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Abstract

Genetically Encoded Fragment-Based Discovery (GE-FBD) from Phage-Displayed Macrocyclic Libraries with Genetically Encoded Unnatural Pharmacophores †

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Abstract: Genetically encoded macrocyclic peptide libraries with unnatural pharmacophores are valuable sources for the discovery of ligands for many targets of interest. Traditionally, the generation of such libraries employs "early-stage" incorporation of unnatural building blocks into the chemically or translationally produced macrocycles. Here, we describe a divergent late-stage approach to such libraries starting from readily available starting material: genetically encoded libraries of peptides. A diketone linchpin 1,5-dichloropentane-2,4-dione converts peptide libraries displayed on phage to 1,3-diketone bearing macrocyclic peptides (DKMP): shelf-stable precursors for Knorr pyrazole synthesis. Ligation of diverse hydrazine derivatives onto DKMP libraries displayed on phage that carries silent DNA-barcodes yields macrocyclic libraries in which the amino acid sequence and the pharmacophore are encoded by DNA. The "late" nature of the 1,3-diketone and hydrazine ligation reaction makes it a favorable approach to graft irreversible and reversible covalent ligands, as well as other chemical fragments with minor modifications. Selection of this library against therapeutically important protein targets can enrich macrocycles containing fragments that target the protein of interest. The macrocycle can help to form favorable interactions with the protein target and increase the binding affinity when compared to the ligand or the pharmacophore alone. This methodology can graft diverse pharmacophores into many existing genetically encoded phage libraries and significantly increase the value of such libraries and aid in molecular discoveries for challenging protein targets.