**Research Title**

Synthesis of cyclopeptides as potential anti-malarials by on-resin cyclization

**Applicant Name**

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**Present Title**

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Prof. Hironobu Hojo

**Summary**

Following our ongoing interest in the synthesis of cyclic peptides as antimalarials, we explored intramolecular NCL assisted by the use of N-alkylcysteine at the peptide C-terminus as an \( N \rightarrow S \) acyl migration device. Fmoc-based solid phase peptide synthesis (SPPS), using amino-PEGA resin was selected to prepare the desired compounds. N-terminal Cys-containing peptides using NCL conditions allowed the cyclization-cleavage reactions and consecutive \( S \rightarrow N \) shift rendering cyclic peptides without the addition of thiol cofactors.

![Fig. 2 On-resin intramolecular NCL using PEGA resin and Fmoc strategy](image)

During the visit of Ph D student Laura Posada, three cyclic hexapeptides were obtained in 18 to 23 % overall yield after purification by preparative RP-HPLC.

The obtained cyclic peptides were evaluated *in vitro* in two independent experiments against *P. falciparum* 3D7 (SYBR Green assay) using artesunate as positive control (EC\(_{50}\) = 0.012 ± 0.003 μM).

The compounds are not active, showing EC\(_{50}\) > 10 μM.

In conclusion, we have developed a procedure for on-resin cyclization with concomitant cleavage from the resin by using tandem reactions of \( N \rightarrow S \) acyl migration and subsequent intramolecular NCL of peptides containing EtCys obtained by Fmoc/SPPS. The procedure could be applied to obtain cyclic peptides of varying ring size and sequences with a wide range of applications.

The training in the use of these methodologies and the equipment at Prof. Hojo laboratory, improved the experience of Ph D student Laura Posada and of the Medicinal Chemistry group, Department of Organic Chemistry at Universidad de la República, Uruguay.

*Deadline: May 15, 2020

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