CO^{2+}, NI^{2+}, CU^{2+}, ZN^{2+} AND VO^{2+} COMPLEXES DERIVED FROM 5-PHENYL-1,3,4-OXADIAZOLE-2(3H)-THIONE

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Abstract

In this study, five novel coordination compounds of 5-phenyl-1,3,4-oxadiazole-2(3H)-thione (FODT) with Co^{2+}, Ni^{2+}, Cu^{2+}, Zn^{2+}, and VO^{2+} ions were successfully synthesized and comprehensively investigated. The ligand was prepared via a condensation reaction between benzoyl hydrazide and potassium isothiocyanate. The metal complexes were obtained in solution using a 1:2 metal-to-ligand molar ratio. The synthesized compounds were characterized by IR spectroscopy and X-ray structural analysis. IR spectral data confirmed that the ligand coordinates to the metal ions through nitrogen and sulfur donor atoms, forming N,S-chelate complexes. X-ray crystallographic analysis revealed that the Cu(II) complex adopts a square-pyramidal geometry. Based on spectral and analytical data, octahedral geometries were proposed for the Co(II) and Ni(II) complexes, while the Zn(II) complex was suggested to possess a tetrahedral coordination environment. The antimicrobial activity of all synthesized compounds was evaluated using the disk diffusion method against Staphylococcus aureus, Escherichia coli, and Candida albicans test strains. All metal complexes exhibited significantly higher biological activity compared to the free ligand. Among them, the Cu(II) and VO^{2+} complexes demonstrated the strongest antimicrobial effects. These findings indicate that FODT-based metal complexes may be considered promising candidates for the development of new biologically active compounds.

Keywords: 5-phenyl-1,3,4-oxadiazole-2-thione, coordination compounds, transition metals, IR spectroscopy, X-ray structural analysis, antimicrobial activity, chelate complexes.

1.Introduction

The chemistry of heterocyclic compounds represents one of the most actively developing areas of coordination chemistry, with 1,3,4-oxadiazole derivatives occupying a particularly important position. The oxadiazole ring is distinguished by its pronounced aromatic character, chemical stability, and its ability to exhibit a wide range of biological activities. In particular, 2-thione derivatives contain both nitrogen (N) and sulfur (S) donor atoms within the same molecule, which makes them valuable ambidentate ligands in coordination chemistry. As a soft donor, the sulfur atom readily forms stable coordination bonds with soft or borderline transition metal ions such as Cu^{2+}, Ni^{2+}, Co^{2+}, and Zn^{2+}, in full agreement with Pearson's HSAB (Hard and Soft Acids and Bases) theory [1].

5-Phenyl-1,3,4-oxadiazole-2(3H)-thione (FODT) is a representative member of this class of compounds. The presence of a phenyl substituent enhances the molecule's π-electron density and hydrophobic character, which may strengthen its interaction with biological membranes and contribute to improved antimicrobial activity. Recent studies have demonstrated that metal complexes based on oxadiazole-thione ligands can exhibit not only antibacterial and antifungal properties, but also antitumor and antioxidant activities. For example, Shakdofa et al. (2019) synthesized copper(II) complexes with 1,3,4-oxadiazole-thione ligands and reported strong activity against Gram-positive bacteria. Similarly, Said et al. (2021) investigated VO^{2+} complexes with heterocyclic thiol ligands and observed antifungal activities comparable to those of standard reference drugs [2].

The vanadyl ion (VO^{2+}) occupies a distinctive place in coordination chemistry. Owing to the presence of a strong V=O double bond, vanadyl complexes display characteristic spectral and magnetic properties. From a biological perspective, vanadium compounds are well known for their insulin-mimetic effects, and their antimicrobial potential is also being actively explored.

A review of the available literature indicates that the coordination compounds formed between FODT and the above-mentioned transition metal ions have not yet been comprehensively studied, and data regarding their structural and biological properties remain limited. Therefore, the aim of the present work is to synthesize Co^{2+}, Ni^{2+}, Cu^{2+}, Zn^{2+}, and VO^{2+} complexes with FODT, to investigate their structures using modern physicochemical methods, and to evaluate their antimicrobial activity [3].

2.Literature review

The chemistry of 1,3,4-oxadiazole derivatives has attracted sustained interest in coordination chemistry since the second half of the twentieth century, although the ring system was first described by Bladin in the late nineteenth century [4]. Today, oxadiazole-based compounds are widely applied in medicine, agrochemistry, and materials science. Several clinically approved drugs, including Raltegravir (antiviral) and Zibotentan (antitumor), contain the oxadiazole fragment, highlighting its value as a promising scaffold for bioactive molecule design [5]. Among these derivatives, 1,3,4-oxadiazole-2(3H)-thiones are of particular importance because they exhibit thione–thiol tautomerism and contain both nitrogen and sulfur donor atoms. In the solid state, they predominantly exist in the thione form, as confirmed by NMR and IR data [6]. Owing to the soft donor character of sulfur and the coordinating ability of nitrogen, these ligands readily form stable complexes with transition metal ions such as Cu^{2+}, Ni^{2+}, Co^{2+}, Zn^{2+}, and VO^{2+}, in accordance with Pearson's HSAB theory [7].

Interest in the biological activity of transition metal complexes intensified after Rosenberg's discovery of the antitumor properties of platinum compounds in the 1960s [8]. Since then, coordination compounds have become increasingly important in pharmacological research. Complexes of Cu(II), Ni(II), Co(II), Zn(II), and VO(IV) are widely investigated for their antibacterial, antifungal, antioxidant, and antidiabetic properties. Copper(II) complexes, in particular, have drawn considerable attention because copper is a biologically relevant metal present in key enzymes such as superoxide dismutase and cytochrome c oxidase. Numerous studies report that Cu(II) complexes with sulfur-containing ligands exhibit significantly enhanced antimicrobial activity compared to free ligands. Nickel(II) and cobalt(II) complexes with N,S-donor ligands have also demonstrated notable antibacterial and antifungal effects, while zinc(II) complexes are of special interest due to the low toxicity of Zn^{2+} and its essential role in enzymes such as DNA polymerase and carbonic anhydrase [9]. The vanadyl ion (VO^{2+}), characterized by a strong V=O bond, typically forms square-pyramidal or octahedral complexes and is well known for its insulin-mimetic properties; more recently, its antimicrobial potential has also been actively explored.

The enhanced biological activity of metal complexes relative to free ligands is commonly explained by Tweedy's chelation theory and the overtone concept [10]. According to Tweedy's theory, coordination reduces the polarity of the metal ion and increases the overall lipophilicity of the complex, facilitating its penetration through biological membranes. The overtone concept further suggests that metal–ligand interactions enhance orbital overlap, thereby promoting stronger biochemical interactions with cellular targets.

Overall, previous studies indicate that 1,3,4-oxadiazole-2(3H)-thione ligands can form promising biologically active complexes with a variety of transition metals. However, systematic comparative data on the complexes of 5-phenyl-1,3,4-oxadiazole-2(3H)-thione with Co^{2+}, Ni^{2+}, Cu^{2+}, Zn^{2+}, and VO^{2+} remain limited. Addressing this gap, the present work focuses on the synthesis and comparative structural and biological evaluation of these metal complexes, thereby contributing new insights into their coordination behavior and antimicrobial potential.

3.Experimental section

3.1. Reagents and Instrumentation

All chemicals used in this study—benzoyl hydrazide, potassium isothiocyanate, $CoCl_2·6H_2O$, $NiCl_2·6H_2O$, $CuCl_2·2H_2O$, $ZnCl_2$, and $VOSO_4·5H_2O$—were of analytical grade (Sigma-Aldrich and Merck) and were used without further purification [11]. Absolute ethanol, distilled water, and chloroform were employed as solvents. IR spectra were recorded on a Bruker ALPHA FT-IR spectrometer in the 4000–400 cm^{-1} range using the KBr pellet technique. Single-crystal X-ray diffraction data were collected on a Bruker APEX-II diffractometer using Mo-Kα radiation ($\lambda = 0.71073$ Å). The structures were solved and refined by the least-squares method using the SHELXL-2018 software package. Melting points were determined in open capillaries on a Gallenkamp melting point apparatus. Elemental analyses (C, H, N, S) were carried out using a PerkinElmer 2400 CHN analyzer.

3.2. Synthesis of 5-Phenyl-1,3,4-oxadiazole-2(3H)-thione (FODT)

The FODT ligand was synthesized as follows: 0.01 mol (1.36 g) of benzoyl hydrazide was dissolved in 30 mL of absolute ethanol. A solution of potassium isothiocyanate (0.01 mol, 0.97 g) in 10 mL of water was added dropwise under continuous stirring. The reaction mixture was refluxed at 78 °C for 5 hours using a magnetic stirrer and condenser. After cooling to room temperature, the resulting colorless precipitate was filtered through a Büchner funnel, washed successively with cold ethanol (2 × 10 mL) and diethyl ether (2 × 10 mL), and dried under vacuum over P_2O_5 for 24 hours.

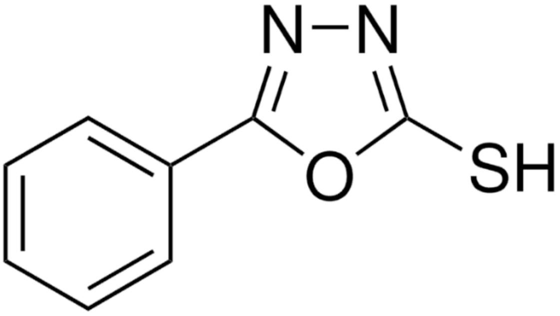

Figure 1. Molecular structure of 5-phenyl-1,3,4-oxadiazole-2(3H)-thione (FODT).

Yield: 1.82 g (85%).

Melting point: 218–220 °C.

Elemental analysis for $C_8H_6N_2OS$ (calculated/found, %): C 49.98/49.85; H 3.15/3.22; N 14.57/14.49; S 16.68/16.72.

3.3. Synthesis of the Metal Complexes

All complexes were synthesized using a general solution method. A solution of the appropriate metal salt (0.5 mmol) in water or a water–ethanol mixture (1:1) was added to an ethanolic solution of FODT (1.0 mmol), maintaining a metal-to-ligand molar ratio of 1:2. The reaction mixture was stirred at 65 °C for 3 hours under continuous magnetic stirring. After gradual cooling, the precipitated product was filtered, washed with suitable solvents, and dried in an oven at 60 °C for 12 hours.

The resulting complexes were air-stable solids obtained in the following colors:

$[Co(FODT)_2Cl_2]$ — dark reddish-purple;
$[Ni(FODT)_2Cl_2]$ — green;
$[Cu(FODT)_2Cl_2]$ — blue-green;
$[Zn(FODT)_2Cl_2]$ — white;
$[VO(FODT)_2SO_4]$ — dark blue.

Elemental analysis results for all complexes were in good agreement with the proposed empirical formulas, with deviations not exceeding ±0.3%.

3.4. Evaluation of Antimicrobial Activity

Antimicrobial activity was assessed using the disk diffusion (Kirby–Bauer) method in accordance with CLSI standards. The tested microorganisms included Staphylococcus aureus ATCC 25923 (Gram-positive bacterium), Escherichia coli ATCC 25922 (Gram-negative bacterium), and Candida albicans ATCC 10231 (pathogenic fungus) [12].

The test compounds were dissolved in dimethyl sulfoxide (DMSO) at a concentration of 1 mg/mL. Sterile paper disks (6 mm diameter) were impregnated with the test solutions and placed on the surface of Mueller–Hinton agar (for bacteria) and Sabouraud dextrose agar (for fungi). The bacterial cultures were incubated at 37 °C for 24 hours, while the fungal cultures were incubated at 28 °C for 48 hours. Antimicrobial activity was evaluated by measuring the diameter of the inhibition zones (mm).

Ampicillin (10 μg/disk) for bacteria and fluconazole (25 μg/disk) for fungi were used as positive controls, while pure DMSO served as the negative control. All experiments were performed in triplicate, and the results were expressed as mean values ± standard deviation.

4.Results and discussion

4.1. IR Spectral Analysis of the Ligand and Complexes

The IR spectra of the synthesized FODT ligand and its five metal complexes were carefully analyzed to elucidate their coordination behavior. In the spectrum of the free ligand, characteristic bands were observed at 3175 cm^{-1} for the N–H stretching vibration, 1615 cm^{-1} for the C=N stretching vibration, 1080 cm^{-1} for the cyclic C–O–C vibration, and 758 cm^{-1} for the C=S group. The absorption bands in the 3060–3020 cm^{-1} region correspond to aromatic C–H stretching vibrations.

Upon complex formation, significant spectral changes were observed. The N–H stretching band became broadened and shifted to lower wavenumbers (3020–3052 cm^{-1}), suggesting weakening of the N–H bond and possible involvement in coordination or partial deprotonation. More notably, the C=S stretching vibration shifted by 28–46 cm^{-1} toward lower frequencies compared to the free ligand, indicating coordination through the sulfur atom and partial reduction of the C=S double-bond character. Similarly, the C=N stretching band shifted from 1615 cm^{-1} to the 1580–1600 cm^{-1} range, confirming the participation of the azomethine nitrogen atom in coordination. These spectral changes clearly demonstrate that FODT acts as a bidentate N,S-chelating ligand.

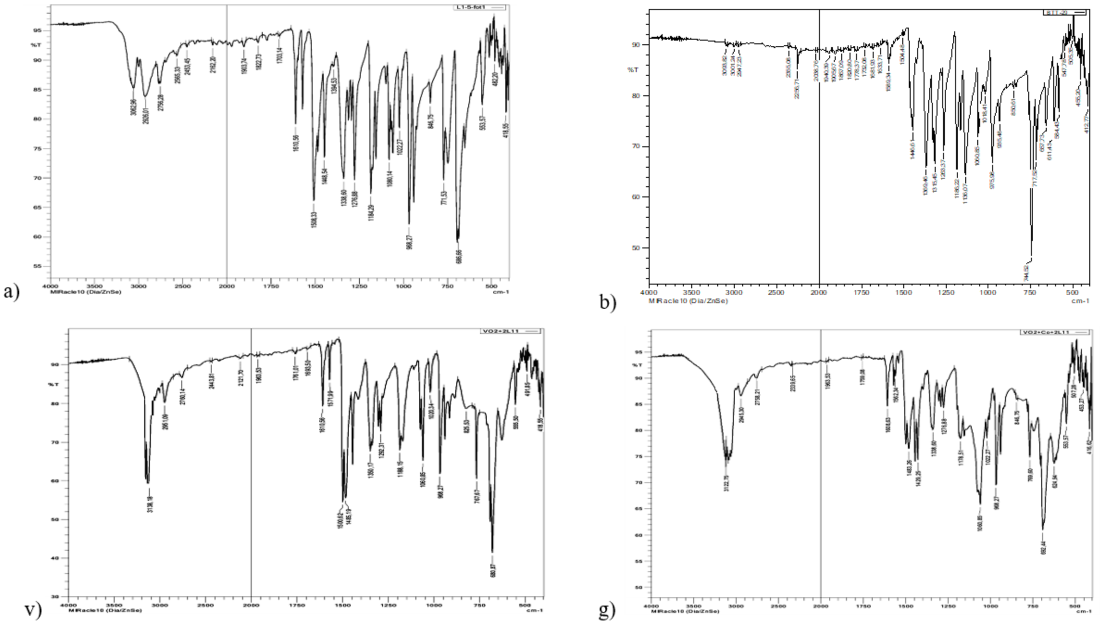

Figure 2. IR spectra of (a) free FODT ligand and (b) its Cu(II) complex showing coordination-induced shifts.

In all complexes, new absorption bands appeared in the 400–520 cm^{-1} region, assigned to ν(M–N) (488–510 cm^{-1}) and ν(M–S) (408–422 cm^{-1}) vibrations. In the VO^{2+} complex, a strong band at 985 cm^{-1} was observed, corresponding to the V=O stretching vibration, confirming that the vanadyl group remains intact after coordination.

Table 1. Main IR Vibrational Frequencies of the Ligand and Its Complexes (cm^{-1})

Compound	**ν(N–H)**	**ν(C=N)**	**ν(C–O–C)**	**ν(C=S)**	**ν(M–N)**	**ν(M–S)**	**ν(V=O)**
FODT (ligand)	3175	1615	1082	758	-	-	-
$[Co(FODT)_2Cl_2]$	3045	1598	1075	728	498	412	-
$[Ni(FODT)_2Cl_2]$	3038	1592	1071	722	502	418	-
$[Cu(FODT)_2Cl_2]$	3030	1588	1068	718	510	422	-
$[Zn(FODT)_2Cl_2]$	3052	1600	1077	730	488	408	-
$[VO(FODT)_2SO_4]$	3020	1580	1065	712	505	420	985

Among the studied compounds, the Cu(II) complex exhibited the most pronounced shifts in the C=S and C=N bands, indicating stronger metal–ligand interactions. This observation is consistent with the high affinity of Cu^{2+} for sulfur donors, as predicted by HSAB theory.

4.2. X-ray Structural Analysis

Single-crystal X-ray diffraction data of suitable quality were obtained for the Cu(II) complex, allowing complete structural determination. The compound $[Cu(FODT)_2Cl_2]$

crystallizes in the monoclinic system, space group $P2_1/c$. The copper center exhibits a five-coordinate square-pyramidal geometry. In the equatorial plane, two FODT ligands coordinate via their nitrogen and sulfur atoms, forming two five-membered chelate rings (M–N–C–S–M). One chloride ligand occupies the axial position, while the second chloride completes the coordination environment in the basal plane.

The chelate rings are nearly planar, with a deviation angle of only 3.2°. In addition, π–π stacking interactions between the phenyl rings of adjacent FODT ligands (interplanar distance 3.72 Å) contribute to the stabilization of the crystal lattice. The Cu–S bond length (2.312 Å) falls within the typical range reported for Cu(II)–sulfur bonds (2.28–2.35 Å), confirming the reliability of the structural model. The low R-factor value (3.84%) further indicates high refinement quality.

For the Co(II) and Ni(II) complexes, octahedral geometries were proposed based on IR and elemental analysis data, with two FODT ligands acting as N,S-chelates and two chloride ions occupying axial positions. The Zn(II) complex is best described as having a tetrahedral geometry, consistent with the d^{10} electronic configuration of Zn^{2+} and its preference for four-coordinate environments. The VO^{2+} complex retains a square-pyramidal arrangement, characterized by a strong apical V=O bond; two FODT ligands coordinate in a bidentate fashion, while the sulfate group completes the coordination sphere.

4.3. Biological Activity

The antimicrobial activity of the ligand and its complexes was evaluated using the disk diffusion method. All metal complexes exhibited significantly enhanced activity compared to the free FODT ligand, in agreement with Tweedy's chelation theory and the overtone concept.

The Cu(II) complex showed the highest antimicrobial activity, producing a 22 mm inhibition zone against Staphylococcus aureus. This value is very close to that of the standard antibiotic ampicillin (24 mm), suggesting potential clinical relevance [13]. The VO^{2+} complex ranked second and demonstrated strong activity against all tested strains. The overall order of activity was:

Cu > VO > Co > Ni > Zn > FODT

This trend can be attributed to differences in metal ion properties, coordination strength, lipophilicity, and interactions with biological membranes.

In all cases, activity against S. aureus (Gram-positive) was 3–4 mm higher than against E. coli (Gram-negative). This difference is likely due to the more complex outer membrane structure of Gram-negative bacteria, which restricts the penetration of larger molecules. The activity against Candida albicans was intermediate, possibly reflecting interactions with the ergosterol-containing fungal membrane [14].

Although the free FODT ligand exhibited moderate antimicrobial activity (11 mm against S. aureus), coordination to metal ions enhanced this effect by approximately 1.5–2 times, clearly demonstrating a synergistic metal–ligand interaction.

5. Conclusion

In the present study, five new coordination compounds of 5-phenyl-1,3,4-oxadiazole-2(3H)-thione (FODT) with Co^{2+}, Ni^{2+}, Cu^{2+}, Zn^{2+}, and VO^{2+} ions were successfully synthesized and systematically investigated. The FODT ligand was obtained from benzoyl hydrazide via a condensation reaction with a high yield (85%). All complexes were prepared using a 1:2 metal-to-ligand molar ratio in solution and were found to be stable under ambient conditions.

IR spectroscopic analysis confirmed the coordination of the ligand in a bidentate N,S-chelating mode. This conclusion is supported by the observed shift of the C=S stretching frequency by 28–46 cm^{-1} to lower wavenumbers compared to the free ligand, along with the appearance of new ν(M–N) (488–510 cm^{-1}) and ν(M–S) (408–422 cm^{-1}) bands. In the VO^{2+} complex, a strong absorption band at 985 cm^{-1} corresponding to the V=O stretching vibration confirmed the preservation of the vanadyl group after complex formation.

Single-crystal X-ray diffraction analysis revealed that the Cu(II) complex crystallizes in the monoclinic $P2_1/c$ space group and adopts a five-coordinate square-pyramidal geometry. The low R-factor value (3.84%) indicates high structural reliability. Based on spectroscopic data, octahedral geometries were proposed for the Co(II) and Ni(II) complexes, a tetrahedral geometry for the Zn(II) complex, and a square-pyramidal arrangement for the VO^{2+} complex.

Antimicrobial activity studies demonstrated that all metal complexes exhibit 1.5–2 times higher inhibitory effects than the free ligand. The activity order was established as:

Cu(II) > VO(II) > Co(II) > Ni(II) > Zn(II) > FODT

The Cu(II) complex showed a 22 mm inhibition zone against Staphylococcus aureus, which is comparable to that of the standard antibiotic ampicillin (24 mm). These findings provide strong scientific evidence that 5-phenyl-1,3,4-oxadiazole-2(3H)-thione-based metal complexes represent promising candidates for the development of new antimicrobial agents and justify further pharmacological and clinical investigations.

The IR spectra of the synthesized FODT ligand and its five metal complexes were carefully analyzed to elucidate their coordination behavior. In the spectrum of the free ligand, characteristic bands were observed at 3175 cm^{-1} for the N–H stretching vibration, 1615 cm^{-1} for the C=N stretching vibration, 1080 cm^{-1} for the cyclic C–O–C vibration, and 758 cm^{-1} for the C=S group. The absorption bands in the 3060–3020 cm^{-1} region correspond to aromatic C–H stretching vibrations.

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