© 2019 IJSRST | Volume 6 | Issue 4 | Print ISSN: 2395-6011 | Online ISSN: 2395-602X
Themed Section: Science and Technology
DOI :https://doi.org/10.32628/IJSRST

Synthesis, Characterization and Biological Activity of Metal Complexes of Novel Schiff Base Bearing Imidazole Moeity

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ABSTRACT

Synthesis of novel metal complexes by reaction of 3-((E)-benzylidene)-amino)-5-(2,5-dimethoxybenzylidene)-2-phenyl-3,5-dihydro-4H-imidazol-4-one with different metal chlorides is accomplished. All the newly synthesized metal complexes were characterized and studied using various techniques viz. ESI Mass, IR, UV and Elemental Analyses. Antimicrobial activity of all metal complexes was evaluated against selected strains of bacteria and fungi.

Keywords: 4H-imidazol-4-one, Schiff base, Metal complexes, Anti-bacterial activity, Anti-fungal activity

I. INTRODUCTION

Imidazol derivatives are an important class of heterocyclic compounds that are known to possess important biological properties. Many drugs and medicinally active compounds incorporate imidazole ring in their scaffold and have been reported to possess a broad spectrum of biological activities such as antifungal [1-3], anti-microbial [4-9], antiviral, anticancer & anti-inflammatory [10-13] activities.

Imidazol derivatives as the ligand easily coordinate to the transition metal ions and have been widely investigated in medicinal field [14, 15]. Metal complexes of Schiff bases bearing imidazole ring have been shown to exhibit difference in activities and may give rise to better medicines [16-19].

In view of above observations, it was thought worthwhile to synthesize new imidazole bearing Schiff base and study its metal complexes to evaluate their biological activity profile.

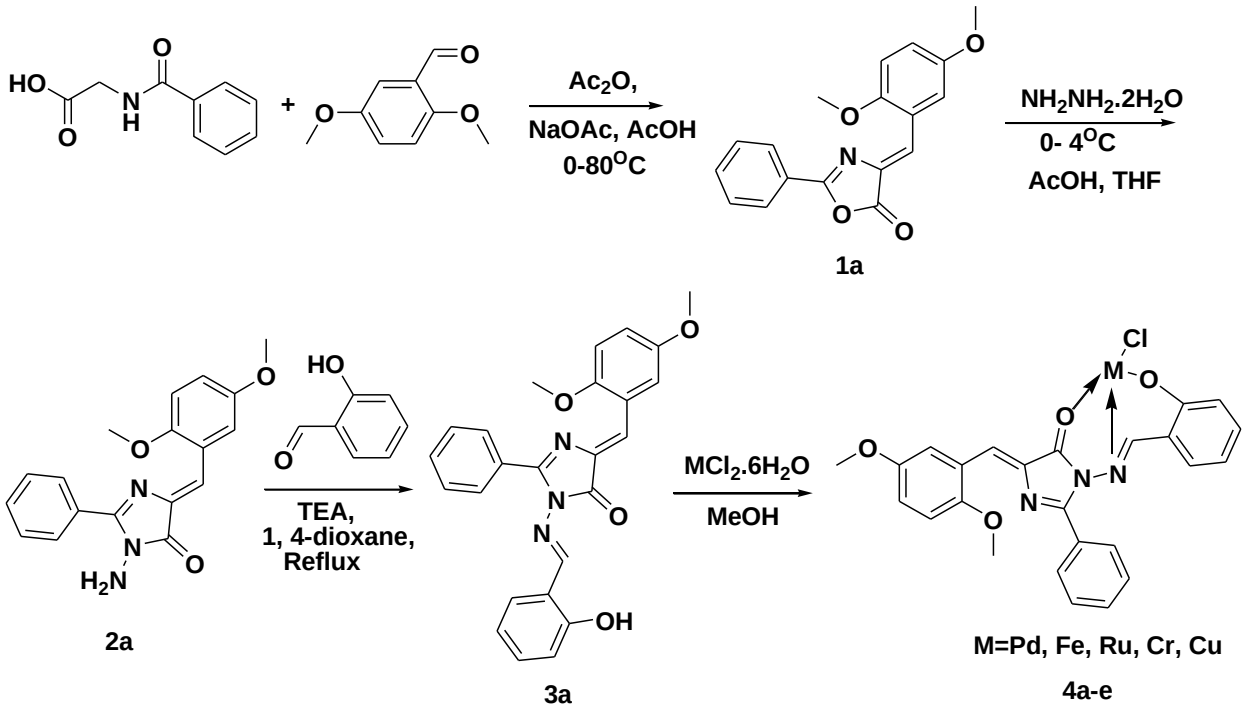
Novel Schiff base 3-((E)-benzylidene)-amino)-5-(2,5-dimethoxybenzylidene)-2-phenyl-3,5-dihydro-4H-imidazol-4-one bearing imidazole ring and arylidene linkage was synthesized which was reacted with different metal halides to form novel metal complexes. Characterization and bioactivity evaluation of all metal complexes was performed which is reported herein.

II. RESULTS AND DISCUSSION

Chemistry

Different metal complexes of a novel Schiff base 3-((E)-benzylidene)-amino)-5-(2,5-dimethoxybenzylidene)-2-phenyl-3,5-dihydro-4H-imidazol-4-one **(3a)** were synthesized. The Schiff base **(3a)** was synthesized in three steps starting from reaction of Hippuric acid and 2,5-dimethoxybenzaldehyde to furnish **(1a)** which on reaction with hydrazine hydrate furnished arylidene **(2a)** which on reaction with 2-hydroxybenzaldehyde furnished imidazole bearing Schiff base **(3a)** **(Reaction Scheme-1)**. Schiff base **(3a)** was reacted with different

metal chlorides to furnish the title metal complexes **(4a-e)**.



Reaction Scheme-1: Synthesis of Schiff base metal complexes **(4a-e)**

Spectral discussion

The ligand **3a** and all the newly synthesized metal complexes **(4a-e)** were characterized by different spectroscopic methods and elemental analyses. The characteristic spectral data confirmed the proposed structures.

A strong band observed at 1690 cm^{-1} in the free ligand was attributed to ν (C=O) of carbonyl group. This band shifted to a lower wavenumber side in all the complexes which indicates the participation of the carbonyl oxygen in bonding with metal ions. A medium to strong intensity band at 1597 cm^{-1} in the free ligand was attributed to ν (C=N) stretch of the azomethine group. Coordination of the Schiff's base to the metal ions through the nitrogen atom is expected to reduce electron density in the azomethine link and lower them (C=N) absorption frequency. This band shifted to a lower wave number side in all the complexes which indicates the participation of the azomethine nitrogen in coordination with metal ions. The medium intensity band at 948 cm^{-1} in the free ligand is assigned to ν (N–N) stretching vibration of hydrazine residue. This band in the complexes shift slightly to higher wave number side conforming involvement of one of the nitrogens of –N–N– in bonding with the metal ions. This indicates that carbonyl oxygen and azomethine nitrogen atoms are involved in coordination.

Antimicrobial evaluation

The Schiff base **(3a)** and all the metal complexes **(4a-e)** were screened for their antibacterial activity against Escherichia coli, Pseudomonas aeruginosa, Staphylococcus aureus, Bacillus subtilis and antifungal activity against Candida albicans, Aspergillus niger by broth dilution method [20]. The results are summarized in **Table 1**. The activities were compared with those of some known drugs, viz. Ampicillin, Chloramphenicol, Ciprofloxacin, Norfloxacin (antibacterial) and Griseofulvin, Nystatin (antifungal).

Antibacterial activity						Antifungal activity	
Minimal inhibition concentration (MIC) (microgram/ml)							
Sr. no.	Compound	E.c.	P.a.	S.a.	B. s.	C. a.	A. n.
3a	Ligand	100	125	250	200	500	500
4a	Pd complex	200	200	250	250	500	1000
4b	Ru complex	100	250	100	250	>1000	>1000
4c	Fe complex	200	125	62.5	100	1000	500
4d	Cr complex	62.5	125	200	100	500	1000
4e	Cu Complex	200	125	200	100	250	1000
Standard drugs (MIC microgram/ml)							
Antibacterial						Antifungal	
Gentamycin		0.05	1	0.25	1	Drug	C. a.	A. n.
Ampicillin		100	100	250	250			
Chloramphenicol		50	50	50	50			
Ciprofloxacin		25	25	50	50	Nystatin	100	100
Norfloxacin		10	10	10	100	Greseo-fulvin	500	100

Table 1: Antibacterial and antifungal evaluation of **3a** and **4a-e**.

The ligand **3a** as well as complexes **4b**, **4c** and **4d** depicted promising antibacterial activity against more than one bacterial strains which shows their potential for broad-spectrum activity. Further, the ligand **3a** showed good antifungal activity as compared to the standard drugs Nystatin and Greseofulvin. Complex **4e** showed excellent antifungal activity against Candida albicans as compared to the standard drug Greseofulvin. All the metal complexes showed moderate to good antifungal activity against Candida albicans.

III. EXPERIMENTAL AND METHODS

Thin-layer chromatography was accomplished on 0.2-mm precoated plates of silica gel G60 F254 (Merck). Visualization was made with UV light (254 and 365 nm) or with an iodine vapor. IR spectra were recorded on a FTIR-8400 spectrophotometer using DRS prob. 1H (400 MHz), NMR spectra were recorded on a Bruker AVANCE II spectrometer in CDCl3 and DMSO. Chemical shifts are expressed in δ ppm downfield from TMS as an internal standard. Mass spectra were determined using direct inlet probe on a GCMS-QP 2010 mass spectrometer (Shimadzu). Solvents were evaporated with a BUCHI rotary evaporator. Melting points were measured in open capillaries and are uncorrected. The electronic spectra were recorded on Shimadzu UV-1700, UV-Visible spectrophotometer. C, H and N analyses were taken on the Euro EA elemental analyser, EA-3000, RS -232.

Procedure for the synthesis of Schiff base **3a**

To Hippuric acid (5 mmol) in a round bottom flask, was added sodium acetate (10 mmol) and acetic anhydride (10 mmol) and the resulting mixture was stirred for half an hour. After getting homogenous mixture, 2,5-dimethoxybenzaldehyde (5 mmol) was added and refluxed until the completion of reaction as monitored by TLC. The reaction mass was then cooled at room temperature and methanol was added. The reaction mixture was kept overnight in the refrigerator and resulting precipitates were filtered. Resulted oxazolone 1a was reacted with 80% hydrazine hydrate using THF as a solvent in presence of catalytic amount of gla. acetic acid under stirring. The reaction was monitored by TLC and after the completion of the reaction, resulting precipitates were filtered, washed with water and dried to get the compound **2a**, which was further refluxed with 2-hydroxybenzaldehyde using 1,4-dioxane as solvent to get the compound **3a**. Crude **3a** was recrystallized with methanol.

M.P.: 230-232 ºC, Anal. $C_{25}H_{21}N_3O_4$: Calc. C, 70.25%; H, 4.95%; N, 9.83%; O, 14.97%; Found: C, 70.45%; H, 4.88%; N, 9.68%; O, 14.92%, MS: m/z: 427 (M), 1H NMR (400 MHz, DMSO), δ ppm: 9.46 (s, 1H), 9.11 (s, 1H), 8.35 (s, 1H), 7.95- 7.00 (m, 12H), 3.89 (s, 3H), 3.83 (s, 3H) IR (KBr): υ cm-1: 3552 (O-H), 1638 (C=N), 1364 (C-N).

General procedure for the synthesis of metal complexes **(4a-e)**

Metal complexes **(4a-e)** were prepared by mixing appropriate amount of ligands in methanol and an aqueous solution of the corresponding metal chlorides in 1:1 molar ratio and 1:2 molar ratio. The reaction mixture was refluxed on a water bath for 6-8 hours in presence of catalytic amount of gla. AcOH is added to adjust acidic pH range. The completion of the reaction was monitored by TLC. After the completion of reaction, the approximately 50% solvent was removed from hot solution and remaining mass was allowed to cooled at room temperature. The solid complexes formed were filtered, washed with hot water (10 mL, 4-5 times) and ethyl alcohol (10 mL, 3-4 times), and finally dried in vacuum desiccators over anhydrous CaCl2.

Pd(II) Complex **4a**: yield (56%). M.P.>300˚C.; UV/Vis: λmax = 235, 250, 311,411 nm; IR (KBr): υ cm-1 = 1688 (C=O), 1535 (C=N), 1250 (C-O), 972

(N-N); ESI-MS: *m/z* = 950; C50H42N6O8Pd: Anal. Calcd. C, 65.90; H, 4.63; N, 9.16; M, 6.25; Found C, 65.94; H, 4.65; N, 9.23; M, 6.13.

Fe(II) Complex **4b**: yield (80%). M.P.>300˚C; UV/Vis: *λ*max = 248, 295, 368nm; IR (KBr): *υ* cm-1 = 1669 (C=O), 1541 (C=N), 1222 (C-O), 969 (N-N); ESI-MS: *m/z* = 911; C50H42N6O8Fe: Anal. Calcd. C, 65.90; H, 4.63; N, 9.16; M, 6.25; Found C, 65.94; H, 4.65; N, 9.23; M, 6.13.

Ru(III) Complex **4c**: yield (68%). M.P.>300˚C; UV/Vis: *λ*max = 251, 289, 333, 555 nm; IR (KBr): *υ* cm-1 = 1656 (C=O), 1559(C=N), 1220 (C-O), 957 (N-N); ESI-MS: *m/z* = 674; C25H25Cl3N3O6Ru: Anal. Calcd. C, 44.81; H, 3.76; N, 6.26; M, 15.08; Found C, 44.76; H, 3.73; N, 6.26; M, 15.06.

Cr(III) Complex **4d**: yield (70%). M.P.>300˚C; UV/Vis: *λ*max = 355, 425 nm; IR (KBr): *υ* cm-1 = 1650 (C=O), 1548 (C=N), 1230 (C-O), 970 (N-N); ESI-MS: *m/z* = 940.; C50H42ClN6O8Cr: Anal. Calcd. C, 38.52; H, 2.28; N, 5.28; M, 20.08; Found C, 63.73; H, 4.49; N, 8.92; M, 13.58.

Cu(II) Complex **4e**: yield (61%). M.P.>300˚C; UV/Vis: *λ*max = 245, 269, 425 nm; IR (KBr): *υ* cm-1 = 1668 (C=O), 1562 (C=N), 1236 (C-O), 955 (N-N).; ESI-MS: *m/z* = 918; C50H42ClN6O8Cu: Anal. Calcd. C, 65.35;H, 4.65; N, 9.18; M, 6.90; Found C, 65.39; H, 4.61; N, 9.15; M, 6.92.

IV. CONCLUSION

Facile synthesis of various metal complexes of imidazole functionalized Schiff base was achieved successfully. The Schiff base ligand and newly synthesized metal complexes exhibited moderate to good antimicrobial activity, which makes them suitable and promising leads for further structural modification in order to develop new classes of antimicrobial compounds.

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Cite this article as :

Jalpa G. Gadara, Manhar V. Parsania, "Synthesis, Characterization and Biological Activity of Metal Complexes of Novel Schiff Base Bearing Imidazole Moeity", International Journal of Scientific Research in Science and Technology (IJSRST), Online ISSN : 2395-602X, Print ISSN : 2395-6011, Volume 6 Issue 4, pp. 429-434, July-August 2019.
Journal URL : https://ijsrst.com/IJSRST229417