

Medicinal Chemistry & Computer Aided Drug Designing

November 02-04, 2015 Atlanta, USA

Design of novel, selective and bioavailable ligands for closely related receptors and pharmacophores: Conformational and topographical considerations

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Proopiomelanocortin (POMC) is a primordial animal gene that produces many of the key hormones and neurotransmitters critical for survival and reproduction. It also is involved in many of our most common degenerative diseases. It produces several hormones and neurotransmitters, including α -MSH, β -MSH, γ -MSH, ACTH, β -endorphin, β -lipotropin, etc., that target 5 melanocortin receptors (MC1R, MC2R, MC3R, MC4R and MC5R) as well as 3 opioid receptors and others. In the case of the melanocortin receptors, MC1R, MC3R, MC4R and MC5R, α -MSH (or δ -MSH) is the primary hormone/neurotransmitter and a common pharmacophore -His-Phe-Arg-Trp- is involved in agonist activation of the 4 receptors. This raises difficult problems in ligand design of agonists and antagonists for these 4 receptors which are involved in many diseases, including pigmentary diseases, feeding behavior diseases, sexual dysfunction, melanoma cancer, heart disease and many others. We have obtained highly potent and selective agonists and antagonists for the receptors that are stable and bioavailable. This required a combination of conformational and topographical considerations in peptide and peptidomimetic design. Several examples of successful applications of these considerations will be presented.

Biography

Regents Professor Victor J. Hruby received his Ph.D. from Cornell University and did his Postdoctoral Studies at Cornell University Medical Center with Nobel Laureate Vincent du Vigneaud. Currently, he is a Regents Professor at the University of Arizona with appointments in four other departments and programs. He has over 1,200 publications, serves on the editorial boards of numerous journals, and has been a member of several NIH Study Sections. Dr. Hruby's major research interests are in the chemical biology, conformation-bioactivity relationships, drug design, molecular mechanisms of information transduction of peptide hormones and neurotransmitters and their ligands that modulate health and disease. He has won numerous awards for his accomplishments including most recently the ACS Ralph F. Hirschmann Award, the ACS Arthur C. Cope Scholar Award, and the APS Murray Goodman Award.

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