Abstract

Charles University

Faculty of Pharmacy in Hradec Králové

Department of Pharmaceutical Chemistry and Pharmaceutical Analysis

Student: Martina Hoppová

Supervisors: PharmDr. Marta Kučerová, Ph.D.; Dr. Rafael Peláez Lamamie de Clairac Arroyo

Title of diploma thesis: Synthesis of new antimitotic agents

Cancer is one of the main causes of death all around the world and therefore the development of new chemotherapeutic drugs is one of the major areas of pharmaceutical research. The effort is to obtain an agent that would be highly effective, target the neoplastic tissue, and have advantageous pharmacological properties and minimum side effects.

Rapid proliferation is one of the main features of cancerous growth, thus influencing mitosis as the phase of cell division may be a convenient way for cancer treatment. Tubulin is a protein, which rapidly polymerizes into microtubules and again depolymerizes and beside others it forms mitotic spindle during mitosis, and according to its important role, tubulin is an attractive target for antitumoral agents. Many drugs inhibiting polymerization or stabilizing already formed microtubules are actually in clinical practice, and research regarding new antimitotics interacting with tubulin is going on at the same time. Such an example is natural combretastatin A-4 binding to the colchicine binding site in tubulin and its numerous synthetic analogues under investigation.

The aim of this work is the synthesis and evaluation of compounds that are supposed to be hybrids of tubulin inhibitors (naphthalenesulfonamides) and alkylphospholipids (alkylphosphonates esterified with alcohols with several polar heads: 2-(dimethylamino)ethan-1-ol, 1-methylpiperidin-4-ol, choline, and 3-(diethylamino)propan-1-ol), designed as dual anticancer agents. The alkylphospholipids are less potent but more water-soluble agents. The effort of this work was therefore to prepare effective agents with good aqueous solubility and targeting the cancerous tissue.

This work is based on a five-step synthetic procedure, which starts with the synthesis of naphthalenesulfonamide and their alkylation with α,ω-dihalogenated alkanes with four to six carbons. The terminal halogens react subsequently with triethyl phosphite to yield the corresponding ethyl phosphonates which are hydrolyzed to the phosphonic acids and re-esterified. All the products were purified, characterized, and submitted for biological evaluation,

except some 1-methylpiperidin-4-ol and choline esters which could not be completely purified. The synthetic route efficiently affords the products.