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# BIOMEDICINAL STUDIES OF SOME NEWLY SYNTHESIZED DIORGANOTIN (IV) DICARBOXYLATES

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The present manuscript elaborates only the biomedicinal efficacy of some newly synthesized and characterized diorganotin(IV)dicarboxylates. The organotin complexes were synthesized by standard yumethods followed by their characterization with the help of sophisticated instrumentation to understand the geometry and structure. The reported compounds screened for the first time for biological efficacy like as antimicrobial activity against different pathogenic bacterial and fungal strains and in-vitro antitumor activity human breast and mammary cancer cell line. It was found that the compounds show remarkable antitumor and antimicrobial activity against pathogenic strains.

**Keywords**: Diorganotin (IV) dicarboxylates, antitumor, antibacterial, antifungal activity.

## INTRODUCTION

Organotin compounds are those compounds containing at least one bond between tin and carbon. The first organotin compound, diethyltindichloride, was synthesized by Frankland in 1849 [1]. The second attempt was made by Lowing in 1852 [2] when he established that ethyl iodide when react with tin/sodium alloy, gave oligomeric diethyl tin oxide and with halogens, gave diethyltindihalides. Organotin compounds, particularly the hydrides, oxides and amides are finding increasing use as reagents in organic synthesis. A number of trialkyltin (IV) compounds are also used industrially in various biological applications, and some dialkyltin(IV) compounds are used for catalyzing certain organic reactions, and as a stabilizers for poly(vinyl chloride).Tin forms predominantly covalent bonds to other elements, but these bonds exhibit a high degree of ionic character with tin usually acting as electropositive. The alkyl groups are usually introduced by complete alkylation of tin tetrachloride with an organometallic reagent, then the various alkyltinchlorides, $R_nSnCl_{4-n}$ (n =1-4), are prepared by the redistribution reaction. Other functional groups are then introduced by nucleophilic of the chloride. Organotin compounds show ionic nature, thus offer dissimilar chemical properties. A useful quick source of references for the synthesis, properties, reactions and application of about 1000 selected organotin compounds is available in the Dictionary of Organometallic Compounds [3]. The recent developments are reviewed in special periodical reports and journals related to organometallic chemistry [4] covering structural aspects of organotin carboxylates [5-7]. Over the last 30 years, research

the chemistry of organometallic compounds of tin in +4 oxidation state has represented one of the most prolific areas of chemical activity. However, the last 10 years have been a steady growth in the number of investigations into the chemistry of organometallic of tri- and diorganotin species.

## EXPERIMENTAL

The organotin compounds were synthesized by the earlier reported method [8]. Tetraorganotin compound as base material can be synthesized by the reaction of respective haloarene with tin tetrachloride and sodium metal in inert atmosphere. The synthesis of base material diorganotin (IV) dichloride was carried out by cleavage of the base material, tetraorganotin, with metal halides at 180°C for two hour by fixing an air condenser. The semisolid mass was extracted with hot pet-ether (40-60°C) and recrystallised with same solvent.

$$4R\text{-}X + SnCl_4 + 8Na \xrightarrow{\text{Toluene/Benzene}} R_4Sn + 4NaX + 4NaCl$$

$$R_4Sn + SnCl_4 \xrightarrow{180°C} 2R_2SnCl_2$$

$$R_2SnCl_2 + 2HL \xrightarrow{Et_3N} R_2SnL_2 + 2Et_3N.HCl$$

R = ($C_6H_5$), ($C_6F_5$), ($C_6H_4F$), HL = Respective carboxylic acid

The preparation of diorganotin (IV) dicarboxylates was carried out by the reaction of $R_2SnCl_2$ and suitable carboxylic acid in presence of triethylamine, as HCl acceptor, under room temperature and nitrogen atmosphere. The biomedicinal screening of the entire newly synthesized compound was performed by the standard reported methods. The experimental details are as follows.

### Antitumor Activity

The in-vitro antitumor activity of these compounds was carried out by MTT-Method [9]. This method was performed to estimate the effect of compounds on the growth of cell. The human breast adenocarcinoma (MCF-7) and mammary cancer (EVSA-7) cell lines were used for this purpose. The principle behind this assay depends upon the reduction of tetrazoleum salt. The yellow colored tetrazoleum MTT [3-(4,5-dimethylthiazolyl-2)-2, 5-diphenyl tetrazoleum bromide] was reduced partially by metabolically active cells by the action of dehydrogenase enzyme to generate NADH and NADPH as reducing equivalents. The resulting intracellular purple Colour zone was solubilized and quantified by spectrophotometer. The MTT was first dissolved in Phosphate buffer saline at a concentration of 5 mg/ml. The MTT solution (50 µl) was added to each well of 96 well culture plate containing 100 µl of culture medium and incubates at 37°C for 4 hrs. The medium was then removed carefully without disturbing the crystals of purple colored zone. 50 ml of DMSO was then added to each well and mixed thoroughly to dissolve the crystals of the zone. The plate was then read on a micro ELISA plate reader at a wavelength of 570 nm to find out the optical density and cell count value.

### Antibacterial Activity

Antibacterial activity of the synthesized compound was carried out by disc diffusion method [10] using ampicillin as standard. The filter paper (Whatmann No.1) sterile disc of 5 mm

diameter, impregnated with the test compounds (10 μg/ml of ethanol) along with standard were placed on the nutrient agar plate at 37°C for 24 hrs in BOD incubator. The inhibition zone around the dried impregnated disc was measured after 24 hrs. The activity was classified as highly active (dia = > 15 mm), moderately active (dia = 10-15 mm) and slight active (dia = 5-10 mm). The diameter less than 5 mm was regarded as inactive.

**Antifungal Activity**

The antifungal activity of the compound was tested by agar plate diffusion method [11], using ampicillin as standard. Two concentrations of the test compounds viz., 50 and 100 μg/ml were prepared and tested against two pathogenic fungal strains, Aspergillus flavus and Aspergillus nigar. The one ml of each compound was poured into a Petri dish containing 20-25 ml of molten potato dextrose-agar medium. As the medium solidify, Petri dishes were inoculated at 37°C for 96 hrs in BOD incubator. After 96 hrs the colony diameter was measured and % inhibition was calculated using standard method.

## RESULTS AND DISCUSSION

All the reactions were conducted at room temperature under nitrogen condition and the final products were recrystallized in petroleum ether (40-60°C) or in benzene. The complexes were white and off-white in color, obtained as a solid mass which subsequently crystallized with benzene/pet-ether. The complexes have sharp melting point and were soluble in chloroform and acetonitrile.

**Infrared Spectroscopy:**

Infrared spectra of the investigated compounds have been recorded from their KBr pellets in range 4000-400cm$^{-1}$.The coordinating mode of the acids (R'COOH) towards the diorganotin (IV) derivatives can be compared with the infrared spectra of free acids, their metal salts and organotin compounds. Frequencies assigned to $\nu_{asym}$(COO) and $\nu_{sym}$(COO) have been identified in free ligand acids and the synthesized compounds. They are reported together with bands assigned to ν(Sn-C) and ν(Sn-O) in table. The explicit feature observed in the spectra of all the compounds in absence of the broadband in range 2504-3034 cm$^{-1}$, which appears in free ligand acid as ν(O-H)-position thus indicating metal ligand bond formation through this site. Moreover, absorption bands which appear in the synthesized compounds in the range 498-427 cm$^{-1}$ and 597-501 cm$^{-1}$, assigned to Sn-O and Sn-C bonds, respectively, which support the formation of complexes.

**UV Spectra:**

The electronic spectra obtained for representative compound was recorded in chloroform in the range 200-400nm. The UV absorption due to COO group appears at 274+6 and 294+2.

**$^1$HNMR Spectroscopy:**

$^1$HNMR spectra for synthesized compounds have been recorded in $CDCl_3$ and DMSO solution. $^1$HNMR response signals of the protons attached to the phenyl moieties of the

ligands have been assigned by their distinct multiplicities, J -values and comparisons with the results obtained from the incremental method.

**$^{13}$C NMR Spectroscopy:**

$^{13}$C NMR Spectra recorded in $CDCl_3$ and DMSO solutions of the free ligands and their respective diorganotin (IV) derivatives. The $^{13}$C NMR Spectral data for the R group attached to the tin atom where R = Ph, ($C_6F_5$) and (f-$C_6H_4$) were assigned by comparison with related analogues as model compounds, combined with the ″J [$^{119}$Sn, $^{13}$C] coupling constants. The positions of the phenyl, pentafluorophenyl and p-fluorophenyl carbon signals undergo minor variations in the complexes as compared to those observed in the free acids and their sodium salts. The carboxylate carbon shifts to lower fields almost in all the complexes indicates the participation of the carboxyl group (COO) in the coordination to tin (IV).

**$^{119}$Sn NMR Spectroscopy:**

The possibility of detecting the presence of coordinative different organotin (IV) moieties was explored by acquisition of $^{119}$Sn NMR spectra for all the investigated compounds. The $^{119}$Sn NMR spectra were recorded in $CDCl_3$ solution, a non-coordinating solvent. The $^{119}$Sn chemical shift values obtained for the diorganotin (IV) compounds show higher coordination. The geometric data calculated are consistent with tetrahedral geometries for the diorganotin(IV) species, for which earlier results indicated five-coordination consistent with the skew-trapezoidal bipyramidal geometries, a lower coordination number become apparent arising from the asymmetric coordination mode of the carboxylate ligands.

**Antitumor Activity**

The antitumor activity of diorganotin (IV) dicarboxylate was studied against the human breast cancer (MCF-7) and mammary cancer cell lines (EVSA-7). Compound shows moderate to high antiproliferative activity against the cell lines. They inhibit the growth of about 35-40% of tumor. The variation in activity is due to variable kind of carboxylate as ligands. The carboxylate having fluorine contents show higher efficacy. It was found that the compounds generally interact with nitrogenous bases of nucleotides of nucleic acid and inhibit the cell division by interfering the replication and transcription of DNA molecules. The compounds may also affect the multienzyme complexes responsible for replication and transcription of DNA thus causing a stop of proliferation of the cells.

**Antibacterial Activity**

The antibacterial activity of these compounds was tested against three human pathogenic bacteria: Pseudomonas auruginosa, Staphylococcus aureus and Klebsiela pneumoniae using 10 μg/ml concentration of the test compound. It was found that compound shows high activity against pseudomonas auruginosa, Klebsiela pneumoniae and against Staphylococcus aureus. The variability in the bacterial activity is due to presence of different kinds of carboxylate group as ligand. The chloride containing carboxylate ligands are more effective than the simple carboxylate ligands.

**Antifungal Activity**

The antifungal activity of these compounds was tested against two fungal strains: Aspergillus flavus and Aspergillus niger at 50 μg/ml and 100 μg/ml respectively of the test compounds. It was so amazing that these compound so much higher efficacy against the fungal strains. Again the activity is due to presence of different kinds of carboxylate which shows higher activity against different fungal strains. The presence of chloride group in carboxylate molecule enhances the activity. At 100 μg/ml concentration, all the compounds show high activity against Aspergillus flavus and Aspergillus niger. The carboxylate ligand definitely play important role in controlling the fungal infections.

**Conclusion**

The newly synthesized diorganotin(IV)dicarboxylates were novel and show prominent antimicrobial activity against pathogenic bacterial and fungal strains showing potential efficacy against antimicrobial resistance. The said compounds also show potential antitumor activity against mammary and breast cancer cell line in-vitro.

**Table-1 Antitumor activity of diorganotin (IV) dicarboxylate**

| S. No. | Compounds | MCF-7 Cell No. x $10^4$ | EVSA-7 Cell No. x $10^4$ | Activity |
|---|---|---|---|---|
| 1 | $(C_6H_5)_2Sn(OOC.CH_3)_2$ | 11.69±1.04 | 11.82±1.06 | Negative |
| 2 | $(C_6H_5)_2Sn(OOC.CH_2Cl)_2$ | 9.17±0.90 | 8.67±0.69 | Positive |
| 3 | $(C_6H_5)_2Sn(OOC.CHCl_2)_2$ | 8.79±0.52 | 8.42±0.46 | Positive |
| 4 | $(C_6H_5)_2Sn(OOC.CCl_3)_2$ | 12.31±1.02 | 12.39±1.03 | Negative |
| 5 | $(C_6H_5)_2Sn(OOC.CF_3)_2$ | 8.95±0.67 | 8.55±0.62 | Positive |
| 6 | $(C_6F_5)_2Sn(OOC.CH_3)_2$ | 11.59±1.06 | 11.29±1.02 | Negative |
| 7 | $(C_6F_5)_2Sn(OOC.CH_2Cl)_2$ | 9.29±0.88 | 9.89±0.92 | Positive |
| 8 | $(C_6F_5)_2Sn(OOC.CHCl_2)_2$ | 12.79±1.20 | 12.69±1.16 | Negative |
| 9 | $(C_6F_5)_2Sn(OOC.CCl_3)_2$ | 11.52±1.02 | 11.82±1.06 | Negative |
| 10 | $(C_6F_5)_2Sn(OOC.CF_3)_2$ | 9.19±0.92 | 9.29±0.88 | Positive |
| 11 | $(FC_6H_4)_2Sn(OOC.CH_3)_2$ | 9.17±0.90 | 8.67±0.69 | Positive |
| 12 | $(FC_6H_4)_2Sn(OOC.CH_2Cl)_2$ | 8.95±0.67 | 8.55±0.62 | Positive |
| 13 | $(FC_6H_4)_2Sn(OOC.CHCl_2)_2$ | 8.79±0.52 | 8.42±0.46 | Positive |
| 14 | $(FC_6H_4)_2Sn(OOC.CCl_3)_2$ | 11.52±1.02 | 11.82±1.06 | Negative |
| 15 | $(FC_6H_4)_2Sn(OOC.CF_3)_2$ | 9.19±0.92 | 9.29±0.88 | Positive |
| 16 | Negative control | 10.21±1.01 | 10.22±1.01 | – |
| 17 | Positive control | 40.26±3.23 | 41.23±3.28 | – |

**Table-2: Antibacterial Activity of diorganotin (IV) dicarboxylate**

| S. N. | Compounds | Control | Pseudo monas aerugin osa | Staphyloco cc us aureus | Klebsiela pneumon iae |
|---|---|---|---|---|---|
| 1 | $(C_6H_5)_2Sn(OOC.CH_3)_2$ | – | +++ | ++ | ++ |
| 2 | $(C_6H_5)_2Sn(OOC.CH_2Cl)_2$ | – | ++ | + | ++ |
| 3 | $(C_6H_5)_2Sn(OOC.CH\ Cl_2)_2$ | – | ++ | + | ++ |
| 4 | $(C_6H_5)_2Sn(OOC.CCl_3)_2$ | – | ++ | ++ | ++ |
| 5 | $(C_6H_5)_2Sn(OOC.CF_3)_2$ | – | + | ++ | + |
| 6 | $(C_6F_5)_2Sn(OOC.CH_3)_2$ | – | +++ | + | ++ |
| 7 | $(C_6F_5)_2Sn(OOC.CH_2Cl)_2$ | – | ++ | + | ++ |
| 8 | $(C_6F_5)_2Sn(OOC.CHCl_2)_2$ | – | ++ | + | +++ |
| 9 | $(C_6F_5)_2Sn(OOC.CCl_3)_2$ | – | + | +++ | ++ |
| 10 | $(C_6F_5)_2Sn(OOC.CF_3)_2$ | – | +++ | ++ | ++ |
| 11 | $(FC_6H_4)_2Sn(OOC.CH_3)_2$ | – | ++ | + | ++ |
| 12 | $(FC_6H_4)_2Sn(OOC.CH_2Cl)_2$ | – | ++ | ++ | ++ |
| 13 | $(FC_6H_4)_2Sn(OOC.CHCl_2)_2$ | – | + | ++ | + |
| 14 | $(FC_6H_4)_2Sn(OOC.CCl_3)_2$ | – | +++ | + | ++ |
| 15 | $(FC_6H_4)_2Sn(OOC.CF_3)_2$ | – | ++ | + | ++ |

**+ = 6-10 mm; ++ = 10-14 mm; +++= >14 mm; – = Inactive**

**Table-3: Antifungal Activity of diorganotin (IV) dicarboxylate at 50 μg/ml conc.**

| S. N. | Compounds | Aspergillus flavus Col. Dia. (mm) | % Inhibition | Aspergillus niger Col. Dia. (mm) | % Inhibition |
|---|---|---|---|---|---|
| 1 | $(C_6H_5)_2Sn(OOC.CH_3)_2$ | 0.7 | 76.6 | 0.5 | 75.0 |
| 2 | $(C_6H_5)_2Sn(OOC.CH_2\ Cl)_2$ | 0.5 | 83.3 | 0.4 | 80.0 |
| 3 | $(C_6H_5)_2Sn(OOC.CHCl_2)_2$ | 0.5 | 83.3 | 0.4 | 80.0 |
| 4 | $(C_6H_5)_2Sn(OOC.CCl_3)_2$ | 0.6 | 80.0 | 0.7 | 65.0 |
| 5 | $(C_6H_5)_2Sn(OOC.CF_3)_2$ | 0.7 | 76.63 | 0.6 | 70.0 |
| 6 | $(C_6F_5)_2Sn(OOC.CH_3)_2$ | 0.8 | 73.3 | 0.8 | 60.0 |
| 7 | $(C_6F_5)_2Sn(OOC.CH_2Cl)_2$ | 0.7 | 76.6 | 0.7 | 65.0 |
| 8 | $(C_6F_5)_2Sn(OOC.CHCl_2)_2$ | 0.2 | 93.3 | 0.7 | 65.0 |
| 9 | $(C_6F_5)_2Sn(OOC.CCl_3)_2$ | 0.2 | 93.3 | 0.7 | 65.0 |
| 10 | $(C_6F_5)_2Sn(OOC.CF_3)_2$ | 0.4 | 86.7 | 0.6 | 70.0 |
| 11 | $(FC_6H_4)_2Sn(OOC.CH_3)_2$ | 0.7 | 76.63 | 0.6 | 70.0 |
| 12 | $(FC_6H_4)_2Sn(OOC.CH_2Cl)_2$ | 0.8 | 73.3 | 0.8 | 60.0 |

| | | | | | |
|---|---|---|---|---|---|
| 13 | $(FC_6H_4)_2Sn(OOC.CHCl_2)_2$ | 0.7 | 76.6 | 0.7 | 65.0 |
| 14 | $(FC_6H_4)_2Sn(OOC.CCl_3)_2$ | 0.2 | 93.3 | 0.7 | 65.0 |
| 15 | $(FC_6H_4)_2Sn(OOC.CF_3)_2$ | 0.2 | 93.3 | 0.7 | 65.0 |
| 16 | Control | 3.0 | – | 2.0 | – |

**Table-4: Antifungal Activity of diorganotin (IV) dicarboxylate at 100 μg/ml conc.**

| S. N. | Compounds | Aspergillus flavus Col. Dia.(mm) | % Inhibition | Aspergillus niger Col. Dia. (mm) | % Inhibition |
|---|---|---|---|---|---|
| 1 | $(C_6H_5)_2Sn(OOC.CH_3)_2$ | 0.1 | 96.7 | 0.2 | 90.0 |
| 2 | $(C_6H_5)_2Sn(OOC.CH_2Cl)_2$ | 0.2 | 93.3 | 0.1 | 95.0 |
| 3 | $(C_6H_5)_2Sn(OOC.CHCl_2)_2$ | 0.1 | 96.7 | 0.1 | 95.0 |
| 4 | $(C_6H_5)_2Sn(OOC.CCl_3)_2$ | 0.4 | 86.7 | 0.2 | 90.0 |
| 5 | $(C_6H_5)_2Sn(OOC.CF_3)_2$ | 0.2 | 93.3 | 0.2 | 90.0 |
| 6 | $(C_6F_5)_2Sn(OOC.CH_3)_2$ | 0.1 | 96.7 | 0.4 | 80.0 |
| 7 | $(C_6F_5)_2Sn(OOC.CH_2Cl)_2$ | 0.2 | 93.3 | 0.3 | 75.0 |
| 8 | $(C_6F_5)_2Sn(OOC.CHCl_2)_2$ | 0.1 | 96.7 | 0.3 | 75.0 |
| 9 | $(C_6F_5)_2Sn(OOC.CCl_3)_2$ | 0.1 | 96.7 | 0.2 | 90.0 |
| 10 | $(C_6F_5)_2Sn(OOC.CF_3)_2$ | 0.2 | 93.3 | 0.3 | 85.0 |
| 11 | $(FC_6H_4)_2Sn(OOC.CH_3)_2$ | 0.1 | 96.7 | 0.4 | 80.0 |
| 12 | $(FC_6H_4)_2Sn(OOC.CH_2Cl)_2$ | 0.2 | 93.3 | 0.3 | 75.0 |
| 13 | $(FC_6H_4)_2Sn(OOC.CHCl_2)_2$ | 0.1 | 96.7 | 0.3 | 75.0 |
| 14 | $(FC_6H_4)_2Sn(OOC.CCl_3)_2$ | 0.1 | 96.7 | 0.1 | 95.0 |
| 15 | $(FC_6H_4)_2Sn(OOC.CF_3)_2$ | 0.2 | 93.3 | 0.3 | 85.0 |
| 16 | Control | 3.0 | – | 2.0 | – |

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