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New titanocene derivatives with high antiproliferative activity against breast cancer cells

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ABSTRACT

The synthesis and characterization of some new titanocene-complexes, having a ethenyl-phenoxide or a benzyl group as substituents of the cyclopentadienyl rings, are reported. The synthesized compounds have been evaluated for their cytotoxic potential against two human breast cancer cell lines, that is: MCF7 and SkBr3. Most of these compounds have shown significant cytotoxic effects, compared to cisplatin, in MTT-based cell tests.

The remarkable antitumor activity shown by *cisplatin* and other platinum complexes[1–6] has meant that new metal-based anticancer drugs have become a noteworthy subject of research. Among all synthesized compounds, a great deal of research has been focused on titanium-based complexes, whose cytotoxic activity against solid tumors is well known.

Budotitane, [*cis*-diethoxybis(1-phenyl-1,3-butanedionato)-titanium(IV)], proved to be very promising in the preclinical evaluation phase, but did not pass phase I clinical trials, due to its rate of hydrolysis.[7]

Titanocene dichloride (Cp_2TiCl_2), (Fig. 1a), is much more resistant in this respect, shows moderate antiproliferative activity in vitro, but promising results in vivo,[8,9] reaching phase II clinical trials. Unfortunately, its efficiency in patients with metastatic renal cell carcinoma or metastatic breast cancer was too low to be pursued.[10,11] As proposed by Sadler and co-workers, titanocene dichloride is able to interact with DNA, binding to phosphate groups instead of binding to nucleotides and nitrogen bases, as does *cisplatin*.[12] Moreover, the titanium(IV) ion, by binding to specific iron(III), forms a strongly-bound complex with transferrin, a protein of human plasma, and thus it is supplied to tumor cells as this complex.[12]

A lot of analogues of titanocene containing aromatic groups linked to the Cp have been synthesized.[13] One of the most interesting of this series, is bis-[(*p*-methoxybenzyl)cyclopentadienyl]-titanium-dichloride (titanocene Y), shown in Figure 1a. Its antiproliferative activity was studied in 36 human tumor cell lines[14] and in explanted human tumors.[15–17] In vitro and ex vivo experiments show that prostate, cervix and kidney tumors are a major target for this novel class of titanocene. Furthermore, titanocene Y has been tested on MCF-7 breast cancer cells, revealing a promising medium–high cytotoxic activity with IC_{50} values of 76 μM.[16]

The oxalate complex obtained from titanocene Y by a simple anion exchange reaction was reported to have 13-fold increased activity in relation to titanocene Y during in vitro studies against the LLC-PK pig kidney cells.[14]

Recently, some of us have reported the synthesis and cytotoxic activity of some titanocene complexes. We have also verified, by substituting chlorine atoms, the influence of other leaving ligands on the activity of the complexes.[18] Some of the synthesized compounds showed a good cytotoxicity, in particular, the complexes bis-[methoxy-ethenyl-cyclopentadienyl]-titanium-dichloride (**T_2**) and [methoxy-ethenyl-cyclopentadienyl]-titanium trichloride (**T_1**) (Fig. 1a) gave IC_{50} values very similar to *cisplatin* on MCF-7, comparable to the ones reported for titanocene Y.[19,20]

Complex **T_1** has been the first example of half-titanocene complex with interesting cytotoxic activity. Therefore, lately, we have synthesized a series of novel half-titanocene complexes and tested them for their regulatory effects on MCF-7 and SkBr3 breast cancer cells.[19] Some of these compounds elicited relevant repressive effects on both cell lines if compared to *cisplatin*. These data provide

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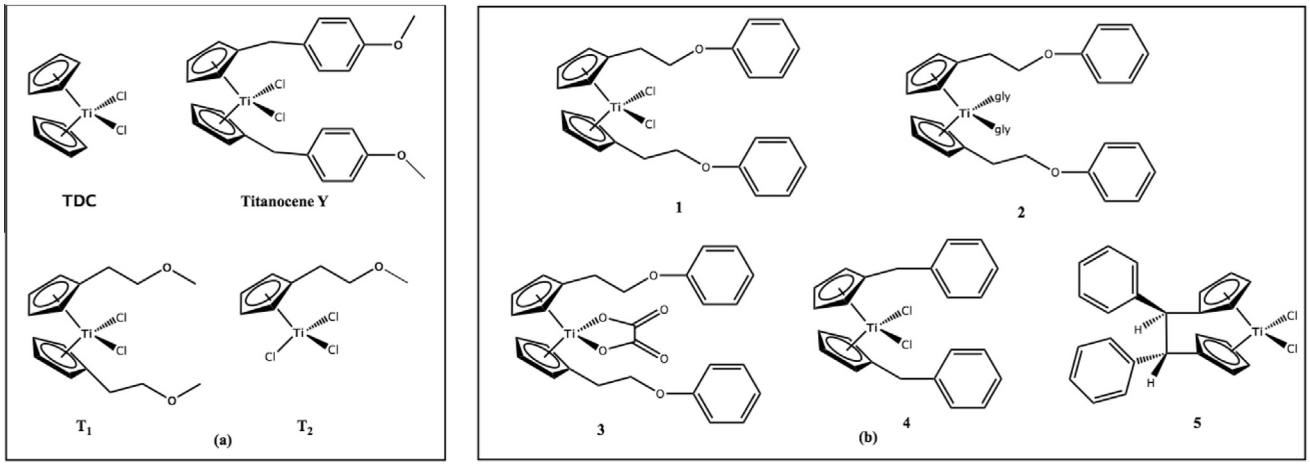
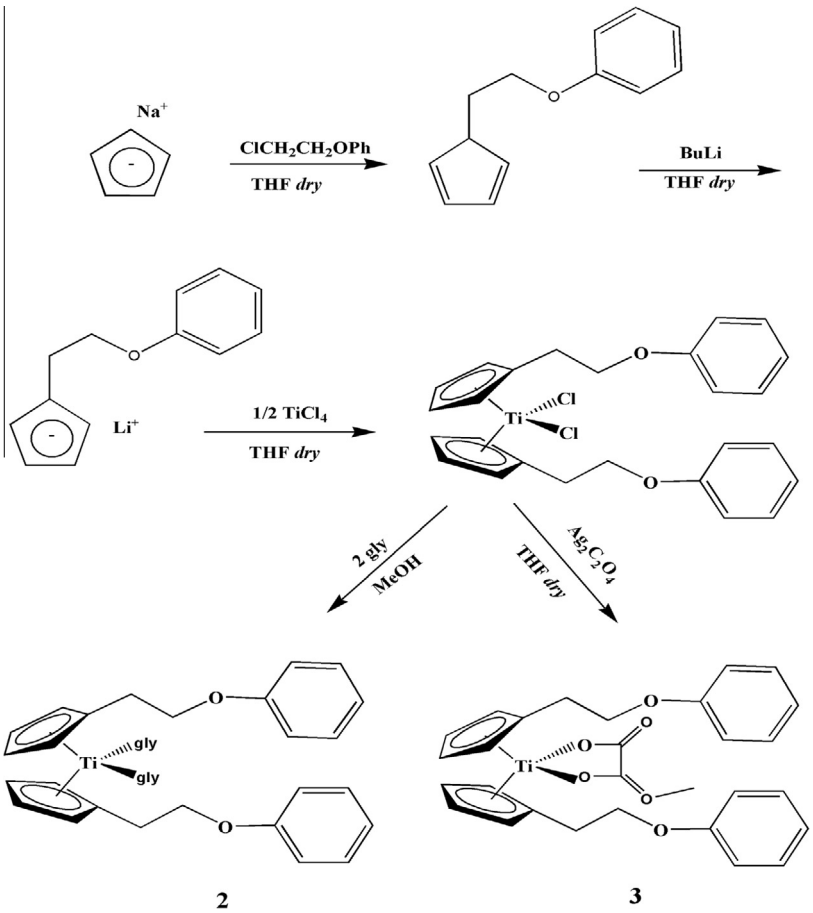


Figure 1. (a) Titanocene dichloride (TDC); bis-[(*p*-methoxybenzyl)cyclopentadienyl]titanium dichloride (titanocene Y); bis-[methoxy-ethenyl-cyclopentadienyl]-titanium-dichloride ($\mathbf{T_2}$) and [methoxy-ethenyl-cyclopentadienyl]-titanium trichloride ($\mathbf{T_1}$); (b) structures of synthesized complexes.

evidence that the presence of coordinating groups on cyclopentadienyl ring (substituted aryl or even the phenyl itself) are important for the biological effectiveness of these compounds.[19]

In order to understand if different ether groups can influence the intramolecular coordination and consequently the stability of the titanocene complexes and whether the ether group is essential for their cytotoxic activity, we synthesized several new-titanocene complexes (Fig. 1b), having as ligands the 2-cyclopentadienyl-ethoxy-benzene [Cp-CH_2CH_2-O-Ph] or the cyclopentadienyl-benzyl [Cp-CH_2-Ph], and we evaluated their potential antiproliferative effects on MCF7 and SkBr3 breast cancer cells.

In particular, the aim of this paper is to report the synthesis and the characterization by nuclear magnetic resonance (NMR), mass spectroscopy and elemental analysis of bis-[2(cyclopentadienyl-ethoxy-benzene)]-titanium-dichloride (**1**) and of the homologous complexes obtained by the substitution of chlorides with glycinate (**2**) and oxalate (**3**) and of bis-cyclopentadienyl-benzyl-titanium-dichloride (**4**). In addition we have also synthesized the



Scheme 1. Synthetic route for the preparation of ligands and complexes **1**–**3**.