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# Synthesis, Characterization and Cytotoxic Activity of Diorganotin(IV) Complexes with 4*H*-Pyrido[1,2-*a*]pyrimidin-4-one Derivatives

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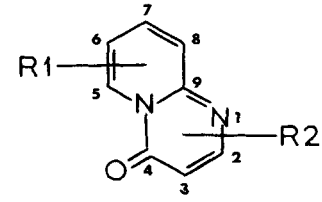
**The coordination behaviour of the diorganotin(IV) compounds $R_2SnCl_2$ (where R = Me, Ph) with 4*H*-pyrido [1,2-*a*] pyrimidin-4-one derivatives (L) has been described. The complexes $R_2SnCl_2 \cdot L$ obtained have been characterized physicochemically and spectroscopically. The pyrimidin-4-one ligands were found to coordinate with $R_2SnCl_2$ species in a monodentate fashion, mainly via the oxygen atom of the 4-one group or possibly via the nitrogen atom of the —C=N linkage (the less sterically hindered nitrogen of the pyrimidine derivative) to give pentacoordinate tin complexes. Of the complexes selected to be screened against five tumour cell lines, some exhibited significant *in vitro* activity.**

**Keywords: organotin; pyrimidin-4-one derivatives; complexes; cytotoxicity**

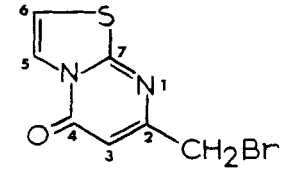
## INTRODUCTION

Organotin(IV) compounds and their complexes with various ligands have found many applications in biomedicine, and several articles and reviews dealing with their anti-pathogenic bacteria and antitumour activities have been reported.[1–6]

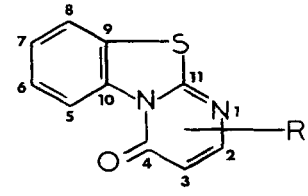
In view of the importance of such complexes, as a combination of our previous work[7–9] we describe in the present work the preparation and properties of $R_2SnCl_2$ complexes of some 4*H*-pyrido[1,2-*a*]pyrimidin-4-one derivatives (Scheme 1) as donating ligands having multiple donor sites and examine the cytotoxic activity of some of these complexes against five tumour cell lines.




L1 : R1 = H , R2 = 2 - $CH_2Br$
L2 : R1 = 7- $CH_3$ , R2 = 2 - $CH_2Br$
L3 : R1 = 8- $CH_3$ , R2 = 2 - $CH_2Br$
L4 : R1 = H , R2 = 3 - $CH_3COO$
L5 : R1 = 7- $CH_3$ , R2 = 3 - $CH_3COO$




L6




L7 : R = 2 - $CH_3$
L8 : R = 3 - $CH_3COO$

**Scheme 1** The ligands used in coordination with $R_2SnCl_2$ compounds.

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## EXPERIMENTAL

### General

The $^1$H NMR spectra were recorded at Yarmook University, Irbid, Jordan, on a Bruker-WH 80 DS spectrometer, using $CDCl_3$ as solvent with TMS as internal standard. IR spectra were recorded on an SP2000 spectrometer in the range 200–4000 $cm^{-1}$ using Nujol mull and CsI discs. Analysis of the complexes was carried out using a CHN Analyser, Type 1106 (Carlo Erba). Electronic spectra were recorded on a Uv/Vis spectrophotometer, Shimadzu Koyoto model 160 (Japan), using DMF as solvent. Conductivity measurements were carried out on $10^{-3}$ molar solutions of the complexes in ethanol, nitromethane and DMF at room temperature (25 °C), using a conductivity meter, model 4070 (Jenway).

### Preparation of starting materials

The compounds $Me_2SnCl_2$ and $Ph_2SnCl_2$ were prepared by standard methods.[10,11] The ligands, 4*H*-pyrido[1,2-*a*]pyrimidin-4-ones, $L^1$–$L^8$ (Scheme 1), were prepared by a standard method.[12] The structures of the ligands were established by NMR.

### Preparation of complexes $R_2SnCl_2 \cdot L$

The complexes were prepared according to the following standard method.

The diorganotin(IV) compound $R_2SnCl_2$ (R = Me or Ph) (1 mmol) was dissolved in the minimum volume of dry chloroform and then added to a solution of the pyrimidin-4-one ligand (L), prepared by dissolving the ligand (1 mmol) in the minimum volume of chloroform at ambient temperature or if necessary under moderate heating.

The resulting solution was evaporated to *ca* one-quarter of its original volume by direct heating on a hotplate. N-Hexane was added to the point of turbidity and the mixture was left in the refrigerator for several hours. The crystalline product thus formed was filtered off, washed several times with n-hexane and dried under vacuum for several hours. The yield was almost quantitative. Melting points were sharp and elemental analysis was used for characterization.

### Biological tests

#### Cell lines

Hep-2 (human carcinoma of larynx), HeLa (human cervical carcinoma), RD (human embryonal rhabdomyosarcoma), $L_{20B}$ (mouse L-cells containing human polio-virus receptors[13]) and BGM (African green monkey cells) were kindly supplied by Al-Basheer Hospital, Amman, Jordan. All cells except $L_{20B}$ were maintained in minimum essential medium (MEM) and supplemented with 5% fetal calf serum (ICN–Flow Laboratories, UK), L-glutamine and antibiotics (100 units of penicillin and 100 μg $ml^{-1}$ of streptomycin. $L_{20B}$ cells were maintained in Dulbecco's MEM (DMEM) (Sigma Chemical Co., USA) and supplemented with 10% fetal calf serum and antibiotics.

#### Cytotoxicity tests

MTT (3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide) colorimetric assay was performed in a 96-well plate.[14,15] The above cell lines ($1 \times 10^6$ cells $ml^{-1}$) were seeded in each well with 100 μl of growth medium and 10% fetal calf serum and antibiotics. After overnight incubation (37 °C, 5% $CO_2$), 10 μl of the sample solution was added to each well and incubated for 48–72 h. Then 10 μl of MTT (5 mg $ml^{-1}$) was added to each well and the plates were incubated for a further 4 h. Later, 25 μl of 10% SDS–0.01 M HCl solution was added to each well. The optical density was recorded using a microplate reader at 540 nm. Three separate sets of controls containing the solvents (10% DMSO) were used in each plate. The $IC_{50}$ (μg $ml^{-1}$) was calculated using the probit test.

## RESULTS AND DISCUSSION

The physical properties of the diorganotin(IV) complexes are listed in Table 1 and the $^1$H NMR data of the complexes $Me_2SnCl_2 \cdot L$ are listed in Table 2. The elemental composition of the complexes prepared is clearly assigned to a 1:1 ratio of organotin compound to ligand, i.e. $R_2SnCl_2 \cdot L$.

From Scheme 1 (Ligands $L_1$–$L_5$) it can be seen that only two active donor sites, i.e. the N-1 and O atoms of the pyrimidin-4-one ring, occur and it appears that the remaining nitrogen atom of the pyrimidine nucleus would be inactive from the

**Table 1** The physical properties and analysis of the diorganotin complexes $R_2SnCl_2 \cdot L^x$

| Complex | Colour | M.p. (°C) | Analysis (%): Found (Calcd) | | | Selected IR bands[a] ($cm^{-1}$) | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | C | H | N | $\nu$(C=N) ($\Delta\nu$) | $\nu$(C=O) ($\Delta\nu$) | $\nu$(Sn–O) $\nu$(Sn–N) | $\nu$(Sn–C) | $\nu$(Sn–Cl) | UV/Vis $\lambda_{max}$ (nm) |
| $Me_2SnCl_2 \cdot L^1$ | Off-white | 88–90 | 28.7 (28.8) | 3.0 (2.8) | 6.0 (6.1) | 1578 m (0) | 1722 s (27) | 434 w | 567 m | 291 m | 376 |
| $Ph_2SnCl_2 \cdot L^1$ | White | 126–128 | 43.0 (43.25) | 3.0 (2.9) | 5.0 (4.8) | 1582 m (4) | 1722 s (27) | 450 m | 234 w | 280 w | 275, 309, 376 |
| $Me_2SnCl_2 \cdot L^2$ | Pale yellow | 82–84 | 30.0 (30.5) | 3.0 (3.2) | 5.7 (5.9) | 1595 m (10) | 1722 s (27) | 492 w | 552 m, sh | 280 m | 267 |
| $Ph_2SnCl_2 \cdot L^2$ | Yellow | 137–139 | 44.1 (44.2) | 3.2 (3.2) | 4.9 (4.7) | 1583 m (−2) | 1700 s (5) | 455 m | 267 m | 300 m | 209, 275, 309, 384 |
| $Me_2SnCl_2 \cdot L^3$ | Off-white | 90–92 | 30.3 (30.5) | 3.0 (3.2) | 5.8 (5.9) | 1590 m (10) | 1682 s (−13) | 434 m | 502 w | 296 s, sh | 275, 309, 378 |
| $Ph_2SmCl_2 \cdot L^3$ | Milky | 100–102 | 44.55 (44.2) | 3.05 (3.2) | 4.8 (4.7) | 1583 w (3) | 1655 s (−40) | 452 m | 238 w | 271 s, sh | 208, 275, 309, 378 |
| $Me_2SnCl_2 \cdot L^4$ | Yellow | 79–81 | 35.0 (34.0) | 3.45) (3.3) | 6.7 (6.6) | 1585 m (5) | 1710 s, 1776 m (−10), (56) | 449 m | 494 w | 280 w | 386 |
| $Ph_2SnCl_2 \cdot L^4$ | Pale yellow | 128–129 | 48.0 (48.2) | 3.2 (3.3) | 5.1 (5.1) | 1580 s (0) | 1695 s, 1765 m (−25), (45) | 470 m | 245 w | 293 m, sh | 386 |
| $Me_2SnCl_2 \cdot L^5$ | Pale yellow | 135–136 | 35.3 (35.6) | 3.8 (3.7) | 6.25 (6.4) | 1580 m (−7) | 1670 m, 1740 s (−20), (−5) | 486 m | 537 m, sh | 286 m | 384 |
| $Ph_2SnCl_2 \cdot L^5$ | Pale yellow | 177–179 | 49.0 (49.1) | 3.45 (3.6) | 5.1 (5.0) | 1591 s (4) | 1685 m, 1740 s (−5), (−5) | 494 m | 245 w | 270 w | 251, 384 |
| $Me_2SnCl_2 \cdot L^6$ | Pale yellow | 149–151 | 23.0 (23.2) | 2.5 (2.44) | 6.1 (6.0) | 1572 m (12) | 1670 s (−15) | 479 m | 569 m | 265 s, sh | 275, 309, 349, 480 |
| $Ph_2SnCl_2 \cdot L^6$ | Off-white | 154–156 | 37.9 (38.7) | 2.7 (2.55) | 4.9 (4.8) | 1560 m (0) | 1685 s (0) | 457 s, sh | 242 w | 280 s, sh | 275, 309, 349, 397 |
| $Me_2SnCl_2 \cdot L^7$ | White | 216–218 | 36.0 (35.8) | 3.3 (3.2) | 6.0 (6.4) | 1575 m (−12) | 1695 m (15) | 490 w | 577 m, sh | 270 s, sh | 275, 309 |
| $Ph_2SnCl_2 \cdot L^7$ | Pale yellow | 223–224 | 49.0 (49.3) | 3.1 (3.2) | 4.9 (5.0) | 1575 m (−12) | 1695 s (15) | 480 m | 245 w | 285 s | 275, 308, 349 |
| $Me_2SnCl_2 \cdot L^8$ | Creamy | 164–165 | 35.2 (35.0) | 3.1 (2.9) | 5.7 (5.8) | 1573 m (−17) | 1670 m, 1740 s (−20), (−10) | 468 w | 547 w | 296 s, sh | 275, 312, 349 |
| $Ph_2SnCl_2 \cdot L^8$ | Creamy | 177–178 | 46.9 (47.7) | 3.3 (3.0) | 4.4 (4.6) | 1575 w (−15) | 1672 m, 1740 m (−18), (−10) | 449 m | 554 w | 290 m, sh | 267, 317, 346 |

[a] IR spectra recorded with Nujol mull: s, strong; m, medium; w, weak; sh, shoulder. $\nu$(C=C) values appeared at *ca* 1620 $cm^{-1}$. ($\Delta\nu$) values were measured as $\nu_{complex} - \nu_{ligand}$.

viewpoint of steric hindrance. In addition, ligands $L^4$ and $L^5$ might have an additional coordination site, i.e. the O atom of the CO group ($CH_3COO$). In the case of ligands $L^6$, $L^7$ and $L^8$) an additional possible coordination site is available (the S atom); nevertheless, tin metal (considered to be in the border region of the soft–hard Lewis acid concept) usually coordinates to hard Lewis bases, e.g. O or N, sites. Therefore, coordination of sulphur with tin in this case was excluded and this is clear from the IR spectral data. On this basis, we discuss the interaction between $R_2SnCl_2$ and the pyrimidin-4-one derivatives.

## NMR spectra

The $^{119}Sn$–CH coupling constant is a very good indicator for the evaluation of the coordination number of tin.[16] It is very clear from the $^2J$ ($^{119}Sn$–CH) values, which range from 68.5 to 71.5 Hz (Table 2), that the ligand has coordinated to tin in a monodentate fashion,[7,17,18] regioselectively, via the most reactive donor site of this ligand, to give pentacoordinate tin species. The $^1H$ NMR signals of the organic residues of the $Me_2SnCl_2$ · pyrimidine complexes remained almost constant when compared with the free pyrimidine using the same solvent.[12] Furthermore, the $^{13}C$ NMR spectrum for the complex $Me_2SnCl_2 \cdot L^8$ showed additional support for our argument; $\delta_{Me} = 7.1$ ppm and $J(^{119}Sn-^{13}C) = 560$ Hz. The coupling constant obtained is typical for pentacoordinate tin species.[16,17,19] The carbon-13 NMR signals of the rest of the organic moiety were similar in their chemical shifts to those of the free ligand, apart from C-4 (Scheme 1) in which the chemical shift in the free ligand (157.7 ppm) was shifted downfield by *ca* 7 ppm ($\delta = 164.5$ ppm), confirming that coordination of this ligand with $Me_2SnCl_2$ takes place via the O atom of C-4.

## IR spectra

Since these pyrimidin-4-one derivatives serve as monodentate ligands in their coordination with tin, and the most likely donor sites are either N-1 or O of C-4 of the ligand, one would expect that the values of $\nu$(C=N) or $\nu$(C=O) modes of the ligands before and after complexation should show which site of the ligand was involved in the coordination. However, if we take into consideration that the coordination of these ligands with tin via O of C-4, or N-1, would result in a significant change in the $\nu$(C=O) and $\nu$(C=N) values respectively, one can predict, from Table 1, the type of interaction between these ligands and $R_2SnCl_2$. Moreover, the band appearing in the region 430–490 $cm^{-1}$ is tentatively attributed to $\nu$(Sn–O) or $\nu$(Sn–N); they are close together and rather difficult to separate. Other absorption

**Table 2** $^1H$ NMR data[a], $\delta$ (ppm) and $J$ (Hz) for $Me_2SnCl_2 \cdot L^x$ complexes

| | | Ligand ($L^x$) assignments | | | | | | |
|---|---|---|---|---|---|---|---|---|
| $L^x$ | δMe $^2J$ ($^{119}Sn$–CH) | δ(HC-2) | δ(HC-3) | δ(HC-5) | δ(HC-6) | δ(HC-7) | δ(HC-8) | δ(others) |
| $L^1$ | 1.23 s (69) | — | 6.6 s | 9.0 d[b] $J=7.0$ | | 7.7–7.8 m (2H) | 7.3 d $J=7.5$ | $CH_2$, 4.4 s (2H) |
| $L^2$ | 1.23 s (70.1) | — | 6.5 s | 9.0 d $J=7.1$ | 7.03 dd $J=7.5, 4.0$ | — | 7.5 d $J=4.0$ | $CH_2$, 4.35 s (2H) $CH_3$, 2.60 s (3H) |
| $L^3$ | 1.25 s (71.2) | — | 6.6 s | 8.95 d[b] $J=7.1$ | 7.08 t $J=7$ | 7.65[b] $J=7.5$ | — | $CH_2$, 4.4 s (2H) $CH_3$, 6.6 s (3H) |
| $L^4$ | 1.23 s (71.4) | 9.075 | — | 9.3 d[b] $J=7.0$ | | 7.8–8.0 m (2H) | 7.45 d[b] $J=6.6$ | $CH_3$, 3.95 s (3H) |
| $L^5$ | 1.22 s (68.7) | 9.03 s | — | 9.16 d $J=7.1$ | 7.15 d $J=7.1$ | — | 7.6 d $J=1.5$ | $CH_3$, 2.58 s (3H) $CH_3COO$, 3.95 s (3H) |
| $L^6$ | 1.21 s (69) | — | 6.4 s | 8.0 d $J=7.1$ | 7.1 d** $J=7.1$ | — | — | $CH_2$, 4.3 s (3H) |
| $L^7$ | 1.21 s (68.4) | — | 6.26 s | | 7.4–7.7 m (2H) | 9.05 dd $J=2.0, 5.0$ | 7.4–7.7 m (1H) | $CH_3$, 2.4 s (3H) |
| $L^8$ | 1.20 s (69.1) | 8.8 s | — | 9.18 dd $J=9.0, 1.4$ | | 7.5–7.9 m (2H) | — | $CH_3COO$, 4.0 s (3H) |

[a] downfield from internal TMS at room temperature: s, singlet; d, doublet; dd, doublet of doublets, m, multiplet signals.
[b] Poorly resolved doublet of doublets.

**Table 3** Cytotoxic activities of $Me_2SnCl_2 \cdot L^x$ complexes against different tumour cell lines

| | $IC_{50}$ ($\mu g\ ml^{-1}$) | | | | |
|---|---|---|---|---|---|
| $L^x$ | Hep-2 | HeLa | RD | $L_{20B}$ | BGM |
| $L^1$ | 1.5 | 1.7 | 0.16 | >10 | 0.17 |
| $L^3$ | 2.3 | 1.4 | 0.9 | >10 | 2.2 |
| $L^4$ | 5.5 | 7.5 | 4.9 | >10 | 5.9 |
| $L^6$ | 2.5 | 3.2 | 0.35 | >10 | 0.85 |
| $L^7$ | 9 | 6.8 | >10 | >10 | 0.85 |
| $L^8$ | >10 | >10 | >10 | >10 | >10 |
| Cisplatin | 1.8 | 5.3 | >10 | >10 | >10 |

bands due to $\nu$(Sn–Cl), $\nu$(Sn–C) (for C aliphatic and aromatic) and $\nu$(C=C) modes were also observed and assigned.

The UV/vis spectral data of the complexes showed absorption bands at maxima at *ca* 210, 275, 310 and 380 nm which are due to charge-transfer transitions of the ligands. The *d–d* transitions caused by the metal are usually unobservable due to obscuring by the ligand charge-transfer bands. In the present case, only a few complexes showed absorption bands at maxima at *ca* 400 and 480 nm due to *d–d* transitions.

Molar conductivities for $10^{-3}$ M solutions of the complexes ($R_2SnCl_2 \cdot L$) in three different solvents, ethanol, nitromethane and DMF, were in the ranges 4–27, 11–25 and 5–57 $\Omega^{-1}\ cm^2\ mol^{-1}$ respectively. These figures suggest non-conductive species,[20] i.e. non-ionic complexes, $[R_2SnCl_2 \cdot L]$, in the solvents used.

## Cytotoxicity tests

All selected complexes for cytotoxicity tests, i.e. $Me_2SnCl_2 \cdot L$ were already purified before testing, by recrystallization from chloroform/hexane. Their cytotoxic activities against different cell lines are shown in Table 3. The complexes tested showed variable cytotoxic activities against the cell lines used in the present study. However, the only cell line that was resistant to all complexes at the concentrations used was $L_{20B}$. Furthermore, the complex $Me_2SnCl_2 \cdot L^8$ showed no cytotoxic activity against the cell lines used ($IC_{50} > 10\ \mu g\ ml^{-1}$).

The most notable activity was demonstrated by the complex $Me_2SnCl_2 \cdot L^1$ (Table 3). The $IC_{50}$ value of this complex is superior to that of cisplatin (Bristol–Myers, USA), expecially against the RD and Hela cells. Other complexes showed moderate cytotoxic activities and can be arranged according to their activity in the ligand sequence as follows: $L^3 > L^6 > L^4$ and $L^7$.

Based on these results, the following conclusion can be drawn. Ligands containing the $CH_2Br$ moiety enhanced the cytotoxicities whereas ones containing $CH_3$ or $CH_3COO$ reduced them. Nevertheless, *in vivo* investigations are required to confirm such activities.

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