Title

Structure-based design of peptide boronate immunoproteasome selective inhibitors

Authors

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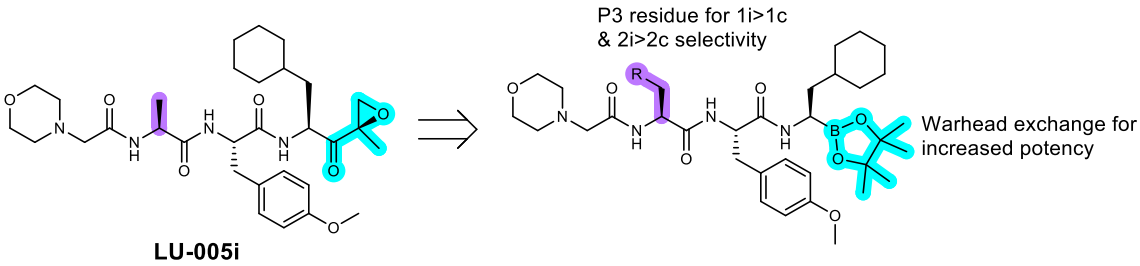
Abstract oral / poster presentation (*oral presentation*)

The ubiquitin-proteasome system lies at the core of protein homeostasis within the cell and specifically the 20S proteasome core particle has been proven as a drug target in a variety of hematological cancers, as well as a being investigated as a potential target in auto-immune diseases. With three distinct catalytically active sites and two different isoforms of note – the constitutive- and immunoproteasome – selective inhibition of one of these two isoforms has proven challenging. As of now, clinically utilized inhibitors (Bortezomib, Carfilzomib) do not discriminate between the constitutive and immunoproteasome and are typically associated with severe side-effects including neuropathy and cardiac disfunction.[1] The first notable clinically relevant inhibitor with an improved immuno-selectivity is Zetomipzomib, which is undergoing clinical trials for lupus nephritis.[2] This increased immuno-selectivity has seemingly reduced the clinically-observed side-effects.

Previously, our group has shown that substitution of the epoxyketone electrophilic trap with a boronic acid, drastically increases the potency of the natural product proteasome inhibitor, epoxomicin (about 10-fold).[3] Based on these observations, we modified an in-house developed inhibitor with a somewhat favorable selectivity pattern, LU-005i, and introduced a boronate electrophilic trap. Further structural optimization at the P3 residue, based on insights made in the past, led to the generation of inhibitors that show a significantly improved immuno-selectivity for β1i and β2i as well as a drastic increase in potency compared to their epoxyketone counterparts.



References (*max 3*)

1. Arastu-Kapur, S. *et al.* Non-Proteasomal Targets of Proteasome Inhibitors Bortezomib and Carfilzomib. *Blood* **112**, 2657 (2008).
2. Parikh, S. V. *et al.* Zetomipzomib (KZR-616), a First-in-Class Selective Immunoproteasome Inhibitor for the Treatment of Lupus Nephritis: Preliminary Results From the Phase 2 MISSION Study: TH-PO487. *Journal of the American Society of Nephrology* **33**, 184 (2022).
3. Verdoes, M. *et al.* Mixing of peptides and electrophilic traps gives rise to potent, broad-spectrum proteasome inhibitors. *Org. Biomol. Chem.* **5**, 1416–1426 (2006).