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Investigations of the possible pharmacological effects of organotin(II) complexes

Ashu Chaudhary [a], A.K. Singh [b], R.V. Singh [a,*]

[a] Department of Chemistry, University of Rajasthan, Jaipur 302 004, India
[b] Department of Chemistry, Indian Institute of Technology, New Delhi 110 016, India

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Abstract

Antitumour, antifertility and histopathological investigations were carried out on male rats by the use of organotin complexes. The organotin complexes were synthesized by the alkylation of $[Sn(TAML^n)Cl_2]$ ($n = 1$–4 and $TAML^n$ represents the tetraazamacrocyclic ligands) in the presence of CH_3I or C_2H_5Br. The structures of all the complexes have been established on the basis of elemental analyses, conductivity measurements, IR, ^1H NMR, ^{13}C NMR, ^{119}Sn NMR and X-ray spectral data. The antitumour effect of the compounds was examined on swiss mice. The results obtained clearly indicated that the compounds, $[C_2H_5Sn(TAML^3)C_5H_5N]$ and $[C_2H_5Sn(TAML^4)C_5H_5N]$ display effective antitumour activity. The emphasis has been given on *in vivo* study on male albino rats (*Rattus norvegicus*) by performing serum analyses, blood analyses and fertility test.

Keywords: Antitumour; Antifertility; Organotin complexes; Tetraazamacrocyclic complexes; Pharmacological effects

1. Introduction

Many organometallic compounds exhibit interesting antitumour activity against several human cancer cell lines, and organotin compounds are a widely studied class of metal based antitumour drugs. Their intensive investigations have led to the discovery of compounds with excellent *in vitro* antitumour activity, but in many cases there is disappointingly high *in vivo* toxicity [1,2]. Organotin complexes have a wide range of pharmacological applications. The use of organotin(IV) halides as antiinflammatory agents against different types of oedema in mice has been reported [3]. Organotin(IV) complexes are also used in agriculture. They are efficient fungicides and bactericides [4,5]. Research in the antitumour activity of organotin compounds started in the 1970s. The potential of such compounds as antitumour agents have been studied by several workers [6–9]. Since 1980, United States National Cancer Institute has tested over 1000 tin compounds and 170 of these were found to be active. An extensive list of organotin compounds which were tested against P388 Lymphocyte Leukemia showed great promise as possible antitumour agents. The diorganotins are the largest group of tin compounds studied for antitumour activity. Organotins chelated to oxygen/nitrogen donating ligands have been found to be active towards a number of tumour cells. The results of such testings showed that these oxygen containing organotins are even more effective than cisplatin [10].

This work stemmed from our interest in the development of a systematic synthetic methodology of the preparation of a new series of diorganotin complexes possessing antitumour activity. Rapidly expanding population and limited sources are thought to be the most pressing global problems today. This rapid increase in the world population has multiplied the benefits of economical and technological advancement. Fertility control is very essential for maintaining satisfactory standards in the developing countries. There is an increasing international recognition

* Corresponding author. Fax: +91 141 2704677.
E-mail addresses: rvsjpr@hotmail.com, singh-rv@uniraj.ernet.in (R.V. Singh).

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for the need to control human fecundity. Needless to say there is an immediate need for an inexpensive, safe and effective as well as universally acceptable contraceptive. For the evolution of such an ideal method for control of human fertility it is necessary that the reproductive process of both, i.e., male and female should be more intensively investigated.

The male, an integral part of the family unit, has largely been sidelined by family planners. Currently, efforts are being made to develop a male contraceptive agent, which would inhibit fertility without affecting sex accessory function and libido. In this endeavor, a variety of synthetic compounds have been evaluated in males of laboratory species of mammals [11,12]. The results obtained are also encouraging. Therefore, this approach may form the basis for clinical regulation of male fertility in future. Inorganic compounds have also been investigated and applied for antifertility activity only and have not been screened for toxicological effect [13–16]. A series of diorganotin macrocycles with various nitrogen/oxygen containing ligands have been found to possess significant antitumour activity [17]. It has also been reported that diorganotin complexes containing methyl/ethyl group cause loss of testicular germ cells in rats and rabbits and decreased libido and impotency were noted in men occupationally exposed to tin [18]. Similarly N_4 tetraamide ligands exhibit a broad spectrum of antimicrobial, antiinflammatory, analgesic and antifertility activity. Also, the peculiar behaviour of organotin complexes in chemical and biochemical processes has led us to synthesize such type of complexes and screened them for their antitumour and antifertility activities so as to contribute in the field of bioinorganic chemistry and their clinical uses. In this context the present communication deals with the synthesis, antitumour screening and contraceptive efficacy of organotin complexes. The complexes were screened for their antifertility efficacy at biochemical and histopathological levels.

2. Experimental

2.1. Synthesis

2.1.1. Materials and methods

All the solvents used were of high purity and distilled before use. $SnCl_2$ (BDH), malonic acid, succinic acid, glutaric acid and adipic acid (Fluka) and 1,9-diaminononane (E. Merck) were used as obtained.

2.1.2. Synthesis of the complex $[Sn(TAML^1)Cl_2]$

The reaction was carried out in 1:2:2 molar ratios. A magnetically stirred solution of $SnCl_2$ in methanol was added to a solution of 1,9-diaminononane. The reaction mixture was stirred for 30 min and then the methanolic solution of malonic acid was added. The resultant mixture was stirred over night to yield solid product which was removed by filtration, washed several times with the same solvent and vacuum dried. The compound was recrystallized in benzene. The purity of the compound was checked by thin layer chromatography (TLC) on silica gel-G. However, if the same reaction is carried out under microwave conditions of green chemistry, the product was formed within 5 min and which is also an advantage of the new technique from the environmental as well as from the economic points of view.

Same procedure has been used for the synthesis of $[Sn(TAML^2)Cl_2]$, $[Sn(TAML^3)Cl_2]$ and $[Sn(TAML^4)Cl_2]$ (TAML represents the tetraazamacrocyclic ligand). The reagents used were succinic acid, glutaric acid and adipic acid, respectively, in place of malonic acid.

2.1.3. Synthesis of the organotin(II) complexes

The reaction was carried out in 1:1 molar ratio. In a Shlenk tube, a saturated methanolic solution of $[Sn(TAML^1)Cl_2]$ was taken, stirred and pyridine was added. The stirred suspension was then cooled at 5 °C and stirred for 35 min. To this suspension, sodium hydroxide (0.006 mol) followed by CH_3I (0.003 mol) were added. The solution was gradually warmed to 20 °C and then stirred further for 40 min. The solution was refluxed till the volume remain half then stirred, filtered and finally dried.

Same procedure has been used for the synthesis of $[RSn(TAML^n)C_5H_5N]$, where $n = 2$–4, $R = CH_3$ and C_2H_5. The reagents used were $[Sn(TAML^2)Cl_2]$, $[Sn(TAML^3)Cl_2]$ and $[Sn(TAML^4)Cl_2]$ along with CH_3I/C_2H_5Br.

2.1.4. Physical measurements and analytical methods

The molecular weights were determined by the Rast Camphor Method. Conductivity measurements in dry dimethylformamide were performed with a conductivity Bridge type 305. Nitrogen and chlorine were estimated by the Kjeldahl's and Volhard's method, respectively. Tin was estimated as tin oxide gravimetrically. Infrared spectra of the precursors and their organotin(II) complexes were recorded in the range 4000–200 cm^{-1} with the help of a Nicolet-Magna FTIR-550 spectrophotometer as KBr pellets. Multinuclear magnetic resonance spectra were recorded on a FX 90Q JEOL spectrometer operating at 90 MHz. ^1H NMR spectra were recorded in DMSO–d_6 (deuterated dimethylsulphoxide) at 89.55 MHz using tetramethylsilane (TMS) as an internal standard. ^{13}C NMR were recorded in dry DMSO (dimethylsulphoxide) using TMS as the internal standard at 22.49 MHz. ^{119}Sn NMR spectra were recorded at 33.35 MHz using DMSO–d_6 as the solvent. The chemical shifts were determined relative to the external reference tetramethyltin and are supposed to be accurate to ±1 ppm. Carbon and hydrogen analyses were performed at Regional Sophisticated Instrumentation Center, Central Drug Research Institute, Lucknow.

2.2. Antibacterial activity

The synthesized compounds were evaluated for *in vitro* inhibitory activity against the bacteria *Pseudomonas*