International Journal of ChemTech Research
CODEN (USA): IJCRGG, ISSN: 0974-4290, ISSN(Online):2455-9555
Vol.10 No.6, pp 321-326, 201

Biological Importance of Zn(II) and Hg(II) Ternary Complexes Derived From 2-Substituted Benzothiazoles and Amino Acids

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Abstract : Biological important ternary complexes of the type [Zn(L-L)(A-A)] and [Hg(L-L´)(A-A)] have been synthesized and characterized by molecular weight determination, magnetic measurements, infrared studies. Based on the studies, a tetrahedral geometry has been proposed for the complexes which are coloured, thermally stable, monomeric and non-electrolytic in nature. The ligands and their metal complexes are tested against pathogenic fungi Aspergillus niger and Fusarium oxysporum to assess their fungicidal properties. The antifungal activity data reveals that metal complexes are found more fungi-toxic than the parent ligands.
Keywords : Benzothiazole, Spectral studies, Conductivity, Antifungal activity.

Introduction

Benzothiazole compounds having bicycling ring system because of its occurrence in biologically active molecules found extensive application in the field of medicinal agents for antitumor, antimaleria, fungicide, anti-HIV, antiviral and analgesic[1-3]. New developments in use of benzothiazole derivatives both natural and synthetic are key components for radiolabeling of PET imaging for detecting disease like Alzheimer[4]. Furthermore, the ligands forms stable complex with different transition metal ions[5] and reacts towards biological system [6]. Other industrial application of benzothiazole found in textile dyeing, processing of rubber, as an antioxidant, fungicide [6,7]. It has been reported in literature that benzothiazole, its bio-isosters have potential against bacteria's such as Gram-negative, Gram-positive and yeast[8]. In this paper, synthesis of 2-Substituted Benzothiazoles *viz. 2-(2´-hydroxynaphthyl) benzothiazole (HNBT), 2-(2´-hydroxyphenyl) benzothiazole(HPBT),2-(2´-mercaptophenyl)benzothiazole (MPBT)* and amino acids *(*Glycine, Alanine ligands) along with Zn(II) ternary complex.

Materials & Methods:

The chemicals and all the solvents were purchased from Merck and double distilled before use.

Physical Measurements

Microanalysis was carried out at the CDRI Lucknow, India. IR spectra were recorded (with KBr pellets) on a SHIMADZU 8400 SPIR spectrophotometer. UV visible spectrophotometer, Gouy balance and Systronics Conductivity Bridge Model 305were used for recording of electronic spectra, magnetic moments and molar conductance respectively. The method of Rast Camphor was used for determination of molecular

weights. Kjeldahl method, Messenger's method and Volhard's method were used for determination of nitrogen, sulfur and chloride respectively. Gravimetrically analysis was used for estimation of zinc[9].

Synthesis of 2-Substituted Benzothiazoles (HPBT,HNBT, MPBT):

The preparation of HPBT, HNBT, MPBT was carried out in the laboratory using condensation of o-aminothiophenol (0.01 mol) with salicylic acid (0.01 mol) and thiosalicylic acid (0.01 mol) in polyphosphoric acid (25 ml). This mixture was heated under reflux and constant mixing for 3 hour at 250 C and this temperature cooled to 100° C. The alkalinity of the resultant mixture is maintained using NaOH. The final product filtered, washed, dried and recrystallized from alcohol.

Preparation of Zn(II) Ternary Complex

HPBT,MPBT and HNBT (0.004 mol each) was mixed with a solution of ZnCl2 in dry alcohol (30 ml) and refluxed using pyridine with constant stirring for 3h and kept at room temperature for 12 hours. This solution was filtered, recrystallized from alcohol and dried. The analytical and physical properties are shown in table 1 and 2.

Table-1: Analytical and physical properties of Ternary Complexes of Zn (II) of 2-substituted benzothiazoles and glycine.

S. No.	Reactant(g) Ligands			Molar Ratio	Complex and Colour	M.P. ^{0}C	Elemental Analysis Found (Calcd.)					Mol. Wt. Found (Calcd.)
	Metal halide	Glycine	Sub. benzothiazole				C	H	N	S	Zn	
1.	$ZnCl_2$ (0.95)	$C_2H_5NO_2$ (0.52)	HPBT $C_{13}H_9NOS$ (1.58)	1:1:1	$Zn(C_{15}H_{12}N_2O_3S)$ Yellowish	224	49.06 (49.26)	3.16 (3.31)	7.48 (7.66)	8.61 (8.77)	17.60 (17.88)	362.24 (365.78)
2.	$ZnCl_2$ (0.95)	$C_2H_5NO_2$ (0.52)	HNBT $C_{17}H_{11}NOS$ (1.93)	1:1:1	$Zn(C_{15}H_{12}N_2O_3S)$ Creamish	239	54.72 (54.89)	3.20 (3.39)	6.53 (6.74)	7.43 (7.71)	15.64 (15.73)	413.71 (415.79)
3.	$ZnCl_2$ (0.95)	$C_2H_5NO_2$ (0.52)	MPBT $C_{13}H_9NS_2$ (1.69)	1:1:1	$Zn(C_{15}H_{12}N_2O_3S)$ Whitish	231	47.01 (47.19)	2.92 (3.17)	7.10 (7.34)	16.67 (16.80)	16.98 (17.13)	379.12 (381.80)

Table-2 Analytical and physical properties of Ternary Complexes of Zn (II) of 2-substituted benzothiazoles and alanine

S. No.	Reactant(g) Ligands			Molar Ratio	Complex and Colour	M.P. ^{0}C	Elemental Analysis Found (Calcd.)					Mol. Wt. Found (Calcd.)
	Metal halide	Alanine	Sub. benzothiazole				C	H	N	S	Zn	
1.	$ZnCl_2$ (0.95)	$C_3H_7NO_2$ (0.62)	HPBT $C_{13}H_9NOS$ (1.58)	1:1:1	$Zn(C_{16}H_{14}N_2O_3S)$ Whitish	227	50.52 (50.61)	3.51 (3.72)	7.22 (7.38)	8.32 (8.44)	17.10 (17.23)	375.98 (379.76)
2.	$ZnCl_2$ (0.95)	$C_3H_7NO_2$ (0.62)	HNBT $C_{17}H_{11}NOS$ (1.93)	1:1:1	$Zn(C_{20}H_{16}N_2O_3S)$ Light blue	235	55.71 (55.89)	3.60 (3.75)	6.38 (6.52)	7.25 (746)	15.08 (15.21)	425.21 (429.82)
3.	$ZnCl_2$ (0.95)	$C_3H_7NO_2$ (0.62)	MPBT $C_{13}H_9NS_2$ (1.69)	1:1:1	$Zn(C_{16}H_{14}N_2O_2S_2$ Whitish	227	48.40 (48.55)	3.44 (3.56)	6.92 (7.08)	16.05 (16.20)	16.39 (17.01)	391.12 (395.82)

Table3: Antifungal screening data of the 2-Substitutedbenzothiazole ligands

Compound	Average % inhibition data of the 2-Substituted benzothiazole ligands.					
	Aspergillus niger			Fusarium oxysporum		
	50	100	200	50	100	200
HPBT	34	46	58	36	48	60
HNBT	35	47	60	37	50	61
MPBT	46	58	68	48	61	70
Bavistin (Standard)	86	98	100	87	99	100

Biological Activity

Radial growth method is employed for the biological activity of ligands (HPBT,HNBT and MPBT) and their Zn (II) ternary complexes using fungi, namely *Aspergillus niger* and *Fusarium oxysporum* in the test solution of dimethylformamide of concentration 50, 100 and 200 ppm. Measuring the fungus colony diameter after 72 hours, results in linear growth. The calculated results of antifungal activity of the ligands and Zn(II) ternary complex was compared with the conventional fungicide Bavistin and shown in table 3.

Results and Discussion

Infrared Spectra

The important IR spectral bands and their tentative assignments are presented in table 4 and 5.

Table-4 IR spectral data (cm^{-1}) of 2-substitutedbenzothiazoles

S.No.	Ligand	*v*(O-H)	*v*(S-H)	*v*(C-O) (Exo)	*v*(C-S) (Endo)	*v*(C-S) (Exo)	*v*(C=C)	*v*(C=N)	Heterocyclic Breathing mode
1.	HPBT	3330	-	1235	735	-	1590	1620	850
2.	HNBT	3345	-	1232	740	-	1580	1615	855
3.	MPBT	-	2560	-	730	1282	1582	1612	845

Table-5 IR spectral data (cm^{-1}) of ternary complexes of Zn (II) of 2-substitutedbenzothiazoles and glycine/alanine

S.No.	Complex	*v*NH_2 Asymm. Symm.	*v*(C=O)	*v*(C=C)	*v*(C=N)	*v*(Zn←N)	*v*(Zn-O)	*v*(Zn←S)
1.	[Zn(HPBT)(Gly)]	3345 3268	1662	1585	1604	450	525	-
2.	[Zn(HPBT)(Aly)]	3341 3266	1660	1583	1602	445	522	
3.	[Zn(HNBT)(Gly)]	3343 3267	1658	1584	1600	440	520	-
4.	[Zn(HNBT)(Aly)]	3338 3263	1656	1581	1598	437	517	
5.	[Zn(MPBT)(Gly)]	3335 3258	1655	1578	1596	430	515	350
6.	[Zn(MPBT)(Ala)]	3332 3255	1650	1575	1595	428	512	346

The ligands HNBT, HPBT, MPBT, Gly and Ala act as bidentate ligands in the Zn(II) ternary complex using oxygen and sulfur as donor atoms. The broad band at 3345-3330 cm^{-1} (Table 4) are attributed to *vas*(O–

H) vibration of –OH group of the free ligands (HNBT and HPBT) disappears in the respective ternary Zn (II) complex indicating the deprotonation of the -OH group and simultaneous formation of Zn-O bonds. This gets further support by the appearance of new bands of medium intensity in the region 525-512 cm^{-1} (Table 5) due to *ν*(Zn-O) vibrations respectively. The absorption band in the region 2560 cm^{-1} due to *ν*(S-H) vibration of –SH group of the free ligand MPBT, disappeared in the IR spectra of respective ternary Zn(II) complexes, suggesting the deprotonation of –SH group and simultaneously formation of Zn-S bonds due to the appearance of non-ligand vibrations respectively. This get further supported by the appearance of bands of medium intensity in the region 350-346 cm^{-1} assignable to *ν*(Zn-S) vibrations respectively. In the IR spectra Zn(II) complex the broad band's observed in the region 3335-3345 cm^{-1} are assigned to *vas*(N–H) and *vs*(N–H) vibrations of–NH2 group of glycine/alanine, indicating the coordination due to support by the appearance of non-ligand bands of medium intensity in the region 450-428 cm^{-1} due to *ν*(Zn←N) vibrations [10,11] respectively. The absorption bands appeared in the region 1650-1662 cm^{-1} in the IR spectra of all these ternary Zn(II) complexes are assignable to *ν*(C=O) stretching vibration of coordinated –COO^- group of the glycine/alanine moiety. The IR spectra of free ligand (HPBT,HNBT and MPBT) exhibit medium intense bands in region 1620-1612 cm^{-1} due to *ν*(C=N) stretching vibration [12], are shifted to the lower wave number by 10-20 cm^{-1} and becoming larger and sharper in the spectra of respective ternary Zn(II) complex, indicating the coordination through tertiary nitrogen atom of benzoxazolyl/benzothiazole moiety with the Zn atom [13,14]. It further conformed by the appearance of non-ligand bands in the region 450-428 cm^{-1} *ν* (Zn←N)[15,16] vibrations in all these ternary complexes.

^{1}H NMR spectra

The bonding pattern in the resulting ternary Zn(II) complexes have been further conformed by ^{1}H NMR spectra of the ternary complexes and their starting materials (HPBT, HNBT, MPBT, glycine and alanine) in DMSO-d6 using tetramerhylsilane as the internal standard. The ^{1}H NMR spectra of the free ligand glycine/alanine show a broad singlet (Table 6) at δ3.68-3.77ppm due to –NH_2 proton, is shifted down field in the respective ternary Zn(II) complexes, suggesting the coordination through nitrogen atom of –NH_2 group with Zn atom. The broad singlet in the region δ10.30-10.33ppm assigned to –OH proton of the free ligand HPBT,HNBT,MPBT and glycine/alanine disappearing in the ^{1}H NMR spectra of corresponding ternary Zn(II) complexes indicating thereby the deprotonation of –OH group and coordination of the phenolic oxygen to the Zn atom.

Table-6 ^{1}H NMR spectral data (δ, ppm) of ternary complexes of Zn (II) of 2-substituted benzothiazoles and glycine/alanine

S.No.	Complexes	-NH_2 (bs)	-CH_3 (d)	-CH_2 (s)	-CH (q)	Aromatic (m)
1.	[Zn(HPBT)(Gly)]	3.70	-	3.64	-	6.99-8.45
2.	[Zn(HPBT)(Ala)]	3.68	1.29		3.68	6.99-8.45
3.	[Zn(HNBT)(Gly)]	3.73	-	3.63	-	7.15-8.49
4.	[Zn(HNBT)(Ala)]	3.71	1.30		3.66	7.13-8.47
5.	[Zn(MPBT)(Gly)]	3.77	--	3.61	-	7.23-8.54
6.	[Zn(MPBT)(Ala)]	3.75	1.33		3.65	7.20-8.50

The ^{1}H NMR spectra of free ligand MPBT exhibit singlet at δ 4.50-4.52 ppm due to –SH (thiophenolic proton), dis appeared in the spectra of respective ternary Zn(II) complex, suggesting the deprotonation of the –SH group and coordination of thiophenolic sulphur to the Zn atom. The ^{1}H NMR spectra of ternary Zn(II) complexes exhibit doublet at δ1.29-1.33ppm due to –CH_3 proton, quintet at δ3.65-3.68 ppm due to –CH proton of alanine and singlet at δ3.61-3.64 ppm due to –CH_2 proton of glycine. Aromatic protons observed at δ 6.96-8.58 ppm as multiplet in the ^{1}H NMR spectra of ligands (HPBT,HNBT and MPBT) shifted down field (δ 0.5-1.5ppm) in the spectra of respective ternary Zn(II) complexe which may be possibly due to deshielding on coordination of ligand molecules with Zn atom[17,18].

Magnetic Studies:

The room temperature magnetic moments of the ternary Zn(II) complex indicates the diamagnetic nature of the Zn(II) ions. The zero value of the magnetic moments of the complex is the characteristic of Zn(II) in the distorted tetrahedral structure.

Biological Activity

The three ligands (HPBT,HNBT and MPBT) and their Zn(II) ternary complex were screened against pathogenic fungi *Aspergius niger* and *Fusarium oxysporum,* to assess their growth inhibitory potential as antifungal agents. The antifungal screening data (Table 3) reveal that the Zn(II) ternary complex are more fungitoxic than the parent ligands (HPBT,HNBT and MPBT). The enhanced activity of the Zn(II)/Hg(II) ternary complexes may be ascribed to the increased lipophilic nature of these complexes arising due to the chelation [19,20]. The toxicity increased as the concentration was increased. The antifungal activity data also reveals that Zn(II) ternary complexes of MPBT and Gly/Ala are more fungitoxic than the complexes of HPBTand HNBT [17] ligands, respectively.It conform that complexes of soft acids are more active because it can bind to the –SH group of the cell enzyme more strongly. This can be explained by chelation theory. Due to chelation, the lipophilic nature of the metal increases which subsequently favour its permeation through the semipereable defences of cell membrane of microorganisms and thereby, impairing normal cell process[21,22].

Conclusion

Synthesis of 2-Substituted Benzothiazoles viz. 2-(2´-hydroxynaphthyl) benzothiazole (HNBT), 2-(2´-hydroxyphenyl)benzothiazole(HPBT), 2-(2´-mercaptophenyl)benzothiazole (MPBT) and amino acids *(*Glycine, Alanine ligands) along with Zn(II) ternary complex have been described. The structure has been established based on the spectral studies. The ligand biological activity found to be less than the complexes which proves that the effectiveness of metal is more than the antimicrobial behavior of ligand.

Acknowledgement

The authors are thankful to Amity University Rajasthan for their full support in this study.

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