Scientific paper

Synthesis, Characterization and Antimicrobial Study of Novel 4-{[(8-Hydroxyquinolin-5-yl)methyl]amino}benzenesulfonamide and Its Oxinates

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Abstract

A novel 4-{[(8-hydroxyquinolin-5-yl)methyl]amino}benzenesulfonamide (HQMABS) was synthesized by optimized reaction of 4-aminobenzenesulfonamide with 5-chloromethyl-8-hydroxyquinoline hydrochloride (CMHQ). Various oxinates of HQMABS were also prepared using Mn(II), Fe(II), Co(II), Ni(II), Cu(II), and Zn(II) metal salts. All compounds were analyzed by physicochemical, thermogravimetric and spectroscopic techniques. Antimicrobial activity was carried out using agar-plate method against various strains of bacteria (*Staphylococcus aureus, Bacillus subtillis, Pseudomonas aerugionsa, and Escherichia coli*) and spores of fungi (*Aspergillus niger* and *Aspergillus flavous*). The results showed significantly higher antimicrobial activity of HQMABS compared to the parent 8-hydroxyquinoline and sulfonamide, while oxinates of HQMABS showed milder activity.

Keywords: 8-Hydroxyquinoline (oxine), sulfonamide, oxinates, antibacterial and antifungal activity.

1. Introduction

Among the hydroxyquinolines, the chemistry of 8-hydroxyquinolines (8HQs) has drawn considerable attention due to their diverse biological properties[1,2] such as antiamoebic,[3,4] antiseptic and disinfectant,[5,6] antimalarial,[7] antiallergic,[8] antitubercular,[9] pesticidal,[10] antiplaque,[11] antineoplastic,[12] anticancer,[13] antileishmanial[14] and antifungal efficiency.[15–17] 8HQ has been found to be non-carcinogenic and is employed for *in vitro* assays as well as genetic toxicity.[18] It also has remarkable effects similar to the antibiotic lomofugin, which rapidly and selectively inhibits the RNA synthesis in yeast.[19] Iron bound to the lipophilic chelator (8HQ), results in substantial DNA-strand breakage of cultured human lung cells.[20]

Biological and pharmacological chelating agents like 8-hydroxyquinoline based ligands and chelates are in progress in coordination studies.[21] 8HQs showed the above mentioned biological properties, which might be due to their ability to chelate with the metal ions, essential for metabolism,[17] where OH group of 8HQ acts as an acid. The metal chelates of 8HQs (oxinates) were reported to be biologically active due to their lipid solubility and possess comparable activity against bacteria and fungi. The activity of oxinates could be explained by assuming that these complexes first penetrate the cell-wall due to their lipid solubility and at the site of action undergoes dissociation to 1:1 8HQ complex which will then become a toxic entity by combining with the metal binding sites of enzymes as well as by blocking the same.[22,23]

In addition to these, due to the excellent pharmacological activities, the synthetic antibacterial sulfonamides have been well-known since 1935, but their toxicity and microbial resistance do not allow them to be used in the treatment of disease.[17]

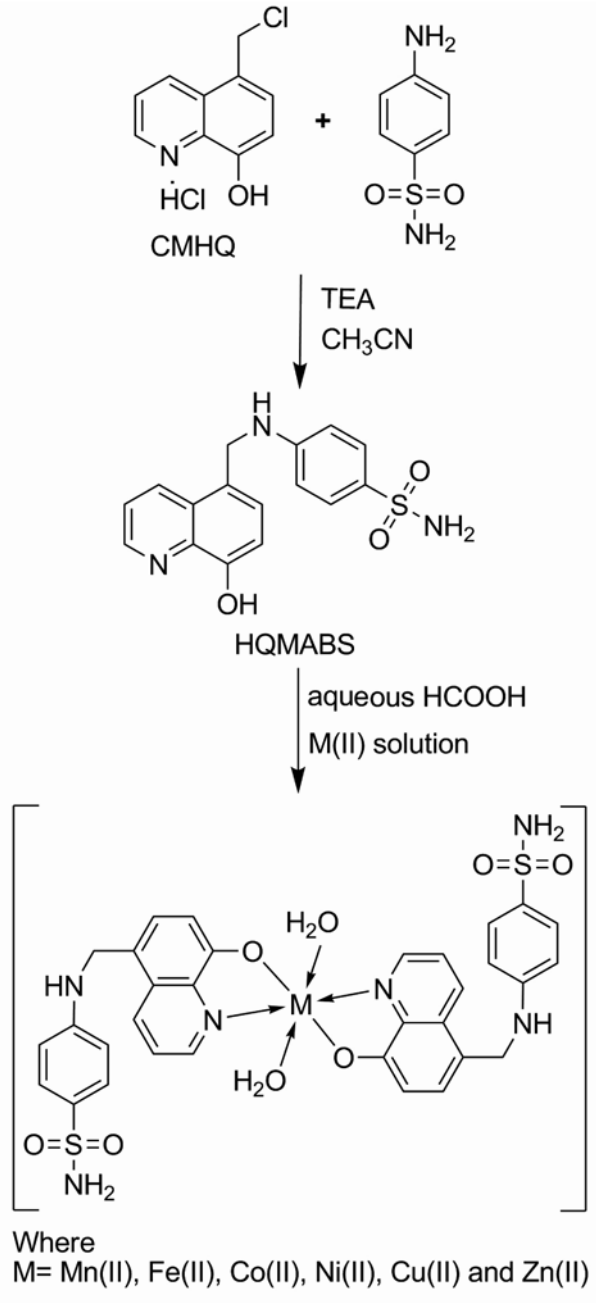
Thus, looking to the prominent biological activities of sulfonamides and 8-hydroxyquinoline derivatives, it was thought interesting to bring these two biologically active moieties within a single molecular framework, with a view to study their additive effects on the chemical and

biological properties. Therefore, the present communication comprises synthesis, characterization and comparative biological study of 4-{[(8-hydroxyquinolin-5-yl) methyl]amino}benzenesulfonamide and its oxinates.

2. Experimental

2. 1. Materials and Methods

All the chemicals used were of analytical grade and purified by standard methods prior to use. Nutrient-agar, potato dextrose agar and sulphanilamide were purchased from Hi-Media Chemicals, India. Chloride, nitrate, and sulphate metal(II)-salts were used in their hydrated form.



Scheme 1: Proposed route for the synthesis of HQMABS and $[M(HQMABS)_2(H_2O)_2]$.

Silica gel F_{254} TLC plates (20 × 20 cm) were purchased from Merck (India). The elemental analyses were performed with Vario EL CHN elemental analyzer. The FT-IR spectra were recorded on Perkin Elmer Spectrum GX spectrophotometer using KBr pellets. The ^{1}H and ^{13}C (APT) NMR spectra were recorded on Bruker 400 MHz instrument using DMSO-d_6 as solvent, and TMS as internal reference standard. The MS-CI spectrum of HQMABS was recorded on Shimadzu LC-MS 2010 eV spectrometer in acetonitrile. Diffuse electronic spectra were recorded on Beckman DK-2A spectrophotometer using MgO as a reference. Magnetic moments were determined by the Gouy method using mercury tetrathiocyanatocobaltate(II) $[HgCo(NCS)_4]$ as calibrant (χ_g = 1644 × 10^{-6} cgs units at 20 °C) and the diamagnetic correction was made using Pascal's constant.[24] The thermogravimetric analyses were carried out using Perkin Elmer Thermogravimetry Analyzer at a heating rate of 10 °C per minute in air. The metal contents of the complexes were analyzed by EDTA titration after decomposing the organic matter with $HClO_4$, H_2SO_4 and HNO_3 (1:1.5:2.5) mixture.[25] The melting point of HQMABS was checked by standard open capillary method and is uncorrected.

The ligand HQMABS was synthesized using 5-chloromethyl-8-hydroxyquinoline hydrochloride[4] (CMHQ) as a starting material by the modification of reported method[26] and its metal(II) complexes were synthesized using previously reported procedure.[27] The outline for the synthesis of HQMABS and its M(II) oxinates is shown in Scheme 1.

2. 2. Synthesis of 4-{[(8-Hydroxyquinolin-5-yl)methyl]amino}benzenesulfonamide (HQMABS)

To a solution of 4-aminobenzenesulphonamide (7.11 g, 41.34 mmol) and triethylamine (9.68 g, 95.61 mmol) in acetonitrile (75 ml), 5-chloromethyl-8-hydroxyquinoline hydrochloride (10 g, 43.45 mmol) was added slowly in portions at room temperature under continuous stirring and refluxed for 2 hours. The reaction mixture was then poured into ice-cold water to afford off-white solid, which was filtered, washed with hot water, and crystallized from ethanol. Isolated crystals were dried under vacuum to obtain colorless crystals of HQMABS. R_f = 0.65, chloroform: methanol: ammonia (70:29:1). Yield, 9.96 g (87.8%); m.p. = 287 °C; MS–CI, m/z 330.0 (M+H) for $C_{16}H_{15}N_3O_3S$ (329.40). The physicochemical parameters, characteristic FT-IR frequencies, and NMR spectral data (^{1}H and ^{13}C) are presented in Tables 1–3.

2. 3. Synthesis of metal(II) oxinates [M(II)(HQMABS)$_2$(H$_2$O)$_2$; M = Mn(II), Fe(II), Co(II), Ni(II), Cu(II), Zn(II)]

A hot solution of metal(II) salt (2.5 mmol) in 50% aqueous formic acid (2.5 ml) was added drop-wisely with continuous stirring to the hot 20% aqueous formic acid solution (20 ml) of HQMABS (5 mmol). With the proper adjustment of the pH (~8.5) using 50% NH_4OH solution, the resultant mixture was further digested for 4 hours in the water bath. The obtained solid product was filtered, washed with hot water, and subsequently with small quantity of ethanol, acetonitrile, and dried in a vacuum desiccator. The physicochemical parameters, and characteristic FT-IR frequencies of metal(II) oxinates are summarized in Tables 1–2.

3. Results and Discussion

5-Chloromethyl-8-hydroxyquinoline hydrochloride (CMHQ) was prepared by chloromethylation of 8-hydroxyquinoline. Considerable difficulties were faced to obtain high purity of CMHQ even after washing the crude CMHQ by concentrated hydrochloric acid and acetone.[4] Another obstacle while working with CMHQ was the use of inorganic base catalysts like sodium/potassium bicarbonate, sodium/potassium hydrogen carbonate, and sodium hydroxide. They leads to either a slow reaction or produce 5-hydroxymethyl-8-hydroxyquinoline in quantitative yield.[4] To overcome these obstacles a triethylamine (TEA) was used as a scavenger in the formation of HQMABS in a quantitative yield while reacting CMHQ with sulphanilamide.

The synthesized 4-{[(8-hydroxyquinolin-5-yl) methyl]amino}benzenesulfonamide (HQMABS) appears as colourless crystals. It is partially soluble in acetone, methanol, ethanol and acetonitrile, while it is soluble in polar organic solvents like dimethylformamide (DMF), dimethylsulphoxide (DMSO), organic acids and pyridine. All metal(II) oxinates [M(II)(HQMABS)$_2$(H$_2$O)$_2$] have characteristic colour, are stable in air, and are practically insoluble in water, ethanol, methanol, chloroform and hexane. On the other hand, slight solubility has been observed in DMF as well as in DMSO, and was difficult to obtain single crystal suitable for the X-ray diffraction analysis.

3. 1. Characterizations

The Mass spectrum of HQMABS was recorded in acetonitrile as solvent using chemical ionization technique and the molecular ion peak was observed at m/z 330.0, which confirmed the proposed molecular formula $C_{16}H_{15}N_3O_3S$ of the ligand.

The results of elemental analysis of ligand HQMABS and it's metal(II) oxinates are given in Table 1

Table 1. Physicochemical parameters of the ligand (HQMABS) and metal complexes.

Compound (Empirical formula)	Molecular weight	Colour	Yield (%)	m.p.[a] (ºC)	Elemental analysis, % observed (calculated)				μ_{eff} B.M. (calc.)	E_a (kcal/mol)
					C	H	N	S	metal		
HQMABS ($C_{16}H_{15}N_3O_3S$)	329.40	White	87.8	287	58.21 (58.34)	4.48 (4.59)	12.54 (12.76)	9.63 (9.74)	–	–	12
[Mn(HQMABS)$_2$(H$_2$O)$_2$] ($MnC_{32}H_{32}N_6O_8S_2$)	746.71	Brown	87	>300	51.50 (51.47)	4.37 (4.32)	11.23 (11.25)	8.61 (8.59)	7.28 (7.22)	5.48 (5.92)	7.5
[Fe(HQMABS)$_2$(H$_2$O)$_2$] ($FeC_{32}H_{32}N_6O_8S_2$)	748.61	Dark brown	84	>300	51.34 (51.43)	4.31 (4.26)	11.23 (11.16)	8.57 (8.64)	7.46 (7.51)	5.18 (4.90)	8.6
[Co(HQMABS)$_2$(H$_2$O)$_2$] ($CoC_{32}H_{32}N_6O_8S_2$)	751.69	Dark green	88	>300	51.13 (51.01)	4.29 (4.38)	11.18 (11.25)	8.53 (8.59)	7.84 (7.77)	4.76 (3.87)	8.5
[Ni(HQMABS)$_2$(H$_2$O)$_2$] ($NiC_{32}H_{32}N_6O_8S_2$)	751.45	Dark red	91	>300	51.15 (51.22)	4.29 (4.19)	11.18 (11.21)	8.53 (8.47)	7.81 (7.86)	3.17 (2.83)	8.9
[Cu(HQMABS)$_2$(H$_2$O)$_2$] ($CuC_{32}H_{32}N_6O_8S_2$)	756.29	Dark green	89	>300	52.86 (50.82)	4.18 (4.26)	11.18 (11.11)	8.59 (8.48)	8.51 (8.40)	1.87 (1.73)	8.4
[Zn(HQMABS)$_2$(H$_2$O)$_2$] ($ZnC_{32}H_{32}N_6O_8S_2$)	758.17	Darkyellow	82	>300	50.69 (50.61)	4.25 (4.35)	11.08 (11.17)	8.46 (8.53)	8.63 (8.60)	D[b]	8.8

[a] Melting points are uncorrected. [b] D = diamagnetic.

and were in good agreement with their predicted molecular formula showing that the oxinates have 1 : 2 metal to ligand ratio.

3. 2. FT-IR Spectra

The FT–IR spectra of HQMABS and its oxinates demonstrating all the important stretching and bending vibrations in appropriate region are summarized in Figure 1 and Table 2.

trum of HQMABS also shows the important bands at 1598 cm^{-1} for C=N, at 1500 cm^{-1} for C=C and at 1475 cm^{-1} for C–C bond, assigned to the aromatic skeletal stretching vibrations of parent heterocyclic ring.[28] Furthermore, two strong bands of S=O appeared at 1318 and 1144 cm^{-1} due to the asymmetric and symmetric stretching vibrations, suggesting the presence of the SO_2NH_2 group.[29] The N–H stretching vibrations appeared near 3200 cm^{-1}, while N–H and C–N bending vibrations appeared at 1659 and 1260 cm^{-1}, respectively.

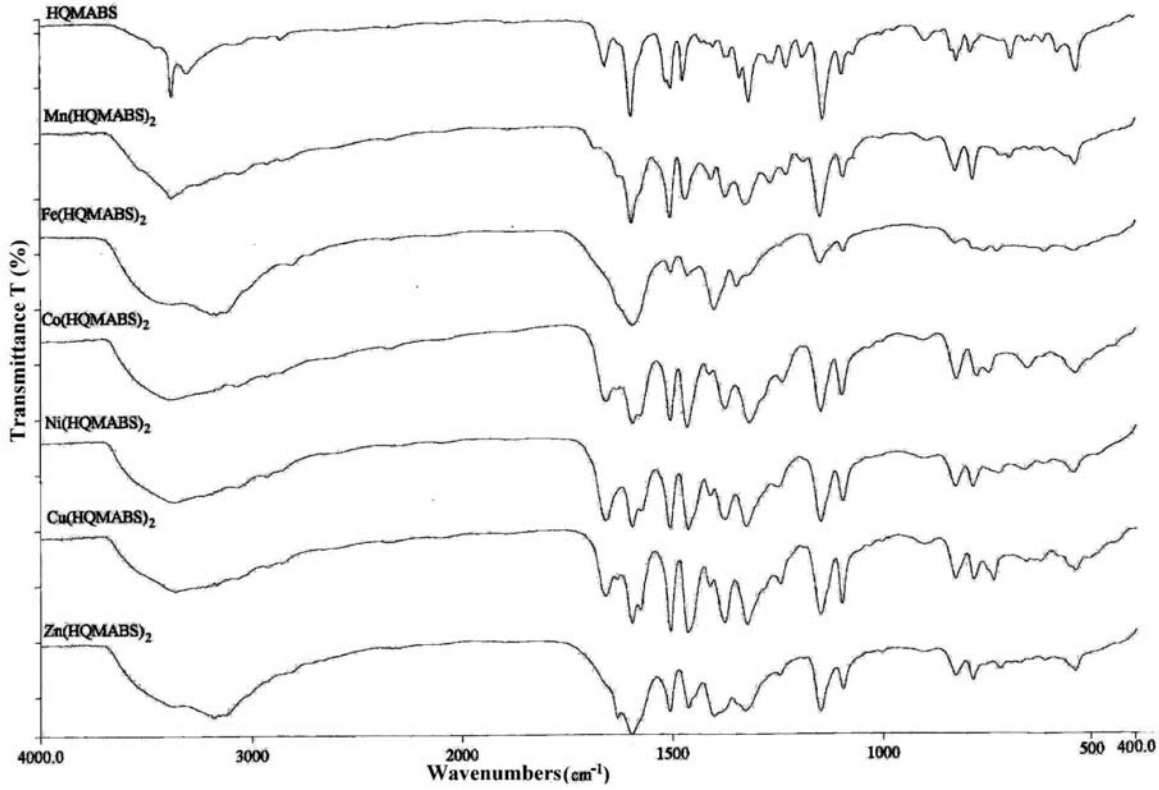


Figure 1. FT–IR spectra of HQMABS and its various oxinates.

Table 2. FT-IR spectral frequencies of M(II)$(HQMABS)_2$ (in cm^{-1}).

Compound	O–H	C=N	O–M	C –O→M	M→N	M→N
$[Mn(HQMABS)_2(H_2O)_2]$	3381	1597	1406	1095	721	544
$[Fe(HQMABS)_2(H_2O)_2]$	3400	1595	1401	1096	731	546
$[Co(HQMABS)_2(H_2O)_2]$	3383	1595	1411	1098	750	541
$[Ni(HQMABS)_2(H_2O)_2]$	3372	1596	1405	1096	727	549
$[Cu(HQMABS)_2(H_2O)_2]$	3360	1596	1410	1091	739	544
$[Zn(HQMABS)_2(H_2O)_2]$	3401	1597	1402	1095	725	545
HQMABS; 3401,1401 (O–H); 3200 (N–H); 2864 ($–CH_2–$), 1599 (C=N), 1144 (S=O), 1098 (C–O–H)						

In the spectrum of HQMABS the absorption band at 3379 cm^{-1} belongs due to O–H stretching vibration and the strong band at 1400 cm^{-1} to O–H bending vibration and C–O stretching vibration.[28] The CH_2 group shows C–H stretching vibration band at 2964 cm^{-1}. The IR spec-

However, a comparison of IR spectra of ligand and its metal(II) coordinated oxinates showed some significant characteristic differences.[30] One of the considerable differences to be expected, was the presence of more broadened band in the region of 2700–3400 cm^{-1} for the chelates. As

the oxygen atom of the OH group of the ligand forms a coordination bond with the metal ions, the broadening of this band may be attributed to the presence of coordinated water molecules.[31] The band due to the C=N stretching vibration at around 1600 cm^{-1} was shifted to lower frequency, whereas, the band at 1400 cm^{-1} in the spectrum of HQMABS assigned to in-plane OH deformation was shifted towards higher frequency in the spectra of the chelates due to the formation of M–O bond.[32] This has been further confirmed by the presence of a weak band at 1100 cm^{-1} for C–O–M stretching mode, while bands around ~730 cm^{-1} and ~545 cm^{-1} correspond to the M → N vibration.[33] All these characteristics features of the FT-IR studies unveil the formation of HQMABS and metal(II) oxinates.

3. 3. NMR Spectra

The ^{1}H and ^{13}C NMR spectral data of the ligand (HQMABS) and its Zn(II) complex [Zn(II)$(HQMABS)_2$] are compared in Table 3 along with their assignments.[34–36] The ^{1}H and ^{13}C NMR spectra for other complexes could not be carried out due to their low solubility in DMSO-d_6.

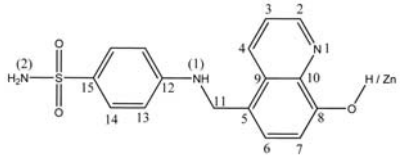
3. 3. 1. ^{1}H NMR Spectra

The ^{1}H NMR spectrum of HQMABS exhibited a broad singlet at δ 9.73 ppm due to the OH proton.[35] Disappearance of this signal in the spectrum of Zn(II) complex suggested that this proton has been lost due to coordination of oxygen atom to the metal ion.[36] The H^2 signal of the Zn(II) complex appeared at low magnetic field (δ 9.00) compared to that of ligand (δ 8.89), suggesting the involvement of N^1 in the formation of complex. $N^{(1)}H$ and $N^{(2)}H_2$ protons in ligand gave triplet at δ 6.87 and singlet at δ 6.92 ppm, respectively, and appeared as broad singlets at δ 6.88 ppm in the Zn(II) complex. This confirms that neither of the nitrogen atoms are involved in the complex formation as the chemical shifts remains unchanged in ligand as well as in the complex. The absorptions of aromatic protons of quinoline and phenyl ring are found in the aromatic region, and all quinoline protons are slightly downfield shifted, except H^7 which is upfield shifted.[37]

3. 3. 2. ^{13}C APT NMR Spectra

In the ^{13}C NMR spectrum of HQMABS all aromatic carbon absorptions were observed in between δ 110.72–153.20 ppm and absorption of C^{11} atom appeared at δ 43.97 ppm.[34,35] The C^2 and C^5 signals (δ 148.31 and 124.73 ppm) of HQMABS were upfield shifted (δ 144.85 and 120.67 ppm) in the complex, while C^8 and C^{10} signals (δ 151.76 and 139.41 ppm) underwent a downfield shift (δ 158.31 and 144.44 ppm) in Zn(II)$(HQMABS)_2$, indicating coordination of Zn with N^1 and oxygen attached to C^8 of quinoline ring.[34–36]

Table 3. ^{1}H and ^{13}C NMR spectral data of HQMABS and Zn(II)$(HQMABS)_2$.



	^{1}H NMR[a] δ, ppm			^{13}C APT NMR[b] δ, ppm	
	HQMABS	Zn(II)$(HQMABS)_2$		HQMABS	Zn(II)$(HQMABS)_2$
H^2	8.89 [d, 4.0]	9.00 [d, 4.4]	C^2	148.31	144.85
H^3	7.62 [dd, 8.4, 4.0]	7.80 [dd, 8.8, 4.0]	C^3	122.21	122.34
H^4	8.50 [d, 8.4]	8.72 [d, 8.8]	C^4	133.13	135.91
H^6	7.45 [d, 8.0]	7.51 [d, 8.4]	C^5	124.73	120.67
H^7	7.05 [d, 8.0]	6.63 [d, 8.4]	C^6	127.45	129.89
C^8–OH	9.73 [bs]	–	C^7	110.72	113.40
H^{11}	4.66 [d, 5.2]	4.58 [s]	C^8	151.76	158.31
C^{11}–$N^{(1)}H$	6.87 [t, 5.2]	6.88 [bs]	C^9	129.59	130.39
H^{13}	6.72 [d, 8.8]	6.73 [d, 8.8]	C^{10}	139.31	144.44
H^{14}	7.52 [d, 8.8]	7.54 [d, 8.8]	C^{11}	43.97	43.76
$–SO_2N^{(2)}H_2$	6.92 [bs]	6.88 [bs]	C^{12}	153.20	153.37
			C^{13}	111.49	111.70
			C^{14}	127.81	127.95
			C^{15}	130.76	130.94

[a] Superscript number shows the position of carbon to which hydrogen atoms are attached. Multiplicities and coupling constants (in Hz) are given in brackets (s= singlet, bs = broad singlet, d = doublet, t= triplet, dd = doublet of doublet). [b] Superscript number shows the position of carbon atom.

3. 4. Diffuse Electronic Spectral and Magnetic Properties Data

The diffuse electronic spectra of $[Cu(HQMABS)_2(H_2O)_2]$ exhibited two bands at 26215 cm^{-1} due to charge transfer and broad band having maxima at 15590 cm^{-1} due to the $^2E_g \rightarrow {}^2T_{2g}$ transition. The broadening of the signal might be due to Jahn-Teller distortion. The absorption bands of the diffuse electronic spectra and value of their magnetic moment favours a tetragonally distorted octahedral geometry around Cu(II) ion.[38,39] The $[Ni(HQMABS)_2(H_2O)_2]$ complex shows three weak absorption bands at 9891, 16055, and 24510 cm^{-1} corresponding to the characteristic transitions $^3A_{2g} \rightarrow {}^3T_{2g}$, $^3A_{2g} \rightarrow {}^3T_{1g}(F)$, and $^3A_{2g} \rightarrow {}^3T_{1g}(P)$, while $[Co(HQMABS)_2(H_2O)_2]$ exhibits three absorption bands at 9810, 15520, and 22100 cm^{-1}, respectively, due to $^4T_{1g}(F) \rightarrow {}^4T_{2g}(F)$, $^4T_{1g}(F) \rightarrow {}^4A_{2g}(F)$, and $^4T_{1g}(F) \rightarrow {}^4T_{1g}(P)$ transitions. The absorption bands of the diffuse electronic spectra and values of their magnetic moments showed an octahedral geometry around Ni(II) and Co(II) ions.[40,41] The spectra of $[Mn(HQMABS)_2(H_2O)_2]$ showed weak bands at 16789, 18453, and 23806 cm^{-1} assigned to the $^6A_{1g} \rightarrow {}^4T_{1g}$, $^6A_{1g} \rightarrow {}^4T_{2g}$, and $^6A_{1g} \rightarrow {}^4A_{1g}, {}^4E_g$ transitions, and magnetic moment value suggesting an octahedral geometry for the Mn(II) ion. The spectrum for $[Fe(HQMABS)_2(H_2O)_2]$ showed bands at 18958 and 36783 cm^{-1} assigned to the $^5T_{2g} \rightarrow {}^3E_g$ and $^5T_{2g} \rightarrow {}^3T_{1g}$ transitions, suggesting its octahedral geometry in support of magnetic moment value around Fe(II) ion. As the spectrum of $[Zn(HQMABS)_2(H_2O)_2]$ was not well resolved, it was not well-interpreted even though magnetic moment value showed that it is diamagnetic in nature as expected.[27] The magnetic moment values of all the M(II) oxinates are given in Table 1.

3. 5. Thermogravimetric Analysis

The thermogravimetric analysis (TGA) for the HQMABS and its oxinates were carried out within the temperature range of 40 to 900 °C in air at a heating rate of 10 °C/min to establish their compositional difference as well as to ascertain the nature of associated water molecules. The TGA curves (Figure 2) showed that HQMABS follows single-step thermal decomposition. The initial weight loss of 1% might be due to loosely held solvent in HQMABS. Up to 74% of the weight loss commenced in the range of 150–550 °C and further slow degradation took place up to 900 °C.

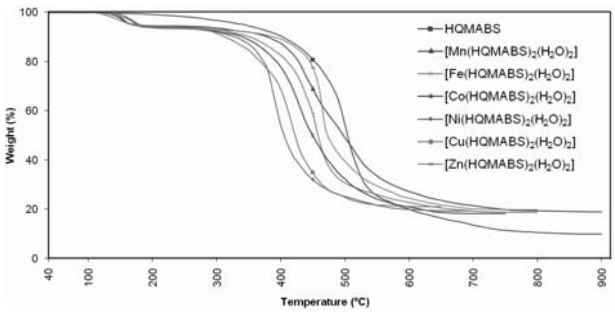


Figure 2. Thermogravimetric curves of HQMABS and its oxinates.

Similarly, examination of the TGA data of oxinates showed two-step thermal decomposition. The initial weight loss may be due to the solvent molecules or loosely held moisture trapped inside the oxinates, whereas the weight loss observed in the range of 125–180 °C may be attributed to the two coordinated water molecules.[42] This also satisfies the six coordination sites of the metal ions in metal(II) oxinates. For metal(II) oxinates the maximum weight loss has been observed in the temperature range of 210–900 °C, and the remaining weight corresponds to a mixture of metal oxide and some ashes as ultimate pyrolysis products.

There is also a remarkable difference in the mode of thermal degradation for HQMABS and its oxinates. $[M(II)(HQMABS)_2(H_2O)_2]$ have shown fast decomposition pattern as compared to HQMABS. These results of thermal behavior can be explained by the fact that the decomposition of chelates was catalytically induced by the metal ions.[43]

The energy of activation (E_a) for thermal decomposition of HQMABS and its oxinates was estimated by the reported method using following equation:[44]

$$\ln[\ln(1/y)] = (E_a/RT + 1) \ln T + \text{constant}$$

E_a was computed from the slope ($-E_a/R$) of the plot of ln[ln (1/y)] versus (ln T), and is given in Table 1. The energy of activation for HQMABS has been found to be 12 kcal/mol, while the activation energy for oxinates is between 8.8–10.9 kcal/mol.

3. 6. Antimicrobial Activity

The synthesized ligand 4-{[(8-hydroxyquinolin-5-yl)methyl]amino}benzenesulfonamide (HQMABS) and its oxinates $[M(II)(HQMABS)_2(H_2O)_2]$ were subjected for their *in vitro* antimicrobial activity against the gram-positive bacteria (*Staphylococcus aureus and Bacillus subtillis*), gram-negative bacteria (*Pseudomonas aerugionsa and Escherichia coli*) by using agar nutrient as medium, and against fungi (*Aspergillus niger* and *Aspergillus flavous*) using potato dextrose agar as medium. A stock solution was prepared by dissolving compounds in DMSO as 10% solution. The antibacterial and antifungal activities were performed at a concentration of 25 μg/ml, using agar-plate method,[45] and DMSO as control for comparison of antibacterial and antifungal activities with parent 8HQ and sulphanilamide. The results of measured zone of inhibition (in mm) of comparative biological study for HQMABS and its oxinates against each of species are summarized in Table 4.

Table 4. Antimicrobial activities of studied compounds.

Compound	Zone of inhibition, mm[a]					
	S.aureus	***B.subtillis***	***E.coli***	***P.aerugionsa***	***A.niger***	***A.flavous***
HQMABS	34	35	31	28	37	32
Sulphanilamide	18	14	20	19	24	22
8HQ	24	22	26	22	21	19
$[Mn(HQMABS)_2(H_2O)_2]$	16	13	13	14	12	11
$[Fe(HQMABS)_2(H_2O)_2]$	22	19.5	21	19	23	21
$[Co(HQMABS)_2(H_2O)_2]$	17	15	16	17	13.5	18
$[Ni(HQMABS)_2(H_2O)_2]$	18	16	14	19	17	15
$[Cu(HQMABS)_2(H_2O)_2]$	19.5	22	21	20	20	19.5
$[Zn(HQMABS)_2(H_2O)_2]$	13	15	11	12	12	15

[a] Zone of inhibition obtained upon extraction of control (DMSO) ≈ 11.

Results of antimicrobial study revealed that ligand HQMABS exhibited higher activity than parent molecules (sulphanilamide, 8HQ, and oxinates). The enhancement of the antimicrobial activity of HQMABS might be due to the synergetic effect[17] of sulphanilamide and 8HQ. The membrane of gram-positive bacteria allows 8HQs to transfer the metal across the intact plasma membrane of endothelial cells rapidly and increase their sensitivity. The outer membrane of gram-negative bacteria might serve as a selective barrier for 8HQs, obstructing their passage in the cell and hence show lesser sensitivity. Therefore, it is presumed that HQMABS exert their biological activities similarly to 8HQ as a membrane-active agent through metal-ion chelation.[46] The biological activity of compounds also depends on the nature of the ligand, concentration, lipophilicity, nature of metal ion, coordinating sites and geometry of the complex. As the mechanism of inhibition by 8HQs and oxinates might be different, it was observed that all the M(II) oxinates showed moderate or lesser activity as compared to HQMABS.

4. Conclusion

The novel 4-{[(8-hydroxyquinolin-5-yl)methyl] amino}benzenesulfonamide (HQMABS) and its octahedral metal(II) oxinates (1 : 2 metal to ligand ratio) were synthesized and characterized, and showed good antibacterial and antifungal activities compared to 8-hydroxyquinoline and sulphanilamide. This might be due to the additive biological effect of parent molecules and/or due to the metal chelating properties. Among the oxinates, Fe(II) and Cu(II) chelates showed better activity, but were found less active than HQMABS.

5. Acknowledgements

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Povzetek

V prispevku je opisana priprava 4-{[(8-hidroksikinolin-5-il)metil]amino}benzensulfonamida (HQMABS) z optimizirano reakcijo med 4-aminobenzensulfonamidom in 5-klorometil-8-hidroksikinolin hidrokloridom. Z uporabo kovinskih soli ionov Mn(II), Fe(II)**,** Co(II), Ni(II), Cu(II) in Zn(II) so bili pripravljeni tudi različni oksinati HQMABS. Vse spojine so bile analizirane in okarakterizirane z fizikalno-kemijskimi, termo-gravimetričnimi in spektroskopskimi tehnikami. Prav tako je bila testirana protimikrobna aktivnost pripravljenih spojin na različnih bakterijah (*Staphylococcus aureus, Bacillus subtillis, Pseudomonas aerugionsa in Escherichia coli*) in sporah gob (*Aspergillus niger* in *Aspergillus flavous*). Rezultati so pokazali precej višjo protimikrobno aktivnost HQMABS kot pri 8-hidroksikinolinu in sulfonamidu, medtem ko oksinati HQMABS kažejo zmerno aktivnost.

Supplementary Material

NMR spectra (^{1}H and ^{13}C APT) of HQMABS and [Zn(HQMABS)$_2$(H$_2$O)$_2$]

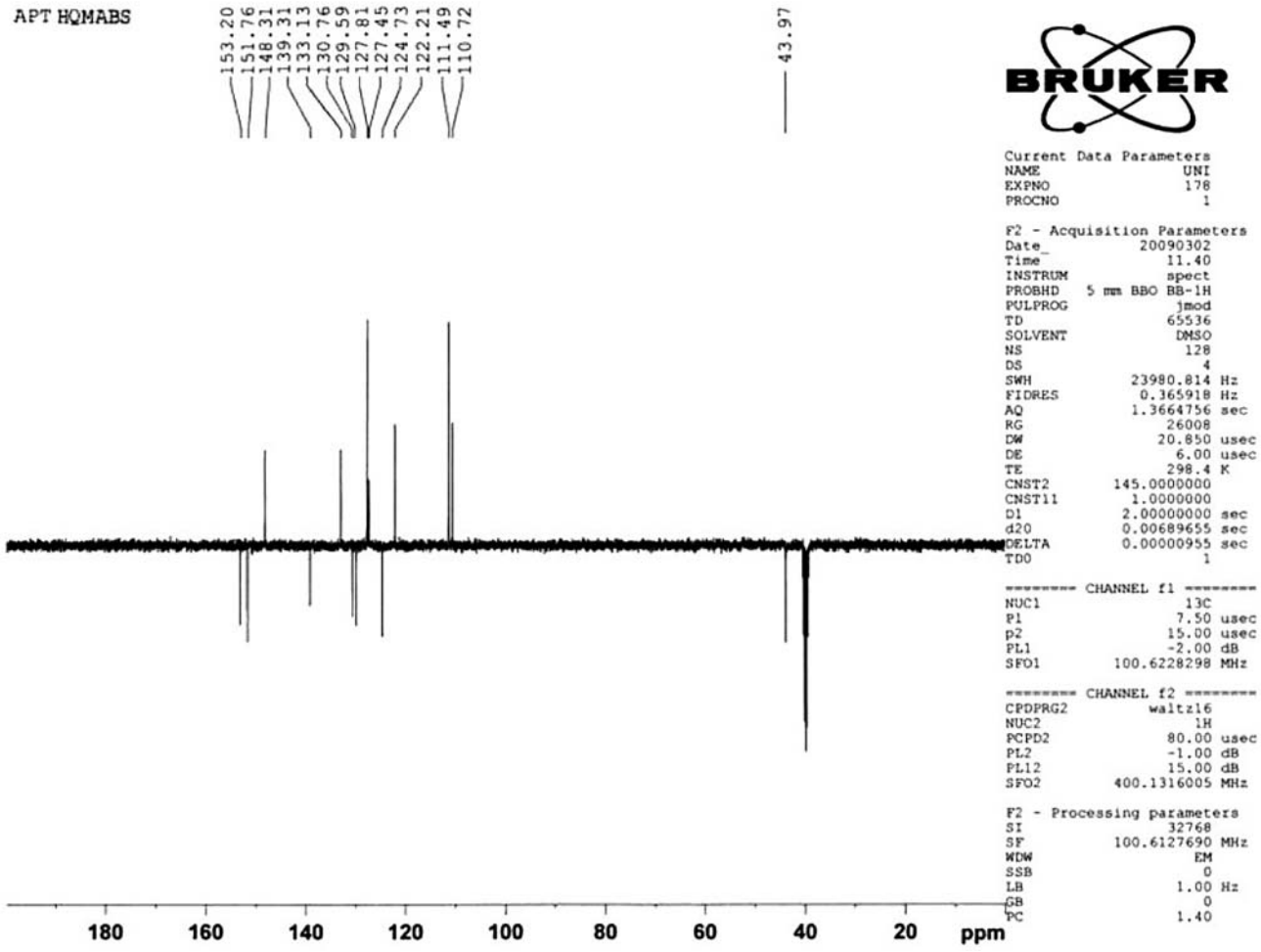

Figure 1. ^{13}C NMR APT spectrum of HQMABS.

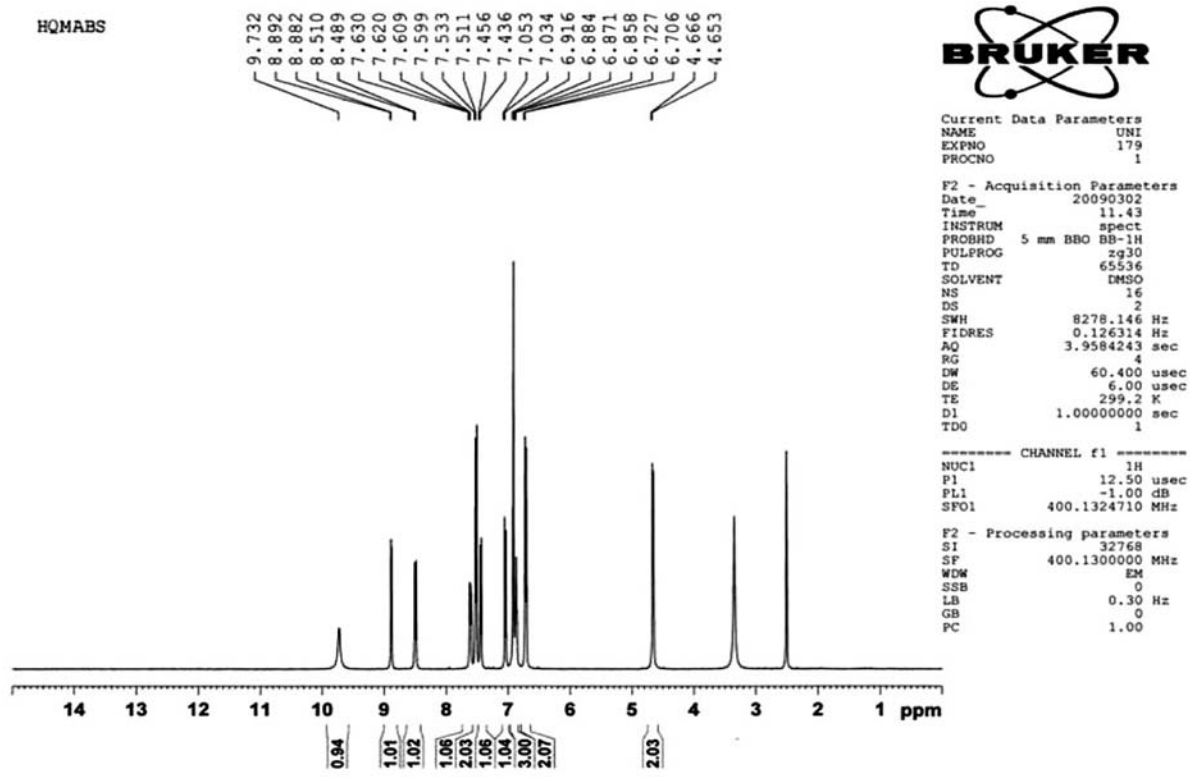

Figure 2. ^{1}H NMR spectrum of HQMABS.

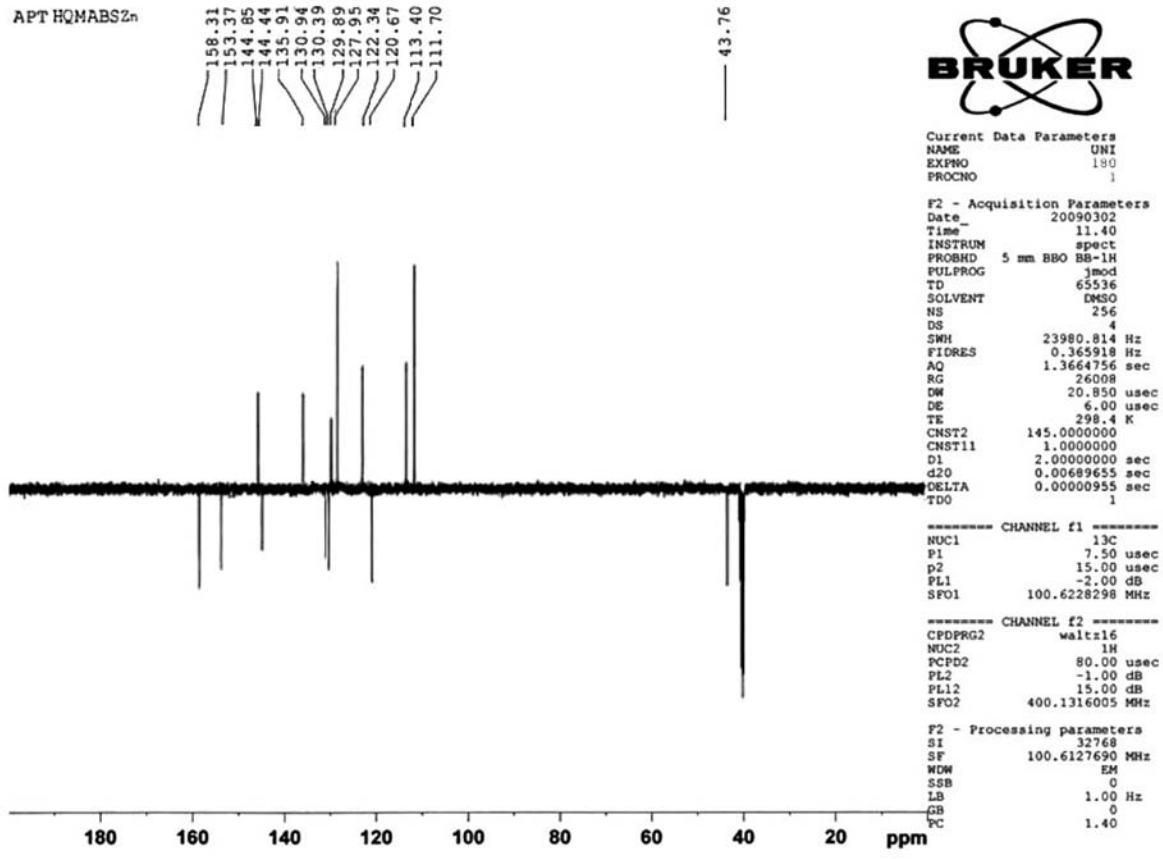

Figure 3. ^{13}C NMR (APT) spectrum of $[Zn(HQMABS)_2(H_2O)_2]$.

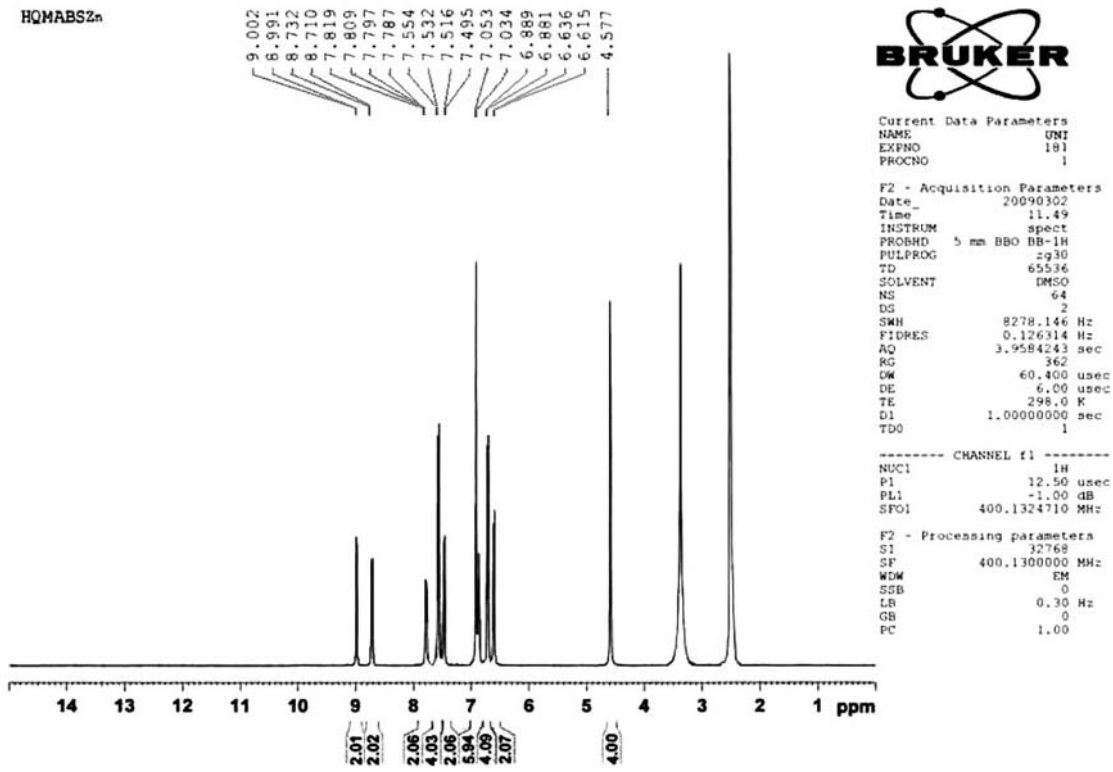

Figure 4. ^{1}H NMR spectrum of $[Zn(HQMABS)_2(H_2O)_2]$.

Diffuse electronic spectra:

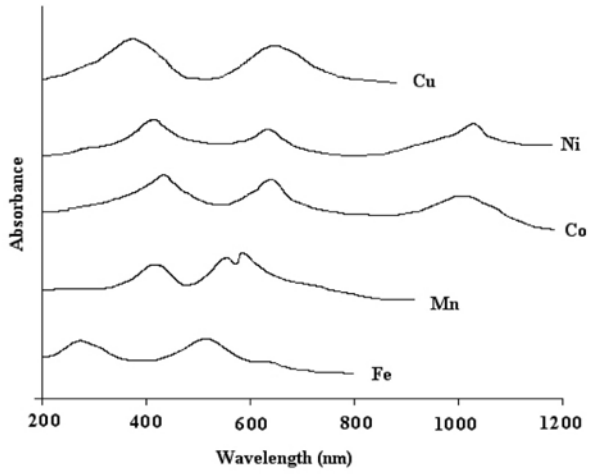

Figure 5. Diffuse electronic spectra of M(II)-oxinate.

Magnetic properties data

Magnetic Susceptibility (μ_{eff}) calculation

Calibration of gouy tube

1. Weight of the empty gouy tube without magnetic field (a) = 11.50826 gm.
2. Weight of the empty gouy tube with magnetic field (b) = 11.50338 gm.
3. Apparent change in weight (b – a) = (– c) = ÿ – 0.00488 gm.
4. Weight of tube + water (d) = 11.96516 gm.
5. Weight of water = Volume of water (d – a) = V = 0.4569 gm.
6. Weight of tube + calibrant without magnetic field (e) = 12.09474 gm.
7. Weight of tube + calibrant with magnetic field (f) = 12.13664 gm.
8. Weight of calibrant (e – a) = W = 0.58648 gm.
9. Apparent change in weight (f – e) = dw = 0.0419 gm.
10. Apparent change in weight with diamagnetic correction = (f – e) – (– c) = w = 0.04678 gm.

Tube constant β was determined from the following equation.

$$\beta = \frac{\chi W - kV}{w}$$

Where, χ = Magnetic susceptibility of the calibrant $Hg[Co(CNS)_4] = 16.44 \times 10^{-6}$ at 20 °C
W = Weight of calibrant
k = Volume susceptibility of air = 0.029×10^{-6}
V = Volume of water
w = Apparent change in weight

$$\beta = \frac{[(16.44 \times 10^{-6})\ 0.58648] - [(0.029 \times 10^{-6})\ 0.4569]}{0.04678}$$

$\beta = 2.05811 \times 10^{-4}$

Magnetic susceptibility (μ_{eff}) calculation for Cu complex

11. Weight of the tube + compound without magnetic field (g) = 11.80136 gm.
12. Weight of the tube + compound with magnetic field (h) = 11.79918 gm.
13. Weight of compound = (g – a) = W = 0.2931 gm.
14. Apparent change in weight = (h – g) = dw = –0.00218 gm.
15. Apparent change in weight with diamagnetic correction = (h – g) – (– c) = w w = 0.002700 gm.

Magnetic susceptibility of the compound determined from the following equation.

$$\mu_g = \frac{kV + \beta w}{W}$$

Where, W = Weight of compound
w = Apparent change in weight
β = Tube constant

$$\mu_g = \frac{[(0.029 \times 10^{-6})\ 0.4569] + [(2.05811 \times 10^{-4})\ 0.002700]}{0.2931}$$

$\mu_g = 1.94111 \times 10^{-6}$ gm.

$\mu_M = \mu_g \times$ Molecular Weight of compound
Where, Molecular Weight of Cu Complex = 756.29 gm.
$= 1.94111 \times 10^{-6} \times 756.29$
$\mu_M = 1.46804 \times 10^{-3}$ gm.

$$\mu_{eff} = 2.83 \sqrt{\mu_M T}$$

Where T = Absolute temperature = 298 °K

$$\mu_{eff} = 2.83 \sqrt{1.46804 \times 10^{-3} \times 298}$$

$\mu_{eff} = 1.8718$ B.M.

NOTE : Magnetic susceptibility (μ_{eff}) calculations for Mn(II), Fe(II), Co(II) and Ni(II) complex were obtained similarly.