Ph.D. Thesis Review

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Ph.D. thesis title: Design, synthesis and evaluation of novel inhibitors of class II PI4Ks and RIPK2/3 kinases

Reviewer: Assoc. Prof. Miroslav Soural, Ph.D.

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The submitted thesis is targeted to the field of medicinal chemistry. It consists of two main research projects with the joint motif being the quinazoline mioety as the central scafffold in the protein kinases inhibitors. In the first project, author has focused on the development of potential II PI4Ks inhibitors. After a rational design of target compounds using molecular docking experiments, author has developed a modular synthetic route to disubstituted aminoquinazolines, which was subsequently applied to prepare the series of derivatives for biological evaluation of inhibitory activity and selectivity to different human PI4Ks. This effort led to discovery of a lead compound with an improved biological profile compared to the previously reported inhibitor. Also co-crystallizion with PI4K2B was succesfully accomplished. In the second project, author has focused on development of potential inhibitors of RIPK2 and RIPK3. Again, the molecular docking experiments were used to design the target compounds followed by a development of a straightforward synthesis of trisubstituted quinazolines. The biological evaluation of the synthesized compounds furnished some potent and selective RIPK2 inhibitors and dually acting RIPK2/3 inhibitors. For the best compounds, microsomal stability was performed as well as evaluation of potential off-targets using the panel of diverse protein kinases.

Formally, the thesis is divided to five sections. In the first chapter, author briefly summarizes a key information from the field of protein kinases. The following two chapters are devoted to the description of the corresponding projects. Each chapter deals with the information about the target kinase and rationale for the scientific goal, followed by discussion on the obtained results. In the next two chapters, author provides experimental procedures and analytical data for the synthesized compounds. Finally, the list of references is added. In my humble opinion, all the five parts are carefully and clearly written and they contain only a negligible amount of formal shortcomings and typos.

I have to appreciate a multidisciplinarity of the both projects. Although author did not perform all of the experiments by himself, he managed to combine the received data and he made a rational

conclusions for further development. In the synthetic part, author has done a respectable amount of work. Results from the thesis have been already published in high quality journals and Mbilo Misehe is the first author of each paper which demonstrates his key role in the both projects.

I am convinced that the published data will be useful for the scientific community working in the field of protein kinases inhibitors and will serve for further development of selective inhibitors. For all of these reasons, **I do recommend the thesis for the defense procedure.**

Further comments and topics for discussion:

1) In the both projects, author has critically discussed the obtained data, however I was missing the more detailed vision of how the results could be applied for further investigation. Could author provide some possible future directions?
2) With respect to the results summarized in the section 2.8, it may be concluded that benzotriazole scaffold might be a suitable scaffold for the C-7 position. What is author´s opinion?
3) I feel that final compounds from the second project may suffer from limited solubility causing problems with administration in the stage of *in vivo* experiments. If this is true, can author suggest some approaches to improve their solubility in water?
4) A mechanistic suggestion of the Dimroth rearrangement, which author provides in the Scheme 10, is very similar to original paper of Chandregowda. Nevertheless, it predicts the conversion of **83** to **84** instead of a addition of water to **83**. This is certainly possible, however some detail is missing in the mechanistic scheme. Please make a correction. Can you suggest some method which might be applicable to prove that Dimroth rearrangement really takes place in the preparation of compound **87**?

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Reviewer´s signature

In Olomouc 4. 1. 2024

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