RESEARCH PAPER

Synthesis, Characterisation and Evaluation of DFT and Antimicrobial activity of Benzamide derivatives of Novel Co(II) and Cu(II) complexes of Mannich Base

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ABSTRACT

This paper reports the theoretical and practical creation of a newly synthesised Mannich base ligand (L) and its metal complexes. Benzamide, benzaldehyde, and dicyclohexylamine (1:1:1 mole ratio) produced the ligand N-(dicyclohexylaminobenzyl)benzamide. Mononuclear complexes were isolated as a result of the ligand's interaction with Co(II) and Cu(II) metal ions in a 1:1 (ligand: metal) mole ratio. With a variety of analytical and spectroscopic methods, examination of the ligands and their metal complexes was performed. The ligand and metal complex's magnetic susceptibility, elemental analysis, molar conductance, FT-IR, UV-Vis spectra, mass spectra, 1H-NMR, 13C-NMR, and TGA were examined. One coordinate mononuclear compound with the generic formula [MLX_2] was characterised. The geometry of the ligand and its metal complexes is suggested by the results of density functional theory (DFT) calculations. The antimicrobial activity of every synthesised chemical was tested experimentally against bacterial and fungal strains, which demonstrated moderate to strong antimicrobial activity.

Keywords: Mannich base, Metal complex, DFT, Benzamide, Antimicrobial activity.

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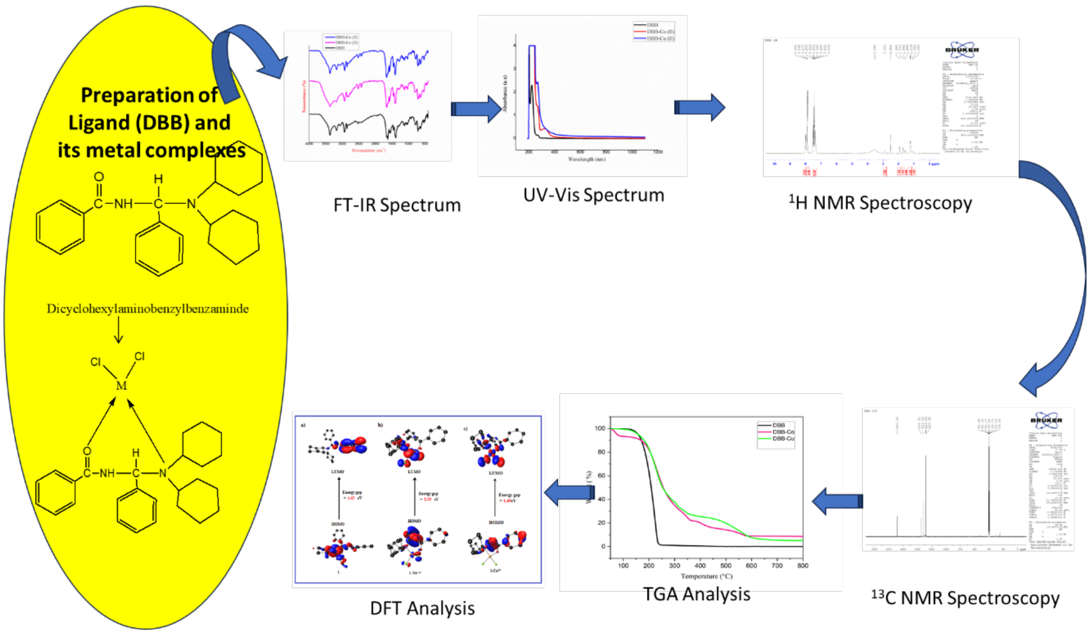


Introduction

Some of the most important types of coordination compounds are found in biological systems. The use and significance of inorganic compounds have been extremely beneficial in the medical industry. Coordination compounds are essential components of the active sites of enzymes and are found in many biomolecules. It is estimated that approximately half of all proteins contain a chemical. Examining the structures and binding properties of various Mannich base complexes may lead to a better insight into complicated bodily functions. Several drugs have shown improved efficacy as metal chelates rather than as organic molecules[1-3]. Heterocyclic compounds, especially N-based ligands, are essential for many biological processes and are present in many vitamins and pharmaceuticals[4]. The literature review indicates that the synthesis of metal complexes of (dicyclohexylaminobenzyl)benzamide has garnered considerable attention in recent decades, and its metal complexes seem to be important in the growth of coordination chemistry[5]. The metal complexes of mannich bases belong to a class of substances that have been studied less frequently. However, additional work has recently been conducted on the biological activity of these chemicals[6]. Numerous Mannich base complexes have promising biological activities, including antioxidant, anti-tubercular, antibacterial, anti-inflammatory, analgesic, anticancer, and anticonvulsant properties[5,7-13]. Recent research has highlighted significant changes in the reactivity of coordination molecules, particularly in substituted benzamide chelate reactions. These changes are primarily driven by the interaction of benzamides with various metal complexes, which can alter their chemical behaviour and reactivity[14]. The diverse mannich bases prepared from secondary amines condensing with assorted aldehydes and amides have been the subject of numerous studies[11,15]. Benzamide is an important structural element in many naturally occurring chemicals with potential biological activity. Numerous details regarding the chemical, biological, and toxicological properties of Mannich bases can be found in the literature[16-18]. Studies have also revealed the enormous importance of the implications of transition metal complexes in the form of drugs for the treatment of a range of human diseases. Advances in inorganic chemistry have enhanced the use of metal complexes as therapeutic agents. In contrast, metal complexes behave differently from non-metals in living organisms. Mannich base derivatives containing a bridge N-atom exhibit several biological characteristics, including antibacterial properties[19,20]. The byproducts of Mannich base reactions include polymers, pigments, dyes, dispersants, and natural macromolecular materials for lubricating oil and petroleum sector additives[21]. Computational research is an important step that can be used to forecast experimental outcomes for a chemical that is fully known, study reaction pathways, and more. Gaussian 09 software[22,23] is a computational research tool that aims to identify relationships between chemical structures and properties. This paper presents the synthesis and structural characterisation of N-(dicyclohexylaminobenzyl)benzamide. The mannich base ligand and its metal ions were analysed using FT-IR, NMR, DFT, and elemental analysis. To establish the optimal parameters for the most stable ligand and its metal complexes of vibration frequencies, HOMO and LUMO energies were observed. The antimicrobial activity of all target compounds was determined by the agar well diffusion method.

Experimental

Materials and Methods

The chemicals required were supplied by Sigma Aldrich. The unrevised melting point of the synthesised compound was assessed with open capillary tubes. The ligand and complexes (CHN) were elementally analysed using the Coleman N analyser and the Carlo Erba 1108 CH analyser. At ambient temperature, the metal(II) complexes' molar conductivities were evaluated in DMSO solutions (10^{-3} M). Infrared spectra were recorded using KBr pellets and a Spectrum One Perkin

Elmer FT-IR spectrometer. Using a Perkin-Elmer EZ 301 spectrophotometer, UV-visible spectra were captured. The ^{1}H and ^{13}C NMR spectra of the material were documented at 400 MHz using a Bruker TopSpin spectrometer.

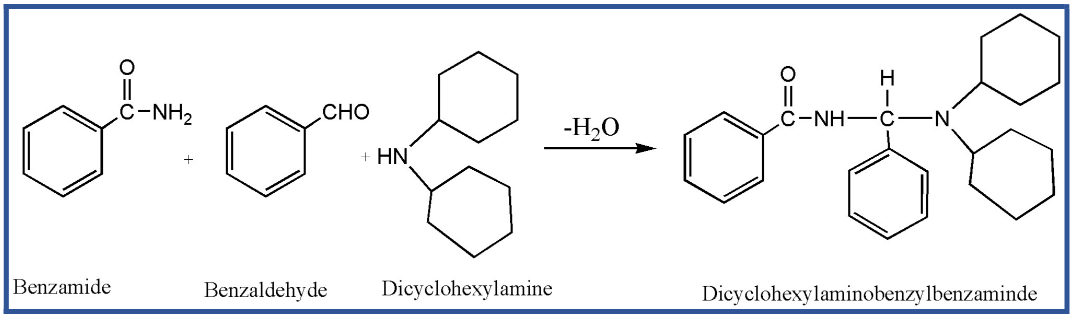


Figure 1. Structure of Mannich base (DBB)

Synthesis of Mannich base ligand (DBB)

The preparation of N-(dicyclohexylaminobenzyl)benzamide (DBB) was performed by the mannich condensation reaction involving dicyclohexylamine, benzaldehyde, and benzamide in an identical mole ratio (Figure 1). 4.00 mL (0.025 mol) of dicyclohexylamine was added at room temperature after the reaction between benzamide (3.10 g, 0.025 mol) and benzaldehyde (3.00 mL, 0.025 mol) had started. The reaction mixture was stirred constantly for 30 to 40 minutes as each drop was added[24]. This process to fix the ratio of reactants (amide, aldehyde, and amine) as 1:1:1 in Mannich base synthesis is guided by experimental pilot studies. After filtering, the colourless precipitate (86% yield) was dried and recrystallised from ethanol (m.p. 110 - 118 °C).

Synthesis of Metal Complexes

In 20 millilitres of heated

ethanol, the synthesized ligand (DBB) (0.61 g, 0.01 mol) was dissolved. Separately on a heated plate, the metal chloride solutions (Co(II) and Cu(II)) of the same molarity in ethanol are continuously stirred. The ligand solution is now gradually added to each of the metal complex solutions in turn, agitated for two hours, and then allowed to evaporate and concentrate. The coloured precipitate was obtained, and the resulting solution was kept undisturbed such that the complexes could form in two to three days[25]. After being cleaned with a tiny bit of ethanol, it was dried and kept for later use in desiccators (Figure 2).

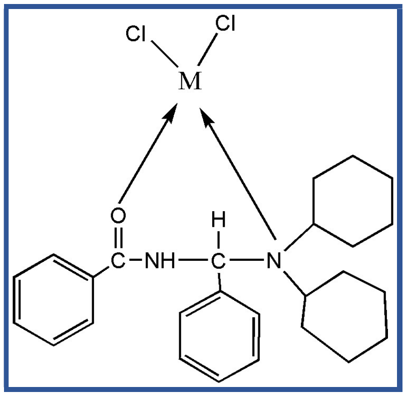


Figure 2. The ligand and its metal complexes' suggested structure (M=Co, Cu)

DFT calculation

The lowest energy geometry was derived using density functional theory (DFT) using Gaussian 09 software[26]. Using the DFT/B3LYP/63-11-G level of theory, the geometry was optimized to provide the ligand and its metal complexes with the lowest energy structure.

Antimicrobial activity

At 25, 50, 75, and 100 µg/mL concentrations, the newly synthesized Mannich base Ligand (DBB) and its metal complexes were assessed on nutritional agar plates using the disc diffusion method. Two strains of gram-positive bacteria, *Staphylococcus aureus* and *Bacillus subtilis*, two strains of gram-negative bacteria, *Escherichia coli* and *Pseudomonas aeruginosa*, and two strains of fungi, *Candida albicans* and *Aspergillus niger* were tested. Discs containing 25, 50, 75, and 100 µg of the chemical each were put on top of the nutrient agar plate. Next came the application of 0.1 mL of sterile microbe culture, which was cultured for 24 hours at 37 °C[27].

Results and Discussion

In a 1:1 (metal: ligand) ratio, the reaction of Co(II) and Cu(II) with two equivalents of HL in a water/ethanol mixture results in pale pink (DBB-Co(II)) & blue (DBB-Cu(II)) metal complexes. The organic ligand and metal complexes under study were clarified by elemental analysis, FT-IR, UV-Vis, magnetic, and molar conductance measurements. All of the target compounds were characterized using mass spectroscopy, ^{1}H-NMR, ^{13}C-NMR, and thermogravimetric analysis. The calculated molecular weight of the synthesized molecule agreed with the measured m/e values. As a result, it was discovered that the computed values of the prepared compound's structure closely matched the experimentally acquired data (Table 1). DBB has the chemical formula $C_{26}H_{34}N_2O$.

Table 1. Physicochemical and Analytical data of ligand and complexes

Molecular Formula	**Colour**	**Yield**	**M.P °C**	**Mol. Wt**	**μ_{eff} B.M**	**Λ_m ohm^{-1} cm^2 mol^{-1}**	**Calc. (Found) %**				
							C	**H**	**N**	**O**	**M**
DBB	Light Yellow	86	110	390	….	….	79.96 (79.95)	8.77 (8.76)	7.17 (7.15)	4.10 (4.09)	-
DBB-Co(II)	Pale pink	82	193	449	3.9	24	69.47 (69.45)	7.62 (7.60)	6.23 (6.22)	3.56 (3.55)	13.11 (13.10)
DBB-Cu(II)	Pale Green	79	212	454	1.9	32	68.77 (68.75)	7.55 (7.54)	6.17 (6.15)	3.52 (3.50)	13.99 (13.96)

Spectral Characterisation Methods

FT-IR Spectroscopy

One of the best scientific methods for confirming the existence of functional groups in chemical compounds is FT-IR spectroscopy. The FT-IR spectra of the ligand and its metal complexes are shown in Figure 3. The υ(NH), amide υ(C=O), and υ(C-N-C) of the dicyclohexylamine group have been identified as the bands 3371, 1624, and 1182 cm^{-1} in the FT-IR of the (dicyclohexylaminobenzyl)benzamide ligand (DBB). In the Co(II) and Ni (II) complexes, the υ(NH) band was observed in the regions of 3370 and 3371 cm^{-1}. The amide υ(C=O) and υ(C-N-C) of the dicyclohexylamine bands at 1658 and 1660 cm-1 and 1179 and 1180 cm^{-1} exhibited notable negative shifts with comparatively low intensity, indicating coordination between the nitrogen of the ligand and the oxygen of the amide moiety[28,29]. Table 2 describes the Mannich base ligand (L) and the complexes' FT-IR spectra. Around 530 and 528 cm^{-1}, some additional bands were found; they are ascribed to the υ(M-O) complexes moiety.

Table 2. IR spectral data - DBB and their complexes

Assignment	ν_{N-H}	ν_{C-H} **(Ar)**	$\nu_{C=O}$	$\nu_{C=C}$ **(Ar)**	ν_{C-N} **(Ar)**	ν_{C-N-C}	ν_{M-O}	ν_{M-N}	ν_{M-X}
DBB	3203	3059	1624	1542	1308	1170	-	-	-
DBB-Co(II)	3401	2937	1603	1564	1307	1137	538	474	449
DBB-Cu(II)	3390	2937	1602	1555	1307	1139	538	477	448

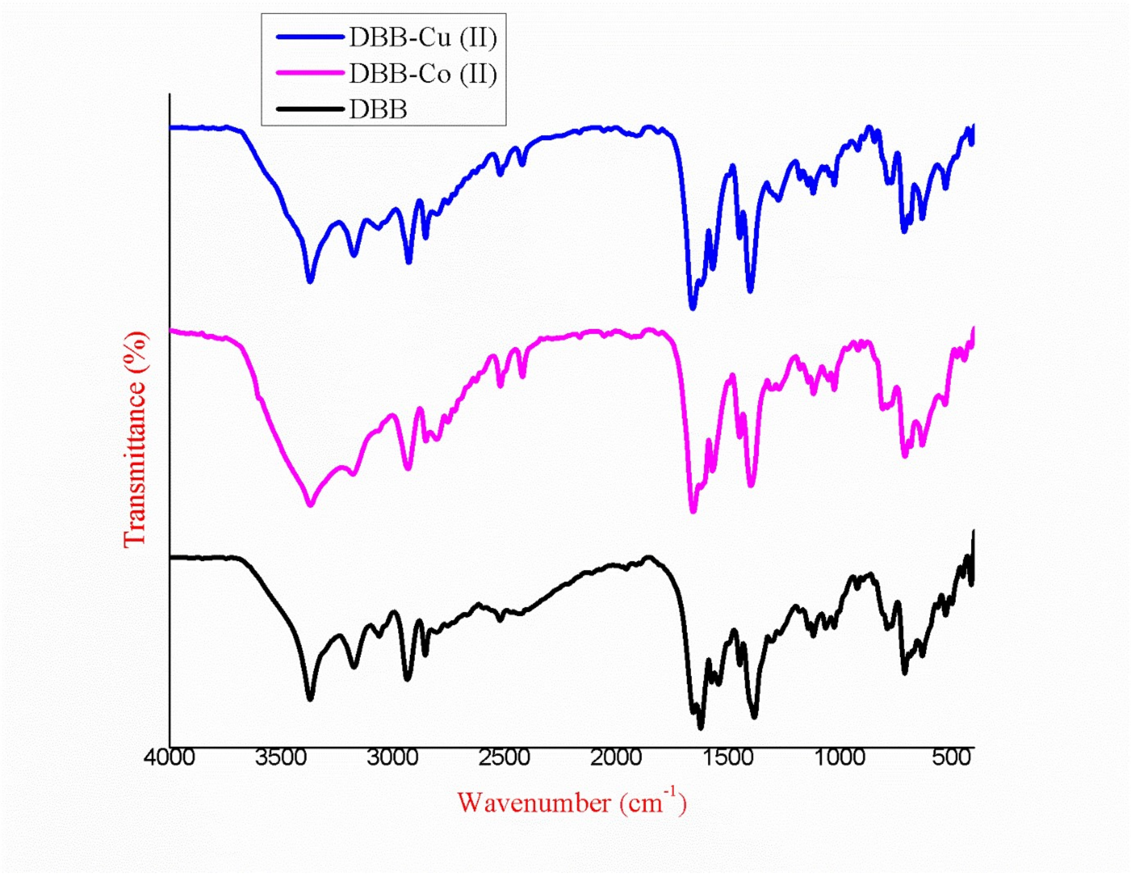


Figure 3. FT-IR spectra - DBB, Co(II) and Cu(II) complexes

UV-Vis spectrum

The UV-Visible spectrometer was used to record absorbance in the UV-visible area in DMSO solution (Figure 4)[30]. The ligand exhibited two distinct absorbance peaks at 203 (35610 M^{-1} cm^{-1}) nm and 224 (42562 M^{-1} cm^{-1}) nm, which were caused by the n→π* and π→π* transitions, respectively. The Co(II) complex exhibits three absorbance bands at 223 (43564 M^{-1} cm^{-1}) nm, 268 (53650 M^{-1} cm^{-1}) nm, and 324 (67435 M^{-1} cm^{-1}) nm. These bands can be attributed to the σ→σ*, π→ π*, and n→ π* transitions, as well as the ligand-to-metal charge transfer. The Co(II) complex has a magnetic movement value of 3.9 BM. The tetrahedral geometry is confirmed by this kind of absorption. With a maximum of three absorbance peaks at 225 (43907 M^{-1} cm^{-1}) nm, 262 (54375 M^{-1} cm^{-1}) nm, and 270 (56721 M^{-1} cm^{-1}) nm, the Cu(II) complex of DBB displays a band belongs to $\sigma \rightarrow \sigma^*$, $\pi \rightarrow \pi^*$, and $n \rightarrow \pi^*$ for tetrahedral geometry for the complex, and the magnetic movement values fall at 1.9 B.M, and is consistent with a mononuclear Cu(II) (d_9) centre in a tetrahedral environment.

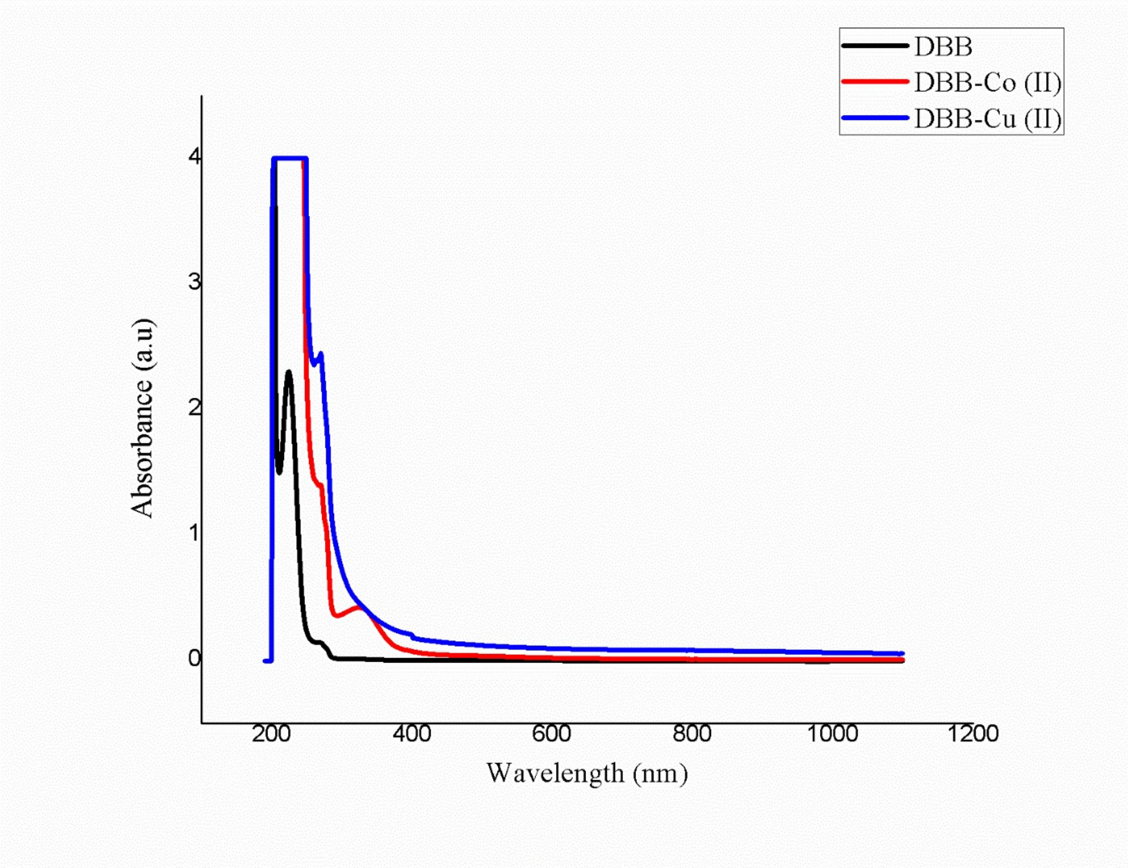


Figure 4. UV-Visible spectra - DBB and its complexes (Co(II) & Cu(II))

Mass spectroscopy

The mass spectrum of the Mannich base ligand (HL) shows the molecular ion peak at m/z = 347 (Figure 5). Some fragmentations and their corresponding abundances are included in the experimental section. Molecular ion peaks are visible in the mass spectra of the metal complexes [$CoLCl_2$] and [CuLCl] at m/z = 449 and 454, respectively. Ion production is the cause of this peak at m/z = 175.

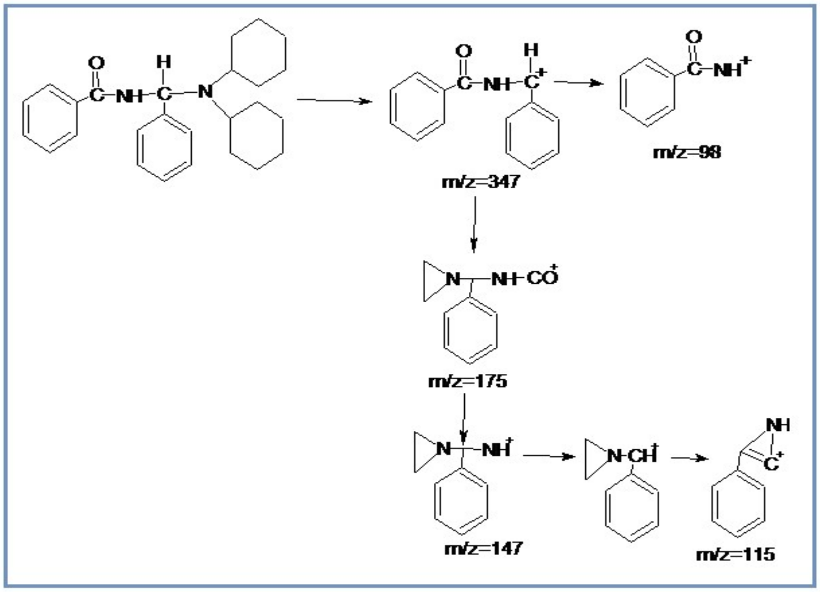


Figure 5. Fragmentation Pattern of DBB

NMR Spectroscopy

^{1}H NMR Spectroscopy

^{1}H-NMR spectra of the ligand DBB, which were captured in DMSO-d_6, are shown in Figure 6. The proton NMR signals of dicyclohexylamine, benzaldehyde, and benzamide are also given for comparison, along with the chemical shifts for DBB, which are shown in Table 3. There are four primary proton types seen in the Mannich base ligand (HL). The weak singlet is produced by the N-H proton chemical shift that takes place at δ 7.89-7.99 ppm. The aromatic protons of the benzamide and benzaldehyde moieties are responsible for the numerous signals between δ 7.37 and 7.99 ppm. The chemical shift at δ 2.50-1.06 ppm is caused by the proton of the (CH_2-N-CH_2) parts of the dicyclohexylamine moiety. The protons in the dicyclohexylamine ring indicate a chemical shift between δ 1.94 and 1.06 ppm. The N-CH-N proton created as a result of the Mannich base's synthesis is responsible for the chemical shift δ 3.54[31].

Table 3. ^{1}H NMR signals for Dicyclohexylamine, Benzamide and DBB

Assignment	Dicyclohexylamine	Benzamide	DBB
NH Protons	0.7	8.05	-
-NCHN-Protons	-	-	3.54
Aromatic Protons	-	7.92	7.37-7.99
$N(CH)_2$ Protons	2.50	-	2.50
CH_2 Protons of cyclohexyl rings	1.94-1.06	-	1.94-1.06

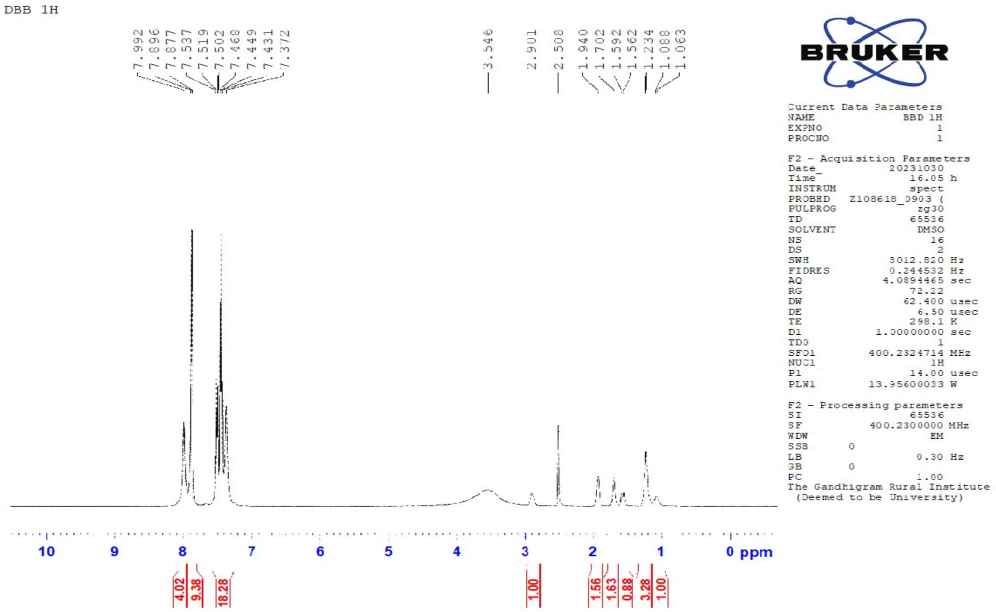


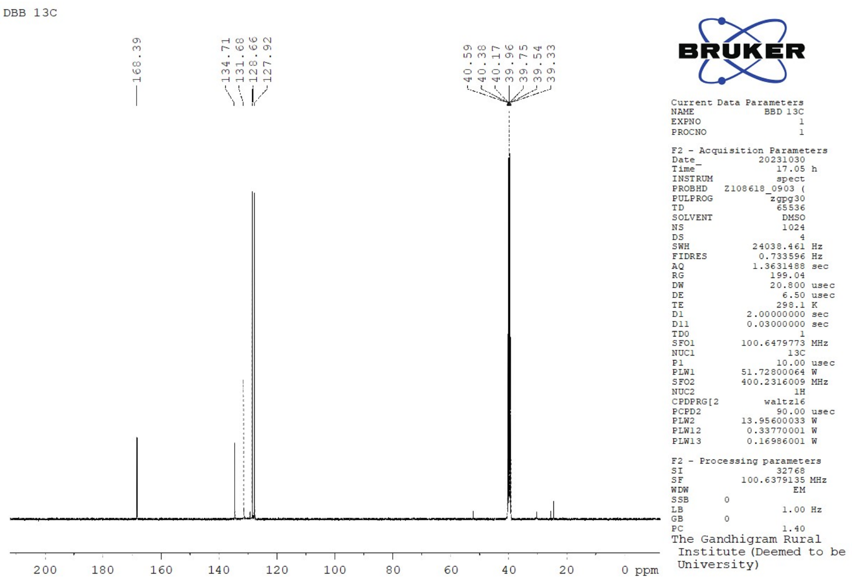
Figure 6. ^{1}H- NMR Spectrum of ligand (L)

^{13}C NMR Spectroscopy

The ^{13}C NMR spectra of DBB were recorded in DMSO-d_6 (Figure 7). The carbonyl carbons of benzamide are responsible for the signal seen at 169.39 ppm (Table 4). Absorption seen at δ 131.68 to δ 127.92 ppm indicates other aromatic carbons of benzaldehyde in DBB. The dicyclohexylamine moiety's N$(CH_2)_2$ carbon exhibited absorption at δ 40.59 - 39.93 ppm. A signal at δ 134.71 ppm is caused by the benzaldehyde-CH [32]. group that joins the benzamide and dicyclohexylamine ring (N-CH-N). The number of ^{13}C NMR signals of DBB and the designated locations of the various carbon atoms in the molecule are consistent with the proposed structure of DBB

Table 4. ^{13}C NMR signals for Dicyclohexylamine, Benzamide and DBB

Assignment	**Dicyclohexylamine**	**Benzamide**	**DBB**
Carbonyl carbons	-	168.39	169.39
Bridgehead aromatic carbons	-	-	134.71
Other Aromatic carbons	-	130.12	131.68, 128.66,127.92
-NCHN- carbons	41.64	-	40.59
CH_2 carbons of cyclohexyl rings	39.33-41.38	-	39.33-40.38



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SFO2           400.2316009 MHz
NUC2                    1H
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PLW12           0.33770001 W
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WDW                     EM
SSB      0
LB                    1.00 Hz
GB       0
PC                    1.40
The Gandhigram Rural
 Institute (Deemed to be
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Figure 7. ^{13}C- NMR Spectrum of ligand (L)

Thermal Analysis (TGA)

Thermal examinations (TGA) have been carried out to understand the thermal stabilities and decomposition patterns of metal chloride complexes. The Co(II) and Cu(II) complexes with mannich base ligand were heated to 800°C in a nitrogen atmosphere. The TGA patterns of the ligand, Co(II), and Cu(II) are shown in Figure 8. The ligand, DBB, is a thermally stable substance. At temperatures between 125 and 240 °C, the ligand began to slowly decompose, resulting in a weight loss of 97.18%, which was the result of one water molecule (found: 97.18, Calc: 97.10%). There are three stages in the decomposition of the Co(II) complex. The Co(II) metal complex underwent first-stage disintegration with an endothermic peak in the temperature range of 65.93-150 °C (found: 5.03%; calculated: 5.01%). 145–360 °C was the second stage of decomposition (found: 70.09 %; calc: 70.03 %). The third stage of breakdown occurs between 360 °C and 540 °C (found: 9.77%; calcified: 9.75%). The Cu(II) complex decomposes in two stages. The mass changed by 72.45% in the first stage of the decomposition temperature range of 131.49-390 °C (found: 72.55%: Calc: 71.97%), and the weight decreased by 18.19% in the second stage of the decomposition temperature range of 390-600 °C (found: 18.19%: Calc: 18.06%).

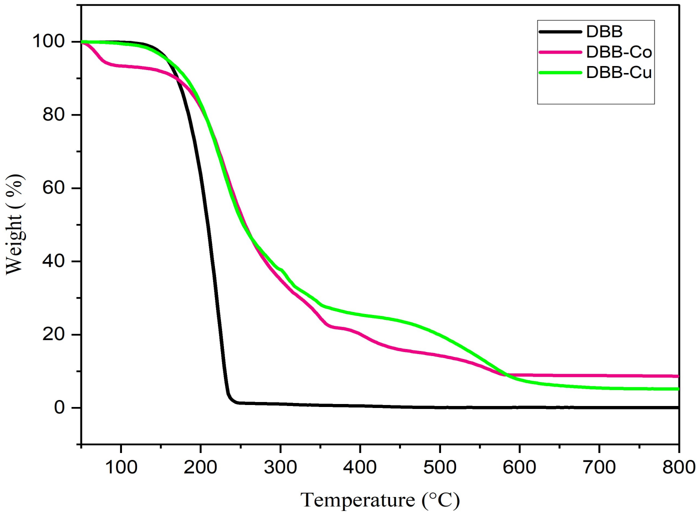

Figure 8. TGA analysis – DBB & its metal complexes

DFT Calculation

Figure 9 displays the optimized structures of the mannich base ligand (DBB) and the metal complexes (Co(II) and Cu(II)). We chose the density functional theory (DFT) approach utilising the B3LYP/6311++G(d,p) basic set for the gas phase calculation since DBB and metal complexes Co(II) and Cu(II) underwent geometry optimisation to analyse molecular structure behaviour inside the gas phase[22,23]. The frontier molecular orbital (FMO) structure of synthetic molecules is depicted in Figure 6. The LOMO is dispersed across the benzamide moiety, while the HOMO is focused on the dicyclohexylamine moiety. In the metal complexes of Co(II) and Cu(II) ions, Figure 10 shows the HOMO distributed around the dicyclohexylamine moiety, with very little contribution from the metal ions. The complexes (Co(II) and Cu(II)) have HOMO-LUMO energy gaps of 2.39 eV and 1.49 eV, respectively, and the mannich base, DBB, has the HOMO-LUMO energy gap of 4.43 eV. The order of the energy band gap is DBB > DBB-Co II > DBB-Cu II.

Molecular Electrostatic Potential

N-(dicyclohexylaminobenzyl)benzamide's molecular electrostatic potential has been computed using the optimised geometry under the B3LYP/6-311++G(d,p) model chemistry. The colour charge on the DBB surface changes from red to blue, reflecting the charge of each atom in the molecular electrostatic potential. Red colour regions are used to identify the most negative colours, while severe blue colour regions are used to identify the most positive colours. Of the 63 atoms that make up DBB, 34 are hydrogen atoms, all of which should be positively charged, because the point charges of each atom are linked to the molecule's electrostatic potential. The metal complexes have been compared to different atomic charges that have been calculated[33]

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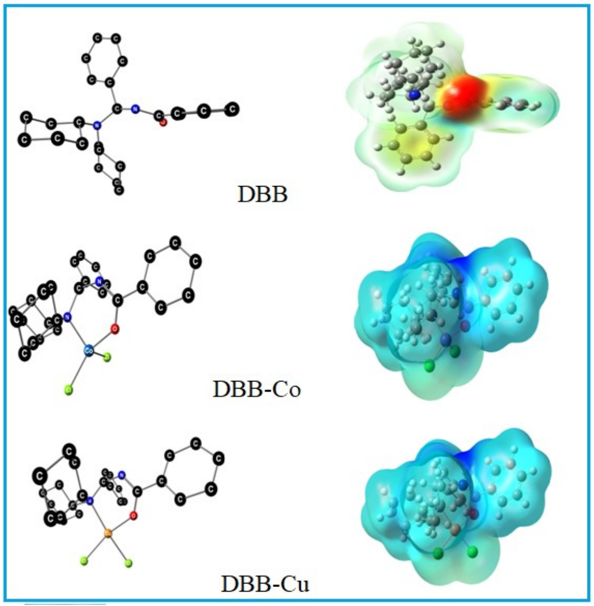

Figure 9. Optimised structure of DBB, Co^{2+} and Cu^{2+} complexes

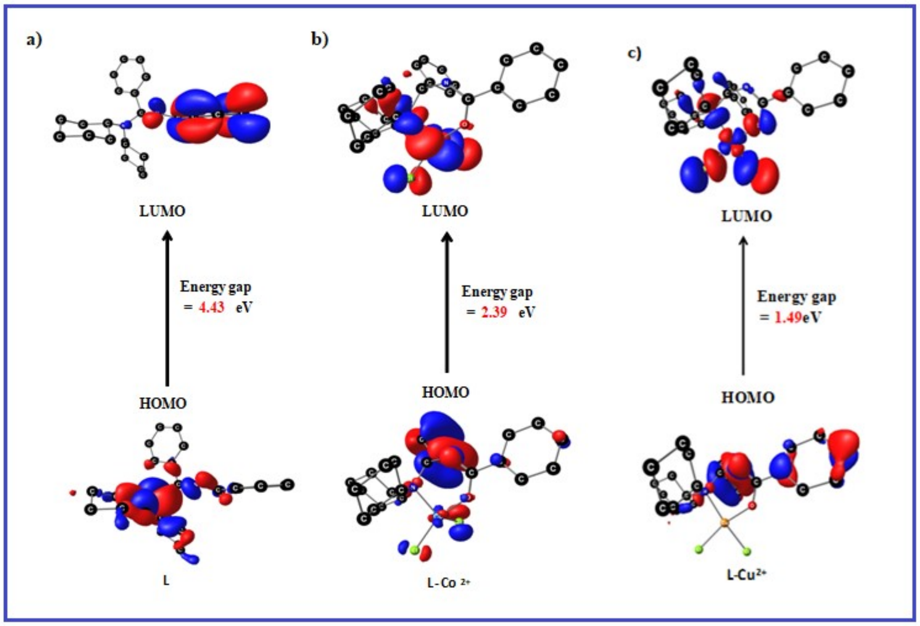

Figure 10. HOMO and LUMO of DBB, Co^{2+} and Cu^{2+} complexes

Biological Activity

The results of DBB and metal complexes' antibacterial activities are displayed in Tables 5a & 5b. Nystatin is used for antifungal activity, Amikacin is used as a positive standard, and DMF serves as a negative control. According to the findings, the metal complexes exhibited greater antibacterial and antifungal efficacy against every bacterium and fungus species examined when compared to DBB[11]. The aforementioned exceptional antimicrobial activities were due to the electron-donating substituent OH and NH groups[22]. Chelation theory might be used to interpret the complexes' high activity, particularly that of the Cu(II) complex[7]. The chelation hypothesis states that metal complexes can go through an organism's cell membrane. This could be connected to the metal ion's decreased polarity as a result of donor groups partially sharing the metal's positive charge[34].

Table 5(a). Antibacterial Activities - DBB and its Co(II) and Cu(II) complexes

Compound	**Zone of Inhibition (mm)**							
	E.coli				**S.aureus**			
	Conc. of compound (µg/mL)				**Conc. of compound (µg/mL)**			
	25	**50**	**75**	**100**	**25**	**50**	**75**	**100**
DBB	10	13	18	21	11	13	15	17
DBB-Co(II)	12	15	19	20	12	14	14	15
DBB-Cu(II)	13	17	21	22	14	15	16	18
Amikacin	8	-	-	-	-	-	-	-
Tetracyclin	-	-	-	-	8	-	-	-

Table 5(b). Antifungal Activities - DBB and its Co(II) and Cu(II) complexes

Compound	**Zone of Inhibition (mm)**							
	A.niger				**C.albicans**			
	Conc. of compound (µg/mL)				**Conc. of compound (µg/mL)**			
	25	**50**	**75**	**100**	**25**	**50**	**75**	**100**
DBB	8	13	14	18	8	14	15	16
DBB-Co(II)	9	15	16	18	10	15	17	19
DBB-Cu(II)	11	17	18	20	12	17	19	22
DBB	8	-	-	-	-	-	-	-

Conclusions

The successful synthesis of the novel Mannich base ligand N-(dicyclohexylaminobenzyl)benzamide and its Co(II) and Cu(II) complexes has been achieved and characterised comprehensively through various analytical, spectroscopic, and thermal methods. The results confirm the formation of stable mononuclear complexes with the proposed [MLX_2] stoichiometry and well-defined geometries, supported by both experimental evidence and DFT calculations. Spectroscopic analyses revealed the coordination behaviour of the ligand, while magnetic and molar conductance data verified its mononuclear nature. Thermal and spectral data further validated the structural stability of the complexes. The biological evaluation indicated that both the ligand and its metal complexes possess significant antimicrobial activity, with the metal complexes exhibiting enhanced potency compared to the free ligand. These findings highlight the promising potential of the synthesised Mannich base and its metal (II) complexes as bioactive compounds with applications in medicinal and coordination chemistry.

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