

# Zinc (II) complexes of sulfonamides as antibacterial agents: Design, characterization and biological activity

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**Abstract** – Since the introduction of Cisplatin, coordination complexes are of the prime interest of medicinal scientists in the last few decades. In the present work, sulfonamide derivatives were synthesized by reaction of TosCl with L-amino acids (N1-N4). Novel Zinc (II) complexes have been efficiently synthesized by reacting sulfonamide derivatives with metal chloride in good to excellent yields (N5-N8). These compounds and their complexes are characterized by IR, <sup>1</sup>HNMR, <sup>13</sup>CNMR, MS, Elemental analysis and x ray crystallography. Interestingly, out of all complexes N8 has shown the enhanced antibacterial activity in comparison with standard drug ciprofloxacin.

**Keywords** – Sulfonamide derivatives, antibacterial, p-toluene sulfonylechloride, metal chloride

## 1. Introduction

Agomelatine Amino acids are the essential part of life and are the most biologically active organic molecules. Complexes of amino acids with the transition metal ions are very fascinating concerning biological evaluations. Some of the transition metal complexes along with the amino acids are being widely used as different models to study the pharmacodynamic or for escalating the pharmacological actions and minimizing the unwanted effects of drugs [1] Additionally; L-amino acids are mostly concerned in the intracellular metabolism and specific transport systems of plasma membrane. On the other hand, evidences have shown that some of them plays vital role for myocardial function and endurance during ischemia / reperfusion stress for example, glutamic acid and aspartic acid [2,3]. The metal complexes of some amino acids from D- or L- isomers of lysine, proline, tryptophan, histidine and arginine have won great importance to treat malaria, diabetes and also serve as an important co-enzyme in reversible oxidation-reduction systems [4-7].

The complexes of Cu (II) with glucuronic acid have been shown to possess anti-inflammatory, antiviral activities while Mn (II) complexes with amino acids have been used to treat various allergies, anemia and heart diseases [8-13]. The organometallic compounds containing antimony as metallic centre has proved its major use against the leishmanial protozoan for many decades [14,15].

Our long standing interest in amino acids and tosylates has encouraged us to incorporate metals as a centre. In the present study novel Zn (II) complexes of tosylated amino acids has been synthesized, characterized and evaluated for their antibacterial activity. We have synthesized tosylates in a simple and efficient way and we investigated their biological studies.

### Chemistry

Various coordination complexes of amino acids derivatives were synthesized by reacting them with metal

II chlorides. The tosylates and their coordination complexes are fully characterized. We already reported the anti diabetic activity of some novel thiohydantoin and hydantoin [16]. We have modified our procedure to prepare the tosylates and extended to prepare their Zinc complexes. Interestingly we are also reporting the crystal structure of the N4 in this report. Cambridge Crystallographic Data Centre (CCDC) reference No is 948810. The selected bond angles for N4 structure are given in the Table 1.

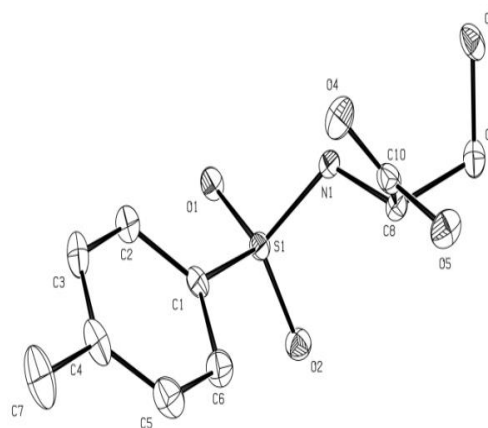


Figure 1: ORTEP diagrams for compounds N4. Thermal ellipsoids are shown at the 50% probability level. Hydrogen atoms are omitted for clarity.

Table 1: bond lengths for X-ray structure of N4

S1	O2	1.4362(14)	C7	H7a	0.9800
S1	O1	1.4413(14)	C7	H7b	0.9800
S1	N1	1.6200(17)	C7	H7c	0.9800
S1	C1	1.7623(19)	N1	C8	1.462(3)
C1	C2	1.387(3)	N1	H1	0.79(3)
C1	C6	1.389(3)	O3	C9	1.434(3)
C6	C5	1.394(3)	O3	H12	0.81(3)
C6	H6	0.9500	C9	C8	1.528(3)
C2	C3	1.389(3)	C9	H10	0.97(3)
C2	H2	0.9500	C9	H11	0.98(3)
C5	C4	1.392(4)	C8	C10	1.522(3)
C5	H5	0.9500	C8	H13	0.94(3)
C3	C4	1.391(3)	C10	O4	1.202(3)
C3	H3	0.9500	C10	O5	1.323(3)
C4	C7	1.515(3)	O5	H20	0.82(3)

## 2. Materials and Methods

All the chemicals used were of analytical grade and are purchased from Sigma Aldrich. Melting points were recorded by using a capillary tube on a digital Gallenkamp (SANYO) apparatus and were uncorrected. FTIR spectra were recorded using Bruker FTIR (4000-400  $\text{cm}^{-1}$ ),  $^1\text{H}$  NMR and  $^{13}\text{C}$ NMR spectra were determined on Bruker AV400RG spectrophotometer using  $\text{CDCl}_3$ ,  $\text{CD}_3\text{CN}$  and DMSO as internal solvents. Elemental analysis was done on a LECO- 183 CHNS analyzer. Mass spectra recorded by Bruker GCMS

### 2.1. Crystal Structure Determination

The crystallographic data for compound N4 was collected on a Bruker APEX II equipped with a Incoatec  $\mu\text{mS}$  Micro source and a Quazar MX monochromator. Cell refinement and data reduction were done using SAINT. An empirical absorption correction, based on the multiple measurements of equivalent reflections, was applied using the program SADABS. The space group was confirmed by XPREP routine in the program SHELXTL. The structures were solved by direct methods and refined by full matrix least-squares and difference Fourier techniques with SHELX-97 [17i-v]. All non-hydrogen atoms were refined with anisotropic displacement parameters. Hydrogen atoms were set in calculated positions and refined as riding atoms with a common

thermal parameter.

### 2.2. General Procedure

#### 2.2.1. Synthesis of Ligands (N1-N4)

Synthesis of Ligands is done by following the method described in literature with some modifications [18, 19]. L-Amino acid (1mmol, 1eq) and potassium carbonate (0.5mmol, 0.5eq) were dissolved in 20 ml of distilled water with continuous stirring. Solution of p-toulenesulfonyl chloride (1mmol, 1eq) in (5 ml) of freshly distilled 1, 4 dioxane was added to the previous mixture. The resultant mixture was refluxed for 2 hrs and then cooled to room temperature. The pH was adjusted at 1-2 with the help of 2N hydrochloric acid. The precipitates were obtained after 48-72 hours, filtered, washed with distilled water and recrystallized from methanol by slow evaporation.

#### 2.2.2. Synthesis of Zn (II) Complexes (N5-N8)

2mmol (1 eq) of ligand (N1-N4) was dissolved in 10 ml of methanol. 1.2 mmol (0.6 eq) of zinc chloride was dissolved in 10 ml of methanol. Zinc solution was added to ligand solution and then stirred for 2 hrs at 60°C on oil bath. The reaction mixture was cooled to room temperature, precipitates were obtained after 5-12 hrs, filtered, washed with cold ethanol and recrystallized in chloroform-hexane (1:1) mixture [20]. The synthesis of ligands and their complexes is given in Figure 2.

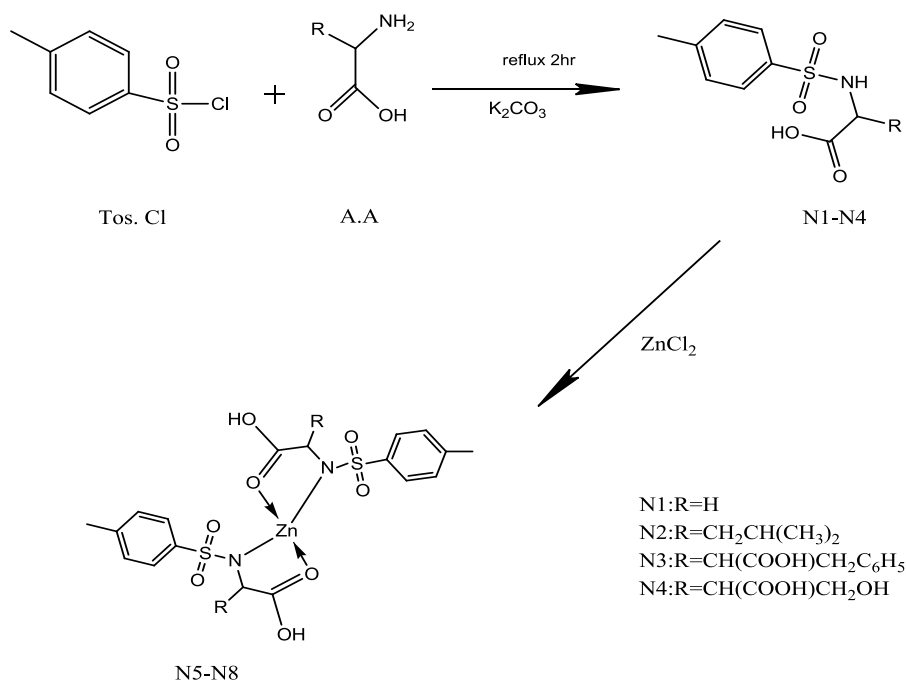


Figure 2. Synthesis of Ligands and their Complexes

#### 2-(4-methylphenylsulfonamido) acetic acid (N1) Glycine

Yield 90 %; white crystalline powder; melting point.151-152 °C. IR (4000-400cm<sup>-1</sup>): 3400 (OH), 3240 (N-H), 1680 (C=O), 1545, 1474 (aromatic C=C), 1293 (SO<sub>2</sub> Stretch). <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>CN): δ ppm 7.75 (d, J=8 Hz, 2H, Ar. H), 7.40 (d, J=8Hz, 2H, Ar. H), 7.74 (1H, OH), 5.94(s, 1H, NH), 3.74 (s, 2H, CH<sub>2</sub>), 2.36 (s, 3H, Ar.CH<sub>3</sub>). <sup>13</sup>C NMR (CD<sub>3</sub>CN): δ = 169 (C-9), 137 (C-4), 135 (C-1), 128 (C-3, C-5), 125 (C-2, C-6), 47 (C-8), 20.8 (C-7). GCMS, m/z (%): 229 (M<sup>+</sup>), 185, 91 (100), 88.

#### 4-methyl-2-(4-methylphenylsulfonamido) pentanoic acid (N2) Leucine

Yield 88 %; off white solid; melting point.120°C. IR (4000-400cm<sup>-1</sup>): 3380 (OH), 3279 (N-H), 1682 (C=O), 1580, 1474 (aromatic C=C), 1287 (SO<sub>2</sub> Stretch). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ ppm 7.78 (1H, OH), 7.75 (d, J=8 Hz, 2H, Ar. H), 7.40 (d, J=8 Hz, 2H, Ar. H), 5.53 (s, 1H, NH), 2.36 (s, 3H, Ar. CH<sub>3</sub>), 1.78–1.93 (m, 1H, CH), 1.46 (m, 1H, CH), 0.92 (s, 6H, CH<sub>3</sub>). GCMS m/z (%); 285 (M<sup>+</sup>), 229, 184, 157, 140, 106, 91 (100), 86.

#### 2-(4-methylphenylsulfonamido)-3-phenyl propanoic acid (N3) (Phn-ala)

Yield 85 %; off white powder; melting point.139 °C. IR (4000-400cm<sup>-1</sup>): 3461 (OH), 3270 (N-H), 1678 (C=O), 1541, 1461 (aromatic C=C), 1265 (SO<sub>2</sub> stretch). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ ppm 7.68 (d, J=8 Hz, 2H, Ar. H), 7.36 (d, J=8 Hz, 2H, ArH), 7.35 (1H, OH), 7.10- 7.26 (m, Ph) 5.53 (s, 1H, NH), 4.10 (m 1H CH), 3.10,3.00(each dd, 2H), 2.36 (s, 3H, Ar. CH<sub>3</sub>), GCMS, m/z (%): 319 (M<sup>+</sup> 1) 275, 227, 165, 159, 155, 147, 119, 91 (100), 75.

#### 3-hydroxy-2-(4-methylphenylsulfonamido) propanoic acid (N4) Serine

Yield 89 %; colorless crystals; melting point. 225°C. IR (4000-400cm<sup>-1</sup>): 3360 (OH), 3258 (N-H), 1690 (C=O), 1592, 1463 (aromatic C=C), 1206 (SO<sub>2</sub> stretch). <sup>1</sup>H NMR (400 MHz, DMSO<sub>3</sub>) δ ppm 7.78 (s, 1H, OH), 7.50 (d, J=8.2 Hz, 2H, Ar. H), 7.13 (d, J=8.2 Hz, 2H, ArH), 5.10 (1H, NH), 3.76 (m, 2H, CH<sub>2</sub>), 3.58 (s, 1H, OH), 3.17 (s, 1H, CH), 2.28 (s, 3H, CH<sub>3</sub>). GCMS, m/z (%): 260 (M<sup>+</sup>), 215, 156, 91, 61.

#### Zinc (II) complex of N1 (N5) glycine

Yield 85 %; white solid; melting point.215-220 °C. IR (4000-400cm<sup>-1</sup>): 1665 (C=O), 1547, 1477 (aromatic C=C), 1270 (SO<sub>2</sub> stretch), 532 (M-N), 440 (M-O). <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>CN): δ ppm 7.74 (d, J=8 Hz, 4H, Ar. H), 7.40 (d, J=8Hz, 4H, Ar. H), 4.20(s, 2H, CH<sub>2</sub>), 2.36 (s, 3H, Ar.CH<sub>3</sub>). Elemental analysis for C<sub>18</sub>H<sub>18</sub>N<sub>2</sub>O<sub>8</sub>S<sub>2</sub>Zn: Calculated, C (41.50), H (3.89), N (5.51). Found C (41.67), H (3.42), N (5.39).

#### Zinc (II) complex of N2 (N6) lucine

Yield 83 %; colorless solid; melting point.105 °C. IR (4000-400cm<sup>-1</sup>):1670 (C=O), 1545, 1473 (aromatic C=C), 1260 (SO<sub>2</sub> stretch), 538 (M-N), 446 (M-O). <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>CN): δ ppm 7.77 (d, J=8.02 Hz, 4H, Ar. H), 7.40 (d, J=8Hz, 4H, Ar. H), 4.43(s, 2H, CH<sub>2</sub>), 2.44(s, 3H, Ar.CH<sub>3</sub>), 1.78–1.93 (m, 2H, CH), 1.45-1.41 (m, 2H, CH), 0.9 (s, 6H, CH<sub>3</sub>). Elemental analysis for C<sub>26</sub>H<sub>30</sub>N<sub>2</sub>O<sub>8</sub>S<sub>2</sub>Zn: Calculated, C (47.11), H (5.13), N (4.81). Found C (48.02), H (5.46), N (4.27).

#### Zinc (II) complex of N3 (N7) phen-alanine

Yield 73 %; off white solid; melting point. 180°C. IR (4000-400cm<sup>-1</sup>):1672 (C=O), 1535, 1460 (aromatic C=C), 1275 (SO<sub>2</sub> stretch), 533 (M-N), 432 (M-O). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ ppm 7.66 (d, J=8 Hz, 8H, Ar. H), 7.34 (d, J=7.8 Hz, 8H, Ar. H), 7.33-7.31 (m, Ar. H), 3.80-3.78 (m 2H CH) 2.43 (s, 6H, Ar. CH<sub>3</sub>), 2.64 (m 4H CH<sub>2</sub>). Elemental analysis for C<sub>32</sub>H<sub>30</sub>N<sub>2</sub>O<sub>8</sub>S<sub>2</sub>Zn: Calculated, C (54.08), H (4.50), N (4.18). Found C (54.91), H (4.76), N

(4.37).

Zinc (II) complex of N4 (N8) serine

Yield 88 %; white solid; melting point.163-168 °C. IR (4000-400cm<sup>-1</sup>): 3230 (OH), 1668 (C=O), 1585, 1457 (aromatic C=C), 1197 (SO<sub>2</sub> stretch), 542 (M-N), 428 (M-O). <sup>1</sup>H NMR (400 MHz, DMSO<sub>3</sub>) δ ppm 7.50 (d, J=8 Hz, 4H, Ar. H), 7.15 (d, J=8 Hz, 4H, ArH), 3.75-7.72 (m, 4H, CH<sub>2</sub>), 3.61 (s, 2H, OH), 3.22 (s, 2H, CH), 2.27 (s, 6H, CH<sub>3</sub>). Elemental analysis for C<sub>20</sub>H<sub>22</sub>N<sub>2</sub>O<sub>10</sub>S<sub>2</sub>: Calculated, C (41.42), H (3.82), N (4.83). Found C (40.72), H (3.88), N (4.40)

### 2.3. Antibacterial bioassay (in vitro)

Synthesized compounds and their novel coordination complexes (N1-N8) were evaluated for in vitro antibacterial studies against 4 ATCC bacterial strains, including Gram negative bacterial strains Escherichia coli, Salmonella typhi, Pseudomonas putida and Gram positive bacterial strain Staphylococcus aureus using the agar well diffusion method [21-24]. Mueller Hinton Agar (MHA) was used to conduct bioassays using fresh inoculums of these strains which were prepared and diluted with the help of normal saline (sterilized). Using sterilized cotton swabs, a homogenous microbial lawn was prepared. Sterilized metallic borer was used to dig the wells (6mm size) in the inoculated plates.

The sample concentration (1 mg/ml in DMSO) for each sample was used. A broad spectrum antibiotic, ciprofloxacin (1mg/ml), an effective drug against number of Gram negative and Gram positive microbial strains was decided to use as standard. The plates were incubated for a period of 24 hrs at 37 °C. Antimicrobial activity of the N1-N8 was determined by measuring the zone of inhibition. These activities were performed three times and reported as Mean of all the three readings.

## 3. Results and Discussion

The FTIR data confirm the formation of ligands and their Zn (II) complexes. IR spectra were recorded in the range of 4000–400cm<sup>-1</sup> and important bands for the

structural assignments are given in the characteristic vibrational frequencies which have been identified by comparing the spectra of the complexes with their precursors. The presence of sulfonamides assembly of N1-N4 have been confirmed by the presence of sharp and well-built bands of NH at 3300-3240 and Stretching bands of SO<sub>2</sub> were found in the region of 1300-1190 cm<sup>-1</sup>. It is noteworthy here that disappearance of the NH peaks in case of N5-N8 is a further confirmation of complexes, indicating that the sulfonamide has been deprotonated. New peaks appeared in the range of 400-500 and 500-560 which may be assigned to M-O and M–N respectively [25-30].<sup>0</sup> Evaluation of FT-IR spectra for the tosylated amino acids (N1-N4) and their novel Zinc (II) complexes (N5-N8) showed that these sulfa derivatives behave as bidentate ligands leading to the formation of five membered ring system.

The <sup>1</sup>H and <sup>13</sup>CNMR are integrated, new peaks are carefully assigned. Interestingly, diamagnetic Zn (II) complexes signals were having downfield effects due to amplified coordination through amino-N and carboxylate-O of the ligands [31,32]. It is noteworthy here that N7 is comparatively weaker complex and more acidic than N5, due to the presence of phenyl ring. It is also noted that due to the hydrophobic character of the phenyl ring, N7 observed to be less soluble in water. Deuterated solvents (CDCl<sub>3</sub>, CD<sub>3</sub>CN, and DMSO) did not show any binding effect on the spectra of the ligands nor the complexes. The results for elemental analysis of the newly synthesized complexes is well complied and are within acceptable range. As far as the antibacterial screening is concerned the sulfonamide derivatives (N1-N8) have some anti bacterial effect but this effect is almost doubled when zinc is inserted as metal centre. Compound N8 was found to be most active antibacterial agent probably due to the presence of polar OH group. Table 2 represents the inhibitory zone (mm) of N1-N8. Graphical representation of the results is illustrated in Figure 3.

Table 2: Zone of inhibition of N1-N8 measured in mm.

Code	S.t	S.a	E.c	P.p
N1	–	–	15	11
N2	6	8	9	14
N3	–	6	7	17
N4	9	18	15	16
N5	18	20	19	13
N6	15	18	24	17
N7	10	22	25	24
N8	27	18	28	25
DMSO	–	–	–	–
Ciprofloxacin	25	20	25	25

S.t (Salmonella typhi), S.a (Staphylococcus aureus), E.c (Escherichia coli), P.p (Pseudomonas putida), (-)= No activity

#### 4. Conclusion

Tosylated amino acids behave as bidentate ligands which lead to the formation of relatively stable metal complexes. Newly synthesized Zinc complexes of sulfonamide derivatives were observed to be more active against bacterial strains than their parent ligands. We investigated the much enhanced activity of N8, probably due to the presence of more binding sites which ultimately leads to increased drug receptor interaction.

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