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Triorganotin(IV) derivatives of umbelliferone (7-hydroxycoumarin) and their adducts with 1,10-phenanthroline: synthesis, structural and biological studies

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Abstract

New triorganotin(IV) derivatives of the general formula $R_3Sn(Umb)$ (where, R = Me, *n*-Bu and Ph; Umb = umbelliferone anion) have been synthesized using sodium salt method. Further, the adducts of the general formula $R_3Sn(Umb) \cdot phen$ (where R = Me and Ph; phen = 1,10-phenanthroline) have also been synthesized by the interaction of the triorganotin(IV) derivatives of umbelliferone with 1,10-phenanthroline. The bonding and coordination behavior of these derivatives are discussed on the basis of IR, NMR (^1H, ^{13}C and ^{119}Sn), and ^{119}Sn Mössbauer spectroscopic studies. These investigations indicate that umbelliferone acts as a monoanionic bidentate ligand in $R_3Sn(Umb)$ coordinating through O(7) and O(1) in the solid-state. These polymeric $R_3Sn(Umb)$ derivatives (where R = Me and *n*-Bu) have been proposed to have a *trans*-trigonal bipyramidal geometry with the three R groups in equatorial positions, while the axial positions are occupied by a phenolic oxygen and the O(1) atom from the adjacent molecule. A pseudotetrahedral geometry has been suggested for $Ph_3Sn(Umb)$. A distorted octahedral geometry around tin has been proposed for $R_3Sn(Umb) \cdot phen$, in which umbelliferone anion acts as a monodentate ligand coordinating through phenolic oxygen O(7). The newly synthesized derivatives have been assayed for their anti-inflammatory, cardiovascular and anti-microbial activities. The average LD_{50} values >1000 mg kg^{-1} of these derivatives indicate their safety margin. Among all the compounds tested, $Ph_3Sn(Umb) \cdot phen$ has been found to show potent anti-inflammatory activity with low mammalian toxicity and mild hypotensive activity.

Keywords: Triorganotin(IV); Umbelliferone; 7-Hydroxycoumarin; 1,10-Phenanthroline; ^{119}Sn Mössbauer; Biological activity

1. Introduction

Coumarin (1, 2-benzopyrone) is a widely distributed natural product [1] with low human toxicity [2] and short half-life (1–1.5 h) [3]. It has been suggested [4] that coumarin may be a pro-drug and its major biotransformed product 7-hydroxycoumarin, also known as umbelliferone, is an active drug. It is used as a fixative and enhancing agent in perfumes and is added to toilet soaps and detergents, toothpaste, tobacco products and some alcoholic beverages [5].

Coumarin and its derivatives have a wide spectrum of bioactivities including anticoagulant, estrogenic, dermal photosensitizing, vasodilator, molluscacidal, anthelmintic, sedative, hypnotic, analgesic, hypothermic [6], antimicrobial [7], anti-inflammatory [8], antifungal [9] and antiulcer [10] activities. In vitro, coumarin and its derivatives inhibit the proliferation of several human tumor cell lines, viz., coumarin

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retards the development of renal [11] and prostate carcinoma [12,13], and prevents the recurrence of melanoma [14]; coumarins and 7-hydroxycoumarins exhibit cytotoxic effects against the lung adenocarcinoma cell lines KB [9], A549 [15], SK-LU-1, 1.3.15, 3A5A and A-427 [16]. Coumarin has undergone clinical trials for the treatment of the lymphoedema following breast cancer treatment and in the treatment of lung and kidney carcinoma, having been used both in isolation [17] and in combination with cimetidene, as an antineoplastic treatment [2,11,18].

In view of the wide biological importance of the coumarins, it is worthwhile to synthesize and characterize their metal complexes, which may be explored as potentially active metallopharmaceuticals. Despite of the good complexing ability of 7-hydroxycoumarin, limited studies on the transition metals and lanthanides with 7-hydroxy- and dihydroxycoumarin derivatives [19–28] have been carried out. The study of the interaction of coumarin derivatives with organometallic compounds of group IV is, therefore, indispensable.

Among non-platinum chemotherapeutic metallopharmaceuticals, organotin(IV) compounds have emerged as potential biologically active compounds in the last two decades [29,30]. The present study aims to find out coordination behavior of umbelliferone with triorganotin(IV) compounds, and to screen their biological activity with the final goal to synthesize potential metallopharmaceuticals.

In view of this, here we report the synthesis and structural studies of some triorganotin(IV) derivatives of umbelliferone or 7-hydroxycoumarin. In order to see their interaction with nitrogen-donor ligands, 1,10-phenanthroline adducts of these triorganotin(IV) derivatives have also been synthesized. The newly synthesized compounds have been assayed for per oral toxicity, anti-inflammatory, cardiovascular and anti-microbial activities.

2. Experimental

2.1. Materials

All the reactions were carried out under an anhydrous nitrogen atmosphere. Methanol, petroleum ether (b.p. 40–60 °C) and hexane (b.p. 60–80 °C, fraction from petroleum) (E. Merck) were dried and distilled before use. Tri-*n*-butyltin(IV) chloride, trimethyltin(IV) chloride, triphenyltin(IV) chloride (Merck–Schuchardt), and 1,10-phenanthroline (Sigma–Aldrich) were used as received. Umbelliferone was synthesized by the reported method [31] using malic acid (Sisco Chem.), resorcinol (E. Merck) and conc. sulphuric acid (E. Merck).

2.1.1. Synthesis of triorganotin(IV) derivatives of umbelliferone

Umbelliferone (0.98 g; 6.0 mmol) was dissolved in the minimum amount (35 ml) of dry methanol. To this was added sodium methoxide, prepared by dissolving sodium (0.14 g; 6.0 mmol) in methanol (10 ml). The resulting solution was refluxed for 2–3 h with constant stirring. A hot methanolic solution of tri-*n*-butyltin(IV) chloride (1.96 g; 6.0 mmol)/trimethyltin(IV) chloride (1.20 g; 6.0 mmol)/triphenyltin(IV) chloride (2.20 g; 6 mmol) in a 1:1 molar ratio was added to the solution of the preformed sodium salt of umbelliferone. The resulting mixture was further refluxed with constant stirring for another 9–10 h, and was then centrifuged and filtered in order to remove the sodium chloride formed. The excess of solvent was removed under reduced pressure. The semi-solid mass thus obtained was solidified by trituration with hexane and recrystallized from methanol–hexane (1:2 v/v) mixture.

2.1.2. Synthesis of 1,10-phenanthroline adducts of triorganotin(IV) derivatives of umbelliferone

1,10-Phenanthroline (0.60 g; 3.0 mmol) and the triorganotin(IV) derivative of umbelliferone (3.0 mmol) were dissolved separately in the minimum amount of methanol and then mixed. The resulting mixture was refluxed for 20 h. The excess of solvent was removed under reduced pressure. The crude product thus obtained was solidified by trituration with petroleum ether and recrystallized with methanol–petroleum ether (1:2 v/v) mixture.

2.2. Measurements and biological studies

The melting points of the synthesized compounds were determined on a Toshniwal capillary melting point apparatus and are uncorrected. Carbon, hydrogen, nitrogen and tin analysis and conductance measurements were carried out as reported previously [32]. IR and Far IR spectra of the solid compounds were recorded on the same instrument [32] as reported previously. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DRX-300 (300 MHz) FT NMR spectrometer at the Central Drug Research Institute, Lucknow, India, using DMSO-d_6 or $CDCl_3$ or CD_3OD as solvent and TMS as the internal standard. ^{119}Sn NMR spectra were recorded in CD_3OD on a Bruker Avance (500 MHz) FT NMR spectrometer using tetramethyltin as the internal reference at the Tata Institute of Fundamental Research, Mumbai, India. ^{119}Sn Mössbauer spectra were recorded on Mössbauer spectrometer model MS-900 (Ranger Scientific Co., Burelson, TX) according to the procedure reported previously [32], at the Department of Chemistry and Physics, University of The District of Columbia, Washington, DC. Anti-inflammatory,

cardiovascular and acute toxicity studies were carried out according to the previously reported methods [32].

2.2.1. Anti-microbial activity

The compounds were tested in vitro for their anti-microbial activity against Gram-positive (*Staphylococcus aureus Mau 29/58*, *Staphylococcus aureus Mau 78/71*, *Bacillus subtilis 18/64*) and Gram-negative (*Escherichia coli 326/71*, *Escherichia coli*) bacteria as well as the yeast (*Candida albicans Pn-10*) and the mould (*Microsporum gypseum*) by the standard dilution method in sabouraud agar medium [33]. The minimum inhibitory concentration (MIC) values in μg/ml were reported. The anti-microbial activities were also tested by the standard plate diffusion method using Muller–Hinton and sabouraud agar (Imuna, Sarisske Michalany, Slovak Republic) for the Gram-positive bacteria *Bacillus polymyxa* and Gram-negative bacteria *Salmonella typhii*.

3. Results and discussion

The reactions of triorganotin(IV) chloride with the sodium salt of umbelliferone (formed according to Eq. (1a)) in a 1:1 molar ratio led to the formation of the compounds according to Eq. (1b). Triorganotin(IV) derivatives of umbelliferone, on reaction with 1,10-phenanthroline in a 1:1 molar ratio (Eq. (2)) afforded the corresponding adducts:

$$(\mathrm{Umb})\mathrm{H} + \mathrm{NaOMe} \rightarrow \mathrm{Na(Umb)} + \mathrm{MeOH} \quad (1a)$$

$$\mathrm{Na(Umb)} + \mathrm{R_3SnCl} \rightarrow \mathrm{R_3Sn(Umb)} + \mathrm{NaCl} \quad (1b)$$

(where, R = Me, *n*-Bu and Ph),

$$\mathrm{R_3Sn(Umb)} + \mathrm{phen} \xrightarrow{1:1} \mathrm{R_3Sn(Umb)\cdot phen} \quad (2)$$

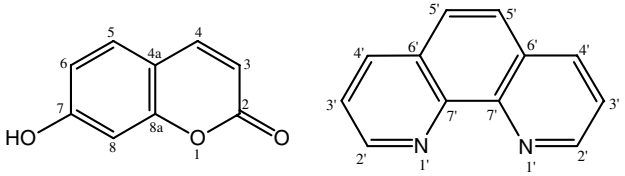
(where, R = Me and Ph).

The reaction between triorganotin(IV) chloride and umbelliferone (Eq. (1b)) was found to be quite feasible and required 9–10 h of reflux. The adduct formation of these triorganotin(IV) derivatives of umbelliferone with nitrogen-donors is rather difficult. The reaction between triorganotin(IV) derivatives of umbelliferone and 2,2′-bipyridyl did not take place, and the reactants were recovered even after refluxing them for 30 h. However, the adducts of 1,10-phenanthroline with triorganotin(IV) derivatives of umbelliferone have been isolated (Table 1), but *n*-Bu_3Sn(Umb) did not form the adduct with 1,10-phenanthroline under similar reaction conditions (see Scheme 1).

All of the synthesized compounds are brown colored powders (except *n*-Bu_3Sn(Umb) which is semi-solid and Ph_3Sn(Umb) · phen which is yellow colored solid), and obtained in good yields (70–80%). The compounds are stable towards air and moisture, and are soluble in dimethylsulphoxide and methanol, but sparingly soluble in chloroform and other organic solvents. The analytical data of the compounds are presented in Table 1 and correspond to the proposed stoichiometry. The molar conductance of 10^{-3} M solution of the compounds in methanol lie in the range 0.00–0.20 Ω^{-1} cm^2 mol^{-1}, indicating their non-electrolytic nature.

3.1. Infrared spectral studies

The characteristic infrared absorption frequencies (in cm^{-1}) and their assignments are presented in Table 2. The infrared spectrum of umbelliferone exhibits two strong bands at 1682 and 1233 cm^{-1}, which may be assigned to ν_{as}(C═O) and ν_s(C═O), respectively. The low carbonyl frequency (1682 cm^{-1}) is presumably due to intermolecular hydrogen bonding of the 7-hydroxyl



(Umb)H: Umbelliferone phen : 1,10-Phenanthroline

Scheme 1.

Table 1
Characteristic properties of triorganotin(IV) derivatives of umbelliferone and their 1,10-phenanthroline adducts

Compound number	Compound (empirical formula)	Yield (%)	Melting point (°C)	Analysis (%): found (calculated)			
				Sn	C	H	N
1	Me_3Sn(Umb) $[C_{12}H_{14}O_3Sn]$	72	80–82	36.22 (36.53)	44.11 (44.36)	4.11 (4.34)	–
2	*n*-Bu_3Sn(Umb) $[C_{21}H_{32}O_3Sn]$	75	Semi-solid	25.98 (26.31)	55.99 (55.90)	7.11 (7.15)	–
3	Ph_3Sn(Umb) $[C_{27}H_{20}O_3Sn]$	80	208–210d	23.11 (23.22)	63.80 (63.44)	3.79 (3.94)	–
4	Me_3Sn(Umb) · phen $[C_{24}H_{22}O_3N_2Sn]$	74	55–57	23.20 (23.50)	56.80 (57.06)	4.42 (4.39)	5.60 (5.55)
5	Ph_3Sn(Umb) · phen $[C_{39}H_{28}O_3N_2Sn]$	78	67–68	16.80 (17.17)	67.89 (67.75)	4.00 (4.08)	4.01 (4.05)

Table 2
Characteristic IR frequencies[a,b] (in cm^{-1}) of umbelliferone, triorganotin(IV) derivatives of umbelliferone and their 1,10-phenanthroline adducts

Assignments	UmbH	1	2	3	4	5
ν_{as}(C═O)	1682vs	1697vs	1688s	1686s	1704vs	1720vs
ν_{s}(C═O)	1233vs	1235s	1237s	1233s	1233s	1233s
ν_{as}(C–O) (phenolic)	1561vs	1598vs	1601vs	1599vs	1593vs	1592vs
ν_{s}(C–O) (phenolic)	1318vs	1334s	1341s	1319s	1336s	1336s
ν_{as}(Sn–C)	–	620w	599	286m	620m	281m
ν_{s}(Sn–C)		–	–	228m	543w	217s
ν(Sn–O)	–	548m	564m	615w	585m	578w
ν(Sn ← O)		490m	538m	560w	–	–
ν(Sn ← N)	–	–	–	–	464m	451s

[a] vs, Very strong; s, strong; m, medium; w, weak.
[b] Complex number as indicated in Table 1.

hydrogen either with O(1) or with O(2). The ν_{as}(C–O) (phenolic) has been assigned at 1561 cm^{-1} as a very strong band in umbelliferone. In the IR spectra of triorganotin(IV) derivatives of umbelliferone, there is a significant shift in ν_{as}(C–O) (phenolic) (by 38 ± 1 cm^{-1}), which clearly indicates the participation of the phenolic oxygen (after its deprotonation) in bonding with the triorganotin moiety. The coordination by O(2) should significantly shift the carbonyl stretching frequency to lower wave numbers. In triorganotin derivatives studied, coordination by O(2) is ruled out as ν_{as}(C═O) undergoes a small shift to higher wave numbers (1686–1697 cm^{-1}) whereas the ν_{s}(C═O) remains almost unaffected. The small shift in ν_{as}(C═O) to higher wave numbers in compounds **1**, **2** and **3** is also indicating the absence of intermolecular hydrogen bonding (as observed in umbelliferone) as well as participation of O(1) in coordination. Appearance of new bands due to ν(Sn–O) and ν(Sn ← O) (Table 2) also confirms the bonding of tin with phenolic oxygen and O(1), respectively, in the triorganotin(IV) derivatives.

In the IR spectra of the adducts, ν_{as}(C═O) is further shifted to higher wave numbers (1704–1720 cm^{-1}), whereas ν_{s}(C═O) does not change. Furthermore, the ν(Sn ← O) in the region 550–500 cm^{-1} is not observed in compounds **4** and **5**. These changes in the IR spectra may be due to non-coordination of O(2) and O(1) as well as absence of intermolecular hydrogen bonding in compounds **4** and **5**. Further, the bonding of 1,10-phenanthroline to tin is supported by the appearance of a new band near 450 cm^{-1} in compounds **4** and **5**, which may be assigned to ν(Sn ← N).

3.2. ^{119}Sn Mössbauer spectral studies

^{119}Sn Mössbauer spectral data of compounds **1**–**5** are given in Table 3. Mössbauer spectra of all the triorganotin(IV) derivatives exhibit a doublet centered in the isomer shift (IS) value range 1.25–1.42 mm s^{-1} and the quadrupole splitting (QS) values in the range 2.62–3.17 mm s^{-1} show that the electric field gradient around tin nucleus is generated by the inequalities in the tin–oxygen σ bonds and is also due to geometric distortions. A possible geometry around the tin atom in R_3Sn(Umb) (where R = Me and *n*-Bu) is a distorted trigonal bipyramidal in which umbelliferone anion acts as bidentate ligand coordinating through O(7) and O(1). A possibility of intermolecular coordination of O(2) with central tin atom of adjacent molecule is ruled out on the basis of IR spectra as ν_{as}(C═O) is shifted to higher wave numbers in these compounds. Further, Me_3Sn(Umb) and *n*-Bu_3Sn(Umb) have ρ values of 2.5 and 2.8, respectively, which also suggest the coordination number of tin either 5 or 6. The three possible isomers (Fig. 1) of R_3SnOX (where, X = O/N; OX are the donor sites of the ligands) have been reported [34] to have different QS values: QS for isomer (a) 1.7–2.3 mm s^{-1}; for (b) 3.0–3.9 mm s^{-1}; for (c) 3.5–4.1 mm s^{-1}.

Table 3
^{119}Sn Mössbauer data (at 80 K) of the triorganotin(IV) derivatives of umbelliferone and their 1,10-phenanthroline adducts[a]

Compound number	QS (mm s^{-1})	IS (mm s^{-1})	ρ (QS/IS)	τ_1(L)	τ_2(R)
1	3.17	1.25	2.5	1.08	1.38
2	3.31	1.42	2.8	1.03	1.12
3	2.62	1.29	2.0	1.06	1.21
4	3.27	1.26	2.6	1.20	1.46
5	2.81	1.20	2.3	1.09	1.82

QS, quadrupole splitting; IS: isomeric shift relative to $BaSnO_3$ and tin foil (splitting 2.52 mm s^{-1}); τ_1(L), half line-width left doublet component; τ_2(R): half line-width right doublet component.
[a] Complex number as indicated in Table 1.

In the trialkyltin(IV) derivatives of umbelliferone studied, the observed values of IS (1.25–1.42 mm s^{-1}) and QS (3.17–3.31 mm s^{-1}) lie in the range typical of *trans*-trigonal bipyramidal coordination (Fig. 1(b)) of tin as found in R_3SnO_2 fragments of triorganotin(IV) carboxylates [35]. The QS value in the range of 3.0–3.1 mm s^{-1} were also found in the trimethyltin(IV) derivatives of amino acids with *trans*-trigonal bipyramidal geometry and the tin atom with amino-bridged intermolecular interactions [36]. Thus, the tin atom configuration as shown in Fig. 2 in which three organic groups are in the equatorial positions and the phenolic oxygen and O(1) from an adjacent molecule are axial, can be proposed for compounds **1** and **2**. This polymeric structure may be responsible for low solubility of these derivatives in non-polar solvents. On the other hand, Ph_3Sn(Umb) has ρ value of 2.0, which is a borderline case, and its QS (2.62 mm s^{-1}) value is slightly lower than those typical for *trans*-trigonal bipyramidal (3.0–3.9 mm s^{-1}), but substantially higher than those for *cis*-trigonal bipyramidal (1.7–2.3 mm s^{-1}) (Fig. 1(a)) and pseudotetrahedral (1.00–2.41 mm s^{-1}) arrangements [35]. These results are readily rationalized if compound **3** has either structure (a) of Fig. 1 or pseudotetrahedral as shown in Fig. 3. Because of the bigger size of phenyl groups and steric strain introduced in the molecule, a pseudotetrahedral structure with very weak Sn–O(1) interactions has been proposed for Ph_3Sn(Umb) (Fig. 3).

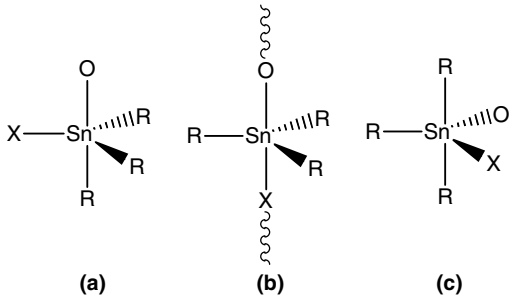


Fig. 1. Structures of possible isomers for $R_3Sn(OX)$ (OX = donor sites of the ligand).

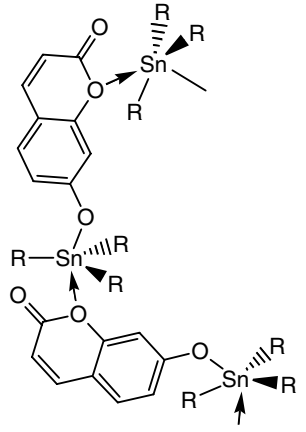


Fig. 2. Proposed structure of the R_3Sn(Umb) derivatives (where R = Me or *n*-Bu).

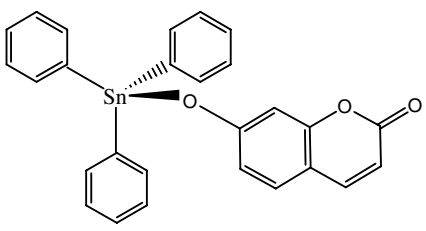


Fig. 3. Proposed structure of Ph_3Sn(Umb).

The possible geometry around tin in the adducts with 1,10-phenanthroline is distorted octahedral in which umbelliferone anion acts as monodentate ligand coordinating through the phenolic oxygen, and strong nitrogen-donor, 1,10-phenanthroline (as revealed from the IR spectra), occupies two coordinating sites around tin. The ρ values of the adducts also indicate the coordination number of tin greater than four. $R_3Sn(Umb)\cdot$phen may have either *fac*- or *mer*-octahedral environment consisting of three organic groups, phenolic oxygen and two phenanthroline nitrogen atoms around tin (Fig. 4(a) and (b)).

3.3. Solution NMR spectral studies

^1H, ^{13}C and ^{119}Sn NMR chemical shifts along with coupling constants obtained from solutions of compounds **1**–**5** are summarized in Tables 4–6, respectively. The chemical shifts of umbelliferone and 1,10-phenanthroline [37] are also given in the tables for comparison. The assignments of ^1H and ^{13}C resonances are based on ^1H–^{13}C HMBC experiment. The ^1H–^{13}C HMBC spectrum of Ph_3Sn(Umb) (in CD_3OD) is given in Fig. 5, which shows correlations between the carbon atoms and protons of the umbelliferone residue as well as those of the organotin moiety.

The assignment of resonances is difficult in 1D NMR spectra of the compounds due to double ring structure of umbelliferone, which can be interpreted with the help of a 2D NMR spectrum. In addition, there is a complex overlapping pattern in the aromatic region in the triphenyltin(IV) derivative as both phenyl groups and umbelliferone moiety give resonances in this region, which can be distinctly identified with the help of a HMBC spectrum.

In ^1H NMR spectra of the triorganotin(IV) derivatives, all the characteristic resonances of umbelliferone are slightly shifted upfield (lower δ values). The resonances of C-7 in the triorganotin(IV) derivatives of umbelliferone shift slightly (δ 162.1–157.0 ppm) compared to the ligand (δ 160.3 ppm). All the magnetically

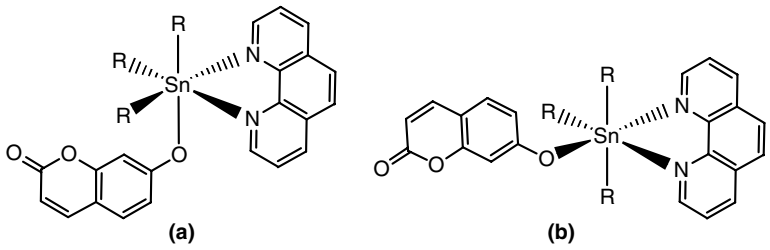
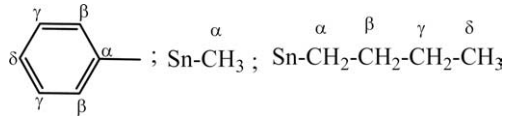


Fig. 4. Octahedral structures of $R_3Sn(Umb) \cdot phen$ (where R = Me and Ph).

Table 4
^1H NMR spectral data[a,b] of umbelliferone, its triorganotin(IV) derivatives, and 1,10-phenanthroline and its adducts with triorganotin(IV) derivatives of umbelliferone

Atom number	UmbH[c]	Phen[c]	**1** (DMSO-d_6)	**2** ($CDCl_3$)	**3** (DMSO-d_6)	**3** (CD_3OD)	**4** (DMSO-d_6)	**5** (DMSO-d_6)
H-3	6.22d [9.5]	–	6.00d [9.0]	6.12d [9.0]	5.89d [9.6]	5.93d [9.6]	5.99d [9.3]	6.17d [5.7]
H-4	7.95d [9.5]	–	7.80d [9.0]	7.63d [9.0]	7.63d [9.0]	7.62 [9.0]	7.80m	8.06d [7.0]
H-5	7.55d [9.0]	–	7.35d [9.0]	7.27d [9.0]	7.11d	7.20d	7.35d [8.4]	7.95d [6.6]
H-6	6.82d [9.0]	–	6.54d [9.0]	6.64d [6.0]	6.74d	6.62d	6.54d [8.1]	6.7dbr
H-8	6.75s	–	6.44s	6.57s	6.18s	6.50s	6.42sbr	6.77dbr
H-2′	–	9.35d	–	–	–	–	9.09d [3.0]	9.09d [3.0]
H-3′	–	8.25dd	–	–	–	–	7.80m	7.79, 7.77dd [4.2, 4.5]
H-4′	–	9.12d	–	–	–	–	8.50d [8.1]	8.50d [8.1]
H-5′	–	8.35s	–	–	–	–	8.00s	7.99s
H-α	–	–	0.47s [72.0][d], 0.02s [35.1][d]	1.32mbr	–	–	0.47s [70.0][d]	–
H-β	–	–	–	1.61mbr	7.90d [7.0] [72.0][e]	7.70d [7.0] [72.0][e]	–	7.48–7.32m[f]
H-γ	–	–	–	1.32mbr	7.34d [9.0]	7.28d [9.0]	–	
H-δ	–	–	–	0.89t	7.38d	7.34d	–	

s, Singlet; d, doublet; dd, doublet doublet; dbr, doublet broad; m, multiplet; mbr, multiplet broad.



[a] Complex number as indicated in Table 1.
[b] The values of coupling constants in Hz are given in square brackets.
[c] Ref. [37].
[d] $^2J(^1H–^{119/117}Sn)$.
[e] $^3J(^1H–^{119/117}Sn)$.
[f] Strongly overlapping multiplets.

non-equivalent alkyl/phenyl carbons of the organic groups attached to tin, and those of the ligands (umbelliferone and 1,10-phenanthroline) have also been successfully identified and are given in Table 5.

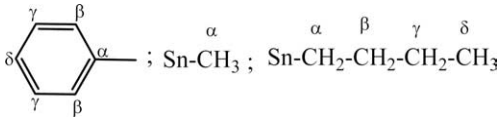
$Me_3Sn(Umb)$ shows two signals for methyl groups in its ^1H (δ 0.47 ppm; ^2J ($^1H–^{119}Sn$) = 72.0 Hz and δ 0.02 ppm; $^2J(^1H–^{119}Sn)$ = 35.1 Hz) as well as in ^{13}C (δ 3.3 ppm; $^1J(^{13}C–^{119}Sn)$ = 498.0 Hz and δ −8.9 ppm) NMR spectra which could be due to the decomposition of $Me_3Sn(Umb)$ in DMSO-d_6 according to the following reaction:

$$2Me_3Sn(Umb) \xrightarrow{Solvent} Me_4Sn + Me_2Sn(Umb)_2 \cdot solvent \quad (3)$$

The ratio of mutual integral intensities of ^1H NMR signal is 12:1 for signals at δ 0.47 ppm and at δ 0.02 ppm, respectively, suggesting that the degree of conversion of Eq. (3) is very less. Me_4Sn appears at δ 0.02 ppm as suggested by its low $^2J(^1H–^{119}Sn)$ value (35.1 Hz), which corresponds well to a tetrahedral structure [37,38]. In the solid-state, umbelliferone anion in $Me_3Sn(Umb)$ acts as a monoanionic bidentate ligand coordinating through O(7) and O(1) of umbelliferone, but in the presence of strongly coordinating solvent DMSO, weak interaction of C(1)O disrupts and now umbelliferone anion is coordinating through O(7) only, the fifth coordinating site being occupied by the solvent molecule. The $^1J(^{13}C–^{119}Sn)$ (498.0 Hz) and $^2J(^1H–^{119}Sn)$ (72.0 Hz) values as well as calculated ∠Me–Sn–Me (120.4°) using the equation given by Lockart and Manders [38] correspond to a pentacoordinate trigonal bipyramidal geometry for $Me_3Sn(Umb) \cdot solvent$ with three methyl groups in equatorial plane and oxygen donor atom of monodentate umbelliferone anion and solvent

Table 5
^{13}C NMR spectral data[a] of umbelliferone, its triorganotin(IV) derivatives, 1,10-phenanthroline and its adducts with triorganotin(IV) derivatives of umbelliferone in DMSO-d_6

Carbon number	UmbH[b]	Phen[b]	**1**	**2** [in $CDCl_3$]	**3**	**3** [in CD_3OD]	**4**	**5**
C-2	161.2	–	166.5	166.7	161.0	163.9	161.2	162.0
C-3	111.2	–	108.9	110.7	112.0	111.0	108.6	111.3
C-4	144.3	–	144.9	144.0	144.8	146.2	145.4	144.8
C-5	129.5	–	129.3	128.6	127.5	129.9	129.3	128.5
C-6	113.0	–	115.9	117.3	114.0	115.6	116.2	113.3
C-7	160.3	–	161.1	162.1	158.0	157.0	161.2	157.0
C-8	102.1	–	103.5	105.8	103.0	104.2	103.6	102.2
C-4a	111.2	–	109.3	112.4	112.0	112.6	108.6	111.3
C-8a	155.4	–	156.2	156.1	151.0	146.2	156.4	145.3
C-2′	–	147.7	–	–	–	–	150.2	150.0
C-3′	–	127.3	–	–	–	–	126.9	127.9
C-4′	–	141.4	–	–	–	–	144.9	144.6
C-5′	–	125.4	–	–	–	–	123.7	123.5
C-6′	–	129.2	–	–	–	–	128.6	128.4
C-7′	–	137.4	–	–	–	–	136.7	136.5
C-α	–	–	3.3 [498][c], −8.9	16.8 [453][c]	144.8 [n.o.][c]	142.5 [750][c]	2.5 [n.o.][c]	144.8[f] [n.o.][c]
C-β	–	–	–	27.6 [20][d]	136.4 [45][d]	137.3 [45][d]	–	136.3[f] [45][d]
C-γ	–	–	–	26.9 [66][e]	128.0 [n.o.][e]	129.6 [75][e]	–	128.9[f] [76][e]
C-δ	–	–	–	13.4	128.5	130.4	–	129.7[f]



[a] Complex number as indicated in Table 1.
[b] Ref. [37].
[c] $^1J(^{13}C–^{119/117}Sn)$.
[d] $^2J(^{13}C–^{119/117}Sn)$.
[e] $^3J(^{13}C–^{119/117}Sn)$.
[f] Strongly overlapping signals.

Table 6
^{119}Sn NMR spectral data of the synthesized compounds[a]

Compound number	Solvent	δ (in ppm)
1	CD_3OD	43.6 (2.0,−140.0)
2	$CDCl_3$	−11.3
3	CD_3OD	−176.9
4	$CDCl_3$	25.3
5	CD_3OD	−475.2

[a] Compound number as indicated in Table 1.

molecule in axial positions. A similar $^1J(^{13}C–^{119}Sn)$ coupling constant of about 500 Hz was observed in methanol-d_4 solutions of the trimethyltin derivative of N-benzoyl-gylcylglycine [39] where a five-coordinated trialkyltin moiety in a trigonal plane is proposed as structural motif. Further, the ^{119}Sn NMR spectrum of $Me_3Sn(Umb)$ recorded in CD_3OD also shows two signals at δ 43.64 ppm (broad) and δ 2.05 ppm (sharp) and a very weak signal at δ −140.0 ppm (Table 6). The presence of additional ^{119}Sn resonances is also in accordance with the decomposition reaction (Eq. (3)), a process which is favoured by the nucleophilic complexation by the solvent molecule, which weakens one of the Sn–CH_3 bond which becomes prone to methyl group redistribution. The additional signal at δ 2.05 ppm is attributed to Me_4Sn and the very low intensity signal at δ −140.0 ppm may be due to pentacoordinate trigonal bipyramidal $Me_2Sn(Umb)_2 \cdot$ solvent in solution. Recently, some pentacoordinate trimethyltin(IV) derivatives of dipeptides have also been reported to undergo similar type of decomposition in solution [40]. *n*-$Bu_3Sn(Umb)$ shows a sharp signal in its ^{119}Sn NMR spectrum at δ −11.3 ppm (Table 6), which is indicative of its pentacoordinate trigonal bipyramidal structure. $Ph_3Sn(Umb)$ exhibits a broadened signal at δ −176.9 ppm in its ^{119}Sn NMR in CD_3OD. This value is very close to the value reported for Ph_3Sn(IV)–Gly–Leu (−170 ppm), which has been assigned a pseudotetrahedral structure [32]. Therefore, a pseudotetrahedral structure can be proposed for $Ph_3Sn(Umb)$ in solution.

In ^{119}Sn NMR spectrum of $Me_3Sn(Umb) \cdot phen$, a single resonance at δ 24.0 ppm is observed, which is in the range of pentacoordinate trimethyltin(IV) compounds. The ^1H NMR spectrum of compound **4** also shows a single signal at δ 0.47 ppm for all the methyl groups with $^2J(^1H–^{119}Sn)$ value of 70.0 Hz, which also supports the presence of pentacoordinate trimethyltin moiety with three methyl groups in equatorial plane in

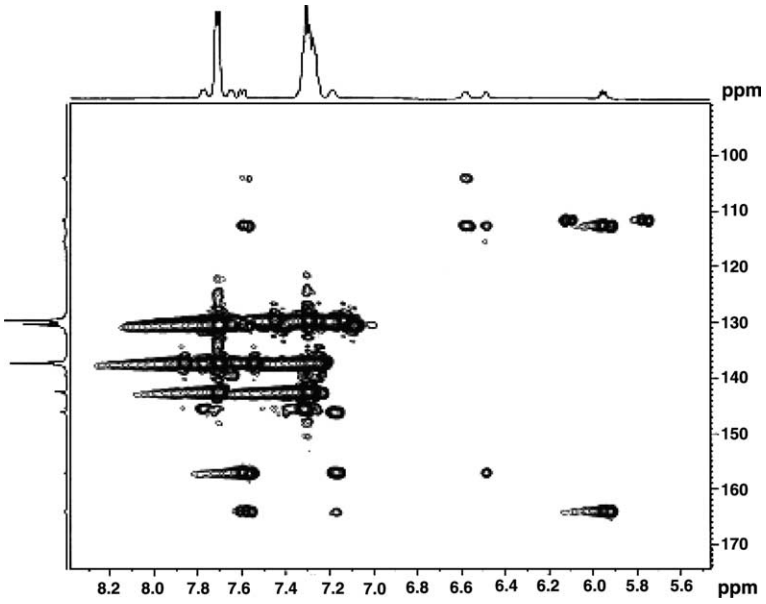


Fig. 5. HMBC (^{1}H–^{13}C) spectrum of $Ph_3Sn(Umb)$.

solution. It seems that the hexacoordinated $Me_3Sn(Umb) \cdot phen$ dissociates in solution giving the pentacoordinate trimethyltin(IV) derivative of umbelliferone. On the other hand, $Ph_3Sn(Umb) \cdot phen$ does not show any chemical shift in the region of $Ph_3Sn(Umb)$ (~ -200 ppm), clearly indicating change of structure upon adduct formation and preventing the decomposition of the adduct in solution. The tin shielding in ^{119}Sn NMR spectra increases markedly with increase in coordination number and tin shifts are normally higher with phenyl compared to alkyl substituents [41]. Therefore, a six-coordinated octahedral structure may be retained in solution for $Ph_3Sn(Umb) \cdot phen$ considering its higher ^{119}Sn chemical shift ($\delta = -475.2$ ppm) in CD_3OD. Due to strongly overlapping pattern of the signals in its ^{1}H and ^{13}C NMR spectra, it could not be possible to resolve and assign the signals of two types of phenyl groups attached to tin in *fac*- or *mer*-octahedral structure. This observation may be due to almost similar electron density around each phenyl group in the octahedral complex as umbelliferone and 1,10-phenanthroline both have heteroaromatic rings.

3.4. Biological studies

3.4.1. Anti-inflammatory activity

The anti-inflammatory activity (% inhibition) of the synthesized compounds was conducted on adult albino rats (body weight 120–160 g) of Froster Charles species against carrageenan induced edema in the doses of 50 mg kg^{-1} given orally. The results are presented in Table 7. The activity of the standard drug phenylbutazone is included for the comparison. The compounds exhibit anti-inflammatory activity of varying degree (9.2–50.8% inhibition). Trimethyltin(IV) derivative of umbelliferone is more active than the phenyl analogue. The activity increases upon adduct formation with 1,10-phenanthroline. Among tested compounds, $Ph_3Sn(Umb) \cdot phen$ has been found to possess the most potent activity (50.8% inhibition), which has been found to be more potent than that of the reference drug, phenylbutazone (38.4% inhibition).

A number of studies [42,43] of the triorganotin compounds, R_3SnX and diorganotin compounds, R_2SnXY indicated that the marked biological activity of the organotins may be due to the transport of either more active species ($R_nSn^{(4-n)+}$, where $n = 2$ or 3) or the molecule as a whole across the cellular membrane, and X or XY group influences only the readiness of delivery of the active part R_3Sn^{+}/R_2Sn^{++} into the cell [42]. Further, the studies on structure-activity correlation of organotin(IV) compounds reveal that the biologically active compounds should have available coordination positions at tin and relatively stable ligand–tin bonds, viz., Sn–N [44] (bond length >2.39 Å) and Sn–S bonds. These bonds should have low hydrolytic decomposition. Thus, it can be proposed that the same mechanism may be involved in the observed activity of the studied organotin(IV) derivatives.

The analysis of the data of Table 7 indicates that the anti-inflammatory activity of the studied compounds is influenced by the nature of ligand environment and organic groups attached to tin. The least activity of $Ph_3Sn(Umb)$ (9.2% inhibition) may be due to the different geometry (pseudotetrahedral) of this compound as compared to other trialkyltin(Umb) which have trigonal bipyramidal structure. Further, the activity of the triorganotin(IV) derivatives of umbelliferone is enhanced

Table 7
LD_{50}, anti-inflammatory and cardiovascular activities of triorganotin(IV) derivatives of umbelliferone and their 1,10-phenanthroline adducts

Compound number	LD_{50} (mg kg^{-1})	Anti-inflammatory activity[a] (% inhibition)	Change in mean blood pressure[b] (mm Hg)			Duration (min)	Change in resting HR bpm	Effect on pressor responses[c]	
			Control mean ± SE	Immediate mean ± SE	Delayed mean ± SE	Mean ± SE		CO	NA
1	>1000	25.1	132.0 ± 6	122.0 ± 6**	–	4.6 ± 1.14	–	–	–
3	>1000	9.2	131.8 ± 10	112.4 ± 8***	–	12.4 ± 2.50	–	–	–
4	>1000	28.2	137.0 ± 6	117.6 ± 4*	–	13.2 ± 3.27	↑↓	↓	↓
5	>1600	50.8	143.8 ± 9	120.0 ± 7***	124.0 ± 9	16.2 ± 1.30	↑↓	–	↓
Phenylbutazone	–	38.4	–	–	–	–	–	–	–

↓ Inhibited; ↑ potentiated.
[a] Dose = 50 mg kg^{-1} p.o.
[b] Dose = 2.5 mg kg^{-1} i.v.
[c] CO, carotid occlusion; NA, noradrenaline.
* $p < \pm 0.05$.
** $p < \pm 0.01$.
*** $p < \pm 0.001$.

upon the adduct formation with 1,10-phenanthroline. This may be due to the presence of Sn–N bonds which tend to dissociate relatively more easily as compared to Sn–O bonds in $R_3Sn(Umb)$ as a part of the mechanism for inhibition.

3.4.2. Acute toxicity studies

The acute toxicity (LD_{50}) was studied on albino mice (body weight 20–25 g) of either sex. The LD_{50} values of the studied compounds are given in Table 7. All of the compounds have LD_{50} values greater than 1000 mg kg^{-1} suggesting the safety margin of these derivatives. Further, $Ph_3Sn(Umb) \cdot phen$ shows LD_{50} value even greater than 1600 mg kg^{-1}. It has been observed that the organotin(IV) derivatives of umbelliferone and their adducts with 1,10-phenanthroline are much less toxic than the organotin(IV) derivatives of simple α-amino acids [45] (<50 mg kg^{-1}) and peptides [32,46] (>500–800 mg kg^{-1}), indicating that umbelliferone and 1,10-phenanthroline lower the toxicities but enhance the activities of the resulting organotin(IV) derivatives.

3.4.3. Blood-pressure lowering (cardiovascular) activity

The blood pressure lowering activity of the synthesized compounds was carried out on either adult dogs (body weight 10–20 kg) or on cats (body weight 3–4 kg) of either sex. The results are presented in Table 7. The trialkyltin(IV) derivatives of umbelliferone exhibited mild hypotensive activity of varying degree (10–20 mm Hg) and duration (5–15 min) without affecting the carotid occlusion (CO) and noradrenaline (NA) response. Such a profile of pharmacological effect is indicative of direct vasodilator action of these compounds. $Ph_3Sn(Umb) \cdot phen$ showed hypotensive activity (23 mm Hg) which lasted for about 15 min. This compound inhibited the NA response without affecting CO response. $Me_3Sn(Umb) \cdot phen$ showed mild blood pressure lowering activity, with inhibition of both CO and NA responses.

The results suggest that $Ph_3Sn(Umb) \cdot phen$ can act as an effective anti-inflammatory agent (50.8% inhibition) as it is least toxic (LD_{50} > 1600 mg kg^{-1}) and has mild hypotensive activity (23 mm Hg that lasted for ~15 min).

3.4.4. Anti-microbial activity

Minimum inhibitory concentrations (MIC in μg ml^{-1}) determined by the standard dilution method are given in Table 8. The studied compounds showed mild activities against different microbes. $Ph_3Sn(Umb)$ and $Me_3Sn(Umb)$ show good activity against *Staplylococcus aureus* (strains 1 and 2) and *Bacillus subtilis*, *Candida albicans* and *Microsporum gypseum*, respectively. However the anti-microbial activities of the triorganotin(IV) derivatives of umbelliferone against certain microbes are slightly enhanced (Table 8) upon adduct

Table 8
Anti-microbial activity data (by standard dilution method)

Compound	MIC (in μg/ml)						
	1	**2**	**3**	**4**	**5**	**6**	**7**
Me_3Sn(Umb)	>25.0	>25.0	2.0	>25.0	>25.0	5.0	5.0
Ph_3Sn(Umb)	10.0	2.0	>25.0	>25.0	>25.0	>25.0	>30.0
Me_3Sn(Umb) · phen	2.0	2.0	>25.0	>25.0	10.0	5.0	5.0
Ph_3Sn(Umb) · phen	>25.0	2.0	>25.0	10.0	10.0	5.0	>30.0

1, *Staphylococcus aureus Mau 29/58*; **2**, *Staphylococcus aureus Mau 78/71*; **3**, *Bacillus subtilis 18/6*; **4**, *Escherichia coli 326/71*; **5**, *Escherichia coli*; **6**, *Candida albicans Pn-10*; **7**, *Microsporum gypseum*.

formation with 1,10-phenanthroline. The zone of inhibition by standard plate diffusion method also suggested mild activity against *Bacillus polymyxa* and *Salmonella typhii*.

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