Exploiting Nature's Rich Source of Proteasome Inhibitors as Starting Points in Drug Development

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One of our research focuses is the analysis of interactions between enzymes and their ligands, as well as elucidation of their catalytic mechanisms. Particularly natural products are promising therapeutic drugs due to their target-oriented stepwise optimization. The recently approved anti-cancer blockbuster carfilzomib (Kyprolis®), a 20S proteasome inhibitor which was derived from the streptomyces metabolite epoxomicin, reflects one of the most prominent examples. The breakthrough of this discovery was only possible by conjoining academic research with industrial optimization procedures. Nowadays, identification of promising novel lead motifs requires a systematic comparison of ligands by combining structural, functional and cellular disciplines. Moreover, future trends in proteasomal drug development have to address enhanced selective properties against distinct proteasome-types. Here, the immunoproteasome is a prime example to be a beneficial rationale for the treatment of autoimmune disorders including rheumatoid arthritis or multiple sclerosis. Therefore, depending on the field of application, bioactive molecules, their distinct derivatives as well as their straightforward simple and cheap production are of general interest. The herein presented status quo let us await many further interesting stories on drug development and their clinical applications for the next decades implementing protein crystallography at the intersection of chemistry, biology and medicine.