *Asian J. Chem. 22(7)*, 5601 (2010).
24. J.Y. Kim, M.J. Jun and W.Y. Lee, *Polyhedron, 15*, 3787 (1996).
25. R.N. Pandey and Sheo Shankar Kumar, *J. Ultra Chem. 7(2)*, 271 (2011).
26. R. Prabhakaran, A. Geetha, M. Thilagavathi, R. Karvembu, V. Krishnan, H. Bertagnoli and K. Natarajan, *J. Inorg. Biochem, 98*, 2131 (2004).
27. B.G. Tweedy, *Phytopathology, 55*, 910 (1964).
28. W. Rehman, F. Samanand I. Ahmad, *Russ. J. Coord. Chem. 34*, 678 (2008).