

Synthesis, Characterization and Biological Evaluation of Schiff Base Transition Metal Complexes Derived from 4-Nitrobenzene-1,2-diamine and 5-Chloroisatin

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A series of transition metal complexes of the type $[MLX_2]$, where $M = \text{Mn(II), Fe(II), Co(II), Ni(II)}$, $X = \text{Cl}^-/\text{CH}_3\text{COO}^-$ and $L =$ Schiff base derived from 4-nitrobenzene-1,2-diamine and 5-chloroisatin have been synthesized and characterized by elemental analysis, molar conductance, IR, UV-visible, magnetic moments measurement, ^1H & ^{13}C NMR and mass spectral studies. On the basis of physico-chemical studies and spectral evaluation, an octahedral geometry have been proposed for all metal(II) complexes. The antimicrobial activity of ligand and its metal complexes have been additionally screened against bacteria and fungi. Metal(II) complexes show good activity as compared to ligand towards studied microorganisms and also metal complexes checked for their catalytic properties for benzylation of phenol.

Keywords: Schiff base, Transition metal(II) complexes, 4-Nitrobenzene-1,2-diamine, 5-Chloroisatin, Antimicrobial activity.

INTRODUCTION

Interest in the bioinorganic chemistry of transition metals have increased recently, with the discovery of two new metallo-enzymes which contain nickel at their active sites, bringing to six the number of established metal containing enzymes [1]. Isatin (1*H*-indole-2,3-dione) is an endogenous polyfunctional heterocyclic compound, which consist two type of carbonyl groups *i.e.* keto and lactum [2,3]. Isatin due to its *cis*- α -dicarbonyl moiety is a potentially good substrate for the synthesis of transition metal complexes either alone or deprotonated, it has also been found in mammalian tissues [4-6]. Isatin pharmacophore is used to prepare large number of heterocyclic compound and used as a starting material for synthesis of infinite drug molecules [7,8].

Isatin is a good class of biologically active compounds with tolerance to humans [9,10] and a good platform for structure modification and derivatization of other compounds. Isatin derivatives exhibit biological actions including anticancer [11], antidepressant [12], antifungal [13], anti-HIV [14], anti-inflammatory [15], anticonvulsant [16], antimicrobial [17], antiviral [18] and antitubercular [19,20]. 5-Substituted isatin

of Schiff base has been found to be biological active against *P. aeruginosa* [21]. It has been found that the nature of substituent at 2- or 3-position of indole plays an important role in modulating their anti-inflammatory action [22-26]. At present time the coordination of Schiff bases with transition metal ions has been extensively studied in medicine and diagnostics [27]. Substituted heterocyclic compounds in combination with transition metal salts generate coordination compound, which possess enhance pharmacological properties [28], nucleolytic activity [29], molecular magnets, catalysts [30-32], *etc.*

On account of these importance of metal complexes, herein, the synthesis, characterization and antimicrobial activities of transition metal(II) complexes of Schiff base obtained by the condensation of 5-chloroisatin and 4-nitrobenzene-1,2-diamine in molar ratio (2:1) in ethanol is reported. Moreover, two of the synthesized Schiff base metal (II) (Cu^{2+} & Ni^{2+}) complexes were utilized as catalysis for benzylation of phenol.

EXPERIMENTAL

All the synthetic chemicals utilized were of reagent grade and utilized as received. 4-Nitrobenzene-1,2-diamine and

5-chloroisatin were procured from Sigma-Aldrich. Hydrated metal(II) salts, methanol, ethanol and diethyl ether were purchased from Qualigens. IR spectra were recorded utilizing KBr plate ($4000\text{--}400\text{ cm}^{-1}$) on a Shimadzu 8300 IR spectrometer. Electronic assimilation spectra in the range $200\text{--}900\text{ nm}$ were acquired in ethanol on a Systronic UV-Visible spectrometer. ^1H NMR of ligand (in $\text{DMSO-}d_6$) was recorded on a Bruker Advance II 400 NMR spectrometer regarding TMS. The mass spectra were recorded on Agilent Q-TOF LC-MS mass spectrometer. The molar conductance estimation were resolved in DMSO (10^{-3}M) at room temperature utilizing Jenway Model 4070 conductivity meter.

Synthesis of Schiff base ((3'Z)-3,3'-(4-nitro-1,2-phenylene)-bis(azan-1-yl-1-ylidene)bis(5-chloroindolin-2-one) (1): Ethanolic solution (50 mL) of 4-nitrobenzene-1,2-diamine (0.755 g, 5 mmol) and ethanolic solution (50 mL) of 5-chloroisatin (1.81 g, 10 mmol) were mixed dropwise with constant stirring. The subsequent arrangement was mixed for 0.5 h and afterward refluxed in 100 mL round bottom flask at $60\text{--}80^\circ\text{C}$ for 3 h. The progress of the reaction response was observed by TLC using chloroform:methanol (95:5). The solid compound was separated off, washed with water, ethanol and diethyl ether and finally dried in vacuum desiccator over anhydrous CaCl_2 (Scheme-I). Yield: 65.5%, m.p.: 262°C , brownish solid. Anal. calcd. (found) for $\text{C}_{22}\text{H}_{11}\text{N}_5\text{O}_4\text{Cl}_2$ (m.w. 479.02): C, 55.02 (55.23); H, 2.31 (2.18); N, 14.58 (14.61).

Synthesis of $[\text{MnL}(\text{OAc})_2]$ complex (1): Ligand (L) (0.479 g, 1 mmol) in hot ethanol (30 mL) and ethanolic solution of $\text{Mn}(\text{OAc})_2 \cdot 4\text{H}_2\text{O}$ (0.245 g, 1 mmol) were mixed dropwise for 1 h. The subsequent solution was refluxed in 100 mL round bottom flask for 6 h and then separated out the dim dark grey coloured solid, washed with cold ethanol and afterward with diethyl ether, dried in vacuum desiccator over anhydrous CaCl_2 . Yield: 64.5%; m.p.: 262°C (dec.). Anal. calcd. (found) % for $\text{C}_{26}\text{H}_{17}\text{N}_5\text{O}_8\text{Cl}_2\text{Mn}$ (m.w. 653.98): C, 47.80 (47.67); H 2.62 (2.57); N, 10.72 (10.68); Mn, 8.41 (8.38); Cl, 10.85 (10.90). Molar conductance: $8.2\ \Omega^{-1}\text{ cm}^2\text{ mol}^{-1}$. μ_{eff} : 4.85 B.M. UV-Vis (DMF) λ_{max} : 625, 504, 482 and 375 nm.

Synthesis of $[\text{FeLCl}_2]$ complex (2): Hot ethanolic solution of ligand (0.479 g, 1 mmol) in 30 mL and $\text{FeCl}_2 \cdot 2\text{H}_2\text{O}$ (0.1628 g, 1 mmol) in 20 mL ethanol were mixed together. The subsequent solution was refluxed in 100 mL round bottom flask for 6–7 h. The dark black solid was washed with cold ethanol (5 mL) and dried in vacuum desiccator over anhydrous CaCl_2 . Yield 49%; m.p.: 285°C (dec.). Anal. calcd. (found) % for $\text{C}_{22}\text{H}_{11}\text{N}_5\text{O}_4\text{Cl}_4\text{Fe}$

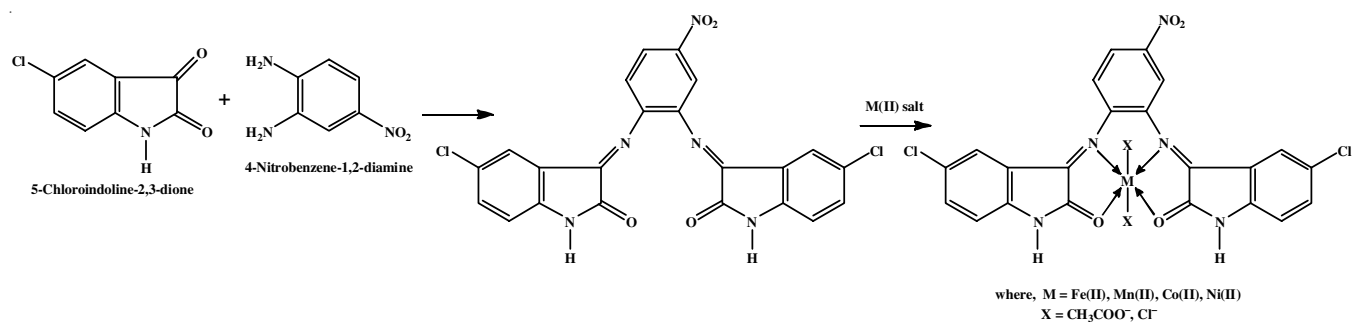
(m.w.: 604.89): C, 43.53 (43.43), H, 1.83 (1.79); N, 11.54 (11.51); Fe, 9.20 (9.23); Cl, 23.36 (23.39). Molar conductance: $7.9\ \Omega^{-1}\text{ cm}^2\text{ mol}^{-1}$. μ_{eff} : 5.12 B.M. UV-Vis (DMF) λ_{max} : 672 and 554 nm.

Synthesis of $[\text{CoL}(\text{OAc})_2]$ complex (3): To hot ethanolic solution of ligand (0.479 g, 1 mmol) in 30 mL and the solution of $\text{Co}(\text{OAc})_2 \cdot 2\text{H}_2\text{O}$ (0.249, 1 mmol) in 20 mL ethanol were mixed for 0.5 h and then refluxed in round bottom flask for 6 h. The dark brown solid washed with ethanol, diethyl ether and dried in desiccator over anhydrous CaCl_2 . Yield 66.1%; m.p.: 295°C (dec.). Anal. calcd. (found) % for $\text{C}_{26}\text{H}_{17}\text{N}_5\text{O}_8\text{Cl}_2\text{Co}$ (m.w.: 657.98): C, 47.51 (47.41); H 2.61 (2.56); N, 10.66 (10.57); Co, 8.97 (8.89), Cl, 10.79 (10.87). Molar conductance: $3.5\ \Omega^{-1}\text{ cm}^2\text{ mol}^{-1}$. μ_{eff} : 4.2 B.M. UV-Vis (DMF) λ_{max} : 807, 610, 450 and 378 nm.

Synthesis of $[\text{NiLCl}_2]$ complex (4): An ethanolic solution of $\text{NiCl}_2 \cdot 6\text{H}_2\text{O}$ (0.237 g, 1 mmol) in 30 mL was mixed to a hot solution of ligand (0.479, 1 mmol) in 30 mL ethanol. The solution was refluxed in round bottom flask for 8 h. The light brown coloured solid product was obtained and then washed with cold ethanol, diethyl ether and finally dried in vacuum desiccator. Yield 59.9%; m.p.: 292°C (dec.). Anal. calcd. (found) for $\text{C}_{22}\text{H}_{11}\text{N}_5\text{O}_4\text{Cl}_4\text{Ni}$ (m.w.: 606.89): C, 43.33 (43.31), H, 1.82 (1.80), N, 11.48 (9.57); Ni, 9.62 (9.67), Cl, 23.25 (23.32). Molar conductance: $5.6\ \Omega^{-1}\text{ cm}^2\text{ mol}^{-1}$. μ_{eff} : 3.31 B.M. UV-Vis (DMF) λ_{max} : 678, 490 and 373 nm.

Biological activities

Antimicrobial activity: Antimicrobial screening of all the metal(II) complexes were evaluated using agar well diffusion method [33]. The biological activity of ligand and its metal complexes and standard drugs (antibacterial Imipenem and antifungal miconazol) were studied against the *Staphylococcus aureus*, *Bacillus subtilis* (Gram-positive) and *Pseudomonas aeruginosa*, *Escherichia coli*, *Salmonella typhi* (Gram-negative) and fungi *Rizoctonia* sp., *Aspergillus* sp., *Penicillium* sp. All strains were obtained from Microbial Type Collection and Gene Bank, Institute of Microbial Technology (IMTECH) Chandigarh, India. The solution of different concentration 1, 1.5 and 2 mg/mL of each compound (free ligand, its metal(II) complexes and standard drug Imipenem and miconazole) in DMSO was prepared for testing against spore germination of fungi and bacteria. Centrifuged pellets of microorganism from a 24 h old culture containing approximately 10^4 cfu/mL were spread on the surface of Muller-Hinton agar media plates. Wells with 6 mm diameter



Scheme-I: Synthesis of Schiff base ligand and its transition metal(II) complexes

made, then solution of test compound was filled to the wells. The plates were incubated at 30 °C for 24 h. The activity of the compounds was determined by measuring diameter of the inhibition zone (in mm) each test was carried in triplicate [33,34].

Catalytic studies of cobalt(II) and nickel(II) complexes towards benzoylation of phenol: The catalytic activities of newly synthesized Co(II) and Ni(II) complexes were tested for conversion towards the benzoylation of phenol. Both the complexes indicated great reactant action. The activity of cobalt (II) complex was by one way or another more noteworthy than that of nickel(II) complex. So as to show up at reasonable response conditions for most extreme change to phenyl benzoate, an ideal catalyst load was utilized. Likewise, the impact of response temperature and time on the transformation productivity was examined.

RESULTS AND DISCUSSION

Condensation reaction of 5-chloroisatin (2 mol) with 4-nitrobenzene-1,2-diamine (1 mol) in ethanol at 60-80 °C gives Schiff base ligand in a moderate yield (**Scheme-I**). The synthesized ligand and its metal complexes are stable at room temperature in solid state. The ligand is soluble in common organic solvents while metal(II) complexes are soluble in DMSO and DMF.

IR spectral studies: The key IR spectral bands of ligand and its metal(II) complexes are given in Table-1. The IR spectra of the ligand showed the absorption at 1615 cm⁻¹, demonstrating the nearness of azomethine group vibration $\nu(\text{C}=\text{N})$. There is no stretching of unreacted NH₂ group in IR spectra of ligand demonstrate the amalgamation of proposed ligand. The IR spectra of metal(II) complexes show huge changes when coordinated with the free ligand. In the IR spectra of all the metal(II) complexes, groups of azomethine group ($-\text{C}=\text{N}$) moved by 5-10 cm⁻¹, proposing coordination through nitrogen atom of azomethine group. This is additionally upheld by the nearness of new groups in the range of 490-475 cm⁻¹, which demonstrate the coordination of nitrogen to the metal $\nu(\text{M}-\text{N})$ vibration. No band was appeared 1711 cm⁻¹ in the IR spectra of metal(II) complexes. The coordination of oxygen molecule of carbonyl group is additionally demonstrated by the appearance of new band at 540-506 cm⁻¹, which might be due to $\nu(\text{M}-\text{O})$ vibration. In the IR spectra of complexes of $[\text{MnL}(\text{OAc})_2] \cdot 2\text{H}_2\text{O}$ and $[\text{CoL}(\text{OAc})_2] \cdot 2\text{H}_2\text{O}$, the two characteristic bands appeared in the range 1565-1350 cm⁻¹, which might be due to $\nu(\text{COO}^-)$. A contrast between the frequencies is 215 cm⁻¹, which is more than 144 cm⁻¹ and proves the coordination of acetate group as unidentate ligand to the metal.

¹H NMR spectral studies: The ¹H NMR analysis of ligand was recorded in DMSO-*d*₆ and its values are given in Table-2. In ¹H NMR range of the ligand, no sign was observed related to essential amine proton, which recommend the arrangement of ligand.

Electronic spectral studies: The electronic spectra of Mn(II) complex shows an absorption band in the region 486-441 and 540-510 nm attributed to ${}^6\text{A}_{1g} \rightarrow {}^4\text{T}_{2g}$ and ${}^6\text{A}_{1g} \rightarrow {}^4\text{T}_{1g}$

TABLE-1
KEY IR SPECTRAL BANDS (cm⁻¹) OF LIGAND
AND ITS METAL(II) COMPLEXES

Compound	(-OH/ H ₂ O)	(C=N) azo	(C=O)	(M-N)	(M-O)
L	—	1615	1711	—	—
$[\text{MnL}(\text{OAc})_2] \cdot 2\text{H}_2\text{O}$	3428	1609	1698	455	530
$[\text{NiLCl}_2]$	—	1606	1702	460	507
$[\text{FeLCl}_2]$	3432	1608	1704	473	518
$[\text{MnL}(\text{OAc})_2] \cdot 2\text{H}_2\text{O}$	3435	1610	1695	479	522

TABLE-2
¹H NMR SPECTRAL DATA OF THE LIGAND (DMSO-*d*₆)

Compound	¹ H NMR (δ , ppm)
Ligand L	6.33-7.72 (m, 9H, Ar-H), 7.8 (d, 1H, N-H)

(G) transition, respectively which indicate the octahedral geometry of the complex [35]. The magnetic moment value for Mn(II) complex was found to be 4.85 B.M.. The electronic spectrum of Fe(II) complex displays two absorption bands at 710-672 and 590-554 nm, which are assigned to ${}^5\text{T}_{2g} \rightarrow {}^5\text{E}_g$ transitions. Also the band at 390 nm is assigned to L $\rightarrow$ M charge transfer. The observed magnetic moment of 5.12 B.M. is consistent with an octahedral geometry. The electronic spectra of cobalt(II) complex indicated three groups at 1200-1051, 700-622 and 489-433 nm, which might be due to ${}^4\text{T}_{1g} \rightarrow {}^4\text{T}_{2g}$ (F), ${}^4\text{T}_{1g} \rightarrow {}^4\text{T}_{1g}$ (P) and ${}^4\text{T}_{1g} \rightarrow {}^3\text{A}_{2g}$ (F), respectively, magnetic moment values in the range 3.2-3.5 B.M. suggesting an octahedral geometry around Co(II) ion [36-38]. The nickel(II) complex displayed three bands at 1145-1054, 706-695 and 461-443 nm attributed due to ${}^3\text{A}_{2g}$ (F) $\rightarrow$ ${}^3\text{T}_{2g}$ (F) (ν_1), ${}^3\text{A}_{2g}$ (F) $\rightarrow$ ${}^3\text{T}_{1g}$ (F) (ν_2) and ${}^3\text{A}_{2g}$ (F) $\rightarrow$ ${}^3\text{T}_{2g}$ (P) (ν_3) and magnetic moment is 3.12 B.M., which indicate that nickel(II) complex also exhibits the octahedral geometry.

Mass spectral studies: The proposed atomic fragments of synthesized complexes were confirmed by contrasting their sub-atomic weight and *m/z* values. The molecular weight of ligand and its metal(II) complexes were found to be: (i) *m/z* = 479.02 (ligand); (ii) *m/z* = 652.98 [Fe(II) complex], (iii) *m/z* = 651.98 [Mn(II) complex], (iv) *m/z* = 655.97 [Co(II) complex], (v) *m/z* = 654.98 [Ni(II) complex]. These information in great concurrence with proposed sub-atomic ratio for these complexes.

Molar conductance: All the metal (II) complexes were dissolved in DMSO and molar conductivity of 10⁻³ M at room temperature. The molar conductance values of all the complexes lies in the range 15-30 ohm⁻¹ cm² mol⁻¹ related to non-electrolytic nature of all complexes [38].

Impact of catalyst amount on the reaction kinetics of phenol benzoylation: The impact of catalyst using different concentration at different temperature on the yield of phenyl benzoate is shown in Tables 3 and 4. The catalyst load which indicated the most elevated reaction during the test response was utilized for the fixed amount of phenol (0.01 mol, 0.94 g) and benzoyl chloride (0.01 mol, 1.41 g). At concentration of 2.5 $\times$ 10⁻⁵ mol gave similar results in the two cases with about 58.33% and 36.73% transformation to phenyl benzoate at 313 K for Co(II) and Ni(II) complexes, respectively. Lower catalyst amount yields poor transformation. The transformation incre-

TABLE-3
EFFECT OF CATALYST AMOUNT ON % YIELD OF
PHENYL BENZOATE (REACTION TEMPERATURE
313 K) AND REACTION TIME 30 min

Catalyst load (mol)	[CoL(OAc) ₂]	[NiLCl ₂]
1.0×10^{-5}	26.14	30.73
2.0×10^{-5}	45.23	32.45
2.5×10^{-5}	65.25	36.73

TABLE-4
EFFECT OF TEMPERATURE ON CONVERSION
% YIELD OF PHENYL BENZOATE, REACTION
TIME 30 min, CATALYST LOAD 1×10^{-5} mol

Temperature (K)	[CoL(OAc) ₂]	[NiLCl ₂]
300	41.85	32.48
313	92.88	37.12
318	45.21	33.02

ments with catalyst however in the long run reduces at high temperature.

Biological activity studies

Antifungal activity: The antifungal activity of synthesized Schiff base ligand and its metal(II) ion complexes exhibited a considerable enhancement against *Aspergillus* sp., *Rizoctonia* sp. and *Penicillium* sp. at 1.0, 1.5 and 2.0 mg/mL concentration (Table-5). The activity is greatly enhanced at the higher concentration. The metal complexes show better activity than the ligand [39]. The antifungal results of the compounds were also compared with the standard antifungal drugs miconazole.

Antibacterial activity: The Schiff base ligand, its metal complexes, standard drug Imipenem and DMSO solution control were screened for their antibacterial activity against the bacteria *Staphylococcus aureus* and *Bacillus subtilis* and *Pseudomonas aeruginosa*, *Escherichia coli* and *Salmonella typhi*. From the bactericidal activity, it is apparent that all the metal(II) complexes

were more effective towards Gram-positive strains than Gram-negative strains because the walls of Gram-negative cells are more complexed than Gram positive cells. Antibacterial activity of all the complexes towards Gram-positive and Gram-negative bacteria is quite significant. Further, the ligand showed moderate while its metal(II) complexes exhibited moderate to high activities as compared to standard drug towards the all organism (Table-6). This may be due to the presence of -NH group, which plays an important role in the biological activity and this group is believed to impart the transformation reaction in biological system. Coordination reduces the polarity of the metal ions due to the partial sharing of its positive charge with the donor group within the chelate ring system [40]. This process, in turn increases the lipophilic nature of the central metal atom, which subsequently favours its permeability through the lipid layer of cell membrane and blocking the metal binding sites on enzymes of microorganism [41,42]. In the present study, low activity of the some metal(II) complexes is due to their low lipophilicity, because of which penetration of the complex through the lipid membrane was decreased and hence, they could neither block nor inhibit the growth of the microorganism.

Conclusion

In this work, four transition metal(II) complexes of Schiff base have been synthesized and characterized by elemental analysis, spectral techniques such as FTIR, ¹H & ¹³C NMR, UV/visible and mass spectral studies. The spectral data of newly synthesized compounds are in the favour of an octahedral geometry of the complexes. The antimicrobial (antibacterial and antifungal) studies revealed that the metal(II) complexes were more biologically active than free ligand. Among the synthesized metal(II) complexes, Ni(II) complex [Ni(C₂₂H₁₁N₅O₄Cl₂)OAc₂] shows best antimicrobial activity against the tested microorganisms. The industrial applications of Co(II) and Ni(II)

TABLE-5
FUNGICIDAL SCREENING DATA OF THE SYNTHESIZED LIGAND AND ITS METAL(II) COMPLEXES

Compound	Inhibition of spore germination (%)								
	<i>Aspergillus</i> sp. (mg/mL)			<i>Penicillium</i> sp. (mg/mL)			<i>Rizoctonia</i> sp. (mg/mL)		
	1.0	1.5	2.0	1.0	1.5	2.0	1.0	1.5	2.0
C ₂₂ H ₁₁ N ₅ O ₄ Cl ₂	42	50	55	23	31	36	44	50	53
[Mn(C ₂₂ H ₁₁ Cl ₂ N ₅ O ₄)OAc ₂]	51	61	78	54	59	71	48	51	60
[Ni(C ₂₂ H ₁₁ Cl ₂ N ₅ O ₄)OAc ₂]	82	86	93	72	77	86	68	72	79
[Co(C ₂₂ H ₁₁ Cl ₂ N ₅ O ₄)OAc ₂]	62	66	71	55	59	67	56	58	60
[Fe(C ₂₂ H ₁₁ Cl ₂ N ₅ O ₄)OAc ₂]	75	85	87	65	70	82	59	64	66
Miconazole (standard)	57	69	100	65	78	83	76	82	94

TABLE-6
BACTERICIDAL SCREENING DATA OF THE SYNTHESIZED LIGAND AND ITS METAL(II) COMPLEXES (INHIBITION ZONE IN mm)

Microorganism	Ligand	Mn(II) complex	Ni(II) complex	Co(II) complex	Fe(II) complex	Imipenem (std. drug)
Gram-positive						
<i>Staphylococcus aureus</i>	32	41	82	52	58	100
<i>Bacillus subtilis</i>	33	40	80	48	56	100
Gram-negative						
<i>Escherichia coli</i>	09	36	59	22	48	100
<i>Salmonella typhi</i>	09	38	54	21	31	100
<i>Pseudomonas aeruginosa</i>	06	32	51	30	35	100

Excellent activity (90-100% inhibition), Good activity (60-70% inhibition), Significant activity (30-50% inhibition), negligible activity (08-20% inhibition).

complexes were studied for their catalytic activities towards benzoxylation of phenol. The conversion of phenol to phenyl benzoate was enhanced by increasing the loaded catalyst. The conversion data showed that both complexes have only mild conversion efficiency.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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