DATE: 23th April 2019

SUMMARY of
2018 RESEARCH RESULTS REPORT
For International Collaborative Research with IPR, Osaka University

Research Title		**International Collaborative Research with IPR, Osaka U**
Applicant	**Name**	**Gloria Serra**
	Affiliation	**Facultad de Química, Universidad de la República, Uruguay**
	Present Title	**"New Investigations for the Synthesis of Anti-malarial Cyclopeptides"**
Research Collaborator (Host PI)		**Prof. Hironobu Hojo**

Summary

In the search for new drug candidates with antiparasitic activity, the Uruguayan group reported the synthesis and biological evaluation as antimalarials, of cyclopeptidic analogs of natural products. The obtained results are very promising as several macrocyles showed nanomolar EC_{50} against *P. falciparum* and a high selectivity for the parasite.

The specific aims of the research at Institute of Protein Research (IPR) were the synthesis of peptides by solid phase peptide synthesis (SPPS) and the study of on resin-macrocyclization using S-N acyl shift to obtain potential cyclopeptidic anti-malarials. Another aim for Prof. Serra was to gain experience in the use of the available equipment at IPR.

First, the conditions for on resin cyclization were studied to obtain *Cyclo Cys-Phe-Ala-Phe-Ala-Phe*. Fmoc strategy on Amino PEGA resin was used to obtain the hexapeptide. The dipeptide Fmoc-Phe-NEt-Cys(Trt)-OH was anchored to the resin followed by iterative Fmoc-SPPS. After deprotection using 50% TFA, a mixture of urea/ AcOH in CH_3CN:H_2O was added to perform the macrocyclization reaction *via* S-N acyl shift. NMR and MS analysis allowed us to conclude that the cyclohexapeptide was obtained in good yield (50%) and good purity.

Then, two cyclopeptides: *Cyclo Cys-Phe-Ala-Phe-Ala-Ala* and *Cyclo Cys-NMeAla-Phe-NMeAla-Ala* were prepared using the described methodology, in 40 and 46% yield and good purities.

The three cyclopeptides were evaluated against *Plasmodium falciparum* showing EC_{50}> 1 μM.

On-resin "Native Chemical Ligation" methodology, allowed the synthesis of cyclopeptides in good purity and good yield. Novel cyclopeptides will be obtained, using this methodology, in order to evaluate them as anti- malarial compounds.

***Deadline: May 17, 2019**
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