*Arch. Pharm. Res.* **15**(2), 187-189 (1992)

# Synthetic β-Lactam Antibiotics VI. Antibacterial Activity of Some 7β-[-(2-Aminothiazol-4-yl)-2-(methoxyimino)acetamido]-3-(pyrrolidinium) methylcephalosporins

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*(Received May 26, 1992)*

In the preceding paper[1], we reported the synthesis and biological properties of cephalosporins having quinoliniumthiomethyls at the C-3 position and demonstrated that quinoliniumthiomethylcephalosporins exhibited an extended antibacterial spectrum including antipseudomonal activity, especially strong antiGram-positive activity. With the aim of elaboration to optimize the antibacterial potency of the quaternary ammonium cephalosporins, we have studied the modification of substituents in the pyrrolidine ring of cefepime 1 which is characterized by its potent activity[2]. In this paper we describe the synthesis, structure-activity relationships and biological property of cefepime derivatives having several kinds of substituents in the pyrrolidine.

The compounds **4a-4g** tested were prepared as outlined in Scheme 1. The 3-substituted pyrrolines **3a-3c** were prepared by the previously reported methods[3,4]. 3,4-Disubstited pyrrolidine **3d-3g** were synthesized from 3,4-dimethoxycarbonyl-1-methylpyrrolidine[5] as a starting material using the proper reaction conditions such as reduction with LAH, basic hydrolysis, or reaction with dimethylamine. Cefotaxime 2 was silylated with N-methyl-N-(trimethylsilyl) trifluoroacetamide and iodized with trimethylsilyl iodide followed by addition of tetrahydrofuran to

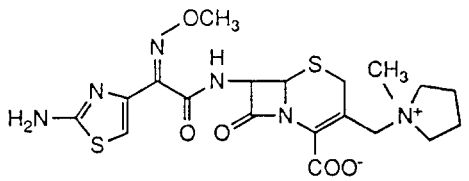
**Table I. NMR spectral data in DMSO-$d_6$ of cephalosporins**

| Compound | | | | O<br>\|\|<br>−CN− | | | Pyrrolidine | |
|---|---|---|---|---|---|---|---|---|
| No. | 3-$CH_2$ (2H, ABq) | 6-H (1H, d) | 7-H (1H, dd) | (1H, d) | $-OCH_3$ (3H, s) | Thiazole (1H, s) | N-$CH_3$(3H, s) | Other protones |
| **4a** | 4.40 | 5.27 | 5.88 | 9.65 | 3.85 | 6.74 | 3.05(1.5H)<br>3.03(1.5H) | 8.23(1H, t), 8.08(1H, s)<br>3.62(3H, m), 3.24(1H, m)<br>2.69(2H, m), 2.21(2H, m)<br>1.87(1H, m) |
| **4b** | 4.40 | 5.26 | 5.88 | 9.65 | 3.84 | 6.74 | 2.98(1.5H)<br>2.97(1.5H) | 3.57(2H, m), 3.32(2H, m)<br>2.94(1H, m), 2.34(2H, m) |
| **4c** | 4.45 | 5.28 | 5.87 | 9.63 | 3.83 | 6.73 | 2.98(3H) | 3.60(4H, m), 2.93(1H, m)<br>2.40(2H, brm) |
| **4d** | 4.43 | 5.27 | 5.87 | 9.63 | 3.83 | 6.74 | 3.13(3H) | 3.60(8H, m), 2.70(2H, m) |
| **4e** | 4.43 | 5.28 | 5.89 | 9.65 | 3.84 | 6.75 | 3.18(3H) | 3.71(4H, m), 2.96(2H, m) |
| **4f** | 4.48 | 5.26 | 5.86 | 9.65 | 3.88 | 6.75 | 3.02(3H) | 3.91(3H, s), 3.63(4H, m)<br>3.03(2H, m), 2.82(3H, s)<br>2.67(3H, s) |
| **4g** | 4.47 | 5.27 | 5.88 | 9.65 | 3.84 | 6.75 | 3.00(1.5H)<br>2.98(1.5H) | 8.20(1H, brs), 3.72(2H, m)<br>3.52(2H, m), 2.98(2H, m)<br>2.66(3H, d) |

**Table II.** ***In vitro*** **antibacterial activity (MIC, μg/ml) of cephalosporins**

| Organism | 4a | 4b | 4c | 4d | 4e | 4f | 4g | Cefotaxime | Cefepime* |
|---|---|---|---|---|---|---|---|---|---|
| Sptreptococcus pyogenes 308 A | 0.025 | 0.049 | 0.098 | 0.049 | 0.098 | 0.098 | 0.049 | 0.007 | 0.007 |
| Streptococcus pyogenes 77 A | 0.049 | 0.049 | 0.098 | 0.049 | 0.098 | 0.098 | 0.013 | 0.007 | 0.007 |
| Streptococcus faecium MD 8b | 100 | 100 | >100 | >100 | >100 | > | >100 | 50 | >100 |
| Staphylococcus aureus SG 511 | 3.125 | 25 | 25 | 6.25 | 25 | 25 | 25 | 1.563 | 3.125 |
| Staphylococcus aureus 285 | 12.5 | 25 | 50 | 25 | 100 | 100 | 50 | 3.125 | 6.25 |
| Staphylococcus aureus 503 | 1,563 | 12.5 | 12.5 | 3.125 | 25 | 12.5 | 12.5 | 1.563 | 1.563 |
| Escherichia coli 055 | 0.025 | 0.025 | 0.098 | 0.049 | 0.098 | 0.195 | 0.025 | 0.013 | 0.049 |
| Esterichia coli DC 0 | 0.049 | 0.025 | 0.195 | 0.098 | 0.098 | 0.195 | 0.049 | 0.049 | 0.098 |
| Esterichia coli DC 2 | 0.098 | 0.049 | 0.195 | 0.098 | 0.195 | 0.195 | 0.049 | 0.007 | 0.098 |
| Esterichia coli TEM | 0.098 | 0.1195 | 0.391 | 0.195 | 0.781 | 0.781 | 0.391 | 0.025 | 0.098 |
| Esterichia coli 1507 E | 0.049 | 0.025 | 0.195 | 0.195 | 0.195 | 0.195 | 0.049 | 0.025 | 0.098 |
| Pseudomonas aeruginosa 9027 | 6.25 | 12.5 | 50 | 12.5 | 50 | 100 | 25 | 12.5 | 6.25 |
| Pseudomonas aeruginosa 1592 E | 3.125 | 12.5 | 25 | 6.25 | 25 | 50 | 12.5 | 12.5 | 3.125 |
| Pseudomonas aeruginosa 1771 | 1.563 | 6.5 | 6.25 | 3.125 | 25 | 50 | 6.25 | 6.25 | 1.563 |
| Pseudomonas aeruginosa 1771 M | 0.195 | 0.195 | 0.781 | 0.391 | 3.125 | 3.125 | 0.781 | 0.049 | 0.195 |
| Salmonella typhimurium | 0.049 | 0.049 | 0.195 | 0.098 | 0.098 | 0.195 | 0.049 | 0.025 | 0.049 |
| Klebsiella oxytoca 1082 E | 1.563 | 12.5 | 12.5 | 12.5 | 12.5 | 12.5 | 12.5 | 0.781 | 1.563 |
| Klebsiella aerogenes 522 E | 0.049 | 0.025 | 0.098 | 0.098 | 0.049 | 0.098 | 0.025 | 0.013 | 0.049 |
| Enterobacter cloacae P 99 | 1.563 | 25 | 25 | 3.125 | 100 | >100 | 25 | 100 | 6.25 |
| Enterobacter cloacae 1321 E | 0.013 | 0.013 | 0.049 | 0.049 | 0.049 | 0.098 | 0.013 | 0.007 | 0.025 |

Cefepime* using a reference was synthesized in this lab.



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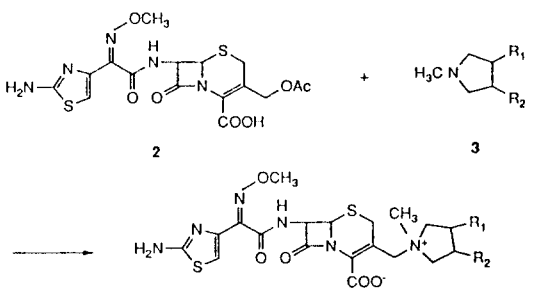

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destory excess trimethylsilyl iodide. To this mixture was added pyrroline derivatives **3a-3g** which was treated wih N-methyl-N-(trimethylsilyl) trifluoroacetamide in acetonitrile. After completion of the reaction, the silylated cephalosporins was hydrolyzed by treatment with methanol to give the corresponding cephalosporins in 39-58% yields[6]. The NMR spectral data of the compounds are shown in Table I.

The *in vitro* antibacterial activity of compounds **4a-4g** was determined by the standard two fold agar dilution method. The result is given in Table II in comparison with those of cefotaxime and cefepime as MIC (μg/ml). As shown in the Table, some compounds have potent activity with expanded spectra against Gram-positive and Gram-negative organisms including Pseudomonas aeruginosa. Against

| | $R_1$ | $R_2$ |
|---|---|---|
| a | $CH_2NCHO$ | H |
| b | COOH | H |
| c | $CNH_2$ | H |
| d | $CH_2OH$ | $CH_2OH$ |
| e | COOH | COOH |
| f | $CN(CH_3)_2$ | $CO_2CH_3$ |
| g | $CN(CH_3)_2$ | COOH |

**Scheme 1.**

Gram-positive bacteria, all compounds displayed slightly inferior to that of cefotaxime and compounds **4a** and **4d** showed comparable activity with cefepime. Against Gram-negative bacteria, the activity of compounds **4a**, **4d** was comparable to those of cefotaxime and cefepime. In a series of compounds the enhancement effect of lipophilic functions in the pyrrolidine on Gram-positive antibacterial activity was not detected. Hydrophilic functions in the pyrrolidine showed decrease of the activity against Gram-positive bacteria while retaining Gram-negative antibacterial activity. Among 7 compounds, only **4a** showed activity fairly comparable to cefepime and modification of this compound is under study now.

## ACKNOWLEDGEMENTS

The authors wish to thank Dr. Eunrhan Woo at the KIST for the MIC data. This work was fully supported by the Ministry of Science and Technology.

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