SUSTAINABLE SYNTHESIS OF IL-17A-TARGETED CHEMICAL LIBRARY USING ACOUSTIC DROPLET EJECTION AND DIRECT-TO-BIOLOGY SCREENING

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SUMMARY

Unsustainability in organic synthesis remains a frontier problem in academic research. The conventional methods for organic synthesis are slow, resource-intensive, and generate large quantities of waste. It is a need of the hour to implement uncharted methodological advances in green synthesis. Moreover, the current therapeutic landscape for IL-17A mediated-autoimmune diseases includes biologics available for clinical use. Therefore, this research thesis is formulated to devise and implement an innovative, accelerated organic synthesis of preliminary small-molecule candidate inhibitors of interleukin 17A (IL-17A).

IL-17A is a challenging target due to its flat, featureless protein-protein interaction interface. The current approaches to synthesize bisamide-containing small molecules rely on multi-step organic synthesis that uses coupling reagents in large quantities and generates products with low atom economy. Therefore, the Ugi four-component reaction was employed to incorporate the bisamide moiety into a chemical library of 1536 compounds, achieving an average atom economy of approximately 95 percent and demonstrating the reaction's greenness.

To accelerate this workflow, a miniaturized and automated synthetic platform based on acoustic droplet ejection was implemented. An Echo liquid handler was used to transfer the Ugi reaction components at the nanolitre scale, enabling the preparation of a 1536-member bisamide-containing compound library. The selected library members were subsequently assessed by UPLC-MS to confirm the presence of the expected Ugi products, and the library proceeded to biological evaluation.

To obtain an initial evaluation of compounds, the library was subjected to preliminary direct-to-biology screening against IL-17A using a Dianthus-based single-dose binding assay. This screening campaign revealed several compounds that exhibited binding-compatible responses, which were selected as preliminary hit candidates for further investigation. These prioritized compounds are currently under resynthesis on the milligram scale for full characterization, and further assays will be performed to assess their functional pharmacology.

This workflow provides an innovative, accelerated platform for generating and prioritizing bisamide-containing small molecules as binding candidates targeting the challenging IL-17A protein-protein interaction interface.