STSM Dafni Graikioti

Title: Libraries of analogues of Eucalyptus G-endoperoxides, antiparasite activities, mechanisms of action.

Description of the STSM main achievements and planned follow-up activities

During this 6-week internship 2 final alkynyl compounds were synthesized and 6 intermediate compounds were prepared. In particular, propargyl alkylation of the endoperoxides (**DG-03** and **DG-04**) and the synthesis of two alkylating precursors-2-Azidoethanol (**DG-11**) and 2-Bromoethyl methanesulfonate (**DG-12**)-were accomplished.

The future objectives of the project can be resumed as follows:

i. Synthesis of the -OMe endoperoxides via the n-butyllithium procedure (known)[5].
ii. Application of this procedure for the coupling of **DG-03** and **DG-04** with **DG-12** and **DG-07**.
iii. Deprotection of *N*-Boc of the endoperoxides **DG-03** and **DG-04** and coupling with **DG-07**, propargyl and butynyl bromide.
iv. Synthesis of ≃10 mg each derivative for biological studies on strains of *P.falciparum*.

References:

1. Ruiz, J.; Azema, J.; Payrastre, C.; Baltas, M.; Tuccio, B.; Vial, H.; Andre-Barres, C., Antimalarial bicyclic peroxides belonging to the G-factor family: mechanistic aspects of their formation and iron (II) induced reduction. *Curr Top Med Chem* **2014,** 14, (14), 1668-83.
2. Najjar, F.; Gorrichon, L.; Baltas, M.; André-Barrès, C.; Vial, H., Alkylation of natural endoperoxide G3-factor. Synthesis and antimalarial activity studies. *Org Biomol Chem* **2005,** 3, (9), 1612-4.
3. Wang, C.-G.; Chong, A.; Yunpeng, L.; Liu, X.; Goto, A., Metal-Free Fast Azidation by Using Tetrabutylammonium Azide: Effective Synthesis of Alkyl Azides and Well-Defined Azido-End Polymethacrylates. *Chemistry - A European Journal* **2019,** 25.
4. Park, S.-H., Acceleration of azidation by microwave irradiation. *Bulletin of the Korean Chemical Society* **2003,** 24, (2), 253-255.
5. Pepe, D. A.; Toumpa, D.; André-Barrès, C.; Menendez, C.; Mouray, E.; Baltas, M.; Grellier, P.; Papaioannou, D.; Athanassopoulos, C. M., Synthesis of Novel G Factor or Chloroquine-Artemisinin Hybrids and Conjugates with Potent Antiplasmodial Activity. *ACS Med Chem Lett* **2020,** 11, (5), 921-927.

STSM outcome form

STSM application number	Home institution & country	Host institution & country	*OneHealthdrugs* WG	Objective of the collaboration	Results of the collaboration and related GAPG
COST-STSM-CA21111	**University of Patras** University Campus, GR26504 Rion, Achaia, Greece	**Laboratoire de Chimie de Coordination du CNRS** - UPR8241 Inserm ERL 1289 Équipe "Nouvelles molécules antipaludiques et approches pharmacologiques" 205 route de Narbonne - BP 44099 - 31077 Toulouse Cedex, France	Working Group 1: Compound libraries coordination and integration of compound design	Title: Libraries of analogues of Eucalyptus G-endoperoxides, antiparasite activities, mechanisms of action. Objectives: • Synthesis and elaboration of endoperoxide G3 compounds which bear terminal alkynes or azides. • Biological studies for each derivative on strains of *P.falciparum*.	*Results:* • Two final alkynyl compounds were synthesized and six intermediate compounds were prepared. *GAPGs:* • Synthesis of the -OMe endoperoxides via the n-butyllithium procedure. • Deprotection of the *N*-Boc of the endoperoxides and coupling with terminal alkynes and azides. • Synthesis of ≃10 mg of each derivative for biological studies on strains of *P.falciparum*.

Image 2. *Syncarpic acid crystals.*

Image 1. *Synthesis of the G3 endoperoxides.*