

DATE: Day 14 Month April Year 2020

SUMMARY of
2019 RESEARCH RESULTS REPORT
For International Collaborative Research with IPR, Osaka University

Research Title		Synthesis of cyclopeptides as potential anti-malarials by on-resin cyclization
Applicant	Name	Gloria Serra
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	Present Title	Associate Professor, PhD in Chemistry
Research Collaborator (Host PI)		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*→*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*→*N* shift rendering cyclic peptides without the addition of thiol cofactors.

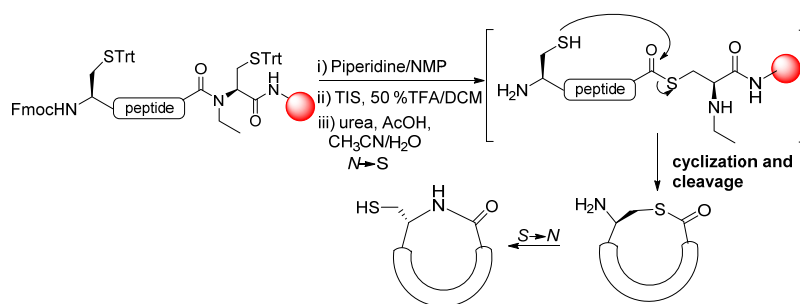


Fig. 2 On- resin intramolecular NCL using PEGA resin and Fmoc strategy

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 ($EC_{50} = 0.012 \pm 0.003 \mu\text{M}$). The compounds are not active, showing $EC_{50} > 10 \mu\text{M}$.

In conclusion, we have developed a procedure for on-resin cyclization with concomitant cleavage from the resin by using tandem reactions of *N*→*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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*Please describe this summary within 1 sheet. Please DON'T add some sheets.

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