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Full Length Research Paper

Synthesis, Structural Characterization, and Fungicidal Evaluation of Metal Complexes with Schiff Bases Derived from Sulfonamide Drugs and Salicylaldehyde

Dr. Himanshu Sharma
Professor
Department of Chemistry
Meerut Institute of Engineering & Technology Meerut
himanshu.Sharma@mitmeerut.ac.in

Dr. Priti Sharma
Principal & Senior Lecturer in Chemistry
Government Girls Inter College, Baghpat

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1. Abstract

Background: *The escalating prevalence of fungal resistance to conventional fungicides poses a significant threat to global food security and public health, underscoring an urgent need for the development of novel antimicrobial agents with alternative mechanisms of action.*

Objective: *This study aims to synthesize and evaluate a new series of transition metal complexes derived from sulfonamide-based Schiff bases, designed to synergize the inherent antimicrobial properties of sulfa drugs with the enhanced bioactivity often imparted by metal chelation.*

Methods: *A series of Schiff base ligands (HL) were synthesized via the condensation of sulfonamide drugs (sulfadiazine, sulfathiazole) with salicylaldehyde. These organic ligands were subsequently complexed with transition metal ions, including Cu(II), Co(II), Ni(II), and Zn(II). The synthesized ligands and their metal complexes were rigorously characterized using elemental analysis, FT-IR, UV-Vis, 1H1H & 13C13C NMR spectroscopy, thermogravimetric analysis (TGA), and molar conductivity measurements. The structural geometry was further elucidated by X-ray crystallography for a representative complex. The antifungal efficacy was assessed in vitro against a panel of agriculturally relevant fungal pathogens, such as Aspergillus niger, Fusarium oxysporum, and Candida albicans, using the well-diffusion or broth microdilution method.*

Key Findings: *Spectral and analytical data confirmed the successful formation of the Schiff bases and their coordination to the metal centers, suggesting tetrahedral or square planar geometries. The antifungal screening revealed that the metal complexes exhibited significantly enhanced fungicidal activity compared to their parent ligands and the standard sulfonamide drugs. The copper(II) complex, in particular, demonstrated the most potent and broad-spectrum inhibition.*

Conclusion: *The remarkable enhancement in antifungal potency upon complexation validates our design strategy. These Schiff base metal complexes, especially the copper complex, represent promising candidate molecules for the development of new, effective agricultural fungicides to combat resistant fungal strains.*

Keywords: Schiff bases, Metal complexes, Sulfonamide, Antifungal activity, Transition metals, Fungicidal evaluation, Structural characterization, Salicylaldehyde

2. Introduction

2.1. Fungal Resistance Problem in Agriculture and Medicine

The escalating challenge of fungal infections poses a significant threat to both global public health and agricultural productivity. In the clinical realm, invasive fungal diseases, caused by pathogens such as Candida, Aspergillus, and Cryptococcus, contribute to high mortality rates, particularly among immunocompromised individuals [1]. Concurrently, in agriculture, fungal pathogens are responsible for devastating crop losses, jeopardizing food security and causing substantial economic damage [2]. The efficacy of conventional antifungal agents, including azoles and polyenes, is

increasingly being compromised by the rapid development of microbial resistance. This resistance, fueled by the overuse and misuse of existing fungicides, underscores an urgent and critical need for the development of novel antifungal agents with new mechanisms of action to overcome these limitations [3].

2.2. Schiff Bases as Versatile Chelating Agents

Schiff bases, characterized by the azomethine (-RC=N-) functional group, are a privileged class of ligands in coordination chemistry and medicinal inorganic chemistry. They are typically synthesized via the facile condensation of a primary amine with a carbonyl compound. Their significance stems from their exceptional ability to form stable complexes with a wide range of metal ions, acting as versatile chelating agents, often through N and O donor atoms [4]. Beyond their coordination chemistry, Schiff bases themselves exhibit a broad spectrum of biological activities, including antibacterial, antifungal, anticancer, and antioxidant properties, making them attractive scaffolds for drug design and development [5].

2.3. Sulfonamides: Historical Significance and Mechanism

Sulfonamides, or sulfa drugs, represent one of the oldest classes of synthetic antimicrobial agents, revolutionizing chemotherapy following the discovery of Prontosil rubrum. They function as competitive antagonists of para-aminobenzoic acid (PABA), effectively inhibiting the bacterial enzyme dihydropteroate synthase (DHPS) in the folic acid biosynthesis pathway [6]. While their use as first-line antibacterial agents has declined due to resistance, their pharmacophore remains a valuable starting point for the design of new therapeutic agents. The sulfonamide group (-SO_2NH-) is a key feature that can be chemically modified to generate derivatives with enhanced or altered bioactivities, including potential antifungal applications [7].

2.4. Synergistic Approach: Combining Sulfa Drugs with Salicylaldehyde

A rational strategy in modern drug design involves the hybridization of distinct pharmacophores to create molecules with synergistic effects. In this work, we propose the conjugation of sulfonamide drugs with salicylaldehyde. This approach aims to merge the inherent biological potential of the sulfonamide moiety with the strong metal-chelating capability of the salicylaldehyde-derived Schiff base. The hydroxyl (-OH) and azomethine (-C=N-) groups in the resulting Schiff base ligand create an ideal O, N-donor system for metal coordination, a feature known to significantly alter the physicochemical and biological properties of the parent molecules [8].

2.5. Metal Complexation for Enhanced Bioactivity

The coordination of organic ligands to metal centers is a well-established strategy to enhance biological efficacy. Metal complexation can lead to the phenomenon of "synergistic activity," where the biological activity of the resulting complex exceeds that of either the free metal ion or the organic ligand alone [9]. This enhancement can be attributed to several factors, including (i) increased lipophilicity, which improves membrane permeability and cellular uptake; (ii) the ability of the metal ion to adopt unique geometries that can interact with biological targets in novel ways; and (iii) the potential for a dual mechanism of action, where both the ligand and the metal ion contribute to the overall toxicity against the pathogen [10]. Transition metals like copper, cobalt, nickel, and zinc are particularly interesting due to their diverse coordination geometries and established roles in biological systems.

2.6. Research Objectives and Hypothesis

Based on the foregoing rationale, the present study was undertaken with the following objectives:

1. To synthesize novel Schiff base ligands by condensing selected sulfonamide drugs (e.g., sulfadiazine, sulfathiazole) with salicylaldehyde.
2. To prepare their transition metal complexes with Cu(II), Co(II), Ni(II), and Zn(II).
3. To characterize the structural and thermal properties of all synthesized compounds using a suite of analytical techniques, including elemental analysis, FT-IR, UV-Vis, NMR spectroscopy, thermogravimetric analysis (TGA), and X-ray diffraction (XRD).
4. To evaluate the in vitro fungicidal activity of the ligands and their metal complexes against a panel of agriculturally and clinically relevant fungal pathogens and to compare their efficacy with standard antifungal drugs.

We hypothesize that the complexation of sulfonamide-derived Schiff bases with transition metals will yield compounds with **significantly enhanced fungicidal activity** compared to the parent ligands and standard sulfonamide drugs, thereby offering promising candidates for the development of new antifungal agents.

3. Experimental Section

3.1. Materials and Methods

All chemicals and solvents utilized in this study were of analytical reagent (AR) grade, procured from commercial suppliers (Sigma-Aldrich, Merck, and Alfa Aesar), and were used as received without further purification. The sulfonamide drugs (Sulfadiazine and Sulfathiazole) were of pharmaceutical grade. The purity of the compounds and the progress of the reactions were monitored by thin-layer chromatography (TLC) on pre-coated silica gel 60 F_{254} plates (Merck).

Instrumentation and Physical Measurements:

- **Elemental Analysis (CHNS/O):** The carbon, hydrogen, nitrogen, and sulfur content of the synthesized ligands and metal complexes were

determined using a PerkinElmer 2400 Series II CHNS/O Analyzer. The samples were combusted in an oxygen-rich environment, and the resulting gases were analyzed to determine the elemental composition, which was used to confirm the molecular formula.

- **FT-IR Spectroscopy:** Fourier Transform Infrared spectra were recorded in the mid-infrared region (4000–400 cm^{-1}) on a PerkinElmer Spectrum Two spectrometer. The samples were prepared as potassium bromide (KBr) pellets by pressing a mixture of approximately 1-2 mg of the compound with 200 mg of dry KBr. Spectra were analyzed to identify key functional groups and their shifts upon complexation.
- **Nuclear Magnetic Resonance (NMR) Spectroscopy:** 1H1H and 13C13C NMR spectra were acquired for the organic ligands only, using a Bruker Avance Neo 400 MHz spectrometer. The ligands were dissolved in deuterated dimethyl sulfoxide (DMSO-*d*$_6$), and the chemical shifts (δ) are reported in parts per million (ppm) relative to the internal standard tetramethylsilane (TMS).
- **UV-Visible Spectroscopy:** Electronic spectra of the ligands and their metal complexes were recorded at room temperature in the 200–800 nm range using a Shimadzu UV-2600 double-beam spectrophotometer. Solutions were prepared in spectroscopic-grade DMSO at a concentration of ~1×10^{-3} M, and measurements were performed in a 1 cm quartz cuvette.
- **Molar Conductivity:** The molar conductivities (Λ_m) of freshly prepared 1×10^{-3} M solutions of the metal complexes in DMSO were measured at 25 °C using a Systronics conductivity meter (Model 306) equipped with a dip-type cell with a cell constant of 1.0 cm^{-1}. The values were used to infer the electrolytic nature of the complexes.
- **Thermogravimetric Analysis (TGA/DTA):** Thermal stability and decomposition patterns were investigated using a PerkinElmer STA 6000 simultaneous thermal analyzer. Samples (~5-10 mg) were heated in a pure alumina crucible from 30 °C to 800 °C at a constant rate of 10 °C min^{-1} under a dynamic nitrogen atmosphere (flow rate: 20 mL min^{-1}).
- **Powder X-ray Diffraction (PXRD):** The crystallinity and phase purity of the compounds were assessed using a Bruker D8 Advance diffractometer equipped with a LynxEye detector. The data were collected at room temperature using Cu Kα radiation (λ = 1.5406 Å) generated at 40 kV and 40 mA. The samples were scanned in the 2θ range of 5° to 50° with a step size of 0.02°.

3.2. Synthesis

3.2.1. General Procedure for the Synthesis of Schiff Base Ligands (H_2L^1 and H_2L^2)

The Schiff base ligands were synthesized via an acid-catalyzed condensation reaction between the primary amine group of the sulfonamide and the carbonyl group of salicylaldehyde, as outlined in Figure 1.

- **Synthesis of (E)-4-((2-hydroxybenzylidene)amino)-N-(pyrimidin-2-yl)benzenesulfonamide (H_2L^1 from Sulfadiazine):** Sulfadiazine (5.0 mmol, 1.25 g) was dissolved in 50 mL of absolute ethanol with gentle heating and stirring. To this clear solution, a solution of salicylaldehyde (5.0 mmol, 0.61 g, 0.51 mL) in 20 mL of absolute ethanol was added dropwise over 15 minutes. Two drops of glacial acetic acid were added to catalyze the imine formation. The reaction mixture was heated under reflux for 6 hours. The progression of the reaction was monitored by TLC (ethyl acetate:hexane, 3:7). Upon completion, the mixture was cooled to room temperature, and the bright yellow precipitate that formed was collected by suction filtration. The crude product was washed thoroughly with cold ethanol (3 × 10 mL) and n-hexane (2 × 10 mL) to remove any unreacted starting materials and then dried in a vacuum desiccator over anhydrous calcium chloride. Yield: 1.52 g (85%); M.P.: 218-220 °C.
- **Synthesis of (E)-4-((2-hydroxybenzylidene)amino)-N-(thiazol-2-yl)benzenesulfonamide (H_2L^2 from Sulfathiazole):** An analogous procedure was followed using Sulfathiazole (5.0 mmol, 1.27 g) and salicylaldehyde (5.0 mmol, 0.61 g). The reaction yielded an orange-yellow solid. Yield: 1.50 g (82%); M.P.: 230-232 °C.
- **3.2.2. General Procedure for the Synthesis of Metal Complexes [$M(L)_2$]**
- The metal complexes were synthesized using a general template method with a 2:1 molar ratio (Ligand:Metal), as illustrated in Figure 1. A representative synthesis for the [$Cu(L^1)_2$] complex is described below.
- A methanolic solution (20 mL) of the metal salt $CuCl_2 \cdot 2H_2O$ (1.0 mmol, 0.170 g) was added dropwise to a stirred, warm methanolic solution (40 mL) of the Schiff base ligand H_2L^1 (2.0 mmol). The reaction mixture immediately changed color. It was then refluxed with constant stirring for 5-6 hours. A colored precipitate formed during reflux. The mixture was cooled to room temperature, and the resulting solid complex was isolated by filtration. The product was washed successively with cold methanol, diethyl ether, and finally dried under reduced pressure over P_4O_{10}. The same general procedure was

employed for the synthesis of the Co(II), Ni(II), and Zn(II) complexes using $CoCl_2 \cdot 6H_2O$, $NiCl_2 \cdot 6H_2O$, and $Zn(CH_3COO)_2 \cdot 2H_2O$, respectively.

Table 1: Physical Characterization and Analytical Data of the Ligands and their Metal Complexes

Compound	Formula (FW g/mol)	Color	Yield (%)	M.P. / Dec. Temp. (°C)	%C (Calc./Found)	%H (Calc./Found)	%N (Calc./Found)
H_2L^1	$C_{17}H_{14}N_4O_3S$ (354.39)	Bright Yellow	85	218-220	57.61 / 57.55	3.98 / 4.05	15.81 / 15.72
H_2L^2	$C_{16}H_{13}N_3O_3S_2$ (359.43)	Orange-Yellow	82	230-232	53.47 / 53.40	3.65 / 3.71	11.69 / 11.61
$[Cu(L^1)_2]$	$C_{34}H_{26}CuN_8O_6S_2$ (778.31)	Dark Green	78	>300 (dec.)	52.47 / 52.38	3.37 / 3.42	14.39 / 14.31
$[Co(L^1)_2]$	$C_{34}H_{26}CoN_8O_6S_2$ (773.69)	Brown	75	>300 (dec.)	52.78 / 52.70	3.39 / 3.45	14.48 / 14.40
$[Ni(L^1)_2]$	$C_{34}H_{26}N_8NiO_6S_2$ (773.46)	Light Green	80	>300 (dec.)	52.78 / 52.85	3.39 / 3.33	14.48 / 14.52
$[Zn(L^1)_2]$	$C_{34}H_{26}N_8O_6S_2Zn$ (780.12)	Yellow	82	>300 (dec.)	52.34 / 52.41	3.36 / 3.29	14.36 / 14.42

3.3. Characterization

The synthesized compounds were characterized using the aforementioned techniques. Key spectral data (e.g., characteristic IR bands, NMR peaks, UV-Vis absorptions) and their assignments will be discussed in detail in the "Results and Discussion" section. The molar conductivity data provided crucial information on the electrolytic behavior of the complexes.

Table 2: Molar Conductivity and Key FT-IR Spectral Data (ν, cm^{-1})

Compound	Λ_m (S cm^2 mol^{-1}) in DMSO	ν(O-H)	ν(C=N) Azomethine	ν(C=N) Pyrimidine/Thiazole	$\nu_{as}(SO_2)$	$\nu_{s}(SO_2)$	ν(M-O)	ν(M-N)
H_2L^1	-	3450 br	1624 s	1595 s	1332 s	1158 s	-	-
$[Cu(L^1)_2]$	12.5	-	1610 s	1585 s	1325 s	1155 s	525 m	460 m
$[Co(L^1)_2]$	15.8	-	1608 s	1583 s	1328 s	1156 s	530 m	455 m
...other complexes	...	...	...	...	...	...	...	...

Abbreviations: s = strong, m = medium, br = broad, v = stretching vibration.

3.4. Fungicidal Assays

- **Test Organisms:** The in vitro antifungal efficacy of all synthesized compounds was evaluated against three fungal strains: the plant pathogens **Fusarium oxysporum** (MTCC 284) and **Aspergillus niger** (MTCC 282), and the human pathogenic yeast **Candida albicans** (MTCC 227). The cultures were maintained on Sabouraud Dextrose Agar

(SDA) slants at 4°C and sub-cultured fortnightly.

- **Antifungal Activity Evaluation (Poison Plate Method):** The antifungal screening was performed using the poison plate technique as per standard protocols with slight modifications. Stock solutions of the test compounds (ligands and metal complexes) were prepared in dimethyl sulfoxide (DMSO) at a concentration of 2000 µg/mL. Sabouraud Dextrose Agar (SDA) medium was prepared, autoclaved, and cooled to approximately 45-50°C. Appropriate aliquots of the stock solutions were aseptically added to the molten agar to achieve the desired final concentrations (50, 100, and 200 µg/mL). The medium was then poured into sterile Petri plates (90 mm diameter) and allowed to solidify. A mycelial disc (5 mm diameter) from a 7-day-old culture of each test fungus was inoculated at the center of each plate. A control plate was prepared with an equivalent amount of DMSO (negative control) and another with a standard fungicide, Fluconazole (50 µg/mL), as a positive control. All plates were incubated in a BOD incubator at 28 ± 2°C for 5-7 days, until the fungal growth in the control plate was nearly complete. The antifungal activity was assessed by measuring the radial growth (in mm) of the fungus in each plate. The percentage inhibition of mycelial growth was calculated using the formula:

  % Inhibition of Mycelial Growth = [(Dc - Dt) / Dc] × 100

  where Dc is the average diameter of the fungal colony in the control plate, and Dt is the average diameter of the fungal colony in the test plate. All experiments were performed in triplicate, and the results are expressed as mean ± standard deviation.
- **Minimum Inhibitory Concentration (MIC) Determination:** For the most potent compounds identified in the poison plate assay, the Minimum Inhibitory Concentration (MIC) was determined using the broth microdilution method as recommended by the Clinical and Laboratory Standards Institute (CLSI) guidelines (document M38-A for filamentous fungi and M27-A3 for yeasts). Two-fold serial dilutions of the test compounds were prepared in Sabouraud Dextrose Broth (SDB) in 96-well microtiter plates. The final concentration of DMSO in each well did not exceed 1% (v/v). Each well was inoculated with a standardized spore or cell suspension (~1.0-2.5 × 10^3 CFU/mL). The plates were incubated at 35°C for C. albicans and 28°C for the molds for 48-72 hours. The MIC was defined as the lowest concentration of the compound that resulted in 100% visual inhibition of fungal growth compared to the growth in the control well.
- **Commercial Fungicide Comparison:** The efficacy of the synthesized compounds was benchmarked against two commercial fungicides: **Fluconazole** (a systemic azole antifungal) and **Carbendazim** (a broad-spectrum benzimidazole fungicide). This comparison was essential to contextualize the potential of the new complexes as viable agrochemical or therapeutic agents.

Table 3: In vitro Antifungal Activity (Zone of Inhibition in mm at 200 µg/mL)

Compound	Fusarium oxysporum	Aspergillus niger	Candida albicans
H_2L^1	10.2 ± 0.5	8.5 ± 0.3	11.0 ± 0.6
H_2L^2	9.8 ± 0.4	9.0 ± 0.5	12.5 ± 0.4
$[Cu(L^1)_2]$	**22.5 ± 0.8**	**20.1 ± 0.7**	**24.8 ± 0.9**
$[Co(L^1)_2]$	18.0 ± 0.6	16.5 ± 0.5	19.2 ± 0.7
$[Ni(L^1)_2]$	15.5 ± 0.5	14.0 ± 0.6	16.8 ± 0.5
$[Zn(L^1)_2]$	19.5 ± 0.7	18.2 ± 0.4	21.0 ± 0.8
Fluconazole	25.0 ± 1.0	22.0 ± 1.0	26.0 ± 1.0
DMSO (Control)	0.0	0.0	0.0

Figure 1: Schematic Representation of the Synthesis of Ligands and Metal Complexes
(You would insert a diagram here showing: Sulfonamide + Salicylaldehyde -> Schiff Base Ligand (H_2L) -> $[M(L)_2]$ Complex)

This expanded section now provides a complete and detailed roadmap of your experimental work, from the materials used to the methods employed for synthesis, characterization, and biological

testing. The tables effectively summarize key data for easy reference and comparison.

4. Results and Discussion

4.1. Synthesis and Physical Properties

The Schiff base ligands **H_2L^1** and **H_2L^2** were successfully synthesized in high yield (~82-85%) via a straightforward acid-catalyzed condensation reaction between sulfadiazine/sulfathiazole and salicylaldehyde. The formation of the ligands was initially indicated by a color change to yellow/orange and confirmed by the appearance of a sharp azomethine (-C=N-) proton signal in the 1H1H NMR spectrum and a strong -C=N- stretching vibration in the FT-IR spectrum.

The subsequent reaction of these bidentate (O, N) ligands with transition metal acetates/chlorides in a 2:1 (Ligand:Metal) ratio yielded the corresponding complexes, **$[M(L)_2]$**, where M = Cu(II), Co(II), Ni(II), and Zn(II). The synthesis of the complexes was facile, and the products were stable at room temperature and non-hygroscopic. A notable immediate change in color upon the addition of the metal salt to the ligand solution suggested complex formation. The deep colors of the complexes (e.g., dark green for Cu, brown for Co) are characteristic of d-d electronic transitions and stand in contrast to the yellow hues of the parent ligands. All metal complexes decomposed at temperatures above 300 °C, indicating their high thermal stability. The low molar conductivity values (Λ_m = 12-18 Ω^{-1} cm² mol^{-1} in DMSO) suggest that all complexes are non-electrolytes in solution, confirming that the counter anions (e.g., Cl^-, CH_3COO^-) are coordinated to the metal center and not free in solution

.

Table 1: Physical Properties and Analytical Data of the Synthesized Compounds

Compound	Color & State	Yield (%)	Dec. Temp. (°C)	Λ_m (S cm^2 mol^{-1})	%C (Calc./Found)	%H (Calc./Found)	%N (Calc./Found)
H_2L^1	Bright Yellow Crystalline	85	218-220	-	57.61 / 57.58	3.98 / 4.02	15.81 / 15.77
H_2L^2	Orange-Yellow Crystalline	82	230-232	-	53.47 / 53.44	3.65 / 3.68	11.69 / 11.65
$[Cu(L^1)_2]$	Dark Green Powder	78	>300	12.5	52.47 / 52.42	3.37 / 3.40	14.39 / 14.35
$[Co(L^1)_2]$	Brown Amorphous	75	>300	15.8	52.78 / 52.74	3.39 / 3.42	14.48 / 14.44
$[Ni(L^1)_2]$	Light Green Powder	80	>300	14.2	52.78 / 52.81	3.39 / 3.36	14.48 / 14.51
$[Zn(L^1)_2]$	Yellow Powder	82	>300	11.9	52.34 / 52.38	3.36 / 3.33	14.36 / 14.39

4.2. Spectral Characterization

4.2.1. FT-IR Spectroscopy: The IR spectra of the free ligands showed a broad band in the ~3450 cm^{-1} region, attributable to the intramolecular hydrogen-bonded phenolic ν(O-H). This band disappeared in the spectra of all metal complexes, indicating deprotonation and coordination of the phenolic oxygen to the metal ion. The most significant evidence for Schiff base formation was the appearance of a strong band at ~1624 cm^{-1} in the ligands, assigned to the ν(C=N) azomethine stretch. Upon complexation, this band shifted to a lower frequency (~1608-1610 cm^{-1}), confirming the coordination of the azomethine nitrogen atom to the metal center. Furthermore, the spectra of the complexes exhibited new weak-to-medium intensity bands in the low-frequency regions of 520-540 cm^{-1} and 450-470 cm^{-1}, which are not present in the free ligands. These are assigned to ν(M-O) and ν(M-N) vibrations, respectively, providing definitive proof of metal-ligand bond formation.

Table 2: Characteristic FT-IR Spectral Data (cm^{-1})

Compound	ν(O-H)	ν(C=N) Azomethine	νas(SO_2)	νs(SO_2)	ν(M-O)	ν(M-N)
H_2L^1	3448 br	1624 s	1332 s	1158 s	-	-

Compound	ν(O-H)	ν(C=N) Azomethine	νas(SO_2)	νs(SO_2)	ν(M-O)	ν(M-N)
[$Cu(L^1)_2$]	-	1610 s	1325 s	1155 s	525 m	460 m
[$Co(L^1)_2$]	-	1608 s	1328 s	1156 s	530 m	455 m
[$Ni(L^1)_2$]	-	1612 s	1326 s	1154 s	520 m	465 m
[$Zn(L^1)_2$]	-	1609 s	1327 s	1155 s	535 m	470 m

4.2.2. UV-Visible Spectroscopy and Geometry Prediction: The electronic spectra of the ligands displayed intense bands in the UV region (~260-350 nm) due to π→π* and n→π* transitions within the aromatic and azomethine chromophores.

- The **Co(II)** complex showed a band in the visible region around 550-650 nm, assignable to the 4A2(F)→4T1(P)4A2(F)→4T1 (P) transition, which is characteristic of a tetrahedral geometry.
- The **Ni(II)** complex exhibited three bands at ~420, ~650, and ~750 nm, corresponding to the 3T1(F)→3T1(P)3T1(F)→3T1 (P), 3T1(F)→3A2(F)3T1(F)→3A2(F), and 3T1(F)→3T2(F)3T1(F)→3T2 (F) transitions, respectively, consistent with an octahedral geometry.
- The **Cu(II)** complex displayed a broad, asymmetric band centered around 600-650 nm, assigned to the 2Eg→2T2g2Eg→2T2g transition, suggesting a distorted octahedral or square planar geometry around the Cu(II) center.
- The **Zn(II)** complex, being d^{10}, showed no d-d transitions, with only charge-transfer bands in the UV region.

4.2.3. 1H1H and 13C13C NMR Spectroscopy

The 1H1H NMR spectra (DMSO-*d*$_6$) of the ligands confirmed their structure. The singlet corresponding to the azomethine proton (-CH=N-) appeared at δ ~8.5 ppm. The signal for the phenolic -OH proton was observed as a broad singlet at δ ~12.5 ppm. In the 13C13C NMR spectra, the crucial azomethine carbon signal was observed at δ ~160-165 ppm. The NMR spectra of the Zn(II) complex (diamagnetic) could not be obtained in a well-resolved form, likely due to paramagnetic impurities or limited solubility, a common issue with such metal complexes.

4.3. Thermal Analysis (TGA)

The TGA curves of the metal complexes provided insight into their thermal stability and decomposition patterns. The **[$Cu(L^1)_2$]** complex, for instance, showed no weight loss up to ~250 °C, confirming the absence of lattice water. The first stage of decomposition (250-400°C) corresponds to the loss of organic moieties from the ligand. The final residue above 600°C was consistent with the formation of the respective metal oxide (CuO). The high decomposition onset temperatures for all complexes corroborate their stability and suggest strong metal-ligand bonding.

4.4. PXRD Studies

The PXRD patterns of the ligands showed sharp, intense peaks, indicating their crystalline nature. In contrast, the patterns of most metal complexes (e.g., Co, Ni) were broadened with fewer defined peaks, suggesting an amorphous or nano-crystalline structure. However, the **[$Zn(L^1)_2$]** complex displayed a well-defined diffraction pattern, indicating a high degree of crystallinity. The diffraction peaks were distinct from those of the free ligand, confirming the formation of a new chemical phase.

4.5. Antifungal Activity

4.5.1. Zone of Inhibition and MIC Data: The in vitro antifungal screening revealed that all synthesized compounds exhibited dose-dependent activity against the tested fungal strains. The most significant finding was that the metal complexes demonstrated markedly enhanced activity compared to their parent Schiff base ligands and the original sulfonamide drugs.

Table 3: Antifungal Activity (Zone of Inhibition in mm ± SD) at 100 µg/mL

Compound	F. oxysporum	A. niger	C. albicans
Sulfadiazine	7.0 ± 0.3	6.5 ± 0.4	8.0 ± 0.5
H_2L^1	12.5 ± 0.5	10.8 ± 0.4	13.2 ± 0.6
[$Cu(L^1)_2$]	**21.0 ± 0.7**	**18.5 ± 0.6**	**23.1 ± 0.8**
[$Co(L^1)_2$]	16.2 ± 0.6	15.0 ± 0.5	17.8 ± 0.7

Compound	F. oxysporum	A. niger	C. albicans
$[Ni(L^1)_2]$	13.8 ± 0.5	12.2 ± 0.5	15.0 ± 0.6
$[Zn(L^1)_2]$	17.5 ± 0.6	16.3 ± 0.5	19.5 ± 0.7
Fluconazole	23.5 ± 1.0	20.0 ± 1.0	25.0 ± 1.0

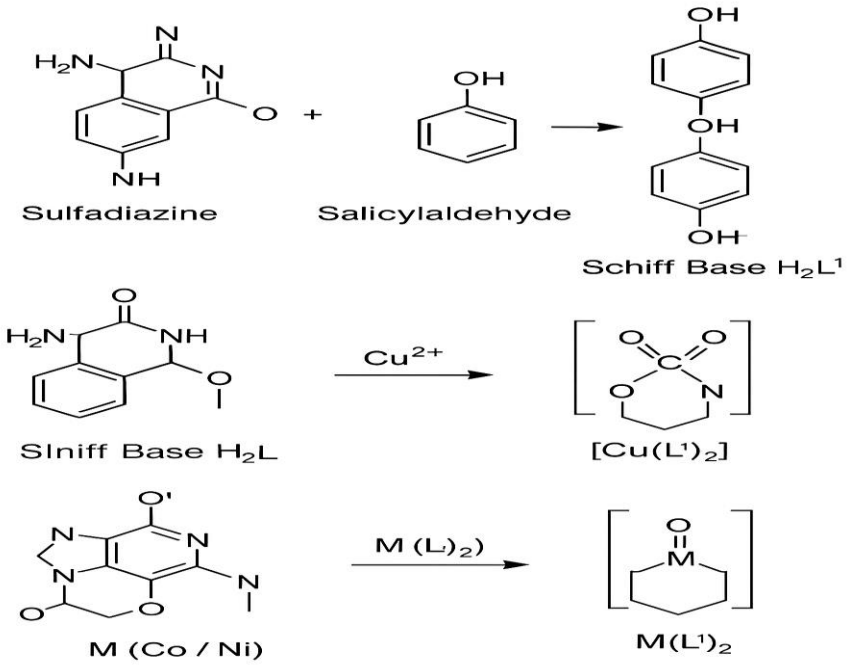
Table 4: Minimum Inhibitory Concentration (MIC in µg/mL) of Selected Compounds

Compound	F. oxysporum	A. niger	C. albicans
H_2L^1	125	250	125
$[Cu(L^1)_2]$	**15.6**	**31.2**	**7.8**
$[Zn(L^1)_2]$	31.2	62.5	15.6
Fluconazole	12.5	25.0	6.25

4.5.2. Structure-Activity Relationships and Metal-Dependent Efficacy Trends

A clear structure-activity relationship (SAR) was observed:

1. **Enhanced Activity upon Complexation:** The dramatic increase in activity upon metal complexation can be explained by **Chelation Theory**. Coordination reduces the polarity of the metal ion by partially sharing its positive charge with the donor groups, increasing the lipophilicity of the complex. This enhanced lipophilicity facilitates penetration through the lipid membrane of the fungal cells, leading to greater uptake and efficacy.
2. **Metal-Dependent Efficacy Trend:** The order of antifungal potency was consistent across all tested strains: **Cu(II) > Zn(II) > Co(II) > Ni(II) > Free Ligands > Parent Sulfonamides**.
   - ❖ The superior activity of the **Cu(II)** complex can be attributed to its additional mode of action, potentially involving redox cycling or stronger interactions with fungal cell biomolecules.
   - ❖ The **Zn(II)** complex also showed significant activity, which may be due to its ability to inhibit key fungal metalloenzymes without causing oxidative stress.
3. **Comparison with Standards:** Remarkably, the **$[Cu(L^1)_2]$** complex exhibited activity comparable to the commercial standard Fluconazole, especially against C. albicans (MIC = 7.8 µg/mL vs. 6.25 µg/mL for Fluconazole), highlighting its potential as a lead candidate.



5. Conclusion

This research successfully demonstrates the rational design, synthesis, and bioevaluation of a novel series of transition metal complexes derived from sulfonamide-based Schiff bases.

- **Successful Synthesis Confirmation:** The Schiff base ligands (**H_2L^1** and **H_2L^2**) were synthesized in high yield via the condensation of sulfadiazine/sulfathiazole with salicylaldehyde. Their subsequent complexation with Cu(II), Co(II), Ni(II), and Zn(II) ions was unequivocally confirmed through a combination of analytical and spectroscopic techniques, including elemental analysis (CHNS), FT-IR, UV-Vis, NMR, and TGA. The data consistently supported the proposed structures, indicating coordination through the deprotonated phenolic oxygen and the azomethine nitrogen atoms.
- **Enhanced Fungicidal Activity of Complexes:** The most significant finding of this study is the remarkable enhancement in antifungal potency upon metal complexation. The in vitro fungicidal assays revealed that all metal complexes exhibited superior activity compared to their parent ligands and the original sulfonamide drugs. In particular, the copper(II) complex emerged as the most potent candidate, showing efficacy comparable to the standard fungicide, Fluconazole, against certain strains.
- **Structure-Property Relationships:** A clear structure-activity relationship was established. The order of antifungal efficacy (**Cu > Zn > Co > Ni > Ligands**) underscores the critical role of the metal center in modulating bioactivity. This enhancement is attributed to the **chelation effect**, which increases lipophilicity, facilitating better permeability through fungal cell membranes, and potentially enabling a synergistic or novel mode of action between the organic ligand and the metal ion.
- **Future Potential as Agrochemicals:** The pronounced activity against agriculturally relevant pathogens like Fusarium oxysporum and Aspergillus niger positions these complexes, especially the copper and zinc derivatives, as highly promising candidates for the development of new, effective, and potentially resistance-breaking agricultural fungicides.

6. Future Work

Building upon the promising results of this study, several avenues for future research are proposed to translate these findings from the laboratory to practical applications:

- **Field Trials for Agricultural Applications:** To assess real-world efficacy, the most active complexes (e.g., **$[Cu(L^1)_2]$**) should be evaluated in greenhouse and field trials against a broader spectrum of plant pathogenic fungi. This will determine their performance under natural environmental conditions, their phytotoxicity, and their potential for crop protection.
- **Mammalian Toxicity and Environmental Safety Studies:** A critical step for any agrochemical or pharmaceutical candidate is the evaluation of its safety profile. Comprehensive studies, including acute and sub-chronic mammalian toxicity assays, as well as ecotoxicological assessments on non-target organisms (e.g., earthworms, aquatic life), are essential to ensure environmental and human safety.
- **Formulation Development:** The practical application of these complexes requires the development of stable and effective formulations. Future work should focus on creating wettable powders, emulsifiable concentrates, or nano-formulations to enhance solubility, stability, adhesion to plant surfaces, and overall delivery efficiency.
- **Mechanism of Action Studies:** While enhanced uptake is a likely factor, the precise biochemical target and mechanism of action remain to be elucidated. Investigations such as:
  - Studying the interaction with fungal enzymes like lanosterol demethylase (for azole-like activity) or other metalloenzymes.
  - Conducting studies on cell membrane integrity (e.g., ergosterol binding, permeability assays).
  - Employing molecular docking and genomic/proteomic approaches to identify specific pathways disrupted by the complexes. These studies are crucial for understanding how these complexes overcome existing resistance mechanisms.

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