（様式５）Form 5

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

Inhibitory activities of WQ-3810 and its analogs against DNA gyrase of *Mycobacterium leprae*
（らい菌のＤＮＡジャイレースに対する WQ-3810 とその類縁体の阻害活性）

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Background

Mycobacterium leprae causes leprosy and ofloxacin is used to control this bacterium. However, specific amino acid substitutions in DNA gyrases of *M. leprae* interferes with the effect of ofloxacin. Therefore, reliable drug should be designed for the quinolone-resistant leprosy. WQ-3810 is newly developed fluoroquinolone with the novel R1 group and this molecular structure showed strong bactericidal activity in both of quinolone susceptible and resistant bacterial pathogens. Though, the molecular structural characteristics of the compound might have a benefit for the higher bactericidal activity against quinolone resistant leprosy than current quinolone remedy, it has not been analyzed in *M. leprae*, yet.

Methodology/principal findings

Concentration for 50% inhibitory activity (IC_{50}) against DNA gyrase of *M. leprae* was calculated for analyzing the utility of WQ-3810 against quinolone resistant leprosy instead of measuring the minimum inhibitory concentration (MIC). Then, those calculated IC_{50}s of WQ-3810 was compared with those of ofloxacin (OFX) and moxifloxacin (MFX) which is current remedy for leprosy. In further, IC_{50}s of those WQ-compounds (WQ-3334, WQ-4064 and WQ-4065) which has similar molecular structure with WQ-3810 were analyzed and compared with those of WQ-3810. Additionally, *in silico* study was carried out to understand the molecular interaction between drug and DNA gyrase, and those simulated results were discussed with experimental result.

The experimental study showed that superiority of WQ-3810 against quinolone-resistant DNA gyrase of *M. leprae* bearing the amino acid substitution in GyrA than current leprosy remedy (OFX and MFX). Indeed, this beneficial inhibitory activity against quinolone-resistant DNA gyrase of *M. leprae* was also found in those of WQ-3334 which has same R1 group (6-amino-3,5-difluoropyridin-2-yl) with WQ-3810.

in silico study showed that, unlike OFX and MFX, WQ-3810 have a specific association between a R1 group in WQ-3810 and aspartic acid at position 464 in the subunit B of DNA gyrases, which is might enhance the inhibitory effect of WQ-3810.

Conclusions/significance

WQ-3810 and WQ-3334 which is the analog compound showed reliable inhibitory activity with the novel R1 group (6-amino-3,5-difluoropyridin-2-yl) against quinolone-resistant DNA gyrase of *M. leprae*. The utility of R1 group might related with a specific association with GyrB. This understanding may help to design the new fluoroquinolone that contribute to overcome the emergence of not only quinolone resistant leprosy but also other antimicrobial resistant pathogenic bacteria.