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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,