Reviewer's Dissertation Thesis Report

Dissertation Thesis Title:	**Synthesis, Biological Profiling and Photophysical Properties of Polycyclic Hetero-Fused 7-Deazapurine Nucleosides**
PhD Student:	**Chao Yang**
Reviewer:	Mgr. Radim Nencka, Ph.D.

Chao Yang's Ph.D. thesis discusses new 7-deazapurin nucleoside derivatives with annulated heterocyclic moieties in the position 7 and 8 that have been designed as compounds with potential biological activity, in particular, antiviral and antineoplastic activities. However, these biological properties were not the only focus of the dissertation, and a significant part of the work was also devoted to the applicability of the compounds as fluorescent probes for nucleic acid labelling and their usability in primer extension experiments. In general, the overall concept of the thesis corresponds very well with the focus of the group supervisor (Prof. Michal Hocek) and is in principle a logical continuation of the work of the whole group. However, in many aspects the PhD. candidate showed that he tried to choose innovative approaches, especially in the synthetic part of the thesis.

The structure of the whole work is traditionally conceived and covers all formal parts. The work is written in English, which, in my opinion, is at a high level and also in terms of style, I did not find any major defects. The whole work is relatively readable.

The first part of the thesis is devoted to the introduction to modified nucleoside derivatives. In this introduction, the PhD candidate describes modifications of individual parts of the nucleoside/nucleotide molecule. He demonstrates what modifications of nucleobase, sugar part and phosphate moiety led to new compounds or even drugs with antiviral or cytostatic activity. In addition, he illustrates that combinations of modifications of nucleosides and nucleotides very often also lead to new substances with interesting biological properties. In the following part of the introduction, the PhD candidate tried to summarize the work that was done in the field of nucleosides with modified 7-deazapurine in Michal Hocek group and then briefly comments on the work of other groups on derivatives with bulky modifications on nucleobase. In the last part of the introduction, he discusses synthetic approaches to nucleosides with fused 7-deazapurine nucleobases and subsequently synthetic approaches to sulfonium salts and their use in cross-coupling reactions. Overall, the introduction to this dissertation is quite comprehensive and it gives the reader a good overview of the topics and objectives discussed in the next text.

It is clear from the Results and Discussion section that the PhD candidate has drawn on his two publications in writing this text and he has tried to include some unpublished data and his observations from the course of the work. This makes the whole the text quite clear and readable, with very few formal or factual errors or

ambiguities. The first part of the experimental work is undoubtedly nice chemistry, although it is not groundbreaking and, in many ways, it is rather routine, these days. However, for me personally, it is a very nice reminder of what I myself dealt with in my dissertation and therefore I know that this work requires a great deal of experimental skill and self-discipline. As I find Negishi coupling of pyrimidines being an underappreciated methodology worth developing further, the second part is really interesting for me. The candidate showed interest in the latest trends and was able to focus on a very exciting segment of the whole research field, to the extent that he described a new cross-coupling on pyrimidines, which is involved in the preparation of new leaving groups based on a sulfonium salt.

This dissertation undoubtedly builds on the very fine work that the PhD candidate was able to publish. Especially on the very nice and innovative work in J. Am. Chem. Soc. which in itself is a good start for a career in the field of organic synthetic and bioorganic chemistry.

In conclusion, I am convinced that Chao Yang has done a decent job on the field of synthetic and applied chemistry and he proved that he deserves the PhD title, and therefore I recommend this work for defense.

Mgr. Radim Nencka, PhD.

The most important questions for the author:

1. The statement that the second synthetic step (**1** to **2**) gave 88% of compound **2** caught my attention, because comp **2** should have somewhat higher MW than substance **1**. However, in the experimental section, the author starts with 410 mg of starting substance **1** and gets 332 mg of substance **2**. Is the yield really right?
2. On page 50/54 author says that azidopyridine is necessary for the next step (**2** to **3/ 8** to **9**). If this is the case, why does he show the tetrazol form as the starting substance in the Table 1/3? What is the mechanism of this reaction and why can it not be based on the tetrazol precursor?
3. What is the predicted mechanism of action for the antiviral activity of the most potent of the first **6e** series? Is the activity not rather due to a non-selective effect on the cells?
4. I assume that compound **17** is the same ate complex as the substance shown in Scheme 12.

- Is there any new information known about the structure of these complexes?
- How do compounds prepared by deprotonation using lithiation (BuLi/tBuLi) or the common Turgo Grignard reagent (iPrMgCl/Br)-RZnCl, RZnBr behave?
- Is there any difference between these and the R_2Zn species for ease or efficiency of the Negishi reaction?
- Are RZnCl precursors capable of giving similar yields?
- And what about Kumada coupling and sulfonium precursors?