New titanocene complexes inhibit human topoisomerase I and II and induce MCF-7 cells death by apoptosis

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The remarkable antitumor activity shown by many platinum complexes has produced a strong interest in research of new organometallic compounds having pharmacological anticancer action. Among the many metal compounds synthesized and tested, those based on titanium have received considerable attention because of their cytotoxic activity against solid tumors. For instance, the titanocene dichloride (Cp_2TiCl_2), resulted very promising in preclinical evaluation phase, but did not pass the phase I and II clinical trials because of its modest efficacy in patients with metastatic renal cell carcinoma or metastatic breast cancer. Differently from *cis*-platinum, the mechanism of action of titanocene dichloride, as proposed by Sadler and coworkers, involves the interaction with the phosphate groups of DNA, instead of nucleotides and nitrogen bases. Thus, the results obtained with Cp_2TiCl_2 allowed significant research activities in the development of new titanium complex with higher cytotoxic activity. These properties were improved by titanocene derivatives having polar side chain attached to the Cp ligands, *e.g.*: alkoxo, amino or carboxylic acid and esters chains. Moreover, the scientific research have been directed toward the development of titanocenes containing aromatic groups linked to the Cp. One of the most interesting of these compounds is the titanocene Y (bis-[(p-methoxybenzyl)-cyclopentadienyl]-titanium-dichloride), which revealed promising medium-high cytotoxic activity on breast cancer cell line MCF-7. Titanocene complexes obtained by replacing the substituent methoxy-aryl of cyclopentadienes of titanocene Y with ethenyl-methoxide or ethenyl-phenoxide were recently synthesized and tested. These substitutions with groups more strongly coordinating and therefore able to more effectively stabilize the cationic species have been proved to increase their cytotoxic activities. Taking into account these considerations, we synthesized new titanocene complexes holding lipophilic groups (for instance a methyl group on benzyl carbon) in order to improve their performance against some tumor cell lines with respect to already reported complexes with cyclopentadienyl-benzyl ligands. Other substitutions have been made, introducing a 5-methoxy naphthyl group to further stabilize the titanocene complexes and give, possibly, a greater capacity coordinating to the reactive sites of DNA. These new complexes have been tested on breast cancer cell lines MCF-7 and normal breast cell line MCF-10A. The obtained results showed a good antiproliferative activity on breast cancer cells, for some of the tested compounds, together with lower toxic effects on normal breast cells, compared to *cis*-platin. These effects could be ascribed to the inhibition of human topoisomerase I and II activity, as confirmed by a specific enzymatic assay. Further studies are needed to clarify the detailed molecular mechanism underlying breast cancer cell death.