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Annex No. 10 to the MU Directive on Habilitation Procedures and Professor Appointment Procedures

HABILITATION THESIS REVIEWER'S REPORT

Masaryk University	
Applicant	Mgr. Jakub Švenda, PhD
Habilitation thesis	Synthetically modified complex natural products
Reviewer	Prof. Dr. Karl Gademann, Dipl. Chem. ETH Full Professor of Organic Chemistry and Chemical Biology
Reviewer's home unit, institution	Department of Chemistry, Universität Zürich, Switzerland

Evaluation Report on the Scholarly Contributions of Dr. Jakub Švenda

Dear members of the Habilitation committee panel, dear colleagues

I understand that Dr. Jakub Švenda is considered for habilitation at your university. I have been contacted by Professor Vladimir Sindelar from Masaryk University with respect to an assessment of his academic performance, to which I am happily responding with this letter.

I am a full professor holding a chair in chemistry at the University of Zurich, and I finished my rotating term as the chair of the department of chemistry of the University of Zurich, which encompasses ca. 25 group leaders and over 250 persons in various functions and levels. Throughout my professional career that involved positions at ETH Zurich, Harvard University, EPFL Lausanne, the University of Basel, and now the University of Zurich, I have evaluated research proposals and scientists on many occasions. For example, I served as dean of research to the faculty of science at the University of Basel, being co-responsible for strategic planning and resource allocation in the natural sciences and mathematics. In this function, I was also involved in each tenure committee in the faculty of mathematics and sciences, and I was also involved in each committee for promotion of assistant professors to associate professors, and for the promotion of associate professors to full professors. Currently, I am a member of the research council of the Swiss National Science foundation as one out of four members in chemistry, and in this function, I am shaping both future directions in project funding, but also serve as reviewer to proposals in the sciences and engineering division. For all these reasons, I think I am well qualified to assess the scientific excellence of the candidate in a fair and professional manner. I should also state that I have not personally met the candidate, but I was aware of his work through reading of the current literature.

Dr. Jakub Švenda has made significant contributions to the field of synthetic organic chemistry, with a particular focus on the total synthesis of complex natural products and the development of innovative synthetic methodologies. His work demonstrates a high level of scholarly excellence, creativity, and a profound understanding of organic synthesis, as evidenced by the habilitation file and the three attached publications under review. This

report aims to highlight the strengths of his studies, emphasizing the impact of his research on the field and its potential applications in medicinal chemistry and pharmaceutical development.

A Short Synthesis of (+)-Actinobolin and Its Analogues

In this publication (Angew. Chem. Int. Ed. 2022, 61, e202116520), Dr. Švenda presents a concise nine-step synthesis of the naturally occurring protein synthesis inhibitor (+)-actinobolin. Traditionally, the synthesis of such complex molecules required lengthy procedures with multiple steps, often exceeding sixteen stages. Dr. Švenda's approach reduces this significantly, achieving the synthesis in just nine steps with an impressive overall yield of 18%.

Strengths:

- **Innovative Synthetic Strategy:** The synthesis leverages a convergent approach that features the conjugate addition of an α-amino radical derived from **5** in the key fragment-coupling step. This method simplifies the assembly of densely functionalized and stereochemically complex structures.
- **Use of Readily Available Building Blocks:** By utilizing (−)-quinic acid, L-threonine, and L-alanine as principal components, the synthesis is both cost-effective and efficient. These readily available natural products contribute nearly the entire atom content of (+)-actinobolin.
- **Facilitation of Analog Synthesis:** The streamlined process has practical implications for the preparation of analogs. Dr. Švenda demonstrates this by synthesizing difluoroactinobolin and other analogs, expanding the potential for developing new antibacterial agents (as shown on Scheme 4).
- **Biological Relevance:** The synthesized analogs exhibit significant activity in inhibiting protein synthesis in bacterial ribosomes, highlighting the potential for therapeutic applications. The work bridges the gap between synthetic chemistry and biological function.

Convergent Assembly of the Tricyclic Labdane Core for Forskolin-like Molecules

In the publication Angew. Chem. Int. Ed. 2023, 62, e202213183, Dr. Švenda addresses the challenge of synthesizing forskolin-like molecules by introducing a new synthetic strategy that assembles the tricyclic labdane core from pre-functionalized cyclic building blocks.

Strengths:

- **Convergent Synthetic Approach:** The method departs from previous linear synthetic routes by employing a convergent strategy (of e.g. coupling **A2** and **C1**) that enhances efficiency and flexibility. This allows for the modular assembly of complex structures.
- **Stereoselective Michael Addition:** The key fragment-coupling step utilizes a stereoselective Michael addition to compound **10**, achieving excellent control over three newly created contiguous stereocenters, including all-carbon quaternary centers. This demonstrates advanced proficiency in stereochemical control.
- **Ring-Opening Metathesis Paired with Ring Closure:** The innovative use of silyl enol ether-promoted ring-opening metathesis, paired with ring closure, enables the

concise assembly of the tricyclic core. This methodological advancement opens new avenues for synthesizing complex terpenoids.

- **Generation of Diverse Analogs:** The approach facilitates the late-stage functionalization of intermediates, resulting in a variety of forskolin-like molecules. This diversity is crucial for exploring structure-activity relationships and potential pharmaceutical applications.

A Concise Synthesis of Forskolin

The publication in Angew. Chem. Int. Ed. 2017, 56, 12586 showcases a 24-step total synthesis of racemic forskolin, a complex diterpene with significant biological activity. Previous syntheses of forskolin were lengthy and not very efficient, but Dr. Švenda's route provides a more practical approach.

Strengths:

- **Strategic Oxidative Transposition:** The synthesis features a strategic allylic transposition, allowing for the installation of the syn-1,2-diol function of forskolin. This step addresses stereochemical challenges and reduces the need for protecting group manipulations.
- **Stepwise Assembly of the Isoxazole Ring:** The construction of the sterically hindered isoxazole ring in compound **9** is achieved through a stepwise process, overcoming obstacles associated with the molecule's dense functionalization.
- **Citric Acid-Modified Upjohn Dihydroxylation:** The application of citric acid-modified Upjohn dihydroxylation to a tetrasubstituted olefin **10** demonstrates Dr. Švenda's ability to adapt and optimize existing methodologies for challenging substrates.
- **Scale and Practicality:** The synthesis delivers gram-scale quantities of forskolin, making it valuable for further research and potential therapeutic exploration.

Overarching Strengths Across the Publications

- **Methodological Innovation:** Across all three studies, Dr. Švenda exhibits a strong ability to develop and refine synthetic methods. His work often involves overcoming significant synthetic challenges, such as controlling stereochemistry in complex molecules and developing novel reactions.
- **Stereochemical Mastery:** The precise control over configuration in complex settings is a hallmark of his work. This is crucial in natural product synthesis, where the biological activity is often highly dependent on stereochemistry.
- **Bridging Chemistry and Biology:** By not only synthesizing complex natural products but also exploring their biological activities, Dr. Švenda effectively bridges the gap between organic synthesis and medicinal chemistry. His work on actinobolin analogs and forskolin-like molecules provides valuable insights into their mechanisms of action.
- **Contribution to Medicinal Chemistry:** The ability to synthesize analogs of biologically active compounds opens up opportunities for drug development. His synthetic routes allow for modifications that are difficult or impossible to achieve

through semisynthesis, potentially leading to new therapeutics with improved efficacy and selectivity.

- **Educational Impact:** The detailed methodologies and strategic approaches presented in his publications serve as valuable educational resources for the scientific community. They provide templates for tackling complex synthetic challenges.

Conclusion

Dr. Jakub Švenda's research contributions are marked by significant innovation, deep understanding of complex synthetic chemistry, and a clear vision for the application of his work in medicinal chemistry. His ability to devise efficient synthetic routes to complex natural products like (+)-actinobolin and forskolin, as well as their analogs, demonstrates strong skill and creativity.

His work not only advances the field of organic synthesis but also has meaningful implications for the development of new antibacterial agents and therapeutics. By enabling the synthesis of novel analogs, he opens up possibilities for the discovery of compounds with improved biological properties.

The scholarly excellence displayed in these publications reflects Dr. Švenda's expertise and his significant contributions to the field. His research is characterized by methodological rigor, innovation, and a commitment to advancing both science and potential therapeutic applications. The supportive and collaborative nature of his work further underscores his suitability for habilitation, as he exemplifies the qualities of a leading researcher and educator in the field of synthetic organic chemistry.

Recommendation

Based on the strengths highlighted in his studies, Dr. Jakub Švenda's scholarly work merits strong support for his habilitation. The amount of his work regarding quantity and quality would also likely qualify him for a similar degree at my university. His contributions significantly advance the field and demonstrate his capability as an independent researcher of high caliber. His innovative approaches and successful synthesis of complex natural products position him as a valuable asset to the scientific community.

Reviewer's questions for the habilitation thesis defence.

1. The innovative use of α-amino radical conjugate addition in the nine-step synthesis of (+)-actinobolin is noteworthy for accessing a complex skeleton quickly. However, the drawback are challenges in the stereochemical control and overall efficiency of the process. Can you comment on these challenges, and how broadly this strategy is applicable to other complex natural products with similar stereochemical complexity?

2. The candidate discusses the outlook of the forskolin derivatives in their ACIE 2023 publication briefly. As the deletion of a methyl group impacts activity (as was also recently demonstrated by Professor Shenvi at the Scripps Research Institute for

salvinorin A), do you think that this could be a general strategy applicable to a range of natural products?

Conclusion

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

Date: Zürich, 26. September 2024

Signature:

Prof. Dr.Karl Gademann