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SUMMARY of
2017 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	**"Synthesis of macrocycles with anti- malarial activity"**
Research Collaborator (Host PI)		**Prof. Hironobu Hojo**

Summary

As part of the Uruguayan group search for new drug candidates with antiparasitic activity, we have reported the synthesis and biological evaluation as antimalarials, of macrocyclic analogs of natural products. The obtained results are very promising as several macrocyles showed submicromolar activities against *P. falciparum* K1 and a high selectivity (SI > 125) for the parasite. In addition three of them, containing N-methylamino acids, showed nanomolar activity and excellent SI (unpublished results). Considering that macrocyclization is a slow and low yielding reaction, the exploration of new methodologies to improve this process is of great interest.

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 macrocyclization reaction using routes based on S-N acyl shift. It is important to note that the research plan involved the use of Prof. Hojo synthetic method for the peptide thioester.

Another aim for Prof. Serra was to gain experience in the use of the available equipment at IPR.

Fmoc strategy of Solid Phase Peptide Synthesis was used to obtain peptides. Two methodologies were explored to obtain cyclopeptides:

i) Using thiophenol promoting the cleavage from the resin and then solution cyclization.

N-(Et)Cys was used to perform the formation of thioester intermediate thorough the "N-S acyl shift" reaction promoted by acid. Then, reaction with thiophenol produces the peptide and cleavage from the resin. Finally, HOOBt was used to obtain cyclopeptides.

ii) On-resin cyclization v*ia* the formation of thioester derived from an N-terminal Cys.

This methodology was studied using urea, acetic acid in CH_3CN: H_2O. Even though, the formation of cyclopeptide, was observed, new experiments have to be developed in order to stablish the scope of this reaction.

All the reactions were analyzed using RP-HPLC and purification of the obtained cyclopeptides was realized using a preparative column by RP-HPLC.

Mass spectra analysis was used to determine the formation of the desired cyclopeptides.

We can conclude that: i) "Native Chemical Ligation" methodology, using thiophenol and HOOBt, allowed the synthesis of cyclopeptides in good purity but in low yield; ii) New experiments are needed in order to determine the scope of on-resin cyclization to obtain this type of cyclopeptides.