University of Salerno

Department of Chemistry and Biology “A. Zambelli”

XXXII Doctoral Cycle in Chemistry

Ph.D. thesis in:

Chiral Bioactive Cyclopeptoids: Concepts and Purposes

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Thesis Abstract

Peptides are an endless source of inspiration for medicinal chemistry, as these biomacromolecules regulate a number of biological activities, acting as hormones, neurotransmitters, signalling molecules and so on. They show high affinity towards therapeutic targets and few side-effects. However, peptides have their drawbacks due to their extreme metabolic instability and low bioavailability.[1] Pharmacokinetics and pharmacodynamic properties can be enhanced with *N*-amide substitution (mainly, alkylation)[2] and/or using a cyclic scaffold;[3] in this way, the resistance to *endo*-peptidases is ensured, and the cell permeability is increased, thanks to the improved lipophilicity.

In the vast realm of the peptidomimetics, peptoids emerge as compounds able to overcome most of the peptides' synthetic drawbacks mentioned before, while providing the enormous therapeutic and pharmaceutical potential. α-Peptoids,[4] oligomers of *N*-alkyl glycines, are easily synthesized *via* solid-phase, usually applying a "sub-monomeric" protocol.[5] The cyclization of such oligomers, described for the first time by Kirshenbaum and co-workers,[6] and widely applied by our research group,[7] leads to macrocyclic derivatives with even more interesting properties, including stable secondary structures in the solution state.

Given the outstanding potential of cyclic peptoids, the main topic of this research project has been the synthesis of congeners of cyclic natural derivatives with a cyclic peptoid scaffold. According to this purpose, we investigated the capability of a series of cyclic hexa- and octapeptoids of mimicking some interesting natural cyclodepsipeptides with cytotoxic and anthelmintic activity. Moreover, the structural rigidity our macrocycles led to an extended investigation about the conformational control in the solution state. With the aim to generate in a stereodirected fashion single conformational enantiomer of the two possible, we conceived a central-to-conformational chirality transfer (with the introduction of a single or multiple stereogenic centres either on the backbone or on the side-chains). The potential of cyclopeptoids as scaffolds, has been explored utilizing the cyclotrimeric architecture which was functionalized with biologically interesting moieties. We prepared a series of catechol-based siderophores, obtaining interesting results in terms of selectivity towards iron(III), and two series of compounds functionalized with polyaromatic units, capable to act as cytotoxic agents towards human cancer cell lines. Lastly, we exploited the well-known capability of alkali metals complexes of cyclic peptoids to act as catalysts, studying the macroring opening polymerization of lactides leading to polylactides, an emerging class of biodegradable polymers.

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[1] a) Di L., *AAPS J.* **2015**, *17*, 1, 134-143; b) Erak M., Bellmann-Sickert K., Els-Heindl S., Beck-Sickinger A. G., *Bioorg. Med. Chem.* **2018**, *26*, 2759-2765.

[2] Biron E., Chatterjee J., Ovadia O., Langenegger D., Brueggen J., Hoyer D., Schmid H. A., Jelinek R., Gilon C., Hoffmann A., Kessler H., *Angew. Chem. Int. Ed.* **2008**, *47*, 2595-2599.

[3] a) Walport L. J., Obexer R., Suga H., *Curr. Opin. Biotech.* **2017**, *48*, 242-250; b) Bock J. E., Gavenonis J., Kritzer J. A., *ACS Chem. Biol.* **2013**, *8*, 488-499.

[4] Simon R. J., 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., Tans R., Frankel A. D., Santi D. V., Cohen F. E., Bartlett P. A., *Proc. Natl. Acad. Sci. USA* **1992**, *89*, 9367-9371.

[5] a) Zuckermann R. N., Kerr J. M., Kent S. B. H., Moos W. H., *J. Am. Chem. Soc.* **1992**, *114*, 10646-10647; b) Culf A. S., Ouellette R. J., *Molecules* **2010**, *15*, 5282-5335.

[6] Shin S. B. Y., Yoo B., Todaro L. J., Kirshenbaum K., *J. Am. Chem. Soc.* **2007**, *129*, 3218-3225.

[7] a) Maulucci N., Izzo I., Bifulco G., Aliberti A., De Cola C., Comegna D., Gaeta C., Napolitano A., Pizza C., Tedesco C., Flot C. De Riccardis F., *Chem. Commun.* **2008**, 3927-3929; b) De Cola C., Licen S., Comegna D., Cafaro E., Bifulco G., Izzo I., Tecilla P., De Riccardis F., *Org. Biomol. Chem.* **2009**, *7*, 2851-2854; c) Comegna D., Benincasa M., Gennaro R., Izzo I., De Riccardis F., *Bioorg. Med. Chem.* **2010**, *18*, 2010-2018; d) De Cola C., Fiorillo G., Meli A., Aime S., Gianolio E., Izzo I., De Riccardis F., *Org. Biomol. Chem.* **2014**, *12*, 424-431; e) Lepage M. L., Schneider J. P., Bodlenner A., Meli A., De Riccardis F., Schmitt M., Tarnus C., Nguyen-Huynh N.-T., Francois Y.-N., Leize-Wagner E., Birck C., Cousido-Siah A., Podjarny A., Izzo I., Compain P., *Chem. Eur. J.* **2016**, *22*, 5151-5155.