

Target identification and lead optimization: fungal secreted aspartic proteinase inhibitors as a paradigm

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Candida albicans (*C. albicans*), the most virulent representative of the *Candida spp.*, can cause severe mucosal and life-threatening systemic infections in immuno-compromised hosts. In particular, the secreted aspartic proteinases (Saps), encoded by the SAP gene family with ten members, appear to play a major role in *Candida albicans* virulence. It has been shown that SAP1-3 contribute significantly to tissue damage and invasion of oral epithelium and cutaneous epidermis, while SAP4-6 are important for systemic infections. In contrast to the usual mode of action of antifungal drugs, to interfere with fungal cell wall production, our group identified a major virulence factor, namely the Saps as a prospective target for intelligent drug design.

By x-ray crystallography we solved the crystal structures of Sap1, Sap3 and as first member of the second subgroup Sap5. On this basis we performed molecular modelling studies of possible Sap-inhibitors with special regard to size and structure also addressing electric charges of the active centre of the different Sap's. We took special care to identify regions of similarity to the human aspartic proteinases to prevent cross-reactivity. 9 Inhibitors belonging to 3 inhibitor libraries were obtained by production of statine and usage of the protecting group strategy. These 9 inhibitors were tested in a fluorescence assay to evaluate their inhibitory potential regarding the different Saps. Keeping the results in mind additional new inhibitors were synthesized and tested.

The newly-synthesized inhibitors inhibit the tested Saps, as pepstatin A, in nanomolar range.

