SYNTHESIS, BIOLOGICAL EVALUATION AND MOLECULAR MODELLING OF NEW MraY INHIBITORS WITH AN AMINORIBOSYL URIDINE STRUCTURE AND AN OXADIAZOLE

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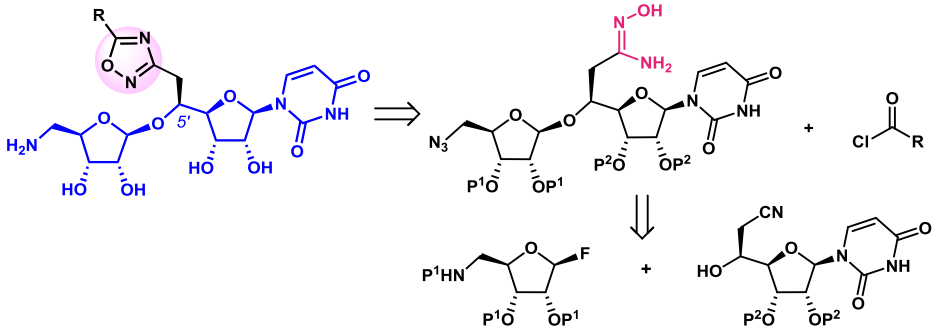
Widespread antibiotic resistance available on the market is steadily eroding the effectiveness of existing treatment option. Furthermore, the dramatic worldwide rise of multidrug-resistant infections is also a global health threat. [1] Therefore, it has an urgent need to develop innovative antibiotics for targeting bacterial infections. Peptidoglycan, whose biosynthesis is known to be a well-established target for antibiotic development and involves enzymes demonstrated essential for bacterial survival, is responsible for maintaining cell shape. MraY, one of these enzymes, involved in the early stages of peptidoglycan biosynthesis,[2] is a trans-membrane protein which catalyzes the first membrane step of peptidoglycan biosynthesis. Because its inhibition can lead to cell lysis and no drugs have been developed to target MraY, MraY is considered a highly promising target for the discovery of new antibiotics.

Several families of natural MraY inhibitors are known, such as muraymycins[3]. Notably, these compounds display a common aminoribosyl uridine scaffold that is important for their biological activity. In the continuity of previous studies, [4] we performed the synthesis of a panel of new MraY inhibitors (Figure) by anchoring through an oxadiazole linker, various substituents on this amino ribosyl uridine scaffold. Indeed, our docking experiments predict important interactions of this linker with key aminoacids of the active site, such as His325. The synthesis of these compounds relies on a glycosylation reaction between a fluororibose and a cyanouridine derivative followed by the formation of the oxadiazole through *O*-acylation of an amidoxime with variously substituted acyl chlorides and microwave-promoted cyclisation, as key steps. The synthesis and the biological evaluation (*in vitro* and *in cellulo*) of this panel of innovative MraY inbititors will be presented.



Structure and retrosynthesis of the synthesized inhibitors

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