CNRS UMR9018 METSY
Metabolic and systemic aspects of oncogenesis for new therapeutic approaches

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Evaluation of the PhD thesis by Ms. Kamila BUZUN
« Molecular mechanism of anticancer activity of novel 4-thiazolidinone derivatives »

General Remarks:

The thesis of Ms. Kamila Buzun is dedicated to the study of new potential anticancer drugs.

The thesis is introduced by a concise literature review. Ms Buzun has briefly introduced the notions essential for the understanding of the subject. I was initially surprised by the shortness of the introduction, but then I realized that most of the subjects were covered by two review papers published by the applicant. I would recommend including these two reviews in the introduction section, to help the reader and to better separate the literature and the experimental sections of the thesis.

The first review "*DNA topoisomerases as molecular targets for anticancer drugs*" published in the Journal of Enzyme Inhibition and Medicinal Chemistry extensively describes known topoisomerase I and II inhibitors and their application in clinics.

My only regret is that Ms. Buzun did not discuss the "dark side" of topoisomerase inhibitors, their ability to induce secondary cancers, e.g. treatment-related leukemias. My question would be whether all described topoisomerase-targeting drugs have the same ability to induce these treatment-related cancers?

The second review entitled "*Autophagy Modulators in Cancer Therapy*" was published in the International Journal of Molecular Sciences. It briefly discusses recent advances in the vast field of autophagy research and summarized autophagy-targeting drugs and their application fields.

In the first part of the experimental paper «*Synthesis and Anticancer Activity Evaluation of 5-[2-Chloro-3-(4-nitrophenyl)-2-propenylidene]-4-thiazolidinones*» published in Molecules, the applicant described the synthesis of several 4-thiazolidinone derivatives and then evaluated their anticancer activity using a panel of cancer cells with non-proliferating human blood lymphocytes used as a control. The author identified the most efficient compounds with a potential therapeutic activity against several cancers at sub-nanomolar doses.

It is regretful that the author did not use proliferating normal cells (primary human cell lines or transformed non-cancerous cell lines) as controls to assess the potential secondary effects of action of the described compounds. Another question concerns Figure 5 of the paper. The data for compound 2j seems to be missing at the concentration of 2uM. Finally, it would be

helpful to discuss the potential mechanisms of action of the synthesized compounds in more details.

The paper "*2-{5-[(Z,2Z)-2-Chloro-3-(4-nitrophenyl)-2-propenylidene]-4-oxo-2-thioxothiazolidin-3-yl}-3-methylbutanoic Acid as a Potential Anti-Breast Cancer Molecule*", International Journal of Molecular Sciences is devoted to synthesis and evaluation of an anticancer activity of another 4-thiazolidinone Les-3331 with a potential activity against breast cancer. This time, the author used a more appropriate control, human skin fibroblasts. Ms. Buzun also investigated the mechanism of anticancer activity of Les-3331 using a variety of methods, including molecular docking. The compound was found to have a DNA topoisomerase II binding capacity.

My question is whether, according to docking results, Les-3331 would prevent DNA topoisomerase II binding to DNA, similarly to ICRF-193 or rather block its complex with DNA similarly to etoposide?

Another question is the decrease in DNA topoisomerase II protein levels in Les-3331-treated cells. Does this occur on a transcriptional level or *via* protein degradation? Were any additional experiments done to find this out?

I am a little bit disappointed by the absence of general discussion and perspectives section; this would be particularly suitable in this work where the applicant has identified new potential anticancer compounds. Whether this work will continue to carry these compounds to a pre-clinical stage? What is missing and/or necessary to achieve this? Can the compounds studied in this work be improved, and if yeas, in what way? What are the general perspectives of Ms. Buzuns's work?

The remarks do not question the scientific value of MS. Buzun's thesis. Kamila Buzun is the first author in all cited papers and her input in the work is beyond any doubt, as confirmed by the co-authors' statements. Given the fundamental importance of the project and the perspectives opened by this work, I consider that MS. Buzun fully deserves the title of Doctor of the Medical University of Bialystok, and give a favourable opinion to the public defence.

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Request for distinction

of the PhD thesis by Ms. Kamila BUZUN
« Molecular mechanism of anticancer activity of novel 4-thiazolidinone derivatives »

The PhD thesis of Ms. Kamila Buzun dedicated to the study of new potential anticancer drugs is comprised of four publications in high impact journals.

During her PhD thesis work, Ms. Buzun synthesized several 4-thiazolidinone derivatives and then evaluated their anticancer activity using a panel of cancer cells. The author identified several efficient compounds with a potential anticancer therapeutic activity at sub-nanomolar doses and studied the molecular mechanisms of their action.

The thesis is well written and well documented; it opens new perspectives for development of 4-thiazolidinone-based anticancer drugs.

Kamila Buzun is the first author in all cited papers and her input in the work is beyond any doubt, as confirmed by the co-authors' statements. Given the fundamental importance of the project and the perspectives opened by this work, I believe that it should be distinguished.

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