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Towards the Development of Sequence-Selective Artificial Proteases

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Abstract. The development of artificial sequence-selective proteolytic metal complexes is endeavoured by use of encoded combinatorial chemistry.

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The selective recognition, binding and cleavage of peptides and proteins play important roles in many biologically important processes. Thus, a lot of research has been dedicated to understanding naturally occurring recognition and cleavage events. As a result, several highly selective artificial receptors binding single amino acids have been synthesized [1]. With the upcoming of combinatorial chemistry [2], even the discovery of natural as well as synthetic receptors for small peptides has become possible [3]. For example, the screening of a dye-marked cyclodextrin analogue against an encoded tripeptide library revealed the ability of cyclodextrin to bind to the dipeptides L-Phe-D-Pro and D-Phe-L-Pro [4]. Combinatorial screenings have also led to the development of a new class of two-armed receptors (**1**–**3**) which recognize certain tripeptides with the highest sequence selectivity so far observed for synthetic receptors [5].

Remarkably, small changes in the structures of these receptors cause significant differences in their binding preferences. Such highly selective binding could not have been predicted easily by rational design, thus demonstrating the power of combinatorial chemistry as a tool for the study of selective intermolecular interactions.

Whereas these examples show the progress in the design of selective receptors for peptides, the design of artificial peptidases has proven to be more difficult.

My present research aims at the development of metal complexes capable of

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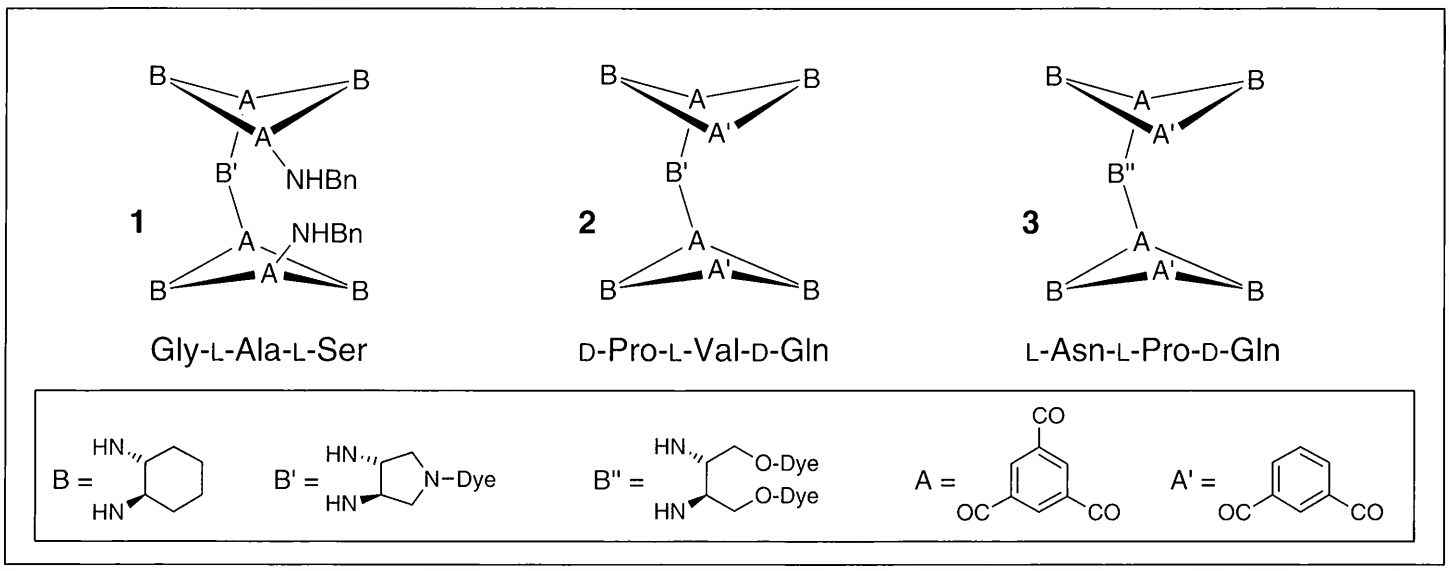

Figure. *Two-armed receptors bind tripeptides selectively*

cleaving small peptides sequence-selectively. Combining combinatorial chemistry with the use of metal complexes as proteolytic agents, libraries of metal complexes will be generated in order to find specific proteolytic receptors. The members of such libraries will be screened for their ability to bind and cleave the peptide L-Ala-γ-D-Glu-L-Lys-D-Ala-D-Ala, an essential peptide for the cell-wall synthesis of gram-postitive bacteria. Apart from the development of selective proteolytic receptors, the research is designed to yield a deeper understanding into non-covalent intermolecular recognition events between peptides as well as peptide-metal complexation.

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[1] See, for example: a) A. Galan, D. Andreu, A.M. Echavarren, P. Prados, J. de Mendoza, *J. Am. Chem. Soc.* **1992**, *114*, 1511; b) K.-S. Jeong, A.V. Muehldorf, J. Rebek, Jr., *ibid.* **1990**, *112*, 6144.

[2] a) A. Furka, F. Sebestyen, M. Asgedom, G. Dibo, *Int. J. Pept. Protein Res.* **1991**, *37*, 487; b) M.H.J. Ohlmeyer, R.N. Swanson, L.W. Dillard, J.C. Reader, G. Asouline, R. Kobayashi, M.H. Wigler, W.C. Still, *Proc. Natl. Acad. Sci. USA* **1993**, *90*, 10922.

[3] For reviews, see: a) D.R. Liu, P.G. Schultz, *Angew. Chem. Int. Ed. Engl.* **1999**, *38*, 36; b) W.C. Still, *Acc. Chem. Res.* **1996**, *29*, 155.

[4] a) M. Maletic, H. Wennemers, Q. McDonald, R. Breslow, W.C. Still, *Angew. Chem. Int. Ed. Engl.* **1995**, *35*, 1490; b) H. Wennemers, W.C. Still, *Tetrahedron Lett.* **1994**, *35*, 6413.

[5] H. Wennemers, S.S. Yoon, W.C. Still, *J. Org. Chem.* **1995**, *60*, 1108.