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Review of the doctoral thesis of Kavya Kondaka entitled "Yeast DNA Topoisomerase II as a model molecular target for novel antifungal compounds" prepared at Gdańsk University of Technology (supervisor: Ph.D., D. Sc., Eng. Iwona Gabriel, Gdańsk Tech Professor)

The PhD thesis of M. Sc. Kavya Kondaka constitutes a comprehensive study focused on the potential use of fungal topoisomerase II as a selective molecular target in the antifungal drug design. The topic addressed in this dissertation is timely due to the need of seeking new therapeutic approaches for fungal infections. Fungal pathogens pose a serious threat to the public health, as they are becoming increasingly common and resistant to available treatments. They cause infections that can lead to severe morbidity and even mortality, particularly in immunosuppressive patients. It is noteworthy that this dissertation was developed at the Faculty which boasts long-standing expertise and considerable success in researching fungal enzymes as potential molecular targets in the treatment of fungal infections.

The reviewed PhD dissertation takes the form of a thematically coherent series of four multi-authored scientific papers (ranging from two to seven authors), published in recognized journals (*Molecules*, *Scientific Reports* and *European Journal of Medicinal Chemistry*) between 2022 and 2026. In my opinion, a selected form of the PhD thesis is justified, especially because all four papers comprehensively describe a full set of research - from a literature review and studies of clinically used topoisomerase II inhibitors to the design, synthesis, and testing of new topoisomerase II inhibitors antifungal activity. The cumulative impact factor of these papers is 21.1 according to the *Journal Citation Reports* database, corresponding to 560 points on the ministerial list, which reflects the high quality of the conducted research. It is noteworthy that the PhD candidate is the first author of three of these papers, which underscores her substantial

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contribution to their preparation. This is further confirmed by the detailed descriptions of the author's role in the research provided in the reviewed dissertation (co-authors' statements were not included). M. Sc. Kavya Kondaka performed the majority of the laboratory experiments related to the antifungal evaluation of the tested compounds, including enzyme inhibition assays, antifungal susceptibility testing (MIC and MFC determination), ROS detection, flow cytometry-based oxidative stress analyses as well as investigations of *Candida albicans* morphological transformation and biofilm formation. She contributed to the interpretation of experimental results as well as the results of bioinformatic analyses. In addition, she was involved in the preparation of figures, tables, and supplementary materials, conducted an extensive literature review and contributed substantially to the writing of the manuscripts. To date, the doctoral candidate's contribution to conceptualisation has been limited to review papers, with no demonstrated involvement in the conceptualisation of experimental research projects.

The dissertation begins with declaration of authorship and abstract of PhD thesis in both Polish and English followed by acknowledgments, content of doctoral dissertation, a list of publications comprising the doctoral thesis together with presentation of the PhD candidate's role in the performed research, Introduction, Chapter 3 entitled as *Yeast Topoisomerase II as a model organism*, aim and objectives of the research, texts of 4 publications comprising the doctoral thesis and a summary of the findings presented in each one, list of abbreviations, summary, a second set of acknowledgments (in this case, referring to co-founders), scientific achievements of M. Sc. Kavya Kondaka, references listing 205 positions, where almost half of the papers were published within last 10 years and appending included list of figures and list of tables.

In Introduction section, the PhD candidate presented the current challenges in antifungal therapy and highlighted fungal DNA topoisomerase II as a promising therapeutic target. She discussed the enzyme's role, its differences from the human counterpart, and recent advances in the design and optimisation of selective topoisomerase II inhibitors with antifungal potential. In Chapter 3, the doctoral candidate complemented the Introduction by further developing the discussion of yeast topoisomerase II as a model system and a fungal-specific drug target. In my opinion, to avoid unnecessary separation of related concepts, this material should be integrated into the Introduction section. Both sections are written clearly and concisely, presenting the information necessary to understand the further parts of the dissertation.

The aim of the reviewed doctoral thesis was to verify the hypothesis that fungal topoisomerase II can serve as a molecular target for antifungal chemotherapy. It is clearly defined and well aligned with both the title and the overall content of the dissertation.

In the first publication, M. Sc. Kavya Kondaka presented a comprehensive and well-structured review of fungal topoisomerase II as a potential drug target, highlighting the urgent need to develop novel antifungal strategies in response to the increasing prevalence of drug resistance. Although fungal and human topoisomerase II enzymes share a high degree of structural similarity, they differ significantly in several regions. These differences provide opportunities for the design of selective inhibitors that specifically target the fungal enzyme. The paper provides a solid conceptual foundation for the research presented in this thesis.

In the next publication, the doctoral candidate investigated a panel of eleven antitumor drugs, targeting human topoisomerase II, to assess their potential for repurposing as antifungal agents. Such approach, known as drug repurposing, is widely recognised as a rapid, cost-effective, and reduced-risk strategy for the development of new treatment options. Although most of the tested compounds proved to be potent inhibitors of yeast Topoisomerase II, only a few exhibited significant antifungal activity. Among them, idarubicin emerged as the most promising compound, effectively inhibiting the growth of both reference fungal strains and clinical fluconazole-resistant *Candida glabrata* isolates. Overall, the results demonstrate that fungal topoisomerase II represents a promising target for antifungal therapy, and the described drugs, particularly idarubicin, may serve as a valuable scaffold for the development of novel antifungal agents.

The third publication focused on a comparative structural analysis of fungal and human topoisomerase II enzymes to support structure-based antifungal drug design. The studies, which included sequence analysis, molecular dynamics simulations, and phylogenetic comparisons, enabled the identification of unique structural features in fungal topoisomerase II compared with the human enzyme. These studies provide valuable insights into the structural determinants that may be exploited for the design of selective antifungal inhibitors.

In the last publication M. Sc. Kavya Kondaka focused on design, synthesis, and biological evaluation of novel bisacridine derivatives as potential antifungal agents targeting fungal topoisomerase II. The synthesised compounds were studied for yeast topoisomerase II inhibition, antifungal activity, and selectivity over the human enzyme. Among the tested derivatives, IKE16 demonstrated the strongest inhibition of yeast topoisomerase II, with

favorable selectivity over the human counterpart and moderate *in vitro* antifungal activity. Notably, although IKE18, IKE19, and IKE21 were weaker enzyme inhibitors, they exhibited significant antifungal effects and were able to overcome fluconazole resistance. Moreover, IKE18 and IKE19 showed higher selectivity indices. Considering the results of experimental studies and in silico analyses, the PhD candidate proposed a possible mechanism underlying the observed activity profile of the investigated compounds, suggesting their distinct mode of interaction with fungal topoisomerase II.

I read M. Sc. Kavya Kondaka's doctoral dissertation with great interest. Despite the high quality of the PhD thesis, the doctoral candidate was unable to avoid errors and editorial flaws during the editing process for instance:

- term "yeast topoisomerase" should be translate as drożdżowa topoizomeraza instead of drożdżówa topoizomeraza (pages 2, 5);
- page 106-107, references 13 and 24 are the same;
- page 65, it should be binding instead of "biding".

After reading this dissertation, the following comments and questions occurred to me and need further explanation:

- Second publication and its accompanying description lack information regarding the source of the investigated drugs and their physicochemical characteristics.
- Did you consider including to research described in this publication any antitumor drugs containing acridine derivatives?
- The descriptions of some procedures are not always precise enough for instance:
    - In the second publication we can find information: "MIC parameters were determined according to the previously described method[24]" but in reference 24 there are only a few sentences that do not bring sufficient details and citation of the next reference. I believe it would be beneficial to referee to the second citation directly.
    - In the forth publication – it is unclear why Scheme 1 shows more synthesis steps than those described in the Materials and Methods section (4.1.1).The description of the purification procedures for the compounds under study is too brief. The conditions used for the HPLC analyses, as well as representative HPLC, MS, and ^{1}H NMR spectra, are missing.

The shortcomings mentioned do not detract from the substantive value of the dissertation, in which M. Sc. Kavya Kondaka, presented very valuable findings.

In summary, the topic addressed in this dissertation is both interesting and timely. The thesis is well structured, and its aim was clearly defined and successfully achieved. The obtained results have undoubtedly expanded the current knowledge of yeast DNA topoisomerase II and demonstrated that this enzyme represents a promising target for the development of novel antifungal drugs. The dissertation contains clear elements of scientific novelty, as evidenced by the valuable publications arising from this work.

The doctoral candidate's academic achievements include five publications in *JCR*-indexed journals (she is the first author on three of them) and five poster presentations at scientific conferences, including three international conferences. M. Sc. Kavya Kondaka completed two internships funded by the Polish National Agency for Academic Exchange (NAWA) and was a four-time recipient of scholarships from the IDUB programme. Notably, the research conducted as part of her doctoral studies was funded by the National Science Centre (OPUS grant).

I am fully convinced that the reviewed doctoral thesis fulfils the requirements for a doctoral dissertation specified in the Act of 20 July 2018 – Law on Higher Education and Science, as amended. I therefore recommend the Council of the Chemical Sciences Discipline of Gdańsk University of Technology allow M. Sc. Kavya Kondaka to the subsequent stages of the doctoral procedure.

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