

External review of PhD thesis

Title: New C-H activations and cross-coupling reactions for modification of deazapurine nucleobases

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Reviewer: prof. RNDr. Jan Hlaváč, Ph.D.

The PhD thesis is focused on chemistry of deazapurine derivatives including development of C-H activation methods for their functionalization, mainly introducing of amino, imido, silyl and phosphonyl groups via chemo- and regioselective manner. Combination of this derivatization with Suzuki-Miyaura cross-coupling reactions was then studied as a tool for preparation of modified deazapurine scaffolds. The topic of the thesis belongs to the modern and perspective fields of new therapeutics research with significant importance in medicinal chemistry.

The aim of the work was a development of direct C-H amination/imidation, silylation, phosphonation of deazapurines and modification of 6 and 7-(het)aryl 7-deazapurines by aqueous Suzuki-Miyaura cross-coupling reactions. The thesis is standardly segmented to Introduction, Specific aims of the project, Results and discussion, Conclusion, Experimental section and References, what is supplemented by Acknowledgement, Abstract and List of abbreviations.

The Introduction reviews the current state of knowledge with focus on biological activity of 1-,3-,7-,9-deazapurines and synthesis of 7-deazapurine derivatives mainly by modification of the basic scaffold. The important part is the survey of C-H activation methods not only of deazapurines, but also purines and other aromatic compounds. This Introduction is written very well with appropriate ratio of apt description and adequate briefness. My only formal remark could be implementation of subchapter 1.3.5. C-H activation strategies to chapter 1.3. Synthesis of substituted 7-deazapurines. Because it is the most important chapter with respect to the thesis goals and it describes reactions predominantly on other than deazapurine substrates, it is worthy of being separate chapter of the Introduction.

The Aims of the thesis are written clearly with defined and controllable outputs. My only rebuke to this part is the missing of a scheme with general final structures and/or reactions to get an idea about aims via eyes of chemists.

The Results and discussion part is written very readably, it describes in sufficient details all important experiments planned with appropriate sense and usefulness. The author deserves praise for systematic optimization of the reactions and step by step finding the conditions giving the very good or at least acceptable yields of the product. My remarks to this chapter have formal character, e.g.:

- I missed the description of concrete substituents in the schemes (e.g. Scheme 5). This drawback causes difficult orientation, which products were formed from which starting compounds as well as what is the substitution for concrete compound (e.g. **13**, which must be elucidate from the text).
- The formal mistakes include combination of subscript and superscript for designation of substituents R in schemes (see e.g. combination of both in Scheme 5).
- Starting compound **28g** in comparison to product **42d** in the Table 12 is not substituted by bromine, what should be described or noted in the table.
- Table 15: The excitation wavelengths are not mentioned
- Table 17: The scheme should include both types of deprotection conditions

The questions regarding to this chapter are summarized in the end of this review.

The thesis is concluded by chapter Conclusion well summarizing the results.

In summary, the author showed his ability to solve synthetic problems, characterize the compounds and study their properties as well as summarize the results in logic and readable report in level of PhD students. He achieved significant results already resulted in five articles in impacted journals (always the first author) and I am convinced of his sufficient experience to get a PhD degree and therefore I recommend the thesis for the defense.

The questions:

1. Chapter 3.1.1. : Preparation of amides derived from cmp. **10a** via acylchlorides was not successful due to decomposition of deazapurines in acidic medium. Have you tried an application of activated esters?
2. Chapter 3.1.2. : The author describes unsuccessful decomposition of 8-imidyl derivatives by hydrazine, what should be in accordance with instability of cmp **10a**. But the instability of **10a** in presence of bases is not discussed. Can the author briefly describe the stability of deazapurines in various media, mainly in presence of bases?
3. Chapter 3.2.1. ; Table 14: Is it possible to explain the different reactivity or achieved yields of thiophen-2-yl and 3-yl respectively in combination with F and Cl substituents?

In Olomouc, November 25th, 2007

prof. RNDr. Jan Hlaváč, Ph.D.