

## Synthesis, Characterization and Biological Effect of Anions [NO<sub>3</sub><sup>-</sup>, SO<sub>4</sub><sup>2-</sup>, C<sub>2</sub>O<sub>4</sub><sup>2-</sup>, or CH<sub>3</sub>CO<sub>2</sub><sup>-</sup>] on Co(II) and Ni(II) Chelates of Tridentate Schiff-base Ligands

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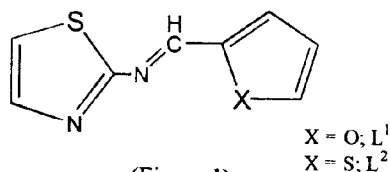
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**Summary:** Furane- and thiophene-2-carboxylaldehyde undergo condensation reaction with 2-aminothiazole to give tridentate NNO and NNS Schiff base ligands, respectively. The synthesized Schiff base ligands have been further used for their complexation reaction with Co(II) and Ni(II) having the same metal ion (cation) but different anions. Structural elucidation of these Schiff base ligands and its metal complexes having the same metal ion (cation) but different anions, [NO<sub>3</sub><sup>-</sup>, SO<sub>4</sub><sup>2-</sup>, C<sub>2</sub>O<sub>4</sub><sup>2-</sup> or CH<sub>3</sub>CO<sub>2</sub><sup>-</sup>] have been done on the basis of their physical, analytical and spectral data. In order to evaluate the effect of anions, these compounds have also been screened for their varied antibacterial activity against bacterial species, *Escherichia coli*, *Staphylococcus aureus* and *Pseudomonas aeruginosa*.

### Introduction

Due to the presence of thiazole and related compounds in the histidyl residue of proteins have gained a considerable interest [1-4]. It also provides a potential binding sites for metal chelation. A limited research work is only available on the coordination and chelating properties of such significant compounds. Sherman and Dickson have reported [5] compounds of 2-amino-4-(5-nitro-2-furyl)thiazole and their various chloro, hydroxy and methoxy derivatives and observed [6-8] that these compounds exhibited antibacterial activity *in vitro*, particularly against *Staphylococcus aureus*, *Salmonella* and *Escherichia coli*. A number of reports [9,10] and patent [11] similarly, have described the preparation and antibacterial properties of a variety of hydroxy-aryliminomethylthiazole, hydroxynaphthylthiazole-2-yl-thiazolidone and  $\alpha$ -substituted benzylamino-thiazoles and their derivatives.



(Figure 1)

However, no work so far, is reported on the synthesis and antibacterial properties of furane- and thiophene derived Schiff base ligands of thiazole. We have previously reported the synthesis and characterization [12-14] of some novel thiazole based

compounds and their biological role upon chelation with different transition metal ions. The present work is an extension of our previous studies in which the same ligands (Figure 1) have been used for the complexation to give chelates of the type [M(L)<sub>2</sub>]X<sub>n</sub> where M = Co(II) and Ni(II), L = L<sup>1</sup> and L<sup>2</sup> and, X<sub>n</sub> = NO<sub>3</sub><sup>-</sup>, SO<sub>4</sub><sup>2-</sup>, C<sub>2</sub>O<sub>4</sub><sup>2-</sup> or CH<sub>3</sub>CO<sub>2</sub><sup>-</sup> where n = 1 or 2. These chelates having the same metal ion (cation) but different anions have been further investigated for their participating role on the biological activity against bacterial species, *Escherichia coli*, *Staphylococcus aureus* and *Pseudomonas aeruginosa*.

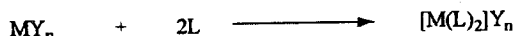
### Results and Discussion

#### Physical Properties

The Schiff base ligands were prepared by reacting equimolar amounts of the respective 2-furane- and 2-thiophenecarboxaldehyde with 2-aminothiazole in ethanol. The structures of these ligands were established [14] with the help of their IR, <sup>1</sup>H NMR, <sup>13</sup>C NMR and microanalytical data.

All the metal complexes (1-16) (Table 1) of these Schiff base ligands were prepared by the stoichiometric reaction of the respective metals as their nitrate, sulfate, acetate and oxalate salts, and the ligands in the molar ratio M:L = 1:2. The proposed reaction is represented by the following equation:

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M = Co(II) or Ni(II)

L = L<sup>1</sup> or L<sup>2</sup>

Y = NO<sub>3</sub><sup>-</sup>, SO<sub>4</sub><sup>2-</sup>, C<sub>2</sub>O<sub>4</sub><sup>2-</sup> or CH<sub>3</sub>CO<sub>2</sub><sup>-</sup>

n = 1 or 2

Their elemental analyses suggest monomer nature of these complexes. All the synthesized complexes are air stable, non-hygroscopic solids and decompose without melting.

IR spectra of the Schiff bases showed the absence of bands at 1735 and 3420 cm<sup>-1</sup> due to carbonyl ν(C = O) and ν(NH<sub>2</sub>) stretching vibrations and, instead, appearance of a strong new band at ~1635 cm<sup>-1</sup> assigned [16-18] to the azomethine ν(C = N) linkage. It however, suggested that amino and aldehyde moieties of the starting reagents no more exist and have been converted into their respective Schiff base ligands. The comparison of the infrared spectra of the ligands and their metal chelates

indicated that the ligands were coordinated to the metal atom in three ways, thus representing the ligands to act as tridentate.

a) The band appearing at 1635 cm<sup>-1</sup> due to the azomethine vibration shifted to lower frequency by ~5-10 cm<sup>-1</sup> indicating participation of the azomethine nitrogen in complexation.

b) The band at 1615 assigned to thiazole ring ν(C = N) nitrogen also shifted to lower frequency by ~10-15 cm<sup>-1</sup> which was indicative of the coordination of thiazole ring nitrogen in chelation.

c) Further conclusive evidence of the coordination of these tridentate Schiff base ligands with the metals, was shown by the appearance of weak low frequency new bands at ~360-365, ~455-460 and 525-530 cm<sup>-1</sup> (Table 2). These were, assigned [19] to the metal-sulfur ν(M-S) in thienyl compounds, metal-oxygen ν(M-O) in furanyl derivatives and metal-nitrogen ν(M-N) of thiazole

Table I. Physical and Analytical Data of the Metal(II) Chelates

No	Metal chelate/ Mol. Formula	Yield (%)	M.p (°C) (decomp)	B.M. (μ <sub>eff</sub> )	C	H	N
1	[Co(L <sup>1</sup> ) <sub>2</sub> (NO <sub>3</sub> ) <sub>2</sub> ] C <sub>16</sub> H <sub>12</sub> CoN <sub>6</sub> O <sub>8</sub> S <sub>2</sub> [347.4]	62	220-222	4.3	55.3 (55.6)	3.5 (3.5)	24.2 (24.1)
2	[Co(L <sup>1</sup> ) <sub>2</sub> (SO <sub>4</sub> ) <sub>2</sub> ] C <sub>16</sub> H <sub>12</sub> CoN <sub>4</sub> O <sub>8</sub> S <sub>2</sub> [479.1]	58	224-226	4.7	40.1 (40.5)	2.5 (2.6)	11.7 (11.5)
3	[Co(L <sup>2</sup> ) <sub>2</sub> (C <sub>2</sub> O <sub>4</sub> ) <sub>2</sub> ] C <sub>18</sub> H <sub>12</sub> CoN <sub>4</sub> O <sub>8</sub> S <sub>2</sub> [447.1]	60	221-223	4.4	48.3 (48.7)	2.7 (2.8)	12.5 (12.1)
4	[Co(L <sup>2</sup> ) <sub>2</sub> (CH <sub>3</sub> CO <sub>2</sub> ) <sub>2</sub> ] C <sub>20</sub> H <sub>18</sub> CoN <sub>4</sub> O <sub>8</sub> S <sub>2</sub> [533.1]	62	227-229	4.9	45.0 (45.3)	3.4 (3.3)	10.5 (10.6)
5	[Co(L <sup>2</sup> ) <sub>2</sub> (NO <sub>3</sub> ) <sub>2</sub> ] C <sub>16</sub> H <sub>12</sub> CoN <sub>6</sub> O <sub>8</sub> S <sub>2</sub> [570.9]	57	222-224	4.5	33.6 (33.5)	2.1 (2.5)	14.7 (14.4)
6	[Co(L <sup>2</sup> ) <sub>2</sub> (SO <sub>4</sub> ) <sub>2</sub> ] C <sub>16</sub> H <sub>12</sub> CoN <sub>4</sub> O <sub>8</sub> S <sub>2</sub> [542.9]	58	218-220	4.8	35.4 (35.7)	2.2 (2.1)	10.3 (10.4)
7	[Co(L <sup>2</sup> ) <sub>2</sub> (C <sub>2</sub> O <sub>4</sub> ) <sub>2</sub> ] C <sub>18</sub> H <sub>12</sub> CoN <sub>4</sub> O <sub>8</sub> S <sub>2</sub> [534.9]	60	212-214	4.5	40.4 (40.6)	2.2 (2.5)	10.5 (10.4)
8	[Co(L <sup>2</sup> ) <sub>2</sub> (CH <sub>3</sub> CO <sub>2</sub> ) <sub>2</sub> ] C <sub>20</sub> H <sub>18</sub> CoN <sub>4</sub> O <sub>8</sub> S <sub>2</sub> [564.9]	62	226-228	4.6	42.5 (42.7)	3.2 (3.0)	9.9 (9.8)
9	[Ni(L <sup>1</sup> ) <sub>2</sub> (NO <sub>3</sub> ) <sub>2</sub> ] C <sub>16</sub> H <sub>12</sub> NiN <sub>6</sub> O <sub>8</sub> S <sub>2</sub> [347.2]	60	223-225	3.3	55.3 (55.5)	3.5 (3.4)	24.2 (24.3)
10	[Ni(L <sup>1</sup> ) <sub>2</sub> (SO <sub>4</sub> ) <sub>2</sub> ] C <sub>16</sub> H <sub>12</sub> NiN <sub>4</sub> O <sub>8</sub> S <sub>2</sub> [478.9]	62	215-218	3.1	40.1 (40.2)	2.5 (2.7)	11.7 (11.5)
11	[Ni(L <sup>2</sup> ) <sub>2</sub> (C <sub>2</sub> O <sub>4</sub> ) <sub>2</sub> ] C <sub>18</sub> H <sub>12</sub> NiN <sub>4</sub> O <sub>8</sub> S <sub>2</sub> [446.9]	58	222-224	3.5	48.3 (48.5)	2.7 (2.5)	12.5 (12.7)
12	[Ni(L <sup>2</sup> ) <sub>2</sub> (CH <sub>3</sub> CO <sub>2</sub> ) <sub>2</sub> ] C <sub>20</sub> H <sub>18</sub> NiN <sub>4</sub> O <sub>8</sub> S <sub>2</sub> [532.9]	60	217-219	3.3	45.0 (44.8)	3.4 (3.3)	10.5 (10.3)
13	[Ni(L <sup>2</sup> ) <sub>2</sub> (NO <sub>3</sub> ) <sub>2</sub> ] C <sub>16</sub> H <sub>12</sub> NiN <sub>6</sub> O <sub>8</sub> S <sub>2</sub> [570.7]	58	223-225	3.6	33.6 (33.7)	2.1 (2.0)	14.7 (14.9)
14	[Ni(L <sup>2</sup> ) <sub>2</sub> (SO <sub>4</sub> ) <sub>2</sub> ] C <sub>16</sub> H <sub>12</sub> NiN <sub>4</sub> O <sub>8</sub> S <sub>2</sub> [542.7]	62	218-220	3.5	35.4 (35.2)	2.2 (2.5)	10.3 (10.0)
15	[Ni(L <sup>2</sup> ) <sub>2</sub> (C <sub>2</sub> O <sub>4</sub> ) <sub>2</sub> ] C <sub>18</sub> H <sub>12</sub> NiN <sub>4</sub> O <sub>8</sub> S <sub>2</sub> [534.7]	60	223-225	3.4	40.4 (40.5)	2.2 (2.4)	10.5 (10.7)
16	[Ni(L <sup>2</sup> ) <sub>2</sub> (CH <sub>3</sub> CO <sub>2</sub> ) <sub>2</sub> ] C <sub>20</sub> H <sub>18</sub> NiN <sub>4</sub> O <sub>8</sub> S <sub>2</sub> [564.7]	62	227-229	3.5	42.5 (42.6)	3.2 (3.3)	9.9 (10.2)

Infrared spectra

Table II. IR and UV-Visible Spectral Data of the Metal(II) Chelates

No	IR (cm <sup>-1</sup> )	$\lambda_{max}$ (cm <sup>-1</sup> )
1	1630 (HC = N), 1605 (C = N), 455 (M-O), 525 (M-N)	30210, 18525, 7880
2	1625 (HC = N), 1610 (C = N), 460 (M-O), 525 (M-N)	30575, 17550, 8615
3	1630 (HC = N), 1610 (C = N), 460 (M-O), 530 (M-N)	30545, 17950, 8430
4	1630 (HC = N), 1605 (C = N), 455 (M-O), 525 (M-N)	30450, 17670, 7910
5	1630 (HC = N), 1610 (C = N), 455 (M-O), 525 (M-N)	30275, 18255, 8535
6	1630 (HC = N), 1605 (C = N), 455 (M-O), 530 (M-N)	30365, 18110, 8215
7	1630 (HC = N), 1605 (C = N), 460 (M-O), 525 (M-N)	30525, 17745, 8110
8	1630 (HC = N), 1605 (C = N), 365 (M-S), 530 (M-N)	30270, 18345, 8455
9	1630 (HC = N), 1605 (C = N), 360 (M-S), 525 (M-N)	28530, 15345, 9315
10	1630 (HC = N), 1605 (C = N), 365 (M-S), 525 (M-N)	29210, 16255, 10145
11	1630 (HC = N), 1605 (C = N), 365 (M-S), 525 (M-N)	28645, 15565, 9665
12	1630 (HC = N), 1605 (C = N), 360 (M-S), 525 (M-N)	29115, 15785, 9735
13	1630 (HC = N), 1605 (C = N), 365 (M-S), 525 (M-N)	28775, 15660, 9660
14	1630 (HC = N), 1605 (C = N), 365 (M-S), 525 (M-N)	28880, 15775, 9545
15	1630 (HC = N), 1605 (C = N), 360 (M-S), 525 (M-N)	28715, 16110, 9325
16	1630 (HC = N), 1605 (C = N), 360 (M-S), 525 (M-N)	28535, 15445, 9835

Magnetic Moments and UV-Visible Spectra

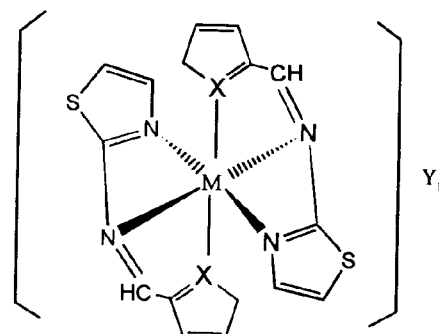
Antibacterial Properties

moiety respectively. These new bands were observable only in the spectra of the metal complexes and not in the spectra of its uncomplexed Schiff bases thus confirming participation of these hetero groups (S, O or N) in the coordination.

The room temperature magnetic moment of the solid cobalt(II) complexes was found to be in the range (4.3-4.9 B.M), indicative [20] of three unpaired electrons per Co(II) ion in an octahedral environment. The nickel(II) complexes also showed  $\mu_{eff}$  values in the range (3.1-3.6 B.M), indicative [21] of two unpaired electrons per Ni(II) ion for their ideal octahedral configuration.

The electronic spectra of the Co(II) chelates showed three bands observed at 7,880-8,615, 17,550-18,525 and 30,210-30,575 cm<sup>-1</sup> which may be assigned to  $4T_{1g} \rightarrow 4T_{2g}(F)$ ,  $4T_{1g} \rightarrow 3A_{2g}(F)$  and  $4T_{1g} \rightarrow 4T_{1g}(P)$  transitions respectively and are suggestive [22, 23] of the octahedral geometry around the cobalt ions. The Ni(II) complexes exhibited three spin-allowed bands at 9,315-10,145, 15,345-16,255 and 28,530-29,210 cm<sup>-1</sup> assignable [24,25] respectively, to the transitions  $3A_{2g}(F) \rightarrow 3T_{2g}(F)(v_1)$ ,  $3A_{2g}(F) \rightarrow 3T_{1g}(F)(v_2)$  and  $3A_{2g}(F) \rightarrow 3T_{2g}(P)(v_3)$  which are suggestive [26] of their octahedral geometry (Fig 2).

The title Schiff base ligands and their metal chelates were evaluated for their antibacterial activity against bacterial species *Escherichia coli* (a), *Staphylococcus aureus* (b) and *Pseudomonas aeruginosa* (c). The compounds were tested at a concentration of 30  $\mu$ g/0.01 mL in DMF solution using the paper disc diffusion method [15]. The



X = O; L<sup>1</sup>, X = S; L<sup>2</sup>  
 Y = NO<sub>3</sub><sup>-</sup>, SO<sub>4</sub><sup>2-</sup>, C<sub>2</sub>O<sub>4</sub><sup>2-</sup> or CH<sub>3</sub>CO<sub>2</sub><sup>-</sup>  
 n = 1 or 2  
 M = Co(II) or Ni(II)

Fig. 2: Proposed Structure of the Metal(II) Chelate

susceptibility zones were measured in mm and the results are reproduced in Table III. The susceptibility zones measured were the clear zones around the discs killing the bacteria.

All the Schiff bases and their complexes individually exhibited varying degrees of inhibitory effects on the growth of the tested bacterial species. The antibacterial results evidently show that the activity of the Schiff base ligands became more pronounced when coordinated to the metal ions. When the same metal chelate having different anions was individually screened, the degree of potency varied. From the obtained data reproduced in Table III, it was generally observed that the order of potency in comparison to the metal(II) complexes having chloride anion evaluated and reported earlier

[14] and to the results of the present studies against the same tested bacterial species under the same conditions were found to follow the order of potency as:



On the basis of these observations, it is strongly claimed that different anions dominantly effect the biological behavior of the metal chelates. It is however, suspected that factors such as solubility, conductivity, dipole moment and cell permeability mechanisms are certainly influenced by the presence of these anions present in the metal chelates that may be the possible reasons for increasing this activity/potency. However, our *in vitro* studies are in progress, which would help us in determining the actual mechanism involved in enhancing this activity due to the presence of anions.

Table III. Antibacterial Activity Data of the Schiff bases and its Metal(II) Chelates

Schiff Base/ Chelate	Microbial Species		
	a	b	c
L <sup>1</sup>	++	+	+
L <sup>2</sup>	++	+	++
1	+++	++	+++
2	+++	+++	++
3	+++	++	+++
4	+++	++	++
5	++++	+++	+++
6	+++	+++	+++
7	++++	++	+++
8	++	+++	+
9	+++	+++	+++
10	+++	+++	+++
11	+++	+++	++
12	++	+++	++++
13	+++	++	+++
14	+++	+++	+++
15	+++	++++	++
16	++	+++	+++

a= *Escherichia coli*, b= *Staphylococcus aureus*,  
c= *Pseudomonas aeruginosa*

Inhibition zone diameter mm (% inhibition): +, 6-10 (27-45 %); ++, 10-14 (45-64 %); +++, 14-18 (64-82 %); +++, 18-22 (82-100 %). Percent inhibition values are relative to inhibition zone (22 mm) of the most active compound with 100 % inhibition.

### Experimental

All chemicals and solvents used were of Analar grade. IR spectra in KBr discs were recorded on a Philips Analytical PU 9800 FTIR spectrophotometer. UV-Visible spectra were obtained in DMF on a Hitachi U-2000 double-beam spectrophotometer. Conductance of the metal complexes was determined in DMF on a YSI-32 model conductometer. C, H and N analyses were

carried out by Butterworth Laboratories Ltd. Magnetic measurements were done on solid complexes using the Gouy method. Melting points were recorded on a Gallenkamp apparatus and are uncorrected. The antibacterial studies were carried out with the help of the Department of Pathology, Qaid-e-Azam Medical College, Bahawalpur.

### Preparation of Schiff Base Ligands

The Schiff base ligands were prepared and characterized as reported [14] earlier.

### Preparation of Metal Complexes

An ethanol solution (20 mL) of the appropriate metal(II) salt (0.001 mol) was added to a stirred warm ethanol solution (15 mL) of the respective Schiff base ligand (0.002 mol). The mixture was refluxed for 2 h, then cooled, filtered and reduced to nearly half its volume. The concentrated solution was left standing overnight at room temperature which resulted in the formation of a solid product. The product thus obtained was filtered, washed with ethanol, then with ether and dried. Crystallization with aqueous ethanol (50 %) gave desired metal complexes (Table I).

### Antibacterial Studies

The synthesized metal(II) chelates in comparison to its free Schiff base ligands were screened for their antibacterial activity against pathogenic bacterial species, *Escherichia coli*, *Staphylococcus aureus* and *Pseudomonas aeruginosa*. The paper disc diffusion method reported [14,15] elsewhere was adopted for the determination of antibacterial activity.

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