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SYNTHESIS, CHARACTERIZATION, MICROBIAL EVALUATION OF MIXED LIGAND COMPLEXES DERIVED FROM HYDRAZONES OF CYCLOHEXANONE AND BENZOPHENONE USING TRANSITION METAL IONS

Deepankar Sharma[a] and Purnima Nag[a,*]

[a]*Department of Chemistry, Jaipur National University, Jaipur, 302017, Rajasthan, India*
**Email: purnima_nag007@yahoo.com*

ABSTRACT:
The chemical interaction of 2,4-dinitrophenylhydrazones of Cyclohexanone and Benzophenone with chlorides of transition metals i.e.; Mn(II), Co(II), Ni(II), Cu(II) and Zn(II) resulted in mixed ligand complexes of the type $[M(C_{31}H_{28}N_8O_8)(H_2O)_2Cl_2]$. The hydrazones were prepared using green synthetic route by avoiding conc. H_2SO_4. Novel mixed ligand complexes have been analyzed, characterized and compared with parent ligands on the basis of chemical analysis and spectral studies.
The antimicrobial activities carried out on bacterial strains *Escherichia coli*, *Bacillus subtilis*, *Staphylococcus aureus* and fungal strain *Candida albicans* showed the appreciable activity of all these complexes against these strains.

KEYWORDS: Mixed Ligand Complexes; Transition metal ions; 2,4-dinitrophenylhydrazones; Antimicrobial activity.

INTRODUCTION:

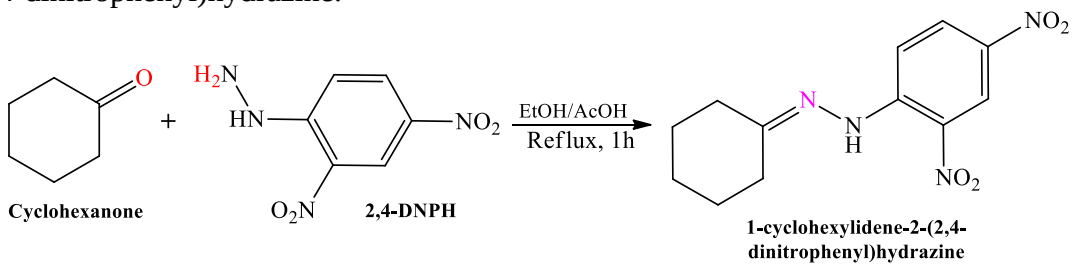
Mixed ligand metal complexes have often fascinated researchers since they are different from conventional metal complexes. Such complexes are known and defined to include minimum two different type of ligand systems attached to the same metal.[i-vii] In fact, mixed ligand metal complexes may vary in their expected behavior and properties due to the presence of more than one type of ligand system. Hydrazones as ligands are versatile in nature owing to their analytical importance[viii] and applications in medicinal chemistry.[ix] They are significant as pharmacophoric cores of variety of antinociceptive, anti-inflammatory as well as antiplatelet drugs.[x] Hydrazones and their complexes bring attention as they demonstrate great diversification of reactivity and their significance in multiple areas of research i.e.; pharmaceutical, biological and materialistic chemistry.[xi-ix]
Considering the advantages of transition metal complexes and in progression of our recent work focused on such complexes with Schiff base and oxime derivatives;[xx, xxi] herein, we highlight and reportthe syntheses, characterization, antimicrobial significance of some novel mixed ligand transition metal complexes derived from hydrazones of Cyclohexanone andBenzophenoneusing transition metals viz. Mn(II), Co(II), Ni(II), Cu(II) and Zn(II).

MATERIALS AND METHODS

Benzophenone, cyclohexanone, 2,4-dinitrophenylhydrazine and metal(II) chlorides were used as procured (purchased from Sigma-Merck and Fisher Scientific). Carbon, Nitrogen and Hydrogen were registered on a C, H, N and S II series 2400 analyzer (Perkin-Elmer). Metals and Cl were estimated using literature methods.[xxii] IR spectra were registered on a Spectrum Version: 10.4.00 spectrophotometer (Perkin Elmer) in the standard region 4000-400cm^{-1}, using KBr. ^{1}H-NMR spectra were registered on a Bruker Ascend 300 MHz system using d_6-DMSO as solvent and TMS as reference. Spectral studies (^{1}H-NMR, IR) were carried out at *MNIT, Jaipur*. Antibacterial activities were carried out at *Seminal Applied Sciences Pvt. Ltd., Jaipur* and antifungal activities were carried out at *Dr. B. Lal Clinical Laboratory Pvt. Ltd. - CIRD, Jaipur.*

Synthesis of Cyclohexanone-2,4-dinitrophenylhydrazone

An ethanolic solution of 2,4-Dinitrophenylhydrazine (4.20g, 21.197 mmol), cyclohexanone (2.08 g, 21.197 mmol) and 2-3ml of glacial acetic acid were mixed and refluxed for an hour (Scheme 1). The contents were cooled; obtained precipitate was filtered off under reduced pressure and washed twice with ethanol to obtain the desired solid product 1-cyclohexylidene-2-(2,4-dinitrophenyl)hydrazine.

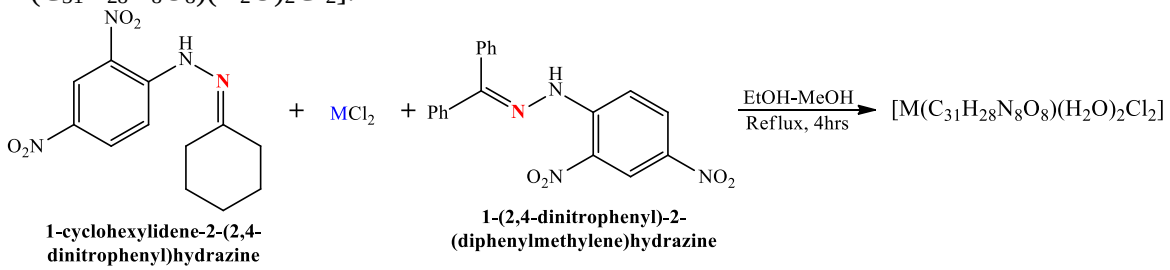


Scheme 1. Green synthesis of Cyclohexanone-2,4-dinitrophenylhydrazone

A similar procedure resulted in synthesis of Benzophenone (2,4-dinitrophenyl)hydrazone.

Synthesis of mixed ligand Zn-complex, [Zn($C_{31}H_{28}N_8O_8$)$(H_2O)_2Cl_2$]

Ethanolic solution of $ZnCl_2$ (3.800 g, 27.882 mmol), methanolic solution of 1-cyclohexylidene-2-(2,4-dinitrophenyl)hydrazine (7.758 g, 27.882 mmol) and methanolic solution of 1-(2,4-dinitrophenyl)-2-(diphenylmethylene)hydrazine (10.103 g, 27.882 mmol) were mixed and refluxed for 4 hours. The contents were cooled; obtained precipitate was filtered off under reduced pressure and washed twice with ethanol to obtain the corresponding Zn-complex [Zn($C_{31}H_{28}N_8O_8$)$(H_2O)_2Cl_2$].



Scheme 2. Synthesis of mixed ligand complexes, [M($C_{31}H_{28}N_8O_8$)$(H_2O)_2Cl_2$]

A similar procedure resulted in synthesis of Mn-complex [Mn($C_{31}H_{28}N_8O_8$)$(H_2O)_2Cl_2$], Co-complex [Co($C_{31}H_{28}N_8O_8$)$(H_2O)_2Cl_2$], Ni-complex [Ni($C_{31}H_{28}N_8O_8$)$(H_2O)_2Cl_2$] and Cu-complex [Cu($C_{31}H_{28}N_8O_8$)$(H_2O)_2Cl_2$].

RESULTS AND DISCUSSION

The chemical interaction of 2,4-dinitrophenylhydrazone of Cyclohexanone ($C_{12}H_{14}N_4O_4$) and 2,4-dinitrophenylhydrazone of Benzophenone ($C_{19}H_{14}N_4O_4$) with transition Metal(II) chlorides in 1:1:1 molar ratios resulted in mixed ligand complexes $[M(C_{31}H_{28}N_8O_8)(H_2O)_2Cl_2]$ (where; M = metal i.e.; Mn/Co/Ni/Cu/Zn). All these colored complexes are obtained in 67-81% yield; soluble in coordinating solvents such as Dimethyl sulfoxide and Dimethylformamide. They have been analyzed using elemental analysis (where found and calculated values vary with less than ±3%); characterized and compared with free ligands using IR, 1H-NMR spectral findings. The physical data for the mixed ligand complexes are provided in Table 1.

Table 1

Physical data for the synthesized mixed ligand complexes

Mixed Ligand Complex	**% Yield**	**State and Color**	**M.p. (°C)**
$[Mn(C_{31}H_{28}N_8O_8)(H_2O)_2Cl_2]$	67	Reddish brown solid	184-186
$[Co(C_{31}H_{28}N_8O_8)(H_2O)_2Cl_2]$	74	Dark pink solid	176-178
$[Ni(C_{31}H_{28}N_8O_8)(H_2O)_2Cl_2]$	69	Dark blue solid	190-192
$[Cu(C_{31}H_{28}N_8O_8)(H_2O)_2Cl_2]$	81	Dark green solid	204-206
$[Zn(C_{31}H_{28}N_8O_8)(H_2O)_2Cl_2]$	77	Orange solid	182-186

IR Spectra

IR spectra of free ligands were studied comparatively with spectra of complexes to determine the binding mode of metals to hydrazones. The spectra of complexes show characteristic bands around 3295-3215 cm^{-1}, 915-870 cm^{-1} attributed to ν(N-H) and ν(N-N), respectively;[xxiii-xxv] which are at lower frequency as compared to free ligand systems. Bands in the spectra of ligands around 1780-1765cm^{-1} assignable to ν(C=N) have shifted to lower values 1735-1710 cm^{-1} in the spectra of complexes (Table 2), which depicts coordinating behavior of azomethine nitrogen towards metal ions. The peaks registered around 3495-3450 cm^{-1} along with peaks in the region 840-820cm^{-1} accounts for the presence of water coordination towards metal ions.[xxiv]Additionally; new peaks observed in the spectra of complexes around 585-445 cm^{-1} attributed to ν(Metal-N) confirms the metal-ligand interaction.

Table 2

IR spectral for the synthesized mixed ligand complexes

Metal Complex	**ν(N-H)**	**ν(H_2O)**	**ν(C=N), azomethine**	**ν(N-N)**	**ν(Metal-N)**
$[Mn(C_{31}H_{28}N_8O_8)(H_2O)_2Cl_2]$	3215	3460, 840	1710	915	520
$[Co(C_{31}H_{28}N_8O_8)(H_2O)_2Cl_2]$	3295	3450, 825	1735	900	490
$[Ni(C_{31}H_{28}N_8O_8)(H_2O)_2Cl_2]$	3290	3475, 820	1725	910	585
$[Cu(C_{31}H_{28}N_8O_8)(H_2O)_2Cl_2]$	3265	3495, 835	1710	885	445
$[Zn(C_{31}H_{28}N_8O_8)(H_2O)_2Cl_2]$	3280	3490, 830	1720	870	470

^{1}H-NMR Spectra[xxiv]

In spectra of complexes, the singlet peaks in the region δ11.11-10.92 ppm can be associated to the >NH protons, which signify that no deprotonation of N-H bonds occurred during formation of complexes. The broad multiplet signals in the spectra of complexes between δ 8.92-7.33 ppm are ascribed to the aromatic ring protons in the ligands. Moreover, the medium intensity signals in the region δ 2.49-1.47 ppm have been attributed to the $>CH_2$ moiety of the cyclohexane ring in spectra of mixed ligand complexes.

Antimicrobial Activity

In-vitro antimicrobial screening of the mixed ligand metal complexes were registered against bacterial strains viz. *Escherichia coli, Bacillus subtilis, Staphylococcus aureus* and fungal strain *Candida albicans* incorporating Kirby-Bauer well diffusion method,[xxvi] using MH agar media. Discs were incubated at 37°C overnight. Standard laboratory cultured strains of *Escherichia coli, Bacillus subtilis, Staphylococcus aureus* and *Candida albicans* were used. The extracts were dissolved in DMSO (Dimethyl sulphoxide) at 5mg/mL, 10mg/mL concentrations and 100µl of the test compound was used in the 6mm sized well. Ciprofloxacin (5mg/mL) and Itraconazole (5mg/mL) were used as standards for analyzing inhibition zone reflected by the test compounds against bacterial strains and fungal strain; respectively. The antimicrobial results (Table 3) suggested the appreciable activity of all these complexes against these strains (Figure 1). It has been noticed that the Zn-complex shows an overall better activity against *Escherichia coli, Bacillus subtilis, Candida albicans;* while, Cu-complex shows maximum activity against *Staphylococcus aureus* compared to other complexes at similar concentrations.

Table 3

Antimicrobial activity data for the synthesized mixed ligand complexes

Metal Complexes at Concentration		**Zone of Inhibition (in mm)**			
		B. subtilis	***E. coli***	***S. aureus***	***C. albicans***
$[Mn(C_{31}H_{28}N_8O_8)(H_2O)_2Cl_2]$	$5mgmL^{-1}$	15	17	14	19
	$10mgmL^{-1}$	19	19	18	24
$[Co(C_{31}H_{28}N_8O_8)(H_2O)_2Cl_2]$	$5mgmL^{-1}$	12	13	9	11
	$10mgmL^{-1}$	15	20	13	15
$[Ni(C_{31}H_{28}N_8O_8)(H_2O)_2Cl_2]$	$5mgmL^{-1}$	10	11	8	13
	$10mgmL^{-1}$	14	15	12	16
$[Cu(C_{31}H_{28}N_8O_8)(H_2O)_2Cl_2]$	$5mgmL^{-1}$	12	14	16	17
	$10mgmL^{-1}$	16	19	21	25
$[Zn(C_{31}H_{28}N_8O_8)(H_2O)_2Cl_2]$	$5mgmL^{-1}$	17	19	13	23
	$10mgmL^{-1}$	21	26	20	29

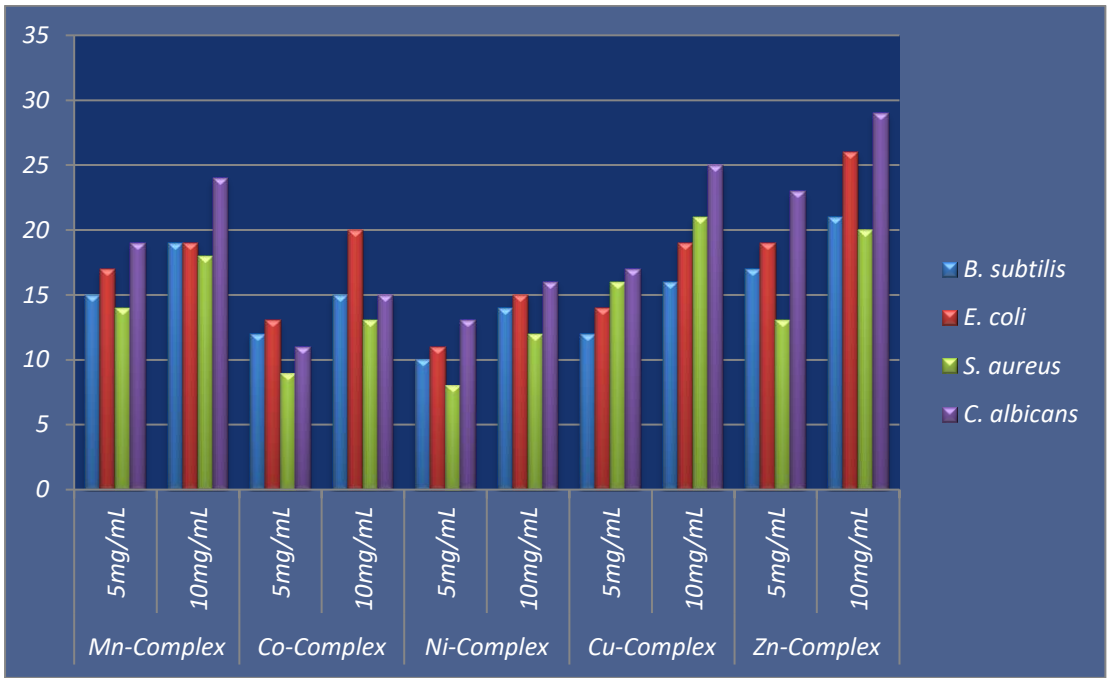


Figure 1. Antimicrobial activities of thesynthesized mixed ligand complexes

CONCLUSION

In the present work, we have reported mixed ligand metal complexes synthesized by chemical interaction of Cyclohexanone-2,4-dinitrophenylhydrazone and Benzophenone-2,4-dinitrophenylhydrazone with transition metal chlorides. Keeping in view the aforementioned results, observations and findings; we propose the following coordination (Figure 2) for the complexes $[M(C_{31}H_{28}N_8O_8)(H_2O)_2Cl_2]$. The microbial screening of these synthesized mixed ligand complexes depicts their overall appreciable activity against *Escherichia coli*, *Bacillus subtilis*, *Staphylococcus aureus* and *Candida albicans.* It has been observed that these complexes possess are more antifungal character as compared to their antibacterial properties.

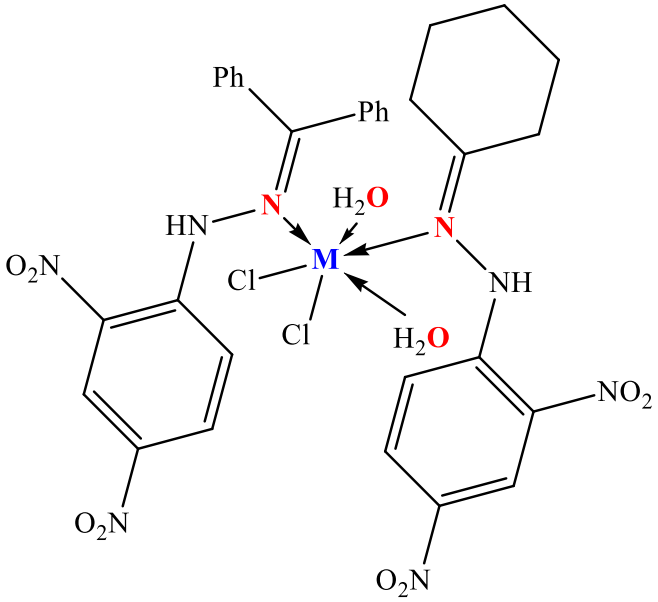


Figure 2. Probable coordination for the synthesized mixed ligand complexes (where; M = Mn/Co/Ni/Cu/Zn)

REFRENCES

i. El-Halim H.F.A.; Mohamed G.G. and Anwar M.N.; "Antimicrobial and anticancer activities of Schiff base ligand and its transition metal mixed ligand complexes with heterocyclic base"; Appl. Organometal. Chem.; 2018, **32**, 1.

ii. Abdel-Rahman L.H.; Abu-Dief A.M.; Ismail N.M. and Ismael M.; "Synthesis, characterization, and biological activity of new mixed ligand transition metal complexes of glutamine, glutaric, and glutamic acid with nitrogen based ligands"; Inorg. And Nano-Met. Chem.; 2017, **47**, 467.

iii. Devi J. and Batra N.; "Synthesis, characterization and antimicrobial activities of mixed ligand transition metal complexes with isatin monohydrazone Schiff base ligands and heterocyclic nitrogen base"; Spectrochim. Act. Part A: Mol. and Biomol. Spec.; 2015, **135**, 710.

iv. Siddiqi Z.A.; Sharma P.K.; Shahid M.; Khalid M. and Kumar S.; "Synthesis, spectral characterizations and biological studies of transition metal mixed ligand complexes: X-ray crystal structures of [Cu(oda)(Bipy)(H_2O)].4H_2O and [VO(oda)(Bipy)].2H_2O"; J. Mol. Str.; 2011, **994**, 295.

v. Babu M.S.S.; Reddy K.H. and Krishna P.G.; "Synthesis, characterization, DNA interaction and cleavage activity of new mixed ligand copper(II) complexes with heterocyclic bases"; Polyhedron; 2007, **26**, 572.

vi. Panchal P.K. and Patel M.N.; "Synthesis, Structural Characterization, and Antibacterial Studies of Some Mixed-Ligand First Row d-Transition Metal Complexes"; Synt. and React. in Inorg. and Met.-Org. Chemistry; 2004, **34**, 1277.

vii. Aly M.M. and Al-Shatti N.I.; "Supramolecular and metallosupramolecular coordination compounds of nickel(II) with the half units of vicinal oxime-imine ligands; mixed ligand complexes of the metal ion"; Trans. Met. Chem.; 1998, **23**, 361.

viii. Terra L.H.S.A.; da Cunha Areias M.C.; Gaubeur I.: Encarnacion M. and Suez-Iha V.; "Solvent extraction-spectrophotometric determination of nickel (II) in natural waters using di-2-pyridyl ketone benzoylhydrazone"; Spectrosc. Lett.; 1999, **32**, 257.

ix. Maurya M.R.; Agarwal S.; Abid M.; Azam A.; Bader C.; Ebel M. and Rehder D.; "Synthesis, characterisation, reactivity and in vitro antiamoebic activity of hydrazone based oxovanadium (iv), oxovanadium (v) and μ-bis (oxo) bis {oxovanadium (v)} complexes"; Dalton Trans.; 2006, 937.

x. Cunha A.C.; Figueiredo J.M.; Tributino J.L.M.; Miranda A.L.P.; Castro H.C.; Zingali R.B.; Fraga C.A.M.; de Souza M.C.B.V.; Ferreira V.F. and Barreiro E.J.; "Antiplatelet properties of novel N-substituted-phenyl-1, 2, 3-triazole-4-acylhydrazone derivatives"; Bioorg. Med. Chem.; 2003, **11**, 2051.

xi. Dilworth J.R.; "The coordination chemistry of substituted hydrazines"; Coord. Chem. Rev.; 1976, **21**, 29.

xii. Zelenin K.N.; Khorseeva L.A. and Alekseev V.V.; "Physiologically active complexes of hydrazones"; Pharm. Chem. J.; 1992, **26**, 395.

xiii. Mizobe Y.; Ishii Y. and Hidai M.; "Synthesis and reactivities of diazoalkane complexes"; Coord. Chem. Rev.; 1995, **139**, 281.

xiv. Koivisto B.D.; Hicks R.G.; "The magnetochemistry of verdazyl radical-based materials"; Coord. Chem. Rev.; 2005, **249**, 2612.

xv. Popov L.D.; Morozov A.N.; Shcherbakov I.N.; Tupolova Y.P.; Lukov V.V. and Kogan V.A.; "Metal complexes with polyfunctional ligands based of bis (hydrazones) of dicarbonyl compounds"; Russ. Chem. Rev.; 2009, **78**, 643.

xvi. Manzura C.; Fuentealba M.; Hamon J.R. and Carrillo D.; "Cationic organoiron mixed-sandwich hydrazine complexes: Reactivity toward aldehydes, ketones, β-diketones and dioxomolybdenum complexes"; Coord. Chem. Rev.; 2010, **254**, 765.

xvii. Narasimhan B.; Kumar P. and Sharma D.; "Biological activities of hydrazide derivatives in the new millennium"; Acta Pharm. Sci.; 2010, **52**, 169.
xviii. Paterson B.M. and Donnelly P.S.; "Copper complexes of bis (thiosemicarbazones): from chemotherapeutics to diagnostic and therapeutic radiopharmaceuticals"; Chem. Soc. Rev.; 2011, **40**, 3005.
xix. Kobayashi S.; Mori Y.; Fossey J.S. and Salter M.M.; "Catalytic enantioselective formation of C− C bonds by addition to imines and hydrazones: A ten-year update"; Chem. Rev.; 2011, **111**, 2626.
xx. Sharma D. and Nag P.; "Synthesis, Characterization and Preliminary Antifungal Activity of Some Co(II) and Zn(II) Complexes Derived From Oximes of 2-Acetyl Aromatic Heterocycles"; Orbital: Electron. J. Chem.; 2021, **13**, 48.
(b) Sharma D. and Nag P.; "Anticandidal activity of some Zn(II) and Pb(II) complexes"; Mor. J. Chem.; 2020, **8**, 326.
xxi. Nag P. and Sharma D.; "Synthesis, characterization and anticandidal activity of dioxomolybdenum(VI) complexes of the type $[MoO_2\{ON=C(CH_3)Ar\}_2]$ and $[MoO_2\{OC(R)CHC(R')=NC_6H_5\}_2]$"; Heliyon; 2019, **5**, e01729.
xxii. Jeffery G.H.; Bassett J.; Mendham J. and Denney R.C.; Vogel's Textbook of Quantitative Chemical Analysis, Longman Scientific & Technical, Britain; 1989.
xxiii. Silverstein R.M.; Bassler G.C. and Movril T.C.; Spectroscopic identification of organic compounds, 4th Ed., Wiley, New York; 1981.
xxiv. Raman N.; Ravichandran S. and Thangaraja C.; "Copper(II), cobalt(II), nickel(II) and zinc(II) complexes of Schiff base derived from benzil-2,4-dinitrophenylhydrazone with aniline"; J. Chem. Sci.; 2004, **116**, 215.
xxv. Deshmukh R.G.; Sawant D.C. and Pingale S.G.; "Synthesis and Characterization of Zn(II), Cd(II), Hg(II) and Pd(II) Complexes of N″-[(1E,2Z)-2-(hydroxyimino)-1-phenylpropylidene]thiocarbohydrazide"; Asian J. Chem.; 2008, **20**, 1723.
xxvi. Brown D.F.J. and Kothari D.; "Comparison of antibiotic discs from different sources"; J. Clin. Pathol. (London); 1975, **28**, 779.

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