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Synthesis and Antibacterial Activities of Novel C(3)-Aminopyrimidinyl Substituted Cephalosporins

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Cephalosporins have been widely used for treating diseases caused by pathogenic bacteria in human. However most of the cephalosporin antibiotics are no longer useful against respiratory tract infections due to the resistance problems, especially, caused by penicillin-resistant *Streptococcus pneumoniae* (PRSP).[1]

In the previous paper,[2,3] we described the synthesis and antibacterial activities of cephalosporins which possess aminopyrimidiniumyl, or pyrimidiniumyl group at the 3-position of cephem nucleus. Those compounds exhibited well balanced activities against Gram-positive and Gram-negative bacteria, but showed moderate activities against respiratory tract pathogens. As a part of our research program on new cephalosporins possessing improved antibacterial activities against respiratory tract pathogens such as PRSP, *H. influenzae* and *M. catarrhalis* while maintaining potent antibacterial activities against Gram-positive and Gram-negative strains, we introduced vinyl spacer at the C-3 position of cephem nucleus and thus synthesized a new series of cephalosporins with a C(3)-substituted aminopyrimidinyl group. Thus, we have prepared a series of novel compounds which possess pyrimidinyl group at the 3-position of cephem nucleus (Figure 1). We report herein the synthesis of these compounds and their antimicrobial activities.

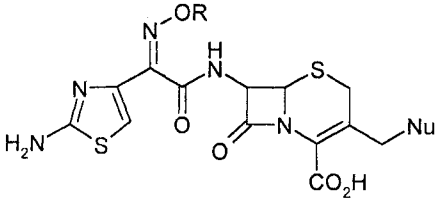
Chemistry

The compounds **1** from acid **3** and *p*-methoxybenzyl 7-amino-3-chloromethyl-3-cephem-4-carboxylate (7-ACLE) **4** were prepared as follows (Scheme 1). The acid **3** was added to the methylene chloride solution containing 7-ACLE and pyridine at −20°C, then phosphorous oxychloride ($POCl_3$) was added to the solution to afford the coupling product **5**. Then the chloride **5** was displaced with nucleophiles (pyrimidinylthiol group) in DMF. Finally, removal of the protecting groups with trifluoroacetic acid (TFA) and anisole afforded the cephalosporins **1**. Nucleophiles shown in Figure 1 were prepared by the methods presented in the previous papers.[3,4] Spectral data for the cephalosporin **1d** is given below.

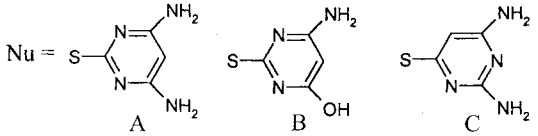
Spectra for **1d**: IR (nujol) 1770 cm^{-1} (carbonyl on β-lactam ring); ^1H NMR (δ, D_2O) 3.29 (ABq, 2H, J= 15.1 Hz), 4.07 (ABq, 2H, J=13.5 Hz), 4.96 (d, 1H, J= 2.5 Hz), 5.37 (s, 1H), 5.42 (s, 1H), 5.62 (d, 1H, J=2.5 Hz), 6.81 (d, 1H, J=7.8 Hz), 6.91 (d, 1H, J=7.8 Hz), 7.01 (s, 2H); FAB-MS m/z 563 $(M+H)^+$.

The compounds **2** were prepared from chloride **5** *via* allyl chloride **6** (Scheme 2). After preparation of Wittig reagent by treatment of triphenylphosphine and sodium iodide to the chloride **5**, ylide was prepared by using 1 N sodium hydroxide. Reaction of the ylide with the chloroacetaldehyde afforded (*Z*)-propenyl chloride **6**. Then the allyl chloride **6** was first replaced with iodide to produce (*E*)-propenyl iodide[5] and the (*E*)-iodide was displaced with nucleophiles (aminopyrimidines) in DMF. Finally, removal

Fig. 1.



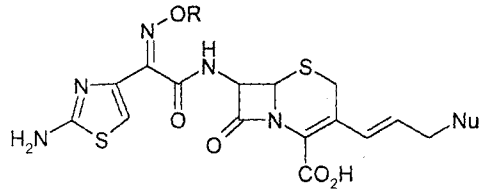
1



No	R	Nu
1a	H	A
1b	H	C
1c	propargyl	C
1d	allyl	C
1e	CH_2CN	C
1f	CH_2CH_2F	C
1g	CH_2OCH_3	C
1h	imidazolyl-4-methyl	C
1i	Me	C
1j	Me	B

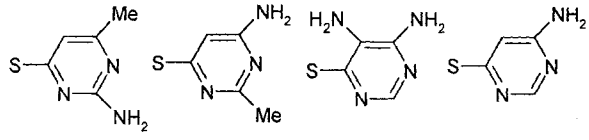
For thiol C: purchased from Aldrich Co.

Fig. 2. Novel C-3-substituted cephalosporins **2** with various C-3 substituents.



2

Nu =

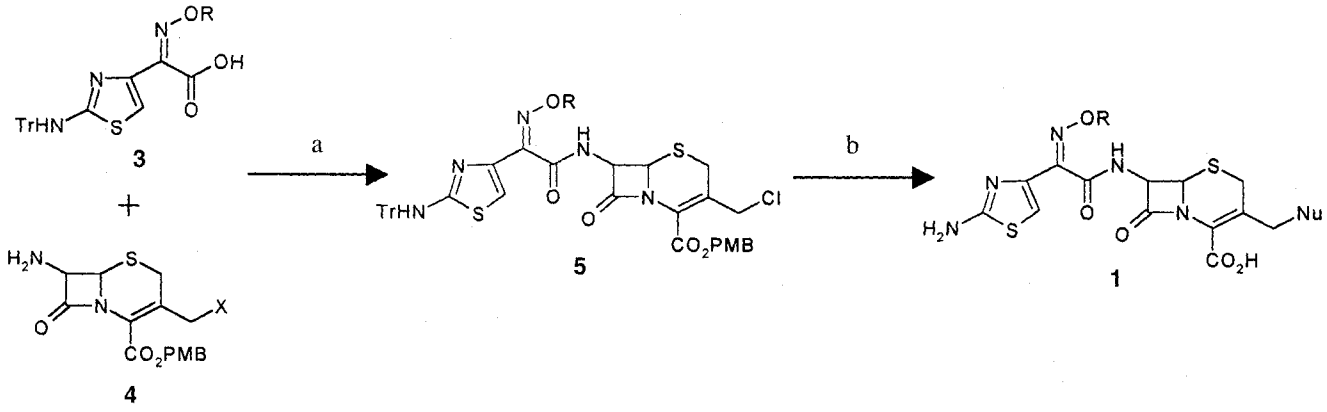


D E F G

No	R	Nu
2a	Me	D
2b	Me	E
2c	Me	F
2d	Me	C
2e	Ethyl	C
2f	Propargyl	G
2g	Propargyl	E
2h	Propargyl	D
2i	Propargyl	F
2j	Propargyl	C

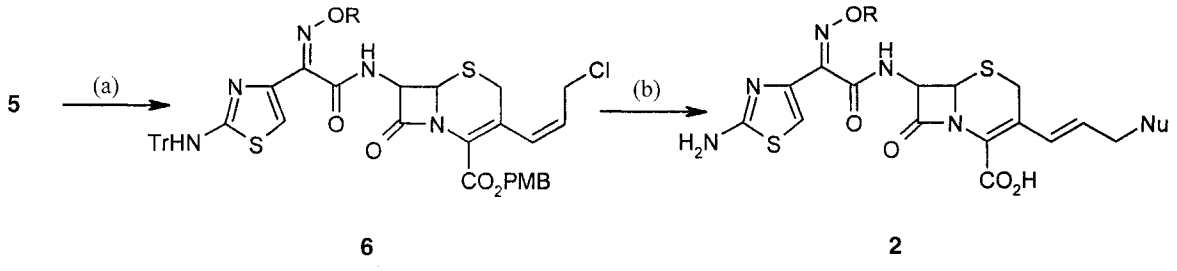
For thiol C: See Figure 1

Scheme 1.



a) Pyridine, $POCl_3$, −20°C; b) NaI, Nucleophiles; CF_3CO_2H, Anisole

Scheme 2.



6 2

a) PPh_3, NaI; 1 N NaOH; $ClCH_2CHO$; b) NaI, Nucleophiles; CF_3CO_2H, Anisole
R=Methyl, ethyl, or propargyl, Tr=triphenylmethyl, PMB=*p*-methoxybenzyl

Table 1. Antibacterial activities of cephalosporins **1** (MIC, μg/ml).

Compound	*S.a.1*	*S.a.2*	*E.c.1*	*E.c.2*	*K.p.*	*P.v.*	*S.p.*	*M.c*	*H.i.*
1a	0.25	8	0.031	2	0.25	0.13	4	0.031	0.5
1b	0.13	2	0.031	2	0.13	0.063	2	0.031	0.25
1c	0.25	4	0.063	4	0.5	0.063	0.5	0.016	0.031
1d	0.25	4	0.063	4	1	0.13	0.25	0.016	0.016
1e	0.5	4	0.063	4	0.25	0.063	1	0.016	0.063
1f	0.5	4	0.063	2	0.5	0.063	0.5	<0.008	0.016
1g	0.5	4	0.063	8	0.5	0.063	1	0.016	0.031
1h	0.5	4	0.031	2	0.13	0.031	0.5	<0.008	0.031
1i	0.5	4	0.063	4	0.25	0.063	2	0.016	0.063
1j	2	16	0.031	8	0.13	0.063	4	0.031	0.25
CDN	0.063	4	0.031	2	0.13	0.031	4	0.016	0.5

Abbreviations: *S.a.1*, *Staphylococcus aureus giorgio*, methicillin susceptible; *S.a.2*, *Staphylococcus aureus* 77, methicillin resistant; *E.c.1*, *Escherichia coli* 3190Y; *E.c.2*, *Escherichia coli* TEM3 3455E; *K.p.*, *Klebsiella pneumoniae* 2011E; *P.v.*, *Proteus vulgaris* 6059; *S.p.*, *Streptococcus pneumoniae* PN010, penicillin resiatant; *M.c.*, *Moraxella catarrhalis* 25240; *H.i.*, *Haemophilus influenzae* HIN003, beta-lactamse producing strain; CDN, cefdinir

of the protecting groups with trifluoroacetic acid (TFA) and anisole afforded the cephalosporins **2**. Nucleophiles shown in Figure 2 were prepared by the methods presented in the previous papers.[6,7] Spectral data for the cephalosporin **2d** are given below.

Spectra for **2d**: IR (nujol) 1770 cm^{-1} (carbonyl on β-lactam ring); ^1H NMR (δ, D_2O) 3.53 (ABq, 2H, J= 15.0 Hz), 3.70 (m, 2H), 4.00 (s, 3H), 5.22 (d, 1H, J= 2.5 Hz), 5.81 (d, 1H, J=2.4 Hz), 6.02 (m, 1H), 6.72 (d, 1H, J=7.8 Hz), 7.00 (s, 1H); FAB-MS *m/z* 563 $(M+H)^+$.

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. In general, most of the compounds in Table 1 showed better antibacterial activities than those of the reference (cefdinir). This series of new C-3-substituted cephalosporins exhibited good antibacterial activities against Gram-positive bacteria such as *S. aureus* and excellent activities against Gram-negative organisms including *E. coli*. It is worthwhile to note that the compounds **1** having C-3 pymidinylthio methyl group showed excellent activity (MIC; 0.031~0.13) against *M. morganii* compared to that of cefdinir (MIC; 8). Oxime-substituted cephalosporins **1c~h** except methyl-substituted compounds **1i** and **1j** exhibited similar potency against

Table 2. Antibacterial activities of cephalosporins **2** (MIC, μg/ml).

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

Abbreviations: See footnote in Table 1.

Gram-positive and negative bacteria including *M. catarrhalis* to the compounds **1a**- and **1b**-unsubstituted oxime. However the antibacterial activities against penicillin resistant *S. pneumoniae* and *H. influenzae* of the compounds **1c**~**h** exhibited much better activities than those of the compounds **1a** and **1b**. Among these series of compounds, cephalosporins **1c** (propargyloxime), **1d** (allyloxime), **1f** (fluoroethyl) and **1h** (imidazolyl-4-methyl) exhibited the most balanced antibacterial activity profiles against the major respiratory tract pathogens including PRSP. Overall, the compounds **1c**~**h** displayed much better antibacterial activities against penicillin resistant *S. pneumoniae* and *H. influenzae* than those of the cefdinir, but gave comparable activities against *M. catarrhalis* compared to cefdinir.

The compounds **2** in Table 2 showed well balanced activities against both Gram-positive and Gram-negative strains including major respiratory tract pathogens. In general, cephalosporins **2** series showed similar activities to the cephalosporins **1**, but demonstrated much better activities against PRSP which is the most important pathogens in community acquired respiratory tract pathogens. The compounds **2** displayed much better antibacterial activities against penicillin resistant *S. pneumoniae* and *H. influenzae* than those of the cefdinir, but gave comparable activities against *M. catarrhalis* compared to cefdinir. When R group was substituted on the oxime with methyl (**2a**~**2d**), the overall antibacterial activities against most of the strains were similar. The results are the same in the case of propargyl-substituted cephalosporins (**2f**~**2j**). Substitution on oxime with different kinds of alkyl group (methyl, ethyl, propargyl) also gave similar antibacterial activities against most of the strains. When the aminopyrimidinethiols were compared, the antibacterial activities of 2-amino-4-methyl-6-thio-compounds (**2a**, **2h**) against one of the most important strain, PRSP, were better than those of 2-methyl-4-amino-6-thio-compounds (**2b**, **2g**). It is worthwhile to note that the compound **2d** bearing methyl-substituted oxime was significantly more active than the compound **2e** which contain the ethyl on the oxime against Gram-negative strains. Among these series of compounds, cephalosporins with 2-amino-4-methyl-6-thio-moiety **2a** and **2h** exhibited the most balanced antibacterial activity profiles.

In conclusion, 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 PRSP, *H. influenzae* and *M. catarrhalis*. The MIC data on the compounds **1c**, **1d**, **1f**, **1h**, **2a** and **2h** proved that these compounds deserve further evaluation for new antibiotics against respiratory tract pathogens.

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