SYNTHESIS AND BIOLOGICAL ACTIVITY OF 3-VINYLTHIO- AND 3-VINYLTHIOMETHYLCEPHEM DERIVATIVES

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The synthesis and biological properties of some 3-vinylthio- and 3-vinylthiomethylcephem derivatives are described. Both series possess potent antibacterial activity. Among them, 3-[(Z)-2-cyanovinylthiomethyl]cephem derivative was found to have an expanded antibacterial spectrum.

Recently we have studied the synthesis and biological properties of cephalosporins with a 1-hydroxyethyl moiety in the 7 position, which is well-known as the unique side chain of many carbapenem antibiotics.1,2 We reported that 7α-(1-hydroxyethyl)cephem derivatives, which had an electron-withdrawing group at the 3 position, possessed potent β-lactamase inhibitory activity. This finding of a substituent effect led us to investigate the biological properties of cephalosporin derivatives having other substituents which are characteristic in carbapenem antibiotics.

As shown in Fig. 1, we were interested in the vinylthio substituents, which are the C-2 side chains of many natural occurring carbapenem compounds such as N-acetyldehydrothienamycin (3),3 AB-110-D (4).4 In cephem compounds, little is known about the substituent effect of vinylthio(methyl) moiety at the C-3 position on the biological property in contrast to well-known heterocyclic thio(methyl)cephem derivatives.5 Thus, we prepared two new types of derivatives, 3-vinylthiocephem (1) and 3-vinylthiomethylcephem (2).

Chemistry

Initially, we attempted to introduce the vinylthio moiety to the C-3 position employing an addition-elimination reaction of lithium vinylthiolate (7), which was derived from 2-ethoxy-1,3-oxathiolane (6) as described by TANIMOTO and his co-workers,6 to 3-methylsulfonyloxycephem (16).5 However, this treatment afforded only β-isomer of 16 and degradation products due to the strongly basic condition. We then employed silver thiolate as described by BATESON and his co-workers.7 Various silver vinylthiolates 5a~5f

Fig. 1. Structures of compounds 1~4.

<table>
<thead>
<tr>
<th>R₁</th>
<th>R₂</th>
<th>R₃</th>
<th>R₄</th>
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<tbody>
<tr>
<td>Et</td>
<td>-NHAc</td>
<td>-NHAc</td>
<td>(H₂)nSCH=CHR₂</td>
</tr>
<tr>
<td>Allyl</td>
<td>H</td>
<td>-NHAc, H</td>
<td>(H₂)nSCH=CHR₂</td>
</tr>
<tr>
<td>X</td>
<td>CH, N</td>
<td>CH, N</td>
<td>CH, N</td>
</tr>
<tr>
<td>n</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

† As silver salts 5a~5f are explosive, particular attention should be given to these compounds.
Scheme 1. Synthesis of silver salts 5a~5f.

5a AgSCH=CHNHAc

Scheme 2. Reaction of silver salts 5a-5f with 3-methylsulfonyloxy cephems 16 or 3-chloromethylcephems 17.

a) LDA, b) AgNO₃, c) Ph₃CSH, tert-BuOK, d) CH₃I, e) Ph₃CSH, l NaOH, f) PCl₅, g) Ph₃CSH, Et₃N.

were synthesized as shown in Scheme 1. Silver acetamidovinylthiolate (5a) was obtained from triphenylmethylthiol and bromoacetaldehyde diethylacetal via several steps as E,Z mixture (E : Z, 3 : 2). Lithium vinylthiolate (7) reacted with silver nitrate in the dark to give crude silver vinylthiolate (5b). 3-Ethynylpyridine (8) was treated with triphenylmethylthiol and potassium tert-butoxide to give 3-[(Z)-2-(triphenylmethylthio)vinyl]pyridine (9) in 60% yield. The Z assignment of the vinyl moiety was based upon the observed coupling constant (Jcis = 12 Hz) in ¹H NMR. Detritylation of 9 with silver nitrate gave silver salt 5c. Compound 9 reacted with methyl iodide to give 1-methyl-3-pyridinium compound 10 in 90% yield. Compound 10 was also converted to silver salt 5d in a similar manner. Silver (Z)-2-cyanovinylthiolate 5e was derived from propionamide (11) in the same manner as that of 5c. The (E)-isomer 5f was prepared by the treatment of (E)-2-chloroacrylonitrile (14) with triphenylmethylthiol and triethylamine followed by reaction with silver nitrate.

As shown in Scheme 2, these silver salts 5a~5f were treated with 3-methylsulfonyloxy cephems 16 or 3-chloromethylcephems 17 and sodium iodide in the dark to give 3-vinylthiocephems 18 (n=0) or 3-vinylthiomethylcephems 19 (n=1), respectively. In these reactions, the treatment of E,Z mixture of 5a
Scheme 2. General synthetic route of 3-vinylthio- and 3-vinylthiomethylcephem derivatives, 1 and 2.

with 16 afforded only Z-isomer of 18, and the other treatment of 5b~5f with 16 or 17 gave 18 or 19 with retention of the configuration. The protecting groups in 18 and 19 were removed in usual fashion to give 1 and 2, that is, the N-formyl groups were deprotected with concentrated hydrochloric acid in methanol, the diphenylmethyl groups were removed with trifluoroacetic acid and anisole, respectively.

Biological Results and Discussion

The in vitro antibacterial activities of the 3-vinylthiocephem derivatives 1a~1e against selected Gram-positive and Gram-negative bacteria are shown in Table 1. Compound 1a, which has (Z)-2-(acetamido)vinylthio group at the C-3 position, corresponding to the C-2 side chain of carbapenem compound 4, showed greater activity against Staphylococcus aureus 209P JC-1 than ceftizoxime (CZX), which has no substituent at the 3 position, moderate activity against Escherichia coli NIHJ JC-2 and Klebsiella pneumoniae 12, and weak activity against Pseudomonas aeruginosa IAM 1095. The antibacterial spectra of compounds 1b~1e were similar to that of compound 1a. 3-Pyridinium compounds, 1d-1 and 1d-2 were potent activity against S. aureus 209P JC-1, E. coli NIHJ JC-2, and K. pneumoniae 12, but less active against P. aeruginosa IAM 1095 than the corresponding 3-pyridine compounds, 1c-1 and 1c-2.

The antibacterial spectra of 7/S-(2-aminothiazol)cephem compounds (1c-2 and 1d-2, X=CH) were similar to those of the corresponding 7£-(5-amino-1,2,4-thiadiazol)cephem compounds (1e-1 and 1d-1, X= N).

The MICs of the 3-vinylthiomethylcephem derivatives, 2c~2f are shown in Table 2. The antibacterial spectra of 2c-1 and 2c-2 are similar to that of the 3-vinylthiocephem derivatives, and in comparison between 1c and 2c, the vinlythiomethylcephem derivatives, 2c-1 and 2c-2 have twice to eight times less activity against S. aureus 209P JC-1, E. coli NIHJ JC-2 and K. pneumoniae 12 than the corresponding vinylthiocephem derivatives, 1c-1 and 1c-3. The antibacterial activity of 3-pyridinium compound 2d had improved activity in comparison to the corresponding 3-pyridine compound 2c-1.
Table 1. MICs of 3-vinylthiocephem derivatives 1a~1e.

<table>
<thead>
<tr>
<th>Compound No.</th>
<th>R₁</th>
<th>X</th>
<th>R₂</th>
<th>MIC (µg/ml)</th>
<th>S.a</th>
<th>E.c</th>
<th>K.p</th>
<th>P.a.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>Et</td>
<td>N</td>
<td>NHAc</td>
<td>0.78</td>
<td>0.39</td>
<td>1.56</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>1b</td>
<td>Et</td>
<td>N</td>
<td>H</td>
<td>1.56</td>
<td>0.39</td>
<td>0.78</td>
<td>12.5</td>
<td></td>
</tr>
<tr>
<td>1c-1</td>
<td>Et</td>
<td>N</td>
<td></td>
<td>0.39</td>
<td>0.10</td>
<td>0.78</td>
<td>6.25</td>
<td></td>
</tr>
<tr>
<td>1c-2</td>
<td>Et</td>
<td>CH</td>
<td></td>
<td>0.78</td>
<td>0.10</td>
<td>0.78</td>
<td>3.13</td>
<td></td>
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<tr>
<td>1c-3</td>
<td>Allyl</td>
<td>N</td>
<td></td>
<td>0.20</td>
<td>0.20</td>
<td>0.78</td>
<td>12.5</td>
<td></td>
</tr>
<tr>
<td>1d-1</td>
<td>Et</td>
<td>N</td>
<td></td>
<td>0.20</td>
<td>0.05</td>
<td>0.39</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td>1d-2</td>
<td>Et</td>
<td>CH</td>
<td></td>
<td>0.20</td>
<td>0.05</td>
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<tr>
<td>1e</td>
<td>Allyl</td>
<td>N</td>
<td>CN</td>
<td>0.78</td>
<td>0.20</td>
<td>0.78</td>
<td>25</td>
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</tr>
<tr>
<td>CZX</td>
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<td></td>
<td></td>
<td>6.25</td>
<td>≤0.025</td>
<td>≤0.025</td>
<td>50</td>
<td></td>
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<tr>
<td>IPM</td>
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<td></td>
<td></td>
<td>≤0.025</td>
<td>0.78</td>
<td>0.10</td>
<td>0.78</td>
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</tbody>
</table>

Abbreviations: S.a., Staphylococcus aureus 209P JC-1; E.c., Escherichia coli NIHJ JC-2; K.p., Klebsiella pneumoniae 12; P.a., Pseudomonas aeruginosa IAM 1095.

Mueller-Hinton agar 10⁻²; stamp method; 37°C, 18 hours.

Table 2. MICs of 3-vinylthiomethylcephem derivatives 2c~2f.

<table>
<thead>
<tr>
<th>Compound No.</th>
<th>R₁</th>
<th>X</th>
<th>R₂</th>
<th>E,Z</th>
<th>MIC (µg/ml)</th>
<th>S.a</th>
<th>E.c</th>
<th>K.p</th>
<th>P.a.</th>
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<tr>
<td>2c-1</td>
<td>Et</td>
<td>N</td>
<td></td>
<td>Z</td>
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<td>0.78</td>
<td>3.13</td>
<td>6.25</td>
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<td>Allyl</td>
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<td></td>
<td>Z</td>
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<td>0.78</td>
<td>3.13</td>
<td>3.13</td>
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</tr>
<tr>
<td>2d</td>
<td>Et</td>
<td>N</td>
<td></td>
<td>Z</td>
<td>0.78</td>
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<td>3.13</td>
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<tr>
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<td>Allyl</td>
<td>N</td>
<td>CN</td>
<td>Z</td>
<td>0.78</td>
<td>0.10</td>
<td>0.78</td>
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<td></td>
</tr>
<tr>
<td>2e-2</td>
<td>Allyl</td>
<td>CH</td>
<td>CN</td>
<td>Z</td>
<td>0.39</td>
<td>0.39</td>
<td>1.56</td>
<td>1.56</td>
<td></td>
</tr>
<tr>
<td>2f</td>
<td>Allyl</td>
<td>N</td>
<td>CN</td>
<td>E</td>
<td>0.78</td>
<td>0.10</td>
<td>0.78</td>
<td>3.13</td>
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<tr>
<td>CZX</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>6.25</td>
<td>≤0.025</td>
<td>≤0.025</td>
<td>50</td>
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<tr>
<td>IPM</td>
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<td></td>
<td></td>
<td>≤0.025</td>
<td>0.78</td>
<td>0.10</td>
<td>0.78</td>
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</tbody>
</table>

Abbreviations: See Table 1.

Mueller-Hinton agar 10⁻²; stamp method; 37°C, 18 hours.
Table 3. Binding affinities of 1c-3, 2c-2, CZX, and IPM for PBPs in *Escherichia coli* NIHJ JC-2.

<table>
<thead>
<tr>
<th>Compound No.</th>
<th>n</th>
<th>1A (µg/ml)</th>
<th>1B (µg/ml)</th>
<th>2 (µg/ml)</th>
<th>3 (µg/ml)</th>
<th>4 (µg/ml)</th>
<th>5 (µg/ml)</th>
<th>6 (µg/ml)</th>
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<tbody>
<tr>
<td>1c-3</td>
<td>0</td>
<td>0.47</td>
<td>0.22</td>
<td>1.9</td>
<td>0.036</td>
<td>8.5</td>
<td>&gt;25</td>
<td>5.8</td>
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<tr>
<td>2c-2</td>
<td>1</td>
<td>0.015</td>
<td>2.1</td>
<td>&gt;25</td>
<td>0.04</td>
<td>&gt;25</td>
<td>&gt;25</td>
<td>&gt;25</td>
</tr>
<tr>
<td>CZX</td>
<td></td>
<td>0.020</td>
<td>0.1</td>
<td>&gt;25</td>
<td>0.012</td>
<td>&gt;25</td>
<td>&gt;25</td>
<td>&gt;25</td>
</tr>
<tr>
<td>IPM</td>
<td></td>
<td>0.2</td>
<td>0.6</td>
<td>&lt;0.1</td>
<td>9.8</td>
<td>&lt;0.1</td>
<td>0.3</td>
<td>0.6</td>
</tr>
</tbody>
</table>

* Concentration required to inhibit binding of [14C]benzylpenicillin to each protein by 50%.

Interestingly, we found that (Z)-2-cyanovinylthiomethyl compounds, 2e-1 and 2e-2 have potent activity against *P. aeruginosa* IAM 1095, while the corresponding (E)-isomer 2f and (Z)-cyanovinylthio derivative 1e have lower activity.

As a result, compound 2e-1 has an expanded antibacterial spectra against both Gram-positive bacteria and Gram-negative bacteria including *P. aeruginosa*, and among 3-vinylthio(methyl)cephem derivatives, (1-methyl-3-pyridinio)vinylthio compounds, 1d-1 and 1d-2 have the most potent activity against *S. aureus* 209P JC-1, *E. coli* NIHJ JC-2, and *K. pneumoniae* 12.

Table 3 showed the effect of the C-3 substituents of cephem derivatives, 1c-3 and 2c-2 upon their affinity for the penicillin-binding proteins (PBPs) of *E. coli* NIHJ JC-2. The 3-vinylthiomethyl compound 2c-2 has strong affinity for PBPs 1A, 1B, and 3, and its affinity pattern is similar to that of CZX. However, the corresponding 3-vinylthiocephem compound 1c-3 has good affinity not only for PBPs 1A, 1B, and 3, but also for PBP 2, which is the primary target for carbapenems such as imipenem (IPM). For the present, it is uncertain how the difference in the affinity profiles between 1c-3 and 2c-2 is reflected in the antibacterial activity although it is a notable feature.

**Experimental**

MP’s were measured with a Yanagimoto micro melting point apparatus and are uncorrected. IR spectra were recorded with a Hitachi 260-10 spectrometer. ¹H NMR were recorded using a Hitachi R-90H spectrometer. Chemical shifts (δ) are recorded in ppm from sodium 2,2-dimethyl-2-silapentane-5-sulfonate (DSS) (in D₂O) or TMS (in CDCl₃ and DMSO-d₆) as internal standard.

**Preparation of Silver Vinylthiolates 5b~5f**

**Silver Vinylthiolate (5b)**

To a solution of *N,N*-diisopropylamine (3.39 ml, 19.5 mmol) in dry THF (80 ml) was added 1.55 M n-butyllithium solution in hexane (12.6 ml) at −60°C in nitrogen atmosphere. The mixture was stirred at 0°C for 30 minutes. To this solution was added a solution of 2-ethoxy-1,3-oxathiolane (6)⁶ (3 ml, 19.5 mmol) in dry THF (5 ml) at −60~−70°C. After additional 30 minutes at −65°C, the mixture was poured into a solution of silver nitrate (8.46 g, 49.8 mmol) in a mixture of water (20 ml) and methanol (80 ml) at 0°C. After stirring for 30 minutes in the dark, the mixture was adjusted to pH 6.5 with dilute sulfuric acid. The precipitate was collected by filtration, washed with water, methanol, and diethyl ether successively, and dried in vacuo to give crude silver salt 5b (7.41 g) as a brown solid.
3-[(Z)-2-(Triphenylmethylthio)vinyl]pyridine (9)

To a solution of triphenylmethylthiol (1.41 g, 5.1 mmol) and 3-ethynylpyridine (8) (0.5 g, 4.8 mmol) in dry THF (10 ml) was added potassium tert-butoxide (571 mg, 5 mmol) at room temperature. The mixture was refluxed for 2 hours. After being cooled to room temperature, the reaction mixture was poured into ice water. The mixture was extracted with ethyl acetate. The extract was washed with saturated aqueous sodium chloride, dried over magnesium sulfate, and evaporated in vacuo to give a crystalline powder. The crystalline powder was washed with ethanol and dried to give 9 (1.1 g, 60%): MP 140-141°C; IR (Nujol) cm⁻¹ 1590, 1560, 1470, 1450, 1410; ¹H NMR (CDCl₃) δ 6.03 (1H, d, J=11 Hz), 6.27 (1H, d, J=11 Hz), 7.13-7.23 (1H, m), 7.27 (15H, m), 7.90 (1H, dt, J=2 and 8 Hz), 8.40 (1H, dd, J=2 and 5 Hz), 8.63 (1H, d, J=2 Hz).

Silver (Z)-2-(3-Pyridinyl)vinylthiolate (5c)

To a solution of 9 (690mg, 1.81 mmol) in a mixture of THF (3ml), methanol (5ml), and pyridine (0.147 ml, 1.82 mmol) was added dropwise a solution of silver nitrate (371 mg, 2.18 mmol) in water (20ml) at room temperature. The mixture was stirred at 0°C for 1 hour in the dark. The precipitate was collected, washed with methanol, and dried over phosphorus pentoxide to give crude 5c (487 mg) as a brown solid: IR (Nujol) cm⁻¹ 1590, 1580, 1560, 1420.

1-Methyl-3-[(Z)-2-(triphenylmethylthio)vinyl]pyridinium Iodide (10)

To a solution of 9 (5g, 13.1 mmol) in dichloromethane (100ml) was added methyl iodide (8.3ml, 133 mmol) at room temperature. The mixture was stirred at room temperature for 6 hours. The precipitate was collected by filtration, washed with diethyl ether, and dried in vacuo to give 10 (6.64g, 97%) as a colorless solid: IR (Nujol) cm⁻¹ 1570, 1500, 1445, 1445; ¹H NMR (DMSO-d₆) δ 4.33 (3H, s), 6.35 (1H, d, J=12 Hz), 6.55 (1H, d, J=12 Hz), 7.00-7.40 (15H, m), 8.40 (1H, dd, J=5 and 8 Hz), 8.57 (1H, d, J=8 Hz), 8.73 (1H, d, J=5 Hz), 8.90 (1H, s).

Silver (Z)-2-(1-Methyl-3-pyridinio)vinylthiolate Nitrate (5d)

This compound was derived from compound 10 as described for 5c from 9.

(Z) -3-Triphenylmethylthioacrylamide (12)

To a mixture solution of propionamide (11) (1.0g, 14.5mmol) in THF and water (1:1, 20ml) was added triphenylmethylthiol (4.2g, 15.2mmol) at 0°C. The mixture was stirred at 0-10°C for 30 minutes and poured into ice water. The precipitate was collected by filtration and dried over phosphorus pentoxide in vacuo to give 12 (4.2g, 84%) as a colorless solid: IR (Nujol) cm⁻¹ 3380, 3180, 1640, 1570.

(Z) -2-Triphenylmethylthioacrylonitrile (13)

To a mixture of 12 (3.0g, 8.7mmol) and DMF (40ml) was added phosphorus pentachloride (3.65 g, 17.5 mmol). The mixture was stirred at 20°C for 30 minutes, poured into ice water, and extracted with ethyl acetate. The organic layer was washed with saturated aqueous sodium chloride, dried over magnesium sulfate, and evaporated in vacuo to give 13 (2.85g, 77%) as a colorless solid: IR (Nujol) cm⁻¹ 2200; ¹H NMR (DMSO-d₆) δ 5.65 (1H, d, J=10 Hz), 6.88 (1H, d, J=10 Hz), 7.00-7.67 (15H, m).

Silver (Z)-2-Cyanovinylthiolate (5e)

This compound was derived from compound 13 as described for 5e from 9.

(Z)-2-Triphenylmethylthioacrylonitrile (15)

To a solution of (E)-2-chloroacrylonitrile (14) (100mg, 1.14mmol) in THF (2.0ml) was added triphenylmethylthiol (0.332 g, 1.2 mmol) and triethylamine (0.175 ml, 1.26 mmol) at 0°C. The mixture was stirred at room temperature for 16 hours, poured into ice water and extracted with ethyl acetate. The extract was washed with saturated aqueous sodium chloride, dried over magnesium sulfate, and evaporated in vacuo to give 15 (0.37g, 100%) as a solid: IR (Film) cm⁻¹ 2210, 1560, 1440; ¹H NMR (DMSO-d₆) δ 5.26
Silver (E)-2-Cyanovinylthiolate (5f)

This compound was derived from compound 15 as described for 5e from 9.

IR (Nujol) cm⁻¹ 2210, 1540, 920, 860.

General Procedure for the Synthesis of 3-Vinylthio- and 3-Vinylthiomethylcephem Compounds, 18 and 19

To a mixture of crude silver salt 5 (20 g) and acetonitrile (90 ml) was added sodium iodide (8.77 g, 58.5 mmol) at room temperature in the dark. The mixture was stirred for 30 minutes at room temperature in dark and cooled to 0°C. To the mixture was added 3-methylsulfonyloxy- or 3-chloromethylcephem, 16 or 17 (9.9 mmol), at 0°C. The mixture was stirred for 30 minutes at 0°C. The precipitate was filtered off. The filtrate was evaporated in vacuo. The residue was added to a mixture of ethyl acetate and water. After stirring, the organic layer was separated, washed with saturated aqueous sodium chloride, dried over magnesium sulfate, and evaporated in vacuo. The residue was purified by silica gel column chromatography to give 3-vinylthio- or 3-vinylthiomethylcephems, 18 or 19.

General Procedure for Deformylation of Compounds 18 and 19

To a mixture of 18 or 19 (2.0 mmol, X=CH) in methanol (25 ml) was added conc hydrochloric acid (6.0–8.0 mmol) at room temperature. The mixture was stirred at 30–35°C for 1 hour. After neutralization with 5% aqueous sodium hydrogen carbonate, the mixture was evaporated in vacuo and the residue was added to a mixture of ethyl acetate and water. The organic layer was separated, washed with saturated aqueous sodium chloride, dried over magnesium sulfate, and evaporated in vacuo. The residue was purified by silica gel column chromatography to give 7-aminothiazol compounds 20 or 21.

General Procedure for Deprotection of Diphenylmethyl Group of Compounds, 18–21

To a mixture of diphenylmethyl ester (18–21, 1.0 g) and anisole (1.0 ml) in dichloromethane (2.0 ml) was added TFA (3.0 ml) under ice-cooling. The mixture was stirred at the same temperature for 1 hour and poured into diisopropyl ether (100 ml). The precipitate was collected by filtration and purified by column chromatography (Diaion HP-20; 30 ml, eluent; 2-propanol-water, 1:10) followed by freeze-drying to give 1 or 2.

7β-[(Z)-2-(5-Amino-1,2,4-thiadiazol-3-yl)-2-ethoxyiminoacetamido]-3-[(Z)-2-(acetamido)vinylthio]-3-cephem-4-carboxylic Acid (1a)

MP 125°C (dec); IR (Nujol) cm⁻¹ 3300, 3250, 1770, 1670, 1610; ¹H NMR (DMSO-d₆) δ 1.23 (3H, t, J = 7 Hz), 2.00 (3H, s), 3.50 and 3.80 (2H, ABq, J = 18 Hz), 4.15 (2H, q, J = 7 Hz), 5.13 (1H, d, J = 5 Hz), 5.33 (1H, d, J = 8 Hz), 5.70 (1H, dd, J = 5 and 8 Hz), 7.14 (1H, dd, J = 8 and 11 Hz), 8.00 (2H, s), 9.40 (1H, d, J = 7 Hz), 9.70 (1H, d, J = 11 Hz).

7β-[(Z)-2-(5-Amino-1,2,4-thiadiazol-3-yl)-2-ethoxyiminoacetamido]-3-vinylthio-3-cephem-4-carboxylic Acid (1b)

MP 145°C (dec); IR (Nujol) cm⁻¹ 1765, 1670, 1525; ¹H NMR (DMSO-<sup>d</sup>₆) δ 1.21 (3H, t, J = 7 Hz), 3.48 and 3.84 (2H, ABq, J = 18 Hz), 4.11 (2H, q, J = 7 Hz), 5.12 (1H, d, J = 5 Hz), 5.33 (1H, d, J = 16 Hz), 5.40 (1H, d, J = 10 Hz), 5.72 (1H, dd, J = 5 and 8 Hz), 6.54 (1H, dd, J = 10 and 16 Hz), 7.98 (2H, s), 9.42 (1H, d, J = 8 Hz).

7β-[(Z)-2-(5-Amino-1,2,4-thiadiazol-3-yl)-2-ethoxyiminoacetamido]-3-(2-pyridyl)vinylthio]-3-cephem-4-carboxylic Acid (1c)

MP 171°C (dec); IR (Nujol) cm⁻¹ 3300, 3250, 1770, 1670, 1610; ¹H NMR (DMSO-d₆) δ 1.27 (3H, t, J = 7 Hz), 3.66 and 4.12 (2H, ABq, J = 18 Hz), 4.20 (2H, q, J = 7 Hz), 5.23 (1H, d, J = 5 Hz), 5.87 (1H, dd, J = 5 and 8 Hz), 6.71 (1H, d, J = 11 Hz), 6.89 (1H, d, J = 11 Hz), 7.48 (1H, dd, J = 5 and 7.5 Hz), 7.95 (1H, dd, J = 2 and 7.5 Hz), 8.13 (2H, brs), 8.49 (1H, d, J = 5 Hz), 8.68 (1H, brs), 9.58 (1H, d, J = 8 Hz).
7β-[\((Z)\)-2-(2-Aminothiazol-4-yl)-2-ethoxyiminoacetamido]-3-[(Z)-2-(3-pyridyl)vinylthio]-3-cephem-4-carboxylic Acid (1c)

IR (Nujol) cm\(^{-1}\) 1770, 1660, 1530; \(^1\)H NMR (DMSO-\(d_6\)) \(\delta\) 1.27 (3H, t, \(J = 7\) Hz), 3.50–4.40 (4H, m), 5.27 (1H, d, \(J = 5\) Hz), 5.87 (1H, dd, \(J = 5\) and 8 Hz), 6.77 (1H, s), 6.80 (1H, d, \(J = 12\) Hz), 6.93 (1H, d, \(J = 12\) Hz), 7.50–7.83 (1H, m), 7.83–8.50 (3H, m), 8.50–8.90 (2H, m), 9.67 (1H, d, \(J = 8\) Hz).

7β-[\((Z)\)-2-Allyloxyimino-2-(2-aminothiazol-4-yl)acetamido]-3-[(Z)-2-(3-pyridyl)vinylthio]-3-cephem-4-carboxylic Acid (1c-3)

IR (Nujol) cm\(^{-1}\) 1760, 1630, 1530; \(^1\)H NMR (DMSO-\(d_6\)) 6 3.62 and 4.17 (2H, ABq, \(J = 18\) Hz), 4.67 (2H, m), 4.90–5.60 (2H, m), 5.20 (1H, d, \(J = 5\) Hz), 5.67–6.10 (1H, m), 5.90 (1H, dd, \(J = 5\) and 8 Hz), 6.80 (1H, s), 7.10–7.60 (1H, m), 7.70–8.00 (1H, m), 8.10 (2H, brs), 8.47 (1H, m), 8.67 (1H, brs), 9.63 (1H, d, \(J = 8\) Hz).

7β-[\((Z)\)-2-(5-Amino-1,2,4-thiadiazol-3-yl)-2-ethoxyiminoacetamido]-3-[(Z)-2-(1-methyl-3-pyridinio)-vinylthio]-3-cephem-4-carboxylate (1d-1)

IR (Nujol) cm\(^{-1}\) 1775, 1670, 1605, 1520; \(^1\)H NMR (DMSO-\(d_6\)) \(\delta\) 1.27 (3H, t, \(J = 7\) Hz), 3.20–3.80 (2H, m), 3.90–4.50 (2H, m), 4.37 (3H, s), 5.07 (1H, d, \(J = 5\) Hz), 5.60 (1H, dd, \(J = 5\) and 8 Hz), 6.65 (1H, d, \(J = 10\) Hz), 7.05 (1H, d, \(J = 10\) Hz), 7.80–9.00 (5H, m), 9.20 (1H, brs), 9.40 (1H, d, \(J = 8\) Hz).

7β-[\((Z)\)-2-(2-Aminothiazol-4-yl)-2-ethoxyiminoacetamido]-3-[(Z)-2-(1-methyl-3-pyridinio)-vinylthio]-3-cephem-4-carboxylate (1d-2)

IR (Nujol) cm\(^{-1}\) 1760, 1650, 1600, 1520; \(^1\)H NMR (DMSO-\(d_6\)) \(\delta\) 1.20 (3H, t, \(J = 7\) Hz), 3.00–3.80 (2H, m), 4.13 (2H, q, \(J = 7\) Hz), 4.37 (3H, s), 5.07 (1H, d, \(J = 5\) Hz), 5.60 (1H, dd, \(J = 5\) and 8 Hz), 6.62 (1H, d, \(J = 10\) Hz), 6.67 (1H, d, \(J = 10\) Hz), 7.05 (1H, d, \(J = 10\) Hz), 7.27 (2H, brs), 7.80–8.20 (1H, m), 8.30–8.60 (1H, m), 8.77 (1H, d, \(J = 6\) Hz), 9.27 (1H, brs), 9.43 (1H, d, \(J = 8\) Hz).

7β-[\((Z)\)-2-Allyloxyimino-2-(5-amino-1,2,4-thiadiazol-3-yl)acetamido]-3-[(Z)-2-(3-pyridyl)vinylthio]-3-cephem-4-carboxylic Acid (1e)

IR (Nujol) cm\(^{-1}\) 2200, 1760, 1660, 1605, 1510; \(^1\)H NMR (DMSO-\(d_6\)) \(\delta\) 3.68 and 4.12 (2H, ABq, \(J = 18\) Hz), 4.67 (2H, m), 5.00–5.50 (3H, m), 5.60–6.20 (2H, m), 5.90 (1H, d, \(J = 10\) Hz), 7.77 (1H, d, \(J = 10\) Hz), 8.10 (2H, brs), 9.60 (1H, d, \(J = 8\) Hz).

7β-[\((Z)\)-2-(5-Amino-1,2,4-thiadiazol-3-yl)-2-ethoxyiminoacetamido]-3-[(Z)-2-(3-pyridyl)vinylthio]-3-cephem-4-carboxylic Acid (2c-1)

MP 156–160°C (dec); IR (Nujol) cm\(^{-1}\) 3300, 3200, 1770, 1670, 1620, 1580, 1530, 1250, 1230, 1180; \(^1\)H NMR (D\(_2\)O) \(\delta\) 1.30 (3H, t, \(J = 7\) Hz), 3.47–4.03 (2H, m), 4.37 (2H, q, \(J = 7\) Hz), 5.20 (1H, d, \(J = 5\) Hz), 5.87 (1H, d, \(J = 5\) Hz), 6.30 (1H, d, \(J = 11\) Hz), 6.67 (1H, d, \(J = 11\) Hz), 7.10–7.40 (1H, m), 7.60–7.80 (1H, m), 8.07–8.30 (1H, m), 8.30–8.50 (1H, m).

7β-[\((Z)\)-2-(5-Amino-1,2,4-thiadiazol-3-yl)-2-ethoxyiminoacetamido]-3-[(Z)-2-(3-pyridyl)vinylthiomethyl]-3-cephem-4-carboxylic Acid (2c-2)

MP 156–160°C (dec); IR (Nujol) cm\(^{-1}\) 3300, 3200, 1770, 1670, 1620, 1580, 1530, 1250, 1230, 1180; \(^1\)H NMR (D\(_2\)O) \(\delta\) 3.60 (2H, brs), 3.60–4.30 (2H, m), 4.63 (2H, m), 5.00–5.50 (2H, m), 5.20 (1H, d, \(J = 5\) Hz), 5.60–6.30 (1H, m), 5.80 (1H, dd, \(J = 5\) and 8 Hz), 6.47 (1H, d, \(J = 11\) Hz), 6.83 (1H, d, \(J = 11\) Hz), 7.47 (1H, m), 7.93 (1H, m), 8.10 (2H, brs), 8.43 (1H, m), 8.63 (1H, m), 9.57 (1H, d, \(J = 8\) Hz).

7β-[\((Z)\)-2-(5-Amino-1,2,4-thiadiazol-3-yl)-2-ethoxyiminoacetamido]-3-[(Z)-2-(1-methyl-3-pyridinio)-vinylthiomethyl]-3-cephem-4-carboxylic Acid (2d)

IR (Nujol) cm\(^{-1}\) 1755, 1660, 1590; \(^1\)H NMR (D\(_2\)O) \(\delta\) 1.30 (3H, t, \(J = 7\) Hz), 3.47–4.57 (4H, m), 4.37 (3H, s), 4.73 (2H, q, \(J = 7\) Hz), 5.30 (1H, d, \(J = 5\) Hz), 5.80 (1H, d, \(J = 5\) Hz), 6.50 (1H, d, \(J = 11\) Hz), 7.03 (1H, d, \(J = 11\) Hz), 7.77–8.13 (1H, m), 8.30–8.80 (3H, m).
7β-[{(Z)-2-Allyloxyimino-2-(5-amino-1,2,4-thiadiazol-3-yl)acetamido]-3-[(Z)-2-cyanovinylthiomethyl]-3-cephem-4-carboxylic Acid (2e-1)

MP 166°C (dec); IR (Nujol) cm⁻¹ 3250, 2210, 1765, 1670, 1615; ¹H NMR (DMSO-d₆) δ 3.60 (2H, br s), 3.80 and 4.25 (2H, ABq, J=14 Hz), 4.67 (2H, m), 5.20 (1H, d, J=5 Hz), 5.17~6.20 (3H, m), 5.70 (1H, d, J=11 Hz), 7.75 (1H, dd, J=5 and 8 Hz), 7.75 (1H, d, J=11 Hz), 8.10 (2H, br s), 9.50 (1H, d, J=8 Hz).

7β-[{(Z)-2-Allyloxyimino-2-(2-aminothiazol-4-yl)acetamido]-3-[(Z)-2-cyanovinylthiomethyl]-3-cephem-4-carboxylic Acid (2e-2)

MP 148°C (dec); IR (Nujol) cm⁻¹ 3300, 2220, 1770, 1670, 1620; ¹H NMR (DMSO-d₆) δ 3.53 (2H, br s), 3.60 and 4.20 (2H, ABq, J=13 Hz), 4.57 (2H, m), 5.10~6.20 (4H, m), 5.17 (1H, d, J=5 Hz), 5.67 (1H, d, J=11 Hz), 6.70 (1H, s), 7.70 (1H, d, J=11 Hz), 9.60 (1H, d, J=8 Hz).

7β-[{(Z)-2-Allyloxyimino-2-(5-amino-1,2,4-thiadiazol-3-yl)acetamido]-3-[(E)-2-cyanovinylthiomethyl]-3-cephem-4-carboxylic Acid (2f)

MP 136°C (dec); IR (Nujol) cm⁻¹ 3300, 2220, 1770, 1675, 1620; ¹H NMR (DMSO-d₆) δ 3.35~4.33 (4H, m), 4.69 (2H, d, J=5 Hz), 5.15~6.20 (4H, m), 5.22 (1H, d, J=5 Hz), 5.75 (1H, d, J=15 Hz), 7.91 (1H, d, J=15 Hz), 8.15 (2H, br s), 9.67 (1H, d, J=8 Hz).

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References