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Synthesis, Characterization and Biological Activities of Mercury(II) Ternary Complexes of 2-Substituted Benzothiazoles Derivatives

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Biological important ternary complexes of type [HgL(A-A)] [where L = 2-(2'-hydroxynaphthyl)benzothiazole (APBT), 2-(2'-hydroxyphenyl)benzothiazole (HPBT), 2-(2'-mercapto-phenyl)benzothiazole (MPBT)] (A = glycine or alanine) have been synthesized and characterized by m.w. determination, magnetic measurements, infrared and NMR studies. A tetrahedral geometry has been proposed for the present mercury(II) complexes. All the complexes are coloured, thermally stable, monomeric and non-electrolytic in nature. The ligands and their metal complexes showed biological activity against pathogenic fungi *Aspergillus niger* and *Fusarium oxysporum*. The antifungal activity data revealed that mercury(II) complexes are found more fungi-toxic than the parent ligands.

Keywords: Benzothiazole, Amino acids, Mercury(II) complexes, Antifungal activity.

INTRODUCTION

In recent years, the synthesis of transition metal compounds, as important semiconductors materials, has attracted wide attention due to their physical and chemical properties in various fields, such as catalysis, sensors, solar cells, photo detector, light emitting diodes, and laser communication, have made them very attractive [1-4]. Linear complexes of mercury(II) forms stable complexes with two sulfur donor ligands. However, Hg^{II}-thiol bonds are labile and for higher Hg-S coordination numbers, the structures are flexible, often with distorted trigonal or tetrahedral coordination structures [5].

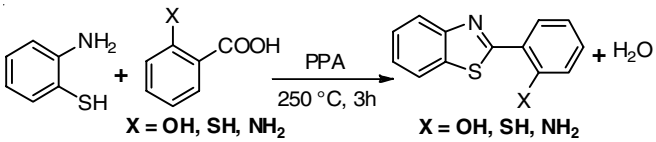
Benzothiazole derivatives played an important role in structural formation of many biological, dye compounds and pharmaceutical [6-10]. They used as cytotoxic agents [11], cathepsin S inhibitors [12], HIV reverse transcriptase inhibitors [13], estrogen receptor agonists [14], selective peroxisome proliferator activated receptor antagonists [15], anticancer agents [16] and orexin-1 receptor antagonists [17]. Benzothiazole derivatives are used as both natural and synthetic are key components for radiolabeling of PET imaging for detecting disease like alzheimer [18].

Furthermore, benzothiazole derivatives as ligand forms stable complex with different transition metal ions [19] and also showed promising biological activities [20]. Other industrial applications of benzothiazole found in textile dyeing, processing of rubber, as an antioxidant, fungicide, *etc*. [20,21]. It has been reported in literature that benzothiazole, its bio-sisters have potential against bacteria's such as Gram-negative, Gram-positive and yeast [22]. Pal *et al*. [23] also reported the synthesis of Zn(II) complex of benzothiazole derivatives having potential antifungal and antibacterial activities. In this article, we reported a synthetic protocol for the synthesis of 2-substituted benzothiazoles *viz*. 2-(2′-hydroxynaphthyl)benzothiazole (APBT), 2-(2′-hydroxyphenyl)benzothiazole (HPBT), 2-(2′-mercapto-phenyl)benzothiazole (MPBT) and amino acids (glycine, alanine) along with Hg(II) ternary complex.

EXPERIMENTAL

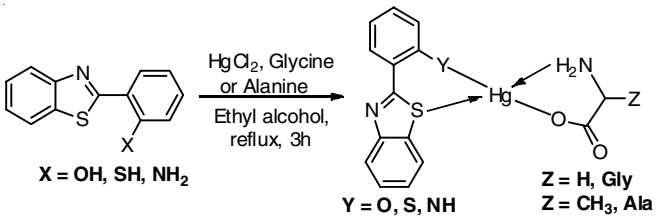
The chemicals and the solvents were purchased from CDH and double distilled before use. Microanalysis was carried out at Department of Chemistry, Rajasthan University, Jaipur, India. IR spectra were recorded (using KBr pellets) on a SHIMADZU 8400 SPIR spectrophotometer. UV-visible spectrophotometer, Gouy balance and Systronics Conductivity Bridge Model 305 were used for recording of electronic spectra, magnetic moments and molar conductance, respectively. The rast camphor method was used for determination of molecular weights. Gravimetric analysis was used for estimation of mercury [24].

Synthesis of 2-substituted benzothiazoles: The synthesis of 2-(2′-hydroxynaphthyl)benzothiazole (APBT), 2-(2′-hydroxyphenyl)benzothiazole (HPBT), 2-(2′-mercapto-phenyl)benzothiazole (MPBT) was carried out by condensing *o*-aminothiophenol (0.01 mol) with salicylic acid (0.01 mol), thiosalicylic acid (0.01 mol) and anthranilic acid (0.01) in polyphosphoric acid (PPA) (25 mL). This mixture was heated under reflux with constant stirring for 3 h at 250 °C and cooled at room temperature. The alkalinity of the resultant mixture is maintained using NaOH. The final product filtered, washed, dried and recrystallized from alcohol (**Scheme-I**).



Scheme-I: Synthesis of benzothiazole derivatives

Synthesis of Hg(II) ternary complexes: The corresponding ligand *viz.*, 2-(2′-Hydroxynaphthyl)benzothiazole (APBT), 2-(2′-hydroxyphenyl)benzothiazole (HPBT) or 2-(2′-mercapto-phenyl)benzothiazole (MPBT) (0.004 mol each) was mixed with a solution of $HgCl_2$, amino acids (glycine or alanine) and pyridine in dry alcohol (30 mL) and refluxed it with constant stirring for 3 h and kept at room temperature for 12 h. This solution was filtered, recrystallized from alcohol and dried under vacuum (**Scheme-II**).



Scheme-II: Synthesis of Hg(II) ternary complex of benzothiazole derivatives and amino acids

Biological activity: Radial growth method is employed for the biological activity of ligands (HPBT, APBT and MPBT) and their Hg (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 h, results in linear growth. The calculated results of antifungal activity of the ligands and Hg(II) ternary complex was compared with the conventional fungicide bavistin.

RESULTS AND DISCUSSION

IR studies: The IR spectral bands and their tentative assigned peaks are presented in Tables 1 and 2. The ligands APBT, HPBT, MPBT with glycine or alanine amino acid act as bidentate ligands in Hg(II) ternary complex using oxygen, sulfur and nitrogen as donor atoms. The broad band at 3340-3328 cm^{-1} (Table-1) are attributed to ν(O-H) vibration of -OH group of the free ligands (HPBT) disappears in the respective ternary Hg(II) complex indicating the deprotonation of the -OH group and simultaneous formation of Hg-O bonds. The formation of Hg-O bond further support by the appearance of new bands of medium intensity in the region 535-521 cm^{-1} (Table-2) due to ν(Hg-O) vibrations respectively. The IR peak in the region 2582 cm^{-1} due to ν(S-H) vibration of -SH group of free ligand MPBT, disappeared in the IR spectra of respective ternary Hg(II) complexes, suggested the deprotonation of -SH group and simultaneously formation of Hg-S bonds due to the appearance of non-ligand vibrations, respectively. This is further supported by the appearance of bands of medium intensity in the region 357-352 cm^{-1} assignable to ν(Hg-S) vibrations, respectively. In the IR spectra Hg(II) complex the broad band's observed in the region 3355-3348 cm^{-1} are assigned to ν(N-H) and ν(N-H) vibrations of -NH_2 group of glycine/alanine, indicating the coordination due to support by the appearance of non-ligand bands of medium intensity in the region 455-437 cm^{-1} due to ν(Hg←N) vibrations [25,26]. The absorption bands appeared in the region 1672-1655 cm^{-1} of IR spectra for all these ternary Hg(II) complexes, which is assignable to ν(C=O) stretching vibration of coordinated carboxylate group of glycine/alanine moiety. The IR spectra of free ligand (HPBT, APBT and MPBT) exhibit medium intense bands in region 1615-1592 cm^{-1} due to ν(C=N) stretching vibration [27], are shifted to the lower wave number by 10-20 cm^{-1} and becoming larger and sharper in the spectra of respective ternary Hg(II) complex, indicated the

TABLE-1
KEY IR BANDS (cm^{-1}) OF 2-SUBSTITUTED BENZOTHIAZOLES

Ligand	ν(O-H)	ν(S-H)	ν(C-O) (Exo)	ν(NH_2) asym/sym	ν(C-S) (Exo)	ν(C=C)	ν(C=N)	Heterocyclic breathing mode
HPBT	3340	–	1231	–	–	1586	1617	853
MPBT	–	2570	1214	–	1279	1589	1621	861
APBT	–	–	–	3369/3251	–	1591	1615	869

TABLE-2
KEY IR BANDS (cm^{-1}) OF TERNARY COMPLEXES OF Hg(II) OF 2-SUBSTITUTEDBENZOTHIAZOLES AND AMINO ACIDS

Complex	ν(NH_2) asym./sym.	ν(C=O)	ν(C=C)	ν(C=N)	ν(Hg←N)	ν(Hg-O)	ν(Hg←S)
[Hg(HPBT)(Gly)]	3348, 3267	1672	1586	1615	455	535	363
[Hg(HPBT)(Aly)]	3342, 3267	1669	1581	1608	445	529	360
[Hg(MPBT)(Gly)]	3339, 3265	1663	1580	1601	443	519	359
[Hg(MPBT)(Aly)]	3337, 3258	1665	1576	1597	441	521	346
[Hg(APBT)(Gly)]	3334, 3265	1650	1571	1594	433	526	365
[Hg(APBT)(Ala)]	3331, 3255	1655	1579	1592	437	511	361

TABLE-3
^{1}H NMR DATA (δ) OF TERNARY COMPLEXES OF MERCURY(II) OF 2-SUBSTITUTED BENZOTHIAZOLES AND GLYCINE/ALANINE

Complexes	-NH_2 (bs)	-CH_3 (d)	-CH_2 (s)	-CH (q)	Aromatic (m)
[Hg(HPBT)(Gly)]	3.77	-	3.65	-	6.98-8.40
[Hg(HPBT)(Ala)]	3.63	1.26	-	3.65	6.94-8.43
[Hg(MPBT)(Gly)]	3.71	-	3.61	-	7.12-8.45
[Hg(MPBT)(Ala)]	3.74	1.30	-	3.64	7.13-8.50
[Hg(APBT)(Gly)]	3.75	-	3.63	-	7.21-8.56
[Hg(APBT)(Ala)]	3.73	1.38	-	3.62	7.23-8.55

coordination through secondary oxygen atom of benzoxazolyl moiety with Hg atom [28,29]. It is further confirmed by the appearance of non-ligand bands in the region 455-437 cm^{-1} in all these ternary complexes [30,31].

^{1}H NMR studies: The bonding pattern in the resulting ternary Hg(II) complexes have been further confirmed by ^{1}H NMR spectra of the ternary complexes and their ligands (substituted benzothiazoles and amino acids) in DMSO-d_6 using tetramethylsilane as the internal standard. The ^{1}H NMR spectra of the free ligand glycine/alanine show a broad singlet (Table-3) at δ 3.60-3.75 ppm due to -NH_2 proton, is shifted to down field (δ 3.63-3.77 ppm) in the respective ternary Hg(II) complexes, suggesting the coordination through nitrogen atom of -NH_2 group with Hg atom. The broad singlet in the region δ 10.28-10.31 ppm assigned to -OH proton of the free ligand HPBT, APBT, MPBT and glycine/alanine disappearing in the ^{1}H NMR spectra of corresponding ternary Hg(II) complexes indicating thereby the deprotonation of -OH group and coordination of the phenolic oxygen to Hg atom.

The ^{1}H NMR spectra of free ligand MPBT exhibited a singlet at δ 4.48-4.50 ppm due to -SH (thiophenolic proton), disappeared in the spectra of respective ternary Hg(II) complex, suggesting the deprotonation of -SH group and coordination of thiophenolic sulphur to Hg atom. The ^{1}H NMR spectra of ternary Hg(II) complex exhibited doublet at δ 1.26-1.30 ppm due to -CH_3 proton, quintet at δ 3.62-3.65 ppm due to -CH proton of alanine and singlet at δ 3.61-3.65 ppm due to -CH_2 proton of glycine. Aromatic protons observed at δ 6.98-8.55 ppm as multiplet in the ^{1}H NMR spectra of ligands (HPBT, APBT and MPBT) shifted down field (δ 0.5-1.5ppm) in the spectra of respective ternary Hg(II) complex, which may be possibly due to deshielding on coordination of ligand molecules with Hg atom [32,33].

Magnetic studies: The magnetic moment values ofternary Hg(II) complex at room temperature indicates the diamagnetic nature of Hg(II) ions. The zero value of magnetic moments of the complex is the characteristic of Hg(II) in the distorted tetrahedral structure.

Biological activity: Three ligands [2-(2′-hydroxynaphthyl)-benzothiazole (APBT), 2-(2′-hydroxyphenyl)benzothiazole (HPBT), 2-(2′-mercaptophenyl)benzothiazole (MPBT)] and their Hg(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-4) revealed that Hg(II) ternary complexes showed greater antifungal activity than the parent ligands (HPBT, APBT and MPBT). The enhanced activity of Hg(II) ternary complexes may be ascribed to the increased lipophilic nature of these complexes arising due to the chelation [34,35]. The toxicity increased as the concentration was increased. The antifungal activity data also revealed that Hg(II) ternary complexes of APBT and gly/ala showed more antifungal activity than Hg complexes of HPBT and MPBT ligands with amino acids, respectively. It also confirmed that complexes of soft acids are more active because -NH_2 group of APBT ligand can bind to the cell enzyme more strongly. This can be explained by chelation theory. Due to chelation, the lipophilic nature of metal increases which subsequently favour its permeation through the semipereable defences of cell membrane of microorganisms and thereby, impairing normal cell process [36,37].

TABLE-4
ANTIFUNGAL SCREENING DATA OF
2-SUBSTITUTED BENZOTHIAZOLE LIGAND

Compound	Average % inhibition					
	Aspergillus niger			*Fusarium oxysporum*		
	50	100	200	50	100	200
HPBT	36	45	62	37	47	64
MPBT	38	44	63	34	56	68
APBT	46	51	69	48	68	76
[Hg(HPBT)(Gly)]	32	46	52	31	43	56
[Hg(HPBT)(Aly)]	31	42	58	37	45	52
[Hg(MPBT)(Gly)]	30	48	61	38	47	59
[Hg(MPBT)(Aly)]	34	42	63	36	49	61
[Hg(APBT)(Gly)]	47	54	71	47	71	79
[Hg(APBT)(Ala)]	46	56	73	45	74	81
Bavistin (standard)	86	96	103	87	99	105

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