Design and synthesis of 3 series of mono and multimeric radiotracers targeting tumor microenvironment and designed as selective theranostic agents

In this project we focused on the design, synthesis, and optimization of novel molecules of biomedical interest with particular relevance in the tumor microenvironment. [1] The developement of new strategies to counteract such a disease is of paramount importance. Among synthetic strategies known to date, the use of Multi-Target Directed Ligands (MTDLs) has emerged as particularly effective, and associated to benefits such as improved patient compliance, therapeutic outcomes and predictable pharmacokinetics and pharmacodynamics. [2] In this context, the project was carried out by the development of two different series of inhibitors, with the first targeting both Carbonic Anhydrases (CA) and Fibroblast Activation Protein (FAP), incorporating a radiolabeling chelator, and the latter obtained incorporating in the same compound the CA inhibition moiety and the radiolabeling chelator (**Figure 1**).

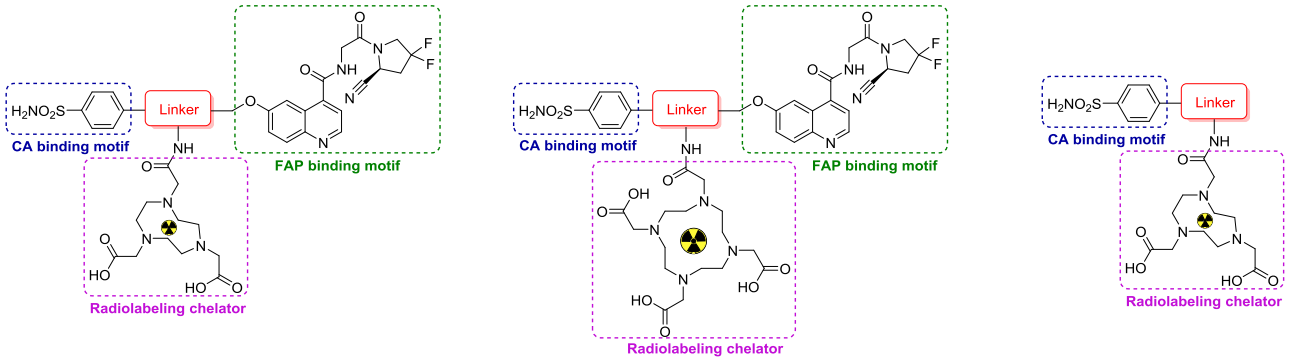

Figure 1: General structure of synthesized compounds.

Carbonic Anhydrases (CA, EC 4.2.1.1) [3-4] are a superfamily of metalloenzymes encoded by eight unrelated gene families that reversibly catalyze the hydration of carbon dioxide to bicarbonate and protons. Among the eight CA families, 15 α-CA isoforms are expressed in humans. CAs are crucial in hypoxic tumors as are relevant to prevent too low intracellular pHs which in turn will trigger necrotic and apoptotic events. [5] The second target for this project is the Fibroblast activation protein-α (FAP-α; EC 3.4.14.5) [6], which is endowed with peptidase activity and expressed on the cell surface of cancer-associated fibroblasts (CAFs) in the tumor stroma. FAP plays a crucial role in tumor progression, growth and metastasis. [7] Although FAP is expressed in specific healthy tissues, [8] it is significantly upregulated in tumors. [9] In this project, two distinct series of derivatives were synthesized: The first bearing both pharmacophores and the chelating agent NOTA or DOTA; the second one bearing only the benzenesulfonamide moiety for the inhibition of carbonic anhydrases isoforms with the chelating agent NOTA.

References:

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