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Synthesis and Antibacterial Activities of Novel C(3)-Aminopyrimidinyl Substituted Cephalosporins Including Against Respiratory Tract Pathogens†

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Abstract—The variety of cephalosporins **1** and **2** which possessed C(3)-aminopyrimidinyl substituents were prepared and evaluated for their antibacterial activities. They exhibited excellent in vitro activities especially against respiratory tract pathogens such as penicillin resistant *Streptococcus pneumonia*, *Moraxella catarrhalis* and *Haemophilus influenza*.

The cephalosporin antimicrobial agents continue to play a major role in the treatment of bacterial infections such as respiratory tract pathogens. Recently, new oral cephalosporin antibiotics with excellent activities against Gram-positive and Gram-negative bacteria such as ceftibutene,[1] cefdinir,[2] and FK041[3] have been developed and introduced to clinical practice. However most of the cephalosporin antibiotics are no longer available against respiratory tract infections due to resistance problems, especially caused by penicillin-resistant *Streptococcus pneumonia* (*PRSP*).[4] In a previous paper,[5] we described the synthesis and antibacterial activities of cephalosporins which possess ((aminopyrimidiniumyl or aminopyrimidinyl)thio)methyl group at the 3-position of cephem nucleus. Those compounds exhibited good activities against Gram-negative strains, but showed moderate activities against Gram-positive bacteria. We wish to synthesize new cephalosporins which have not only a broad spectrum of antibacterial activities, but also excellent activities against major respiratory tract community pathogens such as *PRSP, H. influenza* and *M. catarrhalis*. A new class of cephalosporins bearing C(3)-aminopyrimidinyl substituents was found to exhibit well balanced activities against Gram-positive and Gram-negative bacteria including the above major respiratory tract pathogens. Thus, we have prepared a series of novel compounds which possess the aminopyrimidinyl group at the 3-position of cephem nucleus (Figs. 1 and 2). We report herein the synthesis of these compounds and their antimicrobial activities.

Chemistry

The compounds **1** from 3-methanesulfonylcephalosporin **3** and aminothiazole **6** were prepared as follows (Scheme 1). The synthesis of the amine **5** started from the 3-methanesulfonylcephalosporin **3**. The amine **3** was treated with substituted pyrimidinethiols at −60 °C, then warmed-up to ambient temperature for 8 h to produce 3-thiopyrimidine **4**. The diphenylmethyl group at the C-4 position of the compound **4** was removed by trifluoroacetic acid (TFA) and anisole to afford the amine **5**. The C-5 chlorination of aminothiazole ring in compound **6** with *N*-chlorosuccinimide, protection of amine to *t*-butyl carbamate, hydrolysis of ethyl ester using sodium hydroxide and finally tritylation of hydroxylamine produced the acid **7**. When X = CH, no chlorination step was needed. Also when the R group was propargyl, alkyloxime was prepared by the addition of propargyl bromide instead of using trityl chloride. The activated ester **8** was synthesized from the acid **7** by the addition of diethyl chlorothiophosphate in the presence of triethylamine. Coupling of the amine **5** and the activated ester **8** was carried out with treatment of *N,O*-bistrimethylsilylacetamide and pyridine in dichloromethane to give the coupled product **9**, which was treated

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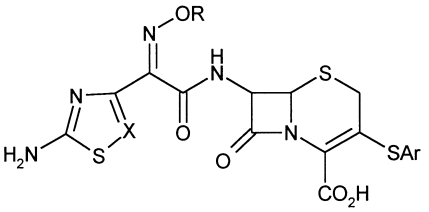

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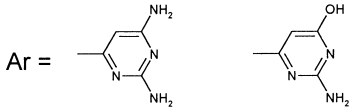
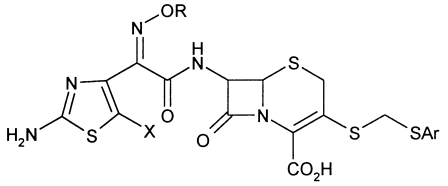


A B

Compounds	R	X	Ar	Compounds	R	X	Ar
1a	Me	CH	A	**1e**	Et	N	A
1b	H	CH	A	**1f**	H	CHCl	A
1c	Propargyl	CH	A	**1g**	H	CHCl	B
1d	Et	CH	A	**1h**	H	CH	B

Figure 1.



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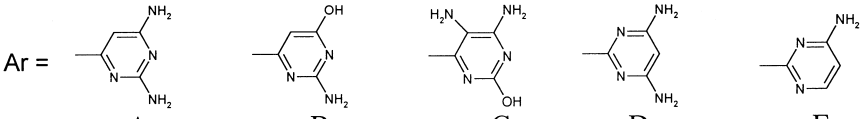


A B C D E

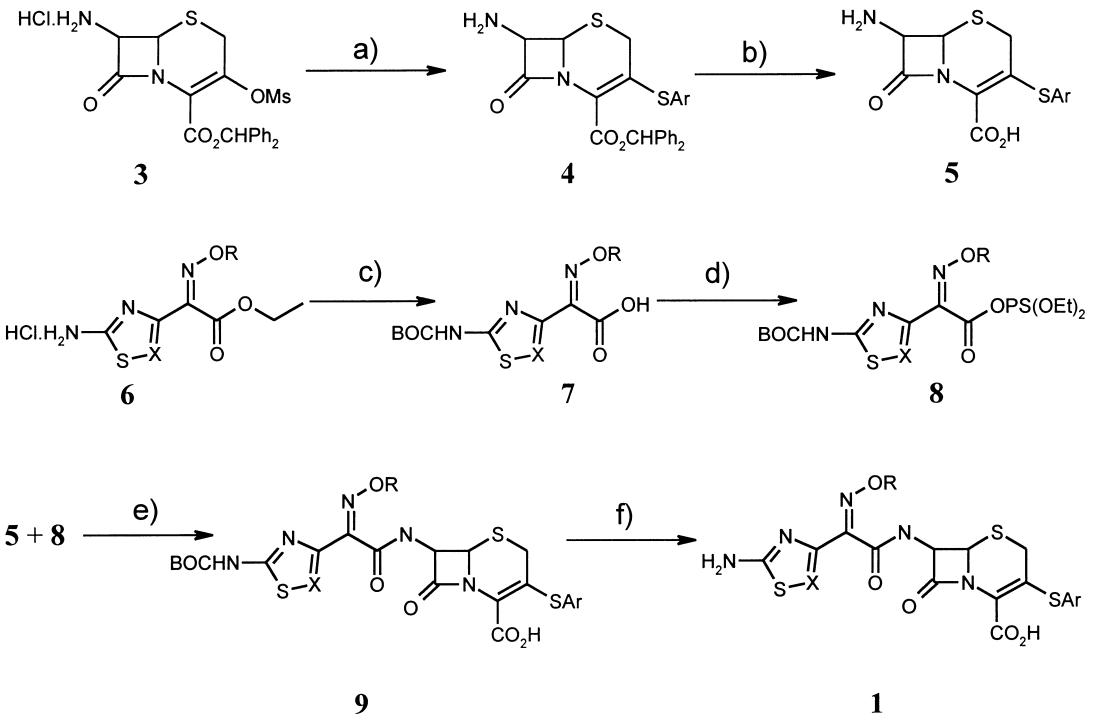
Compounds	R	X	Ar	Compounds	R	X	Ar
2a	H	H	A	**2e**	H	Cl	C
2b	Me	H	A	**2f**	H	H	D
2c	H	Cl	A	**2g**	H	Cl	E
2d	H	Cl	B	**2h**	H	Cl	D

Figure 2.

with TFA and anisole to afford the final products **1**. Nucleophiles shown in Figure 1 were prepared using the methods presented in the previous papers.[6a,b] Spectral data for the cephalosporin **1a** are given below.

Spectra for **1a**: IR (Nujol) 1770 cm^{-1} (carbonyl on β-lactam ring); ^1H NMR (δ, D_2O) 3.68 (ABq, 2H, $J=17.6$ Hz), 4.08 (s, 3H), 5.41 (d, 1H, $J=4.9$ Hz), 5.81 (d, 1H, $J=4.9$ Hz), 5.85 (s, 1H), 7.02 (s, 1H); Mass (FAB, m/e) 523.

The compounds **2** from the 3-hydroxycephalosporin **10** and the aminothiazole **12** were prepared as follows (Scheme 2). The synthesis of the 3-acetate **11** started from the commercially available 3-hydroxycephalosporin **10**.[7] The enol ester **10** was treated with chlorodiphenylphosphate and thiolacetic acid to afford, after removal of phenylacetyl group, the amine **11**. The C-5 chlorination of the aminothiazole ring in compound **12** with *N*-chlorosuccinimide, protection of amine to *t*-butyl carbamate, hydrolysis of ethyl ester using sodium hydroxide and finally tritylation of hydroxylamine produced the acid **13**. When X = H in **13**, no chlorination step was needed. Also when R = Me, no tritylation step was required. The acid **13** was added to the amine **11** and pyridine at −20 °C, then the subsequent addition of phosphorous oxychloride ($POCl_3$) afforded the coupling product **14**. A one-pot sequential hydrolysis/alkylation of compound **14** gave C-3 chloromethylthio cephalosporin, which was displaced with nucleophiles (pyrimidinethiols) in DMF to furnish the compound **15**. Finally, removal of the protecting groups with trifluoroacetic acid (TFA) and anisole afforded the



Scheme 1. (a) Substituted aminopyrimidine A or B, THF, DMF, −60 °C to RT; (b) TFA, anisole, 0 °C to RT; (c) (1) when R = Me or Et, X = H; BOC_2O, DMAP; NaOH, H_2O, EtOH, (2) when R = propargyl, X = H; BOC_2O, DMAP, CH_2Cl_2; NaOH, H_2O, EtOH; propargyl bromide, K_2CO_3, DMF, (3) when R = H, X = H; BOC_2O, DMAP, CH_2Cl_2; NaOH, H_2O, EtOH; TrCl, K_2CO_3, DMF, (4) when R = H, X = Cl; *N*-chlorosuccinimide, DMF; BOC_2O, DMAP, CH_2Cl_2; NaOH, H_2O, EtOH; TrCl, K_2CO_3, DMF; (d) diethyl chlorothiophosphate, Et_3N, CH_2Cl_2, 0 °C to 40 °C; (e) *N,O*-bistrimethylsilylacetamide, pyridine, CH_2Cl_2, **7**, 0 °C to 10 °C; (f) TFA, anisole, 0 °C to RT.

cephalosporins **2**. Nucleophiles shown in Figure 2 were prepared by the methods presented in the previous papers.[5,6b,8a,b] Spectral data for the cephalosporin **2c** are given below.

Spectra for **2c**: IR (Nujol) 1765 cm^{-1} (carbonyl on β-lactam ring); ^1H NMR (δ, D_2O) 3.73 (ABq, 2H, $J = 17.3$ Hz), 4.42 (ABq, 2H, $J = 14.0$ Hz), 5.21 (d, 1H, $J = 4.6$ Hz), 5.87 (d, 1H, $J = 4.6$ Hz), 6.04 (s, 1H); Mass (FAB, m/e) 589.

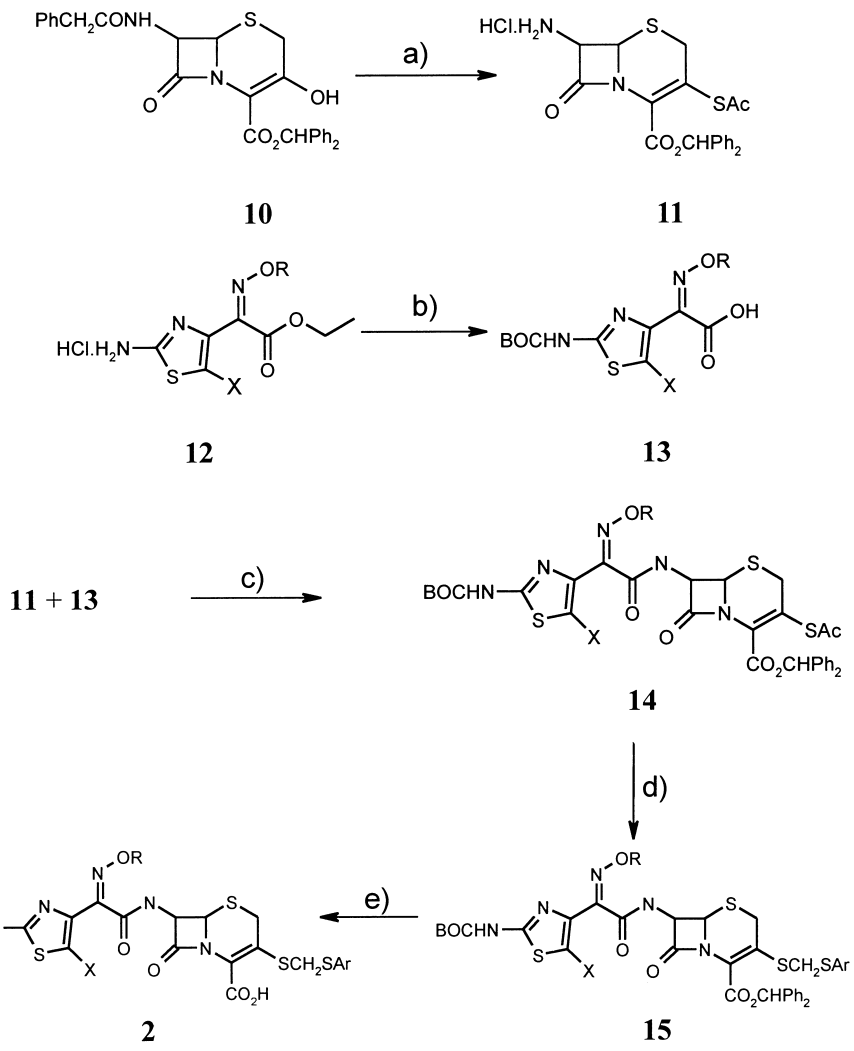
Antibacterial Activities and Discussion

Agar dilution method was used to determine the minimal inhibitory concentration (MIC) of compounds against selected organisms. The MIC values for cefdinir against the same strains are shown for comparison. This series of new C-3-substituted cephalosporins exhibited comparable antibacterial activities to cefdinir against the Gram-positive bacteria such as methicillin resistant *S. aureus* and against Gram-negative organisms including *E. coli*. In general, the cephalosporins **2** showed better activities in *S. aureus* and *E. faecalis* compared to the cephalosporins **1**. When *M. catarrhalis* 25240 was employed in cephalosporins **2**, all of the in vitro antibacterial activities (MIC) of compounds **2** were 0.008 μg/mL or less. Most of the compounds in Table 1 showed much better antibacterial activities in the respiratory tract pathogens, *PRSP*, *M. catarrhalis* and *H. influenza*, than those of the reference (cefdinir). It is worthwhile to note that the compounds **1** series showed

Table 1. Antibacterial activities of cephalosporins **1** (MIC, μg/mL)[a]

Compounds	*S.a.*1	*S.a.*2	*E.f.*	*E.c.*	*K.p.*	*P.v.*	*S.p.*	*M.c.*	*H.i.*
1a	0.5	4	>64	0.031	0.5	0.016	0.5	<0.008	0.016
1b	0.25	2	8	0.031	1	0.031	0.5	<0.008	0.13
1c	0.5	4	32	0.13	2	0.031	0.25	0.016	0.031
1d	0.5	4	64	0.13	2	0.063	0.5	<0.008	0.063
1e	1	4	64	0.063	2	0.063	0.25	<0.008	0.13
1f	0.25	2	2	0.25	2	0.5	1	<0.008	0.5
1g	0.25	2	8	0.063	1	0.063	0.5	nd[b]	0.016
1h	0.5	4	4	0.5	8	0.5	1	<0.008	1
Cefdinir	0.063	4	8	0.031	0.13	0.031	4	0.016	0.5

[a]*S.a.*1, *Staphylococcus aureus giorgio*, methicillin susceptible; *S.a.*2, *Staphylococcus aureus* 77, methicillin resistant; *E.f.*, *Enterococcus faecalis* 29212; *E.c.*, *Escherichia coli* 3190Y; *K.p.*, *Klebsiella pneumonia* 2011E; *P.v.*, *Proteus vulgaris* 6059; *S.p.*, *Streptococcus pneumonia* PN010, penicillin resiatant; *M.c.*, *Moraxella catarrhlis* 25240; *H.i.*, *Haemophilus influenza* HIN003, beta-lactamase producing resistant strain.
[b]nd, not detected.



Scheme 2. (a) $ClP(O)(OPh)_2$, Hunig's base, MeCN; AcSH, triethylamine, MeCN; PCl_5, pyridine, then isobutyl alcohol, $-10\sim-15\,^{\circ}C$; (b) (1) when R = Me, X = H; BOC_2O, DMAP; NaOH, H_2O, EtOH, (2) when R = H, X = H; BOC_2O, DMAP; NaOH, H_2O, EtOH; TrCl, K_2CO_3, DMF, (3) when R = H, X = Cl; *N*-chlorosuccinimide, DMF; BOC_2O, DMAP; NaOH, H_2O, EtOH; TrCl, K_2CO_3, DMF; (c) pyridine, $POCl_3$, CH_2Cl_2, $-20\,^{\circ}C$; (d) ICH_2Cl, morpholine, pyridine, PhH, DMF, $-20\,^{\circ}C$; NaI, DMF, aryl thiol; (e) TFA, anisole, $0\,^{\circ}C$ to RT.

4 to 16 times better activities against *PRSP* compared to that of cefdinir. Oxime-substituted **1a, 1c–e** and unsubstituted **1b** cephalosporins having 2,6-diaminopyrimine at C-3 exhibited similar potency against both Gram-positive and Gram-negative bacteria including *respiratory tract pathogens*. When 2-amino-4-hydroxy substituted pyrimidine at C-3 was employed, the antibacterial activities against *PRSP* and *H. influenza* were better in 5-chloro-substituted aminothiazole **1g** than in 5-H aminothiazole **1h**. Overall, most of the compounds **1** displayed much better antibacterial activities against penicillin resistant *S. pneumonia, M. caterrhalis* and *H. influenza* than those of the cefdinir.

In general, the compounds **2a**–**2d** (4-pyrimidinethiol substituents) in Table 2 showed better antibacterial activities than those of the cephalosporins **2e**–**2g** (2-pyrimidinethiol substituents). This series of new C-3 substituted cephalosporins exhibited good antibacterial activities against Gram-positive bacteria such as *S. aureus* including methicillin resistant *S. aureus*. It is worthwhile to note that the compounds **2a,c,d** showed excellent activity against *E. faecalis* compared to that of cefdinir. The compounds **2c–e,g,h** which possessed 5-chloro (X = Cl) in aminothiazole ring showed lack of efficacy in Gram-negative bacteria such as *Klebsiella pneumonia* and *Proteus vulgaris* compared to **2a,b,f** which had 5-H (X = H) in the aminothiazole ring. However **2c–e,g,h** exhibited good and balanced activities against respiratory tract pathogens, *PRSP*, *H. influenza* and *M. catarrhalis*, compared to the cephalosporins **2a,b,f**. Among those five compounds, **2c** and **2d** showed the most balanced antibacterial activities against both Gram-positive and Gram-negative bacteria including *PRSP*, *H. influenza* and *M. catarrhalis*. Some of the compounds shown in Table 2 exhibited good pharmacokinetic value and bioavailability. In particular, the compound **2c** showed excellent oral absorption (C_{max} ~13.8 μg/mL) and half life (139 min) in rats (20 mg/kg administration). Based on the MIC value and the pharmacokinetic data, the compound **2c** proved that this compound deserves further evaluation for new oral antibiotics especially against respiratory tract pathogens.

Table 2. Antibacterial activities of cephalosporins **2** (MIC, μg/mL)[a]

Compounds	*S.a.*1	*S.a.*2	*E.f.*	*E.c.*	*K.p.*	*P.v.*	*S.p.*	*M.c.*	*H.i.*
2a	0.13	1	1	0.031	0.5	0.031	0.5	2	0.5
2b	0.25	4	64	0.063	0.5	0.016	0.13	0.5	1
2c	0.13	1	1	0.25	1	0.25	0.25	0.13	0.5
2d	0.13	1	1	0.25	2	0.13	0.5	0.063	0.031
2e	0.5	4	4	0.25	1	0.25	2	0.13	0.016
2f	0.13	1	4	0.063	0.5	0.031	1	1	1
2g	0.25	2	2	1	8	0.5	1	0.5	0.25
2h	0.5	4	4	1	8	1	1	0.13	0.016
Cefdinir	0.063	4	8	0.031	0.13	0.031	4	0.5	0.5

[a]*S.a.*1, *Staphylococcus aureus giorgio*, methicillin susceptible; *S.a.2*, *Staphylococcus aureus* 77, methicillin resistant; *E.f., Enterococcus faecalis* 29212; *E.c., Escherichia coli 3190Y; K.p., Klebsiella pneumonia* 2011E; *P.v., Proteus vulgaris* 6059; *S.p., Streptococcus pneumonia* PN010, penicillin resistant; *M.c., Moraxella catarrhalis* MCA027, beta-lactamase producing resistant strain; *H.i., Haemophilus influenza* HIN003, beta-lactamase producing resistant strain.

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