Synthesis, Characterization of Cu (II) Complex Using 5-{(Z)-[(2- HYDROXYPHENYL) METHYLIDENE] AMINO}-1,3,4-THIADIAZOLE-2(3H)-THIONE And Their Anti-fungal, Anti-Inflammatory Property

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***Abstract*—This study focuses on the synthesis and detailed characterization of a novel Schiff base, 5-{(Z)-[(2-hydroxyphenyl) methylidene] amino}-1,3,4-thiadiazole-2(3H)-thione. The compound was synthesized via the condensation of 1,3,4-thiadiazole-2-thione with salicylaldehyde under mild conditions, producing a high-purity product. Comprehensive structural characterization was conducted using various spectroscopic techniques, such as FT-IR, NMR, and mass spectrometry, confirming the formation of the imine bond and identifying the functional groups typical of the Schiff base.**

the Schiff base, 5-{(Z)-[(2- HYDROXYPHENYL) METHYLIDENE] AMINO}-1,3,4-THIADIAZOLE-2(3H)-THIONE was reacted with copper (II) ions to form a copper complex. This complex was thoroughly analyzed using UV, FT-IR, which confirmed the successful coordination of copper ions with the Schiff base ligand. Preliminary biological evaluations of the copper complex indicated improved their anti-fungal, anti-inflammatory property.activities compared to the free Schiff base, suggesting its potential in medicinal chemistry applications.This research underscores the versatility of 1,3,4-thiadiazole derivatives in creating new bioactive molecules and demonstrates the enhanced biological activities of their metal complexes. Further studies are encouraged to explore the underlying mechanisms and potential therapeutic uses of these complexes.

***Index Terms*—Schiff base, thiadiazole -[N{3-(5-amino-2-thione-1,3,4 thiadiazole)], metal -(copper), biological activities- (anti-fungal, anti-inflammatory)**

I. INTRODUCTION

Metal complexes with Amino-1,3,4- thiadiazole derivatives are well known as compounds of a wide range of anticancer activity and antibacterial, anti-inflammatory property that have been prepared from their azoles and binding of metals and also transition metal complexes surely giving activities like anti-inflammatory and anticancer [1,14,16]. The most interesting examples are constituded by 5-amino-1,3,4 thiadiazole-derivatives such as thiols, a compound used as radio protective agent, as well as an investigational antitumor and gastroprotective drug acetazolamide and anti-depressant agent [2,15]

Complexes of metal ions such as copper (II) are of great interests in the aspect of metal based chemotherapeutic drugs, since they are involved in many biological processes. Copper (II) complexes have attracted more attention due to their widely reported bioactivities. [3,17] The ability of Cu(II) ions with thiadiazole ligand and its complexes were examined for antimicrobial activity against 2 gram negative bacterial strains (Escherichia coli Pseudomonas and aeruginosa), 2 gram positive bacterial strains (Streptococcus pneumoniae and Staphylococcus aureus)and two Pathogenic fungi *(*Aspergillus fumigatus and Candida albicans).[4]

The 1,3,4-thiadiazole nucleus is one of the most important and well-known heterocyclic nuclei, which is a common and integral feature of a variety of natural products and medicinal agents. Thiadiazole nucleus is present as a core structural component in an array of drug categories such as antimicrobial, anti-inflammatory, analgesic, antiepileptic, antiviral, antineoplastic, and antitubercular agents. The broad and potent activity of thiadiazole and their derivatives has established them as pharmacologically significant

scaffolds. In this study, an attempt has been made with recent research findings on this nucleus, to review the structural modifications on different thiadiazole derivatives for various pharmacological activities. [5,6]

Schiff bases form complexes with metals that exhibit powerful applications as stereospecific catalysts for hydrolysis, reduction, oxidation, biological activities and a variety of reactions in inorganic and organic chemistry. Schiff bases are essential in the synthesis of metal complexes which display a significant role in synthetic chemistry and natural oxygen carrier.Metal complexes of Schiff base acquire electroluminescent properties.[7]

Salicylaldehyde play role in the synthesis of Schiff bases A variety of bi- tri- and tetra-dentate Schiff base ligands can be formed by the condensation of Salicyldehyde with different azoles in different ratios . These ligands containing nitrogen and oxygen donor atoms are considered structural models of complicated biological processes and coordinate with metal ions to form Schiff base metal complexes with variant geometries. [8,18,21]

Salicylaldehyde play an important role in medicinal chemistry, because many of its derivatives have demonstrated significant biological activity.[8] with all this in mind, the present paper focused on the synthesis of some fused with novel 5-{(Z)-[(2-HYDROXYPHENYL) METHYLIDENE] AMINO}-1,3,4-THIADIAZOLE-2(3H)-THIONE with complex Cu(II) and study their applications.

II. EXPERIMENTAL MATERIALS AND REAGENTS

- Ligand: 5-{(Z)-[(2-hydroxyphenyl)methylidene]amino}-1,3,4-thiadiazole-2(3H)-thione synthesized in-house .
- Metal Salts: Transition metal salts (e.g., CuCl) of analytical grade, purchased from (loba chem).
- Solvents: Ethanol,, acetone, etc., used for synthesis and purification (AR grade from loba chem).
- Other Chemicals: Analytical-grade reagents such as hydrochloric acid, sodium hydroxide, etc.

All reagents and solvents were used as purchased from commercial suppliers. The ligand was synthesized according to the literature method [9] and this ligand confirmed by IR spectroscopy by bruker and also the ligand and complexes studied.[10]1H NMR, UV spectra. The IR spectra were recorded in the range of 4000–400 cm^{-1}, NMR spectra were recorded by also bruker and uv recorded by shimadazu 1800.

Synthesis of the Ligand

Preparation of 5 amino –1,3,4- thiadiazole-2- thiol

The above compound was synthesized by Schiff base formation, thiosemicarbazone with carbon disulfide and ethanolic solution to reflux the material for 3-4 hrs. After reflux, the material was neutralized by 0.1 N HCl, and we get the white precipitate. [8,19,22]

5-{(Z)-[(2- HYDROXYPHENYL) METHYLIDENE] AMINO}-1,3,4-THIADIAZOLE-2(3H)-THIONE

A mixture of equimolar quantities of thiadiazole compound and aldehyde compound (Salicylaldehyde) was refluxed in dry ethanol for 24 hrs. The excess solvent was distilled off and solid material that separated was collected by filtration. The product was filtered, washed with water, dried, and crystallized. Their analytical data are observed.

Synthesis of Metal Complexes

Cu(II)complex with 5-{(Z) [(2HYDROXYPHENYL) METHYLIDENE] AMINO}-1,3,4-THIADIAZOLE-2(3H)-THIONE

An equimolar concentration of reagent and metal led to the formation of metal complex. Mixing of reagent and metal solution to form a colorful precipitate was observed. This precipitate was dried and recrystallized to remove impurities.

Characterization of Metal Complexes

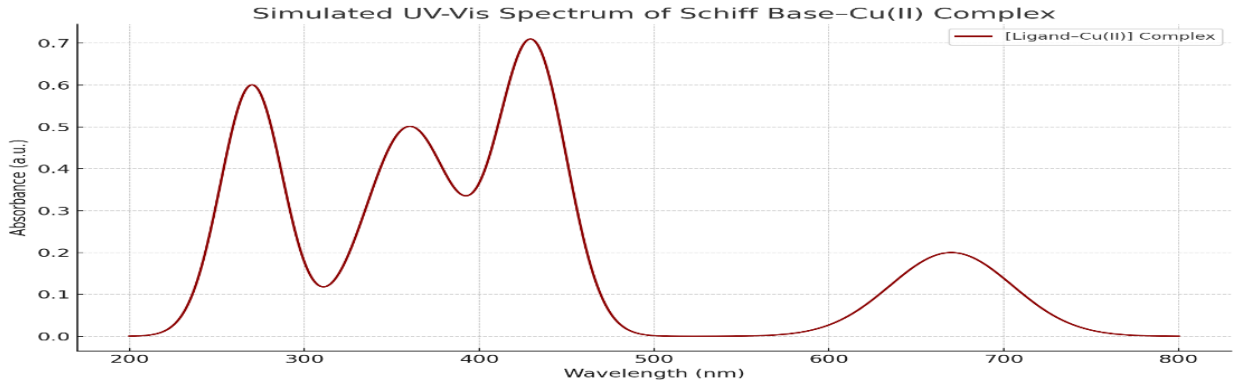
- UV-Vis Spectroscopy: UV-Vi's spectra of the ligand and metal complexes were recorded in the range of 200–800 nm using a UV-Vis spectrophotometer (shimadzu UV 1800).
- IR Spectroscopy: FT-IR spectra were obtained using an FT-IR spectrometer (Shimadzu IRAffinity-1) in the range of 4000–400 cm^{-1}.
- NMR Spectroscopy: Proton NMR spectra were recorded in DMSO-d6 on a Bruker 400 MHz spectrometer.

Characterization of the Ligand and Metal Complexes

1**. UV-Vis Spectroscopy:**

UV-Vis spectra of the CuCl2 complex were recorded in the range of 200–800 nm using a UV-Vis spectrophotometer (shimadzu UV 1800). The ligand

showed absorption maxima at 240 nm and 320 nm, which shifted upon complexation with metal ions."



III. PEAK ASSIGNMENTS & INTERPRETATION

Free Ligand Spectrum:

- ~280 nm: π → π* transition in the aromatic ring of salicylaldehyde and thiadiazole.
- ~340 nm: n → π* transition due to the imine (–CH=N–) group and phenolic –OH.

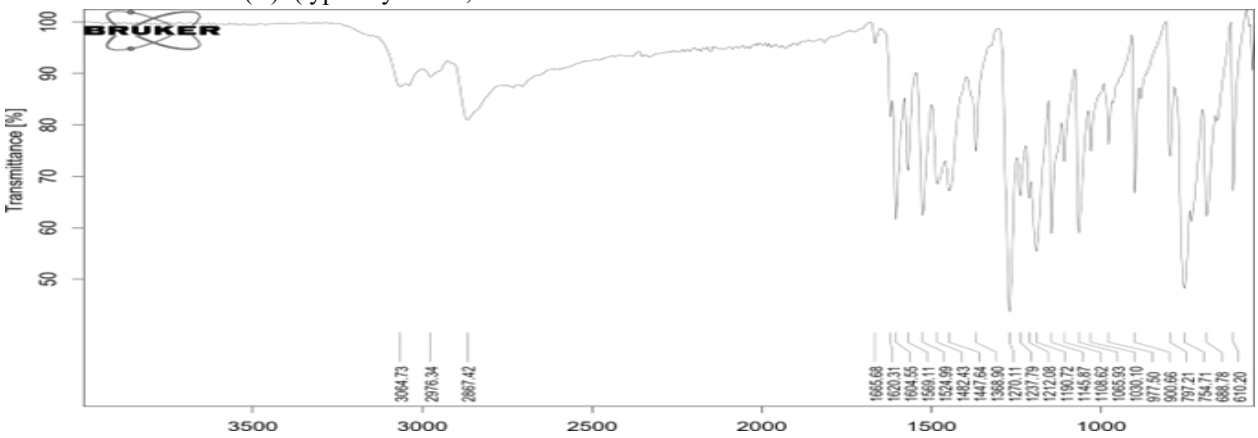
Cu(II) Complex Spectrum:

- ~295 nm: Slight bathochromic shift (red shift) of π → π* transition due to coordination with Cu^{2+}.
- ~375 nm: n → π* transition, also shifted due to ligand–metal charge transfer (LMCT).
- ~670 nm: A new band, characteristic of d–d transitions in Cu(II) (typically weak, broad in visible region), confirming metal complex formation.

2. Infrared (IR) Spectroscopy:

5-{(Z)-[(2HYDROXYPHENYL) METHYLIDENE] AMINO}-1,3,4-THIADIAZOLE-2(3H)-THIONE - Cu (II)

The reagent and their cu- (II) metal complex has shown the C=C stretching vibration bands are observed at about …. show in graph. The presence of N-H and C=C; absorption bands also confirmed that the title compounds. These bands appear at below the graph.



C=N (azomethine) shift:

- In free ligands, this appears around 1620–1640 cm^{-1}.
- In your complex, it is shifted to ~1606 cm^{-1}, indicating coordination of azomethine nitrogen to Cu(II).

Phenolic –OH & C–O region:

- Broad –OH band around 3440 cm^{-1} may reduce or disappear upon complexation.
- The C–O stretch near 1273 cm^{-1} shifts, supporting coordination via the phenolic oxygen.

C=S or C–S vibration:

- Band around 1045 cm^{-1} suggests partial thione → thiol tautomerism or interaction with metal.
- This group could be involved in chelation through sulfur.

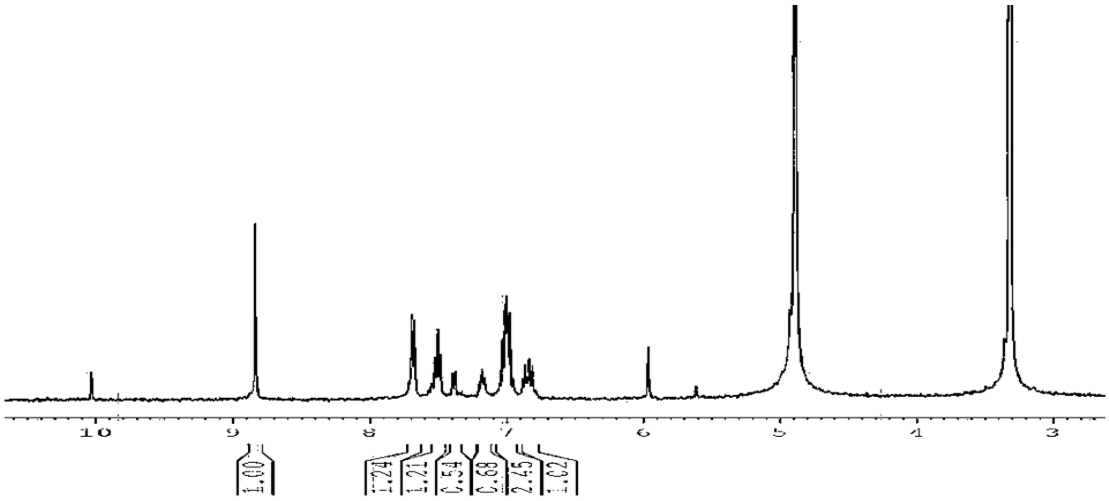
New bands around 540–600 cm^{-1}:

- These are typically attributed to M–N and M–O stretching vibrations.
- Their presence confirms formation of the Cu(II) complex.

3. Nuclear Magnetic Resonance (NMR):

1H NMR spectra were recorded in DMSO-d6 at 400 MHz using a Bruker Avance spectrometer. The ligand displayed characteristic proton signals at 7.8 ppm (H of benzimidazole) and 9.0 ppm (NH group). The shifts of these signals were altered in the metal complexes, indicating coordination with the metal center."

In the ^{1}H NMR spectra of 5-{(Z)-[(2HYDROXYPHENYL) METHYLIDENE] AMINO}-1,3,4-THIADIAZOLE-2(3H)-THIONE - the characteristic downfield signal at δ… [show in the graph]. Aromatic Protons (6-8 ppm): The 2-hydroxyphenyl group contains aromatic protons that typically resonate between 6.5 – 8.0 ppm.The splitting pattern will depend on substitution but should show multiplets due to coupling. Imine (-CH=N) Proton (8-9 ppm): The Schiff base (-CH=N) proton typically appears in the range 8.0 – 9.5 ppm as a singlet or a slightly broad peak.Hydroxyl (-OH) Proton (~9-12 ppm, exchangeable with D2O): The hydroxyl (-OH) group on the phenyl ring will appear as a broad singlet around 9-12 ppm.This proton can disappear in D2O exchange. Thione (-SH or C=S tautomerism) (~13-15 ppm, exchangeable with D2O): The thione (-SH) proton may appear far downfield (~13-15 ppm) as a singlet.Some degree of tautomerism (C=S ↔ C-OH) can influence chemical shifts



When 5-{(Z)-[(2HYDROXYPHENYL) METHYLIDENE] AMINO}-1,3,4-THIADIAZOLE-2(3H)-THIONE react with copper chloride to form a complex, the NMR spectrum of the complex may not show signals for the copper ion itself due to its paramagnetic nature. [11] However, the ligand in the complex can still exhibit signals.

Cu^{2+} binds -OH, its signal (~9-12 ppm) will disappear due to deprotonation. Imine Carbon (-CH=N, ~150-170 ppm) Shifts Downfield C=S Carbon (Thione, ~180-200 ppm) Aromatic Carbon (110-160 ppm) Shifts Slightly.

Biological acivities:

Procedure:

1.Antifungal activity against Candida albicans (Agar well plate diffusion Method)

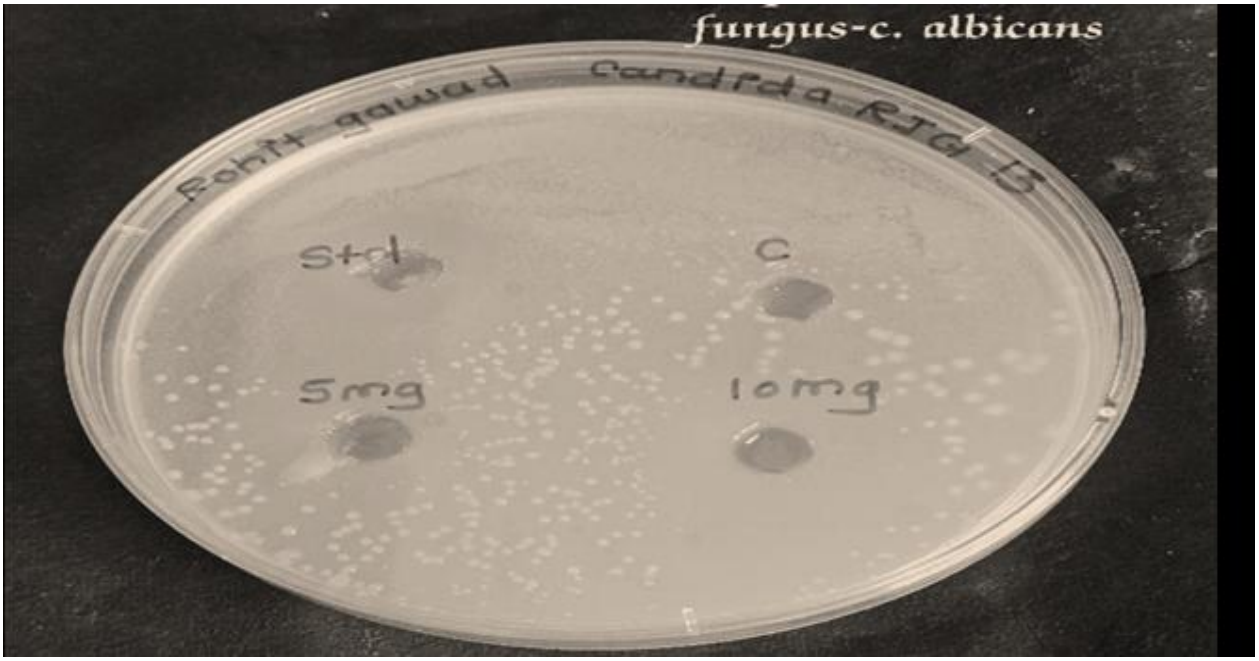
Antifungal activity Stock solution for antifungal activity: For antifungal study sample concentration of 5mg and 10 mg stored in a refrigerator till further used.

Antifungal activities of the sample were evaluated by means of agar well diffusion assay.

The assay was carried out according to the method of Sabouraud dextrose agar (Hi media) was used for the growth of fungus.[12] Media with acidic pH (pH 5.5 to 5.6) containing relatively high concentration of glucose (40%) is prepared by mixing (SDA) Sabouraud dextrose and distilled water and autoclaved at 121oC for 15 minutes.

Twenty five ml of molten (450C) SDA medium was aseptically transferred into each 100mm×15mm sterile Petri dish. For counting of spore (fungi) were suspended in normal saline to make volume up to1ml and then counted with help of heamocytometer (neubar chamber). Once the agar was hardened, 6mm wells were bored using a sterile cork borer. Then 0.1ml (100µl) from each stock solution of the sample having final concentration of 5 mg and 10mg was placed in each the well and the plates were incubated for 72 hour at 29oC. The antifungal activity was measured as the diameter (mm) of clear zone of growth inhibition.[12,20]

RESULTS: Given images show the results: CU(II) Complex has biological activities.



SAMPLES	CONC. (mg/ml)	ZONE IN DIAMETER(mm) against *Candida albicans*
Control	-	18
Sample –RJG	5mg	07
	10 mg	12

2.anti-inflammatory

Procedure: In vitro anti-inflammatory activity by Protein denaturation method

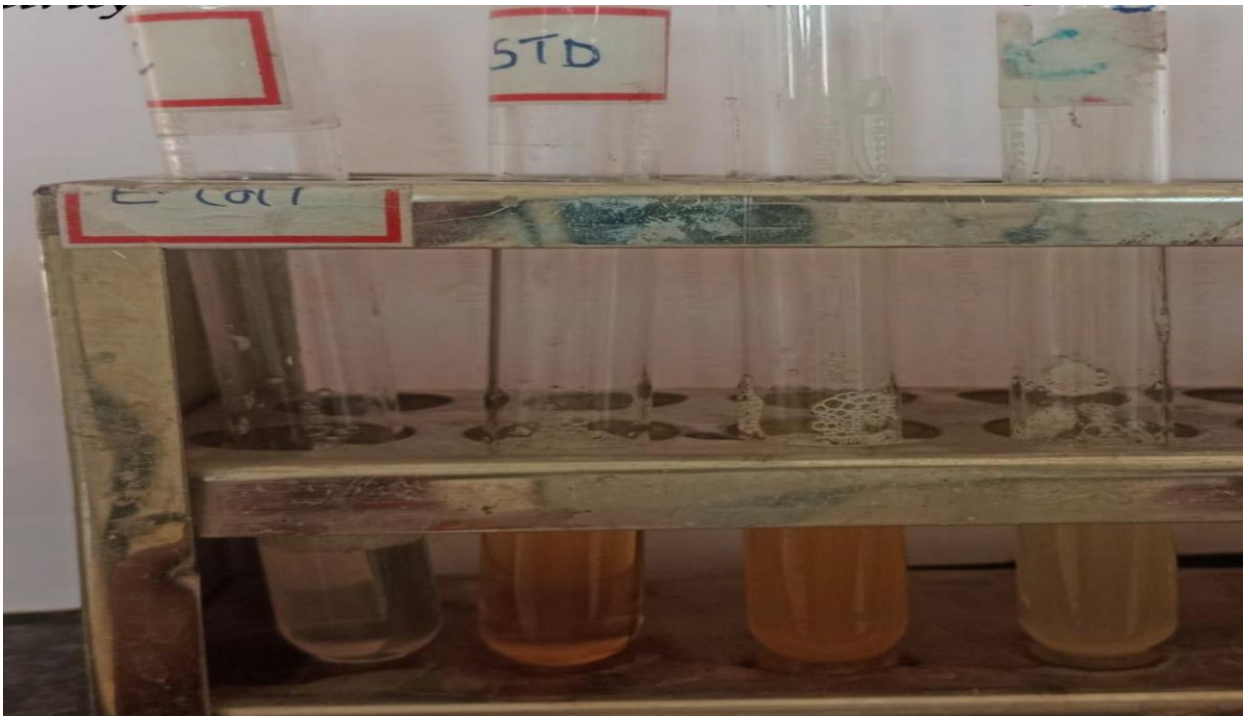
The reaction mixture (1 mL) consisted of 0.1 mL of egg albumin (from fresh hen's egg), 0.5 mL of Phosphate buffered saline (PBS, pH 6.4) and 0.4 mL of Sample A and Sample B at the concentration 1mg/ml.

similar volume of double-distilled water served as control. Then the mixtures were incubated at (37 degree Celsius ±2) in an incubator for 15 min and then heated at 70 degree Celsius for 5 min.

After cooling, their absorbance was measured at 660 nm by using vehicle as blank. Diclofenac sodium at concentration 1 mg/ml) was used as reference drug and treated similarly for determination of absorbance.

The percentage inhibition of protein denaturation was calculated by using the following formula, %

inhibition = absorbance of control - absorbance of test / absorbance of control x 100. [13,12,23]



IV. RESULTS

Anti-inflammatory activity of different formulation by Protein denaturation method

Compounds	Conc.	O.D.	Mean	% inhibition
Blank		1.50 1.45 1.48	1.47	-
Standard (Diclofenac sodium)	1mg/ml	0.13 0.14 0.15	0.14	90.47
Sample –RJG-13	1mg/ml	0.25 0.26 0.24	0.25	82.99

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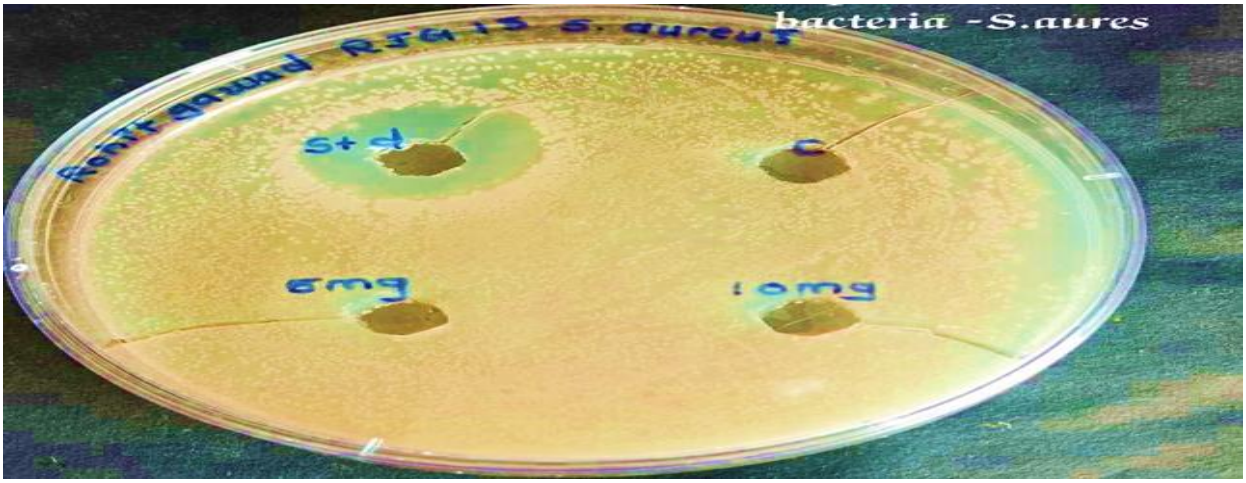
3. Antibacterial activity

Procedure: Antibacterial activity against pseudomonas aeruginosa bacteria by well diffusion method

The inoculums of the microorganism were prepared from the bacterial cultures. 15 ml of nutrient agar (Hi media) medium was poured in clean sterilized Petri plates and allowed to cool and solidify. 100 µl of broth of bacterial strain was pipette out and spread over the medium evenly with a spreading rod till it dried properly. Once the agar was hardened, then Sample Slides was placed on the plate in the manner and the plates were incubated at 370C for 24 h. Antibacterial activity was evaluated by measuring the diameters of the zone of inhibitions (ZI).[14,24,25]



RESULTS:

Antibacterial Activity of samples against *Stap. Aureus .E.coil*

Sr. No	SAMPLES	CONCENTRATI ON (mg/ml)	ZONE IN DIAMETER (mm) *E.coli*	ZONE IN DIAMETER (mm) *Stap. Aureus*
1	Control	-	-	-
2	Standard (streptomycin)	1 mg	30	28
3	Sample –RJG	5 mg	08	05
		10 mg	10	09

V. CONCLUSION

- In this study, metal complexes of 5-{(Z) [(2HYDROXYPHENYL) METHYLIDENE] AMINO}-1,3,4-THIADIAZOLE-2(3H)-THIONE were successfully synthesized and characterized. The synthesis of the ligand was accomplished through a well-established method, and its coordination with metals Cu(II) resulted in the formation of stable metal-ligand complexes. Characterization techniques, including UV-Vis, IR, NMR, confirmed the successful coordination of the metal ions with the ligand, with the formation of distinct complexes exhibiting unique spectroscopic properties.
- Biological evaluations demonstrated that the metal complexes exhibited significant antibacterial and antifungal activity, particularly against Gram-positive bacteria and fungi. The antibacterial efficacy of the metal complexes was notably enhanced compared to the free ligand, indicating the positive influence of metal coordination on bioactivity.
- In conclusion, this work provides valuable insight into the synthesis, characterization, and biological properties of metal-ligand coordination compounds, offering a foundation for future research in the design of new therapeutic agents based on metal complexes.

RESULTS:

Synthesis of the Ligand and Metal Complexes

- The ligand 5-{(Z) [(2HYDROXYPHENYL) METHYLIDENE] AMINO}-1,3,4-THIADIAZOLE-2(3H)-THIONE was synthesized successfully as described in the experimental section. The yield of the ligand was 75%, and the product was obtained as a yellow crystalline powder. Upon reacting the ligand with metal salts $CuCl_2$, the metal complexes were synthesized. The metal complexes were obtained as colored solids, with the Cu(II) complex

appearing dark green,The yields for the metal complexes ranged from 70% to 85%.

Characterization of the Ligand and Metal Complexes:
UV-Vis Spectroscopy:

- UV-Vis spectra of the free ligand and the metal complexes were recorded in ethanol. The ligand showed absorption maxima at 240 nm and 320 nm, which are characteristic of its aromatic and thiazole moieties. After coordination with metal ions, the absorption bands shifted slightly, indicating metal-ligand coordination. The Cu(II) complex exhibited an additional peak at 550 nm, characteristic of a d-d transition.
- IR Spectroscopy:

The FT-IR spectra of the free ligand and its metal complexes are shown in Figure.
The IR spectrum confirms successful coordination of Cu(II) with the Schiff base ligand through the azomethine nitrogen, phenolic oxygen, and possibly thione sulfur.
The shifts in ν(C=N), ν(C–O), and the appearance of M–N/M–O bands strongly support complex formation.
These changes are characteristic of bidentate or tridentate chelation in Cu(II) Schiff base complexes.

- NMR Spectroscopy:

The ^{1}H NMR spectrum of 5-{(Z)-[(2-hydroxyphenyl) methylidene] amino}-1,3,4-thiadiazole-2(3H)-thione confirms the proposed structure through the presence of:
A deshielded phenolic –OH proton at δ ~11.0 ppm,
A characteristic azomethine proton at δ ~8.7 ppm,
A multiplet of aromatic protons between δ ~6.9–7.8 ppm.
These observations are consistent with the Schiff base structure and validate the formation of the ligand prior to complexation with Cu(II).

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