Photochemical Rearrangement of Macrocyclic α-Azido Ketones: Synthesis of High Value-Added Compounds and Process Automatization.

This project compiles a collection of innovative approaches aiming to reveal the underrated potential of light-induced rearrangements of α-azides as the beginning of an entire light-mediated reaction cascade. Several different research directions will be pursued, with the common purpose of demonstrating the attractiveness and usefulness of the proposed reactivity in the synthesis of structurally diverse macrocycles with drug intercalation motifs. The proposed transformation will be conducted in a continuously flowing stream. To accomplish this, a self-made, automated, remotely controlled setup allowing the reaction to be carried out in flow with precise real-time monitoring by UV-Vis and/or IR will be constructed. The proposed synthesis of medicinally relevant, high-value macrocycle compounds, primarily based on photochemical transformation, which proceeds under sustainable conditions without any catalysts or additives, fits perfectly within the assumptions of the European Union directive on *Chemicals Strategy for Sustainability Towards a Toxic-Free Environment*. Additionally, executing the synthesis in a fully automated, continuously flowing stream will minimize operational steps, significantly reduce costs, shorten production times, and limit the amount of waste produced.

In recent years, macrocyclic compounds defined as ring systems consisting of 12 or more atoms have emerged as increasingly important therapeutic candidates in drug discovery. Natural-product-derived macrocycles, of which over 100 exist as FDA-approved drugs, have demonstrated excellent efficacy as antibiotics and anticancer drugs. Macrocycles possess unique structural properties that make them excellent synthetic targets and show great potential to succeed where small molecules have failed. Recognizing the huge potential and growing interest in drugs based on macrocyclic compounds, the development of a sustainable protocol for their preparation is of critical importance.

In the current grant application, we propose a fully automated, green, and sustainable protocol for synthesizing structurally diverse, high-value-added macrocycles with drug intercalation motifs. This synthesis will be achieved within a continuously flowing stream. The proposed strategies are grounded in a light-induced reaction cascade that encompasses rearrangements of α-azides, Fries-type rearrangement, and Wolf-rearrangement. This photochemical transformation proceeds with excellent atom economy, without the need for any catalysts or additives, and offers a practical avenue to generate macrocycles with unprecedented architectures.

We believe that the innovative solutions outlined above will notably expand the existing state of the art in complex macrocycle synthesis. Moreover, these solutions will offer a valuable pathway for crafting intricate organic molecules from basic starting materials for the wider research community. Anticipating the outcomes from this project, we envision that the results will significantly enhance the field of chemistry concerning photo-induced ring-expansion of α-azides. This approach holds immense potential as a powerful tool for generating chemically, biologically, and medically vital organic compounds.