MAKING THE UNDRUGGABLE *DRUGGABLE*: SYNTHETIC PROLIN-DERIVED MODULES (ProMs) AS BUILDING BLOCKS FOR RATIONAL AND LIBRARY-BASED DRUG DEVELOPMENT

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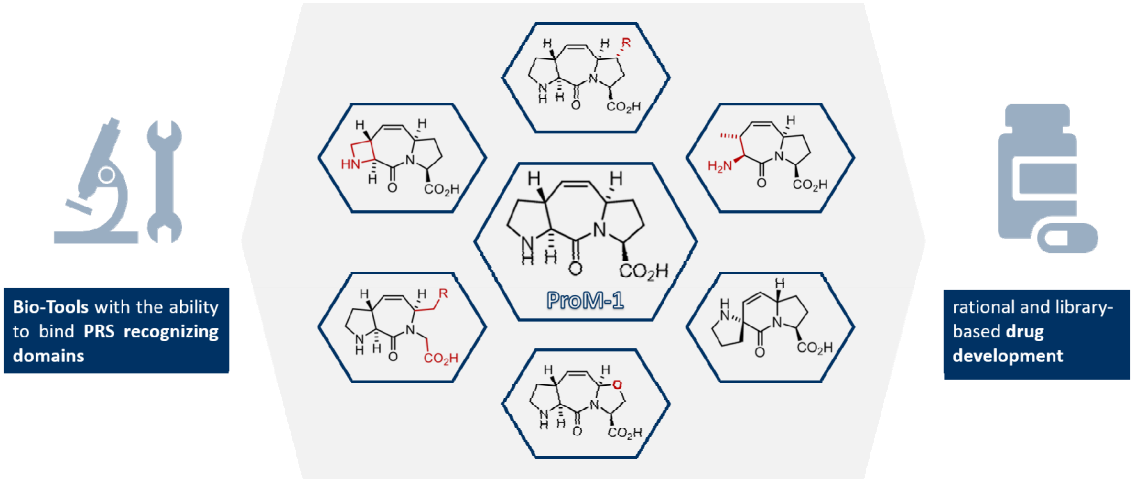
Protein domains specialized in the recognition of proline-rich segments (PRS) adopting a polyproline type II helix (PPII) conformation are particularly abundant, yet so far undruggable.[1] Moreover, these domains often play a key role in disease-related cellular malfunctions (e.g. the expansion of invasive cancer), making small-molecule competitors of PRS urgently needed.

We designed and established efficient syntheses of proline-derived modules (ProMs), i.e. polycyclic dipeptide units structurally rigidified in a PPII conformation.[2] These were then used as building blocks in the synthesis of tailored small molecule ligands, which selectively bind to the target domain with remarkable affinity.

As a proof of concept, we developed a highly selective, ProM-based inhibitor of protein-protein interactions involving Ena/VASP, a target of choice for the development of an antimetastatic drug. Furthermore, *in vivo* studies revealed that treating highly invasive breast cancer cells with this ProM-inhibitor caused a strong suppression of cell motility and chemotaxis, as reflected by an inhibition of cancer cell invasion by 66%.[3]



[1] L. Ball, R. Kühne, J. Schneider-Mergener, H. Oschkinat, *Angew. Chem. Int. Ed.* **2005**, *44*, 2852.

[2] (a) J. Zaminer, C. Brockmann, P. Huy, R. Opitz, C. Reuter, M. Beyermann, C. Freund, M. Müller, H. Oschkinat, R. Kühne, H.-G. Schmalz, *Angew. Chem. Int. Ed.* **2010**, *40*, 7111; (b) C. Reuter, R. Opitz, et. al. R. Kühne, H.-G. Schmalz, *Chem. Eur. J.* **2015**, *21*, 8464; (c) S. Chiha, A. Soicke, M. Barone, M. Mueller, J. Bruns, R. Opitz, J.-M. Neudoerfl, R. Kuehne, H.-G. Schmalz, Eur. J. Org. Chem. 2018, 2018, 455-460.

[3] R. Opitz, M. Müller, C. Reuter, et. al. H.-G. Schmalz, R. Kühne, *PNAS* **2015**, *112*, 5011.