



**PhD position starting on October 2020 in Montpellier (France)
3 years doctoral fellowship (Contrat Doctoral)**

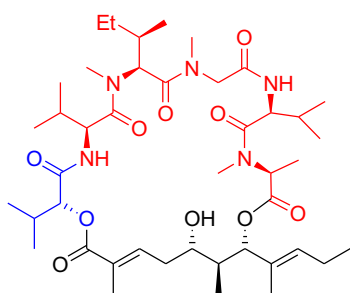
Synthesis and SAR studies of Cytotoxic Cyclic Depsipeptides

Research laboratory: Institut des Biomolécules Max Mousseron (IBMM), Université de Montpellier (France). Team F10 : Stereoselective synthesis and modified amino acids.

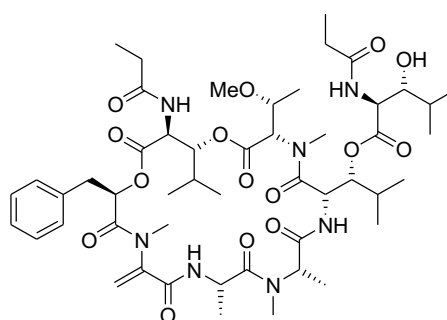
Research theme: Asymmetric organic synthesis, unnatural amino acids and peptides, total synthesis of natural products, structural analogues

Profile: The candidate will hold a solid formation in asymmetric organic synthesis. Scientific curiosity, interest, motivation, rigor and ability to work in team are also essential.

A variety of cyclic depsipeptides of marine origine, like Aurilide C and Sameuramide A, with anticancer properties, have been isolated and explored during the last years.^{1,2} Because of their promising drug-like properties, including good membrane permeability and biostability, synthetic and medicinal chemistry studies are of interest. These molecules, correctly re-designed and possibly conjugated to be more selective against malignant cells, could be used either in cotherapy with other anti-tumor molecules, or as a palliative treatment against tumors that have become resistant to other medications. Key structural elements include several unusual aminoacids fused together in a macrocycle and in some cases a polyketide chain.



Aurilide C



Sameuramide A

Strong from our experience in the total synthesis, in solution and solid phase, of another depsipeptide, Oxoapratoxin A,³ we wish to develop a new route for the synthesis of natural depsipeptides. This would provide access to large quantities of these compounds that nature provides in low doses. This flexible route will also allow access to non-natural analogs of these compounds for the purpose of conducting a structure-activity relationship study (SAR) that allows the identification of the minimal active structure and important moieties for the activity. We also hope to improve the anticancer activity of natural products with synthetic analogs. The compounds will be gradually tested for their cytotoxicity on different cell lines. The results of

these tests will guide us in terms of the structural modifications to be envisaged. We can thus discern between the bricks, at the level of the structure of our products, those which are essential for the biological activity of the compounds and those which have no influence. We also plan to combine the cyclodepsipeptides synthesized with a molecule vector, showing tumour cells affinity, to transport them specifically to targeted cells.

In addition, the synthesis strategy can also be carried out using deuterium-labeled raw materials to produce stable isotopic analogs, allowing their use as referents for accurately measuring the amount of internalized bioactive compounds and establishing a dose / activity correlation overcoming the cellular type.

The candidate for this doctoral contract in France will benefit from an interdisciplinary team gathering complementary expertise in asymmetric synthetic organic chemistry (Dr. Xavier Salom-Roig) and peptide chemistry (Dr. Florine Cavelier) from the Institut des Biomolécules Max Mousseron (IBMM, Université de Montpellier, France).

The institute and the scientific environment

The Institute of Biomolécules Max Mousseron (IBMM, <https://ibmm.umontpellier.fr/>), led by Pr. Pascal Dumy, is a CNRS research unit associated with the University of Montpellier and the School of Chemistry of Montpellier. It is one of the four institutes forming BALARD Chemical division of Languedoc-Roussillon.

The activities of research and innovation focus on the essential biomolécules such as lipids, nucleosides, nucleotides and nucleic acids, amino acids, peptides and proteins, glycosides, biopolymers, prebiotic molécules and fluorinated molécules. The research programs conducted on biomolécules concern their design, synthesis and pharmacology.

The institute has the essential equipment for organic chemistry and analysis, including analytical and preparative LC/MS dedicated to peptides, technical platform (Laboratory of physical measurements, LMP) provides complementary facilities: six NMR spectrometers from 200 to 600 MHz, liquid and solid samples, H/C/P/N/Si detection, multidimensional analyses (NOESY-COSY-DEPT...), variable temperature, HR-MAS; four Mass spectrometers with various ionization/mass analyzer configurations: ESI-APCI/QqTof, ESI/QqQ, MALDI/Tof-Tof, EI-CI/Q, low and high resolution analyses, hyphenated techniques (LC/MS, LC/MS/MS, GC/MS); four chromatography systems : Liquid chromatography (HPLC, UPLC, NanoLC) and gas chromatography coupled to mass spectrometers for qualitative and quantitative analyses of complex mixtures; Elemental Analyses C/H/N/S/O content measurement by combustion or pyrolysis. Polarimeter and spectropolarimeter: optical rotation, circular dichroism, UV/Visible, fluorescence measurements.

Applications before 30/06/2020: Please, send cover letter, CV, 2 recommandation letters and transcripts of Master studies to

Dr. Xavier Salom-Roig (Xavier.Salom-Roig@umontpellier.fr) and

Dr. Florine Cavelier (Florine.Cavelier@umontpellier.fr)

1.-Masato Kaneda, Shinsaku Kawaguchi, Nobutaka Fujii, Hiroaki Ohno, and Shinya Oishi, *Med. Chem. Lett.* **2018**, *9*, 365–369.

2.- Koshi Machida, Daisuke Arai, Ryosuke Katsumata, Satoshi Otsuka, Jun K. Yamashita, Tao Ye, Shoubin Tang, Nobuhiro Fusetani, Yoichi Nakao, *Bioorganic & Medicinal Chemistry* **26** (2018) 3852–3857.

3.-Arnaud Gilles, Jean Martinez, Florine Cavelier, *J. Org. Chem.* **2009**, *74*, 4298-4304.