TherAza : New triazamacrocycles based bioconjugates for diagnosis and therapy

PhD Project : 1er octobre 2018 – 30 septembre 2021
Financement : 50% CDE / 50 % ARED

CEMCA - UMR CNRS 6521 Université de Bretagne Occidentale, 6 avenue Victor Le Gorgeu, C.S. 93837 - 29238 BREST CEDEX 3 – France ; Fax : 33 (0)2 98 01 70 01
Site web: http://www.umr6521.cnrs.fr/

Context : Polyazacycloalcanes like 1,4,7-triazacyclononane (tacn) are characterized by their excellent complexing properties for ionic substrates, explaining their involvment in numerous applications. In medicinal research, applications of their metallic complexes are directed towards diagnosis imaging (MRI, PET and Optic Imaging), therapy with radiotherapy or photodynamic therapy (PDT). This wide applications spectrum allows to understand the importance of controling the chemistry of these compounds.
Our group is expert in polyazacycloalcanes chemistry area and has already described derivatives of tacn chelators of Copper (II) for PET imaging and radiotherapy applications (respectively with radioisotopes Copper-64 and Copper-67) and also of Zinc(II) characterized as a MRI sensor for Zn(II) detection. We are now developing luminescent probes for optic imaging that requires the synthesis of tacn based sophisticated platforms.

Objectives : For having effectiveness in the aimed applications, the different triazamacrocyclic chelates have to be drived to the target by conjugation to a biospecific vector (peptide, antibody,…). Chelators design has to be extended to the bifunctional analogues having the functions for chelating the metallic cation and also for binding easily to the vector. Despite the synthesis difficulties, one mean consists in introducing a supplementary function called coupling function or bioconjugation function on one of the chelating arm. These methods are promising but remain time-consuming and not much profitable because of the numerous steps in the synthesis and require to be studied and adapted for each considered chelator.

Project : The project consists in introducing these coupling functions directly on the « waked » macrocycle by developing a « tacn C-functionalization » method allowing to place the functional arm for biocoupling on a carbon atom of the macrocycle.
The aim of this project is to develop a tacn C-functionalization method allowing to place the functional arm reserved for bio-coupling on one of the carbon atoms of the macrocycle. We will thus be able to synthesize our chelators for different applications in imaging and therapy from only one adjustable derivative. The rare exemples of a such synthesis in the literature present the major default to contain numerous steps giving low yields and thus no real prospects for an industrial transfer of the applications in health. Our aim requires to elaborate a competitor and easy-to-run method, capable of producing bioconjugable platforms in the range of gram quantities.
This work will be done in collaboration with Pr Mark Bartholomä from University of Fribourg in Germany for the bioconjugation of our chelates to a neuro-polypeptide derivative of Bombesin and for the study of the properties of the radiopharmaceutical

The candidate will possess skills in organic synthesis and in the study of macrocyclic chemistry for metal cations complexation. Knowledges of biological applications in health area would be appreciated.

References : A. Guillou, L. M. P. Lima, M. Roger, D.Esteban-Gómez, R. Delgado, C. Platas-Iglesias, V. Patinec, R. Tripier, *Eur. J. Inorg. Chem*, **2017**, 2435. M. Le Fur, M. Beyler, N. Le Poul, L. M. P. Lima, Y. Le Mest, R. Delgado, C. Platas Iglesias, V. Patinec, R. Tripier, *Dalton Trans*, **2016**, 45, 7406. M. Roger, L.M.P. Lima, M. Frindel, C. Platas-Iglesias, J.F. Gestin, R. Delgado, V. Patinec, R. Tripier, *Inorg. Chem.*, **2013**, 9, 5246. M. Regueiro-Figueroa, S. Gündüz, V. Patinec, N. K. Logothetis, D. Esteban-Gómez, R. Tripier, G. Angelovski, and C. Platas-Iglesias, *Inorg. Chem.*, **2015**, 54, 10342. E. Molnár, N. Camus, V. Patinec, G. Rolla, M. Botta, G. Tircso, F. Kalman, T. Fodor, R. Tripier, C. Platas-Iglesias, *Inorg. Chem.*, **2014**, 10,5136.