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A NEW ORAL CEPHALOSPORIN ANTIBIOTIC: DISCOVERY OF LB10827

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As an antimicrobial agent class, the cephalosporins have a proven tract record. Because they inhibit target proteins that do not exist in human, they exhibit true selective toxicity. For several decades, cephalosporins have been the most important consideration in clinics for treating infectious diseases not only because of their effectiveness but also of their safeties. Community acquired bacterial pneumonia caused by *Streptococcus pneumoniae* has been a common cause of mortality worldwide. However, most of the cephalosporin antibiotics are no longer available against respiratory tract infections due to the resistance problems, especially, caused by penicillin-resistant *Streptococcus pneumonia(PRSP)*. So, there are growing needs for novel effective antimicrobials which have excellent activity against major pathogens of respiratory tract infection including multi-drug resistant strains. As a part of our research program on new cephalosporins possessing improved antibacterial activities against respiratory tract pathogens such as *PRSP, H. influenza and M.catarrhalis* while maintaining potent antibacterial activities against Gram-positive and Gram-negative strains, we introduced methyl-, allyl- or thiomethylthiopyrimidines at the C-3 position of cephem nucleus. We report herein the synthesis of these compounds and their antimicrobial activities including pharmacokinetic profiles and *in vivo* efficacy.

The synthesis of LB10827 was shown in schemes 1,2 and 3. Other kinds of cephalosporin antibiotics will be presented at the symposium. For the synthesis of LB10827 series, coupling partners **2**, **4** were synthesized from comercially available compounds **1** and **3**, respectively. Coupling product **5** from **2** and **4** was accomplished by known procedure, then removal of acetate by morpholine and substitution reaction with chloroiodomethane gave chloromethylsulfide product **6**. The compound was then reacted with 2,6-diamino-4-thiopyrimidine to afford the coupled material. Finally, removal of all protecting group by trifluoroacetic acid inanisole produced **7** (LB10827).

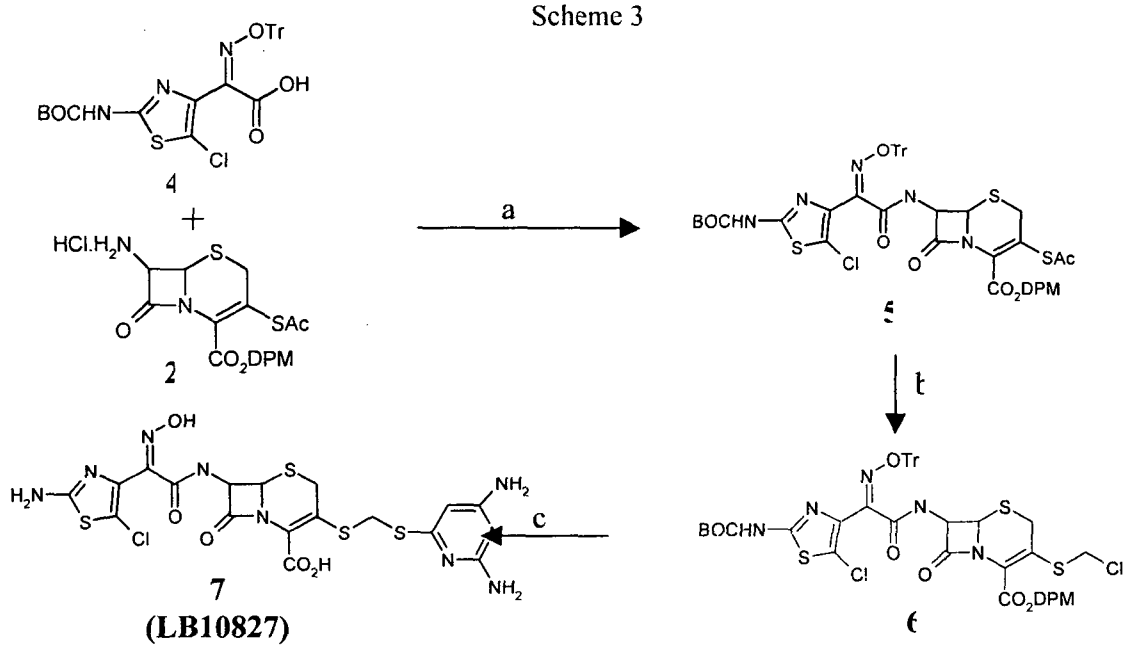
Scheme 1

1. ClP(O)(OPh)$_2$, Hunig's base, AcSH; 2. PCl_5, pyridine, 1,3-butanediol

Scheme 2

1. *N*-Chlorosuccinimide, DMF; 2. Boc_2O, DMAP: 3. NaOH, H_2O, EtOH; 4. TrCl, Et_3N, DMF

Scheme 3



a) pyridine, POCl3; b) morpholine, ICH2Cl, Hunig's base, DMF;

c) NaI, 2,4-diamino-6-thiopyrimidine, DMF; TFA, Anisole

This series of new C-3-substituted cephalosporins including LB10827 exhibited good antibacterial activities against Gram-positive bacteria such as *S. aureus* and against Gram-negative organisms including *E.coli*. Especially, selected antibacterial activities of LB10827 against respiratory tract pathogens were shown in Table 1. Compared to other oral cephalosporins, penicillin and macrolide, LB10827 showed excellent and balanced activities against major respiratory tract strains including penicillin resistant *Streptococcus pneumonia*. LB10827 showed the most potent antibacterial activity among the compounds tested against all strains of *Streptococcus pneumoniae*. The MIC values of LB10827 against penicillin-resistant strains of pneumococci were 0.25 μg/ml. Although clarithromycin and other β-lactam antibiotics showed excellent activity against penicillin-susceptible strains of pneumococci, they had limited or no activity against penicillin-resistant strains (MIC_{90}: 2 ~ >32 μg/ml). LB10827 was also very active against *Haemophilus influenzae* and *Moraxella catarrhalis* (MIC: 0.5 and 0.13 μg/ml, respectively). The enhanced activity of LB10827 against *S. pneumoniae* as well as *H. influenzae* and *M. catarrhalis* suggested that it would be a promising agent for the treatment for respiratory tract infections. As shown in Figure 1, LB10827 showed long half life (139 min) and high Cmax (13.8 ug/ml) at 20 mg/kg dose in rat. The compound also exhibited high bioavailability (56%).

Table I. Antibacterial activity of LB10827 and other oral compounds against respiratory strains

Strains	LB10827	Cefuroxime	Cefprozil	Cefdinir	Cefditoren	Amox/clav	Clarithromycin
S. pneumoniae [a] PN010	0.25	4	4	4	0.5	1	> 64
S. pneumoniae [a] PN020	0.25	4	8	8	1	2	0.5
M. catarrhalis [b] 25240A	≤ 0.008	0.13	0.13	0.016	≤ 0.008	≤ 0.008	0.13
M. catarrhalis [c] MCA027	0.13	2	8	0.5	1	0.5	0.25
H. influenzae [b] HIN009	0.25	0.5	1	0.25	≤ 0.008	0.5	8
H. influenzae [c] HIN003	0.5	1	4	0.5	0.031	4	8

[a]. Penicillin resistant *pneumococcus*

[b]. β-lactamase non producing strain

[c]. β-lactamase producing strain

The *in vivo* activity of LB10827 was compared with those of amox/clav, cefdinir and trovafloxacin in rat and mouse pneumonia infection models(Figure 2). LB10827 dramatically reduced the viable cells in the lungs of all three groups. Furthermore, 2mg/kg dose of LB10827 showed better *in vivo* activity than 10mg/kg of amox/clav and 50mg/kg of cefdinir or trovafloxacin. Similar efficacy was also observed in a mouse pneumonia model that was induced by intranasal instillation of same strain to C57BL/6 mice. LB 10827 was as effective as amox/clav and more effective than the other comparator antibiotics. These studies showed that LB10827 was the most potent agent among test compounds against pneumonia infection in rat and mouse models. And the *in vivo* activities of LB10827 were well correlated with its excellent *in vitro* antibacterial activities (MIC against *S. pneumoniae* type III: LB10827, 0.008; amox/clav, 0.031; cefdinir, 0.063; trovafloxacin, 0.25 μg/ml).

Figure 1. Cp profile of LB10827 in Rat(20 mg/kg IV & PO)

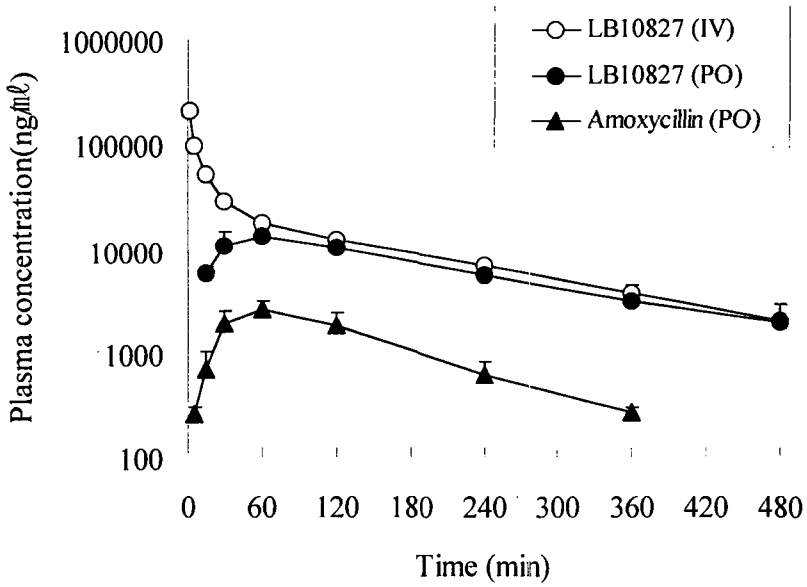
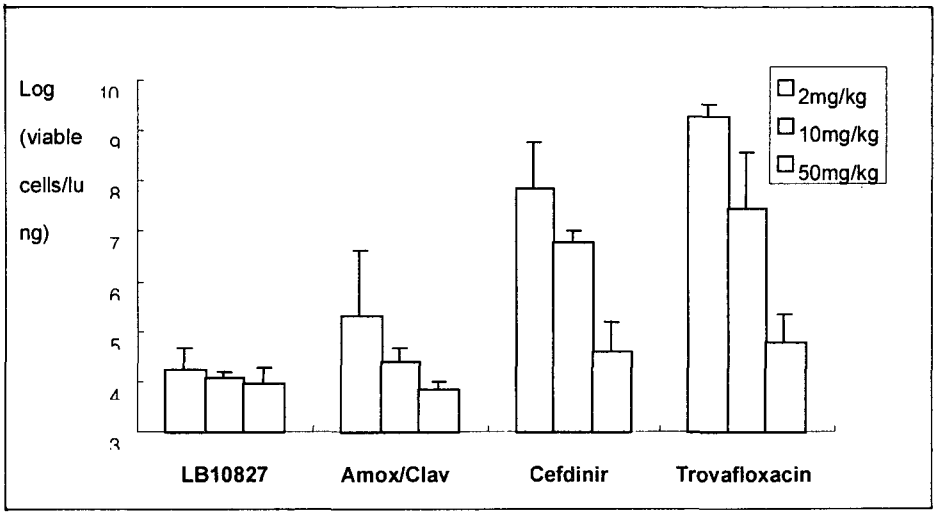


Figure 2. In vivo therapeutic efficacy of LB10827 against acute pneumonia caused by *S. pneumonia* in neutropenic rat model



In conclusion, LB10827 showed well balanced antibacterial activities against G(+) and G(-) strains including respiratory tract pathogens such as *S. pneumonia*, *H, influenza* and *M. catarrhalis*. It also showed excellent pharmacokinetic profiles and good bioavailability. In in vivo infection model using mice and rats, LB10827 were well correlated with its excellent antibacterial activities and showed the most potent therapeutic efficacy among the test compounds such as augmentin, cefdinir and trovafloxacin.