

DESCRIPTION FOR THE GENERAL PUBLIC (IN ENGLISH)

Degradation of proteins is essential for regulation of critical biological processes and maintenance of cellular homeostasis. The ubiquitin-proteasome system is responsible for degradation of most intracellular proteins, such as damaged, mutated, oxidized and short-lived regulatory proteins. Due to the broad spectrum of its substrates, the proteasome controls key cellular processes like cell cycle progression, apoptosis, transcription, oncogenesis and others. The core of this system is 20S proteasome. Dysfunction of the ubiquitin-proteasome system underlie, directly or indirectly, the pathogenesis of numerous human diseases, such as cancer, autoimmune and neurodegenerative diseases. Because of its implication in pathological processes proteasome has become an important therapeutic target, especially for cancer.

It has been shown that malignant cells are more susceptible for the proteasome inhibition than normal cells, likely because they exhibit increased activity of the proteasome. This finding has been led to development of many inhibitors of proteasome, designed as potential anticancer drugs. The most common proteasome inhibitors are orthosteric, covalently binding compounds. They target the active center of the enzyme, directly blocking degradation of all substrates. Three of such inhibitors (bortezomib, carfilzomib and ixazomib) have been approved for the treatment of multiple myeloma and lymphoma. Despite the success in the treatment of hematological cancers, they possess many drawbacks, including quite high cytotoxicity. In addition, many patients treated with these drugs relapse or develop resistance.

Allosteric, noncompetitive inhibitors can be a promising alternative to orthosteric inhibitors used in cancer therapy. This new type of modulators binds to a site/s distinct from the active center and by conformational changes influence the affinity of the proteasome to substrates. This mode of action could provide more precise and specific control of the proteasome, thus displaying higher efficacy and lower toxicity. Allosteric inhibitors used in combination with orthosteric inhibitors or other conventional anticancer drugs could also improve efficiency of the treatment.

One of the first known allosteric inhibitors of the proteasome was naturally occurring peptide PR39. As a preliminary work we have obtained a set of PR39 analogs, some of which inhibit the activity of the proteasome in a nanomolar range. The main objective of this project is optimization of the structure of PR39 analogs to design more efficient and stable under proteolytic conditions allosteric inhibitors of the proteasome activity.

The obtained compounds could serve in the future as the lead structures for development of new, specific proteasome inhibitors to treat diseases characterized by increased activity of the proteasome, particularly for cancer.