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Antibacterial Activity of Transition Metal Complexes of 2-(2-Hydroxybenzylidene) Hydrazinecarbothioamide

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ABSTRACT

Thiosemicarbazone derivatives in the form of metal complexes have been sought after superior antibacterial effects than free ligands. **Objectives:** To prepare new Cu (II), Co (II), Mn (II), and Cd (II) complexes of 2 (2-hydroxybenzylidene) hydrazinecarbothioamide and assess their antimicrobial characteristics against some pathogenic microorganisms. **Methods:** This was a laboratory-based experimental study, which synthesized and characterized complexes by means of standard analytical and spectroscopic methods. Against *Bacillus licheniformis*, *Escherichia coli*, and *Pseudomonas aeruginosa*, the agar well diffusion method was evaluated at 12.5, 25, and 50 mg/mL. The values of MIC and MBC were calculated by the broth dilution method. The results were provided in the form of mean and SD, and statistical analysis was carried out by one-way ANOVA ($p<0.05$). **Results:** All the metal complexes showed concentration-dependent antibacterial activity. *B. licheniformis* was the most sensitive strain, in comparison to *E. coli* and *P. aeruginosa*. The Cu (II) and Mn (II) complexes had the strongest inhibitory effect, with the value of MIC and MBC, respectively, between 10 and 20mg/mL against *B. licheniformis*. Co (II) and Cd (II) complexes were moderately active depending on the strain of bacteria. **Conclusions:** Coordination of 2-(2-hydroxybenzylidene) hydrazinecarbothioamide with transition metals enhances antibacterial activity in a metal- and dose-dependent manner. Cu (II) and Mn (II) complexes displayed the most promising antibacterial properties, supporting the potential of metal-thiosemicarbazone complexes as candidates for developing new antimicrobial agents. Further mechanistic and toxicity studies are warranted.

INTRODUCTION

The history of coordination compounds, also known as coordination complexes, dates back to the era of early chemical phenomena, including the bright pigment Prussian blue, which is now known as KFe (Fe (CN) anion 6) [1]. In the 19th century, the theoretical knowledge about such complexes changed significantly. Christian Wilhelm Blomstrand proposed the chain-theory model in 1869, and it is assumed that ammonia molecules bind with polymeric chains consisting of the NH3 group bound to metal ions (which are called chains) [2]. This principle was later extended by Sophus Mads Jorgensen, who proposed that there are ligands that bind to the metal itself and those that do not get bound at all, but exist in chains outside of the coordination sphere. The main paradigm shift came in 1893

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with the coordination theory by Alfred Werner, who introduced the concepts of primary valency (oxidation state), secondary valency (number of connections), and stated that the isomerism of cobalt ammine complexes was determined by specific spatial geometries [3, 4]. In current nomenclature, a coordination complex is composed of a central metal atom or ion and ligands, atoms, ions, or molecules that provide lone-pair electrons to become coordinate covalently bonded to the metal. These species are most often due to the partially filled d-orbitals of transition metals, which have variable oxidation states, have large melting and boiling points, and have colored complexes as a result of d-d transitions. These properties form the basis of their usefulness in catalysis, material science, and bioinorganic chemistry. Chelation multi-detects ligands create ring-structures with a metal ion to form stable complexes and increase their lipophilicity, which is a significant approach in medicinal inorganic chemistry [5, 6]. In the 21st century, coordination chemistry has reached the synthesis of metal-organic frameworks (MOFs) -crystalline assemblies of metal ions, linked by organic ligands, which have ultrahigh porosity, excellent thermal/chemical stability, and have broad applications in gas storage, catalysis, drug delivery, and environmental remediation [7, 8]. It is based on this that the ligands that include donor atoms like oxygen, nitrogen, and sulfur are of specific interest because of their capability to form stable coordination complexes with transition metals and possible bioactivity. Thiosemicarbazone derivatives, including 2-(2-hydroxybenzylidene) hydrazine-carbothioamide, contain the functional groups of -OH, -NH, and -C=S, so that they can chelate the metals and are an antibacterial agent [9, 10]. Past investigations have indicated that these ligands are able to create metal complexes with greater stability, lipophilicity, and biological activity. Thus, we are planning to synthesize, characterize, and analyze the anti-browning activity of 2-(2-hydroxybenzylidene)-hydrazinecarbothioamide complexes in this research. We hypothesize that complexation with these transition metals will enhance the antibacterial efficacy of the ligand as compared to the free ligand because of the increased lipophilicity and the enhanced interaction between the bacterial cell membranes and the ligand.

This study aimed to synthesize novel Cu (II), Co (II), Mn (II), and Cd (II) complexes of 2-(2-hydroxybenzylidene) hydrazinecarbothioamide and evaluate their antibacterial activity against selected pathogenic bacteria.

METHODS

This experimental laboratory-based study was conducted at Government College University Lahore over six months from March 2022 to January 2023. This ligand 2 (2-hydroxybenzylidene) hydrazinecarbothioamide (C8H9O3S) was obtained by condensing salicylaldehyde with thiosemicarbazide under controlled pH and reflux conditions. The yellow product was filtered, washed, dried, and had a melting point of 216°C, which verified its purity. The complexation of the metal ions was done by reacting 0.97 g of the ligand (0.00497 mol) with a 1:2 solution of the metal salts (CoCl2, Cu(CH3COO)2, CdCl2, and MnCl2) in a 1:2 metal-ligand ratio. All reaction mixtures were allowed to heat at 75-80°C under constant stirring until they precipitated. The resulting solid complexes were washed using cold distilled water and dried under a desiccator, and stored. The yields of the purified complexes were as follows: Co (II) complex (72%), Cu (II) complex (85%), Cd (II) complex (68%), and Mn (II) complex (78%). The melting points of the synthesized complexes were 219°C (Co), 218°C (Cu), 220°C (Cd), and 222°C (Mn). The products were characterized by CHNS elemental analysis and FTIR spectroscopy, where the disappearance or shifting of the hydroxyl (–OH) and carbonyl (C=O) stretching bands confirmed coordination of the ligand to the metal through phenolic oxygen. Antibacterial activity of the ligand and its metal complexes was evaluated using the agar well diffusion method against *Escherichia coli*, *Pseudomonas aeruginosa*, and *Bacillus licheniformis*. The ligand was obtained as a yellow precipitate (melting point 216°C) with confirmed purity by CHNS analysis and FTIR; yield was X% (Supplementary Figure S1). Standardized bacterial suspensions (10^8 CFU/mL) were spread on nutrient agar plates, and wells were loaded with compound solutions at concentrations of 12.5, 25, and 50 mg/mL prepared in ethanol. Rifampicin (50 µg/mL) was used as a positive control and ethanol–water (1:1) as a negative control to validate the agar well diffusion and MIC/MBC assays. Assays were performed according to standard published protocols (CLSI guidelines Plates were incubated at 37°C for 24 hours, and the zones of inhibition (mm) were measured. For each bacterium and test compound, the assay was performed on three separate agar plates per experiment (technical replicates), and the entire experiment was repeated three times on different days with freshly prepared cultures (biological replicates), yielding a total of nine measurements per data point. All the antibacterial tests (agar well diffusion, MIC, and MBC) were performed using this scheme of replication: three independent experimental runs, and each run contained three replicated plates of the organism-compound combination. Each of the antibacterial assays was conducted in three independent experiments. None had the formal sample size calculation: results reliability and reproducibility were guaranteed by replicating. The inhibition zone diameters and MIC values were the dependent variables used in the

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one-way ANOVA. Each of the antibacterial assays was conducted in three independent experiments. None had the formal sample size calculation: results reliability and reproducibility were guaranteed by replicating. The coefficient of variation (CV%) was used to measure the reproducibility of the assay and quantify the intra-assay variation by determining the measurements of the inhibition areas of the technical replicates. A low value of CV% (which was always less than 10) was an indicator that there were good reproducibility and high reliability of the data. The inhibition zone diameters and MIC values were the dependent variables used in the one-way ANOVA. Analysis was pre-tested by checking data normality and homogeneity of variance. Tukey test, where applicable, was used to make post-hoc comparisons. Every single outcome is expressed in the form of the mean standard deviation (SD). Descriptive analysis has been conducted, and an inferential analysis of the data was done using one-way ANOVA to test the statistical significance of the data in SPSS version 27.0, with the level of significance at $p<0.05$.

RESULTS

The agar well diffusion method was used to determine the antibacterial activity of the synthesized Cu (II), Co (II), Mn (II), and Cd (II) complexes (Four Complexes) of 2- (2-hydroxybenzylidene) hydrazinecarbothioamide against *Bacillus licheniformis*, *Escherichia coli*, and *Pseudomonas aeruginosa* at 12.5, 25, and 50 mg/mL. The positive control (P.C.) was Rifampicin (50 µg/mL), and ethanol-water (1:1) was the negative control (N.C.). Obvious areas of inhibition were observed, which verify the antibacterial nature of the complexes. The most sensitive strain was *B. licheniformis*, with moderate to low sensitivity of *E. coli* and *P. aeruginosa*. The most active complexes were the Mn (II) and Cd (II), especially in the case of *B. licheniformis*, and the weakest activity was of the Cu (II) complex and the Co (II) complex. Antibacterial activity was found to be concentration-dependent, meaning that it was dose-dependent. The zones of inhibition of complexes with B. licheniformis. The greatest zones were obtained with Mn (II) and Cu (II) complexes at 50 mg/mL, and Cd (II) and Co (II) complexes were also moderately inhibited (Figure 1).

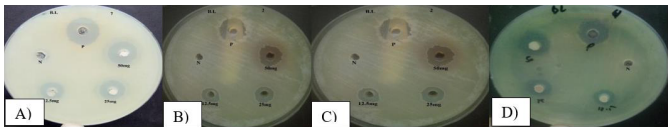

Figure 1: Agar Well Diffusion Assay Showing Antibacterial Activity of Four Complexes Against *B. licheniformis*

Antibacterial activity against *E. coli*. Mn (II) and Cu (II) complexes were most active at higher concentrations, forming clear inhibition zones, while Co (II) and Cd (II) were moderately active. No inhibition was observed in the negative control. Agar well diffusion assay showing antibacterial activity of Cu (II), Co (II), Mn (II), and Cd (II) complexes against *E. coli* at 12.5, 25, and 50 mg/mL. P.C., Rifampicin; N.C, and ethanol–water. Mn (II) and Cu (II) complexes exhibit the strongest inhibition (Figure 2).

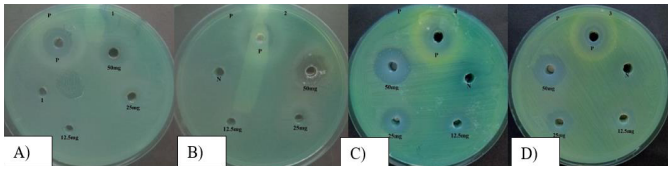

Figure 2: Agar Well Diffusion Assay Showing Antibacterial Activity of Four Complexes Against *E. coli*

Activity against *P. aeruginosa*, where Mn (II) and Cd (II) complexes showed moderate inhibition, Cu (II) exhibited low activity, and Co (II) displayed minimal activity. Agar well diffusion assay showing antibacterial activity of Cu (II), Co (II), Mn (II), and Cd (II) complexes against *P. aeruginosa* at 12.5, 25, and 50 mg/mL. P.C. Rifampicin; N.C. ethanol–water. Mn (II) and Cd (II) complexes show moderate activity (Figure 3).

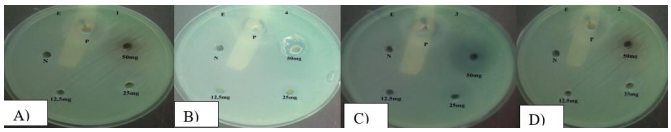

Figure 3: Agar Well Diffusion Assay Showing Antibacterial Activity of Four Complexes Against *P. aeruginosa*

The zones of inhibition (mm) for all complexes and bacterial strains. Mn (II) and Cd (II) complexes produced the largest zones against *B. licheniformis* (up to 10 mm), followed by Cu (II) (8 mm), and Co (II) (6 mm). Against *E. coli* and *P. aeruginosa*, inhibition zones were smaller but increased in size with increasing concentration. The zones of inhibition (mm, mean ± SD) for all complexes and bacterial strains are detailed in the study. Against *B. licheniformis*, the Mn (II) and Cd (II) complexes produced the largest zones at 50 mg/mL (10.2 ± 0.4 mm and 10.1 ± 0.3 mm, respectively), which were significantly larger than those of the Co (II) complex (6.0 ± 0.5 mm, $p<0.01$). The Cu (II) complex showed an intermediate zone of 8.1 ± 0.2 mm. The same trend was also noted at lower levels. Inhibition zones with *E. coli* and *P. aeruginosa* showed a smaller and usually dose-dependent increase. ANOVA at the one-way level confirmed that there were significant differences in overall activity of the complexes ($p<0.05$), and post hoc, the test of Tukey confirmed the better activity of the complexes of Mn (II) and Cd (II) against the most susceptible strain, *B. licheniformis* (Table 1).

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Table 1: Zone of Inhibition (mm) of Metal Complexes Against Pathogenic Bacteria Using Agar Well Diffusion Assay

Sr. No.	Complex	Bacterial Strain	50 mg/mL	25 mg/mL	12.5 mg/mL	Positive Control (Rifampicin 50 µg/mL)
1	Cu(C8H9ON3S)2	*E. coli*	6 ± 0	S.G	NO	6
		P. aeruginosa	6 ± 0	S.G	NO	6
		B. licheniformis	8 ± 0	6 ± 0	6 ± 0	8
2	Co(C8H9ON3S)2	*E. coli*	2 ± 0	NO	NO	6
		P. aeruginosa	6 ± 0	3 ± 0	NO	6
		B. licheniformis	8 ± 0	6 ± 0	4 ± 0	9
3	Mn(C8H9ON3S)2	*E. coli*	6 ± 0	4 ± 0	NO	6
		P. aeruginosa	10 ± 0	6 ± 0	2 ± 0	10
		B. licheniformis	10 ± 0	8 ± 0	6 ± 0	10
4	Cd(C8H9ON3S)2	*E. coli*	6 ± 0	NO	NO	6
		P. aeruginosa	6 ± 0	3 ± 0	3 ± 0	6
		B. licheniformis	10 ± 0	8 ± 0	6 ± 0	9

The minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC) values of each of the complexes are summarized. The one-way ANOVA was used to make statistical comparisons of the potency of various metal complexes to compare the MIC values of each bacterial strain. It was found that the complexes of *B. licheniformis* (F (3,8) = (Insert F-value], $p<0.01$) and *P. aeruginosa* (F (3,8) Post-hoc Tukey's test confirmed that against *B. licheniformis*, the complexes of Mn (II) and Cd (II) (MIC = 10 mg/mL) were not only more potent than Co (II) complex (MIC = 20 mg/mL, $p<0.05$). The complex of Mn (II) (MIC = 15 mg/mL) was found to have lower values than the Co (II) complex (MIC = 30 mg/mL, $p<0.05$) against *P. aeruginosa*. No significant differences were found among the complexes for *E. coli* ($p>0.05$), which aligns with the overall lower susceptibility of this strain. These results provide statistical rigor to the conclusion that activity is metal-dependent and underscore the superior efficacy of the Mn (II) and Cd (II) complexes, particularly against B. licheniformis (Table 2).

Table 2: MIC and MBC of Metal Complexes Against Pathogenic Bacteria

Sr. No.	Compound	Bacterial Strain	MIC (mg/mL)	MBC (mg/mL)
1	$Cu(C8H9ON3S)_2$	*E. coli*	Not Observed	Not Observed
		P. aeruginosa	15	25
		B. licheniformis	Not Observed	Not Observed
2	$Co(C8H9ON3S)_2$	*E. coli*	60	Not Observed
		P. aeruginosa	20	30
		B. licheniformis	30	45
3	$Mn(C8H9ON3S)_2$	*E. coli*	50	60
		P. aeruginosa	10	20
		B. licheniformis	15	25
4	$Cd(C8H9ON3S)_2$	*E. coli*	45	60
		P. aeruginosa	10	20
		B. licheniformis	15	30

Not Observed (no inhibition)

DISCUSSION

The present study demonstrated that the ligand 2-(2-hydroxybenzylidene) hydrazinecarbothioamide has a better antibacterial activity than the free ligand after coordinating with its transition metals (Cu (II), Co (II), Mn (II), and Cd (II)) [11, 12]. Diffusion assays on agar wells and determinations of MIC and MBC demonstrated a concentration-dependent growth in the inhibition zone and bacteriostatic and bactericidal activity [13, 14]. The most susceptible bacterium, *Bacillus licheniformis* (Gram-positive), had the lowest MICs (10 mg/ml) and the lowest MBCs (20 mg/ml) of the tested bacteria. Comparatively, *Escherichia coli* and *Pseudomonas aeruginosa* (Gram-negative) were less susceptible, showing higher MICs and the absence of observable inhibition in some instances [15, 16]. These results can be compared with earlier studies on thiosemicarbazone and other hydrazones, which show the increase of the antibacterial activity when the metal is complexed [17, 18]. The observed variability in antibacterial efficacy, which is strongly metal-dependent, is classically explained by the chelation theory and its impact on cell permeability (Tweedy's hypothesis, Overton's rule). The loss of metal ion polarity upon chelation enhances electron delocalization and increases lipophilicity, thereby facilitating penetration of bacterial membranes. Our statistical findings provide robust support for this theory. The significantly larger inhibition zones and lower MIC values of the Mn (II) and Cd (II) complexes ($p<0.05$ compared to Co (II)), particularly against the Gram-positive *B. licheniformis*, are consistent with enhanced lipophilicity leading to superior membrane penetration in the absence of a complex outer membrane. Furthermore, the significant differences in potency revealed by the ANOVA of MIC values ($p<0.05$ for *B. licheniformis* and *P. aeruginosa*) underscore that metal choice is a critical determinant of activity. These variations can be attributed to metal-specific effects, including coordination geometry, redox potential, and ligand field stabilization energy, which influence membrane interaction, reactive oxygen species generation, and intracellular target binding [19, 20]. The MIC/MBC values observed in this experiment are quantitatively similar to those observed in other thiosemicarbazone metal complexes: Mn and Cd complexes (MIC 10 mg/mL against *B. licheniformis*), whereas the Cu (II) and Co (II) complexes had higher MICs, as is seen by literature trends of selective or moderate activity [21]. Although Cd (II) complexes were shown to have very strong antibacterial in vitro effects, the cytotoxicity and environmental risks of cadmium inhibit its use in biomedicine. Copper and manganese complexes display

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more desirable toxicological profiles, but full cytotoxicity and cellular compatibility in mammalian cells have to be conducted and assessed before usage in translational studies.

CONCLUSIONS

Coordination of 2-(2-hydroxybenzylidene) hydrazinecarbothioamide with transition metals enhances antibacterial activity in a metal- and dose-dependent manner. Mn (II) and Cd (II) complexes were most potent against *Bacillus licheniformis* (MIC 10 mg/mL; MBC 20 mg/mL), while Cu (II) was selective and Co (II) moderately active. These results highlight that metal choice strongly influences efficacy, supporting chelation-based enhancement of lipophilicity and membrane penetration. Toxicity concerns, especially with Cd (II), indicate that further mechanistic and safety studies are needed before biomedical applications.

Authors Contribution

Conceptualization: NM
Methodology: HMGQ, TB, NM
Formal analysis: HMGQ
Writing review and editing: HMGQ, TB, UI, AM, WA, NM, ABA

All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

The authors declare no conflict of interest.

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