TOFIQ Journal of Medical Sciences, TJMS, Vol. 3, Issue 2, (2016), 64-75 ISSN: 2377-2808

TOFIQ Journal of Medical Sciences

SYNTHETIC, SPECTROSCOPIC AND ANTIBACTERIAL STUDIES OF CO(II),NI(II),CU(II),ZN(II),CD(II)AND HG (II),MIXED LIGAND COMPLEXES OF TRIMETHOPRIME ANTIBIOTIC AND ANTHRANILIC ACID

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Abstract

Mixed ligand complexes of bivalent metal ions, viz ; M= Co(II),Ni(II),Cu(II), Zn(II), Cd (II), and Hg(II) of the composition $[M(Anth)_2(TMP)]$ in 1:2:1 molar ratio, (where . AnthrH= Anthranilic acid ($C_7H_7NO_2$) and Trimethoprime (TMP) = ($C_{14}H_{18}N_4O_3$) have been synthesized and characterized by repeated melting point determination, Solubility, Molar conductivity ($\mathbf{\Lambda_m}$),determination the percentage of the metal (M%) in the complexes by (AAS), FT-IR, magnetic susceptibility measurements [µeff (BM)] and electronic spectral data. The two ligands and their metal complexes have been screened for their bacterial activity against selected microbial strains (Gram +ve) & (Gram -ve).

Key words: Trimethoprim, , Complexes, Anthranilic Acid and Antimicrobial

1. Introduction

Mixed ligand complexes plays an important role in numerous medicine, chemical and biological systems like antioxidant,water softening, ion exchange resin, photosynthesis in plants, removal of undesirable and harmful metals from living organisms electroplating, dying also great importance in the field of environmental chemistry[1-7]. Development of antimicrobial drugs was wide as one of the great medical success story of the twentieth century[8].

Research are being undertaken in fields such as cancer[9], diabetes[10], metal-mediated antibiotics, antibacterial, antiviral, antiparasitic and radiosensitizers[11], In continuation of our efforts[12, 13] to progress metal-based therapeutics agents, the synthesis, characterization, and antibacterial studies of Anthranilic acid and trimethoprim are presented.

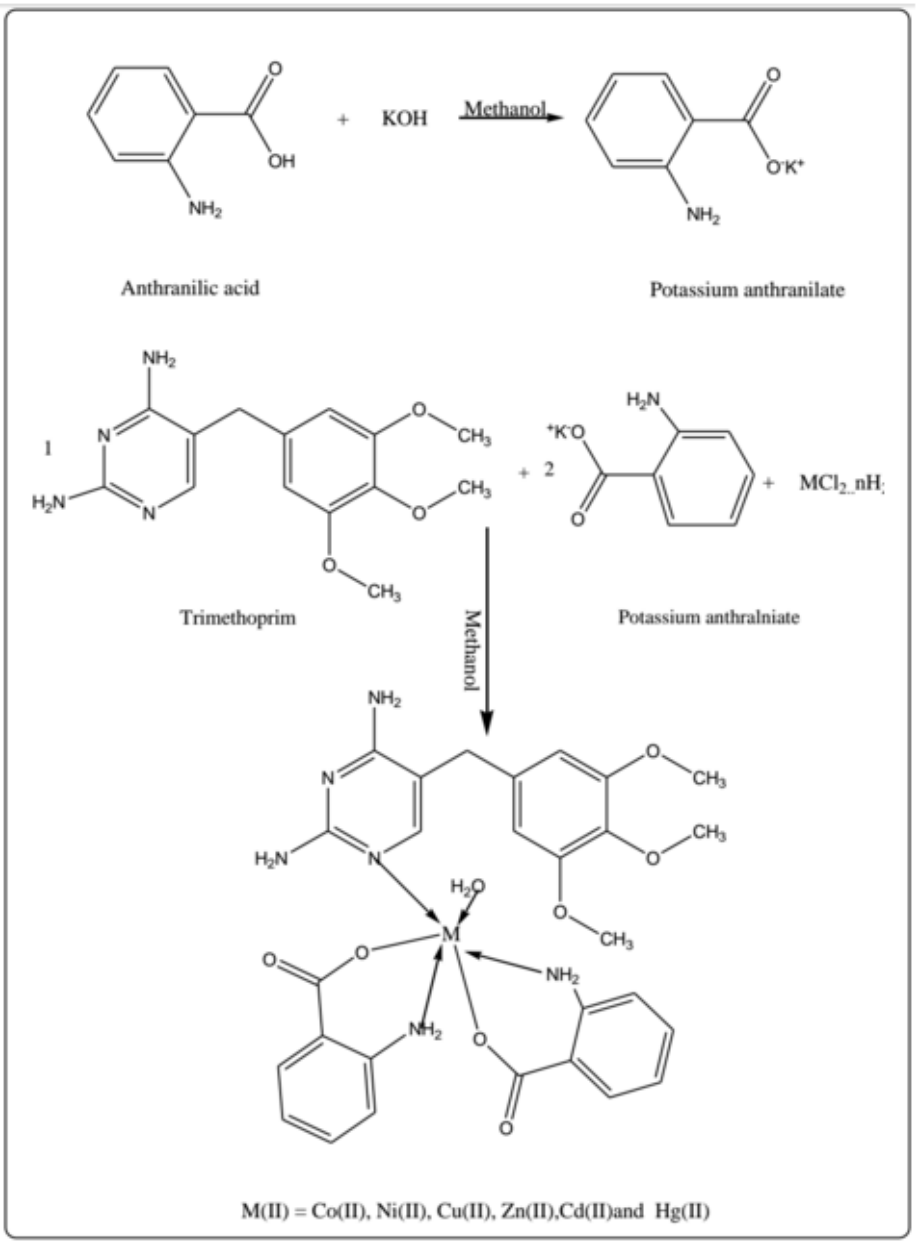
2. Experimental[12, 13]

2.1. Chemicals

All chemicals used were of reagent grade and were used as received.$CoCl_2$.6H, NiCl2.6H2O,CuCl2. $2H_2O$, $CdCl_2.H_2O$,$HgCl_2$, $ZnCl_2$, Na OH (supplied by either Merck or Fluka) ethanol, methanol, dimethylforamaide, dimethyl sulfoxide and KBr, from (B.D.H). Trimethoprime powder DSM (Spain) and Anthranilic acid from Riedial- Dehaen.

2.2 Synthesis of (Mixing ligands) complexes with some metal ions

A solution of the metals containing[0.237g, 0.237g, 0.170g, 0.136g, 0.201g and 0.271g (1 mmol)] of $CoCl_2.6H_2O$,$NiCl_2.6H_2O$,$CuCl_2.2H_2O$,$ZnCl_2$,$CdCl_2.H_2O$ and $HgCl_2$ in methanol (10ml) respectively was added gradually with stirring to methanolic KOH solution (0.112g,2mmol) of the anthranilic acid.(0.290g ,1mmol) of Trimethoprime (TMP) was added to the mixture in each case by using stoichiometric amount (1:2:1) Metal:K^+ $Anth^-$:(TMP) moler ratio. The mixture was refluxed with constant stirring for an hour. The mixture was cooled at room temperature pale precipitate was formed, filtered and recrystallized from ethanol dried at room temperature according to the following reaction :(scheme 1)



Scheme (1): Schematic representation preparation of the Complexes [M(Anth)$_2$(TMP)]

3. Results and Discssion

3.1. Characterization of Metal Complexes.

The complexes were prepared by reacting the respective metal Chloride with the ligands using 1:1:2 mole ratios, [TMP: M: 2 Anth] , i.e. one mole of Trimethoprim [TMP] , one mole of metal Chloride and two moles of Anthranilic acid [Anth.H][12, 13]. The formula weights and melting points are given in Table (1). It was found that all the complexes were appeared as powders and stable in air at room temperature with higher melting points revealing that the

complexes are much more stable than their [AnthH & TMP] ligands indicating formation of complexes.

All these complexes are colored solids, insoluble in common organic solvents but soluble in DMF and DMSO. The conductivity values for the complexes (in DMSO,10^{-3} M,25°C), ranging in the (3.1-19.9) $\Omega^{-1}mol^{-1}cm^{2}$ region, indicate that the complexes are non electrolytes[11]. The test for Chloride ion (Cl) with $AgNO_3$ solution was (-negative)[11-13]. The calculated and experimental values of (M%) in each complex are in fair agreement as shown in Table (1).

Table (1): The Physical Properties & Atomic Absorption Results of the [(TMP- Metal-Anth)] Complexes

Compounds Chemical Formula)	M. wt Calc	Color	Yield %	M .p°c (de) °c	Λ_m Ω^{-1} cm^2 mol	Metal% Theory (exp)
Anth.H	137.14	Pale-yellow	–	146	6.2	–
[Co(Anth) $_2$(TMP)(H_2O)]	620.96	Brown	66	280	3.66	9.49 (9.01)
[(Ni(Anth)$_2$(TMP)(H_2O)]	621.27	Blue	63	265	13.3	9.47 (10.50)
[(Cu(Anth) $_2$(TMP)(H_2O)]	625.57	Green-blue	75	285	19.9	10.15 (10.13)
[(Zn(Anth) $_2$(TMP)(H_2O)]	627.96	Yellow	60	290	11.3	10.41 (10.56)
[(Cd(Anth) $_2$(TMP)(H_2O)]	674.99	White	70	240	3.66	16.65 (16.11)
[Hg(Anth) $_2$(TMP)(H_2O)]	763.16	Yellow	59	112	5.0	26.28 25.73

3.2. FT-IR spectra of [(TMP), (Anth)] ligands & [Co(Anth)$_2$(TMP) (H_2O)] (1), [Ni(Anth)$_2$(TMP)(H_2O)] (2), [Cu(Anth)$_2$(TMP)(H_2O)] (3), [Zn(Anth)$_2$(TMP)(H_2O)] (4), [Cd(Anth)$_2$(TMP)(H_2O)] (5), and [Hg(Anth)$_2$(TMP)(H_2O)] (6) complexes.

The I.R spectrum of the Trimethoprim (TMP) which used as a primary ligand exhibits strong bands at (3471, 3319) cm^{-1} ascribed to stretching vibration of primary amine υ(NH_2) asym &sym respectively[12, 13]. A sharp very strong frequency band at 1633 cm^{-1} & 1508cm^{-1} in (TMP) assigned to the pyrimidine nitrogen ν(C=N). The absorption bands at 1263 and 1236 cm^{-1} which account for

C-O-C str. (asym.) and C-O-C str. (sym.) respectively[14, 15]

The FT-IR spectrum of the [Anth.H] which used as a secondary ligand Table (3-25) exhibits bind the metal ion as a bidentate monobasic fashion through (COO-) & (NH_2) donors, while (TMP) bind the metal ion as a mono dentate ligand through the (N) atom[14]. The FT-IR spectra assignments bands for compounds (1), (2), (3), (4), (5) and (6),. are summarized in Table (4). The assignments have been carried out based on comparison of the spectra data with of similar compounds (6,11)..New weak intensity bands were observed in the regions (509-586) cm^{-1} & (424-478) cm^{-1} may be ascribed to M-N and M-O vibrations, respectively[15, 16].

The FT-IR spectra of all the complexes exhibited peaks around (3305- 3213) cm^{-1} and in the range (1627-1623) cm^{-1}. These peaks can be appointed to OH (stretching & bending) vibration, which indicate the presence of coordinated water molecule in the complexes. The coordinated between the (H_2O) molecules and the (M^{+2}) resulted in the appearance of vibrational bands at range (756-759) cm^{-1} ($M-OH_2$) in the all complexes[12, 13] and all complexes adopt an octahedral geometry as proposed.

Table (2): Infrared spectral data(wave number ύ) cm^{-1} for the Trimethoprim

υ (N-H) $_{asym}$	υ (N-H) $_{sym}$	υ (C=N) Pyrimidine(N)	υ (C-O-C)$_{asym}$ Str	υ (C-O-C)$_{sym}$ Str	υ (-OCH_3)
3471vs	3319	1633vs 1508vs	1263s	1236s	1128vs

Table (3): FT-IR Spectrum Data of the L-Anthranilic acid

(NH_2) $_{asym,sym}$ Str	υ ($N-H_3^+$)	υ C=O Str (carbox.)	υ(-COO^-)$_{asym.}$	υ(-COO^-)$_{sym.}$	Δυ (-COO^-)$_{asmy-smy}$
3321 s 3240	3101s	11716	1662s	1485s	177

Table (4): Infrared spectral data(wave number ύ) cm^{-1} for the mixed $[M(Anth)_2(TMP)(H_2O)]$ complexes

Compounds	υ (OH-H_2O)	υ(N-H_2) asym & sym	υ (C-H) arom.	υ(C-H) aliph	Pyrimidine Nitrogen (C=N)	υ_{asy} COO υ	□υ υ_{as} COO- - υ_{as} COO	υ(C=C) arom.	υ(C-C) aliph.	υ –*OH* H_2O	υ (M-N)	υ(M- N)	(M-O)
1) Co	3410	3305 3226	3136	2935,	1616	1538	211	1492 s	1242	756	586	516	470
2) Ni	3448	3305 w 3217 w	3028	2939, 2835s	1605	1543	216	1492	1237v s	756	586	516	478
3) Cu	3406	3275 3236	3124	2936 2835	1600	1550	227	1500	1238v s	759	567	516	424
4) Zn	3406	3298 3213	3128	2935s 2835	1616	1543	226	1492	1238	756vs	563	513	428
5) Cd	3425	3329 3224	3140	2935 s 2835	1616	1589	189	1531	1238	756vs	567	509	455
6) Hg	3420	3352 s 3217	3065	2939, 2835 Vs	1627s	1593	220	1492 s	1238s	759	578	528	451

3.3 .The (UV-Vis spectra) of the free (TMP) and ((Anth.H)) and $[M(Anth)_2(TMP)(H_2O)]$ complexes were carried out as DMSO (10^{-3} M) solutions and corrected magnetic moment (μeff) in Bohr magneton units are given in Table 5. The μeff for the all M(II) in this study as expected for six coordinated M (II) species suggest an octahedral geometry. These employments are in agreement with the literature values[12, 13, 17, 18].

Table5: Electronic Spectral data, magnetic moment μ_{eff} (BM)of the [M(Anth)$_2$(TMP)(H$_2$O)]complexes

Compound	λ_{max} nm	ύ cm^{-1}	ε_{max} $Mol^{-1}.L.cm^{-1}$	Assignments	μ_{eff} (BM)
TMP	257	38910	2431	$\pi \rightarrow \pi^*$	-
Anth.H	245 332	41322 30120	1857 1924	$\pi \rightarrow \pi^*$ $n \rightarrow \pi^*$	-
[Co(Anth)$_2$(TMP)(H$_2$O)]	301 773 821	33222 12936 12180	1651 76 66	Charge transfer $^4T_1g \rightarrow T_1g^{(p)}$) υ_3 $^4T_1g \rightarrow {}^4A_2g^{(f)}$ υ_2	4.34
[(Ni(Anth)$_2$(TMP)(H$_2$O)]	276 624 663 706 821	36231 16025 15082 14164 12180	1950 81 68 55 37	Ligand Field $^3A_2g^{(F)} \rightarrow {}^3T_1g^{(p)}$ υ_3 $^3A_2g^{(F)} \rightarrow {}^3T_1g^{(f)}$ υ_2 $^{3A2g(F)} \rightarrow {}^{3T2g(F)}$ υ_1	2.73
[(Cu(Anth)$_2$(TMP)(H$_2$O)]	289 345 813	34602 28985 12300	1484 1198 15	Ligand Feild CT 2Eg → 2T2g	1.75
[(Zn(Anth)$_2$(TMP)(H$_2$O)]	325	30769	1934	C.T	Diamagnetic
[(Cd(Anth)$_2$(TMP)(H$_2$O)]	318	31446	2245	C.T	Diamagnetic
[Hg(Anth)$_2$(TMP)(H$_2$O)]	247 343	40485 29154	2399 1824	C.T C.T	Diamagnetic

3.4 . The Proposed Molecular Structure for Studying [M(Anth)$_2$(TMP)(H$_2$O)] Complexes :

Studying complexes on bases of the above analysis, spectral observations suggesting the octahedral geometry for all the prepared complexes which exhibited coordination number six and may be formulated as:[M(Anth)$_2$(TMP)(H$_2$O)],

M=Co(II),Ni(II),Cu(II),Zn(II),Cd(II)and Hg(II).

The general structure of the complexes is 3D as is shown in Figure (1) .Accordingly, we can deduce that the (Athr$^-$) binds the M(II) as bidentate fashion (NO$^-$) .The bonding sites are the Nitrogen (amine group) & Oxygene the carboxylato group ,while (TMP) binds the M(II) as mono dentate. through the (N) atom of the pyrimidine group .

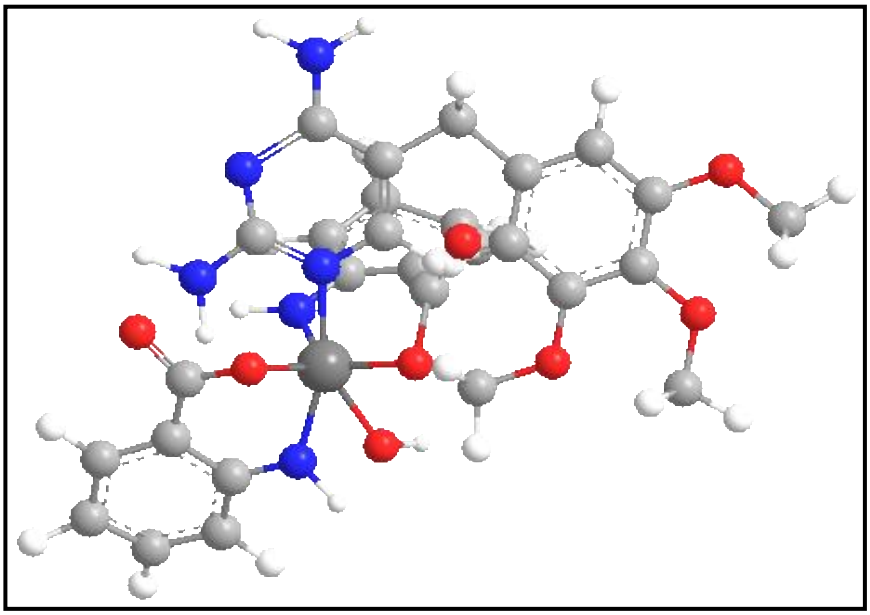


Figure (1): 3D molecular modeling proposed $[M(Anth)_2(TMP)\ (H_2O)]$ complexes

3.5. Bacterial activities of the $[M(Anth)_2(TMP)(H_2O)]$complexes :

M=Co(II),Ni(II),Cu(II),Zn(II),Cd(II)and Hg(II)

Antimicrobial activity were expressed in terms of millimeter (mm) by measuring inhibition zone diameters (ZI) and contrasted with the DMSO solvent (as control) and the values have been tabulated. Tables (6), Chart (1) and Figure (2)

Compounds (ligads & complexes), were screened for their in vitro antibacterial activity against (2Gram-negative (-) =,*Escherichia coli, , and Pseudomonas aeruginosa*) and (2 Gram-positive (+) =*Bacillus subtilis* and *Staphylococcus aureus*) bacterial strains[20, 21.]
Generally the (ZI) mm compounds were in the following order;
Metal complexes > Anth.H > TMP = DMSO.

The (ZI) of the(TMP) show inactive to weak active against the growth of three bacteria but (Anth.H) show moderately active to highly active.The $[Co(Anth)_2(TMP)(H_2O)]$show highly activity against 3-organisms uses except *Pseudomonas*.
All complexes show highly antibacterial activity against *Bacillus.*

$[M(Anth)_2(TMP)(H_2O)]$, M=Ni(II),Cu(II),and Zn(II)]complexes ,shows active antibacterial against *E-coli* and *Pseudomonas*.

$[Cd(Anth)_2(TMP)(H_2O)]$ and $[Hg(Anth)_2(TMP)(H_2O)]$ shows very good antibacterial activity against all bacteria .

The increased inhibition activity of the metal complexes can be explained on the basis of Tweedy's chelation theory[13,14].In metal complexes, on chelation the polarity of the metal ion will be reduced to a greater extent due to the overlap of the ligand orbital[20, 21].

Table (6):Biological activity of the mixed $[M(Anth)_2(TMP)(H_2O)]$ complexes (ZI) (mm)

Compound	N_o in Petri dish	*E-coli*	*Pseudomonas*	*Staphylococcus aureus*	*Bacillus*
Control(DMSO)	c	5	7	5	6
TMP	_	4	0	5	10
Anth.H	_	18	9	21	13
$[Co(Anth)_2(TMP)(H_2O)]$	1	11	0	12	37
$[Ni(Anth)_2(TMP)(H_2O)]$	2	0	0	11	26
$[Cu(Anth)_2(TMP)(H_2O)]$	3	0	0	22	30
$[Zn(Anth)_2(TMP)(H_2O)]$	4	0	0	12	35
$[Cd(Anth)_2(TMP)(H_2O)]$	5	20	33	0	36
$[Hg(Anth)_2(TMP)(H_2O)]$	6	27	18	39	40

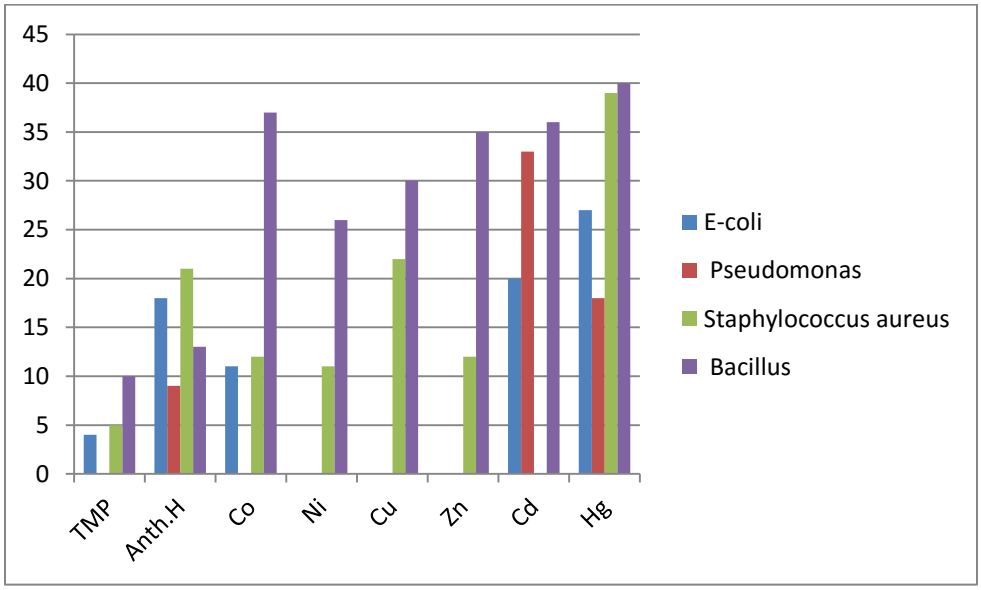


Chart (1) : The (ZI) mm of mixed

[Trimethoprim-Metal Chloride–Athranilic acid]Complexes

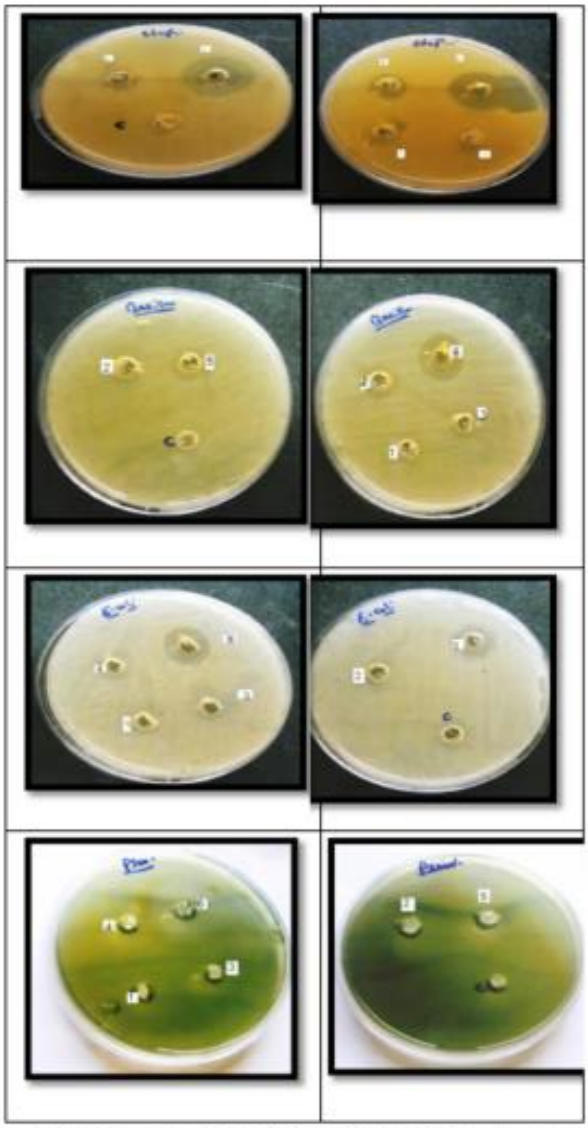


Figure (2) Photograph of Antimicrobial Activity of compounds

References

1. Mrinalinil L. and Manihar Singh A.K., (2012).”Mixed ligand Co(III) complexes with 1-amidino-O-methyl urea and amino acids”, J., Res. Chem. Sci., 2(1), 45-49.
2. Girgaonkar M.V. and Shirodkar S.G., (2012), “synthesis, characterization and biological studies of Cu(II) and Ni(II) complexes with new bidentate schiff’s base ligands as 4-hydroxy-3-(1-(arylimino)ethyl) (arylimino)ethyl)Chromen-2-one”, Res. J. Recent Sci., 1(ISC-2011), 110-116 ,
3. Agarwal Ram K., Sharma Deepak and Agarwal Himanshu. (2006), “Synthesis, biological, spectral and thermal investigation of Cobalt (II) and Nickel (II) complexes of N-isoniotinamido-2,4-dichlorobenzaldimine”, J. Bioinorganic Chemistry and Applications., 1 (9),2863–2875.
4. Gupta Y.K., Agarwal S.C., Madnawat S.P. and Ram Narain., (2012), “Synthesis, characterization and antimicrobial studies of some transition metal complexes of Schiff bases, Res. J., Chem. Sci., 2(4), 68-71 .
5. Sankhala K.and Chaturvedi A., (2012) “Microwave assisted synthesis, characterization and antibacterial activity of some arsenic(III) derivatives of O-alkyl or O-aryl tri thio phosphates, J., Res. Chem. Sci., 2(5), 57-65 .
6. Gazala Mohamed H. and Ben Hander. (2012), “Ternary complexes of Cobalt(II) involving Nitrilotriacetic acid and some biological active ligands, J., Res. Chem. Sci., 2(3), 12-20.
7. Rajasekar K., Ramchandramoorthy T.and Paulraj A., (2012) “Microwave assisted synthesis, structural characterization and biological activities of 4-aminoantipyrine and thiocynate mixed ligand complexes“, J., Res. Pharmaceutical Sci., 1(4), 22-27.
8. Cook B. M., Mohandas N., and Copel R. L., (2004) “Malaria and the red blood cell membrane,” Seminars in Hematology, vol. 41,. 173– 188. 9. Hartinger C. G., Jakupec M. A., Zorbas-Seifried S.(2008), “KP1019, a new redox-active anticancer agent-preclinical development and results of a clinical phase I study in tumor patients,” J., Chemistry and Biodiversity, 5, (10). 2140–2155.
9. Garoufis A., Hadjikakou S. K., and Hadjiliadis N., (2009) “Palladium coordination compounds as anti-viral, anti-fungal, anti-microbial and anti-tumor agents,” J., Coordination Chemistry Reviews, 253, (. 9-10), 1384–1397.
10. Taghreed, H. Al-Noor, Ahmed. T.AL. Jeboori, Manhel R.Aziz, (2014), J., International Technical Research and Applications, 2, (4) 187-192
11. Geary W. J., (1971), “The Use of Conductivity Measurements in Organic Solvents for the Characterization of Coordination Compounds”. J., Coord. Chem. Rev.; 7, 81-122.
12. Taghreed. H. Al-Noor , Lekaa K. Abdul Karim , ,(2015) “Synthesis, Physico-Chemical and Antimicrobial Activities Co(II),Ni (II) ,Cu(II), Zn(II),Cd(II) and Hg(II) Mixed-Ligand Complexes of L- Alanine and Trimethoprim Antibiotic“J., Chemistry and Materials Research.,7 (.5),82-91.
13. Taghreed. H. Al-Noor , Lekaa K. Abdul Karim ,(2015) “Synthesis, Physico-Chemical and Antimicrobial Activities Co(II),Ni (II) ,Cu(II), Zn(II),Cd(II) and Hg(II) Mixed- Ligand Complexes of L- Prolin and Trimethoprim Antibiotic“ , J., Chemistry and Materials Research ,7(3) ,32-39.
14. 14-William, K. (1991) ((***Organic Spectroscopy***)), 3rd edition, Macmillan Education Ltd, London , 49-54, 60-75

15. Lin-Vien, D., N.B. Colthup, W.G. Fately & J.C. Grasselli (1991) *"**The Handbook of Infraredand Raman Characteristic Frequencies of Organic Molecules**" Academic Press; San Diego.*

16. Nakamoto, K. *(1997) "Infrared and Raman Spectra of Inorganic and Coordination Compounds"*5th Edit., Part B; Wiley; New York.

17. 17. Lever A.B.P.; (1984) "***Inorganic spectroscopy***" Elsevier publishing company 1rd Ed.

18. Shriver & Atkins "Inorganic ***Chemistry***", 3rd Ed.,Freeman, (1999).

19. Abu-El-Wafa, S.M El-Rifs, M.A and Ahmed, F.H (1987) "Formation of metformin complexes with some transition metal ions and their biological activity". J., Inorg. Chim. Acta. 136:127-131

20. Awetz, Melnick and A .Delbrgs .; (2007) *"**Medical Microbiology***" McGraw Hil-USA.

21. Poomalai J., Selladurai P., Subramanian V.i and Rangappan R. (2011), Synthesis, spectral characterization, electrochemical and anti-microbial activities of new binuclear Schiff base metal complexes derived from 3, 3' diaminobenzedine. J., Euro. Chem. 2(4), 480 -484.