Controlling molecular recognition involving peptides and peptidomimetics through fluorination and warhead introduction

Guillaume Compain

[a]*Univ. Bordeaux, CNRS, Bordeaux INP, CBMN, UMR 5248, IECB, 33600, Pessac*

g.compain@iecb.u-bordeaux.fr

Molecular recognition is a phenomenon driven by selective binding of two (or more) molecular partners through a combination of interactions and shape complementary. Molecular recognition underpins many biological processes, including receptor activation, protein-protein interactions, protein-cofactor binding and enzymatic reactions.[1] Achieving highly efficient and selective molecular recognition is essential for drug design. In our laboratory, we explore approaches to control challenging molecular recognition processes, in particular in protein-peptide interactions and protein-like host-guest complexes.

Peptide-based ligands endowed with a covalent mode of action represent emerging modalities for targeting extended protein-protein interaction (PPI) interfaces, where small molecule ligands are not always effective. While covalent ligands typically target cysteine residues, the most reactive nucleophiles in proteins, histidine residues at PPI sites has been largely overlooked. In recent years, we developed a structure-based design to selectively target histidine residues in PPIs using moderate electrophiles, expanding the scope of covalent ligand strategies.[2]

In parallel, host-guest chemistry presents persistent challenges, particularly in achieving stable encapsulation assemblies in aqueous environments. To address this, we investigated the stabilizing effects of fluorination on host-guest complexes in aqueous environment using a oligourea foldamers that form proteomimetic quaternary assemblies in water.[3] These self-assemblies generate a central hydrophobic cavity lined with leucine-type residues that can encapsulate small hydrophobic guests, such as aliphatic alcohols. By incorporating a hexafluorinated leucine analogue,[4] we reshaped the cavity, modulating both its hydrophobicity and volume to enhance molecular recognition. We will discuss the rational design, synthesis, and impact of fluorination on assembly formation and molecular recognition.

References:

[1] (a) M. Maurer, C. Oostenbrink, *J. Mol. Recognit.* **2019**, *32*, e2810; (b) T. Young, R. Abel, B. Kim, B. J. Berne, R. A. Friesner, *Proc. Natl. Acad. Sci.* **2007**, *104*, 808–813.

[2] G. Compain, C. Monsarrat, J. Blagojevic, K. Brillet, P. Dumas, P. Hammann, L. Kuhn, I. Martiel, V. Oliéric, P. Wolff, D. Y. Burnouf, J. Wagner, G. Guichard, *JACS Au*, **2024**, *4,* 432−440.

[3] (a) G. W. Collie, et al., *Nat. Chem.* **2015**, *7*, 871–878; (b) G. W. Collie, R. Bailly, K. Pulka-Ziach, C. M. Lombardo, L. Mauran, N. Taib-Maamar, J. Dessolin, C. D. Mackereth, G. Guichard, *J. Am. Chem. Soc.* **2017**, *139*, 6128–6137.

[4] (a) A. Delamare, G. Naulet, B. Kauffmann, G. Guichard, G. Compain, *Chem. Sci.* **2022**, *13*, 9507–9514; (b) G. Naulet, A. Delamare, G. Guichard, G. Compain, *Eur. J. Org. Chem.* **2023**, e202201148; (c) A. Delamare, G. Naulet, S. Mummadi, G. Guichard, G. Compain, *C. R. Chimie*, **2024**, *27*, 385-394; (d) S. Mummadi, G. Naulet, B. Kauffmann, G. Guichard, G. Compain *J. Org. Chem.* **2026**, *91*, 1, 631–637.