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Synthesis and Characterization of Antifungal and Antibacterial Hg(II) Ternary Complexes of 2-Substituted Benzoxazoles and their derivatives

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Abstract : Biological important ternary complexes of the type [Hg(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 : Benzoxazole, Spectral studies, Conductivity, Antifungal activity.

Introduction:

Benzoxazole derivatives are important structural motifs in many biological, pharmaceutical and dye compounds.[1] They are used as cytotoxic agents,[2]cathepsin S inhibitors,[3] HIV reverse transcriptase inhibitors,[4] estrogen receptor agonists,[5] selective peroxisome proliferator activated receptor antagonists,[6] anticancer agents,[7] and orexin-1 receptor antagonists.[8]Benzoxazole derivatives are used as both natural andsynthetic are key components for radiolabeling of PET imaging for detecting disease like Alzheimer.[9]Furthermore, the ligands forms stable complex with different transition metal ions[10] and also showingbiologicalactivity.[11] Other industrial application of Benzoxazole found in textile dyeing, processing of rubber, as an antioxidant, fungicide.[11-12] It has been reported in literature that Benzoxazole, its bio-sistershave potential against bacteria's such as Gram-negative, Gram-positive and yeast.[13]Pal et al. also synthesized the antifungal and antibacterial compounds of Zn(II) complex of benzothaizole derivatives.[14]In this paper, we are reporting a synthetic protocol forthe synthesis of2-Substituted Benzoxazoles viz. 2-(2´-hydroxynaphthyl)Benzoxazole (APBO), 2-(2´-hydroxyphenyl) Benzoxazole(HPBO),2-(2´-mercaptophenyl)Benzoxazole (MPBO) and amino acids (Glycine, Alanine ligands) along with Hg(II) ternary complex.

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Materials & Methods:

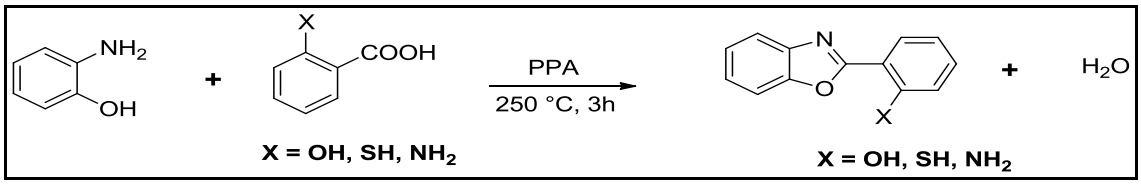
The chemicals and all the solvents were purchased from Merck and double distilled before use.

Physical Measurements

Microanalysis was carried out at the Rajasthan University, Jaipur, 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 Mercury.[15]

Synthesis of 2-Substituted Benzoxazoles (HPBO, APBO, MPBO):

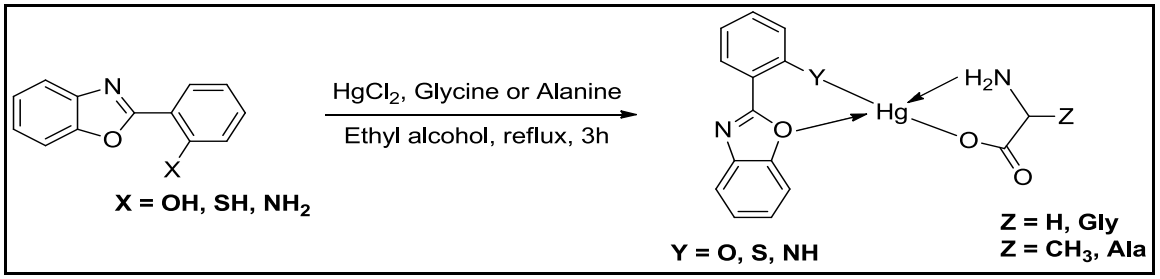
The preparation of HPBO, APBO, MPBO was carried out in the laboratory using condensation of o-aminophenol (0.01 mol) with salicylic acid(0.01 mol),thiosalicylic acid (0.01 mol) andanthranilic acid (0.01) in polyphosphoric acid (25 ml). This mixture was heated under reflux and constant mixing for 3 hour at 250˚ C and cooled at room temperature. The alkalinity of the resultant mixture is maintainedusingNaOH. The final product filtered, washed, dried and recrystallized from alcohol.



Scheme 1: Synthesis of Benzoxazole derivatives

Preparation of Hg(II) Ternary Complex

HPBO,MPBO and APBO (0.004 mol each) was mixed with a solution of $HgCl_2$ in dry alcohol (30 ml) and refluxed using pyridine with constant stirring for 3hours and kept at room temperature for 12 hours. This solution was filtered, recrystallized from alcohol and dried under vacuum. The analytical and physical properties are shown in table 1 and 2.



Scheme 2: Preparation of Hg(II) Ternary Complexof Benzoxazole derivatives

Biological Activity

Radial growth method is employed for the biological activity of ligands (HPBO, APBO and MPBO) and their Hg (II) ternary complexes using fungi, namely *Aspergillusniger*and*Fusariumoxysporum*in the test solution ofdimethylformamide 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 Hg(II) ternary complex was compared with the conventional fungicide Bavistin and shown in table 3.

Results and Discussion

Infrared Spectra

The IR spectral bands and their tentative assigned peaks are presented in table 4 and 5. The ligands APBO, HPBO, MPBO with glycine and alanine amino acid act as bi-dentate ligands in the Hg(II) ternary complex using oxygen, sulfur and nitrogen as donor atoms. The broad band at 3345-3330 cm^{-1} (Table 4) are attributed to *ν*(O–H) vibration of –OH group of the free ligands (HPBO) 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 530-515 cm^{-1} (Table 5) 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 the free ligand MPBO, disappeared in the IR spectra of respective ternary Hg(II) complexes, suggesting the deprotonation of –SH group and simultaneously formation of Hg-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 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 3342-3350 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 458-435 cm^{-1} due to ν(Hg←N) vibrations[16-17] respectively. The absorption bands appeared in the region 1658-1670 cm^{-1} in the IR spectra of all these ternary Hg(II) complexes are assignable to *ν*(C=O) stretching vibration of coordinated carboxylate group of the glycine/alanine moiety. The IR spectra of free ligand (HPBO, APBO and MPBO) exhibit medium intense bands in region 1595-1610 cm^{-1} due to *ν*(C=N) stretching vibration[18], 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, indicating the coordination through secondaryoxygen atom of benzoxazolyl moiety with the Hg atom.[19-20] It further conformed by the appearance of non-ligand bands in the region 458-435cm^{-1}*ν*(Hg←N)[21-22] vibrations in all these ternary complexes.

^{1}H NMR spectra

The bonding pattern in the resulting ternary Hg(II) complexes have been further conformed by ^{1}H NMR spectra of the ternary complexes and their starting materials (HPBO, APBO, MPBO, glycine and alanine) 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 6) at δ3.68–3.77ppm due to –NH_2 proton, is shifted to down field (δ 3.66–3.80 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 δ10.30-10.33ppm assigned to –OH proton of the free ligand HPBO,APBO,MPBO 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 the Hg atom.

The ^{1}H NMR spectra of free ligand MPBO exhibit singlet at δ 4.50-4.52 ppm due to –SH (thiophenolic proton), disappeared in the spectra of respective ternary Hg(II) complex, suggesting the deprotonation of the –SH group and coordination of thio-phenolic sulphur to the Hg atom. The ^{1}H NMR spectra of ternary Hg(II) complexes exhibit doublet at δ1.29-1.33ppm due to –CH_3 proton, quintet at δ3.63-3.68 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 (HPBO,APBO and MPBO) shifted down field (δ 0.5-1.5ppm) in the spectra of respective ternary Hg(II) complexe which may be possibly due to deshielding on coordination of ligand molecules with Hg atom.[23-24]

Magnetic Studies:

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

Biological Activity

The three ligands (HPBO, APBO and MPBO) 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. Theantifungal screening data (Table 3) reveal that the Hg(II) ternary complexes are showing greater antifungal activity than the parent ligands (HPBO, APBO and MPBO). The enhanced activity of the Hg(II) ternary complexes may be ascribed to the increased lipophilic nature of these complexes arising due to the chelation.[25-26]The toxicity increased as the concentration was increased. The antifungal activity data also reveals that Hg(II) ternary complexes of APBO and Gly/Ala are showing more antifungal activity than the Hg complexes of HPBO and MPBO ligands with Gly/Ala amino acids, respectively. It conform that complexes of soft acids are more active because $–NH_2$ group of the APBO ligand can bind to 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 semipermeable defences of cell membrane of microorganisms and thereby, impairing normal cell process.[27-28]

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

S. No.	Reactant(g) Ligands			Molar Ratio	Complex and Colour	M.P. (°C)	Elemental Analysis Found (Calcd.)						M. W. Found (Calcd.)
	Metal Halide	Glycine	Benzoxazole Derivatives				C	H	N	O	S	Hg	
1.	$HgCl_2$ (0.85)	$C_2H_5NO_2$ (0.23)	HPBO $C_{13}H_9NO_2$ (0.66)	1:1:1	$Hg(C_{15}H_{12}N_2O_4)$ Yellowish	239	36.06 (37.15)	2.36 (2.49)	5.56 (5.77)	12.56 (13.19)	---	40.60 (41.37)	479.24 (484.85)
2.	$HgCl_2$ (0.85)	$C_2H_5NO_2$ (0.23)	MPBO $C_{13}H_9NOS$ (0.71)	1:1:1	$Hg(C_{15}H_{12}N_2O_3S)$ Light Yellowish	244	35.78 (35.97)	2.30 (2.41)	5.42 (5.59)	9.11 (9.58)	6.18 6.40	39.88 (40.04)	498.29 (500.93)
3.	$HgCl_2$ (0.85)	$C_2H_5NO_2$ (0.23)	APBO $C_{13}H_{10}N_2O$ (0.65)	1:1:1	$Hg(C_{15}H_{13}N_3O_3)$ Light Greenish	233	36.01 (37.23)	2.52 (2.70)	7.10 (8.68)	9.17 (9.91)	----	40.12 (41.45)	481.24 (483.87)

Table 2: Analytical and physical properties of Ternary Complexes of Hg(II) of 2-substituted benzoxazole and alanine.

S. No.	Reactant(g) Ligands			Molar Ratio	Complex and Colour	M.P. (°C)	Elemental Analysis Found (Calcd.)					M. W. Found (Calcd.)
	Metal Halide	Alanine	Benzoxazole Derivatives				C	H	N	S	Hg	
1.	$HgCl_2$ (0.85)	$C_3H_7NO_2$ (0.27)	HPBO $C_{13}H_9NO_2$ (0.66)	1:1:1	$Hg(C_{16}H_{14}N_2O_4)$ Yellowish	241	40.52 (38.52)	3.56 (2.82)	6.22 (5.61)	-	43.10 (40.20)	510.98 (498.88)
2.	$HgCl_2$ (0.85)	$C_3H_7NO_2$ (0.27)	MPBO $C_{13}H_9NOS$ (0.71)	1:1:1	$Hg(C_{16}H_{14}N_2O_3S)$ Light blue	245	39.71 (37.32)	3.61 (2.75)	6.38 (5.44)	7.25 (6.22)	41.08 (38.95)	525.21 (514.94)
3.	$HgCl_2$ (0.85)	$C_3H_7NO_2$ (0.72)	APBO $C_{13}H_{10}N_2O$ (0.65)	1:1:1	$Hg(C_{16}H_{15}N_3O_3)$ Whitish	235	41.40 (38.60)	3.84 (3.03)	9.92 (8.43)	-	44.39 (40.28)	509.12 (497.88)

Table 3: Antifungal screening data of the 2-Substitutedbenzoxazole ligands

Compound	Average % inhibition data of the 2-Substituted benzothiazole ligands.					
	Aspergillus Niger			*FusariumOxysporum*		
	50	**100**	**200**	**50**	**100**	**200**
HPBO	35	47	61	38	46	62
MPBO	36	48	61	38	51	65
APBO	47	59	68	49	63	73
Bavistin(Standard)	85	97	101	86	100	103

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

S.No	Ligand	*v*(O-H)	*v*(S-H)	*v*(C-O) (Exo)	vNH_2asym/sym	*v*(C-S) (Exo)	*v*(C=C)	*v*(C=N)	Heterocyclic Breathing mode
1.	HPBO	3345	-	1238	-	-	1593	1621	858
2.	MPBO	-	2582	1218	-	1285	1585	1624	863
3.	APBO	-	-	-	3372/3255	-	1586	1618	865

Table 5: IR spectral data (cm^{-1}) of ternary complexes of Hg(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*(Hg←N)	*v*(Hg-O)	*v*(Hg←S)
1.	[Hg(HPBO)(Gly)]	3342 3265	1670	1588	1610	458	530	-
2.	[Hg (HPBO)(Aly)]	3340 3268	1666	1585	1605	450	525	-
3.	[Hg (MPBO)(Gly)]	3340 3263	1660	1581	1597	446	516	357
4.	[Hg (MPBO)(Aly)]	3335 3260	1662	1578	1595	442	522	352
5.	[Hg (APBO)(Gly)]	3338 3261	1652	1574	1592	437	520	-
6.	[Hg (APBO)(Ala)]	3335 3250	1658	1572	1590	435	515	-

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

S.No.	Complexes	-NH_2 (bs)	-CH_3 (d)	-CH_2 (s)	-CH (q)	Aromatic (m)
1.	[Hg (HPBO)(Gly)]	3.80	-	3.64	-	6.96-8.41
2.	[Hg (HPBO)(Ala)]	3.66	1.29	-	3.68	6.94-8.41
3.	[Hg (MPBO)(Gly)]	3.74	-	3.60	-	7.14-8.47
4.	[Hg (MPBO)(Ala)]	3.76	1.32	-	3.65	7.11-8.45
5.	[Hg (APBO)(Gly)]	3.79	-	3.61	-	7.24-8.52
6.	[Hg (APBO)(Ala)]	3.77	1.30	-	3.63	7.21-8.54

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