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PROJECT TITLE: Design and synthesis of new agents against antibacterial resistance

Project description (max 300 words**)**

β-Lactam antibiotics are nowadays the most widely employed drugs in clinical practice for the treatment of bacterial infections. However, their efficacy is being seriously threatened due to the rise and spread of antimicrobial resistance (AMR). AMR represents nowadays a major health problem worldwide, potentially becoming one of the main causes of death in 2050. Among the different antimicrobial resistance mechanisms, one of the most relevant is the expression of the β-lactamase enzymes, which hydrolyze the β-lactam ring of β-lactam antibiotics, thus generating metabolites incapable of binding the transpeptidase enzymes. Among the different resistance mechanisms, the production of β-lactamases, particularly the metallo-β-lactamases (MBLs), significantly compromises the activity of these antibiotics. Despite progress in developing serine-β-lactamase (SBL) inhibitors, no MBL inhibitors are currently available in clinical practice.[1,2]

The aim of the PhD project will be the design and synthesis of broad-spectrum SBL and MBL inhibitors. The PhD activity will be devoted to compound optimization of recently identified proprietary hit compounds [3] as well as the identification of novel prototypes to be embarked in hit-to-lead transition. Standard organic chemistry approaches and synthetic methodologies developed ad hoc will be exploited for the construction of specific structural motifs, also exploiting, whenever required, continuous flow conditions. The possibility, through established collaborations, to assess compounds *in vitro* on several SBL and MBL isoforms will allow efficient cycles of design, synthesis and biological evaluation. Upon detailed structure-activity relationship studies, the best performing compounds will be assessed for their synergistic activity in combination with β-lactam antibiotics on SBL- and MBL-producing clinical isolates. Computational studies will also help to elucidate the interaction of the compounds at the molecular level against selected SBL and MBL isoforms. The optimization of ADME + T will also be pursued to identify the most promising compounds to be interrogated in relevant *in vivo* infection models.

REFERENCES

[1] Mojica M.F., Rossi M.A., Vila A.J., Bonomo R.A. *Lancet Infect. Dis*. **2022**, 22, e28-e34.
[2] Lima L.M, da Silva B. N. M., Barbosa G., and Barreiro E. J *Eur. J. Med. Chem*. **2020**, 208, 112829.
[3] Summa V., Brindisi. M. *et al, J. Med. Chem.* **2025**, manuscript under revisions.

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