

# Synthesis, Structural Characterization and Antimicrobial Activity of New Substituted Oxazole Thiosemicarbazone Ligand and its Co (II) and Ni (II) Complexes

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DOI: [10.36348/sijcms.2023.v06i04.003](https://doi.org/10.36348/sijcms.2023.v06i04.003)

| Received: 18.12.2022 | Accepted: 24.01.2023 | Published: 09.04.2023

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## Abstract

The New ligand 5-methyl-2-(2-thienyl)-1,3-oxazole-4-carbaldehyde thiosemicarbazone (HL)(1) was synthesized. This ligand reacted with Co(II) and Ni(II) chloride in ratio 1:2 metal:ligand afforded two complexes, [Co(LH)]Cl<sub>2</sub> (2) and [Ni(HL)<sub>2</sub>]Cl<sub>2</sub> (3). The ligand and its metal (II) complexes have been characterized by spectroscopic techniques. The X-ray structural studies revealed that the free ligand exist in thione form and remain as neutral tridentate with NNS donor atoms in the tow complexes beside presence of uncoordinated chloride ions in the cavities of the crystal lattice of the complexes. One of these chlorides in complex (2) is hydrogen bonded to a proton of the amine of the ligand. While in complex (3) the chloride bonded to proton of imine (-N<sub>2</sub>H) of the ligand and the coordination environment has a distorted octahedral. The oxazole N and S atoms in the two complexes are *cis* to each other whereas the azomethine N atoms are *trans* coordinated. The ligand and its metal complexes were tested for their *in vitro* biological activity against six standard microorganisms: two Gram positive namely *Bacillus subtilis* and *Micrococcus luteus*, and one Gram negative bacteria *Escherichia coli* and three fungi: *Saccharomyces cerevisiae* (Baker's yeast), *Mucor spec.*, and *Aspergillus niger*, at a concentration 100µg/ml.

**Keywords:** Oxazole, Thiosemicarbazone, Cobalt (II) and Nickel (II) complexes, Crystal structure and biological activity.

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## INTRODUCTION

Thiosemicarbazones (TSCs), with the general formula  $R^1R^2C=N-NH-CS-NR^3R^4$ , are a group of compounds obtained by condensing thiosemicarbazide with carbonyl compounds. These reagents function as good chelating agents and form complexes with several metal ions. Depending on the type of parent aldehyde or ketene used for condensation they can act as unidentate, bidentate or multi dentate chelating agents during complexation with metal ions [1].

Heterocyclic thiosemicarbazones, in addition to their metal complexes, are important because of their possible beneficial biological activity [2]. Among the new classes of compounds under investigation, since the Thiosemicarbazone reported as antituberculous activity [3]. The oxazolyl thiosemicarbazone derivatives

were reported for the first time by Sriram *et al.*, as antimycobacterium agents [4].

However, no studies of the metal in particular, Ni (II) and Co (II) complexes of oxazole thiosemicarbazone or their derivatives have been reported. So, Surveying literature here showed many studies of antimicrobial activity of Ni (II) and Co (II) complexes with other related heterocyclic thiosemicarbazone ligands. For example, vitamin K<sub>3</sub> - thiosemicarbazone (C<sub>12</sub>H<sub>11</sub>N<sub>3</sub>NaO<sub>4</sub>S<sub>2</sub>.5H<sub>2</sub>O, abbreviated as VT), and their cobalt(II) complexes have shown strong inhibitory actions In vitro tests of antibacterial activity [5]. also, the 8-Formyl-7-hydroxy-4-methylcoumarin-3-methyl thiosemicarbazone, 5-Formyl-6-hydroxy coumarin-3-methyl thiosemicarbazone and their cobalt(II) and other metal complexes of type ML<sub>2</sub> have been reported, they were found to be enhanced by Minimum Inhibitory

Concentration (MIC) [6]. Recently, Some of cobalt(II) complexes being one of them, with the ligand *m*-nitrobenzaldehyde-4-(4'-sulfoamidephenyl)-3-thiosemicarbazone exhibited significant activity [7].

Nickel is an essential trace element for bacteria, plants, animals and human. In recent years, a number of researchers have shown some interest in the biological, medicinal and the structural properties of nickel thiosemicarbazone complexes. Some of these complexes have shown a variety of biological activities like antibacterial, antimalarial and antifungal activities [8]. A series of new derivative complexes derived from the reaction of nickel(II) chloride or bromide with thiophene-2, 3-dicarboxaldehyde bis (thiosemicarbazone), showed a noticeable antifungal activity [9].

This work expands that types of research by introducing an unknown heterocyclic thiosemicarbazones ligand based on a 5-methyl-2-(2-thienyl)-1,3-oxazole-4-carbaldehyde thiosemicarbazone ligand (HL) beside its Ni(II) and Co(II) complexes.

## EXPERIMENTAL

### Materials and measurements

All chemicals and solvents were of reagent grade and were purchased from Sigma- Aldrich Chemical Co. and used without further purification.

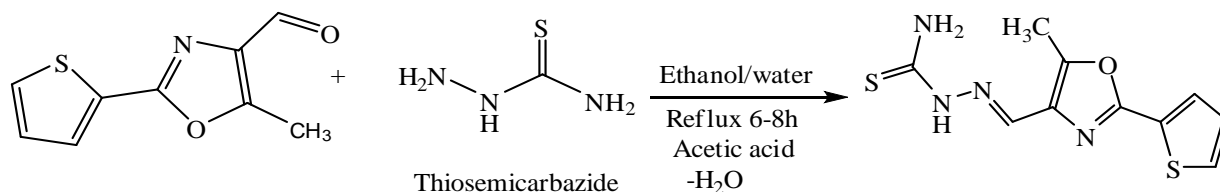
### Instrumentation

The Partial elemental microanalyses of synthesized ligand and complexes for C, N, H, S contents were performed on Euro EA Elemental Analyzer. HL ligand and its metal complexes were mounted on a glass capillary and data collections carried out on a Bruker APEX-II CCD diffractometer. The HL and complexes 1& 2 crystals were kept at 170, 296(2) and 100.15 K respectively during data collection. Using Olex2 [10], the structures were solved by ShelXT [11] (1) and SIR2004 [12] (2) structure solution program using Direct Methods, and refined with the XH (1), ShelXL [13] (1), olex2. refine [14] (2), refinement package using CGLS minimization and Gauss-Newton minimization. IR spectra were recorded as KBr pellets by using a Perkin-Elmer Spectrum RX-

1Spectrophotometer in the wave- number ranging between 200 to 3700  $\text{cm}^{-1}$ . Spectra of  $^1\text{H}$  NMR and  $^{13}\text{C}$  NMR data were recorded at ambient temperature (about 23°C) on Bruker AV-II 300 Spectrometer, operating at 300 MHz for  $^1\text{H}$  and 75.5 MHz for  $^{13}\text{C}$ , with deuterated DMSO. The chemical shifts ( $\delta$ ) are given in ppm relative to TMS and coupling constant (J) are given in Hertz. The solvent signals were used as reference ( $^1\text{H}$ :  $\delta_{\text{H}}$  2.500 ppm residual DMSO-d<sub>5</sub> in DMSO-d<sub>6</sub>,  $^{13}\text{C}$ :  $\delta_{\text{C}}$  39.56 ppm). The UV-visible studies of all compounds in the solid state were performed by using barium chloride as a blank on a Cary 4000 UV-Vis spectrophotometer, in the range (200-900) nm.

### Synthesis of 5-methyl-2-(2-thienyl)-1,3-oxazole-4-carbaldehyde thiosemicarbazone ligand (HL) (1)

5-methyl-2-(2-thienyl)-1,3-oxazole-4-thiosemicarbazone ligand (HL) (1), was prepared by using the following procedure [15]. Equimolar quantities (1:1) of 5-methyl-2-(2-thienyl)- 1,3-oxazole-4-carbaldehyde and thiosemicarbazide, Scheme 1. Thiosemicarbazide (0.18228 g, 2.0 mmol), was dissolved in (approx. 60mL of 60% ethanol-water) by refluxing at 50°C in 250. In the refluxing solution, the aldehyde (0.38644g, 2.0 mmol) solution in ethanol (approx. 30 mL) was added dropwise. The reaction mixture was refluxed for 6-8 h. at 60°C on steam-bath temperature, in the presence of a few drops of glacial acetic acid, a clear solution of the reaction mixture filtered and the filtrate was allowed to cool slowly at room temperature. A yellow crystalline product with crystals suitable for X-ray was separated, washed with cold ethanol and dried in air. The product mass of 0.3485 g corresponds to 61 % yield. FT-IR (KBr,  $\nu$ ,  $\text{cm}^{-1}$ ): 3314(s) ( $\text{N}^1\text{H}_2$ ), 3118(s) ( $\text{N}^2\text{H}$ ), 1604(s) ( $\text{C}^2=\text{N}$ ) (azomethine), 1533(s) ( $\text{C}=\text{N}$ ) (oxazole ring), 819 (s) ( $\text{C}=\text{S}$ ) thione,  $^1\text{H}$  NMR (300 MHz, 300 MHz for  $^1\text{H}$  and 75.5 MHz for  $^{13}\text{C}$ , DMSO-d<sub>6</sub>,  $\delta$ , ppm): 2.55 (s, 3H,  $\text{CH}_3$ ), (7.2 - 7.5) (, 3H, thiophene-H), 11.45 (m, 1H,  $\text{HN}^2\text{CS}$ ), 8.3 & 8.5 (2H,  $\text{CSN}^1\text{H}_2$ ), 8.1 (1H,  $\text{HC}^2=\text{N}$ , azomethine), 12 (1H, -OH) and 3.4 (alkyl), 178.01 (C1, thione), 135.95 (C2, imine), (149- 155) ( C3, C4, C5, oxazole ring), 11.53 (C6) (methyl),  $\delta$  127-131(4C, thiophene ring). Anal. calcd. for  $\text{C}_{10}\text{H}_{10}\text{N}_4\text{OS}_2$ : C, 45.10; H, 3.78; N, 21.04, S, 24.08. Found: C, 43.77, H, 3.63; N, 20.39, S, 23.34%. (Molar mass g/mol).



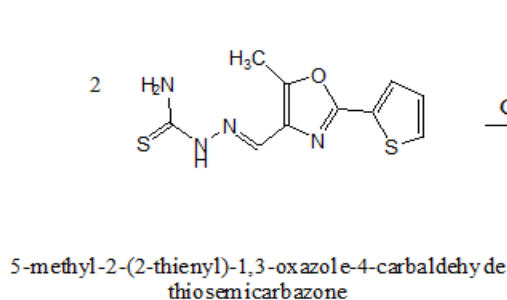
5-methyl-2-(2-thienyl)-1,3-oxazole-4-carbaldehyde

5-methyl-2-(2-thienyl)-1,3-oxazole-4-carbaldehyde thiosemicarbazone

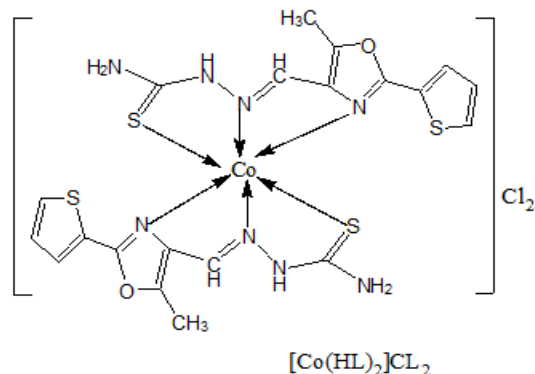
**Scheme 1: Synthesis of the ligand (HL) (1)**

### Synthesis of $[\text{Co}(\text{HL})_2]\text{Cl}_2$ (2)

The complex  $[\text{Co}(\text{HL})_2]\text{Cl}_2$  (2) was prepared according to the following procedure<sup>[16]</sup>.  $\text{CoCl}_2 \cdot 6\text{H}_2\text{O}$  (0.19 g; 0.5 mmol, 10  $\text{cm}^3$ ) was added to an ethanolic solution of the ligand ( $\text{HL}^2$ ) (0.27 g, 1.0 mmol, 20  $\text{cm}^3$ ) under refluxing conditions. The reflux was maintained for 24 h. The resulting solution was concentrated and a dark brown precipitate was filtered off (scheme 2). Recrystallization from a water-ethanol mixture gave crystals suitable for X-ray analysis. 82 % yield. FT-IR (KBr,  $\nu$ ,  $\text{cm}^{-1}$ ): 3297(s) ( $\text{N}^1\text{H}_2$ ), 3113(s) ( $\text{N}^2\text{H}$ ), 1586(s) ( $\text{C}^2=\text{N}$ ) (azomethine), 1634(s) ( $\text{C}=\text{N}$ ) (oxazole ring), 862



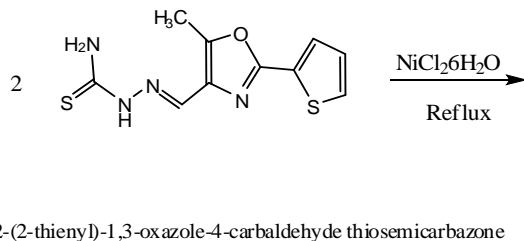
(s) ( $\text{C}=\text{S}$ ) thione, 444 (M-N) azomethine, 487 (M-N) oxazole nitrogen, 656 (M-S) thioamide,  $^1\text{H}$  NMR (300 MHz, 300 MHz for  $^1\text{H}$  and 75.5 MHz for  $^{13}\text{C}$ , DMSO- $d_6$ ,  $\delta$ , ppm): 2.5 (s, 3H,  $\text{CH}_3$ ), (7.3 - 7.7) ( , 3H, thiophene-H), 8.38 & 8.02 (2H,  $\text{CSN}^4\text{H}_2$ ), 8.03 (1H,  $\text{HC}^2=\text{N}$ , azomethine), 179.9 (C1, thione), 136.7 (C2, imine), 141.9 - 158.3 (C3, C4, C6, oxazole ring), 11.08 (C5, methyl), 123-133 (4C, thiophene ring). Anal. calcd. for  $\text{C}_{20}\text{H}_{20}\text{Cl}_2\text{N}_8\text{NiO}_2\text{S}_4$ : C, 36.27; H, 3.04; N, 16.92, S, 19.37. Found: C, 36.96, H, 3.042; N, 15.32, S, 16.73%. (Molar mass g/mol).



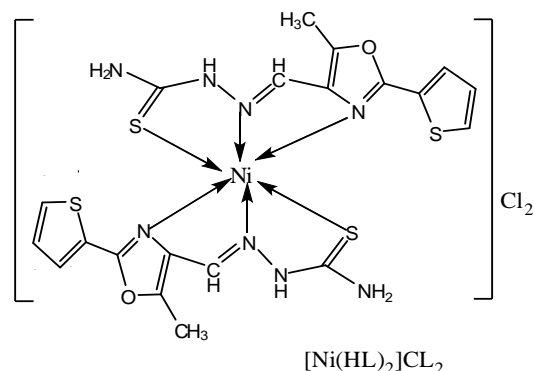
Scheme 2: Synthesis of the complex (2)

### Synthesis of $[\text{Ni}(\text{HL})_2]\text{Cl}_2$ (3)

The  $[\text{Ni}(\text{HL})_2]\text{Cl}_2$  (3) was synthesized by published procedure<sup>[17]</sup> but used ethanol instead of water for dissolving the metal halide. A hot solution of  $\text{NiCl}_2 \cdot 6\text{H}_2\text{O}$  (0.5 mmol, 0.12 g) in 5 mL hot ethanol was added to a boiling solution of the ligand (HL) (1.00 mmol, 0.184 g) in ethanol. The reaction mixture was refluxed on a water bath for 4 h and allowed to cool overnight at room temperature. The green crystals suitable for X-ray analysis were filtered, washed with ethanol and dried in air (scheme 3). 82 % yield. FT-IR (KBr,  $\nu$ ,  $\text{cm}^{-1}$ ): 3276 (s) ( $\text{N}^1\text{H}_2$ ), 3086 (s) ( $\text{N}^2\text{H}$ ),



1598(s) ( $\text{C}^3=\text{N}$ ) (azomethine), 1489(s) ( $\text{C}=\text{N}$ ) (oxazole ring), 863 (s) ( $\text{C}=\text{S}$ ) thione, 454(M-N) azomethine, 491(M-N) oxazole nitrogen, 649(M-S) thioamide,  $^1\text{H}$  NMR (300 MHz, 300 MHz for  $^1\text{H}$  and 75.5 MHz for  $^{13}\text{C}$ , DMSO- $d_6$ ,  $\delta$ , ppm): 2.6 (s, 3H,  $\text{CH}_3$ ), 7.4 - 7.9 (3H, thiophene-H), 8.42 & 8.25 (2H,  $\text{CSN}^1\text{H}_2$ ), 8.05 (1H,  $\text{HC}^3=\text{N}$ , azomethine), 177.08 (C1, thione), 135.45 (C3, imine), 148.6 - 154.9 (C4, C5, C9, oxazole ring), 11.08 (C10, methyl), 126-130 (4C, thiophene ring). Anal. calcd. for  $\text{C}_{20}\text{H}_{20}\text{Cl}_2\text{N}_8\text{CoO}_2\text{S}_4$ : C, 36.26; H, 3.04; N, 16.96, S, 19.36. Found: C, 36.72, H, 3.039; N, 16.69, S, 18.94%. (Molar mass g/mol).



Scheme 3: Synthesis of the complex (3)

### Biological Screening

The ligand HL and its metal complexes were tested for *in vitro* biological activity by using a modified agar diffusion method [18]. All The tested substances were dissolved in DMSO in concentration

(100  $\text{mg mL}^{-1}$ ), and all the tested microorganisms were obtained from a prepared cell suspension of fresh overnight culture of each strain. Cell suspension of 100  $\mu\text{L}$  of each strain was plated on an agar plate, and a sterile cork borer was used to stamp out two holes on

each agar plate, 100  $\mu\text{L}$  of each chemical substance (100  $\text{mg mL}^{-1}$ ) was added into the agar plate holes. The antibacterial activity of the ligand and its metal complexes were performed against *Bacillus subtilis*-ATCC, *Micrococcus luteus*-ATCC as (Gram positive) and *Escherichia coli*-ATCC as (Gram negative). The Agar plate was incubated at 37°C, zone of inhibition (radius “r” in mm, Figure 1) was determined after 20, 24 and 48 h of incubation. Antifungal activity of the synthesized ligand and its corresponding metal complexes in term of their inhibition were tested against three fungi; *Saccharomyces cerevisiae* (Baker’s yeast), *Mucor spec* and *Aspergillus niger*. The agar plate was incubated at 28°C for *Saccharomyces cerevisiae* and at room temperature for *Mucor spec* and *Aspergillus niger*. The zone of inhibition (radius “r” in mm) was determined after 20, 24 and 48 h of incubation.

Experiments were done at Institute of Microbiology, General Microbiology-TU-Dresden-Germany.

## RESULTS AND DISCUSSION

The synthesized ligand 5-methyl-2-(2-thienyl)-1,3-oxazole-4-thiosemicarbazone and its complexes were characterized by using partial elemental analysis, IR, UV-Visible,  $^1\text{H}$  NMR and  $^{13}\text{C}$  NMR spectroscopy and single x-ray diffraction.

### Physical Properties and elemental analysis

The ligand HL (1) and its Co(II) and Ni(II) complexes (2,3) are stable under ambient conditions; they are soluble in dimethyl sulfoxide (DMSO), hot methanol and ethanol. The analytical data for three compounds are in close agreement with the theoretical values obtained, Table 1.

**Table 1: The physicochemical characteristics of the synthesized ligand and its metal complexes**

Complex	Formula	Color	Yield%	Elemental analysis, % found (%calculated)				Molar massg/mol
				C	N	H	S	
HL (1)	$\text{C}_{10}\text{H}_{10}\text{N}_4\text{OS}_2$	Yellow	61.2	43.77 (45.10)	20.39 (21.04)	3.63 (3.78)	23.34 (24.08)	266.34
Co(HL) $_2$ Cl $_2$ (2)	$\text{C}_{20}\text{H}_{20}\text{Cl}_2\text{CoN}_8\text{O}_2\text{S}_4$	Dark brown	82	36.72 (36.26)	16.69 (16.96)	3.039 (3.04)	18.94 (19.36)	662.51
Ni(HL) $_2$ Cl $_2$ (3)	$\text{C}_{20}\text{H}_{20}\text{Cl}_2\text{NiN}_8\text{O}_2\text{S}_4$	Green	65	36.96 (36.27)	15.32 (16.92)	3.42 (3.04)	16.73 (19.37)	662.28

### Crystal structure of the ligand HL

HL crystallizes with one ligand molecule and one ethanol solvent molecule per asymmetric unit in triclinic P-1, Figure 1. Hydrogen bonds between link both molecules: N1–H1A...O2 with donor acceptor (D...A) distances of 3.064(1) Å, O2–HO2...N3 with (D...A = 3.141(2) Å) and O2–HO2...N4 with (D...A = 2.936(2) Å). Note that the thiophenering is disordered in the solid state, caused by a 180° rotation around the C5–C7 single bond. The thionate sulfur atom S1 and hydrazinic atom N3 lie in trans position (E

configuration) to each other with respect to the N2–C1 bond. This is confirmed by the torsion angle of –173.4(2)° of the S1–C1–N2–N3 moiety, which is close to that observed in benzaldehyde thiosemicarbazone derivatives [19, 20]. The thione form in the solid state is also confirmed by the observed bond lengths of 1.686(2) Å for the C1–S1 contact and 1.347(2) Å for C1–N2 contact. The C1–S1 distance is closer to the C=S double bond length (1.62 Å) and the C1–N2 distance is in the range for known thiosemicarbazones with C–N single bonds [21, 22].

**Table 2: Crystal data and structure refinement parameters for HL (1) and complexes (2&3)**

Compound	HL (1)	2	3
Formula	$\text{C}_{10}\text{H}_{10}\text{N}_4\text{OS}_2 \cdot \text{C}_2\text{H}_5\text{OH}$	$\text{C}_{20}\text{H}_{20}\text{Cl}_2\text{N}_8\text{CoO}_2\text{S}_4$	$\text{C}_{20}\text{H}_{20}\text{Cl}_2\text{N}_8\text{NiO}_2\text{S}_4$
Formula Weight	312.41(266.34+46.08)	662.60	665.68
Temperature /K	170(2)	296(2)	100.15
Colour	Yellow	Dark brown	Green
Crystal System	Triclinic	Monoclinic	Monoclinic
Space Group	P-1	C 1 2/c 1	P2/c
Unit cell dimensions/Å, °	a = 7.322(1), $\alpha$ = 100.29(1) b = 10.574(1), $\beta$ = 109.07(1) c = 11.071(1), $\gamma$ = 100.48(1)	a = 16.0051(10), $\alpha$ = 90 b = 12.2354(8), $\beta$ = 116.074(2) c = 16.0067(10), $\gamma$ = 90	a = 11.4715(9) $\alpha$ = 90 b = 10.0746(8) $\beta$ = 101.066(3) c = 13.0986(10) $\gamma$ = 90
Volume/Å $^3$	770.08(9)	2815.6(3)	1485.7(2)
Z; $\rho_{\text{calc}}/\text{g}\cdot\text{cm}^{-3}$	2; 1.347	4, 1.563	4, 1.626
$\mu/\text{mm}^{-1}$	0.352	1.131	1.148
Wavelength/Å	MoK $\alpha$ ( $\lambda$ = 0.71073)	MoK $\alpha$ ( $\lambda$ = 0.71073)	Mo K $\alpha$ ( $\lambda$ = 0.71073)
2 $\theta$ range for data collection/°	4.026 to 58.412	29.0 to 28.999	3.62 to 50.98
Index ranges	-9 $\leq$ h $\leq$ 9, -14 $\leq$ k $\leq$ 11, -14 $\leq$ l $\leq$ 15		
F(000)	326.0	1348	681.9
Reflections collected	12594	8720	15575
Independent reflections	0.0158	3753 [R $_{\text{int}}$ = 0.0395 R $_{\text{sigma}}$ = 0.0323]	2753 [R $_{\text{int}}$ = 0.0401, R $_{\text{sigma}}$ = 0.0498]

Compound	HL (1)	2	3
Data / Restraints / Parameters	3835/43/196		
Final R indexes [ $I \geq 2\sigma(I)$ ]	$R_1 = 0.0411$ , $wR_2 = 0.1058$	$R_1 = 0.0573$ , $wR_2 = 0.1492$	$R_1 = 0.0884$ , $wR_2 = 0.2243$
Final R indexes [all data]	$R_1 = 0.0462$ , $wR_2 = 0.1141$	$R_1 = 0.0645$ , $wR_2 = 0.1520$	$R_1 = 0.1096$ , $wR_2 = 0.2409$
Goodness-of-fit on $F^2$	1.048	1.186	1.150

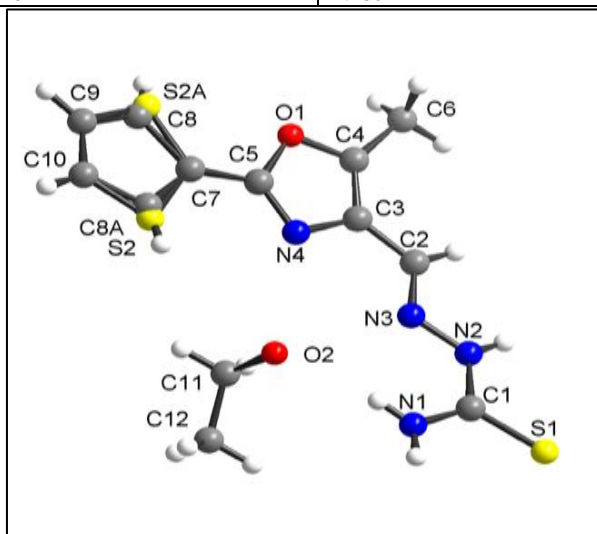


Figure 1: 5-methyl-2-(2-thienyl)-1,3-oxazole-4-carbaldehyde thiosemicarbazone ligand (HL)

#### Crystal structure of the complex $[\text{Co}(\text{HL})_2]\text{Cl}_2$ (2)

In complex  $[\text{Co}(\text{HL})_2]\text{Cl}_2$  (2) the cobalt(II) ion is in an octahedral coordination environment provided by two molecules of the neutral tridentate ligand. The main crystal data and structure refinement parameters are reported in Table 2, with selected bond distances and bond angles summarized in Table 3. Complex (2) crystallized into a monoclinic crystal system with one molecule in the unit cell. The molecular structure together with the atom numbering scheme is shown in Figure 2. The E configuration of the thiosemicarbazone

ligand with respect to C1–N3 bond changed to the Z configuration after coordination to the metal to facilitate the coordination of the thione sulfur and imine nitrogen to Co(II). This is confirmed by the torsion angle of  $172.7(19)^\circ$  for the S1–C1–N3–N2 moiety of the ligand of  $-2.3(4)^\circ$  in the complex. The two azomethine nitrogen atoms N2 and N2<sup>1</sup> are *trans* to each other, and the two oxazoline nitrogen atoms N1 and N1<sup>1</sup> and the thionate sulfur S1 and S1<sup>1</sup> are in the *cis* position. The network structure is stabilized by the intermolecular hydrogen bonding interaction, N4H... ..C11.

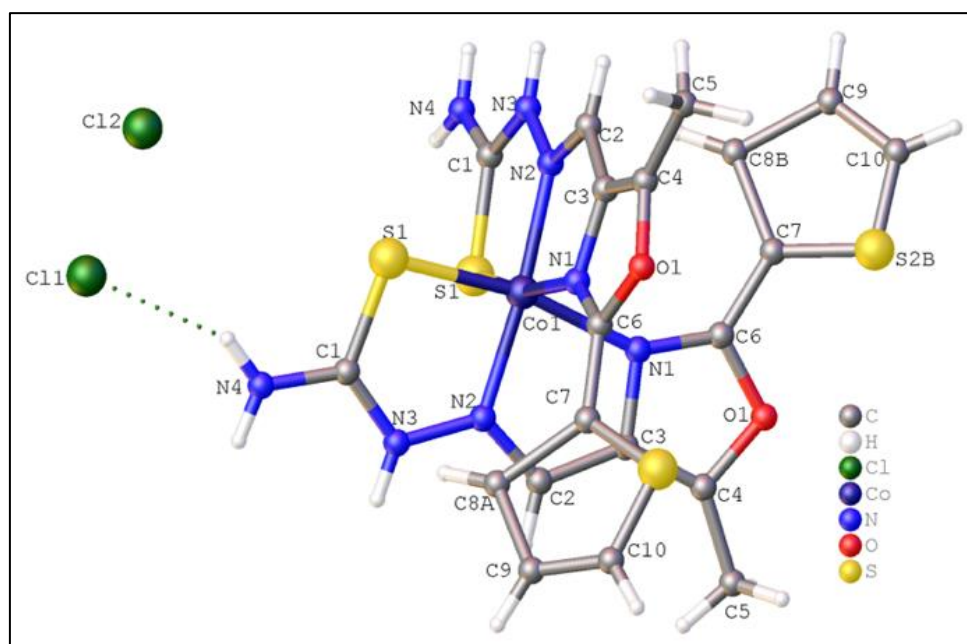


Figure 2: Structure of the  $[\text{Co}(\text{HL})_2]\text{Cl}_2$  (2) complex

**Table 3: Selected bond lengths (Å), bond angles and torsion angle (°) of the complex (2)**

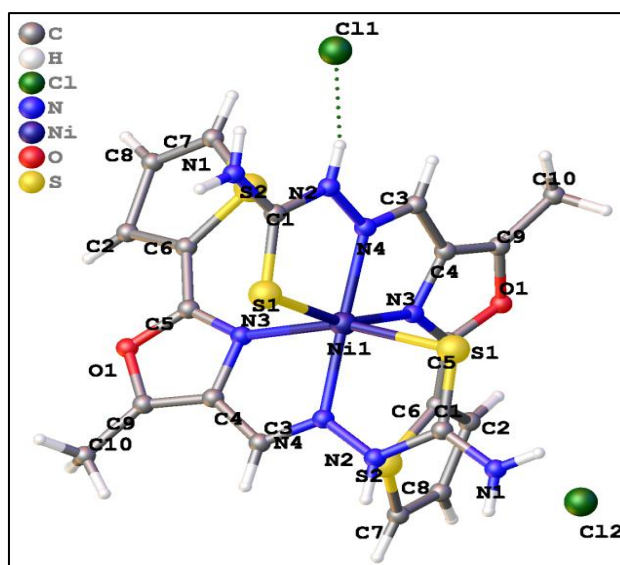
Bond length Å Atom atom length	Bond angle (°) Atom atomatom angle	Torsion angle (°) Atom AAAAngle
Co1 S1 2.1972(9)	S1 <sup>1</sup> Co1 S1 90.86(5)	N2 N3 C1 S1 -2.3(4)
Co1 S1 <sup>1</sup> 2.1972(9)	N1 Co1 S1 <sup>1</sup> 91.36(8)	
Co1 N1 2.017(3)	N1 <sup>1</sup> Co1 S1 91.36(8)	
Co1 N1 <sup>1</sup> 2.017(3)	N1 Co1 S1 168.39(8)	
Co1 N2 2.2078(5)	N1 <sup>1</sup> Co1 S1 <sup>1</sup> 168.39(8)	
Co1 N2 <sup>1</sup> 1.900(3)	N1 Co1 N1 <sup>1</sup> 88.75(16)	
S1 C1 1.900(3)	N2 Co1 S1 85.66(9)	
	N2 <sup>1</sup> Co1 S1 <sup>1</sup> 85.66(9)	
	N2 <sup>1</sup> Co1 S1 90.16(8)	
	N2 Co1 S1 <sup>1</sup> 90.16(8)	
Bond length Å Atom atom length	Bond angle (°) Atom atomatom angle	
Ni1 S1 2.364(2)	S1 Ni1 S1 <sup>1</sup> 97.81(12)	
Ni1 S1 <sup>1</sup> 2.364(2)	N3 Ni1 S1 <sup>1</sup> 88.51(17)	
Ni1 N3 2.166(6)	N3 Ni1 S1 159.90(16)	
Ni1 N3 <sup>1</sup> 2.166(6)	N3 <sup>1</sup> Ni1 S1 <sup>1</sup> 159.90(16)	
Ni1 N4 2.023(6)	N3 <sup>1</sup> Ni1 S1 88.51(17)	
Ni1 N4 <sup>1</sup> 2.023(6)	N3 <sup>1</sup> Ni1 N3 92.0(3)	
	N4 Ni1 S1 93.18(18)	
	N4 Ni1 S1 <sup>1</sup> 81.78(18)	
	N4 <sup>1</sup> Ni1 S1 <sup>1</sup> 81.78(18)	
	N4 Ni1 N4 <sup>1</sup> 172.4(3)	

**Crystal structure of the complex [Ni(HL)<sub>2</sub>]<sub>2</sub>Cl<sub>2</sub>(3)**

The molecular structure of complex [Ni(HL)<sub>2</sub>]<sub>2</sub>Cl<sub>2</sub>(3) along with the numbering sequence is given in Figure 3. The crystal data and structure refinement parameters are reported in Table 2. Selected bond lengths and bond angles are summarized in Table 3.

In this complex the Ni(II) ion is in a distorted octahedral environment. The six coordinate octahedral Ni(II) complex is bonded to two neutral tridentate ligands (HL). Two chloride ions neutralize the two

positive charges of the metal. The structure of [Ni(HL)<sub>2</sub>]<sub>2</sub>Cl<sub>2</sub> is almost identical to a closely related Ni(II) complex [23]. The crystal structure showed that in the complex [Ni(HL)<sub>2</sub>]<sub>2</sub>Cl<sub>2</sub>, thiosemicarbazone is coordinated as an NNS donor ligand with the sulfur atom coordinated in the thione form. The two coordinated azomethine nitrogen atoms are *trans* to each other and the other two sets of identical donor atoms, oxazole nitrogen atoms and thione sulfur atoms are *cis* to each other. Moreover, this molecular structure showed hydrogen bonding between one chloride and the (N2-H).

**Figure 3: Structure of [Ni(HL)<sub>2</sub>]<sub>2</sub>Cl<sub>2</sub> (3) complex**

### IR spectroscopy

The IR spectra of the ligand HL showed band of (C=O) carbonyl of the parent aldehyde at a frequency of 1687  $\text{cm}^{-1}$ , after condensation of aldehyde with thiosemicarbazide, this frequency replaced by 1604  $\text{cm}^{-1}$  which assigned to azomethine group  $\nu(\text{C}=\text{N})$  of the thiosemicarbazone [24]. More evidence of confirmation of thiosemicarbazone, band at 3314  $\text{cm}^{-1}$  (m) attributed to  $\nu(\text{N}1\text{H}_2)$  and 3112  $\text{cm}^{-1}$  (m) which assigned to  $\nu(\text{N}2\text{H})$ . The spectra showed band at 1533  $\text{cm}^{-1}$  which assigned to  $\nu(\text{N}=\text{C}-\text{O})$  oxazole ring. Also, the spectra showed band at 1424  $\text{cm}^{-1}$  (s), 1337  $\text{cm}^{-1}$  (s) and (1277 & 1068)  $\text{cm}^{-1}$  (s), attributed to  $\nu(\text{C}=\text{C})$  oxazole,  $\nu(\text{C}-\text{N})$  oxazole,  $\nu(\text{C}-\text{O}-\text{C})$  respectively, and band at 2968  $\text{cm}^{-1}$  (s) assigned to  $\nu(\text{C}-\text{H})$  oxazole ring. The ligand was existing in thione form in the solid state and this was confirmed by absence of the  $\nu(\text{S}-\text{H})$  stretching in the region 2500-2600  $\text{cm}^{-1}$  in the IR spectrum and appearance of peaks at 1370  $\text{cm}^{-1}$  and 819  $\text{cm}^{-1}$  for  $\nu(\text{C}=\text{S})$ .

The major characteristic bands of the ligand HL (1) and complexes 2&3 are summarized in Table 4. In the case of the Co(II) complex (2) the bands at 3314, 3118, 1604, 1533 and 819 which assigned to  $\nu(\text{N}^1\text{H}_2)$ ,  $\nu(\text{N}^2\text{H})$ ,  $\nu(\text{C}=\text{N})_{\text{azomethine}}$ ,  $\nu(\text{C}=\text{N})_{\text{oxazole nitrogen}}$  and

$\nu(\text{C}=\text{S})$  respectively in the free ligand are shifted to lower or higher frequency 3297, 3113, 1586, 1634 and 862  $\text{cm}^{-1}$  in the complex. This change in frequencies indicated the formation of the complex [25], and a good evidence the new bands appearing at 487, 491 and 656  $\text{cm}^{-1}$  which are assigned to  $\nu(\text{M}-\text{N})_{\text{azomethine}}$ ,  $\nu(\text{M}-\text{N})_{\text{oxazole nitrogen}}$  and  $\nu(\text{C}=\text{S})_{\text{thioamide}}$  respectively.

For the complex 3 the IR spectral analysis showed bands at 3276  $\text{cm}^{-1}$  (s) and 3086  $\text{cm}^{-1}$  (s) are assigned to the  $\nu(\text{N}^1\text{H}_2)$  stretching  $\nu(\text{N}^2\text{H})$  and respectively. The  $\nu(\text{C}=\text{N})$  band of the thiosemicarbazone at 1604  $\text{cm}^{-1}$  shifted to lower frequency 1598  $\text{cm}^{-1}$  in the complex Ni(LH)<sub>2</sub> indicating coordination via the azomethine nitrogen [26]. The shift of the thioamide stretching frequency from 819 to 863  $\text{cm}^{-1}$  indicated thione coordination. The band at 1489  $\text{cm}^{-1}$  is assigned to  $\nu(\text{C}=\text{N})_{\text{oxazole ring}}$  is shifted to a lower frequency indicating the involvement of the nitrogen of the oxazole ring in complexation. Crystal structure supported the involvement of the nitrogen of the oxazole ring in complexation. The new bands at 454, 491 and 649  $\text{cm}^{-1}$  are assigned to  $\nu(\text{M}-\text{N})_{\text{azomethine}}$ ,  $\nu(\text{M}-\text{N})_{\text{oxazole nitrogen}}$  and  $\nu(\text{C}=\text{S})_{\text{thioamide}}$  respectively.

**Table 4: IR frequencies ( $\text{cm}^{-1}$ ) of characteristic groups**

Mode	HL (1)	Co(LH) <sub>2</sub> Cl <sub>2</sub> (2)	Ni(HL) <sub>2</sub> Cl <sub>2</sub> (3)	references
$\nu(\text{N}^1\text{H}_2)$ amine	3314	3297	3276	25&26
$\nu(\text{N}^2\text{H})$ imine	3118	3113	3086	25& 26
$\nu(\text{C}=\text{N})_{\text{azomethine}}$	1604(s)	1586	1598	25& 26
$\nu(\text{C}=\text{N})_{\text{oxazole ring}}$	1533	1634	1489	25& 26
$\nu(\text{C}=\text{S})$ thione	819	862	863	25& 26
$\nu(\text{M}-\text{N})_{\text{azomethine}}$	-	444	454	
$\nu(\text{M}-\text{N})_{\text{oxazole nitrogen}}$	-	487	491	
$\nu(\text{M}-\text{S})_{\text{thioamide}}$	-	656	649	

### <sup>1</sup>H & <sup>13</sup>C NMR Spectroscopy

The <sup>1</sup>H-NMR spectral data of the ligand HL (1) shows the signal of the (N<sup>2</sup>H) proton at  $\delta = 11.45$  ppm, the amino protons (-N<sup>1</sup>H<sub>2</sub>) are shown as two signals at  $\delta$  8.3 and  $\delta$  8.5 ppm, due to the restricted rotation of this group about C<sup>1</sup>- N<sup>1</sup> bond axis caused by the delocalization of the lone pair of electrons on the N<sup>1</sup>H<sub>2</sub> nitrogen [27]. The C<sup>2</sup>H signal is found at  $\delta \approx 8.1$  ppm, and the methyl protons (C<sup>6</sup>H<sub>3</sub>) at  $\delta = 2.6$  ppm. The aromatic protons (thiophene) are found between 7.2 and 7.5 ppm. Smaller signals at  $\delta = 12$  ppm (-OH) and 3.4 ppm (alkyl) are probably caused by traces of ethanol. In Complex(2), the signal attributed to (N<sup>3</sup>HCS) proton (figure 2) was not observed. The spectrum showed two signals at  $\delta$  8.38 and 8.02 ppm which assigned to amine (CSN<sup>4</sup>H<sub>2</sub>) protons. While azomethine (-C<sup>2</sup>H=N-) proton appeared at  $\delta$  8.03 ppm this signal exhibited slightly shift from that in the free ligand. The signal appeared at  $\delta$  2.5 ppm assigned to methyl group (-CH<sub>3</sub>)

[28]. The aromatic protons of thiophene are found at  $\delta$  7.3 to 7.7 ppm.

Spectrum of complex (3) showed signal at  $\delta$  11.4 ppm due to the hydrazide N-H group, even though this signal is slightly downfield shifted from that for parent ligand, these observations are taken as evidence for the N chelate formation. As well as, Presence of this signal at  $\delta$  11.4 ppm in the spectra of the metal complex confirms protonation of the thiosemicarbazone chain and subsequent coordination through the thionate form. Azomethine (-CH=N-) proton is observed at  $\delta$  8.05 ppm, while the two signals observed at  $\delta$  8.42 and 8.25 ppm assigned to -NH<sub>2</sub> proton. The signal appeared at  $\delta$  2.2 ppm assigned to methyl group (-CH<sub>3</sub>) [28]. Aromatic protons of thiophene are found at  $\delta$  7.4 to 7.9 ppm.

The <sup>13</sup>C NMR spectral data of the ligand LH has shown peak at  $\delta$  178.01 ppm attributed to the thione

carbon (C1), whereas the imine carbon (C2) appeared at  $\delta$  135.95 ppm. The oxazole ring carbon atoms showed signals at  $\delta$  (149- 155) ppm. The signal at  $\delta$  11.53 (C6) is assigned to the methyl group. The thiophene carbon ring exhibited signals at  $\delta$  (127-131) ppm.

The  $^{13}\text{C}$  NMR spectra of the  $[\text{Co}(\text{II})(\text{HL})_2]\text{Cl}_2$ (2) and  $[\text{Ni}(\text{II})(\text{HL})_2]\text{Cl}_2$  (3) complexes showed signals at  $\delta$  179.91 and  $\delta$  177.08 ppm respectively, which are assigned to C1-S carbon. The

azomethine ( $-\text{C}2\text{H}=\text{N}$ ) carbon (complex (2)) exhibited a peaks at  $\delta$ 136.7 ppm while in (complex (3))the azomethine ( $-\text{C}3\text{H}=\text{N}$ ) carbon signal found at  $\delta$ 135.45 ppm. The oxazole ring carbon atoms exhibited peaks at  $\delta$ (141.9 – 158.3)ppm and at  $\delta$ (148.6 – 154.9) ppm respectively. Four carbon atoms of thiophene exhibited peaks at  $\delta$ (123 – 133)and  $\delta$ (126 – 130)ppm, Signals at  $\delta$  11.08 and 10.78 ppm are assigned to the methyl group ( $-\text{CH}_3$ )respectively. Signals at  $\delta$  = 18 and 56 ppm are due to ethanol impurities.

**Table 5:  $^1\text{H}$  NMR data of ligand HL (1) and its complexes 2 & 3 in ppm**

Compound	$\delta$ ( $\text{N}^2\text{H}$ )	$\delta$ ( $\text{N}^1\text{H}_2$ )	$\delta$ ( $\text{C}^2\text{H}$ )	( $\text{C}^6\text{H}_3$ )	( $\text{C}^{8,9,10}$ )-H (thiophen ring)	(-OH) ethanol	(alkyl) ethanol
HL <sup>2</sup> (1)	11.45 (m)	8.3 and 8.5	8.1	2.6	7.2 - 7.5	12	3.4
Co(HL) <sub>2</sub> Cl <sub>2</sub> (2)	-	8.38 and 8.02	8.03	2.5	7.3 - 7.7	-	-
Ni(HL) <sub>2</sub> Cl <sub>2</sub> (3)	11.4, 12.2	8.42 and 8.25	8.05	2.60	7.4 – 7.9	-	-

### UV-Vis spectra

The thiosemicarbazone ligand HL has bands at 335, 414, 586, 629 and 728 nm. The band at 335 nm is assigned to  $\pi \rightarrow \pi^*$  transition of the azomethine group. The bands at 414, 575, 629 and 728 nm may be associated to  $n \rightarrow \pi^*$  transition of the azomethine, thioamide, oxazole ring and thiophene. For the complexes 2 and 3 the UV-Vis spectrum showed the intraligand absorption at 349 and 318 nm attributed to the  $\pi-\pi^*$  transition. These bands were shifted to higher energy in complex (2) while complex(3) shifted to lower. This shift on complexation indicates coordination via thioamide bands C=S. The intraligand bands corresponding to  $n-\pi^*$  transition of two complexes are shifted to higher energy. These changes are due to the involvement of thioamide, azomethine nitrogen and oxazole nitrogen atom in coordination [29].

### Biological Activity

The new Co(II) and Ni(II) complexes of heterocyclic thiosemicarbazone ligands and HL were

tested for their in vitro biological activity against six of standard microorganisms: two Gram positive namely *Bacillus subtilis* and *Micrococcus luteus*, and Gram negative bacteria *Escherichia coli* and three fungi that is *Saccharomyces cerevisiae* (Baker's yeast), *Mucor spec.* and *Aspergillus niger*., three compounds were tested at concentration 100  $\mu\text{g}/\text{mL}$  and the Zone of inhibition has been measured in mm after 20, 24 and 48 hours of incubation. The results of antimicrobial activity data of compounds are as given in Table 6. The results showed that the antimicrobial activities of the ligand and its metal complexes exhibited good activity toward all bacteria except at *E.coli*(Gram -negative) (complex 2) and at *M.luteus*(Gram +positive) (complex 3). The results of antifungal activity showed that the ligand and its metal complexes have a good inhibition activity against *Mucor spec.* except complex 2. while only complex 2 exhibited activity toward *Aspergillus niger*. Generally, the ligand HL<sup>2</sup> and their metal complexes exhibited the strongest antimicrobial effect especially Co(II) complex.

**Table 6: Antimicrobial\* screening data of investigated ligand and their Ni(II) and Co(II) complexes**

Compound	Conc. $\mu\text{g}/\text{mL}$	Diameter of inhibition zone in millimeter (mm)					
		Gram + ve: Bacteria		Gram -ve: Bacteria	Baker's yeast	Fungus	
		<i>B. subtilis</i>	<i>M.luteus</i>	<i>E. coli</i>	<i>S.cerevisiae</i>	<i>Mucor spec.</i>	<i>A. niger</i>
HL(1)	100	10	30	40	-	50	-
Co(HL) <sub>2</sub> Cl <sub>2</sub> (2)	100	15	60	-	-	-	30
Ni(HL) <sub>2</sub> Cl <sub>2</sub> (3)	100	10		45	-	50	-

\* Agar diffusion assay method, solvent DMSO/ Gram- positive bacteria: *Bacillus subtilis* and *Micrococcus luteus* Gram-negative bacteria: *Escherichia coli* Fungi: *Saccharomyces cerevisiae* (Baker's yeast), *Mucor spec.* and *Aspergillus niger*

## CONCLUSION

The new ligand, 5-methyl-2-(2-thienyl)-1,3-oxazole-4-carbaldehyde thiosemicarbazone (HL) and its Co(II) and Ni(II) complexes were synthesized and characterized by elemental analysis, IR, ( $^1\text{H}$  &  $^{13}\text{C}$ ) NMR and UV-Vis spectroscopy. The crystal structure of the

free ligand and complexes has been determined by single crystal X-ray diffraction technique. It is examined that in these complexes the ligand has NNS donor tridentate nature, bind to the center metal through the azomethine nitrogen, oxazole nitrogen and thione/thiolate sulfur atom. As well as, the results of the



above studies exhibited considerable distortion from octahedral symmetry. The antimicrobial activity results of the HL ligand and its metal complexes showed good antimicrobial activity toward most selected organism.

## ACKNOWLEDGEMENTS

The authors thank (Technische Universität Dresden, Faculty of Biology) for performing the antibacterial and antifungal tests. MMM gratefully acknowledges a DAAD research grant. special thanks are due to the soul of “the late” Dr. Abdalmoneim Abdalrouf Suliman first supervisor who passed away. very thankful to Prof. Dr. Thomas Doert, also indebted and very grateful to both Dr. Jens Hunger and Dr. Martin Kaiser of the Technical University of Dresden-Germany for carrying out the X-ray analysis.

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