Novel Cephalosporins Having a Benzothiopyran Group 1. Synthesis and Antibacterial Activity of Cephalosporin Derivatives Characterized by Novel C-3 Substituents of Benzothiopyran

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In recent years, a number of cephalosporin antibiotics having a broad spectrum and resistance to β-lactamase have been developed.[1] They have a heterocyclic group and 7β-[2-(2-aminothiazol-4-yl)-(*Z*)-2-alkoxyiminoacetamido]group at 3-position and 7-position of cephalosporin nucleus, respectively, but show weak or moderate antibacterial activity against Gram-positive bacteria including *Staphylococcus aureus* and *Enterococcus faecalis*.

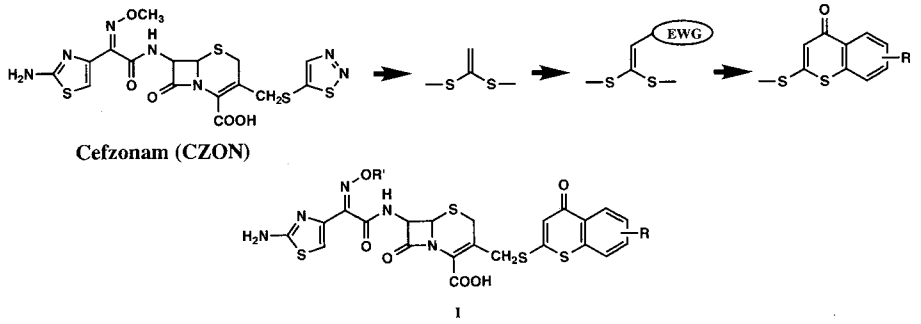
The following were suggested from the structure-activity relationships in the past reports: 1) C-3 side chains involving a ketene dithioacetal moiety provide good anti Gram-positive bacterial activity, as exemplified by cefuzonam (CZON)[2] and 2) electron-withdrawing group linking to C-3 position of cephalosporin nucleus enhance reactivity of β-lactam ring, thus, leading to rise in antibacterial activity.[3~6] These led us consider that the 2-position of 4-oxo-4*H*-1-benzothiopyran nucleus attached to the 3-position of the cephalosporin nucleus through a thiomethyl linkage would be effective in strengthening the activity against both of Gram-positive and Gram-negative bacteria (Fig. 1). Therefore, we designed a novel series of 7β-[2-(2-aminothiazol-4-yl)-(*Z*)-2-alkoxyiminoacetamido]cephalosporins having a 4-oxo-4*H*-1-benzothiopyran-2-ylthiomethyl group at the C-3 position, which bore keten dithioacetal system and α,β-unsaturated ketone system as electron-withdrawing group.

In this paper, we describe the synthesis and antibacterial activity of a novel series of cephalosporins having 4-oxo-4*H*-1-benzothiopyran-2-ylthiomethyl group as C-3 side chain represented by formula **I** (Fig. 1).

Chemistry

The typical procedure is shown in the Scheme 1. Treatment of the sulfoxide (**II**)[7] with the mercaptan (**III**)[8,9] afforded the 3-substituted cephem. After reduction of sulfoxide by PBr_3, the protecting groups of **IV** were removed by treatment with TFA in the presence of anisole to give the desired novel cephalosporins. **1**: ^{1}H NMR (CD_3OD) δ 3.43 (1H, d, J=18 Hz), 3.77 (1H, d, J=18 Hz), 3.96 (3H, s), 4.10 (1H, d, J=13 Hz), 4.70 (1H, d, J=13 Hz), 5.08 (1H, d, J=5 Hz), 5.75 (1H, d, J=5 Hz), 6.83 (1H, s), 7.05 (1H, s), 7.54~7.73 (2H, m), 7.75 (1H, d, J=8 Hz), 8.38 (1H, dd, J=1 and 8 Hz); IR (KBr) cm^{-1} 1765, 1603, 1530; FAB-MS *m/z* 612 $(M+H)^+$.

Fig. 1.



Scheme 1.

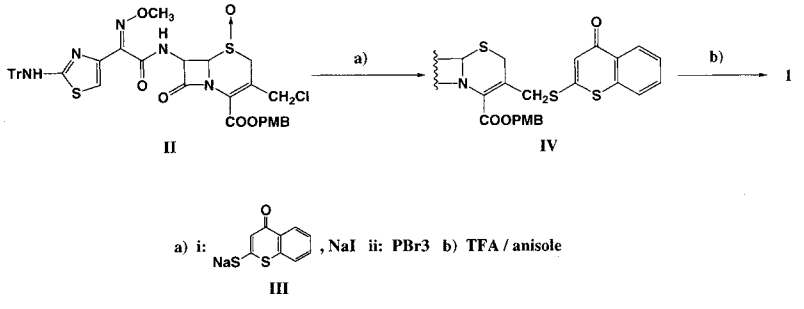
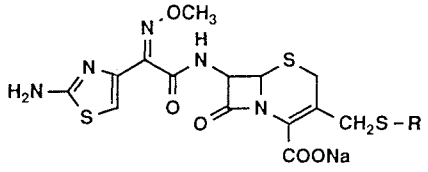
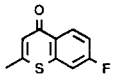
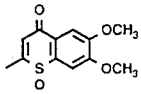
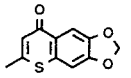
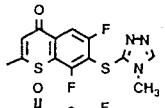
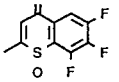
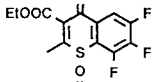
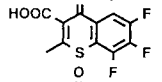
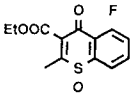
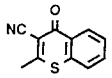


Table 1. *In vitro* antibacterial activity (MIC, μg/ml) of 2-aminothiazol-4-yl-2-(*Z*)-methoxyimino derivatives (**1**～**10**).



Compound No.	R	*S. a.* 209P JC-1	*S. p.* IID692	*E. f.* IID682	*E. c.* NIHJ JC-2	*P. v.* IFO3167	*P. a.* V-1
1		0.10	≤0.0063	12.5	≤0.0063	≤0.0063	3.13
2		0.10	≤0.0063	6.25	≤0.0063	0.025	6.25
3		0.39	≤0.0063	50	0.20	0.10	50
4		0.10	≤0.0063	12.5	0.0125	0.025	12.5
5		0.39	0.025	50	0.05	0.10	25
6		0.20	≤0.0063	25	0.025	0.025	6.25
7		0.39	0.0125	100	0.10	0.39	25
8		6.25	0.05	>100	0.78	0.0125	>100
9		0.39	≤0.0063	25	0.05	0.20	25
10		12.5	0.05	>100	0.05	0.20	25

Abbreviations: *S.a., Staphylococcus aureus*; *S.p., Streptococcus pyogenes*; *E.f., Enterococcus faecalis*; *E.c., Escherichia coli*; *P.v., Proteus vulgaris*; *P.s., Pseudomonas aeruginosa.*

Biological Results and Discussion

The antibacterial activities (MICs) were determined by the standard serial 2-fold agar dilution method using Mueller-Hinton agar against selected organisms.

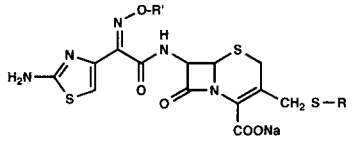
Table 1 summarizes the antibacterial activities of 7β-[2-(2-aminothiazol-4-yl)-(*Z*)-2-methoxyiminoacetamido]-3-(4-oxo-4*H*-1-benzothiopyran-2-yl)thiomethyl-3-cephem-4-carboxylates. Among the compounds, **1**, **2**, **4** and **6** were highly active against Gram-negative and Gram-positive bacteria including *E. faecalis*. This activity was higher than those of **3** and **5**. These data suggested that the introduction of bulky substituents in the benzothiopyran ring resulted in the reduction of the antibacterial activity against Gram-positive and also Gram-negative bacteria.

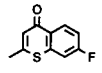
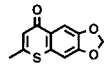
The introduction of electron-withdrawing group to the 3-position of 4-oxo-4*H*-1-benzothiopyran nucleus (**7**, **8**, **9** and **10**) exerted no enhancing effect on the antibacterial activity, although their molecular design was based on the electron-withdrawing effect.The activity of simplified compounds (**1** and **2**) was found to be superior to that of another cephalosporin derivatives bearing substituents on the benzothiopyran ring.

Table 2 shows the effect of the oxime substituent (R′) in a novel cephalosporin on the MIC. The hydroxyimino analogs (**11**, **12** and **15**) were 2- to 4-fold more active against Gram-positive organisms than corresponding methoxyimino analogs. Especially, **11**, **12** and **15** exhibited excellent and moderate antibacterial activity against Gram-positive bacteria including *E. faecalis* and Gram-negative bacteria. It was characteristic that they showed excellent antibacterial activity against *E. faecalis* as compared with other general cephalosporins. The carboxylic acid analogs **13** and **14** were 2- to 10-fold less active than methoxy analog (**2**) against most bacteria except *Proteus vulgaris*.

A comparison of the 4-oxo-4*H*-1-benzothiopyran with another heterocyclic ring system for the activities was indicated in Table 3. The compound **1** was more active than the 4-oxochromen-2-yl group (**16**) and the 4-oxo-3*H*-quinazolin-2-yl group (**17**) against Gram-positive bacteria and Gram-negative bacteria, especially 2- to

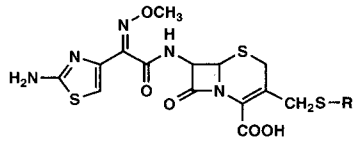
Table 2. *In vitro* antibacterial activity (MIC, μg/ml) of 2-aminothiazol-4-yl-2-(*Z*)-alkoxyimino derivatives.

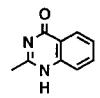
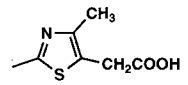


No.	Compound R	R'	*S. a.* 209P JC-1	*S. p.* IID692	*E. f.* IID682	*E. c.* NIHJ JC-2	*P. v.* IFO3167	*P. a.* V-1
11		H	0.05	≤0.0063	6.25	≤0.0063	0.10	50
1		CH_3	0.10	≤0.0063	12.5	≤0.0063	≤0.0063	3.13
12		H	0.05	≤0.0063	6.25	0.025	0.10	100
2		CH_3	0.10	≤0.0063	6.25	≤0.0063	0.025	6.25
13		CH_2COOH	1.56	0.05	>100	0.0125	≤0.0063	12.5
14		$C(CH_3)_2COOH$	0.78	0.10	>100	0.05	≤0.0063	12.5
15		H	0.025	≤0.0063	12.5	0.0125	0.39	50
4		CH_3	0.10	≤0.0063	12.5	0.0125	0.025	12.5

Abbreviations: See footnote in Table 1.

Table 3. The efficacy of antibacterial activity in comparison with cephalosporins having another heterocyclic ring.



R					
Compound No.	1	16	17	CZON	CDZM
S. a. 209P JC-1	0.10	0.20	0.78	0.10	3.13
S. p. IID692	≤0.0063	≤0.0063	≤0.0063	≤0.0063	0.05
E. f. IID682	12.5	50	50	100	100
E. c. NIHJ JC-2	≤0.0063	≤0.0063	0.0125	≤0.0063	≤0.0063
P. v. IFO3167	≤0.0063	0.0125	0.05	≤0.0063	≤0.0063
P. a. V-1	3.13	12.5	50	3.13	12.5

Abbreviations: See footnote in Table 1.

16-fold more active against *E. faecalis* and *P. aeruginosa*. Although **1** showed roughly comparable effects to CZON against almost bacteria tested, it was 4-fold more active against *E. faecalis* than cefodizime (CDZM)[10] and CZON. This excellent anti-*E. faecalis* activity was also superior to those of recent advanced cephalosporins including cefpirome (the MIC against *E. faecalis* IID 682 was 50 μg/ml, data not shown), which was one of the most active cephalosporins against *E. faecalis*.

We found that AM-1601 (**1**) had highly potent antibacterial activity against both Gram-positive and Gram-negative bacteria including *Enterococcus faecalis*.The ring system of α,β-unsaturated ketone was needed for good antibacterial activity and substitution of sulfur atom at the β-position of α,β-unsaturated ketone was essential for the expansion of the antibacterial spectrum.

These results indicate that introduction of 4-oxo-4*H*-1-benzothiopyran-2-yl group at the C-3 side chain of the cephalosporin nucleus leads to expand the spectrum and the 4-oxo-4*H*-1-benzothiopyran nucleus is one of the useful substituents at the C-3 side chain in cephalosporin chemistry.

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