

P003 Linear mimics of the natural proteasome inhibitor
TMC-95A: design, synthesis and biological evaluation
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The use of Velcade® (bortezomib) for treating multiple myeloma has validated proteasomes as a new drug target. We have designed, synthesized and evaluated the biological potential of new potent inhibitors of proteasomes that act in a reversible manner and create no covalent bond with catalytic O⁶Thr1 as do bortezomib, MG-132 and lactacystin. TMC-95A, a cyclic tripeptide metabolite of *Apiospora montagnei*, is a non covalent inhibitor that acts specifically on the three proteasome activities, but its synthesis is complex and time-consuming. Reversible inhibitors have been prepared using more readily synthesized new linear mimics of this natural molecule. Their cytotoxicity for tumor cells has been evaluated. Treatment with one of these linear mimics induces cell cycle arrest and cell death. These new inhibitors which have no reactive group ('warhead'), are easily synthesized. They may have lower negative side-effects and thus open new perspectives in the pharmacological treatment of cancers.