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Development of benzodioxane-benzamides inhibitors of FtsZ as potent broad-spectrum antimicrobial agents

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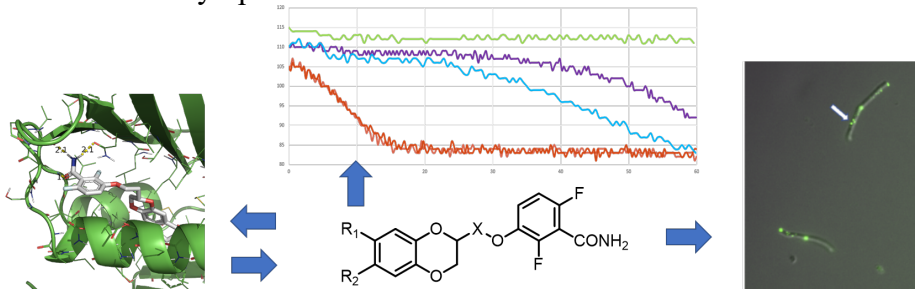
Antimicrobial resistance is a serious worldwide health threat. The identification of novel potential antibiotic targets is one of the ways to slow down its worsening. FtsZ, one of the bacterial cell division machinery proteins, emerged in the last decade for its crucial role in bacterial replication and viability [1]. Benzamide compounds are the most studied and promising FtsZ inhibitors developed so far, due to their high anti-staphylococcal activity, their low cytotoxicity and the interesting results obtained in association with other antibiotic classes [2]. Along these lines, here we report our recent findings on a class of FtsZ inhibitors, containing a 2,6-difluoro-benzamide scaffold linked to a hydrophobically substituted 1,4-benzodioxane ring [3-6]. We firstly validated a robust computational model, which drove us to identify the structural features the 1,4-benzodioxane moiety and the alkoxy linker should possess, in order to perfectly fit the FtsZ binding pocket. We thus developed several interesting compounds, having submicromolar antibacterial activities and showing comparable inhibitory activities towards both Gram-positive (*Staphylococcus aureus* and *Bacillus subtilis*) [3,5] and Gram-negative (*Escherichia coli)* FtsZ. Nevertheless, these derivatives proved to be substrates of *E. coli* efflux pump AcrAB, thus affecting their potencies [4]. These surprising and novel results confirmed how a single molecule can target both species while maintaining potent antimicrobial activity.

We set-up and performed different assays, to firstly validate FtsZ as the target of our class of compounds. Morphometric analysis and fluorescence microscopy let us evaluate the typical alterations of cell division and FtsZ inhibition, as well as the effects on FtsZ localization [6]. Moreover, we took advantages of fluorescence anisotropy to investigate and assess the impact of our derivatives on the kinetics of disassembly of the GTP triggered FtsZ polymers. Furthermore, we used confocal microscopy, to evaluate the shape and the dimension of FtsZ polymers, when in presence or in absence of our compounds in solutions containing crowding agents mimicking the crowded environment in the cytoplasm.



[1] P.J Eswara et al, *eLife* **2018**, 7.
[2] S. Tripathy et al, *Bioorg. Chem*. **2019**, *91*, 103169.
[3] V. Straniero et al, *ChemMedChem* **2020**, *15*, 195–209.
[4] V. Straniero et al, *Antibiotics* **2020**, *9*, 160.
[5] V. Straniero et al, *Antibiotics* **2021**, *10,* 442.
[6] unpublished data