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Contribution	*Oral*	*Slide&Talk*	*Poster*
Session	*Anal Chem*	*Med Chem*	*Pharma Tech & Drug Del*

Design of dual peptidomimetic gelatinase/integrin inhibitors for tumor angiogenesis targeting

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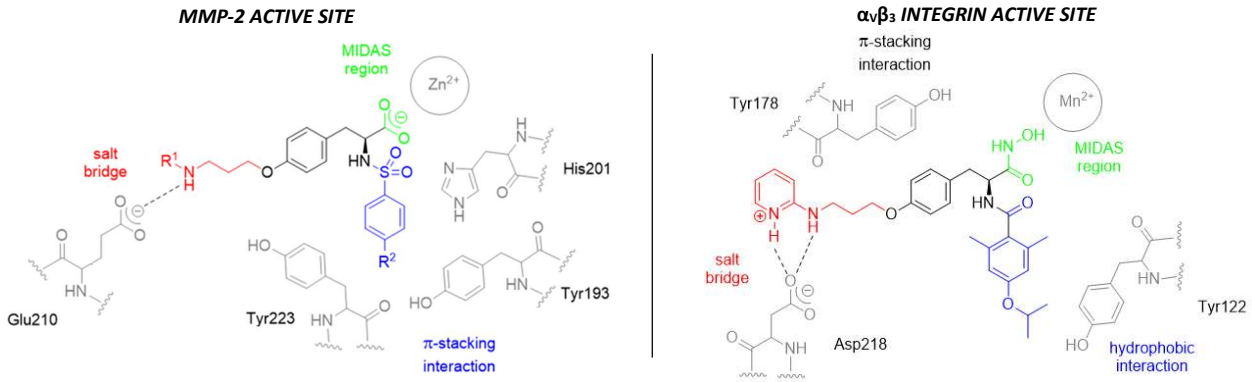
Matrix Metallo-Proteases (MMPs) subfamily of gelatinase are zinc-containing extracellular proteases which are overexpressed in numerous aggressive malignant tumors. Due to their proteolytic activity, they play a role in cellular signalling pathways. $\alpha_V\beta_3$ integrin is a membrane receptor which determine fundamental processes for tumor metastasis such as angiogenesis and cellular migration. These two classes of macromolecules can interact each other, resulting to the important aforementioned event for tumor cells to generate metastasis process.



We reasoned that *L*-Tyrosine-derived inhibitors of $\alpha_V\beta_3$ integrin[1] display a similar pharmacophore to those of MMPs inhibitors. Thus, we synthesized molecules analogous to those reported, equipped with appropriate functional groups (an α-arylsulfonamide group, a terminal basic group, and an α-chelating group), to verify if it were possible to obtain integrin/gelatinase multitarget inhibitors. Molecular docking calculations were performed to identify the ligand-protein interactions between a selected synthesized molecule and MMP-2. The pool of synthesized molecules was assayed toward MMP-2 and MMP-9, as well as toward $\alpha_V\beta_3$ integrin. Some tested molecules demonstrated to possess optimum inhibitory activity toward both classes of macromolecules, suggesting their potential as effective multitarget inhibitors.

References

[1] D. Heckmann, B. Laufer, L. Marinelli, V. Limongelli, E. Novellino, G. Zahn, R. Stragies, H. Kessler, Breaking the Dogma of the Metal-Coordinating Carboxylate Group in Integrin Ligands: Introducing Hydroxamic Acids to the MIDAS To Tune Potency and Selectivity, *Angew. Chem. Int. Ed.*, 2009, 48, 4436.