Communication in Physical Sciences, 2025, 12(7):2060-2075

Synthesis, Characterization, and ADME/T Prediction of (2Z)-2-[2-(2,4-Dinitrophenyl)hydrazinylidene]-1,2-diphenyle-than-1-ol (DPHD) and Its Copper(II) Complex

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Received: 12 July 2025/Accepted 19 October 2025/Published online: 17 October 2025
https://dx.doi.org/10.4314/cps.v12i7.7

Abstract : *The hydrazone ligand (2Z)-2-[2(2,4-dinitrophenyl)hydrazinylidene]-1,2-diphenylethan-1-ol (DPHD) and its Cu(II) complex were synthesized and characterized using physical and spectroscopic techniques. The newly synthesized compounds are coloured and crystalline with high yield (>70%) with melting points ≥ 100 ℃. The spectroscopic result has indicated a square planar geometry for the copper complex being coordinated by azomethine nitrogen, imine nitrogen, and two nitro groups. Both were soluble in dimethyl sulfoxide (DMSO), sparingly soluble in methanol and ethanol while being insoluble in hexane. The ligand was sparingly soluble in water while its complex was insoluble. SwissADME and ProTox-II in silico predictions of ADME/T showed that both DPHD and its copper complex showed compliance with the Lipinski's Rule of Five signifying promising oral drug-likeness. Complexation improved the gastrointestinal absorption and aqueous solubility of its copper complex, but it increased the predicted acute toxicity (LD_{50} = 900 mg/kg) and synthetic complexity relative to the free ligand. Both drugs are not blood-brain-barrier permeant and have acceptable pharmacokinetic characteristics of possible drug-drug interaction via inhibitory effect on various cytochrome P450. These findings concluded that the copper complex has a better bioavailability but altered toxicity, highlighting the need for experimental toxicity testing and further recommends preclinical investigation of its therapeutic role.*

Keywords: *Dinitrophenylhydrazone, Copper complex, ADME/T, pharmacokinetics, in silico*

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1.0 Introduction

Hydrazone-type compounds containing an azomethine (C=N) linkage constitute an important class of organic compounds with broad pharmaceutical and coordination chemistry relevance, playing a pivotal role in the discovery of new therapeutic agents. The hydrazone moiety, due to its extended conjugation and the presence of electron-donating nitrogen atoms, is capable of participating in resonance stabilization, hydrogen bonding, and metal coordination (Romero et al., 2015). These versatile structural and electronic characteristics endow hydrazones with the ability to bind to diverse metal centers, influencing their geometry, redox properties, and biological response**.** Hydrazone derivatives have demonstrated significant therapeutic potential, including antimicrobial, antioxidant, anti-inflammatory, and anticancer activities (Tumosienė et al., 2025; Işik et al., 2022). Among the various classes of hydrazones, dinitrophenylhydrazones have recently gained increased scientific attention due to their intriguing chemical and biological properties. The incorporation of a 2,4-dinitrophenyl (2,4-DNP) moiety into hydrazone ligands significantly alters their electronic distribution, chemical reactivity, and biological function. The electron-withdrawing nitro groups in the ortho and para positions of the phenyl ring increase the electrophilicity of the molecule and enhance its resonance stabilization and acidity (Nishiwaki, 2020). Such electronic effects promote facile deprotonation, radical stabilization, and efficient metal coordination, making 2,4-DNP-substituted hydrazones particularly suitable scaffolds for metal-based drug design and biological studies.

Currently, the synthesis of transition metal complexes of hydrazones is widely reported in the scientific literature. The growing interest in this area stems from the remarkable enhancement of biological activities observed in hydrazone–metal complexes compared to the parent ligands (Czyżewska et al., 2024). Metal coordination not only influences the physicochemical behavior of hydrazones but also modifies their lipophilicity, membrane permeability, and redox potential—properties essential for effective drug delivery and pharmacological performance**.** Complexation between a bioactive ligand and a transition metal can thus amplify or modulate therapeutic outcomes by influencing the compound’s solubility, stability, and biochemical reactivity (Ugochukwu et al., 2021; Otuokere et al., 2020).

Notably, copper(II) hydrazone complexes exhibit diverse pharmacological and biochemical activities, such as DNA intercalation, reactive oxygen species (ROS) modulation, enzyme inhibition, and redox-mediated cytotoxicity, all of which are critical for selective therapeutic targeting (Mahfouz et al., 2025; Otuokere et al., 2022; Edozie et al., 2020; Otuokere et al., 2019). Their square-planar or distorted geometries also contribute to their high binding affinity toward biological macromolecules**.** Despite advances in synthetic methodologies and the increasing number of studies on copper(II) complexes of hydrazones, particularly those bearing the 2,4-dinitrophenyl substituent, a comprehensive understanding of their pharmacokinetic behavior, bioavailability, and toxicity is still limited.

The Absorption, Distribution, Metabolism, Excretion, and Toxicity (ADME/T) profiling of a compound is a critical predictive tool in modern drug design, providing insight into oral bioavailability, systemic stability, and safety (Eberendu et al., 2025; Asogwa et al., 2024; Eberendu et al., 2024; Xiao et al., 2022; Otuokere et al., 2019). Although computational tools such as SwissADME and ProTox-II are now routinely used for in silico pharmacokinetic modeling, their application to hydrazone-based copper(II) complexes remains underrepresented in the literature. Literature reveals limited integration of detailed spectroscopic and physicochemical characterization with in silico ADME/T prediction, particularly for ligands like (2Z)-2-[2-(2,4-dinitrophenyl)hydrazinylidene]-1,2-diphenylethan-1-ol (DPHD), whose molecular structure and electronic configuration could profoundly influence drug-likeness and toxicity outcomes. This constitutes a critical knowledge gap that must be addressed to guide rational design of safer and more efficient metal-based therapeutics.

Hence, the present study is designed to synthesize and characterize the hydrazone ligand DPHD and its copper(II) complex, and to systematically predict their pharmacokinetic and toxicity profiles using advanced in silico ADME/T tools**.** By integrating multi-spectroscopic characterization techniques (UV–Vis, FTIR, NMR, and elemental analysis) with computational pharmacokinetic modeling, this study seeks to establish the structural, electronic, and biological interplay between the ligand and its metal complex. The ADME/T predictions are expected to provide vital insights into absorption potential, solubility, metabolic stability, predicted acute toxicity, and overall drug-likeness, allowing for a rational assessment of their therapeutic viability.

Ultimately, this holistic approach not only bridges the identified research gap but also contributes to the foundational understanding of hydrazone–metal systems as potential leads in medicinal and coordination chemistry. The results of this study are expected to enhance future development of copper-based pharmacophores with optimized bioavailability, reduced toxicity, and improved therapeutic efficiency.

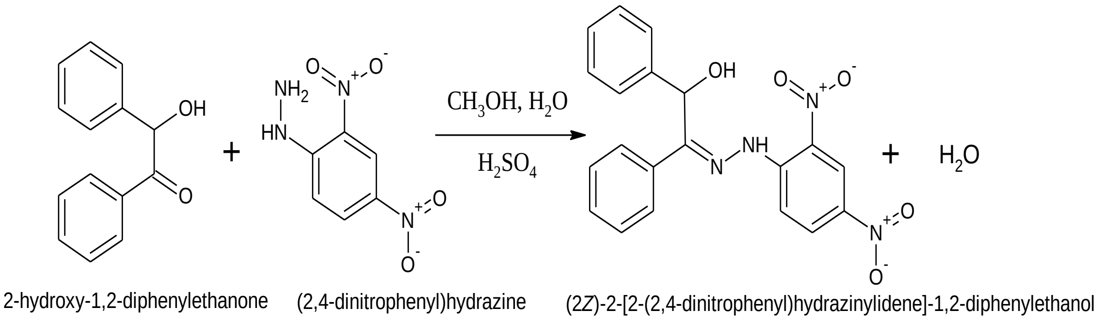
2.0 Materials and methods

2.1 Chemicals and solvents

The chemicals and reagents used in this study are of analytical grades supplied by sigma-Aldrich and were used as obtained without further purification.

2.2 Synthesis of DPHD

The ligand (DPHD) was prepared following the reported procedure by Eberendu *et al*. (2024). To the warm clear solution obtained by filtering a warmed mixture of 1.98 g (0.010 mol.) of 2,4-DNP, 10 mL of concentrated sulphuric acid, 15 mL of water, 25 mL of methanol, and 1.50 g (0.010 mol.) of the carbonyl compound 2-hydroxy-1,2-diphenylethanone was added and heated just to boiling. The precipitates formed were allowed to cool to room temperature before they were recrystallized from methanol, dried in a desiccator, and stored in a neatly labeled container. The equation of reaction is shown in Scheme 1.



Scheme 1: Synthesis of DPHD

2.3 Synthesis of [Cu(DPHD)n]

The [Cu(DPHD)n] complex was synthesized following the reported procedure by Eberendu *et al*. (2024). Exactly 1.70 g of $CuCl_2.2H_2O$ (0.010 mol.) metal salt was dissolved in 5 mL of methanol; the mixture was stirred for about 5 minutes. The hydrazone ligand DPHD was then dissolved separately in a hot solution of methanol. The ligand solution containing 3.92 g (0.010 mol.) of DPHD ligand was added to the solution containing the metal salt and stirred. The obtained product was cooled, filtered, recrystallized with methanol solvent, and dried at room temperature. The equation of the reaction is shown in equation (1).

$$\mathrm{CuCl_2.2H_2O} + DPHD \xrightarrow{CH_3OH} [Cu(DPHD)] + 2HCl_2 \qquad (1)$$

2.4 Physical measurements

Melting points were recorded using a Gallenkamp melting point apparatus. Solubility was carried out in test tubes using various solvents such as polar solvents (water, methanol, and ethanol), the non-polar solvent hexane, and dimethylsulfoxide (DMSO). Molar conductivities were checked using an OMEGA digital conductometer (CD5126 by OMEGA industry, UK) at a room temperature of 10-3 M solution in deionized water.

2.5 Characterization

The electronic absorption spectra were recorded using a Thermo Scientific Orion Aquamate 8100 UV-Vis Spectrophotometer in the range 200-800 nm. Infrared spectroscopy was recorded using an Agilent Cary 630 FT-IR (4000-600 cm^{-1}) in KBr pellets. Nuclear magnetic resonance was recorded on Nanalysis-X685 (60 MHz) using $CDCl_3$ as a solvent.

2.6 In silico studies

2.6.1. ADMET predictions

Swiss ADME online platform (http://www.swissadme.ch) was used to determine the ADMET properties, the drug-like characteristics, and possible drug-drug interactions.

2.6.2. Toxicity

The toxicological predictions were produced based on the ProTox-II web tool (tox.charite.de).

3.0 Results and Discussion

Some physical parameters of DPHD and [Cu(DPHD)n] are presented in Table 1. The solubility of DPHD and [Cu(DPHD)n] in some selected solvents is presented in Table 2. The electronic, infrared, ^{1}H NMR, and ^{13}C NMR of DPHD and [Cu(DPHD)n] are presented in Figs. 1, 2, 3, and 4, respectively

Table 1: Some physical parameters of DPHD and [Zn(DPHD)]

Compound	Colour	Yield (%)	Molar Conductance (Sm^{2}mol^{-1})	M.P (°C)
DPHD	Orange	89	111	110
[Cu(DPHD)n]	Greenish yellow	74	141	157

DPHD is orange, while the copper complex is greenish yellow in color (Table 1). Color changes upon complexation indicate coordination changes and altered electronic environments around the central metal ion, typical for metal-hydrazone complexes (Mandewale *et al*., 2019). The yield (Table 1) of DPHD is high (89%), which is typical for pure organic syntheses. The copper complex yield is slightly lower (74%), this variation in percentage yield is as a result coordination challenges and purification losses (Marchetti *et al*., 2022). DPHD has a high molar conductance of 111 Sm^{2}mol^{-1}, indicative of a non-electrolyte or low electrolytic nature, as it's an organic compound without ionic dissociation ((Marchetti *et al*., 2022). The copper complex has a higher conductance (141 Sm^{2}mol^{-1}), consistent with electrolytic behavior in solution (Marchetti *et al*., 2022). DPHD melts at 110°C, while its copper complex has a higher melting point (157°C). This elevation is typical for metal complexes due to enhanced thermal stability from metal-ligand coordination bonds strengthening the lattice structure (Hussain *et al*., 2023).

Table 2: Solubility of DPHD and [Zn(DPHD)]

Compounds	Hexane	Water	Methanol	Ethanol	DMSO
DPHD	IS	SS	SS	SS	S
[Cu(DPHD)n]	IS	IS	SS	SS	S

****Insoluble (IS), Soluble (S), Sparingly Soluble (SS)**

Both DPHD and its copper complex were soluble in dimethyl sulfoxide (DMSO) but were sparingly soluble in methanol and ethanol while being insoluble in hexane. This is due to the polar aprotic characteristics of DMSO solvent and this also confirms the polar and ionic character of these compounds which does not favour solvation in non-polar solvents (Aly *et al*., 2020). The DPHD was sparingly soluble in water while its metal complex was insoluble in water. This solubility pattern indicates limited hydrophilicity of these compounds and do not dissolve well in typical alcohols or water but dissolve in strongly coordinating polar solvents like DMSO (Otuokere and Robert, 2020).

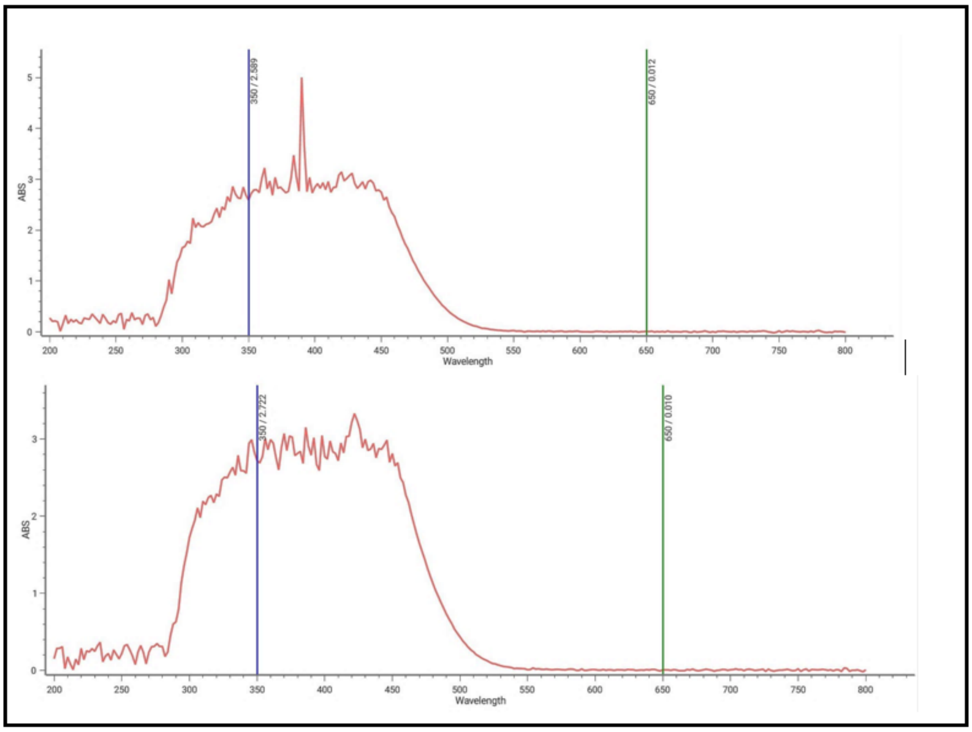


Fig. 1: Electronic spectra of DPHD and [Cu(DPH

Both DPHD and [Cu(DPHD)n] spectra (Figure 1) exhibit absorbance peaks around 305-400 nm, likely corresponding to π→π* or n→π* electronic transitions typical of hydrazone ligands (Tadewos *et al*., 2022) . There is a slight red-shift (bathochromic shift) of the absorption maximum in [Cu(DPHD)n] relative to DPHD, suggesting metal coordination influences electron distribution in the ligand (Marchetti *et al*., 2022). The peak at at λ = 425 nm for the complex [Cu(DPHD)n] point to new ligand-to-metal charge transfer (LMCT) or d-d transitions characteristic of copper complex (Marchetti *et al*., 2022; Aly.and Fathalla, 2019). Studies further report that such spectral features, including red-shifts and increased absorbance intensity, may be associated with improved biological activities of copper hydrazone complexes compared to free ligands (Moreira *et al*., 2025).

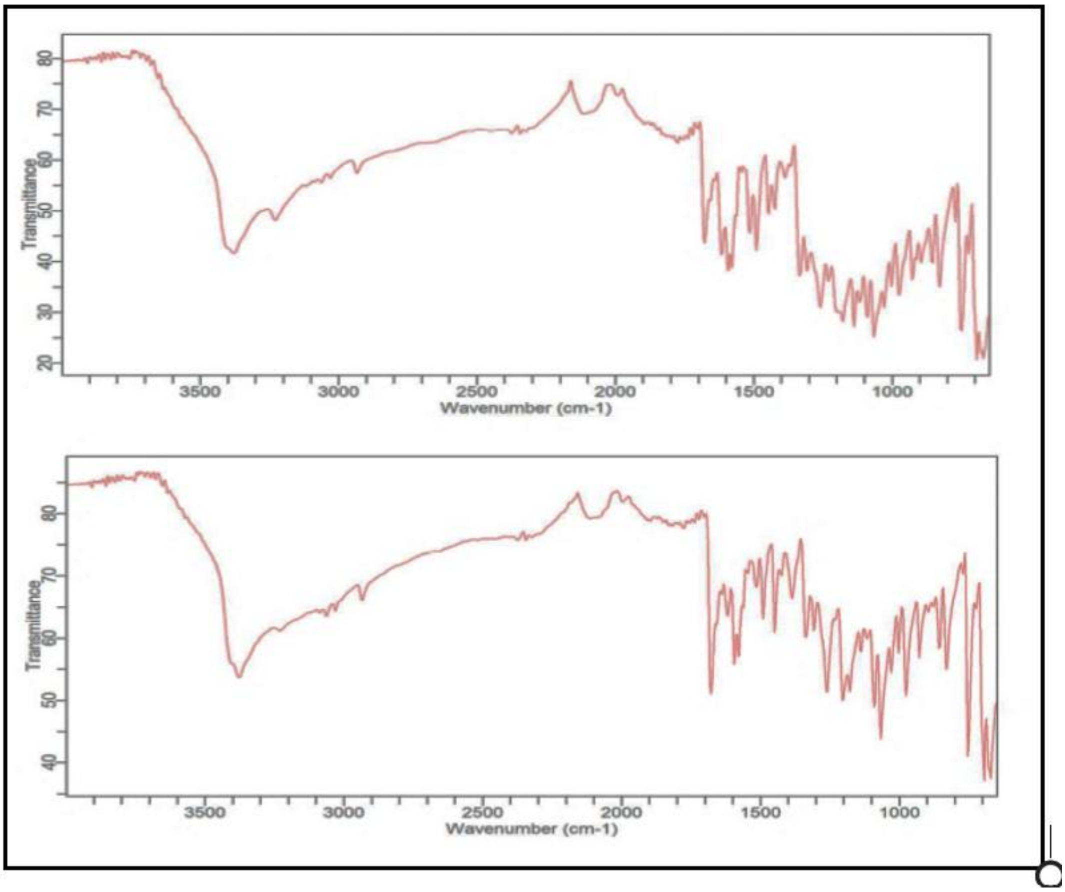


Fig. 2: FTIR spectra of DPHD and [Cu(DPHD)n]

The DPHD infrared spectrum (Fig. 2) shows a strong absorption band at 1650 cm^{-1}, which was attributed to the azomethine (C=N) vibration, as has been reported previously with hydrazone ligands (Moreira *et al*., 2025). In coordination with zinc in [Cu(DPHD)n] (Figure 2), this band changes to a lower wavenumber at (1610 cm^{-1}) indicating metal bonding through the azomethine nitrogen. A red shift of this type indicates an increase in electron density in the C=N bond, thus leading to a weakened bond and a lower vibrational frequency which is consistent with Schwitall *et al*. (2024) who reported similar behavior for hydrazone compounds. In the DPHD spectrum, weak broad bands at 3380 and 3227 cm^{-1} are assigned to hydroxyl (-OH) and amine (-NH) stretching vibrations, respectively (Riaz *et al*., 2023). In the [Cu(DPHD)n] complex, the -OH stretching band remained at 3380 cm^{-1}, suggesting that the -OH group remains protonated and does not participate in coordination. This is further supported by the absence of a shift in the C–O stretching band from 1259 cm^{-1} in DPHD to a different position in the complex, reflecting no coordination-induced changes in the C–O bond (Manimaran *et al.*, 2021). Notably, the NH band shifted up to 3235 cm^{-1} for [Cu(DHPD)n], indicating the coordination of the ligand to the metal through the nitrogen atom of the amine group (Abdel-Rahman *et al.*, 2023). The ligand's characteristic aromatic nitro (NO_2) vibration at 1386 cm^{-1} also shifts to 1338 cm^{-1} in the [Cu(DPHD)n]. This suggested the participation of the NO_2 functionality in coordination with zinc (Bhaskar *et al.*, 2020). Such shifts in nitro group vibrations upon complexation have been widely documented, reflecting changes in electron distribution within the aromatic ring and substituents upon metal binding (Bhaskar *et al.*, 2020).

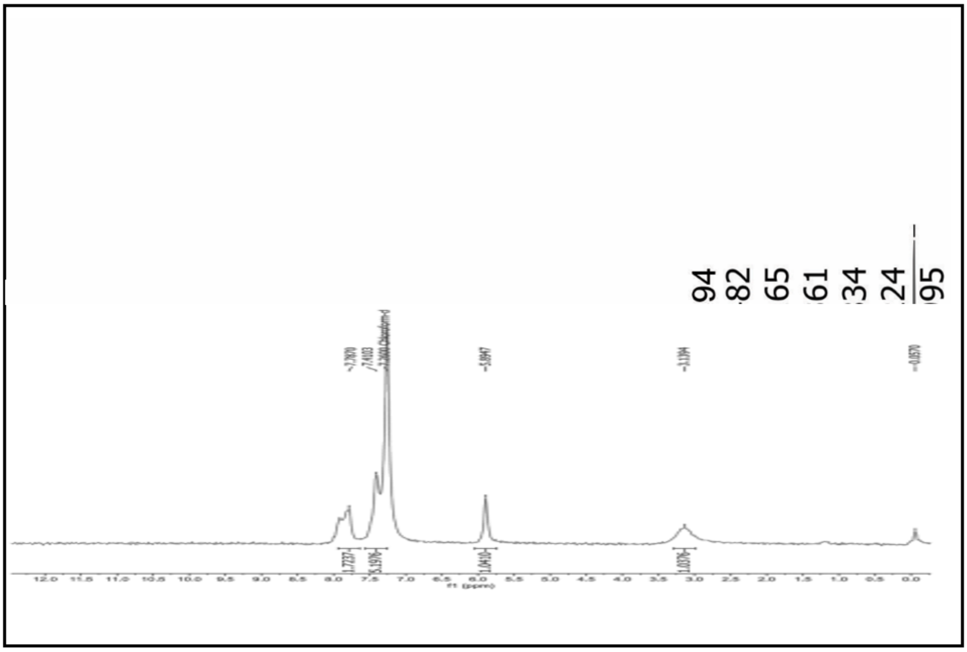


Fig. 3: ^{1}H NMR spectra of DPHD and [Cu(DPHD)n]

The ^{1}H NMR spectra of DPHD and its zinc complex [Cu(DPHD)n] (Fig. 3) display characteristic aromatic proton signals from phenyl groups and the 2,4-dinitrophenyl (2,4-DNP) moiety in the range δ 7.3–7.9 ppm, consistent with previously reported chemical shifts for aromatic protons in similar ligands (Badal *et al.*, 2020). The hydrazone azomethine proton (HC=N-) showed as a distinct peak at δ 8.5 ppm in the free ligand DPHD, corroborating literature values for imine protons (Shah *et al.*, 2022). In [Cu(DPHD)] spectrum, this azomethine proton signal is either broadened or overlapped with nearby aromatic proton resonances, indicative of coordination through the N atom of the C=N group. This behavior aligns with observations reported in similar metal complexes, where coordination results in peak shifts or broadening due to changes in electron density and exchange processes involving the azomethine proton (Pîrnău *et al.*, 2025).

The recorded chemical shifts are in good agreement with previously reported hydrazone frameworks supporting the successful synthesis and structural integrity of the newly synthesized compounds.

Both ^{13}C NMR spectra (Fig 4) prominently display the chloroform-d ($CDCl_3$) solvent peak around 77 ppm, appearing as a characteristic triplet due to deuterium coupling, consistent with standard NMR solvent behavior (Tiwari *et al.*, 2025). The free ligand DPHD exhibits multiple distinct peaks between 127 and 129 ppm, typical of aromatic carbons in phenyl or heteroaromatic rings, aligning with reported values in the literature for similar aromatic systems (Yayli *et al*., 2021). Upon coordination to Cu in [Cu(DPHD)n], the aromatic carbon signals in the 127-129 ppm range exhibit changes in intensity and slight chemical shift variations compared to the free ligand. This trend is commonly reported in metal-ligand coordination studies, where metal binding alters electron density and the local magnetic environment of aromatic carbons, often resulting in peak broadening and reduced intensity due to slower molecular tumbling or paramagnetic effects (Yayli *et al*., 2021). Notably, the C=N carbon signal, appears around δ 133.93 ppm in ^{13}C NMR of DPHD, which is highly deshielded due to resonance effects (Ogunniran *et al*., 2015). [Cu(DPHD)n] complex showed a peak at 139.26 ppm, were assigned the imine carbon -C=N. This is consistent with the study of El-Sonbati *et al*. (2021), who reported that coordination of metal ions to the imine nitrogen has a negligible effect on the electron density of the adjacent carbon atom. The peak at 76.40 ppm for DPHD was assigned carbon to which the -OH group is attached (Yayli *et al*., 2021) while for its [Cu(DPHD)n] complex it appeared at 87.83 ppm.

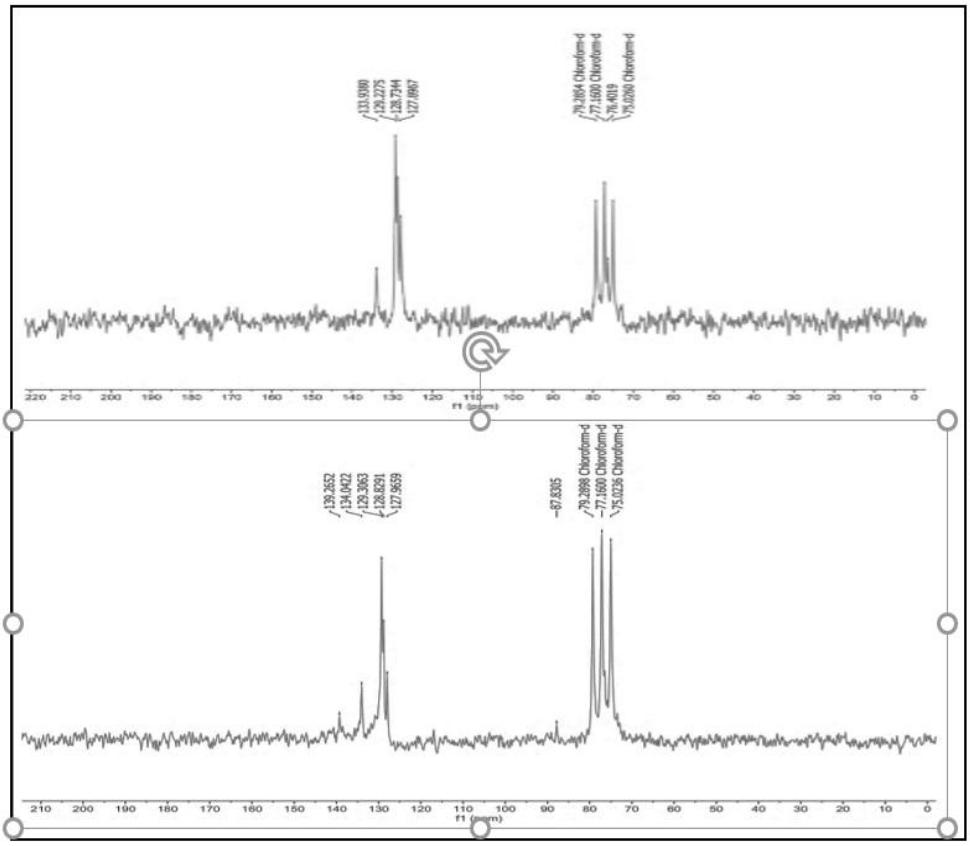


Fig. 4: ^{13}C NMR of DPHD and [Cu(DPHD)n]

The overall distribution of peaks across both the donwfield and upfield regions in the spectra of the compounds strongly confirm the successful synthesis and structural integrity of DPHD and DPHMM ligands and their metal complexes.

Based on the spectroscopic studies, the structures in Fig. 5 have been proposed for the ligand and its metal complex

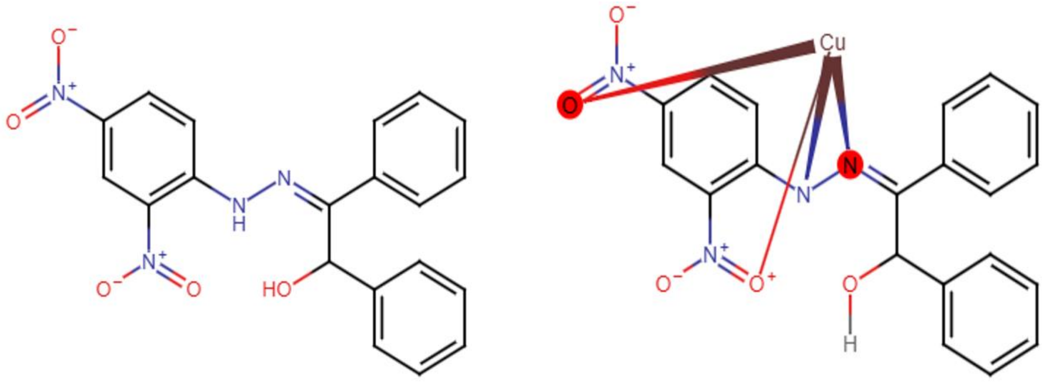
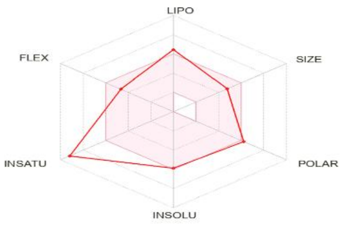
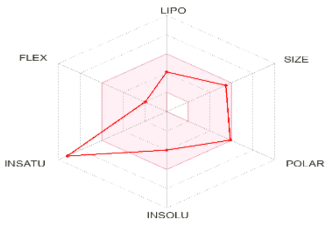


Fig. 5: Proposed structure for DPHD and [Cu(DPHD)n]

Table 3: ADME/T properties of DPHD and [Cu(DPHD)n]

	Physicochemical Properties	
Formular	DPHD	[Cu(DPHD)]
Molecular weight (g/mol)	392.36	454.90
Num. H-bond acceptors	6	5
Num. H-bond donors	2	1
Molar Refractivity	112.02	123.97
TPSA (Å^2)	136.26	127.24
	Lipophilicity	
Log *P*	-0.37	-5.08
	Water Solubility	
Log *S* (ESOL)	-5.89	-3.98
Class	Moderately soluble	Moderately soluble
	Pharmacokinetics	
GI absorption	Low	High
BBB permeant	No	No
P-gp substrate	Yes	Yes
CYP1A2 inhibitor	No	No
CYP2C19 inhibitor	Yes	Yes
CYP2C9 inhibitor	Yes	No
CYP2D6 inhibitor	No	No
CY3A4 inhibitor	No	No
Log K_p (skin permeation) (cm/s)	-4.61	-7.87
	Druglikeness	
Lipinski	Yes, 0 violation	Yes, 0 violation
Bioavailability Score	0.55	0.55
	Medicinal Chemistry	
PAINS	0 alert	0 alert
Synthetic accessibility	4.01	5.92
Bioavailability Radar		





The ADME/T properties of DPHD and [Cu(DPHD)n] (Table 3) reveal several important pharmacokinetic and medicinal chemistry differences that could impact their drug development potential.

Physicochemical Properties: The copper complex [Cu(DPHD)n] exhibits a higher molecular weight (454.90 g/mol) than DPHD (392.36 g/mol), attributable to copper coordination. This leads to decreased hydrogen bond donors (1 vs. 2) and slightly fewer acceptors (5 vs. 6), which can affect molecular interactions and solubility. The molar refractivity increases with complexation (123.97 vs. 112.02), suggesting changes in volume and polarizability. Topological polar surface area (TPSA) decreases from 136.26 Å^2 in DPHD to 127.24 Å^2 in [Cu(DPHD)n], indicating improved membrane permeability and absorption (Veber *et al*., 2002).

Lipophilicity and Solubility: DPHD is more lipophilic (log P = -0.37) compared to the copper complex (-5.08), metal complexation decreased its lipophilicity but increased its hydrophilicity (Lipinski *et al*., 1997). Both compounds are moderately soluble, with [Cu(DPHD)n] demonstrating improved aqueous solubility (log S -3.98 vs. -5.89) on complexation, indicating good solubility and enhanced oral absorption and bioavailability (Veber *et al*., 2002).

Pharmacokinetics

Gastrointestinal (GI) absorption is predicted to be low for DPHD but high for [Cu(DPHD)], likely due to improved solubility and decreased TPSA in the complex. Both are not blood-brain barrier (BBB) permeant, which is advantageous for drugs not intended for CNS purpose. Both compounds are substrates for P-glycoprotein (P-gp) that may be effluxed from intestinal cells in turn reducing bioavailability (Al-Azzam et al., 2022). Cytochrome P450 (CYP) inhibition profiles differ: DPHD inhibits CYP2C19 and CYP2C9, whereas [Cu(DPHD)n] inhibits CYP2C19 only. This variation shows the impact of metal coordination on metabolic pathways and potential drug-drug interactions (Otuokere *et al*., 2025).

Drug-likeness and Synthetic Accessibility

Both compounds satisfy the Lipinski Rule of Five, signifying promising oral drug-likeness. Their bioavailability scores are identical (0.55) indicating moderate oral bioavailability, they could be well absorbed in the human body. The synthetic accessibility score is higher for [Cu(DPHD)n] (5.92 vs. 4.01), indicating moderate synthesis route of drug development which means more synthetic complexity (5).

Toxicity

The predicted LD_{50} of [Cu(DPHD)] (900 mg/kg) is lower than DPHD (2690 mg/kg), indicating higher acute toxicity. The toxicity class of the copper complex is 4, compared to 5 for DPHD, reflecting increased toxicity risk upon metal coordination. This aligns with reports that metal complexes often exhibit altered toxicity profiles that require detailed evaluation (Otuokere et al., 2025).

[Cu(DPHD)n] shows improved GI absorption and water solubility compared to DPHD due to changes in physicochemical properties from copper metal complexation. However, the complex also exhibits higher toxicity and synthetic complexity which are consistent with reported trends in metal-based drug candidates, where enhanced pharmacokinetics may be offset by increased toxicity risks and challenges in synthesis (Otuokere *et al*., 2025; Asogwa *et al*., 2024; Ugochukwu *et al*., 2021).

4.0 Conclusion

This study successfully synthesized, characterized the DPHD ligand and its corresponding metal complex with Cu(II) and further probed into the pharmacokinetic potential of these compounds. The structure of the DPHD ligand and it metal complex were confirmed through the spectral data results which affirmed the effective coordination with the metal ion. The copper complex showed enhanced solubility and improved gastrointestinal absorption but its toxicity was increased relative to the free ligand. The ADME/T predictions support their potential as orally bioavailable drug candidates i.e they could be suitable for oral administration. The srtudy further showed that the metal complex exhibited improved pharmacokinetics at the cost of higher synthetic complexity and toxicity risk which further establishes a foundational understanding of copper hydrazone complexes and their drug-like behavior.

Future studies should explore the *in vitro* and *in vivo* studies and pharmacological effects of the synthesized compounds using suitable animal models. Exploring the formulation of the synthesized compounds into nano-delivery systems in other to improve their solubility, stability, and targeted delivery are advisable. Conducting detailed biological activity tests, such as antioxidant, anti-inflammatory and antimicrobial evaluations, will provide deeper insights into how these compounds can be used medicinally.

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Declaration

Funding sources

No funding

Competing Financial Interests Statement:

There are no competing financial interests in this research work.

Ethical considerations

Not applicable

Data availability

The microcontroller source code and any other information can be obtained from the corresponding author via email.

Authors' Contribution

Unwananobong. F. Robert carried out the experimental work and interpreted the results, drafted the initial manuscript. Ifeanyi E. Otuokere conceptualized and supervised the study, led in result interpretation and contributed to manuscript revision. Jude C. Nnaji supervised the research and critically reviewed the manuscript.