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Supervisor's evaluation and report
on PhD thesis

**Synthesis of Novel Hetero-fused 7-Deazapurine Nucleosides and Nucleotides with
Potential Biological Activity or for the Modifications of DNA and RNA**

author: **Marianne Fleuti**

Marianne Fleuti performed her PhD research project under my supervision from 2016 till 2023. The aim of her PhD thesis was the synthesis of novel nucleosides derived from hetero-fused deazapurine bases. In the first part, she developed the synthesis of two isomeric series of N-methylpyrrazolo-fused deazapurine nucleosides and synthesized a series of derivatives for biological testing. In the second part, she contributed to the study of a new approach for the synthesis of several new types of polycyclic fused deazapurines based on C-H dibenzothiophenation followed by the Negishi cross-coupling and heterocyclization. Unfortunately for her, the five-membered heterocycles which she studied were not reactive for this type of C-H activation and were also quite unstable so this approach did not prove to be useful for the synthesis of tricyclic fused deazapurine bases. In the last part of her thesis, she attempted the synthesis of quinolino- and isoquinoline-fused deazapurine bases and nucleosides. The chemistry was very difficult and out of the 4 possible isomer, only one was feasible to be synthesized, whereas in the other cases the cross-coupling, azidation or cyclization failed. She synthesized a small series of quinolino-fused deazapurine nucleosides which were tested for cytostatic activity. One nucleoside was also converted to triphosphate and tested as substrate for RNA polymerase. The results were published in 2 papers with Marianne Fleuti as the first author (JOC and ACS Omega) and she participated as co-author on one additional paper in JACS.

Marianne is a very tidy, perfectionistic and obstinate person which made her quite difficult to supervise and prevented her from being more efficient. She also fought with mental health issues. The result was that her thesis took longer than it should. On the other hand, she managed to synthesize two series of target nucleosides that were difficult to make and her thesis is in an acceptable shape and scope.

I can conclude that **Marianne Fleuti** fulfilled the requirements for the PhD title and I recommend her thesis for defense and further proceeding to be awarded the PhD degree.

In Prague June 3, 2024

Prof. Ing. Michal Hocek, CSc., DSc.