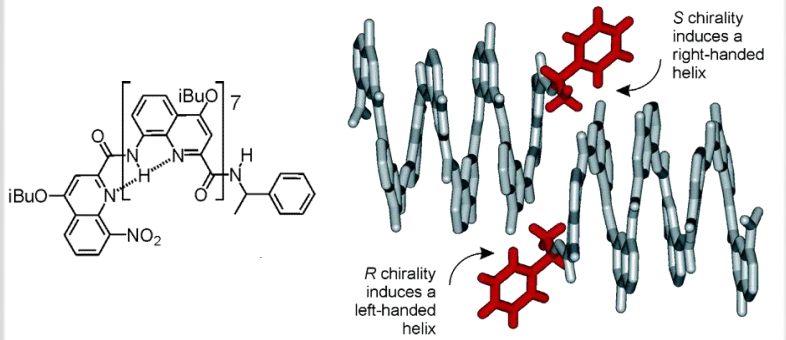
Detection of protein/foldamer interactions by induced chirality

Lucile Fischer

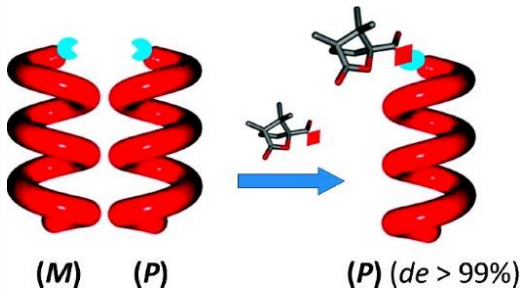
29-11-2021

Induction of chirality in helical amide foldamers @ CBMN

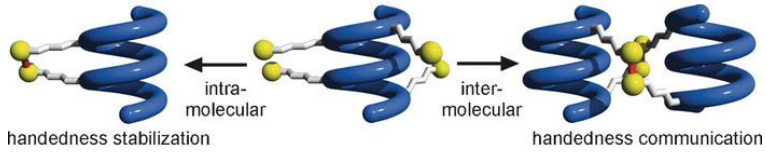
- **Internal inducer**



Dolain *et al*. *JACS*, 2005, *127*, 12943

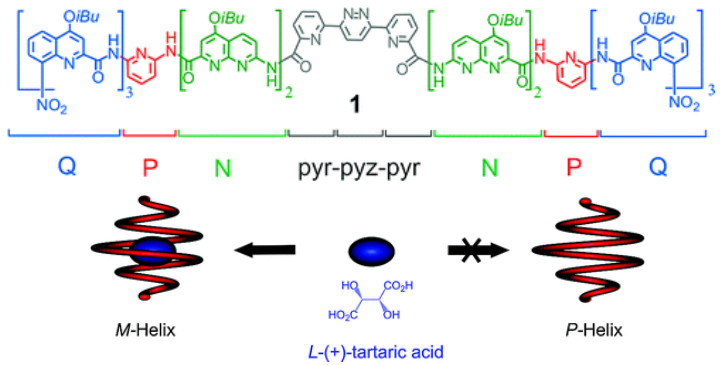


Kendhale *et al*. *JOC*, 2011, *76*, 195

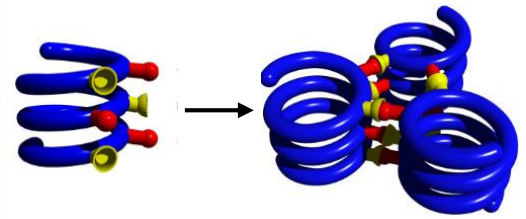


Tsiamantas *et al*. *ACIE,* 2016, *55*, 6848

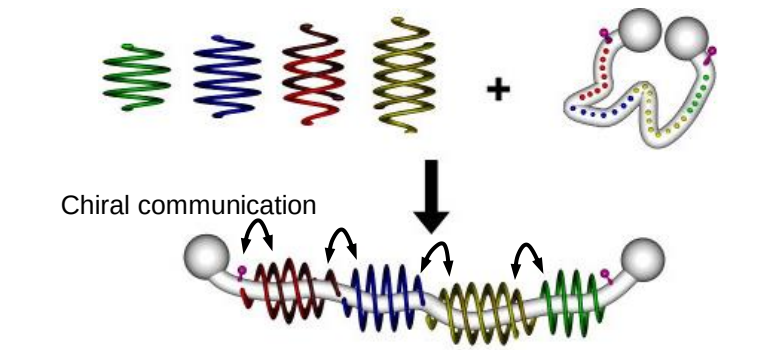
- **External inducer**



Ferrand *et al*., *JACS*, 2010, *132*, 7858



De *et al*. *Nat. Chem*., 2018, *10*, 51

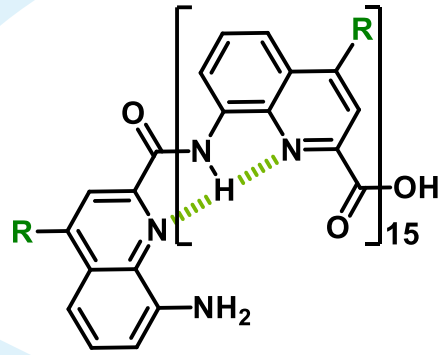


Gan *et al*. *Nat. Nanotech.* 2017, *12*, 447

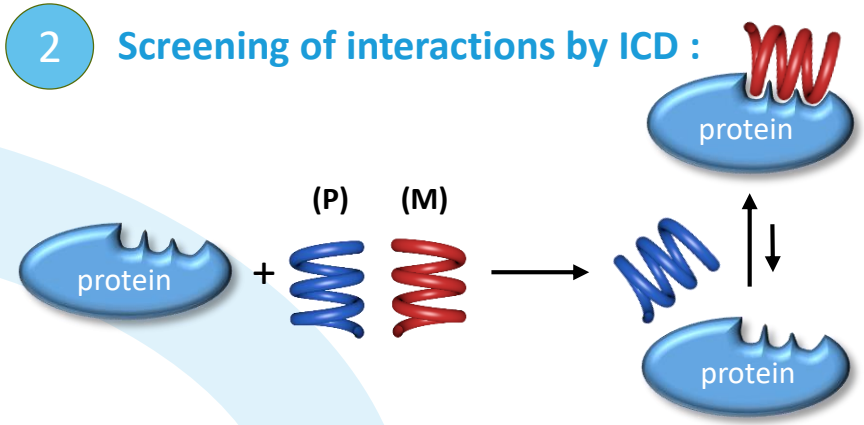
Structure-based design from an iterative process

- **AIM :** **Develop a foldamer able to interact specifically with a protein surface**
- **STRATEGY :** **Obtain structural information by holding foldamer in close contact with the protein surface**

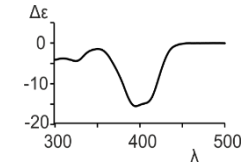
1 **Synthesis of foldamers**

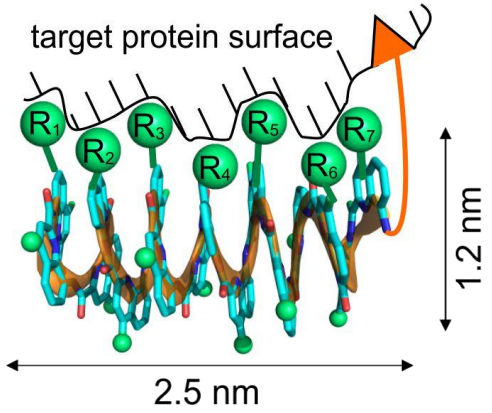


2 **Screening of interactions by ICD :**



⇨ Helix sense bias

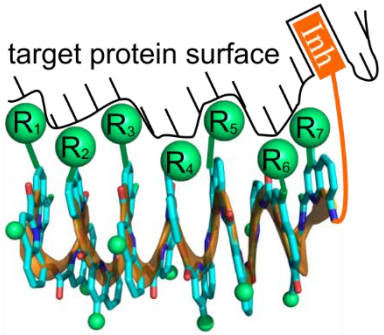


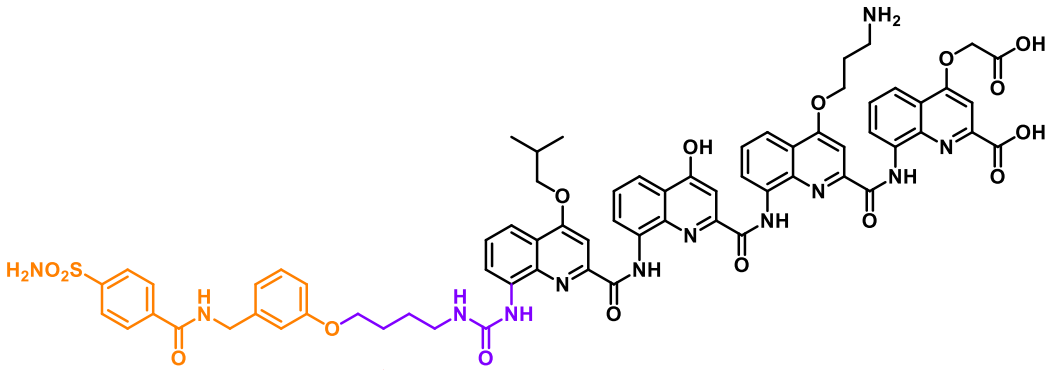


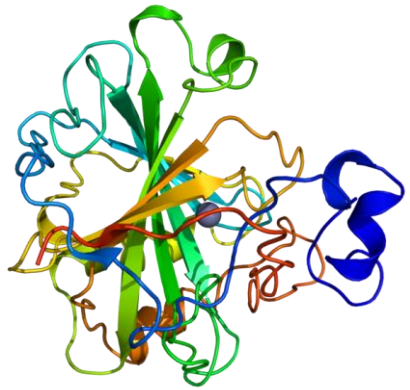
3 **Structural studies (NMR, X-ray)**

4 **Design optimization**

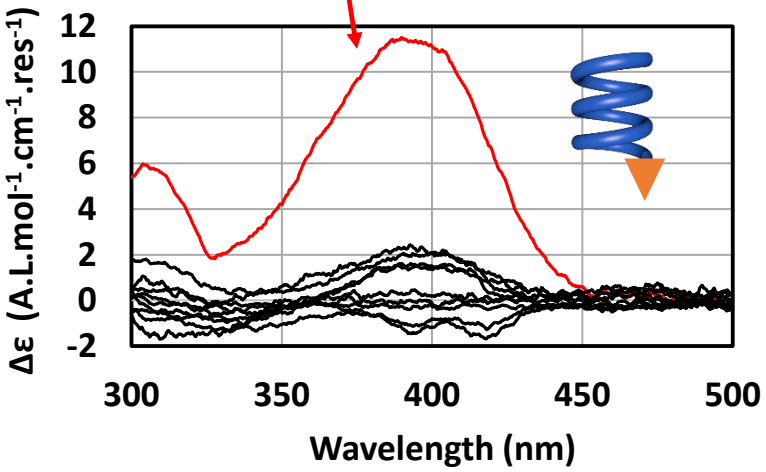
First validation: anchoring via an inhibitor

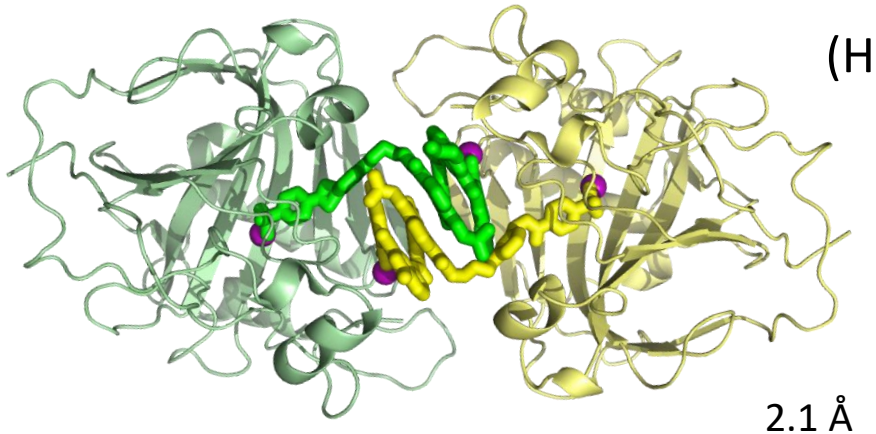






Human carbonic anhydrase II (HCAII) :
production and crystallization easily achieved
⇨ widely used for structural studies of enzymes





$(HCA/\mathbf{F})_2$

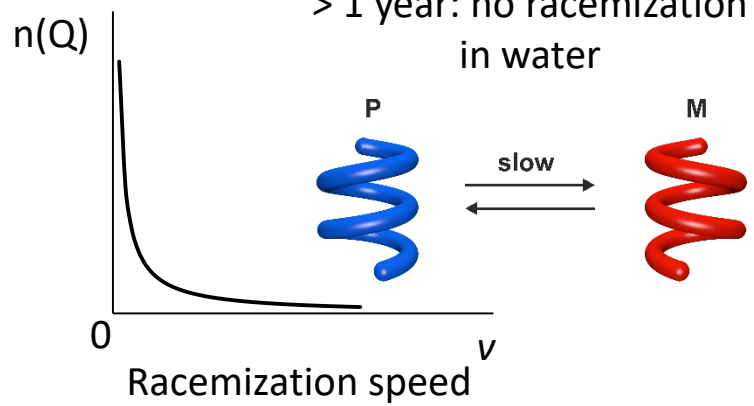
2.1 Å
$P2_1$
PDB: 4LP6

Angew. Chem. Int. Ed., **2014**, *53*, 883

Longer oligomers: overcome locked conformation ?

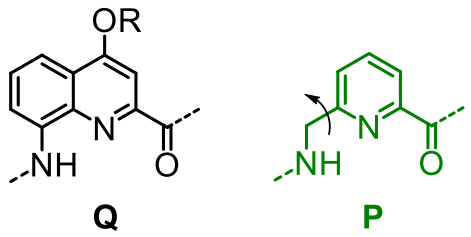
Q 8-mer

> 1 year: no racemization in water



How to introduce flexibility ?

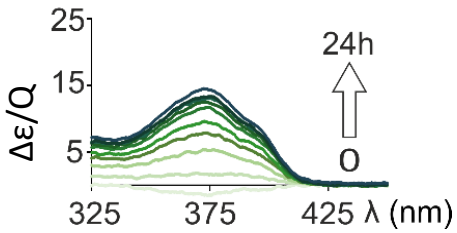
⇨ Introducing aminomethyl pyridine monomers



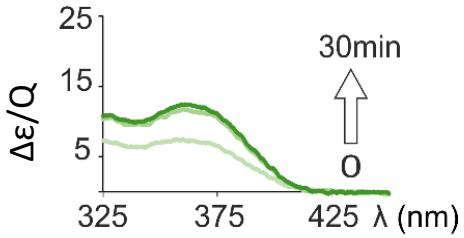
⇨ Same curvature, more flexibility

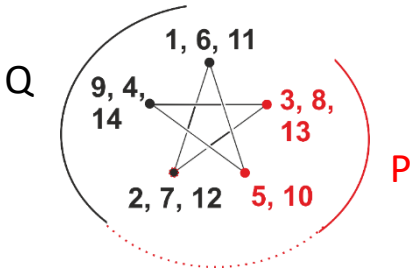
Kinetic study by CD and NMR on diastereomers (internal chiral inducer Phe) :

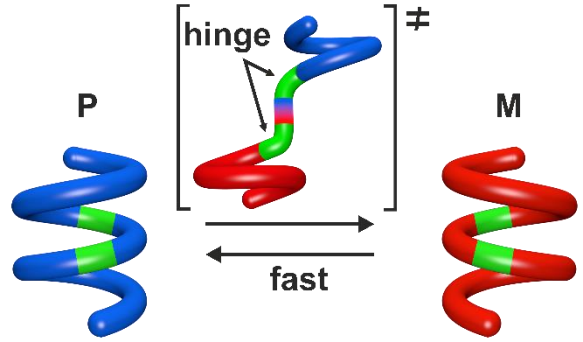
Ac-QPQPQQPQPQQ-Phe



Ac-QPQPPQPQPQQ-Phe



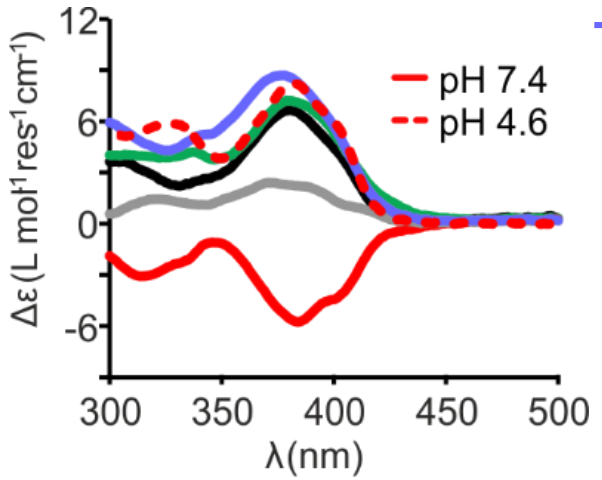




Q_nP_m hybrid foldamer

Eur. J. Org. Chem. **2018**, 5489

Long flexible oligomers interacting with a protein surface



— Inh-Q^{Orn}-P-Q^{Asp}-Q^{Hyd}-P-Q^{sAsp}-P-Q^{Asp}-Q^{Orn}

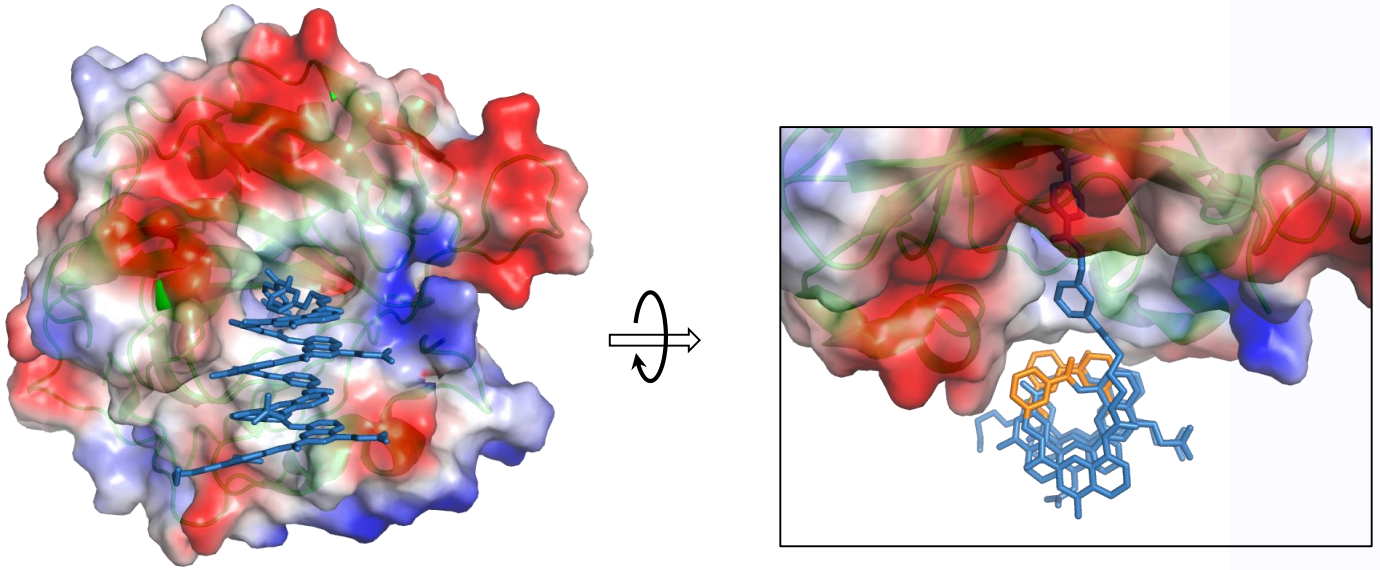
HCA/F_2

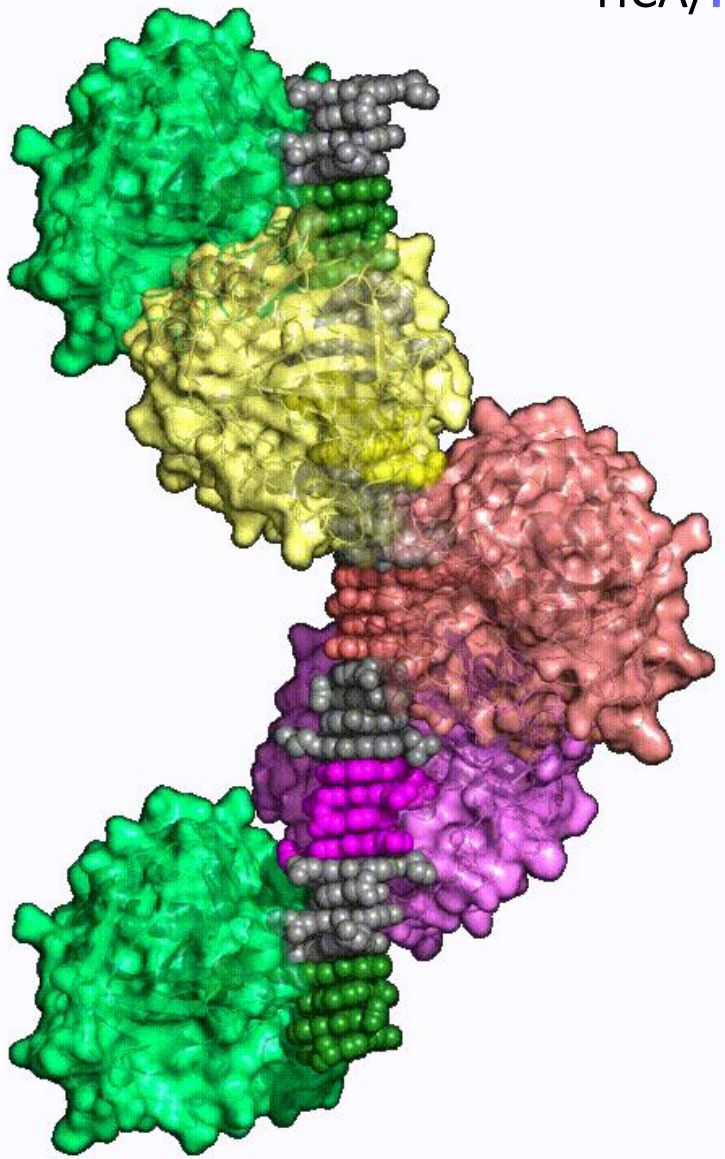
2.9 Å

P4₃

PDB: 6HZX

⇨ **Some interactions are pH dependent**





Chem. Eur. J. **2019**, *25, 11042*