ABSTRACT

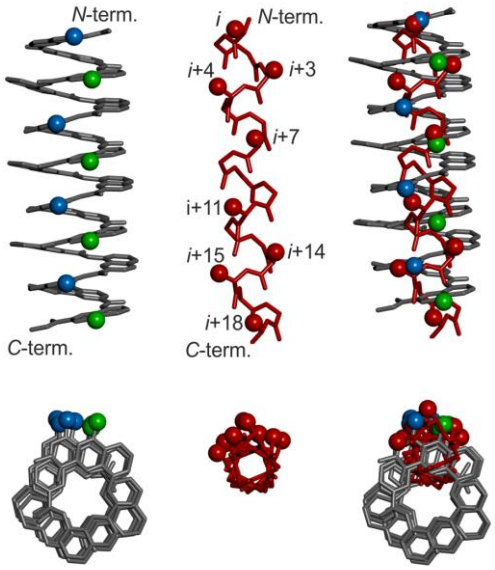
Synthesis and application of quinoline based foldamer building blocks

Name:	*Zwillinger M.[(1)], Kotschy A.[(1)], Csékei M.[(1)]*
[(1)] Affiliation:	*Servier Research Institute of Medicinal Chemistry, Záhony u. 7, 1031 Budapest, Hungary*

Abstract: *Foldamers are considered as new functional polymers with synthetic backbones that may exhibit interesting chemical and biological properties, reaching beyond natural biopolymers. Foldamers have gained interest in several research areas, including medicinal chemistry. However, complete mimicry of the sophisticated structural and functional features of biopolymers by these synthetic macromolecules is beyond the mark today. Efforts in our research are focused on eliminating two major limitations connected to the –otherwise promising– class of helical aromatic oligoamide foldamers.*

The first aim of our work was to increase the variability of quinoline carboxamide foldamers by the design and synthesis of new building blocks, enabling the construction of diverse foldamer libraries. A collection of 20 new monomers has been synthesized bearing proteinogenic sidechains at position 6 or positions 4 and 6 on the quinoline core. Some of the synthesized monomers were used to design helical aromatic oligoamide foldamers displaying α-helix mimetic sidechain patterns, which might eventually allow tackling medicinally relevant protein-protein interactions.[1]

The other, more challenging task was the elaboration of a novel isotope encoding methodology to facilitate mass spectrometric sequence identification in combinatorial foldamer libraries. The final goal of the project is to enable the quick screening of foldamer mixtures against biological targets. An 8-member collection of deuterium labelled building blocks has been synthesized and computational methods have been developed for automatic code generation and deconvolution. The basic principle and toolkit have been validated on a model system and provided promising results.



Comparison of an α-helix mimetic foldamer and an ideal peptide α-helix.

References:

[1] *Zwillinger, M., Reddy, P.S., Wicher, B., Mandal, P.K., Csékei, M., Fischer, L., Kotschy, A., Huc, I. Aromatic Foldamer Helices as α-Helix Extended Surface Mimetics. Chem. Eur. J. 2020. 26(72):17366-17370.*