J. Chem. Soc. Nigeria, Vol. 51, No. 1, pp 079 – 089 [2026] https://dx.doi.org/10.4314/jcsn.v51i1.6

SYNTHESIS, SPECTROSCOPIC CHARACTERIZATION, AND ANTIBACTERIAL ACTIVITY OF Cu[II], Cu[I], AND Ag[I] COMPLEXES OF 5-METHOXY- AND 5-DIFLUOROMETHOXY-2-MERCAPTOBENZIMIDAZOLES

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ABSTRACT

Copper [II], copper[I], and silver[I] complexes of 5-methoxy-2-mercaptobenzimidazole [MTZ] and 5-[difluoromethoxy]-2-mercaptobenzimidazole [FMZ] were synthesized and characterized by elemental analysis, infrared and NMR spectroscopy, and magnetic susceptibility measurements. The complexes exhibited thermal stability, melting/decomposing above 340°C, and were readily soluble in polar aprotic solvents such as DMSO and DMF. The analytical and spectral data confirmed 1:1 metal-to-ligand stoichiometries, with coordination occurring through the azomethine nitrogen and thiol sulphur atoms. The magnetic susceptibility data indicated paramagnetic behaviour for Cu[II] and diamagnetism for Cu[I] and Ag[I] complexes. The *in vitro* antibacterial activity of the complexes was evaluated using the agar well diffusion method against *Staphylococcus aureus*, *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, and *Salmonella typhi*. Among the synthesized compounds, AgMTZ displayed the highest and broadest antibacterial activity, followed by AgFMZ and CuMTZ, suggesting that metal ion type and ligand substitution significantly influence bioactivity. These findings reveal the potential of methoxy- and difluoromethoxy-substituted benzimidazole–metal complexes as promising antimicrobial agents with tunable activity profiles.

Keywords: 2-Mercaptobenzimidazole derivatives, Metal-ligand coordination, Infrared and NMR spectra, Antimicrobial evaluation

INTRODUCTION

Benzimidazole and its derivatives have attracted considerable attention owing to their broad pharmacological, catalytic, and corrosion-inhibitory properties. The incorporation of sulphur functionality at position 2 in the benzimidazole ring system enhances its coordination potential and biological activity, leading to the development of diverse thiol- and thione-containing analogues with important medicinal and industrial applications [1-6]. Thiolated benzimidazoles, such as 2-mercaptobenzimidazole, have been extensively investigated as corrosion inhibitors, antioxidants, and antimicrobial agents. Their adsorption behaviour on metallic surfaces [1-2] and desulfurization pathways under visible light conditions [7] have been reported. Furthermore, their derivatives have exhibited promising antibacterial, antifungal, anticancer, and enzyme inhibitory activities [8-10]. Among the 2-mercaptobenzimidazoles, 5-methoxy-2-mercaptobenzimidazole [MTZ] and 5-[difluoromethoxy]-2-mercaptobenzimidazole [FMZ] stand out as valuable scaffolds due to their electron-donating and -withdrawing

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substituents, respectively, which modulate their reactivity, metal-binding tendencies, and bioactivity. FMZ, a known intermediate in the synthesis of pantoprazole, a clinically approved proton pump inhibitor [11], has been associated with notable cytotoxic and enzyme inhibitory properties [12, 13]. Despite extensive studies on related benzimidazole derivatives [14-17], investigations on the coordination chemistry of MTZ and FMZ with transition metals and their biological activities remain limited. Metal ions such as copper and silver are known for their redox flexibility and intrinsic antimicrobial properties, and their coordination with biologically active ligands often enhances membrane permeability and enzyme inhibition, leading to synergistic bioactivity. Given the growing concern about bacterial resistance to conventional antibiotics, synthesizing and characterizing new benzimidazole–metal complexes could offer alternative leads for novel antimicrobial agents with better efficacy and structural tunability. This research focuses on the synthesis and spectroscopic characterization of Cu[II], Cu[I], and Ag[I] complexes derived from 5-methoxy- and 5-[difluoromethoxy]-2-mercaptobenzimidazole, and to assess their *in-vitro* antimicrobial potential against selected Gram-positive and Gram-negative bacterial strains.

MATERIALS AND METHODS

Materials

All chemicals were of analytical grade and purchased from Sigma-Aldrich. They were used as received without further purification. Melting points were determined on a Gallenkamp melting point apparatus and are reported uncorrected. Infrared spectra were recorded as Nujol mulls on a PerkinElmer FT-IR spectrophotometer within the range 4000–350 cm^{-1}. ^{1}H and ^{13}C NMR spectra were measured in DMSO-d_6 using a Bruker Avance 400 MHz NMR spectrometer, with tetramethylsilane [TMS] as the internal standard.

Synthesis

The reactant ligands, 5-methoxy-1*H*-benzo[*d*]imidazole-2-thiol [MTZ] and 5-[difluoromethoxy]-1*H*-benzo[*d*]imidazole-2-thiol [FMZ] were purchased from commercial supplier and used as received.

MTZ: Faint beige powder, 261-263ºC. IR [KBr, cm^{-1}]: *ν*[N-H] 3306; *ν*[C-$H_{[OCH3]}$] 2837; *ν*[S-H] 2457*vw*; *δ*[N-H] 1641; *ν*[C=C] 1622, 1501; *ν*[-C=N] 1470; *ν*[C-N] 1182, *ν*[C-O] 1266, 1155, *ν*[C-S] 642.

FMZ: Off white powder, 241-243ºC. ^{1}H-NMR [400 MHz, DMSO-d_6]: IR [KBr, cm^{-1}]: *ν*[N-H] 3164; *ν*[C-$H_{[OCHF2]}$] 2885; *ν*[S-H] 2454; *δ*[N-H] 1637; *ν*[C=C] 1626, 1498; *ν*[-C=N] 1469; *ν*[C-N] 1182; *ν*[C-O] 1259, 1149; *ν*[C-F] 1121, 1032; *ν*[C-S] 653.

CuMTZ: was prepared by heating 5-methoxy-2-benzimidazolethiol [200.0 mg, 1.11 mmol] and copper[II] chloride dihydrate [94.6 mg, 0.55 mmol] to reflux in 18 mL

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EtOH for 2 h. The reaction mixture was cooled to room temperature, and the solvent was reduced under vacuum. The mixture was filtered to obtain the precipitate, which was washed with methanol and allowed to dry in air. A yellow powder was obtained [151.5 mg, 50%], Mp > 340ºC. Anal. % cal for $C_{16}H_{14}Cl_2Cu_2N_4O_2S_2$ [556.44]: C 34.54, H 2.54, N 10.07, S 11.53; found C 33.77, H 2.97, N 9.71, S 11.17. IR [KBr, cm^{-1}]: ν[N-H] 3118; ν[C-$H_{[OCH3]}$] 2821; δ[N-H] 1634; ν[C=C] 1618, 1495; ν[-C=N] 1459; ν[C-N] 1191; ν[C-O] 1260, 1155; ν[C-S] 652; ν[Cu-N] 491; ν[Cu-S] 468. Magnetic moment: 2.02 BM.

CuFMZ: was prepared by heating 5-[difluoromethoxy]-2-mercaptobenzimidazole [200.0 mg, 0.93 mmol] and copper [II] chloride dihydrate [78.8 mg, 0.46 mmol] to reflux in 15 mL EtOH for 2 h. The reaction mixture was cooled to room temperature, and the solvent was reduced under vacuum, the resulting precipitate was filtered with methanol and allowed to dry in air. An off-white powder was obtained [141.5 mg, 98%], Mp >340ºC. Anal. % calc for $C_8H_7CuF_2N_2O_2S$ [296.76]: C 32.38, H 2.38, N 9.44, S 10.80; found C 31.89, H 2.12, N 8.94, S 10.38. IR [KBr, cm^{-1}]: ν[O-H] 3462, ν[N-H] 3134; ν[C-$H_{[OCHF2]}$] 2840; δ[N-H] 1634; ν[C=C] 1622, 1496; ν[-C=N] 1458; ν[C-N] 1169; ν[C-O] 1259, 1141; ν[C-F] 1126, 1046; δ[O-H] 809; ν[C-S] 656; ν[Cu-N] 482; ν[Cu-S] 462. Magnetic moment: 0.58 BM.

AgMTZ: was prepared by heating 5-methoxy-2-benzimidazolethiol [200.0 mg, 1.11 mmol] and silver nitrate [188.5 mg, 1.11 mmol] to reflux in 15 mL EtOH for 2 h. The reaction mixture was cooled to room temperature and the resulting precipitate was obtained by filtration, washed with methanol and allowed to dry in air. A white powder was obtained [367.0 mg, 94%], Mp [>340ºC]. Anal. % calc for $C_9H_{12}AgN_3O_5SAg$ [382.14]: C 28.29, H 3.17, N 11.00, S 8.39; found C 27.54, H 2.30, N 10.15, S 8.84. IR [KBr, cm^{-1}]: ν[N-H] 3126; ν[C-$H_{[OCH3]}$] 2812; ν[S-H] 2427; δ[N-H] 1636; ν[C=C] 1618, 1491; ν[-C=N] 1460; ν[NO_3] 1384; ν[C-N] 1172; ν[C-O] 1261, 1152; ν[C-S] 660; ν[Ag-N] 493; ν[Ag-ONO_2] 478; ν[Ag-S] 458. Magnetic moment: 0.18 BM.

AgFMZ: was prepared by heating 5-[difluoromethoxy]-2-mercaptobenzimidazole [200.0 mg, 0.93 mmol] and silver nitrate [157.1 mg, 0.93 mmol] to reflux in 15 mL EtOH for 2 h. The reaction mixture was cooled to room temperature, and the solvent was reduced under vacuum, the resulting precipitate was filtered, washed with methanol and allowed to dry in air. A white powder was obtained [323.0 mg, 99%], Mp [>340ºC]. Anal. % calc for $C_8H_6F_2N_3O_4SAg$ [386.08]: C 24.89, H 1.57, N 10.88, S 8.31; found C 25.70, H 1.42, N 10.15, S 9.05. IR [KBr, cm^{-1}]: ν[N-H] 3058; ν[C-$H_{[OCHF2]}$] 2809; ν[S-H] 2427; δ[N-H] 1637; ν[C=C] 1630, 1496; ν[-C=N] 1464; ν[C-N] 1168; ν[C-O] 1259, 1149; ν[NO_3] 1384; ν[C-F] 1125, 1042; ν[C-S] 664; ν[Ag-N] 491; ν[Ag- ONO_2] 484; ν[Ag-S] 452. Magnetic moment: 0.19 BM.

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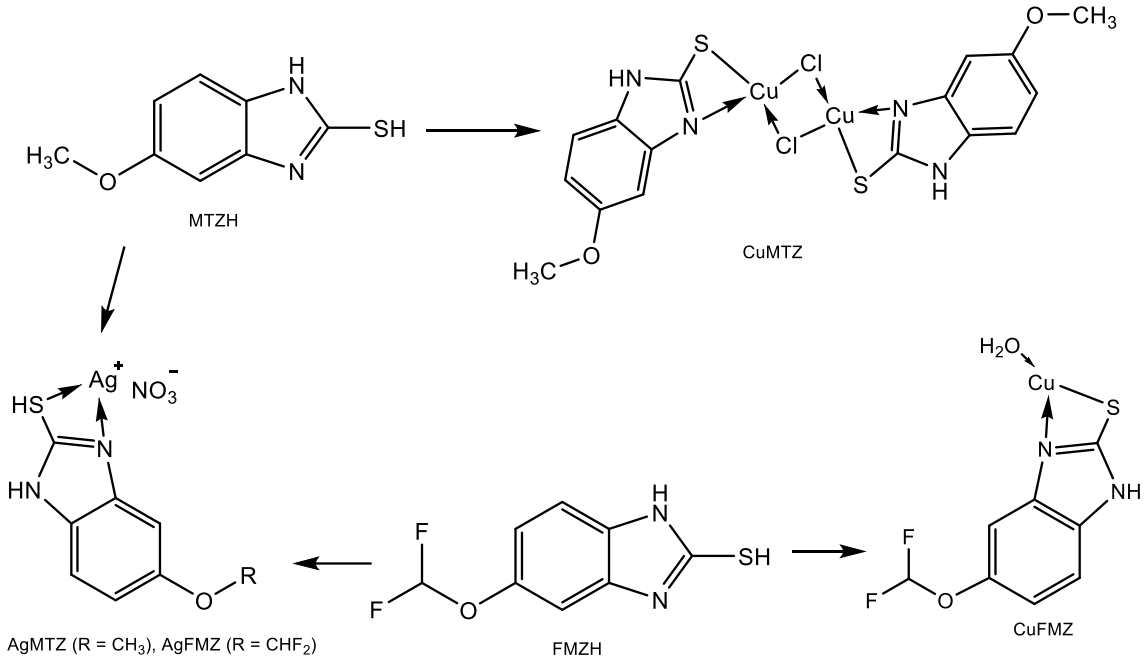


Figure 1: The synthesis scheme and structures of the metal complexes

In vitro Antibacterial Assay Procedure

The *in vitro* antibacterial activity of the synthesized complexes was evaluated using the agar well diffusion method against five bacterial strains, including the Gram-positive *Staphylococcus aureus* ATCC 6571 and Gram-negative *Escherichia coli* ATCC 35218, *Klebsiella pneumonia* ATCC 700303, *Pseudomonas aeruginosa* ATCC 27853 and *Salmonella typhi* ATCC 6571. Ciprofloxacin [10 µg/mL] was used as the reference antibiotic, while DMSO served as the negative control. Bacterial inocula and media were prepared following standard microbiological procedures. A loopful of each bacterial strain was transferred from stock culture into 5 mL of sterile nutrient broth and incubated at 28°C for 18–24 h. The resulting overnight culture was diluted [1:100] by mixing 0.1 mL of culture with 9.9 mL of sterile distilled water. From this dilution, 0.2 mL was introduced into sterile molten nutrient agar and poured aseptically into Petri dishes. After solidification [approximately 45–60 min], wells of 6 mm diameter were made using a sterile cork-borer. Each well was filled with 50 µL [150 µg] of the test solution, prepared by dissolving 3 mg of the compound in 1 mL DMSO. The plates were allowed to pre-diffuse at room temperature for 2 h and subsequently incubated at 26–28°C. Antibacterial activity was evaluated by measuring the diameter of the inhibition zones [mm] around each well. All assays were performed in duplicate to ensure reproducibility.

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RESULTS AND DISCUSSION

Analytical analyses

The ligands and synthesized metal complexes are depicted in **Figure 1**. The complexes exhibited good solubility in polar aprotic solvents such as DMSO and DMF, but were sparingly soluble in nonpolar media. They demonstrated high thermal stability, with melting points exceeding 340°C, while the ligands melted between 240 and 263°C. The empirical formulas of CuMTZ, CuFMZ, AgMTZ, and AgFMZ were established based on CHNS elemental analyses, which showed close agreement between the experimental and theoretical values, thereby confirming the proposed molecular formulations [**Figure 1**]. Except for CuMTZ, which was isolated as a yellow powdery solid, all other complexes were obtained as white to off-white powders. Magnetic susceptibility measurements indicated magnetic moments of 1.42 BM for the monomeric CuMTZ species and 2.01 BM for its dimeric form, consistent with the presence of one unpaired electron in a d^9 Cu[II] center. In contrast, CuFMZ, AgMTZ, and AgFMZ exhibited low magnetic moments of 0.58, 0.18, and 0.19 BM, respectively, suggesting diamagnetic behaviour typical of Cu[I] and Ag[I] complexes.

^{1}H and ^{13}C NMR Spectra

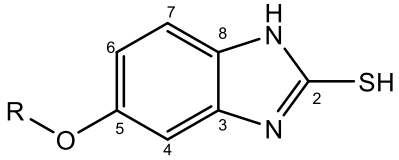
The ^{1}H and ^{13}C NMR spectra of MTZ, FMZ, AgMTZ and AgFMZ were recorded in DMSO-d_6 to investigate the influence of Ag^+ coordination on the ligand framework. The chemical shifts data [δ, ppm] are summarized in **Table 1**. For the free ligands, distinct singlets corresponding to the N–H and S–H protons were observed at 12.40 and 12.36 ppm for MTZ, and at 12.64 and 12.63 ppm for FMZ, consistent with reported values for analogous 2-mercaptobenzimidazole derivatives [3, 9, 16]. Upon complexation, AgMTZ and AgFMZ displayed a downfield shift of the N–H signal to 13.21–13.39 ppm, while the disappearance of the S–H resonance confirmed dative coordination via the thiol sulphur atom. Aromatic proton signals [H4, H6, H7] appeared as multiplets within 6.68–7.16 ppm, whereas the methoxy and difluoromethoxy protons resonated at 3.75 and 7.36 ppm, respectively, as reported in related compounds [3, 4, 18]. These signals exhibited slight downfield shifts [0.02–0.20 ppm] upon complexation, reflecting electron redistribution across the aromatic framework induced by metal binding.

The ^{13}C NMR spectra of the ligands showed characteristic benzimidazole carbon resonances [C2-C8] between 95 and 170 ppm [3, 8, 9], with the most deshielded peaks at C2 [≈170 ppm] and C5 [≈156 ppm], attributable to the inductive effects of neighbouring heteroatoms [19]. In the corresponding Ag[I] complexes, notable upfield shifts [11–27 ppm] were observed for C3 and C8, indicating shielding effects arising from coordination through the N and S donor sites. Conversely, the methoxy and difluoromethoxy carbon resonances [≈56 and ≈117 ppm, respectively]

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[8, 9, 11] remained largely unaffected, confirming that the oxygen atoms of these substituents were not involved in metal coordination.

Table 1: ^{1}H and ^{13}C NMR shifts for the ligands and Ag[I] complexes [400 MHz, DMSO-d$_6$, δ ppm]



R = CH_3, CHF_2

Compound	^{1}H	NH, SH	4	6	7	R
MTZ		12.40, 12.36	6.68	6.73	7.03	3.74
AgMTZ		13.21	6.80	6.79	7.23	3.76
FMZ		12.64, 12.63	6.95	6.96	7.16	7.36
AgFMZ		13.39	7.15	6.98	7.28	7.34

Compound	^{13}C	2	3	4	5	6	7	8	R
MTZ		168.25	133.53	94.92	156.22	110.19	110.43	126.84	56.02
AgMTZ		140.46	116.72	94.95	156.78	112.35	115.51	115.75	55.99
MFZH		169.82	133.24	101.41	146.87	110.55	114.55	130.30	117.18
AgFMZ		147.36	119.68	113.03	147.39	114.55	115.33	117.12	117.12

Infrared Spectra

Infrared spectral analysis provided further insight into the coordination behaviour of the ligands toward the metal ions. The characteristic ν[N–H] stretching vibrations appeared in the range 3306–3058 cm^{-1} in both the ligands and their corresponding complexes, confirming the retention of the benzimidazole N–H group. In CuFMZ, a broad medium-intensity band at 3462 cm^{-1} and an intense absorption at 809 cm^{-1} were assigned to the stretching and bending vibrations of coordinated water molecules. The methoxy [C–H] and methyne [C–H] stretching bands were observed between 2885–2809 cm^{-1} and 2837–2812 cm^{-1}, respectively.

Weak ν[S–H] bands near 2450 cm^{-1} in the free ligands [20] were absent in the copper complexes and slightly shifted to lower frequencies [~2427 cm^{-1}] in the silver complexes, confirming the involvement of the thiol sulphur atom in coordination. The C–S stretching vibrations originally observed at 664–642 cm^{-1} [21] shifted to higher wavenumbers upon complexation, further supporting S-donor participation. The imine ν[C=N] and ν[C–N] bands of the benzimidazole moiety, initially at 1470 and 1182 cm^{-1}, respectively, shifted by 5–14 cm^{-1}

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in the complexes, indicative of metal–nitrogen coordination.

The *ν*[C–O] absorptions of the methoxy and difluoromethoxy substituents appeared as medium bands between 1266–1149 cm^{-1} and remained unchanged after complexation, suggesting that oxygen atoms were not involved in chelation. Aromatic ring vibrations were observed within 1630–1491 cm^{-1}, while the asymmetric and symmetric *ν*[C–F] stretches in FMZ and its complexes occurred at 1126–1121 cm^{-1} and 1046–1032 cm^{-1}, respectively. A strong absorption at 1384 cm^{-1} in the silver[I] complexes was attributed to the uncoordinated nitrate ion [22-24]. The metal–ligand stretching vibrations were identified within 497–468 cm^{-1}, confirming coordination through nitrogen and sulphur donor atoms. Bands attributable to ν[M–Cl], typically observed below 400 cm^{-1}, were not detected due to instrumental limitations.

Antibacterial Assay

The summary of the inhibition zone diameters [mm] of CuMTZ, AgMTZ, and AgFMZ compared with the solvent control and the reference drug, ciprofloxacin, against five bacterial strains is given in Table 2. Ciprofloxacin exhibited the highest antibacterial potency, with inhibition zones ranging from 30 mm for *Klebsiella pneumoniae* to 46 mm for *Escherichia coli*, confirming its broad-spectrum efficacy. Among the tested complexes, AgMTZ exhibited the strongest antibacterial activity with zones of 12–18 mm across the tested organisms, indicating broad-spectrum potential probably resulting from effective interaction with bacterial cell membranes. AgFMZ displayed moderate activity [12–14 mm] against *Staphylococcus aureus*, *E. coli*, and *Pseudomonas aeruginosa*, but lower inhibition [<10 mm] against *K. pneumoniae* and *Salmonella typhi*. CuMTZ showed a more selective antibacterial profile, exhibiting pronounced inhibition against *S. aureus* [19 mm] but minimal activity toward *P. aeruginosa*. These trends highlighted the strain-dependent nature of antimicrobial activity, and exploring the precise mechanisms could lead to novel formulations for resistant pathogens.

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Table 2: The Diameters of Inhibition zones [in mm] of Screened Compounds

Bacteria / Compounds	CuMTZ	AgMTZ	AgMTZ	CIPRO	DMSO
Staphylococcus aureus ATCC 6571	19	12	14	39	6
Escherichia coli ATCC 35218	12	16	12	46	6
Klebsiella pneumoniae ATCC 700303	8	18	7	30	6
Pseudomonas aeruginosa ATCC 27853	6	13	13	32	6
Salmonella typhi ATCC 14028	6	17	9	37	6

CONCLUSION

The synthesis of Cu[II], Cu[I], and Ag[I] complexes of 5-methoxy- and 5-difluoromethoxy-2-mercaptobenzimidazole has been achieved, and their structural features were elucidated through elemental, spectroscopic, and magnetic analyses. The complexes demonstrated enhanced thermal stability compared with the parent ligands. Coordination of the ligands through sulphur and imine nitrogen atoms was supported by infrared and NMR spectroscopic data, as evidenced by the disappearance of *ν*[S–H] and downfield shifts in N-H proton signal, while the methoxy and difluoromethoxy substituents remained non-coordinating. The Cu[II] complex exhibited a paramagnetic nature, while the Cu[I] and Ag[I] analogues were diamagnetic. Antibacterial screening revealed that AgMTZ exhibited the most pronounced and broad-spectrum activity, highlighting the role of the Ag[I] center and ligand environment in modulating biological response. These findings highlight the influence of metal ion type and ligand substitution pattern on biological efficacy and suggest that benzimidazole-based metal complexes hold promise as potential scaffolds for the development of new antimicrobial agents.

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