Unlocking the high-throughput potential of peptidomimetic diversification

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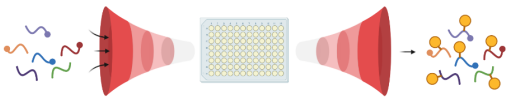
The pharmaceutical industry currently faces a productivity crisis, prompting a renewed interest in peptide therapeutics a highly promising drug modality for challenging targets.[1] Recent advancements in the field have emphasized the remarkable potential of peptidomimetics, surpassing the limitations of their native counterparts by expanding the chemical space beyond the confined twenty canonical amino acids.

A particularly effective strategy employed to enrich chemical and structural diversity involves the lateral diversification of individual residues or peptides.[2] This approach can potentially be strengthened by the power of high-throughput experimentation (HTE), which exponentially enhances the output of a single step when applied across an entire library. Unfortunately, only a handful of studies have thus far reported successful high-throughput lateral diversification of amino acids and peptides.[3-5] Hence, the primary objective of this research endeavor is two-fold: to address the discrepancy in available methods and to acquire insights into the inherent limitations entailed by HTE.

To this goal, two well-established techniques for diversification were selected: the renowned Suzuki-Miyaura cross-coupling and the highly-efficient copper(I)-catalyzed azide-alkyne cycloaddition (CuAAC). This work embraces the optimization of both transformations on individual amino acids at low nanomole scale within the ambit of a high-throughput environment. Subsequently, the feasibility of our methodology has been validated by demonstrating proof-of-concept through the lateral diversification of cyclic in-house peptide mimetics in a 384-well format.



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