

Ph.D. Thesis Review

Ph.D. Thesis title: Preparation of Influenza Neuraminidase and Polymerase Inhibitors

Ph.D. Thesis author: Václav Zima

Supervisor: Aleš Machara

Václav Zima has worked under my supervision for the past five years. His two major projects deal with the preparation of peptidomimetics that disrupt assembly of two peptidic parts of influenza RNA-dependent RNA polymerase, and with the preparation of sialomimetics binding to neuraminidase enzyme of influenza virus. The beginning of both projects were not easy and Mr. Zima struggled with tricky synthetic steps of intended synthetic routes. He eventually attempted his own ideas to sort out all issues and finely he was successful in his effort. Here I have to admit that these three tough years with an eager supervisor behind his back have turned this young colleague into a decent chemist. I realized it later during the past six months when I witnessed the successful preparation of a pair of bicyclic peptides accomplished by Mr. Zima. I intentionally chose the verb *witness* rather than *supervise* since I was just kept informed about how fast the projects progress and Mr. Zima only shared with me his plans for upcoming synthetic steps. But there was nothing to discuss, he managed everything by himself.

Apart from research associated with chemistry of peptidomimetics and sialomimetics Mr. Zima worked on a different project that is related to inhibitors of influenza endonuclease (flavonoids). The preparation of six pivotal compounds required eight synthetic steps for each of them and there was no chance to do it in a modular fashion. Hence he had to perform eight steps, rigorously purify the final product and start all over again with the preparation of its isomer. These achievements clearly indicate that Mr. Zima is able to handle very demanding challenges in a systematic way.

In the past five years Mr. Zima provided many valuable results that supported our interdisciplinary collaboration with biochemists and virologists. His Thesis is dedicated mainly to the preparation of influenza inhibitors. During his Ph.D. two original paper has been co-authored by him so far (*Bioorg. Med. Chem.* and *Eur. J. Med. Chem.*). One follow-up paper reporting on inhibitory potency of flavonoids congeners against influenza endonuclease will be submitted to *International Journal of Molecular Science* in May this year. Other two papers reporting on inhibitory potency of bicyclic, monocyclic and linear peptides against assembly of PA-PB1 subunits of influenza polymerase will be submitted this year as well.

Mr. Václav Zima has met all requirements of Ph.D. study and I do recommend his Thesis to enter the defense procedure.

In Prague 23. 4. 2021



Ing. Aleš Machara, Ph.D.