Title: **Synthetic methodologies for *N*-methylation. Application to solid-phase peptide synthesis.**

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The following project has been focused on an exhaustive bibliographic review (1915-2018) about the different *N*-methylation methodologies of amino acids and peptides in solution and on solid-phase with their applications on natural peptides. The most important application is the improvement of the drugs effectivity against serious illnesses as the cancer.

Depsipeptides are from cyanobacterial origin and, even though they already have a high quantity of *N*-methyl, they are easy enzymatic degradable. For this reason, research has been focused on peptides alkylation and to minimize the effects of this biodegradation. Besides, two key mechanisms have been detailed: the Fischer mechanism and the Mitsunobu mechanism. The databases used were the SciFinder, the Reaxys (Elsevier) and the Wiley Online Library.

In this work, in collaboration with Dra. Judit Tulla and Elisenda Durà the peptide H-Tyr-Ala(*N*Me)-Phe-Ala-OH **71** has been synthesized on solid phase, in the Organic Chemistry Section. The composed amino acids have been prepared in solution for the subsequent couplings to the CTC resin using the Fmoc strategy, the activating agents DIC and the Oxyma Pure. Finally, a treatment with TFA in presence of a low quantity of H_2O has been required to perform the resin cleavage. The results showed that the pure tetrapeptide was obtained with a 38 % of yield.

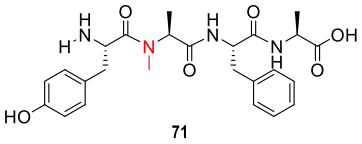

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Figure. Structure of the *N*-methylated tetrapeptide on solid-phase.

The characterization of the products has been performed by HPLC and HPLC-MS analysis. Also, it has been carried out an ultraviolet-visible spectroscopy at 290 nm to quantify the removed Fmoc in the deprotection step, using the Lamber Beer Law.

Keywords: depsipeptides, bioactive peptides, natural products, *N*-methylation.