

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.*

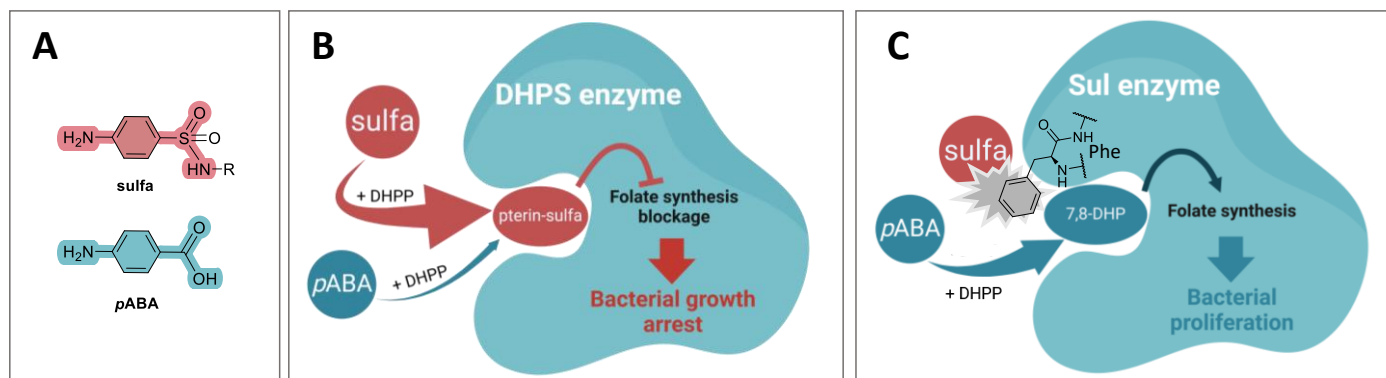


Figure 1. A) Structural similarity between *p*ABA and sulfa is highlighted. B) Mechanism of action of a sulfa drug in the DHPS leading to bacterial growth arrest. C) Inefficiency of a sulfa drug in the Sul enzyme, due to Phe at the entry of the catalytic site, leading to bacterial proliferation.

The recruited M2 student will mainly contribute to accelerating the synthetic work of *p*ABA analogs 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, an enzymatic colorimetric assay is currently being implemented 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 2027.

Required documents: *curriculum vitae*, Master 1 transcripts and recommendation letter(s).

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