Bureš lecture

„New Approaches to Drug Design: Multivalency in Drug Design for the Disease State"

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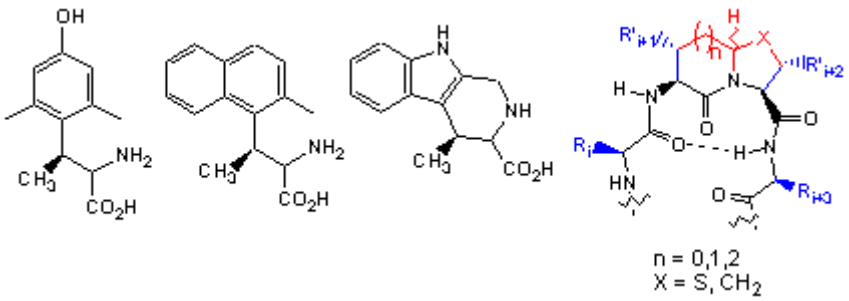
Information about the speaker:

The research group of Prof. Hruby is oriented to the design, synthesis, analysis, conformations, dynamics and structure-biological activity relationships of biologically active peptides and peptide mimetics with special interests in hormones and neurotransmitters that affect human behavior. They are interested in the rational design of anti-hormones (inhibitors) based on conformation, in hormone and neurotransmitter receptors (GPCRs), in brain chemistry, in the design and asymmetric synthesis of conformationally constrained amino acids, peptides and peptide mimetics, and in the use of NMR and other physical methods to examine peptide and peptidomimetic conformations. They seek to understand the physical-chemical basis for information transduction and for these important molecules in biological systems, and utilize synthetic organic chemistry, structural chemistry, bio-organic chemistry, analytical chemistry, physical chemistry, and biology to examine the relationships of structure to information transduction. Some projects include:

1. Asymmetric synthesis of topographically controlled amino acids and their derivatives and β-turn mimetics, including the following:



2. Synthesis and conformation-bioactivity relationships of alpha, beta and gamma melanotropins in relation to melanoma cancer, pigmentation, feeding behavior, sexual behavior, energy homeostasis, cardiovascular function, renal function, pain, immune response and learning. Development of conformationally restricted alpha-MSH analogues with extraordinary in vitro and in vivo biological properties including super-potency, super-agonist activity, super-antagonist activity and super prolonged activity. Computer assisted modeling is being used for design of new scaffolds and more potent and selective compounds including agonists and antagonists for several new melanocortin receptors.

3. Design and synthesis of conformationally constrained neuropeptides. Conformationally restricted, cyclic, rigid enkephalin, deltorphin, somatostatin, substance cholecystokinin and dynorphin analogues with high receptor specificity and novel bioactivity profiles are being developed. Using a new design principle, prof. Hruby's group is examining the design of ligands that can treat disease states (e.g. neuropathic pain) by design of ligands with overlapping pharmacophores that can simultaneously interact at different receptor types and with different

pharmacologies. The conformational basis for their selectivity is being investigated as are new analogues that will modulate pain behavior, learning, memory, satiety and other CNS effects. This information is used for de novo peptidomimetic design.

4. Design, synthesis, and biological evaluation of ligands designed to be agonists at μ and/or δ opioid receptors and antagonist at CCK, NK1 or other receptors relevant to prolonged pain, neuropathic pain, tolerance, and drug seeking behavior.

5. Design of multimeric ligands that can act as molecular machines that will recognize the surface of cancer cells, but not of normal cells, for use in medical diagnosis of cancer, molecular imaging, and cancer therapeutics.

Honors

Murray Goodman Scientific Excellence & Mentorship Award, 2011
Arizona Technology Innovator of the Year, 2009
Arthur C. Cope Scholar Award, ACS, 2009
Ralph F. Hirschmann Award, ACS, 2002
Pierce (now Merrifield) Award in Peptide Science, APS, 1993
Doctor Honorus Causa, Free University of Brussels, 1989

Selected Publications from 2002-2011

V.J. Hruby, Designing Peptide Receptor Agonists and Antagonists, Nature Reviews Drug Discovery, 1, 847-858 (2002).

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M. Cai, M. Stankova, S. J.K. Pond, A.V. Mayorov, J.W. Perry, H.I. Yamamura, D. Trivedi, and V.J. Hruby Real Time Differentiation of G-Protein Coupled Receptor (GPCR) Agonist and Antagonist by Two Photon Fluorescence Laser Microscopy, J. Am. Chem. Soc., 126, 7160-7161 (2004).

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D.L. Marks, V.J. Hruby, G. Brookhart and R.D. Cone, The Regulation of Food Intake by Selective Stimulation of the Type 3 Melanocortin Receptor (MC3R), Peptides, 27, 259-264 (2006).

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Molecule Peptide Mimetics Targeting the Melanocortin Receptors, Bioorg. Med. Chem. Letts., 16, 5462-5467 (2006).

T. Yamamoto, P. Nair, P. Davis, S-W. Ma, E. Navratilova, S. Moye, S. Tumati, J. Lai, T.W. Vanderah, H.I. Yamamura, F. Porreca, and V.J. Hruby, Design, Synthesis and Biological Evaluation of Novel Bifunctional C-Terminal Modified for delta/mu Opioid Receptor Agonists and Neurokinin 1 Receptor Antagonists, J. Med. Chem., 50, 2779-2786 (2007).

J. Vagner, L. Xu, H.L. Handl, J.S. Josan, D.L. Morse, E.A. Mash, R.J. Gillies, and V.J. Hruby, Heterobivalent Ligands Crosslink Multiple Cell-Surface Receptors: The Human Melanocortin-4 and δ-Opioid Receptors, Angew. Chem. Int. Ed., 47, 1685-1688 (2008). PMC2716288

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