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Synthesis and Antimicrobial Screening of Metal-ligand Complexes Derivative from (2-chloroquinolin-3-yl)methylene)hydrazine) and their Biological Studies

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ABSTRACT

This study presents the synthesis of a Schiff base ligand, 1,2-bis((2-chloroquinolin-3-yl) methylene)hydrazine, via a condensation reaction between an amine and a carbonyl compound. The resulting ligand was subsequently utilized to synthesize Cu(II), Co(II), and Ni(II) complexes. Characterization of the ligand was performed using analytical techniques such as ^{1}H NMR, FTIR, and mass spectrometry. Further structural analysis of the metal complexes was conducted through spectroscopic methods, including FTIR and UV. Their antifungal activity was assessed *in vitro*, revealing that the Ni(II) complex exhibited the highest efficacy against the tested fungal strains. Additionally, the Zn(II) complex demonstrated notable antifungal properties, with activity ranging from 14–35 µg/mL against *Candida albicans*, *Candida glabrata*, *Aspergillus flavus*, and *Cryptococcus neoformans*. The antibacterial potential of the complexes was also evaluated *in vitro* against three distinct bacterial strains. Compounds 6b and 6h displayed comparable potency to the reference drug Ampicillin against *Escherichia coli*, with IC_{50} values of 46 µg/mL. Furthermore, compound 6 h exhibited similar activity to Ampicillin against *Bacillus subtilis*, with an IC_{50} value of 50 µg/mL.

Keyword: Antibacterial, Antifungal activity, Bis hydrazine, Metal complexes.

INTRODUCTION

The chemistry of transition metal complexes has garnered significant interest due to their catalytic and bioinorganic properties. These complexes are also noteworthy for their potential biological activities, including anticancer[1], antimicrobial[2], antimalarial[3], and antitumor[4]. antibacterial[5], antiviral[6], antinflammatory[7], antioxidant[8]. Schiff base compounds, which are formed through thecompression of prime amines by carbonyl compounds (aldehydes) and the elimination of water molecules, are particularly important in this context. The formation of Schiff bases is often facilitated by the presence of a dehydrating agent (Scheme 1).

The choice of metal integrated into the complex and the particular Schiff base utilized have

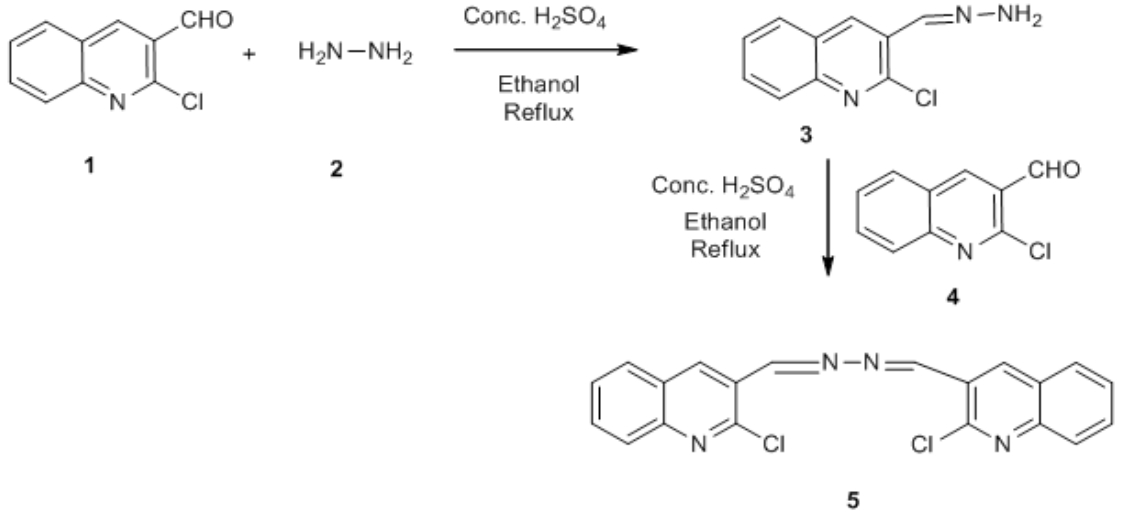
a substantial impression on their biological activity. Metal-Schiff base compounds demonstrate more potent drug action mechanisms than their decently organic counterparts. Owing to the biologically active azomethine group, Schiff bases serve as highly effective ligands for metal compounds. This azomethine structure, with its electron-deficient carbon and electron-rich nitrogen, facilitates diverse electrophilic and nucleophilic reactions at these specific sites[9-11].

Schiff bases that coordinate with oxygen, nitrogen, and other similar donor atoms, and their complexes, have been extensively studied and statedto exhibit a comprehensivevarietyof biological activities, with activity beside bacteria, fungi, and certain types of tumors. These compounds possess numerous biochemical, clinical, and pharmacological properties[12]. The synthesis of the metal complexes followed procedures reported in the literature[13,14].

The chemistry of Schiff bases represents a significant area of study within coordination chemistrybecause of their capacity to form stable multiplexes with various metal ions, leading to applications across multiple disciplines. A notable focus in this field has been the usage of Schiff-base ligands to progress phenoxo-bridged binuclear multiplexes by eitherhomometalliccenters. These Schiff-base complexes are crucial in biomedical, biomimetic, and catalyticorganizationsand also support liquid crystalline phases[15-22]. Schiff bases synthesized from aliphatic aldehydes tend to be more unstable and prone to polymerization compared to those derived from aromatic aldehydes, which exhibit greater stability due to more effective conjugation. Aldehydes, which are less sterically hindered and more electrophilic than ketones, react more readily, facilitating the formation of Schiff bases. The simplicity of synthesis and the ready availability of Schiff bases have made them a subject of considerable interest. The development of several applications in the fields of inorganic[23], bioinorganic[24], organic synthesis[25], environmental[26], and coordination chemistry[27] are the significant interest.

MATERIALS AND METHODS

All the procured substances used were methodical mark, distilled solvents were used. Metal salts were used without further refinement.



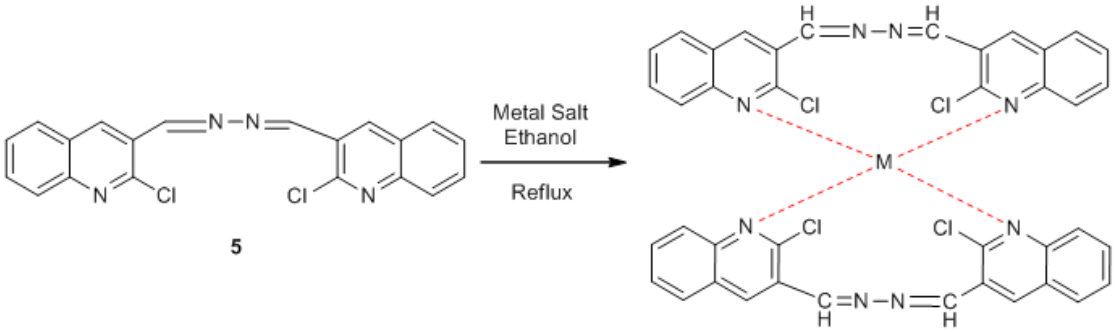
Scheme 1. Synthesis of hydrazine derivative

In 50 mL round bottom flask to stirred solution of compound (1) (1mmol) in ethanol (10 mL) was treated by hydrazine hydrate (2) (6 mmol) and 1-2 drops of rigorous sulphuric acid at room temperature. The reaction mixture was refluxed in a preheated oil bath for four hours, resulting in the formation of 2-chloro-3-(hydrazonomethyl) quinolone (3). Subsequently, an extra 1 mmol of 2-chloroquinolin-3-carbaldehyde (4) and 1–2 drops of concentrated H_2SO_2 were introduced, and the mixture was further refluxed for another four hours. Upon conclusion of the reaction, as observed by T. L.C. by means of an ethyl acetate: n-hexane (3:7) system, the solvent was evaporated. The resulting

crude product was precipitated by adding ice, followed by filtration, drying, and recrystallization from ethanol.The isolated yellow solid was confirmed by NMR and Mass spectroscopic analysis. IR (KBr cm^{-1}): 3402 (OH), 3011 (Ar-H), 1668 (Imine C=N), 1579 (C=C), 1170 (C-O-C).

Preparation procedure

The metal salts (1mmol) were addition the ethyl alcohol solution of the ligand (5) (2 mmol). A some what basic pH of the reaction was carried out in slightly basic condition by adding 1 mmol of ammonia, and then this contentswere refluxedup to 5 to 6 hrs. The development of the reaction was checked by using T.L.C. and also monitored the colour changes. The subsequent yield was poured on petri dish and cool, filtration and dehydrated (6a-h). Each product was recrystallized from ethanol andthen take out its melting point, confirmed by IR and UV spectroscopy. Physical data of synthesized compounds are shows in Table 1.



5 **6a-h**

6a CdL4 **6e** FeL4
6b CoL4 **6f** SrL4
6c CuL4 **6g** ZnL4
6d NiL4 **6h** ZrL4

Table 1: Physical information of manufactured complexes

Entry	Sample codea	Ligand/metal salt	Elemental analysis (%)				
			C	H	N	M	Cl
1	5	Ligand	63.32	3.17	14.77	0	18.73
2	6a	CdL4	55.14	2.76	12.87	12.91	16.31
3	6b	CoL4	58.75	2.94	13.71	7.21	17.38
4	6c	CuL4	58.43	2.92	13.63	7.73	17.28
5	6d	NiL4	58.77	2.93	13.71	7.18	17.39
6	6e	FeL4	58.98	2.94	13.76	6.86	17.45
7	6f	SrL4	56.76	2.83	13.24	10.36	16.79
8	6g	ZnL4	58.29	2.91	13.60	7.94	17.24
9	6h	ZrL4	56.52	2.82	13.19	10.74	16.72

Spectroscopic data of Synthesized metal Complexes

The N-H stretching band of the free ligand exhibited a shift towards lower frequencies in the spectra of all complexes, suggesting the involvement of the N-H group in complex formation. The infrared spectral data (ν, cm^{-1}) for C=N, M-N, and C-H bonds in the metal complexes is provided.

The (6a) complex have Lemon yellow colour solid with melting point 274°C infrared Spectral values (cm^{-1}) 1672 (C=N), 639 (M-N), 3068 (C-H), 3268 (O-H), UV spectra of the (6a) metal complex werenotedin ethanol solvents λ_{max} value is 344.99 nm.

(6b) Complex have grey colour solid with melting point >300^{0}C Infrared Spectral values (cm^{-1}) 1611 (C=N) 687(M-N), 3071(C-H), 3486 (O-H), UV Spectra of the (6b) metal complex were noted in ethanol solvents λ_{max} value is 201.58 nm.

(6c) Complex have yellowish brown colour

solid with melting point 280^{0}C Infrared Spectral values (cm^{-1})1611 (C=N), 687 (M-N), 3072 (C-H), 3407 (O-H), UV spectra of the (6c) metal complex were noted in ethanol solvents λ_{max} value is 385.53 nm.

(6d) Complex have brown colour solid with melting point 2980C Infrared Spectral values (cm^{-1})1580 (C=N), 689 (M-N), 3055 (C-H), 3180 (O-H), UV spectra of the (6d) metal complex were noted in ethanol solvents λ_{max} value is nm.

(6e) Complex have yellow colour solid with melting point >300^{0}C Infrared Spectral values (cm^{-1}) 1581 (C=N), 646 (M-N), 3060 (C-H), 3133 (O-H), UV spectra of the (6e) metal complex were noted in ethanol solvents λ_{max} value is 383.28 nm.

(6f) Complex have white colour solid with melting point >300^{0}C Infrared Spectral values 1610 (C=N), 688 (M-N), 3069 (C-H), 3389 (O-H), UV spectra of the (6f) metal complex were noted in ethanol solvents λ_{max} value is 350.06 nm.

(6g) Complex have yellowish green colour solid with melting point 270^{0}C Infrared Spectral values cm^{-1} 611 (C=N), 689 (M-N), 3070 (C-H), 3497 (O-H), UV spectra of the (6g) metal complex were noted in ethanol solvents λ_{max} value is 203.6 nm.

(6h) Complex have light Yellow colour solid with melting point 286^{0}C Infrared Spectral values 1596 (C=N), 686 (M-N) 3065 (C-H), 3429 cm^{-1} (O-H). UV spectra of the (6h) metal complex were noted in ethanol solvents λ_{max} value is 343.06 nm.

RESULT AND DISCUSSION

Antifungal activity (*in vitro*)

The newly manufactured complexes were evaluated for their *in vitro* Antifungal activity in contradiction of numerous fungal pathogens. MIC standards were resoluteby means of the normal agar technique, with Miconazole helping as the reference drug. Dimethyl sulfoxide was used as the solvent control. The MIC values (µg/mL) for the tested compounds and Miconazole are presented in Table 2. According to the data in Table 1, all synthesized compounds demonstrated decentto reasonable antifungal efficacy in contradiction of the examined fungal strains.

Table 2: Antifungal activity of complexes

Complexes	MIC[a] µg/mL				
	C. albicans	*C. glabrata*	*A. fumigates*	*A. flavus*	*C. neoformans*
6a	51	50	57	37	39
6b	25	28	38	15	16
6c	26	29	38	18	15
6d	28	32	44	20	20
6e	22	24	32	11	10
6f	30	32	41	22	25
6g	35	36	40	18	24
6h	25	24	35	14	14
Miconazole	25	25	35	12	12

[a]Values are theordinaryof threeevaluations

The results revealed that the entire Schiff base metal complex complexes exhibition antifungal activity. The compounds with the decent antifungal outlines were 6b, 6e, and 6h, each awarding at slightestone MIC value reaching between 10-40 µg mL^{-1}. Table 1 results observations show that the Schiff base metal complex compounds are more active than their respective Schiff base. The Ni complex i.e. 6e was found to be highly active towards all the selected fungi strains. A good effectiveness is exhibited by Zn complex i.e. 6 h, which acts in the range 14–35 µg mL^{-1} toward *C. albicans*, *C. glabrata*, *A. fumigates, A. flavusand Cryptococcus neoformans*.

Antibacterial activity (*in vitro*)

The antibacterial properties of the newly manufacturedcomplexeswere assessed *in vitro* against three distinct bacterial strains. MIC standards were measured by means of the normal agar process, with Ampicillin serving as the reference drug and DMSO as the solvent control. The results, as shown in Table 3, indicate that the synthesized compounds exhibited moderate

to strong antibacterial effects in contradiction of *E. coli, B. subtilis*, and *S. aureus*.

Table 3: Antibacterial activity (*in vitro*) data

Compounds	MIC[a] µg/mL		
	E. coli	*B. subtilis*	*S. aureus*
6a	>100	>100	>100
6b	46	48	48
6c	50	50	50
6d	56	60	52
6e	62	55	60
6f	70	70	72
6g	60	55	60
6h	48	50	52
Ampicillin	50	50	48

[a]Values are the ordinary of three evaluations

The consequences ofAntibacterial activity (*in vitro*) as obtainablein Table 3, indicate that the manufactured complexes 6b and 6h were originate to be additional equipotent to that oftypical drug Ampicillin against *Escherichia coli* IC_{50} values 46 µg/mL and 48 µg/mL correspondingly. The synthesized complexes 6 h were found to be equipotent to that of standard drug Ampicillin against *Bacillus subtilis* IC_{50} value 50 µg/mL. It was also noticed that the derivatives with the "Zn" and "Cd" metal in their structure were found to be potent compounds among the other synthesized derivatives.

CONCLUSION

In conclusion, a new ligand was synthesized using aldehydes, vanillin and 2-chloro-3-carbaldehyde,along with amine hydrazine hydrate. This ligand was further utilized for the synthesis of metal-ligand complexes. The anewmanufactured ligand and metal complexes were categorizedby means of various spectroscopic methods, including ^{1}H NMR, Mass spectrometry, IR spectroscopy, UV spectroscopy, and antibacterial and antifungal activity assays. The monodentate Schiff base substituted hydrazineLigand and its metal developments were positively manufactured and categorized using the aforementioned spectroscopic techniques. The antifungal and antibacterial activities of the manufactured metal complexes were evaluated, revealing that the compound Ni exhibited significantly good in vitroantifungal activity against *C. albicans*, *C. glabrata, A. fumigatus*, *A. flavus*, and *C. neoformans*. Complexes with Cd and Zn demonstrated in vitroantifungal activity when compared to the standard drug Miconazole against the fungiform strains *C. albicans* and *C. glabrata*.

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Conflict of interest

We announced no conflicts of interests.

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