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SYNTHESIS, SPECTROSCOPIC AND *IN-VITRO* ANTIMICROBIAL SCREENING OF SOME NOVEL TRANSITION METAL BASED HETEROCHELATES

GAJERA P[1], VADODARIA M[2], RAJA M[1] AND CHOLERA A[1]

1: Assistant Professor, Atmiya University, Rajkot, 360005, Gujarat, India

2: Chemical Research Laboratory, Shri Manibhai Virani & Smt. Navalben Virani Science College (Autonomous), Rajkot - 360005, Gujarat, India

***Corresponding Author: Mr. Prashant Gajera: E Mail: ps9601477204@gmail.com**

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ABSTRACT

New Mn(II), Cu(II) and Zn(II) heterochelates were synthesize by reacting Semicarbazone, Thiosemicarbazone and Antipyrine with 2 amino 3,5 dibromo benzaldehyde. All the synthesized Schiff's base ligands and their heterochelates were examined for their spectroscopic and antimicrobial activities. The structures of Schiff's base ligands were confirmed by ^{1}H NMR, IR, Mass, elemental analysis and their heterochelates were confirmed by IR and FAB mass spectroscopy. All the Schiff's base ligands and heterochelates were screened for in-vitro biological study against Gram positive (*Bacillus subtilis, S. Aureus*) and Gram negative (*E. coli, Pseudomonas aeruginosa*) microorganisms. The results confirmed that transition metal based heterochelates have an immense potential and important for further research work.

Keywords: Semicarbazone, Thiosemicarbazone, Schiff's base, Heterochelates, Antimicrobial studies

INTRODUCTION

Schiff's base ligands were found to be a significant set of chelating agents for complexation in chemistry **[1, 2]**. Schiff's bases are very important category of organic compounds for inorganic chemistry because of their ability to form stable

complex with different transition metals **[3, 4]**. Complexation of Schiff's base gain significance attention due to their broad range of applications such as thermal studies **[5]**, catalytic **[6]** toxicity **[7]**, antibacterial activity **[8, 9]**, antifungal **[10]**, Antitumor activity **[11]**, Antiviral **[12]**, DNA binding **[13]**. In such class of compounds, the C=N moiety is important for biological activity.

On the other hand, complexes of Semicarbazone and thiosemicabazone Schiff's base ligands with transition metal have received considerable interest due to its ability to disrupt DNA synthesis by causing modification in the reductive conversion of ribonucleotides to deoxyribonucleotides **[14]**. Furthermore, Semicarbazone possess good pharmacological activities such as antimicrobial **[15, 16]**, antioxidant **[17]**, anticonvulsant **[18-20]**, antiepileptic **[21]**, antiproliferative **[22]**, antitubercular **[23]**, antiinflammatory **[24]** and as intermediates for the preparation of heterocyclic compounds having potent biological activity **[25]**. Coordination compounds of different geometries and properties can be synthesized easily through nitrogen and sulphur of semi carbazone and thiosemicarbazone Schiff's base ligand to metal centre **[26-30]**.

In view on the consequence of transition metal based complexes and our interest in the science of complexes of semicarbazone and thiosemicarbazone based Schiff's base ligands, here we illustrate here the synthesis, spectroscopic and in-vitro antimicrobial screening of some novel transition metal based heterochelates. The general structure of heterochelate is shown in **Figure 1**.

MATERIAL AND METHODS

Materials

All the chemicals used were of analytical grade and used devoid of further purification. The compounds Semicarbazone and Thiosemicarbazone were purchased from Sigma Ltd (India). The 2 Amino, 3,5 dibromo benzaldehyde was purchased from Almon Industries, Ahmedabad, Gujarat, India and used-without purification.

Detection methods

Elemental analysis (C, H, N) was performed on a model 2400 Perkin-Elmer elemental analyzer. FT-IR spectra were recorded as KBr pallets on Nicolet-400D spectrophotometer. ^{1}H NMR spectra were recorded on Advance 400 Bruker FT-NMR instrument in DMSO-d_6 solvent. The FAB-mass spectrum of heterochelate was recorded with JEOL SX-102/DA-6000 mass spectrometer.

General procedure for synthesis of ligands (L_1-L_3)

A 1:1 molar methanolic solution of 4 amino Antipyrine, Thiosemicarbazone and Semicarbazone (0.001mol) was taken in two necked round bottom flask and stirred for several minutes at reflux temperature. A methanolic solution of 2 amino 3,5 dibromo benzaldehyde (0.001mol) was added drop wise to an above solution and refluxed for further 4 h at 60ºC with constant stirring and check the reaction completion by TLC. After the reaction completion, a product was allowed to stand overnight at room temperature. Then a solid product was crystallized by methanol and washed with diethyl ether so solid material was obtained.

L_1

M.F-$C_{18}H_{16}Br_2N_4O$ Yield 85%; M.P. 209°C; Yellow powder; FT-IR (KBr,cm^{-1}): 3439 ν(N–H), 1640 ν(C=O), 1590 ν(C=N); ^{1}H NMR (400 MHz,DMSO-d_6): δ (ppm) = 2.42 (3H,s,-CH_3); 3.2 (3H,s,N-CH_3); 9.5 (1H,s,-CH); 7.3 (2H,s,-NH_2); 7.3-7.6 (7H,c,Ar-H), Elemental analysis found (%) C, 46.65; H, 3.55; Br, 34.49; N, 12.13; O, 3.52 calculated for $C_{18}H_{16}Br_2N_4O$: C, 46.58; H, 3.47; Br, 34.43; N, 12.07; O, 3.45.

L_2

M.F-$C_8H_8Br_2N_4S$ Yield 76%; M.P. 212°C; Cream white powder; FT-IR (KBr,cm^{-1}): 3466 ν(N–H), 1082 ν(C=S), 1543 ν(C=N); ^{1}H NMR (400 MHz,DMSO-d_6): δ (ppm) = 11.3 (1H,s,-CH); 8.2 (1H,s,-NH); 6.3 (2H,s,-NH_2); 7.4-8.1 (2H,dod,Ar-H), Elemental analysis found (%) C, 27.35; H, 2.36; Br, 45.44; N, 15.99; S, 9.18 calculated for $C_8H_8Br_2N_4S$: C, 27.29; H, 2.29; Br, 45.39; N, 15.91; S, 9.11.

L_3

M.F-$C_8H_8Br_2N_4O$ Yield 82%; M.P. 206°C; White powder; FT-IR (KBr,cm^{-1}): 3491 ν(N–H), 1676 ν(C=O), 1597 ν(C=N); ^{1}H NMR (400 MHz,DMSO-d_6): δ (ppm) = 6.8 (1H,s,-CH); 6.8 (1H,s,-NH); 6.1 (2H,s,-NH_2); 5.0 (2H,s,-NH_2); 7.4-7.5 (2H,dod,Ar-H), Elemental analysis found (%) C, 28.67; H, 2.47; Br, 47.63; N, 16.74; O, 4.82 calculated for $C_8H_8Br_2N_4O$: C, 28.60; H, 2.40; Br, 47.56; N, 16.68; O, 4.76.

General procedure for the synthesis of Heterochelates

A general process has been accepted for the synthesis and isolation of all the heterochelates. A hot methanolic solution of metal (II) acetate salt (0.001mol) was added drop wise with continuous stirring to the solution of respective ligands (0.001mol) in1:2 molar ratios. The mixture was heated for 4 h at 70 ºC and left overnight at room temperature. The colored solid product was obtained washed with water, methanol and then dried it in desiccators.

RESULTS AND DISCUSSION

The structure of all the prepared Schiff's base ligands and heterochelates were carried out using elemental analysis, IR, ^{1}H NMR and FAB-Mass spectra. The ^{1}H NMR data of Schiff's base ligands are given in experimental section. The analytical and physical data of heterochelates are given in **Table 1**. Heterochelates were sparingly soluble in methanol and completely soluble in DMF and DMSO. All the heterochelates were stable in air for extended period of time.

^{1}H NMR spectra of ligands

The ^{1}H NMR spectra of ligands L_1 & L_2 are shown in **Figure 2** and **Figure 3** respectively. The ^{1}H NMR spectra of ligand L_1 & L_2 shows a singlet peak at 9.57 and 11.33 δppm assigned to imine group proton (HC=N). The ^{1}H NMR spectra of ligand L_1 shows two singlet for three proton each at 2.4-2.5 and 3.2-3.3 δppm indicates the presence of two $–CH_3$ group. Aromatic protons for both the ligands are obtained in the range of 7.3 to 8.2 δppm. The peak for Aromatic $–NH_2$ protons in ligand L_2 is observed for two protons at 6.3 δppm. The peak for –NH proton may merge in aromatic region so it is difficult to separate it out. As numbers of protons are exactly match with molecular formula of the compound.

Infrared Spectra

The IR data for Schiff's base ligands (L_1-L_3) and its transition metal heterochelates are given in **Table 2**. The IR data of ligands were comparing with the IR data of heterochelates to confirm the binding modes of ligands with metal. The Schiff's base ligands (L_1-L_3) shows a sharp and strong band of a υ(C=N) of the acyclic azomethine group in the range of 1540 to 1600 cm^{-1}. The observed lower energy shift of this band in the heterochelates and appearing in the range of 1510 to 1580 cm^{-1} indicate the co-ordination of azomethine nitrogen **[31]**. The υ(C=O) band is visible in the spectra of ligand L_3 at 1676 cm^{-1}. The IR spectra of heterochelates demonstrate an impressive negative move of 15-20 cm^{-1} indicates the coordination through the oxygen atom of ligand. However, the disappearance of amidic NH_2 band and the appearance of anilinic NH band in the range of 3410 to 3460 cm^{-1} proved the formation of heterochelates **[32]**.

FAB Mass Study of Heterochelate

The verified mass spectrum **Fig. 4** and the molecular ion peak for the heterochelate $[Cu(L_3)_2]$ were used to confirm the molecular formula for the proposed heterochelate. The proposed fragmentation pattern is shown in **Scheme (1)**. The first peak at m/z=736 represents the molecular ion peak of heterochelate. Scheme (1)

demonstrates the possible degradation path way for the investigated heterochelate. The primary fragmentation of the heterochelate take place due to the loss of two CH_3N_2O molecule from the species **(a)** to give species **(b)** with peak at m/z=619 as base peak with maximum intensity. Further degradation yields species **(c)** with loss of remaining part of molecule $C_7H_6Br_2N_2$. Species **(c)** further degrade to a stable species **(d)** may be due to the loss of CuO. The calculated molecular weight for all the suggested degradation steps was exactly match with the expected values **[33]**.

Antimicrobial activity

Antimicrobial screening of all the ligands and heterochelates were carried out by Cup borar method using Peniclillin as a standard. A stock solution of 10 mg mL^{-1} was made by dissolving compound in least amount of DMSO and making it up to the mark with double distilled water. The medium was made up by dissolving bacteriological agar (20 g) and Luria broth (20 g; SRL, India) in 1-liter distilled water. The mixture was autoclave for 15 min at 120ºC and then distributed into sterilized Petri dishes, allowed to solidify and then used for inoculation. The target microorganism cultures were prepared separately in 15 mL of liquid Luria broth medium for activation. Inoculation was done with the help of micropipette with sterilized tips; 100 µL of activated strain was placed onto the surface of an agar plate and spread evenly over the surface by means of a sterile, bent glass rod. Then two wells having diameter of 10 mm were made using a sterilized borer in each plate. Application of disks Sterilized stock solutions (10 mg mL^{-1}) were used for the application in the well of earlier inoculated agar plates. When the disks were applied, they were incubated at 30ºC (Gram+ve) and 37ºC (Gram-ve) for 24 h. The zone of inhibition was then measured (in mm) around the disk shown in **Figure 5**. The control experiments were performed with only the equivalent volume of solvents without added test compounds and the zone of inhibitions was measured (in mm) shown in **Table 3 [34]**.

Applications

All the prepared Schiff's base ligands namely L_1-L_3 and their transition metal (Mn, Cu and Zn) based heterochelates were monitored against different gram +ve and –ve bacterial strains. The antimicrobial screening data (**Table 3**) shows that heterochelates exhibit more inhibitory effects compare to parent Schiff's base ligands. The ligand (L_1) and heterochelate $Mn(L_1)_2$ are much powerful bactericides against *E.coli* and *P. aeruginosa* respectively. While ligand L_3 and its heterochelates i.e. $Cu(L_3)_2$ and $Zn(L_3)_2$

found much active against *Bacillus subtilis* and *S. Aureus* bacteria respectively. The enhanced activities of the heterochelates as compared to ligands can be explained on the basis of overtone concept **[35]** and chelation theory **[36]**.

Table 1: Analytical and physical data of Heterochelates

Compounds Chemical Formula	Formula Weight	Colour	(%Yield)	Analysis (%) Found (Cal)					
				C	H	N	O/S	Br	M
$Mn(L_1)_2$	983	Brown	(80)	44.00	3.31	11.42	3.28	32.52	5.63
$C_{36}H_{32}N_8O_2Br_4Mn$				(43.98)	(3.28)	(11.40)	(3.25)	(32.51)	(5.59)
$Cu(L_1)_2$	992	Black	(78)	43.60	3.27	11.33	3.24	32.23	6.43
$C_{36}H_{32}N_8O_2Br_4Cu$				(43.59)	(3.25)	(11.30)	(3.23)	(32.22)	(6.41)
$Zn(L_1)_2$	994	Yellow	(71)	43.53	3.26	11.31	3.26	32.19	6.61
$C_{36}H_{32}N_8O_2Br_4Zn$				(43.51)	(3.25)	(11.28)	(3.22)	(32.16)	(6.58)
$Mn(L_2)_2$	759	Black	(83)	25.35	2.13	14.79	8.48	42.13	7.27
$C_{16}H_{16}N_8S_2Br_4Mn$				(25.32)	(2.12)	(14.76)	(8.45)	(42.11)	(7.24)
$Cu(L_2)_2$	768	Dark brown	(68)	25.07	2.11	14.63	8.37	41.67	8.30
$C_{16}H_{16}N_8S_2Br_4Cu$				(25.03)	(2.10)	(14.60)	(8.35)	(41.64)	(8.28)
$Zn(L_2)_2$	769	Light orange	(85)	24.99	2.13	14.59	8.34	41.57	8.54
$C_{16}H_{16}N_8S_2Br_4Zn$				(24.97)	(2.10)	(14.56)	(8.33)	(41.54)	(8.50)
$Mn(L_3)_2$	727	Brown	(79)	26.45	2.25	15.44	4.43	43.99	7.58
$C_{16}H_{16}N_8O_2Br_4Mn$				(26.44)	(2.22)	(15.42)	(4.40)	(43.97)	(7.56)
$Cu(L_3)_2$	736	Dark green	(74)	26.16	2.21	15.24	4.37	43.48	8.67
$C_{16}H_{16}N_8O_2Br_4Cu$				(26.13)	(2.19)	(15.23)	(4.35)	(43.45)	(8.64)
$Zn(L_3)_2$	737	Cream white	(74)	26.10	2.21	15.23	4.35	43.37	8.90
$C_{16}H_{16}N_8O_2Br_4Zn$				(26.06)	(2.19)	(15.20)	(4.34)	(43.35)	(8.87)

Table 2: IR data of ligands and heterochelates

Compounds	ν(N-H)	ν(C=N)	ν(C=O) Or ν(C=S)
L_1	3439	1590	1640
$Mn(L_1)_2$	3430	1566	1600
$Cu(L_1)_2$	3418	1554	1604
$Zn(L_1)_2$	3413	1564	1601
L_2	3466	1543	1082
$Mn(L_2)_2$	3458	1512	1061
$Cu(L_2)_2$	3438	1520	1055
$Zn(L_2)_2$	3439	1533	1070
L_3	3491	1597	1676
$Mn(L_3)_2$	3446	1579	1656
$Cu(L_3)_2$	3444	1569	1672
$Zn(L_3)_2$	3460	1577	1674

Table 3: Antimicrobial effects of the ligands and their heterochelates

Sr. No.	Compounds	Gram +Ve (mm)		Gram –Ve (mm)	
		B. subtilis	*S. Aureus*	*E. coli*	*P. aeruginosa*
Ref. Drug	Penicillin	27	21	25	23
1	L_1	8	7	6	9
2	$Mn(L_1)_2$	13	14	18	12
3	$Cu(L_1)_2$	13	11	16	15
4	$Zn(L_1)_2$	12	15	11	14
5	L_2	6	7	6	8
6	$Mn(L_2)_2$	17	14	15	12
7	$Cu(L_2)_2$	13	15	10	11
8	$Zn(L_2)_2$	11	13	16	15
9	L_3	10	7	8	7
10	$Mn(L_3)_2$	15	13	14	12
11	$Cu(L_3)_2$	18	17	15	17
12	$Zn(L_3)_2$	19	18	13	15

f

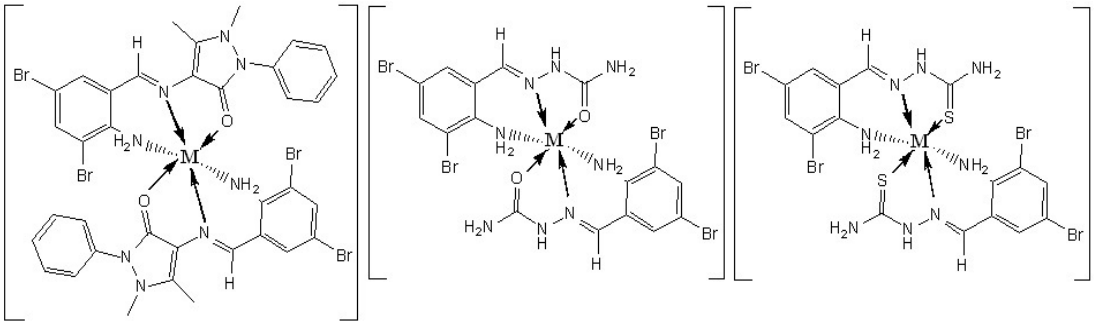


Figure 1: Proposed structure of Heterochelates

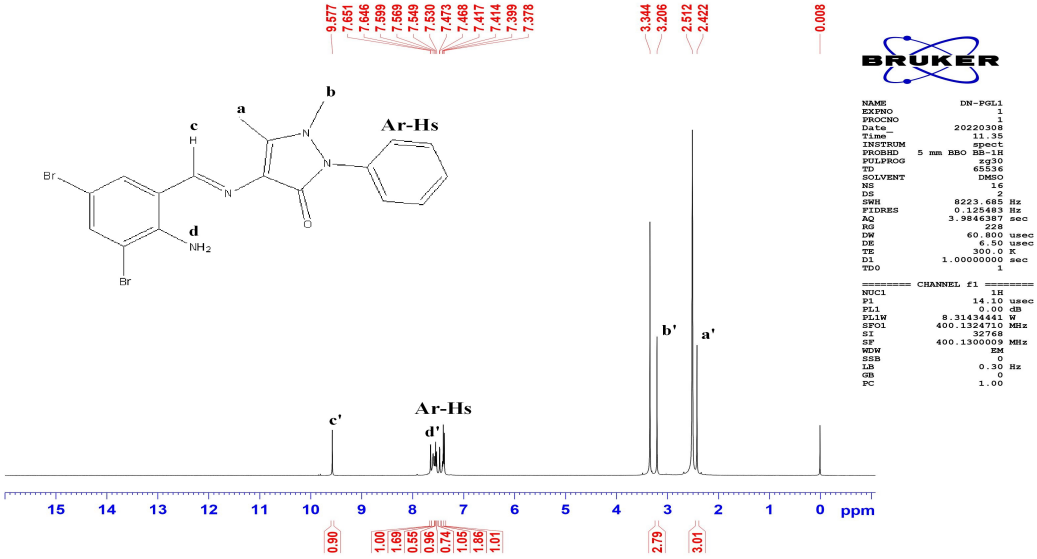


Figure 2: ^{1}H NMR Spectrum of Ligand L_1

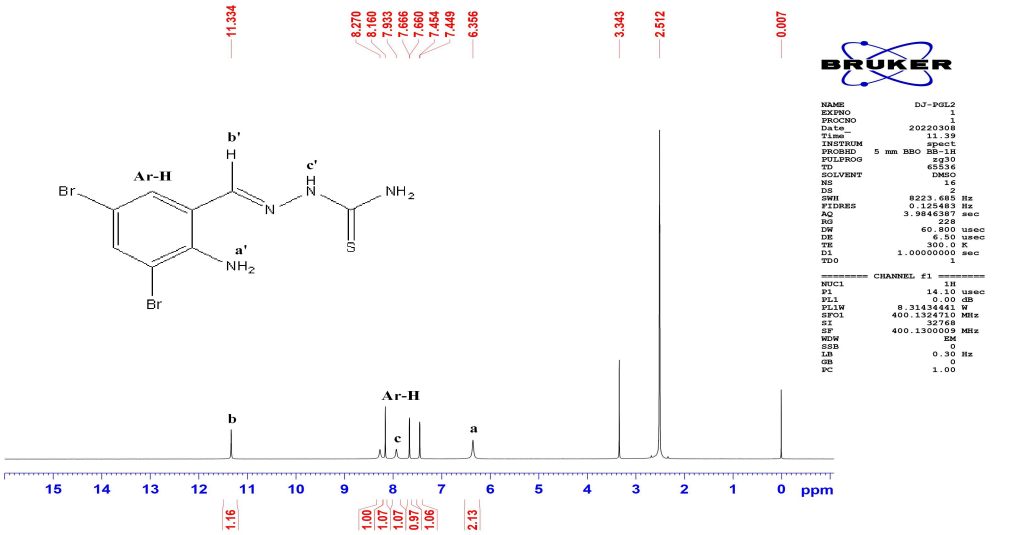


Figure 3: ^{1}H NMR Spectrum of Ligand L_2

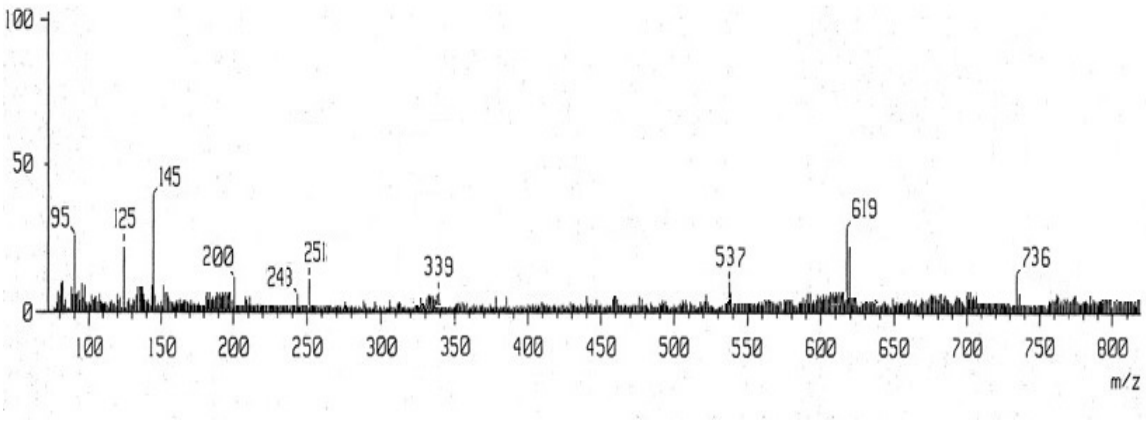


Figure 4: FAB Mass Spectrum of $Cu(L_3)_2$

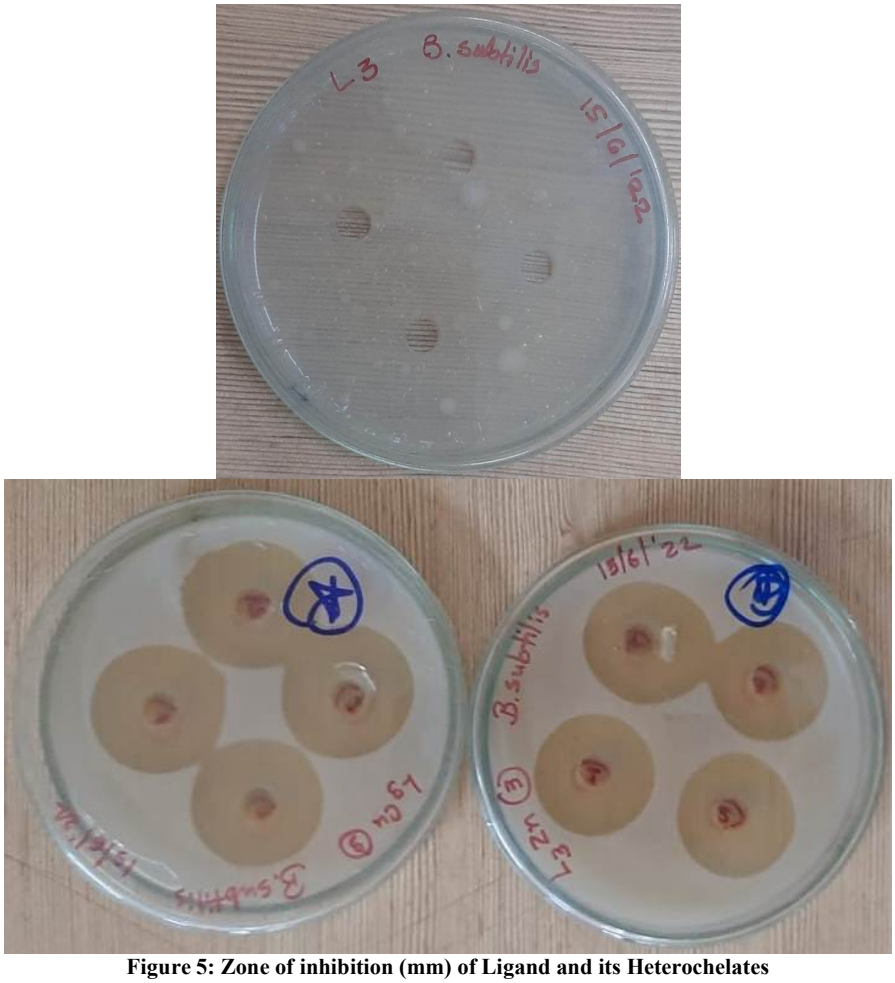
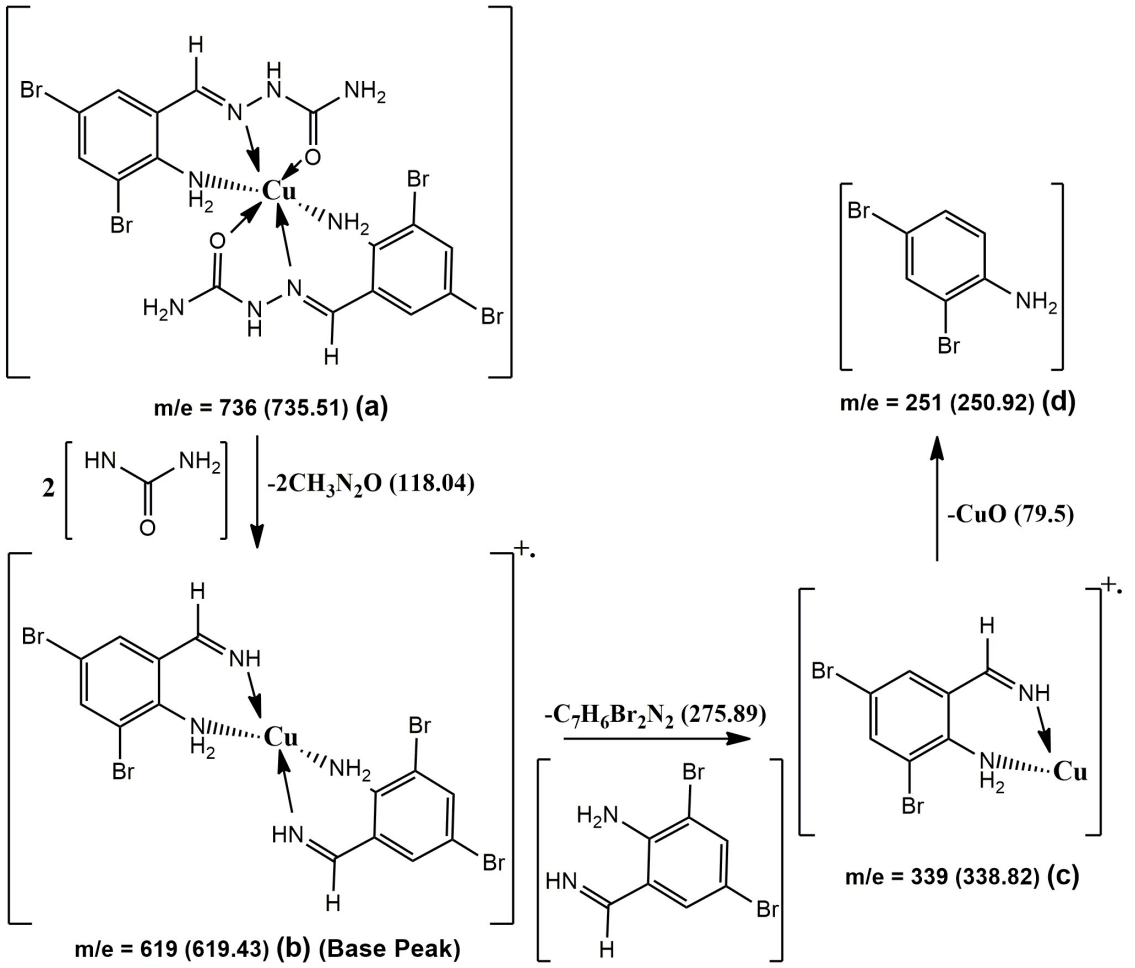


Figure 5: Zone of inhibition (mm) of Ligand and its Heterochelates



Scheme 1: The Suggested Fragmentation pattern for $Cu(L_3)_2$

CONCLUSION

In current effort, we create some novel carbazone and thiocarbazone based Schiff's base ligands and their heterochelates with transition metals. All the synthesized ligands and its heterochelates were confirming with ^{1}H NMR, IR and Mass Spectral studies and characterized their properties. All the synthesized compounds were screened for their antimicrobial activity. The heterochelates exhibit strong activities against Gram positive (*Bacillus subtilis, S. aureus*) and Gram negative (*E. coli, Pseudomonas aeruginosa*) microorganisms in comparison with their respective ligands. The heterochelates having potent activity against one or more bacteria establishing a novel class of transition metal based bactericidal agents for advance research.

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