Journal of the Serbian Chemical Society
JSCS-info@shd.org.rs • www.shd.org.rs/JSCS
J. Serb. Chem. Soc. *83* (4) 425–437 (2018)
JSCS–5086
UDC 546.814–039.7+542.913:547.963.32:
543.42:57–188:615.279/.28
Original scientific paper

Design, synthesis and biological evaluation of organotin(IV) complexes of flumequine and cetirizine

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(Received 3 December 2016, revised 1 June, accepted 6 June 2017)

Abstract: Six new organotin(IV) derivatives $[Me_3SnL_1]$ (**1**), $[Bu_3SnL_1]$ (**2**), $[Ph_3SnL_1]$ (**3**), $[Me_3SnL_2]$ (**4**), $[Bu_3SnL_2]$ (**5**) and $[Ph_3SnL_2]$ (**6**) (where HL_1 = = 9-fluoro-6,7-dihydro-5-methyl-1-oxo-1*H*,5*H*-pyrido[3,2,1-*ij*]quinoline-2-carboxylic acid (flumequine) and HL_2 = 2-[2-[4-[(4-chlorophenyl)phenylmethyl]--1-piperazinyl]ethoxy] acetic acid (cetirizine)) were synthesized and characterized by elemental analysis, FT-IR spectroscopy, multinuclear ^{1}H-, ^{13}C- and ^{119}Sn-NMR, mass spectrometry and thermal analysis techniques. The obtained data reveal trigonal-bipyramidal geometry in case of complexes **1**, **2**, **4** and **5**, and tetrahedral geometry for complexes **3** and **6** around the tin atom, whereas in complexes **3** and **6** the carboxylate ligand act as monodentate ligand through one of its oxygen atoms while it acts as bidentate ligand through two oxygen atoms for complexes **1**, **2**, **4** and **5**. The antibacterial and antifungal efficacies of complexes **1**–**6** were assessed and the majority of the compounds showed good activities. The present research showed that the trimethyltin(IV) derivatives were particularly more effective than tributyltin(IV) and triphenyltin(IV) derivatives against all the bacterial and fungal strains. Antioxidant and DNA binding studies were also performed and promising results were obtained.

Keywords: organotin(IV) complexes; spectroscopy; antioxidant; antimicrobial; DNA binding.

INTRODUCTION

The synthetic chemistry of organotin(IV) complexes has become an active field of research because of their vast antimicrobial and industrial applications. Such compounds could be utilized as critical thermal stabilizers of plastics, and

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https://doi.org/10.2298/JSC161203070I

as catalysts and biocides.[1–3] Organotin(IV) carboxylates could be used for multipurpose, *e.g.*, as catalysts for esterification,[4] silicone curing,[5] structuring polyurethane,[6] antifouling paints,[7] PVC stabilizers[8] and transesterification from vegetable oil to biodiesel.[9] Moreover, they could be used to synthesize multipurpose medicinal compounds that could operate as useful anti-bacterial and anti-fungal drugs. They also gave considerable responses as anti-tumor and anti-cancer drugs,[10,11] because of their ability to bind with the phosphate of DNA in tumors, causing, thereby, damage.[12] Their antibacterial action may generally be associated with the organotin(IV) moieties and the attached ligands,[10,13,14] since the natural ligands facilitate the action of the complexes over the cell membranes. In general, the triorganotin compounds are famous for showing higher activities over their di- and mono-organotin analogues, which may be attributed to their capacity to bind with proteins.[15,16] According to Hadjiliadis and co-workers, organotins exhibit significant *in vitro* antiproliferative activity which, in some cases, is higher than the corresponding activity of cisplatin or other drugs used for clinical treatment in cancer chemotherapy.[17] Similarly, Gielen thoroughly worked with and discussed the anticancer and especially human anticancer behavior of organotin compounds, which showed significant response.[18,19] Gómez-Ruiz and co-workers compared the response of organometallic drugs with cisplatin. Although organometal drugs have shown good results, they have some significant side effects that require solving.[20] In this context, Gomez-Ruiz and Ferragut published new tin(IV) carboxylate complexes that showed increased antiproliferative activity and cytotoxicity against various human tumor cell types relative to that shown by an established tin complex, In addition, novel organotin compounds overcome multidrug resistance.[21] An extensive review was published on the significant and promising behavior of nano-structured materials functionalized with metallodrugs in the treatment of cancer.[22] Organotin compounds were found to be highly cytotoxic to lymphoma cell lines with lower toxicity towards the HeLa cervical cancer cell line and distinctive behavior towards different mammalian cell lines.[23] Gómez-Ruiz and Kaluđerović studied novel nanostructured mesoporous silica SBA-15 as a carrier system for organotin compounds against different cancer cells and *in vivo*, and observed a promising response and improved therapeutical properties.[24,25]

The quinolones are an important class of antibiotics that has a rich history of medicinal chemistry applied towards improving bacterial spectrum and adverse side effect profiles.[26] Of these, flumequine is mainly used for veterinarian purposes for the medication of enteric infections (all infections of the intestinal tract), and can be used to treat cattle, swine, chickens and fish.[27] In addition, it has occasionally been utilized in some countries to treat urinary tract infections.[28] On the other hand, cetirizine is another remarkable drug. It is a second-generation antihistamine prescribed for the curing of hay fever, allergies, angio-

edema and urticarial.[29] It is a significant metabolite of hydroxyzine and a racemic particularly H_1 receptor antagonist.[30] Cetirizine is usually restrained from crossing the blood-brain barrier and, consequently, has diminished impact on the central nervous system in contrast to first-generation drugs, for example, it has less possibility to induce sleepiness or to interfere with memory creation.[31] Keeping in mind the above aspects and in continuation of previous research work,[32–37] herein the synthesis and biological activities of organotin(IV) complexes of flumequine and cetirizine are reported to evaluate further their biological significance in comparison to their previous function as patent drugs.

EXPERIMENTAL

Materials and methods

Organotin(IV) hydroxides, R_3SnOH (R = CH_3, *n*-C_4H_9 and C_6H_5) were purchased from Sigma–Aldrich (USA) and used without further purification. Flumequine (**HL_1**) and cetirizine (**HL_2**) were purchased from Mac and Rains Pharmaceutical Industry, Sundar, Lahore, Pakistan. The utilized analytical grade solvents, methanol, *n*-hexane, chloroform, toluene, diethyl ether, and dichloromethane obtained from Merck, DMSO from Lab Scan and petroleum ether Riedel-de Haen, were dried before use as per standard methods.[38]

The melting points of the samples were determined in capillary tubes using a Stuart SMP3 apparatus. The IR spectra were recorded on a PerkinElmer 1000 FTIR spectrophotometer in the wavenumber range 4000 to 400 cm^{-1}. The elemental composition (C, H, N, Cl and F) of the complexes was determined using a Leco CHNS-932 natural analyzer (USA). The percentage of Sn was determined by ICP-OES (Thermo iCap 6300). The ^{1}H-, ^{13}C- and ^{119}Sn-NMR spectral measurements were realized at 400, 75 and 100 MHz, respectively, using a Bruker ARC 400 MHz FT-NMR spectrometer. The thermogravimetric analyses were performed on Mettler Toledo microanalysis TGA instrument at heating rate of 10 K/min in O_2 environment and the mass spectrometric analyses were realized on an Agilent G1974A MALDI mass spectrometer.

All the characterization data of the synthesized complexes are provided in the Supplementary material to this paper.

Synthesis of triorganotin derivatives

Stoichiometric quantities of the respective medicinal ligands (**HL_1** and **HL_2**) and the appropriate organotin hydroxide (trimethyltin, tributyltin and triphenyltin) in toluene were refluxed in a two-necked flask fitted with a Dean and Stark apparatus for 12–15 h with continuous azeotropic removal of water. The progress of the reaction was monitored through thin layer chromatography. The reaction mixture was allowed to cool to room temperature and then evaporated under reduced pressure until the formation of a thick concentrate, which was allowed to solidify normally. The crude synthesized products were recrystallized using a mixture of *n*-hexane:chloroform (1:4) to obtain the target products **1**–**6** in powder form.

Biological studies

The antibacterial activities of the ligands and their organotin(IV) derivatives (**1**–**6**) were investigated against five bacterial strains, *i.e*., *Escherichia coli* (ATCC 25922), *Bacillus subtilis* (ATCC 19659), *Staphylococcus aureus* (ATCC 25923), *Pseudomonas aeruginosa* (ATCC 27853) and *Micrococcus luteus* (ATCC 9341). The agar well-diffusion method was used for the antibacterial studies. Broth culture (0.75 mL) having *ca*. 10^6 colony-forming units

(CFU) per mL of the test strain was added to 75 mL of nutrient, *i.e*., prepared agar medium, at 45 °C, blended well, transferred to 14 cm sterile Petri plates, left to solidify and 8 mm wells dug with a sterile metallic borer. At this point, a DMSO solution of test sample (100 μL) at concentration of 1 mg mL^{-1} was added to the required wells. DMSO served as the negative control, and cefixime (1 mg mL^{-1}) as the positive control. They were incubated aerobically at 37 °C for 24 h after which zones of inhibition (mm) were measured. Triplicate measurements were performed for each bacterial strain.[39]

The agar tube dilution method was utilized to evaluate the antifungal behavior of the synthesized complexes **1**–**6**. The antifungal assay was carried out against distinctive fungal strains, *Trichophyton longiformis* (ATCC 28188), *Candida albicans* (ATCC 10231) and *Aspergillus flavus* (ATCC 9643). The tubes containing hardened Sabouraud dextrose agar (SDA) and triorganotin(IV) carboxylates (**1**–**6**) having concentration of 200 mg/ mL were inoculated with 4 mm diameter of inoculums, taken starting with seven days old fungus culture grown in SDA at 28 °C. DMSO and terbinafine (200 mg/mL) were utilized as negative and positive controls, respectively. Each experiment was carried out in three replicates. The tubes were incubated at 28 °C for seven days. Growth in the media was determined by measuring linear growth (mm) and growth inhibition was calculated with reference to negative control.[40]

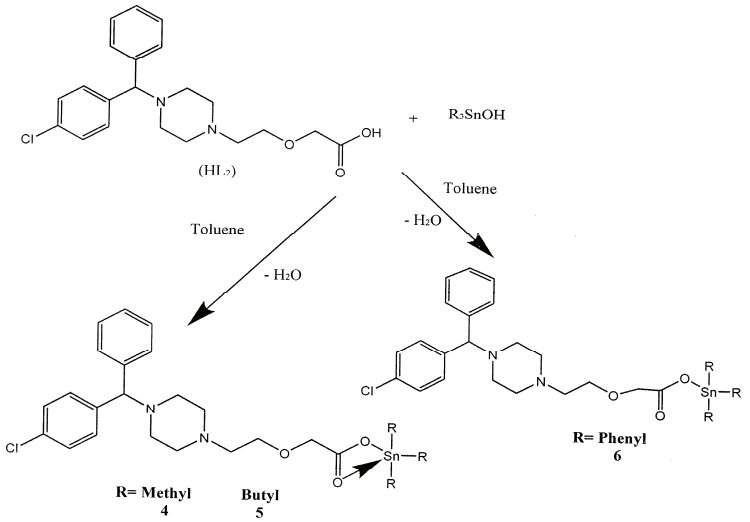
The antioxidant studies of the ligands and derivatives were determined by using a free radical scavenging method taking the 2,2-diphenyl-1-picrylhydrazyl ($DPPH^{\bullet}$) stable radical as the action agent. Different concentrations of test mixtures (12.5, 25, 50 and 100 μg) and standard gallic acid were taken in separate test tubes and the volume for every test tube was adjusted to 100 μL by the addition of pure DMF. In the tubes containing the sample solutions in DMF, 5 mL a methanolic solution of $DPPH^{\bullet}$ (0.1 mM) was added. The tubes were left standing for 30 min and then the absorbance at 517 nm was measured. Control tests were performed in a similar manner without the test samples. The reduction of $DPPH^{\bullet}$ was calculated relative to the measured absorbance of the control samples. Radical scavenging activity was calculated by the formula given as: % scavenging of $DPPH^{\bullet}$ = [(Control OD – Sample OD) / control OD]×100.[41]

DNA binding studies by the viscosity method were performed using an Ubbelohde viscometer at 23±1 °C. The average flow times were calculated from three readings to avoid error. The values of viscosity were found out from the difference of flow time of solution – 50 μM of DNA with compound using (1:1) mixture of DMSO and Tris-HCl at concentration of $1x10^{-5}$ M (t), from flow time of DNA solution alone (t_0) using the following formula, $\eta = t - t_0$.[42] The viscosity data is presented as graph of $(\eta/\eta_0)^{1/3}$ *vs*. binding ratio ([compound]/[DNA]) where η represents the viscosity of DNA in the presence of complex and η_0 is the viscosity of DNA in the absence of the complex.

RESULTS AND DISCUSSION

Triorganotin(IV) complexes of flumequine and cetirizine were synthesized by reacting the respective trialkyltin hydroxide (R_3SnOH, R = methyl, *n*-butyl, phenyl) in a 1:1 mole ratio with the appropriate ligand in dry toluene under reflux conditions, as shown in Scheme 1. The purities of the compounds were checked by thin layer chromatography. The synthesized compounds **1**–**6** were creamy white and stable in moist air. They were characterized by FTIR, multinuclear ^{1}H-, ^{13}C- and ^{119}Sn-NMR spectroscopy in combination with elemental analysis and

melting point determinations. The thermal stability of the synthesized complexes was determined through TG-DSC analysis. Furthermore, the biocidal activities of the complexes were evaluated as compared to those of the parent ligands.



Scheme 1. Method of synthesis of complexes **1**–**6**.

IR spectroscopy

The infrared spectra for all the synthesized complexes were recorded in the standard range of 4000–400 cm^{-1} on KBr discs. The absorption bands were assigned after correlation with reported values.[43] In the spectra, medium to weak peaks in range 403–459 cm^{-1} were assigned to Sn–O bonds, while peaks in the region 510–526 cm^{-1} gave an indication of Sn–C bonds. The formation of the complexes because of deprotonation of the –COOH group of the ligand was authenticated by the absence of a broad ν(OH) band in the 3434–3424 cm^{-1} region. The $\Delta\nu$ values ($\Delta\nu = \nu(COO)_{asy} - \nu(COO)_{sym}$) demonstrate the mode of coordination of the carboxylate ligands to the tin moiety. Hence, values for $\Delta\nu$ less than 200 cm^{-1} indicate bidentate coordination (trigonal bipyramidal geometry) while values of $\Delta\nu$ greater than 200 cm^{-1} indicate monodentate coordination (tetrahedral geometry) for a carboxylate ligand.[44] In present study, complexes **1**, **2**, **4** and **5** possess bidentate and complexes **3** and **6** possess monodentate mode of coordination in solid state as shown by their respected $\Delta\nu$ values. The coordination around the tin atom may be affected by the bulkiness of the ligands as well as the size of the alkyl/aryl groups attached to the tin atom. $\Delta\nu$ indicated that both ligands are potentially bidentate, but in **3** and **6** they are attached to tin in a monodentate manner due to bulky nature of phenyl groups. The $\nu_{asym}(COO)$ values around 650 cm^{-1} also confirms the Sn–O bond formation.

NMR studies

The ^{1}H-NMR of all the complexes were recorded in deuterated DMSO. The spectral positions of the distinct protons were identified as per their intensities, pattern and the number of protons.[43] In the ^{1}H-NMR spectra of all the organotin derivatives, the carboxylic acid hydrogen near 11–12 ppm was absent due to the formation of organotin complexes. In addition, the chemical shift values of complexes were shifted downfield as compared to those for the ligands, which is also confirmation of bond formation. Two consecutive multiplets due to three phenyl groups attached to the tin atom and halophenyl group protons of the attached ligands were resolved in range 7–8 ppm. The multiplets in all the compounds due to the aryl protons of the ligands were found slightly upfield due to the attachment of halogens in compounds **3** and **6**. When butyl or methyl groups were attached to tin, the values were recorded in the expected ranges as 0.9–1.6 ppm and 0.3–0.7 ppm, respectively, in complexes (**1**, **2**, **4** and **5**).

The ^{13}C-NMR data explicitly show the carbon attached to the tin and other carbons that differentiate the organotin derivatives. The numbers of signals found were in accordance with the presence of magnetically non-equivalent carbon atoms. The shifting in the resonance position of carboxylic carbon suggested bonding of oxygen to the tin atom. The carbonyl carbon peak was found around 160–180 ppm in all the compounds. All the phenyl carbons were resolved in the range 125–135 ppm. The aromatic carbons of triphenyltin showed signals of sufficient interest by which the environmentally different phenyl groups could be identified as compared to aryl–Cl signals that were slightly deshielded.[45] The chemical shift of the triphenyltin unit in region 125–135 ppm is characteristic due to the tetrahedral geometry of compounds **3** and **6**. In addition, some new signals in NMR spectra of complexes **2** and **5** were found in range 13–36 ppm as compared to NMR spectra of ligands for *n*-butyl carbons and signals at 15 and 13.5 ppm were found due to methyl carbons in complexes **1** and **4**, respectively.

Amongst the synthesized compounds, single sharp resonances were observed in the ^{119}Sn-NMR spectra for **1**, **2**, **4** and **5** in the range –90 to –190 ppm, which indicated the five-coordinated geometry around tin, while compounds **3** and **6** showed peaks in range of +200 to –60 ppm indicating tin as four-coordinated, which is well in accordance with reported work.[45] The NMR data of the these complexes in liquid state as well as FTIR in solid state well supported each other and the respective geometries are presented in Scheme 1.

Thermal studies

Thermal studies were performed on all the synthesized complexes **1**–**6**. Thermogravimetric analysis (TGA) revealed that complexes **1**, **2**, **4** and **5** undergo decomposition in three steps, while complexes **3** and **6** undergo decomposition in two steps. The first step involves the loss of two methyl groups for **1**

and **4**, loss of all butyl groups for **2** and **5** and loss of three phenyl groups for **3** and **6**. The second step involves the loss of the third methyl group and a halogen atom for **1** and **4**, and loss of a halogen atom for **2** and **5**, while it is the SnO_2 formation step for **3** and **6**. The third and final step involves the formation of SnO_2 for **1**, **2**, **4** and **5**. The mass loss data are given in Table I. The total mass left in TGA curves supports the formation of SnO_2 after the decomposition.[46]

TABLE I. Data for the thermal decomposition of complexes **1**–**6**

Compound	Step No.	TG step temperature range, K	Mass loss, %		Type of loss
			Observed	Calculated	
$(CH_3)_3Sn(HL_1)$	I	305–501	7.20	7.05	Loss of 2 Me groups
(**1**)	II	504–592	15.20	15.03	Loss of Me and F atom
	III	595–923	64.70	64.56	Formation of SnO_2
$(C_4H_9)_3Sn(HL_1)$	I	330–540	31.10	31.03	Loss of 3 Bu groups
(**2**)	II	543–610	34.60	34.47	Loss of F atom
	III	613–973	72.70	72.51	Formation of SnO_2
$(C_6H_5)_3Sn(HL_1)$	I	463–673	37.75	37.83	Loss of three phenyl groups
(**3**)	II	763–963	75.20	75.33	Formation of SnO_2
$(CH_3)_3Sn(HL_2)$	I	315–510	5.50	5.41	Loss of 2 Me groups
(**4**)	II	513–605	14.80	14.62	Loss of Me and Cl atom
	III	608–943	73.00	72.74	Formation of SnO_2
$(C_4H_9)_3Sn(HL_2)$	I	320–550	25.10	25.15	Loss of 3 Bu groups
(**5**)	II	552–622	30.60	30.39	Loss of Cl atom
	III	625–953	78.10	77.86	Formation of SnO_2
$(C_6H_5)_3Sn(HL_2)$	I	473–673	30.50	31.30	Loss of three phenyl groups
(**6**)	II	773–973	79.00	79.54	Formation of SnO_2

Biological studies

The DPPH method was used to check the antioxidant behavior of the synthesized complexes based on their radical scavenging ability. $DPPH^{\bullet}$ is a stable free radical that is used for the determination of the scavenging activity of a compound. The decrease in the absorbance of $DPPH^{\bullet}$ at 517 nm caused by an antioxidant helps to determine the reduction capability.[47] The data revealed that some of the synthesized complexes were fairly active while the others were moderately active as shown in Fig. 1, which gives the IC_{50} values of the compounds (the concentration of a compound that reduces the absorption of $DPPH^{\bullet}$ by 50 %). Gallic acid was used as a standard. The trimethyltin(IV) derivatives have shown better activities as compared to all the other complexes and neutral ligands.

DNA binding studies

Viscometric measurements are a useful technique to determine drug–DNA interactions. It clearly describes the type of interaction between a molecule and the DNA whether through intercalation or electrostatic mode of interaction. During

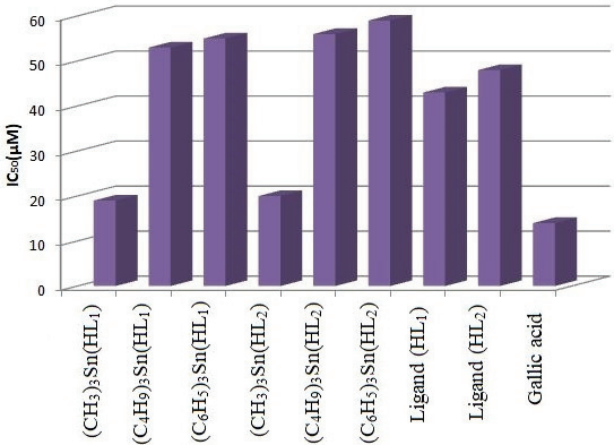


Fig. 1. Antioxidant activities of compounds **1**–**6**.

intercalation, the viscosity of DNA solution increases as the DNA helix lengthens. In the other case, the viscosity of the DNA solution decreases with increasing concentration of binding molecule, which is due to electrostatic interaction (out-binding mode) of the incoming molecule. When the relative specific viscosities (η/η_0) were plotted against concentrations (molecule/salmon-sperm DNA (SS-DNA)), it was observed that there was positive change in (η/η_0) with increasing concentration of the synthesized compounds (**1**–**6**), as shown in Fig. 2. The gradual increase in the viscosity of the solution indicates the intercalative mode of interaction between synthesized compounds and the salmon-sperm DNA.[48]

Antimicrobial activity

The synthesized complexes (**1**–**6**) were checked against five bacterial strains, *i.e*., *Escherichia coli*, *Bacillus subtilis*, *Staphylococcus aureus*, *Pseudomonas aeruginosa* and *Micrococcus luteus*, and three fungal strains, *i.e*., *Trichophyton longiformis*, *Candida albicans* and *Aspergillus flavus*. The data showed moderate activity both against the different bacterial strains, Fig. 3 and the fungal strains, Fig. 4. In both cases, the ligands showed lower activity as compared to those of the standard drug.

The bioassay results demonstrated that the metal complexes showed considerable increases in activity against most of the bacterial and fungal strains as compared to the ligands, which is in accordance with the Tweedy chelation theory.[49] The data suggest that the activity spectrum for trimethyltin(IV) and triphenyltin(IV) derivatives is most enhanced one than rest of the compounds which may be attributed to their electron donor/back donation ability.

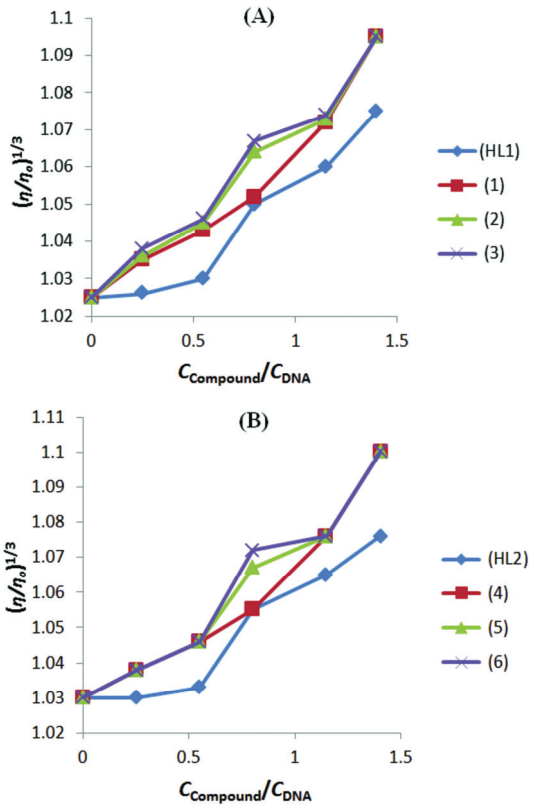


Fig. 2. Effects of increasing concentration of ligand and complexes **1**–**6** on the relative viscosity of SS-DNA at 25 °C. [SS-DNA] = 1.60×10^{-4} M.

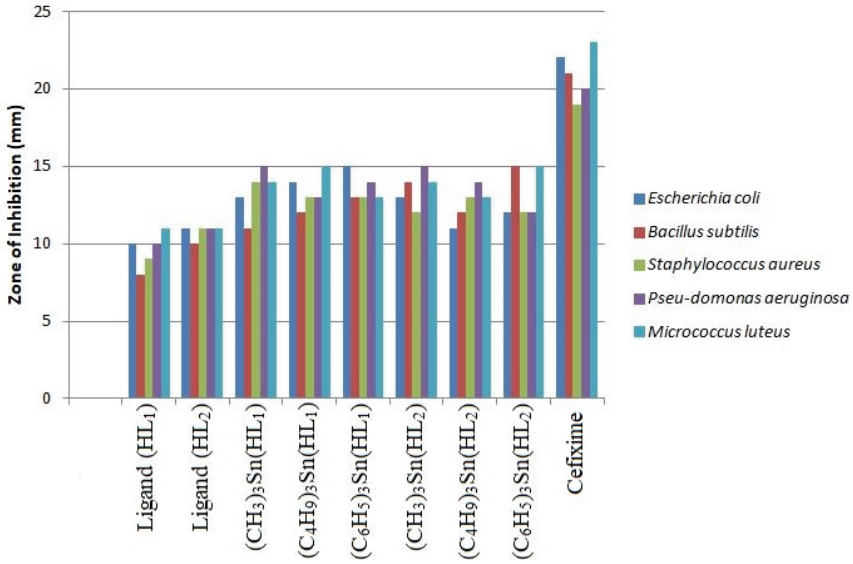


Fig. 3. Antibacterial data for the ligands, complexes **1**–**6** and the standard drug.

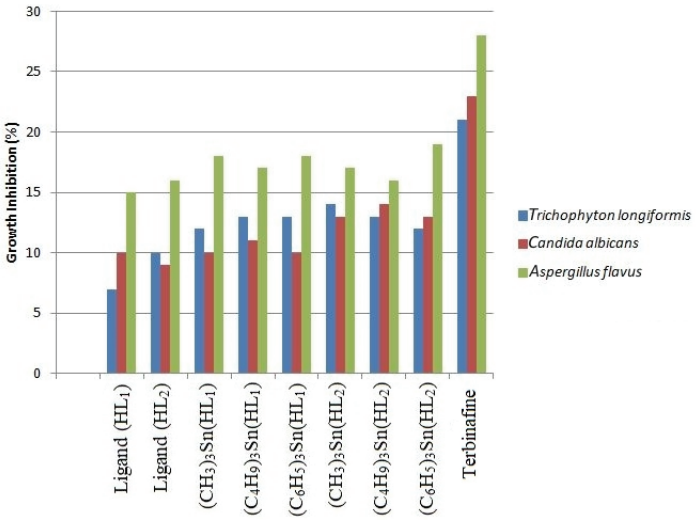


Fig. 4. Antifungal data for the ligands, complexes **1**–**6** and the standard drug.

CONCLUSIONS

Six new organotin(IV) derivatives of flumequine and cetirizine were successfully synthesized and characterized using spectroscopic techniques, such as FTIR, multinuclear ^{1}H-, ^{13}C- and ^{119}Sn-NMR spectroscopy, mass spectrometry and TGA-DSC studies together with elemental analysis and ICP-OES measurements,. The results of elemental analysis and ICP-OES indicate great concurrence between the observed and calculated percentages of all the examined elements. The FTIR spectral data clearly showed that the ligands behaved as monodentate with tetrahedral geometric shapes for **3** and **6**, due to the presence of bulky phenyl groups in the organotin(IV) moieties and for the compounds **1**, **2**, **4** and **5**, the ligands coordinated with tin in a bidentate manner, due to the presence of less bulky groups, had trigonal-bipyramidal geometry. The NMR spectral data explicitly confirmed the presence of distinct protons and carbons in the proposed structures and ^{119}Sn-NMR data for **1**–**6** authenticated the geometric shapes of all the synthesized compounds. The mass spectrometry data were in agreement with the proposed molecular formulae for all the synthesized complexes. The thermal data supported that the end product of thermal degradation was SnO_2 after the decomposition of all the complexes, which was also an indicator for existence of Sn–O linkages in all the complexes. The DNA binding studies for **1**–**6** indicate an intercalation mode of interaction between the anticipated drug and DNA. The synthesized compounds **1**–**6** were also evaluated for their possible antibacterial, antifungal and antioxidant activities and promising activities were found, for all the complexes as compared to their respective ligands.

SUPPLEMENTARY MATERIAL

The areas evaluated in the tests and some of the test questions are available electronically at the pages of journal website: http://www.shd.org.rs/JSCS/, or from the corresponding author on request.

Acknowledgments. S. H. I. is thankful to the Higher Education Commission of Pakistan for financial support during the present study for an Indigenous 5000 scholarship batch-5 (Pin No. 085-10718-Ps5-236) and an IRSIP Foreign scholarship. He is also thankful to the Department of Chemistry, University of Engineering and Technology, Lahore and the School of Chemistry, University of Manchester, UK, for providing facilities for the experimental work and analyses.

И З В О Д

ДИЗАЈН, СИНТЕЗА И БИОЛОШКА ИСПИТИВАЊА КОМПЛЕКСА КАЛАЈА(IV) СА ФЛУМЕКВИНОМ И ЦЕТИРИЗИНОМ

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Описана је синтеза шест нових комплекса калаја(IV), Me_3SnL_1] (**1**), [Bu_3SnL_1] (**2**), [Ph_3SnL_1] (**3**), [Me_3SnL_2] (**4**), [Bu_3SnL_2] (**5**) и [Ph_3SnL_2] (**6**) (HL_1 = 9-флуоро-6,7-дихидро--5-метил-1-оксо-1H,5H-пиридо[3,2,1-*ij*]хинолин-2-карбоксилна киселина (флумеквин) и HL_2 = 2-[2-[4-[фенил(4-хлорофенил)метил]-1-пиперазинил]етокси]сирћетна киселина (цетиризин)). Комплекси су окарактерисани применом елементалне микроанализе, FT--IR и NMR (^{1}H, ^{13}C и ^{119}Sn) спектроскопије, масене спектрометрије и термалне анализе. На основу добијених резултата нађено је да комплекси **1**, **2**, **4** и **5** имају тригонално-бипирамидалну геометрију, а комплекси **3** и **6** тетраедарску геометрију. Испитивања антибактеријске и антифунгалне активности комплекса **1**–**6** су показала да већина испитиваних комплекса показује добру активност. Резултати биолошких испитивања су показали да су трифенилкалај(IV) комплекси активнији од триметилкалај(IV) и трибутилкалај(IV) комплекса. Такође, испитивана је антиоксидативна способност комплекса, као и њихова интеракција са ДНК, при чему су добијени резултати који обећавају.

(Примљено 3. децембра 2016, ревидирано 1. јуна, прихваћено 6. јуна 2017)

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