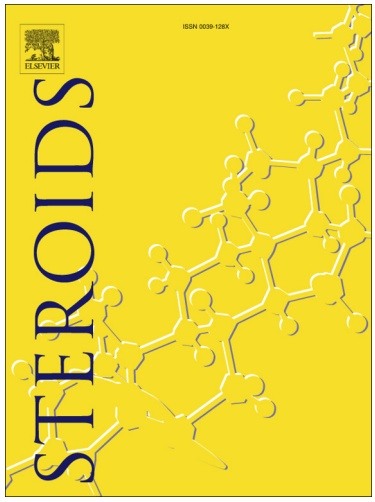

Catalytic cyclometallation in steroid chemistry V: Synthesis of hybrid molecules based on steroid oximes and (5Z,9Z)-tetradeca-5,9-dienedioic acid as potential anticancer agents

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Catalytic cyclometallation in steroid chemistry V[1]: Synthesis of hybrid molecules based on steroid oximes and (5Z,9Z)-tetradeca-5,9-dienedioic acid as potential anticancer agents

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ABSTRACT *Synthetic analogues of natural 5Z,9Z-dienoic acids - hybrid molecules based on the oximes of cholesterol, pregnenolone, and androsterone with 1,14-tetradeca-5Z,9Z-dienedicarboxylic acid - were synthesized for the first time and studied for antitumor activity in vitro. The acid was prepared using catalytic cyclomagnesiation of O-containing 1,2-dienes with Grignard reagent in the presence of Cp_2TiCl_2 as the key step. Using flow cytometry, it was shown for the first time that the new molecules are efficient apoptosis inducers in the HeLa, Hek293, U937, Jurkat, and K562.*

Key words: Cross-cyclomagnesiation; Grignard reagents; Steroid oximes; 5Z,9Z-Dienoic acids; Anticancer activity.

1. Introduction

According to published data [1], aliphatic 5Z,9Z-dienolic acids isolated from marine invertebrates possess a broad spectrum of biological activities such as antimalarial, antibacterial, and antifungal activities. In addition, 5Z,9Z-dienoic acids exhibit high inhibitory activity against human topoisomerases I and IIα [2-6], which are considered as intracellular targets of chemotherapeutic agents that prevent the break repair and thus cause accumulation of damaged DNA molecules and promote tumor cell death [7].

In recent years, more and more publications have addressed the use of cytotoxic steroids for the treatment of cancer; most of these steroids are hybrid molecules in which the cytotoxic substituent in linked to one functional group of the steroid [8-10]. In these molecules, the steroid moiety functions as a cytostatic transport, owing to its lipophilic properties and the ability to easily penetrate the lipid bilayer of biological membranes, thus providing access to definite target proteins and increasing the selectivity of drug action. The results indicate that the direct

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