ABSTRACT (ENGLISH)

Charles University, Faculty of Pharmacy in Hradec Králové. Department of Pharmaceutical Chemistry and Pharmaceutical Analysis

Author: Asal Askari
Supervisor: Assoc. Prof. PharmDr. Jan Zitko, Ph.D.
Consultant: Ghada Bouz, Ph.D.
Title of diploma thesis: Design, Synthesis, and Evaluation of Heterocyclic Compounds with Potential Antimicrobial Activity V

Staphylococcus aureus (*SA*) is one of the most common causes of life-threatening infections. One of the ways to control *SA* infectious is the development of innovative agents, preferably with novel mechanism of action, that are efficient against both drug-sensitive and drug-resistant strains. Quinazolone serves as an essential backbone for many different biologically active compounds. Antistaphylococcal quinazolones (AQs) have established structure activity relationships in the literature. Penicillin binding protein (PBP), DNA topoisomerase, and lactate dehydrogenase are few of the molecular targets for AQs.

With the use of *in silico* docking, we coupled our extensive antibacterial knowledge with what has been described in the literature to create novel, potentially active AQs targeting PBP. As result, we prepared 11 final compounds with ranging lipophilicity between 2.69 and 4.06 by reacting the lactone intermediate, benzoxazinone, with different benzyl amines. Despite the original design as antistaphylococcal active agents, none of the final compounds exerted significant antistaphylococcal activity. As complementary testing, final compounds were screened against a panel of pathogens, including some gram-positive bacteria, gram-negative bacteria, mycobacteria, and fungi. GDM-10 (R = 3-Cl) was among the most active compounds against *M. kansasii* (MIC = 7.81 µg/mL), with extended spectrum of activity to include *Mtb* H37Ra (MIC = 31.25 µg/mL) and *M. avium* (MIC = 31.25 µg/mL), making it the most promising compound. Our results suggest shifting the focus of such designed compounds toward mycobacteria rather than *SA.* Future work shall investigate whether mycobacteria penicillin binding protein is the target of active compounds.

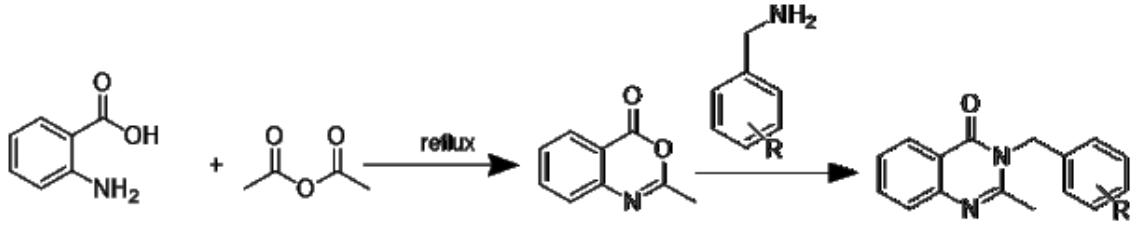

Figure 1. The general procedure and structures of final compounds prepared in this diploma. R= 2,4-diMeO; 3-MeO; 4-MeO; 3-F; 2-Me; 3-Cl; 4-CF_3; 2,4-diCl; 3,4-diCl; etc