Synthesis and Characterization of Mercuric Bromide-Phenothiazine Complexes

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ABSTACT

N-alkylphenothiazines (NAPTZs) are biologically active heterocyclic compounds that find extensive applications in the field of medicine. In the pharmaceutical industry, they are used as psychotherapeutic, antiemetic, and antihistaminic drugs. In this study, complexation reactions of mercuric bromide with NAPTZs as principal ligands have been investigated in MeOH medium. Five mercuric bromide complexes of the NAPTZ ligands namely, chlorpromazine hydrochloride (CP.HCl), promethazine hydrochloride (PM.HCl), ethopropazine hydrochloride (EP.HCl), trifluoperazine dihydrochloride (TF.2HCl) and thioridazine hydrochloride (TR.HCl) have been synthesized. These complexes were subjected to elemental analysis, solubility, molar conductance magnetic susceptibility, I.R, and NMR spectroscopy. The molecular formulations of the complexes have been found to be: $[HgBr_2(CP)_2].4H_2O$; $[HgBr_2(PM)_2].2H_2O$; $[HgBr_2(EP)_2]$; $[HgBr_2(TF)_2].2H_2O$ and $[HgBr_2(TR)_2]$. Tentative molecular structures have been proposed and presented.

Keywords: synthesis, characterization, complexes, mercury(II) bromide, phenothiazines

I. INTRODUCTION

N-alkylphenothiazines (NAPTZs) are biologically active heterocyclic compounds that possess large spectrum of biological applications such as tranquilizers, antihistaminic, antipsychotic, anticholinergic, antiemetic, anti-inflammatory, sedative, cytostatic, antimalarial, antitubercular, analgesic and antimicrobial (antifungal and antibacterial) [1,2]. However, in recent years coordinating behavior of NAPTZs has gained much importance in the pharmaceuticals and chemical analysis [3, 4]. Till date, few studies have been reported for transition metal complexes with phenothiazines [5 - 9]. Recently, *in vivo* studies in rats with ruthenium(II) complexed with N-alkylphenothiazines demonstrated free radical scavenging activity [8]. Similarly, other phenothiazine derivatives were synthesized with Fe(III) and Cu(II) [10]. NAPTZs derivatives such as dioxobridged binuclear niobium(V) and tantalum(V) complexes demonstrated enhanced antifungal activity against Botryodiplodia theobromae, Ceratocystisi paradoxa and Lenzites trabea [11]. These results intrigued us for exploring novel transition metal complexes with mercury(II) bromide.

The rationale for this work was the fact that transition metal-NAPTZ complexes may behave as more potent drug candidates than the free ligands. In the present study an attempt has been made to synthesize and characterize mercury(II) bromide complexes with five phenothiazine derivatives as main ligands (Fig. 1). The ligands employed in the present study include: chlorpromazine hydrochloride (CP.HCl), promethazine hydrochloride (PM.HCl), trifluoperazine dihydrochloride (TF.2HCl), thioridazine hydrochloride (TR.HCl), and ethopropazine hydrochloride (EP.HCl). The synthesized products were subjected to characterization where the ligands were identified as bidendates.

II. EXPERIMENTAL

II.1. Materials and Methods

Mercury(II) bromide and the N-alkylphenothiazine ligands (chlorpromazine hydrochloride, promethazine hydrochloride, thioridazine hydrochloride, ethopropazine hydrochloride and trifluoperazine dihydrochloride) were obtained from Aldrich Chemical Company, USA. Analytical grade methanol, ethanol, diethylether, N,N-dimethylformamide (DMF), dimethylsulphoxide (DMSO), DMSO-d_6 and hydrochloric acid were purchased from Aldrich Chemical Company, USA.

II.2. General Synthetic Procedure for the Complexes

Mercuric bromide-NAPTZ complexes were prepared following the previously described protocol with slight modifications [9]. Briefly, $HgBr_2$ (1 mmol) in methanol was added drop-wise with stirring to a saturated methanolic solution of the N-alkylphenothiazine derivative (2 mmol) at room temperature. The reaction mixture was cooled overnight at -20° C to allow complex precipitation and separation. The precipitated crude product was suction-filtered using a medium porosity sintered glass crucible. The product obtained was washed thrice with small volumes of cold water followed by MeOH. Moisture in the final product was removed by air-drying, vacuum drying and followed by desiccating over anhydrous $CaSO_4$. The crude product was further purified by recrystallization with a hot saturated solution in MeOH.

II.3. Physical Measurements

The purified complexes were initially subjected to physical characterization. The electrical conductance was measured in 1.0 mM DMF solutions with YSI Model 34 Conductance-Resistance meter. A KCl solution (0.02 M) with a specific conductance of 0.00277 Ω^{-1} at 25° C was used as the standard solution to determine the cell constant, k. Mass magnetic susceptibility of the complexes were measured with a Johnson Matthey magnetic susceptibility balance (Catalytic System Division, Wayne, PA), where $Hg[Co(SCN)_4]$ served as calibrant. Purified complexes were subjected to elemental analysis. Infrared (IR) spectra were recorded in Nujol mull and KBr disc (Shimodzu 8400 Fourier transform infrared spectroscopy, NJ). Melting points were determined using a Melt-Temp apparatus (Laboratory Devices, Cambridge, MA). ^{1}H-NMR spectra were obtained (JOEL 300-MHz FT-NMR spectrometer, USA) with DMSO-d_6 as the solvent.

III. RESULTS AND DISCUSSION

III.1. Physical properties of the complexes

Physical properties of the mercuric-NAPTZ complexes are presented in Tables 1. The complexes are colored, microcrystalline, and stable at room temperature, except EP complex. Each of the new complexes possesses a sharp melting point ranging from 5 - 8° C. Some complexes have high melting points, which indicate their greater thermal stability. Most of the complexes blacken before melting. The Hg(II) complexes of CP·HCl, EP.HCl, TR·HCl, PM·HCl, and TF·2HCl, which are slightly soluble in polar solvents such as H_2O and MeOH, are preferentially soluble in DMF and DMSO. Mass magnetic susceptibilities (Xg) of the complexes are in the range of -297 x 10^{-9} to -293 x 10^{-9} cgs at 25 ± 0.5° C (Table 1). The magnetic data are consistent with the d^{10} metal systems, which are of low spin (diamagnetic) type due to the absence of unpaired electrons in the metal *d*-subshell.

III.2. Elemental analysis

The calculated elemental data are in agreement with the experimental results, except for halide ions (Table 2). Tentative molecular formulae are presented in table 2. All complexes are mononuclear with two NAPTZs as principal ligands.

III.3. Infrared spectra

The free NAPTZ ligands, in their hydrochloride form, show a broad band in the 2060-2760 cm^{-1} range. This broad band is assigned to the interaction of the quaternary ammonium ion, $(R_3NH)^+$, with the halide ion. However, the IR spectra of mercuric complexes show that this band was shifted and the intensity was diminished. This result suggests that the exocyclic tertiary N atom is indirectly involved in coordination with the metal ion. In addition, the IR spectra of some complexes show a broad band in the 3200-3680 cm^{-1} range indicating the presence of hydrogen bonding of O-H group of the solvent, H_2O. The bands in the 600-700 cm^{-1} and 715-740 cm^{-1} ranges are attributable to the heterocyclic C-S-C vibrational modes of the NAPTZ ligand. Upon complexation, these bands have undergone a shift suggesting that the sulfur atom is the coordination site for Hg(II). In agreement with the Pearson's HSAB rule, of the two heterocyclic sites, N and S atoms, the softer S atom is preferred over the harder N atom (as base) by the soft acid, Hg(II). Since between the heterocyclic N atom and the exocyclic amino N atom the later is more basic, it preferentially coordinates to Hg(II). Therefore, the NAPTZ provides a heterocyclic S atom and an exocyclic amino N atom as two coordination sites for the Hg(II) center making NAPTZ a bidentate ligand.

III.4. ^{1}H-NMR Spectra

The ^{1}H-NMR spectral data of the free NAPTZ ligands and their mercury(II) complexes recorded in DMSO-d_6 medium are presented in Table 3. The general trends of the NMR spectra for free NAPTZs and their complexes are similar except for few changes due to coordination to the metal center. The reason for the shifts may be attributed to intramolecular rearrangement of NAPTZ and in some cases contamination with water. The strong broad singlet at 3.35 ppm indicates the presence of water. A comparison of the nature of the important peaks/multiplets and their chemical shifts reveals that some of the resonance signals of ligands have experienced small downfield shifts upon coordination with Hg(II). The above spectral changes support the involvement of its side chain N and heterocyclic S as donor atoms. The disappearance of the peak corresponding to R_3NH^+ proton shows that the coordinated NAPTZ ligand in each complex is not in its hydrochloride salt form unlike the free ligand.

III.5. Proposed molecular structures of the complexes

The mercuric bromide-NAPTZ complex crystals were poor in quality such that to permit X-ray crystallographic analysis of the structure. Therefore, tentative mercuric-NAPTZ complex structures for two compounds (Figs. 2 and 3) proposed in this study are based on elemental analysis, mass magnetic susceptibility, spectroscopic, and molar conductance data. As an example, for the CP and EP complexes, the general non-ionic molecular formulations have been determined as $[HgBr_2(CP)_2].4H_2O$ and $[HgBr_2(PM)_2].2H_2O$, respectively**.** The low values of mass magnetic susceptibility (χ_g = -2.92 X 10^{-7} and χ_g = -2.93 X 10^{-7}) indicate the diamagnetic behavior of d^{10} Hg(II) center. The two NAPTZ ligands act as bidentates using their heterocyclic S atoms and the exocyclic amino N atoms as coordination sites. Additionally, there are two monodentate bromide ions forming the Hg(II)-Br bonds. These bonds together make each compound a six-coordinate complex. The distortion in the octahedral geometry of metal chelates is due to the bidentate NAPTZ ligands (Figs. 2 and 3) [9]**.** Mercury(II) being a soft acid unlike zinc(II), prefers to bind to the heterocyclic S atom, which is softer than the heterocyclic N atom. The complexes of TR, PM, and TF have similar octahedral structures.

IV. CONCLUSIONS

In this study, five new mercury(II) complexes of N-alkylphenothiazine derivatives have been synthesized and characterized. All the five mercury(II) complexes are non-electrolytes. Analytical characterization qualitatively supports our proposed structures for the complexes. All the complexes are colored, non-hygroscopic and stable at room temperature for a long period. Of the synthesized mercury(II) complexes, EP complex was an exception with white color. Magnetic susceptibility was helpful in predicting the absence of unpaired electrons in the *d*-subshell of the Hg(II) center of the complexes as expected for a d^{10} metal complex. The proposed molecular structures for the complexes are distorted octahedrons. In each complex, two N-alkylphenothiazines act as bidentate ligands using heterocyclic S atom and exocyclic amino N atom as coordination sites, while the two bromide ions act as monodentates.

V. ACKNOWLEDGMENTS.

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VI. REFERENCES

[1] Mosnaim, A.D; Ranade, V.V; Wolf. M.E; Puente, J: Antonieta, V.M., Phenothiazine molecule provides the basic chemical structure for various classes of pharmacotherapeutic agents, American Journal of Therapeutics. 2006. 13, 261-273

[2] Tanaji N. Bansode, Jayant V. Shelke, Vaijanath G. Dongre, Synthesis and antimicrobial activity of some new N-acyl substituted phenothiazines, European Journal of Medicinal Chemistry, 2009, 44, 5094-5098

[3] Cimpoiu C1, Hodisan S, Toşa M, Paizs C, Majdik C, Irimie FD, Separation of N-alkyl phenothiazine sulfones by HPTLC using an optimum mobile phaseJ Pharm Biomed Anal. 2002 Apr 15;28(2):385-9

[4] Francisco J. Lara; Ana M. García-Campaña; Laura Gámiz-Gracia; Juan M. Bosque-Sendra Fermín Alés-Barrero, Determination of phenothiazines in pharmaceutical formulations and human urine using capillary electrophoresis with chemiluminescence detection, Electrophoresis 2006, 27, 2348–2359

[5] Netkal M. Made Gowda, Ravindra K. Vallabhaneni, Indira Gajula, S. Ananda, Palladium(II)-phenothiazine complexes: synthesis and characterization, Journal of Molecular Structure, 1997, 407, 2(3), 125-130

[6] B. Keshavan, P.G. Chandrashekara, Netkal M. Made Gowda, Synthesis, characterization, and spectral studies of lanthanide(III) nitrate complexes of promethazine, Journal of Molecular Structure, 2000, 553, 193–197

[7] Keshavan, B., Gowda, K., Synthesis of square-planar palladium(II) and platinum(II) complexes with N-alkylphenothiazines, Journal of the Indian Chemical Society, 2001, 7(1), 37-38

[8] Milena Krstića, Sofija P. Soviljb, Sanja Grgurić-Šipkab, Ivana Radosavljević Evansc, Sunčica Borozana, Juan Francisco Santibanezd, Jelena Kocićd, New ruthenium(II) complexes with N-alkylphenothiazines: Synthesis, structure, in vivo activity as free radical scavengers and in vitro cytotoxicity, European Journal of Medicinal Chemistry, 2010, 45 (9), 3669 - 3676

[9] Varun, Debbeti; Tarab J, Ahmad; S, Ananda; Netkal M, Made Gowda, Transition Metal Complexes of Ethopropazine: Synthesis and Characterization, American Journal of Chemistry 2012, 2(6): 294-298.

[10] Simona ANTONESCU, Elena BACU, Nicolae STĂNICĂ, Ovidiu OPREA, Cornelia GURAN, New complex compounds of Fe(iii) and Cu(ii)- With phenothiazines derivatives, U.P.B. Sci.Bull.,Series B, 2010, 72, (4), 145-154.

[11] Boregowda KESHAVAN, Hunasegala KEMPE GOWDA, Synthesis, Spectral and Fungicidal Studies on Dioxobridged Binuclear Niobium(V) and Tantalum(V) Complexes of N-Alkylphenothiazines, Turk J. Chem, 2002, 26, 237-243

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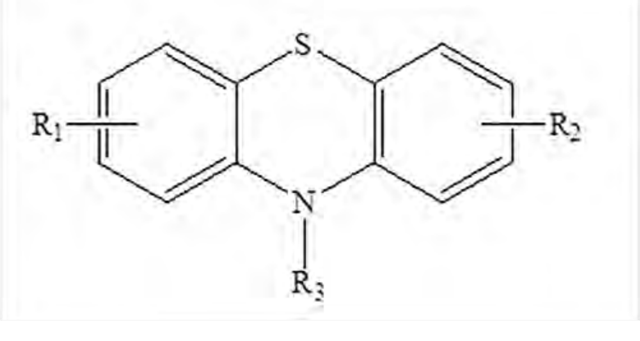

Fig 1. General structure of N-Alkylphenothiazines

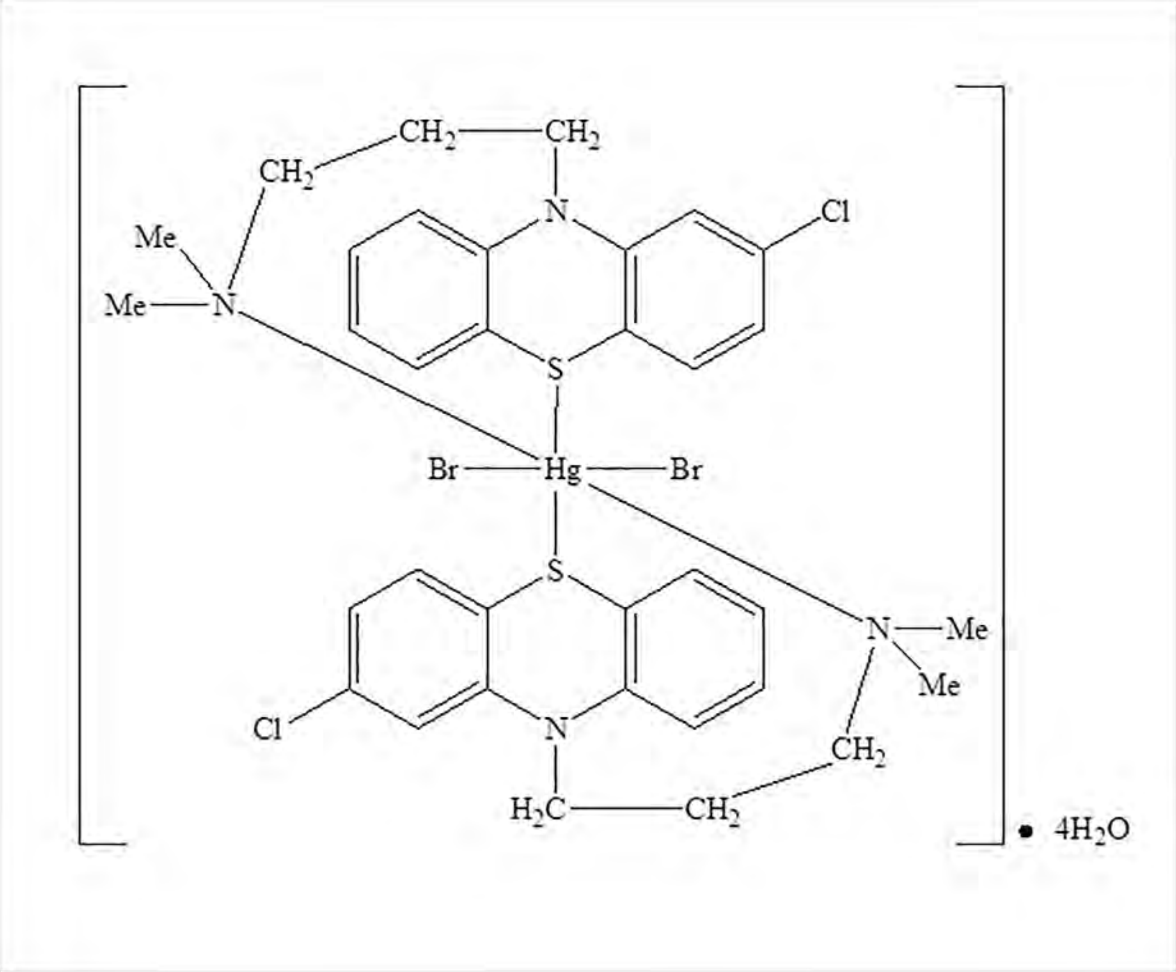

Fig 2. Proposed molecular structure of $[HgBr_2(CP)_2]$ $.4H_2O$

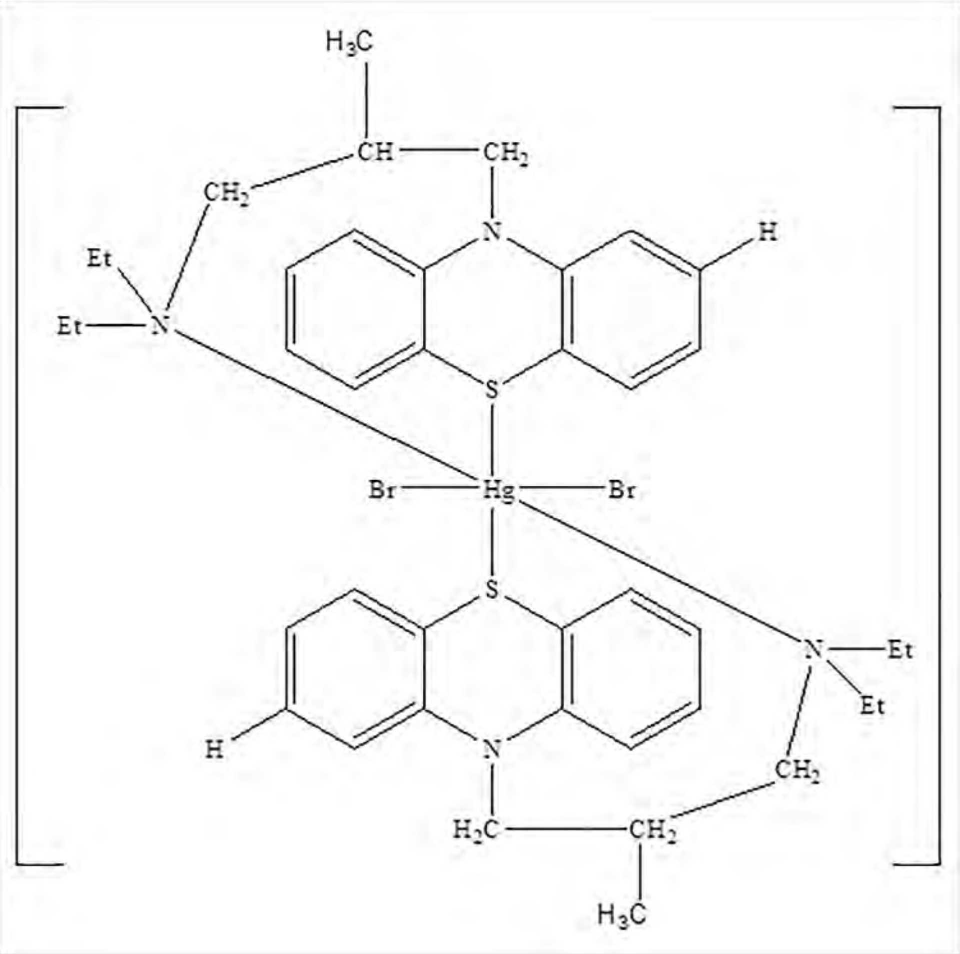

Fig 3. Proposed molecular structure of [$HgBr_2(EP)_2$]

Table 1. Physical properties of complexes

Complex	Melting Point (°C)	Molar conductance in mho cm^2 mol^{-1}	Mass magnetic susceptibility in 10^{-9} cgs	Color (nature of solid)
$HgBr_2$ – CP	102-104	19.17 (Non-electrolyte)	-296.2 (diamagnetic)	greenish microcrystalline
$HgBr_2$ – PM	75-80	28.74 (Non-electrolyte)	-293.7 (diamagnetic)	reddish orange amorphous powder
$HgBr_2$ – TR	75-80	28.74 (Non-electrolyte)	-292.8 (diamagnetic)	blackish brown microcrystalline
$HgBr_2$ – EP	225-230	28.80 (Non-electrolyte)	-292.8 (diamagnetic)	colorless amorphous powder
$HgBr_2$ – TF	210-215	28.06 (Non-electrolyte)	-296.7 (diamagnetic)	greenish yellow microcrystalline

Table 2. Elemental Analysis*

Molecular Formula proposed	% C	% H	%N	% S	% Br
[HgBr$_2$(CP)$_2$].4H$_2$O	26.9	2.63	3.63	4.21	22.8
	(27.2)	(2.59)	(3.69)	(4.20)	(23.5)
[HgBr$_2$(TF)$_2$].2H$_2$O	31.7	3.30	6.10	3.8	12.5
	(32.0)	(3.63)	(6.18)	(3.55)	(13.0)
[HgBr$_2$(TR)$_2$]	38.4	4.40	4.45	4.30	------
	(39.6)	(4.27)	(4.42)	(4.25)	-------
[HgBr$_2$(PM)$_2$]. 2H$_2$O	29.6	2.93	4.01	4.66	22.9
	(29.9)	(2.92)	(4.02)	(4.69)	(22.6)
HgBr$_2$(EP)$_2$	42.4	4.60	5.18	5.96	13.3
	(42.9)	(4.69)	(5.17)	(5.99)	(12.6)

*Theoretical values are in parentheses

Table 3. ^{1}H-NMR spectral data of free NAPTZ ligands and their complexes

Ligand (Complex)	Chemical shift (multiplicity, protons)
CP.HCl [HgBr$_2$(CP)$_2$].4H$_2$O	(a)2.08 (m,2H) (b) 2.68 (s,6H) (c) 3.13 (t,2H) (d) 4.17 (m,2H) (e) 6.95-7.30 (m,7H) [(a) 2.02 (m,2H) (b) 2.74 (m,6H) (c) 3.14 (t,2H) (d) 3.40 (str.S,H$_2$O) (e) 3.96(t,2H) (f) 7.05-7.24(m,7H)]
PM.HCl [HgBr$_2$(PM)$_2$].2H$_2$O	(a)1.22-1.35 (d,3H) (b) 2.50 (STR.S,DMSO peak) (c) 2.70-2.80 (Br s,6H) (d) 3.30-3.40 (Str.s,H$_2$O) (e) 3.60 (m,H) (f) 4.55(m,2H) [(a) 1.23-1.27(str.d.3H) (b) 2.4 2 (str..S, DMSO peak) (c) 2.86 (str.q, 6H) (d) 3.48 (str.S,H$_2$O) (e) 4.07 (s,1H) (f) 4.30 (m,2H)]
TR.HCl [HgBr$_2$ (TR)$_2$]	(a) 1.40 (m, 2H) (b) 1.50-2.10 (m, 6H) (c) 2.30 (m, 3H) (d) 2.65(m, 3H) (e) 3.15(m, 3H) [(a) 1.32(m,2H) (b) 1.50-1.74 (m,6H) (c) 2.20 (m,3H) (d) 2.49 (m,3H) (e) 3.16 (m,3H) (f) 3.42(str.s,H$_2$O)]
EP.HCl [HgBr$_2$ (EP)$_2$]	(a) 3.33 (H$_2$O peak) (b) 6.6-7.05 (m,8H) (c) 8.58 (m,1H) [(a) 1.32 (m, 2H) (b) 6.69-6.98 (m,6H) (c) 8.59 (Br.s,1H)]
TF.2HCl [HgBr$_2$ (TF)$_2$].2H$_2$O	(a)2.07 (m,2H) (b) 2.78 (s,3H) (c) 3.25 (m,2H) (d) 3.58 (m,8H) (e) 4.05 (m,2H) (f) 7.00-7.41 (m,7H) [(a) 2.02 (m,2H) (b) 2.82 (s,3H) (c) 3.16(m,2H) (d) 3.42(str.S,H$_2$O) (e) 4.00-4.15 (m,2H) (f) 7.00-7.50 (m,7H)