INVESTIGATION OF MULTIPOLAR INTERACTIONS IN THE ACTIVE SITE OF THROMBIN

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Due to its rigidity and well-defined binding mode, the enzyme thrombin represents an interesting target to investigate multipolar interactions occurring upon binding of the tricyclic inhibitors developed in the *Diederich* group [1]. With regard to the surprising results obtained during the fluorine scan in the D and S1 pockets, which lead to the discovery of a new type of orthogonal interactions between the fluorine atom and a backbone carbonyl group [2], we became interested in studying related interactions of fluorine, hydroxy and methoxy substituents, respectively, in the oxyanion hole as well as in position 4 of the benzyl ring reaching into the D pocket of the active site (figure 1). For the latter analysis we performed also the synthesis of the bromo and chloro derivatives, additionally envisaging the comparison with the iodo substituted compound.

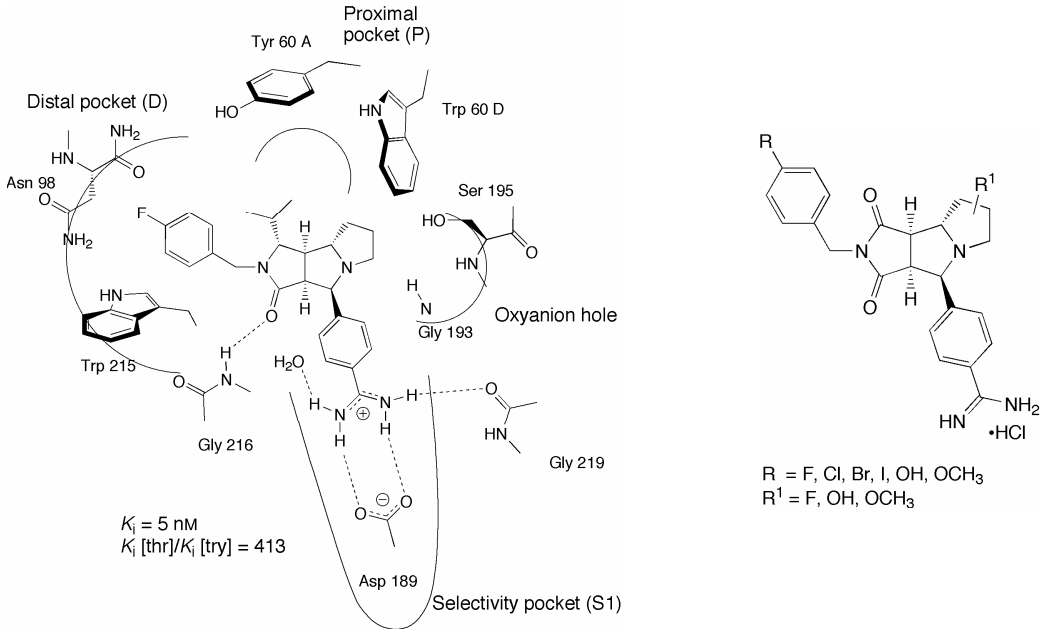

Figure 1: *Our most potent tricyclic inhibitor bound in the active site of thrombin (left) and the substitution pattern for the investigation of the multipolar interactions (right).*

[1] U. Obst, V. Gramlich, F. Diederich, L. Weber, D. W. Banner, *Angew. Chem.* **1995**, *107*, 1874-1877; *Angew. Chem. Int. Ed.* **1995**, *34*, 1739-1742.
[2] J. A. Olsen, D. W. Banner, P. Seiler, B. Wagner, T. Tschopp, U. Obst-Sander, M. Kansy, K. Müller, F. Diederich.