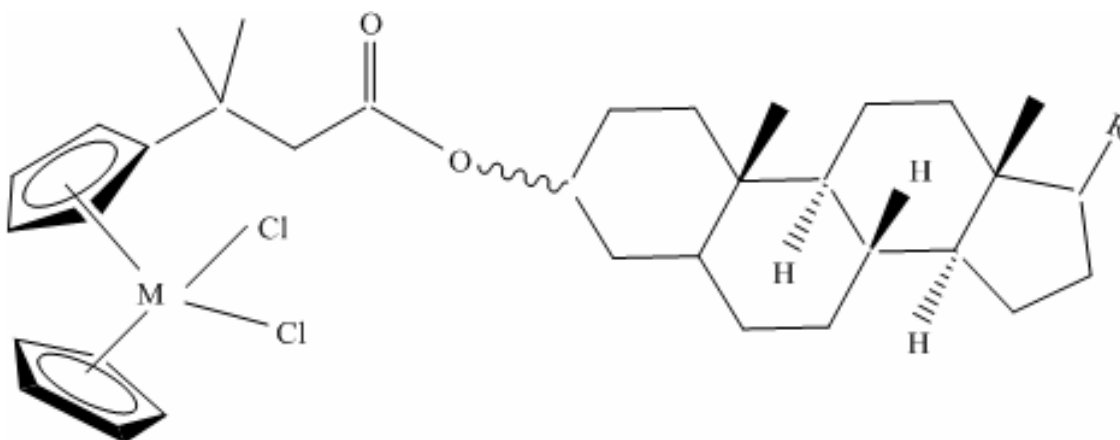


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Design of Metallocene Anticancer Agents

Meléndez's research work entails the design of metal-based drugs and organometallic biosensors. New metallocene drugs which target specific tumors and receptors are developed as tools for treating cancers. To achieve this, steroidal hormones (estrogen, androgen and progesterone derivatives) are attached as pendant groups to the corresponding metallocene, Scheme I. In principle these metallic species will be *target specific drugs* toward hormone dependant cancers such as breast, ovarian and prostate. The mechanistic aspects of these species are studied by spectroscopic methods, molecular modeling and molecular biology methods, and the latter in collaboration with Dr. Matta laboratory as explained below. We examine the binding of drugs to biomolecules such as proteins and oligonucleotides using a wide variety of physical and analytical techniques such as CD, UV-Vis, fluorescence and 2D NMR spectroscopies and electrochemical methods. To explain the experimental results, we use molecular modeling methods.



Scheme I. General structure of metallocene-steroid complex, M = Ti, V, Mo.

In this collaborative project with Dr. Matta laboratory, cytotoxicity and DNA Microarray studies are being performed on the modified complexes to establish structure-activity relationship. Through an active collaboration involving Dr. L.M. Gao; postdoctoral researcher in Dr. Melendez laboratory, and three of his graduate students (Dr. Ramon Hernandez, Idaines Feliciano (M.S.), José Vera (M.S.) and Deborah Acevedo (B.S.) five papers have been published in peer-reviewed international journals, please see publications. Our structure-activity study on these metallic drugs has allowed us to pinpoint which pendant groups are important to improve their anticancer activity.

Publications

1. "Synthesis, Ti(IV) intake by apotransferrin and cytotoxic properties of functionalized titanocene dichlorides" L-M. Gao, R. Hernández, J. Matta and E. Meléndez J. Biol. Inorg. Chem. **2007**, 12(7), 959-967.

2. "Structure-Activity Studies of Ti(IV) Complexes: Aqueous Stability and Cytotoxic properties in colon cancer HT-29 cells" R. Hernández, J. Lamboy, L.M. Gao, J. Matta, F. R. Román¹ and E. Meléndez. *J. Biol. Inorg. Chem.* **2008**, 13, 685-692.
3. "Synthesis, Structure, Electrochemistry and Cytotoxic Properties of Functionalized Ferrocenes" L.M. Gao, R. Hernández, J. Matta and E. Meléndez. *Metal Based Drugs* **2009**, Article ID 420784.
4. "Water-soluble molybdenocene complexes with both proliferative and antiproliferative effects on cancer cell lines and their binding interactions with human serum albumin" I. Feliciano, J. Matta and E. Meléndez. *J. Biol. Inorg. Chem* **2009**, 14(7):1109-17.
- 5.. "Synthesis, Structure and Biological Activity of Amide-Functionalized Titanocenylys: Improving their Cytotoxic Properties" L.M. Gao, J. Matta, A. Rheingold and E. Meléndez. *J. Organometal. Chem.* **2009**, 694, 4134.