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RESEARCH ARTICLE

SYNTHESIS, CHARACTERISATION AND APPLICATIONS OF SOME COMPLEXES OF BENZOXAZOLE DERIVATIVES

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Abstract

The present investigation focuses on the synthesis, characterization and investigation of the biological activities of zinc and copper complexes of benzoxazole compounds from 4-thiocyanatobenzoicacid. Infrared spectra of the above compounds agree well with the reported results. The ^{1}H NMR and ^{13}C NMR spectra of all the compounds prepared provide the expected signals. Out of the complexes synthesized, Cu-Ligand complex shows maximum antimicrobial and anticancer activity.

Keywords

Benzoxazole
4-Thiocyanatobenzoic acid
H NMR,
C NMR.

Introduction

Coordination compounds have been a challenge to inorganic chemists since in the 19th century. Transitions metal complexes with soft or hard donor groups have been used extensively in coordination and organometallic chemistry. They have found extensive application in various fields of human interest like extraction, dyeing, pharmaceutical and water softening [1-4]. Many chelating ligands find extensive applications as reagent and masking agents in various titrimetric, spectrophotometric, chromatographic methods. Benzoxazole derivatives [5] are biologically significant compounds and known to exhibit various biological activities such as anticancer, antimicrobial and anti HIV properties. The present investigation investigator focuses in synthesizing and characterizing some transition metal complexes using benzoxazole compounds as ligands from substituted benzoic acid derivatives.

Experimental

All the chemicals and solvents used were AR grades obtained from Sigma-Aldrich, and Spectrochem. Elemental analysis is performed using Perkin-Elmer analyzer. IR spectra are recorded in KBr using Shimadzu spectrometer ^{1}H-NMR and ^{13}C-NMR [6,7]

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are carried on Bruker AC-400 spectrometer using TMS as an internal standard.

Synthesis of thiocyanate (TC)

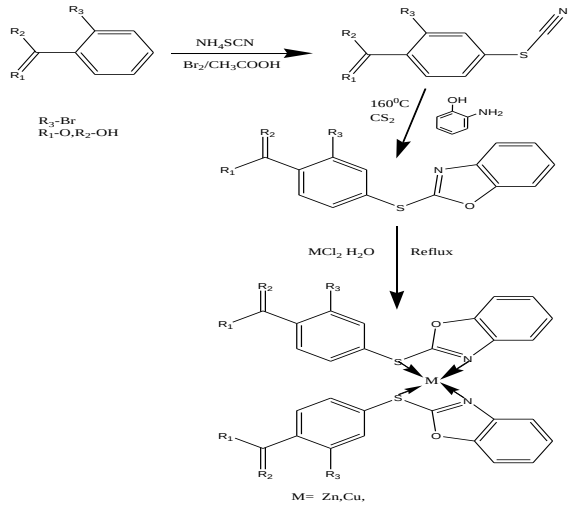
The substituted/unsubstituted benzoic acid (0.5 mol) is dissolved in acetic acid (125 ml) and the solution is added to the solution of ammonium thiocyanate (1.05 mol, 80 g) in glacial acetic acid (250 ml). This solution is cooled to 10-20ºC. To this well stirred solution, a solution of bromine (0.5 mol, 25.7 ml) in acetic acid (250 ml) is added drop wise for thirty minutes and the temperature is maintained below 20ºC. After the addition of bromine, it is kept at room temperature for ten minutes and then it is diluted with an equal amount of water. The solid thiocyanate thus formed is filtered, washed, dried and recrystallized from ethanol, which is further used in the synthesis of benoxazoles.

Synthesis of benzoxazoles

A mixture of thiocyanate TC1-TC5 (0.01 mol), o-aminophenol (0.01 mol, 1.08 g) and carbon disulphide (0.1 mol, 8 ml) is heated in an oil bath at 160ºC for 6 h. The resultant benzoxazole (BOX) is cooled and recrystallized from ethanol.

Synthesis of 4-(benzo[*d*]oxazol-2-ylthio)2-bromobenzoicacid metal complexes

4-(benzo[*d*]oxazol-2-ylthio)2-bromobenzoic acid (0.02 M) is dissolved in ethanol to which solid $M\cdot Cl_2\cdot 6H_2O$ (0.01 M) (where M= Zn/Cu) is added. The resulting reaction mixture is refluxed for 24 h in the presence catalytic amount of NH_3 with continued stirring. After completion of the reaction the resulting solid is filtered, washed with cold methanol and dried at room temperature. The proposed scheme of synthesis of the metal complexes is shown below:



Molecular Docking

The structure of the target protein is downloaded from PDB. The structure of the different compounds are drawn using ChemSketch software and the files are saved as MOL files. Docking studies are done using iGEM DOCK which is a Graphical-Automatic Drug Design System for Docking, Screening and Post-Analysis. Experimental results show that iGEMDOCK keeps the advantages of GEMDOCK and provides graphical-integrated environment for virtual screening and docking. iGEMDOCK, integrates the structure-based virtual screening and post-screening analysis, is a useful system for drug discovery. Absorption Distribution Metabolism Excretion (ADME) properties of the best docked compounds are predicted using the MEDCHEM DESIGNER software.

Results and Discussion

The complexes are isolated as sparingly soluble, coloured products from the reaction medium. They are insoluble in most common organic solvent but soluble in DMF and DMSO. The physical data of complexes prepared are given in Table 1. The molecular weight of the complexes determined by the Rast method are in good agreement with the reported data.The structures of the ligand and complexes are characterised using UV, FT-IR,^{1}H-NMR and ^{13}C-NMR spectral data**.**

Table 1. Elemental analysis and molecular weight of the ligand and complexes.

Compound	Yield (%)	M. Pt (°C)	Molecular Formula	Elemental Analysis (%) Exp. (Calc.)					M wt
				C	H	N	O	S	
Ligand	77	452-453	$C_{14}H_8S$ Br N O_3	48.02 (48.08)	2.30 (2.34)	4.00 (4.06)	13.71 (13.76)	9.16 (9.23)	350
Zn-Ligand	67	656-657	$C_{28}H_{16}$ Br_2 S_2 N_2 O_6 Zn	43.92 (39.25)	2.11 (3.12)	3.66 (3.31)	12.54 (12.70)	9.28 (9.26)	765
Cu-Ligand	71	712-713	$C_{28}H_{16}$ Br_2 S_2 N_2 O_6Cu	44.02 (44.25)	2.11 (2.01)	3.67 (3.11)	12.57 (12.45)	8.39 (8.24)	763

Electronic spectra

The electronic spectra were recorded in DMSO as solvent in the UV-Visible region [8-11]. The UV–Vis. spectra of both L and the complexes are shown below. In the UV spectrum of ligand, two characteristic absorption bands are found. An absorption band at 241 nm is due to the π-π* transition of π electrons present in aromatic ring (C=C) and imine group (−C=N). The strong absorption band at 376 nm is allocated to n-π* transition of non-bonded electrons available in imine group. UV spectra of the complexes also exhibit these characteristic n-π* and π-π* transitions however they slightly differ in position as well as the intensity, which may be the result of coordination of L with

metal centre. Besides, metal complexes reveal an extra and much significant characteristic band that appears as the result of d-d transition. This d-d transition is very useful to predict the geometry of the metal complexes. Cu(II) complex reveals this band at 540nm and it can be assigned to $^2B_{1g} \rightarrow {}^2A_{1g}$ transition, characteristic of d^9 square planar geometry In contrast, Zn(II) complex does not exhibit any d–d band because of its completely filled d^{10} transition. The UV spectrum of the ligand the copper ligand complexes are shown in figure 1(a)

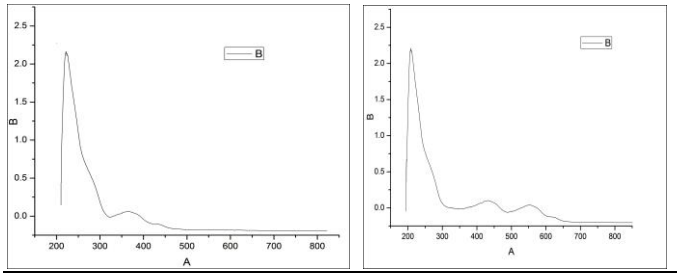


Figure 1. UV-Visible spectrum of (a) ligand and (b) Cu(II) complex.

Infrared spectra

The IR frequencies of the synthesized compounds [12] of the ligand, Zn-Ligand and Cu-Ligand are tabulated in Table 2.

Table 2. IR frequencies of the synthesized ligand, Zn-Ligand and Cu-Ligand.

Compounds	Frequency in cm^{-1}								
	OH	C=N	NH	C-H	C=C	C-O	C-Br	Zn	Cu
Ligand	2962	1682	3290	3361	1482	1142	-	-	-
Zn-Ligand	2922	1680	3100	3001	1399	1275	743	554	
Cu-Ligand	2924	1678	3210	3578	1408	1114	750	-	548

^{1}H-NMR spectra

The ^{1}H-NMR spectra of the synthesized compounds [13] of ligand and Zn-Ligand are tabulated in Table 3 and its corresponding spectrum is shown in Fig. 5. The ^{1}H-NMR spectrum of the compound shows signals indicating the presence of the Ar-H and O-H protons.

Table 3. ^{1}H-NMR signals of the compounds synthesised

Compounds	Ar-H	NH	O-H
Ligand	7.8	2.5	11.2
Zn-Ligand	7.6	3.5	10.8

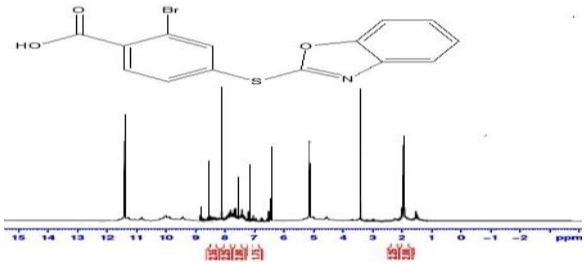


Figure 5. ^{1}H NMR spectrum of ligand.

^{13}C- NMR spectra

The following Table 4 shows the ^{13}C-NMR frequencies of the synthesized compounds which are in good agreement with the proposed structure.

Table 4. ^{13}C-NMR data.

Compounds	sp^2carbon in ppm	Chemical shift of carbonyl carbon in ppm
Ligand	39.67	174
Zn-Ligand	39.56	172

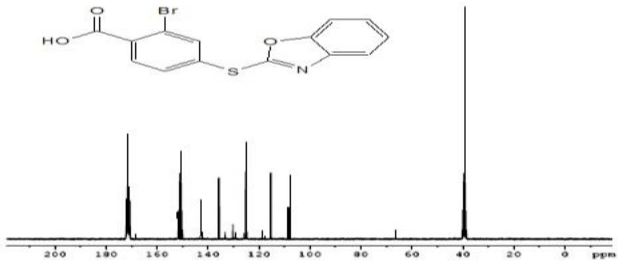


Figure 7.^{13}C-NMR spectrum of ligand.

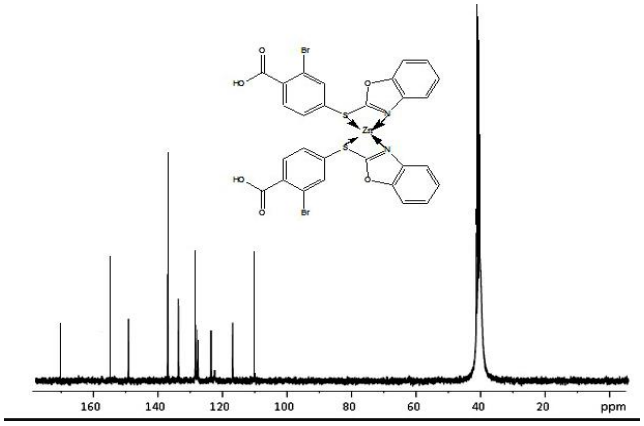


Figure 8. ^{13}C- NMR spectrum of Zn-Ligand.

Antimicrobial activity

The following table shows the anti-microbial activity of the synthesized compounds.

Table 5. Zone of inhibition of synthesized ligand, Zn-Li, Cu-Li against antimicrobial activity.

S.No	Microorganisms	Zone of inhibition in mm			
		Ligand	Zn-Ligand	Cu-Ligand	Standard
1.	*S. aureus* (NCIM 2079)	18	25	21	35
2.	*B. Subtilis* (NCIM 2063)	27	21	32	40
3.	*K. aerogenes* (NCIM 2098)	15	18	24	30
4.	*P. aeruginosa* (NCIM 2036)	25	23	18	40
5.	*A. niger* (NCIM 20105)	17	27	19	35
6.	*C. albicans* (NCIM 3102)	19	18	25	32

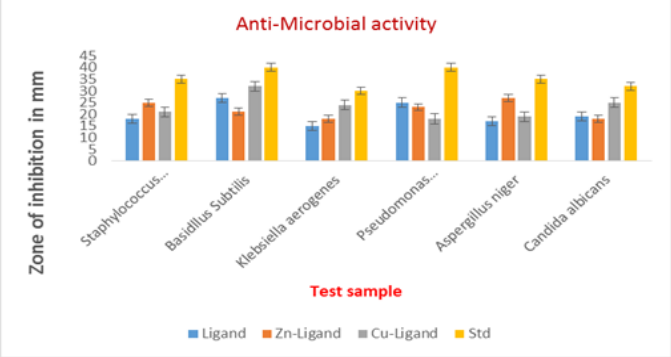


Figure 9. Antimicrobial activity of the synthesized compounds.

Anti-cancer activity

From the table 6 and figure 7 we understand that the maximum anticancer activity is shown by Cu-Ligand compound under 0.25% growth inhibition.

Table 6. Growth of inhibition % against MCF 7 Cell line.

Compounds	% Growth inhibition (µM)				
	0.25	2.5	25	50	100
Ligand	0.1270	4.2358	24.2780	39.2580	67.2351
Zn-Ligand	0.3587	2.1574	19.0210	28.5141	35.8780
Cu-Ligand	0.4540	3.1189	21.0871	37.0120	51.5870

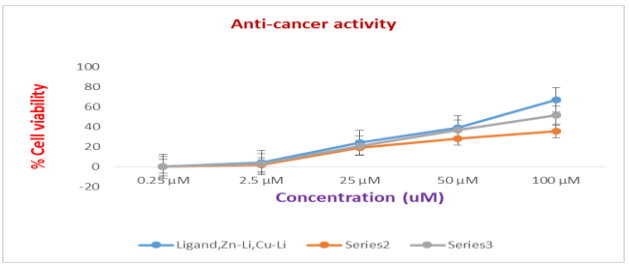


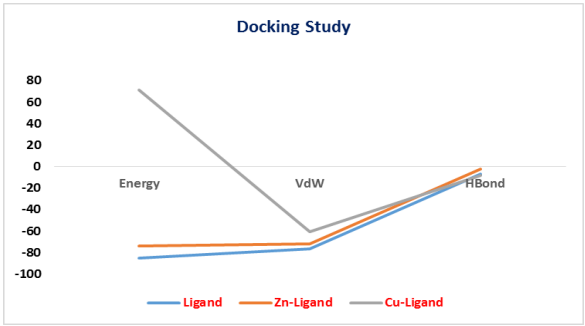
Figure 7. Anticancer activity of the synthesized compounds

Docking studies

The interaction residues and energy values of the synthesised compounds with the target are given in Table 7. Zn-Ligand compound is found to fit well with the binding sites of the target protein. The Zn-Ligand compound has a minimum energy of -84.91. They also interacted with the residues of His 21, Ala54, Ser55, and Tyr65 respectively of binding pocket. Hence the compound can be used to treat inflammation but further research is needed to formulate it as a drug. Further toxicity studies have to be done to ensure the safety and efficacy of the compound to act as a drug in treating inflammation.

Table 7. Energy values of the synthesized compounds.

S.No	Compound	Energy	VdW	HBond	Interaction
1	Ligand	-73.88	-71.85	-2.03	His 21, Tyr54, Ser55, Tyr65
2	**Zn**-Ligand	-84.91	-76.47	-6.81	His 21, Tyr54, Ser55, Tyr65
3	**Cu**-Ligand	71.06	-60.29	-8.57	Gly44, Tyr54, Ser55, Tyr65



Docking study of the synthesized compounds

Conclusions

The present work delves into the synthesis, characterization and investigation of the biological activities of metal complexes of copper and zinc with benzoxazole compounds as ligand. The structures of the ligands and the complexes are confirmed by IR, ^{1}H-NMR and ^{13}C-NMR spectra. The prepared copper complexes show more anticancer and antimicrobial activity than the zinc complexes

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