

Assessment of Doctoral Thesis

**Preparation and Study of Photoprotective and Antimicrobial Properties
of Novel Materials Based on 1,2,3-Triazole**

by David Miličević

(reviewer: Robert Vícha)

The Thesis, that I was invited to review, describes preparation, spectral characterization and biological activities of quinolone-2,4-dione compounds which were substituted with two 1,2,3-triazole rings at positions N1 and C3. This chemistry is an extension of doc. Kafka research group's long-term studies on quinolinedione compounds.

As it is common, the text is divided into three main chapters: Introduction, Results and Discussion, and Experimental part. In Introduction section, the author provides general information regarding history, properties, synthesis and applications of 1,2,3-triazole derivatives. Since the chemistry of 1,2,3-triazoles is extremely rich (SciFinder provides more than 1.333×10^6 compounds), I understand that the selected examples have to represent rather the author's choice than a full insight into this field of chemistry. On the other hand, the examples are representative and adequate to introduce readers to the matter. I appreciate a couple of examples from supramolecular chemistry which demonstrate that triazole ring formation can be used for construction of large molecular architectures.

Reading the Results and Discussion section, it became clear that synthesis of target compounds was the main intention of the work. The preparations from starting compounds to bis(triazole)quinolindiones and subsequent transformations of alcohols to aldehydes and carboxylic acids are described in full details, fluently and clearly. However, the minor branches dealing with ring-opening studies, complexation abilities and photo-protective properties could be more elaborated to emphasize rather a discussion than a description point of view.

The Experimental section is written with a care and I believe that eventual followers will be able to repeat the experiments without any problems.

Indeed, my job is to find flaws and set some questions. Thus here they are:

First of all, I have to say that I did not find any justification of a lot of effort which was paid to prepare target compounds, particularly the aldehydes and acids, throughout the Thesis. Therefore, I encourage the author to present his standpoint during defence and support it with some similar structures and/or original hypothesis regarding expecting properties and/or functions of the target molecules.

Following remarks and questions are page-referenced bellow.

Page 58 Discussion of the C3 substituent influence on the cleavage rate. The author states that electron withdrawing phenyl ring make the C3 atom more sensitive to a nucleophilic attack. Does the author mean that the cleavage starts with a nucleophilic attack of the methoxide anion at the C3 atom of the quinolindione ring? I am asking the author to be so kind and show us his idea of the cleavage mechanism.

Page 59 (and the procedure on the page 103) The author states that acids **20** were formed after acidification of the mixture (within a work up procedure) via hydrolysis of the initially formed methyl esters **19**. However, the acids **20** were isolated in quite high yields (30-70%) and several points are not clear. Author states that mixtures were "neutralized" with HCl. Was the actual pH "neutral" or an excess of HCl was present? How long was the mixture treated with HCl? Was the reaction carried out under inert atmosphere or OH⁻ could be formed via reaction of MeO⁻ with moisture? Were acids **20** (or their salts) detected during alkaline treatment? Since the chapter is called "Ring-opening studies", I would expect more detailed insight into the issue and/or more precise designing of the monitoring procedures and results presentation. Finally, it is not clear what does the statement "transformation was complete" mean. Was an equilibrium reached with significant portion of starting compound or all starting material was consumed?

Page 60 How did you distinguish ring D and ring A of the target bis(triazolo)quinolinediones in the NMR spectra?

Page 66 In my opinion, a bit elaborated study on coordination abilities of bistriazole compounds would be a nice part of this Thesis. I noticed that the author did not prepare the compounds, which displayed some complexations with Ru, as he states on page 67 (By the way, I am wondering who did synthesize these compounds? The compound displayed in the Scheme 44 is included in the published paper from David Miličević *et al.* (*Molecules*, **2018**, 23(9), 2310) along with a claim that experiments were done by DM).

Nevertheless, this section is included in the Thesis and I would be happy if the author provides some further explanations. First of all, how do the NMR spectra indicate that Ru complexes with bistriazole compounds are formed? Additionally, how do the NMR spectra indicate that these complexes are weak? And finally, I counted all the signals in showed aromatic part of ^1H NMR spectrum of free and complexed bistriazole (Figure 24) and there seem to be no additional signals of cymene, which should be coordinated to the Ru, as Scheme 44 suggests. Please, clarify this.

Page 78 The compound **4b** is reported as a DMF solvate. However, there are no signals related to the DMF in lists of ^1H and ^{13}C NMR spectra. On the other hand, one additional band (1654 cm^{-1}) is listed in carbonyl area of IR spectrum (compared with the IR spectrum of the compound **4a**). Please, clarify identity and spectral characterization of this compound.

Page 45 (and many times elsewhere in the text): The yields of new compounds are given in the Schemes. The purity is stated to be determined by TLC and IR. Please explain, how the purity could be determined using IR. Were some authentic samples available for comparison?

Minor comments:

The Tables 13–17 seem to be redundant since all chemical shifts are listed in the experimental section.

The text in Table 18 is not formatted properly.

Throughout the document, some wording could be better, some grammatical and typing errors can be found. However the portion of mistakes is not significant and text is readable and clear.

In conclusion, I can state that the intentions of the work, which are defined on page 41 were achieved, substantial part of the work has been already published or is under consideration by a journal editor. The Thesis matches all formal and scientific requirements and therefore I recommend it for defence.

In Loučka, 24th May 2019