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Synthesis and antiproliferative activity of novel organotin complexes bearing abiraterone drug moiety

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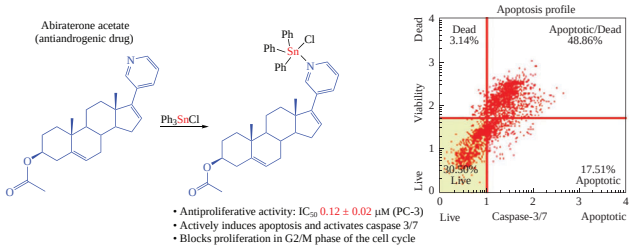
Novel organotin(IV) complexes based on anticancer drug abiraterone acetate and abiraterone incorporating semipolar N➔Sn bond at the pyridine moiety were synthesized and characterized. *In vitro* antiproliferative activity of the complexes against human cancer and normal cell lines was evaluated, the complexes with triphenyltin moiety being the most active (IC_{50} is in the range of 120–430 nM). Compounds actively induced apoptosis and blocked proliferation in the G2/M phase of the cell cycle.



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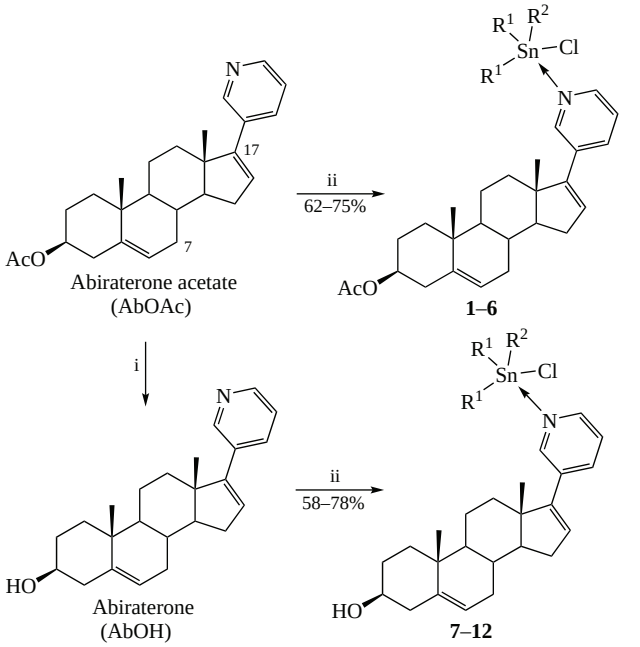
Prostate adenocarcinoma retains a high-risk disease in the male population and is responsible for about 20% of cancer-related deaths. The number of research has proven that prostate cancer is regulated by the androgen receptor (AR). The blocking of AR function can be achieved by competitive antagonists of the cognate ligands (*e.g.*, testosterone, dihydrotestosterone) or by reducing intra-tumoral androgen synthesis.[1,2] Unfortunately, for most patients the resistance to androgen deprivation therapy (ADT) is developed and disease progresses towards castration-resistant prostate cancer (CRPC) after 1.5–3 years. The additional treatment is required as it becomes metastatic (mCRPC). Depending on prostate-specific antigen (PSA) levels and clinical stage, decision is made whether to use radiotherapy or surgery. Photodynamic and photothermal therapies can bring future advances in prostate cancer treatment due to their localized and controlled cytotoxic effect, as well as their low incidence of side effects.[3]

In the metastatic hormone-sensitive prostate cancer setting, three antihormonal agents (abiraterone acetate, apalutamide and enzalutamide) and docetaxel were approved in addition to ADT. Abiraterone acetate (Zytiga) is a specific inhibitor of CYP17A1, a 17-hydroxylase and 17–20 lyase of the cytochrome P450 family, which converts pregnenolone or progesteron into dehydroepiandrosterone and androstendione, respectively. Abiraterone was first approved by the Food and Drug Administration (FDA) in 2011 for late-stage CRPC patients who have received docetaxel.[4,5] Abiraterone requires long-term use of corticosteroids such as prednisolone, and this may be an obstacle for patients with diabetes, hypertension, osteoporosis.[6,7] Various drug combinations are being intensively studied for the treatment of patients with mCRPC.[8]

Since platinum(II)-based chemotherapy exhibits modest activity on CRPC and overall patient survival, the strategy to combine in one molecule 17β-acetyl-testosterone and amino acid platinum(II) complexes linked at the position 7α to the target in order to improve the antiproliferative activity of platinum(II)-based chemotherapy on prostate cancer cells seems highly prospective. Synthesized Pt^{II} complexes exhibited antiproliferative activity (IC_{50}) and median lethal concentration (LC_{50}) at micromolar level on panel of prostate cancer cell lines and cancer cell lines unrelated to prostate cancer.[9] The use of cisplatin and its analogs (carboplatin, oxaliplatin) is limited by the relatively low selectivity of action, side effects as well as resistance in some cancer cell lines.[10] Another method of cancer treatment[11] is photoactivated chemotherapy based on photoinduced transformations of platinum(IV) complexes, *e.g.*, pyridine complex *trans*-$[Pt(Py)_2(N_3)_2(OH)_2]$.

Organotin compounds containing O-, N-, S-coordinating ligands with various mode of biological action are candidates for antitumor agents.[12–14] Organotin complexes with steroid fragments exhibit high activity against various types of human cancer.[15] Mechanisms of organotin action is associated with ability of the compounds to bind with sulfhydryl groups, thereby disrupting DNA replication and transcription leading to cell cycle arrest and inducing the apoptosis.[16] Therefore, the search for new hybrid organotin compounds on the basis of steroid drugs is promising. Recently,[17] we synthesized the Cu, Co, and Zn complexes with abiraterone acetate. In the present work, we report the synthesis of novel organotin complexes **1**–**12** with abiraterone acetate (AbOAc) and abiraterone (AbOH) (Scheme 1) and the study of their biological activity *in vitro*. The antiproliferative properties of new complexes and the correlation between their structure and biological activity are discussed.

New complexes **1**–**12** were synthesized from abiraterone acetate or abiraterone with the corresponding organotin chlorides in EtOH at room temperature (see Scheme 1). The compositions and purity of compounds **1**–**12** were confirmed by IR, ^{1}H, ^{13}C, ^{119}Sn NMR spectroscopy and elemental analysis. The changes of chemical shifts for pyridinyl protons in ^{1}H NMR spectra of the



Scheme 1 *Reagents and conditions*: i, KOH, EtOH, 40 °C, 2 h; ii, $R^1_2R^2SnCl$, EtOH, 50 °C, 4 h.

synthesized complexes in comparison to initial compounds indicate the coordination through pyridine N-donor atom. In general, during coordination with abiraterone and abiraterone acetate the nearest pyridinyl protons to N atom demonstrate the greatest downfield shifts.

The chemical shifts in ^{119}Sn NMR spectra of complexes **1**–**12** varied in the wide range (from +127 to –298 ppm) depending on the chemical environment of Sn atom (Table 1). Noticeable shifts of ^{119}Sn in complexes **1**–**12** were observed in comparison with the signals of the starting organotin chlorides; moreover, the absence the ^{119}Sn signals for the starting organotins also proves their consumption. The upfield signals are attributed to tin with higher electron density due to complexation. It is known that the dissolution of trimethyltin chloride or bromide in donor organic solvents such as acetone, acetonitrile or dioxane affords a 1 : 1 complex.[18] Single crystal X-ray analysis of five-coordinate complex of 4-(dimethylamino)pyridine with tribenzyltin chloride revealed the monomeric structure with a trigonal bipyramid geometry around tin and equatorial benzyl groups.[19]

Chloro(triorganyl)tin complexes **5**, **6**, **11** and **12** manifest only one ^{119}Sn resonance signal that confirms coordination by N atom of pyridinyl ring in complexes. On the contrary, spectra of dichloro(diorganyl)tin complexes **1**–**4** and **7**–**10** contain two ^{119}Sn signals, which indicates the presence of two different kinds of Sn^{IV} centers in solution. Similar results with two types of tin centers have been previously reported for tetranuclear tin complexes.[20]

Table 1 Chemical shifts ^{119}Sn in NMR spectra of starting organotin compounds and complexes **1**–**12** ($CDCl_3$).

Compound	δ_{Sn} (ppm)	Compound	δ_{Sn} (ppm)	Compound	δ_{Sn} (ppm)
Me_2SnCl_2	142.4	**1**	–116.2; –64.0	**7**	–116.1; –65.1
Et_2SnCl_2	129.6	**2**	–139.3; –92.4	**8**	–138.7; –91.0
Bu_2SnCl_2	127.8	**3**	–138.2; –90.9	**9**	–138.1; –90.9
Ph_2SnCl_2	–27.7	**4**	–211.8; –297.6	**10**	–211.9; –297.7
Me_3SnCl	172.7	**5**	120.2	**11**	126.7
Ph_3SnCl	–45.2	**6**	–69.3	**12**	–68.42

The behavior of compounds **6**, **12**, AbOAc and AbOH in acidic (pH 5.5) solution for modeling the hydrolysis process in cancer was studied spectrophotometrically. In the absorption spectra of compounds **6**, **12** and AbOH, no noticeable decrease in optical density was detected during 20 h (see Online Supplementary Materials). In the case of AbOAc at pH 5.5, optical density change was observed within 2 h that was probably due to hydrolysis of the ester group or protonation of the pyridine moiety.

It is known that organotins are capable of promoting oxidative stress in biological substrates by homolytic cleavage of Sn–C bond.[21] Copper ion antioxidant capacity (CUPRAC-test) is frequently applied to evaluate redox-activity of compounds, *e.g.*, antioxidants. Previously,[14] we have shown that the introduction of antioxidant moiety into organotin complexes decreased *in vitro* antiproliferative activity against cancer cells. In order to prove that compounds under study do not possess antioxidant activity, we applied the CUPRAC method. The ability of compounds to one-electron reduction was studied using the spectrophotometric CUPRAC test[22] (see Online Supplementary Materials, Table S1). In fact, compounds **4**, **6**, **10** and **12** demonstrate mild activity due to the presence of phenyl groups at tin atom that can be involved in redox and radical processes. The activity of diphenyl (**4**, **10**) and triphenyltin (**6**, **12**) compounds was similar to that of Ph_2SnCl_2 and Ph_3SnCl. The presence of abiraterone moiety does not influence the ability of organotins to undergo electron transfer.

The results of screening by MTT test for antiproliferative activity of abiraterone-based complexes against cancer PC-3 (prostate), MCF-7 (human breast adenocarcinoma), HCT-116 (colon carcinoma), A-549 (lung cancer) and normal WI-38 (fibroblasts) cells are presented as IC_{50} values (Table 2).[23] The IC_{50} values for the most toxic compound Ph_3SnCl are 0.010 ± 0.001 μM (HCT-116) and 0.07 ± 0.01 (MCF-7) μM.[12] The cytotoxicity of starting dialkyltin chlorides is 1–2 orders lower than that of Ph_3SnCl.[24,25] Compounds **1**–**12** exhibit high activity in micromolar range of concentrations. It was found that the antiproliferative properties of Sn^{IV} complexes depended on the nature of the organyl group at the Sn atom and the cell type: IC_{50} ranges from 0.1 to 12.4 μM, which was lower than that for the ligand AbOAc (IC_{50} ranges from 1.6 to 22.7 μM). Lipophilic compound $Ph_3SnCl \cdot$AbOAc (**6**) turned out to be the most active (IC_{50} = 0.12 ± 0.02 μM) against prostate cancer PC-3 cells. The results demonstrate the selectivity and combined action of the complexes toward prostate cancer cells that opens new prospects for the search of new anticancer drugs.

Table 2 IC_{50} values of compounds AbOAc, AbOH and **1**–**12** on various cell lines.

Compound	IC_{50}/μM				
	PC-3	A-549	MCF-7	HCT-116	WI-38
AbOAc	5.3 ± 1.2	9.4 ± 1.2	22.7 ± 2.0	1.6 ± 0.2	12.4 ± 1.3
1	17.3 ± 2.3	17.6 ± 2.1	20.6 ± 1.9	22.2 ± 2.3	10.3 ± 0.8
2	25 ± 3.0	23.7 ± 2.3	14.6 ± 1.3	5.3 ± 0.4	6.7 ± 0.7
3	0.9 ± 0.2	1.3 ± 0.2	1.1 ± 0.1	0.7 ± 0.1	0.7 ± 0.1
4	2.0 ± 1.2	2.3 ± 0.2-	2.6 ± 0.3	1.45 ± 0.03	2.1 ± 0.1
5	22.1 ± 2.0	18.2 ± 1.9	21.8 ± 2.1	16.2 ± 1.7	11.1 ± 1.2
6	0.12 ± 0.02	0.21 ± 0.03	0.23 ± 0.04	0.32 ± 0.04	0.22 ± 0.03
AbOH	18.4 ± 2.5	22.9 ± 1.8	38.8 ± 4.1	25.7 ± 2.3	14.0 ± 1.3
7	12.1 ± 1.4	41.3 ± 3.7	22.6 ± 1.9	62.2 ± 4.5	39.3 ± 3.7
8	33 ± 4	15.3 ± 1.4	17.2 ± 1.5	38.6 ± 3.1	8.1 ± 0.9
9	2.6 ± 0.4	1.5 ± 0.3	1.1 ± 0.2	2.0 ± 0.1	1.1 ± 0.1
10	2.3 ± 0.3	2.8 ± 0.4	1.9 ± 0.1	1.5 ± 0.2	2.2 ± 0.2
11	17.3 ± 1.9	32.2 ± 3.5	29.7 ± 3.1	45.8 ± 5.1	25.4 ± 3.4
12	0.12 ± 0.03	0.31 ± 0.02	0.43 ± 0.03	0.3 ± 1.2	0.25 ± 0.05

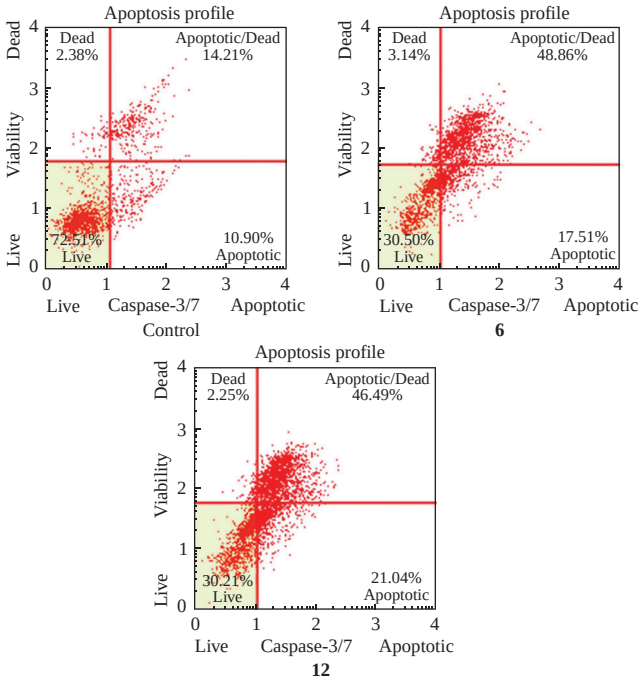


Figure 1 Cytometry studies of caspase 3/7 activation by compounds **6** and **12** on the HCT116 cell line after 24 h.

Mechanism of cell death that is related to Annexin V/7-AAD reactivity was determined for compounds **6**, **12** and cisplatin in HCT116 cells using the Muse® AnnexinV & Dead Cell Kit by flow cytometry.[26] Compounds **6**, **12** were shown to activate apoptosis significantly (see Online Supplementary Materials, Figures S17 and S18). After 24 h treatment with the compounds, the percentage of viable cells was almost halved and the population of apoptotic cells increased by 44 and 38% for **6** and **12**, respectively. The maximum cell pool was observed at the late apoptosis stage (32.5 and 31.6% for compounds **6** and **12**, respectively). After treatment for 48 h with the compounds, the number of cells in late apoptosis increased significantly up to 59% for **6** and 70% for **12**, while the number of viable cells was less than 20% of the entire population.

Caspase-1 is a cysteine protease that plays a central role in propagating the process of programmed cell death (apoptosis) in response to the proapoptotic signals. Caspases called effector ones act further downstream and direct cellular breakdown through cleavage of structural proteins (Caspase-3 and Caspase-7). Thus, activation of caspase 3/7 is a hallmark of the apoptosis. It has been discovered that majority of cells 48.9% (**6**) and 46.5% (**12**) are found in the stage of late apoptosis or dead by apoptotic mechanisms (Figure 1).

To determine the effect of compounds **6**, **12** on the cell cycle arrest, the propidium iodide (PI) assay was also performed on the HCT116 cell lines. The cell cycle phases, namely, the distribution of cells in the G1/G0-, S- and G2/M-phases of the cell cycle was assessed by determining the relative content of DNA in the cells using nuclear DNA intercalating stain PI. The effect of compounds **6**, **12** on the distribution of HCT116 cells over the phases of the cell cycle was studied. A slight decrease in the cell population in the S phase and an accumulation of cells in the G2/M phase were found compared to the control (from 8.8% in the control to 12.7% for **6** and 13.4% for **12**) after 24 h of cell treatment (Figure S3). Thus, both compounds with triphenyltin moiety affect the HCT116 cell cycle.

In conclusion, diphenyl and especially triphenyltin complexes with abiraterone ligands demonstrated the highest antiproliferative activity. Lipophilic compound $Ph_3SnCl{\cdot}AbOAc$ (**6**) turned out to be the most active one ($IC_{50} = 0.12 \pm 0.02$ μM) in PC-3 cells. Triphenyltin complexes **6** and **12** were shown to induce apoptosis significantly and they also affected the cell cycle. The noticeable increase of cancer cells in G2/M phase was detected.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2024.01.007.

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