Synthesis and Activity of Benzotriazolium Cephalosporins

JAE CHUL JUNG, MYOUNG GOO KIM, MOO JE SUNG, YONG KEY CHOI, SANG GEUN AN, SEA HAN OH, SEONG SOO YIM and CHI JANG MOON*

R & D Center, Dae Woong Pharmaceutical Co., Ltd., 223-23 Sangdaewon-Dong, Sungnam, Kyonggi-Do 462-120, Korea

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β-Lactam antibiotics are still among the most beneficial compounds for the treatment of often otherwise fatal infections. Aminothiazolyl cephalosporins having 3'-quarternary ammonium moiety, such as cefpirome and cefepime,[1,2] show better antibacterial activity against Gram-positive and Gram-negative bacteria, including *Pseudomonas aeruginosa*, than that of the third generation cephalosporins.[3]

Recently, it was reported that aminothiadiazolyl and aminothiazolyl cephalosporins having the delocalization of the positive charge of the condensed-heterocyclic azolium moiety[4,5] lead to an expanded antibacterial activity. In this paper, we wish to describe the synthesis and the antibacterial activity of 7β-[2-(2-aminothiazol-4-yl)-2(*Z*)-methoxyiminoacetamido] cephalosporins bearing 1-substituted-benzotriazol-3-ium methyl groups at the 3'-position in the cephalosporin nucleus (Scheme 1).

A general synthetic method for the preparation of 7β-[2-(2-aminothiazol-4-yl)-2(*Z*)-methoxyiminoacetamido]-3-[(1-substituted-benzotriazol-3-ium)methyl]-3-cephem-4-carboxylate (**4**) is shown in Scheme 1.

1-Substituted-benzotriazole compounds (**2**) were prepared according to the known procedure.[6~8] *p*-Methoxybenzyl 7β-[2-(2-tritylaminothiazol-4-yl)-2(*Z*)-methoxyiminoacetamido]-3-chloromethyl-3-cephem-4-carboxylate (**1**) was readily prepared according to the previously reported method.[2] The general procedure is as follows: 1-(2-Hydroxyethyl)benzotriazole (**2f**, 0.20 g, 1.2 mmol) was added to the solution of chloromethyl cephem (**1**, 0.78 g, 1 mmol) and KI (0.25 g, 1.5 mmol) in DMF (1 ml) at room temperature. After being strirred at room temperature for 10 hours, the reaction mixture was poured into toluene to afford *p*-methoxybenzyl 7β-[2-(2-tritylaminothiazol-4-yl)-2(*Z*)-methoxyiminoacetamido]-3-[(1-(2-hydroxyethyl)benzotriazol-3-ium)methyl]-3-cephem-4-carboxylate iodide (**3f**). Finally, the removal of all protecting groups with TFA and anisole, and then purification by column chromatography on DIAION HP-20 give 7β-[2-(2-aminothiazol-4-yl)-2(*Z*)-methoxyiminoacetamido]-3-[(1-(2-hydroxyethyl)benzotriazol-3-ium)methyl]-3-cephem-4-carboxylate (**4f**) in 35.8% yield from **1**. The structure of **4f** was confirmed by ^{1}H NMR spectrum: ^{1}H NMR (80 MHz, DMSO-d_6 + D_2O) δ 3.38 (m, 2H, C-2), 3.88 (s, 3H, $-OCH_3$), 4.31 (t, 2H, $-CH_2-$), 4.83~5.07 (m, 3H, $-CH_2-$, C-7), 5.54 (m, 1H, C-6), 6.02 (d, 2H, C-3), 6.74 (s, 1H, thiazol), 7.35~8.01 (m, 4H, C_6H_4).

Table 1 shows the antibacterial activity of 1-substituted benzotriazol-3-ium cephalosporins. From examples of Table 1, **4a** has the best activity against Gram-positive and Gram-negative bacteria including *Pseudomonas aeruginosa*, but **4a** shows less activity than cefpirome against *Streptococcus faecium* MD 8B. Also **4b** has excellent activity against Gram-positive bacteria including *Streptococcus faecium* MD 8B and Gram-negative bacteria, and shows somewhat better activity than cefpirome and somewhat less activity than ceftazidime against *Pseudomonas aeruginosa*. With increasing the size of the benzotriazole substituent (**4b**→**4c**→**4d**), the activity is diminished mainly against *Pseudomonas aeruginosa*. This could be due to decreasing cell wall penetration. When the compound contains electron donating group like **4f**, it is still comparable to cefpirome and shows somewhat better activity than **4c** against Gram-positive and Gram-negative bacteria. However, the compound carrying electron withdrawing group like

Scheme 1. Synthetic routes to cephalosporins.

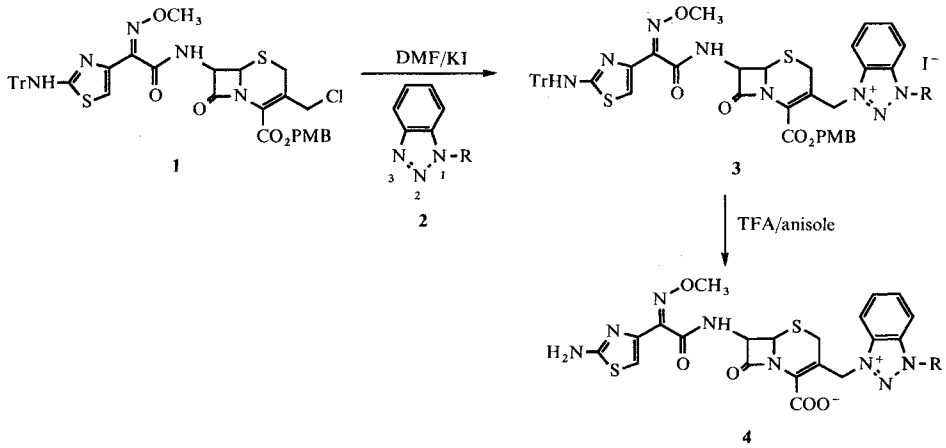

Table 1. Antibacterial activity of the cephalosporins **4** (MIC: μg/ml).

Compound	R	S.p. 77A	S.f. MD88	S.a. SG 511	E.c. TEM	P.a. 9027	P.a. 1592E	K.o. 1082E	K.a. 1512E
4a	NH_2	0.004	100	0.195	0.013	1.563	1.563	0.049	0.025
4b	CH_3	0.004	12.5	0.195	0.025	3.125	1.563	1.563	0.025
4c	CH_2CH_3	0.004	>100	0.781	0.098	3.125	3.125	3.125	0.195
4d	$CH_2CH{=}CH_2$	0.007	>100	0.781	0.049	3.125	6.25	1.563	0.195
4e	CH_2CN	0.013	>100	1.563	0.025	3.125	12.5	3.125	0.391
4f	CH_2CH_2OH	0.004	>100	0.391	0.049	3.125	3.125	3.125	0.098
Ceftazidime		0.195	50	6.25	0.049	1.563	0.781	0.781	0.098
Cefpirome		0.098	25	0.391	0.049	3.125	3.125	3.125	0.025

S.p.: *Streptococcus pyogenes*, S.f.: *Streptococcus faecium*, S.a.: *Staphylococcus aureus*, E.c.: *Escherichia coli*, P.a.: *Pseudomonas aeruginosa*, K.o: *Klebsiella oxytoca*, K.a.: *Klebsiella aerogenes*.

4e exhibits reduced antibacterial activity.

In summary, **4a** and **4b** have excellent and well-balanced antibacterial activity against Gram-positive and Gram-negative bacteria including *Pseudomonas aeruginosa*, and these cephalosporins have been selected as candidates for further biological evaluation.

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