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A review of the doctorate thesis entitled „Derivatives of Pyrazinecarboxylic Acid as Potential Antimycobacterial Active Drugs” written by MSc Ghada Bouz under supervision of Prof Martin Doležal and assoc. Prof Jan Zitko as an advisor

Tuberculosis, an infectious disease of bacterial etiology remains leading cause of death worldwide. However recently it has lost its dishonorable position for modern world maladies like diabetes or cardiovascular disorders, tuberculosis remains one of the most deadly bacterial infection. It is really bitter, that in modern world, century after first antibacterial drugs have appeared, more than million people die from infections caused by Mycobacterium every year. Low activity of used drugs, emerging resistance and lack of novel drugs are factors that are responsible for this situation. Another one, probably most important one is poor healthcare accessibility in developing countries where tuberculosis is the most common. The same is the reason of low interest in developing new drugs among industry which hampers the research. Thus, more independent research carried out in universities are particularly important and valuable. Group of professor Doležal from Pharmaceutical Faculty of Charles University is well known for great efforts in this field,



resulting in numerous publications, projects and priceless knowledge in chemistry and pharmacology of potential antimycobacterials. The thesis, written by MSc Ghada Bouz that has been submitted for my evaluation perfectly fits into this trend. Ms. Bouz devoted her scientific interest to search for novel derivatives of pyrazine carboxylic acid that could have better activity than still widely used pyrazinamide (PZA).

The thesis itself has been prepared as a commentary on five scientific articles that were published by Ms. Bouz, mostly as a first and corresponding author. One publication is a review dealing with zebrafish (*Danio rerio*) as an animal model suitable for in vivo screening of new drugs, vaccines and also pharmacological studies. This work, although not directly connected with the main focus of the experimental research is quite important for this review. Synthetic and systematic point of view is an indispensable aspect of matured scientific attitude. Ability to combine facts and creating additional value from previous observation in thorough study is rare attribute of adepts of modern and more technical teaching. I strongly believe that this review written on the basis of pharmaceutical light and drug design is relevant and will be found interesting by scientific community.

On the other hand experimental paper that have been published as part of this thesis are typical, sound and solid works on design and development of new bioactive molecules. Synthetic plans of Ms. Bouz were supported on former research that deals with derivatives of amino and phenylcarbamoyl-pyrazine-2-carboxylic acids. Analysis of structures and activities of PZA based drugs led author to propose ureidopyrazines and benzenesulfonamides as novel moieties. It should be noted here that the more rationale target-based strategy is not available in this research. The vague nature of PZA activity that is generally a result of multitarget interactions forced more or less intuitive design. Nevertheless analysis of plausible mechanism of action was undertaken in this work. For example docking to enzymes that were selected on the basis of substrate similarity. By the way in commentary it should be clearly noted the source of structure and some more detail of the study (e.g. page 13). Certainly, without a biochemical verification the results should not be considered as a proof, but may provide a hint for further design. Introduction



of acylurea moiety (ureidopyrazines) is appealing modification resulting in pyrazine having two type linkers amide and retro-amide. These derivatives were designed on the basis of wide biological activity of these compounds. Indeed acylureas were claimed a privileged structures in literature. Here, these compounds were found promising reaching one of the highest micromolar activity with good selectivity. In page 16 author state that ureidopyrazines were synthesized in pressurized vials in microwave reactor. Here I would like to as if the pressure was controlled and how important it is for reaction.

An important part of commentary that has been included in this thesis are ongoing research and future plans. I honestly commend this part as it confirms the continuity of the idea and applicability of the results obtained so far. It is good that author can recognize his own results as a direction of future research. Here Ms. Bouz pointed out quinoxaline derivatives and hybrid compounds, combining pyrazinamide and p-aminosalicylic acid moiety as structure of interest. These leading structures has been designed on the basis of structure-activity relationship analysis that has been done in this work. Interestingly first preliminary results may suggest a successful approach as highly active compounds were obtained.

The editorial work that has been done on this thesis, in my opinion deserves complements. I was able to find only few misspelled words or odd fragments, that arisen probably during re-edition of the text. Dissertation begins with list of abbreviation and most of them are separately explained in the text. However GPS1 in Table 1 is used without explanation and its function is described rather sketchy. Introduction describes problem of tuberculosis along with therapeutic possibilities

As a general remark I think that the commentary could be more comprehensive. Author is very sketchy in some fragments, particularly those regarding experimental procedures and methodology. All necessary data are available in publications that were attached to this thesis, nevertheless I think that deeper discussion would be beneficial.



In conclusion it should be stressed out that the dissertation written by MSc Ghada Bouz is well prepared and scientifically sound. Candidate undertaken big part of laboratory work and the experimental methodology is well designed and managed. Conclusions are supported by results that have been published in series of papers published in recognized journals. In my opinion the scientific achievements of MSc Ghada Bouz fully confirm her development and attitude as young devoted scientists. Therefore it is my great pleasure to request the Scientific Council of Pharmaceutical Faculty of Charles University to award her with the PhD degree.

