Indian Journal of Biochemistry & Biophysics
Vol. 59, February 2022, pp. 189-196

Anti pathogenic studies of new mixed ligand metal chelates

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Received 11 August 2021; *revised 19 January 2022*

Drug discovery aimed at the methodical extermination of life-threatening bacterial infection, especially considering the emergence of multi-drug resistance of pathogenic bacteria has remained a challenge for medicinal inorganic chemistry. In this article, the mixed ligand complexes of Cu (II), Co (II), and Ni (II) containing heterocyclic ligands were synthesized and characterized by IR, LC-MS, UV, and TG-DTA. Complexes are screened for Anti-microbial activity against human pathogenic bacteria.

Keywords: Heterocyclic ligands and anti-microbial activity, Life-threatening bacterial infection, Mixed ligand complexes, Multi-drug resistance, Pathogenic bacteria

In recent years, the world's mortality rate has increased due to multi -resistance to antibiotics in treating infectious diseases that are directly related to bacteria[1-3]. Therefore, there is a necessity to develop new Antibacterial drugs with excellent mechanisms and structural activity[4-6]. Numerous challenges encountered in antibiotic chemistry can overcome in bioinorganic chemistry[7]. Coordination chemistry of transition metals with biologically active ligands is important in metallo-enzymes and other biological activities[8]. In most cases, complexation of metal with ligands shows higher bioactivities than the free ligands[9] and drug resistance and some side effects are reduced[10]. Chelating ligands containing donor atoms like O, S, and N have high biocidal actions of the metal complexes[11-13]. When a metal ion chelates with ligands the polarity of the metal ion gets reduced appreciably, due to the overlap of ligand orbital and partial sharing of its positive charge with metal atoms. Hence the lipophilicity of the complexes increases due to delocalization of the π-electron on the chelating ring[14-15]. Consequently, the metal complexes easily penetrate into the cell membrane of microbes blocking the enzymes of organisms; in some cases, metal complexes also block the synthesis of proteins which restricts further growth of organisms. It has been found that mixed ligand complexes are more active biologically than the ligand itself hence they are used in fighting microbial infections[16-22]. This makes the researchers interested in the synthesis of mixed ligand complexes.

In this review various kinds of mixed ligand complexes are synthesized with metal atoms of Cu(II), Ni(II), Co(II) and ligands such as Riboflavin, Tyrosine, Arginine, Bipyridyl, Phenyl- acetic acid as primary ligands NCO, N_3 are selected as secondary ligands and focus is placed on antibacterial activities on six pathogens: *Shigella sonnei* NK4010 (Gram-negative), *Salmonella enterica serovar* C6953 (Gram-negative), *Aeromonas hydrophilla* DH1585 (Gram negative), *Vibrio cholera* 010 *gawa* CO855 (Gram negative), *Klebsiella pneumonia* MTCC109 (Gram negative), *Micrococcus luteus* MTCC106 (Gram positive).

Materials and Methods

Chemicals

All chemicals reagents and solvents are procured from renowned companies and were of analytical grade used as received without further purification.

Instruments

IR spectra are obtained with a Shimadzu IR Prestige 21 FT-IR spectrophotometer. Electronic spectra are recorded on LABINDIA UV3000+ UV/Vis spectrophotometer. LC-MS spectra are recorded on AGILANT QQQ (ESI-MS). Mass spectrometer. TG-DTA spectra are obtained using SDT Q600 V20.9 BUILD 20.

Synthesis of metal complexes

Riboflavin complexes

Coordination compounds of complexes 1 and 2 were prepared by the addition of 1 mM solutions of

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metal salts C_1 (Cobalt nitrate 0.129 g), C_2(Nickel nitrate 0.058 g) added to ligand Sodium hydroxide solution of Riboflavin at constant stirring for 30 min at room temperature. The precipitate are filtered, washed with methanol solution, and dried.

Amino acid complexes

Coordination compounds of complexes 3 and 4 were prepared by the addition of 1 mM solutions of metal salts C_3 (Nickel sulphate hexahydrate 0.262 g), C_4 (Copper nitrate 0.241 g) added to 1 mM solutions of L_3(Bipyridyl 0.156 g), L_4 (Arginine 0.774 g and Sodium azide 0.069 g) at room temperature under constant stirring for 30 min. The precipitate formed is filtered, washed with methanol solution and dried.

Bipyridyl complexes

Coordination compounds of complex 5 and 6 were prepared by the addition of 1mM solution of metal salt Copper per chlorate hexahydrate (0.37 g) added to a 1 mM methanolic solution of the ligand L_5 (Bipyridyl 0.156 g) at room temperature and L_6 (Sodium isocyanate 0.081 g) added at 60°C for 30 min. The precipitate formed is filtered, washed with methanol solution and dried.

Phenyl acetic acid complexes

Coordination compounds of complex 7, 8 and 9 were prepared by the addition of 0.5 mM solution of Copper per chlorate hexahydrate (0.185 g) added to 0.5 mM solution of the ligand L_6 (phenyl acetic acid 0.068 g), 1mM solution of ligand L_7 (Sodium thiocyanate 0.04 g), 1 mM solution of ligand L_8 (Sodium Azide 0.03 g), 0.5 mM solution of L_9 (Ortho phenyl diamine 0.054 g) under constant stirring at 60°C for 30 min. The precipitate formed is filtered, washed with methanol solution and dried.

Antimicrobial activity using disc diffusion assay

Complexes are tested against human pathogenic bacteria isolates determined by the disk diffusion method in Mueller-Hinton Agar[23], the method is essentially a qualitative or semi- quantitative test indicating sensitivity or resistance of microorganisms to the test materials as well as the bacteriostatic or bactericidal activity of a compound. These complexes are screened for Anti Pathogenic activity against six pathogens.

Shigella sonnei NK4010 (Gram negative), *Salmonella enterica serovar* C6953 (Gram negative), *Aeromonas hydrophilla* DH1585 (Gram negative), *Vibrio cholera.*

Results and Discussion

Physico-chemical properties

The colour, yield, molecular weights, physical appearance, solubility of their complexes are shown in (Table 1).

IR-spectra

The main stretching frequencies of the IR spectra are listed in (Table 2).

Table — 1 Physio-chemical properties

S. No	Complexes	Colour	Yield (%)	Mol.Wt	Physical Appearance	Solubility
1	Complex 1	Green	0.43 g (72%)	507.36	Precipitate	DMF
2	Complex 2	Yellow	1 g (75%)	471.09	Precipitate	DMF
3	Complex 3	Brown	0.38 g (64%)	613.28	Crystals	DMF
4	Complex 4	Blue	0.163 g (34%)	409.14	Crystals	DMF
5	Complex 5	Blue	0.25 g (49%)	472.68	Crystals	DMF
6	Complex 6	Blue	0.23 g (38%)	331.82	Crystals	DMF
7	Complex 7	Sky blue	0.187 g (63%)	406.86	Precipitate	DMSO
8	Complex 8	Greenish Blue	0.168 g (59%)	580.05	Precipitate	DMSO
9	Complex 9	Dark brown	0.147 g (48%)	650.02	Crystalline precipitate	DMSO

Table 2 — IR-spectra

S. No	Compounds	ν (N-H) cm^{-1}	ν (C=O) cm^{-1}	ν (C=N) cm^{-1}	ν (O-H) cm^{-1}	ν (COO^-) cm^{-1}	ν (N_3) cm^{-1}	ν (NCO) cm^{-1}	ν (ClO_4) cm^{-1}
1	Complex 1		1635	1528	3385				
2	Complex 2		1647	1544	3384				
3	Complex 3	3261		1575		1446			
4	Complex 4	3385			3122	1479			
5	Complex 5		1603	1557	3439				1087
6	Complex 6					1411		2199	
7	Complex 7				3569			2259	
8	Complex 8		1741		3408		2051		
9	Complex 9			1514	3383				1087

LC-MS

Mass spectra

The most important peaks in the LC-MS spectral data of all complexes are listed in (Table 3).

Electronic spectral analysis

The electronic spectra of the complexes showed strong absorption bands in the Ultraviolet-Visible region (200-800 nm), allocated to the transitions π→π* and n →π *, verifying coordination of metal ions to the ligand are listed in (Table 4).

Thermal analysis

Thermo gravimetric analysis of the complexes was used to obtain information about the thermal stability of the complexes. The results of the thermal analysis of the metal complexes are given in (Fig. 1 & Table 5).

Evaluation of antimicrobial activity

The antimicrobial activity of metal complexes was performed by using different bacteria and the results are summarized in (Table 6).

These complexes showed better activity against six human pathogens: *Shigella sonnei* NK4010 (Gram negative), *Salmonella Enteric serovar* C6953 (Gram negative), *Aeromonas hydrophilla* DH1585 (Gram negative), *Vibrio cholera* 010 *gawa* CO855 (Gram negative), *Klebsiella pneumonia* MTCC109 (Gram negative), *Micrococcus luteus* MTCC106 (Gram positive). This indicates their usefulness as broad-spectrum antibacterial agents (Fig. 2).

Table 3 — Mass Spectra

S. No	Complex	*m/z*
1	Complex 1	377 [Ribo]
		505 [Co(Ribo)4H_2O]
2	Complex 2	377[Ribo]
		450 [Ni(Ribo)H_2O]
3	Complex 3	597[Ni(Tyr)$_2$Bpy]H_2O
		613 [Ni(Tyr)$_2$Bpy]2H_2O
4	Complex 4	175 [Arg]
		237 Cu[Arg]
		410 [Cu(Arg)$_2$]
5	Complex 5	318 [Cu(Bpy)] ClO_4
		375 [Cu(Bpy)(H_2O)$_3$] ClO_4
		474[Cu(Bpy)(H_2O)$_3$] (ClO_4)$_2$
6	Complex 6	219 [Cu(Bpy)]
		261 [Cu(Bpy)(NCO)]
		307[Cu(Bpy)(NCO)$_2$]
7	Complex 7	380[Cu(PAA)$_2$NCO]
		425[Cu(PAA)$_2$(NCO)$_2$]
		447 [Cu(PAA)$_2$(NCO)$_2$$H_2O$]
8	Complex 8	416 [Cu(PAA)$_2$(N_3)$_2$]
		551 [Cu(PAA)$_3$(N_3)$_2$]
9	Complex 9	169 [Cu]ClO_4
		648 [Cu(PAA)$_2$(OPD)$_2$$ClO_4$]

It was found that these transition metal complexes are having cytotoxicity against human cancer cell line MCF-7, A-431, HepG-2 and anti-microbial activity against *E. coli*, *S. aureus* and antifungal activity against *R. oligospores* as mentioned in previous papers[24-38]. Among the above -mentioned complexes [Cu (Bpy)(H_2O)$_3$]ClO_4^- (**9**) makes it more active against human pathogens due to the presence of N-donors in the Bipyridyl and presence of ClO_4^- which are the general functional groups present in antibacterial agents[39].

Conclusion

This review reveals that the complexes are effective Anti cancer agents as well as Anti-microbial agents. These complexes are well characterized by using FT-IR, LC-MS, UV-Vis, and TG-DTA. This spectral data has supported the above concerned geometry of the complexes. The ligands of the complex coordinate with metal ion *via* O and N. The mixed ligand complexes showed a broad range of antimicrobial activity against six pathogenic species: *Shigella sonnei* NK4010 (Gram negative), *Salmonella entericaserovar* C6953 (Gram negative), *Aeromonas hydrophilla* DH1585 (Gram negative), *Vibrio cholera* 010 *gawa* CO855 (Gram negative), *Klebsiella pneumonia* MTCC109 (Gram negative), *Micrococcus luteus* MTCC106 (Gram positive) at 150 µL concentration as well as *E. coli*, *S. aureus* and *R. oligospores*. The outcomes of our study suggest that the ligands bearing N-donors have great potency as antibacterial agents hence among the nine

Table 4 — Electronic spectral analysis

S. No	Complex	Frequencies	Assigning	Geometry
1	Complex 1	280 nm	π→π*	Distorted
		380 nm	n →π *	Octahedral
2	Complex 2	275 nm	π→π*	Square planar
		350 nm	n →π *	
3	Complex 3	280 nm	π→π*	Distorted
		360 nm	n →π *	Octahedral
4	Complex 4	283 nm	π→π*	Square planar
		384 nm	n →π *	
5	Complex 5	280 nm	π→π*	Square
		400 nm	n →π *	pyramidal
6	Complex 6	280 nm	π→π*	Square planar
		350 nm	n →π *	
7	Complex 7	280 nm	π→π*	Square
		350 nm	n →π *	pyramidal
8	Complex 8	280 nm	π→π*	Square
		360 nm	n →π *	pyramidal
9	Complex 9	280 nm	π→π*	Square
		380 nm	n →π *	pyramidal

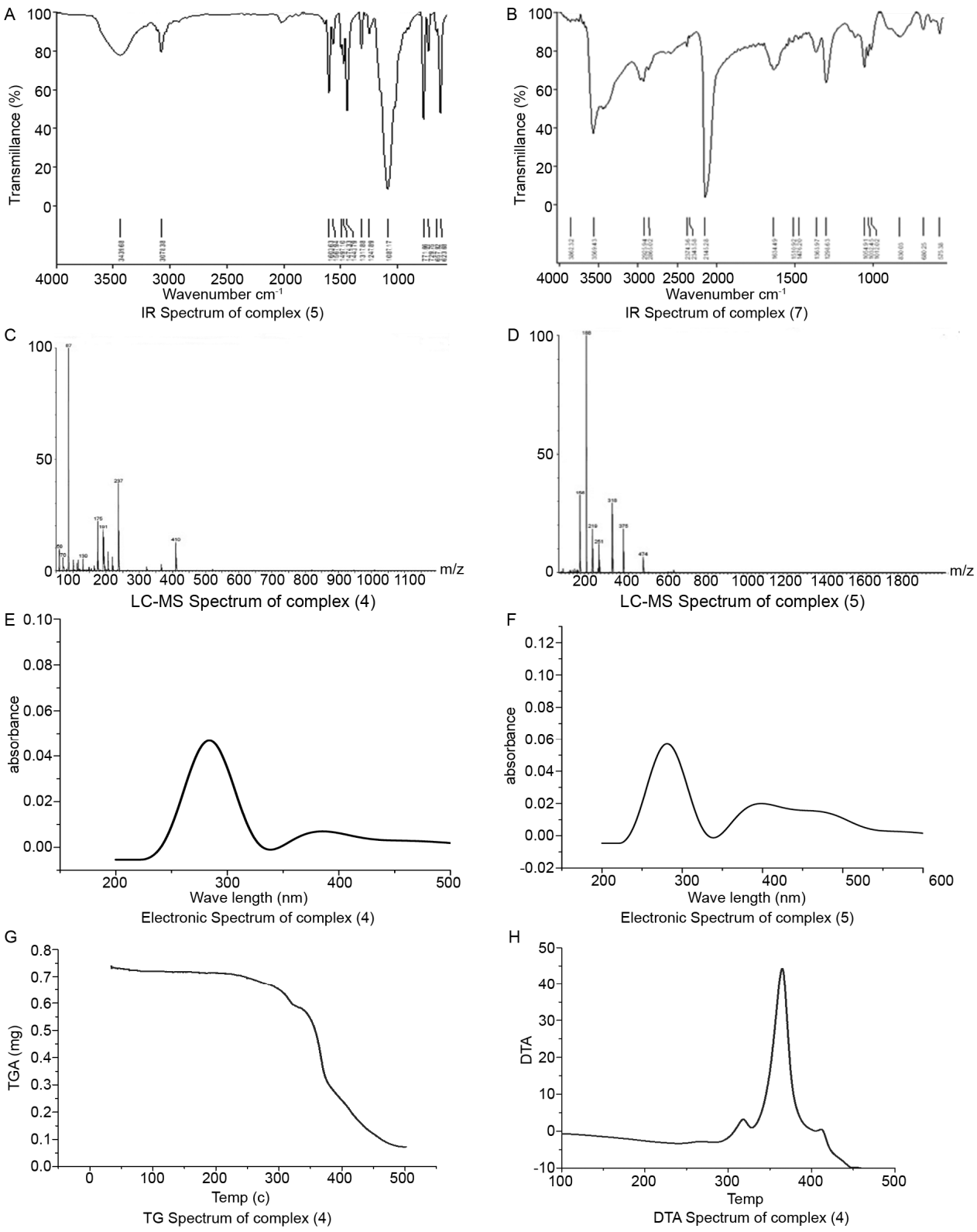

Fig 1 — (A) IR Spectrum of complex (5); (B) IR Spectrum of complex (7); (C) LC-MS Spectrum of Complex (4); (D) LC-MS Spectrum of Complex (5); (E) Electronic Spectrum of Complex (4); (F) Electronic Spectrum of Complex (5); (G) TG Spectrum of complex (4); and (H) DTA Spectrum of complex (4)

Table 5 — Thermal analysis

S. No	Compounds	TG range	DTA range	N	Mass found	Loss Calculated
1	$[Co(Ribo)4H_2O]$	100-200°C	150°C		14%	16.7%
		200-300°C	250°C	3	52.5%	59.5%
		300-500°C	450°C		86.4%	89.3%
2	$[Ni(Ribo)2H_2O]$	50-150°C	100°C	3	6.7%	6.8%
		250-300°C	280°C		84.3%	84.9 %
3	$[Ni(Tyr)_2Bpy]2H_2O$	50-100°C	90°C		3%	5%
		200-300°C	200°C	3	26%	30%
		300-500°C	300°C		60%	60%
4	$[Cu(Arg)_2]$	40-110°C	110°C		8.7%	9%
		120-290°C	290°C	3	35%	33%
		300-495°C	460°C		43%	42.2%
5	$[Cu(Bpy)(H_2O)_3](ClO_4)_2$	100-200°C	150°C	2	3.8%	4%
		350-400°C	380°C		96.2%	98.4%
6	$[Cu(Bpy)(NCO)_2]$	50-220°C	240°C	2	71.9%	71.3%
		250-300°C	300°C		94.1%	94.1%
7	$[Cu(PAA)_2(NCO)_2H_2O]$	50-200°C	100°C		11.5%	11.7%
		200-300°C	220°C	3	16.1%	17.1%
		300-500°C	460°C		45.6%	46.6%
8	$[Cu(PAA)_3(N_3)_2]$	50-250°C	250°C	2	10.09%	10.63%
		280-400°C	280°C		57.2%	57.9%
9	$[Cu(PAA)_2(OPD)2ClO_4]$	200-250°C	220°C	2	14.2%	14.6%
		250-400°C	250°C		64.2%	67.8%

Table 6 — Evaluation of Antimicrobial activity

S. No.	Compound (Sample No.)	Concentration	Growth inhibition zones (in diameter) of pathogenic bacteria					
			Shigella sonnei NK4010	*Salmonella enterica serovar typhi* C6953	*Aeromonas hydrophilla IDH1585*	*Vibrio cholera*; O1 Ogawa C0835	*Klebsiella pneumonia* MTCC109	*Micrococcus luteus* MTCC106
0	CR	150 µL	20 mm	11 mm	14 mm	14 mm	12 mm	8 mm
1	$[Co(Ribo)4H_2O]$ (**3**)	150 µL	12 mm	7 mm	-	10 mm	7 mm	10 mm
2	$[Ni(Ribo)2H_2O]$ (**5**)	150 µL	14 mm	7 mm	-	-	10 mm	-
3	$[Ni(Tyr)_2Bpy]2H_2O$ (**6**)	150 µL	14 mm	-	-	10 mm	-	-
4	$[Cu(Arg)_2]$ (**8**)	150 µL	14 mm	7 mm	-	10 mm	-	-
5	$[Cu(Bpy)(H_2O)_3]ClO_4^-$ (**9**)	150 µL	34 mm	25 mm	20 mm	28 mm	16 mm	24 mm
6	$[Cu(Bpy)(NCO)_2]$ (**10**)	150 µL	20 mm	7 mm	10 mm	16 mm	-	12 mm
7	$[Cu(PAA)_2(NCO)_2H_2O]$ (**13**)	150 µL	16 mm	7 mm	-	16 mm	-	10 mm
8	$[Cu(PAA)_3(N_3)_2]$ (**14**)	150 µL	16 mm	7 mm	-	10 mm	-	10 mm
9	$[Cu(PAA)_2(OPD)2ClO_4]$(**15**)	150 µL	18 mm	11 mm	-	16 mm	-	11mm

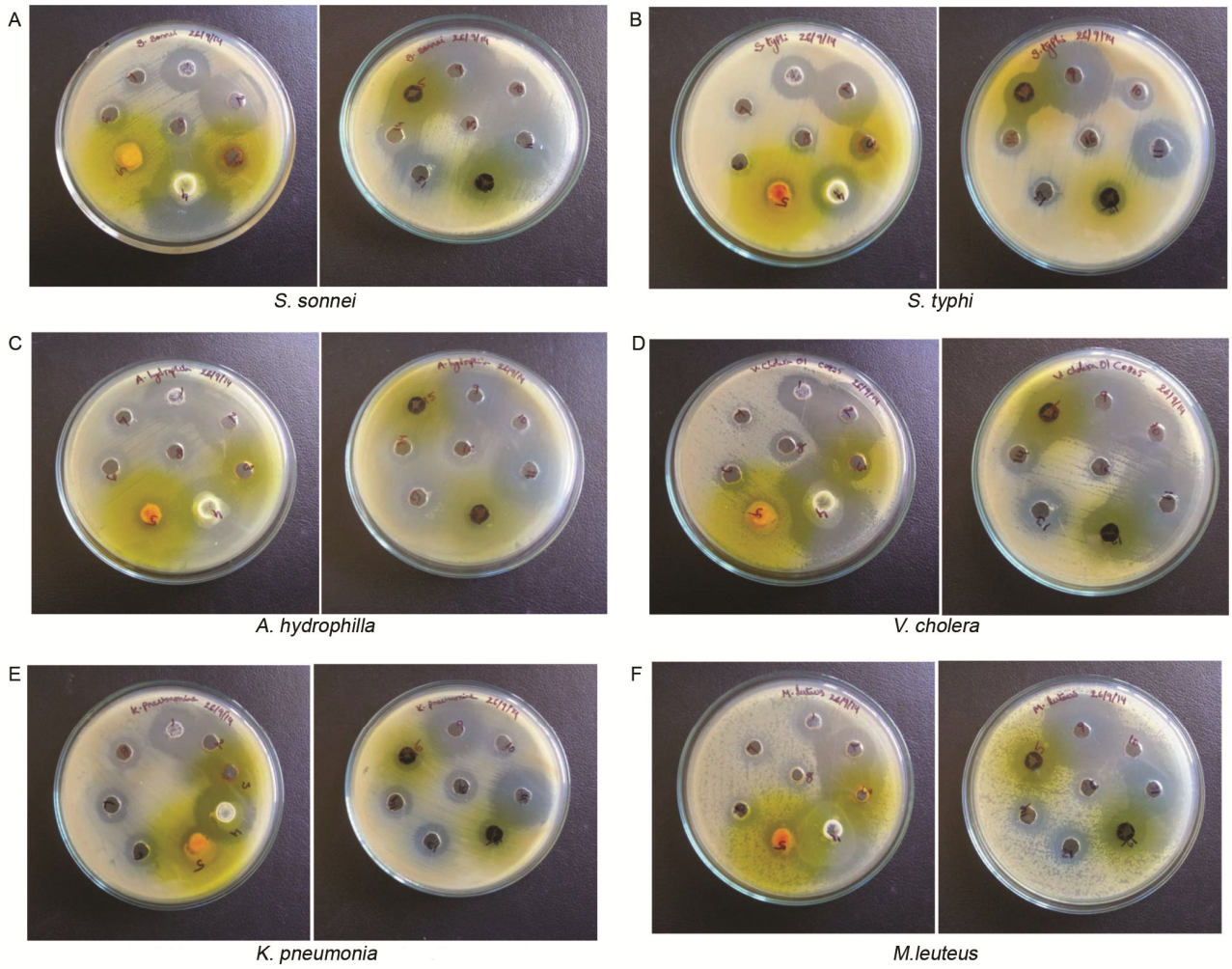

Fig. 2 — (A) Inhibition zones for complex 1-9 against *S. sonnei*; (B) Inhibition zones for complex 1-9 against *S. typhi*; (C) Inhibition zones for complex 1-9 against *A. hydrophilla*; (D) Inhibition zones for complex 1-9 against *V. cholera*; (E) Inhibition zones for complex 1-9 against *K. pneumonia*; and (F) Inhibition zones for complex 1-9 against *M. leuteus*

complexes prepared [Cu (Bpy) $(H_2O)_3$] ClO_4^- (**9**) has shown better activity compared to other complexes which might be a suitable strategy to develop novel therapeutic tool for development of new metal based drug. Further studies of these complexes explore its clinical inference to life threating infection.

Acknowledgement

B. Kishore Babu and K. Mohana Rao (JRF) acknowledge grants from the Ref No: 42-354/2013 UGC (INDIA), New Delhi. We are grateful for the technical assistance provided by the Department of Engineering Chemistry at the Andhra University, Visakhapatnam (INDIA) and the University of Hyderabad for providing the spectral data. B. Anil Kumar (JRF) acknowledges for the grants from the Ref No: SB/EMEQ-436 Dated 21-03-2016, New Delhi.

Conflict of interest

All authors declare no conflict of interest.

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