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Click Chemistry for advancing the development of dual RGD integrin/MMP ligands

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Through the process of angiogenesis, tumor cells generate new blood vessels to ensure supply and a route of elimination of waste metabolites. So, tumor cells can grow and spread out to the body generating metastasis. Integrin receptors and Matrix Metallo-Proteases (MMPs) are proteins deeply involved in tumor cell invasion and metastatic diffusion, interacting each other to facilitate these processes [1]. Indeed, Integrins are responsible of cellular adhesion with the extracellular matrix (ECM), while MMPs have a role in tissue remodeling and in the degradation of several structural proteins in the ECM.

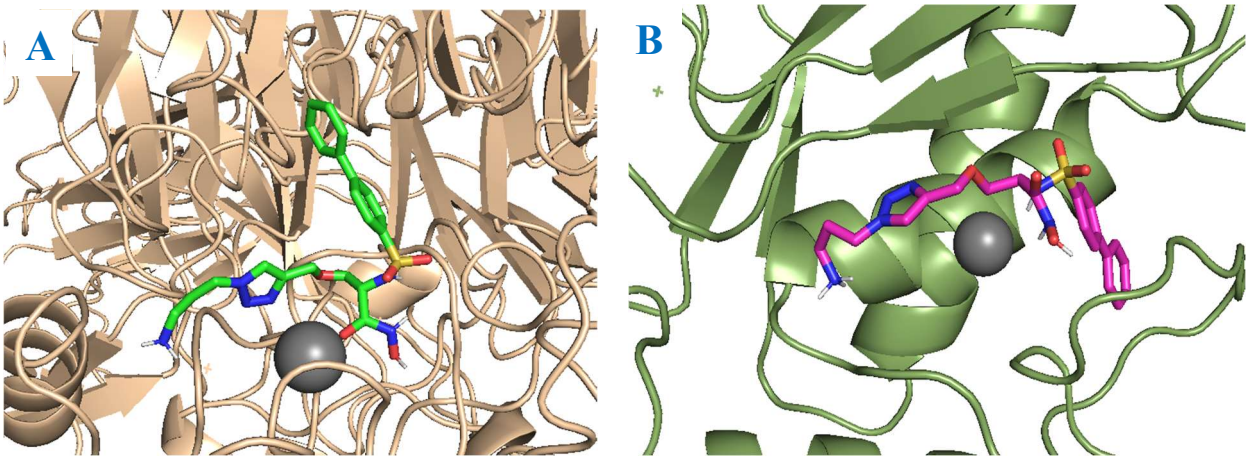

Figure 1 – Molecular Docking studies of a selected ligand toward $\alpha_v\beta_3$ Integrin receptor (Figure A) and MMP-2 (Figure B)

Recently, we developed *L*-tyrosine-derived dual RGD integrin/MMP ligands [2], that demonstrated the similarity of the active sites of these two proteins and the possibility of targeting both with a ligand possessing three main Functional Groups (FGs): a chelating FG for interacting with the metal ion, a basic FG for establishing a salt bridge with acidic amino acid residues, and a hydrophobic moiety for penetrating a lipophilic pocket. In this view, we reasoned exploiting the click chemistry for synthesizing novel compounds as dual RGD integrin/MMP ligands possessing the aforementioned interacting FGs and the triazole ring as central scaffold, resulting in the identification of a serine-derived compound with significant bioactivity.

References

[1] S. Quintero-Fabián, R. Arreola, E. Becerril-Villanueva, J.C. Torres-Romero, V. Arana-Argáez, J. Lara-Riegos, M.A. Ramírez-Camacho, M.E. Alvarez-Sánchez. Role of Matrix Metalloproteinases in Angiogenesis and Cancer. *Front. Oncol.* **2019**, 9, 1370.

[2] L. Baldini, E. Lenci, F. Bianchini, A. Trabocchi. Identification of a Common Pharmacophore for Binding to MMP2 and RGD Integrin: Towards a Multitarget Approach to Inhibit Cancer Angiogenesis and Metastasis. *Molecules*. **2022**, 27, 1249.