Exploitation of macrocyclic chemical space by multicomponent reaction (MCR) and their applications in medicinal chemistry
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Summary

English Summary

Nederlandse samenvatting
Summary, concluding remarks and future perspectives

Macrocycles have been regarded as a novel potential class of drug candidates in-between biologics and small molecules. For the approximately 30,000 described diseases (incl. orphan diseases) only a small fraction can be pharmacologically treated. While recent sequencing of human, parasitic, bacterial and viral genomes as well as immense progress in individual whole-genome sequencing for personalized medicine has provided a wealth of novel drug targets, very few small molecule drugs for post-genomic identified targets are currently in development. Current chemical space of screening libraries is not sufficient to deliver leads in areas of difficult post-genomic targets that are often involved in protein-protein interactions. The historical growth of targeted (towards main pharmaceutical targets GPCRs, kinases etc.) screening collections, the recently observed reductionism in the use of organic reactions as well as the disregard of chemical space wealth of natural products have most likely contributed to this observation.

Peptidic macrocycles are a well-introduced drug class, however with limitations regarding high molecular weight and mostly poor bioavailability. Synthetic macrocycles have recently emerged as a novel class of drugs that lie between biologics and traditional small molecules, potentially combining the best of both worlds. However, for the regular use of synthetic macrocycles in drug discovery, three main problems have to be solved, which the research in this thesis is focused on 1: The difficult synthetic access towards a large and diverse macrocyclic chemical space which we solved by the design of synthetic pathways for the convergent synthesis of multiple macrocyclic (MC) classes using modular multicomponent reaction chemistries and a mix-and-match approach including classical organic reactions; 2: the majority of MCs does not show sufficient passive membrane permeations, a prerequisite to discover molecules for intracellular targets like protein-protein interactions and to have the option to develop oral medications with drug-like properties. we investigated the conformational and chemical property space of the above MC scaffolds to understand the Structure-Penetration-Relationship and to build predictive models for passive penetration; 3: the potential chemical space of MC is very poorly reflected in the current screening collections in terms of numbers and diversity.

These issues we have covered during in this thesis. We have introduced several 1- or 2-step general macrocycle syntheses from common building blocks where from available building blocks millions of macrocycles can be synthesized. Furthermore, we have investigated the 3D structures of the different artificial macrocycle scaffold classes we have introduced by methods of X-ray crystallography. As a result of our study of the macrocycles, we have leveraged the novel artificial macrocycle space and have found potent inhibitors of protein-protein interactions such as p53-MDM2.

In chapter 1, artificial macrocycles recently became popular as a novel research field in drug discovery. As opposed to their natural twins, artificial macrocycles promise to have better control on synthesizability and control over their physicochemical properties resulting in drug-like properties. Very few synthetic methods allow for the convergent, fast but diverse access to large macrocycles chemical space. One synthetic technology to access
artificial macrocycles with potential biological activity, multicomponent reactions, is reviewed here, with a focus on our own work. We believe that synthetic chemists have to acquaint themselves more with structure and activity to leverage the design aspect of their daily work.

**In chapter 2 and 3,** the design and synthesis of head-to-tail linked artificial macrocycles using the Ugi-reaction has been developed. This synthetic approach of just two steps is unprecedented, short, efficient and works over a wide range of medium (8-11) and macrocyclic (≥12) loop sizes. The substrate scope and functional group tolerance are exceptional. Using this approach, we have synthesized 39 novel macrocycles by two or even one single synthetic operations. The properties of our macrocycles are discussed with respect to their potential to bind to targets that are not druggable by conventional, drug-like compounds. As an application of these artificial macrocycles, we highlight potent p53-MDM2 antagonism.

**In chapter 4 and 5.** A concise two-step synthesis of tetrazole containing macrocycles from readily accessible starting materials is presented. The first step comprises a chemoselective amidation of amino acid derived isocyanocarboxylic acid esters with unprotected symmetrical diamines to afford diverse α-isocyano-ω-amines. In the second step, the α-isocyano-ω-amines undergo an Ugi tetrazole reaction to close the macrocycle. Advantageously, this strategy allows short access to 11-19-membered macrocycles in which substituents can be independently varied at three different positions. Also, the direct non-peptidic macrocycle synthesis of α-isocyano-ω-amines via the classical Ugi 4-component reaction (U-4CR) is introduced. Where the α-isocyano-ω-amines undergo a U-4CR with a high diversity of aldehydes and carboxylic acids in a one-pot procedure. This synthetic approach is short, efficient and leads to a wide range of macrocycles with different ring sizes.
In chapter 6 and 7, we address a general, unprecedented, rapid, and highly diverse macrocycle synthesis pathway via the union of two orthogonal MCRs, e.g., the linker α-isocyanano-ω-carboxylic acids were synthesized by MCR-1 and the subsequent macro ring closure by MCR-2. In the first part, we synthesized α-isocyanano-ω-carboxylic acids of different lengths by using an Ugi reaction then the final ring closure is performed via Ugi 4-component reaction of α-isocyanano-ω-carboxylic acids. In the second part, macrocyclic depsipeptides can be convergently synthesized by a sequence of an Ugi reaction followed by an intramolecular Passerini 3-component reaction.

In chapter 8, a short reaction pathway was devised to synthesize a library of artificial macrocycles of size 18 to 27. The 5-step reaction sequence involves ring opening of a cyclic anhydride with a diamine, esterification, coupling with an amino acid isocyanide, saponification and finally macro ring closure using an Ugi- or alternatively Passerini-multicomponent reaction. Three out of the five steps allow for the versatile introduction of linker elements, side chains and substituents with aromatic, heteroaromatic and aliphatic character. The versatile pathway is described for 15 different target macrocycles on a mmol scale. Artificial macrocycles have recently become of high interest due to their potential to bind to difficult post-genomic targets.
In chapter 9, protein-protein interactions (PPIs) are important targets for understanding fundamental biology and development of therapeutic agents. Based on different physicochemical properties, numerous pieces of software (e.g., POCKETQUERY, ANCHORQUERY, and FTMap) have been reported to find pockets on protein surfaces and have applications in facilitating the design and discovery of small molecular weight compounds binding to these pockets. Also, we discuss a pocket-centric method of analyzing PPI interfaces, which prioritize their pockets for small-molecule drug discovery and the importance of multicomponent reaction (MCR) chemistry as starting points for undruggable targets. The authors also provide their perspectives on the field.

I believe that my groundbreaking work in the area of artificial macrocycles will form the foundation of many more discoveries in the area of drug discovery.

**Macrocycles are magic.**