Arch Pharm Res Vol 22, No 6, 579-584, 1999 Medicinal Chemistry

Synthesis and *In Vitro* Antibacterial Activity of Quaternary Ammonium Cephalosporin Derivatives Bearing Oxazolidinone Moiety

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(Received June 20, 1999)

Several oxazolidinones having amine moiety were prepared to form a quaternary ammonium salt with cephalosporin nucleus, and antibacterial activity of the quaternary ammonium cephalosporin derivatives bearing oxazolidinone moiety were examined particularly with expectation of dual activity. However, the cephalosporin-oxazolidinone compounds revealed rather weaker antibacterial activity *in vitro* than their parent oxazolidinone and cephalosporin without showing any characteristic activity as expected.

Key words: Oxazolidinone, Quaternary ammonium cephalosporin, Antibacterial activity

INTRODUCTION

After the discovery of oxazolidinone derivative, Dup-721 (Gregory *et al.*, 1989) which showed excellent activity against Gram-positive bacteria including resistance strains, Pharmacia & Upjohn has intensively worked on development of new oxazolidinone antibacterial agents, and discovered linezolid and eperezolid (Bricker *et al.*, 1996). These compounds showed potent antibacterial activity *in vitro* and *in vivo* against numerous Gram-positive pathogens including methicillin-resistant *Staphylococcus aureus* (MRSA), methicillin-resistant *Staphylococcus epidermidis* (MRSE), quinolone-resistant *Staphylococcus aureus* (QRSA), vancomycin-resistant *Enterococci* (VRE), and multidrug-resistant *Myco-bacterium tuberculosis* (MDRTB) strains. Currently, linezolid is in phase III clinical trials for the treatment of Gram-positive infections. However, the oxazolidinones currently under development have no activity against Gram-negative bacteria including *Pseudomonas aeruginosa*.

In general, it was reported that cephalosporin derivatives having a quaternary ammonium moiety at the 3-position showed broad antibacterial spectrum with enhancing activity against Gram-negative bacteria including *Pseudomonas aeruginosa* (Sugiyama *et al.*, 1992). This prompted us to investigate that the quarternization at the 3-position of cefotaxime with the oxazolidinone group might have led candidate compounds showing dual antibacterial activity of cephalosporin and oxazolidinone derivatives as in the case that Hoffman La Roche (Geor-gopapadakou *et al.*, 1989) attempted a similiar approch with quinolone and cephalosporin moieties.

Therefore, we have been interested in synthesis of new antibacterial agents to expand the antibacterial spectrum of the oxazolidinones to Gram-negative and *Pseudomonas* strains as well as increasing activity against Gram-positive bacteria.

In this paper, we wish to describe the design and synthesis of several new oxazolidinones having amine moiety and quaternary ammonium cephalosporin derivatives (Fig. 1) attached by oxazolidinone groups at the 3-position of cefotaxime. *In vitro* antibacterial activity of these oxazolidinone-cephalosporin compounds were

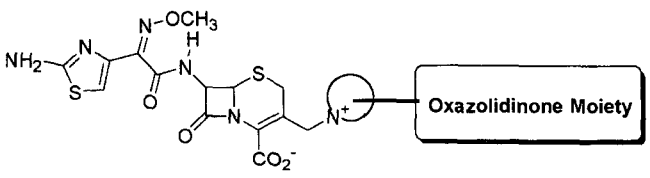

Fig. 1. Quaternary Ammonium cephalosporin antibiotics bearing oxazolidinones

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examined particularly with expecting dual antimicrobial character revealing oxazolidinone's and cephalosporin's activity.

MATERIALS AND METHODS

Materials

All starting materials were obtained from commercial suppliers, and used without further purification. All solvents used for reaction were freshly distilled from proper dehydrating agents. ^{1}H NMR spectra were recorded on a Gemini Varian-300 (300 MHz) spectrometer. Chemical shift are reported in parts per million (δ) down field relative to tetramethylsilane as an internal standard. Melting points were measured with a Thomas Hoover capillary melting point apparatus. IR spectra were taken on a Perkin Elmer 16F PC FT-IR spectrometer. Mass spectra were obtained on a HP590 GC/MS 5972 MSD spectrometer. HPLC analysis were done at 254 nm on a Waters 840 HPLC system equipped with a Waters WISP injection system and a Merck μ-Bondpack C18 reverse-phase column (LiChroCART100RP-18,10 μm).

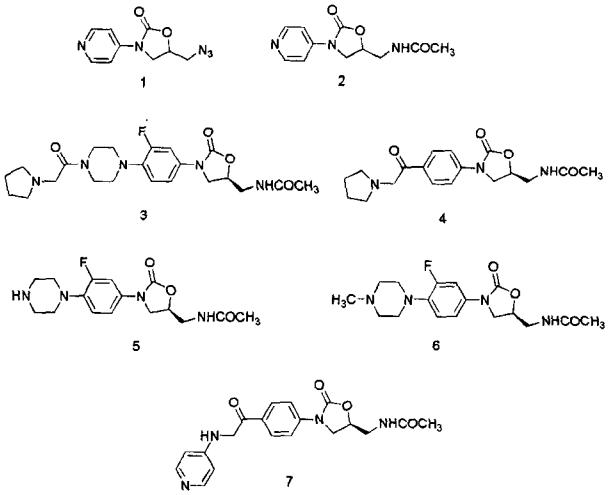
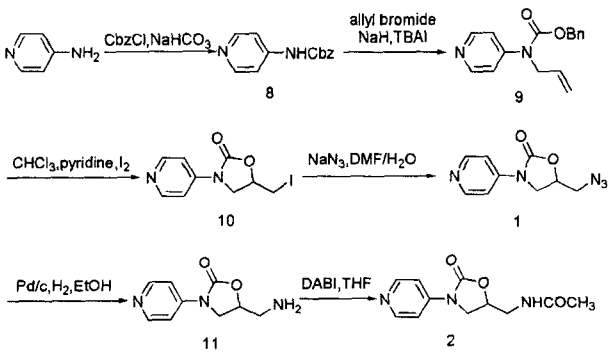


Fig. 2. Synthesized oxazolidinone derivatives



Scheme 1. Synthesis of oxazolidinone **1** and **2**

Chromatographic purification was carried out by flash chromatography using Kieselgel 60 (230~400 mesh, Merck). Antibacterial activities were obtained by agar dilution method.

Synthesis of oxazolidinone derivatives

Oxazolidinone derivatives were summarized in Fig. 2. Compound **1** and **2** were prepared by the similiar manner of known procedures (Gregory *et al.*, 1989) as shown in Scheme **2**.

Compound **3**, **4** and **7** were prepared by reaction of amines and chloroacetyl compound of oxazolidinone known in the literature (Gregory et *al.*, 1989; Bricker et *al.*, 1996). Compound **5** and **6** were also synthesized by the known method (Bricker *et al.*, 1996 and 1995).

Benzyl *N*-allyl-*N*-(4-pyridyl)carbamate (9)

4-(*N*-benzyloxycarbonyl)amino pyridine (**8**) (1 g, 4.38 mmol ; Kim *et al.*, 1985) was dissolved in THF (44 ml), and NaH (1.1 eq, 0.2 g) added under nitrogen atmosphere. After stirring the mixture for 30 min., *n*-Bu_4NI (0.1 eq, 0.16 g) and allyl bromide (1.1 eq, 0.42 ml) were added, and the solution was stirred for 2 h at room temperature. The reaction was terminated by quenching with H_2O (1 ml). Most of solvent was evaporated, and CH_2Cl_2 (100 ml) and H_2O (100 ml) were added to the residue. The organic layer was dried, and evaporated to obtain 0.94 g (82 %) of yellow oily product. The crude product was used for the following reaction without further purification. IR (KBr) cm^{-1} ;1011, 1485, 1530, 1690, 2360, 3421. ^{1}H NMR (300 MHz, $CDCl_3$) ; δ 8.51 (d, *J*=4.8 Hz, 2 H), 7.36 (s, 5 H), 7.28 (d, *J* =4.8 Hz, 2 H), 5.92 (m, 1 H), 5.24(s, 2H), 5.15 (m, 2 H), 4.37 (d, *J*=1.8 Hz, 2 H).

5-(Iodomethyl)-3-(4-pyridyl)-1,3-oxazolan-2-one (10)

Benzyl *N*-allyl-*N*-(4-pyridyl)carbamate (**9**) (0.75 g, 2.8 mmol) was dissolved in pyridine (15 eq, 3.4 ml) and $CHCl_3$ (56 ml), and iodine (15 eq, 10.7 g) was added to the solution. The reaction mixture was stirred for 3 h at 50°C. Resulted suspension was filtered off, and washed the filter cake with $CHCl_3$. The filtrate was treated with 20% $Na_2S_2O_3$ solution, and dried over anhydrous hydrous sodium sulfate to obtain yellow oily product (0.17 g, 19.3 %). mp 119-120; IR (KBr) cm^{-1} ; 438, 676, 990, 1086, 1746, 2940. ^{1}H NMR (300 MHz, $CDCl_3$) ; δ 8.55 (d, *J*=1.8 Hz, 2 H), 7.47 (d, *J*=1.8 Hz, 2 H), 4.78 (m, 1 H), 4.18(m, 1 H), 3.78 (m, 1 H), 3.49 (m,1 H), 3.37(m, 1 H).

5-(Azidomethyl)-3-(4-pyridyl)-1,3-oxazolan-2-one (1)

5-(Iodomethyl)-3-(4-pyridyl)-1,3-oxazolan-2-one(**10**) (0.17 g, 0.54 mmol) was dissolved in DMF (5 ml) and water

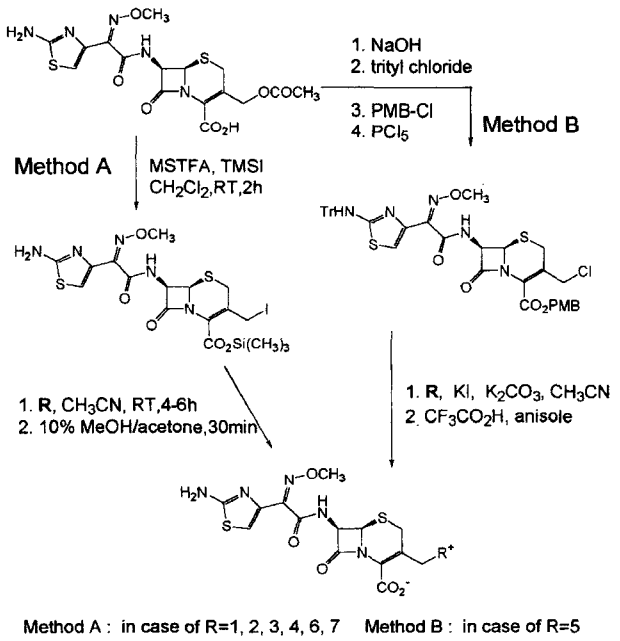
(0.4 ml), and NaN_3 (4 eq, 0.14 g) added to the solution. The reaction mixture was stirred for 6 h at 60°C, and poured into water and then extracted with EtOAc. Dried organic layer was concentrated to obtain product (0.1 g, 85%) as white solid. mp 83-87; IR (KBr) cm^{-1} ; 450, 1754, 2106, 3030. ^1H NMR (300 MHz, $CDCl_3$) ; δ 8.56 (d, *J*= 4.8 Hz, 2 H), 7.48(d, *J*=4.8 Hz, 2 H), 4.84 (m, 1 H), 4.09 (t, *J*=9 Hz, *J'*=18 Hz, 1H), 3.74 (dd, *J*=4.5 Hz, 4.8 Hz, 1 H), 3.60 (dd, *J*=4.2 Hz, 4.2 Hz, 1 H).

5-(Aminomethyl)1-3-(4-pyridyl)-1,3-oxazolan-2-one (11)

5-(Azidomethyl)-3-(4-pyridyl)-1,3-oxazolan-2-one(**1**) (0.1 g, 0.46 mmol) was dissolved in EtOH (15 ml), and added 10% Pd-C (20 mg). The reaction mixture was stirred for 2 h at room temperature under 40 psi hydrogen pressure. The mixture was filtered with celite, and the filtrate was concentrated to obtain yellow oily product (0.07 g, 78.4 %), and next reaction was proceeded without further purification. IR (KBr) cm^{-1} ; 1751, 2103, 3016. ^1H NMR (300 MHz, $CDCl_3$) ; δ 8.47 (d, *J*=9 Hz, 2 H), 7.43 (d, *J*=4.8 Hz, 2 H), 4.69 (m, 1 H), 3.99 (t, *J* =8.7 Hz, *J'*=4.8 Hz, 1 H), 3.83 (dd, *J*=6.6 Hz, 1 H), 3.08 (dd, *J*=4.8 Hz, 4.2 Hz, 1 H), 2.93 (dd, *J*=4.8 Hz, 4.8 Hz, 1 H).

5-(Acetamidomethyl)-3-(4-pyridyl)-1,3-oxazolan-2-one(2)

To a solution of 5-(aminomethyl)-3-(4-pyridyl)-1,3-oxazolan-2-one (**11**) (0.096 g, 0.497 mmol) dissolved in dried anhydrous THF (10 ml) added *N,N'*-diacetylbenzimidazolone (0.5 eq, 0.0 54g), and refluxed the reaction mixture for 3 h. After cooling the reaction mixture, precipitated solide was filtered off. The filtrate was purified by column chromatography (EtOAc : MeOH=2 : 1) to obtain product (0.08 g, 64 %) as white solid. mp 186-188. IR (KBr) cm^{-1} ; 432, 1102, 1666, 1758, 3032. ^1H NMR (300 MHz, $CDCl_3$) ; δ 8.47 (d, *J*=4.2 Hz, 2 H), 8.23 (m, 1 H), 7.53 (d, *J*=4.8 Hz, 2 H), 4.77 (m, 1 H), 4.12 (t, *J*=12 Hz, *J'*=9 Hz ,1 H), 3.73 (dd, *J*=6.6 Hz, 1 H), 3.43 (m, 2 H), 1.82(s, 3 H).



Scheme 2. Synthesis of Quaternary Ammonium Cephalosporin

Synthesis of quaternary ammonium cephalosporin derivatives

Quaternary ammonium cephalosporins were synthesized by quaternization of cephalosporin iodide intermediate generated *in situ* with oxazilidinone amines as shown in Scheme 2.

Method A : 7-[2-(2-Aminothiazol-4-yl)-2(Z)-methoxyiminoacetamido]cephalosporanic acid (cefotaxim; 0.16 g, 0.36 mmol) was suspended in methylene chloride (5 ml) under nitrogen atmosphere, and *N*-methyl-*N*-(trimethylsilyl)-trifluoroacetamide (2 ml, 3 eg) was added. The mixture was stirred for 1 h at room temperature, and then added trimethylsilyl iodide (0.15 ml, 3 eg). The resulting solution was stirred for 1 h, then solvent was evaporated *in vacuo* to afford a viscous yellow oil. The oily residue was dissolved in acetonitrile (1 ml), and THF (0.1 ml) was added to destroy excess of TMSI. To the resulting solution added oxazolidinone derivatives (1.5 eq) dissolved in acetonitrile (5 ml), and stirred for 3-4 h at room temperature, and then 5% MeOH/acetone (5 ml) was added to precipitate hydrogen iodide salt of product. The solid washed with CH_2Cl_2 (5 ml × 2) and acetone (5 ml × 2). The crude HI salt was dissolved in 10% aqueous $NaHCO_3$ solution and chromatographed by eluting with 80% acetonitrile/water. Eluted solution containing product was dried by freezing dryer to obtain colorless or pale yellow amorphous solid. The purity was examined on a HPLC (eluent : 10% acetonitrile/H_2O, flow rate : 1 ml/min). The compound **1A**~**4A** and **6A** ~ **7A** were prepared by the method A.

7-{[2-(2-Amino-1,3-thiazol-4-yl)-2-(methoxyimino) acetyl]amino}-3-({4-[5-(azidomethyl)-2-oxo-1,3-oxazolan-3-yl]-1-pyridiniumyl}methyl)-6-oxo-7,7a-dihydro-2H,6H-azeto[2,1-b][1,3]thiazine-4-carboxylate (1A) mp 250 °C. IR (KBr) cm^{-1}; 988, 1122, 1227, 1491, 1735, 2109; ^1H NMR (300 MHz, DMSO-d_6) ; δ 9.47 (br, 2 H), 8.43 (dd, *J*=6 Hz, 2 H), 8.25(t, 1 H), 7.52 (dd, *J*=6 Hz, 2 H) ,7.18 (br, 2 H), 6.69 (s, 1 H), 5.62 (d, 1 H), 5.12 (d, 1 H), 4.49 (m, 1 H), 4.56 (q, 2 H), 4.16 (t, 1 H), 3.95 (s, 3 H), 3.71 (dd, *J*=9 Hz, 1 H), 3.65 (q, 2 H), 3.39 (dd, *J*=9 Hz, 2 H).

3-[(4-{5-[(Acetylamino) methyl]-2-oxo-1,3-oxazolan-3yl}-1-pyridiniumyl) methyl]-7-{[2-(2-amino-1,3-thiazol-4-yl) -2-(methoxyimino)acetyl]amino}-6-oxo-7,7a-dihydro-2H, 6H-azeto[2,1-b][1,3]thiazine-4-carboxylate (2A) mp 250 °C. IR (KBr) cm^{-1} ; 1003, 1097, 1277, 1347, 1481, 1571, 1745; ^1H NMR (300 MHz, DMSO-d_6) ; δ 9.47 (br, 2 H), 8.43 (dd, *J*=6Hz2H), 8.25 (t, 1 H), 7.52 (m, 2 H), 7.18 (br, 2 H), 6.69 (s, 1 H), 5.62 (m, 1 H), 5.12(m, 1 H), 4.49 (m, 1 H), 4.56 (q, 2 H), 4.16 (t, 1H), 3.95 (s, 3 H), 3.71 (dd, 1 H,), 3.65 (q, 2 H), 3.39 (dd, *J*=9 Hz, 2 H), 1.82 (s, 3 H).

7-{[2-(2-Amino-1,3-thiazol-4-yl)-2-(methoxyimino) acetyl]amino}-3-(N1-[(3-{3-fluoro-4-[4-(2-tetrahydro-1H-1-pyrrolylacetyl)piperazino]phenyl}-2-oxo-1,3-oxazolan -5-yl)methyl]acetamide)-6-oxo-7,7a-dihydro-2H,6H-azeto[2,1-b][1,3]thiazine-4-carboxylate (3A) mp 205°C. IR (KBr) cm^{-1} ;843, 973, 1097, 1242, 1486, 1581, 1740 ; ^1H NMR (300 MHz, DMSO-d_6) ; δ 9.56 (br, 2 H), 9.12 (d, 1 H), 8.25 (t, 1 H), 7.50(d, 1 H), 7.19 (d, 1 H), 7.17 (br, 2 H), 7.07 (m, 1 H), 6.87 (s, 1 H), 5.95 (d, 1 H), 5.28 (d, 1 H), 5.05 (m, 2 H), 4.06 (m, 1 H), 3.87 (s, 3 H), 3.70 (m, 2 H), 3.67 (m, 2 H), 3.42 (m, 2 H), 2.83 (m, 8 H), 1.83 (s, 3 H), 1.69 (m, 8 H).

3-({1-[2-(4-{5-[(Acetylamino)methyl]-2-oxo-1,3-oxazolan-3-yl}phenyl)-2-oxoethyl]tetrahydro-1H-1-pyrroliumyl}methyl)-7-{[2-(2-amino-1,3-thiazol-4-yl)-2-(meth -oxyimino)acetyl]amino}-6-oxo-7,7a-dihydro-2H,6H-azeto[2,1-b][1,3]thiazine-4-carboxylate (4A) mp 189°C. IR (KBr) cm^{-1} 838, 938, 1092, 1262, 1347, 1451, 1581, 1735, 2358. ^1H NMR (300 MHz, DMSO-d_6) δ ; 9.56 (br, 2 H), 9.12 (d, 1 H), 8.01 (d, 2 H), 7.61 (d, 2 H), 7.17 (br, 2 H), 6.87 (s, 1 H), 6.51(t, 1 H), 5.95 (d, 1 H), 5.28 (d, 1 H), 5.05 (m, 2 H), 4.81 (m, 1 H), 4.09 (t, 1 H), 3.93 (s, 2 H), 3.87 (s, 3 H), 3.81(m, 1 H), 3.62(m, 2 H), 2.65 (m, 4 H), 2.10 (s, 3 H), 1.81(m, 4 H).

3-{[4-(4-{5-[(Acetylamino) methyl]-2-oxo-1,3-oxazo-lan-3-yl}-2-fluorophenyl) -1-methylhexahydropyrazin-1-ium-1 -yl]methyl}-7-{[2-(2-amino-1,3-thiazol-4-yl)-2-(meth-oxyimino)acetyl]amino}-6-oxo-7,7a-dihydro-2H,6H-azeto [2, 1 -b][1,3]thiazine-4-carboxylate (6A) mp 177°C. IR (KBr) cm^{-1} ; 1152, 1526, 1755, 3335; ^1H NMR (300 MHz, DMSO-d_6) δ ; 9.56 (br, 2 H), 9.35 (d, 1 H), 8.24 (t, *J*=3 Hz, 1 H), 7.49 (d, *J*=9 Hz, 1 H), 7.17 (br, 2 H), 7.16 (d, *J*=3Hz, 1 H), 7.12 (t, *J*=9 Hz, 1 H), 6.89(s, 1 H), 5.93 (d, *J*=6Hz, 1 H), 5.04 (d, *J*=6Hz, 1 H), 4.71 (m, 1 H), 4.52 (q, 2 H), 4.07 (t, 1 H), 3.81 (s, 3 H), 3.71 (t, *J*=6.6 Hz, 1 H), 3.62(q, 2 H), 3.39 (m, 2 H), 3.05 (m, 4 H), 2.56 (m, 4 H), 2.11 (s, 3 H), 1.82 (s, 3 H).

3-[(4-{[2-(4-{5-[(Acetylamino) methyl]-2-oxo-1,3-oxa-zolan-3-yl}phenyl)-2-oxoethyl]amino}-1-pyridiniumyl) methyl]-7-{[2-(2-amino-1,3-thiazol-4-yl)-2-(methoxyimino) acetyl]amino}-6-oxo-7,7a-dihydro-2H,6H-azeto [2,1-b] [1,3]thiazine-4-carboxylate (7A) mp 234°C. IR (KBr) cm^{-1}; 1661, 1765, 3405; ^1H NMR (300 MHz, DMSO-d_6). 9.56 (br, 2 H), 9.35 (d, 1 H), 8.69 (d, 1 H), 8.26 (m, 3 H), 8.06 (d, *J*=7.1 Hz, 2 H), 7.77 (d, *J*=7.2 Hz, 2 H), 7.17 (br, 2 H), 6.89 (d, *J*=7.2 Hz, 2 H), 6.87 (s, 1 H), 5.95 (d, 1 H), 5.90 (s, 2 H), 5.18 (d, 1 H), 5.08 (m, 2 H), 4.81 (m, 1 H), 4.20 (m, 1 H), 3.92 (s, 3 H), 3.83 (m, 1 H), 3.45 (m, 2 H), 1.82 (s, 3 H).

3-{[4-(4-{5-[(Acetylamino)methyl]-2-oxo-1,3-oxazo-lan-3-yl}-2-fluorophenyl)piperazino]methyl}-7-{[2-(2-amino-1,3-thiazol-4-yl)-2-(methoxyimino) acetyl] amino}-6 -oxo-7,7a-dihydro-2H, 6H-azeto[2,1-b][1,3] thiazine-4-carboxylate (5A, Method B)

7-[2-(2-Aminothiazol-4-yl)-2(*Z*)-methoxyiminoacetamido] cephalosporanic acid (cefotaxim : 0.16 g, 0.36 mmol) was suspended in water (3 ml) and MeOH (2 ml) at -5 °C, and 1 N NaOH aqueous solution (4.5 ml) was slowly added. After the reaction mixture become clear solution, tritylchloride in 10 ml acetone was slowly added by maintaining pH=7 with 10% aqueous NaOH solution. After stirring 30 min, reaction was terminated by adding ethyl acetate (50 ml). The organic layer was separated after the solution acidified at pH 2, and the orgainc layer was dried by $MgSO_4$.

p-Methoxybenzylchloride added to the dried solution, and stirred for 2 h at room temperature. The precipitated solid was filtered off, and filterate concentrated to obtain oily residue. Suspended PCl_5 (2.5 eq) and pyridine (2.5 eq) in CH_2Cl_2 (10 ml) was added to the oily residue in the 5 ml CH_2Cl_2 at -10°C, and the reaction mixture was stirred for 2 h at the same temperature. The reaction mixture was cooled to -40°C, and MeOH (10 ml) was slowly added, and then water (5 ml) and toluene (20 ml) were added for 2 h with vigorous stirring under ice bath. Resulted solid was filtered and washed with isopropylalcohol and diethyl ether to obtain 7-((*Z*)-2-methoxyimino-2-(2-tritylaminothiazole-4-yl)acetamido-3-chloromethyl-3-cephem-4-carboxylate. To suspension of 7-((*Z*)-2-methoxyimino-2-(2-tritylaminothiazole-4-yl)acetamido)-3-chloromethyl-3-cephem-4-carboxylate and KI (1.5 eq) in acetonitrile (25 ml) added 4-(4-{5-[(acetylamino)methyl]-2-oxo-1,3-oxazolan-3-yl}-2-fluorophenyl) piperazinomethy (1 eg) and K_2CO_3 at room temperature. After stirred the reaction mixture for 2 h, solid was filtered off, and water (5 ml) was added to the filtrate to precipitate the coupled product. Obtained solid was stirred for 1 h at 0°C in anisole (10 ml) and CF_3CO_2H (2 eg), and poured into isopropylether. Precipitated solid was filtered, and dissolved in a mixture of water and EtOAc, and adjusted to pH=7.2 with $NaHCO_3$. The aqueous layer was chro- matographed on a column of dianion HP-20 using 80% water/acetone to obtain pale yellow product. mp 177°C. IR (KBr) cm^{-1} 1666, 1744, 3292; ^1H NMR

Table I. *In vitro* antimicrobial activity of cephalosporins (MIC, μg/ml)

Compounds	*S.p.1*	*S.p.2*	*S.f.*	*S.a.1*	*S.a.2*	*S.a.3*	*E.c.1*	*E.c.2*	*E.c.3*	*E.c.4*	*E.c.5*	*P.a1*	*P.a2*	*P.a3*	*P.a4*	*S.t.*	*K.o.*	*K.a.*	*En.c.1*	*En.c.2*
CPR	0.013	0.007	1.563	0.78	0.78	0.098	0.025	0.013	0.049	0.049	0.025	3.12	1.56	0.78	0.391	0.049	1.56	0.025	3.125	0.013
12	0.049	0.049	25	6.25	12.5	3.125	0.098	0.391	0.195	0.391	0.391	50	50	25	3.125	12.5	25	0.195	50	0.098
13	0.781	0.391	50	25	50	12.5	3.125	6.25	6.25	6.25	6.25	50	50	50	25	6.25	25	3.125	50	3.125
14	0.195	0.195	100	25	50	12.5	6.25	50	1.563	50	50	100	100	100	25	25	100	25	100	6.25
15	0.025	0.049	50	12.5	50	12.5	0.781	1.563	3.125	3.125	1.563	50	50	50	12.5	1.563	6.25	0.781	50	0.781
16	0.098	0.781	3.125	6.25	12.5	3.125	12.5	6.25	6.25	25	25	100	100	100	25	12.5	12.5	25	25	6.25
17	1.563	1.563	100	100	100	100	25	100	12.5	100	50	100	100	100	100	50	100	50	100	25
18	0.049	0.049	50	6.25	25	3.125	0.195	0.391	0.049	0.781	0.391	100	100	12.5	1.563	0.391	6.25	0.781	100	0.098

Abbreviations:CPR:cefpirome,*S.p.1,Streptococcus pyogenes* 308A; *S.p.2,Streptococcus pyogenes* 77A; *S.f.,Streptococcus faecium* MD8b; *S.a.1,Streptococcus aureus* SG511; *S.a.2,Streptococcus aureus* 285; *S.a.3,Streptococcus aureus* 503; *E.c.1,Escherichia coli* 055; *E.c.2,Escherichia coli* DC 0; *E.c.3,Escherichia coli* DC2; *E.c.4,Escherichia coli* TEM; *E.c.5,Escherichia coli* 1507E; *P.a.1, Pseudomonas aeruginosa* 9027; *P.a.2,Pseudomonas aeruginosa* 1592E; *P.a.3,Pseudomonas aeruginosa* 1771; *P.a.4,Pseudomonas aeruginosa* 1771M; *S.t., Salmonella typhimurium*; *K.o.,Klebsiella oxytoca* 1082E; *K.a.,Klebsiella aerogenes* 1522E; *En.c.1,Enterobacter cloacae* P99; *En.c.2,Enterobacter cloacae* 1321E

(300 MHz, DMSO-d_6) δ 9.56(br, 2H), 9.35 (d, 1 H), 8.24 (t, *J*=3 Hz, 1 H), 7.49 (d, *J*=9 Hz, 1 H), 7.17 (br, 2 H), 7.16 (d, *J*=3 Hz, 1 H), 7.12 (t, *J*=9 Hz, 1H), 6.89 (s, 1 H), 5.93 (d, *J*=6 Hz, 2H), 5.04 (d, *J*=6 Hz, 1H), 4.71(m, 1 H), 4.52 (q, 2 H), 4.07(t, 1 H), 3.81(s, 3H), 3.71 (t, *J*=6.6 Hz, 1 H), 3.62(q, 2 H), 3.39 (m, 2 H), 3.01 (m, 4 H), 2.57 (m, 4 H), 1.82 (s, 3 H).

Antibacterial activity

Antibacterial activity of the cephalosporin-oxazolidinone quarternary ammonium salts was determined by an agar dilution method, and are summarized in Table I. All of the compounds did not show any dual antibacterial activity as expected. On the contrary, the activities were much more weaker than the parent cefotaxim and oxazolidinone itself. However, most of compounds show a moderate antibacterial activity against *Streptococcus pyogenes* 308A and 77A strains while the compound **5A**, which is not quaternary ammonium salt, showed best activity against tested pathogens.

RESULTS AND DISCUSSION

Several new cephalosporin-oxazolidinone quaternary ammonium compounds were easily synthesized by the general method with oxazolidinone pharmacophore having amine moiety. The coupling reaction to form quarternary ammonium salt was carried out by the method **A** while the compound **5A** was prepared by the method **B**.

The antibacterial activity of all the compounds was unexpectedly weaker than the parent cefotaxime and oxazolidinones without showing any dual activity character against Gram-positive and Gram-negative strains. It is supposed to be attributed by the big molecular size and strong polarity, and consequently hard to penetrate cell membrane of microorganisms. However, compound **5A**, which is not quarternary salt but *N*-substituted tertiary amine compound with C-3' position of cepha-losporin, showed better acitivity against *Escherichia coli* DC2 than the others due to less polar character of the molecule.

In conclusion, chemical combination of oxazolidinone and cephalosporin antibacterials seems not to be a promising approach for further investigation on new antibacterials.

ACKNOWLEDGEMENTDS

This work was supported by Korea Ministry of Science and Technology, and we would like to thank Ms. Seon Hee Seo for assistance in biological testing.

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