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Review

Metallocenes as target specific drugs for cancer treatment

Enrique Meléndez *

University of Puerto Rico, Department of Chemistry, P.O. Box 9019, Mayagüez, PR 00681, USA

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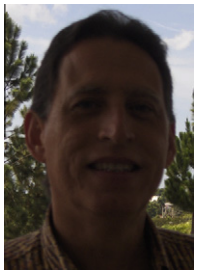
ABSTRACT

The application use of organometallic compounds into the cancer research was established in the late 1970s by Köpf-Maeir and Köpf. This new research area has been developed for the past 30 years. In the early 1980s, Jaouen and coworkers recognized the potential application of organometallic compounds vectorized with pendant groups that can deliver the drug to certain specific receptors. This is what is called nowadays target specific drugs. This review will focus on metallocenes vectorized with steroids derivatives of hormones, nonsteroidal and selective endocrine modulator.



Enrique Meléndez's research work entails the design of metal-based drugs and organometallic biosensors. New metallocene drugs for target specific tumors are developed as tools for treating hormone-dependent cancers. To achieve this, steroidal hormones (estrogen, androgen and progesterone derivatives) are attached as pendant groups to the corresponding metallocenes. The mechanistic aspects of these species are studied by spectroscopic methods such as NMR, UV–Vis, Fluorescence spectroscopy, electrochemistry and Molecular Modeling techniques. Another area of interest, in collaboration with the Material and Engineering Department, is the development of electrochemical biosensors. The principal objective of this work is to develop an electrochemical biosensor based on conducting polymers electrode functionalized with ferrocene to detect substrate such as glucose and other biologically important analytes.

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* Tel.: +1 787 832 4040x2524; fax: +1 787 265 3849.
E-mail address: enrique.melendez@upr.edu

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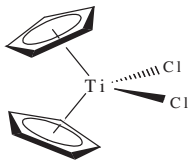
1. Introduction

The first report on the anti-tumor properties of titanocene dichloride (**I**), Cp_2TiCl_2, (Scheme 1) in 1979 by Köpf-Maier and Köpf, revolutionized the idea regarding metal-based drugs and the previous concept that organometallic complexes, under aqueous and physiological media and their application to biology and medicine were incompatible [1]. This report opened a new exciting area of research: BioOrganometallic Chemistry. In the early 1980's, Köpf-Maier and Köpf continued investigating the biological activity of other metallocenes and found that many metallocenes such as Cp_2MX_2 (M = Ti, V, Nb, Mo; X = halides and pseudo-halides), Cp_2Fe^+ and main group $(C_5R_5)_2M$ (M = Sn, Ge; R = H, CH_3) exhibited anti-tumor activity against a wide variety of tumor cells (among them Ehrlich ascites tumor, B16 melanoma, colon 38 carcinoma, Lewis lung carcinoma) with less toxic effects than the well reputed cis-platin [2–7]. Cp_2TiCl_2 was the most active species in colon, breast and lung cancers reaching phase I and II clinical trials [8–12] but its low response in metastatic cancers discourage its further investigation and the clinical trials were abandoned.

In the subsequent years, different strategies were pursued by several research groups to modify structure and improve anti-tumor activity from replacing X ancillary ligands with hydrophilic one to functionalization of the Cp ring with hydrophobic or hydrophilic groups and bioactive molecules. The last strategy has been very attractive to tailor organometallic complexes with predetermined properties. Perhaps the most exciting among these strategies is the functionalization of the Cp ring with pendant groups to develop target specific drugs. In particular, pendant groups that can be recognized by a receptor and function as an antagonist to certain types of hormone dependent cancers have attracted the attention of various investigators. Currently, there are several organic compounds as selective receptor modulators (SRM) to cancers with high receptor expression, in particular to hormone dependent such as breast, ovarian and prostate cancers [13–18]. In a similar manner, metal-based drugs that either behaves as SRM or antagonist to these receptors can be developed and it is the subject of this review.



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Scheme 1.

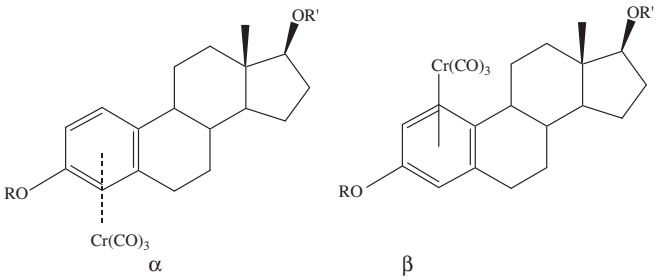
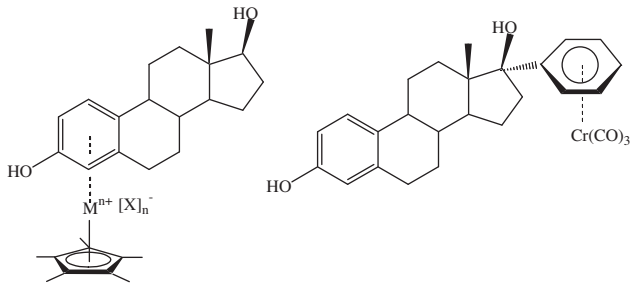
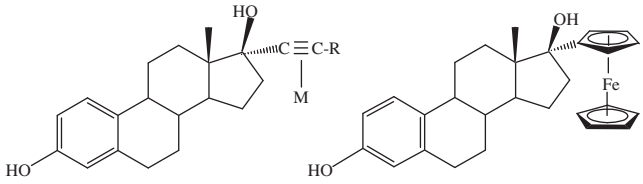


Fig. 1. α- and β-(3-*O*-R-l7β-*O*-R′-Estradiol)$Cr(CO)_3$ diasteroisomers.



M = Ru, Rh; X = CF_3SO_3, PF_6, BF_4

Fig. 2. Structures of organometallic-labeled estradiol at the A-ring (left) and 17α-position of the 17β-estradiol.



M = $Co_2(CO)_6$, $Mo_2Cp_2(CO)_4$, $Os_3(C)_{10}$, $Ru_3(CO)_{10}$

R = H, Me

Fig. 3. Structures of 17α-organometallic labeled 17β-estradiol.

2. Target specific drugs for breast and prostate cancers

2.1. Precedents: an overview

The idea of target specific drugs relies heavily on the fact that certain cancers, in the initial stages, express higher amount of hormone receptor. The principle is to synthesize a species that can be recognized by the receptor and behaves as an antagonist, impairing the receptor function. Certain structural scaffolds and properties are needed to obtain this property. The most important one are the organic moiety that can be recognized by the receptor and the organometallic group that can express its cytotoxic activity and impair the protein function.

The idea of incorporating an organometallic functionality to a hormone was originally explored in the early 1980's by Jaouen and coworkers and the precedents discussed in this Overview section belongs exclusively to G. Jaouen research. We discuss in this

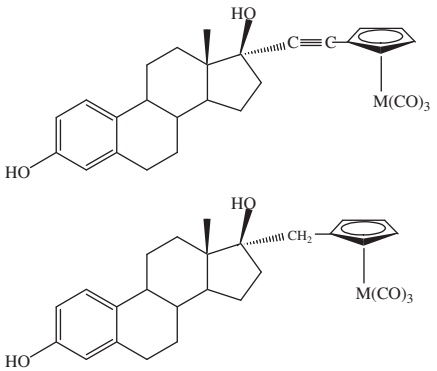


Fig. 4. Structure of 17α-[(R-C_5H_4)$M(CO)_3$]-17β-estradiol. M = Mn, Re; R = CH_2, C_2.