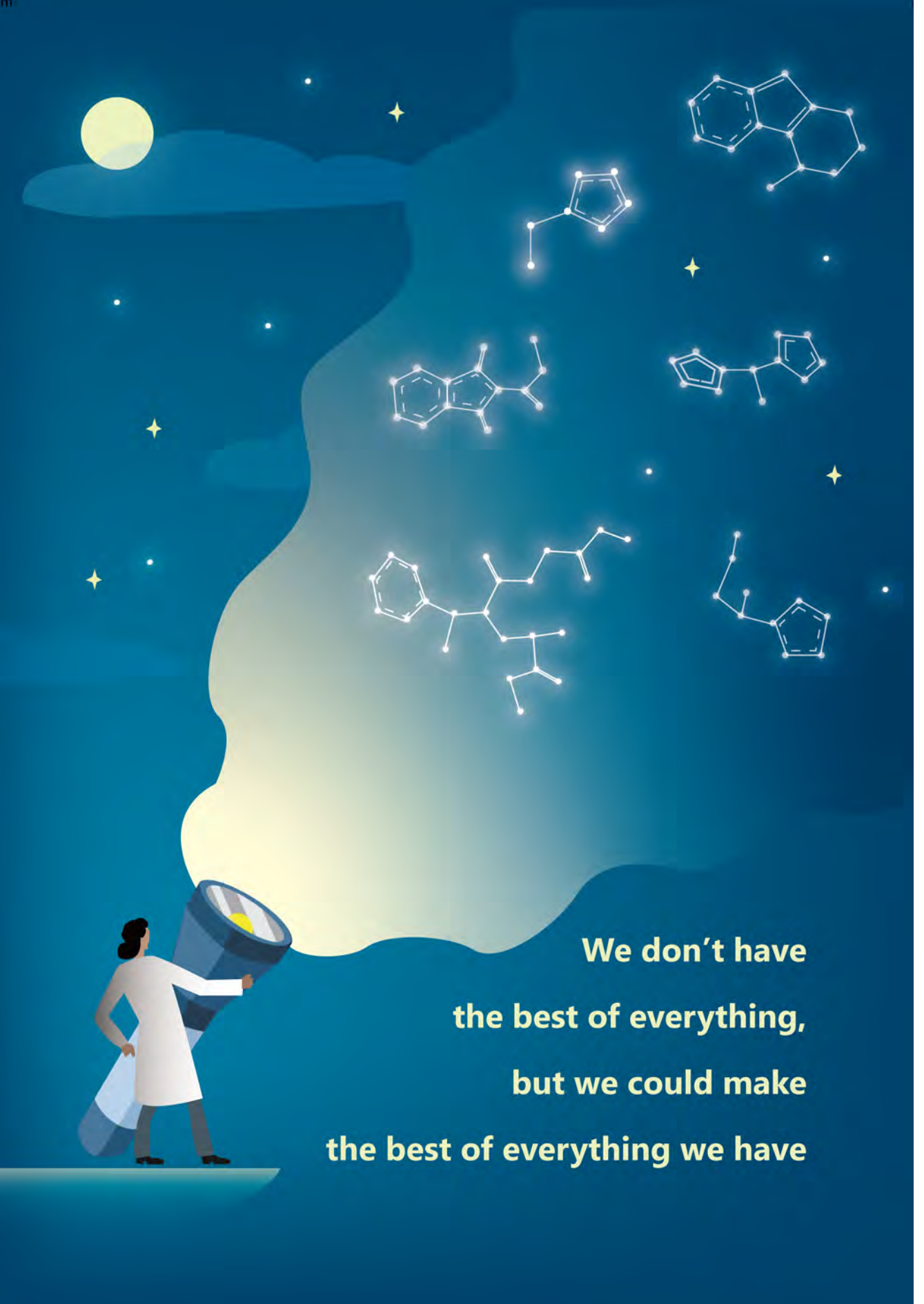
We don't have
the best of everything,
but we could make
the best of everything we have

Summary

MCR chemistry is an emerging and promising tool for organic synthesis and medicinal chemistry. In this thesis, we enriched the probable scaffolds of MCR by exploring its isocyanide, aldehyde and acid substrates. Besides, post-cyclization of MCR products was performed as well and generated an efficient methodology towards drug-like compounds. The discovery of IL-17A antagonists through MCRs was accomplished in the last chapter, indicating the broad applicability of MCRs in the drug development process.

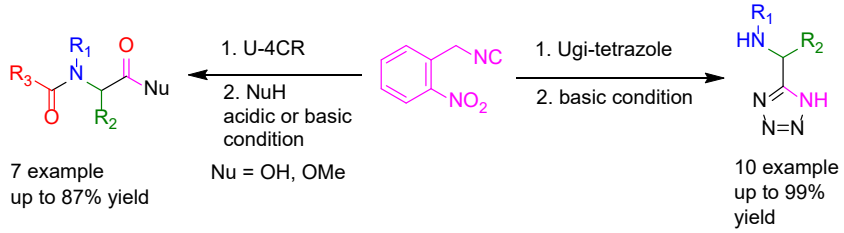

Figure 1. 2-Nitrobenzyl isocyanide as a universal isocyanide in Ugi reactions

In **Chapter1**, 2-Nitrobenzyl isocyanide is reported as a universal convertible isocyanide with extensive applicability in both Ugi-4CR and Ugi-tetrazole reactions. The cleavage of this isocyanide from 17 examples in both acidic and basic conditions is presented. Additionally, this isocyanide has various handling and synthetic advantages, such as easy to prepare, odorless, stable and easy to handle as a solid.

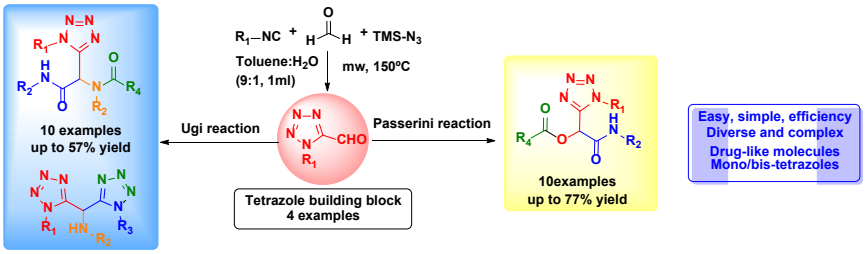

Figure 2. tetrazole building blocks in MCR chemistry

In **Chapter2**, the building block approach to introduce the tetrazole moiety into multicomponent reactions towards the synthesis of diverse and complex drug-like molecules is presented. The tetrazole building block was efficiently and directly accessed by using a three component reaction between cost-efficient and commercially available starting materials. Further synthetic utility of this novel tetrazole building block was demonstrated by introducing a tetrazole moiety into different MCRs that have already

found important uses in the drug discovery industry. This method subsequently fulfills the ever-increasing demand for the tetrazole-based compound libraries and novel scaffolds that are otherwise difficult to access through other methods.

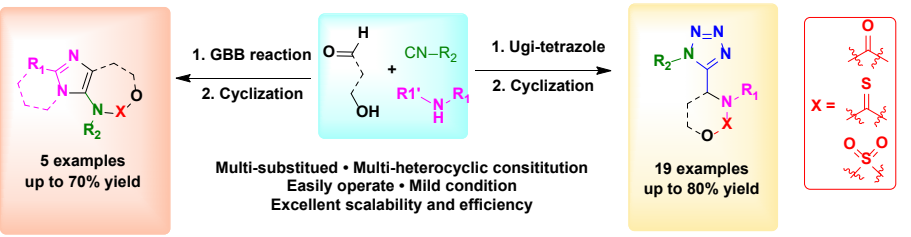

Figure 3. Scaffolding-induced property modulation of chemical space

In **Chapter3**, A two-step approach, which involves a multicomponent reaction followed by cyclization, is reported to achieve the transition from basic moieties to charge neutral cyclic derivatives. A series of multi-substituted oxazolidinones, oxazinanones, oxazepanones as well as their thio- and sulfur-derivatives are synthesized from readily available building blocks with mild conditions and high yields. Like no other method, MCR and cyclization allow for the collective transformation of a large chemical space into a related one with different properties.

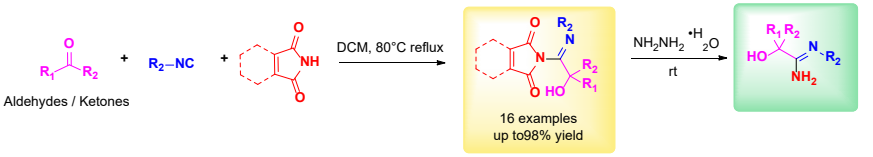

Figure 4. Phthalimide as the acid component in the passerini reaction

In **Chapter4**, an approach to introduce phthalimide and its derivatives into Passerini reaction towards the synthesis of diverse and complex molecules is presented. This method subsequently provides a fresh orientation of involving NH-based acid component into MCRs and fulfills the ever-increasing demand for the novel scaffolds.

In **Chapter5**, a review, illustrating the benefits, classification, and recent researches upon PROTACs is presented. Co-crystal structures, computational tools, kinetics of PROTACs, and specific cases including homoPROTACs, Tau-PROTACs and PROTACs in clinical trials, are explained as well.

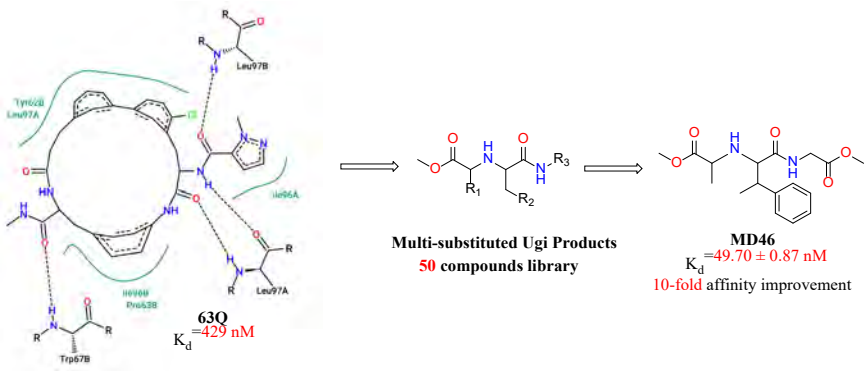

Figure 5. Amino acid derivatives as a scaffold for the discovery of IL-17A binders

In **Chapter6**, we describe the initial development of a series of small molecule antagonists targeting the IL-17A:IL17RA interaction, though an anchor based designed to mimic the hydrogen bind of macrocycle 63Q with the Leu97A/B and Trp68B of IL17A. 12 initial hits were identified from a primary ligand series of 40 members, as determined by differential scanning fluorimetry (DSF) screening. Initial hit **MD01** and derivative **MD09** were further cross-validated in a microscale thermophoresis (MST) binding assay. We then optimized and synthesized ten derivatives from the identified hits, and measured the binding affinity (Kd) with IL17A. Of these 10 optimized compounds, 4 displayed good MST biding curves, with that of **MD46** measured as 49nM. After three-round of random docking, three repeated full binding posed showed a conserved hydrogen bond with Trp67 as we predicted and another hydrogen bonds with Glu97A instead of Leu97A. The chiral separation and bioactivity test of the most active compounds are still ongoing.

Overall, this thesis demonstrates both the targeted exploration of MCR building blocks towards the synthesis of diverse scaffolds and their applications in small molecule drug discovery. In the past decades, researches regarding the methodology investigation and the post-modification of MCRs toward various heterocycles emerge endlessly. Besides the development in the organic chemistry field, the applications of MCRs in medicinal chemistry gain extensive attention on account of their efficiency, low cost, and multiformity properties. The discovery of macrocycles and PROTACs could be beneficial toward the "undarguable" targets, which have flat surfaces and are difficult to bind. The multi-substitution property of MCRs could benefit In the development of these

techniques via fragment-based drug discovery. However, multi-substitution always correspond to multi-chiral centers. How to cope with steric hindrance and remote chiral centers toward oriented synthesis is still a big challenge for chemists.