学位論文内容の要旨
Abstract of the dissertation

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学位論文題名
The title of the doctoral dissertation

Evaluation of the efficacy of novel quinolones against quinolone-resistant *Mycobacterium avium*

（キノロン耐性 *Mycobacterium avium* に対する新規キノロン剤の有効性の評価）

Mycobacterium avium is an opportunistic pathogen belonging to the *Mycobacterium avium* complex (MAC) that causes chronic pulmonary diseases (CPD). Moxifloxacin (MXF), a 4th-generation fluoroquinolone (FQ), is a recommended second-line treatment for MAC infections. However, *M. avium* resistance to MXF is becoming more widespread. Therefore, it is crucial to suggest new FQs with higher efficacy and lower adverse effects to treat MAC-PD. This thesis presented the efficacy of the potential and promising candidate drugs developed by two different pharmaceutical companies for the treatment of FQ-resistant *M. avium* infections.

Chapter I highlighted the inhibitory effect of WQ-3810 on recombinant wild-type (WT) and mutant DNA gyrases of *M. avium* and comparison of the IC_{50}s of WQ-3810 with those of ciprofloxacin (CIP), levofloxacin (LVX), and MXF, showing a stronger inhibitory effect than CIP and LVX and comparable to or superior to MXF for both WT and mutant DNA gyrases. In addition, the antimicrobial activity of WQ-3810 against 11 *M. avium* clinical isolates, including FQ-resistant isolates were lower than that of other existing FQs. Furthermore, WQ-3810 showed a synergistic interaction in combination with isoniazid (INH). So, the overall characteristics of WQ-3810 demonstrated greater effectiveness than three other FQs, suggesting that it is a promising option for treating FQ-resistant *M. avium* infections.

Chapter II presented the inhibitory effect of DC-159a and sitafloxacin (STFX) on recombinant WT and mutant DNA gyrases of *M. avium* and comparison of the IC_{50}s of both drugs with those of CIP, LVX, and MXF, showing a greater inhibitory effect than existing FQs. Moreover, both drugs showed low minimum inhibitory concentrations against clinical isolates, especially those resistant to FQs. Those results indicate that DC-159a and STFX have a strong inhibitory profile against *M. avium* DNA gyrase A, suggesting that they may be used as a promising treatment for MAC-PD.

Overall, all three drugs have shown an excellent inhibitory activity on mutant DNA gyrase

and promising antibacterial activities for FQ-resistant *M. avium.*