

Ph.D. Review Report
PhD thesis „Development of novel cholinesterase modulators“

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Reviewer: prof. Stanislav Mičuda, MD, PhD.

1. General description

The thesis is properly structured document fulfilling requirements for this type of scientific work, and contain all necessary issues: Introduction, Aims, Discussion, Conclusions, References, Enclosed publications etc. The thesis span over 228 pages with additional three enclosed highly impacted articles where Mr. Górecki is the first author. The extent and content of all chapters is appropriate, and satisfactory. The introduction presents all necessary information to justify the aims of the research. Dedicated methods are innovative and corresponds with the objectives of thesis. Discussion explains all findings achieved during postgraduate studies of the student. Referred citations are mainly from the last ten years, and they support actual relevance of solved scientific problems together with a proper orientation of the author within the recent sources of scientific data.

Overall scientific performance: Scopus refers to 12 publications of the author, 88 total citations and the *h-index* of 5.

2. Scientific content

The data presented by the author in the thesis and enclosed articles further extends continuous scientific work of the research group within the development of acetylcholinesterase inhibitors and reactivators. Author presents methods of synthesis that yielded tacrine-phenothiazine derivatives, AChE and the NMDA dual-targeting tacrine derivatives, Cys-targeted insecticides, mono-quarternary permanently charged and others AChE reactivators. I should appreciate combination of chemical synthetic methods with biological screening to predict potency, efficacy and toxicity of obtained compounds.

The scientific content of thesis is current and relevant in the context of up-to-date development of potential therapeutic modalities for Alzheimer's disease and organophosphate intoxication.

3. Remarks to thesis:

Table 8 and 9 presents different IC₅₀ values for the same AChE inhibitors and values are somewhat mixed between individual compound – please explain.

4. Questions:

- Huge extent of presented scientific work indicates contribution of many scientists. Could the author specify his contribution to obtained results?
- Could the author explain which of presented compounds are considered for further *in vivo* testing and which selection criteria have been used? Are some data already available? How the authors overcome poor solubility of obtained agents?
- Why the drug toxicity was tested on HepG2 cells?
- Combination of tacrine and phenothiazine may be interesting in penetration into CNS and inhibitory potency at AChE. However, phenothiazines are known for direct inhibitory effect at M receptors, which may counteract positive effect of cumulating acetylcholine and produce numerous adverse drug reactions in patients such as confusion and memory impairment. Have the author considered this discrepancy?
- Are there available any *in vivo* data which may confirm selectivity of synthesized insecticides on target species? How it could be tested?

Conclusion:

In my opinion, the thesis fulfils all formal requirements at excellent level. Scientific content of thesis corresponds with the approved topic of postgraduate work of the student. The aims of the work have been accomplished successfully by using appropriate methods. Conclusions are correct with obvious scientific contributions to current knowledge within the topic. Publication activity of author is exceptional. The thesis meets all the requirements imposed on the dissertation work in the field. I recommend PhD thesis presented by Mr. Górecki for defense; after successful process, I recommend granting him an academic title „Ph.D.“.

Hradec Králové; May 29th, 2019

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