Fast and Green: High Throughput Experimentation, Scalable Library Synthesis-Enabled Covalent Drug Candidates

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High-throughput screening of small molecule libraries is critical in early-stage drug discovery, yet millimolar-scale synthesis and purification remain challenging. We present a scalable and innovative method for parallel compound synthesis using a modified Ugi four-component reaction (Ugi-4CR) with ammonia, enabling precipitation-driven purification and eliminating the need for chromatography. Supported by custom-designed filtration devices and commonly available instrumentation, this workflow enabled the rapid synthesis of ~1,200 high-purity acrylamide compounds designed for covalent drug discovery. Library quality was evaluated using NMR, UPLC-UV-MS, and acoustic droplet ejection mass spectrometry (ECHO-MS), to assess compound integrity and stability. This approach significantly reduces time, cost, and solvent use, offering a sustainable and efficient strategy for generating diverse, high-quality screening libraries for both pharmaceutical and academic applications.

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Man, Machine and Multicomponent Reactions

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Peptide scaffolds are gaining momentum in the field of drug discovery. However, when it comes to selectivity and potency of the compounds, large libraries of diversified analogs are required, which is a synthetically lengthy, challenging, and resource-intensive process. To address this problem, we combined multicomponent reaction (MCR) and miniaturization technology for the rapid assembly of diverse chemical libraries from simple precursors. Here we developed a pyrazole based peptidomimetics and macrocyclic peptide library using acoustic droplet ejection technology. Chemical synthesis of this library is designed to occur in 1536-well microplates, in DMSO at nano scale, to facilitate the direct high-throughput screening of these compounds without purification. This study exemplifies how organic chemists can exploit state-of-the-art technologies to markedly increase throughput and confidence in the preparation of drug-like molecules in a span of short duration.