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Victor J Hruby

University of Arizona, USA

Conformational and dynamic considerations in drug design for G-protein coupled receptors

Most natural ligands for G-Protein Coupled Receptors are peptides, and most of these peptides are linear peptides with multiple conformations in aqueous solution. There are good biological reasons for this, not the least of which is that different conformations are utilized during their biological life. However, they require a specific conformation for their interaction with their membrane bound receptors. Moreover, many of these hormones and neurotransmitters can interact with several receptor subtypes and virtually all native ligands are agonists. For drug design, it often is necessary to design ligands that are highly receptor selective, and often both agonists and antagonists are needed for various medical and biological applications. We have been developing a strategy to deal with the above drug design requirements which includes the following: 1) determining the basic pharmacophore; 2) discovering antagonists; 3) computer assisted homology modeling of receptor ligand interactions for receptor selectivity and agonist vs. antagonist efficacy; 4) conformation constraint by novel cyclization, backbone modification and chi space constraints; 5) monovalent and multivalent ligands depending upon biological and medical application; 6) enhanced bioavailability including blood brain penetration or not. We will illustrate these strategies in the design of ligands for the treatment of prolonged and neuropathic pain, pigmentary disorders, sexual dysfunction and cancer, as time permits.

Biography

Victor J Hruby is a Regents Professor in the Department of Chemistry and Biochemistry at the University of Arizona. He received his PhD at Cornell University in Theoretical Organic Chemistry and did a Postdoctoral studies with Nobel Laureate Vincent du Vigneaud. He has been a Professor at University of Arizona since 1968 where he has joint appointments in the Neuroscience Program, Medical Pharmacology, and Bio5 among others. His research interests are in the chemistry, biophysics, molecular pharmacology, molecular biology of peptide hormones and neurotransmitters and their receptors, transduction systems and in the design, synthesis and bio evaluation of novel ligands for the treatment of degenerative diseases.

hruby@email.arizona.edu

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