

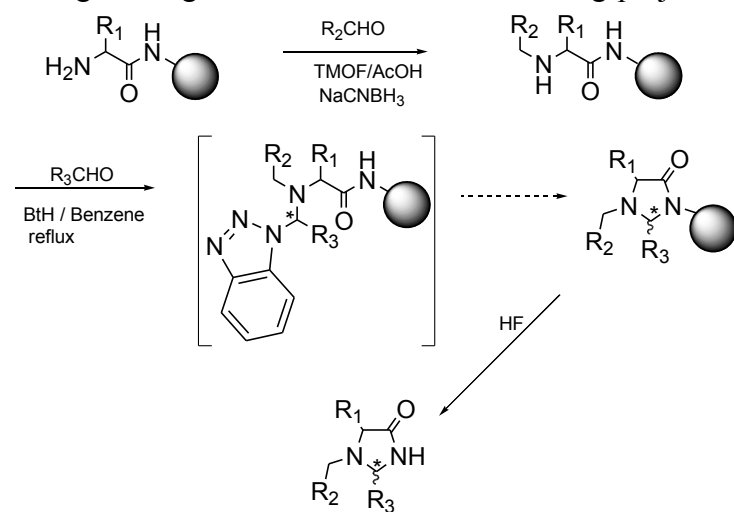
# Research Statement

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My research interests lie in general in the utilizing and developing organic chemistry as a tool to answer questions arising in biomedical and biological disciplines. The most excitement for me comes from useful applications in mapping of biological interactions, targeting biological processes or modifying biological responses, in other words everything that can result in better understanding of life.

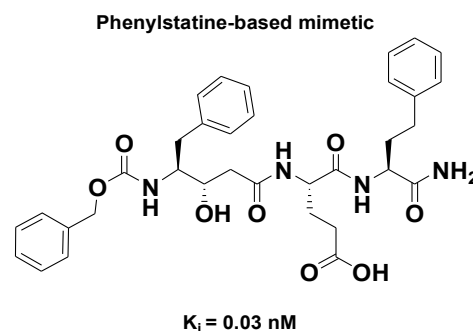
At the beginning of my carrier I got an opportunity to learn basics of peptide chemistry and solid phase methodology on its peak at the time when combinatorial chemistry was born. Back then, before I even considered pursuing a PhD degree, I had participated in the development of several automated synthesizers<sup>1</sup> and performed many methodological experiments using principles of solid phase synthesis. My interest in science was influenced by the inspiring personality of Dr. Michal Lebl, the restless scientist and enthusiastic inventor who later become my PhD mentor. Besides exploring alternative solid supports (e.g. cotton carrier<sup>2</sup>) for solid phase and combinatorial synthesis I was experimenting with various cleaving<sup>3</sup> and coupling<sup>4</sup> methods for solid phase synthesis.

Since the beginning, my research has always been centered on applications. Learning about interesting biological properties of peptides<sup>5</sup> initiated my interest in peptidomimetic molecules. Peptidomimetics are a remarkably interesting class of compounds that are designed to take shape of naturally occurring peptides with modified properties, mainly improved stability while maintaining or enhancing biological activity. Design and development of peptidomimetics is a classical process of medicinal chemistry that can be focused on a large variety of biological targets. One of the most interesting projects I had been involved in was targeted on finding



*Scheme 1* Solid phase synthesis of 1,2,5-trisubstituted 4-imidazolidinones

libraries featuring peptidomimetic moieties as reduced bond, hydroxyethylene isostere, phenylstatine and



*Figure 1* The most potent inhibitor identified in the library (inhibitory activity against wild type HIV-1PR).

novel inhibitors of HIV-1 protease mutants<sup>6</sup>. Drug resistant mutants primarily isolated from patients carried resistance to clinically used and FDA approved protease inhibitors such as Ritonavir, Indinavir and Saquinavir. HIV-1 protease is profound for its ability to mutate so that with each new inhibitory drug a new resistant mutant of the protease is generated. The project was collaboration between the group of Dr Thomas Klimkait in the Institute of Medical Microbiology in Basel, Switzerland and the group of Dr Jan Konvalinka in the Institute of Organic Chemistry and Biochemistry in Prague, Czech Republic. I was invited to design structures of peptidomimetics and execute chemistry tasks. Several narrowly focused

phenylnorstatine were synthesized on solid phase. They were screened and evaluated using combinatorial deconvolution methods. Several novel inhibitors were identified with high inhibitory activity and little or no specificity for individual mutated strains (Fig. 1 shows the best hit identified in the library). This project gave me a greatly positive experience with team work in an international interdisciplinary environment.

When I accepted a postdoctoral position with Dr Richard Houghten at the Torrey Pines Institute for Molecular Studies (TPIMS) in San Diego, I continued to pursue my interests in peptidomimetic chemistry. Scientific freedom of the institute with its enigmatic founder provides excellent environment for research. This time a motif of an imidazolidinone-constrict that forces a peptide to change its conformation was my main focus. At first we developed a method based on solid phase synthesis<sup>7</sup> (Scheme 1) providing a reliable tool to generate combinatorial libraries<sup>8</sup>. Screening of the libraries against various targets is one of the central functions of TPIMS. I was personally interested in how the incorporation of this moiety will affect opioide activity of peptide-ligand Leu-enkephalin<sup>9</sup>. Five positional analogs of Leu-enkephalin were designed and synthesized. The strongest effect was observed for an analog with C-terminal backbone constriction that gives bioactive conformation improving binding ( $K_i = 4$  nM, compare to 24 nM of Leu-enkephalin) (Fig.2).

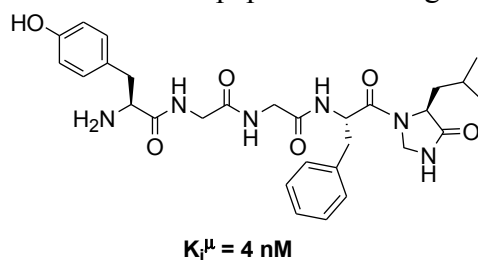
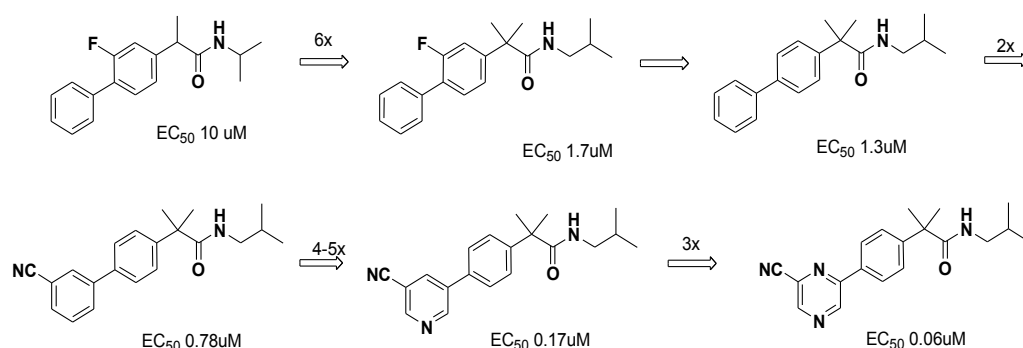


Figure 2 The most potent Leu-enkephalin analog (activity on  $\mu$ -opioid receptor).

In the process of searching for challenging opportunities in biotech rich San Diego, I found myself interested in trying industrial environment. I accepted a position with Senomyx, Inc., a company focused on development of “taste enhancers”. The company created proprietary taste receptor-based assay systems using isolated human receptors for umami and sweet taste (GPCR family). The program involved initial process of vast library screenings, followed by lead optimization and medicinal chemistry structure-activity studies. Since I was engaged with the company from early beginning, I could enjoy all the transformations the chemistry group went through. Most of the time I spent as a medicinal chemist and my most fruitful project was optimization of sweet agonists based on biaryl scaffold<sup>10</sup> (Scheme 2 and 3). Work at the company resulted in several patents covering novel sweeteners with nanomolar activities, umami compounds and also compounds enhancing sweet taste with no sweetness on their own.

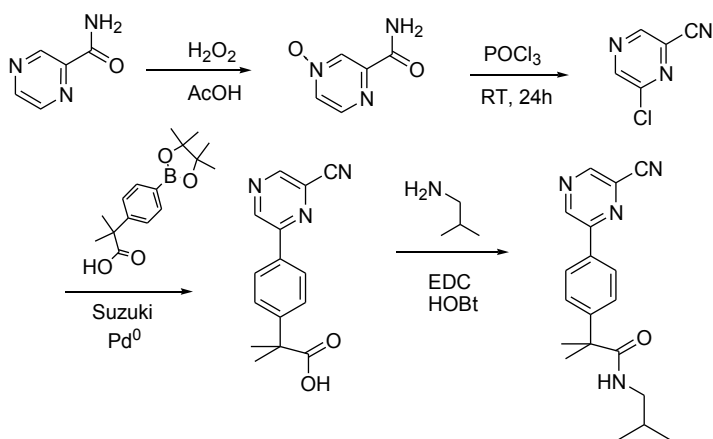


Scheme 2 Optimization of sweet agonist in biaryl series

To better describe my synthetic experience I have to mention that in the time between finishing PhD and starting the postdoc overseas I joined a group of Dr Ivan Rosenberg at the

Institute of Organic Chemistry and Biochemistry in Prague, Czech Republic as a scientist. This well established group is focused on chemistry of nucleotides and nucleosides. I took an opportunity to learn more synthetic organic chemistry and started development of pyrrolidine analogs of nucleosides<sup>11</sup>.

Recently I have joined the group of Dr John A. Katzenellenbogen at the University of Illinois at Urbana-Champaign. I have been given an opportunity to enjoy again an academic environment and close contact with students. Dr Katzenellenbogen group research is focused on the study of estrogen receptors (ER $\alpha$  and ER $\beta$ ), their function and regulation. Main synthetic directions include steroid hormone analogs, design of small molecule ligands, radiolabeled compounds for PET imaging studies, and also novel structure and hormone-dendrimer conjugates. Working on several projects in this group enriched my experience and refreshed my spirit. I have realized my ambition as an independent researcher that I would like to pursue. Ideally, my research would be focused on peptidomimetics. The key aspect would be identification of novel peptidomimetic structures and evaluation and optimization of their biological activities. I still maintain several active collaborations with experimental groups with unique biological targets and established testing methods (Dr Jiri Jiracek - Betaine-homocysteine methyl transferase, Dr Martin Fusek – Cathepsin D, Dr Jan Konvalinka – HIV-1PR, Human Glutamate Carboxypeptidase II, Dr Richard A. Houghten – several research areas). The research would include the whole process from design of potentially bio-active compounds, to structure-activity relationship studies and structure optimization. Involving all modern tools based on biological data, crystallographic experiments or molecular modeling, in other words available tools of medicinal chemistry. I am a big fan of team work and interdisciplinary collaborations. I would like to implement these principles in my research.



*Scheme 3 Synthetic scheme for preparation of the top sweetener*

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