Ph.D. Thesis Review

Ph.D. thesis author: MSc. Chao Yang

Author´s affiliation: Faculty of Science, Charles University Prague

Ph.D. thesis title: Synthesis, Biological Profiling and Photophysical Properties of Polycyclic Hetero-Fused 7-deazapurine Nucleosides

Reviewer: Assoc. Prof. Miroslav Soural

Reviewer´s affiliation: Faculty of Science, Department of Organic Chemistry, Palacky University Olomouc

Contact e-mail: miroslav.soural@upol.cz

The submitted thesis is targeted to the field of modified nucleosides. Author has focused on two subprojects aiming to the preparation and study of 7-deazapurine analogues. First, he designed and synthesized derivatives with annelated benzothiophene scaffold. The series of C6-modified (according to the purine scaffold numbering) nucleosides was prepared using conventional synthetic method and the fluorescence properties were examinated. Next, a selected nucleotide was prepared and studied as the fluorescent label in oligonucleotides. Finally, the whole set of prepared derivatives was tested for antiviral and cytotoxic properties. In the second part of his work, author has focused on developent of original method to access the key intermediates for base-modified nucleosides using Negishi coupling *via* sulfonium salts. After a careful optimization, he succeeded and prepared the set of diverse (hetero)arylated-dichloropyrimidines. Some of them were successfully converted to desired nucleosides containing one, two or three fused/nonfused thiophene scaffolds. As in the previous case, a selected compound was studied as the fluorescence label in oligonucleotides and the whole set of prepared derivatives was screened for their cytotoxic and antiviral activities.

The submitted thesis has 209 pages and is standardly divided to individual chapters. The Theoretical part deals with modified nucleosides and represents - in my opinion - very nice, though brief overview of this area. I also appreciate addition of the last subchapter devoted to the chemistry of sulfonium salts to give some background necessary for the second aim of the Ph.D. thesis. The both aims are then rationally specified in an individual chapter followed by the Results and Discussion part, which describes the synthesis development and study of physico-chemical and biologial properties. In my opinion, this part is logically and clearly written. After Conclusion, the Experimental part follows with all standard analytical data (NMR, HRMS), followed by selected NMR spectra and the list of 142 references.

The whole text is carefully written and contains only a negligible amount of formal errors (such as „adamantly“ in list of abbreviations; page 32: „menbered“; page 37 and elsewhere: „[4,5-b]“-b should be in italics), thus the thesis is at high level of formal quality. The quantity of summarized results clearly shows that author has worked on the project with the real engagement. The thesis contains highly valuable and

original findings applicable for further research in the field of modified nucleosides. This can be undoubtedly supported by the fact that the results were already published in prestigious scientific journals. **Overall, author proved his competences in the field of advanced organic synthesis and its use in challenging, multidisciplinary projects. For this reason, and with respect to quality of the thesis, I do recommend to enter the defence procedure.**

Specific comments and topics for discussion:

1) Author claims that azidation gave a mixture of azidoderivatives and tetrazolopyrimidines (**2a**/**2b**, **8a**/**8b**) in different ratios. I wonder how the assignment of signals was done. Could author show an example of spectra an its analysis?
2) Table 1/Table 3 shows the conversion of only tetrazol, not azidoderivative. Why? Can author suggest the mechanistic conversion of **2a** to **3**? What should be the role of Rhodium catalyst?
3) Could author make more comments (or eventually show data of corresponding, previously studied analogues) on the selection of specific substituents for series **6a-h** (Scheme 11) and **12a-h** (Scheme 14).
4) On the page 57, author reports that „Importantly, 1,4-dioxane must be used…“ Why is it so?
5) On the page 47, author gives a rationale for design of target compounds. However, it´s well known that sulphurous heterocycles are isosteric, or even bioisosteric with the corresponding carbocycles: i. e. thiophene - benzene, benzo[*b*]thiophene – naphthalene etc. Thus very close similarity in properties of compounds **6**/**12** and the previously studied naphtho-fused analogues would be quite expectable. Could author explain how should the presence of sulfur instead of C=C improve the properties?
6) The use of (het)arylsulfonium salt is very nice alternative (although limited only to electron-donating groups). However I am a bit confused with the limited applicability toward five membered heterocycles (Scheme 16). Could author provide more details instead of just „negative results“?

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Reviewer´s signature

Katedra organické chemie
Přírodovědecká fakulta Univerzity Palackého v Olomouci
17. listopadu 1192/12 | 771 46 Olomouc | T: 585 634 406
orgchem@orgchem.upol.cz
www.orgchem.upol.cz

Department of Organic Chemistry
Faculty of Science | Palacký University Olomouc | Czech Republic
17. listopadu 1192/12 | CZ 771 46 Olomouc | T: +420 585 634 406
orgchem@orgchem.upol.cz
www.orgchem.upol.cz