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Exploring the Antimicrobial Potential of Newly Synthesized Cobalt (II) Thiosemicarbazone Complexes

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Abstract: Four novel Cobalt(II) aryl thiosemicarbazone complexes with the general formula $[Co(Ligand1)_2Cl_2]$, $[Co(Ligand2)_2Cl_2]$, [Co(Ligand3) 2Cl2], and $[Co(Ligand4)_2Cl^2]$ have been successfully synthesized. Here, Ligand1 refers to 4-Phenyl-3-buten-2-one thiosemicarbazone (PBTSC), Ligand2 is 4-Hydroxy-3-methylbenzaldehyde thiosemicarbazone (HMBTSC), Ligand3 represents 4-Methoxybenzaldehyde thiosemicarbazone (MBTSC), and Ligand4 denotes Propiophenone thiosemicarbazone (PTSC). The ligands were prepared via the reaction of thiosemicarbazide with substituted aromatic aldehydes and ketones, utilizing microwave irradiation methods. Subsequent complexation with Cobalt(II) ions yielded the final metal complexes. The synthesized complexes were thoroughly characterized using elemental analysis, melting point determination, FTIR, and UV-visible spectroscopy. Additionally, both the ligands and their respective metal complexes were evaluated for their in vitro antibacterial activity against two microbes i.e., *S. aureus* and *E. coli*.

Keywords: Microwave assisted Synthesis, Cobalt(II), Thiosemicarbazones, Antimicrobial activity.

1. Introduction

The synthesis and exploration of transition metal complexes have long captivated the interest of researchers due to their diverse structural properties and significant applications in various fields such as catalysis, material science, and medicine. [1] Among these, cobalt(II) complexes hold a prominent place, largely because of their unique chemical versatility and biological relevance. [2] The ability of cobalt to form stable complexes with a wide range of ligands has led to its extensive use in designing compounds with tailored properties, including catalytic efficiency, magnetic behavior, and antimicrobial activity. [3]

Aryl thiosemicarbazones, a class of sulfur- and nitrogen-containing organic compounds, have attracted attention as versatile ligands for transition metals. [4] Their ability to coordinate through both sulfur and nitrogen atoms allows them to form stable chelates with metals, leading to the development of complexes with unique electronic and structural properties. [5] The presence of an aryl group further enhances their potential by introducing electronic and steric effects that can influence the properties of the resulting metal complexes. In particular, cobalt(II) aryl thiosemicarbazone complexes have emerged as promising candidates for applications in medicinal chemistry, particularly as antibacterial and anticancer agents, owing to their ability to interact with biological macromolecules and disrupt cellular processes. [6]

Cobalt plays a vital role in biological systems, most notably as a central component of vitamin B12, which is essential for various metabolic processes. [7] This biological significance has spurred interest in cobalt-based complexes for therapeutic applications. Cobalt(II) complexes are particularly intriguing because of their redox properties, which allow them to participate in electron transfer reactions and generate reactive oxygen species

(ROS). [8] These properties make them suitable candidates for antimicrobial and anticancer therapies, as they can disrupt essential cellular functions in pathogenic microorganisms or cancer cells. [9]

The antimicrobial properties of cobalt complexes have been extensively studied, and their efficacy against a wide range of bacteria and fungi has been demonstrated. [10] The coordination of cobalt with ligands such as thiosemicarbazones enhances its bioactivity, as the ligands can modulate the lipophilicity, electronic structure, and overall stability of the complexes. [11] These factors influence the ability of the complexes to penetrate microbial membranes, interact with cellular targets, and exhibit antimicrobial effects. [12]

Thiosemicarbazones are Schiff base derivatives characterized by the presence of a thiocarbonyl group (-C=S) and an azomethine group (-C=N). These ligands exhibit a remarkable ability to coordinate with transition metals due to their multiple donor atoms, typically sulfur and nitrogen. [13] The incorporation of an aryl group into the thiosemicarbazone structure enhances their chemical properties by introducing aromaticity, which can increase stability and influence electronic interactions. [14]

The versatility of aryl thiosemicarbazones as ligands stems from their ability to form bidentate or tridentate coordination modes, depending on the metal center and the reaction conditions. [15] This flexibility enables the formation of a variety of metal-ligand geometries, ranging from square planar to octahedral structures. [16] Furthermore, aryl thiosemicarbazones are known for their biological activity, including antimicrobial, antiviral, and anticancer properties. [17] These activities are often attributed to their ability to chelate metals and disrupt critical biological pathways in target organisms. [18]

The rise of antimicrobial resistance has created an urgent need for new antibacterial agents with novel mechanisms of action. [19] Metal complexes have emerged as promising candidates in this regard, as they can disrupt microbial processes through multiple pathways. [20] The antibacterial activity of cobalt(II) complexes is often attributed to their ability to generate ROS, which can damage microbial membranes, proteins, and DNA. [21] Additionally, the metal centers in these complexes can interact with essential enzymes or other cellular components, leading to the inhibition of microbial growth. [22]

Aryl thiosemicarbazone ligands further enhance the antibacterial properties of cobalt(II) complexes by increasing their lipophilicity and facilitating their penetration into bacterial cells. [23] The ability of these complexes to target multiple cellular pathways reduces the likelihood of resistance development, making them attractive candidates for combating multidrug-resistant bacteria. [24]

The results of this study are expected to have significant implications for the design and development of new metal-based antimicrobial agents. [25] The synthesis of cobalt(II) complexes with aryl thiosemicarbazone ligands represents a promising approach to addressing the challenges posed by antimicrobial resistance. [26] Additionally, the use of microwave-assisted synthesis highlights the potential for green chemistry principles to be applied in the preparation of metal complexes, paving the way for more sustainable practices in coordination chemistry. [27] Furthermore, the insights gained from this research may inspire the exploration of other transition metal complexes with thiosemicarbazone ligands, broadening the scope of their applications in medicine and beyond. [28]

2. Material And Methods

All chemicals and solvents used in the study were of analytical reagent (AR) grade, procured from Sigma-Aldrich and E. Merck, and utilized without further purification. The purity of the synthesized compounds was confirmed using thin-layer chromatography (TLC). Infrared (IR) spectra were recorded on a Bruker Optic Model Alpha FT-IR spectrometer (Zn-Se optics, ATR) within the range of 4000-500 cm^{-1} using KBr discs. Magnetic susceptibility measurements were performed using a vibrating sample magnetometer (VSM), model 155, at a field strength of 5500 Gauss. Microwave-assisted synthesis was conducted using a domestic microwave oven (Model KENSTAR-OM20ACF, 2450 MHz, 800 W) and a Green Microwave Biochemical Reactor (GMBR) at the Green Chemistry Research Centre (GCRC), P.G. Department of Chemistry, Government Dungar College (NAAC-A Grade), MGS University, Bikaner, Rajasthan. UV-visible absorption measurements were carried out using an ECIL Double Beam UV-Visible Spectrophotometer (Model UV 5704SS) equipped with a quartz cell of 10 mm light path.

All biological activity assays were conducted under aseptic conditions using a horizontal laminar airflow system at the Biotechnology and Infection Research Facility (BIFR), Bikaner.

Microwave Irradiation Synthesis of Ligands

Four ligands were synthesized via microwave-assisted methodology: Ligand1 (4-Phenyl-3-buten-2-one thiosemicarbazone, PBTSC), Ligand2 (4-Hydroxy-3-methylbenzaldehyde thiosemicarbazone, HMBTSC), Ligand3 (4-Methoxybenzaldehyde thiosemicarbazone, MBTSC), and Ligand4 (Propiophenone thiosemicarbazone, PTSC). In a typical synthesis, a mixture containing thiosemicarbazide (0.01 mol), aldehyde or ketone (0.01 mol), and glacial acetic acid (2 mL) in water or water-alcohol mixture was placed in an Erlenmeyer flask capped with a funnel. This setup was irradiated in a microwave oven at 200 W for 2-5 minutes.

The progress of the reaction was monitored using thin-layer chromatography (TLC). Upon completion, the reaction mixture was cooled to room temperature, and the precipitated solid was filtered off. The crude product was then recrystallized from redistilled ethanol to obtain the purified ligand.

Microwave Irradiation Synthesis of the Complexes

For the novel synthesis of Co (II) thiosemicarbazone complexes, a slurry of ligands (i.e. PBTSC, HMBTSC, MBTSC, PTSC) (0.02 mol) was prepared in water or in water-ethanol mixture. In this, a solution of cobalt chloride hexahydrate (0.01mol in 30 ml ethanol) was added. The resulting mixture was irradiated in a microwave oven for 2 to 10 minutes at medium power level (600W) maintaining the occasional shaking. The mixture was cooled to 25 °C and poured into ice chilled methanol and dried in vacuum over P_2O_5.

Antimicrobial Activity

A saturated solution of Nutrient agar (75 g) was prepared in double distilled water, and it was autoclaved for 15 min, then poured in Petri plates in the laminar. After its solidification loan of bacteria (i.e. Staphylococcus aureus and Escherichia coli) against which antimicrobial activity is to be investigated was applied. Solutions were prepared of all the four ligands and their complexes with Co (II). A separate paper disc was soaked in each solution for 10 minutes. Thus, prepared paper disc was placed into Petri plate and finally prepared Petri plates were kept in incubator at 37°C for 24 hours. After 24 hours, Petri plates were removed and checked for measuring zone of inhibition in mm.

3. Results And Discussion

Ligands and complexes were identified on the basis of elemental analysis and spectral studies. Colour, yield and elemental analysis data are represented in Table 1.

Infrared Spectra

Infrared spectrum data for all ligands and complexes each row illustrates the synthesis of a chemical and its cobalt complex. The band at ν(C=N) for the ligand is 1683 cm^{-1}, whereas for the complex it is 1680 cm^{-1}, indicating a drop in the C=N stretching frequency upon complex formation. The IR frequency range of 1556-1683 cm^{-1} for ν(C=N) in all the ligand and complexes suggests coordination of the thiosemicarbazone C=N formation in each complex. This minor shift suggests that the azomethine nitrogen is involved in coordination with cobalt, as metal binding weakens the C=N bond. The N-N stretching frequency rises in the complexation, indicating that nitrogen atoms in the thiosemicarbazone framework are affected by coordination with cobalt. The infrared frequency range of 1069-1170 cm^{-1} for ν(N-N) in all ligands and complexes indicates the coordination of thiosemicarbazone N-N formation in each complex. For the ν(N-N) bond complex, the ligand exhibits a stretching frequency of 1076 cm^{-1}, whereas the complex shows a stretching frequency of 1102 cm^{-1}. [29-33] For the ν(C=S) bond in the ligand, a stretching frequency of 1336 cm^{-1} is observed, while in the complex, the stretching frequency shifts to 1316 cm^{-1}. In the complex, coordination is shown via the sulfur atom, as the electron density of sulfur moves towards cobalt, therefore weakening the C=S bond. The IR frequency range of 1258-1352 cm^{-1} for ν(C=S) in all complexes indicates coordination through the thiosemicarbazone C=S group in each complex. For the δ(C=S) bond in the ligand, a bending frequency of 852 cm^{-1} is observed, which shifts to 836 cm^{-1} in the complex. in this complex, supporting the involvement of the sulfur atom in coordination with cobalt. The IR frequency range of 819-883 cm^{-1} for δ(C=S) in all ligands and complexes indicates coordination through the thiosemicarbazone C=S group in each complex. [34-37]

For the $\nu(^2$N-H) and $\nu(^4$N-H) bond in the ligand, a stretching frequency of 3195 cm^{-1} and 3469, 3353 cm^{-1} is observed, which shifts to 3195 cm^{-1} and 3469, 3370 cm^{-1} in the complex. These values remain largely unchanged, indicating that the N-H bonds are not significantly affected by complexation. [38-41] In all the

complexes, the presence of a band in this region corresponds to NH vibration which indicates that the ligand is coordinated in the neutral form. The IR frequency range of 3153-3208 cm^{-1} for $\nu(^2N\text{-}H)$ and 3378-3469, 3243-3370 cm^{-1} for $\nu(^4N\text{-}H)$ in all ligands and complexes indicates coordination through the thiosemicarbazone NH group in each complex. [42-44]

For the ν(M-N) bond in the complex, a stretching frequency of 485 cm^{-1} (M-N) and 435 cm^{-1} (M-S) is observed, in all the complexes. These new peaks confirm the formation of M-N and M-S bonds, confirms cobalt coordination with nitrogen and sulfur atoms. The IR frequency range of 455-488 cm^{-1} (M-N) and 435-460 cm^{-1} (M-S) is observed in all complexes indicates coordination through the thiosemicarbazone M-N, and M-S group in each complex. The presence of a band in the range 435-460 cm-1 is assigned to v(Co-S) band is evidence of coordination of S to central metal atom. The chloro complexes show v(Co-Cl) band at 338-370 cm-1, it is assigned for terminal chloro ligands in thiosemicarbazone complexes. [45-46]

The vibrational spectra of all ligands indicate that the IR spectroscopic results demonstrate that thiosemicarbazone ligands coordinate to cobalt via the azomethine nitrogen and thiocarbonyl sulfur atoms in every case. The alterations in ν(C=N), ν(N-N), ν(C=S), and δ(C=S) frequencies, together with the appearance of ν(M-N) and ν(M-S) bands in the complexes, validate this coordination characteristic. The ligands do not coordinate via the amino N-H groups, as seen by the unchanged N-H stretching frequencies. The N, S-donor arrangement is uniform across all complexes, indicating a consistent bonding behavior for cobalt with each thiosemicarbazone ligand. [47-49]

Magnetic Moments and Electronic Spectra

The magnetic susceptibility measurements have been carried out in the polycrystalline state at 25 °C and the results are presented in Table 3. The magnetic moments of the complexes lie in the range 4.62-5.09 BM, which correspond to three unpaired electrons. This indicates a quartet ground state term ^4F (S = 3/2) which is the case of Co (II) (d^7) and it may be obtained weak field octahedral configuration.[50] The efficient magnetic moment (μ_{eff}) for each complex, expressed in Bohr Magnetons (BM), provides insight into the electrical arrangement and geometry of the cobalt(II) ion inside each complex. High-spin cobalt(II) complexes with a d^7 electron configuration often exhibit a magnetic moment ranging from 4.7 to 5.2 BM, attributable to the presence of three unpaired electrons.[51] All values fall within the expected range for high-spin Co(II) complexes, suggesting an octahedral or distorted octahedral geometry with unpaired electrons contributing to the observed magnetic moments. The slight variations may be attributed to ligand field strength differences, which can cause minor variations in magnetic moment.[52]

The electronic spectral assignments of four cobalt (II) thiosemicarbazone complexes are given in table 3. and. All the Co (II) thiosemicarbazone complexes show a $\pi \rightarrow \pi^*$ band in the range 35500-36600 cm^{-1} and an $n \rightarrow \pi^*$ band in the range 31800- 34500 cm^{-1} due to the transition involved in thiosemicarbazone moiety.[53]

The ground state term for Co (II) (d^7 electronic configuration) is $^4T_{1g}$ or ^4E_g in octahedral coordination depending on whether the complex is high spin or low spin. The electronic spectra of cobalt (II) thiosemicarbazone complexes shows three bands due to spin allowed transitions at 9000-10000 cm^{-1}, 18000-18800 cm^{-1}, 20000-2100mag0 cm^{-1} which correspond to $^4T_{1g}(F) \rightarrow {}^4T_{2g}(F)$ (ν_1), $^4T_{1g}(F) \rightarrow {}^4A_{2g}(F)$ (ν_2) and $^4T_{1g}(F) \rightarrow {}^4T_{1g}(P)$ (ν_3) respectively, expected for distorted octahedral geometry around Co(II).[54-56]

Table 1: Physico-chemical Data of Co(II)-thiosemicarbazone Complexes

S. No.	Complexes	Colour	M. P. (ºC)	Yield %	Elemental analysis Calculated (Found) %		
					C	H	N
1	PBTSC	Pale yellow	190	67	60.24 (59.90)	19.16 (19.03)	5.97 (5.92)
2	HMBTSC	Light brown	198	64	51.65 (51.47)	20.07 (19.81)	5.29 (5.23)
3	MBTSC	Orange	180	61	51.65 (51.58)	20.07 (19.91)	5.29 (5.24)
4	PTSC	Dark red	202	69	57.94 (57.88)	20.27 (20.22)	6.32 (6.27)

5	$[Co(PBTSC)_2Cl_2]$	Light Brown	204	56	46.48 (46.37)	4.61 (4.50)	14.78 (14.65)
6	$[Co(HMBTSC)_2Cl_2]$	Brown	198	55	39.42 (39.31)	4.04 (3.95)	15.32 (15.19)
7	$[Co(MBTSC)_2Cl_2]$	Pink	200	60	39.42 (39.36)	4.04 (3.93)	15.32 (15.22)
8	$[Co(PTSC)_2Cl_2]$	Greenish Brown	206	63	44.12 (44.02)	4.81 (4.72)	15.43 (15.30)

Table 2: Vibrational Spectral Assignments (cm^{-1}) of Co (II)-thiosemicarbazone complexes

S. No.	Compound	ν(C=N)	ν(N-N)	ν(C=S)	δ(C=S)	$\nu(^2$N-H)	$\nu(^4$N-H)	ν(M-N)	ν(M-S)
1	PBTSC	1683	1076	1336	852	3195	3469, 3353		
	$[Co(PBTSC)_2Cl_2]$	1680	1102	1316	836	3195	3469, 3353	485	435
2	HMBTSC	1663	1069	1352	845	3167	3393, 3243		
	$[Co(HMBTSC)_2Cl_2]$	1605	1107	1294	819	3167	3393, 3243	455	446
3	MBTSC	1605	1110	1351	883	3153	3378, 3370		
	$[Co(MBTSC)_2Cl_2]$	1556	1170	1338	835	3153	3378, 3370	488	460
4	PTSC	1623	1096	1315	843	3208	3390, 3313		
	$[Co(PTSC)_2Cl_2]$	1610	1137	1258	822	3208	3390, 3313	466	455

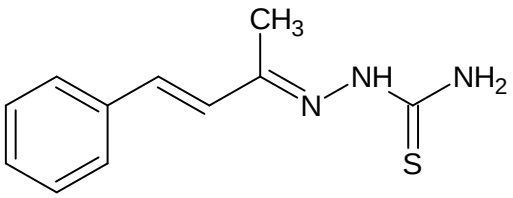
Table 3: Magnetic Moments and Electronic Spectral Data of Co (II)-thiosemicarbazone Complexes

S. No.	Complex	μ_{eff} (BM)	Electronic Spectral Bands λ_{max} (cm^{-1})	Tentative assignments	Expected Geometry
1	$[Co(PBTSC)_2Cl_2]$	4.81	35085, 31843, 29981, 24725, 24030, 20676, 19029, 18750, 18132, 9416	$^4T_{1g}(F)\rightarrow{}^4T_{2g}(F)$, $^4T_{1g}(F)\rightarrow{}^4A_{2g}(F)$, $^4T_{1g}(F)\rightarrow{}^4T_{1g}(P)$	Distorted Octahedral
2	$[Co(HMBTSC)_2Cl_2]$	4.62	36533, 33278, 31499, 30255,26706, 25940, 24786, 20025, 18778, 9941	$^4T_{1g}(F)\rightarrow{}^4T_{2g}(F)$, $^4T_{1g}(F)\rightarrow{}^4A_{2g}(F)$, $^4T_{1g}(F)\rightarrow{}^4T_{1g}(P)$	Distorted Octahedral
3	$[Co(MBTSC)_2Cl_2]$	4.89	35844, 34446, 32573, 25975, 24751, 23980, 20833, 18067, 174820, 9853	$^4T_{1g}(F)\rightarrow{}^4T_{2g}(F)$, $^4T_{1g}(F)\rightarrow{}^4A_{2g}(F)$, $^4T_{1g}(F)\rightarrow{}^4T_{1g}(P)$	Distorted Octahedral
4	$[Co(PTSC)_2Cl_2]$	5.09	35583, 32260, 27545, 24965, 24271, 22936, 20365, 19921, 18364, 9972	$^4T_{1g}(F)\rightarrow{}^4T_{2g}(F)$, $^4T_{1g}(F)\rightarrow{}^4A_{2g}(F)$, $^4T_{1g}(F)\rightarrow{}^4T_{1g}(P)$	Distorted Octahedral

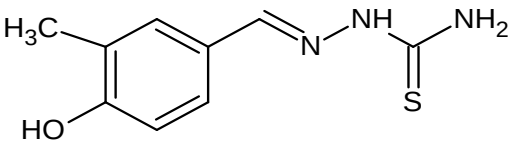
Table 4: Antibacterial activity of synthesized compounds

S. No.	Compounds	Zone of inhibition (in mm)	
		S. aureus	***E. coli***
1	PBTSC	15	8
2	HMBTSC	21	10
3	MBTSC	15	0

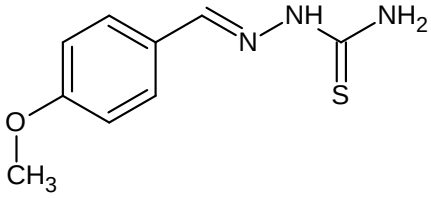
4	PTSC	12	0
5	$[Co(PBTSC)_2Cl_2]$	0	0
6	$[Co(HMBTSC)_2Cl_2]$	12	0
7	$[Co(MBTSC)_2Cl_2]$	14	0
8	$[Co(PTSC)_2Cl_2]$	0	0



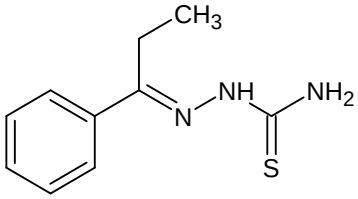
PBTSC



HMBTSC

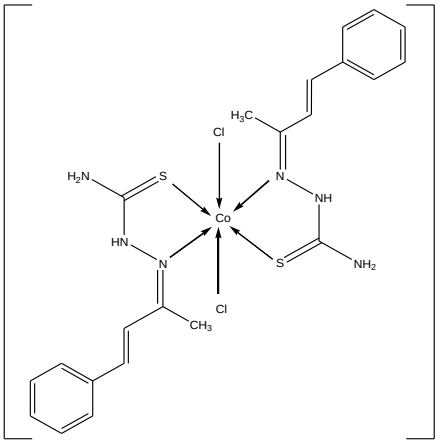


MBTSC

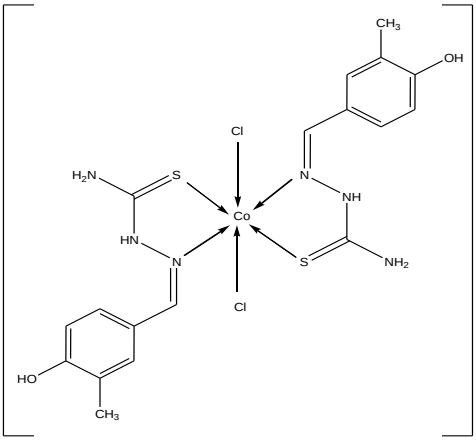


PTSC

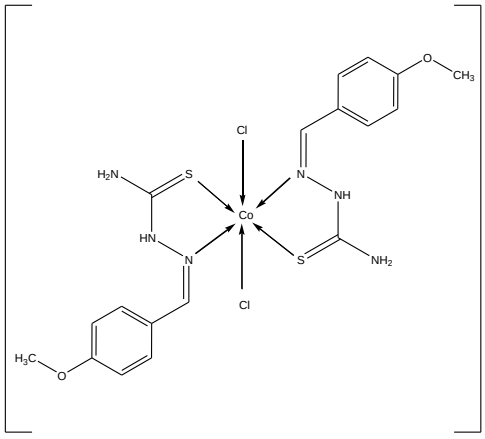
Figure 1: Structure of Ligands



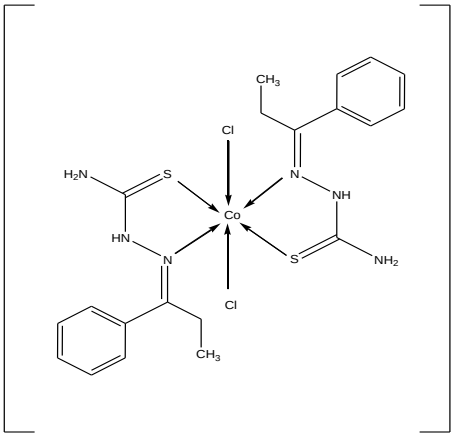
$[Co\text{-}(PBTSC)_2]Cl_2$



$[Co\text{-}(HMBTSC)_2]Cl_2$



$[Co\text{-}(MBTSC)_2]Cl_2$



Complex $[Co\text{-}(PTSC)_2]Cl_2$

Figure 2: Tentative Structures of Co (II) Complexes

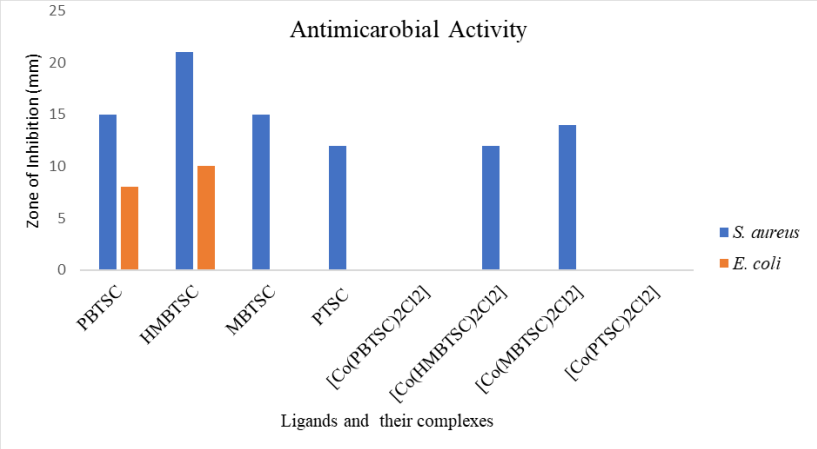


Figure 3: Graphical Presentation of Antimicrobial Activity

4. Conclusion

The thiosemicarbazone ligands and their cobalt(II) complexes were characterized using elemental analysis, spectral studies, and magnetic moment measurements. Based on the obtained data, the thiosemicarbazone ligands exhibit bidentate coordination, binding through the azomethine nitrogen and the thione sulfur atoms. Among the ligands, HMBTSC showed the highest antibacterial activity against both *S. aureus* and *E. coli*, indicating its potential as a standalone antimicrobial agent. The cobalt(II) complexes generally displayed reduced antibacterial activity compared to their free ligands. For instance, [Co(HMBTSC)2Cl2] showed lower activity against *S. aureus* (12 mm) than its free ligand HMBTSC (21 mm). None of the synthesized cobalt(II) complexes exhibited activity against *E. coli*, suggesting that complexation may adversely affect the ligands' ability to target gram-negative bacteria. [Co(PBTSC)2Cl2] and [Co(PTSC) 2Cl2] were in active against both bacterial strains, indicating that these complexes might lack the structural or electronic properties necessary for antibacterial activity.

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Conflict of Interest Statement

The authors certify that they have NO affiliations with or involvement in any organization or entity with any financial interest or non-financial interest in the subject matter or materials discussed in this manuscript.

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