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Cd (II) complex of some novel 5-nitroimidazole derivatives: Synthesis, characterization and antibacterial activity

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ABSTRACT

Background: Bacterial resistance development to the existing drugs has encouraged the search for novel targets. The novel metal complexes and their derivatives may represent an interesting approach for designing new antibacterial drugs. This may be due to the dual mechanism of both ligands and metal ion interacting in different stages of life cycle of bacteria.The aim of the present work was to synthesize a novel series of Cd (II) complexes of 2-(1-substituted-5-nitro-1*H*-imidazol-2-yl)-1-substitutedethanone and evaluate their *in-vitro* antibacterial activity. **Methods:** The metal-ligand complexes of cadmium have been synthesized in good yield. Synthesized complexes were evaluated *in-vitro* for their antibacterial activity by agar well diffusion method. **Results:** All the synthesized compounds were characterized by IR, ^{1}H NMR, mass spectra and molar conductance. Some of the metal complexes were found to be moderately active against Gram-positive bacteria, *B. pumilus* ATCC 14884 and *S. aureus* ATCC 29737. **Conclusion:** Cd (II) complexes of 2-(1-substituted-5-nitro-1*H*-imidazol-2-yl)-1-substitutedethanone have been synthesized and characterized. The synthesized complexes show inhibitory activity against only Gram-positive bacteria.

KEYWORDS: Cadmium (II) complex; 5-nitroimidazole; Antibacterial activity.

1. INTRODUCTION

It is well known that chelating ligands containing N, O and S atoms play a key role in the coordination of metals at the active sites of numerous metallobiomolecules[1]. Literature survey also reveals that coordination of metal ions to biologically active compounds may enhance their activities[2, 3]. Imidazole derivatives have often been used as chelating ligands in the field of coordination chemistry and their metal complexes are of special interest for many years because of the variety of ways in which they are bonded to metal ions. It was found that the complexes of transition metal salts with imidazole derivatives showed greater antimicrobial activity than the ligands applied alone [4-6].

There is substantial interest in the coordination chemistry of cadmium complexes because of the toxic environmental impact of cadmium[7, 8]. Some cadmium complexes with various ligands were found to show biological properties, such as antibacterial and antifungal activities [9, 10].

Following all these observations and as a part of our continuing work on 5-nitroimidazole complexes containing N and O donor atoms[11-13] and in light of the importance of Cd ion metal, herewith, we are reporting the synthesis and characterization of cadmium (II) complexes of the 2-(1-substituted-5-nitro-1*H*-imidazol-2-yl)-1-substitutedethanone derivatives. The development of resistance to current antibacterial therapy needs the discovery of more effective agents. So in continuing effort to find more potent antibacterial agent, herein, antibacterial activity of the prepared metal-ligand complexes was evaluated against two gram (+)ve bacterial strains and one gram (-)ve isolate.

2. MATERIALS AND METHODS

2.1. Chemicals and reagents

All the chemicals and solvents (reagent grade) obtained commercially from Loba company used without further purification. All the ligands were prepared following the same procedure described in a previous paper [12].

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2.2. Physical measurements

All the melting points were determined in open capillaries and are uncorrected. Molar conductance was measured on Conductivity Bridge, Systronics. IR spectra were recorded in KBr on Shimandzu Fourier Transform Infrared 8400S spectrophotometer. Mass spectra were recorded on Micromass Q-T, TOF MS ES+4.73e^3. Proton NMR were recorded in DMSO-d_6 on Bruker advance II at 400 MHz using Tetramethylsilane (TMS) as reference standard and the chemical shift are presented in ppm.

2.3. General procedure for the synthesis of metal complexes:

A solution of $CdCl_2$ (5 mM) prepared in hot methanol (50 mL) was added to solution of appropriate ligand (10 mM) dissolved in 50 mL methanol. The pH of the mixture then adjusted to 8-10 with the help of conc. ammonia. The brown colored solution thus formed, refluxed for 4-5 h and then allowed to stand at room temperature to get crystalline compounds. The product then filtered, washed with cooled absolute ethanol, recrystallized from acetonitrile or methanol and dried under vacuum.

Cd(NIMP)$_2$:

Bluish crystals; Yield: 87%; m.p. 212-214 °C; IR (KBr, cm^{-1}): 2977, 2800, 2270, 1570, 1365, 495; MF: $C_{30}H_{34}CdN_6O_{10}S_2$ (815.17); MS: *m/z* 815(M^+); Em ($\Omega^{-1}cm^2mol^{-1}$): 2.20.

Cd(NIMPCl)$_2$:

Brown crystals; Yield: 82%; m.p. 208-210 °C; IR (KBr, cm^{-1}): 2980, 2850, 2250, 1558, 1361, 484; ^{1}H NMR (DMSO-d_6, δ): 1.28 (t, 6H, -$SO_2CH_2CH_3$), 3.20 (q, 4H, -$SO_2CH_2CH_3$), 3.72 (t, 4H, -$CH_2CH_2SO_2C_2H_5$), 4.30 (s, 4H, N=C-CH_2-COAr), 4.90 (t, 4H, N-$CH_2CH_2SO_2C_2H_5$), 7.60-7.84 (m, 8H, Ar-H), 7.87 (s, 2H, C-4 of imidazole); MF: $C_{30}H_{32}Cl_2CdN_6O_{10}S_2$ (884.06); Em ($\Omega^{-1}cm^2mol^{-1}$): 1.60.

Cd(NIMMCl)$_2$:

Reddish brown crystals; Yield: 72%; m.p. 240-243 °C; IR (KBr, cm^{-1}): 2900, 2850, 2248, 1570,1350, 500; MF: $C_{30}H_{32}Cl_2CdN_6O_{10}S_2$ (884.06); MS: *m/z* 884 (M^+), 886 (M^{+2}), 888 (M^{+4}); Em ($\Omega^{-1}cm^2mol^{-1}$): 1.25.

Cd(NIMOCl)$_2$:

Red crystals; Yield: 62%; m.p. 246-248 °C; IR (KBr, cm^{-1}): 2900, 2850, 2230, 1550, 1345, 520; MF: $C_{30}H_{32}Cl_2CdN_6O_{10}S_2$ (884.06); Em ($\Omega^{-1}cm^2mol^{-1}$): 1.10.

Cd(NIMF)$_2$:

Dark brown crystals; Yield: 73%; m.p. 232-235 °C; IR (KBr, cm^{-1}): 2980, 2900, 2270, 1545,1360, 510; ^{1}H NMR (DMSO-d_6, δ): 1.40 (t, 6H, -$SO_2CH_2CH_3$), 3.15 (q, 4H, -$SO_2CH_2CH_3$), 3.66 (t, 4H, -$CH_2CH_2SO_2C_2H_5$), 4.26 (s, 4H, N=C-CH_2-COAr), 4.96 (t, 4H, N-$CH_2CH_2SO_2C_2H_5$), 6.54 (d, 2H, C-4 of furan), 6.75 (d, 2H, C-3 of furan), 7.59 (s, 2H, C-5 of furan), 8.10 (s, 2H, C-4 of imidazole); MF: $C_{26}H_{30}CdN_6O_{12}S_2$ (795.09); Em ($\Omega^{-1}cm^2mol^{-1}$): 1.50.

Cd(NIMDF)$_2$:

Brown crystals; Yield: 72%; m.p. 217-218 °C; IR (KBr, cm^{-1}): 2980, 2900, 2270, 1545, 1360, 525; ^{1}H NMR (DMSO-d_6, δ): 3.82 (s, 6H, N-CH_3), 4.30 (s, 4H, N=C-CH_2-COAr), 6.54 (d, 2H, C-4 of furan), 6.75 (d, 2H, C-3 of furan), 7.59 (s, 2H, C-5 of furan), 7.98 (s, 2H, C-4 of imidazole); MF: $C_{20}H_{18}CdN_6O_8$ (582.80); MS: *m/z* 582 (M^+); Em ($\Omega^{-1}cm^2mol^{-1}$): 2.60.

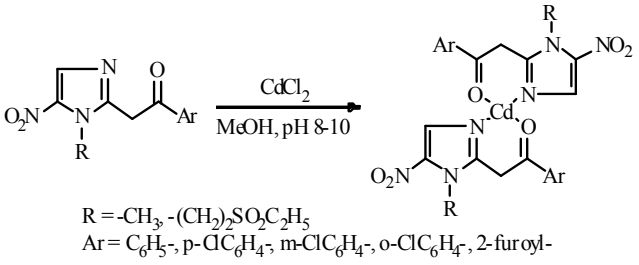
Cd(NIMDP)$_2$:

Red crystals; Yield: 78%; m.p. 222-225°C; IR (KBr, cm^{-1}): 2980, 2900, 2270, 1555, 1340, 512; MF: $C_{24}H_{22}CdN_6O_6$ (602.88); MS: *m/z* 602 (M^+); Em ($\Omega^{-1}cm^2mol^{-1}$): 2.00.

3. RESULTS AND DISCUSSION

3.1. Synthetic approach

The designed metal-ligand complexes were obtained in reasonably good yield by treating various 2-(1-substituted-5-nitro-1*H*-imidazol-2-yl)-1-substitutedethanone (ligand) with cadmium chloride under reflux condition in alkaline pH using methanol as solvent. A synthetic route is shown in scheme 1. All the complexes were air-stable, crystalline solids, soluble in DMSO, DMF and insoluble in all other solvents.



Scheme 1 Synthetic route of metal-ligand complex

3.2. Characterization:

The characterization of complexes have been achieved satisfactory by physical methods and spectral (IR, NMR, mass and conductance) studies.

Preliminary characterization of the ligand and its cadmium complexes was performed by IR spectroscopy. The appearance of new strong signals at about 1700 cm^{-1} confirmed the formation of ligand. The IR spectra of the complexes exhibit a sharp band at 2250-2000 cm^{-1} due to carbonyl group; a positive shift with respect to the corresponding absorption of the free ligand indicates the coordination of the ligand

via N of imidazole and carbonyl O to the metal ion. A signal at 3096-2800 cm^{-1} in the ligand spectrum was ascribed to C-H groups. Two strong signals at 1570-1540 and 1366-1358 cm^{-1} were assigned to the asymmetric and symmetric vibrations of the NO_2 groups of the ligand, respectively. In the spectrum of metal-ligand complex, a new sharp signal at 600-480 cm^{1} was observed that could be assigned to M-O vibrations.

A ^1H NMR spectral study could be considered as a powerful technique for confirming a proposed structure. Accordingly, the ^1H NMR spectra of the ligand and its Cd (II) complexes were recorded. The detailed assignments of the proton of the cadmium complexes confirmed the anticipated structure. The ^{1}HNMR (DMSO-d_6) spectra of metal-ligand complex, displays a triplet and quartet at δ 1.28-1.40 and 3.15 ppm for ethyl group (-$SO_2C_2H_5$), two triplets at δ 3.66-3.89 and 4.96 ppm for two methylene groups (N-$(CH_2)_2SO_2C_2H_5$), a singlet at δ 4.26-4.30 for methylene group (-N=C-CH_2-CO-Ar) and a singlet for proton at C-4 of imidazole ring between δ 7.87-8.1 ppm. All the aromatic protons were found between δ 6.54 to 7.94 ppm as multiplet. In mass spectra of ligand and ligand metal complexes, molecular ions corresponds to molecular weight were observed. The fragmentation routes primarily involved losses of NO (M-30), NO_2 (M-46) and HNO_2 (M-47) from the molecular ion. The higher molecular weight of the compound and results of mass spectroscopy confirms metal to ligand ratio 1:2 perfectly.

The molar conductance values of the synthesized metal-ligand complexes were determined in 10^{-3} M DMF and were in the range of 1.10-2.60 $\Omega^{-1}cm^2mol^{-1}$, which confirms non-electrolytic nature of the complexes[14].

3.3. Antibacterial activity:

All the newly synthesized metal-ligand complexes were tested for their *in vitro* growth inhibitory activity against *B. pumilus,S. aureus* and *S. aboney*. The antibacterial activities of the complexes were evaluated by agar well-diffusion method under standard conditions using Mueller-Hinton agar medium[15]. Sufficient amount of Muller Hinton agar medium were poured into each Petri plate and plates were swabbed with inoculum of microorganisms and kept for 15 minutes. The wells were bored into the seeded agar plates using a sterile cork borer of 8 mm diameter. Then these bores were loaded with synthesized compounds (100 µg/mL) reconstituted in dimethyl sulfoxide. All the plates were incubated at 37 °C for 24h then zone of inhibition were measured (mm). DMSO was used as a negative control, whereas ciprofloxacin and tinidazole were used as positive control. This procedure was done in triplicate for each organism. The results of antibacterial activity are summarized in Table 1.

Table 1. Antibacterial activity of metal-ligand complexes

	*Zone of inhibition (mm)		
	Gram positive		Gram negative
Metal-Ligand Complex	*B. pumilus* ATCC 14884	*S.aureus*ATCC 29737	*S.aboney* NCTC 6017
$Cd(NIMP)_2$	ND#	ND	ND
$Cd(NIMPCl)_2$	ND	ND	ND
$Cd(NIMMCl)_2$	ND	ND	ND
$Cd(NIMOCl)_2$	ND	ND	ND
$Cd(NIMF)_2$	12	10	ND
$Cd(NIMDF)_2$	10	8	ND
$Cd(NIMDP)_2$	12	20	ND
Tinidazole	ND	ND	ND
Ciprofloxacin	28	32	31

**Average of triplicate reading (conc. 100 µg/mL) , #ND - Zone of inhibition not detected*

4. CONCLUSION

The Cd (II) complexes of 2-(1-substituted-5-nitro-1*H*-imidazol-2-yl)-1-substitutedethanone were synthesized by direct reaction of the free ligand with cadmium chloride under reflux condition in good yield. It is evident from antibacterial screening that the some of the investigated compounds displayed moderate *in-vitro* antibacterial activity against Gram-positive bacteria only. In the case of Gram-negative isolate, none metal-ligand complexes exhibited inhibitory activity. This occurs may be due to the difference in the cell wall structure of gram (+)ve and gram (-)ve bacteria.

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