**Barbara Mikulak-Klucznik**

**Automatic analysis of chemical reactions
and its use in computer-assisted
and automated synthesis of organic compounds**

**Promotor: Prof. dr Bartosz A. Grzybowski|**

**ABSTRACT**

In recent years, computer-aided organic chemistry is experiencing its renascence and the challenges it is facing are greater than ever before. The rapidly changing climate, exhaustion of natural resources, as well as delays in the supply chains caused by the SARS-CoV-2 pandemic create increased demand for new, more effective methods of synthesis and separation of organic compounds. These methods include, *inter alia*, increasing the efficiency of chemical processes via development of new types of chemical reactions, creating optimal synthetic plans for desired compounds as well as the construction of integrated experimental systems for automated synthesis and separation.

The beginnings of computer-assisted organic chemistry date back to the 1960s, when
E. J. Corey started his work on the first program for retrosynthetic analysis – LHASA. Despite initial enthusiasm, both this and subsequent programs failed to generate useful analyzes and did not gain popularity among chemists. The reason for the limite planning prowess of these early solutions was, among others, insufficient computing power and the lack of advanced algorithmic tools. The situation has changed dramatically during the last few years, when Prof. Grzybowski and his team developed the most extensive program for retrosynthetic analysis – *Chematica/Synthia*™.

Retrosynthetic plans generated by Chematica have been validated by experiment, in multiple syntheses of medically-important targets. Taking an important and in many ways a crucial step forward, the subject of my research was to investigate the possibility of using the program for the retrosynthesis and laboratory validation of natural products with a high degree of structural complexity – which I demonstrated by performing the key part of the total synthesis of (*R,R,S*)-tacamonidine. This work was published in *Nature*1.

In the second part of my research, I focused on the problem of automatic synthesis and separation of organic compounds. Using a new type of rotating reactor based on out-of-equilibrium solvent systems held in a multilayer configuration by centripetal forces,
I developed a method of automated, selective extraction of organic compounds, which
I demonstrated on the example of phenylalanine extraction using the D2EHPA carrier. This work was published in *Nature*2.

1 Mikulak-Klucznik, B. *et al.* Computational planning of the synthesis of complex natural products *Nature* **588**, 83–88 (2020).

2 Cybulski, O. *et al.* Concentric liquid reactors for chemical synthesis and separation. *Nature* **586**, 57–63 (2020).