Cyclopeptides for Sustainable Weed Management with Low Ecotoxicological Impact

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The increase in agricultural production has brought with it new challenges, one of which is the increasing emergence of herbicide-resistant weeds. The other problem is that most of the currently used herbicide exhibit ecotoxicity in both terrestrial and aquatic environments. These herbicides that reach water bodies, combined with various hydrological alterations and global warming, promote the proliferation of cyanobacteria and limit water use, whether for human or animal consumption or for recreational activities. Over the years, natural products have served as a source of inspiration for the development of bioactive molecules. A significant number of natural products derived from amino acids, among them, cyclopeptides, have been described with herbicidal activity and could be considered as an alternative for sustainable agriculture. For example, tentoxin, a cyclotetrapeptide isolated from the fungus *Alternaria alternata* produces chlorosis on a variety of soybean and corn weeds.

Our goal is to develop new, potentially eco-friendly herbicides that selectively control weeds in economically relevant crops and minimize the risk of promoting cyanobacterial blooms. To achieve this, we proposed the synthesis of tetra- and penta- cyclopeptides analogues to natural products with herbicidal activity.

We will present the peptides preparation employing solid phase peptide synthesis (SPPS) using 2-chlorotrytil resin (2-CTC) and Fmoc strategy. These peptides were cyclized through solution-phase macrocyclization to obtain the corresponding tetra- and penta- cyclopeptides (Figure 1). A library of more than 30 products was obtained and subjected to biological evaluation. Furthermore, we will show the promising results as herbicides against *Lolium multiflorum, Conyza spp.*, and cyanobacterial activity against *Microcystis aeruginosa*, as well as the ecotoxicity assessments involving an eukaryotic alga, *Daphnia magna* and *Vibrio fisheri*.

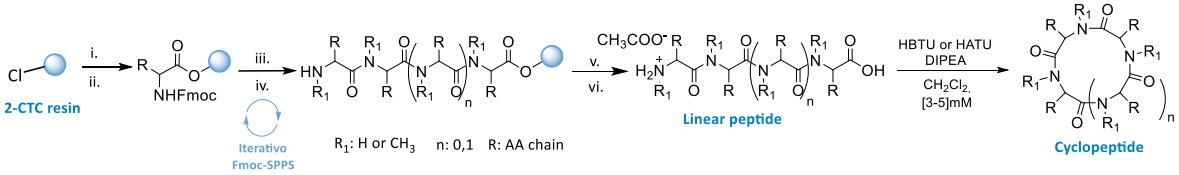

Figure 1. Solid phase peptide synthesis and macrocyclization in solution phase. i. Fmoc-AA-OH (2eq.) in DCM; ii. MeOH; iii. Fmoc-AA-OH, HATU or HBTU in DMF; iv. 4-DMAP 20% in DMF; v. 4-DAMP 20% in DMF; vi. TFA 1% in DCM.

References:

Irabuena C, Posada L, Colombo S, Aubriot L, Rey L, Villalba J, Badagian N, Brena B, Scarone L, Davyt D, Serra G. ACS Omega. 2024 Apr 25;9(18):20167-20175.

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