Design and synthesis of peptidomimetic inhibitors for the M1 family of zinc aminopeptidases

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[†]*In memory of our beloved collaborator Dionisios*

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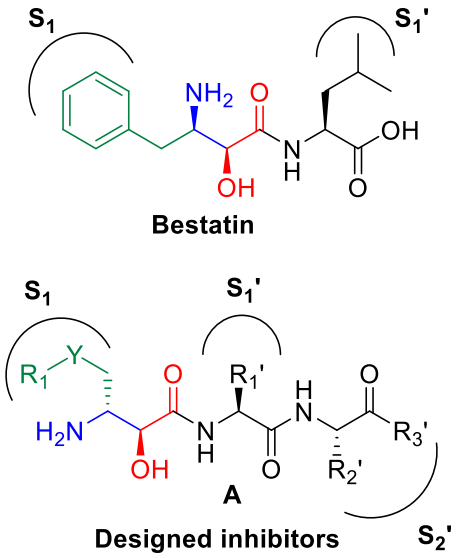
Bestatin (ubenimex) is a well-characterized inhibitor of aminopeptidases, enzymes that catalyze the catabolism of the N-terminus of a variety of peptide substrates. It was discovered in 1975 by Umezawa who isolated it from cultures of the *Streptomyces olivoreticuli* in a search of aminopeptidase B inhibitors.[1] Bestatin is an approved drug in Japan where it has been used for more than 30 years mainly as a complementary chemotherapeutic agent in the treatment of acute myeloid leukemia. We have undertaken the design, the synthesis and the biochemical evaluation of bestatin-based compounds as inhibitors of M1 zinc aminopeptidases. Initially, we target endoplasmic reticulum aminopeptidases ERAP1 and ERAP2, which are involved in hydrolysis of precursor antigenic peptides,[2] and the insulin-dependent aminopeptidase IRAP that is implicated in hydrolysis of the peptide hormones, such as oxytocin, vasopressin and angiotensin III.[3]

Bestatin was selected due to the flexibility offered by the α-hydroxy-β-amino acid scaffold as zinc-chelating group with the required stereochemistry for the design of potent M1 aminopeptidase inhibitors. A new synthetic methodology that deviates from existing, linear-step methods offers the flexibility to introduce a variety of functional groups through common intermediates, requiring a small number of synthetic steps. Using structure-based selection of appropriate functional groups (R_1 and R_1'–R_3' in the Scheme) for the corresponding subsites of each enzyme (S_1, S_1', S_2') we seek to maximize inhibitor potency while obtaining selectivity for individual members of the M1 aminopeptidase family.



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