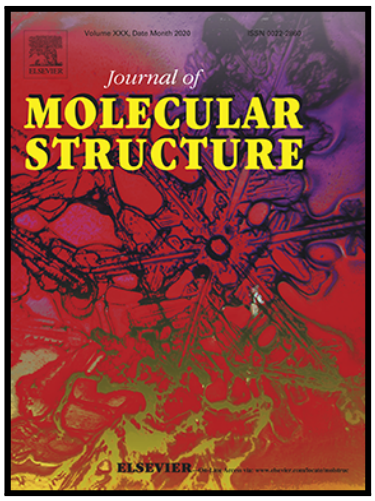

Organotin(IV) derivatives based on 2-((2-methoxyphenyl)carbamoyl)benzoic acid: Synthesis, spectroscopic characterization, assessment of antibacterial, DNA interaction, anticancer and antileishmanial potentials

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Highlights

- Synthesis of novel organotin(IV) carboxylates
- Spectroscopic characterizations and structural elucidation
- Interaction with SS-DNA *via* intercalative mode of interaction
- *In vitro* antibacterial, anticancer, and antileishmanial activity

Organotin(IV) derivatives based on 2-((2-methoxyphenyl)carbamoyl)benzoic acid: Synthesis, spectroscopic characterization, assessment of antibacterial, DNA interaction, anticancer and antileishmanial potentials

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Abstract

A series of ten organotin(IV) carboxylate derivatives of 2-((2-methoxyphenyl)carbamoyl)benzoic acid were prepared and confirmed by FTIR, CHN analysis and single crystal XRD (SCXRD) as well as by NMR and mass spectrometry. The microelemental CHN analysis results give a close matching with those of the theoretical values of CHN atoms. The results of the solid state SCXRD for the complex **3** reveals trigonal bipyramidal geometry (TBG) with slight distortion for the R_3SnL derivatives. Further confirmation about the 5-coordinated TBG may also be achieved from the τ value which is 0.87 for the complex **3**. It is obvious from the crystal structure of the complex **3** that the involvement of the O1 of the carboxylate moiety and O3 of the amide moiety with Sn atom are responsible for formation of the polymeric structure having 5-coordinated TBG. The values of Δν obtained from FTIR analysis prove the 5- and 6-coordinated environments around the Sn atom for the R_3SnL and R_2SnL_2 derivatives, respectively. The comparison of SCXRD value (124.8º) and that of ^{13}C NMR value (123º) for C-Sn-C angle in complex **3** is the best confirmation of 5-coordinated TBG for the R_3SnL derivatives. The evaluated compounds interact with DNA by an intercalative type of binding as displayed by the results obtained from UV-vis. and viscosity measurements. The results of the antimicrobial activity of the evaluated compounds in

comparison to the standard drugs demonstrate that the tested compounds possess good antimicrobial potentials. The cytotoxicity results obtained against H-157 and BHK-21 cell lines using Sulforhodamine B based method show that compound **1** has the maximum activity among the studied compounds and its activity is comparable to that of the vincristine. The small IC_{50} value for the compound **1** as compared to the standard antileishmanial drug, Amphotericin B, proves the efficiency of the tested compounds for the treatment of *leishmania* disease.

Keywords: Organotin(IV) carboxylate; spectroscopic analysis; DNA binding; Antibacterial activity; Cytotoxicity; Antileishmanial activity

1. Introduction

The flexible molecular structures and diverse biochemical applications attract the attention of scientists towards the organometallics compounds among which, organotin compounds deserve keen importance because of their structural and strong biological activity [1]. Organotin compounds having Sn-C bonds with general representation R_nSnX_{4-n} either with R = aliphatic or aromatic groups can easily be prepared and handled under normal conditions [2]. From literature study it has been found that the toxicity of organotin(IV) compounds in biological system is dropped while their lipophilicity is enhanced as a result of an enhancement both in size as well as substituents on the Sn atom [3].

Among the various organotin compounds, the most widely studied are the organotin(IV) carboxylates because of distinct advantages of the carboxylate moiety. The carboxylate moiety possesses the coordination ability *via* the oxygen atoms and coordinates to metal atom either through a monodentate, bidentate (isobidentate or anisobidentate), or a bridging manner [1, 4]. The display of wide range of biological properties (e.g., antimicrobial, antitumor, anticancer and antileishmanial etc) makes the organotin(IV) attractive for researchers as these are highly toxic even at very minimum dose. Regarding the coordinating ability of carboxylates ligands toward organotin compounds, the researcher have diverted their attention toward the development of structurally modified new carboxylate and their organotin(IV) derivatives [5] as the

organotin(IV) carboxyalte complexes adopts several geometries like octahedral, trigonal bipyramidal and tetrahedral [6]. Organotin derivatives with carboxylate ligands possess the highest cytotoxicity against human tumor cell lines than with thiolato or dithiocarbamato ligands [7].

Organotin(IV) compounds with different coordinating ligands particularly with carboxylate derivatives are studied in order to know about the relation between the coordination fashion and their cytotoxicity. It is found that organotin(IV) compounds interact with membrane proteins or glycoproteins or with cellular proteins. They also interact with DNA and alter the intracellular metabolism of the phospholipids of the endoplasmic reticulum [8]. The most demanding objective of the medicinal chemistry is to develop novel and targeted metal based anticancer agents. Organotin(IV) compounds are considered best for this purpose as they have explored excellent antitumor potential [9] and their activity is mainly depends both on the nature and number of the R group coordinated to Sn. Gielen *et al*., has reported that the activity of the most of these compounds against colon and breast carcinoma cell lines depends on the organic moiety attached to Sn atom [10]. Structure Activity Relationship (SAR) has explored that these compounds possess some promising properties (such as expansion in coordination number of Sn (4-8), Ligand-Sn stable bonds, slow hyrdolytic decomposition etc) which make them attractive for the researchers [11].

The protozoan parasitic disease called *leishmaniases* is also challenging the attention of Scientists as it is ranked by WHO as the 6^{th} among the major infectious diseases worldwide [12, 13]. Both first and second-lines drugs are used for the cure of the *leishmaniases* [14]. The researchers are working for the identification and preparation of novel agents to overcome the parasite resistance and toxicities problem at effective therapeutic doses [15]. In this regard, organotin(IV) carboxylate derivatives are applied here against *leishmania* major.

In linkage with our earlier research, we are reporting the preparation and characterization of ten new 2-(2-methoxyphenylcarbamoyl)benzoic acid based organotin(IV) complexes. The newly

designed samples were tested for exploration of their antibacterial activity against different human pathogens. They were also tested for interaction with DNA as well as their cytotoxic activity was checked against lung carcinoma and kidney fibroblast cell lines. Moreover, these compounds were also tested for their antileishmanial potential against *leishmania* major.

2. Experimental section

2.1. Materials and methods

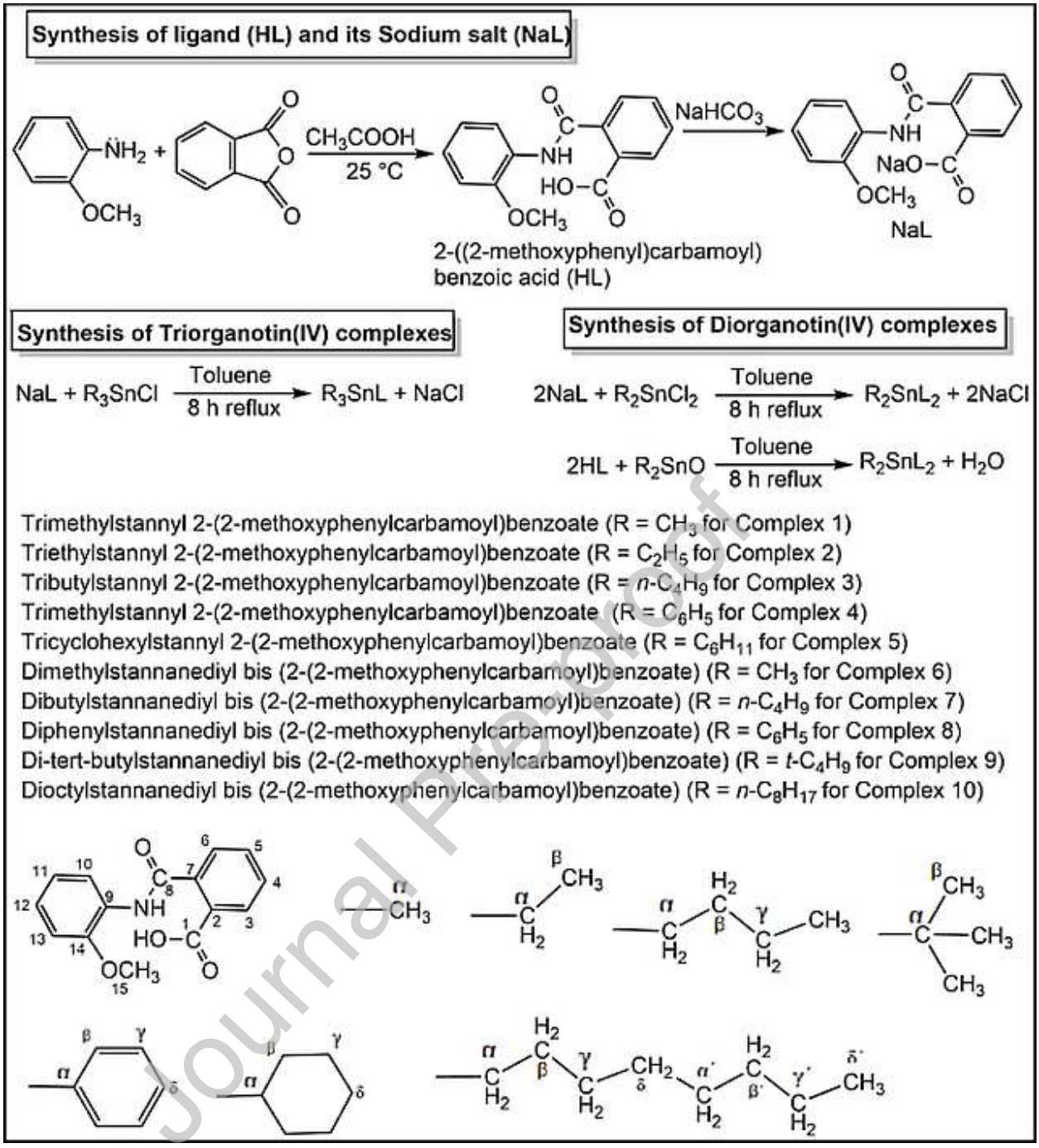
The required reactants and solvents were purchased for sigma Aldrich, Fluka and RDH. Melting point was determined by UK made Gallenkamp apparatus while IR, NMR and Mass spectra were recorded by Thermo Nicolet-6700 FTIR, JEOL ECS (400 MHz) Spectrophotometers and Thermo Scientific executive, respectively. The percentage elemental compositions were determined by CE-440 Elemental Analyzer while single crystal samples were analyzed by Bruker Apex II CCD diffractometer at 296 K. The crystal structures were solved and refined by SHELXTL [16] and SHELX 2012 [17]. The interaction of the evaluated compounds with DNA was performed by Shimadzu1800UV-visible Spectrophotometer.

2.2. Synthesis of 2-((2-methoxyphenyl)carbamoyl)benzoic acid (HL), Sodium salt (NaL) and Organotin(IV) carboxylate derivatives

The ligand 2-((2-methoxyphenyl)carbamoyl)benzoic acid was prepared according to the reported method [9, 18, 19] and shown in Scheme 1. 20 mmol of each of 2-methoxyphenyl aniline and phthalic anhydride were dissolved in analytical grade glacial CH_3COOH which were then mixed together. After mixing the mixture was stirred at 25 °C till the presence of precipitate in the flask. After the appearance of precipitate the stirring was further continued for few minutes and then was filtered. The reaction product was washed with CH_3COOH to eliminate the unreacted reactant and also with distilled H_2O to eliminate any phthalic acid formed in the experiment. The product was then air dried and fine crystals were obtained from acetone after the slow evaporation of the solvent.

Sodium salt of the 2-((2-methoxyphenyl)carbamoyl)benzoic acid was prepared as a result of obtaining a clear solution after the reaction of 2-((2-methoxyphenyl)carbamoyl)benzoic acid suspended in distilled H_2O with NaOH. The required product was obtained by evaporating the water through Rotary evaporator.

The organotin(IV) carboxylate complexes were prepared by following the previously reported method [20-23]. Both tri and di organotin(IV) carboxylate complexes were obtained from the reaction between NaL and R_3SnCl/R_2SnCl_2 in 1:1 (in case of R_3SnCl) or 2:1 (in case of R_2SnCl_2) molar ratio using analytical grade toluene as a solvent by stirring and refluxing for about 6-8 h as shown in Scheme 1. The required products were obtained after evaporating the toluene through Rotary evaporator which was air dried and dissolved in chloroform for crystallization. In case of octyltin complex, instead of NaL, 2-((2-methoxyphenyl)carbamoyl)benzoic acid (HL) was used and the reaction was carried out in Dean and Stark apparatus which is used to remove the water formed in the experiment.



Scheme 1: Procedure for HL, NaL and organotin(IV) derivatives synthesis. For the explanation of NMR data, the numbering of HL as well as R groups attached to Sn is also given here.

2.3. Determination of DNA-compound interaction

The interaction of the Salmon sperm DNA (SS-DNA) with the representative compounds was determined by UV-vis. Spectroscopy and viscosity measurements. The SS-DNA solution was prepared by dissolving a small quantity of sodium salt of SS-DNA (about 0.2 mg) in deionized H_2O and was stirred at 25 °C for 24 h to obtain a clear homogeneous solution which was stored at

4 °C. The concentration of this solution was determined by measuring its absorbance at 260 nm and using the molar absorptivity of SS-DNA, 6600 M^{-1} cm^{-1}. By this way the concentration of DNA solution was 1.8×10^{-4} M and also was sufficiently free of protein as the value of the A_{260}/A_{280} ratio was 1.8. The compound-DNA interaction study was carried out by varying the concentration of the DNA while that of the compound was kept constant. The reference cell also contains the same concentration of DNA to eliminate the effect of DNA alone [24-28].

The binding mode of the interaction between DNA and compound was find out through viscosity measurements by varying the concentration of the DNA and keeping the concentration of the compound constant [29-31].

2.4. Determination of biological potential

The biological activity of the designed compounds was determined in term of antibacterial activity against seven different bacterial strains namely *E. coli*, *S. marcesscens*, *K. pneumoniae*, *S. epidermidis*, *S. pyogenes*, *P. aeruginosa* and *S. aureus* using agar well diffusion assay. The anticancer activity against H-157 and BHK-21 cell lines was carried out using SRB (Sulforhodamine B) based Skehan´s method with 100, 10, 1, 0.1 μM concentrations of the compounds. The antileishmanial activity against *leishmania* major was performed using amphotericin B as a reference drug. All the above mentioned biological activities are done following exactly the same procedure as discussed in our earlier reported papers [1, 4].

3. Results and discussion

In this paper we have explored the synthesis of ten new organotin(IV) carboxylate complexes derived from 2-((2-methoxyphenyl)carbamoyl)benzoic acid. All the prepared compounds are air and moisture stable and are obtained in good yield. The IUPAC names of the synthesized compounds are given in Scheme 1 while their physical data including melting point, percentage yield, molecular formula and weight along with CHN elemental compositions are given in Table 1. The newly designed compounds are soluble at room temperature in MeOH, EtOH, $CHCl_3$, DMSO. Their sharp M. point is the indication of the purity of these synthesized compounds.

Table 1: Physical and percentage CHN data of the prepared compounds

Comp. No	Yield (%)	M. point (°C)	F. weight	Formula	C, cal./found	H, cal./found	N, cal./found
HL	89	140-142	271.1	$C_{15}H_{13}NO_4$	66.4 (66.2)	4.8 (4.8)	5.2 (5.2)
1	77	117-119	434	$C_{18}H_{21}NO_4Sn$	49.8 (49.4)	4.9 (4.8)	3.2 (3.1)
2	80	102-104	476.1	$C_{21}H_{27}NO_4Sn$	53.0 (53.2)	5.7 (5.7)	2.9 (2.7)
3	87	112-114	560.3	$C_{27}H_{39}NO_4Sn$	57.9 (57.8)	7.0 (6.8)	2.5 (2.3)
4	81	97-99	620.3	$C_{33}H_{27}NO_4Sn$	63.9 (63.5)	4.4 (4.3)	2.3 (2.6)
5	73	198-200	638.4	$C_{33}H_{45}NO_4Sn$	62.1 (62.0)	7.1 (7.3)	2.2 (2.4)
6	76	130-132	689.3	$C_{32}H_{30}N_2O_8Sn$	55.8 (56.0)	4.4 (4.4)	4.1 (4.2)
7	82	120-122	773.5	$C_{38}H_{42}N_2O_8Sn$	59.0 (58.9)	5.5 (5.5)	3.6 (3.7)
8	77	Decompose	813.4	$C_{42}H_{32}N_2O_8Sn$	62.0 (62.3)	4.2 (4.3)	3.4 (3.6)
9	76	178-180	773.5	$C_{38}H_{42}N_2O_8Sn$	59.0 (58.7)	5.4 (5.3)	3.6 (3.5)
10	78	138-140	885.7	$C_{46}H_{58}N_2O_8Sn$	62.4 (43.8)	6.6 (6.4)	3.2 (3.2)

3.1. FTIR analysis

Table 2 demonstrates the important peaks observed in the FTIR spectra of the synthesized compounds. The distinct OH peak observed in the spectrum of the 2-((2-methoxyphenyl)carbamoyl)benzoic acid at 3200 cm^{-1} confirm its formation. This distinct OH peak was missing in the spectra of the NaL as well as in that of the organotin(IV) carboxylate complexes which is the indication of the deprotonation of the 2-((2-methoxyphenyl)carbamoyl) benzoic acid and attachment of the carboxylate moiety to Sn atom confirming the formation of desired complexes. The NH peak at 3368 cm^{-1} observed in the spectrum of the 2-((2-methoxyphenyl)carbamoyl)benzoic acid is also present in the spectra of its complexes slightly at higher wavelength compared to its position in ligand. This shift in the position of NH peak toward higher wave number may be due to the fact that during completion electron density is transferred from the ligand to Sn metal because of its electropositive nature. The complexation was further confirmed by the observation of two new peaks for Sn-C and Sn-O peaks at 540-585 cm^{-1} and 440-467 cm^{-1}, respectively. In case of complex **4** the Sn-C peak was observed in far IR region at 267 cm^{-1} that is because of the Sn-Ph mass effect [32].

Δν decides about the binding nature of the carboxylate moiety as well as coordination environment about the Sn atom. A decrease in the value of νCOO_{asym} while an increase in the value of νCOO_{sym} is observed during the complexation and as a result the value of Δν also decreases [10]. The values of νCOO_{asym} and νCOO_{sym} for the ligand are 1594 cm^{-1} and 1332 cm^{-1} with a Δν value of 272 cm^{-1}. The value in complexes is 1500-1567 cm^{-1} and 1345-1377 cm^{-1} with Δν value smaller than that of the ligand (272 cm^{-1}). According to the literature, a reduction in the value of Δν occurs when there is shift of coordination from four to five or higher number. The value of Δν for complexes **1** and **2**, i.e., Me_3SnL and Et_3SnL derivatives, so the carboxylate moiety possess a bidentate bridging coordination mode as Δν of complex ≤ Δν of NaL while in complexes **3-5**, i.e., Bu_3SnL, Ph_3SnL and Cy_3SnL derivatives the carboxylate moiety possess a monodentate mode as Δν of complex > Δν of NaL [33]. This is because of the three bulky butyl, phenyl and cyclohexyl group attached to Sn atom. A redistribution of electron density and increase in the value of νCOO_{sym} takes place in complexes where the carboxtylate moiety has monodentate nature [33]. The SCXRD for the Bu_3SnL (complex **3**) also support the FTIR data in the carboxylate moiety is in coordinated to Sn atom in a monodentate fashion.

Table 2: Important FTIR peaks (ν, cm^{-1}) of the prepared compounds

Comp. No.	C-Sn	O-Sn	O=C	COO_{sym}	COO_{asym}	Δν	OH	NH
HL	-	-	1707	1383	1597	214	3200	3368
NaL	-	-	1678	1370	1559	189	-	3399
1	540	444	1694	1372	1554	182	-	3370
2	556	457	1687	1368	1552	184	-	3380
3	575	460	1690	1377	1570	193	-	3377
4	267	445	1691	1347	1547	200	-	3381
5	562	460	1685	1328	1530	202	-	3386
6	550	450	1680	1371	1506	135	-	3382
7	540	440	1688	1369	1504	135	-	3381
8	278	458	1700	1352	1500	148	-	3372
9	554	462	1701	1362	1502	140	-	3380
10	585	467	1716	1354	1505	151	-	3390

3.2. NMR analysis

The multinuclear NMR spectra (^{1}H, ^{13}C and ^{119}Sn) of the prepared compounds were analyzed in d_6-DMSO. The numbering pattern of the ligand 2-((2-methoxyphenyl)carbamoyl)benzoic acid and the organic moieties attached to Sn atom are shown in Scheme1. The ^{1}HNMR and ^{13}C/^{119}SnNMR data are given in Table 3 and 4, respectively.

The formation of the ligand 2-((2-methoxyphenyl)carbamoyl)benzoic acid was confirmed through ^{1}HNMR (Table 3) by the presence of the two distinct singlets for OH peak of the carboxylic group and NH at 13.0 ppm and 9.09 ppm, respectively. The chemical shift values for remaining aromatic protons appear in their respective regions. The formation of the complexes was confirmed by comparing their spectra with that of the ligand 2-((2-methoxyphenyl)carbamoyl)benzoic acid in which the carboxylic group OH was absent in the spectra of the complexes. Furthermore, the presence of some new peaks for the organic moieties attached to Sn atoms also confirms their formation. For complexes **1** and **6**, coupling was observed between the ^{119}Sn and ^{1}H nuclei for which the $^{3}J[^{119}\text{Sn-}^{1}\text{H}]$ value was calculated which has the value of 62 Hz and 100 Hz that lies in the range of 5-coordinated and 6-coordinated environment at Sn atom, respectively [34]. The $^{3}J[^{119}\text{Sn-}^{1}\text{H}]$ values were converted into $\theta_{\text{C-Sn-C}}$ using the famous Lockhart´s equation to know about the geometry of the complexes [35]. For complex **1** (triorganotin derivatives), $\theta_{\text{C-Sn-C}}$ = 113° while for complex **6** (diorganotin derivatives), $\theta_{\text{C-Sn-C}}$ = 147°. These values also lie in the range of 5-coordinated and 6-coordinated environment at Sn atom, respectively.

In ^{13}CNMR spectrum of the ligand 2-((2-methoxyphenyl)carbamoyl)benzoic acid, the two informative peaks for C1 (carboxylic group carbon) at 167.5 ppm and C8 (amide group carbon) appear at 169.2 ppm were shifted down field in the spectra of the complexes as a result of transfer of electron density for the ligand to the electropositive Sn metal center. In ^{13}C NMR spectra of the complexes, ^{1}J coupling between ^{119}Sn and ^{13}C nuclei, $^{1}J[^{119}\text{Sn-}^{13}\text{C}]$, were also observed that are helpful in geometry determination around Sn center as shown in square

brackets in Table 4. These ^{1}J coupling values were also converted into $\theta_{C\text{-}Sn\text{-}C}$ angle as shown in {} brackets in Table 4. Both the values of ^{1}J and $\theta_{C\text{-}Sn\text{-}C}$ for mention complexes for in the range of 5-coordinated and 6-coordinated for tri- and di-organotin derivatives respectively.

The ^{119}Sn NMR is used for the prediction of geometry of Sn containing complexes. The data of ^{119}Sn NMR data of the prepared complexes is given in Table 4. The chemical shift of ^{119}Sn is highly dependent on the nature of the attached alkyl/aryl group and the electronegativity of the ligand bonded to Sn atom as well as temperature employed in the experiments [36]. A sharp single peak was observed in the ^{119}Sn NMR spectra of the complexes. For the trimethyl- (complex **1**), triethyl- (complex **2**) and tributyltin (complex **3**) complexes the ^{119}SnNMR the signal for Sn NMR peak appear in low field (highly shielded) region compared to the normal range of 5-coordination which may be due electron withdrawing and donating ability of the groups attached to ligand as well as electronegativity of the substituent at the tin atom. Also it has been found in the literature that the presence of a group having lone pair electron or π electrons of multiple bonds then SN NMR peak in high shielded region appears due to partial filling of vacant 5d orbital of Sn atom [34]. For complexes **4** and **5** the value of Sn NMR lies in the normal range of 5-coordniated environment. While for diorganotin derivatives (complexes **6-10**) the Sn NMR peak appears in the normal range of 6-coordinated environment.

Table 3: ^{1}H NMR peaks (chemical shift in ppm) for the prepared compounds

Comp. No	Proton No.											
	OH	**H3**	**H4**	**H5**	**H6**	**NH**	**H10**	**H11**	**H12**	**H13**	**H15**	**α, β, γ, δ**
HL	13.10 , s	7.91, d (6.4)	7.94, m	7.88, m	7.35, d (6.4)	9.09 , s	7.18, d (7.2)	6.98, t (3.6)	7.05, t (3.6)	6.80, d (8)	3.77, s	-
1	-	8.14, d (8.0)	7.90, m	7.86, m	7.37, d (6.4)	9.57 , s	7.02, d (7.6)	6.89, t (4.0)	6.99, t (3.6)	6.80, d (8)	3.74, s	0.18 (α, s [62][a], {113°}[b])
2	-	8.18, d (6.4)	7.93, m	7.87, m	7.71, d (6.4)	8.82 , s	7.43, d (7.2)	6.98, t (3.8)	7.10, t (3.6)	6.74, d (8.4)	3.73, s	0.97 (α, q), 1.14 (β, t (3.8))
3	-	8.19, d (7.2)	7.90, m	7.86, m	7.64, d (7.2)	8.88 , s	7.25, d (7.2)	6.92, t (3.6)	7.08, t (3.6)	6.88, d (7.2)	3.74, s	1.0 (α, t (4.0)), 1.21 (β, m), 1.49 (γ, m), 0.79 (δ, t (3.6))
4	-	8.05, d (8.0)	7.94, m	7.76, m	7.60, d (7.2)	8.85 , s	7.22, d (7.6)	6.99, t (3.8)	7.06, t (3.8)	6.87, d (7.6)	3.70, s	7.15 (β, d (8.0)), 7.40 (γ, m), 7.53 (δ, m)
5	-	8.06, d (6.4)	7.90, m	7.85, m	7.68, d (6.4)	8.97 , s	7.34, d (7.2)	6.90, t (3.6)	7.11, t (3.6)	6.70, d (8.4)	3.70, s	1.21 (α, m), 1.80 (β, m), 1.60 (γ, m), 1. 48 (δ, m)
6	-	8.10, d (8.0)	7.95, m	7.96, m	7.47, d (6.4)	9.01 , s	7.32, d (7.6)	6.99, t (4)	7.12, t (3.6)	6.80, d (8)	3.73, s	0.63 (α, s [100], {147°})
7	-	8.11, d (7.2)	7.93, m	7.87, m	7.60, d (7.2)	8.98 , s	7.20, d (7.2)	6.97, t (3.6)	7.10, t (3.6)	6.86, d (7.2)	3.73, s	1.12 (α, t (3.6)), 1.56 (β, m), 1.40 (γ, m), 0.89 (δ, t (3.6))
8	-	8.05, d (8.0)	7.95, m	7.89, m	7.76, d (8.0)	9.09 , s	7.18, d (8.0)	7.00, t (3.8)	7.07, t (3.6)	6.74, d (8.0)	3.70, s	7.14 (β, d (3.6)), 7.33 (γ, m), 7.45 (δ, m)
9	-	8.10, d (7.2)	8.0, m	7.93, m	7.34, d (7.2)	9.23 , s	7.14, d (7.2)	6.88, t (3.2)	7.19, t (3.2)	6.98, d (7.2)	3.72, s	1.19 (β, s)
10	-	7.81, d (7.2)	7.94, m	7.89, m	7.35, d (7.2)	9.08 , s	7.18, d (8.4)	6.92, t (3.6)	7.04, t (3.6)	6.75, d (8.4)	3.75, s	1.32 (bs, α),1.51 (bs, β,γ,δ), 1.17 (bs, α',β',γ'), 0.79 (t, δ', 3.4)

a) 2*J*[119/117Sn-1H] in Hz. b) C-Sn-C bond angle calculated while using 2*J*(119Sn-1H) in Hz. All the symbols used α, β, γ, δ, etc used are explained in Scheme 1.

Table 4: ^{13}C NMR data (chemical shift in ppm) of the prepared Compounds

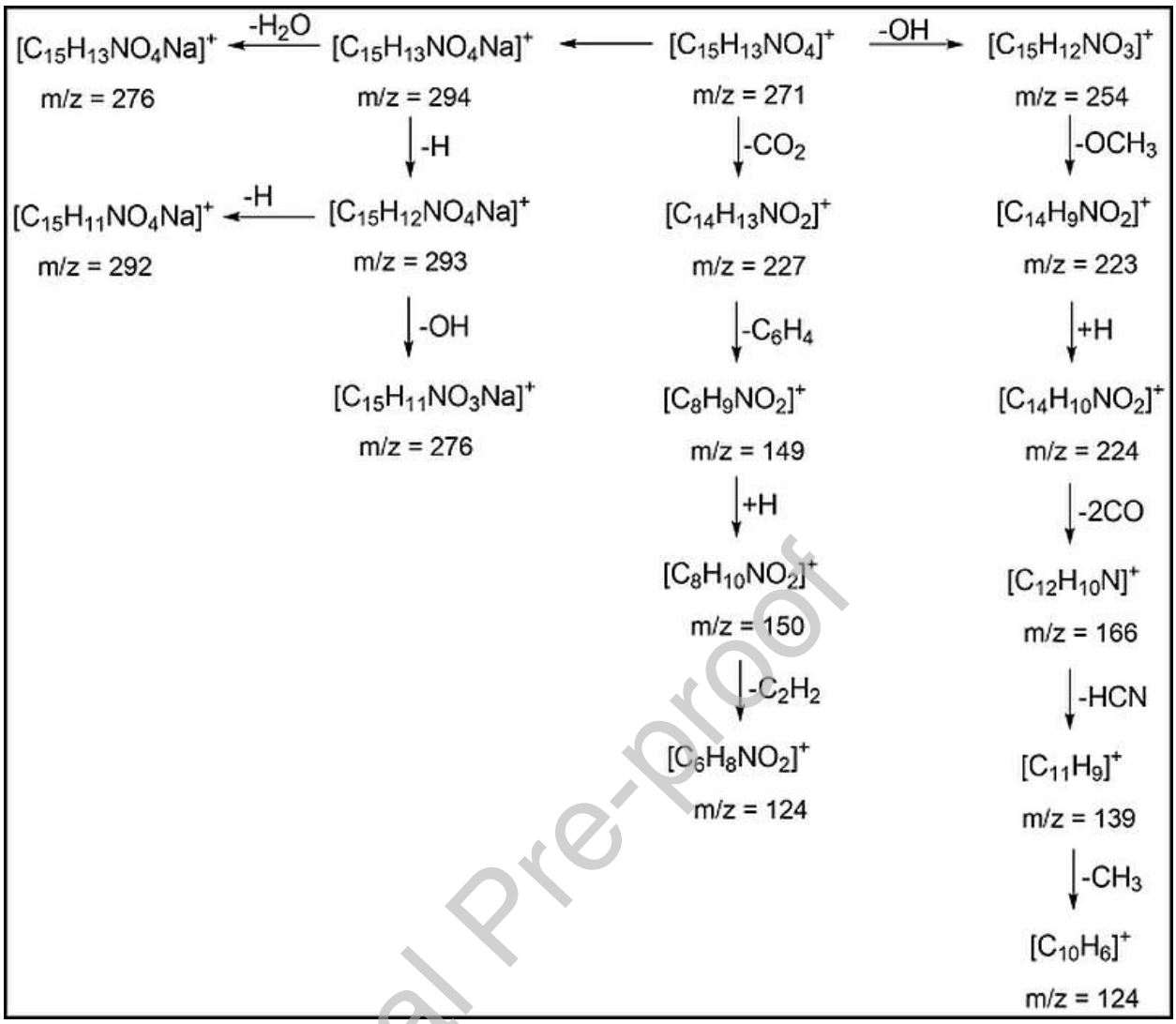
Comp. No.	Carbon No.										$C_{\alpha, \beta, \gamma, \delta, \alpha', \beta', \gamma', \delta'}$	^{119}Sn
	C_1	C_{2-7}	C_8	C_9	C_{10}	C_{11}	C_{12}	C_{13}	C_{14}	C_{15}		
HL	167.5	129.9, 129.8, 135.3, 139.1, 127.9, 130.7	169.2	124.0	123.1	120.6	125.3	111.8	150.8	56.3	-	-
1	170.7	129.4, 129.1,135.8, 137.3, 128.6, 129.7	174.7	124.4	121.8	120.7	128.3	111.4	149.7	56.2	-0.7 C_α [440, 421][a], {115°}[b]	-16.7
2	170.7	129.8,129.6,135.2, 138.3,128.5, 130.2	175.3	124.4	121.2	120.7	128.0	111.3	149.5	56.1	11.1 C_α [486, 465], {119°}, 10.6 C_β [31]	-18.3
3	170.8	129.7, 129.5,135.6, 137.9,128.5,130.1	175.0	124.3	121.1	120.6	128.0	111.3	149.4	56.1	19.1 C_α [472, 460], {122°}, 28.2 C_β[27], 27.1 C_γ [77], 14.1 C_δ	-20.6
4	170.7	129.8, 128.7,135.5, 138.2,128.4, 130.5	175.0	124.5	121.7	120.8	128.1	111.4	149.7	56.1	143.6 C_α [664], {117°}, 136.7 C_β [46], 129.4 C_γ [51], 128.8 C_δ	-226.4
5	170.6	129.6, 129.2,135.1, 137.2,128.0,130.0	174.8	124.4	121.6	120.6	128.2	111.4	149.5	56.1	27.3 C_α [672]. {118°}, 29.4 C_β[70], 31.0 C_γ[28], 35.1 C_δ	-200.0
6	170.7	130.2, 129.7,136.0, 138.1,128.7,131.1	175.0	124.3	121.1	120.6	128.0	111.3	149.4	56.1	0.9 C_α [820], {149°}	-284.9
7	170.8	130.2, 129.4,135.9, 137.8,129.0,130.8	175.0	124.4	121.4	120.6	128.1	111.3	149.4	56.1	20.0 C_α [640], {139°}, 27.6 C_β[46], 26.3 C_γ [63], 14.2 C_δ	-277.6
8	167.4	131.3, 130.9, 135.4, 138.1,129.4, 132.1	174.4	124.1	121.4	120.7	128.3	111.1	155.8	56.3	146.7 C_α, 136.7 C_β, 128.7 C_γ [59], 128.4 C_δ	-272.2
9	167.9	130.0, 129.6, 135.4, 137.2,128.5, 130.9	172.7	124.1	121.1	120.5	128.2	111.5	150.0	56.1	30.6 C_α, 30.1 C_β	-289.3
10	167.4	131.3, 130.9, 135.3, 139.1,129.4, 132.1	170.5	124.0	121.1	120.7	128.2	112.8	155.8	56.3	25.1 C_α, 28.6 C_β, 29.5 C_γ, 31.9 C_δ, 33.4 $C_{\alpha'}$, 22.7 $C_{\beta'}$, 29.2 $C_{\gamma'}$, 14.5 $C_{\delta'}$	-295.5

a) $1J$[119/117Sn-13C] in Hz. b) C-Sn-C bond angle calculated while using $1J$(119Sn-13C) in Hz. All the symbols used α, β, γ, δ, etc used are explained in Scheme 1.

3.3. Mass Spectrometry

For 2-((2-methoxyphenyl)carbamoyl)benzoic acid the fragmentation pattern is given in Scheme 2, in which the presence of the molecular ion peak, $[C_{15}H_{13}NO_4]^+$ at m/z of 271, conform the formation of the proposed compound. The molecular ion undergoes the fragmentation which give rise to the fragment $[C_{14}H_{13}NO_2]^+$ with m/z = 227 by the carbon dioxide molecule. The resulting fragment on further subsequent lose of C_6H_4, H and C_2H_2 units to produce the base peak, $[C_6H_8NO_2]^+$ with m/z = 124. The other fragmentation pathways are presented in detail in Scheme 2.

The formation of the organotin(IV) carboxylate derivatives by mass spectrometry was confirmed by the presence of the molecular ion peak in their mass spectra. In addition to the molecular ion peak, some peak present in the fragmentation of the 2-((2-methoxyphenyl)carbamoyl)benzoic acid were also there in the spectra of the organotin(IV) complexes. These organotin(IV) carboxylate complexes have followed the fragmentation pattern of our previously reported organotin(IV) analogous [34]. Thus here we have just mention the molecular ion fragment of synthesized organotin(IV) carboxylate complexes along with their m/z value as well as relative abundance, i.e., $[C_{18}H_{21}NO_4Sn]^+$, m/z = 435 (32) for complex **1**, $[C_{21}H_{27}NO_4Sn]^+$, m/z = 477 (21) for complex **2**, $[C_{27}H_{39}NO_4Sn]^+$, m/z = 561 (5) for complex **3**, $[C_{33}H_{27}NO_4Sn]^+$, m/z = 621 (16) for complex **4**, $[C_{33}H_{45}NO_4Sn]^+$, m/z = 639 (15) for complex **5**, $[C_{32}H_{30}N_2O_8Sn]^+$, m/z = 690 (13) for complex **6**, $[C_{38}H_{42}N_2O_8Sn]^+$, m/z = 774 (9) for complex **7**, $[C_{42}H_{34}N_2O_8Sn]^+$, m/z = 814 (5) for complex **8**, $[C_{38}H_{42}N_2O_8Sn]^+$, m/z = 774 (9) for complex **9** and $[C_{46}H_{58}N_2O_8Sn]^+$, m/z = 886 (2) for complex **10**.



Scheme 2: Mass fragmentation pathway of 2-((2-methoxyphenyl)carbamoyl)benzoic acid

3.4. Crystal analysis of 2-((2-methoxyphenyl)carbamoyl)benzoic acid and Complex 3

The crystal data for title compound, 2-((2-methoxyphenyl)carbamoyl)benzoic acid, ArN(H)C(=O)PhC(=O)OH, with Ar = 2-methoxyphenyl is given in Table 5. Figure 1 presents the molecular structure of the 2-((2-methoxyphenyl)carbamoyl)benzoic acid. Selected geometric parameters are collated in Table 5 including bond lengths and angles. A difference of 0.12 Å occurs in the C—O bond lengths of carboxylic acid, i.e., C1—O1=1.3203(19) Å and C1—O2= 1.201(2) Å which is consistent with the literature value of similar compounds [37, 38]. The significant difference in bond length of C—O confirms the protonation at O1 atom. Twists in the molecule are observed at about the C8—C7 bond as well as C9—N1 bond. The twist inC8—C7 bond is seen in the values of the N1—C8—C7—C6 [88.63(17)°] and N1—C8—C7—C2 [-

92.64(17)°] torsion angles while that in N1—C9 bond is seen in the values of the N1—C9—C10—C11 [177.93(15)°], N1—C9—C14—C13 [-177.80(15)°] torsion angles.

Significant H-bonding interactions were observed in the molecule. An intermolecular H-bonding interaction between hydroxy-O—C—H· · ·O (amide carbonyl) hydrogen bonds [O1—H1· · ·$O3^1$: H1· · ·$O3^1$ = 1.880 Å, O1· · ·$O3^1$ = 2.7017(17) Å with angle at H1 = 179(3)° for symmetry operation (1) +X,1/2-Y,1/2+Z] resulting in the formation of supramolecular structure (along c-axis) as shown in Figure 2. The amide residue form weak H-bonding *via* amide-N—H· · ·O (carboxylic) hydrogen bonds [N1—H1· · ·O2: H1· · ·O2 = 3.293 Å, N1· · ·O2 = 3.042(2) Å with angle at H1 = 95.4°] resulting in the formation of six-member ring. The amide residue also form weak H-bonding *via* amide-N—H· · ·O (methoxy) hydrogen bonds [N1—H1A· · ·O4: H1A· · ·O4 = 2.5727(19) Å, N1· · ·O4 = 2.140 Å with angle at H1 = 110°] resulting in the formation of five-member ring. The only identified points of contact to link the tapes into a three-dimensional architecture are weak π (phenyl)· · ·O (amide carbonyl) [C10—H10· · ·O3: H10· · ·O3 = 2.939 (2) Å with angle at H10 = 120°.

The crystallographic asymmetric unit of complex 3 is shown in Figure 3A while part of its polymeric structure is shown in Figure 3B. The crystal data for the complex **3** complex is given in Table 5. The Sn center is coordinated by three butyl groups and two oxygen atoms (O1 of the carboxylic group and O3 of amide carbobyl group) resulting in polymeric structure in the carboxylate moiety has a monodentate behavior due to bulky group attached to Sn center and the complex exist in TBG as shown in Figure 3B. The resulting coordination geometry is distorted as evidenced from its τ value of 0.86. The τ value for an ideal TBG is 1. Sum of the three basal angles around the Sn atom is 356.6° while the value of the axial position angle is 177.13°. This slight distortion in the geometry as evidenced from the basal and axial angles may caused by the presence of three bulky butyl groups attached to Sn center.

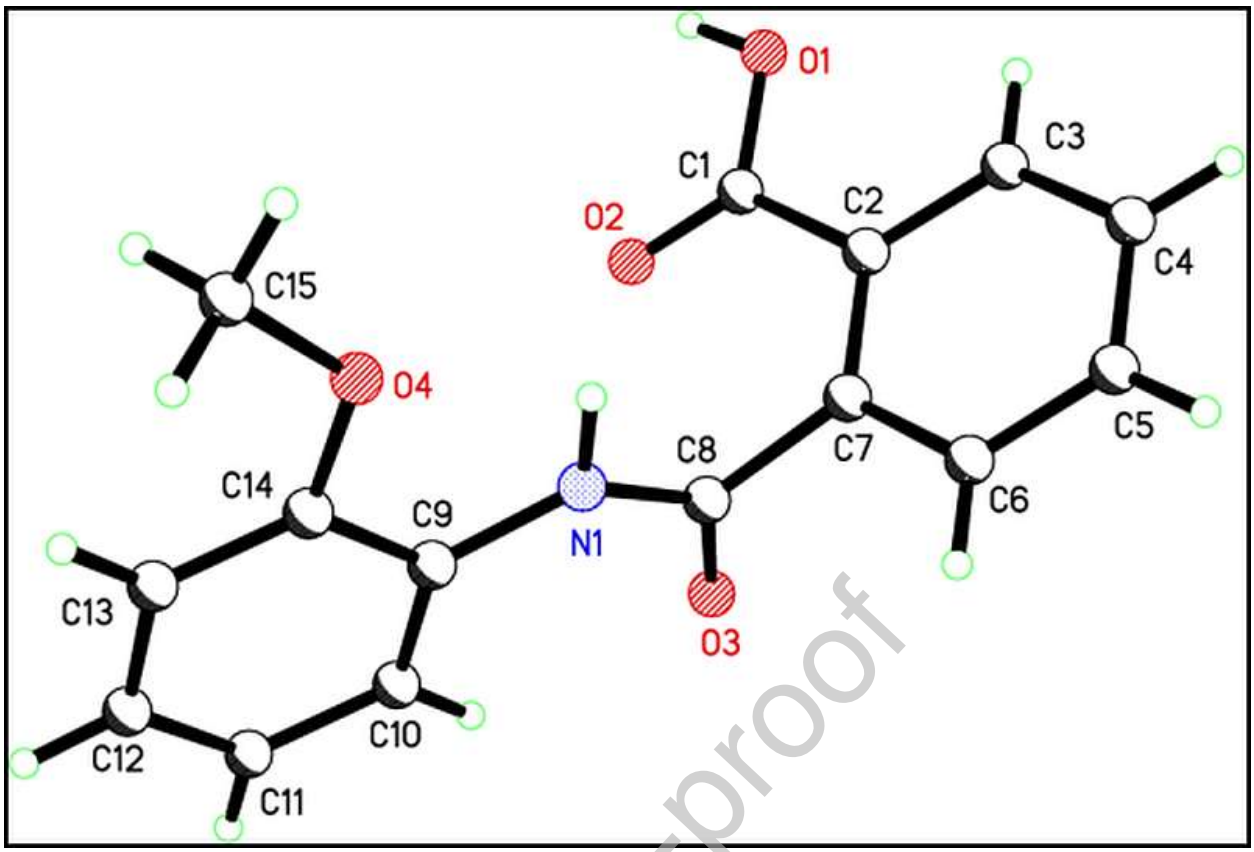


Figure 1: Molecular structure of the 2-((2-methoxyphenyl)carbamoyl)benzoic acid along with the crystallographic numbering pattern.

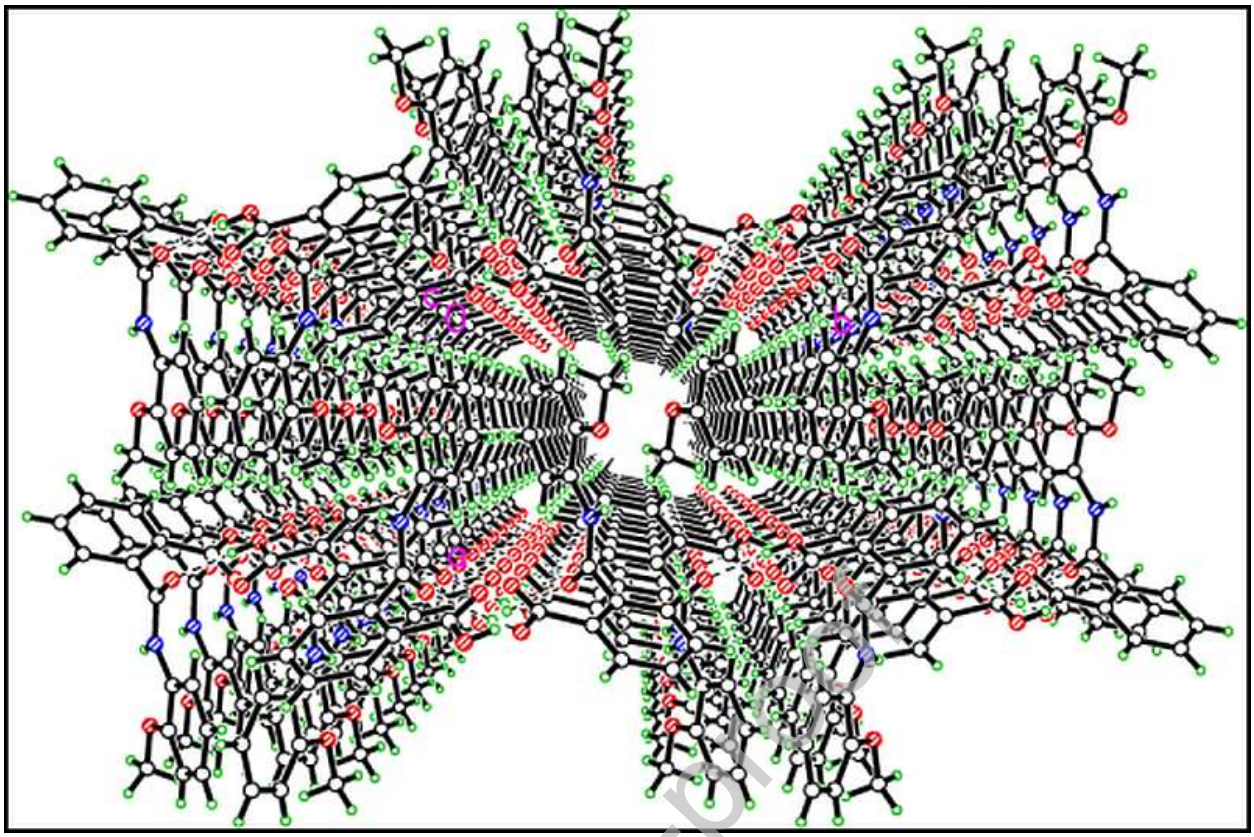


Figure 2: Packing diagram with unit cell of the 2-((2-methoxyphenyl)carbamoyl)benzoic acid viewed along c-axis. Dotted lines show the interactions responsible for supramolecular structure.

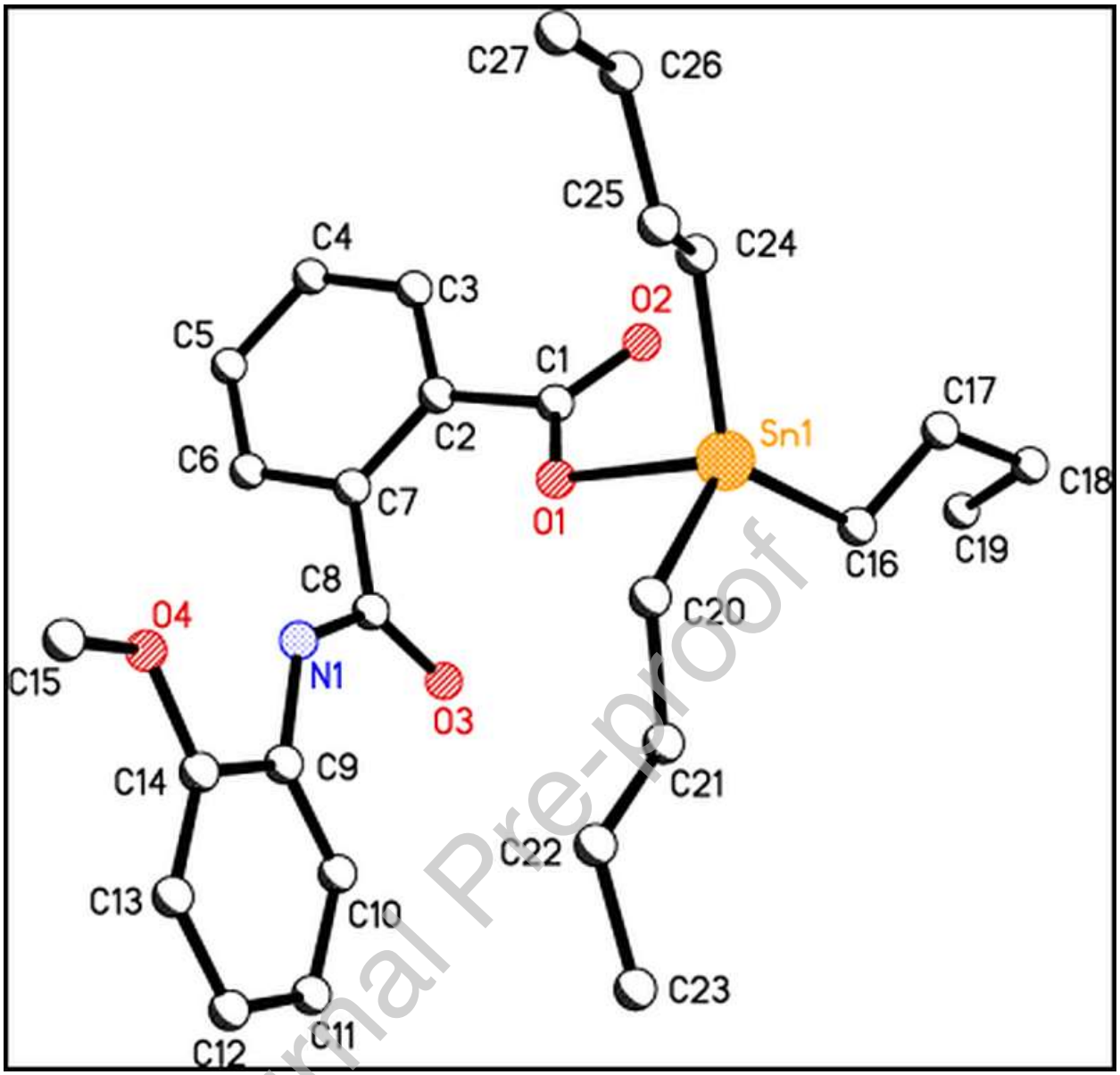


Figure 3A: Asymmetric unit of complex **3** along with crystallographic numbering pattern. All H-atoms have been omitted for clarity.

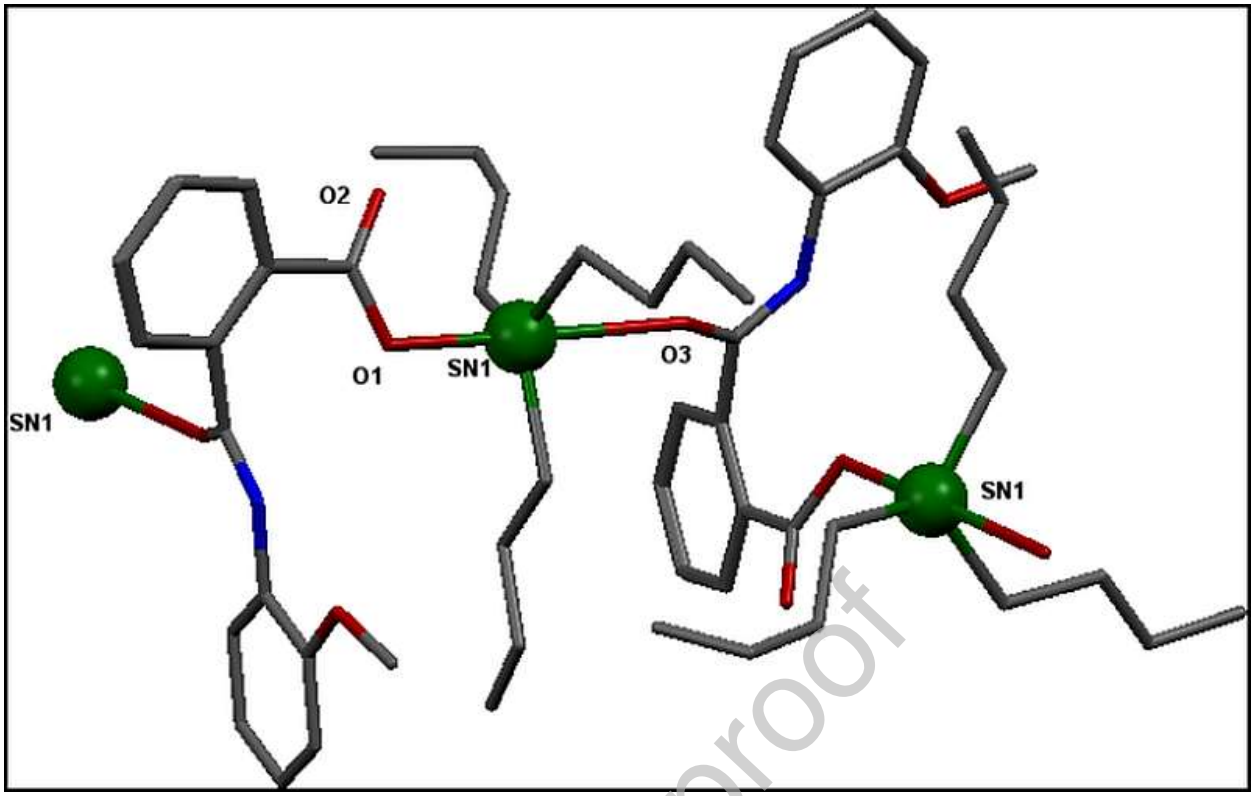


Figure 3B: Part of the polymeric chain of complex **3** showing the 5-coordinated trigonal bipyramidal geometry. The H-atoms are excluded for clarity.

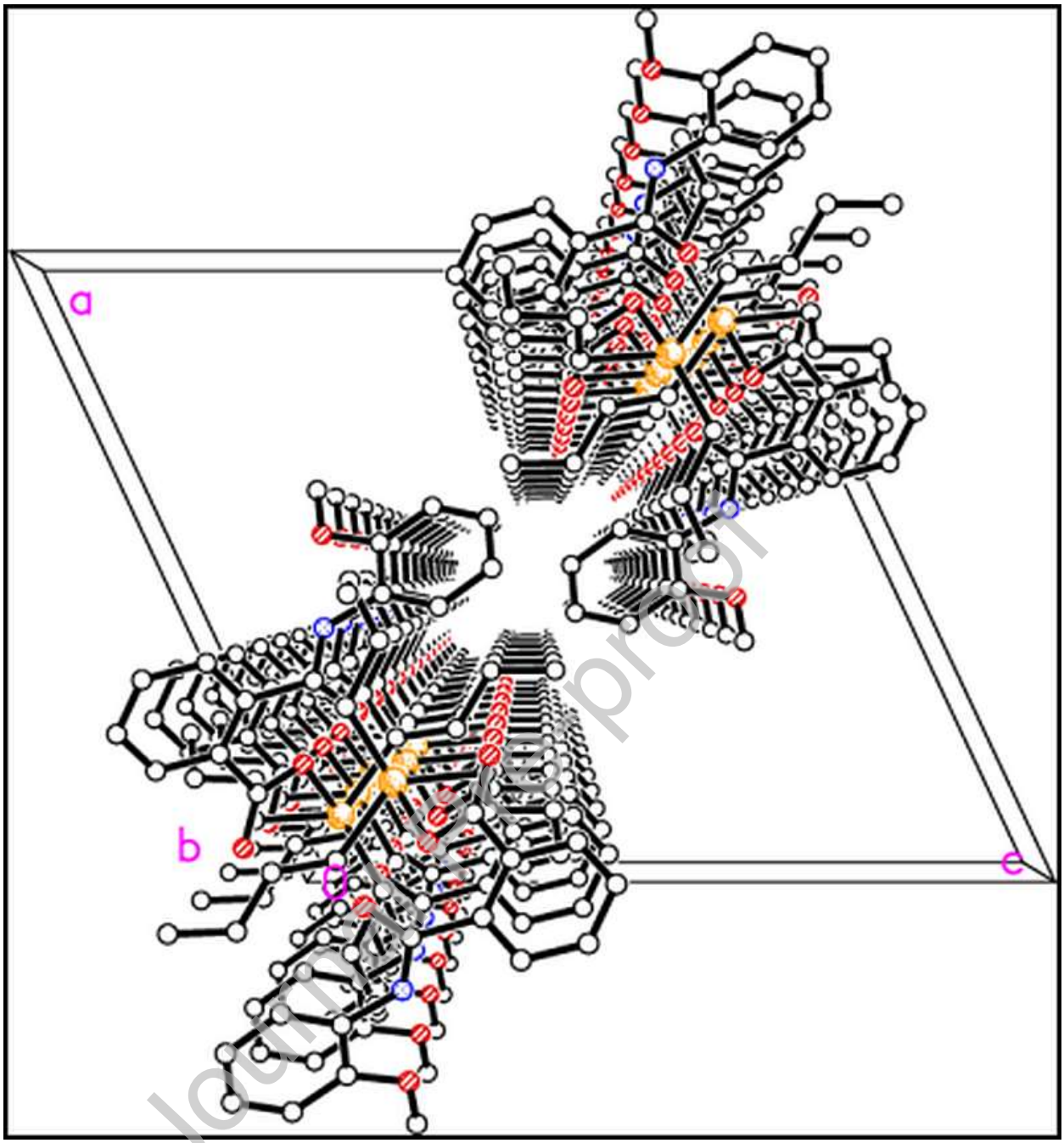


Figure 4: Packing structure along with unit cell of complex **3** viewed along b-axis.

Table 5: Crystal data for HL and complex **3**

Parameters	**HL**	**Complex 3**
Empirical formula, weight	$C_{15}H_{13}NO_4$, 271.26	$C_{27}H_{39}NO_4Sn$, 560.28
T/K	296(2)	296(2)
Crystal system with space group	Monoclinic, $P2_1/c$	Monoclinic, C2/c
a, b, c	9.0919(8), 14.3579(10),	21.5086(19), 12.6104(11),

	10.4720(9)Å	23.096(2)Å
α, β, γ	90, 107.506(4), 90	90, 115.175(4), 90°
V, Z	1303.71(19)Å^3, 4	5669.2(9)Å^3, 8
ρ_{calc}	1.382mg.mm^{-3}	1.313mg.mm^{-3}
μ	0.101mm^{-1}	0.931mm^{-1}
F(000)	568.0	2320.0
Size	0.32 × 0.22 × 0.16mm^3	0.35 × 0.25 × 0.22mm^3
2θ range for data collection	4.7 to 54.24°	3.84 to 52°
λ	MoKα radiation (0.71073Å)	MoKα radiation (0.71073Å)
N(hkl)$_{measured}$, N(hkl)$_{collected}$, R_{int}	10501, 2868, 0.0331	11040, 5559, 0.0234
Data/restraints/parameters	2868/0/183	5559/12/324
S on F^2	1.038	1.049
Final R indexes [I>=2σ(I)]	R_1 = 0.0397, wR_2 = 0.0992	R_1 = 0.0464, wR_2 = 0.1114
Final R indexes [all data]	R_1 = 0.0600, wR_2 = 0.1102	R_1 = 0.0746, wR_2 = 0.1316
CCDC number	2027516	2027515

Table 6: Selected bond lengths and bond angles for HL and complex **3**

Bond lengths (Å) for HL			
C1—O1	1.3203(19)	O2—C1	1.201(2)
C1—C2	1.487(2)	C3—C2	1.399(2
C8—N1	1.332(2)	C9—N1	1.413(2)
C8—O3	1.2299(19)	O4—C14	1.367(2)
O4—C15	1.422(2)	C11—C10	1.386(3)
Bond angles (°) for HL			
O1—C1—O2	122.99(14)	O2—C1—C2	123.15(14)
O1—C1—C2	113.85(13)	C1—C2—C3	121.12(13)
N1—C8—C7	114.69(13)	C8—N1—C9	130.18(13)
C9—C14—C13	120.29(15)	O4—C14—C9	114.62(14)
Bond lengths (Å) for complex 3			
O1—Sn1	2.141(3	C16—Sn1	2.120(7)
O3—Sn1	2.623(4)	C20—Sn1	2.142(6)
C1—C2	1.494(6)	C24—Sn1	2.129(6)
C1—O1	1.279(5)	C1—O2	1.221(6)

Bond angles (°) for complex 3			
O1—Sn1—C16	99.8(2)	C16—Sn1—O3	82.1(2)
O1—Sn1—C20	92.3(2)	C20—Sn1—O3	88.71(19)
O1—Sn1—C24	95.84(18)	C24—Sn1—O3	81.30(18)
O1—Sn1—O3	177.13(12)	C16—Sn1—C20	118.5(2)
O1—C1—O2	123.9(5)	C16—Sn1—C24	124.8(3)
O1—C1—C2	115.7(4)	C20—Sn1—C24	113.3(2)

Table 7: Hydrogen-bond angles and bond lengths (°, Å) for HL and complex **3**

D—H···A	D—H	H···A	D···A	D—H···A
HL				
O1—H1···O3^{i*}	0.82	1.88	2.7017(17)	179.0
N1—H1A···O4	0.86	2.14	2.5727(19)	110.0
C10—H10···O3	0.93	2.36	2.939(2)	120.0
Complex				
N1—H1···O4^{i}	0.8600	2.4100	3.254(6)	166.00
N1—H1···O4	0.8600	2.1800	2.599(6)	109.00
C12—H12···O2^{ii}	0.9300	2.4700	3.310(8)	150.00
C10—H10···O3	0.9300	2.3000	2.887(7)	121.00

*Symmetry transformations for **HL**: (i) +X,1/2-Y,1/2+Z. Symmetry transformations for **complex 3**: (i) -X,+Y,1/2-Z; (ii)-1/2+X,1/2-Y,-1/2+Z

3.5. Results of biological activities

3.5.1. Antibacterial activity results

Table 8 presents the antibacterial potential of the designed compounds against seven various bacterial strains using agar well diffusion assay. The data shows that among the screened compounds, compounds **1-3** and **9** are highly active against all the tested bacterial strains and among these four highly active compounds, trimethyl derivative, i.e., compound **1** (26.0 ± 0.0 mm against *K. pneumoniae*, 20.0 ± 0.0 mm against *S. pyogenes*, 14.0 ± 0.57 mm against *S. epidermidis*, 10.0 ± 0.0 mm against *S. aureus*, 26.0 ± 0.0 mm against *S. marcesscens*, 22.0 ± 0.0 mm against *P. aeruginosa*, 26.0 ± 0.0 mm against *E. coli*) is the most active one due to smallest size of methyl group attached to Sn center as the size of the organic moiety plays an important

role in biological system. All the other compounds are active against all strains except few ones. The lowest activity among the organotin(IV) carboxylate complexes is shown by the octyl derivative, i.e., compound **10**, (3.0±0.0 mm against *S. epidermidis* and inactive against other strains) due to long chain octyl group attached to Sn center having lowest lipophobic (or highest lipophilic) character [34]. The data clearly demonstrate that the evaluated compounds especially compounds **1-3** and **9** are more active that the reference drugs, tetracycline, penicillin G, ampicillin and amoxicillin which indicates that the evaluated compounds may after *in vivo* studies be used as antibacterial drugs for the treatment of bacterial diseases.

Table 8: Evaluation of antibacterial potential of the screened compounds

Comp. #	Zone of inhibition in mm (Mean ± Standard deviation) of the evaluated compounds against bacterial strains						
	K. pneumoniae	***S. pyogenes***	***S. epidermidis***	***S. aureus***	***S. marcesscens***	***P. aeruginosa***	***E. coli***
HL	R	2.3 ± 0.33	3.0 ± 0.0	R	R	2.3 ± 0.33	11.0 ± 0.0
1	26.0 ± 0.0	20.0 ± 0.0	14.0 ± 0.57	10.0 ± 0.0	26.0 ± 0.0	22.0 ± 0.0	26.0 ± 0.0
2	26.0 ± 0.0	17.0 ± 0.0	10.6 ± 0.5	10.0 ± 0.0	15.0 ± 0.0	15.0 ± 0.0	26.0 ± 0.0
3	13.3 ± 2.8	7.0 ± 0.2	22.0 ± 1.7	10.3 ± 0.5	10.0 ± 0.0	19.0 ± 1.7	25.0 ± 0.0
4	R	1.3 ± 0.5	17.0 ± 1.0	20.0 ± 0.0	14.6 ± 2.5	20.0 ± 0.0	21.0 ± 0.0
5	R	17.0 ± 0.0	10.0 ± 0.0	R	5.0 ± 0.0	10.0 ± 0.0	11.0 ± 0.0
6	R	15.0 ± 0.0	13.0 ± 0.0	R	5.0 ± 0.0	5.0 ± 0.0	7.0 ± 0.0
7	R	15.0 ± 0.0	20.0 ± 0.0	8.6 ± 8.6	7.0 ± 0.0	20.0 ± 0.0	26.0 ± 0.0
8	R	10.0 ± 0.0	13.0 ± 0.0	10.0 ± 0.0	8.0 ± 0.0	15.6 ± 1.1	19.0 ± 0.0
9	25.0 ± 0.0	12.6 ± 0.33	18.3 ± 0.88	15.0 ± 0.0	21.6 ± 0.66	22.0 ± 0.0	26.0 ± 0.0
10	R	R	3.0 ± 0.0	R	R	R	R
Tetracycline[a]	14 ± 1.00	0	10 ± 2.00	0	0	6 ± 1.20	2 ± 1.71
Penicillin G[a]	0	0	0	0	8 ± 1.30	6 ± 1.70	0
Ampicillin[a]	6 ± 1.03	0	0	0	8 ± 1.10	0	0
Amoxicillin[a]	6 ± 1.35	0	2 ± 1.54	0	6 ± 1.50	6 ± 1.00	0

Growth inhibition was recorded as 0 for no sensitivity; 1-5 for low sensitivity; 6-10 for moderate effect;11-25 for high sensitivity. Rindicates (resistant, means have no effect on the test bacterial strain). a) Reference drugs

3.5.2. Cytotoxic activity results

Table 9 consists of the cytotoxicity data of the newly designed compounds against H-157 and BHK-21 cell lines using SRB (Sulforhodamine B) based method. The data describes that all the evaluated compounds are active against the tested cell lines and generally the R_3SnL derivatives have lower IC_{50} (or higher activity) than their R_2SnL_2 analogues due to their stronger toxic action on NCS (central nervous system) [34]. Among the R_3SnL derivative the most active compound is **1** (Me_3SnL) and its activity (IC_{50}: 1.96 ± 0.18 µM against H-157 and 1.89 ± 0.01 µM against BHK-21) is comparable to that of the vincristine (IC_{50}: 1.08 ± 0.09 µM), used as a reference drug. The least active one is the $C_8H_{17}SnL_2$, i.e., Compound **10** (IC_{50}: 8.43 ± 0.65 µM against H-157 and 13.9 ± 0.03 µM against BHK-21) which follow the general trends of toxicity [39].

Table 9: Cytotoxicity data against H-157 and BKH-21 cell lines of the screened compounds

Comp. #	H-157/IC_{50} ± SEM (µM)	BHK-21/IC_{50} ± SEM (µM)
HL	10.2 ± 0.41	14.6 ± 0.15
1	1.96 ± 0.18	1.89 ± 0.01
2	2.49 ± 0.06	4.07 ± 0.51
3	5.64 ± 0.07	8.45 ± 0.08
4	4.73 ± 0.50	6.34 ± 0.17
5	6.81 ± 0.26	3.28 ± 0.09
6	3.49 ± 0.01	2.33 ± 0.07
7	7.09 ± 0.12	7.07 ± 0.06
8	4.58 ± 0.09	11.4 ± 0.04
9	4.22 ± 0.32	3.11 ± 0.06
10	8.43 ± 0.65	13.9 ± 0.03
Vincristine	1.08 ± 0.09	1.08 ± 0.09

3.5.3. Antileishmanial activity results

Table 10 summarizes the results of antileishmanial activity of the evaluated compounds. As shown in the table, the synthesized compounds have displayed a significant antileishmanial

potential against the *leishmania* major. Compound **1** (Me_3SnL) has shown the maximum activity which is evidenced from its IC_{50} value (0.48 ± 0.02µM). Its activity is also slightly higher that the amphotericin B (0.49 ± 0.04 µM) used as a reference drug.

Table 10: Antileishmanial data against the of the screened compounds

Comp. #	IC_{50} ± SEM (µM)
HL	4.91 ± 0.05
1	0.48 ± 0.02
2	1.66 ± 0.05
3	1.97 ± 0.02
4	1.73 ± 0.01
5	3.31 ± 0.09
6	2.56 ± 0.03
7	3.46 ± 0.06
8	2.68 ± 0.08
9	2.09 ± 0.03
10	3.69 ± 0.06
Amphotericin B	0.49 ± 0.04

3.6. Study of interaction between compound and DNA

The interaction study between the representative compounds and DNA was performed by UV-vis. spectroscopy as well as by viscosity measurements.

3.6.1. Results of UV-vis. study

The results of the Uv-vis. study of the 2-((2-methoxyphenyl)carbamoyl)benzoic acid (HL) and compound **3** are mentioned in Figures 5 and 6, respectively. Both HL and compound **3** displayed a strong peak at 276.80 nm and 288.60 nm, respectively as a result of π-π* transition in the ligand molecule. Upon the addition of various concentration of DNA to solutions of HL and compound 3, a hypochromic shift along with 4 nm bathochromic shift was observed as shown in

Figures 5 and 6. These two changes (hypochromic shift and bathochromic shift) occur when the compound interact with DNA *via* an intercalative mode [24, 25, 30, 31, 40].

The binding constant for the compounds interacted with DNA was measured form the ratio of intercept to slope of the plot of $A_o/A\text{-}A_o$ *vs.* 1/[DNA] as shown in the inner part of the Figures 5 and 6. The value of binding constant falls in the general range of the compounds having the intercalative binding mode with DNA [24, 25, 30, 31, 40].

3.6.2. Results of viscosity measurements

UV-vis. Spectroscopy data of compound-DNA interaction was further supported by the viscosity measurement for the compound-DNA adduct. It is found that when a compound interact with DNA *via* intercalation mode, then the viscosity of compound-DNA adduct is increased as a result of the entrance of the planar part of compound into the DNA bases causing the lengthening of DNA bases [24, 25, 30, 31, 40]. In the present study, a remarkable increase in the relative viscosity of compound-DNA adduct was observed (Figure 7) suggesting an intercalative mode of interaction.

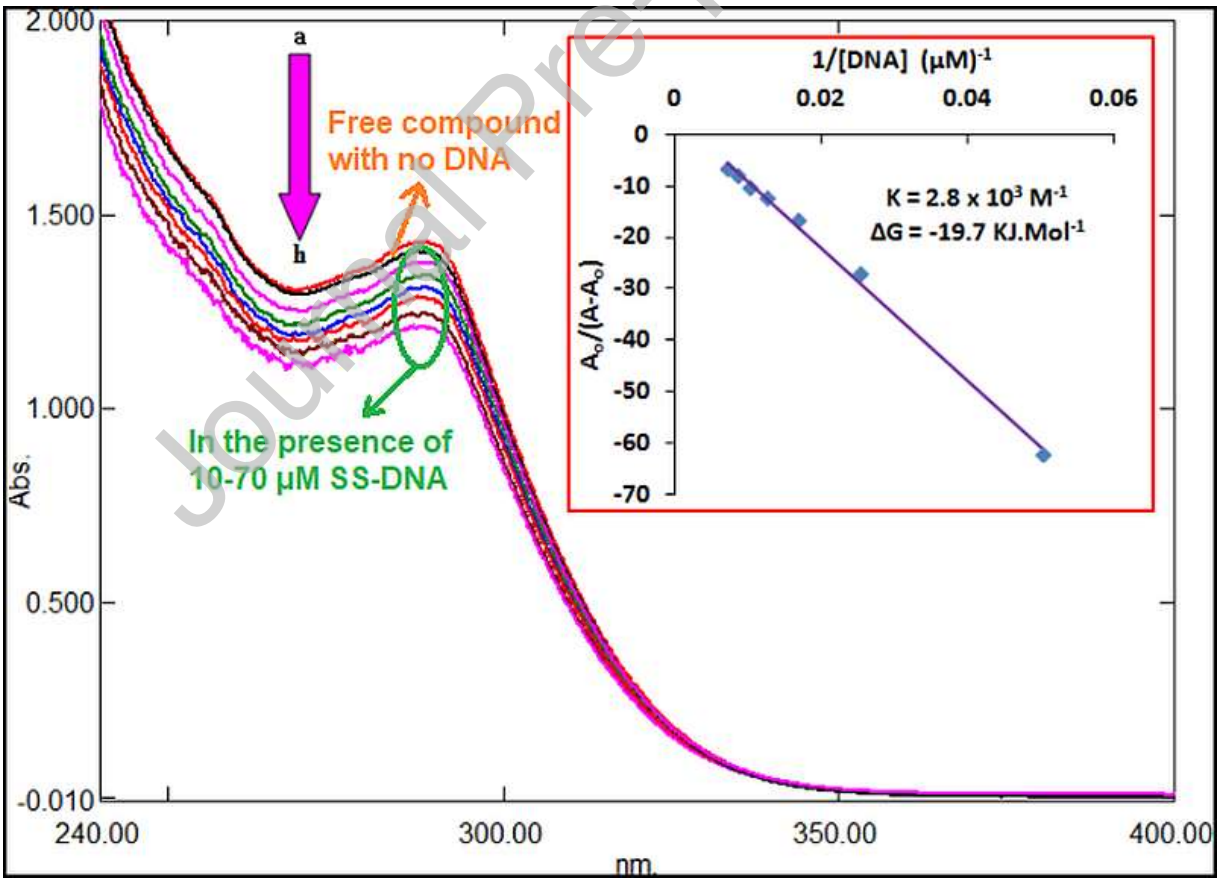


Figure 5: Absorption spectrum of 2 x 10^{-4} M of 2-((2-methoxyphenyl)carbamoyl)benzoic acid interacted with increasing concentration of SS-DNA (10-70 μM)

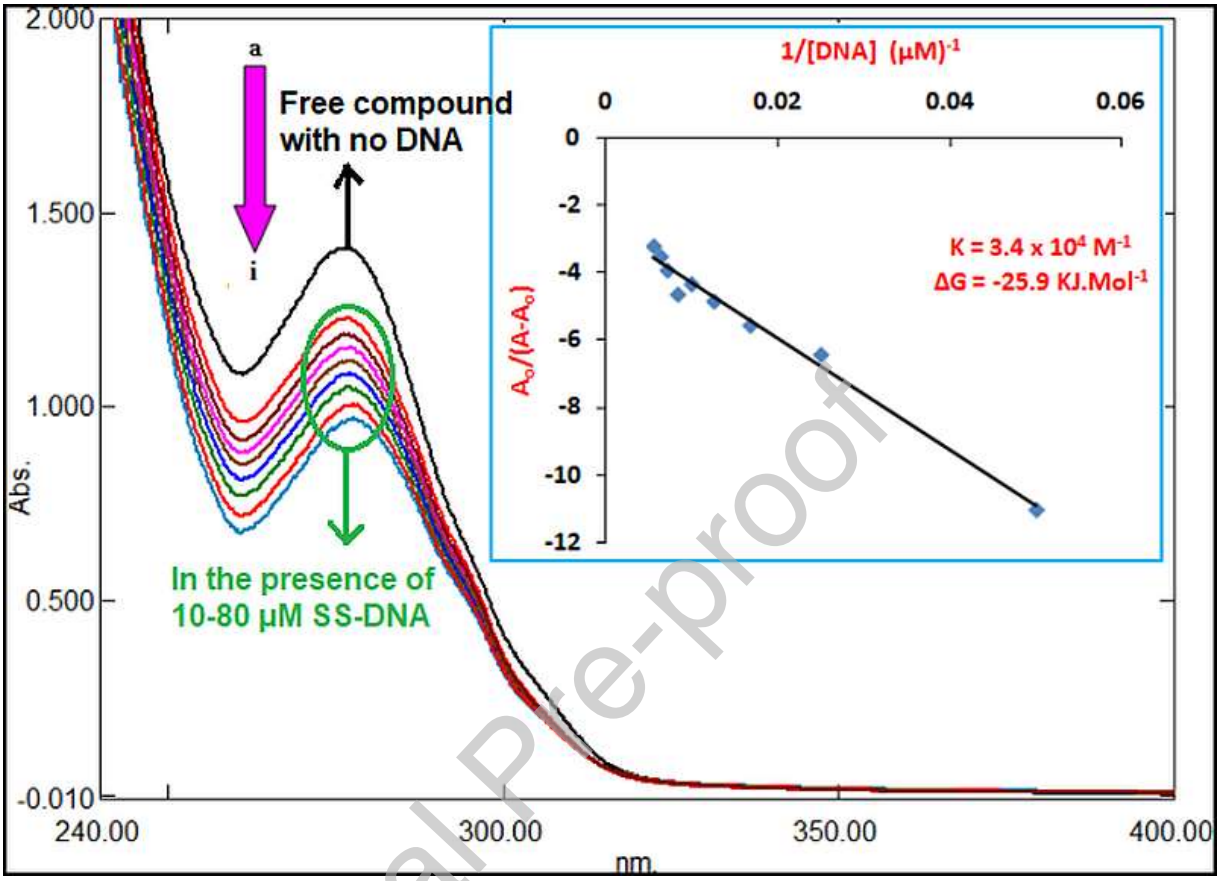


Figure 6: Absorption spectrum of 2.1 x 10^{-4} M of complex **3** interacted with increasing concentration of SS-DNA (10-80 μM)

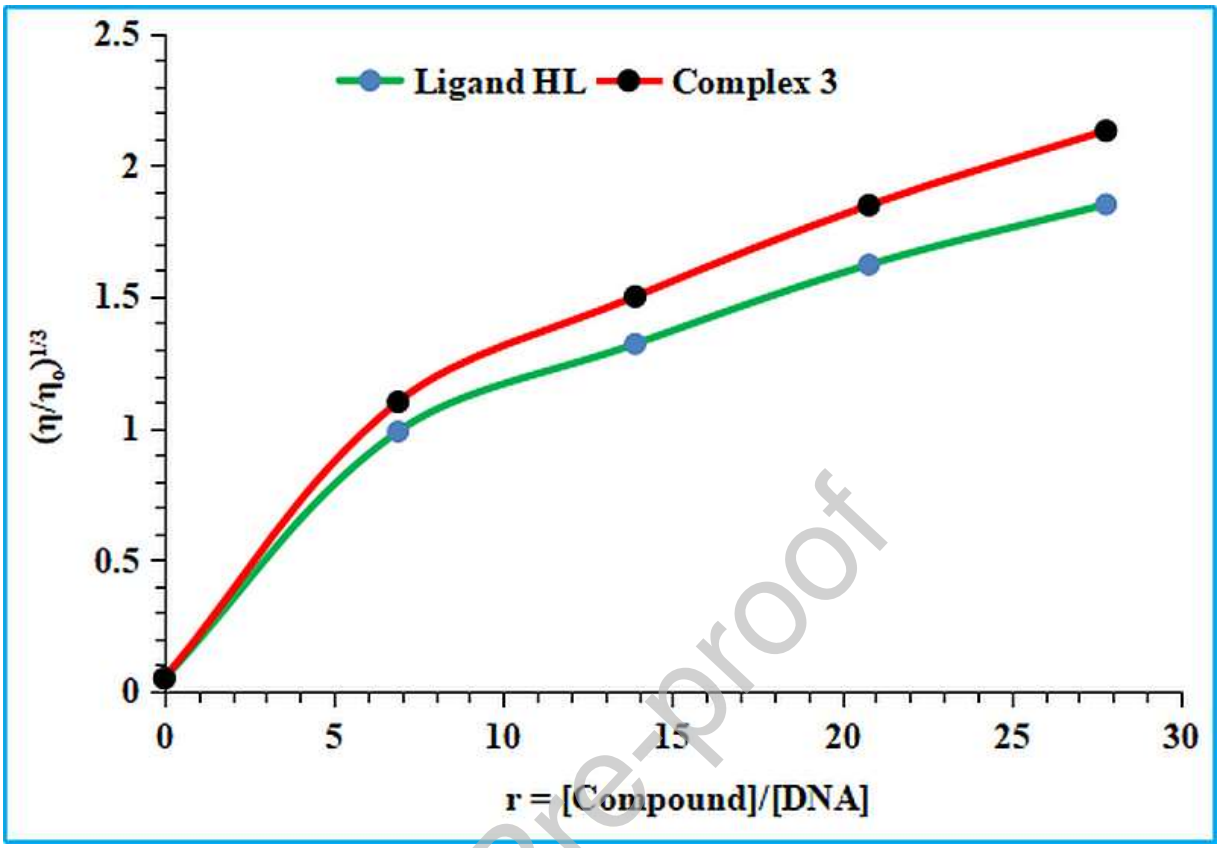


Figure 7: Plot of relative viscosity *vs*. Compound/DNA concentration

Conclusion

Ten Sn(IV) compound based on 2-((2-methoxyphenyl)carbamoyl)benzoic acid are successfully prepared and fully characterized using various instruments such as FTIR, NMR, Mass spectrometer and SCXRD. The ligand, 2-((2-methoxyphenyl)carbamoyl)benzoic acid, behaves as monodentate while coordinated to Sn atom in complexes as evidenced from FTIR and SCXRD data. The SCXRD result for Bu_3SnL complex displays a distorted TBG in which the three Bu groups are present at the equatorial positions while the axial positions are occupied by two oxygen atoms one from carboxylic moiety (O1) while the other oxygen from the amide carbonyl group (O3). The results of the biological activities explore that the overall all the synthesized compounds are biological active. Among the screened compounds, complex**1** (Me_3SnL) has shown the most promising anticancer (IC_{50}: 1.96 ± 0.18 µM against H-157cell lineand 1.89 ± 0.01 µM against BHK-21 cell line), antileishmanial (IC_{50}: 0.48 ± 0.02 µM) and antibacterial potentials .The interaction between the DNA and two representative compounds (2-

((2-methoxyphenyl)carbamoyl)benzoic acid and complex **3**), studied by UV-vis. spectroscopy and viscometry, has displayed that there is an intercalative type of binding.

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Author Contribution Statement

Muhammad Sirajuddin: Writing- Original draft preparation, Conceptualization, Methodology, Software,

Saqib Ali: Supervision

Muhammad Nawaz Tahir: Crystal analysis

Conflict of interest

There is no Conflict of interest.

Regards

Dr. Muhammad Sirajuddin

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Graphical abstract