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Artigo

SYNTHESIS AND BIOLOGICAL ACTIVITY OF NEW SERIES OF ORGANOTIN(IV) ESTERS WITH N,N-DIACETYLGLYCINE

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A bioactive N,N-diacetylglycine (NNDAG) and new organotin(IV) complexes (OTCs) (**1-7**) were synthesized. Spectroscopic techniques were employed to characterize NNDAG and OTCs. FTIR was employed to verify N,N protection of glycine by acetyl groups. The disappearance of υ(OH) at 3000-2600 cm^{-1} showed de-protonation of free ligand. The Δυ 150<200 cm^{-1} of OTCs **4**-**7** verified bidentate coordination with tetrahedral geometry. The Δυ of OTCs **1** and **3** was <200 cm^{-1} exhibiting *trans*-octahedral geometry while OTC **2** dimer was assigned a unique sinusoidal view. The ^{1}H NMR spectra of OTCs verified their synthesis by de-protonation of NNDAG and no chemical shift was found downfield for carboxylic acid proton. The ^{13}C, ^{119}Sn NMR and Mass spectrometric data also supported FTIR and ^{1}H NMR descriptions. The OTCs **4**, **5**, **6** and **7** (500 ppm) proved twice as active against *Escherichia coli* as the standard antibiotic enoxacin (1000 ppm). The promising property of the OTCs (**4**, **5**, **6** and **7**) is clearly due to their tetrahedral. The OTCs **4** and **5** exhibited excellent activity against *M. minimum* and good activity against *T. castaneum.* LD_{50} of all the compounds were determined and OTCs **4**, **5** and **7** were found to be active.

Keywords: N,N-diethylglycine; organotin(IV); complexes; antibacterial; insecticide.

INTRODUCTION

Organotin(IV) complexes (OTCs) have been investigated on account of broad spectrum of their uses in daily field of life. Particularly, organotin(IV) esters have been given importance on account of their applications in the fields of pesticide, antibacterial, and antitumor agents, wood preservatives, among others.[1-4]

On the other hand, amino acids and their derivatives show antioxidant activity and enhanced hormonal immunity which inhibits lactic acid level. Interestingly, glycine acts as antioxidant as well as improves hormonal immune system. Therefore, ligand N,N-diacetylglycine has been synthesized on the basis of potential of glycine described in the literature.[3-5]

The organotin(IV) esters have been given special attention in the recent years due to their excellent pharmacological importance.[5,6] Moreover, organotin esters of amino acids and N-protected amino acids have been reported as biocides for example, tricyclohexyltin(IV) alaninate is used as fungicide and bactericide and trialkyltin(IV) derivatives of both amino acids and N-acetylamino acids play as intermediate role for the synthesis of peptides.[7-9] In the last two decades very little literature is found on the organotin(IV) esters of N-protected amino acids.[10-14] On account of broad spectrum of applications of organotin(IV) carboxylates as well N-protected amino acids and interesting finding of our earlier research work here we report the spectroscopic characterization, and preliminary biological investigation of OTCs of N,N-diacetylglycine.[15-17] The toxicity bioassays were also studied in addition to antibacterial and insecticidal bioassays of all **1-7** OTCs against Escherichia coli, *Pseudomonas aeruginosa, Klebsiella pneumonia* and *Salmonella typhi* strains with clinical interest and *Monomorium minimum*, *mealybug* and *tribolium castaneum* pests insects, respectively.[18]

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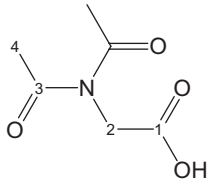
EXPERIMENTAL

Materials and instruments

Glycine, di-n-butyltin(IV) oxide, triphenyltin(IV) chloride, tricyclohexyltin(IV) chloride and triethylamine of Merck Chemicals were used as such. The di- and tri-benzyltin(IV) chloride were prepared according to reported procedure.[19] All organic solvents were dried as per reported procedures.[20] The FTIR spectra were carried out on a JASCO 302-ghgA spectrometer by KBr sampling technique from 4000-400 cm^{-1}. Finnigan MAT 12 spectrometer was used to record EI-MS spectra for the determination of % m/z. Bruker AM 400 NMR was used to record ^{1}H, ^{13}C and ^{119}Sn spectra at HEJ Institute of Chemical Sciences, University of Karachi. The chemical shifts were reported relative to $(CH_3)_4Si$ and $(CH_3)_4Sn$ signal used as internal standards. Enoxacin as reference drug was used to determine antibacterial activity using disc diffusion method. Half maximal lethal dose (LD_{50}) of compounds was determined by Brine Shrimp hatching method as reported.[21]

Synthesis of N,N-diacetylglycine (NNDAG)

Glycine 5 g (66.7 mmol) and acetyl chloride 10.0 mL (133.4 mmol) were added in 100.0 mL dioxane and refluxed for 6 hours of reaction time. The solvent was removed under vacuum and the product was obtained in *n*-hexane (Scheme **1**).[22]



Scheme 1. *Structure of N, N-diacetylglycine (NNDAG)*

Yield: 60%, m.p.: 220 °C, Solubility: H_2O, CH_3OH, CH_3CH_2OH, and $CHCl_3$. CHN analysis (%) antipyrene: C, 45.2 (45.2); H, 5.7 (5.7) and N, 8.7 (8.8), theoretical values are given in the parenthesis. FTIR (KBr) cm^{-1}: OH: 3000-2600 b; CO (acetyl): 1770 mw; CO (carbonyl): $1730_{asym,}$sp, 1610_{sym} msp; C-O (ether linkage): 1080 sp. ^{1}H NMR ($CDCl_3$) δ: OH: 9.7 s; H-2: 3.90 s; H-3: 2.35 s. ^{13}C NMR ($CDCl_3$) δ: C-1: 169.22; C-2: 42.45; C-3: 171.90; C-4: 21.68. MS m/z: $[HO_2CCH_2N(COCH_3)_2]^+$ M^+ 159 (10%); $[OCCH_2N(COCH_3)_2]^+$ 142 (15%); $[CH_2N(COCH_3)_2]^+$ 114 (100%); $[CH_2N$- $(COCH_3)]^+$ 71 (27%); $[CH_2NCH_3)]^+$ 56 (38%); $[CH_2N]^+$28 (45%).

Synthesis of organotin(IV) complexes

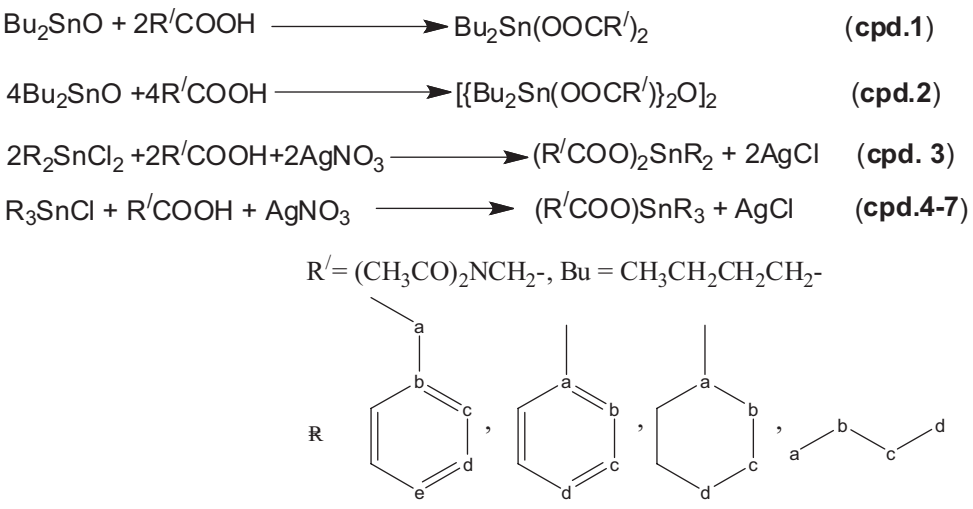
Diorganotin(IV) complexes (**1** and **2**) have been synthesized by taking dibutyltin(1V) oxide and N,N-diacetylglycine in 2:1 (monomer) and 1:l (dimer) molar ratios in ethanol and toluene (3:1, v/v) with the azeotropical removal of water. The appropriate molar ratio (2:1/1:1) of silver salt of NNDAG and the corresponding organotin(IV) chloride were refluxed for 6 h in chloroform to synthesized compounds **3-7**. The solvent were removed under vacuum. The synthesized compounds were recrystallized in different solvents. OTCs have been synthesized by adopting the procedures as cited in literature and given in Scheme **2.**[2,15-17,23]

The compounds are soluble in organic solvents and stable on room temperature. The analytical data is accordance to the proposed stoichiometric ratio of complexes.

Dibutyltin(IV)-di-N,N-diacetylglycine(monomer) (**1**): $[(C_4H_9)_2Sn\{O_2CCH_2N(COCH_3)_2\}$: N,N-diacetylglycine 1 g (6.29 mmol) was reacted with dibutyltin(IV) oxide 0.47 g (3.14 mmol) in 2:1 ratio in 66.0 mL ethanol and 33.0 mL toluene. Recrystallized in chloroform and ethanol in 1:2 ratio. Yield: 78%. m.p.: 202-204 °C. Solubility: CH_3OH, CH_3CH_2OH, $CHCl_3$ and CCl_4. CHN analysis (%) antipyrene: C, 43.7 (43.7); H, 6.2 (6.2) and N, 5.8 (5.10), theoretical values are given in the parenthesis. FTIR (KBr) υ(cm^{-1}): CO(acetyl): 1765 mw; CO (carbonyl): $1620_{asym,}$sp, 1470_{sym} msp; Δυ:150; C-O(ether linkage): 1025 sp; Sn–C: 517 w; Sn–O: 498 sp. ^{1}H NMR ($CDCl_3$) δ: H-2: 3.82 s; H-4: 2.35 s; H-a: 1.04 t (7); H-b: 1.59 m; H-c: 1.26 m; H-d: 0.90 t (7). ^{13}C NMR ($CDCl_3$) δ: C-1: 172.73; C-2: 40.10; C-3: 168.50; C-4: 21.78; C-a: 23.50; C-b: 27.13; C-c: 26.48; C-d: 13.55. ^{119}Sn NMR $(CH_3)_4Sn$:-190.35. MS m/z: $[(C_4H_9)_2Sn\{O_2CCH_2N(CH_3CO)_2\}_2]^+$ M^+ 548 (4%); $[(C_4H_9)Sn\{O_2CCH_2N(CH_3CO)_2\}_2]^+$ 491 (53%); $[(C_4H_9)_2Sn\{O_2CCH_2N(CH_3CO)_2\}]^+$ 390 (100%); $[(C_4H_9)_2Sn\{CH_2N(CH_3CO)_2\}]^+$ 346 (37%); $[Sn\{O_2C$-$CH_2N(CH_3CO)_2\}_2]^+$ 400 (21%); $[Sn\{CH_2N(CH_3CO)_2\}_2]^+$ 312 (27%); $[(C_4H_9)_2Sn]^+$232 (15%); $[(C_4H_9)Sn]^+$ 175 (30%); [Sn/SnH]$^+$ 119/120 (5%); $[CH_3CH_2$- $CH_2]^+$ 43 (55%); $[CH_3CH_2]^+$ 29 (33%); $[CH_3]^+$ 15 (14%).

Dibutyltin(IV)-di-stannoxane-di-N-acetylglycine (dimer) (**2**): $[\{(C_4H_9)_2SnO_2$- $CCH_2N(COCH_3)_2\}_2O]_2$: N,N-diacetylglycine1 g (6.29 mmol) was reacted with dibutyltin(IV) oxide 0.94 g (6.29 mmol) in 2:1 ratio in 66.0 mL ethanol and 33.0 mL toluene. Recrystallized in chloroform and n-hexane in 1:2 ratio. Yield: 72%. m.p.: 220 °C. Solubility: CH_3OH, CH_3CH_2OH, $CHCl_3$ and CCl_4. CHN analysis (%) antipyrene: C, 41.3 (41.3); H, 6.4 (6.4) and N, 3.4 (3.4). FTIR (KBr) υ(cm^{-1}): CO (acetyl): 1755 w; CO (carbonyl): $1608_{asym,}$sp, 1455_{sym} msp; υΔ: 143; C-O(ether linkage): 1018 sp; Sn–C: 522 m; Sn–O: 490 sp. ^{1}H NMR ($CDCl_3$) δ: H-2: 4.00 s; H-4: 2.36 s; H-a: 1.91 t (7); H-b: 1.61 m; H-c: 1.27 m; H-d: 0.94 t (7). ^{13}C NMR ($CDCl_3$) δ: C-1: 173.73; C-2: 41.19; C-3: 170.44; C-4: 22.51; C-a: 29.50; C-b: 27.59; C-c: 26.63; C-d: 14.10. ^{119}Sn NMR $(CH_3)_4Sn$: -210.4, -216.2. MS m/z: $[\{(C_4H_9)_2SnO_2CCH_2N(CH_3CO)_2\}_2$ $O]_2^+$ M^+; $[(C_4H_9)_2SnO_2CCH_2N(CH_3CO)_2]^+$ 390 (58%); $[(C_4H_9)_2SnCH_2N(CH_3CO)_2]^+$346 (38%); $[(C_4H_9)$ $SnO_2CCH_2N(CH_3CO)_2]^+$ 333(16%); $[SnO_2CCH_2N(CH_3CO)_2]^+$ 276 (34%); $[SnCH_2N(CH_3CO)_2]^+$ 232 (45%); $[(C_4H_9)_2Sn]^+$ 229 (100%); [Sn/SnH]$^+$ 119/120 (13%); $[CH_3CH_2CH_2]^+$ 43 (70%); $[CH_3CH_2]^+$ 29(27%); $[CH_3]^+$ 15 (42%).

Dibenzyltin(IV)-di-N,N-diacetylglycine (**3**): $[(C_6H_5CH_2)_2Sn\{O_2C$ $CH_2N(COCH_3)_2\}_2]$: N,N-diacetylglycine 1 g (6.29 mmol) and $AgNO_3$ 1.06 g (6.29 mmol) were reacted with dibenzyltin(IV) chloride 1.16 g (3.14 mmol) in 2:1 ratio in 100.0 mL chloroform. Recrystallized in chloroform and benzene in 1:2 ratio. Yield: 79%. m.p.: 166 °C. Solubility: DMSO, CH_3OH, CH_3CH_2OH, $CHCl_3$ and CCl_4. CHN analysis (%) antipyrene: C, 50.5 (50.5); H, 4.9 (4.9) and N, 4.5 (4.5). FTIR (KBr) υ(cm^{-1}): CO (acetyl): 1760 m sp; CO (carbonyl): $1635_{asym,}$sp, 1462_{sym} msp; Δυ: 173; C-O (ether linkage): 1032 m;Sn–C: 515 m; Sn–O: 505 w. ^{1}H NMR ($CDCl_3$) δ: H-2: 3.80 s; H-4: 2.10 s; H-a: 2.87 s; H-c: 7.05 t (7); H-d: 7.37 m; H-e: 7.80 t (7). ^{13}C NMR ($CDCl_3$) δ C-1: 171.34; C-2: 39.23; C-3: 169.89; C-4: 21.62; C-a: 20.14; C-b: 136.19; C-c: 127.60; C-d: 130.34; C-e: 125.53. ^{119}Sn NMR $(CH_3)_4Sn$: -127.5. MS m/z (%): $[(C_6H_5CH_2)_2Sn\{(O_2CCH_2N(CH_3CO)_2\}_2]^+$ M^+ 616 (7%); $[(C_6H_5CH_2)Sn\{O_2CCH_2N(CH_3CO)_2\}_2]^+$ 525 (77%); $[(C_6H_5CH_2)_2Sn\{O_2CCH_2N(CH_3$- $CO)_2\}]^+$458 (100%);



Scheme 2. *Synthesis of organotin(IV) complexes*

$[Sn\{O_2CCH_2N(CH_3CO)_2\}_2]^+$ 434 (10%); $[(C_6H_5CH_2)_2Sn\{CH_2N(CH_3CO)_2\}]^+$ 414 (57%); $[Sn\{CH_2N(CH_3CO)_2\}_2]^+$ 346 (41%); $[(C_6H_5CH_2)_2Sn]^+$ 300 (15%); $[(C_6H_5CH_2)Sn]^+$ 209 (55%); [Sn/SnH]$^+$ 119/120 (10%); $[C_6H_5CH_2]^+$ 91 (48%); $[C_6H_5]^+$ 77 (18%).

Tribenzyltin(IV)-N,N-diacetylglycine (**4**): $[(C_6H_5CH_2)_3SnO_2CCH_2N(COCH_3)_2]$: N,N-diacetylglycine 1 g (6.29 mmol) and $AgNO_3$ 1.06 g (6.29 mmol) were reacted with tribenzyltin(IV) chloride 2.64 g (6.29 mmol) in 1:1 ratio in 100.0 mL chloroform. Recrystallized in chloroform and ethanol in 1:2 ratio. Yield: 82%. m.p.: 191 °C. Solubility: $(C_2H_5)_2O$, CH_3CH_2OH and $CHCl_3$. CHN analysis (%) antipyrene: C, 58.9 (58.9); H, 5.3 (5.3) and N, 2.5 (2.5) the calculated values are in the parenthesis. FTIR (KBr) υ(cm^{-1}): CO (acetyl): 1753 m w; CO (carbonyl): $1660_{asym.}$sp, 1488_{sym} msp; Δυ: 188; C-O (ether linkage): 1050 m; Sn–C: 510 m; Sn–O: 498 w. ^{1}H NMR ($CDCl_3$) δ: H-2: 3.92 s; H-4: 2.25 s; H-a: 2.64 s; H-c: 7.73 t (7); H-d: 7.29 m; H-e: 7.91 t. ^{13}C NMR ($CDCl_3$) δ: C-1: 168.66; C-2: 40.25; C-3: 170.35; C-4: 21.57; C-a: 19.87; C-b: 138.10; C-c: 129.18; C-d: 128.43; C-e: 124.93. ^{119}Sn NMR $(CH_3)_4Sn$: -142.71. MS m/z: $[(C_6H_5CH_2)_3SnO_2CCH_2N(COCH_3)_2]^+$ M$^+$ 549 (7%); $[(C_6H_5CH_2)_2SnO_2CCH_2N(COCH_3)_2]^+$ 458 (100%); $[(C_6H_5CH_2)_3Sn]^+$ 391 (72%); $[(C_6H_5CH_2)SnO_2CCH_2N(COCH_3)_2]^+$ 367 (50%); $[SnO_2CCH_2N(COCH_3)_2]^+$ 276 (40%); $[(C_6H_5CH_2)_2Sn]^+$300 (57 %); $[SnCH_2N(COCH_3)_2]^+$ 232 (45%); $[(C_6H_5CH_2)Sn]^+$ 209 (52%); [Sn/SnH]$^+$ 119/120 (8%), $[CH_2N(COCH_3)_2]^+$ 114 (38%); $[C_6H_5CH_2]^+$ 91 (34%); $[C_6H_5]^+$ 77 (12%); $[CH_2N(COCH_3)]^+$71 (30%).

Tributyltin(IV)-N,N-diacetylglycine (**5**): $[(C_4H_9)_3SnO_2CCH_2N(COCH_3)_2]$: N,N-diacetylglycine 1 g (6.29 mmol) and $AgNO_3$ 1.06 g (6.29 mmol) were reacted with tributyltin(IV) chloride 2.04 g (6.29 mmol) in 1:1 ratio in 100.0 mL chloroform. Recrystallized in chloroform. Yield: 85%. m.p.: 105 °C. Solubility: CH_3OH, CH_3CH_2OH, $CHCl_3$ and THF. CHN analysis (%) antipyrene: C, 48.2 (48.2); H, 7.8 (7.8) and N, 3.1 (3.1). FTIR (KBr) υ(cm^{-1}): CO (acetyl): 1765 m w; CO (carbonyl): $1674_{asym.}$sp, 1515_{sym} msp; Δυ: 159; C-O (ether linkage): 1043 m; Sn–C: 517 m; Sn–O: 505 w. ^{1}H NMR ($CDCl_3$) δ: H-2: 3.77 s; H-4: 2.55 s; H-a: 0.76 t; H-b: 1.39 m; H-c: 1.25 m; H-d: 0.88 t (7). ^{13}C NMR ($CDCl_3$) δ: C-1: 172.95; C-2: 40.11; C-3: 170.61; C-4: 21.71; C-a: 16.50; C-b: 27.12; C-c: 26.30; C-d: 13.56. ^{119}Sn NMR $(CH_3)_4Sn$: 123.7. MS m/z: $[(C_4H_9)_3SnO_2CCH_2N(COCH_3)_2]^+$ M$^+$ 447 (4%); $[C_4H_9)_2SnO_2CCH_2N(COCH_3)_2]^+$390 (100%); $[C_4H_9)SnO_2CCH_2N(COCH_3)_2]^+$333 (35%); $[C_4H_9)_3Sn]^+$ 289 (85%); $[SnO_2CCH_2N(COCH_3)_2]^+$276 (39%); $[(C_4H_9)_2Sn]^+$ 233 (22%); $[SnCH_2N(COCH_3)_2]^+$232 (49%); $[(C_4H_9)Sn]^+$ 175 (45%); $[CH_2N(COCH_3)_2]^+$114 (37%); [Sn/SnH]$^+$ 119/120 (5%); $[CH_2N(COCH_3)]^+$71 (17%); $[CH_3CH_2]^+$ 29 (25%); $[CH_3]^+$ 15 (8%).

Triphenyltin(IV)-N,N-diacetylglycine (**6**): $[(C_6H_5)_3SnO_2CCH_2N(COCH_3)_2]$: N,N-diacetylglycine 1 g (6.29 mmol) and $AgNO_3$ 1.06 g (6.29 mmol) were reacted with triphenyltin(IV) chloride 2.42 g (6.29 mmol) in 1:1 ratio in 100.0 mL chloroform. Recrystallized in chloroform and ether in 1:2 ratio. Yield: 78%. m.p.: 126 °C. Solubility: $(C_2H_5)_2O$, CH_3CH_2OH, $CHCl_3$ and THF. CHN analysis (%) antipyrene: C, 56.7 (56.7); H, 4.5 (4.5) and N, 2.7 (2.7), the calculated values are in the parenthesis. FTIR (KBr) υ(cm^{-1}): CO (acetyl): 1745 m w; CO (carbonyl): $1656_{asym.}$sp, 1471_{sym} msp; Δυ: 185; C-O (ether linkage): 1027 m; Sn–C: 547 m; Sn–O: 512 w. ^{1}H NMR ($CDCl_3$) δ: H-2: 3.80 s;H-4: 2.78 s; H-b: 7.64. t (7); H-c: 7.28 m; H-d: 7.15 t (7). ^{13}C NMR ($CDCl_3$) δ: C-1: 172.26; C-2: 40.73; C-3: 170.45; C-4: 21.37; C-a: 135.61; C-b: 133.54; C-c: 131.18; C-d: 130.39. ^{119}Sn NMR $(CH_3)_4Sn$: -99.29. MS m/z: $[(C_6H_5)_3SnO_2CCH_2N(COCH_3)_2]^+$ M$^+$ 507 (5%); $[(C_6H_5)_2SnO_2CCH_2N(COCH_3)_2]^+$ 430 (100%); $[(C_6H_5)SnO_2CCH_2N(COCH_3)_2]^+$ 353 (21%); $[(C_6H_5)_3Sn]^+$ 349 (25%); $[SnO_2CCH_2N(COCH_3)_2]^+$ 276 (32%); $[(C_6H_5)_2Sn]^+$ 272 (30%); $[SnCH_2N(COCH_3)_2]^+$ 232 (38%); $[CH_2N(COCH_3)_2]^+$ 114 (43%); $[(C_6H_5)Sn]^+$ 195 (36%); [Sn/SnH]$^+$ 119/120 (17%); $[(C_6H_5)]^+$ 77 (24%).$[CH_2N\text{-}(COCH_3)]^+$71 (17%).

Tricyclohexyltin(IV)-N,N-diacetylglycine (**7**): $[(C_6H_{11})_3SnO_2CCH_2N(CH_3CO)_2]$: N,N-diacetylglycine 1 g (6.29 mmol) and $AgNO_3$ 1.06 g (6.29 mmol) were reacted with tricylohexyltin(IV) chloride 2.64 g (6.29 mmol) in 1:1 ratio in 100.0 mL chloroform. Recrystallized in chloroform. Yield: 76%. m.p.: 112 °C. Solubility: $(C_2H_5)_2O$, CH_3OH, CH_3CH_2OH and $CHCl_3$. CHN analysis (%) antipyrene: C, 54.7 (54.7); H, 7.8 (7.8) and N, 2.6 (2.6). FTIR (KBr) υ(cm^{-1}): CO (acetyl): 1747 mw; CO (carbonyl): 1645_{asym}sp, 1490_{sym} msp; Δυ: 155; C-O (ether linkage): 1035 m; Sn–C: 540 m; Sn–O: 518 w. ^{1}H NMR ($CDCl_3$) δ: H-2: 3.76 s; H-4: 2.81 s; H-a: 1.14. t (7); H-b: 1.35 m; H-c: 1.55 m; H-d: 1.81m. ^{13}C NMR ($CDCl_3$) δ: C-1: 172.17; C-2: 39.35; C-3: 168.71.; C-4: 21.57; C-a: 22.69; C-b: 28.89; C-c: 26.44; C-d: 25.50. ^{119}Sn NMR $(CH_3)_4Sn$: 9.1. MS m/z: $[(C_6H_{11})_3SnO_2CCH_2N(COCH_3)_2]^+$ M$^+$ 525 (3%); $[(C_6H_{11})_2SnO_2CCH_2N\text{-}(COCH_3)_2]^+$ 442 (100%); $[(C_6H_{11})_3Sn]^+$ 367 (75%); $[(C_6H_{11})SnO_2CCH_2N(COCH_3)_2]^+$ 340 (44%); $[(C_6H_{11})_2Sn]^+$ 284 (52%); $[SnO_2CCH_2N(COCH_3)_2]^+$ 276 (30%); $[SnCH_2N\text{-}(COCH_3)_2]^+$ 232 (22%); $[CH_2N(COCH_3)_2]^+$ 114 (27%); $[C_6H_{11}Sn]^+$ 201 (42%); [Sn/SnH]$^+$ 119/120 (15%); $[C_6H_{11}]^+$ 83 (30%); $[CH_2N(COCH_3)]^+$ 71 (11%).

Bioactivity studies

Antibacterial bioassay

For the purpose antibacterial activity, glassware was sterilized at 150 °C for 20 minutes before use. The microbial specimens were accumulated as swabs of pus, blood, urine, sputum, siemen etc. from the Bahawal Victoria Hospital (BVH) of Bahawalpur. *E. coli, P. aeruginosa, K. pneumonia* and *S. typhi* were isolated and used for the purpose of antibacterial activity. MacConkey agar (10.0 g) and C.L.E.D mediums (10.0 g) in 250.0 mL distilled water and autoclaved which is used for preparation of Petri plates. The strains were inoculated and incubated at 37 °C. The ligand and OTCs methanolic solutions of 200 and 500 ppm were prepared. The pregnant discs were soaked in test solutions and dried and autoclaved as well. All the prepared petri plates were, incubated at 37 °C for 24 h.

Insecticidal bioassay

Monomorium minimum, *mealybug* and *tribolium castaneum* insects were selected to determine % toxicity rate as per reported method.[15] While *in vitro* LD_{50} values were analyzed by Probit statistical method.[21]

Brine shrimp bioassay

The lethality assays on the OTCs were carried out. LD_{50} was determined according to the literature.[24]

RESULTS AND DISCUSSIONS

FTIR study

FTIR successfully employed to verify 2:1 molar ratio of acetyl chloride and glycine respectively. The 3500-3100 cm^{-1} region was remained transparent for N-H moiety that is the indication of N,N-protection of glycine by acetyl groups whereas the OH broad band appeared at 3000-2600 cm^{-1} and C–H stretching of CH_3 of acetyl group occurred at 2961 cm^{-1}. The important $υ(CO)_{sym.}$ $υ(CO)_{asym.}$ υ(Sn–C), and υ(Sn–O) were observed in the region as reported in

the literature.[24] The reaction among $\{R_2Sn\text{-}(IV)\}^{2+}/\{R_3Sn(IV)\}^{+}$ and ligand was confirmed by the absence of the broad band of υ(OH) at 3000-2600 cm^{-1} showing the de-protonation of free ligand and presence of υ(Sn–O) in the range of 520-400 cm^{-1} given the indication of ligand metal complexation.[25-29] The involvement of the COO group in the coordination can be concluded by the shifting of υ(COO) band of the complexes to lower wave number as compared to that of the free ligand.[30] The difference between the $\upsilon(COO)_{asym}$ and $\upsilon(COO)_{sym}$ bands, Δυ(COO) of bidentate carboxylate group is below 200 cm^{-1} while unidentate carboxylate is above 200 cm^{-1}.[31] The characteristic $\upsilon(COO)_{asym}$ and $\upsilon(COO)_{sym}$ vibrations of the carboxylic group appeared at 1655 ± 20 and 1490 ± 20 cm^{-1}, respectively, for tri-organotin(IV) complexes **4-7**. The Δυ(COO) vibrations values are about 170 ± 15 cm^{-1} indicating the covalent bonding of the metal-oxygen bond.[32] The increasing of asymmetric and decreasing of symmetric stretching values of compounds than ligand while Δυ in the complexes was also larger than the Δυ of ligand, suggested that SnR_3 groups are bidentate coordinated to the oxygen of COO group of NNDAG which is also similar to the reported general pattern of coordination: $\upsilon_{asym(OTCs)} < \upsilon_{asym(ligand)} \upsilon_{sym(OTCs)} < \upsilon_{sym\ (ligand)} \Delta\upsilon_{(OTCs)} > \Delta\upsilon_{\ (ligand)}$.[16,33,34] The Sn-C stretching frequency at 510, 517, 547, and 540 cm^{-1} for benzyl, butyl, phenyl and cyclohexyl groups suggested the presence of all three organic groups in the equatorial positions of the polymeric trigonal bipyramidal structure in Figure **1**.[34,35]

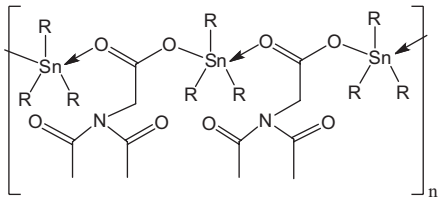


Figure 1. *Polymeric trigonal bipyramidal structure of tri-organotin(IV) complexes (**4-7**)*

The characteristic $\upsilon(CO)_{asym.}$ and $\upsilon(CO)_{sym.}$ vibration of monomeric compounds **1** and **3** appeared at 1620±15 and 1462±8 cm^{-1}, respectively,[33-35] while Δυ value of CO was < 200 cm^{-1} exhibit bidentate bonding to NNDAG with *trans*-octahedral geometry (Figure 2).[16,36] Very sharp band at 634 cm^{-1} of compound **2** recommend Sn-O-Sn-O ring dimeric networking with endo and exo Sn(IV) atoms that proposed the hexa coordination geometry given in Figure **3** and the general observed pattern for υCO in accordance with literature is as follow: $\upsilon_{asym(comp.)} < \upsilon_{asym(lig.)}$, $< \upsilon_{sym(comp.)} < \upsilon_{sym(lig.)}$, $\Delta\upsilon_{(comp.)} > \Delta\upsilon_{\ (lig.)}$.[15,16,36]

^{1}H NMR study

The CH_3CO protons of NNDAG resonated at 2.30-1.5 ppm and O–H proton shifted at downfield region 11.3 ppm indicating the N,N-protected of glycine. Interestingly no N–H chemical shift was observed in the ^{1}H NMR spectra of ligand. It is facile and more convenient route that can be used to protect glycine at NN site is not found in the literature. The ^{1}H NMR study of OTCs (**1–7)** successfully verified their synthesis by de-protonation of NNDAG ligand and no chemical shift was found at downfield for carboxylic acid proton. All data is given in experimental part. The $–CH_2$ chemical shifting is found at 3.71-4.00 ppm while CH_2 of benzyl at 2.64-2.87 ppm is seen as reported.[16,36-39] The proton signal of phenyl, cyclohexyl and aromatic proton of benzyl were found at range 7.32-8.23 ppm. Two molar stoichiometric ratio of NNDAG was used to synthesize OTCs **1**, and **3** are confirmed by ^{1}H NMR data and the literature evidences supported octahedral geometry (Figure **2**).[31,40]

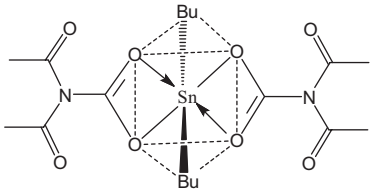


Figure 2. *Octahedral geometry of monomer **1**, and **3***

In case of compounds **2** the endo- and exocyclic Sn(IV) centers were difficult to identify as reported in literature because there is no distinct signals of butyl group attached to endo- and exocyclic tin(IV) centers giving the equal status to endo and exo tin(IV) centers.[16,17,41,42] It is obviously due to six coordination sites of each endo and exotin(IV) atom with chemically equivalent nature. Hence it might be purposed that dimer have a ladder topology with sinusoidal view from one unit to other that linked with each other through oxygen atom of carboxylate of one unit to Sn(IV) atom of other unit as we reported previously and shown in Figure 3.[15,31]

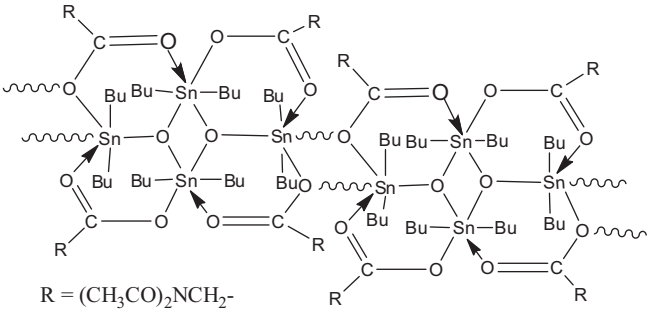


Figure 3. *Sinusoidal view of compound **2** exhibiting weakly bonded two dimer units*

For triorganotin(IV) compounds (TOTCs) **4-7,** the ^{1}H NMR spectra (data can be seen in experimental part) show the chemical shift that verifying the tetrahedral structure in $CDCl_3$ solvent and established the coordination of oxygen of carboxylic group to tin(IV) centers (Figure **4**) with support of literature as well.[41,42]

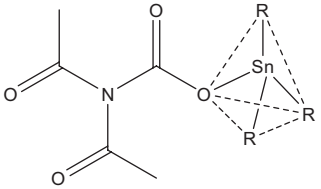


Figure 4. *Tetrahedral geometry of triorganotin(IV) complexes (**4-7**)*

^{13}C NMR study

The ^{13}C NMR spectra of NNDAG data can be seen in experimental part. According to Scheme 1, all the carbon atoms 1, 2, 3, 4 were resonated at the specified chemical shifts as reported in the literature.[16,17,31] The C-1of COOH gave ^{13}C signal at 169.22 ppm and whereas the C-4 of CH_3 at 21.68 ppm is confirming the synthesis of NNDAG. All the OTCs have COO values at down field up to 173.73 ppm as well confirmed carboxylate carbon (C-1) bonding to tin(IV) atom. The ^{13}C chemical shift of butyl, phenyl, benzyl and cyclohexyl (C-a, C-b, C-c, C-d, C-e) were observed at range 13.55-27.13, 130-140 and 22-30 ppm, respectively.[16,17,41]

^{119}Sn NMR study

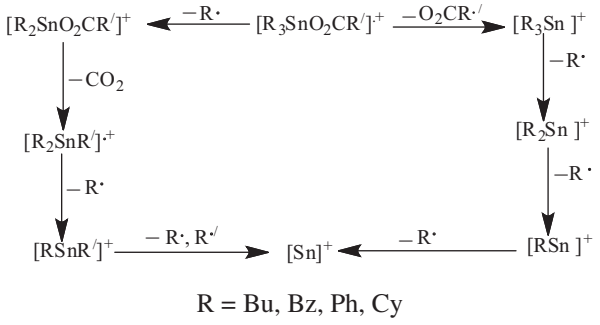
The ^{119}Sn chemical shifts of the tribenzyl-, tributyl-, triphenyl-, and tricyclohexyl-tin(IV) carboxylates were at -142.71, 123.7, -99.29, and 71.21 ppm indicating a tetrahedral environment. [43,44] While dibutyl- and dibenzyl-tin(IV) complexes exhibited ^{119}Sn chemical shift at -190.35 and -238.32 ppm respectively confirming the *trans* octahedral arrangement (Figure **2**).[45] While pair of ^{119}Sn resonance peaks of equal intensities at -210.4 and -216.2 were confirming the endo- and exo-cylic status of tin(IV) respectively that substantiated the sinusoidal view of compound **2** given in Figure **3**.[15,23]

Mass spectral study

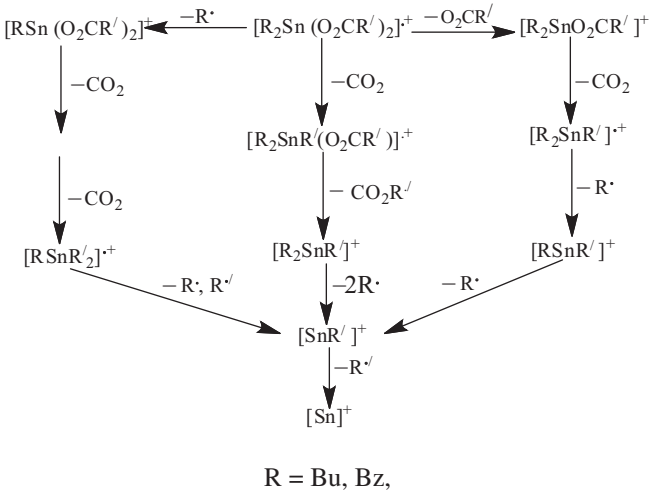
Molecular ion peak at m/z 159 is the actual mass of ligand NNDAG is true evidence of existence of two moles of acetyl groups at N terminal of glycine is the most important step toward synthesis of NNDAG through this new and facile route to protect N terminal. In the organotin(IV) derivatives major fragmentation was observed due to the loss of the ligand moiety from the tin(IV) derivatives. Successive loss of R groups (Bu, Bz, Ph) during fragmentation was happened until the Sn^{4+} ion was resulted. In an alternative route, R groups were eliminated first and next one molecule of CO_2 removed as per revealed in literature.[23,46] Further, the remaining substituents were defragmented on same pattern as given in Schemes **3** and **4**.

Antibacterial activity

The results related to antibacterial activity is given in Table **1.** The OTCs **4**, **5**, **6** and **7** (500 ppm) is promising more than two fold activity than the standard antibiotic enoxacin (1000 ppm). The compounds **1**, **2** and **3** reflected good activity at 500 ppm dose whereas the NNDAG is too less promise as given in selected petri plate of *E. coli* (Figure **5**) and the comparative zone of inhibition of OTCs **1**-**7** versus bacterial strains is given in Figure **6**. It is obvious that promising property of OTCs (**4**, **5**, **6** and **7**) is due to tetrahedral geometry of tin(IV) atom that bears CO oxygen free for coordinate with corresponding metal ions of enzymatic system of strains as well the tin(IV) metal ions has more vacant coordination site to block the metabolites to protein synthesis along with ribosomal sub units of bacterial strains.[47-50] From this study following trend of OTCs may be concluded for the antibacterial inhibition: TOTCs (alkyl) > TOTCs (aryl) > dimer > monomer > ligand.



Scheme 3. *Fragmentation pattern of triorganotin(IV) complexes*



Scheme 4. *Fragmentation pattern of diorganotin(IV) complexes*

Insecticide activity

The OTCs **4** and **5** have excellent activity against *M. minimum* and *T. castaneum* but remained insignificant against *Mealy bug*. The LD_{50} value and the results are given in Table **2**.

Cytotoxicity study

Cytotoxicity was evaluated using brine shrimp lethality assay (Table **3**). LD_{50} of all compounds were carried out against brine shrimp larvae using standard statistical procedure Probit analysis. OTCs **4**, **5** and **7** were found to be active.

Table 1. Antibacterial bioassay

Compounds (500 ppm)	*E. coli*		*P. aeruginosa*		*K. pneumoniae*		*S. typhi*	
	Inhibition (mm)	Results	Inhibition (mm)	Results	Inhibition (mm)	Results	Inhibition (mm)	Results
NNDAG	10	+	8	+	7	+	9	+
1	18	++	15	++	13	++	14	++
2	22	+++	18	++	16	++	15	++
3	15	++	13	++	12	++	14	++
4	25	+++	22	+++	20	++	19	++
5	39	++++	33	+++	29	+++	28	+++
6	35	++++	30	+++	27	+++	30	+++
7	32	++++	31	++++	23	++	25	++
*Standard	28	+++	29	+++	30	+++	34	++++

where - = no result, + = insignificant, ++ = significant, +++ = more significant, ++++ = most significant. *enoxacin = 1000 ppm doze.

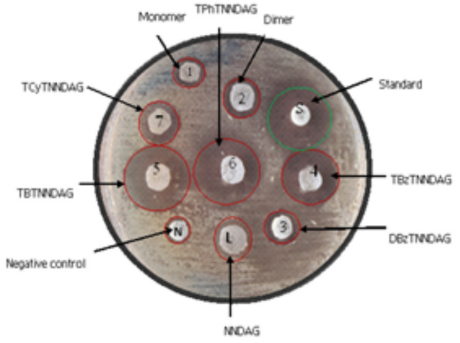


Figure 5. *Selected experimental petri plates against E. coli*

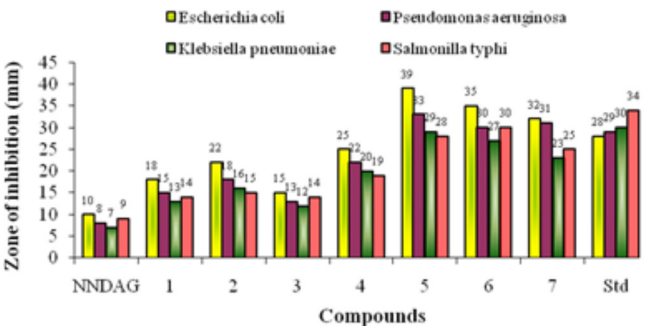


Figure 6. *Comparison of antibacterial activity*

Table 2. Insecticidal bioassay

*Compounds	Type of insects (% Death) µg/mg														
	Monomorium minimum						*Tribolium castaneum*							*Mealy bug*	
	1000	700	400	100	10	LD_{50}	Result	1000	700	400	100	10	LD_{50}	Result	Result
NNDAG	10	10	10	-	-	-	-	10	10	-	-	-	-	-	-
1	80	70	60	40	30	140.48	+	80	60	60	40	20	100.00	+	-
2	100	100	80	70	20	28.18	++	60	60	40	40	30	350.80	++	-
3	80	80	80	80	40	35.48	++	90	90	60	60	10	79.43	++	-
4	100	100	90	80	60	6.60	++	90	80	70	70	40	35.48	++	-
5	100	100	90	70	50	1.00	+++	100	100	80	60	30	28.18	+++	-
6	90	90	60	30	30	39.81	++	70	70	50	50	20	141.48	++	-
7	90	80	80	80	30	39.81	++	80	70	50	40	20	100.00	++	-

* compounds and flour are in w/w % ratio; where: - = no result, + = insignificant, ++ = significant, +++ = more significant, ++++ = most significant.

Table 3. Brine shrimp LD_{50} bioassay

Compounds	% Death at dose (µg/mg)					LD_{50}	Results
	1000	700	400	100	10		
NNDAG	20	20	10	-	-	-	+
1	40	30	20	20	20	-	++
2	90	80	70	70	60	7.94	++++
3	30	30	10	10	10	-	++
4	90	80	80	80	60	3.16	++++
5	100	100	100	90	70	3..98	++++
6	100	100	70	70	50	10.00	++
7	90	90	90	90	60	3.16	+++

where: ++++ = more significant, +++ = significant – = no activity.

CONCLUSIONS

A new series of monomeric organotin(IV) esters **1, 3** dimeric organotin(IV) esters **2** and triorganotin(IV) esters **4-7,** were synthesized with N,N-diacetylglycine. All the complexes were more active than the ligand and some were even more active than standard used. The following trend may be concluded for the antibacterial inhibition; OTCs (alkyl) > OTCs (aryl) > monomeric organotin(IV) esters > monomer organotin(IV) esters > ligands, the bacterial strains were inhibited as: *E. coli* > *P. aeruginosa* > *K. pneumonia* > *S. typhi.* While the rate of toxicity and LD_{50} values have following order: *T. castaneum* > *M. minimium* > *Mealybug* in cotton plant. LD_{50} against Brine Shrimp larvae were found to be active for dimer and inactive for monomer while OTCs esters have very narrow range of LD_{50} values of 3-10 µg/mg.

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