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Synthesis and characterization of Schiff bases of pyrazole aldehyde and their metal complexes of Cu(II), Ni(II) and Co(II)

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Synthesis of some novel metal complex of different transition metal likes Co, Cu and Ni have been carried out with (E)-5-(3-(3-(4-chlorophenyl)-1-phenyl-1H-pyrazol-4-yl)acryloyl)-2-hydroxybenzamide ligand with the appropriate metal salts i.e. $Co(CH_3COO)_2 \cdot 6H_2O$, $Ni(CH_3COO)_2 \cdot 6H_2O$ and $Cu(CH_3COO)_2 \cdot 2H_2O$. The structure conformation of ligand molecule is done by using various spectroscopic techniques such as ^1H NMR, IR and mass. The thermal analyses of synthesized metal complexes are carried out by TGA and DTA under inert gas atmosphere. Further, antimicrobial activity of these synthesized metal complexes are also checked against some selected bacterial and fungal strains and good to moderate biological activity of the metal complexes against selected bacterial and fungal strains are observed in DMF and DMSO solvents.

Keywords: Transition metal complexes, Schiff base, Anti microbial activity, Pyrrazole aldehyde

In many countries, the treatment of many diseases causes by various microorganisms still remains as an important and challenging problem as day by day, the microorganisms are becoming more and more resistive against drug present in the market. Further, the numbers of microbial pathogens are also increasing which causes serious effect on the health. Due to drug resistant microbial pathogens, the new compounds have been synthesized by various chemists in order to find out new effective leading molecules[1]. Literature shows that the pyrazole derivatives possess various biological and pharmaceutical activities in medicinal field[2-5]. Pyrazole is the one of the five member heterocyclic ring having two adjacent nitrogen atoms. Pyrazole derivatives showed biological activities such as anticancer[6], antimalarial[7], antiulcer[8], antihypertensive[9], antiinflammatory[10], antidiabetic[11], etc.

Nowadays, the chemistry of metal complexes is gaining importance due to their incredible biological and pharmaceutical activities[12-14]. The biological activities of pyrazole scaffolds may be further enhanced by preparation of metal complexes of such pyrazole ligand with various transition metals[15,16]. Among the transition metals, copper, nickel and cobalt are most common metals used in synthesis of metal complexes[17-19]. The copper is one of the trace elements uses in the formation and activity function of many enzymes, proteins, DNA and essential for life. The structural modification could enhance solubility and stability of heterocyclic compounds in the biological medium and enhanced biological activities.

In the present work, the synthesis of some transition metal complexes such as Ni(II), Cu(II), Co(II), with pyrazole heterocyclic compound as ligand molecule was carried out in alcoholic medium. The structure conformation of ligand molecule was done through ^1H NMR, infrared (IR) and mass spectral data. Thermal analysis of the synthesized metal complexes was done through thermogravimetric analysis (TG) and differential thermal analysis (DTA) in inert atmosphere. The antimicrobial screening was also studied for all synthesized metal complexes against selected bacterial and fungal strains in *N,N*-dimethyl formamide (DMF) and dimethyl solfoxide (DMSO) solvent by agar well diffusion method.

Materials and Methods

Chemicals

The various chemicals used in the synthesis as well as in antimicrobial screening were analytical reagent grade and purchased from Spectro Chem Pvt. Ltd. and used as received. For metal complexes formation, the metal salt such as $Co(CH_3COO)_2 \cdot 6H_2O$, $Ni(CH_3COO)_2 \cdot 6H_2O$ and $Cu(CH_3COO)_2 \cdot 2H_2O$ were

supplied by LOBA Chem Pvt. Ltd. and used as received. The reaction progress and the purity of synthesized metal complexes were checked through the thin layer chromatography (TLC, Provided by MERCK Pvt. Ltd.) in which silica gel pre-coated on aluminum foil was used.

Instruments

The structure confirmation of ligand molecule was done by ^{1}H NMR, IR and mass spectral data. The ^{1}H NMR spectra were taken on a Bruker Avance III at 400 MHz frequency. For ^{1}H NMR spectra, deuterated DMSO was used as solvent and tetra methyl silane (TMS) as an internal standard. IR analysis of pyrazole ligand was carried out on IRaffinity-1S (Shimadzu FTIR spectrophotometer) by solid phase method and in moisture free atmosphere. Mass analysis was carried out by using direct inlet probe method on SHIMADZU GC-MS spectrometer.

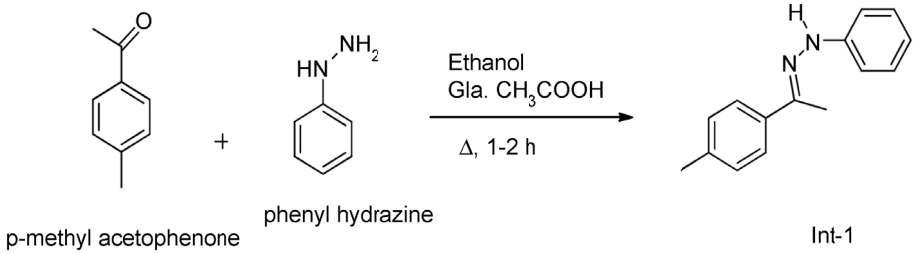
TG thermograms of the complexes were recorded on a Shimadzu DTG-60H instrument in nitrogen atmosphere with flow rate 100 mL/min. For TG analysis, sample was put into open silica pan and heated from room temperature to 1000 °C with empty silica pan as the reference. For all compounds, the heating rate was 10 °C min^{-1}. Before the analysis, the DTG-60H instrument was calibrate with standard indium and zinc metals.

Synthesis of (E)-1-phenyl-2-(1-(p-tolyl)ethylidene)hydrazine (Int-1)

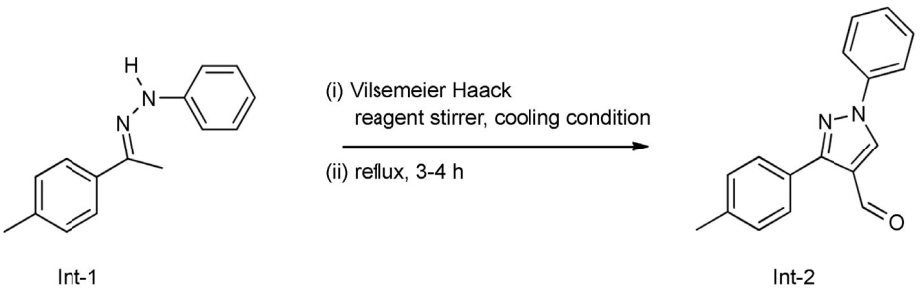
The solution of p-methyl substituted acetophenone (0.01 mmol) and phenyl hydrazine (0.011 mmol) in ethanol was refluxed for 2-3 h. The reaction progress was checked by TLC pre-coated with fine silica gel on aluminum foil using hexane and ethyl acetate (5:5) as mobile phase. After completely refluxed, the reaction mass was poured into crushed ice with constant stirring. The obtained solid was filtered, washed with cold water and dried under vacuum. The obtained crude product was used in next step without further any purification. The reaction scheme is shown in Scheme 1.

Synthesis of 1-phenyl-3-(p-tolyl)-1H-pyrazole-4-carbaldehyde (Int-2)

Int-1 (0.01 mmol) was dissolved in minimum quantity of anhydrous DMF and the solution was cooled in ice bath. To this solution, Vilsemeier-Haack reagent (mixture of phosphorus oxychloride ($POCl_3$, 0.18 mmole) and DMF (0.06 mmol)) was added dropwise with constant stirring in same cooling condition. After complete addition of reagent, the solution was allowed to stir additionally for 1 h in ice bath and then was refluxed for 3 to 4 h. The TLC was used to determine reaction status using mixture of hexane:ethyl acetate (4:6) as mobile phase. After completion of reaction, the reaction mixture was poured into crushed ice with constant stirring and was stirred for overnight in order to separate out all pyrazole aldehyde. The obtained solid product was filtered, washed with cold water and dried under vacuum. The reaction scheme is shown in Scheme 2.



Scheme 1— Scheme for synthesis of (E)-1-phenyl-2-(1-(p-tolyl)ethylidene)hydrazine



Scheme 2 — Scheme for synthesis of 1-phenyl-3-(p-tolyl)-1H-pyrazole-4-carbaldehyde

Synthesis of (Z)-5-(3-(1,3-diphenyl-1H-pyrazol-4-yl)acryloyl)-2-hydroxybenzonitrile (Int-3)

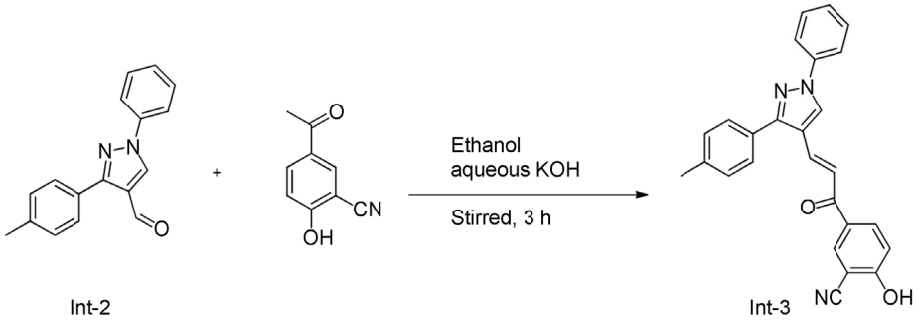
The solution of Int-2 (0.01 mmol) and 4-hydroxy-3-cyano-acetophenone (0.01 mmol) was prepared in ethanol and in this solution 5 ml aqueous solution of potassium hydroxide (50 % w/v) was added dropwise. After complete addition of alkali solution, the mixture was stirred for 3 h at room temperature. The clear solution was observed which is then converted into viscous solution. The reaction monitored through pre-coated TLC using hexane: ethyl acetate (3:7) as mobile phase. After completion of reaction, the reaction mixture was poured into crushed ice and allow to stirrer for 2-3 h. The solution was then neutralized with diluted hydrochloric acid solution. The obtained solid product was filtered, washed with cold water and dried under vacuum. The reaction scheme is shown in Scheme 3.

Synthesis of (E)-2-hydroxy-5-(3-(1-phenyl-3-(p-tolyl)-1H-pyrazol-4-yl)acryloyl)benzamide (OPD-1) ligand:

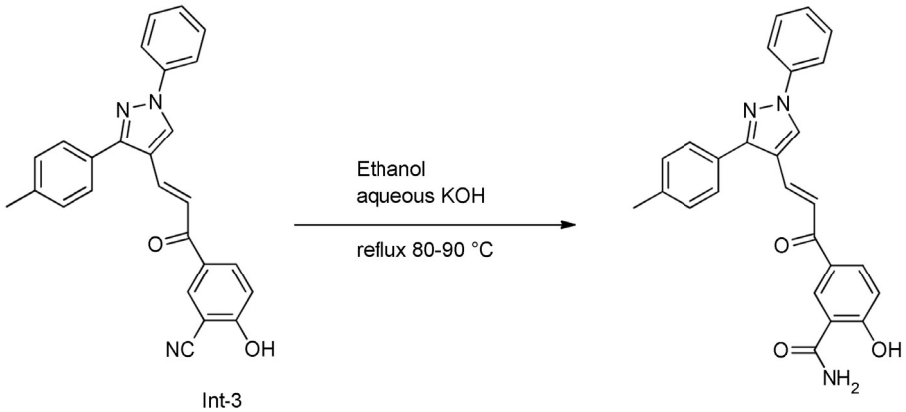
Int-3 (0.01 mmol) was dissolved in minimum quantity of ethanol and to this aqueous KOH (0.10 mmol) was added dropwise with constant stirring. After complete addition of alkali solution, the resultant mixture was refluxed in water bath for time. The progress of reaction was checked by TLC using hexane: ethyl acetate (3:7) mixture as mobile phase. The reaction mixture was poured into cold water and neutralized by dilute hydrochloric acid solution. The obtained precipitate was filtered, washed with cold water and dried under vacuum. Yield: 61%, molecular formula: $C_{26}H_{21}N_3O_3$, molecular weight: 423, retardation factor (R_f): 0.65 The reaction scheme is shown in Scheme 4.

Preparation of metal complexes

For metal complex formation, the appropriate transition metal salt likes $Co(CH_3COO)_2 \cdot 6H_2O$, $Ni(CH_3COO)_2 \cdot 6H_2O$, and $Cu(CH_3COO)_2 \cdot 2H_2O$ (0.10 mmol) was dissolved in minimum quantity of distilled water. To this solution, the pre-prepared solution of ligand molecule (0.10 mmol in ethanol) was added dropwise. After compete addition of ligand solution, the resultant mixture was refluxed at 60-70 °C for 8-10 h with constant stirring. The status of metal complex formation was monitored by TLC using hexane:ethyl acetate (3:7) mixture as mobile phase. After refluxing, the obtained mixture was allowed to stand at room temperature for 8 to 9 h to develop coloured metal complex crystal. After complete



Scheme 3 — Scheme for synthesis of (Z)-5-(3-(1,3-diphenyl-1H-pyrazol-4-yl)acryloyl)-2-hydroxybenzonitrile



Scheme 4 — Scheme for synthesis of (E)-2-hydroxy-5-(3-(1-phenyl-3-(p-tolyl)-1H-pyrazol-4-yl)acryloyl)benzamide (OPD-1) ligand

precipitation, extra solvent was removed by using rotary evaporator and the product was filtered, washed with cool methanol and dried under vacuum. The reaction scheme is shown in Scheme 5.

Results and Discussion

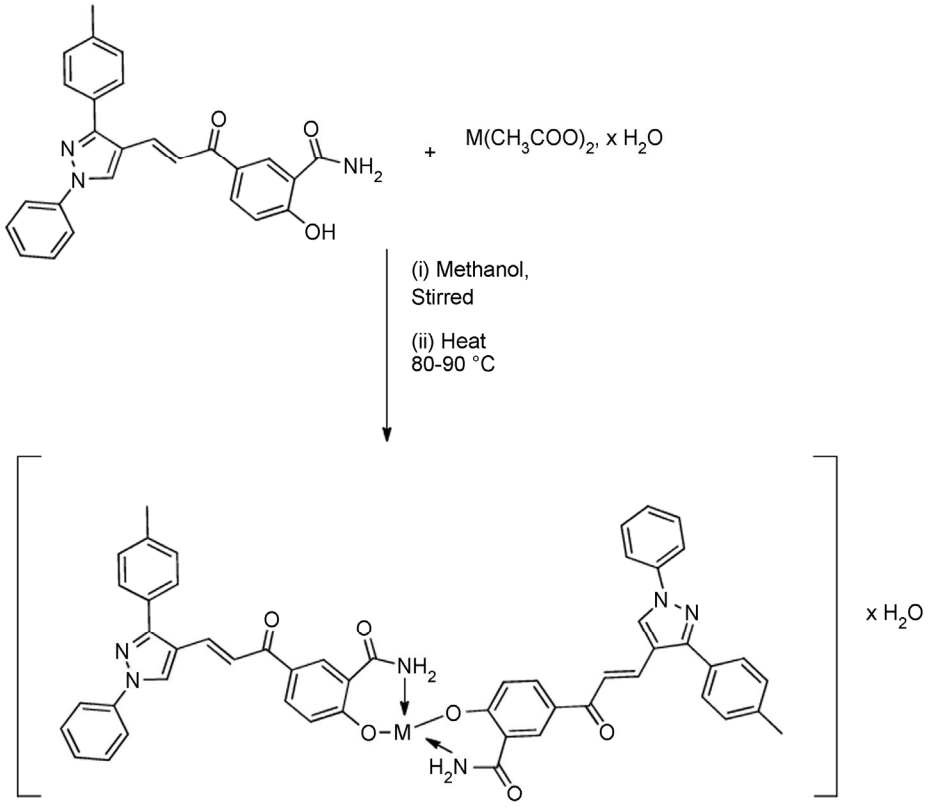
Spectral analysis of ligand

^{1}H NMR spectrum of OPD-1 is shown in Fig. 1. Here it is observed that the proton peak of methyl group present in free ligand molecule shows peak in up field at δ 2.406 ppm. The proton peak of amino group is observed in deshielding region i.e. in down field at δ 9.296 ppm due to effect of nitrogen atom. The characteristics proton peak of hydroxyl group is also observed in deshielding region at δ 8.753 ppm as singlet. Other peaks of aromatic protons are observed in their appropriate region with appropriate splitting. This gives the conformation of synthesis of heterocyclic molecules.

In IR spectrum of OPD-1 as shown in Fig. 2, the bands observed at 3385.07, 3311.78 and 3197.98 cm^{-1} are due to N-H stretching of amino group present in molecule. The N-H stretching of amide group is observed in the region of 3310-3335 cm^{-1}. The peaks observed in this region are broad which indicates the merger of N-H stretching peak with –OH stretching peak. The broad band in the region 3300-3400 cm^{-1}; shows the presence of free hydroxyl group. The characteristics carbonyl stretching peaks are observed at 1707 and 1668 cm^{-1}. These absorbance peaks show that the presence of two type carbonyl group in the molecules. The alkane (-CH-) stretching absorbance peaks are observed at 3150-2800 cm^{-1}. In mass spectrum of OPD-1 as shown in Fig. 3, the molecular ion peak is obtained at 423 m/z.

Spectral analysis of complex

Fig. 4 shows the IR spectrum of OPD-1 Cu, complex. The comparison of IR spectrum of ligand molecule with that of metal complex shows that the N-H stretching of amide group is observed at 3385.07, 3311.78 and 3197.98 cm^{-1} in free ligand



Scheme 5 — Scheme for synthesis of metal complexes

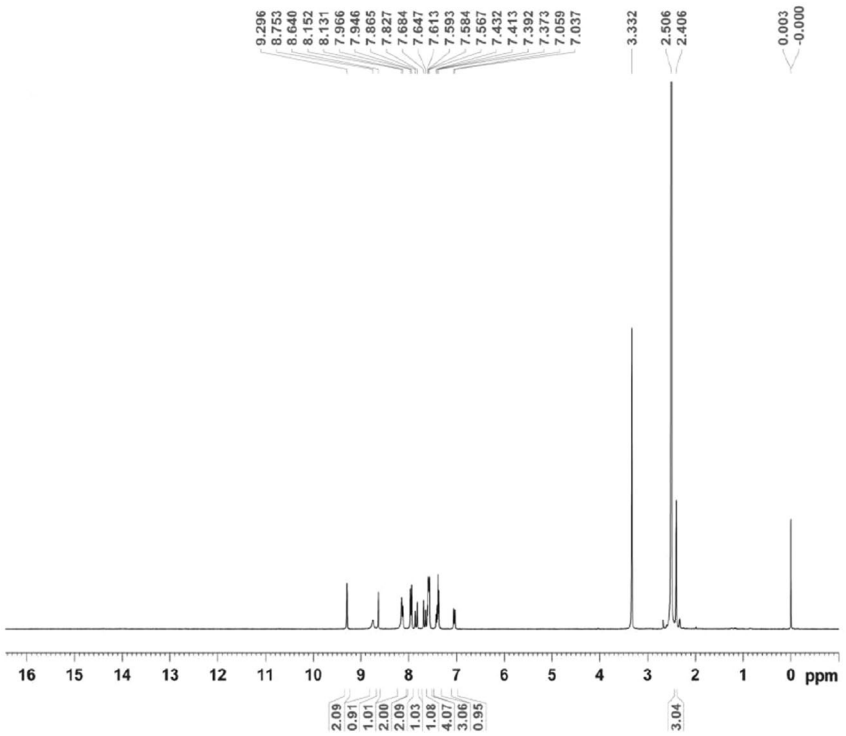


Fig. 1 — ^{1}H NMR spectrum of OPD-1

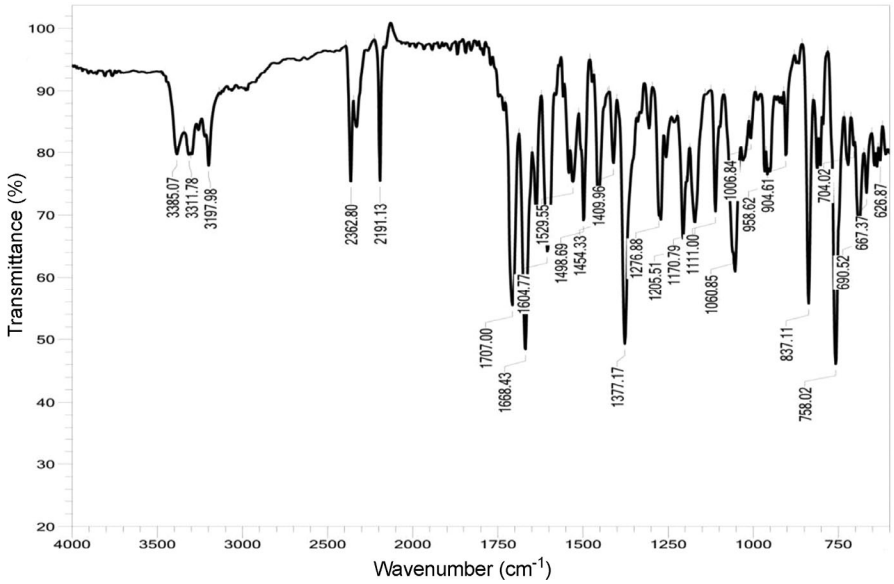


Fig. 2 — IR spectrum of OPD-1

molecule. However, in the IR spectrum of metal complex, less intense N-H stretching of amide group is observed. The less intensity of stretching peak indicates the coordination of the amide group with the transition metal. Further, on comparison of IR spectrum of pure ligand and metal complex, it is observed that the hydroxyl group shows broad peak in case free ligand which got disappear in metal complex. This indicates that in metal complex, the transition metal forms coordinate covalent bond with hydroxyl and amide group of ligand molecules. The change in the absorption frequency of these groups indicates that the metal is attached with oxygen and nitrogen atoms of the ligand.

Thermal analysis of the complex

The TG analysis of metal complexes gives information about metal complex formation, weight loss with the temperature, degradation pattern, etc. The thermal stability of a compound depends on its structure. In the studied compounds, ligand moiety is same for all the compounds but central metal is different as shown in Table 1. Various thermal properties such as initial decomposition temperature, the decomposition temperature range and percentage weight loss for all the complxes are determined from the thermograms are given in Table 2. Hence, in the present study, the variation in thermal stability may be due to nature of different substitutions.

From TG and DTA plots of OPD-1 Cu complex (Fig. 5), it is observed that the degradation of metal complex is a multistep process. In TG curve, the first notable change in mass was obtained around 115 °C which indicates removal of water molecules present in metal complex. The weight loss at this temperature is observed around 3.43% which is approximately equal to two water molecules. This practical weight loss of 3.43% is in accordance with the theoretical weight loss of 3.45%. It also confirms that the water molecule in metal complexes are present in non-bounded form. After evaporation of water molecules, the TG curve become stable upto 180 °C and then it gradually decreases with increase in the temperature. In the second step, the degradation of heterocylic ligand takes place. The ligand molecule is containing benzene ring along with nitrogen as heteroatom. The second degradation step is gradually decreased with increase in the temperature indicates that the ligand molecules degrade stepwise and continuous. From TG curve, it is observed that the metal complex degrade up to 40% at 300 °C. At 1000 °C temperature almost 91% weight loss observed and approximate 9% was remains in sample pan. In the present study, in the DTA plot (Fig. 5), first an endothermic peak is observed at about 115 °C which

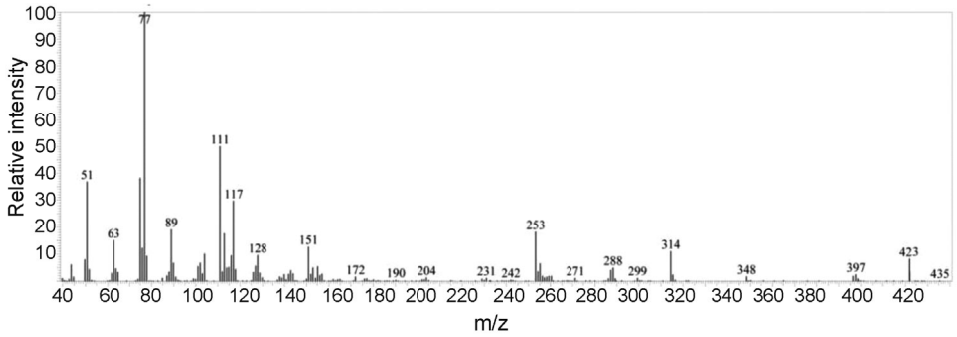


Fig. 3 — Mass spectrum of OPD-1

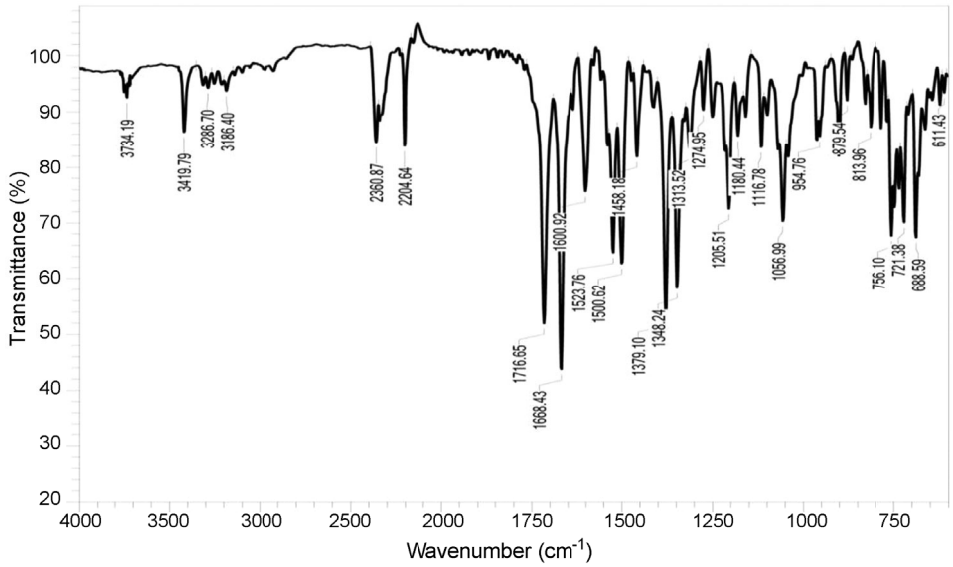


Fig. 4 — IR spectrum of OPD-1 Cu complex

Table 1 — Some physical parameters of synthesized metal complexes

Code	Metal	Ligand substitution	Molecular formula	Molecular weight	Melting point (°C)
OPD-1 Cu	Cu(II)	p-CH_3	$C_{52}H_{44}O_8N_6Cu$	944	325
OPD-1 Ni	Ni(II)		$C_{52}H_{48}O_{10}N_6Ni$	974	336
OPD-1 Co	Co(II)		$C_{52}H_{48}O_{10}N_6Co$	975	332

Table 2 — Some thermodynamic parameters evaluated from TG thermograms for synthesized metal complexes

Complex	Sample amount (mg)	Stage	Initial decomposition temperature (°C)	Temperature range (°C)	Mass loss from TG	Theoretical mass loss	Probable assignment	Residual weight at 1000 °C (mg)
OPD-1 Cu	5.621	1	100	0-115	3.43	3.81	Loss of two water molecules	0.528
		2		115-300	87.18	87.77	Loss of parts of ligand molecule	
		3		300-900	90.61	91.58	Loss of parts of ligand molecule	
OPD-1 Ni	4.892	1	120	0-140	7.15	7.39	Loss of four water molecules	0.417
		2		140-350	84.59	84.95	Loss of parts of ligand molecule	
		3		350-900	91.74	92.34	Loss of parts of ligand molecule	
OPD-1 Co	5.921	1	115	0-135	7.13	7.38	Loss of four water molecules	0.513
		2		135-300	84.29	84.94	Loss of parts of ligand molecule	
		3		300-850	91.33	92.32	Loss of parts of ligand molecule	

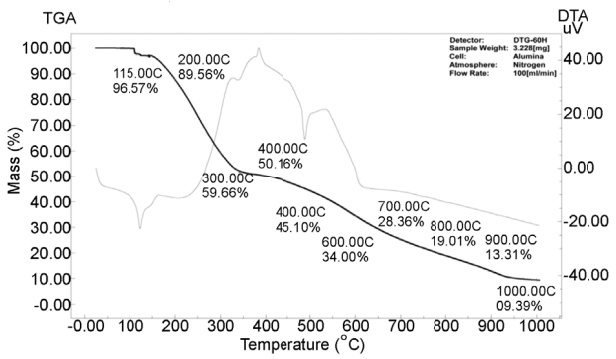


Fig. 5 — TG and DTA plots of OPD-1 Cu complex

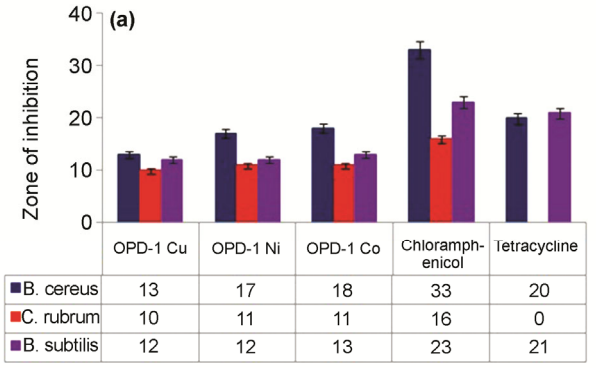
indicates that the change in metal complexes. The second broad peak is start after 300 °C which indicates continuous change in metal complexes.

Antimicrobial, antibacterial and antifungal activity

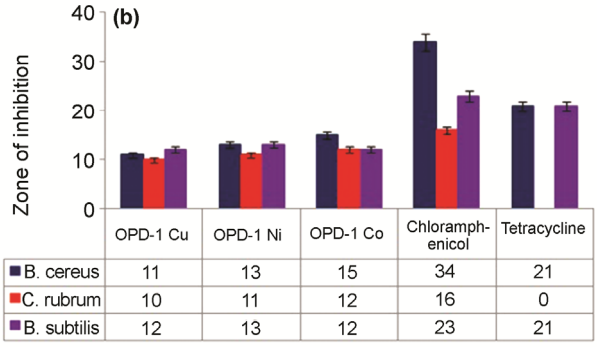
The entire synthesized metal complexes were subjected for antimicrobial activity against selected bacterial and fungal strains in DMF and DMSO solvents. For better understanding, the antimicrobial activity of the synthesized metal complex was compared with standard antibiotics such as chloramphenicol and tetracycline. In case of antifungal activity, as standard antibiotics nystatin and itraconazole were used. For antimicrobial activity, agar well diffusion method was used. In this method, the solution of the synthesized metal complexes were dissolved in appropriate solvent likes DMF and DMSO and then injected in growing colony of microorganisms in Petriplates. The organisms were maintained on nutrient agar and MGYP medium (Hi Media, INDIA) for bacteria and fungi, respectively, at 4 °C and were sub-cultured before use. For the antimicrobial activity, solution of synthesized metal complex was prepared in dry DMF and DMSO in range of concentration 20 μg/mL.

The crystalline products were subjected to antibacterial activities against some selected gram positive likes *Bacillus cereus (BC), Corynebacte riumrubrum* (*CR*) and *Bacillus subtilis* (*BS*). As gram negative four strains like *Klebsiella pneumoniae* (*KP*), *Staphylococcus typhimurium* (*ST*) and *Pseudomonas aeruginosa* (*PA*) were selected. The synthesized compounds were also subjected for antimicrobial activity against selected fungal strains like *Candida albicans* (*CA*), *Candida glabrata* (*CG*) and *Cryptococcus neoformans* (*CN*). The organisms were maintained on nutrient agar and MGYP medium (Hi Media, India) for bacteria and fungi respectively, at 4 °C and were sub-cultured before use.

The graphical representations of antibacterial activity of synthesized metal complexes against selected bacterial strains are given in Fig. 6 (a) and (b) for DMF and DMSO media, respectively. From the Fig. 6a, it is observed that all the synthesized metal complexes showed inhibition against selected bacterial strains. Further, it is observed that the OPD-1 Co complex (metal complex of cobalt with ligand) showed higher inhibition against all gram positive bacterial strains in DMF. However, OPD-1 Cu (metal complex of copper with ligand) and OPD-1



	OPD-1 Cu	OPD-1 Ni	OPD-1 Co	Chloramph-enicol	Tetracycline
B. cereus	13	17	18	33	20
C. rubrum	10	11	11	16	0
B. subtilis	12	12	13	23	21



	OPD-1 Cu	OPD-1 Ni	OPD-1 Co	Chloramph-enicol	Tetracycline
B. cereus	11	13	15	34	21
C. rubrum	10	11	12	16	0
B. subtilis	12	13	12	23	21

Fig. 6 — Antimicrobial screening of synthesized metal complex against selected positive bacterial strains in (a) DMF and (b) DMSO

Ni (metal complex of nickel with ligand) showed lower inhibition as compared OPD-1 Co complex. It is clear that against *Corynebacterium rubrum* in DMF, OPD-1 Ni and OPD-1 Co complexes showed maximum and almost same extent of inhibition. Against *Bacillus subtilis*, OPD-1 Cu and OPD-1 Ni showed same extent of inhibition in DMF. However, none of the metal complex showed higher inhibition as compared to standard antibiotics.

From the Fig. 6b, it is observed that the again OPD-1 Co showed higher inhibition against *Bacillus cereus* and *Corynebacterium rubrum* in DMSO. In DMSO, all metal complexes also exhibited inhibition but low as compared to standard antibiotics. Against *Bacillus subtilis,* OPD-1 Ni showed higher in inhibition as compared to rest of two metal complexes, OPD-1 Cu and OPD-1 Co. Out of the three complexes, OPD-1 Cu, showed minimum inhibition against *Bacillus cereus* and *Corynebacterium rubrum* in DMSO. Hence, it is clear that solvent also plays an important role in antibacterial activity.

The zone of inhibition plots of synthesized metal complex against some selected gram negative bacterial strains in DMF and DMSO are shown in Fig. S1 in Supplementary Data. It is observed that all the synthesized metal complexes showed good to moderate biological activity against *Klebsiella pneumonia,* and *Staphylococcus typhimurium*. OPD-1 Co complex showed maximum inhibition whereas OPD-1 Ni showed minimum inhibition against all three tested bacterial strains in DMF. However, none of the metal complex showed inhibition higher than that of standard antibiotics used as reference material in anti microbial study. In DMSO, once again OPD-1 Co complex showed higher inhibition against all three selected gram negative bacterial strains in compare to OPD-1 Cu and OPD-1 Ni complex.

The antifungal activity of the metal complexes against selected fungal strains in DMF and DMSO are graphically shown in Fig. S2 (Supplementary Data). From this figure, it is observed that all compounds showed good to moderate inhibition against selected fungal strains in DMF and DMSO solvents. From Fig. S2a, it is observed that the OPD-1 Co complex showed the maximum and OPD-1 Cu showed the minimum inhibition against *Candida albicans*, *Candida glabarata* and *Cryptococcus neoformans* in DMF. As shown in Fig. S2b, OPD-1 Ni complex showed the maximum inhibition against *Candida albicans* and *Cryptococcus neoformans* in DMSO. OPD-1 Cu complex showed the minimum inhibition against *Candida albicans*, *Candida glabarata* and *Cryptococcus neoformans* in DMSO. However, in comparison with reference compounds, all synthesized complexes show lower antifungal activity. Antimicrobial activities of all the metal complexes were carried out by Agar well diffusion method in preparative petridishes as shown in Fig. S3 in Supplementary Data.

Conclusions

In the present study, transition metal complexes such as Cu(II), Co(II) and Ni(II) were prepared with synthesized (E)-2-hydroxy-5-(3-(1-phenyl-3-(p-tolyl)-1H-pyrazol-4-yl)acryloyl)benzamide. From thermal study of metal complexes, it is observed that degradation of these metal complexes is a multi step process and the metal complexes are stable up to 300 °C. From the degradation pattern and loss of %residue it is concluded that in copper metal complex have two coordinate water molecules where as in cobalt and nickel metal complexes have four coordinate water molecules. Further, from the antimicrobial screening; it is observed that the metal complexes showed good to moderate biological activity against selected bacterial and fungal strains in DMF and DMSO.

Supplementary Data

Supplementary Data associated with this article are available in the electronic form at http://nopr.niscair.res.in/jinfo/ijca/IJCA_60A(03)332-340_SupplData.pdf.

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