MACROCYCLISATION *IN SITU* BY CONFINEMENT: PROOF OF CONCEPT AND APPLICATION TO THE DESIGN OF NEW MACROCYCLIC INHIBITORS OF THE INHA ENZYME

Chebaiki Mélina[ab], Lherbet Christian[a], Mourey Lionel[b], Maveyraud Laurent[b].

[a]*LSPCMIB, UMR-CNRS 5068, Université Paul Sabatier-Toulouse III, 118 Route de Narbonne, 31062 Toulouse Cedex 9, France.*

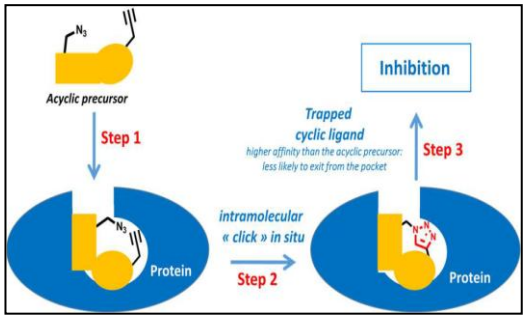
[b]*IPBS, CNRS, 205 Route de Narbonne, BP64182, F-31077 Toulouse, France.*

In 2020, tuberculosis (TB) is the 13th leading cause of death worldwide and the second due to an infectious disease behind COVID-19. In 2020, 9.9 million people contracted tuberculosis, including 1.1 million children.[1] The area of the world most affected by this disease is sub-Saharan Africa and the Western Pacific.[1] This desease is caused by the mycobacterium *Mycobacterium tuberculosis.*[1]

InhA is an essential enzyme for the survival of mycobacteria; it allows the reduction of mycolic acids, lipids forming the bacterial membrane. The main project targets this protein to find new inhibitors.[2,3]

Ligand formation is inspired by KTGS, the kinetic target guided synthesis, a synthesis in which the protein participates in the formation of ligands. It is the most affine ligands that will be formed in the active site. In KTGS, the targets bring in close proximity with the right orientation, affine reagents, so that they react irreversibly. *In situ* click chemistry, first disclosed for the discovery of acetylcholinesterase (AChE) inhibitors, is the most popular kinetic target guided synthesis. It allows protein-templated triazole synthesis from biocompatible alkynes and azides.[4]

In our project, we will apply intramolecular *in situ* click chemistry; the two reactive parts are on the same molecule to form a macrocycle. So, the main objective is to explore the potential of a new concept, the macrocyclisation of acyclic ligands by taking advantage of the confinement provided by the binding pocket of a protein. Based on steric considerations, we predict that an acyclic precursor would reach the protein pocket more easily than its macrocyclic counterpart (step 1). Once housed within the pocket, the confinement should promote proximity of the reactants and facilitate the intramolecular ring closure reaction (step 2) to create a new ligand with enhanced binding properties (step 3).



References:

[1] Global Tuberculosis Report 2021(https://www.who.int/teams/global-tuberculosis-programme/tb-reports/global-tuberculosis-report-2020) (accessed March 26, 2021)

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[4] D.Bosc, *J. Med. Chem*. **2020**, 63, 3817-3833.