

Expert opinion on Dissertation Thesis

Dissertation Thesis entitled "Preparation and Study of Photoprotective and Antimicrobial Properties of Novel Materials Based on 1,2,3-Triazole" was submitted by **David Miličević** as prerequisite for obtaining PhD academic degree. Dissertation itself consists of 115 numbered pages arranged into 7 chapters accompanied with appropriate list of References. In short Introduction the author briefly acquaints reader with the discovery and significance of alkyne-azide [3+2]-cycloaddition giving 1,2,3-triazole derivatives and with its Cu-catalyzed variant. The metal-catalyzed (Cu, Ru) variants are further discussed in detail together with strain promoted cycloaddition involving cyclooctyne derivatives. Third chapter summarizes practical applications of 1,2,3-triazoles especially as coordinating *N*-ligands in metal complexes with various utility. Biological properties of compounds containing 1,2,3-triazole moiety are also described. Then Aims and Objectives are defined which involve multistep synthesis of novel 1,2,3-triazole functionalized quinoline-2,4-diones and their evaluation as photoprotective or antimicrobial agents. The most important is Chapter 5 (30 pages) which summarizes and discusses results obtained by the candidate during his study. This part also compares relevant previous results. Next Chapter 6 describes all experiments and measurements discussed in the previous part. Remaining parts covers short Conclusion, References and short CV.

The thesis itself is written in an intelligible way – only several English errors or unsuitable phrases can be found. However these minor imperfections have no influence on the overall quality of the Dissertation thesis.

The following questions and comments should be appropriately answered during *viva voce*:

1) In Chapter 2.1 the author discusses mechanism of Cu(I)-catalyzed alkyne-azide cycloaddition (CuAAC) but some fundamental works are omitted. Kinetic measurements of CuAAC reaction catalyzed with well-defined mono- and dinuclear Cu(I) phenylacetylide complexes containing NHC ligand(s) has clearly proved participation of dinuclear species (see e.g. L. Jin, D. R. Tolentino, M. Melaimi, G. Bertrand, *Sci. Adv.* **2015**, *1*, e1500304).

2) On page 58 the author explains lower reactivity of 3-methyl derivative. However, his explanation is not correct at all. Phenyl group is definitely not electron-withdrawing substituent (*cf.* Hammett sigma constants). The actual reason for big difference in reactivity lies in much better nucleofugality of C3-carbanion, which is resonance-stabilized not only with carbonyl (C2) and triazolyl moiety but also with phenyl. The rate-limiting step probably involves cleavage of an adduct formed from **5a,b** or **6b** and methoxide in previous faster step (pre-equilibrium).

3) I do not understand why chapter 5.5.1 is included in the Thesis? The author talks about three (not specified) triazole derivatives first but then rejects them as they were not synthesized in his laboratory. Another question concerns metal complex choice. Why only $[\text{RuCl}(\mu\text{-Cl})(\eta^6\text{-}p\text{-cymene})]_2$ was tested for coordination ability with bis-(1,2,3-triazolyl) derivatives? This part should be omitted.

4) The evaluation of photoprotective properties of prepared compounds should be better substantiated. While the biological activities of many triazoles are well known (as illustrated in Chapter 3.5) there is no mention in the text why triazoles should be promising candidates as photoprotective agents. Moreover, only simple UV maxima were measured, which is not enough to judge the expected properties.

5) Today, computer-aided drug design approach is routinely used for searching of new pharmacophores (docking studies etc.). As demonstrated on several examples – 1,2,3-triazole ring is present in several active antimicrobial agents – but again, there is no substantiation why just prepared derivatives should be active.

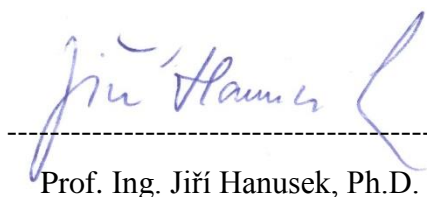
Minor points:

- 1) In Scheme 15 substituents R^1, R^2 are not specified, therefore no information from formulas A and B can be obtained.
- 2) Stereodescriptors *cis*- and *trans*- and letter locants should be always in italics. This is not the case in Fig. 8 or on p. 27/line 11.
- 3) Calyx[4]arenes are calix[4] arenes.

In conclusion, from the point of view of Organic Chemistry the Thesis is well elaborated and brings original results although other tasks were not so successful.

According to §47 Article 4 of the Act No. 111/1998 Coll. on Higher Education Institutions and on the Amendments and Supplements to Other Acts (the Higher Education Act) I can **recommend** this thesis as necessary prerequisite for *viva voce* and after its successful defense for awarding a PhD degree.

In Pardubice 14.5. 2019



Prof. Ing. Jiří Hanusek, Ph.D.

Institute of Organic Chemistry and Technology
Faculty of Chemical Technology, University of Pardubice