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Synthesis, characterization, and anticancer activities examination of tri-organotin (IV) complexes derived from cephalexin schiff base

Abeer Erfan[1], Emad Yousif[1,★], Ahmed Alshanon[2], Mohammed Kadhom[3], Muna Bufaroosha[4], and Ali Shihab[5]

[1]Department of Chemistry, College of Science, Al-Nahrain University, Baghdad 64021, Iraq
[2]Center of Biotechnology Researches, University of Al-Nahrain, Baghdad, Iraq
[3]Department of Environmental Health, College of Energy and Environmental Science, Alkarkh University of Science, Baghdad 10081, Iraq
[4]Department of Chemistry, College of Science, United Arab Emirates University, P.O. Box 15551, Al-Ain 1818, UAE
[5]Department of Chemistry, College of Science, University of Baghdad, Baghdad 10074, Iraq

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Abstract: This study details the synthesis, characterization, and anticancer assessment of novel tri-organotin (IV) complexes derived from a cephalexin Schiff base ligand. The Schiff base and its tri-organotin complexes were examined via different techniques, namely Fourier Transform Infrared (FTIR) spectroscopy, Nuclear Magnetic Resonance (^{1}H, ^{13}C, ^{119}Sn-NMR), Field Emission Scanning Electron Microscopy (FESEM), X-ray diffraction (XRD), and elemental analysis. The anticancer efficacy of the prepared complexes was evaluated against the human breast cancer cell line (MCF-7). The test was conducted via the utilization of an MTT assay to ascertain cytotoxicity and compute the half-maximal inhibitory concentration (IC_{50}). The findings demonstrate that both tri-phenyl and tri-butyl organotin (IV) complexes possess notable anticancer efficacy, presumably attributable to their capacity to induce apoptosis through interactions with DNA and phospholipid metabolism. Structural and morphological analyses indicated that the coordination geometry and ligand characteristics affected the biological activity of the synthesized compounds. Hence, our findings show the potential of organotin (IV) complexes as viable candidates for anticancer drug development.

Key words: organotin (IV) complexes, cephalexin Schiff base, anticancer activity, MCF-7 breast cancer cells, MTT assay

Introduction

The study of organotin compounds began with Sir Edward Frankland, who synthesized diethyltin diiodide and tetraethyltin. Later, subsequent investigations led to the synthesis of more than 800 organotin compounds.[1,2] The applications of organotin (IV) complexes are based on understanding their geometry and coordination structures.[3,4] Organotin complexes have many applications across industrial, biological, agricultural, and medicinal fields.[5-9] Therefore, significant attention is required to improve and evaluate their synthesis

★ Corresponding author
Phone : +964-7705839300
E-mail : emad_yousif@hotmail.com

processes using advanced techniques.[10]

Tin is an abundant metal that is found in numerous inorganic and organometallic compounds. Its outer shell electronic configuration is $5s^2$ $5p^2$, and it exhibits two oxidation states: Sn^{2+} and Sn^{4+}. Tin (II) has a reducing nature that could rapidly oxidize to Tin (IV), which attains the electronic configuration of xenon [11]. Organotin compounds are characterized by the presence of at least one covalent C-Sn bond and tetravalent Sn centers. They are classified as mono-, di-, tri-, and tetra-organotin compounds based on the attached aryl and alkyl groups, as well as anionic groups such as Cl^-, F^-, O^{2-}, OH^-, COO^-, or S^-, which influence the biological activity of organotin (IV) complexes.[12]

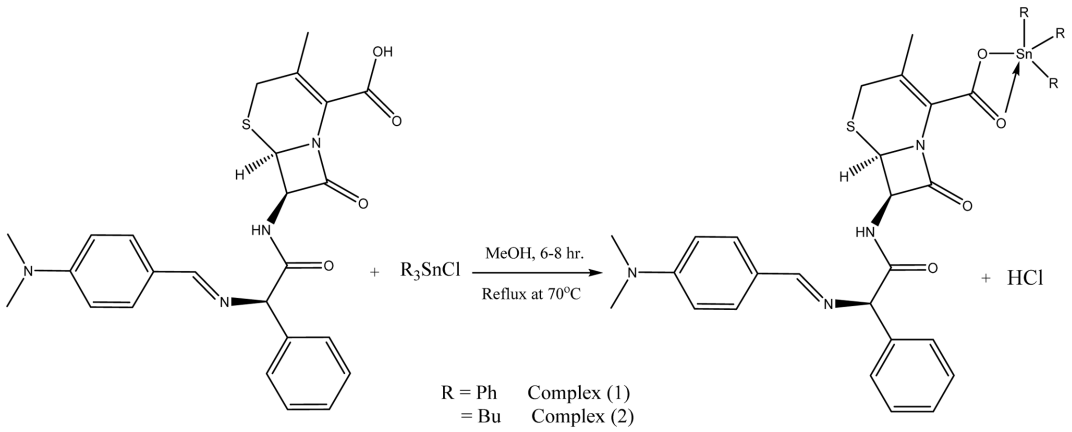
Recently, organotin (IV) complexes gained remarkable attention due to their broad applications in various fields, including medicine, industry, and agriculture. The structure and coordination of organotin (IV) complexes are very important in determining their biochemical activity, particularly for compounds containing Schiff bases. Schiff bases garnered interest because of their ability to cleave DNA, especially those derived from salicylaldehyde. This process is influenced by the electron-deficient metal and the electron-rich ligand, which interact and bind to form stable metal-ligand complexes.[13,14]

Although organotin (IV) complexes exhibit significant biological activity, they frequently demonstrate toxicity at different concentrations. It is affected by the quantity and nature of the anionic groups bonded to the Sn atom.[6,8] For example, trialkyltin (IV) [R_3Sn^+] and triaryltin (IV) [Ar_3Sn^+] derivatives demonstrate significant neurotoxicity. In the R_3Sn^+ series, lower homologs like methyl (Me) and ethyl (E_t) exhibit the highest toxicity when ingested orally. Toxicity diminishes progressively from tri-n-propyl to tri-n-octyl, the latter being entirely non-toxic.[15]

The biological activity of organotin compounds typically adheres to the hierarchy: $RSnX_3 < R_2SnX_2 < R_4Sn << R_3SnX$, with X representing functional groups such as chloride, fluoride, oxide, hydroxyl, carboxylate, or thiolate.[9,10] Complexes with elongated chains generally exhibit lower toxicity compared to those with shorter chains, and aryl groups are usually less toxic than alkyl groups. However, this is contingent upon the organism in question.[16] The anticancer efficacy of these compounds is contingent upon the geometry and coordination of the groups adjacent to the tin atom, along with the chemical and physical properties of the synthesized ligand.[17]

Metal complexes have recently found extensive use in medicine, particularly in the treatment of cancers, rheumatoid arthritis, and gastric conditions, among others.[14,16] As a result, research has increasingly focused on synthesizing new metal-based compounds and exploring their medical applications, especially as anticancer agents, given that cancer remains one of the most threatening diseases.[18] Many studies have evaluated the anticancer activity of organotin compounds against various cancer cell types, including ovarian, breast, lung, epidermoid, lymphoma, cervical, bladder, and germ cell cancers.[12-14] The anticancer effects are primarily attributed to apoptosis induction, the compounds' lipophilicity, and the presence of alkyl and aryl groups in the organotin compounds.[19] These compounds damage cancer cell DNA by interacting with phosphate groups that disrupt DNA structure, protein function, activators, and gene expression. Additionally, the coordination and ligand groups in organotin compounds contribute to their anticancer activity.[20-22]

The precise mechanism of action by which organotin complexes function is not completely understood. The tin complexes exhibit binding to DNA, resulting in structural modification and inhibition of cell division in the tumor cells.[23] Organotin complexes are capable of interacting with DNA nitrogen atoms, phosphate groups, and nucleotide bases through the formation of covalent and coordination bonds with them.[24] They function through binding to DNA phosphate groups and disrupting phospholipid metabolism, leading to apoptosis.[23-25] Tetra-tin complexes cause intracellular generation of ROS and lead to increased oxidative stress that leads to DNA damage and thus induces apoptosis.[26] The lipophilicity and hydrophilicity of organotin complexes, based on their coordination and nature and the number of their associated groups,



Scheme 1. Synthesis of tri-organotin (IV) complexes.

enhance their cell membrane permeability.[27] Their cytotoxicity in cancer cells results in DNA damage, an increase in calcium ion content, inhibition of macromolecule synthesis, induction of linoleic acid oxidation, and inhibition of mitochondrial metabolism.[27-30]

In this study, both triphenyl organotin (IV) complex (Ph_3SnCl) and tributyl organotin (IV) complex (Bu_3SnCl) were synthesized using cephalexin and p-dimethylaminobenzaldehyde as ligands. The cytotoxicity of these complexes was evaluated using the MTT assay against the breast cancer cell line (MCF-7).

2. Experimental

2.1. Chemicals

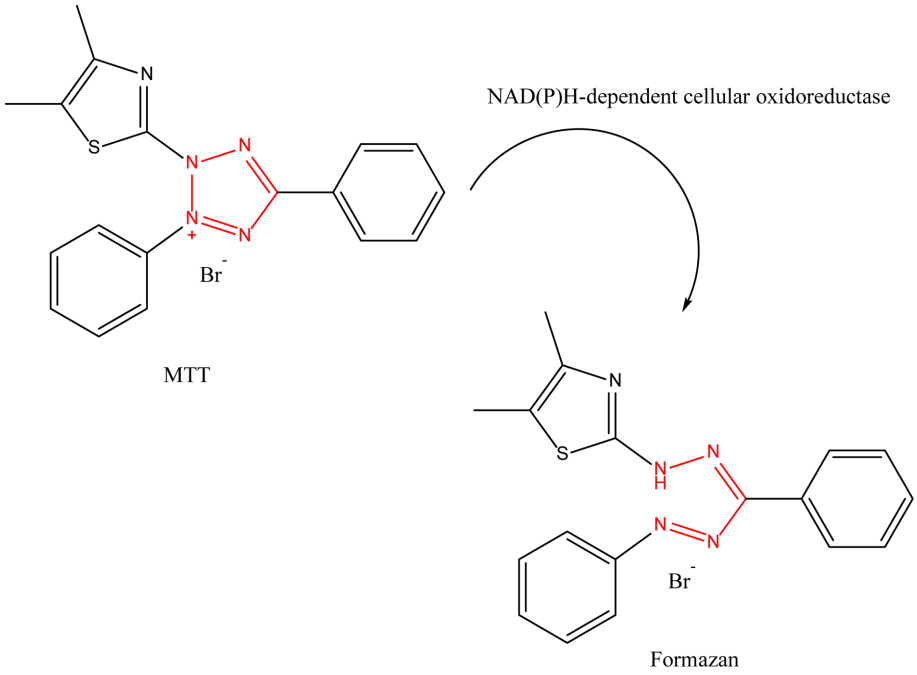
Cephalexin ($C_{16}H_{17}N_3O_4S$, M.wt. 347.39 g/mole, solid, purify: 96 %) was obtained from Scharlau Company. Also, ethanol (CH_3CH_2OH, M.wt. 46.068 g/mole, liquid, purify: 99 %, Scharlau company) and methanol (CH_3OH, M.wt. 32.4 g/mole, liquid, purify: 99 %, GCC company). The organotin compounds; (Tributyltin chloride, $C_{12}H_{27}SnCl$, 325.5 g/mole, liquid, 96 %), (Triphenyltin chloride, $C_{18}H_{15}SnCl$, 385.46 g/mole, Solid, 97 %) and para-dimethylaminobenzaldehyde ($C_9H_{11}NO$, M.wt. 149.19 g/mole, liquid, purify: 97 %) were produce from Fluka company.

Synthesis of Tri-Organotin (IV) Complexes

A mixture of cephalexin (1.0 mmol, 0.35 g) and 4-(dimethylamino) benzaldehyde (1.0 mmol, 0.149 g) in methanol (MeOH, 25 mL) was refluxed with stirring for 3 h. The resulting product was filtered, washed with MeOH, and dried to produce the corresponding Schiff base.[24,31] Two tri-organotin (IV) complexes were synthesized (*Scheme* 1), employing a 1:1 molar ratio of metal to ligand. Ph_3SnCl (0.3855 g, 1.0 mmol) and Bu_3SnCl (0.3255 g, 1.0 mmol) were individually dissolved in 5 mL of methanol. A Schiff base, synthesized and dissolved independently in 5 mL of methanol, was introduced to the agitated solution. The mixture was refluxed at 70 °C for 6 h, then filtered and dried to yield the product as a precipitate.[32,33]

2.3. The activity of anticancer/MTT cytotoxicity assay

The MTT assay is a colorimetric technique and biological tool that utilizes tetrazolium salts [3-(4,5-dimethyl-2-thiazolyl)-2,5-diphenyl-2H-tetrazolium bromide] to measure cell cytotoxicity. The flavin enzyme, found in mitochondria, plays a key role in the reduction of MTT.[28] This method is widely used to evaluate cell viability, cell death, and the cytotoxicity of drugs by measuring absorbance at 540 nm with a colorimeter. There is a direct correlation between metabolically active cells and the resulting color.[29] The MTT assay detects color changes from yellow to purple as formazan is formed. Healthy, rapidly dividing cells generate a significant reduction of



Scheme 2. Flow diagram representing the systematic conversion of MTT to formazan.

formazan, while dead cells show little to no decrease, as illustrated in *Scheme* 2. The intensity of the purple color reflects cell viability, with higher intensity indicating higher cell viability and lower intensity indicating fewer viable cells.[30] The reduction of MTT is also affected by intracellular factors like nicotinamide adenine dinucleotide (NADH), which serves as an electron donor in the reduction process.[28] The cytotoxic effects of cephalexin, Schiff base, and di- and tri-organotin (IV) complexes were assessed using the MTT assay at an absorption of 575 nm using an ELISA reader (Bio-Rad Laboratories GmbH, Feldkirchen, Germany. The MTT assay (triplicate) was performed for each concentration at Al-Nahrain University's Biotechnology Research Center.[18,24]

3. Results and Discussion

3.1. Physical data

Table 1 defines the physical properties of the synthesized triorganotin complexes. The melting points of the two complexes were determined utilizing an Electrothermal capillary apparatus at the Department of Chemistry, College of Sciences, Al-Nahrain University. Elemental analysis of the synthesized triorganotin (IV) complexes was performed using a Vario EL III instrument (Analysis System GmbH, Hanau, Germany). Based on the data in the table below, the found value refers to the percentage of the elements obtained from the experiment measurements, while the calculated values refer to the theoretical data,

Table 1. The Physical Properties of Triorganotin Complexes.

Compounds	Colors	Melting Points(°C)	Yields (%)	Found % (calculated%)					
				C	H	N	O	S	Sn
Ph_3SnL	Orange	125-127	75	61.78 (62.41)	4.49 (4.87)	6.33 (6.77)	7.62 (7.73)	3.44 (3.87)	14.24 (14.34)
Bu_3SnL	Brown	170-173	80	55.94 (57.89)	6.55 (6.83)	7.06 (7.30)	8.11 (8.34)	3.97 (4.18)	15.20 (15.46)

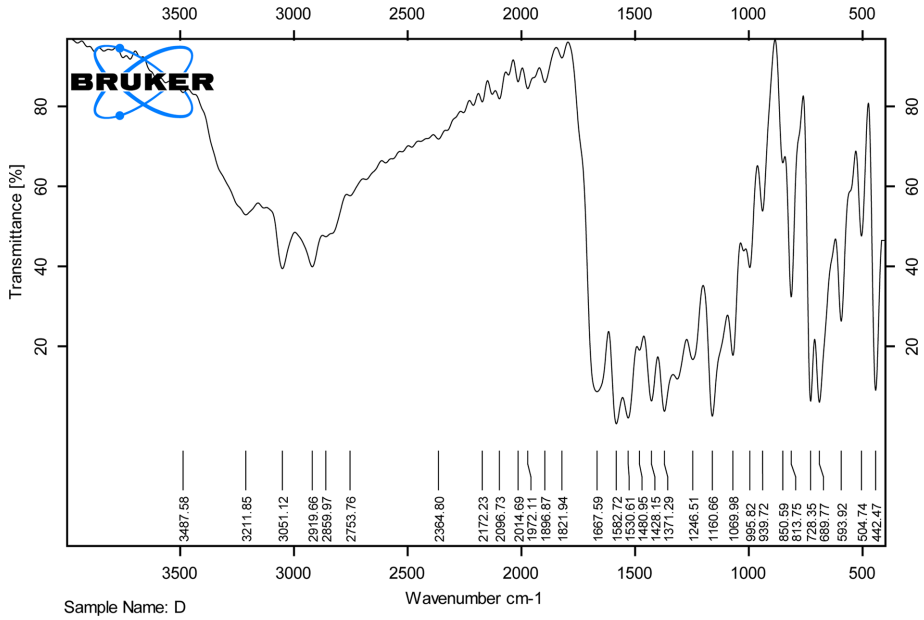


Fig. 1. FTIR spectrum of Ph_3SnL complex.

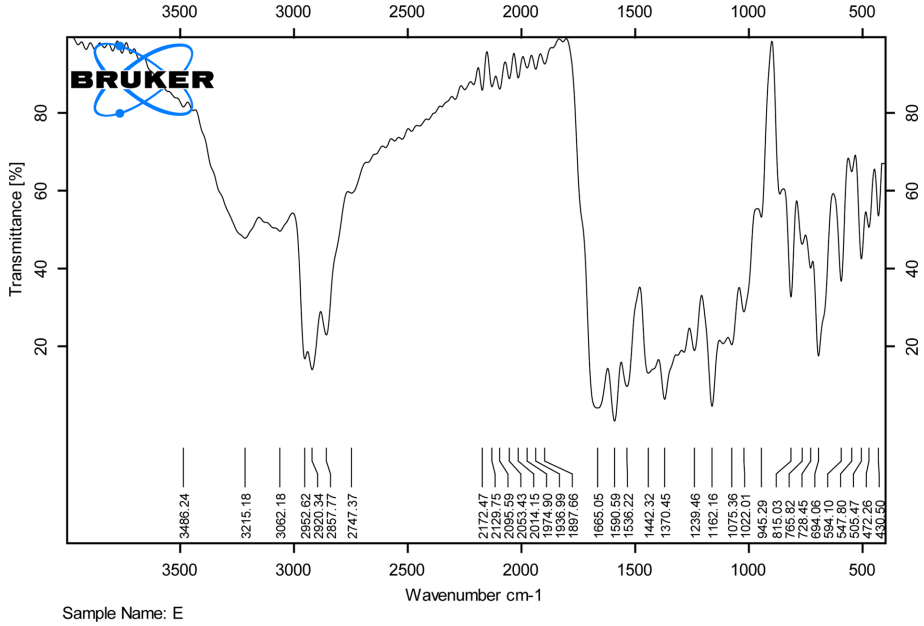


Fig. 2. FTIR spectrum of Bu_3SnL complex.

and the results show agreement with the literature.

3.2. Characterization of functional groups by FTIR spectrum

FT-IR measurements were conducted utilizing KBr discs on a Shimadzu Model 8300 Spectrophotometer (Japan) within the frequency range of 4000 – 400 cm^{-1}. The IR spectra of organotin carboxylate compounds, illustrated in *Figs.* 1 and 2, offer essential insights into the coordination characteristics of the carboxylate

Table 2. The FTIR spectra for some of the various groups in triorganotin (IV) complexes 1,2

No.	Complexes	v (COO) asym	v (COO) sym	Δv	v(Sn-O)	v(Sn-C)
1	Ph_3SnL	1582	1371	211	442	560
2	Bu_3SnL	1590	1370	220	472	547

group. In HL (cephalexin and p-dimethylamino-benzaldehyde, $C_{25}H_{26}N_4O_4S$) and the synthesized complexes, the asymmetric and symmetric (C=O) stretching vibrations were detected within the ranges of 1582 – 1590 cm^{-1} and 1368 – 1371 cm^{-1}, respectively.[24] Reduced IR values for the complexes signify the successful formation of organotin (IV) complexes. The noted reduction in asymmetric (COO^-) frequencies and the rise in symmetric (COO^-) frequencies further validate the establishment of metal-ligand bonds.

The Δv [$\nu_{as}(COO^-) - \nu_s(COO^-)$] value is 221 cm^{-1} for HL and diminishes in the complexes. Literature indicates that a Δv (COO^-) exceeding 350 cm^{-1} signifies monodentate binding, whereas values below 250 cm^{-1} imply a bidentate carboxylate binding mode to the tin metal.[34,35] Furthermore, the emergence of novel absorption bands within the range of 400 to 600 cm^{-1}, indicative of ν(Sn-O) and ν(Sn-C), substantiates the formation of the complexes.[36] The FT-IR data for the triorganotin (IV) complexes is presented in *Table* 2.

3.3. NMR Spectroscopy

The ^1H NMR spectra for Cephalexin, HL, and the synthesized complexes were acquired utilizing DMSO-d_6 as the solvent. The documented chemical shift values corresponded with those cited in earlier studies, validating the bonding modes deduced from the IR spectra.[37] Nuclear magnetic resonance measurements for proton and carbon were performed using a Varian INOVA spectrophotometer at 400 MHz. The principal signal values from the ^1H NMR spectra are depicted in *Figs.* 3 and 4. The lack of the COOH proton signal in the spectra of the complexes signifies deprotonation, corroborating the establishment of a metal-COO bond.[38] In Cephalexin, signals at 8.87 ppm and 8.40 ppm correspond to NH_2 and NH protons, respectively. The

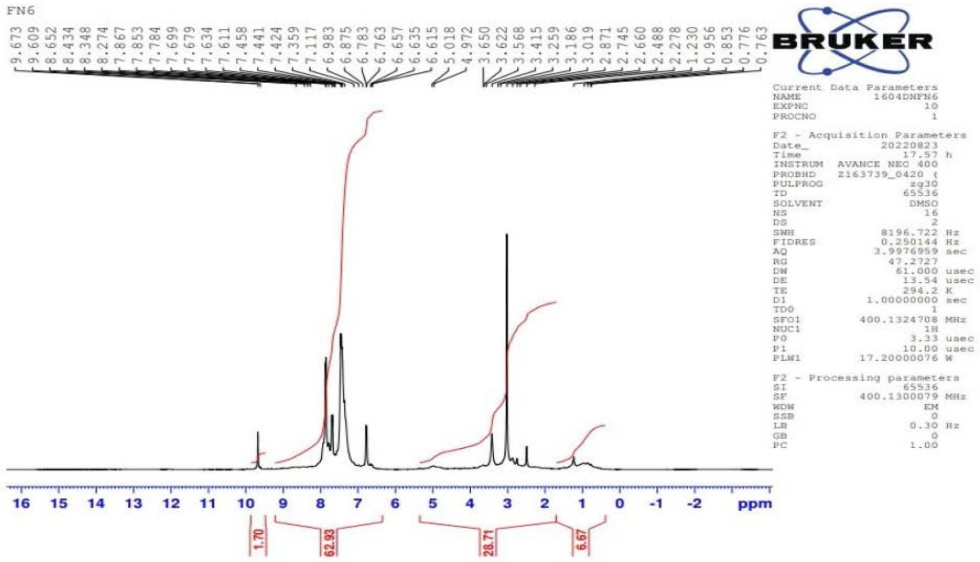


Fig. 3. ^1H-NMR spectrum of Ph_3SnL Complex.

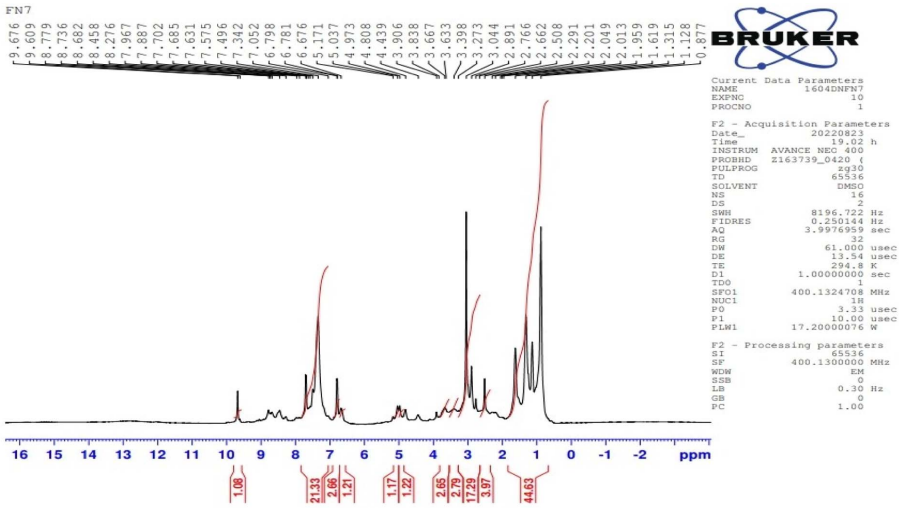


Fig. 4. ^{1}H-NMR spectrum of Bu_3SnL Complex.

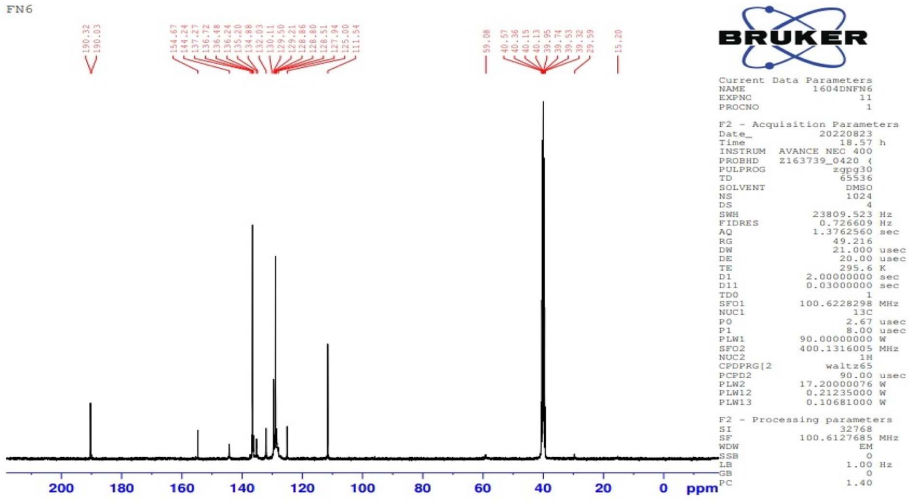


Fig. 5. ^{13}C-NMR spectrum of Ph_3SnL Complex.

NH_2 signal vanishes in the ligand spectrum as a result of C=N bond formation, resonating at 8.70 ppm.[39] A signal at 8.40 – 8.45 ppm corresponds to the proton of the NH group.[40] The spectra for the synthesized complexes show additional signals belonging to the aromatic protons' methylene and methyl groups. The ^{1}H NMR spectra for Ph_3SnL; 8.65 (s, 1H, C=NH), 8.43 (s, 1H, NH), 6.62 – 8.72 (m, Ar-H), 4.97 (d, 1H), 3.02 (s, 6H), 1.23 (s, 3H) and for Bu_3SnL; 8.78 (s, 1H, C=NH), 8.45 (s, 1H, NH), 6.68 – 8.28 (m, Ar-H), 5.17 (d, 1H), 3.04 (s, 6H), 2.50 (s, 3H, CH_3), 1.31 (m, 6H, $3CH_2$), 0.90 (t, 3H, CH_3), 0.88 (s, 3H).

^{13}C NMR spectroscopy was utilized to examine the synthesized complexes, with significant signal values presented in *Figs.* 5 and 6. Supplementary signals detected in the spectra suggest the existence of organic groups bonded to the tin atom. NMR spectroscopy of ^{119}Sn, a crucial method for elucidating the characteristics and reactions of tin (IV) complexes in solution, was also employed. Measurements were conducted using a Bruker DRX300 NMR spectrophotometer (Bruker, Zürich, Switzerland) at 107 MHz, in Tehran,

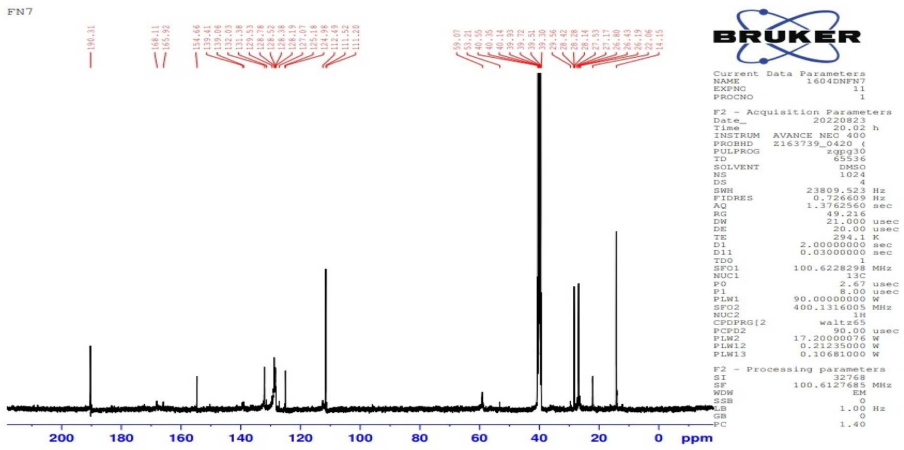


Fig. 6. ^{13}C-NMR spectrum of Bu_3SnL Complex.

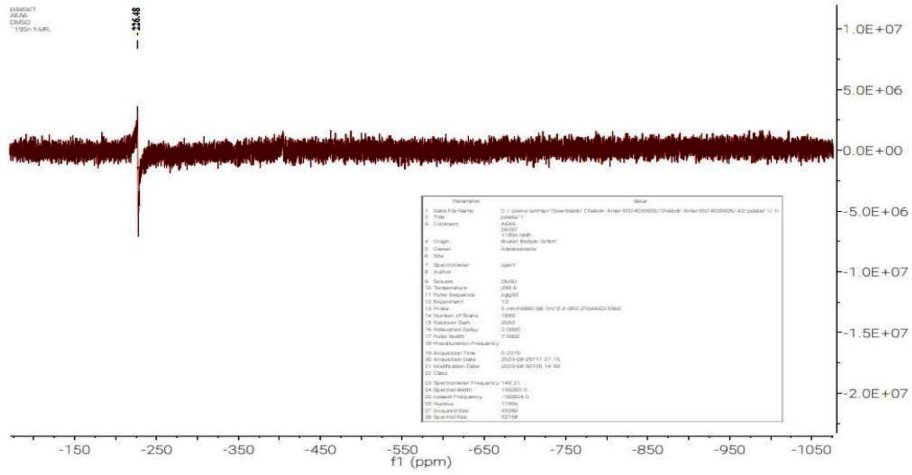


Fig. 7. ^{119}Sn-NMR spectrum of Ph_3SnL complex.

Iran, at 107 MHz, with all compounds solubilized in DMSO-d_6. In the spectrum of free cephalexin, a very low signal occurs between 164 – 167 ppm, which refers to the C=O group, and when the Schiff base formed, there is a new bond occurs, which is the azomethine C=N at 154.66 ppm, which occurs in both complexes that synthesized. The ^{13}C NMR spectra for Ph_3SnL: C=O (190.32), C=N (154.67), Arm. (144.24, 125 – 137.27, 111.54), C-NH (59.08), CH_3, CH_2 (40.13, 29.59, 15.20) and for Bu_3SnL; C=O (190.31), C=N (154.66), ARM (124.98 – 132.03, 111.20), C-NH (59.07), CH_3, CH_2 (40.55 – 39.30, 29.56 – 26.19, 22.06, 14.15).

The synthesized tri-organotin (IV) complexes exhibited ^{119}Sn resonances at -226.48 ppm for Ph_3SnL and -286.45 ppm for Bu_3SnL. ^{119}Sn NMR is a very important technique for describing the coordination around the central atom, which is tin. Increasing coordination number led to an increase in the electron density around the central atom, which causes the resonance signals to move upfield and downfield, respectively. The values indicate five-coordinated geometries surrounding the tin (IV) centers, as illustrated in *Figs.* 7 and [8.41,42] *Table* 3 presents a summary of the ^{1}H NMR, ^{13}C NMR, and ^{119}Sn NMR spectral data.

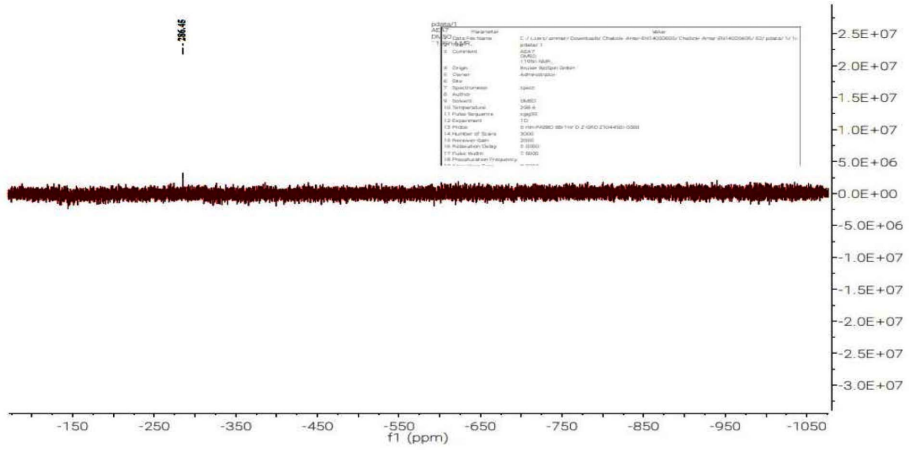
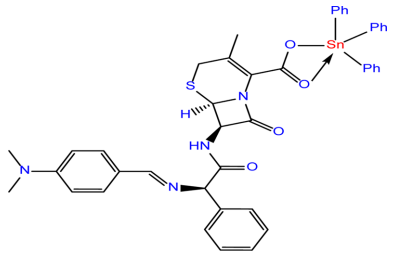
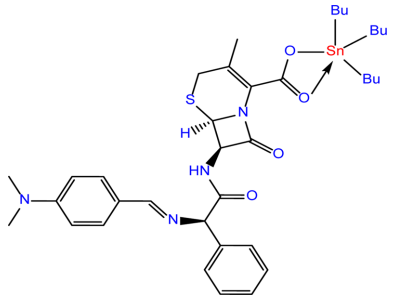


Fig. 8. ^{119}Sn-NMR spectrum of Bu_3SnL complex.

Table 3. ^{1}H-NMR, ^{13}C-NMR, and ^{119}Sn-NMR spectral data for Tri-organotin (IV) complexes

Compound	Structure	^{1}H-NMR (400 MHz: DMSO-d_6, δ, ppm, *J* Hz)
Ph_3SnL		8.65 (s, 1H, C=NH), 8.43 (s, 1H, NH). ^{13}C-NMR (400 MHz: DMSO-d_6, δ, ppm) C=O (190.32), C=N (154.67). ^{119}Sn-NMR (δ ppm) -226.48
Bu_3SnL		^{1}H-NMR (400 MHz: DMSO-d_6, δ, ppm, *J* Hz) 8.78 (s, 1H, C=NH), 8.45 (s, 1H, NH). ^{13}C-NMR (400 MHz: DMSO-d_6, δ, ppm) C=O (190.31), C=N (154.66). ^{119}Sn-NMR (δ ppm) -286.45

3.4. Field emission scanning electron microscopy and energy dispersive X-ray examination

Scanning Electron Microscopy (SEM) is a proficient technique for examining surface characteristics, encompassing variations, particle dimensions, morphology, and uniformity.[43] Field Emission Scanning Electron Microscopy (FESEM) provides improved functionalities, including reduced electrostatic distortion and exceptional spatial resolution of up to 1.5 nm, which is three to six times superior to conventional SEM.[44] The FESEM and Energy Dispersive X-ray (EDX) analyses of Cephalexin, Schiff base, and di- and tri-organotin (IV) complexes were conducted utilizing a TESCAN MIRA3 LMU system (Kohoutovice, Czech Republic) at an accelerating voltage of 15 kV.

FESEM was employed to examine the morphology

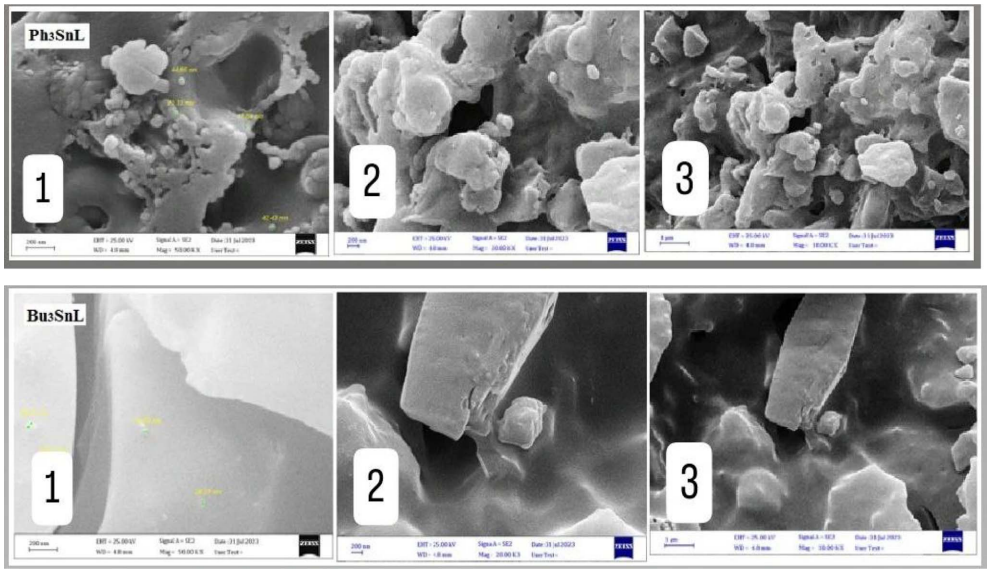


Fig. 9. FESEM images of the tri-organotin (IV) complexes. The figure above shows two cross-sections (1&2) from two different locations on the complex's surface, both were measured at the same size at 200 nm. The third cross-section (3) was measured at 1 μm for greater accuracy (It is true because the Figures are clear).

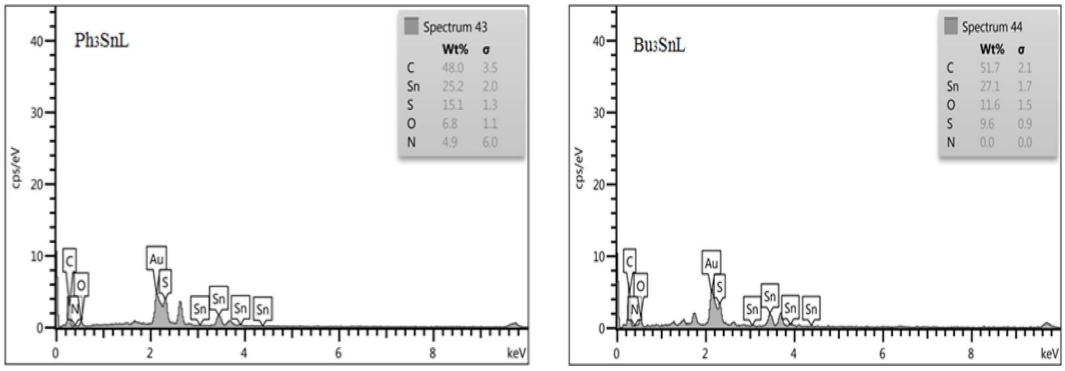


Fig. 10. EDX spectra of the tri-organotin (IV)complexes.

of the synthesized tri-organotin (IV) complexes. *Fig.* 9 illustrates that the complexes exhibited uniform and porous structures. Furthermore, the images revealed the existence of small particle agglomerates, demonstrating variations in both the shape and size of the particles.[45] The particle size ranges were established as 17.86 – 44.66 nm for Ph_3SnL and 22.33 – 93.17 nm for Bu_3SnL. The images of the FESEM show the crystalline distribution and distinct differences in shape and size, which indicate the effect of coordination between the ligand and the tri-organotin complexes. This morphology increased the formation of larger aggregates and the coordination bonds.[17]

EDX microanalysis verified the existence of metals within the complexes. This semi-quantitative method is exceptionally sensitive and is extensively employed in biomedical research to identify elements in diverse compounds and biological tissues.[46,47] The comprehensive findings of the FESEM and EDX analyses are presented in *Figs.* 9 and 10. The EDX shows information about the elements that form the complexes. Here, the EDX spectrum shows the presence of a lot of elements: carbon, tin, sulfur, nitrogen, and oxygen. The presence of Sn in the complexes confirms the

formation of the organotin complexes by coordinating the ligand with the central atom, as shown in *Fig.* 10.[17]

3.5. Application of organotin complexes as anticancer

The cytotoxic effects of the synthesized tri-organotin (IV) complexes were evaluated on MCF-7 (breast cancer) and HDFn (normal human dermal fibroblast) cell lines using the MTT assay. This assay relies on the reduction of tetrazolium salt (3-(4,5-dimethyl-2-thiazolyl)-2,5-diphenyl-2H-tetrazolium bromide) from yellow to purple, a change indicating cell viability and apoptosis. After 24 h of incubation at 37 °C in a CO_2-enriched atmosphere, varying concentrations of cephalexin and the organotin (IV) complexes (12.5, 25, 50, 100, 200, and 400 μg/mL) were administered.

IC_{50} refers to the inhibitory concentration of 50 %, used to measure the concentration of the compounds that are used to inhibit the biological activity at 50 % percentage. IC_{50} differs from IC, which refers to inhibition in general. The IC_{50} values revealed that the organotin (IV) complexes possess anticancer activity, which varies based on structural features, such as the attached chemical groups, geometry, and dosage. The results also indicate a direct correlation between anticancer activity and drug concentration, with significant effectiveness observed at lower concentrations.[48,49] Notably, the IC_{50} analysis showed no cytotoxic effects of the organotin (IV) complexes on HDFn cell lines, suggesting that the synthesized complexes are safe for normal human cells. The

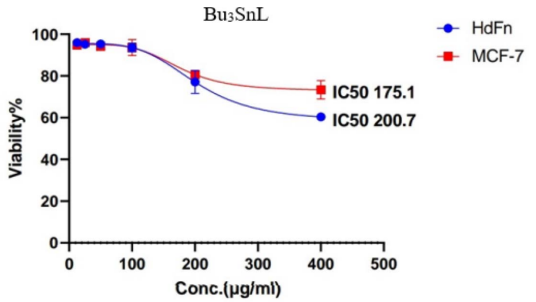


Fig. 11. Dose-dependent cytotoxic effect of Bu_3SnL complex on MCF-7 and HdFn cell lines.

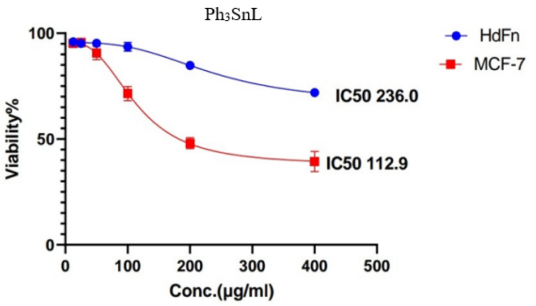


Fig. 12. Dose-dependent cytotoxic effect of Ph_3SnL complex on MCF-7 and HdFn cell lines.

Table 4. Cytotoxic effects of the tri-organotin (IV) complexes at different concentrations (12.5, 25, 50, 100, 200, 400 μg/ml) on MCF-7 cancer cells & HdFn cells

MCF-7 cancer cells							
Complexes	Viability (mean ± SD)						IC_{50}%
	Concentration (μg mL^{-1})						
	12.5	25	50	100	200	400	
Ceph	-----	94.67±0.60	93.98±0.53	89.19±2.41	74.69±2.55	62.92±5.03	180.8
Ph_3SnL (1)	95.17±1.28	95.71±0.8	90.70±3.18	71.489±3.39	48.03±2.5	39.352±4.78	112.9
Bu_3SnL (2)	94.86±0.29	95.949±0.904	94.29±0.82	93.59±3.9	80.67±1.9	73.37±4.42	175.1
HdFn cells							
Complexes	Viability (mean ± SD)						IC_{50}%
	Concentration (μg mL^{-1})						
	12.5	25	50	100	200	400	
Ceph	-----	94.63±0.48	93.86±1.10	90.08±1.04	86.07±3.07	74.88±5.00	194.5
Ph_3SnL (1)	95.949±1.02	95.216±0.82	95.33±1.18	93.59±2.10	84.79±1.20	71.95±0.81	236.0
Bu_3SnL (2)	95.949±1.02	95.216±0.82	95.33±1.18	93.59±2.10	77.083±5.52	60.378±0.81	200.7

anticancer activity results are summarized in *Figs.* 11 and 12, as well as *Tables* 4.

4. Conclusions

This study emphasizes the significant cytotoxic effects of organotin (IV) compounds on both cancerous and normal cell lines. Tri-organotin (IV) complexes were comprehensively characterized using advanced techniques, including FT-IR spectroscopy and proton, carbon, and tin nuclear magnetic resonance, confirming the coordination of the organotin (IV) moieties with the ligand. The cytotoxic efficacy of the synthesized complexes was assessed via the MTT assay on breast cancer cell lines (MCF-7) and HDFn. The results demonstrated significant anticancer effects on MCF-7 cells, particularly at high concentrations. The suggested mechanism of action entails organotin (IV) complexes interacting with nitrogen and phosphate groups in DNA and nucleotide base pairs. These complexes induce apoptotic cell death by binding to DNA phosphate groups and disrupting internal phospholipid metabolism.

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