

## Abstract

*Despite the discovery of cis-platin in the treatment of cancer there has been a considerable exploration on the antitumoral activity of other transition metal complexes. One of the main problems about the application of transition metal complexes for chemotherapy is their potential toxicity. For instance, recently the attention has been focused on titanium based complexes, which could have significant potential effect against solid tumor. The advantage of Ti(IV) complexes is their relative biological compatibility, which mostly leads to mild and revisable side effects. However, the hydrolytic instability of known Ti(IV) complexes and formation of various different species upon water addition makes their therapeutic application problematic, and raises a strong interest in the development of relatively stable Ti(IV) complexes with well defined hydrolytic behavior that demonstrate appreciable cytotoxic activity. Strong ligand binding is also of interest to avoid complete ligand stripping by transferrin, so that the ligand may be used as a target for structure–activity relationship investigations.*

*Titanocene dichloride (Cp<sub>2</sub>TiCl<sub>2</sub>) shows an average antiproliferative activity in vitro but promising results in vivo. Considerable work has been performed in developing therapeutic analogues of Cp<sub>2</sub>TiCl<sub>2</sub> by varying the central metal, the labile ligands (Cl) and the bis-cyclopentadienyl moiety. In particular, small changes to the Cp ligand can strongly affect the hydrolytic stability and water solubility properties of the metallocenes and have an impact on the cytotoxic activity.*

*For a better exploration of the parameters affecting activity and its mechanistic aspects, the synthesis and investigation of particularly designed complexes based on different strongly coordinating ligands has been our main purpose*

*We synthesized novel titanocene and half-titanocene derivatives, having substituted cyclopentadienyl ligands; all the complexes have been fully characterized by NMR, elemental analysis and MS. Additionally we studied the rate of hydrolysis of these complexes. Starting from the reflection that the different activities of the complexes could be related to their different stabilities, the hydrolysis stability represents a first possible indication on the achievable cytotoxic effects of synthesized compounds.*

*The synthesized compounds have been evaluated for their cytotoxic potential against cancer cell lines. Most of these compounds showed significant anti-proliferative effects compared to cisplatin*