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Synthesis and Antibacterial Activity of New Cephalosporin Compounds

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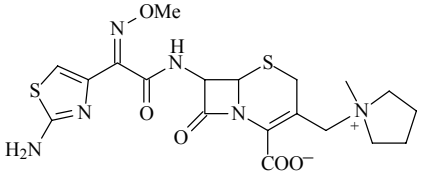
Abstract: Five new cephalosporin compounds were designed and synthesized, and the antibacterial activities were evaluated by the standard serial 2-fold agar dilution method *in vitro*. The results showed that the activities of the compounds **Ia** and **Ib** against ESBL *E. coli* and *K. pneumoniae* are comparable to those of Cefepime.

Keywords: Cephalosporin, synthesis, antibacterial activities.

The fourth generation cephalosporin cefepime **I** exhibited potent antibacterial activity with board antibacterial spectrum[1,2]. Based on the structure of cefepime, we synthesized its analogs **Ia** having fluoro atom at the aminothiazolyl oxime moiety at the 7-position of the cephem nucleus, and **Ib** possessing 1-(2-fluoroethyl) pyrrolidium methyl group at the 3-position. It was reported that cephalosporin derivatives with a quaternary ammonium moiety at the 3-position of the cephem nucleus, showed enhanced antibacterial activity, including MRSA and *P. aeruginosa*[3-5]. This lead us to synthesize compounds **IIa** and **IIb** bearing thiazolyl pyridinium moiety at the 3-position. A novel oxacilin with 5-methyl-3-phenyl isooxazol-4-yl formacyl group at the 6-position of 6-APA showed resistance to β-lactamase activity and broad antibacterial spectrum. Compound **III** was prepared by introduction of 5-methyl-3-phenyl isooxazol-4-yl formacyl group at the 7-position of cephem nucleus instead of the 6-position of 6-APA, and bearing pyridinium methyl group at the 3-position.



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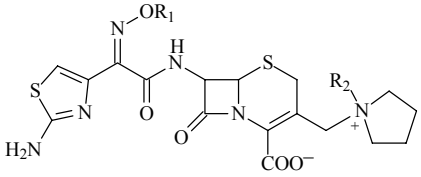

Ia R_1=CH_2CH_2F, R_2=CH_3;
Ib R_1=CH_3, R_2=CH_2CH_2F

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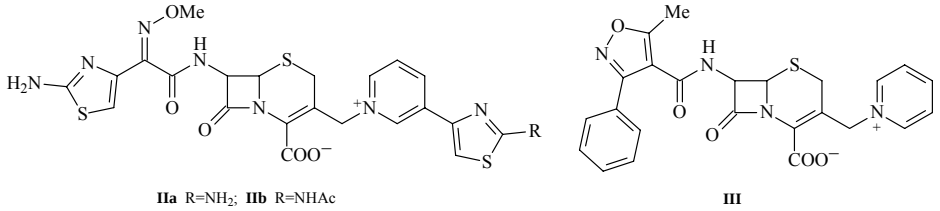
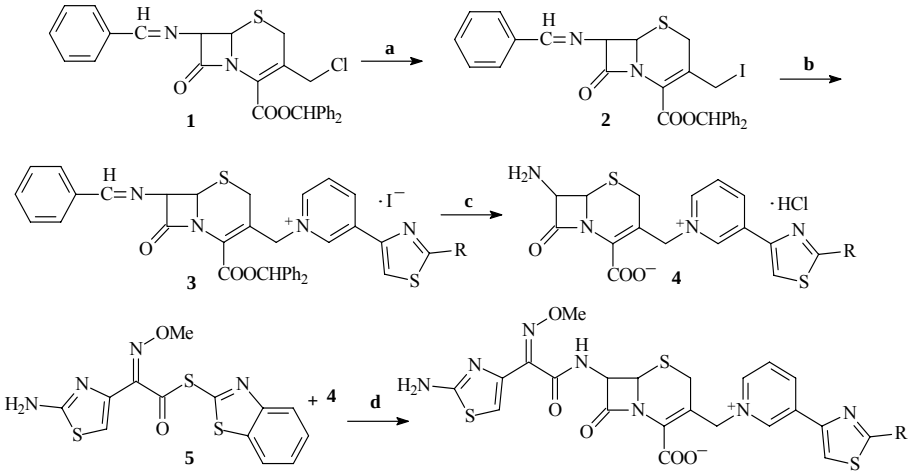


IIa R=NH_2; **IIb** R=NHAc **III**

Scheme 1 The synthetic route of compounds **IIa** and **IIb**

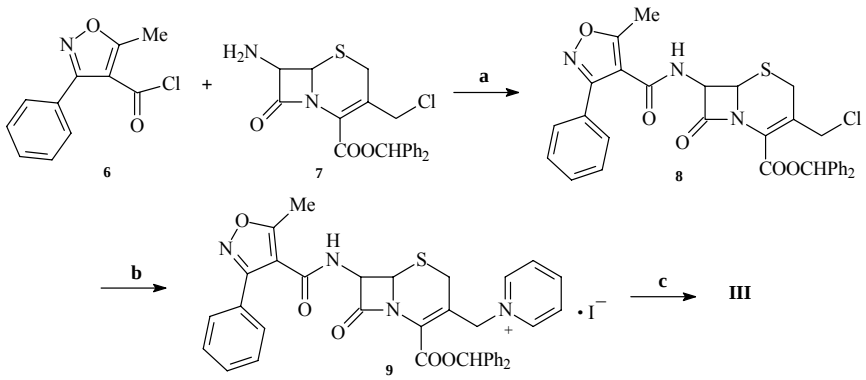


a. NaI/CH_3COCH_3, r.t.; b. 2-amino or 2-acetamido-4-(pyrid-3-yl)thiazole/DMF, r.t.; c. HCl / HCOOH, r.t.; d. $NaHCO_3$/DMF-H_2O, r.t.

Compounds **Ia** and **Ib** were synthesized by using the same method of cefepime[6]. **Ia** was obtained in total yield about 30%. However, replacement of 2-fluoroethyl group for methyl group at the N-position of pyrrolidine significantly decreased the reaction yield (about 5%) of **Ib**. The reason was presumably that the steric hindrance of the2-fluoroethyl group retarded the substitution at 3-position. Compounds **IIa**, **IIb** and **III** were prepared as shown in **Scheme 1** and **Scheme 2**, respectively. Reaction of **1** with NaI gave the corresponding iodide intermediate **2**. The key compound **4** was prepared through **2** by substitution with amino or acetamido pyridyl thiazole, and removal of the protecting groups. The target compounds **IIa** and **IIb** were obtained by reaction of activated thioester **5** with **4**. Compound **7** was acylated with 5-methyl-3-phenyl isooxazole-4-carboxylic acid chloride **6** to give **8**, the chloromethyl group of which was converted into iodomethyl group and followed by substitution with pyridine to give **9**. Removal of the protecting group of **9** offered **III**.

With the general procedures described above, five new cephalosporin compounds were synthesized, and the melting points, MS and ^{1}H-NMR data were listed in **Table 1**.

Scheme 2 The synthetic route of compound **III**



a. $N(C_2H_5)_3/HCCl_3$,0-5℃; b. NaI/CH_3COCH_3, pyridine, r.t.; c. HCl/HCOOH, r.t.

Table 1 The melting points, MS and ^{1}H-NMR data of **Ia-b**, **IIa-b** and **III***

Comp.	mp(℃)	MS(ESI) *m/z*	^{1}H-NMR (D_2O, 500Hz, δ ppm)
Ia	200-201	513.4 (M+1, 100%), 460.3, 428.4, 416.5, 257.4, 227.4, 86.2.	2.20-2.21 (m, 4H), 2.97 (s, 3H), 3.43-3.53 (m, 5H), 3.89 (ABq, 1H, J=16.8Hz), 3.96 (ABq, 1H, J=13.8Hz), 4.48 (t, 1H, J=3.9Hz), 4.58 (t, 1H, J=3.9Hz), 4.47-4.73 (m, 2H), 4.84 (m, 1H), 5.34 (d, 1H, J=4.8Hz), 5.84 (d, 1H, J=4.8Hz), 7.15 (s, 1H).
Ib	193-195	513.4 (M+1), 460.4, 428.3, 396.3, 374.3, 324.3, 118.3 (100%)	2.22-2.24 (m, 4H), 3.48 (ABq, 1H, J=17.1Hz), 3.57-3.67 (m, 6H), 3.89 (ABq, 1H, J=16.8Hz), 4.01 (s, 3H), 4.08 (ABq, 1H, J=13.8Hz), 4.67 (ABq, 1H, J=14.0Hz), 4.80- 5.01 (m, 2H), 5.35 (d, 1H, J=4.5Hz), 5.87 (d, 1H, J=4.5Hz), 7.03 (s, 1H).
IIa	203-205	573.3 (M+1), 479.4, 423.3, 396.3, 279.4, 259.4, 178.4 (100%), 126.2, 99.2, 85.2.	3.26 (ABq, 1H, J=17.7Hz), 3.71(ABq, 1H, J=17.4Hz), 4.06 (s, 3H), 5.32 (d, 1H, J=5.1Hz), 5.39 (ABq, 1H, J=14.4Hz), 5.43 (ABq, 1H, J=14.4Hz), 5.84 (d, 1H, J=5.1Hz), 7.12 (s, 1H), 7.46 (s, 1H), 8.16 (m, 1H), 8.82 (d, 1H, J=8.1Hz), 8.94 (d, 1H, J=5.1Hz), 9.34 (s, 1H).
IIb	179-182	615.5 (M+1), 573.3, 418.3, 396.4, 308.4, 220.4 (100%), 178.4, 126.1.	2.30 (s, 3H), 3.23 (ABq, 1H, J=18.0Hz), 3.72 (ABq, 1H, J=18.0Hz), 4.00 (s, 3H), 5.31-5.39 (m, 2H), 5.64 (ABq, 1H, J=14.4Hz), 7.80 (d, 1H, J=4.8Hz), 7.04 (s, 1H), 7.82 (s, 1H), 8.11 (m, 1H), 8.89 (m, 2H), 9.58 (s, 1H).
III	188-190	477.4 (M+1), 420.3, 398.3, 370.3, 352.4, 186.4, 144.3, 80.2 (100%).	2.64 (s, 3H), 3.20 (ABq, 1H, J=18.0Hz), 3.63 (ABq, 1H, J=18.0Hz), 5.24 (d, 1H, J=4.5Hz), 5.34 (ABq, 1H, J=15.0 Hz), 5.61 (ABq, 1H, J=15.0Hz), 5.80 (d, 1H, J=4.5Hz), 7.54-7.64 (m, 5H), 8.11 (t, 2H, J=7.2Hz), 8.60 (t, 2H, J_1= 7.2 Hz, J_2=8.1Hz), 8.95 (d, 2H, J=8.1Hz).

* MS and ^{1}H-NMR spectra were taken on a Finnigan TSQ-700 and a Varian INOVA-500 spectrometer. Tetramethylsilane was used as an internal standard. Melting points were determined on Yanaco micro melting point apparatus and uncorrected.

Antibacterial Activitives

The antibacterial activities of the target compounds were determined *in vitro* by the standard serial 2-fold agar dilution method with Mueller-Hinton agar as the tested medium. The tested bacteria were ESBL *E. coli* (20 trains) and ESBL *K. pneumoniae*

(20 trains) that were collected from Beijing and Chongqing hospitals. For comparison, the forth generation cefepime was employed as reference drug. All the synthesized compounds expected for **III** exhibited antibacterial activities against both Gram-positive and Gram-negative bacteria. The cefepime analogs **Ia** and **Ib** showed the most potent antibacterial activities, and the MIC_{50} of **Ia** and **Ib** against ESBL *E. coli* and ESBL *K. pneumoniae* were 1 mg/L, 1 mg/L and 4 mg/L, 8 mg/L, respectively. The antibacterial activities of **IIa** and **IIb** were moderate.

Using fluoroethyl group instead of methyl group in aminothiazolyl oxime moiety at the 7-position of cephem nucleus **Ia** or introduction fuoroethyl group at pyrrolidine linked at 3-position **Ib** showed the same antibacterial activities as the reference drug. The antibacterial activities of compounds **Ia** and **Ib** were comparable to those of cefipime. Remaining aminothiazolyl oxime moiety at the 7-position and introducing 2-amino-4-(pyrid-3-yl)thiazole **IIa** or 2-acetamido-4-(pyrid-3-yl)thiazole **IIb** at the 3-position decreased the antibacterial activities, though **IIa** showed little more potent antibacterial activities than **IIb**. It was contrary to our expectation that modification of the 7-position of cephem nucleus by phenyl methyl isooxazole acid chloride and introduction quaternary pyridinium moiety at the 3-position almost did not exhibit antibacterial activities.

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