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Synthesis and in Vitro Antibacterial Activity of 3-[*N*-methyl-*N*-(3-methyl-1,3-thiazolium-2-yl)amino]methyl Cephalosporin Derivatives

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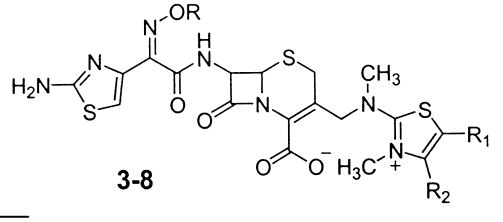
Abstract—The new cephalosporins having *N*-linked quarternary ammonium salt at C-3 position were prepared from the reaction of 2-methylimino-3-methyl-1,3-thiazoline derivatives with cephalosporins. Also antimicrobial activities of those compounds were determined.

In the past decade, even though cephalosporin antibiotics have made remarkable progress and contribution in the treatment of acute disease originated from pathogenic infection in clinics, many efforts still exist to achieve the well-balanced broad-spectrum and to improve β-lactamase stability. Among them, quarternary ammonium cephalosporins having aminothiazole derivatives at C-7 have continuously been paid attention and developed to improve the broad-spectrum activity. The category of these can be devided into pyridinium (ceftazidime,[1] cefpirome,[2] DQ-2556[5]), cyclic quaternary alkyl ammonium (cefclidin,[4] cefepime[3]), and other hetero cyclic ring (cefozofran[6]), and *S*-linked heterocyclic ammonium cephalosporins.[7] However, only a few cases of *N*-linked quaternary ammonium salts[8] of cephalosporin were reported. We found that 2-methylimino-3-methyl-1,3-thiazoline derivatives were easily introduced into the C-3 position of cephalosporin derivatives to form a new type of *N*-linked quaternary ammonium salt. Herein, we report the result of synthesis and antibacterial activities of this new type of cephalosporin.



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The 2-(methylimino)-3-methyl-1,3-thiazoline derivatives (**1b-f**) were conveniently prepared by the reaction of 1,3-dimethylthiourea with α-chloroketone compounds in good to excellent yield, while the 2-bromoacetaldehyde diethyl acetal was used instead of chloroacetaldehyde for the preparation of **1a** according to the modification of literature.[9,10]

Amide **1e** was prepared from ester **1d** under the condition of saturated NH_3 with sodium methoxide in MeOH solution. The compounds **3**–**8**[11] were readily obtained by introduction of **1a**–**f** into C-3 position of 7β-[2-(aminothiazol-4-yl)-2-alkoxyiminoacetoamido]-3-acetoxymethyl-3-cephem-4-carboxylic acid (**2a**–**c**) according to the previously reported method[2c] as shown in Scheme 1. The minimum inhibitory concentrations (MICs) of new cephalosporins against 20 standard strains are summarized in Table 1 and compared with those of cefpirome and cefotaxime as references. MICs were determined by the serial 2-fold agar dilution Muller–Hinton method. Most of the new thiazolium cephalosporins exhibited well-balanced antimicrobacterial activity except *Pseudomonas aeruginosa*. The substituents of thiazolium ring at C-3 side chain did not largely influence the antibacterial activity. However, the activity of **8** against Gram-positive organism is superior to those of other thiazolium cephalosporins. The antimicrobial effect of alkyloxyimino group in the acyl side chain at C-7 position was explored. The **4c** and **6c** with allyloxyimino group was 2-fold Tore active than those of **4a**–**b** and **6a**–**b** with methoxy- and ethoxyimino group against *staphylococcus aureus*.

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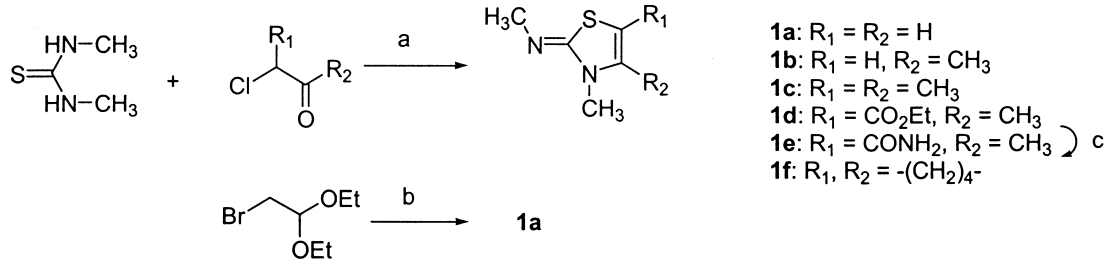
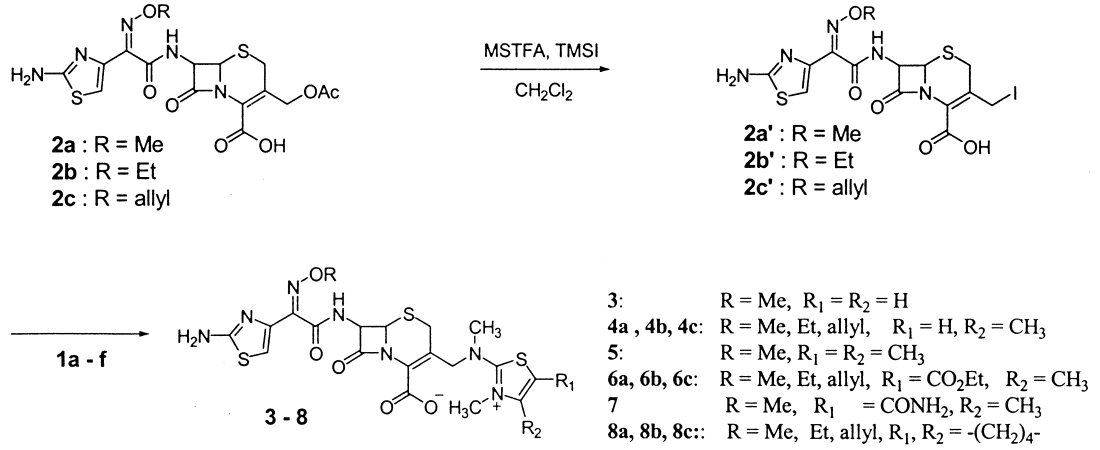


Table 1. In vitro antibacterial activity of new cephalosporins **3–8** (MIC: μg/mL)[a]

Strain	CPR	CTX	3	4a	4b	4c	5	6a	6b	6c	7	8a	8b	8c
S.p. A 308	0.007	0.007	0.007	0.013	0.013	0.013	0.013	0.007	0.007	0.013	0.007	0.007	0.013	0.004
*S.p.*A77	0.007	0.002	0.007	0.004	0.013	0.007	0.007	0.004	0.004	0.013	0.007	0.007	0.007	0.004
S.p. 8b	1.563	100	>100	>100	50	25	>100	25	25	50	12.5	12.5	25	50
S.a. SG511	0.391	1.563	1.563	0.781	0.781	0.391	1.563	1.563	1.563	0.781	0.391	0.391	0.391	0.391
S.a. 285	0.781	3.125	3.125	1.563	1.563	0.781	1.563	1.563	1.563	1.563	0.781	0.781	0.781	0.781
S.a. 503	0.098	0.781	0.391	0.781	0.391	0.195	0.781	0.781	0.781	0.391	0.195	0.195	0.195	0.195
E. coli O 55	0.025	0.007	0.025	0.025	0.025	0.049	0.025	0.049	0.049	0.025	0.025	0.025	0.049	0.049
E. coli DC 0	0.013	0.025	0.098	0.049	0.098	0.195	0.049	0.098	0.098	0.098	0.049	0.049	0.098	0.391
E. coli DC2	0.049	0.013	0.098	0.049	0.025	0.025	0.098	0.049	0.049	0.025	0.025	0.025	0.025	0.025
E. coli TEM	0.049	0.025	0.098	0.049	0.098	0.195	0.049	0.195	0.195	0.098	0.049	0.049	0.195	0.391
E. coli 1507E	0.025	0.025	0.098	0.049	0.098	0.195	0.049	0.098	0.098	0.098	0.049	0.049	0.195	0.391
P.a. 9027	3.125	25	50	25	25	25	50	100	100	25	50	50	25	50
P.a. 1592 E	1.563	12.5	50	25	12.5	12.5	50	50	50	12.5	25	25	25	50
P.a. 1771	0.781	3.125	25	12.5	3.125	6.25	25	25	25	3.125	6.25	6.25	6.25	6.25
P.a. 1771 M	0.391	0.098	1.563	1.563	0.391	0.195	1.563	1.563	1.563	0.391	0.781	0.781	0.391	0.781
S.t.	0.025	0.025	0.098	0.049	0.049	0.098	0.098	0.049	0.049	0.049	0.049	0.049	0.098	0.195
K.o. 1082 E	1.563	1.563	25	6.25	6.25	12.5	6.25	6.25	6.25	6.25	3.125	3.125	3.125	6.25
K.a. 1522 E	0.025	0.025	0.098	0.049	0.049	0.098	0.098	0.049	0.049	0.049	0.025	0.025	0.098	0.195
E.c. P99	3.125	100	50	25	25	25	12.5	3.125	3.125	25	6.25	6.25	6.25	12.5
E.c. 1321	0.013	0.007	0.049	0.013	0.025	0.098	0.013	0.025	0.025	0.025	0.013	0.013	0.049	0.049

[a]Abbreviations: CPR, Cefpirome; CTX, Cefotaxime; S.p. A308, *Streptococcus pyogenes* A308; S.p. A77, *Streptococcus pyogenes* A77; S.p. 8b, *Streptococcus pyogenes* 8b; S.a. SG 511, *Staphylococcus aureus SG* 511; S.a. 285, *Staphylococcus aureus* 285; S.a. 503, *Staphylococcus aureus* 503; *E. coli* O 55, *Escherichia coli* O 55; *E. coli* DC 0, *Escherichia coli* DC 0; *E. coli* DC 2, *Escherichia coli* DC 2; E. coli TEM, *Escherichia coli* TEM; *E. coli 1507E, Escherichia coli* 1507E; P.s. 9027, *Pseudomonas aeruginosa* 9027; P.s. 1592 E, *Pseudomonas aeruginosa* 1592 E; P.s. 1771, *Pseudomonas aeruginosa* 1771; P.s. 1771M, *Pseudomonas aeruginosa 1771 M; S. t., Salmonella typhimurium; K. o. 1082E, Klebsiella oxytoca* 1082 E; K.a. 1522E, *Klebsiella aerogenes* 1522 E; E.c. P99, *Enterobater cloacae* P99; E.c. 1321, *Enterobater cloacae* 1321.



Scheme 1.

In conclusion, the new type of 3-[*N*-methyl-*N*-(3-methyl-1,3-thiazolium-2-yl)amino]methyl cephalosporin derivatives possessed a well-balanced broad spectrum and potent activity against Gram-positive and Gram-negative except *Pseudomonas aeruginosa*.

Acknowledgements

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11. General procedure for **3**–**8**: To the suspension of cefotaxime (0.478 g, 1.00 mmol) in dried CH_2Cl_2 (20 mL) was added MSTFA (0.70 mL, 3.80 mmol) under nitrogen atmosphere at rt. After the reaction solution became clear, TMSI (0.40 mL, 2.80 mL) was added and the resulting solution was stirred for additional 30 min at rt. The solvent was removed in vacuo. Dried acetonitrile (5 mL) and anhydrous THF (0.37 ml, 4.50 mmol), which destructed excess unreacted TMSI, was added to the residue. To this solution was added silylated **1a** (0.128 g, 1.17 mmol) with MSTFA (0.3 mL, 1.6 mmol) dissolved in dried acetonitrile (3 mL), and stirred for 20 hr at rt. The reaction mixture was poured into the mixture of methanol and acetone (5:95, v/v) (40 mL) to precipitate a solid, followed by filtration to afford HI salt of crude **1a** (0.35 g) as an ivory solid. The neutralized solution (pH 6.8) of **1a** with 5% $NaHCO_3$ was directly loaded on silica gel column. Elution with the mixture of the acetonitrile and water (5:1, v/v) gave **1a** (0.10 g, 19%) as an off white solid. Mp 213 °C (dec); ^{1}H NMR (DMSO-d_6, 300 MHz) δ 3.20 (3H, s, N–CH_3), 3.85 (3H, s, OCH_3), 3.90 (3H, s, N^+-CH_3), 4.49 (2H, ABq, J = 14.6 Hz, S–CH_2), 5.00 (1H, d, J = 4.8 Hz, C8–H), 5.60 (1H, dd, J = 4.8, 8.1 Hz, C7–H), 6.73 (1H, s, aminotiazole H), 7.20 (2H, bs, NH_2), 7.25 (1H, d, J = 12.5 Hz), 7.55 (1H, d, J = 12.5 Hz), 9.52 (1H, d, J = 8.1 Hz). Anal. calcd for $C_{19}H_{21}N_7O_5S_3$: C, 43.58; H, 4.04; N, 18.73. Found: C, 43.83; H, 3.76; N, 18.51.