Stabilizing inactive conformations of MALT1 as an effective strategy to inhibit its protease activity

The paracaspase MALT1 (mucosa associated lymphoid tissue lymphoma translocation protein 1) plays an important role in various immune pathways and has been proposed as a therapeutic target for auto-immune disorders as well as cancers (i.e. DLBCL). We explored different mechanisms to inhibit the protease activity of MALT1 and discovered two unrelated chemical scaffolds. Biophysical and structural studies revealed that both scaffolds stabilize the protease in an inactive conformation. While one ligand binds to the allosteric site at the interface between the caspase and the IG3 domain, the other ligand binds to the active site in a so far undescribed mechanism. Iterative structure based drug discovery on one scaffold resulted in the identification of a potent, selective and bioavailable MALT1 inhibitor.