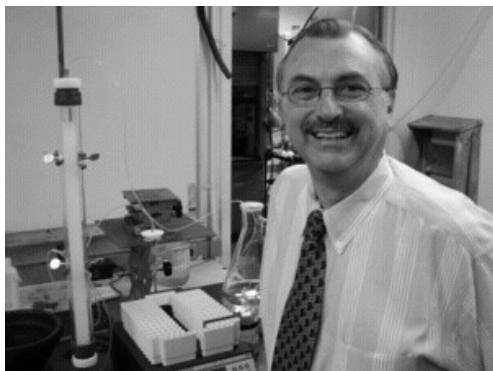


Faculty Profile

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Victor Hruby

Regents Professor Emeritus - Retired

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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 Honoris Causa, Free University of Brussels, 1989

Education and Appointments

- B.S. 1960, University of North Dakota
- M.S. 1962, University of North Dakota
- Ph.D. 1965, Cornell University

Research Interests

- Biochemistry
- Organic
- "Metabolism, Signaling, and Regulation"
- "Theory, Modeling, and Simulation"
- Astrobiology and Astrochemistry
- Bioanalytical
- Bioorganic
- Biophysics
- Chemical Biology
- Protein and Membrane Biochemistry
- Spectroscopy/molecular Structure
- Structural Biology
- Surfaces and Solid State
- Synthesis/Synthetic Methods Development

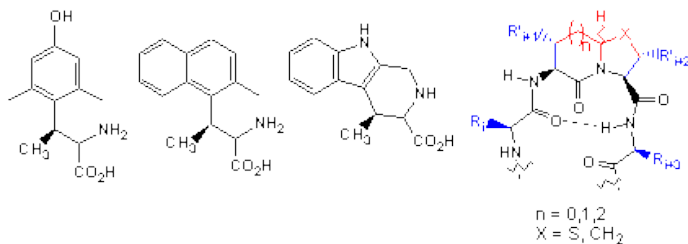
Research Summary

Organic Chemistry, Biochemistry, Chemical Biology and Medicinal Chemistry

Our research group is interested in 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. We are interested in the rational design of antihormones (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. We 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.

We have developed conformationally restricted alpha-MSH analogues with extraordinary in vitro and in vivo biological properties including superpotency, superagonist activity, superantagonist 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 we are 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. We are designing 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.

Selected Publications

- V.J. Hruby, Designing Peptide Receptor Agonists and Antagonists, *Nature Reviews Drug Discovery*, **1**, 847-858 (2002).
- V. J. Hruby, Peptide Science: Exploring the Use of Chemical Principles and Interdisciplinary Collaboration for Understanding Life Processes, *J. Med. Chem.*, **46**, 4215-4231 (2003).
- J. Ying, K.E. Kövér, X. Gu, G. Han, D.B. Trivedi, M.J. Kavarana, and V.J. Hruby, Solution Structures of Cyclic Melanocortin Agonists and Antagonists by NMR, *Biopolymers (Peptide Science)*, **71**, 696-716 (2003).
- 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).
- I.D. Alves, K.A. Ciano, V. Boguslavsky, E. Varga, Z. Salamon, H.I. Yamamura, V.J. Hruby, and G. Tollin, Selectivity, Cooperativity, and Reciprocity in the Interactions Between the δ -Opioid Receptor, Its Ligands, and G-Proteins, *J. Biol. Chem.*, **279**, 44673-44682 (2004).
- V. Subramaniam, I.D. Alves, G.F.J. Salgado, P-W. Lau, R.J. Wysocki, Jr., Z. Salamon, G. Tollin, V.J. Hruby, M.F. Brown, and S.S. Saavedra, Rhodopsin Reconstituted Into a Planar-Supported Lipid Bilayer Retains Photoactivity After Cross-Linking Polymerization of Lipid Monomers, *J. Am. Chem. Soc.*, **127**, 5320-5321 (2005).

I.D. Alves, Z. Salamon, V.J. Hruby, and G. Tollin, Ligand Modulation of Lateral Segregation of a G-Protein-Coupled Receptor into Lipid Microdomains in Sphingomyelin/Phosphatidylcholine Solid-Supported Bilayers, *Biochemistry*, 44, 9168-9178 (2005).

- H.L. Handl, J. Vagner, H.I. Yamamura, V.J. Hruby, and R.J. Gillies, Development of a Lanthanide-Based Assay for Detection of Receptor-Ligand Interactions at the Delta-Opioid Receptor, *Analytical Biochem.*, 343, 299-307 (2005).
- 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).
- J.P. Cain, A.V. Mayorov, M. Cai, H. Wang, B. Tan, K. Chandler, Y.S. Lee, R.R. Petrov, D. Trivedi, and V.J. Hruby, Design, Synthesis, and Biological Evaluation of a New Class of Small 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
- Z. Liu, H. Qu, X. Gu, B.J. Min, J. Nyberg, and V.J. Hruby, Enantioselective Synthesis of anti- β -Substituted γ,δ -Unsaturated Amino Acids: A Highly Selective Asymmetric Thio-Claisen Rearrangement, *Organic Letters*, 10, 4105-4108 (2008). PMC2654228
- T. Yamamoto, P. Nair, N.E. Jacobsen, P. Davis, S-W. Ma, E. Navratilova, S. Moye, J. Lai, H.I. Yamamura, T.W. Vanderah, F. Porreca, and V.J. Hruby, The Importance of Micelle-Bound States for the Bioactivities of Bifunctional Peptide Derivatives for δ/μ Opioid Receptor Agonists and Neurokinin 1 Receptor Antagonists, *J. Med. Chem.*, 51, 6334-6347 (2008). PMC18821747
- A. Juni, M. Cai, M. Stankova, A.R. Waxman, C. Arout, G. Klein, A. Dahan, V.J. Hruby, J.S. Mogil, and B. Kest, Sex-Specific Mediation of Opioid-Induced Hyperalgesia by the Melanocortin-1 Receptor, *Anesthesiology*, 112, 181-188 (2010).
- V.J. Hruby, Organic Chemistry and Biology: Chemical Biology Through the Eyes of Collaboration (A Perspective), *J. Org. Chem.*, 74, 9245-9264 (2009).
- T.M. Largent-Milnes, T. Yamamoto, P. Nair, V.J. Hruby, J. Lai, F. Porreca and T.W. Vanderah, Spinal or Systemic TY005, A Peptidic Opioid Agonist/Neurokinin 1 Antagonist, Attenuates Pain with Reduced Tolerance, *Brit. J. Pharmacol.*, 161, 986-1001 (2010).
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- Y.S. Lee, V. Kulkarni, S.M. Corvell, S-W. Ma, P. Davis, K-E. Hanlon, T.W. Vanderah, J. Lai, F. Porreca, R. Vardanyan, and V.J. Hruby, Development of Potent μ and δ Opioid Agonists With High Lipophilicity, *J. Med. Chem.*, 54 382-386 (2011). PMCID PMC21128594

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