

PhD Program	MEDICINAL CHEMISTRY
Project title:	Preparation of peptide-enediyne conjugates and their potential as DNA cleaving agents.
Research field:	The research project involves synthesis of novel amino acid- and peptide-derived enediyne compounds, investigation of their activity (in the presence of proton donors, metal ions, pH or thermally induced) and DNA-cleavage potential.
Institution where the experimental work will be performed	Ruđer Bošković Institute 10000 Zagreb, Bijenička 54 http://www.irb.hr/en/str/zokb/labs/05_upg/
Supervision	Dr. Ivanka Jerić
Achievement	The candidate will acquire broad knowledge in organic synthesis, spectroscopy and mass spectrometry. That should in turn enable candidate after obtaining a PhD degree to find either academic position in one of these fields, or in chemical or pharmaceutical industry.
Abstract	<p>Chemotherapy is usually the first choice for the treatment of many cancer types. According to the American Cancer Society, more than 100 drugs are currently used for chemotherapy, alone or in combination with other drugs or treatments. Many more have been developed as anticancer drug candidates, but only a few of them are expected to come into clinical practice. These drugs vary widely in their chemical composition, how they are taken, their usefulness in treating specific forms of cancer, and their side effects. The majority of anticancer drugs affects cell division or DNA synthesis and function and can be classified as alkylating agents, antimetabolites, anticancer antibiotics, mitotic inhibitors and plant alkaloids. Enediyne antibiotics, relatively new class of anticancer agents, are subject of great interest and intensive research among the chemists and biologists since their discovery in the middle 80's. They possess an exceptional biological profile due to the unique molecular structure, striking mode of action and high potency. Their structure can be split into three parts; first part is responsible for recognition and delivery into minor groove of the DNA, second part initiates a cascade of chemical reactions leading to conformational changes of enediyne (Z-hexa-1,5-diyne-3-ene) moiety captured within 9- or 10-membered ring. The conformational changes trigger Bergman cyclization and the formation of 1,4-benzene diradical capable of the DNA double helix breakage. Enediyne anticancer antibiotics are extremely potent DNA cleavers, but highly toxic, so there is urgent need for new enediyne-related structures with maximum activity towards tumor cells and minimum toxicity towards normal cells. Also, structural complexity on natural enediynes calls upon synthetically more accessible analogs.</p> <p>Our scope of research is study of amino acid- or peptide-derived enediynes. Amino acids, as carriers of enediyne moiety, have multiple advantages: they are good complexation ligands, an array of side chains provides easy change of molecule properties (e.g. lipophilicity, acidity) and versatility of functional groups enables binding of other molecules. Therefore, enediyne-amino acid conjugates are important tools in studies of Bergman cyclization, a process underlying enediyne activity. Research includes design and synthesis of enediyne-peptide derivatives, their characterization by spectroscopic and mass spectrometric methods, evaluation of their activity (in the presence of proton donors, metal ions, pH or thermally induced). Compounds with good properties will be tested upon DNA-cleavage potential and antiproliferative activity.</p>