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Complexes of Copper (II) with Thiosemicarbazone and Chloroethanol - Synthesis, Characterization and Biological Studies

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Abstract: *Mixed ligand complexes of copper (II) with Thiosemi carbazones of acetophenone /benzophenone /benzaldehyde/ vanillin and chloroethanol as a second ligand are reported. The complexes are characterized by Elemental and thermal analyses, IR, UV-visible, EPRspectralstudies, and magnetic susceptibility studies.Antibacterial, Antifungal activities were carried out on these complexesagainst the bacteria, E.coli, Salmonella typhi, Bacillus subtilis, staphylococcus auerus, Pseudomonas aeruginosa and against the fungi, candida albicans, Trichodermaviridi and Aspergillus niger.The invitro cytotoxicity of the complexes against HT 29 colon cancer cells showed excellent activity with very low IC $_{50}$ values together with significantly higher selectivity index.*

Keywords: *antibacterial, antifungal, anticanceractivities,mixed ligand complexesof Cu (II), Chloroethanoland Thiosemicarbazone complexes.*

I. Introduction

Life threatening infections and diseases, spreading all over the world, day by day, demand development of new antimicrobial agents, that are highly efficient with lesser side effects and equally cost effective.(1).Metal complexes are preferred to simple ligands due to an increased activity and several sulphur containing metal chelates have been reported with significant antibacterial and antifungal activities.(2,3). A large majority sofThiosemicarbazones have been extensively studied, because of their antibacterial,antifungal,antitumor, antiviraland anticanceractivities.(4-12) Transition metal complexes of thiosemicarbazone have attracted chemists due to the presence of hard nitrogen and soft sulphur donor atoms which permits coordination with a metal ion in different binding mode yielding stable and intensely coloured complexes(13) This versatile nature of the ligand has encouraged us to explore the coordination chemistry further and to make mixed ligand complexes along with a second ligand in such a way that it enhancesthe biological activity. In view of the above facts herein we report the synthesis, characterization, antimicrobial and cytotoxicity studies of copper (II)complexesof thiosemicarbazone formed fromacetophenone, benzophenone, benzaldehyde and vanillinin the presence of chloroethanol as a second ligand.The abbreviations aptsc, bptsc, bztscand vantsc representdeprotonated, thiosemicarbazone of acetophenone, benzophenone, benzaldehyde and vanillin respectively. ($R_2C=N-N=C(S^-)-NH_2$)

II. Experimental section

The chemicals employed for the synthesis are of Analar grade. Copper (II) chloride, thiosemicarbazide, acetophenone, benzophenone, benzaldehyde, vanillin, and chloroethanol are pure gradechemicalsfrom Merckand used without further purification.Thiosemicarbazide (0.01m) in hot methanol(50ml) was taken to whichacetophenone/benzophenone/benzaldehyde/vanillin (0.01m) in 20 ml methanol was added and the reaction mixture was refluxed for2 hrs. After that copper chloride (0.01m) in 20 ml methanol and chloroethanol (0.01m) were added simultaneously and stirred for another 30 mins. Green colouredcomplex was formed which was washed several times with alcohol and water , filtered and air dried. The metal content present in the complexes was estimated using ICP-OES (Inductively coupled plasma - optical emission Spectroscopy). The nitrogen and sulphur content were estimated by Kjelhdhal's method and barium sulphate method respectively. The Chloride in the complexes was estimated by standard Vohlhard's method. TG/DSC/DTA were recorded in NETZSCH STA 449F3 thermal analyzer with a heating rate of 10^o/min. Magnetic susceptibility studies were carried out using Vibrating sample magnetometer Lakeshore VSM 7410. UV-Visible absorption spectra of the complexes in DMSO were recorded using a Shimadzu UV 1600 model spectrometer. The IR spectra of the complexes were recorded as KBr disc using SCHIMADZU Spectrometer. The EPR spectra of the complexes were recorded using JES-FA200 electron spin resonance spectrometer in the region from 1000-8000 gauss. The anti-bacterial and anti-fungal studies were done by agar disc diffusion method. The anti-cancer activities were studied by the MTT assay.

III. Results and Discussion

All the copper complexes were green in colour and found to be soluble in DMSO and DMF. The complexes arevery stableat room temperature.The complexes did not precipitate AgCl on reaction with $AgNO_3$ indicating absence of Cl^- counter ions. The molar conductance of the complexes was inthe range 4 - 5 ohm^{-1} cm^2 mol^{-1} indicating the non-electrolytic nature of the complexes. The elemental and thermal analysisdata arefurnished in TABLE-1 which agrees wellwith the proposed composition for the complexes. The thermo grams were run upto 1000^oc and the residual mass percentage obtained as a result of thermal decomposition of the complexes corresponds to metal sulphides in acetophenone and benzaldehyde semicarbazone complexes and oxides in benzophenone and vanillin semicarbazone complexes[17]. The IR and UV-Vis spectral data on thecomplexes are furnished in TABLE-2.The bands in the region 3725-3775 cm^{-1} inthe complexes confirms the presence of coordinated water molecules.The presence of sharp band in the region 1575-1615 cm^{-1} and absence of band around 1700 cm^{-1}confirms the condensation of aldehyde/ ketone with thiosemicarbazide. The bands in the range 3146-3350cm^{-1} confirms the presence of NH_2 group of Thiosemicarbazone.The bands in the range 720-757cm^{-1} and 600-690 cm^{-1} are due to $U_{C\text{-}Cl}$and $U_{C\text{-}S}$of deprotonated chloroethanol and coordinated mono ionic thiosemicarbazonerespectively. The appearance of bands in the region 420-533cm^{-1} confirms Cu-N bond in the complexes.(14)The electronic spectra of the complexes exhibited strong bands around 248-360 nm which are assigned to ligand to metal charge transfer transitionsA weak band observed in the range 590-615nm due to $^2E_g \rightarrow {}^2T_{2g}$ transition confirms the distorted octahedral configuration around the copper ion(15,16)The EPR spectra of the copper complexes show one signal with g values 2.052, 2.165, 2.094 and 2.064for acetophenone, benzophenone, benzaldehyde and vanillin complexes respectively and these values are higher compared to free electron g indicating an appreciable covalency in bonding (18).The VSM plotsshowhysteresisloop indicatingferromagneticnature.

IV. Biological studies

Antibacterial studies

The antibacterial activitiesof allthe complexesagainst five different bacteria were tested by the Agar disc diffusion method.(19) and compared against standard Ampicillin and the diameter of the inhibitory zone are given in TABLE 3As the concentration increases, the activity also increases indicating that the complexes are active.All the complexes may be termed quite good anti-bacterial agents. The benzaldehyde and vanillin complexes do not exhibit any activity against pseudomonasaureginosa. Among these,benzophenonecomplex shows excellent activity against E. coli compared to standard. The acetophenone and vanillin complexes show nearly comparable activity against bacillussubtilis.

Antifungal activities

The anti-fungal activities in terms of the diameter of the inhibitory zone are given in TABLE 4.for allthe complexes against three different fungi namely *candida albicans, Trichodermaviridi,*and *Aspergillus Niger*. Among these, acetophenone complex shows nearly equivalent activity against *Trichodermaviridi* and benzaldehyde complex shows equivalent activity against *candida albicans* compared to standard. All other complexes show good activity against different fungi even at lower concentration.

Anticancer activities

The anticancer activities of the complexes were studied by MTT assay(20) on HT 29 cell line (colon cancer cell). In parallel the activity was tested against Vero cell line(Normal Monkey kidney cell). Table 5 gives IC_{50} of cancer cells and normal cells observed in the presence of the four complexes. The Complexes showed excellent activity even at lower concentrations. The selectivity Index is calculated as the ratio ofIC_{50} of cancer cells to that of normal cells, A lower IC_{50} and a higher selectivity index indicate greater anti-cancer action and lower toxicity to normal cells respectively.The acetophenone complexhas an excellent selectivity index and vanillin complex shows the least activity.

Table-1 Elemental composition and TGA data

Complexes	%N (theo)exp	%Cl (theo)exp	% S (theo) exp	% Cu (theo) exp	% residueTGA (theo)exp
$[Cu(aptsc)(ClCH_2CH_2O)(H_2O)_2]$	(11.2)10.6	(9.3) 9.4	(8.5)8.1	(17.0)16.3	(25.6)26.3
$[Cu(bptsc)(ClCH_2CH_2O)(H_2O)_2]$	(9.6) 9.0	(7.8) 8.1	(7.3)6.5	(14.6)13.8	(18.3)18.7
$[Cu(bztsc)(ClCH_2CH_2O)(H_2O)_2]$	(11.6)10.7	(9.1) 9.8	(8.9)8.1	(17.7)17.0	(26.6)27.4
$[Cu(vantsc)(ClCH_2CH_2O)(H_2O)_2]$	(10.3)10.9	(8.2) 8.7	(7.8)7.2	(15.7)16.1	(19.6)18.8

Table-2 IR (cm^{-1}) and UV-Vis (λ max in nm)spectral data

Complexes	υ_{OH} aquo	υ_{NH2} (tsc)	$\upsilon_{C=N}$	υ_{C-O}	υ_{C-Cl}	υ_{C-S}	υ_{M-N}	λ max (UV Vis)
[Cu(aptsc)($ClCH_2CH_2O$) ($H_2O)_2$]	3725 3421	3349 3249	1615	1028	754	677	533 453	312,360 595
[Cu(bptsc)($ClCH_2CH_2O$)($H_2O)_2$]	3731 3410	3238 3162	1605	1083	773	686	526 431	248,312 601
[Cu(bztsc)($ClCH_2CH_2O$) ($H_2O)_2$]	3741 3416	3233 3146	1610	1094	746	671	529 442	264,320,369 615
[Cu(vantsc)($ClCH_2CH_2O$)($H_2O)_2$]	3776 3472	3257 3150	1575	1029	721	601	536 420	252,293 590

Table 3 Diameter of Inhibitory Zone -Antibacterial studies

Complexes	Bacteria	Inhibiton Zone(mm) Conc(µg)			Standard (1µg/ml)
		1000µg	750 µg	500µg	
[Cu(aptsc)($ClCH_2CH_2O$) ($H_2O)_2$]	E .coli	18	14	11	29
	Pseudomonas aeruginosa	16	16	14	35
	Salmonella typhi	16	15	14	22
	Bacillus subtilis	19	14	13	23
	Staphylococcus aureus	13	12	11	29
[Cu(bptsc)($ClCH_2CH_2O$) ($H_2O)_2$]	E .coli	27	20	17	29
	Pseudomonas auruginosa	23	20	15	35
	Salmonella typhi	14	12	10	22
	Bacillus subtilis	11	8	7	23
	Staphylococcus aureus	20	15	14	29
[Cu(bztsc)($ClCH_2CH_2O$) ($H_2O)_2$]	E .coli	20	18	13	29
	Pseudomonas auruginosa	-	-	-	35
	Salmonella typhi	18	9	8	22
	Bacillus subtilis	18	14	11	23
	Staphylococcus aureus	14	9	6	29
[Cu(vantsc)($ClCH_2CH_2O$) ($H_2O)_2$]	E .coli	15	12	10	29
	Pseudomonas auruginosa	-	-	-	35
	Salmonella typhi	17	15	11	22
	Bacillus subtilis	21	18	12	23
	Staphylococcus aureus	18	13	11	29

Table 4Anti-Fungal Studies

Complexes	Fungi	Zone of Inhibition(mm) Concentration(µg/ml)			Antibiotic (1mg/ml)
		1000µg	750 µg	500µg	
[Cu(aptsc)($ClCH_2CH_2O$) ($H_2O)_2$]	Candida albicans	22	21	19	25
	Trichoderma viridi	27	26	25	28
	Aspergillus niger	20	19	15	22
[Cu(bptsc) ($ClCH_2CH_2O$) ($H_2O)_2$]	Candida albicans	8	7	6	12
	Trichoderma viridi	28	24	19	32
	Aspergillus niger	12	11	10	19
[Cu(bztsc) ($ClCH_2CH_2O$) ($H_2O)_2$]	Candida albicans	9	7	6	9
	Trichoderma viridi	9	8	6	15
	Aspergillus niger	10	9	7	10
[Cu(vantsc) ($ClCH_2CH_2O$) ($H_2O)_2$]	Candida albicans	25	9	6	29
	Trichoderma viridi	20	12	8	24
	Aspergillus niger	15	10	7	15

Table 5 Anticancer studies

Complexes	Ic50 of cancer cell	Ic 50 of normal cells	Selectivity index
[Cu(aptsc)($ClCH_2CH_2O$)($H_2O)_2$]	7.8	500	64
[Cu(bptsc)($ClCH_2CH_2O$)($H_2O)_2$]	31.2	1000	32
[Cu(bztsc)($ClCH_2CH_2O$)($H_2O)_2$]	31.2	1000	32
[Cu(vantsc)($ClCH_2CH_2O$)($H_2O)_2$]	62.5	1000	16

V. Conclusions

Theexcellent antibacterial, antifungal activities of the copper complexes against different bacteria and fungi and a superb cytotoxicity results reveal that they have promising future in the medical field. The hysteresis loops showferromagnetic nature of the complexes, which indicate that these complexes have future applications in magnetic field too.

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