M2 POSITION IN MEDICINAL CHEMISTRY

Host laboratory: équipe COSSBA, UMR CNRS 5246 - ISPB - Faculté de pharmacie de Lyon – 8 avenue Rockefeller – France. COSSBA website.

Duration of the position: 6 months
Title of the project: **Design of *p*ABA competitors as new antibiotics against Sul enzyme-mediated resistance.**

Key words: medicinal chemistry, organic chemistry, antibioresistance, Sul enzymes.

The growing emergence of antibiotic-resistant bacteria poses a major public health challenge, severely limiting the efficacy of existing treatments. An illustrative case of antibiotic resistance is found in sulfonamides (sulfas), a well-established class of antibiotics that act through competitive inhibition of dihydropteroate synthase (DHPS), by mimicking the natural substrate *p*-aminobenzoic acid (*p*ABA, Figure 1A and 1B). Over time, the misuse of sulfas in both humans and animals contributed to the rise of bacterial resistance and resulted in a decreased effectiveness of sulfas in treating infectious diseases they were originally intended for.

Recently, Savchenko, Stogios & coworkers released Sul proteins' crystal structures that revealed, for the first time, molecular and structural basis of Sul-mediated resistance. They showed that the insertion of a phenylalanine (Phe) residue close to the entry of the catalytic site prevents the access of sulfa drugs to the catalytic pocket (mainly by the electron-rich aromatic substituent of the Phe residue, Figure 1C). In summary, a single amino acid insertion provides discrimination between sulfa and *p*ABA, despite strong structural similarities. *Following this rationale, we aim to design novel pABA analogs to act as competitive inhibitors of Sul and DHPS enzymes, thereby blocking folate biosynthesis and impairing bacterial growth.*

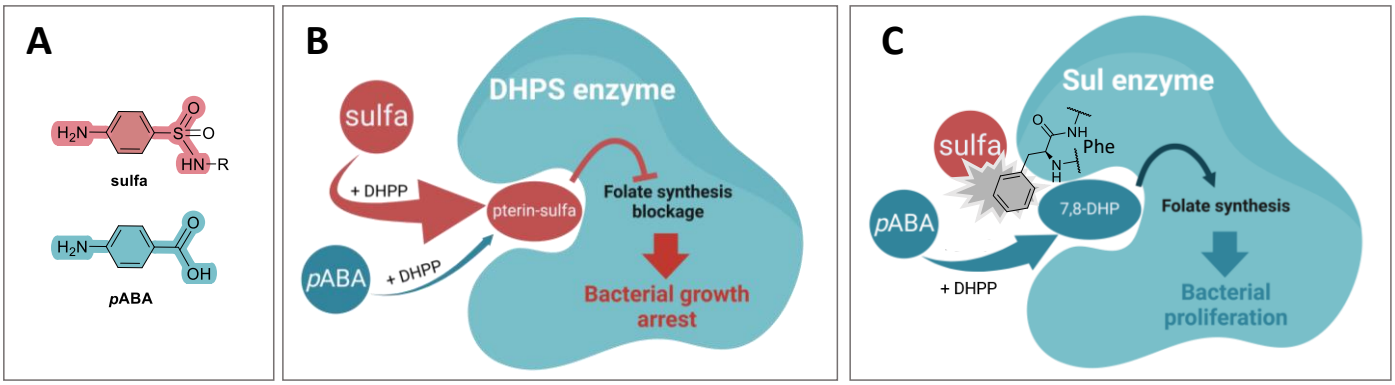

Figure 1. A) Structural similarity between pABA and sulfa is highlighted. B) Mechanism of action of a sulfa drug in the DHPS leading to bacterial growth arrest. C) Inefficiency of a sulfa drug in the Sul enzyme, due to Phe at the entry of the catalytic site, leading to bacterial proliferation.

The design and synthesis of the *p*ABA analogs is performed by the COSSBA team and constitute the core of M. Corneiller's PhD thesis. **The recruited M2 student will mainly contribute to accelerating the synthetic work** to enhance our chance to obtain active compounds. These molecules will subsequently be evaluated through minimal inhibitory concentration (MIC) assays against a panel of bacterial strains, to identify candidates with promising antibacterial activity. In parallel, M. Corneiller will establish an enzymatic colorimetric assay to measure the *in vitro* inhibitory activity of the compounds on both Sul and DHPS enzymes. *If the synthesis is successful, the M2 student can take part in the screening process to have an overview of the global drug discovery workflow.*

To apply

Start date: January 2026.

Required documents: *curriculum vitae*, recommendation letter(s).

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