

Spectral and Biological Studies on Microwave Assisted Synthesized Zn(II) Complex of Schiff Base Derived from Sulphonamides.

MAMTA BHATTACHARYA¹ and PRIYA BUDHANI²

¹Sadhu Vaswani College , Bairagarh. Bhopal-462 030 India.

²Sagar Institute Science & Technology Air Port Road Bhopal India.

<http://dx.doi.org/10.13005/msri/130106>

(Received: November 14, 2015; Accepted: March 03, 2016)

ABSTRACT

A big challenge, academic world and industry is facing the relationship of modern societies to the environment that requires reinventing the manufacture and use of materials. Synthetic methodologies now a day should be designed to use and generate substances that possess little or no toxicity to human health and the environment. The microwave assisted synthesis and characterization of Zn (II) complexes of Schiff bases derived from three diuretic drugs acetazolamide, furosemide and hydrochlorothiazide are reported here. The ligand and complexes have been suitably synthesized and isolated in crystalline form. Molar conductance values suggest the non-electrolytic nature of the complexes. On the basis of elemental analyses, electrical conductivity data and molecular weight data the adducts are assigned to the general composition $[M(L)_2]$. All the adducts are diamagnetic in nature. The IR studies indicate that ligand is coordinated to metal through azomethine nitrogen atom. The diuretic activity of the ligand FSM-SA and complex FSM-SA-Zn was assessed *in vivo* following the protocol of Institutional Animal Ethical Committee norms. While studying the results of the experiment it was concluded the diuretic activity of the FSM-SA and FSM-SA-Zn was found to be more than the parent drug. Partical size studies further suggest that the size of metal complexes is smaller than the drug molecule.

Keywords-Complexes, Schiff base, diuretic, acetazolamide, furosemide and Hydrochlorothiazide.

INTRODUCTION

Green chemistry is an invention, design, development and application of chemical product and processes to reduce or eliminate the use and generation of the substances hazardous to the human health and environment. Microwave assisted organic synthesis is one such component of green chemistry¹.

Schiff bases and their metal complexes have been found to possess important biological and industrial applications. There is enormous interest

presently in the field of coordination chemistry of '3d' transition metal ion with Schiff bases²⁻⁸. Metal ions play a vital role in the biological activity and certain metal complexes of the drug have been found to be more potent than their parent drug⁹. Survey of literature reveals that very few studies have been done on metal complexes of Schiff bases of diuretic drugs. We report herein the synthesis and characterization of some bipoisitive 3d metal ion chelates of diuretic drugs along with the assessment of diuretic activity. In continuation of our previous work on metal complexes of established drugs¹⁰⁻¹² the synthesis and structural studies of (AZM-

SA)₂Zn, (FSM-SA)₂Zn, (HCT-SA)₂Zn complexes are described below.

EXPERIMENTAL

Pure sample of acetazolamidemide (AZM) molecular formula C₄H₆N₄O₃S₂, molecular weight 222.24, was obtained from Shalaks Pharmaceuticals Pvt. Ltd New Delhi. Pure sample of furosemide (FSM) molecular formula C₁₂H₁₁N₂O₅S, molecular weight 330.75, was obtained from Geno Pharmaceuticals Pvt. Ltd., Goa. Pure sample of Hydrochlorothiazide (HCT) molecular formula C₇H₈ClN₃O₄S₂, molecular weight 297.74, was obtained from Novartis India Pvt. Ltd, Mumbai. These drugs were used as such for the synthesis of ligand. Metal salts were Qualigen

chemicals. Solvents used were methyl alcohol and acetone. All the chemicals used were of analytical grade. . Elementa analysis (CHN) were carried out on a Carlo Ebra 1106 Thomas and Coleman analyzer. Conductivity measurments were carried out on Systronics digital direct reading conductivity meter using conductivity cell having cell constant 1.0. The IR spectra of ligand and complexes were recorded in KBr pallets on Perkin Elmer spectrophotometer in the range 4000-400 cm⁻¹. Magnetic susceptibility measurements were done on Vibrating Sample Magnetometer at room temperature. The ¹H NMR spectra of ligand and complexes were run in DMSO d₆ on a Joel-FX-100 Spectrophotometer using TMS as an internal standard. Diuretic activity of FSM-SA and (FSM-SA)₂Cu complex was assessed at Jawahar

Table 1: Synthesis and physicochemical characteristics of ligand and complexes

Ligand\ Complex	Ligand/ metal Ratio	Colour	% Yield	Stability Constant logK (L/mole)	Free energy change - Δ F Kcal/mole)	Molar Conductance (Ω ⁻¹ cm ² mole ⁻¹)
AZM-SA -	Pale yellow	70	-	-	-	-
(AZM-SA) ₂ Zn	2:1	Yellow	32	11.2006	15.6839	15.0
FSM-SA -	Pale yellow	65	-	-	-	-
(FSM-SA) ₂ Zn	2:1	Yellow	32	11.3529	15.996	14.6
HCT-SA -	Yellow	72	-	-	-	-
(HCT-SA) ₂ Zn	2:1	White	65	12.0888	17.038	11.3

Table 2: Analytical data of complexes

Ligand \Complex	Elemental analysis %			Found (Calculated)			m.p°C
	C	H	Cl	N	S	metal	
C ₁₁ H ₁₀ N ₄ O ₃ S ₂	40.66 (40.49)	3.33 (3.06)	-	17.57 (17.17)	9.29 (9.81)	-	212
(C ₁₁ H ₈ N ₄ O ₃ S ₂) ₂ Zn	36.89 (36.50)	2.53 (2.34)	-	14.53 (16.00)	17.21 (17.50)	9.11 (9.70)	150
C ₁₉ H ₁₄ ClN ₂ O ₆ S	52.63 (52.46)	3.66 (3.45)	8.29 (8.16)	6.87 (6.24)	7.33 (7.38)	-	212
(C ₁₉ H ₁₃ ClN ₂ O ₆ S) ₂ Zn	48.22 (48.89)	3.54 (3.01)	7.63 (7.6)	6.75 (6.00)	6.58 (6.88)	7.62 (7.01)	150
C ₁₄ H ₁₁ ClN ₃ O ₅ S ₂	41.22 (41.89)	2.44 (2.74)	8.12 (8.72)	10.55 (10.47)	15.33 (15.96)	-	255
(C ₁₄ H ₁₀ ClN ₃ O ₅ S ₂) ₂ Zn	38.15 (38.85)	2.59 (2.54)	8.77 (8.21)	9.70 (9.71)	14.14 (14.80)	7.86 (7.28)	260

Lal Nehru Cancer Hospital and Research Center, Bhopal, following the protocol and Institutional Animal Ethical Committee norms

General microwave procedure for the synthesis of Schiff bases (AK1-AK5). Synthesis of Ligand (Drug-Schiff base) General microwave procedure for the synthesis of Schiff bases

Equimolar solutions of pure drugs (0.01M) and salicylaldehyde (0.01M) were taken in aqueous methanol mixture (1:1 ratio). Both the solutions were mixed contents were subjected to microwave

irradiation at an interval of 1 min at 400 W for about 8-10 min; The reaction mixture was kept overnight. Crystals of drug-Schiff base (AZM-SA, FSM-SA, HCT-SA) were formed in the reaction mixture, which were washed with 50:50 methanol : water mixture, filtered, dried and weighed. Melting point was recorded

Ligand-Metal ratio and Stoichiometry

To confirm the ligand metal ratio, conductometric titrations using monovariation method were carried out on Systronics conductivity meter 0.01M solution of drug-Schiff base was

Table 3: Infra Red Spectral Bands (cm⁻¹) of (AZM-SA)₂Zn, (FSM-SA)₂ Zn and (HCT-SA)₂Zn complexes

Ligand/ Complex	ν (SO ₂ N)	ν (HC=N)	ν (Phenolic OH)	ν (C-S)	ν (M-O)	ν (M-N)	ν Aromatic S)	ν (C-Cl)	ν Chelate Ring
AZM-SA	1176 vs	1680 vs	3303 vw		-	-	700 m		
(AZM-SA) ₂ Zn	1163 s	1599 s	-		622 s	515 s	700 s		1420 vs
FSM-SA	1142 vs	1672 vs	1620 vs		-	-		789 s	-
(FSM-SA) ₂ Zn	1150 s	1600 vs	-		680 w	583 m		630 s	1400 m
HCT-SA	1152 s	1602 m	3271 m	1059 w	-	-		776 w	-
(HCT-SA) ₂ Zn	1152 m	1580 w	-	1058 w	676 w	609 w		776 w	1427 w

The ¹HNMR spectra of FSM-SA, HCT-SA and (FSM-SA)₂Zn & (HCT-SA)₂Zn complex
The spectra of ligand (FSM-SA) and its metal complexes were recorded in DMSO.

Table 4: (observations for group I) Average volume of urine excreted by control animals (Mice were fed with 0.5ml acidified double distilled water)

S.N.	Vol. of urine (in μ l) Readings at 12:00 noon	Vol. of urine (in μ l) Readings at 3:00 pm	Vol. of urine (in μ l) Readings at 6:00 pm	Average vol. of urine (in μ l)	A1 (X+Y+Z/3)
1.	58.02	136.45	50.52	81.66	
2.	126.04 X 96.47	175.20 Y 166.76	61.56 115.31	120.93 Z 86.41	117.52
3.	23.33	89.80		76.17	
4.	221.25	278.0	151.04	216.97	
5.	63.74	154.37	53.64	90.58	

prepared in 60:40 acetone: water mixture and diluted to 200ml with same solvent. This Schiff base solution was titrated against 0.02M metal solutions using monovariation method. After making volume corrections the results were plotted that suggest the ligand metal ratio to be 2:1. Formation of 2:1 complex was further confirmed by Job's method of continuous variation, modified by Turner and Anderson. The stability constants and free energy change were also calculated.

Synthesis of complexes

0.1M ligand solution was prepared in 60:40 acetone : water mixtures and refluxed for four hours with 0.05M solution of $ZnCl_2$. Fine crystalline compounds appeared in the solutions. Complexes were washed with acetone, filtered, dried and weighed. Melting points were recorded.

Diuretic activity of FSM-SA and (FSM-SA)₂Zn complex

Diuretic activity of FSM-SA and (FSM-SA)₂Cu complex was assessed at Jawahar Lal Nehru Cancer Hospital and Research Center, Bhopal, following the protocol and Institutional Animal Ethical Committee norms. The experiment was carried out

Table 5: (observations for group ii (test gr.) (0.024 g furosemide)

S.N.	Average vol. of urine(in μ l)	A2
Mice 1.	173.29	168.29
Mice 2.	174.96	
Mice 3.	168.96	
Mice 4.	173.29	
Mice 5.	150.96	

Table 7: (observations for group v (test gr.) (0.024 g furosemide Schiff base Zn complex)

S.N.	Average Vol. of urine (in μ l)	A4
Mice 1.	530.88	542.81
Mice 2.	541.81	
Mice 3.	532.48	
Mice 4.	576.92	
Mice 5.	531.98	

on mice. Detailed survey of literature indicated that dose prescribed for human being is also safe in mice²⁵⁻²⁶.

The average volume of urine output for various sets of experiments explains clearly the order of diuretic activities of the drug its Schiff base and metal complexes as follows- (FSM-SA)₂Zn(Complex)>FSM-SA(Schiff base) > FSM(Pure drug)>Water The order is indicating that a metal complex of the drug is more potent diuretic than its Schiff base and pure drug itself.

RESULTS AND DISCUSSION

Ligand-Metal ratio and stoichiometry- The color, melting point, yield percentage, stability constant, free energy change and molar conductance value are summarized in table I & analytical data are summarized in table II. Conductometric studies, monovariation method and Job's method of continuous variation modified by Turner and Anderson²¹⁻²² indicate the formation of 2:1 (L: M) complexes of Schiff base of ligands with Zn ion. .

Table 6: (observations for group ii (tes (0.024 g furosemide Schiff base)

S.N.	Average vol. of urine(in μ l)	A3
Mice 1.	189.23	181.72
Mice 2.	176.49	
Mice 3.	185.83	
Mice 4.	184.05	
Mice 5.	173.00	

Table 8: Comparison of Diuretic Activities of Various Samples

Group	Sample given	Average vol. of urine (in μ l)
A1	(Water)	117.52
A2	(Pure drug Furosemide)	168.29
A3	Furosemide	181.72
	salicyldimine Schiff base	
A4	Furosemide Schiff base	542.81
	Zn complex	

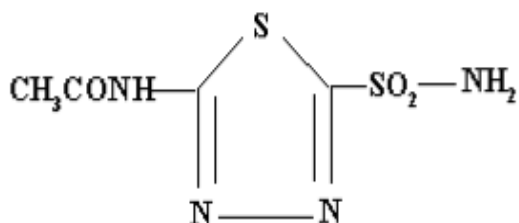
**Structure of Acetazolamide**

Fig. 1

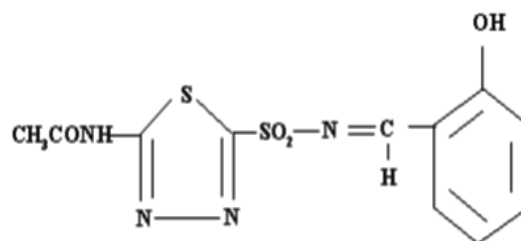
**Structure of Acetazolamide Schiff base**

Fig. 2

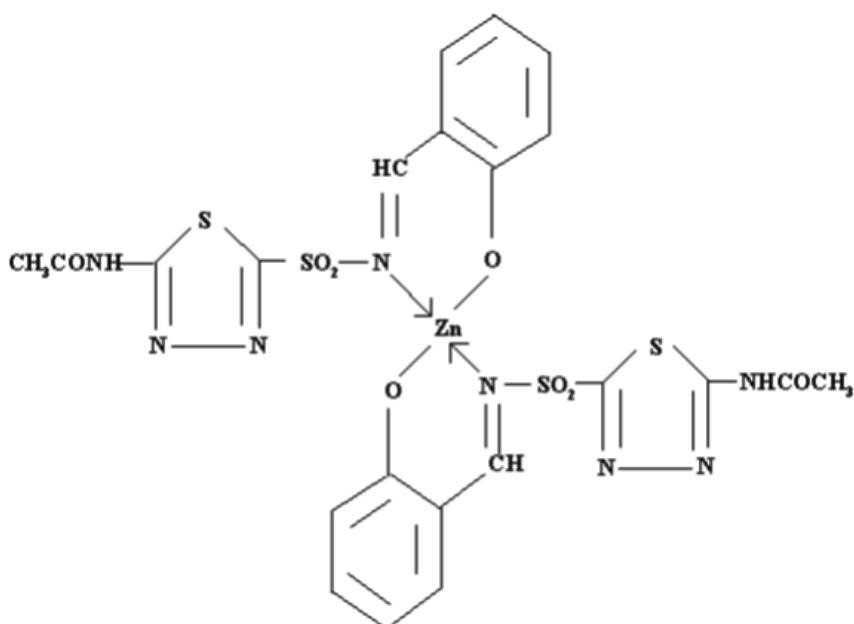
**Structure of Acetazolamide Schiff base Zinc complex**

Fig. 3

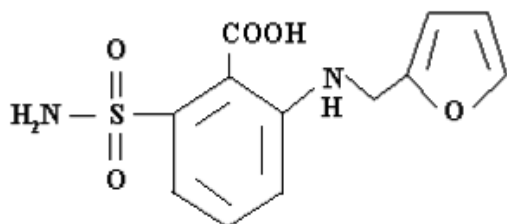
**Structure of Furosemide**

Fig. 4

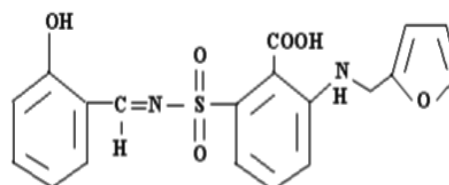
**Structure of Furosemide schiff base(FSD-SB)**

Fig. 5

Analytical data of these complexes are in agreement with the composition.

IR Spectra

Proposed structure of (AZM-SA)₂Zn, (FSM-SA)₂Zn, (HCT-SA)₂Zn complexes were further confirmed by IR spectra data²³⁻²⁸. In the present work the IR spectra of ligands and their metal complexes were recorded on Perkin Elmer Spectrophotometer in KBr pallets.

Bands observed at 1163 cm⁻¹ 1150 cm⁻¹ and 1152 cm⁻¹ are characteristic of SO₂-N group. Absorption bands at 1420cm⁻¹, 1400cm⁻¹ and 1427cm⁻¹ shows the presence of chelate ring. Frequencies at 622 cm⁻¹, 680 cm⁻¹ and 676 cm⁻¹ are characteristics of M-O linkage. Bands at 515 cm⁻¹, 583 cm⁻¹ and 609 cm⁻¹ are characteristic of M-N linkage. Frequencies at 892 cm⁻¹, 805 cm⁻¹ and 859 cm⁻¹ indicate the S-N linkage. Absorption bands of m-w intensity due to azomethine linkage have been observed at 1599 cm⁻¹-1602 cm⁻¹. Azomethine

linkage is produced by the reaction between drug and salicylaldehyde.

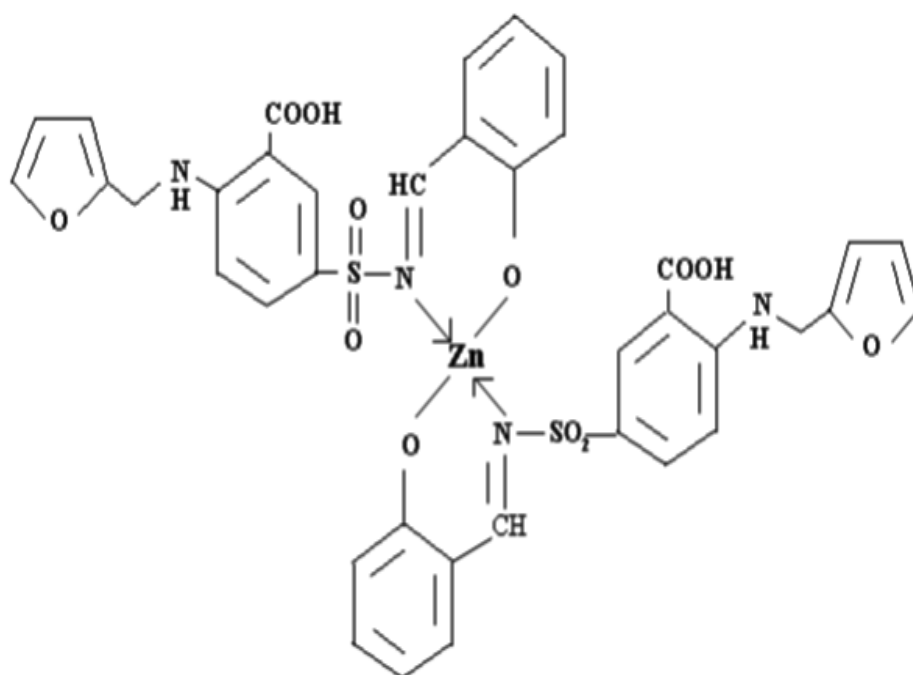
Lowering of azomethine frequencies in the metal complexes indicate its involvement in coordination²⁹. The disappearance of frequencies of phenolic -OH in complexes supports its involvement in complexation.

The ¹HNMR spectra of FSM-SA ,HCT-SA and (FSM-SA)₂Zn & (HCT-SA)₂Zn complex

The spectra of ligand(FSM-SA) and its metal complexes were recorded in DMSO.

FSM-SA

The (N=CH) group proton shows triplet peak at δ (8.59-8.63) ppm, which can be assigned to azomethine(HC=N) proton.³⁰In the ligand (FSM-SA) peaks observed at δ(8.34-8.40)ppm , δ(7.06) ppm and δ(6.36-6.43)ppm are assigned to aromatic protons due to the different environments around the protons.³¹The ligand showed the single peak at



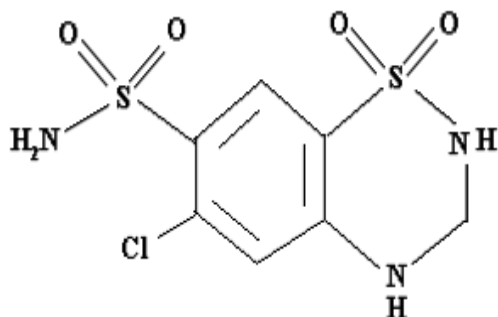
Structure of Furosemide schiff base Zinc complex

Fig. 6

δ (7.62) ppm, that corresponds to proton of benzene ring having -COOH substitution at para position. The spectrum showed the presence of singlet at δ (7.32 ppm) due to (-NH) proton. The signal observed at (4.57-4.59) ppm has been assigned to phenolic -OH proton.³² Peaks observed at δ (3.33) ppm can be attributed to TMS (Tetra Methyl Silane).

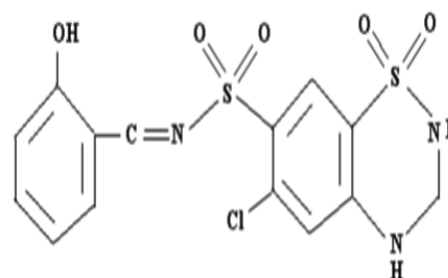
(FSM-SA)₂Zn complex

In The ¹H NMR spectra of (FSM-SA)₂Zn singlet peak observed at δ (9.162) ppm, is corresponds to -NH proton in . Singlet peak observed at δ (8.44) ppm is corresponds to azomethine (NC=H) proton. In spectrum singlet peak observed at δ (7.571) ppm are corresponds to proton of benzene ring



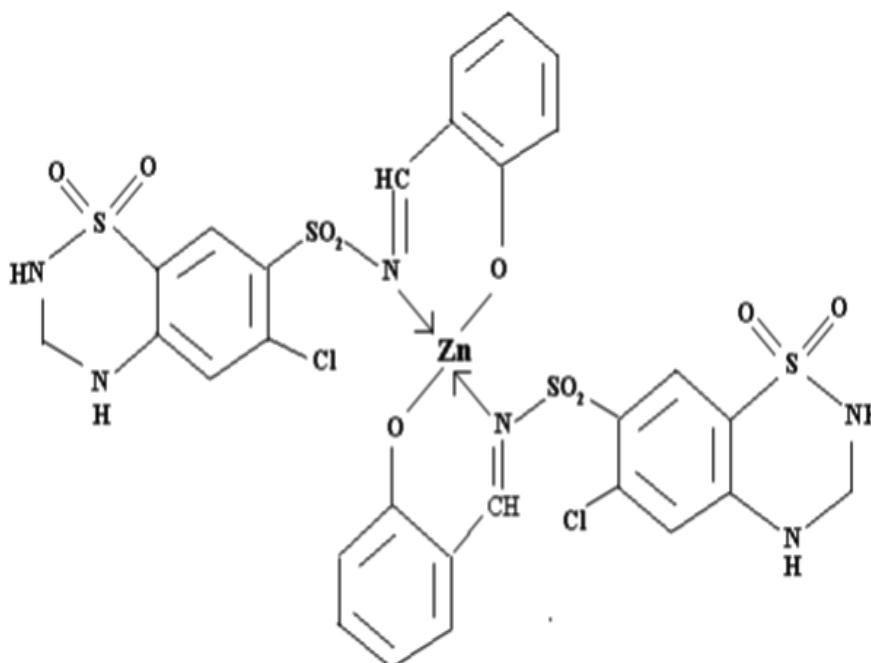
Structure of Hydrochlorothiazide

Fig. 7



Structure of Hydrochlorothiazide Schiff base

Fig. 8



Structure of Hydrochlorothiazide Schiff base Zinc complex

Fig. 9

having - COOH substitution at para position. The spectra showed peaks at δ (6.936)ppm, δ (6.33-6.77)ppm and δ (7.244)ppm due to aromatic proton (*loc. cit.*). In The ^1H NMR spectra of $(\text{FSM-SA})_2\text{Zn}$ singlet peak observed at δ (3.512) ppm is assignable to TMS. The (N=CH) group Proton shows the downfield shifting which supports the coordination of metal to (N=CH) group through nitrogen, which is also supported by IR spectral data. Absence of signal due to phenolic -OH suggests the coordination of phenolic oxygen to the metal. This has also been supported by IR spectral data. The spectra do not show any peak due to coordinated water molecule which indicates square planer geometry of the complexes.

The ^1H NMR spectra of HCT-SA and its $(\text{HCT-SA})_2\text{Zn}$ complex The spectra of ligand(HCT-SA) and its metal complexes were recorded in DMSO.

HCT-SA –The (N=CH) group proton shows a triplet at δ (7.91-7.99) ppm, which corresponds to -NH proton. The peaks observed at δ (7.48) ppm may be attributable to azomethine proton. Spectra of ligand(HCT-SA) showed peak at δ (6.97)ppm which can be assigned to aromatic protons due to the different environments around the protons³². Signal observed at δ (4.70-4.73) ppm has been assigned to phenolic -OH proton. Peaks observed at δ (3.33) ppm can be attributed to TMS (Tetra Methyl Silane).

$(\text{HCT-SA})_2\text{Zn}$

The signal observed at δ (7.959-8.003) ppm in ^1H NMR spectra of $(\text{HCT-SA})_2\text{Zn}$ has been assigned to azomethine (NC=H) proton³⁴. The peaks observed at δ (7.49) ppm in the spectra of $(\text{HCT-SA})_2\text{Zn}$ are attributable to -NH proton³³. The ^1H NMR spectra of $(\text{HCT-SA})_2\text{Zn}$ showed peaks at δ (6.94)ppm due to aromatic proton (*loc. cit.*). Peaks observed at δ (3.33)

ppm may be assigned to TMS. The (N=CH) group Proton shows the downfield shifting which supports the coordination of metal to (N=CH) group through nitrogen³⁴, which is also supported by IR spectral data. In spectra absence of signal due to phenolic OH suggests the coordination of phenolic oxygen to the metal. This has also been supported by IR spectral data. The spectra do not show any peak of coordinated water molecule, which indicates square planer geometry of the complexes.

Diuretic Activity

The average volume of urine output for various sets of experiments is shown in tabulated form- The average volume of urine output for various sets of experiments explains clearly the order of diuretic activities of the drug its Schiff base and metal complexes as follows- $(\text{FSM-SA})_2\text{Zn}(\text{Complex}) > \text{FSM-SA}(\text{Schiff base}) > \text{FSM}(\text{Pure drug}) > \text{Water}$ The order is indicating that a metal complex of the drug is more potent diuretic than its Schiff base and pure drug itself. The average volume of urine output for various sets of experiments explains clearly the order of diuretic activities of the drug its Schiff base and metal complexes as follows-

$(\text{FSM-SA})_2\text{Zn}(\text{Complex}) > \text{FSM-SA}(\text{Schiff base}) > \text{FSM}(\text{Pure drug}) > \text{Water}$ The order is indicating that a metal complex of the drug is more potent diuretic than its Schiff base and pure drug itself.

ACKNOWLEDGEMENT

The authors thank the authorities of CDRI, Lucknow for providing facilities of elemental analysis, IR and electronic spectra. The authors are thankful to Dr. N. Ganesh and Mr. T.M. Malla, Jawahar Lal Nehru Cancer Hospital and Research Center, Bhopal, for providing facilities for *in vivo* testing of diuretic activity of the ligand and the complexes.

REFERENCES

1. Yadav K., Sharma A., Shrivastava *Asian J. Chem*, Vol12, 5779-81 **2012**.
2. De A.K., Deb D., Nath Bhowmik K.R. and Dutta R.N. *J. Indian Chem Soc*, Vol. **86**, 76-82 **2009**.
3. Khan M.H., *Orient. J. Chem*, Vol. **26**, (3), 1155-58 **2010**.
4. Mohan J. Kataria S., *Indian J. of heterocyclic Chem*, **6**, 317 **1997**.
5. Sigel R.K.O., Song B. and Siegl H. *J. Am. Chem.*

- Soc ,119,744 **1997**.
6. Kumar A.,Singh G., Handa R.N.,*Indian J. of Chem*, ,**38A**, 613-617 **1999**.
7. Prakash Anant and Ahmed Shamim, *Orient. J. Chem*, **25**, 2, 391-395 **2009**
8. Prasad Anukul and Rai B.K.. *Orient. J. Chem*, **25**,1, 175-179 **2009**.
9. Singh Sachin etal. *Orient. J. Chem*, **25**, 2, 433-436 **2009**.
10. Bhattacharya M., Iqbal S.A. and Malik S., *Orient. J. Chem*, Vol,**4**, 643-646 **2004**.
11. Iqbal S.A.and Siddiqui S., Qureshi R.and Desnavi A., *Orient. J. Chem* ,1,32 **1985**.
12. Qureshi R. and Iqbal S.A., *Orient. J. Chem*, **3**,13, **1997**.
13. Larkem H.,Larkem A. and Messadi D.,*Egypt J. Chem*, **47**(4),413-426 **2004**.
14. Kamal Kishor, Gupta B.B. and Dheer R. *Indian Drug Review*, Mediworld Pub. Pvt. Ltd, Delhi. Jul-Aug ,**2006**
15. <http://www.pettalk.com>.,
16. Yadav R.,Raikwar D.K. and Shrivastava K.S., *J.Indian Chem Soc*, , Vol.**86**, 195-198 **2009**.
17. <http://www.Wikipedia>, the free encyclopedia,
18. <http://www.patient.co.uk>
19. **Burn J.H. Quart. J. Pharm**,**4**,517 **1931**
20. Aston R. *Toxicol. appl. Pharmacol*, 1,272 **1959**.
21. Job P., *Ann Chim.*, **10** ,113, **1928**
22. Turner S.E., and Anderson, R.C., *J.Am .Chem.,Soc*, 71,912, **1949**.
23. Ahmed Naushad, *Orient. J. Chem*,Vol.26,No.3, 921-929 **2010**.
24. Bellamy L. J., *Chemical Application Of spectroscopy*" (Int.Sci.Pub.) New York, **1956**.
25. Nakamoto K., *Infrared spectra of Inorganic and co-ordination Compounds*, (John Wiley), New York, **1963**.
26. Weissberger A., *Chem. Application of spectroscopy* (Int. Sci. Pub.) New York, **1956**.
27. Rai B.K., *Orient. J. Chem*,Vol.**26**, No.3, 1097-1101 **2010**.
28. Manivanan S. and Manimaran A., *J.Indian Chem Soc*, Vol.**85**, 988-995, **2008**.
29. B.N. Figgis, *Introduction to Ligand Field*, Wiley Eastern, New Delhi, , 279. **1976**.
30. Lever A.B.P.,*Inorg. Electronic Spectroscopy*, Elsevier.____Amsterdam,**1968**.
31. Chukurovali A. Ibrahim Y.and Habibe, "Transition Metal Chemistry",**26**,619-624 **2001**.
32. Hussain A.et.al , *Asian J.of Chem*,**17**(3),1579-1584 **2005**.
33. Al-Nowasiar F.M. et al., *Material Science Research India*,**03**(1), 1-6 **2005**.
34. Pathani S. Mansingh and Kailash C.,*Indian J.Chem*,**34A**,904-907 **1995**.