Communications

Synthesis and Antibacterial Activity of 1,8-Naphthyridine Cephalosporins

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Many of the introduced cephalosporins have a common structural figure. They have a 7β-[(Z)-2-(2-aminothiazole-4-yl)-2-alkoxyiminoacetamido] side chain at C-7' position and have monocyclic or bicyclic nitrogen-containing heterocycles at C-3' position.

Recently, C-3' quaternary ammonium cephalosporins such as cepirome (CPR),[1] ceftazidime (CAZ) and cefepime (CEPM)[2] have shown increased activities against both Gram-positive bacteria and Gram-negative bacteria including *Psudomonas aeruginosa*.[3]

Therefore our efforts have been focused on synthesizing C-3' quaternary ammonium cephalosporins with more enhanced antibacterial activities and better pharmacokinetic profiles than "third-generation" antibacterial agents.

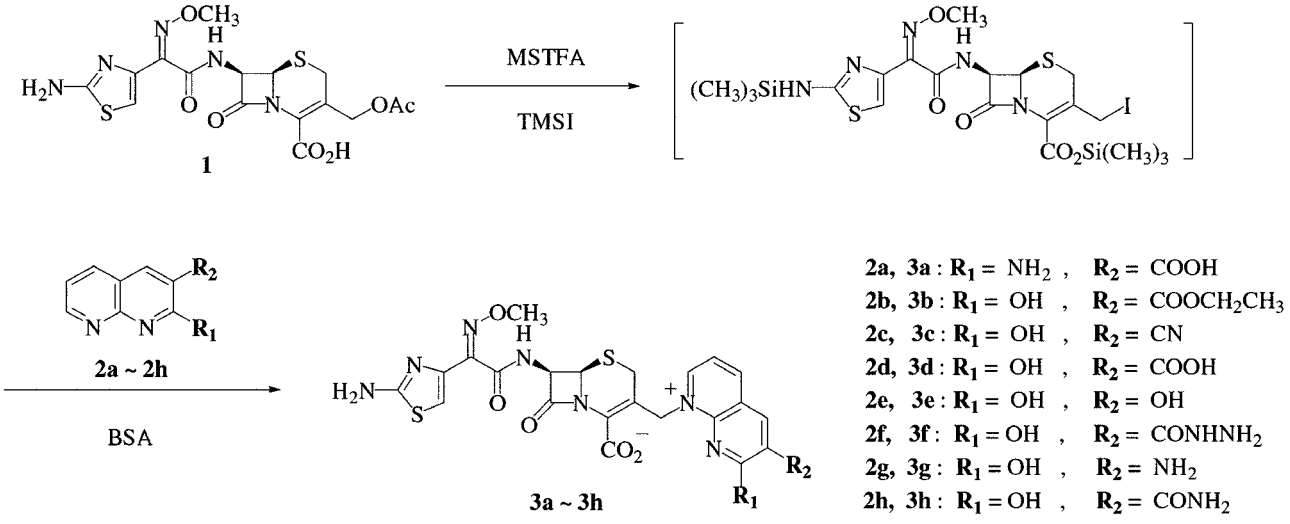
We are interested in substitution at the C-3' position with nitrogen-containing heterocyclic compounds, 1,8-naphthyridine **2**, so we have prepared 1,8-naphthyridine derivatives and a new series of quaternized cephalosporins. In this paper, we wish to describe the synthesis and antibacterial activity of the novel series of cephalosporins having 1,8-naphthyridine moiety at C-3' side chain.

2,3-Disubstituted 1,8-naphthyridine derivatives, **2a-2h**, were prepared either directly by Friedländer reactions, 2-aminonicotinaldehyde with α-methylene compounds using piperidine as catalyst,[4-6] or by subsequent reactions of the bicyclic products.

The quaternary ammonium cephalosporins, 7β-[(Z)-2-(2-aminothiazole-4-yl)-2-methoxyiminoacetamido]-3-[8-(2,3-disubsitituted)-1,8-naphthyridiniummethyl]-3-cephem-4-carboxylic acid inner salt, **3a-3h**, were prepared according to the general method as shown in Scheme 1.[7,8] The silylation of cefotaxime (CTX) **1** was carried out with *N*-methyl-*N*-(trimethylsilyl)trifluoroacetamide (MSTFA) in methylene chloride followed by *in situ* formation of the C-3' iodide with trimethylsilyl iodide (TMSI). The silylated iodo compounds were quaternized with 1,8-naphthyridine **2**, to give products.

The final products, **3a-3h**, were purified by column chromatography using 75% aqueous acetonitrile solution.

The *in vitro* antibacterial activities (MIC, μg/mL) of the new cephalosporins, **3a-3h**, which are against Gram-positive and Gram-negative bacteria were determined by the



Scheme 1. Synthesis of quaternized cephalosporins. Abbreviations: MSTFA, *N*-(methyl)-*N*-(trimethylsilyl)trifluoroacetamide; TMSI, trimethylsilyl iodide; BSA, *N*,*O*-bis(trimethylsilyl)acetamide.

Table 1. *In vitro* antibacterial activity of the cephalosporins. (**3a-3h**)

Compound	MIC (μg/mL)								
	S.a.1	*S.a.2*	*S.p.*	*S.t.*	*E.c.1*	*E.c.2*	*P.a.1*	*P.a.2*	*K.o.*
3a	1.25	0.019	0.019	0.039	0.039	0.075	0.075	0.039	0.019
3b	5	0.075	0.019	0.313	0.156	0.313	0.313	0.039	0.019
3c	2.5	0.075	0.039	0.625	0.313	0.625	0.625	0.039	0.019
3d	2.5	0.075	0.039	0.156	0.039	0.156	0.156	0.039	0.039
3e	5	0.019	0.019	0.075	0.019	0.075	0.313	0.039	0.019
3f	2.5	0.019	0.019	5	0.019	0.313	0.313	0.156	0.039
3g	2.5	0.019	0.019	0.625	0.039	0.075	0.313	0.156	0.019
3h	2.5	0.019	0.019	2.5	0.625	0.156	0.313	0.156	0.075
CAZ	5	2.5	0.313	0.313	0.156	0.313	0.039	0.019	0.019
CTX	1.25	0.019	0.019	0.039	0.039	0.075	0.075	0.039	0.019

Abbreviations: *S.a.1*, *Staphylococcus aureus* KCTC 1928; *S.a.2*, *Staphylococcus aureus subsp. aurues* ATCC 6538P; *S.p.*, *Streptococcus pyrogens* ATCC 21059; *S.t.*, *Salmonella typhimurium* KCTC 1925; *E.c.1*, *Escherichia coli* ATCC 9637; *E.c.2*, *Escherichia coli* KCTC 1923; *P.a.1*, *Pseudomonas aeruginosa* ATCC 15692; *P.a.2*, *Pseudomonas aeruginosa* ATCC 27853; *K.o.*, *Klepsiella oxytoca* ATCC 8724; CAZ, ceftazidime; CTX, cefotaxime.

Mueller-Hinton-agar dilution method.[9,10] The results of MIC test are summarized in Table 1 and it includes those of ceftazidime and cefotaxime for comparison, as well.

Most of the compounds, **3a-3h**, were superior to ceftazidime and comparable to cefotaxime in antibacterial activity against selected Gram-positive bacteria and Gram-negative bacteria. However, They were less active than ceftazidime against *Pseudomonas aeruginosa* ATCC 15692 and *Pseudomonas aeruginosa* ATCC 27853.

Especially the product **3a** possessing 2-amino-1,8-naphthyridine-3-carboxylic acid group showed the best activity against Gram-positive and Gram-negative bacteria and its activity was equal to cefotaxime.

In conclusion, 7β-[(Z)-2-(2-aminothiazole-4-yl)-2-methoxyiminoacetamido]-3-[8-(2,3-disubsitituted)-1,8-naphthyridiniummethyl]-3-cephem-4-carboxylic acid inner salt, **3a-3h**, showed a well-balanced antibacterial spectrum and potent activities against Gram-positive and Gram-negative bacteria. Further studies in this series will be focused on modifying their structure with a broad spectrum of antibacterial activities.

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7. General procedure for **3a**. Cefotaxime (CTX) **1** (500 mg, 1.1 mmol) was suspended in methylene chloride (10 mL) under nitrogen atmosphere. *N*-Methyl-*N*-(trimethylsilyl) trifluoroacetamide (0.8 mL, 4 mmol) was added and the mixture was stirred for 1 hour. The resulting homogeneous solution of cephem trimethylsilyl ester was cooled to 0 ^{o}C and trimethylsilyliodide (0.75 mL, 4.4 mmol) was added. The solution was stirred for 30 minutes and then evaporated *in vacuo* to afford the 3-iodomethyl cephem as a viscous oil. The oily residue was dissolved in acetonitrile (10 mL) and tetrahydrofuran (2 mL). The stirred solution was added, in one portion, to a solution of 2-amino-1,8-naphthyridine-3-carboxylic acid **2a** (196 mg, 1.1 mmol) silylated with *N,O*-bis-(trimethylsilyl)acetamide (1.05 mL, 3.3 mmol) in acetonitrile (10 mL). The reaction mixture was stirred for 3 hours at room temperature and then added to a mixture of methanol (1 mL) and acetonitrile (2 mL) at 0 ^{o}C. The mixture was stirred at 0 ^{o}C for 30 minutes. The precipitated solids were collected by filteration to provide a solid product. Water (10 mL) was added to the solid, and the mixture was neutralized with saturated sodium bicarbonate solution and then concentrated. The residue was purified by column chromatography (eluent : CH_3CN/H_2O = 4/1) over silica gel to give **3a** in 43% yield.
^{1}H-NMR (300 MHz, DMSO-d_6) δ = 6.66 (1H, s), 6.04 (1H, d), 5.80 (1H, q), 5.36-5.01 (2H, ABq), 9.11-8.88 (4H, m), 9.59 (1H, d, J = 8.1 Hz), 7.22 (2H, s), 3.75 (1H, s); ^{13}C-NMR (300 MHz, DMSO-d_6) δ = 165.7, 165.1, 162.9, 162.2, 159.6, 158.7, 155.3, 146.9, 142.7, 140.65, 139.9, 136.7, 135.3, 127.9, 119.1, 114.1, 110.6, 110.1, 108.1, 57.6, 54.0, 52.2; IR (KBr) 3350, 1733, 1676, 1635 cm^{-1}; HRMS (FAB) Calcd for $C_{23}H_{21}N_8O_7S_2$: 585.0975, Found 585.0996.
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