Computer-Assisted Discovery Of Unprecedented One-Pot Reactions And Functional Analogs

M.Sc. Ahmad Makkawi

Promotor: prof. B. A. Grzybowski

The integration of computers into chemistry has revolutionized the field, particularly in problem-solving, data management, and AI-assisted synthesis design. Initially used for simple data storage and calculations, modern computational tools now play a critical role in planning complex synthetic routes, enabled by advances in graph theory, reaction-network algorithms, and quantum chemical modeling. Once met with skepticism, AI has now proven capable of mimicking aspects of human reasoning in organic synthesis.

A key example of this progress is the *Allchemy* software, which was an indispensable companion of my doctoral work, providing synthetic ideas and plans that I subsequently set out to test in the laboratory. Unlike older tools that provide only basic recommendations, such as E.J. Corey's LHASA, Allchemy—a comprehensive platform for *in silico*, retro and forward synthesis—takes a more sophisticated approach by combining several specialized tools. Its different modules work together to tackle complex challenges, such as refining potential drug candidates, studying reaction mechanisms, and even exploring the chemical origins of life. It creates clear, logical reaction pathways and simplifies exploring chemical networks, speeding up molecule discovery. By combining vast reaction knowledge base with physical-organic chemistry principles, it designs and optimizes synthetic routes and strategies for even highly complex targets and can also work at the level of mechanistic steps to invent novel transformations, including multicomponent processes and carbocation rearrangements.

In my first study, I initially focused on one of Allchemy's modules (a.k.a **Mech**), a computational tool that demonstrated its ability to design novel multicomponent reactions (MCRs) and one-pot syntheses by integrating reaction mechanisms with physical-organic chemistry principles. Utilizing this **Mech** module, the algorithm predicted mechanistic pathways defining novel MCRs, estimated kinetic rates, and identified potential by-products. My work was primarily focused on validating and optimizing, through experimental synthesis, these predictions. I successfully generated a range of molecular frameworks, including novel tricyclic scaffolds, and compared direct- and conjugate-addition reactions—highlighting the critical role of HMPA in distinguishing these mechanisms. The study also explored competing

side reactions, which the **Mech** module systematically identified and tracked. Its predictions for reaction selectivity and mechanistic competition aligned closely with experimental results, affirming the model's accuracy. However, while the tool accelerates reaction discovery, it does not eliminate the need for hands-on experimental optimization, emphasizing the importance of keeping the human chemist “in the loop”.

Looking ahead, incorporating radical mechanisms and catalytic cycles will enhance the module’s predictive power further. By combining automated mechanistic exploration with rational filtering, the **Mech** module has proven effective in bridging computational and experimental chemistry, driving innovation in synthetic reaction design.

My second project dealt with the use of Allchemy’s **Analog** module for drug development. Recent computational advances have transformed analog drug design by enabling efficient synthesis of structural analogs using optimized pathways. Generative AI tools like Allchemy-**Analog** integrate molecular property predictions with target similarity to guide *de novo* scaffold design. In this project, I experimentally evaluated the module, which relies on bioisosteric substitutions, retrosynthetic analysis, and guided synthesis to create diverse analogs. The workflow ensured flexibility and addressed functional group limitations through refined protocols and adaptable chemical blocks. My experimental validation focused on designing, synthesizing and testing analogs of Ketoprofen and Donepezil. Seven analogs of Ketoprofen and five of Donepezil were synthesized, most showed micromolar to nanomolar binding affinities. One Ketoprofen analog slightly outperformed the original, and a Donepezil analog achieved a strong 36 nM affinity for AChE, closely matching the parent compound.

These experimental binding affinities aligned with theoretical predictions of Allchemy’s internal neural network (and also with predictions of docking programs) to within an order of magnitude. These results show how computer tools can simplify drug analog design, but reveal we still need better prediction methods for drug development.