学位論文内容の要旨

Abstract of the dissertation

博士の専攻分野の名称：博士（感染症学）　　氏名： Pondpan Suwanthada

Name

学位論文題名

The title of the doctoral dissertation

Study on quinolones-resistant bacteria and novel drugs for them

(キノロン剤耐性細菌とそれらに対する新規薬剤に関する研究)

The growing threat caused by quinolone-resistant non typhoidal *Salmonella* (NTS) and *Campylobacter* species emphasizes the significant challenges in effectively managing bacterial infections. This dissertation conducts a thorough investigation into the mechanisms of quinolone resistance, particularly focusing on amino acid substitutions in DNA gyrase and the role of Plasmid-Mediated Quinolone Resistance (PMQR) genes that is QnrB19 and evaluates potential candidate drugs for treating these resistant infections.

In the first chapter, the complexities of resistance mechanisms are explored. Amino acid substitutions within the quinolone resistance-determining regions (QRDR) of DNA gyrase substantially reduce quinolone susceptibility by diminishing their ability to bind and inhibit DNA gyrase. However, the presence of QnrB19 synergizes resistance further by protecting DNA gyrase from quinolone effects, conferring a high-level of quinolone resistance. The impact of co-existent mechanisms not only challenges the effectiveness of available antimicrobial drugs but also highlights the possibility that bacterial could survive even under pharmacological pressures.

The second chapter investigates novel quinolone derivatives, specifically WQ-compounds, through *in vitro* assays including supercoiling assays and MIC tests. These compounds exhibit strong inhibitory activity against both wild-type (WT) *S.* Typhimurium and *S.* Typhimurium with amino acid substitutions in DNA gyrases, suggesting WQ-3810 and WQ-3334, that have a 6-amino-3,5-difluoropyridine-2-yl group at the R1 position, as potent treatments for quinolone-resistant NTS.

In the third chapter, the investigation was further to *C. jejuni*, assessing the impact of WQ-compounds on both wild-type and mutant strains. Comprehensive tests including supercoiling assays, MIC and *in silico* assay deepen our understanding of the structural-activity relationships of these drugs, showcasing their potential against quinolone-resistant *Campylobacter*. In this chapter, WQ-3334 shows its high inhibitory activity against mutant *C. jejuni* strains, suggesting a promising candidate drug for the treatment of *C. jejuni.*

In conclusion, the additive effect on the co-existing quinolone resistance mechanisms, including amino acid substitutions in DNA gyrase and the presence of QnrB19 was shown in this study and the study on the impact of WQ-compounds which is the novel quinolones against *S.* Typhimurium and *C. jejuni* elucidated that the modification at R1 by 6-amino-3,5-difluoropyridine-2-yl group resulted in strong inhibitory activities against these resistant bacteria as exhibited by the low IC_{50} and MICs. The findings in this thesis advocate for a multi-faceted approach that includes developing new drugs and understanding resistance mechanisms in NTS and *C. jejuni* in depth, to manage and mitigate the impact of antimicrobial resistance effectively.