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Synthesis, characterization and biological studies of organotin (iv) complexes of *2H*- 1,2,3 - triazole entailing carboxylic acid

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Key words: N-arylation, 6-(1',2',3'-triazol-2'-yl) pyridine-3-carboxylic acid, Carboxylates, Organotin (IV) complexes, Biological studies

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Abstract

An efficient and convenient method for the synthesis of 6-(1',2',3'-triazol-2'-yl) pyridine-3-carboxylic acid (1) via *N*-arylation is described. The synthesized azole ligand was further coordinated with a variety of organotin (IV) salts. Structural elucidations of ligand and the complexes thus formed were made by CHN, IR, NMR and MS. The newly synthesized compounds were also screened for antibacterial, cytotoxic and antiurease activities. Comprehensive biological studies revealed that an aryl group within organotin (IV) moiety, as in compound 8, showed excellent biological activities. While the compound with small alkyl group (compound 5) showed an insignificant inhibition indicating weak interactions at the active sites.

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Introduction

Various synthetic and naturally occurring compounds with biomedical properties have five-membered nitrogen-holding ring in their framework (Sadler 1991). Among these, imidazoles, triazoles and their derivatives are reported to be a major class of tunable ligands that exhibit numerous physiological (Girotto, Bechtold *et al.* 2015, Nimal, Aftab *et al.* 2016) and pharmacological properties (Lednicer 2007). These are extensively be used as haem oxygenase or β-lactamase inhibitors, and as antibacterial, antifungal, anticancerous, anti-allergic, anti-HIV, anticonvulsant, anti-inflammatory, antitubercular and antidiabetic agents (Grimmett 1997, Adams, Boehm *et al.* 2001, Nakamura, Kakinuma *et al.* 2004, Babizhayev 2006, Rajasekaran, Murugesan *et al.* 2006, Roman, Riley *et al.* 2007, Congiu, Cocco *et al.* 2008, Venkatesan, Agarwal *et al.* 2008). Owing to their pharmacological properties, the derivatization and *N*-arylation of azoles has become a regular practice in organic synthesis.

A variety of methods for *N*-arylation have been used as Ullmann coupling (Hu, Xie *et al.* 1999), aromatic nucleophilic substitutions (Maiorana, Baldoli *et al.* 1998) and Pd or Cu catalyzed arylations (Beletskaya, Davydov *et al.* 1998). Among these, the transition-metal catalyzed *N*-arylation was regarded as the most efficient and powerful method for the synthesis of such precursors (Prabakaran, Manivel *et al.* 2010). Also the researchers have tried to cope with remarkable shortcomings comprising harsh conditions, weird stoichiometry, high costs of metals and inadequacy in terms of generality for above mentioned synthetic processes. And searched for less expensive, less toxic and more efficient catalytic agents (Corbet and Mignani 2006).

It has been previously reported that a suitable combination of a base and solvent can enhance catalytic activity during *N*-arylation. A wide range of bases used like potassium phosphate (Anderson, Mendez-Perez *et al.* 2003), cesium carbonate (Artamkina, Sergeev *et al.* 2001), sodium methoxide (Prashad, Hu *et al.* 2000) and sodium hydroxide (Huang, Anderson *et al.* 2003) have been reported. The reactions were solely governed by higher boiling solvents like DMF or DMSO at elevated temperature. In the present work, hexadecyltrimethylammonium bromide catalyzed *N*-arylation of 1,2,3-triazole in the presence of 6-chloropyridine-3-carboxylic acid was carried out by using K_2CO_3 as a base. The *N*-arylated moiety thus formed was further coordinated with a variety of organotin (IV) salts.

Both the stability and the structural diversity of organotin (IV) compounds has revolutionized their coordination chemistry and led to their extensive use in various fields of life sciences particularly in medicines (Janiak 2003). Usually high *in vitro* or *in vivo* activity of diorganotin (IV) and triorganotin (IV) compounds depends on the organic moiety (R) or donor ligands (substituting sulfur, nitrogen, oxygen or fluorine) attached to the metal, it can make them highly attractive anticancerous (Gómez-Ruiz, Kaluđerović *et al.* 2008, Abbas, Hussain *et al.* 2013), antioxidant (Pellerito, D'Agati *et al.* 2005), anti-inflammatory etc (Nath, Pokharia *et al.* 2004, Gielen and Tiekink 2005). The activity of the complexes decreases in order of *n*-butyltin > phenyltin > ethyltin > octyltin > cyclohexyltin > acyclovir (Singh, Tawade *et al.* 1999, Khan, Baloch *et al.* 2004) and R_3SnL > R_2SnL_2 > $RSnL_3$ (Ashfaq 2006).

Material and Methods

All the chemicals and reagents in current studies were research grade products, purchased from commercial sources (Merck and Aldrich) and were used either without any further purification or purified where necessary. Analytical grade solvents were dried before use. Gallen Kemp melting point apparatus was used to determine melting point. Bruker Tensor 27 Fourier Transform Infra-Red Spectrophotometer was used in the range of 4000-400 cm^{-1} to collect spectral data. Elemental analyses (CHNS) were carried out on Carlo Erba 2400 automatic analyzer. Multinuclear NMR (^1H and ^{13}C) spectra were recorded on Varian MR Instrument at 300 MHz and/or 400 MHz in $CDCl_3$ or deutrated acetone using tetramethylsilane (TMS) as internal standard. The mass spectra were recorded on JEOL JMS 600-H series (EBE) MS spectrometer.

Procedure for the synthesis of ligand and complexes (1-10)

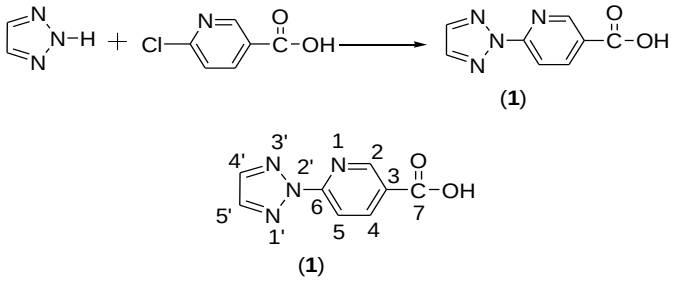
Synthesis of 6-(1',2',3'-triazol-2'-yl)pyridine-3-carboxylic acid (1)

With little modifications, *N*-arylation of 2*H*-1,2,3-triazole co-reacted with 6-chloropyridine-3-carboxylic acid **(**Scheme-1**)**, was accomplished by pre-described method in literature (Hussain, Siddiqui *et al.* 2009).

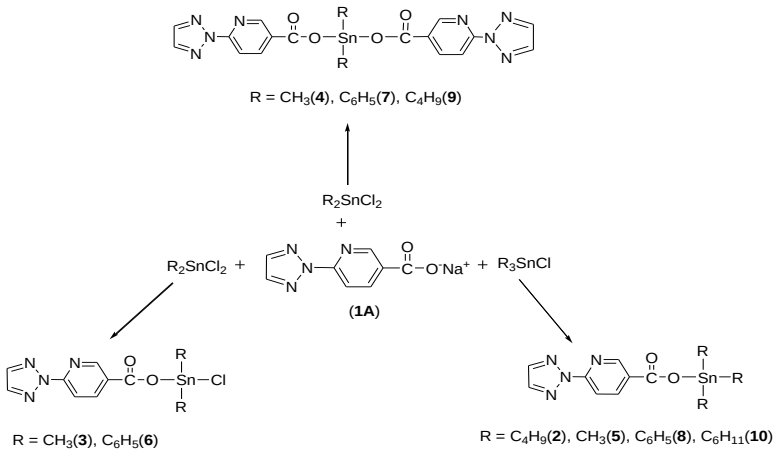
Briefly, a mixture of 2*H*-1,2,3-triazole (0.1 mmol), anhydrous potassium carbonate (0.1mmol), 6-chloropyridine-3-carboxylic acid (0.1 mmol), hexadecyltrimethylammonium bromide (20µg) and dioxin (50ml) was refluxed for the period of 18-22 hours. Consequently the progress of the reaction was monitored via TLC.

Followed by the precipitate formation in crushed ice was taken as strong indication of required product.

Precipitates thus formed were filtered off, dried and recrystallized in n-hexane.



Scheme 1. Preparation and numbering scheme of 6-(1',2',3'-triazol-2'-yl) pyridine-3-carboxylic acid.



Scheme 2. Preparation of di- and tri-oraganotin (IV) carboxylates through Na-salt of 6-(1',2',3'-triazol-2'-yl) pyridine-3-carboxylic acid.

General procedure for the synthesis of complexes (2-10)

The Na-salts of ligand i.e. 6-(1',2',3'-triazol-2'-yl) pyridine-3-carboxylic acid (1A) were further reacted with various organotin (IV) chlorides (Scheme 2). (Hanif, Hussain *et al.* 2010, Hussain, Rauf *et al.* 2010). Suitable dry solvents like toluene, methanol, n-hexane etc. were used for reactions to complete. All the complexes thus isolated were crystalline or amorphous solids, stable at room temperature,

non-hygroscopic and having sharp melting points. The products so obtained were soluble in various organic solvents like benzene, chloroform, DMF and DMSO. Further, ^{1}H, $^{13}CNMR$, IR and mass spectrometry was carried out for their confirmation.

Procedures for biological activities

Cytotoxicity assay

To evaluate inhibitory effects on the growth of *Nauplii* (brine shrimps), cytotoxic activity of the ligand (1) and its corresponding organotin (IV) complexes (2-10) was performed by brine shrimp lethality method (Atta-ur-Rahman and Thomsen 1999, Tariq, Muhammad *et al.* 2013). Briefly, the hatching tray was filled with artificial sea water (salt solution 38g/l) and a porous membrane used to divide the tray into two halves. Brine shrimp eggs were sprinkled in one half of the tray and covered. The second half of the hatching tray was left exposed under artificial light for 1-2 days at 30±3°C (till the eggs hatched) and the larvae moved towards the illuminated part of the tray through the porous membrane. Solutions of test compounds (10mM) were prepared in DMSO. A specific volume of the test solution was poured in a tube and left overnight for evaporation. To this tube, the salt solution was added and the volume made up to 5ml. To this sample tube, 2-4 days old Shrimps, (10 in number) were added via Pasteur pipette. The tubes were incubated overnight and maintained 30±3°C under illumination. Number of the survivors were recorded and cytotoxicity was determined as below:

$$\text{Dead}\,(\%) = \frac{\text{Number of larvae dead}}{\text{Number of larvae added}} \times 100$$

The salt solution served as the negative control and Etoposide as standard drug (positive control). Results of the assay are graphed in Fig. 1.

Antiurease activity

The assay was modified from Berthelot assay and engaged for the determination of antiurease activity (Searle 1984, Watson 2000).

In each well of 96-well plate, a total of 200µl assay volume contained 55µl of phosphate buffer (0.2M) of pH 7 followed by the adding up 10µl test solution and 10µl enzyme mixture (0.015 units). All the contents were pre-incubated at 37°C for 10 minutes. Then 10µl of urea stock solution (80mM) was added in each well and incubation was done at 37°C for further 10 minutes. A pre-reading was taken at 630nm. After that 115µl of phenol hypochlorite reagent was added in each well. (Phenol hypochlorite reagent was made freshly by combining 45µl phenol solution with 70µl alkali solution). For color appearance, incubation was done for 10 minutes at 37°C. Absorbance was taken at 630 nm using 96-well plate reader.

$$\text{Percentage Inhibition} = \frac{(\text{O.D of positive control} - \text{O.D of Sample})}{\text{O.D of positive control}} \times 100$$

The solution having no sample served as a negative control. Wells containing thiourea served as positive control.

Antibacterial activity

Antibiotic sensitivity testing was performed using a standard disc diffusion assay (Bauer, PERRY *et al.* 1959, Kaspady, Narayanaswamy *et al.* 2009) using *E. coli* as an indicator target strain. Briefly, 50µl compound was loaded onto a sterile filter-paper disc (6 mm in diameter). A 50µl simple broth was used as the negative control, and ampicillin (20µg/ml) was used as positive control. After application onto paper discs, the discs were air dried and placed onto the nutrient agar plate, which had been inoculated with a lawn of *E. coli*. After incubation for 24h at 37°C, the antibacterial activity was evaluated by measuring the diameter of the growth-inhibition zones from the edge of each filter paper. The inhibitive radii mean (the clear zone radii in which the tested strains did not grow) was noted.

The percentage inhibition was calculated by the following formula

$$\text{Percentage Inhibition} = \frac{(\text{radius of positive control} - \text{radius of sample})}{\text{radius of positive control}} \times 100$$

Results and discussion

The overwhelming chemistry of organotin (IV) compounds in diverse biological, non-biological and industrial areas has encouraged researchers to explore their novel applications. For this we have developed a facile route to synthesize 6-(1',2',3'-triazol-2'-yl) pyridine-3-carboxylic acid and its organotin (IV) complexes.

The compounds thus formed were characterized via ^{1}H & ^{13}C NMR, IR and MS and screened for their therapeutic aspects. Results of which are given below. Expansion of the findings may lead to the industrial applications of the synthesized moieties.

Spectral interpretation of synthesized compounds (1-10)

6-(1',2',3'-triazol-2'-yl) pyridine-3-carboxylic acid (1)

White Crystalline Solid, 77.3% yield; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 10 (s, 1H, H-2), 8.41 (d, 1H, *J* = 7.7Hz, H-4), 7.62 (d, 1H, *J* = 7.3Hz, H-5), 11.41 (s, H-7), 8.12 (d, 2H, *J* = 6.1Hz, H-4',5'),; ^{13}C-NMR (100 MHz, $CDCl_3$): δ 152.2 (C-2), 127.4 (C-3), 138.01 (C-4), 123 (C-5), 154 (C-6), 170.1 (C-7), 133 (C-4',5'),; IR (KBr, 4000-400cm^{-1}): *υ* 1325 (N-C), 2965 (aromatic ring), 1515 (ring N-N), 1608 (ring C=N); Mass Spectra (m/z%): 190 (50.46) [M^{+}], 122.02 (45.47), 78 (100), 44 (66.81); M.P. 231-233°C. Anal. Calcd. For $C_8H_6N_4O_2$: C, 50.53; H, 3.18; N, 29.46; O, 16.83. Found: C, 51.0; H, 3.3; N, 30.0; O, 16.83.

Tributyltin (IV)-6-(1',2',3'-triazol-2'-yl) pyridine-3-carboxylate (2)

White Amorphous Solid, 51.22% yield; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 9.02 (s, 1H, H-2), 8.4 (d, 1H, *J* = 7.1Hz, H-4), 7.43 (d, 1H, *J* = 7.5Hz, H-5), 8.01 (d, 2H, *J* = 6.3Hz, H-4',5'), 1.34 (t, 6H, $H_{\alpha,\alpha',\alpha''}$), 1.32 (m, 6H, $H_{\beta,\beta',\beta''}$), 1.32 (m, 6H, $H_{\gamma,\gamma',\gamma''}$), 0.97 (t, 9H, $H_{\delta,\delta',\delta''}$); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 151.9 (C-2), 127.4 (C-3), 150.0 (C-4), 123 (C-5), 155.3 (C-6), 173 (C-7), 134.01 (C-4',5'), 14.4 ($C_{\alpha,\alpha',\alpha''}$), (25.4 ($C_{\beta,\beta',\beta''}$), 27 ($C_{\gamma,\gamma',\gamma''}$), 13.8 ($C_{\delta,\delta',\delta''}$); IR (KBr, 4000-400cm^{-1}): *υ* 1675 (COO)$_{asym}$, 1329 *υ* (COO)$_{sym}$, 346 Δ*υ* (COO$_{asym}$ - COO$_{sym}$), 483 (Sn–C), 432 (Sn–O), 1345 (N-C), 2989 (aromatic ring), 1523 (ring N-N), 1615 (ring C=N); Mass Spectra (m/z %): 481.2(64.02) [M+1], 412 (65.21), 335 (49.72), 263 (50.38), 235 (66.23), 291.11 (26.23), 78 (100), 68.22 (64.73), 45.22 (40.58), 29.03 (50.13); M.P. 230 °C. Anal. Calcd. for $C_{20}H_{32}N_4O_2Sn$: C, 50.13; H, 6.73; N, 11.69; O. 6.68; Sn, 24.77. Found: C, 50.5; H, 6.2; N, 10.9; O, 6.68.

Chlorodimethyltin (IV)-6-(1',2',3'-triazol-2'-yl) pyridine-3-carboxylate (3)

White Crystalline Solid, 62.2% yield; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 9.22 (s, 1H, H-2), 7.92 (d, 1H, *J* = 7.5Hz, H-4), 7.3 (d, 1H, *J* = 7.8Hz, H-5), 7.92 (d, 2H, *J* = 6.2Hz, H-4',5'), 0.9 (s, 6H, H_{α}); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 152.0 (C-2), 126.82 (C-3), 137.3 (C-4), 123.2 (C-5), 154 (C-6), 172.5 (C-7), 131.8 (C-4',5'), 0.5 (C_{α}); IR (KBr, 4000-400cm^{-1}): *υ* 1595 (COO)$_{asym}$, 1321 (COO)$_{sym}$, 274 Δ*υ* (COO$_{asym}$ -COO$_{sym}$), 456 (Sn–C), 442 (Sn–O), 1352 (N-C), 3133 (aromatic ring), 1545 (ring N-N), 1631 (ring C=N); Mass Spectra (m/z%): 375.1 (72.8) [M+1], 201.2 (100), 173 (57.9), 28 (46.4), 144.73 (25.9), 78 (47.7), 67.82 (26.6); M.P. 192 °C. Anal. Calcd. for $C_{10}H_{11}ClN_4O_2Sn$: C, 32.17; H, 2.97; Cl, 9.50; N, 15.01; O, 8.57; Sn- 31.79. Found: C, 32.8; H, 3.1; N, 15.5; O, 8.57.

Dimethyltin (IV) bis [6-(1',2',3'-triazol-2'-yl) pyridine-3-carboxylate] (4)

White Crystalline Solid, 57.82% yield; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.82 (s, 2H, H-2), 7.93 (d, 2H, *J* = 7.4Hz, H-4), 7.4 (d, 2H, *J* = 7.9Hz, H-5), 7.72 (d, 4H, *J* = 6.4Hz, H-4',5'), 0.9 (s, 6H, H_{α}); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 152.3 (C-2), 127.5 (C-3), 138 (C-4), 123.1 (C-5), 153 (C-6), 172.4 (C-7), 133 (C-4',5'), 1.6 ($C_{\alpha,\alpha'}$); IR (KBr, 4000-400cm^{-1}): *υ* 1642 (COO)$_{asym}$, 1461 (COO)$_{sym}$, 181 Δ*υ* (COO$_{asym}$ -COO$_{sym}$), 452 (Sn–C), 439 (Sn–O), 1342 (N-C), 3100 (aromatic ring), 1562 (ring N-N), 1628 (ring C=N); Mass Spectra (m/z %): 528.05 (54.2) [M^{+}], 68.22 (82.5), 458.92 (38.4), 78 (45.2), 383.87 (37.4), 339.4 (100), 150 (66.8), 190.1 (24.7); M.P. 221°C. Anal. Calcd. For $C_{18}H_{16}N_8O_4Sn$: C, 41.02; H, 3.06; N, 21.26; O, 12.14; Sn, 22.52. Found: C, 41.8; H, 5.1; N, 20.7.8; O, 12.14.

Trimethyltin (IV)-6-(1',2',3'-triazol-2'-yl) pyridine-3-carboxylate (5)

Brown Amorphous Solid, 92.2% yield; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.92 (s, 1H, H-2), 8.02 (d, 1H, *J* = 7.8Hz, H-4), 7.6 (d, 1H, *J* = 7.5Hz, H-5), 8.01 (d, 2H, *J* = 6.3Hz, H-4',5'), 0.9 (s, 9H, H_{α}); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 150.8 (C-2), 126.7 (C-3), 138.1 (C-4), 123.01 (C-5), 154.2 (C-6), 172.3 (C-7), 133.2 (C-4',5'), 0.3 (C_{α}); IR (KBr, 4000-400cm^{-1}): *υ* 1565 (COO)$_{asym}$, 1298 (COO)$_{sym}$, 267 Δ*υ* (COO$_{asym}$ - COO$_{sym}$), 489 (Sn–C), 433 (Sn–O), 1289 (N-C), 3001 (aromatic ring), 1545 (ring N-N), 1663 (ring C=N); Mass Spectra (m/z %): 353.9 (65.7) [M^{+}], 181 (42.2), 173 (36.9), 144.73 (52.5),

78 (71.5), 67.82 (38.7); M.P. 187 ˚C. Anal. Calcd. for $C_{11}H_{14}N_4O_2Sn$: C,37.43; H,4.00; N, 15.87; O, 9.07; Sn, 33.63. Found: C, 37.8; H, 5.1; N, 16.0; O, 9.07.

Chlorodiphenyltin (IV)-6-(1',2',3'-triazol-2'-yl) pyridine-3-carboxylate (6)

Yellow Amorphous Solid, 67.4% yield; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 9.2 (s, 1H, H-2), 8.1 (d, 1H, *J* = 7.5Hz, H-4), 7.7 (d, 1H, *J* = 7.2Hz, H-5), 8.02 (d, 2H, *J* = 6.9Hz, H-4',5'), 7.3 (m, 10H, Ph-H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 150.8 (C-2), 126 (C-3), 138 (C-4), 121.2 (C-5), 155 (C-6), 173.02 (C-7), 134 (C-4',5'), 129 (C_α), 137.5 (C_β), 128.8 (C_γ); IR (KBr, 4000-400cm^{-1}): *υ* 1602 $(COO)_{asym}$, 1378 $(COO)_{sym}$, 224 Δ*υ* (COO_{asym} - COO_{sym}), 478 (Sn–C), 412 (Sn–O), 1298 (N-C), 3013 (aromatic ring), 1567 (ring N-N), 1662 (ring C=N); Mass Spectra (m/z %): 499.1 (61) [M+1], 68.22 (44.8), 430.1 (100), 77.92 (42.2), 353.23 (51.3), 44 (36.0), 309.21 (86.8), 274.1 (29.8); M.P. 183 ˚C. Anal. Calcd. for $C_{20}H_{15}ClN_4O_2Sn$: C, 48.28; H, 3.04; Cl, 7.13; N, 11.26; O, 6.43; Sn, 23.86. Found: C, 49; H, 3.6; N, 10.9; O, 6.43.

Diphenyltin (IV)bis[6-(1',2',3'-triazol-2'-yl) pyridine-3-carboxylate] (7)

White Crystalline Solid, 57.82% yield; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 9.02 (s, 2H, H-2), 8.4 (d, 2H, *J* = 7.9Hz, H-4), 7.38 (d, 2H, *J* = 7.2Hz, H-5), 7.78 (d, 4H, *J* = 6.7Hz, H-4',5'), 7.42 (m, 10H, Ph-H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 152.01 (C-2), 128.2 (C-3), 136.7 (C-4), 121.9 (C-5), 154.2 (C-6), 172.8 (C-7), 134.01 (C-4',5'), 128.7 (C_α), 138.2 (C_β), 129 (C_γ); IR (KBr, 4000-400cm^{-1}): *υ* 1634 $(COO)_{asym}$, 1452 $(COO)_{sym}$, 182 Δ*υ* (COO_{asym} - COO_{sym}), 475 (Sn–C), 423 (Sn–O), 1288 (N-C), 3013 (aromatic ring), 1556 (ring N-N), 1672 (ring C=N); Mass Spectra (m/z %): 652.1 (78) [M+1], 68.22 (32.4), 585 (31.2), 122.43 (49.4), 462.87 (100), 78 (18.4), 386.52 (26.8), 241.1 (33.0); M.P. 206 ˚C. Anal. Calcd. For $C_{28}H_{20}N_8O_4Sn$: C, 51.64; H, 3.10; N, 17.21; O, 9.83; Sn, 18.23. Found: C, 52.0; H, 3.6; N, 17.8; O, 9.83.

Triphenyltin (IV)-6-(1',2',3'-triazol-2'-yl) pyridine-3-carboxylate (8)

White Amorphous Solid, 74.4% yield; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 9.0 (s, 1H, H-2), 8.2 (d, 1H, *J* = 7.76Hz, H-4), 7.5 (d, 1H, *J* = 7.5Hz, H-5), 7.89 (d, 2H, *J* = 6.9Hz, H-4',5'), 7.27 (m, 15H, Ph-H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 151.0 (C-2), 127.5 (C-3), 137.5 (C-4), 122.4 (C-5), 153 (C-6), 172.01 (C-7), 132.5 (C-4',5'), 127.8 (C_α), 137.8 (C_β), 127.4 (C_γ); IR (KBr, 4000-400cm^{-1}): *υ* 1544 $(COO)_{asym}$, 1242 $(COO)_{sym}$, 302 Δ*υ* (COO_{asym} - COO_{sym}), 483 (Sn–C), 423 (Sn–O), 1345 (N-C), 2989 (aromatic ring), 1523 (ring N-N), 1615 (ring C=N); Mass Spectra (m/z%): 68.04 (47.49), 471.91 (50.8), 78.02 (43.2), 394.72 (58.3), 351.1 (33.2), 77 (53.2), 274.12 (33.01), 197.3 (47.58); M.P. 140-142 ˚C. Anal. Calcd. For $C_{26}H_{20}N_4O_2Sn$: C, 57.92; H, 3.74; N, 10.39; O, 5.93; Sn, 22.02. Found: C, 58.1; H, 4.2; N, 10.5; O, 5.93.

Dibutyltin (IV) bis [6-(1',2',3'-triazol-2'-yl) pyridine-3-carboxylate] (9)

White Crystalline Solid, 70.2% yield; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 9.3 (s, 2H, H-2), 8.08 (d, 2H, *J* = 7.8Hz, H-4), 7.3 (d, 2H, *J* = 7.5Hz, H-5), 8.01 (d, 4H, *J* = 6.3Hz, H-4',5'), 1.35 (t, 4H, $H_{\alpha,\alpha'}$), 1.33 (m, 4H, $H_{\beta,\beta'}$), 1.3 (m, 4H, $H_{\gamma,\gamma'}$), 0.99 (t, 6H, $H_{\delta,\delta'}$); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 152.0 (C-2), 126.8 (C-3), 138.01 (C-4), 123 (C-5), 153 (C-6), 173.2 (C-7), 132.5 (C-4',5'), 21.1 ($C_{\alpha,\alpha'}$), 21.6 ($C_{\beta,\beta'}$), 26.7 ($C_{\gamma,\gamma'}$), 13.8 ($C_{\delta,\delta'}$); IR (KBr, 4000-400cm^{-1}): *υ* 1662 $(COO)_{asym}$, 1490 $(COO)_{sym}$, 172 Δ*υ* (COO_{asym} - COO_{sym}), 462 (Sn–C), 442 (Sn–O), 1276 (N-C), 3010 (Aromatic ring), 1572 (ring N-N), 1662 (ring C=N); Mass Spectra (m/z%): 57.1 (51.3), 556.05 (66.8), 42.9 (54.3), 511.89 (71.6), 68.6 (66.8), 173.8 (54.6), 445.02 (100), 368.1 (34.7), 78.4 (46.8), 324.3 (25.0), 145.05 (18.0), 151.02 (34.2); M.P. 254 ˚C. Anal. Calcd. For $C_{24}H_{28}N_8O_4Sn$: C, 47.16; H, 4.62; N, 18.33; O, 10.47; Sn, 19.42. Found: C, 47.2; H, 5.1; N, 18.9; O, 10.47.

Tricyclohexyltin (IV)-6-(1',2',3'-triazol-2'-yl) pyridine-3-carboxylate (10)

Grey Amorphous Solid, 62.8% yield; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 9.71 (s, 1H, H-2), 7.92 (d, 1H, *J* = 7.5Hz, H-4), 7.44 (d, 1H, *J* = 7.3Hz, H-5), 8.05 (d, 2H, *J* = 6.4Hz, H-4',5'), 1.4 (m, 3H, H_α), 1.6 (m, 12H, $H_{\beta,\beta'}$), 1.49 (m, 12H, $H_{\gamma,\gamma'}$), 1.46 (m, 6H, H_δ); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 151.5 (C-2), 127.71 (C-3), 137.2 (C-4), 122.2 (C-5), 153.62 (C-6), 171.92 (C-7),

133.2 (C-4',5'), 6.5 (C_{α}), 29.2 ($C_{\beta,\beta'}$), 30.0 ($C_{\gamma,\gamma'}$), 28.0 (C_{δ}); IR (KBr, 4000-400cm^{-1}): υ 1596 $(COO)_{asym}$, 1416 $(COO)_{sym}$, 180 $\Delta\upsilon$ (COO_{asym} - COO_{sym}), 482 (Sn–C), 451 (Sn–O), 1301 (N-C), 3000 (aromatic ring), 1577 (ring N-N), 1657 (ring C=N); Mass Spectra (m/z%): 559.2 (49.5) [M+1], 68.02 (67.49), 489 (30.3), 78.11 (43.2), 412.82 (31.67), 44.12 (50.1), 369.1 (20.2), 287 (43.81); M.P. 196 °C. Anal. Calcd. For $C_{26}H_{38}N_4O_2Sn$: C, 56.03; H, 6.87; N, 10.05; O, 5.74; Sn, 21.30. Found: C, 57.3; H, 7.2; N, 10.9; O, 5.74.

Discussion

Vibrational spectroscopy

Infrared spectra of complexes of organotin (IV) moieties provides valuable information regarding the structures of the compounds in the solid state (Nath, Pokharia *et al.*, 2001). The disappearance of vibrations associated with COOH group of free acid is regarded as the coordination of SnR_3 or SnR_2 groups (Ahmed, Ali *et al.* 2002). The specific mode of coordination of carboxylates are assigned through the magnitude of separation ($\Delta\nu$) of the $\nu_{asym}(COO)$ and $\nu_{sym}(COO)$ bands i.e. difference of both frequencies [$\nu_{asym}(COO)$ - $\nu_{sym}(COO)$cm^{-1}]. Where $\Delta\nu$ smaller than 200 cm^{-1} indicates bidentate mode of coordination while greater than 200 cm^{-1} worth unidentate mode (Xie, Yang *et al.* 1996, Badshah, Mahmood *et al.* 1998).

The $\nu_{asym}(COO)$ IR frequencies for compounds 2-10 were found to be in the range of 1544-1675 cm^{-1}, while for $\nu_{sym}(COO)$ these were in the range of 1242-1490 cm^{-1}. The magnitude of separation ($\Delta\nu$) i.e. [$\nu_{asym}(COO)$-$\nu_{sym}(COO)$cm^{-1}] was observed to be 172-346 cm^{-1}. The complexes 2,3,5,6,8 were attributed as unidentate in nature with $\Delta\nu$ in range of 224-346 cm^{-1}, While the bidentate mode of coordination was confirmed for compounds 4,7,9,10 having values 172-182 cm^{-1}. The vibrations for Sn–C, Sn–O moieties and that of nitrogen i.e. C-N, C=N and N-N were observed in their expected regions, as previously reported in literaure. Typically Sn-C and Sn-O peaks were in the range of 456-489 and 412-451 cm^{-1} respectively. As far as ligand nitrogens are concerned, these gave different peaks as C-N, 1276-1352 cm^{-1}, C=N, 1615-1672 cm^{-1} and for N-N, 1523-1577cm^{-1}. Aromatic ring showed typical stretching in the range of 2989-3133 cm^{-1}.

Mass spectrometry

Mass Spectrometry is regarded as the most important technique to assess the reaction proceedings that leads to the confirmation of the structures of synthesized moieties. A uniform fragmentation pattern was observed in all the synthesized compounds i.e. ligand and its organotin (IV) derivatives with few common fragment (ion) peaks, that confirmed the stability of that specific ions. For example [$C_2H_2N_3^{\bullet}$] & [$C_5H_4N^{\bullet}$] with *m/z* 68.01 and 78.12 respectively were appeared in almost all the compounds with high intensity (100% in some cases). Significant molecular ion peaks (with lowest intensity in few exceptions) were also observed in all compounds. It confirms the formation of desired moiety. However, in case of triphenyltin(IV) and dibutyltin (IV) complexes, molecular ion peak was absent. Same behavior was observed for base peaks i.e. appeared in all cases except in triphenyltin (IV) and tricyclotin (IV) derivatives.

NMR spectroscopy

The reaction outcomes were monitored by ^{1}H NMR spectra, designated as sharp signals at room temperature for all the synthesized compounds (1-10). Disappearance of highly deshielded proton peak (at 11 ppm) of the ligand (1) within the complexes was labeled as the strong sign of coordination among ligand and the tin salts. In all the synthesized compounds, the downfield chemical shift value for H-4',5' (7.72-8.12 ppm) can be justified by the presence of two electron withdrawing nitrogen atoms in surroundings. Similarly deshielding of H-2 (8.82-10.0 ppm) is possibly due to the presence of carboxylate in neighborhood. The aromatic protons were also assigned with well resolved coupling. A complex pattern is observed for tri & di-butyl protons of compounds 2 & 9 due to the $-CH_2-CH_2-CH_2-CH_3$ skeleton in the normal reported range (H_{α}, 1.34–1.35 ppm), (H_{β} & H_{γ}, 1.32-1.33 ppm) and (H_{δ}, 0.97–0.99 ppm). The aromatic protons of triphenyltin(IV) in compounds 6, 7 & 8 were also marked as multiplets at

7.3, 7.42 & 7.27 respectively. In case of tricyclohexyltin (IV) (10), multiplets in the range of 1.40-1.6 ppm for different protons were also confirmed.

In ^{13}C NMR of the complexes (2-10), the carboxylate moiety (COO^-) was appeared at highly downfield (171.9-173.2 ppm), obviously due to coordination with metal atom, while the ligand showed its peak at 170.1 ppm. In all the compounds, deshielding of C-2 (150.8-152.2 ppm), C-4',5' (131.8-134.01 ppm) and C-6 (153.3-155 ppm) is possibly due to the presence of nitrogen atoms in the surrounding. In compounds **2** & **9**, an upfield shift was observed for carbon skeleton ($–CH_2–CH_2–CH_2–CH_3$) in the range of C_α - 13.8 & 14.4, C_β - 21.1 & 25.4, C_γ - 26.7 & 27 and C_δ - 13.8. Highly shielding methyl protons in di & tri methyl tin were attributed as $C_{\alpha,\alpha'}$ (21.1), $C_{\beta,\beta'}$ (21.6), $C_{\gamma,\gamma'}$ (26.7), $C_{\delta,\delta'}$ (13.8).

Biological activities

The organotin (IV) compounds have acknowledged as substantial schizonticidal, antimalarial, antifungal, antitumor and most recently proved to be anticancerous. The biological activity of organotin (IV) compounds is mainly governed by the number and nature of the organic groups destined to the central tin atom. The $[R_3Sn\ (IV)]^+$ and $[Ar_3Sn\ (IV)]^+$ derivatives usually employ powerful toxic action on the central nervous system (Pellerito, Nagy *et al.* 2006).

Usually the biocidal activities of the ligand increases upon chelation with suitable metal ions or with organometallics. This is due to an increase in the target oriented nature of the synthesized moieties (Ferrari, Capacchi *et al.* 2001). The organotin (IV) complexes bound preferentially to a phosphate group of the DNA backbone, that may reduce DNA synthesis or directly interact with cell membrane by increasing cytosolic Ca^{2+}concentration etc (Tabassum, Mathur *et al.* 2012). It makes organotin (IV) compounds very promising antifungal (Růžička, Dostal *et al.* 2002, Hussain, Siddiqui *et al.* 2009), antimicrobial (Teoh, Ang *et al.* 1999, Kaspady, Narayanaswamy *et al.* 2009) and antiproliferative (Katsoulakou, Tiliakos *et al.* 2008) etc.

The literature suggests that a potential cytotoxic agent should have an impact on effected cells or tissues but must not harm normal cells (Gielen and Tiekink 2005, Gómez-Ruiz, Kaluđerović *et al.* 2008). "Cytotoxicity" is used to describe the cumulative effect of a compound over a given period of time on cell number, whether due to apoptosis, necrosis, or a reduction in the rate of cell proliferation. A graphical representation of cytotoxic activity of the ligand (1) and its corresponding organotin (IV) complexes (2-10) is given in Fig. 1. From the graph it is clear that, the compound 8 exhibited maximum inhibition i.e. 63.82% while compound 5 remained at bottom line with only 15.88% inhibitory potential.

The complexes revealed significant changes in % inhibition relative to the free ligand i.e. compound 7 (55.74%) & compound 8 (63.82%) showed higher activity compared to the free ligand (50.515%). Although compounds 10, 9, 2, 4 & 5 showed activity lower than that of free ligand. These findings indicate that the complexes are better cytotoxic in nature, which may be related to a decline in unsaturation and size reduction in substituents attached with tin (Hussain, Ali *et al.* 2011).

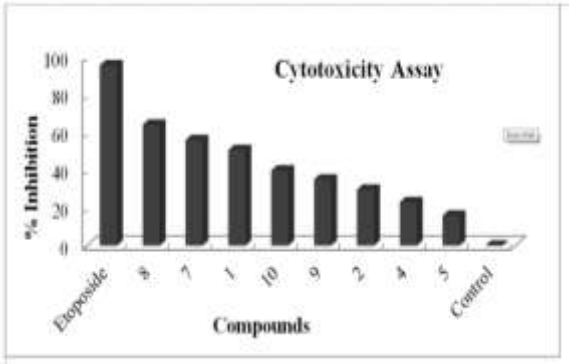


Fig. 1. Cytotoxicity assay profile of ligand and their corresponding organotin (IV) complexes using brine shrimp lethality assay method. Each bar represents the percentage inhibition for 10mM test concentration. A reference drug (positive control) and solvent or negative control (10mM DMSO) are also shown along with synthesised compounds.

Urease is an intracellular as well as an extracellular enzyme, which catalyzes urea hydrolysis and gives carbamate and a molecule of ammonia.

Carbamate is instantly hydrolyzed into ammonia and carbonic acid. Urease is also involved in the catabolism of purines (Watson 2000). So it is important to develop such precursors that can inhibit urease activity.

It has been previously reported (Amtul, Siddiqui *et al.* 2002), that triorganotin (IV) exhibit exceptionally higher antiurease activity than diorganotin (IV) complexes. The results of the antiurease assay of synthesized compounds confirm the above findings (Fig. 2). Here the triorganotin(IV) complex i.e. 10 showed 85.16% inhibition while compounds 8 & 2 depicted 80.92% and 75.45% respectively. Also the compound (5) showed least antiurease activity (61.12% inhibition). From the results, it can be concluded that all the compounds are much good antiureatic agents, as previously described (Hussain, Ali *et al.* 2011).

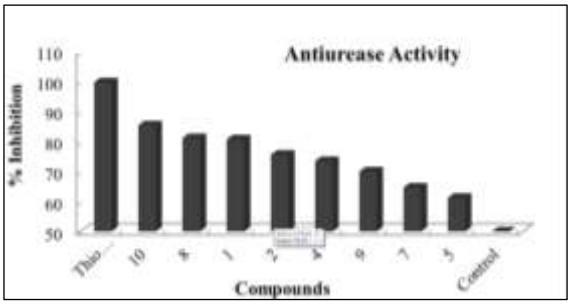


Fig. 2. Antiurease assay profile of ligand and their corresponding organotin (IV) complexes by using Berthelot (phenol-hypochlorite) assay using 96-well plate format. Each bar depicts the percentage inhibition (mm) for a 10mM test concentration. A reference drug (positive control) and solvent or negative control (10mM DMSO) is also shown along with synthesised compounds.

Antibacterial screening test of the synthesized ligand and its organotin (IV) derivatives was carried out against *E.coli* and shown in Fig. 3. It is clear that compounds 8 and 9 exhibited excellent percentage inhibition i.e. 83.2% & 85.7% respectively. While other complexes (7>10>4>2>5) showed inhibition capability in the range of 60.6-78.2%. Usually, good percent inhibition is due to an ease of permeation of the complexes through cell membrane.

The polarity of the central tin atom decreases upon chelation which increases its lipophilic character and an ease of permeation through the lipid layer of cell membrane (Hussain, Ali *et al.* 2011, Yin, Liu *et al.* 2012).

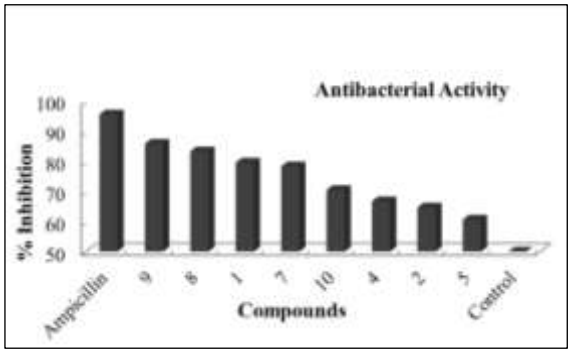


Fig. 3. Antibacterial activity profile of ligand and their corresponding organotin (IV) complexes by using disc diffusion method. Each bar represents the percentage inhibition (mm) for 10mM test concentration. A reference drug (positive control) and solvent or negative control (10mM DMSO) is also graphed along with synthesised compounds.

Conclusion

A facile *N*-arylation of 2*H*-1,2,3-triazole and 6-chloropyridine-3-carboxylic acid was carried out and ligand thus formed was complexed with organotin (IV) salts for the synthesis of mono- and di-coordinated complexes. Molecular structures were confirmed with the help of different spectroscopic data (IR, NMR and MS). Synthesized compounds were pharmacologically screened for antibacterial, antiureatic and cytotoxic assays. Among all organotin (IV) compounds, triphenyltin (IV)-6-(1',2',3'-triazol-2'-yl)pyridine-3-carboxylate (8) exhibited good cytotoxic, antiureatic and antibacterial properties. In contrast trimethyltin (IV)-6-(1',2',3'-triazol-2'-yl) pyridine-3-carboxylate (5) showed worst inhibition against the said biological assays.

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