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Synthesis, Characterization, Antibacterial Activity of New Antimony III Complexes of Some Tosyl-Sulfonamide Derivatives

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Abstract: Present work describes the synthesis of novel coordination complexes of Cl_3Sb III, have been synthesized from 4-methyl-sulfonamido derivatives in good yields. These sulfonamide derivatives were synthesized by reaction of tosyl chloride with L-amino acids. These compounds and their complexes are characterized by IR, ^{1}HNMR, ^{13}CNMR, MS, Elemental analysis and x ray crystallography. Interestingly, out of all complexes N6 has shown the enhanced antibacterial activity in comparison with standard drug Amoxicillin.

Key words: Sulfonamide derivatives · Antibacterial · P-toluene sulfonylchloride · Metal chloride

INTRODUCTION

Amino acids being the important part of life and are the most biologically active organic molecules. It is well known that the complexes of amino acids with transition metal ions are very charming concerning biological assays. To minimize the unwanted effects transition metal complexes with amino acids are being widely used as different models to study the pharmacodynomic and pharmacokinetics. Some of the vital role for myocardial function and endurance during ischemia / reperfusion stress for example, glutamic acid and aspartic acid [1-3] additionally, metal complexes of some amino acids from D- or L- isomers of lysine, proline, histidine, tryptophan and arginine have won greater importance to treat malaria, diabetes and serve as an important co-enzyme in reversible oxidation-reduction systems as well [4-7].

The Cu (II) complexes with glucoronic acid have been shown to possess anti-inflammatory, antiviral activities while Mn (II) complexes with amino acids have been used to treat various anemia, allergies and heart diseases [8-13]. The organometallic compounds containing antimony as metallic centre has proved its major use against the leshminial protozoan for many decades [14-15]. Antimony (III) complexes have gained special interest since 1990, as potential antineoplastic agents, for the first time when Silvestru *et al.* reported anti-tumor activity of Sb(III) complexes [16]. Recently our group has reported Zn II metal complexes with some interesting antimicrobial evaluation of sulfonamides derivatives, with p-toluene sulfonyl chloride and amino acids as precursors [17]. Our long standing interest in amino acids, tosyles and their Zn II complexes has encouraged us to incorporate Cl_3Sb III metal in the complex form. In the present study novel Cl_3Sb (III) complexes of tosylated amino acids derivatives has been synthesized, characterized and also investigated for their antibacterial activity.

RESULTS AND DISCUSSION

The IR spectra have shown the a strong and well build band in the region 3403-3360 confirming the presence of (OH) and (NH) groups in the synthesized compounds (A1-A5) respectively. The data also confirms the synthesis of Sb (III) complexes. In case of A10, the synthesis of this compound was confirmed by the absence of well build band of (OH), which may be due to the deprotonation of carboxyl (OH) group, showing tetra coordinated Sb III complex (A10). The spectra were recorded in the range of 4000–400cm^{-1} 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. In synthesized compounds (A6-A9), the shifting of well build, sharp band of NH at 3300-3240 confirms the presence of metal group. Stretching bands of

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Table 1: Zone of inhibition of A1-A10 (measured in mm).

Code	E.C	P.P	S.T	S.A
A1	10	11	17	19
A2	6	8	9	14
A3	-	6	7	15
A4	12	8	14	-
A5	14	13	17	12
A6	21	24	24	28
A7	15	20	21	20
A8	21	18	20	22
A9	8	11	21	18
A10	11	17	24	24
DMSO	-	-	-	-
Amoxicillin	25	20	25	25

E.C (Escherichia coli), P.P (Pseudomonas putida), S.T (Salmonella typhi), S.A (Staphylococcus aureus), (-) = No activity

SO_2 were found in the region of 1300-1190 cm^{-1}, in case of ligands, while in case complexes (A6-A10), these peaks were shifted towards the lower frequency by 8-30 cm^{-1}, which was clear evidence that the complexes have been synthesized efficiently (A6-A10). IR spectra of ligands as well as complexes (A1-A10) was compared, assigned carefully all the peaks which confirms the formation of complexes.

^{1}H NMR spectrum confirms the formation of compounds (A6-A10). The confirmation of the synthesized compounds is further evidenced by the presence of a singlet at δ 4.91 ppm for –NH proton which clearly indicates that (NH) is not deprotonated (A6-A9), while in case of A6, the carboxyl proton was not observed in the region δ 7.42 which was observed in case of A5, indicating that it is deprotonated and the complex (A6) is formed. All the aromatic protons showed signals in the range between δ 7.78-7.41 ppm in case of compounds (A1-A5) which were shifted to δ 7.68-7.38 in case of complexes (A6-A10). It is noteworthy adding here that all the remaining signals in ^{1}H NMR spectrum also agreed with in the acceptable range and is given in detail in the experimental section.

^{13}C NMR of compound is already given in detail in the experimental section which agrees with the formation of complex (A6-A10). 13C NMR shows shifting of (C10) e.g. (COO) carbon in the range of δ 164-169 in compounds (A6-A10) from δ 176-172 in case of ligands, showing the complex formation (A6-A10). These shifting are further evidence of the complex formation [18]. The results for elemental analysis of the newly synthesized complexes is well complied and are within acceptable range. The elemental analysis data is given in the experimental section in detail. Sulfonamides family may have some anti bacterial effect but this effect is almost doubled when Sb III metal is inserted as metal centre. X ray crystal structure of compound (A1) is given in Fig. 1. Table 1 represents the inhibitory zone (mm) of A1-A10. Graphical representation of the results is illustrated in Figure 2.

Synthesis of Ligands (A1-A5)

3-hydroxy-2-(4-methylphenylsulfonamido) Propanoic Acid (A1) Serine: Yield 89 %; colorless crystals; melting point. 225°C. IR (4000-400cm^{-1}): 3360 (OH), 3258 (N-H), 1690 (C=O), 1592, 1463 (aromatic C=C), 1206 (SO_2 stretch). 1H NMR (400 MHz, $DMSO_3$) 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, CH2), 3.58 (s, 1H, OH), 3.17 (s, 1H, CH), 2.28 (s, 3H, CH3). GCMS, m/z (%): 260 (M^+), 215, 156, 91, 61: Elemental analysis: $C_{10}H_{13}NO_5S$; Calculated (%); C, 46.32, H, 5.05, N, 5.40; Found (%); C, 46.33, H, 5.06, N, 5.41.

***3-methyl-2-(4-methylphenylsulfonamido) butanoic acid (A2valine)*:** Yield 93 %; white crystalline solid; melting point.148°C. IR (4000-400cm^{-1}): 3473 (OH), 3286 (N-H), 1682 (C=O), 1597, 1463 (aromatic C=C), 1329 (SO_2 Stretch). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm, 7.75-7.73 (d, J=8 Hz, 2H, Ar. H), 7.31-7.29 (d, J=8 Hz, 2H, Ar. H), 7.28 (s. 1H, OH), 5.07-5.04 (d, 1H, J=12 Hz, NH), 3.84-3.81 (m, J=8 Hz,1H, CH), 2.43 (s, 3H, Ar. CH3), 2.14–2.11 (m, J=4 Hz, 1H, CHCH), 1.00- 0.98 (d, J=8 Hz, 3H, CH3), 0.90-0.89 (d, J=4 Hz, 3H, CH3). ^{13}C NMR (CD_3CN): δ = 174.35 (C-12), 167.72 (C-1), 143.50 (C-4), 126.30 (C-3, C-5), 125.60 (C-2, C-6), 60.06 (C-8), 31.17 (C-7), 21.20 (C-9), 18.64 (C-10), 16.75 (C-11) GCMS m/z (%); Major peak, 271 (M^+). Elemental analysis: $C_{12}H_{17}NO4S$; Calculated (%); C 53.12, N 5.16, H 6.32, Found (%); C, 53.30, N, 5.10, H 5.89.

***Synthesis of 3-methyl-2-(4-methylphenylsulfonamido) pentanoic acid (A3IsoLeucine)*:** Yield 88 %; off white crystalline powder; melting point.135°C. IR (4000-400cm^{-1}): 3386 (OH), 3288 (N-H), 1680 (C=O), 1580, 1466 (aromatic C=C), 1280 (SO_2 Stretch). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.80 (1H, OH), 7.76 (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. CH3), 1.94-1.80 (m, 1H,J=16 Hz, CH), 1.35 (d, J=8 Hz, 3H, CH3), 0.92 (d, J=4 Hz, 3H, CH3). GCMS m/z (%); 285 (M^+), 229, 184, 157, 140, 106, 91 (100), 86. Elemental analysis: $C_{13}H_{19}NO_4S$; Calculated (%); C 54.72, N 4.91, H 4.91, Found (%); C 57.30, N, 4.20, H, 5.23.

Synthesis of 3-(4-hydroxyphenyl)-2-(4-methylphenylsulfonamido) propanoic acid (A4tyrosine) Yield 80 %; white powder; melting point. 165-168°C. IR (4000-400cm^{-1}): 3470 (OH), 3280 (N-H), 1672 (C=O), 1551, 1455 (aromatic C=C), 1275 (SO_2 stretch).

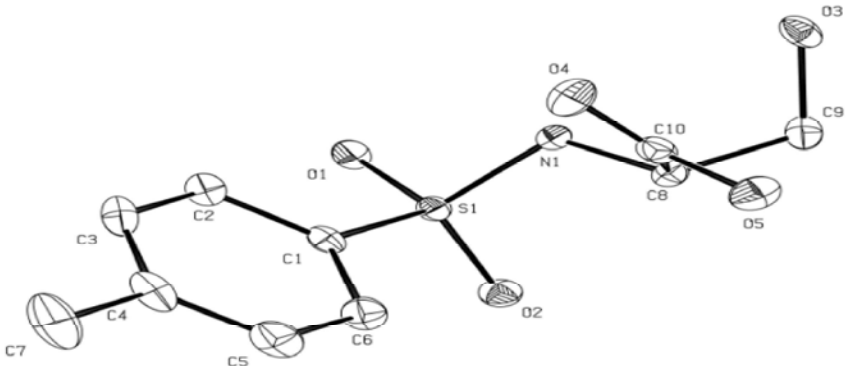

Fig. 1: ORTEP diagrams for compounds A1. Thermal ellipsoids are shown at the 50% probability level. Hydrogen atoms are omitted for clarity

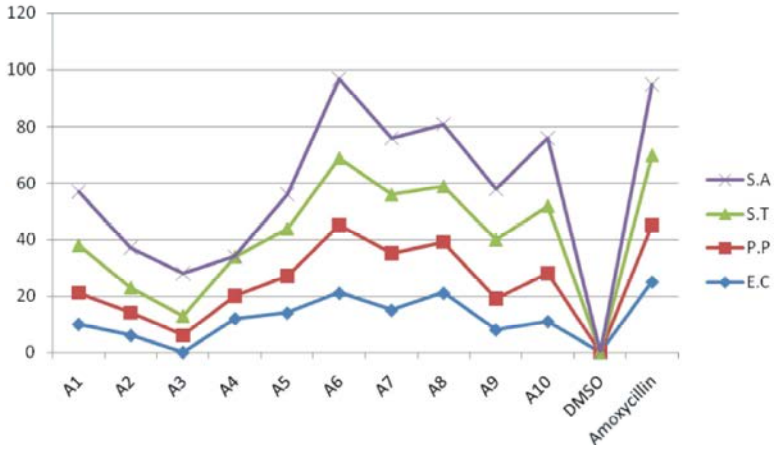

Fig. 2: Graph representing the antibacterial effect of ligands and their complexes (A1-A10)

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.76 (d, J=8.2 Hz, 2H, Ar. H), 7.72 (d, J=8.2 Hz, 2H, 'ArH), 7.46 (d, J=8 Hz, 3H, Ar. H), 7.12 (d, J=8.2. Hz, 2H, 'ArH),5.30 (1H, OH, Ar-OH), 5.53 (s, 1H, NH), 3.90 (m, J=4 Hz, 1H CHCH2), 3.14,3.12(each dd, J=8 Hz, 2H, CH2-Ph), 2.36 (s, 3H, Ar. CH3), GCMS, m/z (%): 336 (M^+1) 275, 227, 165, 159, 155, 147, 119, 91 (100), 75. Elemental analysis: $C_{16}H_{17}NO_5S$; Calculated (%); C 57.30, N 4.17, H 5.11, Found (%); C 57.10, N 4.19, H 5.19.

***Synthesis of 2-(4-methylphenylsulfonamido) propanoic acid (A5Alanine)*:** Yield 91 %; off white crystalline powder; melting point. 130°C. IR (4000-400cm^{-1}): 3415 (OH), 3242 (N-H), 1669 (C=O), 1535, 1464 (aromatic C=C), 1299 (SO_2 Stretch). ^{1}H NMR (400 MHz, CD3CN): δ ppm 7.75 (d, J=8 Hz, 2H, Ar. H), 7.42 (d, J=8Hz, 2H, Ar. H), 7.41 (1H, OH), 5.94 (s, 1H, NH), 3.60 (d, J=5.2 1H, CH), 2.36 (s, 3H, Ar.CH3), 1.38 (d, J=12, 3H, CHCH3). ^{13}C NMR (CD_3CN): δ = 173.95 (C-10), 143.50 (C-1), 135.85(C-4), 128.29 (C-3, C-5), 125.19 (C-2, C-6), 51.98 (C-8), 20.71 (C-7), 18.64 (C-9), Elemental analysis: $C_{10}H_{13}NO_4S$; Calculated (%); C 49.20, N, 5.39, H 7.90, Found (%); C 49.12, N 5.59, H 7.61, GCMS, m/z (%): 243 (M^+).

Synthesis of Cl_3Sb (III) Complex: (A6-A10)

***Synthesis of Sb (III) complex of 3-hydroxy-2-(4-methylphenylsulfonamido) propanoic acid (A6serine)*:** Yield 81 %; colorless needle like crystalline powder; melting point. 240-243°C. IR (4000-400cm^{-1}): 3395 (O-H), 3265 (N-H), 1691 (C=O), 1582, 1459 (aromatic C=C), 1223 (SO_2 stretch). 1H NMR (400 MHz, $DMSO_3$) δ ppm 7.64 (d, J=8 Hz, 2H, ArH), 7.28 (d, J=8 Hz, 2H, ArH), 4.98 (1H, NH), 3.24 (m, 2H, CH2), 3.51 (s, 1H, OH), 3.10 (t, J=8, 1H, CHCH2), 2.41 (s, 3H, ArCH3). Elemental analysis: $C_{10}H_{13}Cl_3NO_5SSb$; Calculated (%); C, 24.64, N, 2.87, H, 2.69, Found (%);C, 24.80, N, 2.46, H, 3.13. GCMS, m/z (%): 488 (M^+) Major Peak.

***Synthesis of Sb (III) metal complex of 3-methyl-2-(4-methylphenylsulfonamido) butanoic acid (A7valine)*:** Yield 86 %; light brown crystalline solid; melting point. 221-224°C. IR (4000-400cm^{-1}): 3380 (O-H), 3266 (N-H), 1702

(C=O), 1548, 1463 (aromatic C=C), 1286 (SO_2 Stretch). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.66 (d, J=8 Hz, 3H, Ar-H, OH), 7.40 (d, J=8 Hz, 2H, Ar- H), 4.96 (s, 1H, NH), 3.22 (dd, J=8 Hz,1H, CH), 2.10–2.08 (m, 1H,J=8, CH), 2.41 (s, 3H, Ar- CH3), 0.92 (d, J=6.8 Hz, 6H, CH3). ^{13}C NMR (CD_3CN): δ = 169.90 (C-12), 168.55 (C-10), 143.22 (C-1), 129.42 (C-4), 127.32 (C-3, C-5), 128.54 (C-2, C-6), 61.10 (C-8), 32.24 (C-7), 21.19 (C-9), 19.18 (C-11). Elemental analysis: $C_{12}H_{17}Cl_3NO_4SSb$; Calculated (%); C, 28.86, N, 2.80, H, 3.43, Found (%);C, 28.99, N, 3.10, H, 2.80. GCMS, m/z (%): 498 (M^+) Major Peak. $C_{24}H_{34}N_2Cl_2O_8S_2Zn$; Calculated (%); C, 42.46, N, 4.13, H, 5.05, Found (%);C, 42.06, N, 4.83, H, 4.12.

***Synthesis of Sb (III) metal complex of 3-methyl-2-(4-methylphenylsulfonamido) pentanoic acid (A8)*:** Yield 76 %; off white block shape crystalline powder; melting point. 124-130°C. IR (4000-400cm^{-1}): 3376 (O-H), 3329 (N-H), 1670 (C=O), 1597, 1454 (aromatic C=C), 1289 (SO_2 Stretch). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.66 (d, J=8 Hz, 3H, Ar. H), 7.39 (d, J=8 Hz, 2H, Ar. H), 5.01 (s, 1H, NH), 2.41 (s, 3H, Ar. CH3), 1.68–1.64 (m, J=8, 1H, CH), 0.90 (s, 6H, CH3). Elemental analysis: $C_{13}H_{19}Cl_3NO_4SSb$; Calculated (%); C, 30.41, N, 2.73, H, 3.73, Found (%);C, 30.11, N, 2.43, H, 3.89. GCMS, m/z (%): 513 (M^+) Major Peak.

***Synthesis of Sb (III) metal complex of 3-(4-hydroxyphenyl)-2-(4-methylphenylsulfonamido) propanoic acid (A9)*:** Yield 71 %; colorless crystalline powder; melting point.190-193 °C. IR (4000-400cm^{-1}): 3403 (0-H), 3277 (N-H), 1549 (C=O), 1514, 1472 (aromatic C=C), 1225 (SO_2 stretch). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.64 (d, J=8 Hz, 3H, Ar. H), 7.29 (d, J=8 Hz, 4H, 'ArH), 7.12-7.10 (dd, J=8.2 Hz, 6H, Ar. H), 7.09 (d, J=8. Hz, 2H, 'ArH), 4.97 (s, 1H, NH), 3.80 (m, 2H, CH), 3.20 (each dd, 4H, CHCH2), 2.41 (s, 3H, Ar-CH3): Elemental analysis: $C_{16}H_{17}Cl_3NO_5SSb$; Calculated (%); C, 34.10, N, 2.49, H, 3.04, Found (%); C, 33.92, N, 2.21, H, 3.26. GCMS, m/z (%): 564 (M^+) Major Peak.

***Synthesis of Sb (III) metal complex of 2-(4-methylphenylsulfonamido) propanoic acid (A10Alanine)*:** Yield 75 %; light grey colorless crystalline powder; melting point.180-183°C. IR (4000-400cm^{-1}): 32320 (N-H), 1656 (C=O), 1596, 1467 (aromatic C=C), 1303 (SO_2 Stretch). ^{1}H NMR (400 MHz, CD3N): δ ppm 7.74 (d, J=8 Hz, 2H, Ar. H), 7.41 (d, J=8Hz, 2H, Ar. H), 4.91 (s, 1H, NH), 3.62 (d, J=8 1H, CH), 2.36 (s, 3H, Ar.CH3), 1.37 (q, J=4.2, 3H, CHCH3). ^{13}C NMR (CD_3CN): δ = 167.89 (C-10), 138.65 (C-4,), 135.19 (C-1), 129.71 (C-3, C-5), 125.29 (C-2, C-6), 47.51 (C-8), 21.83 (C-7), 18.2 (C-9). Elemental analysis: $C_{13}H_{18}ClN_2O_5SSb$; Calculated (%); C, 28.78, N, 5.16, H, 3.34, Found (%);C, 29.08, N, 4.56, H, 4.14, GCMS, m/z (%): Major peak, 542(M^+).

Antibacterial Bioassay (*In vitro*): Synthesized ligands (A1-A5) and their novel coordination complexes (A6-A10) were investigated for in vitro antibacterial evaluation against 4 bacterial strains, including Gram positive bacterial strain Staphylococcus aureus and Gram negative bacterial strains Escherichia coli, Salmonella typhi, Pseudomonas putida, using agar well diffusion method [18-21]. 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). With the help of 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, amoxicillin (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 A1-A10, was determined by measuring the zone of inhibition. These activities were performed three times and reported as Mean of all the three readings.

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 cm^{-1}), ^{1}H NMR and ^{13}CNMR spectra were determined on Bruker AV400RG spectrophotometer using $CDCl_3$, CD_3CN and DMSO as internal solvents. Elemental analysis was done on a LECO- 183 CHNS analyzer. Mass spectra recorded by Bruker GCMS.

General Procedure for the Synthesis of Ligands (A1-A5): Synthesis of Ligands is done by following the method described in literature with some modifications [22, 23, 27] L- Amino acid (1eq, 2mmol,) and potassium carbonate (1mmol, 0.5eq) were dissolved in 15 ml of distilled water along with continuous stirring. A solution of p-toluene sulfonyl chloride (2.02mmol, 1.01eq) in (7 ml)

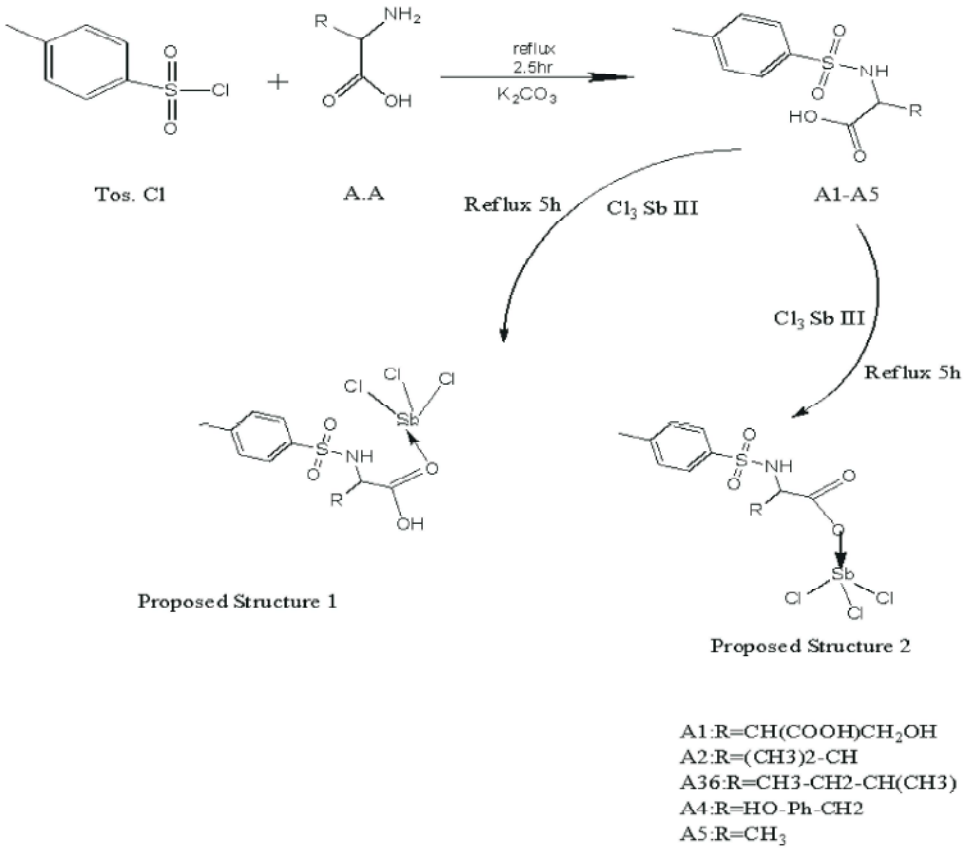

Fig. 3: Synthesis of Ligands and their Complexes

of distilled 1, 4 dioxane was further added to the previous mixture. Resultant mixture was refluxed for 2.5 hrs and then cooled to room temperature. With the help of 2N hydrochloric acid pH of the solution was adjusted at 1-2. Precipitates started to grow in 48-72 hours, which were filtered, washed with the help of distilled water and recrystallized from ethanol: water (2:0.5) by slow evaporation. All the ligands were obtained using the general procedure.

General Procedure for the Synthesis of Cl_3Sb III Complexes (A6-A10): 2mmol (1 eq) of ligand (A1-A5) was dissolved in 10 ml of dry methanol, 2.08 mmol (1.04 eq) of Cl_3Sb chloride was dissolved in 10 ml of methanol. A solution of antimony III chloride in acetone 10 ml was slowly added with constant stirring. The reaction mixture was refluxed for 5 hr at 50°C. The reaction mixture was cooled to room temperature. The precipitates obtained after 5-12 h were filtered washed with cold ethanol and recrystallized in ethanol-hexane (1:1) mixture and dried under slow evaporation [24]. The synthesis of ligands and their complexes is given in Figure 3.

CONCLUSION

Antimony III Chloride complexes with some sulfonamides enhances the antibacterial activity. They formed the relatively stable tetra coordinate complexes in the ligand to metal ration of 1:1. Newly synthesized Cl_3SbIII metal complexes of sulfonamide derivatives were observed to be more active against bacterial strains then their parent ligands. We further investigated the more improved activity of A6, which may be due to the presence of more binding sites, ultimately leads to increased drug receptor interaction.

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Supporting Information: Complete details of the X-ray analyses for compound (A1) have also been deposited at

the Cambridge Crystallographic Data Centre (CCDC) and can be retrieved with the following reference number: 948810.These data can be obtained free of charge via www.ccdc.cam.ac.uk/ data_request/cif, by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, U.K. (fax: +44 1223 336033).

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