SYNTHESIS OF A NOVEL CYCLIC PEPTIDE LIBRARY ENABLED BY C-H FUNCTIONALIZATIONS AND THE DNA-ENCODED LIBRARY TECHNOLOGY

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During the past decades, research in genomics has detected a fascinating number of new disease-related targets that present promising opportunities for therapeutic intervention. Unfortunately, many of these drug targets have proven difficult to address with small molecules that comply to Lipinski's Rule of 5. Thus, medicinal chemists have in recent years started to explore the "beyond Rule of 5" chemical space in search of new starting points for therapeutic development against such challenging drug targets. Here, macrocyclic peptides constitutes an promising compound class that has shown to be able to interact with several different challenging drug targets.

In this project, we employ different Pd-catalyzed, directing-group assisted C–H functionalization reactions to prepare different unnatural amino acid derivatives which we will then use as building blocks in the synthesis of a library of macrocyclic peptides (Mw 900-1500 Da). To streamline this library synthesis, we plan to take advantage of the DNA-encoded library (DEL) technology and carry it out in a split-pool synthesis fashion. With this strategy, we intend to prepare a pilot DEL consisting of 125.000 macrocyclic peptides, in which all library members will be tagged with their unique DNA barcode.