

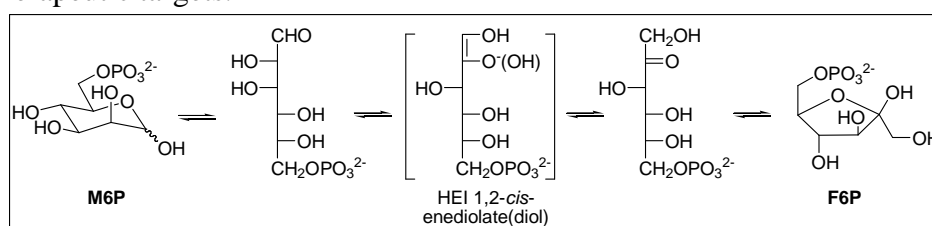
Design, synthesis, kinetic and theoretical structural studies of substrates and inhibitors of phosphomannose isomerases.

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Phosphomannose isomerases (PMIs) are metal-dependent aldose-ketose isomerases catalyzing the reversible isomerization of D-mannose 6-phosphate (M6P) and D-fructose 6-phosphate (F6P, *scheme 1*). As they are essential for the survival of several pathogenic microorganisms, including *Pseudomonas aeruginosa* and *Leishmania mexicana*, PMIs are considered as potential therapeutic targets.



Scheme 1 : Reversible interconversion of M6P and F6P catalyzed by PMIs.

The catalytic reaction proceeds through a proton transfer mechanism and involves a 1,2-cis-enediolate high-energy intermediate (HEI). 5-Phospho-D-arabinonohydroxamate (5PAH), a designed HEI analogue, was recently reported in our laboratory as the most potent inhibitor of PMIs.¹ This molecule is also a powerful inhibitor of phosphoglucose isomerase (PGI) catalyzed reversible isomerization of D-glucose 6-phosphate (G6P) to F6P. Contrary to PGIs, the catalytic mechanism of the PMIs is not well defined yet.

The present work describes a structure-activity relationship study, consisting into the synthesis of several substrate and HEI analogue inhibitors and the kinetic evaluation of their properties towards PMIs. These compounds have been docked into the active site of PMI by energy-minimization using the polarizable molecular mechanics procedure SIBFA (Sum of Interactions Between Fragments *ab initio* computed).² Their structures derive from M6P or 5PAH structures. They are designed by modifications of the chelating part, the phosphate part, or the number of hydroxyl groups. To date, two M6P analogues and five HEI analogues have been designed and synthesized.

In the absence of actual crystal structures of PMI-inhibitor complexes, the conclusions of kinetic and molecular modelling studies are expected to improve our structural and mechanistic knowledge of PMIs. Moreover, this structure-activity relationship study will be the starting point for the design of inhibitors of therapeutic interest that should be endowed with high PMI affinities, selectivity for pathogen PMI vs. human PMI or selectivity for PMI vs. PGI.

¹ Roux, C., Lee, J. H., Jeffery, C. J., Salmon, L., *Biochemistry* 2004, 43, 2926-2934.

² Roux C., Gresh N., Perera L. E., Piquemal J-P., Salmon L., *J. Comput. Chem.* 2007, 401, 279-285.