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Abstract of the doctoral dissertation

The doctoral dissertation entitled "Study of the extended specificity profile of human proteasomes" was carried out in the Department of Biological Chemistry and Bioimaging at the Faculty of Chemistry, Wrocław University of Technology under the supervision of Prof. Marcin Drąg, PhD. The research carried out as part of the dissertation concerns the determination of the substrate preferences of individual catalytic subunits of the human proteasome and immunoproteasome on both the primed and unprimed sides.

The dissertation presented here consists of two main parts: theoretical and research. The theoretical introduction presents a review of the scientific literature on the human proteasome and immunoproteasome. At the beginning, the mechanism of action and physiological significance of the ubiquitin-proteasome system and the structure of the human 26S proteasome are introduced. This section also presents the information gathered so far on the substrate specificity of the catalytic subunits of the proteasome: β1, β2 and β5, and characterizes the substrates and inhibitors specific to them. The human immunoproteasome was then characterized in an analogous manner, describing its structure, the substrate specificity known so far, and the substrates and inhibitors specific to the catalytic subunits β1i, β2i and β5i.

In the research part, the specificity profile of the three catalytic subunits of the human immunoproteasome at positions P4-P2 was determined using hybrid combinatorial substrate libraries. Next, the specificity profile of the human proteasome and immunoproteasome at positions P6-P5 and P1'-P2' was determined. For this purpose, it was necessary to synthesize

further hybrid libraries of fluorogenic susbstrates (positions P6-P5) and IQF-type substrate libraries (positions P1'-P2'). The determined specificity profiles of the two enzymes were compared with each other, and based on the results obtained, a dipeptide inhibitor specific for the β1i subunit of the human immunoproteasome was designed and synthesized.