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SYNTHETIC, CHARACTERIZATION AND BIOLOGICAL APPLICATIONS OF Mo(V) DITHIOCARBAMATE COMPLEXES

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ABSTRACT

Dithiocarbamates are organosulphur compound. They have been reported to show good biological activities as an antimicrobial Schizonticidal, antitumor, antimalarial and as biocidal in agriculture. The Molybdenum complexes viz. $Mo_2C_{10}H_{14}N_2O_2S_6$ and $Mo_2C_{14}H_{20}$ $N_2O_2S_6$ have been synthesized with Sodium Pyrroline/Sodium Piperidino dithio-carbamates, and they are characterized by elemental analysis, Molar Conductance and spectral studies. Antimicrobial activity of Compounds has been carried out against Some bacterial species (viz E.Coli and K. Pneumonial) and Fungal species (viz. A. Niger and C. albicans). The results indicate that Mo(V) Complexes are much more biologically active than Ligand Fragments. Further all the synthesized Compounds were assesed for their anticancer studies against Cancer line human Leukemia K562. Results showed that the complexes are promising chemotherapeutic alternatives in the search of anticancer agents. The studies showed that upon further optimization these complexes could become a leading class of compounds that possess broad spectrum antimicrobial and anti-tumor activities.

KEYWORDS: Mo(V), dithio-Carbamates, characterization, antifungal, antibacterial, anticancer.

INTRODUCTION

Dithio Carbamates are organo sulfur ligands which form stable complexes with Transition metals. The strong metal binding properties of the dithiocarbamates were recognized early by the virtue of insolubility of the metal salts and the capacity of the Molecules to form chelate complexes.

They are capable of stablizing Transition Metals in a wide range of oxidation states and Frequently Stablizethe Metal Centre in an unusually high apparent formal oxidation state Ahmad et al. (2006); Avinishi et al (2014) Chemistry of dithiocarbamates could be dated to start in the early Twentieth Century Precisely in 1930. Commercial application was used as a fungicide for the first time during world war. Other wide applications can be seen in the fields of accelerating vuclanization, acting as flotation agents agriculture (Pesticide), biology, materials science, medicine, organic synthesis, photostablizing Polymers, Protecting radiators, in the field of Nano Science Technology. Moreover they act as therapeutic agents for alcoholism and metal intoxication. Now a days they have also been reported to treat acquired immune depressive syndrome and Cancer. Ayyavoo etal; (2017).

In view of the diverse applications of the dithiocarbamates. Herein we report synthesis, characterization and biological applications like anticancer, antibacterical and antifungal studies of molybdenum compounds with sodium pyrroline (pyrdtc) and sodium piperidino dithiocarbamates (Pipdtc).

The Synthesized Metal Complexes of Molybdonum show enhanced biological activities as compared to free ligands due to drop in polarity of metals after complexation.

Chauhan et al; (2007); Chauhan etal; (2015) Farrugia etal; (1995); Faraglia etal, (2005).

MATERIALS AND METHODS

All reagents used were of AR grade and used as purchased commercially however the solvents were purified by the standard procedure. The ligands were prepared by the reported procedure. Thorn etal (1962). C, H, N and S were analyzed on Carlo-Erba Micro Analyser 1106 Metal Contents were estimated by standard procedure. Vogel, A.I (1978). FTIR was recorded on Thermo Nicolet Avater 370. Electronic spectra on Shimadzu UV-160A spectrophotometer. The Conductance measurement were carried out on a metal CM-180 Eliodigital conductivity meter.

^{1}H and ^{13}C NMR spectra in dimethyl sulfoxide (DMSO) recorded on a Brucker WH 300 (200 MHz) and Varian

Gemini (200 MHz) Spectrometers. using tetramethylsilane (TMS) as an internal reference. The invitro antimicrobial screening effects of the investigated compounds were tested against the bacterial species: Escherichia Coli (E. Coli) and Kebsiella Pneumoniae (K. Pneumoniae) and Fungal species. Aspergillus Niger (A. Niger) and Candida albicans (C. albicans) by using Kirby Bauer Disk diffusion method.

Chloramphenicol and Nystatin were used as the standard antibacterial and antifungal agents. The Test Compounds were dissolved in DMF Solution (which has no inhibition activity and solution soaked in filter paper disk of 5mm diameter and 1 mm thickness. The disks were incubated 24h for bacterial and 72 h for fungal species at 37°C. The minimum inhibitory concentration (MIC) value of the compounds was determined by the Serial dilution method.

The invitro cancer studies of all the compounds were assessed for their antiproliferation test against a panel of selected human cancer cell lives such as K-562 by using SRB (sulforhodamine B) assay concentration of drug used 10, 20, 40 and 80 µg / mL ADR (adrincyin) was As positive control which controls cells with definite structure and clear cell wall without degeneration.

Each drug was assayed inducing 50% growth inhibition (GI_{50}) total growth inhibition (TGI) and 50% cytotoxicity (LC_{50}) after a 48 h incubation period were calculated by linear interpolation from the observed data points. Fricker etal (1996). Garje etal (2003).

Synthesis of metal Complexes

0.001 mol of Sodium Pyrroline/Sodium Piperidino dithiocarbamates was dissolved into minimum quantity of water 0.001 mol ammonium dithiomolybdate solution in 20-30 mL double distilled water added into the dithiocarbamate solution the mixture solution stirred well with the help of magnetic stirrer for 1h then the solution mixture was kept over water bath for 40-50 minutes the resulting solution was cooled 0-5°C to get the light yellow / orange red solid the resulting precipitate was washed with ethanol followed by ether and then dried in vacuo over $CaCl_2$ yield (75-80%).

RESULTS AND DISCUSSION

All the metal complexes were colored, Non-hygroscopic in nature and stable at room temperature. They were insoluble in common organic solvents but soluble in DMF and DMSO. The results of the elemental analysis are in good agreement with the calculated values. The molar Conductance values indicate their Non-Electrolytic Nature. Physical and analytical data of compounds are summarized in table 1. The IR data of the ligands pyrroline and piperidino dithio carbamates show several bands at 1450, 938, 820 and 2965 cm^{-1} due to C – N, C = S, C – S and C – H bond stretching vibrations in the solid state respectively. On complexation the band in the region 934 – 940 cm^{-1} indicating the presence of two terminal oxygen the additional important bands in the IR spectra of metal Complexes of 430 – 450 cm^{-1} suggesting the presence of bridging sulphur atom *v*(M–S)b. Another striking features of the spectra of Molybdenum Complexes was the appearance of the medium intensity stretching vibrations at 330–385 cm^{-1} which confirms that the two metal centres in the binuclear type of complexes are linked to each other through two bridging sulphur atoms showing the M – S – M bonds Nakamoto, K. (1997); Kavounit etal (1982). Ultraviolet-visible (UV–Vis) it is also called electronic spectroscopy because the electronic spectra for ligands of dithio carbamates and its metal complexes are recorded in the UV–Vis region from a range of 200–800 nm. Ligands of dithiocarbamates show three bands relative to intramolecular charge transfer in the ultra-violet region of the electromagnetic spectrum. Bands are π – π* transitions of the N – C = S group, π – π* of S – C = S group and n – π* respectively.

In metal complexes the two transitions from ligands and excitation of metal ions. Transitions from ligands are π – π* and n – π* while transition as a result of excitation of metal ions is called the d – d transition. Metal to ligand charge transfer (MLCT) and ligand to metal charge transfer (LMCT) are due to excitation of an electron from the metal ion to the dithio carbamate ligands and Vice-versa. The Synthesized Compound are Sulphur rich Compounds in which metal ions are S – S bonded this fact is also inagreement with IR studies Lever A.B.P. (1968); Maurya etal (2023).

The ^{1}H NMR Spectrum displayed the chemical shifts of the – CH_2 protons as multiplets for 1.4 -2.2 ppm. The δ (–HC – N) & δ (N – H) were observed in the deshielded region at about 4.1 ppm and 6.8 ppm this deshielding was caused by the high electron density around the sulphur or metal atom via the thioureide π system. The ^{13} C NMR spectrum showed the resonance at 181.05 -1 ppm which were assigned to δ(N^{13} CS_2) of NCS_2 moiety. The signals observed at 114.77 ppm and 127.52 ppm were assigned to C = C bond in the aromatic ring. The spectrum also showed signal for C – N bond from C-NH group at 50.50 ppm. There was only one extra peak at 158 ppm which is assumed to be due to the impurities of the ligand δ (NCS_2) 181.05 – 189 ppm were shifted upfield to about 200 – 201.42 ppm in the metal complexes. This upward shift caused by the delocalisation of an electron cloud from the NCS_2 moiety towards the metal centre.

Gunther, H. (1995), Irobi, etal (1996); Rehman etal 2014. Jerry etal (2022), Freeman R.A (1997).

Table 1: Physical and Analytical data of Compounds.

Compound	No	Colour	% Analysis Found/(Calcd)					M.P. D.T. (O°C)	Molar Conductance Ohm^{-1} cm^2 mol^{-1}
			C	H	N	S	M		
$C_4H_7NS_2Na$	1	White	30.0	4.22	8.10	40.8	—	212	—
			(30.76)	(4.48)	(8.97)	(41.02)			
$C_6H_{10}NS_2Na$	2	White	39.0	4.98	6.99	33.97	—	220	—
			(39.3)	(5.46)	(7.65)	(34.97)			
$Mo_2C_{10}H_{14}N_2O_2S_6$	3	Orange	20.0	2.10	4.50	32.8	31.78	300–	6.82
		Red	(20.8)	(2.43)	(4.86)	(33.3)	(32.98)	306	
$Mo_2C_{14}H_{20}N_2O_2S_6$	4	Light	1.90	2.91	4.12	30.0	29.98	>342	7.53
		Yellow	(2.22)	(3.17)	(4.44)	(30.47)	(30.15)		

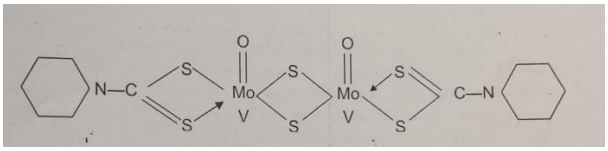

Fig. 1: Structure of Molybdenum Complex with Pipdtc.

BIOLOGICAL APPLICATIONS

In vitro antimicrobial studies the antibacterial and antifungal activity of the ligand and complexes were assayed against some of the bacteria and fungi. DMF is used as Negative control and chloramphenicol is used as a positive standard for antibacterial and Nystatin for antifungal activities. The minimum in inhibitory concentration (MIC) value of the compounds was determined by the serial dilution method and is given in Table 2. The in vitro antimicrobial activity results revealed that Metal Complexes are more microbial toxic than the ligand. The activity order of the Synthesized complexes and ligands are based on the facts that the increase in antimicrobial activity is due to faster diffusion of metal complex as a whole through the cell membrane or due to combined actively effect of the metal and the ligand. dithio-carbamate Molybdenum complexes are highly active due to increasing the delocalization of π electrons into the whole chelate indicating increase in its lipophilicity on chelation, polarity of the the metal ion will be reduced to a greater extent due to overlap of the dithiocarbamate ligand orbital and partial sharing of the positive charge of the metal ion with donor group. Pelczar etal (1998); Stokes etal (1980).

The increased activity of the metal complexes explained on the basis of overtone's concept and Tweedy's chelation theory. Odularu etal (2019); Hou etul (2014); Hedges, A.J. (2002); Papazisis etal (1994); Mosmann, T (1982); Xiao etal (2017).

Table 2: Antimicrobial activity (MIC µg/mL) data.

Compound	Compound Number	Antibacterial Activity		Antifungal Activity	
		E. Coli	K. Pneumoniae	A. niger	C. albicans
C4H7NS2Na	1	40	45	35	38
C6H10NS2Na	2	38	41	30	32
$Mo_2C_{10}H_{14}N_2O_2S_6$	3	25	28	24	22
$Mo_2C_{14}H_{20}N_2O_2S_6$	4	18	20	22	20
Chloramphnicol	5	12	14	—	—
Nystatin	6	—	—	10	12

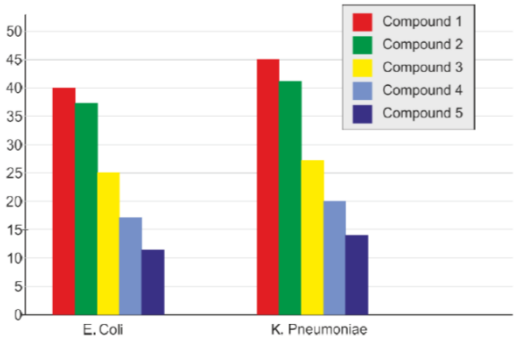

Fig. 2: Antibacterial Studies of Ligand and its metal complexes against E. Coli and K. Pneumoniae.

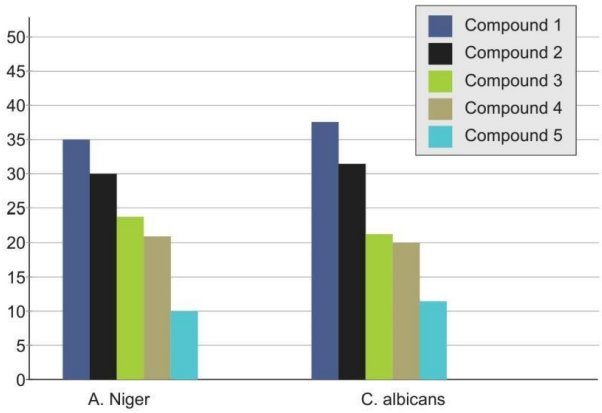

Fig. 3: Antifungal Studies of Ligand and its Metal complexes against A. niger and C. albicans.

In vitro anticancer studies

The data obtained by the SRB assay show that Molybdenum complexes 3 and 4 have inhibitory effects on the growth K562 (Table 3 and 4) (Fig 3). Cancer cells in dose dependent manner.

The antiproliferative effect of tested complexes is likely due to the lipophilicity of the complexes that alleviate the transport of metal complexes into the cell and posteriorly into the organelles where metal may possibly contribute to toxicity by inhibitory cellular respiration and metabolism of biomolecules. The compounds 1 and 2 (ligands) exhibited no cytotoxic effect on cell line. The choice of the coordinated ligand(s) seems to be as important as the choice of metal(s) because besides being the integral part of biologically active complexes.

Keepers etal (1991), Pandaya etal (1999). The pure metal are in active however the activity of metal cations varies on their bioavailability hence delivery methods/solubility and ionization of metal sources are significant parameters to deal metals in biological system possibly this is the reason that bonding of metal cation Mo(V) to biologically compatible ligands enhance the bioavailability and ultimately the activity of metal cation. Gringeri etal (1988); Hogarth etal (2012); Hogarth Graeme (2023); Griffon etal (1995). The photomicrograph of the cells treated with compounds 1, 2, 3, 4 revealed the morphological features of apoptosis consist of membrane blebbing nuclear condensation, cytoplasmic shrinkage, DNA fragmentation, cell wall destruction and formation of apoptotic bodies (Fig 4) morphological images were grabbed using a phasecontrast microscope at × 20 magnifications with a digital camera at 48 h after treatment with the samples. compound 1 and 2 showed negligible cytotoxicity as the cell growth and morphology did not get affected whereas it can be seen clearly that the compounds 3 and 4 affected the normal morphology which rendered, the cells to lose their viability the picture revealed that the cells treated with compound 3 and 4 exhibited apoptotic cellular death as the population of code reduced drastically within the 48h of treatment. The Photomicrograph depicts the treatment of K 562 cell treated with complexes 3 and 4 showed a significant inhibitory effect on the cellular growth.

It was verified that the increased in concentration of complexes leads to higher cytotoxic activities nevertheless results also proved that ADR showed superior cytotoxic activity against the Human Leukemia cell Line K 562.

Table 3: Control growth drug Concentrations (µ g/mL) K562 cell line.

Human Leukemia cell line K562																
% Control growth.																
Drug Concentrations (g/mL)																
Compound Number	**Experiment 1**				**Experiment 1**				**Experiment 1**				**Average Values**			
	10	20	40	80	10	20	40	80	10	20	40	80	10	20	40	80
1	78.3	71.7	66.1	58.0	-74.5	70.6	64.4	58.3	74.9	76.0	65.1	55.6	77.3	73.8	65.3	57.8
2	33.2	31.7	30.3	26.3	-29.7	28.3	26.7	20.6	26.2	24.5	21.8	16.6	29.7	28.2	26.3	21.2
3	20.0	18.1	17.2	17.1	-20.7	20.8	19.3	17.7	17.9	16.3	16.3	15.4	19.6	18.4	17.6	16.8
4	17.1	16.5	15.2	12.8	-18.1	17.5	16.8	13.5	15.4	15.1	14.4	8.4	16.9	16.4	15.5	11.6
ADR	1.4	-5.1	-34.4	-34.8	1.6	–5.9	-12.4	-35.8	–9.8	-14.4	-28.4	-41.1	–2.3	–8.5	-25.1	-37.2

Table 4: Parameters Calculated from graph (Fig 3)K562 cell line.

Compound Number	Drug Concentrations (µ g/mL) Calculated From graph		
	LC50	TGI	GI50
1	> 80	> 80	> 80
2	> 80	> 80	17.0
3	> 80	> 80	< 10
4	> 80	77.3	< 10
ADR	75.5	35.3	< 10

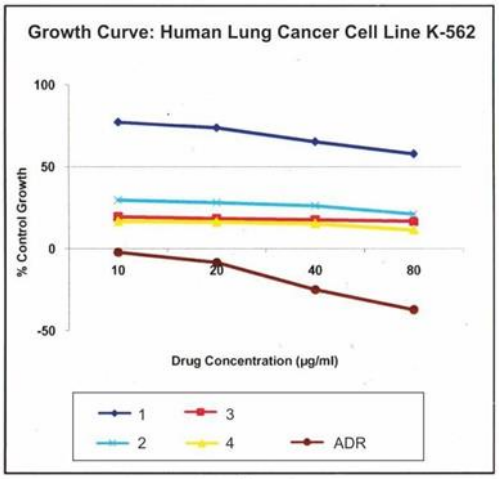

Fig. 4 : Growth Curve human Cancer cell line K-562

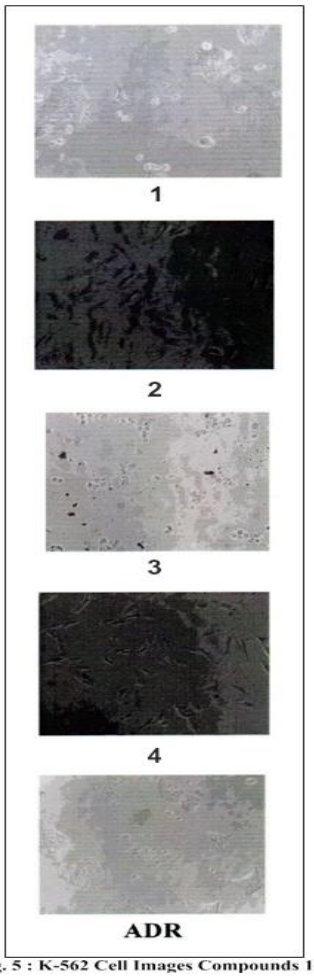

Fig. 5 : K-562 Cell Images Compounds 1-4

CONCLUSION

antibacterial studies suggested that Molybdenum (v) complexes generally have better activity than the ligands and less activity than known antibiotic drugs. Further Metal Complexes exerted growth inhibition on the human cancer cell line showing promise as potential anticancer drugs deserving of further investigation.

FUTURE SCOPE

The output of this research work to report the dithiocalbamate complexes intervention to control cancer disease to its nanoparticles by further characterization technique of SEM, TEM, EDS AND XRD.

Future will entail the uses of complexes to substitute platinum coordination compounds in seleding targets in cytotoxic drug design. The presence of Nitrogen and Sulfur coordination modes has made dithiocarbamates to be successfully applied as anticancer agents future research will review papers on groups of aliphatic and aromatic dithiocarbamates and compare their anticancer activities with each other.

CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

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