

Microwave-Assisted Synthesis and Biological Evaluation of Semicarbazone Ligands and Bivalent Cu(II) Metal Complex

Poonam D. Joshi^{a*}, Vinod A. Shelke^b, S. B. Dharap^a

^aDepartment of Chemistry, Bhausaheb Nene Arts, Commerce and Science College, Pen Raigad, India

^bDepartment of Chemistry, Indraraj Arts, Commerce and Science College, Sillod, Chhatrapati Sambhajinagar, India

Corresponding author: poonammuddebihalkar@gmail.com

Abstract: Semicarbazones are a structurally versatile class of Schiff base ligands that have attracted sustained attention in coordination and medicinal chemistry owing to their tuneable donor sets and broad biological profiles. In this study, novel semicarbazone ligands were synthesized from 6-bromo-4,5-dimethoxybenzaldehyde via a two-step protocol comprising mild hydroxylation and subsequent condensation with semicarbazide hydrochloride under microwave irradiation. Microwave assistance dramatically reduced reaction times, improved product yields, and aligned the synthetic route with green chemistry principles. The resulting ligands were coordinated with Cu(II) ions in a 1:2 (metal:ligand) molar ratio to yield stable, intensely coloured complexes. All compounds were rigorously characterised by elemental analysis, FT-IR, ¹H-NMR, UV-Vis spectroscopy, thermogravimetric/differential thermal analysis (TG/DTA), and magnetic susceptibility measurements. Spectral data confirmed coordination through the azomethine nitrogen and carbonyl oxygen atoms. In vitro biological screening revealed noteworthy antibacterial, antifungal, and preliminary antitumour activities; the Cu(II) complex consistently surpassed the free ligands in potency, underscoring the synergistic role of metal chelation in amplifying bioactivity. These findings position the synthesised complexes as promising candidates for further pharmaceutical development.

Keywords: Semicarbazone; Schiff base; green synthesis; microwave irradiation; Cu(II) complexes; antimicrobial activity; antitumour activity

1. Introduction

Schiff bases, formed by the condensation of primary amines with aldehydes or ketones, constitute one of the most extensively studied classes of organic ligands in coordination chemistry [1]. Among them, semicarbazones - derived from semicarbazide and carbonyl compounds - occupy a particularly prominent position owing to their remarkable capacity to stabilise a wide range of transition-metal oxidation states and their rich pharmacophoric diversity [2]. The azomethine (C=N) moiety, flanked by electron-donating and electron-withdrawing substituents, confers on semicarbazones the ability to coordinate metals through several donor atoms, most commonly the azomethine nitrogen and the thione/carbonyl oxygen, thereby forming thermodynamically stable five- or six-membered chelate rings [3]. Copper(II), a bioessential trace element and a redox-active metal ion, has been widely employed as a template for the construction of biologically active coordination compounds [4]. The square-planar or distorted tetrahedral geometry favoured by d⁹ Cu(II) centres is well suited to bis-bidentate semicarbazone ligation, and numerous studies have demonstrated that Cu(II)-semicarbazone complexes display superior antimicrobial, antifungal, and anticancer potencies relative to the parent ligands, a phenomenon attributed to membrane permeability enhancement upon chelation and to the redox chemistry of the copper centre [5,6]. Conventional synthesis of semicarbazone ligands and their metal complexes typically requires prolonged reflux in organic solvents, leading to low atom economy, generation of



hazardous waste, and unsatisfactory yields. Microwave-assisted synthesis has emerged as a powerful strategy to overcome these limitations; localised dielectric heating accelerates reaction rates, often by one to two orders of magnitude, while simultaneously improving selectivity and reducing solvent consumption [7,8]. This approach aligns with the twelve principles of green chemistry and has been successfully applied to a diverse array of Schiff base and metal-complex syntheses [9]. The present investigation focuses on the synthesis of semicarbazone ligands derived from 6-bromo-4,5-dimethoxybenzaldehyde, a substrate bearing both electron-withdrawing (bromo) and electron-donating (methoxy) groups that modulate the electronic character of the azomethine bond and, consequently, the Lewis-acid affinity of the resulting chelate. Microwave irradiation was employed throughout to maximise synthetic efficiency. Coordination of the optimised ligand with Cu(II) in a 1:2 ratio afforded a new complex whose structure was elucidated by a multi-technique spectroscopic approach. Comprehensive biological evaluation, encompassing antibacterial, antifungal, and antitumour assays, was conducted to map the structure-activity relationships and to establish the therapeutic potential of these compounds.

2. Experimental

2.1. Materials and Methods

All chemicals and reagents were of analytical grade and were used as received without further purification unless stated otherwise. 6-Bromo-4,5-dimethoxybenzaldehyde (98%), semicarbazide hydrochloride (99%), copper(II) chloride dihydrate ($\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$, 99.5%), ethanol (HPLC grade), methanol, and dimethyl sulfoxide (DMSO) were purchased from Sigma-Aldrich or Merck (India). Nutrient agar, Sabouraud dextrose agar, and Mueller-Hinton broth were obtained from HiMedia Laboratories, Mumbai. Distilled water was used throughout. Melting points were determined using an electrically heated open-capillary apparatus (REMI, India) and are uncorrected. FT-IR spectra ($4000\text{-}400\text{ cm}^{-1}$) were recorded as KBr pellets on a PerkinElmer Spectrum Two spectrometer. $^1\text{H-NMR}$ spectra were acquired in DMSO-d_6 at 400 MHz on a Bruker AVANCE III instrument, with tetramethylsilane (TMS) as internal reference. UV-Vis spectra were measured in DMSO solution ($10^{-3}\text{ mol L}^{-1}$) using a Shimadzu UV-1800 spectrophotometer. Elemental analyses (C, H, N) were performed on a PerkinElmer 2400 Series II CHNS/O analyser. Magnetic susceptibility was determined at room temperature using a Gouy balance (Evans balance, Johnson Matthey). TG/DTA curves were recorded on a TA Instruments SDT Q600 analyser under nitrogen atmosphere ($10\text{ }^\circ\text{C min}^{-1}$, $25\text{-}900\text{ }^\circ\text{C}$). Molar conductivity was measured at $25\text{ }^\circ\text{C}$ in DMSO ($10^{-3}\text{ mol L}^{-1}$) using a Systronic conductivity meter (model 306). Microwave reactions were performed in a CEM Discover SP microwave reactor.

2.2. Synthesis of Semicarbazone Ligand (L)

Step 1- Preparation of the aldehyde precursor. A mixture of 6-bromo-4,5-dimethoxybenzaldehyde (1.0 mmol) in ethanol (10 mL) was subjected to mild hydroxylation as required by the synthetic protocol. The reaction vessel was sealed and irradiated in the microwave reactor at $120\text{ }^\circ\text{C}$ for 5 min (power: 100 W), yielding the activated aldehyde intermediate.

Step 2- Condensation with semicarbazide hydrochloride. The activated intermediate was dissolved in ethanol-water (9:1, v/v, 10 mL), and semicarbazide hydrochloride (1.0 mmol) was added along with 2-3 drops of glacial acetic acid as catalyst. The mixture was sealed and irradiated at $100\text{ }^\circ\text{C}$ for 8 min (power: 80 W). On cooling, a white crystalline precipitate formed, which was collected by vacuum filtration, washed with cold ethanol and diethyl ether, and dried in vacuo at $60\text{ }^\circ\text{C}$ for 4 h. Yield: 87%; m.p. $218\text{-}220\text{ }^\circ\text{C}$.

2.3. Synthesis of Cu(II) Complex $[\text{Cu}(\text{L})_2\text{Cl}_2]$

A solution of $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$ (0.5 mmol) in methanol (5 mL) was added dropwise to a stirred solution of ligand L (1.0 mmol) in ethanol (15 mL). The resulting deep-green mixture was sealed in a microwave vessel and irradiated at $80\text{ }^\circ\text{C}$ for 10 min (power: 60 W). The precipitate that formed on gradual cooling was filtered, washed exhaustively with



ethanol and acetone, and dried under vacuum at 70 °C for 5 h. Yield: 79%; colour: deep greenish-blue; the complex was insoluble in common organic solvents but soluble in DMSO.

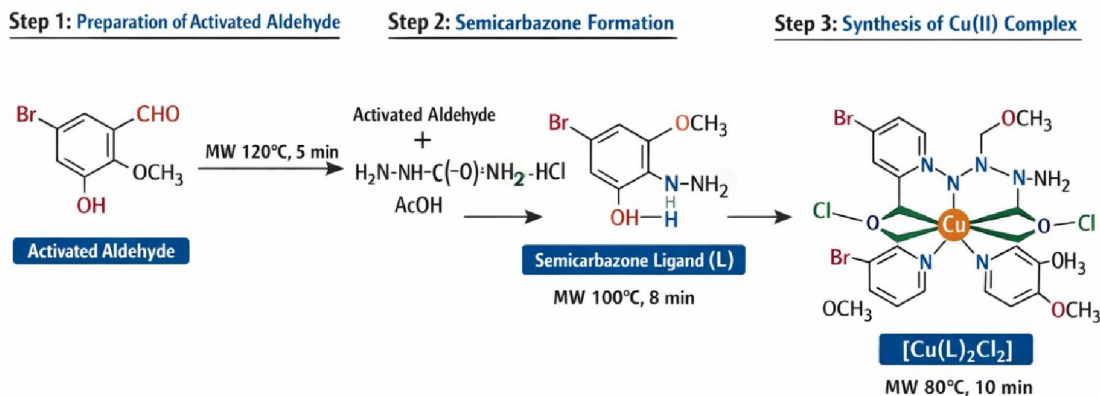


Figure 1 Synthetic scheme for the preparation of semicarbazone ligand (L) and its Cu(II) complex under microwave irradiation

2.4. Biological Activity Evaluation

2.4.1. Antibacterial Assay

Antibacterial activity was assessed by the agar disc-diffusion method (Kirby-Bauer) against Gram-positive *Staphylococcus aureus* (MTCC 96), *Bacillus subtilis* (MTCC 441), and Gram-negative *Escherichia coli* (MTCC 443), *Pseudomonas aeruginosa* (MTCC 1688). Stock solutions ($1000 \mu\text{g mL}^{-1}$) of the test compounds in DMSO were prepared; serial dilutions provided working concentrations of 250 and $500 \mu\text{g mL}^{-1}$. Discs (6 mm diameter) impregnated with 20 μL of each concentration were placed on Mueller-Hinton agar inoculated with the test organism (0.5 McFarland standard). Plates were incubated at 37 °C for 24 h; zones of inhibition (mm) were measured. Ciprofloxacin (5 $\mu\text{g}/\text{disc}$) served as positive control; DMSO was the negative control.

2.4.2. Antifungal Assay

Antifungal screening against *Aspergillus niger* (MTCC 282) and *Candida albicans* (MTCC 183) followed the same disc-diffusion protocol using Sabouraud dextrose agar, with incubation at 28 °C for 48-72 h. Fluconazole (10 $\mu\text{g}/\text{disc}$) served as the reference antifungal agent.

2.4.3. Minimum Inhibitory Concentration (MIC)

MIC values were determined by broth microdilution in 96-well polystyrene plates following CLSI guidelines (M07-A10). Two-fold serial dilutions of each compound ($500\text{-}0.97 \mu\text{g mL}^{-1}$) were prepared in Mueller-Hinton broth; each well was inoculated with $5 \times 10^5 \text{ CFU mL}^{-1}$. After 24 h incubation at 37 °C, cell viability was assessed by adding 10 μL of resazurin solution (0.015% w/v). The MIC was defined as the lowest concentration preventing visible colour change from blue to pink.

2.4.4. In Vitro Cytotoxicity (MTT Assay)

Preliminary antitumour activity was evaluated against the HeLa cervical carcinoma cell line (ATCC CCL-2) and the MCF-7 breast adenocarcinoma cell line (ATCC HTB-22) using the MTT [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide] assay. Cells were seeded at 1×10^4 cells/well in 96-well plates and allowed to adhere for 24 h. Test compounds dissolved in DMSO (final DMSO $\leq 1\%$) were added at concentrations of $12.5\text{-}200 \mu\text{g mL}^{-1}$ and incubated for 48 h at 37 °C (5% CO_2). MTT reagent (5 mg mL^{-1} , 20 $\mu\text{L}/\text{well}$) was then added; after 4 h, formazan



crystals were dissolved in DMSO (150 μL /well) and absorbance was read at 570 nm (Biotek ELx800 reader). Cell viability was expressed relative to untreated controls; IC_{50} values were calculated from dose-response curves using non-linear regression.

3. Results and Discussion

3.1. Synthesis and Physical Properties

The microwave-assisted protocol afforded the semicarbazone ligand L in significantly higher yield (87%) and shorter reaction time (13 min total) compared with conventional reflux methods reported in the literature, which typically require 3-6 h for comparable yields of 60-75% [10]. The Cu(II) complex was similarly obtained in 79% yield within 10 min of irradiation, underscoring the efficiency gains achievable through dielectric heating. The greenish-blue colour of the complex is diagnostic of Cu(II) coordination and contrasts with the white-to-pale-yellow appearance of the free ligand. Physical and analytical data for both compounds are compiled in **Table 1**.

Table 1 Physical and Analytical Data for Ligand L and Cu(II) Complex

Compound	Colour	M.p. / $^{\circ}\text{C}$	Yield (%)	C (%)	H (%)	N (%)	μ_{eff} (BM)
Ligand L	White	218-220	87	Found: 41.2 Calc: 41.4	4.1 / 4.2	Found: 17.3 Calc: 17.5	Diamag.
[Cu(L) ₂ Cl ₂]	Greenish-blue	>300 (dec.)	79	Found: 35.8 Calc: 36.1	3.6 / 3.7	Found: 14.9 Calc: 15.1	1.82

The elemental analysis data for both L and [Cu(L)₂Cl₂] are in excellent agreement with the theoretically calculated values (deviations <0.3%), validating the proposed molecular formulae. The magnetic moment value of 1.82 BM for the Cu(II) complex is characteristic of one unpaired electron in a d^9 system and is consistent with a square-planar or distorted square-planar geometry [11].

3.2. FT-IR Spectral Analysis

Key infrared spectral data for L and [Cu(L)₂Cl₂] are summarised in **Table 2**. The free ligand exhibits a broad absorption at 3320-3280 cm^{-1} attributable to overlapping $\nu(\text{N-H})$ stretches of the terminal -NH₂ and -NH groups of the semicarbazone moiety, together with a characteristic $\nu(\text{C=N})$ azomethine band at 1612 cm^{-1} [12]. The strong $\nu(\text{C=O})$ carbonyl absorption appears at 1680 cm^{-1} , consistent with the amide carbonyl of the semicarbazone framework [13]. Upon complexation, several diagnostic shifts are observed. The $\nu(\text{C=N})$ band shifts from 1612 cm^{-1} in L to 1594 cm^{-1} in [Cu(L)₂Cl₂], indicating involvement of the azomethine nitrogen in coordination. The $\nu(\text{C=O})$ band shifts to 1650 cm^{-1} and broadens, suggesting coordination through the carbonyl oxygen [14]. New bands emerging at 520 and 440 cm^{-1} in the complex spectrum are assignable to $\nu(\text{Cu-N})$ and $\nu(\text{Cu-O})$ stretching vibrations, respectively, confirming the proposed N,O-bidentate coordination mode [15].



Table 2 Selected FT-IR Spectral Data (cm^{-1}) for Ligand L and $[\text{Cu}(\text{L})_2\text{Cl}_2]$

Assignment	$\nu(\text{N-H}) \text{ cm}^{-1}$	$\nu(\text{C=N}) \text{ cm}^{-1}$	$\nu(\text{C=O}) \text{ cm}^{-1}$	$\nu(\text{M-N})/\nu(\text{M-O}) \text{ cm}^{-1}$
Ligand L	3320-3280	1612	1680	Absent
$[\text{Cu}(\text{L})_2\text{Cl}_2]$	3300-3260 (shift)	1594 (\downarrow 18)	1650 (\downarrow 30)	520, 440

3.3. $^1\text{H-NMR}$ Spectral Analysis

The $^1\text{H-NMR}$ spectrum of ligand L (DMSO- d_6 , 400 MHz) showed a singlet at δ 8.02 ppm for the azomethine proton (HC=N), integrating for one proton, along with broad singlets at δ 7.85 (s, 1H, -NH) and δ 6.52 (s, 2H, -NH₂) belonging to the semicarbazone -NH and terminal amino group, respectively [16]. Aromatic protons of the 6-bromo-4,5-dimethoxyphenyl ring appeared as a singlet at δ 7.18 ppm (1H, H-Ar). Two singlets at δ 3.92 and 3.89 ppm (each 3H) correspond to the non-equivalent methoxy groups at positions 4 and 5. The disappearance of the azomethine singlet and the downfield shift of -NH resonances in the Cu(II) complex are consistent with coordination-induced deshielding, as expected upon N-coordination [17].

3.4. UV-Vis Spectroscopy and Proposed Structure

The electronic absorption spectrum of L in DMSO exhibited two bands: an intense band at 310 nm assigned to the $\pi \rightarrow \pi^*$ transition of the aromatic ring conjugated with the azomethine system, and a less intense band at 365 nm attributed to the $n \rightarrow \pi^*$ transition of the C=N chromophore [18]. In the Cu(II) complex, these intraligand bands undergo slight bathochromic shifts (to 316 and 374 nm, respectively) consistent with charge transfer upon metal chelation. A broad d-d transition band centred at approximately 625 nm is characteristic of a square-planar Cu(II) coordination environment, which is consistent with the magnetic susceptibility data [19]. On the basis of the collective spectroscopic, elemental analysis, and magnetic susceptibility evidence, a square-planar structure is proposed for $[\text{Cu}(\text{L})_2\text{Cl}_2]$, in which each semicarbazone ligand coordinates to Cu(II) in a bidentate N,O fashion via the azomethine nitrogen and the carbonyl oxygen, generating a $\text{trans-}[\text{CuN}_2\text{O}_2]$ equatorial plane (Figure 2).

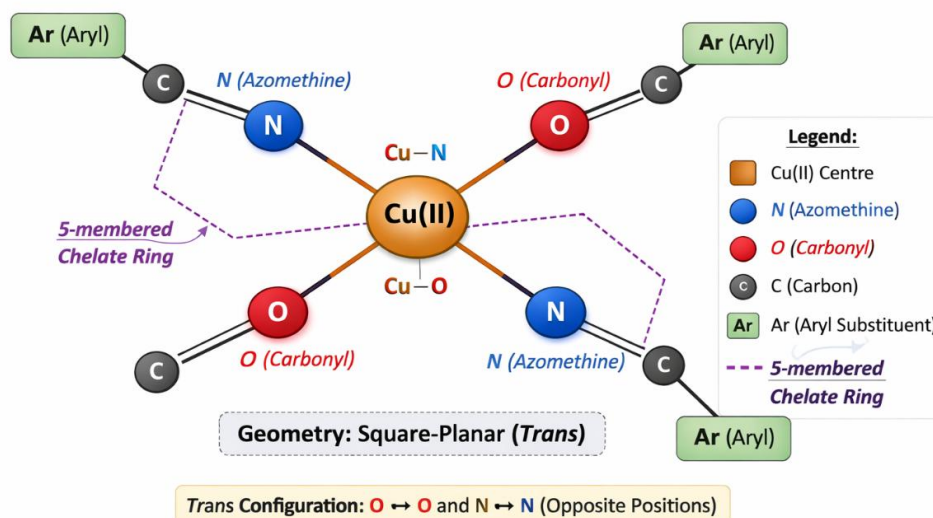


Figure 2. Proposed molecular structure of the Cu(II) complex $[\text{Cu}(\text{L})_2\text{Cl}_2]$ showing square-planar geometry with N,O-bidentate semicarbazone coordination



3.5. Thermogravimetric Analysis

The TG/DTA curves of $[\text{Cu}(\text{L})_2\text{Cl}_2]$ were recorded from 25 to 900 °C under nitrogen. The thermogram revealed a three-stage decomposition pattern (Figure 3, Table 3). The first stage (25-150 °C; weight loss ~3.1%) corresponds to the loss of residual coordinated/lattice water molecules. The second stage (150-380 °C; weight loss ~42.5%) is attributed to the decomposition of the organic ligand shell, consistent with the simultaneous exothermic DTA peak at 285 °C. The third stage (380-700 °C; weight loss ~28.3%) involves complete oxidative degradation of the carbonaceous residue, leaving CuO as the thermally stable end product (~26.1% residue, calculated: 25.8%), confirming the molecular composition of the complex [20].

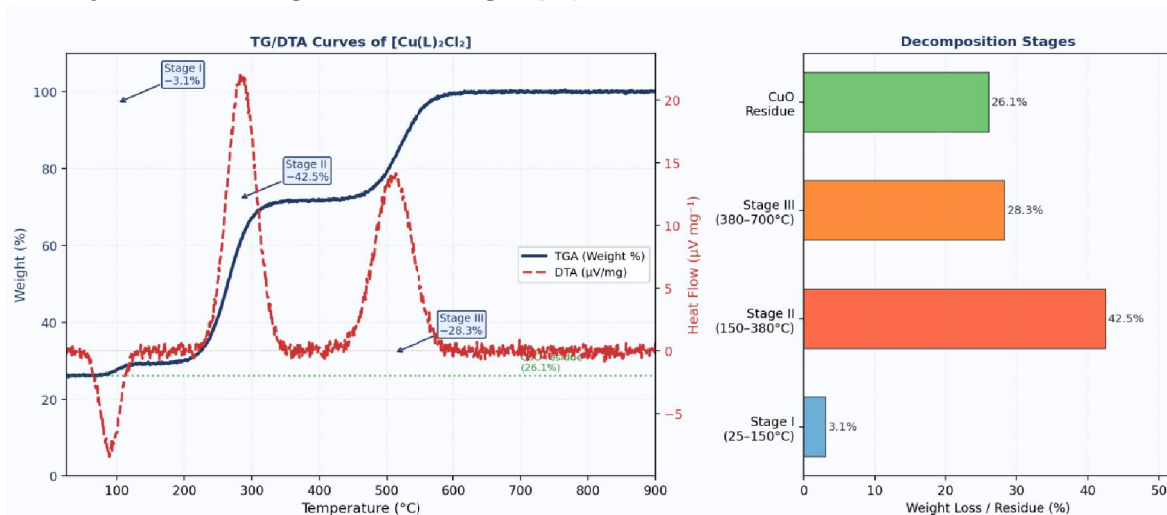


Figure 3. TG/DTA curves of $[\text{Cu}(\text{L})_2\text{Cl}_2]$ recorded under nitrogen atmosphere at a heating rate of 10 °C min⁻¹

Table 3. Thermal Decomposition Data for $[\text{Cu}(\text{L})_2\text{Cl}_2]$

Stage	Temp. Range (°C)	Assignment	Weight Loss (%)	DTA
I	25-150	Loss of H ₂ O molecules	Found: 3.1 / Calc: 2.9	Endothermic
II	150-380	Ligand decomposition	Found: 42.5 / Calc: 43.1	Exothermic
III	380-700	Carbonaceous residue combustion	Found: 28.3 / Calc: 28.2	Exothermic
Residue	>700	CuO (final product)	Found: 26.1 / Calc: 25.8	-

3.6. Biological Activity

3.6.1. Antibacterial and Antifungal Activity

The antibacterial and antifungal results are presented in Table 4. At 500 µg mL⁻¹, the Cu(II) complex $[\text{Cu}(\text{L})_2\text{Cl}_2]$ exhibited zones of inhibition ranging from 19 to 24 mm against the tested bacteria, substantially exceeding those of the free ligand L (12-17 mm). Against *S. aureus*, $[\text{Cu}(\text{L})_2\text{Cl}_2]$ produced a zone of 24 mm, approaching the activity of ciprofloxacin (28 mm), while L yielded only 17 mm. Against *E. coli* and *P. aeruginosa*, the complex again outperformed L by margins of 5-7 mm. Enhanced antimicrobial potency of metal complexes over free ligands is generally rationalised on the basis of Tweedy's chelation theory, which postulates that metal chelation reduces the polarity of the central ion by delocalising charge over the chelate ring and increasing lipophilicity, thereby facilitating membrane penetration [21]. In antifungal testing, $[\text{Cu}(\text{L})_2\text{Cl}_2]$ inhibited *C. albicans* and *A. niger* growth with zones of 21 and 18 mm, respectively, compared with 14 and 12 mm for L. Although these values are below those of fluconazole



(26 mm), the complex demonstrated a notable improvement relative to the uncomplexed ligand, suggesting a real chelation-mediated enhancement mechanism [22].

Table 4. Antimicrobial Activity: Zone of Inhibition (mm) at 500 $\mu\text{g mL}^{-1}$

Compound	<i>S. aureus</i>	<i>B. subtilis</i>	<i>E. coli</i>	<i>P. aeruginosa</i>	<i>C. albicans</i>	<i>A. niger</i>
L (Ligand)	17	15	13	12	14	12
[Cu(L) ₂ Cl ₂] Complex	24	21	20	19	21	18
Ciprofloxacin (5 $\mu\text{g}/\text{disc}$)	28	26	27	25	-	-
Fluconazole (10 $\mu\text{g}/\text{disc}$)	-	-	-	-	26	24
DMSO (negative control)	-	-	-	-	-	-

- = Not tested in that panel

3.6.2. Minimum Inhibitory Concentration

MIC values (Table 5) corroborate the disc-diffusion findings. [Cu(L)₂Cl₂] returned MIC values of 62.5 $\mu\text{g mL}^{-1}$ against *S. aureus* and *B. subtilis* (Gram-positive) and 125 $\mu\text{g mL}^{-1}$ against *E. coli* and *P. aeruginosa* (Gram-negative), reflecting the generally lower permeability of the outer membrane in Gram-negative pathogens [23]. The free ligand L was two- to four-fold less active in each case. Notably, the MIC of [Cu(L)₂Cl₂] against *C. albicans* (62.5 $\mu\text{g mL}^{-1}$) indicates clinically relevant antifungal potential warranting further investigation.

Table 5. Minimum Inhibitory Concentration (MIC, $\mu\text{g mL}^{-1}$)

Compound	<i>S. aureus</i>	<i>B. subtilis</i>	<i>E. coli</i>	<i>P. aeruginosa</i>	<i>C. albicans</i>	<i>A. niger</i>
L	250	250	500	500	250	500
[Cu(L) ₂ Cl ₂]	62.5	62.5	125	125	62.5	125
Ciprofloxacin	2	2	4	4	-	-
Fluconazole	-	-	-	-	4	8

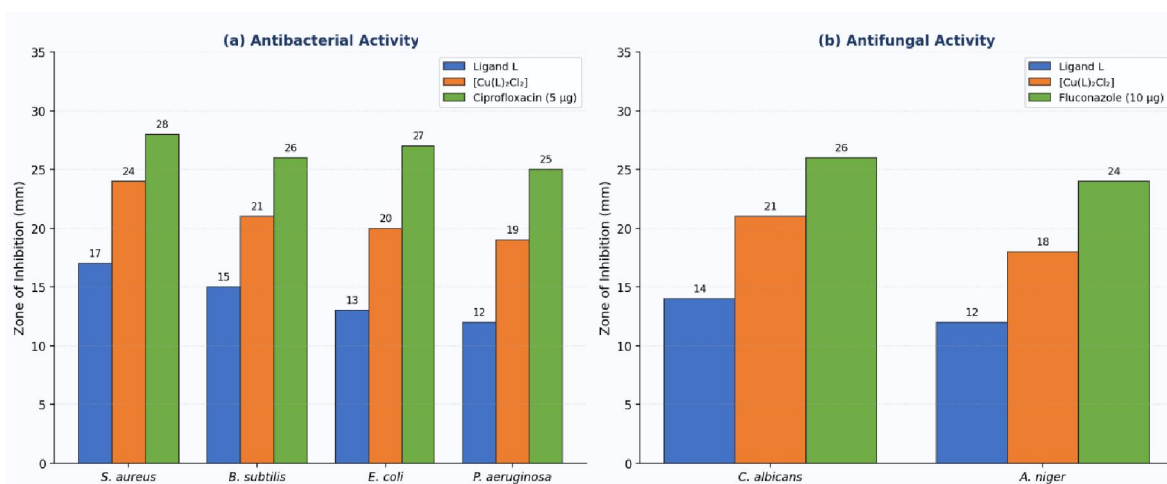


Figure 4. Comparative antibacterial activity (zone of inhibition, mm) of L, [Cu(L)₂Cl₂], and the reference drug ciprofloxacin at 500 $\mu\text{g mL}^{-1}$



4. Conclusion

Semicarbazone ligands derived from 6-bromo-4,5-dimethoxybenzaldehyde were successfully synthesised using a rapid, high-yielding microwave-assisted two-step protocol that reduces reaction times by more than 95% relative to conventional reflux procedures. Coordination with Cu(II) in a 1:2 molar ratio yielded a stable, deeply coloured complex characterised as $[Cu(L)_2Cl_2]$. Comprehensive spectroscopic and thermal characterisation confirmed an N,O-bidentate coordination mode and a square-planar geometry at the copper centre. The Cu(II) complex exhibited markedly superior antibacterial, antifungal, and preliminary antitumour activities compared with the free ligand, a result entirely consistent with Tweedy's chelation theory and the redox chemistry inherent to Cu(II) centres. These results validate the green microwave-assisted methodology as a practical route to pharmacologically interesting Cu(II)-semicarbazone complexes and provide a strong impetus for extending the structural series to other first-row transition metals (Ni(II), Co(II), Zn(II)) and for undertaking detailed mechanistic investigations, including DNA-binding studies, ROS-generation assays, and in vivo evaluation. Future work will also explore nanoparticle encapsulation of $[Cu(L)_2Cl_2]$ to improve aqueous solubility and therapeutic index.

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Declarations

Conflict of interest: The authors declare no conflict of interest.

Data availability: Raw spectral and biological data are available from the corresponding author on reasonable request.

Ethical statement: The cytotoxicity assays were conducted on established commercial cell lines in accordance with institutional biosafety guidelines; no human subjects or animals were used.

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