

# The *in vitro* activity of OPC-17116, a new 5-methyl substituted quinolone against *Burkholderia (Pseudomonas) pseudomallei*

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การทดสอบความไวต่อยาต้านจุลชีพในหลอดทดลองของ OPC-17116 ซึ่งเป็น  
5-methyl substituted quinolone ชนิดใหม่ ต่อเชื้อ *Burkholderia (Pseudomonas) pseudomallei*

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## บทคัดย่อ

จากการทดสอบความไวต่อยาต้านจุลชีพของเชื้อ *Burkholderia (Pseudomonas) pseudomallei* จำนวน 50 สายพันธุ์ด้วยวิธี broth microdilution technique ที่มีต่อยา OPC-17116 ซึ่งเป็น 5-methyl substituted quinolone ชนิดใหม่ พบว่าค่า minimal inhibitory concentration (MIC) มีพิสัยระหว่าง 1-8  $\mu\text{g/ml}$  ค่า MIC<sub>50</sub> และ MIC<sub>90</sub> เท่ากับ 2.6  $\mu\text{g/ml}$  และ 4.0  $\mu\text{g/ml}$  ตามลำดับ

## Abstract

Fifty clinical isolates of *Burkholderia (Pseudomonas) pseudomallei* were tested by broth microdilution technique for susceptibility to OPC-17116, a new 5-methyl substituted quinolone. The minimal inhibitory concentration (MIC) range was 1-8  $\mu\text{g/ml}$ . The MIC<sub>50</sub> and MIC<sub>90</sub> were 2.6  $\mu\text{g/ml}$  and 4.0  $\mu\text{g/ml}$ , respectively.

## Introduction

*Burkholderia (Pseudomonas) pseudomallei* is a causative agent of melioidosis, an endemic infectious disease prevailing in Thailand, some parts of Southeast Asia and North Australia (1). Case incidence in those areas is increasing and changing in spectrum of infection (2). The disseminated septicemic form of melioidosis possesses a high mortality rate, nearly 90% (1).

Treatment with conventional antimicrobial agents such as chloramphenicol, tetracycline, kanamycin or trimethoprim sulfamethoxazole is usually ineffective in patients with the disseminated septicemic form. New antimicrobial agents are needed to reduce the mortality rate of this disease. Therefore, we tested the susceptibility of 50 clinical isolates of *B. pseudomallei* to OPC-17116, a new 5-methyl substituted quinolone in order to determine its possible role in the treatment of melioidosis.

## Material and Method

Fifty clinical isolates of *B. pseudomallei* were collected from blood, sputum and exudate from melioidosis patients in Khon Kaen, Thailand from 1990-1993. The strains had previously been identified and stored at 70°C in Brucella broth with 15% glycerol.

Antimicrobial reference standard powders were obtained from Otsuka Pharmaceutical Co, Ltd. Tokushima, Japan.

Susceptibility testing was performed by a microdilution technique (3). Briefly, two fold dilutions of antibiotics in Mueller Hinton broth (BBL Microbiology system) were dispensed in a sterile U well microdilution tray. The organisms were grown overnight in Mueller Hinton broth for log phase growth. The inoculum size was determined by diluting an overnight growth of bacteria to correspond to 0.5 McFarland turbidity standard and then was further diluted to achieve a final concentration of  $10^5$  CFU/ml. These were inoculated in U well microdilution trays along with control organisms and incubated aerobically for 20-24 hours at 37°C. The MIC was determined as the antibiotic concentration in the first well with no visible growth. Each test was carried out in triplicate with broth control, antibiotic and broth control.

## Results

The broth dilution susceptibility test of OPC-17116 ranged from 1 to 8  $\mu\text{g/ml}$  while MIC 50 and MIC 90 were 2.6  $\mu\text{g/ml}$ , and 4.0  $\mu\text{g/ml}$ , respectively, as shown in Table 1 and Fig 1.

## Discussion

A number of recent *in vitro* studies have tested *B. pseudomallei* strains for susceptibility against new antimicrobial agents (4,5,6,7,8). Potentially useful antimicrobial agents with MIC for 90% of the strains tested below therapeutic levels in serum included imipenem, piperacillin and ceftazidime (4). The susceptibility of quinolones such as ciprofloxacin, amifloxacin, enoxacin, norfloxacin and ofloxacin was tested against *B. pseudomallei* by microdilution technique (5). Ciprofloxacin was the most effective agent with MIC for 90% of the strains tested of 8.0  $\mu\text{g/ml}$ . In our study MIC for 90% of the strains tested of OPC-17116 was 4.0  $\mu\text{g/ml}$ . However, on the basis of achievable levels in blood and susceptibility data of fluoroquinolones, it would not be appropriate for an initial therapy of melioidosis (5). Preliminary pharmacokinetic data suggested that the maximum concentration of OPC-17116 at a steady state of 1.23 mg/L is achievable after 400 mg oral administration (9). Thus, it might be possible to treat selected cases with this drug.

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**Table 1** MIC distribution table of *B. pseudomallei*

MIC ( $\mu\text{g/ml}$ )	Number of isolated bacteria		
	Sample 1	Sample 2	Sample 3
1	2 (4%)*	2 (4%)	2 (4%)
2	13 (26%)	13 (26%)	13 (26%)
4	30 (60%)	30 (60%)	30 (60%)
8	5 (10%)	5 (10%)	5 (10%)
16	0	0	0

\* Numbers in parentheses represent the sensitivity distribution expressed as the percentage of isolated bacteria.

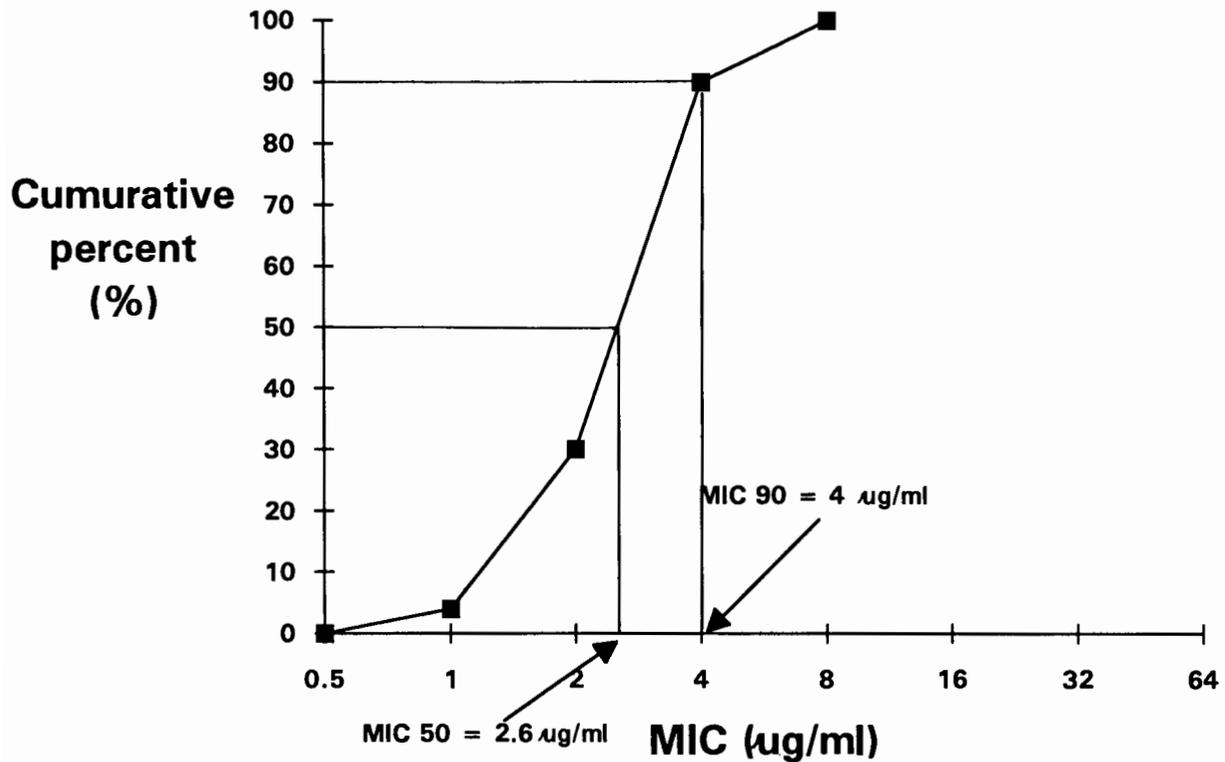


Figure 1 MIC sensitivity distribution of *B. pseudomallei*

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