HABILITATION THESIS REVIEWER'S REPORT

Masaryk University	
Applicant	Mgr. Jakub Švenda, PhD
Habilitation thesis	Synthetically modified complex natural products
Reviewer	Prof. Dr. Mathias Christmann
Reviewer's home unit, institution	Institute of Chemistry and Biochemistry, Freie Universität Berlin

Dr. Jakub Švenda's habilitation thesis demonstrates exceptional skill in the synthesis and modification of complex natural products, significantly advancing the field of synthetic chemistry. His research has not only improved the accessibility of these compounds but also deepened our understanding of their biological activities and therapeutic potential.

1. Pseurotin Synthesis and Analog Development

Jakub has developed concise, enantioselective routes for the synthesis of pseurotins, specifically cephalimycins B and C, and pseurotin A2, starting from a strategy involving enantioselective conjugate addition using nickel(II)-diamine catalysis. Using his approach, he synthesized over forty new pseurotin analogs with immunomodulatory effects. The synthetic work was published in the *Journal of Organic Chemistry* (2021), the biological evaluation was published in *Phytomedicine* (2020).

2. Forskolin Synthesis and Analog Discovery

Dr. Svenda designed and executed an efficient route to these complex terpenoid structure reducing the number of steps from previously over 30 to 24 steps, enabling fully synthetic production of analogs not accessible via semisynthesis. The new analogs exhibited selective adenylyl cyclase stimulation, particularly by modifying the A-ring. This research provided new insights into the structure-activity relationships of forskolin derivatives. The synthetic work has led to two publications in *Angewandte Chemie* (2017 and 2023).

3. Bactobolin Synthesis

The development of new antibiotics is essential to combat the growing threat of antibiotic-resistant bacteria, ensure effective treatment of infections, and protect global public health. Jakub developed two generations of synthetic routes to bactobolin antibiotics, achieving a most concise assembly allowing for analog synthesis. The synthesized analogs were tested for ribosomal selectivity and potency, revealing that structural changes at C3 significantly impact biological activity. From this work, one communication in *Journal of the American Chemical Society* (2020), and one in *Angewandte Chemie* (2022) were published.

4. Acybolin Synthesis

The acybolin family are cryptic natural products synthesized with a complex structure. Their synthesis enables future biological studies to better understand their role in bacterial biosynthesis and might lead to potential antibiotic applications.

Dr. Švenda's work is characterized by its high quality and impact, as evidenced by his publications in top-tier journals. Although his publication record may be smaller compared to researchers in other fields, such as catalysis, the exceptional quality of his work more than compensates for this.

Summary

Dr. Švenda is undoubtedly one of the most promising young chemists in target-oriented synthesis in Europe. His systematic approach to synthesizing complex molecules facilitates further study into their roles in health and disease, paving the way for potential therapeutic applications and diagnostic advancements.

In conclusion, Dr. Jakub Švenda's habilitation thesis represents a significant contribution to the field of synthetic chemistry. His research has expanded the boundaries of what is possible in the synthesis of complex natural products, opening doors for future discoveries and innovations.

Reviewer's questions for the habilitation thesis defence

A) Can you discuss the key innovations that are needed to reduce the complexity of synthetic operations and overall step count of chemical syntheses even further?

B) Could you elaborate on the specific challenges you faced in controlling stereochemistry during the synthesis of the spirocyclic core of pseurotin family? What can be learned from this?

C) Will natural product synthesis be needed in the future? Why not focus on synthetic compound libraries?

Conclusion

The habilitation thesis entitled “Synthetically modified complex natural products” by Jakub Švenda **fulfils** requirements expected of a habilitation thesis in the field of Organic Chemistry.

Date: Signature:

23.09.2024