medical sciences forum

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Abstract

Design, Synthesis and Antimicrobial Activities of Quinoline-Based FabZ Inhibitors as Promising Antimicrobial Drugs †

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† Presented at the 8th International Electronic Conference on Medicinal Chemistry, 1–30 November 2022; Available online: https://ecmc2022.sciforum.net/.

Keywords: antibioresistance; antimicrobial drugs; FabZ; fatty acid biosynthesis; quinolines

At present, antimicrobial resistance is one of the most significant public health challenges. Multi-resistance is particularly worrying in both Gram-negative bacteria, including *Pseudomonas aeruginosa* and *Escherichia coli*, and parasites, such as *Plasmodium falciparum*.

Consequently, the development of new compounds with original and selective antimicrobial modes of action is critical. Fatty acids are essential to maintain the vital integrity of the bacterial membrane. Their biosynthesis involves the fatty acid synthase-II (FAS-II) system, which is exclusively found in microorganisms. Furthermore, the amino-acid sequences of the active sites of FAS-II enzymes are well-conserved in microbial pathogens. As a proof of concept, isoniazid, a well-known antituberculous compound, and afabicin, which is currently in clinical development to treat drug-resistant staphylococci infections, target InhA or FabI FAS-II enzymes. In this work, we focus on another important FAS-II enzyme, FabZ, to design new antimicrobials with limited side effects and minimal chances of cross resistance with existing drugs that target other pathways.

In the Protein Data Bank (PDB), several FabZ 3D structures from different organisms have been reported. Among the known FabZ inhibitors, the NAS91 family, with a quinoline core, inhibits *Pf*FabZ with an IC_{50} value in the micromolar range. Additionally, co-crystal NAS91 family–*Pf*FabZ complex structures are described in the PDB. Based on these data, we have started a FabZ-based drug design study to develop novel quinoline structures. Herein, the in silico study, synthesis of new quinolines and biological results will be presented.

Supplementary Materials: The slides are available online at https://www.mdpi.com/article/10.3390/ECMC2022-13165/s1.

Author Contributions: Conceptualization, P.S., A.D.-K. and J.-P.B.; methodology, P.S., A.D.-K. and L.B.; chemical synthesis, L.B.; biological evaluation, N.L., F.P., V.M. and C.D.; writing—original draft preparation, L.B.; writing—review and editing, L.B., A.D.-K. and P.S.; visualization, P.S. and A.D.-K.; supervision, P.S., A.D.-K. and N.T.; project administration, P.S.; funding acquisition, P.S. All authors have read and agreed to the published version of the manuscript.

Funding: Laurie Bibens was the recipient of a grant from the Agence Innovation Défense and from the Région Hauts-de-France.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Citation: Bibens, L.; Becker, J.-P.; Lemaitre, N.; Peltier, F.; Morel, V.; Damiani, C.; Taudon, N.; Dassonville-Klimpt, A.; Sonnet, P. Design, Synthesis and Antimicrobial Activities of Quinoline-Based FabZ Inhibitors as Promising Antimicrobial Drugs. *Med. Sci. Forum* **2022**, *14*, 88. https://doi.org/10.3390/ECMC2022-13165

Academic Editor: Maria Emília Sousa

Published: 1 November 2022

Data Availability Statement: Not applicable.

Conflicts of Interest: The authors declare no conflict of interest.