PhD position in computational chemistry at Nantes (France)

Design of ligands for the complexation of astatine-211

(Annonce en français en fin de document)

Background:

Astatine-211 is an alpha-emitting radioisotope with a 7.2-hour half-life that holds great promise for cancer therapy. Associated with a specific vector molecule of a type of tumor cell, ^{211}At can be transported as close as possible to tumor sites for delivering its high-energy radioactive radiation, allowing the destruction of targeted cells. ^{211}At is artificially produced using a particle accelerator. In particular, the Arronax cyclotron located in Nantes is one of the most powerful accelerators in the world allowing its production. It is expected to enable clinical applications of ^{211}At in various cancer pathologies in the forthcoming years. In order to produce an ^{211}At-based radiopharmaceutical, chemical synthesis steps are required. As astatine is the heaviest of halogens, synthetic approaches typical of halogens are most often implemented with the formation of astatine-carbon bonds. However, this type of bonding is most often found to be insufficiently stable *in vivo*, and astatine dissociates from its vector before reaching its tumor target, leading to unwanted irradiation of healthy tissues. It is therefore necessary to find alternatives to the astatine-carbon bond.[1]

Astatine is the rarest chemical element on Earth, so it has been studied very little and the possibilities of new developments are numerous. The SAt-Radio project (Stable ^{211}At-labeled radiopharmaceuticals for targeted α therapy) is funded for 5 years from October 2023 by the European Research Council (ERC). The work on astatine carried out over the last 10 years places Nantes Université as a major global player in radiolabeling chemistry with this chemical element of growing interest. The CRCI²NA laboratory (UMR 1307) is one of the few in France to develop cancer therapy modalities using alpha-emitting radiopharmaceuticals. The CEISAM laboratory (UMR 6230) has expertise in modeling the chemistry of radioelements, thanks to bond analysis tools developed locally. These laboratories are working closely together on the SAt-Radio project, which requires an interdisciplinary approach, from chemistry to radiopharmacy and biology. The modeling team currently gathers one associate professor and one postdoc student.

They are working to guide the development of the chemical precursors needed to introduce radionuclides onto biological vectors of interest. The ERC program will be carried out in close collaboration with Dr. François Guérard of the CRCI2NA laboratory for organic synthesis aspects, and with Dr. Gilles Montavon (Subatech, UMR 6457), for analytical aspects.

Hypotheses and research program:

Astatine displays typical characteristics of metals, due to the relativistic effects observed for heavy elements (Z = 85). Several studies have highlighted this metallic character and the ability of some of At oxidized species to form complexes with various ligands.[2,3] However, no complex sufficiently stable for *in vivo* use has been reported to date. The PhD project aims to take advantage of At's metallic character to design radiopharmaceuticals based on chelating agents. Relativistic DFT calculations will be carried out to predict the affinity of simple model ligands for At(I). For the most suitable ligands, a comparison is expected between determined equilibrium constants and measured data in solution. These same ligands will then be assembled into polydentate ligands, with pre-organization to be refined by molecular modeling.

A second part of the PhD will focus on the halogen character of astatine. *N*-heterocyclic carbenes (NHCs) are known to form stable complexes with metals of low oxidation state, which in turn can stabilize the astatide anion (At^-).[4] Molecular modeling can be used to characterize the influence of the nature of the metal (*e.g.* M = Rh(I), Ir(I), Au(I)), as well as the electronic effects of *N*-substituents. In particular, descriptors of the At-M bond (bond energy, bond order and polarity, etc.) will be determined and compared with measured stabilities. The obvious aim is to guide the development of optimal M-NHC motifs, and a selection of the most promising compounds will be proposed for synthesis.

Candidate Profile:

The successful candidate will have a Master degree with honors in chemistry, physical chemistry or a similar degree, and should have a solid background in quantum chemistry with good experience of a current molecular modeling program such as Gaussian, Turbomole, Q-Chem or ADF. A background in coordination chemistry is an asset. He/she must speak English fluently and must be motivated to learn French.

Application:

Candidates will send a cover letter, a detailed CV (indicating marks or ranks of Master 1 and Master 2), as well as the names of two referees to nicolas.galland@univ-nantes.fr.

Refs.

1. F. Guérard, C. Maingueneau, L. Liu, R. Eychenne, J.-F. Gestin, G. Montavon, N. Galland, Acc. Chem. Res., 54, 3264–3275 (2021).

2. F. Bassal, J. Champion, S. Pardoue, M. Seydou, A. Sabatié-Gogova, D. Deniaud, J.-Y. Le Questel, G. Montavon, N. Galland, Inorg. Chem., 59, 13923-13932 (2020)

3. J. Champion, C. Alliot, S. Huclier, D. Deniaud, Z. Asfari, G. Montavon, Inorg. Chim. Acta, 362, 2654–2661 (2009).

4. H. Rajerison, F. Guérard, M. Mougin-Degraef, M. Bourgeois, I. Da Silva, M. Chérel, J. Barbet, A. Faivre-Chauvet, J.-F. Gestin, Nucl. Med. Biol., 41, e23–e29 (2014).