ABSTRACT

Charles University

Faculty of Pharmacy in Hradec Králové

Department of Pharmaceutical Chemistry and Pharmaceutical Analysis

Author: Katharina Zenkerová

Supervisors: Assoc. Prof. PharmD. Jan Zitko, Ph.D.; Prof. Romano Silvestri

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Cancer is a major burden of disease worldwide and it remains one of the most difficult illnesses to treat. Since the percentage of people suffering from cancer is increasing, an enormous effort to design and develop better medicaments is needed.

Microtubules are a key component of the cytoskeleton in most eukaryotic cells and they represent an attractive target for antitumor agents, due to the significant mitosis rate of tumor cells. Since cancer cells usually display higher proliferation rates than normal cells, drugs that interfere with microtubules dynamic equilibrium, also known as antimitotic agents, have become a fruitful approach to develop anticancer agents in clinical use. In fact, agents interfering with microtubules may either inhibit the tubulin polymerization or block microtubules to disassembly, both causing the arrest of cell division and the consequent cell death.

Over the years, a series of compounds, bearing a pyrrole nucleus in their structure, were found to be effective as inhibitors of tubulin assembly. In this context, professor Silvestri et al. have recently described 3-aroyl-1-arylpyrrole (ARAP) derivatives as a new class of potent inhibitors of tubulin. Encouraged by this promising result, the present thesis project is based on the development of new ARAP derivatives with the aim to improve the inhibition of both tubulin assembly and MCF-7 cancer cells growth, by binding the colchicine binding site. Three ARAP derivatives, differently substituted

at positions 1 and 3 of the pyrrole nucleus, were synthesized. The synthetic scheme is based on five different steps.

The first step of the preparation of new ARAP compounds was the Friedel-Craft reaction between 1 (p-Tolylsulfonyl)pyrrole and the appropriate benzoylchloride in dichloromethane, in the presence of anhydrous aluminum chloride at room temperature for 20 min under Argon stream. The resulting acyl intermediate was then hydrolyzed using NaOH 6 M, in ethanol at 80 °C for 4 hours to obtain the appropriate acyl-pyrrole compound. Finally, the acyl-pyrrole intermediate was dissolved in dioxane and it was treated with the suitable protected purine base (previously synthesized) in the presence of cesium carbonate, copper iodide and phenanthroline. The reaction was then heated at 110 °C overnight under Argon to obtain the protected final compound. Subsequent cleavage of the silyl protecting group with trifluoroacetic acid in dichloromethane at room temperature led to the desired ARAP compound. The protected purine base was synthesized treating the suitable purine base with trimethylsilyl chloride in dichloromethane at room temperature overnight.

The activity of this novel small library of 3-aroyl-1-arylpyrrole derivatives will be evaluated on tubulin polymerization *in vitro*, the binding of [^{3}H]colchicine to tubulin and on the MCF-7 breast cancer cell growth.