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Macrocyclic α–Helical Peptide Therapeutic Modality: A Perspective of Learnings and Challenges

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Abstract

Macrocyclic α–helical peptides have emerged as a compelling new therapeutic modality to tackle targets confined to the intracellular compartment. Within the scope of hydrocarbon-stapling there has been significant progress to date, including the first stapled α–helical peptide to enter into clinical trials. The principal design concept of stapled α–helical peptides is to mimic a cognate (protein) ligand relative to binding its target via an α–helical interface. However, it was the proclivity of such stapled α–helical peptides to exhibit cell permeability and proteolytic stability that underscored their promise as unique macrocyclic peptide drugs for intracellular targets. This perspective highlights key learnings as well as challenges in basic research with respect to structure-based design, innovative chemistry, cell permeability and proteolytic stability that are essential to fulfill the promise of stapled α–helical peptide drug development.

Emerging macrocyclic peptide technology platforms to accelerate drug discovery

Building upon the impressive accomplishments credited to basic research and drug development of novel peptides, peptidomimetics and small-molecules having agonist or antagonist activities at G-coupled peptide receptors (e.g., glucagon-like peptide-1, gonadotropin-releasing hormone, melanocortin, opioid, oxytocin, somatostatin and vasopressin [1-3]), the challenge to tackle intracellular targets has achieved success by way of drug discovery campaigns focused on proteases (e.g., HIV protease, HCV protease and proteasome [4-6]) and, more recently, protein–protein interaction target pathways (e.g., p53, Bel-2 family, β-catenin and mutant RAS [7-12]). Rising to be the most propitious modality to modulate key intracellular protein–protein interactions, macrocyclic peptides have attained a “superclass” status to include chemically and/or biologically accessible molecules for modulating targets to advance both basic research and drug development (13-27). Indeed, such macrocyclic peptides realize a huge and diverse chemical space relative to ring size, amino acid (or non-amino acid) composition, and varying linkages to attain covalent cyclization. Furthermore, such strategies are being intensely driven within pharma and biotech in terms of leveraging robust platforms to accelerate macrocyclic peptide drug discovery (Table 1).
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