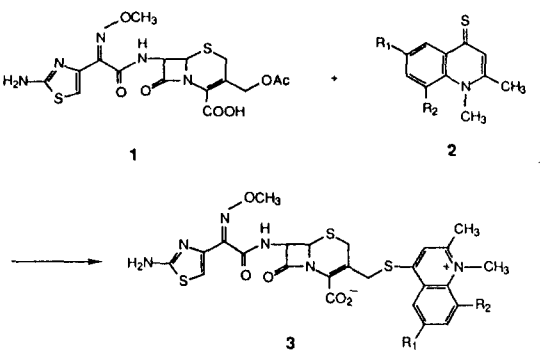
Arch. Pharm. Res. **14**(3), 279-281 (1991)

Synthetic β-Lactam Antibiotics V. Antibacterial Activity of Some 7β-[2-(2-Aminothiazol-4-yl)-2-(methoxyimino)acetamido]-3-(quinolinium)thiomethylcephalosporins

Dongyeol Lim, Sang-Woo Park and Youseung Kim*
Organic Synthesis Lab, Korea Institute of Science and Technology, Cheongryang P.O. Box 131, Seoul 130-650, Korea
(Received September 16, 1991)

In the field of cephalosporins, introduction of quaternary heterocyclic methyl groups at the C-3 position has led to a new class of cephalosporins such as cefepime and cefpirome, the so-called 4th generation cephalosporins which are characterized by their potent activity[1]. Since then many efforts were attempted to synthesize more effective analogs. One of these efforts has been synthesis of quaternary heterocyclic alkylthiocephalosporins using pyridiniumthiomethyls for the C-3 substituent[2-3]. In this paper we wish to report the synthesis and biological activity of the title compounds, the first example of quinoliniumthiomethylcephalosporins.

The compounds **3a-3f** tested were prepared as outlined in Scheme 1. The 4-thioquinolone derivative **2a-2f** from the corresponding anilines and ethyl acetoacetate were prepared by the previously reported methods[4-5]. Reaction between cefotaxime 1 and 4-thioquinolones **2a-2f** in acetonitrile at 65℃ for several hours in the presence of sodium bicarbonate, followed by purification on flash column chromatography to give cephalosporins **3a-3f** in satisfactory yields[6]. The NMR spectral data of the compound were shown in Table I[7].



	R_1	R_2
a	H	H
b	OCH_3	OCH_3
c	OH	H
d	H	OH
e	OCH_3	H
f	OH	OCH_3

Scheme 1.

The *in vitro* antibacterial activity of compounds **3a-3f** was determined by the standard two fold agar dilution method. The result is given in Table II in comparison with that of cefotaxime as MIC/(μg/ml). Cephalosporins bearing a quinoliniumthiomethyl group at the C-3 position exhibited strong activity with widely expanded spectra against Gram-positive and Gram-nagative organisms. All **6** compounds showed superior activity against Gram-positive bacteria and comparable or slightly inferior activity against Gram-negative bacteria to cefotaxime. Against pseudomonas aeruginosa, compounds **3a**, **3d** and **3f** displayed activity comparable to that of cefotaxime. As shown in Table II, cephalosporins **3a** and **3f** were strongly active against Enterobacter cloacae P99 and Streptococcus faecium MD 8b which are resistant to most of cephalosporins including cefotaxime. In a series of compounds, the enhancement effect of hydroxy or methoxy groups substitued at the quinoline ring on the antibacterial activity was not detected.

Among 6 compounds, **3a** was chosen for further evaluation on the basis of its antistaphylococcal, antipseudomonal and antienterobacterial activity. The activity of **3a** against selected MRSA, Enterococcus, Pseudomonas and Streptococcus bacteria

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

Compound No.	3−CH_2 (2H, ABq)	6−H (1H, dd)	7−H (1H, dd)	O H || | −C−N− (1H, d, J=8H)	−OCH_3 (3H, s)	Thiazole (1H, s)	Quinoline N-CH_3(3H, s)	Quinoline −CH_3(3H, s)	Quinoline other protons
3a	4.66	4.99	5.57	9.60	3.86	6.72	4.27	2.98	8.67(1H, m), 8.52(1H, m) 8.20 (1H, m), 7.98(1H, m), 7.38(1H, s)
3b	4.64	5.03	5.68	9.54	3.82	6.82	4.29	2.90	8.54(1H, s), 7.30(1H, s) 7.06 (1H, s), 3.97(3H, s), 3.84(3H, s)
3c	4.58	5.02	5.60	9.58	3.78	6.72	4.22	2.88	8.22(2H, m), 7.61(1H, d) 7.43(1H, s)
3d	4.53	5.01	5.56	9.52	3.82	6.72	4.57	2.82	8.24(1H, s), 7.24(3H, m)
3e	4.66	5.01	5.58	9.53	3.82	6.74	4.27	2.96	8.55(1H, s), 8.43(1H, d) 7.80 (1H, d), 7.50(1H, s), 4.00(3H, s)
3f	4.58	4.98	5.57	9.51	3.81	6.72	4.27	2.84	8.36(1H, s), 7.21(1H, s) 7.04 (1H, s), 4.00(3H, s)

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

Organism	**3a**	**3b**	**3c**	**3d**	**3e**	**3f**	Cefotaxime
Streptococcus pyogenes 308	0.004	0.013	0.013	0.004	0.004	0.004	0.007
Streptococcus pyogenes 77	<0.002	0.004	0.004	<0.002	<0.002	<0.002	0.004
Streptococcus faecium MD 8b	3.125	100	12.5	100	6.25	100	100
Staphylococcus aureus SG 511	0.195	1.563	0.781	0.391	0.781	0.391	1.563
Straphylococcus aureus 285	0.391	3.125	1.563	1.563	1.563	0.391	3.125
Staphylococcus aureus 503	0.195	0.781	0.391	0.391	0.391	0.195	0.781
Escherichia coli O 55	0.049	0.781	0.098	0.098	0.195	0.098	0.007
Escherichia coli DC 0	0.195	3.125	0.781	1.563	1.563	0.781	0.025
Escherichia coli DC 2	0.007	0.098	0.025	0.013	0.049	0.013	0.007
Escherichia coli TEM	0.195	3.125	0.781	1.563	1.563	0.391	0.025
Escherichia coli 1507E	0.195	3.125	0.781	0.391	1.563	0.781	0.025
Pseudomonas aeruginosa 9027	25	100	50	12.5	100	12.5	12.5
Pseudomonas aeruginosa 1592E	25	100	50	12.5	100	12.5	12.5
Pseudomonas aeruginosa 1771	12.5	50	12.5	3.125	25	12.5	6.25
Pseudomonas aeruginosa 1771M	1.563	3.125	3.125	3.125	6.25	1.563	0.049
Salmonella typhimirium	0.391	1.563	0.781	3.125	1.563	1.563	0.049
Klebsiella oxytoca 1082E	0.781	12.5	3.125	3.125	6.25	3.125	0.781
Klebsiella aerogenes 1522E	0.391	3.125	0.781	0.781	1.563	0.781	0.025
Enterobacter cloacae P99	6.25	100	50	100	50	12.5	100
Enterobacter cloacae 132E	0.098	0.781	0.098	0.195	0.391	0.098	0.025

Table III. ***In vitro*** **activities of 3a**

Compound	Organism (no. tested)	MIC-range	MIC. 50	MIC. 90
3a	MRSA (Hoechst) (19)	0.781-50	12.5	25
	Enterococcus I (20)	0.049-1.563	0.098	0.781
	Pseudomonas II (20)	6.25-50	12.5	25
	Streptococcus I (20)	0.002-50	0.025	0.391
Cefotaxime	MRSA (Hoechst) (19)	1.563-100	12.5	25
	Enterococcus I (20)	0.025-12.5	0.098	1.563
	Pseudomonas II (20)	6.20-100	12.5	50
	Streptococcus I (20)	0.002-100	0.025	0.391

is listed in Table III. Based on this result, further studies are in progress to evaluate the compound **3a** and modification of this derivative is under study now.

ACKNOWLEDGEMENTS

This work was fully supported by the Ministry of Science and Technology.

LITERATURE CITED

1. Dürckheimer, W., Blumbach, J., Lattrell, R. and Scheunemann, K. H.: Recent developments in the field of β-lactam antibiotics. *Angew. Chem. Int. Ed. Engl.* **24**, 180 (1985).
2. Kondo, S., Shibahara, S., Okonogi, T., Yoshida, T., Murai, Y., Kudo, T. and Inouye, S.: A new aminothiazolylcephalosporin having 1-carboxyethoxyimino group, ME 1228. *J. Antibiotics* **43**, 62 (1990).
3. Tsuruoka, T., Ogino, H., Iwamatsu, K., Katano, K., Nakabayashi, S., Yoshida, T., Inouye, S. and Kondo, S.: New aminothiazolyglycylcephalosporins with 1,5-dihydroxy-4-pyridone-2-carbonyl group I. Synthesis and biological activity of cephalosporin derivatives to MT 0703. *J. Antibiotics* **43**, 174 (1990).
4. Wright, G. C., Watson, E. J., Ebetino, F. F., Lougheed, G., Stevenson, B. F. and Winterstein, A.: Synthesis and hypotensive properties of new 4-aminoquinolines. *J. Med. Chem.* **14**, 1060 (1971).
5. Knorr, H., Gildemeister, H., Mildenberger, H. and Salbeck, G.: Neue 4-Chinolinol- und 5,6,7,8-Tetrahydro-4-chinolinolabkomm linge mit biozider Wirkung. *Liebigs Ann. Chem.*, 1656 (1982).
6. Kondo, S., Katano, K., Ogino, H., Iwamatsu, K., Nakabayashi, S., Yoshida, T., Komiya, I., Tsuruoka, T. and Inouye, S.: Synthesis and biological activity of (cyclopentenopyridinium)thiomethylcephalosporins. *J. Antibiotics* **43**, 1150 (1990).
7. The peaks of C-2 protons were hardly detected due to water peaks in the range of 3-4 ppm.