Abstract of the PhD Thesis in:

"New Insights into Peptoids' Chemistry: Synthesis, Characterization and Properties"

By

Alessandra Meli

Department of Chemistry and Biology "A. Zambelli"

University of Salerno, Via Giovanni Paolo II, 132, I-84084 Fisciano, Salerno, Italy

My PhD research activity aimed to enrich the realm of peptoids[1] with novel compounds and new insights into their behavior and properties, investigating their potential applications.

A new class of cyclic "arylopeptoids" was synthesized by the insertion of an aromatic ring and a methylene unit into the peptoidic backbone (Chapter 2). Tested as ion transporters of alkali metal cations, protons, and a series of anions through a phospholipid membrane, they highlighted the strong influence of the size of the macrocycle on the ion transport activity.

Exploiting the ion complexation properties of cyclic peptoids, two cyclic hexamers were synthesized with three carboxyethyl side chains each, to promote the formation of Gd^{3+}-complex as MRI-probes (Chapter 3). When carboxyethyl side chains were alternated with methoxyethyl side chains, the cyclic peptoid coordinated Gd^{3+} and displayed good relaxometric properties, as revealed by ^{1}H-relaxometric investigations.[2]

The versatility of peptoids enabled us to explore the field of glycoscience as well. A library of cyclic peptoids, ranging from 4-mer to 16-mer, with appended propargyl groups was synthesized and underwent click chemistry with DNJ azido-derivatives (Chapter 4). This is the first example of cyclopeptoid-based iminosugar click-clusters that showed activity towards α-mannosidases inhibition and the highest multivalent effect in the correspondence of the 36-valent ligand.[3]

This impressive outcome is the result of the modular synthetic approach of peptoids that enables for the insertion of an unlimited numbers and types of side chains.[4]

Taking advantage of such feature, we synthesized a library of cyclic hexapeptoids with methoxyethyl and propargyl side chains, varying in the relative content and positions (Chapter 5). Studying their role in the solid-state assembly of cyclic hexapeptoids, they showed to promote a columnar arrangement in which the propargyl groups are the pillars and the methoxyethyl chains provide intercolumnar interactions and side-by-side contacts.[5]

---

[1] Simon, R., I.; Kania, R., S.; Zuckermann, r., N.; Huebner, V., D.; Jewell, D., A.; Banville, S.; Ng, S.; Wang, L.; Rosenberg, S.; Marlowe, C., K.; Spellmeyer, D., C.; Tan, R.; Frankel, A., D.; Santi, D., V.; Cohen, f., E.; Bartlett, P., A.; Proc. Natl. Acad. Sci., 1992, 82, 9367- 9371.

[2] De Cola, C., Fiorillo, G., Meli, A., Aime, S., Gianolio, E., Izzo, I., De Riccardis, F., *Org. Biomol. Chem.,* **2014,** *12*, 424–431

[3] (a) Lepage, M. L., Meli, A., Bodlenner, A., Tarnus, C., De Riccardis, F., Izzo, I., Compain, P., *Beilstein J. Org. Chem.,* **2014**, 10, 1406-1412; (b) Lepage, M., L.; Schneider, J.; Bodlenner, A.; Meli, A.; De Riccardis, F., Schmitt, M.; Tarnus, C.; Nguyen Huynh, N., Y.; Leize-Wagner, E.; Cousida-Siah, A.; Mitschler, A.; Podjarny, a.; Izzo, I.; Compain, P.; *Chem. Eur. J.,* **2016***,* doi:10.1002/chem.201600338

[4] Zuckermann, R., N.; Kerr, J., M.; Kent, S., B., H.; Moos, W., H.; J. Am. Chem. Soc., 1992, 114, 10646- 10647.

[5] Meli, A., Macedi, E., De Riccardis, F., Smith, V. J., Barbour, L. J., Izzo, I. and Tedesco, C., *Angew. Chem. Int. Ed*., **2016**, doi:10.1002/anie.201511053