UNIVERSITY OF CHEMISTRY AND TECHNOLOGY, PRAGUE
Faculty of Chemical Technology
Department of Organic Chemistry

Expert opinion on the Ph.D. thesis entitled "New C-H activations and cross-coupling reactions for modification of deazapurine nucleobases"

The Ph.D. thesis submitted is focused on the development of novel transformations for the synthesis of 7-deazapurines analogues. As per usual, the dissertation is divided into several parts (*Introduction*, *Specific Aims of the Project*, *Results and Discussion*, *Conclusion*, *Experimental Section*, and *References*). The *Introduction* (31 pages) gives an extensive description of the biological activity of purines and deazapurine nucleobases and their derivatives. Next, synthetic approaches to substituted 7-deazapurines are described. The *Results and Discussion* section forms the most important part of the thesis (34 pages). In the first part, attention is paid to direct transition metal catalyzed C-H amination, silylation, and phosphonation of 7-deazapurines. Then, results obtained during the preparation of 7-deazapurines bearing aryl and hetaryl substituents are described. It should be emphasized that UV absorption spectra, fluorescent properties, and biological activity of prepared 7-deazapurine bases were evaluated.

Overall, the formal level of the thesis fulfills general requirements. Basic terms and concepts are well explained in the introduction. The aims of the work are clearly defined. The thesis has outstanding performance in terms of accomplished experimental results. I would like to point out the enormous number of optimization experiments performed during C-H functionalizations. The preparation of free phosphonic-acid derivatives attracted my attention as an example of a highly difficult, successfully solved problem. It was also nice to see X-ray crystallography data of selected 7-deazapurine analogues. Schemes and tables are arranged in a fashion typical for professional communication. All results and their subsequent conclusions are logically and sufficiently formulated.

On the other hand, some inconsistencies can be found while reading the text. Incorporating scheme into the body of the table in all cases would increase the readability of the text. A complex description of optimization results obtained during Pd/Cu-catalyzed C-H amination (Table 1 and 2, pages 47 and 48) leads to less comprehension of the presented findings. I understand that the main purpose of this thesis is to study the preparation of functionalized 7-deazapurines and test their properties, but including reactivity-explaining type experiments would increase the value of obtained results. For example, C-H phosphonation of 7-unsubstituted-7-deazapurines proceeded smoothly but 7-deazapurine with fluorine atom in positon 7 did not react at all. However, no attempts to explain factors influencing the reactivity of 7-unsubstituted-7-deazapurines are provided. The experimental part is well assembled, and I have no doubts about the reproducibility of the experiments. However, it would be nice to see some attached copies of ^{1}H and ^{13}C NMR spectra of the selected compounds.

The thesis contains minimal grammatical and typographical errors. Here are some examples:

Page 8, ref. 3: "Slavetínská" should be "Slavětínská"
Page 18, line 14: "sdudies" should be "studies"
Page 22, line 6: "5-iodoprimidine" should be "5-iodopyrimidine"

Phone: +420 220 444 245, fax: +420 220 444 288, e-mail: tomas.tobrman@vscht.cz, www.vscht.cz

UNIVERSITY OF CHEMISTRY AND TECHNOLOGY, PRAGUE
Faculty of Chemical Technology
Department of Organic Chemistry

Page 29, line 19: "are play" should be "play"
Page 36, line 29: "wa" should be "was"
Page 60, line 13: "2- 3" should be "2-3"
Page 83, line 13: "20 ml" should be "20 mL"
Page 179, line 4: "Eur. J. *Org. Chem.*" should be "*Eur. J. Org. Chem.*"

The following questions arose while reading this document:

1. It was shown (page 42, scheme 35), that the Arbuzov reaction proceeds on aryl halides, but no example was provided in ref. 136. In my opinion, the Arbuzov reaction is mainly associated with sp^3-hybridized reaction centers unless specific additives/conditions are used (e.g., visible-light activation, *ACS Catalysis* **2016**, *6*, 8410). Please comment on the meaning of the Arbuzov reaction in scheme 35.

2. Mn(III)-catalyzed phosphonation of 7-unsubstituted 7-deazapurines proceeds smoothly (Table 9, page 62). However, the use of 7-fluoro derivative failed to give the expected products. Please comment on the observed reactivity pattern.

3. It is quite surprising that silylation of 9-benzyl-6-phenyl-7-deazapurine gave only a trace amount of bissilylated product **19c** even with an excess of triethylsilane. Do you have any explanation for this observed selectivity?

4. Pd-Catalyzed cross-coupling reaction was used for the preparation of 6-aryl-4-fluoro-7-deazapurines, and then simple chromatography was used to remove traces of palladium. Did you check the palladium content in samples before the biological-screening experiments?

Let me conclude this report by saying that the presented Ph.D. thesis is a collection of high-quality original results. The aims of the thesis were reached, and Mgr. Sabat is the first author of five publications in peer-reviewed journals. Therefore, I recommend accepting this Ph.D. thesis as the basis for defending the Ph.D. academic degree.

In Prague, 15. 11. 2017

Doc. Ing. Tomáš Tobrman, Ph.D.

Phone: +420 220 444 245, fax: +420 220 444 288, e-mail: tomas.tobrman@vscht.cz, www.vscht.cz