Synthetic Cephalosporins. VII.¹⁾ Synthesis and Antibacterial Activity of 7-[(Z)-2-(2-Aminothiazol-4-yl)-2-(3-(3-hydroxy-4-pyridon-1-yl)-3-carboxypropoxyimino)acetamido]-3-(1,2,3-thiadiazol-5-yl)-thiomethyl-3-cephem-4-carboxylic Acid and Its Related Compounds

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Synthesis and antibacterial activity of 7-[(Z)-2-(2-aminothiazol-4-yl)-2-(3-(3-hydroxy-4-pyridon-1-yl)-3-carboxypropoxyimino)acetamido]-3-(1,2,3-thiadiazol-5-yl)thiomethyl-3-cephem-4-carboxylic acid (12a) and its related compounds are described. Compound 12a exhibited excellent antibacterial activity against gram-negative bacteria, including *Pseudomonas aeruginosa*.

Keywords cephalosporins; anti-pseudomonal activity; structure-activity relationships; 3-hydroxy-4-pyridone

We previously reported that 7-[(Z)-2-(2-aminothiazol-4-yl)-2-(1-carboxy-1-methyl)ethoxyiminoacetamido]-3-(3-hydroxy-4-pyridon-1-yl)methyl-3-cephem-4-carboxylic acid showed excellent antibacterial activity against gram-negative bacteria.¹⁾ In particular, the anti-pseudomonal activity of this compound was 10 to 15 times greater than that of ceftazidime (CAZ).²⁾ This finding that the 3-hydroxy-4-pyridon-1-ylmethyl group is a potent substituent in the C-3 side chain of cephalosporin prompted us to test other possibilities of this group as substituents of cephalosporin, with the aim of developing a new efficient cephalosporin. At first, 3-hydroxy-4-pyridon-1-ylacetic acid was introduced to the 7-amino group of cephalosporin, but the resulting compound **5** did not show good activity against gram-negative bacteria. On the other hand, incorporation of 3-hydroxy-4-pyridone moiety into the *O*-alkyl groups of the alkoxyimino 2-(2-aminothiazol-4-yl)acetyl cephalosporin was fruitful. 7-[(Z)-2-(2-Aminothiazol-4-yl)-2-(3-(3-hydroxy-4-pyridon-1-yl)-3-carboxypropoxyimino)acetamido]-3-(1,2,3-thiadiazol-5-yl)thiomethyl-3-cephem-4-

carboxylic acid (**12a**) showed excellent antibacterial activity against *Pseudomonas aeruginosa* as well as gram-negative bacteria. Here we report the synthesis and structure-activity relationships of **12a** and its related compounds.

Results and Discussion

Chemistry 3-Diphenylmethoxy-4-pyrone¹⁾ (**1**) reacted with glycine to produce 3-diphenylmethoxy-4-pyridon-1-ylacetic acid (**2**) in a 57% yield. The coupling reaction of **2** with *p*-methoxybenzyl 7-amino-3-(1,2,3-thiadiazol-5-yl)thiomethyl-3-cephem-4-carboxylate³⁾ (**3**) was carried out using *N,N*-dicyclohexylcarbodiimide as a coupling reagent to give **4**, which, upon treatment with trifluoroacetic acid, produced cephalosporin (**5**). Compound **1** also reacted with DL-homoserine, DL-isoserine and ethanolamine to give the corresponding pyridones **6a**, **7a** and **8a**, respectively.

Chart 1

Chart 2

Chart 3

TABLE I. *in Vitro* MICs ($\mu\text{g/ml}$)

Test organisms	5	12a	12b	12c	CZON	CAZ
<i>Staphylococcus aureus</i> 606	0.78	12.5	25	3.13	0.39	6.25
<i>S. aureus</i> SMITH (1)	0.39	12.5	25	1.56	0.39	3.13
<i>S. epidermidis</i> ATCC14990	0.39	12.5	25	0.78	0.39	6.25
<i>Bacillus subtilis</i> ATCC6633	0.20	3.13	50	0.78	0.39	3.13
<i>Escherichia coli</i> W3630 RGN823	50	0.78	1.56	1.56	0.10	0.39
<i>E. coli</i> No. 29	3.13	<0.025	0.39	0.20	0.05	0.20
<i>Klebsiella pneumoniae</i> GN69	6.25	<0.025	0.39	0.10	0.10	0.10
<i>K. pneumoniae</i> PCI602	3.13	<0.025	0.39	0.10	0.10	0.20
<i>Salmonella typhi</i> O-901-W	3.13	<0.025	0.05	<0.025	<0.025	0.05
<i>S. enteritidis</i> No. 11	3.13	<0.025	<0.025	<0.025	<0.025	0.05
<i>Shigella dysenteriae</i> (SHIGA)	3.13	0.05	0.10	0.05	<0.025	0.05
<i>Proteus vulgaris</i> GN76	>100	<0.025	0.05	0.10	0.20	0.05
<i>Morganella morganii</i> 1510	>100	3.13	6.25	3.13	3.13	12.5
<i>Serratia marcescens</i> GN10857	>100	3.13	3.13	1.56	3.13	0.78
<i>Pseudomonas aeruginosa</i> GN10362	>100	3.13	3.13	>100	50	1.56
<i>P. aeruginosa</i> M-0148	>100	0.78	0.78	>100	50	1.56
<i>P. aeruginosa</i> E-2	>100	0.39	0.78	3.13	25	0.78
<i>P. aeruginosa</i> ML Rms139	>100	0.20	0.39	1.56	25	0.78

Pyridone **6a** and **7a** were converted into the diphenylmethylesters **6b** and **7b** by treatment with diphenyldiazomethane.

A Mitsunobu reaction of **6b**, **7b** and **8a** with *N*-hydroxyphthalimide, and subsequent removal of the phthaloyl groups of **6c**, **7c** and **8b** produced the alkoxyamines **6b**, **7d** and **8c** in good yields. The alkoxyamines were allowed to react with 2-oxo-2-(2-tritylaminothiazol-4-yl)-acetic acid (**9**) to give the α -alkoxyimino acids **10a**, **10b** and **10c**, respectively. Compounds **10a**—**c** were coupled with **3** using POCl_3 as a coupling reagent, and subsequent removal of the protecting groups of **11a**—**c** gave the new cephalosporins **12a**—**c**, respectively, in which **12a** and **12b** were in the form of a 1:1 diastereomeric mixture according to their proton nuclear magnetic resonance ($^1\text{H-NMR}$) spectra.

Antibacterial Activity The minimum inhibitory con-

centrations (MICs) of the new cephalosporins **5** and **12a**—**c** were determined by the standard, two-fold, agar-dilution method. The MIC values of these compounds against several gram-positive and gram-negative bacteria are summarized in Table I and compared with those of cefuzonam (CZON)³⁾ and CAZ (Chart 4).

Compound **5** showed excellent activity against gram-positive bacteria, but poor activity against gram-negative bacteria. However, compounds **12a**—**c** which have a 3-hydroxy-4-pyridone moiety in the *O*-alkyl groups of the 2-alkoxyimino-2-(2-aminothiazol-4-yl)acetamido substituents showed high activity. Compounds **12a** and **12b**, bearing a carboxy group in the *O*-alkyl group, have high activity against gram-negative bacteria. In particular, the anti-pseudomonal activity of **12a** and **12b** was higher than that of CZON and comparable or better than that of CAZ.

Although **12c** showed almost comparable activity to CAZ against *Staphylococcus aureus* and gram-negative bacteria, the activity against *Pseudomonas aeruginosa* was lower.

In conclusion 7-[(*Z*)-2-(2-aminothiazol-4-yl)-2-(3-(3-hydroxy-4-pyridon-1-yl)-3-carboxypropoxyimino)acetamido]-3-(1,2,3-thiadiazol-5-yl)thiomethyl-3-cephem-4-carboxylic acid (**12a**) showed the best anti-pseudomonal activity, as well as broad and excellent activity against gram-negative bacteria, among the tested cephalosporins. The present results, coupled with previous findings,^{1,4} imply that the incorporation of a 3-hydroxy-4-pyridone moiety to cephalosporin tends to improve the anti-pseudomonal activity.

Experimental

Melting points were measured using a Mitamura micro melting point apparatus and are uncorrected. Infrared (IR) spectra were recorded on a JASCO-IR-1 spectrometer. ¹H-NMR spectra were determined with tetramethylsilane as an internal standard on either a Hitachi R-90H NMR spectrometer or a JEOL GX-400 NMR spectrometer, chemical shifts being given in ppm units. Mass spectra (MS) were taken on a Hitachi M-80B mass spectrometer.

3-Diphenylmethoxy-4-pyridon-1-ylacetic Acid (2) Glycine (2.7 g) was dissolved in water (10 ml) containing NaOH (1.4 g) and treated with **1** (1 g) in methanol (10 ml) at room temperature. The mixture was stirred for 20 h at room temperature and concentrated *in vacuo* to 3 ml. The solid was collected by filtration to produce the sodium salt of **2**. The salt was dissolved in water (10 ml), and the solution was adjusted to pH 2.8–3.2 with 5% HCl at 5°C and extracted with CH₂Cl₂. The organic layer was washed with water and brine, dried, and evaporated *in vacuo* to give a pale yellow powder (**2**, 700 mg). mp 179–180°C. IR (Nujol): 1750, 1680 cm⁻¹. ¹H-NMR (90 MHz, CDCl₃-DMSO-*d*₆) δ: 4.38 (2H, s, CH₂), 6.30 (1H, d, *J*=7 Hz, pyridone 5-H), 6.60 (1H, s, CHPh₂), 7.00–7.50 (12H, m, arom.). Field desorption-mass spectrum (FD-MS) *m/z*: 335 (M⁺).

2-(3-Diphenylmethoxy-4-pyridon-1-yl)-4-hydroxybutyric Acid (6a) DL-Homoserine (10 g) was dissolved in water (10 ml) containing NaOH (8.3 g) and treated with **1** (1 g) in methanol (20 ml) at room temperature. The mixture was stirred for 10 h at 80°C and evaporated *in vacuo*. The remaining residue was purified by column chromatography on a Diaion HP-20 using 50% methanol–water as an eluent. The fractions were collected and lyophilized to give the sodium salt (530 mg) of **6a** as a white powder. IR (Nujol): 3200–3300, 1640 cm⁻¹. ¹H-NMR (90 MHz, D₂O, DOH at 4.82) δ: 1.8–3.4 (4H, m, OCH₂CH₂), 4.55–4.75 (1H, m, CH), 6.15 (1H, d, *J*=7 Hz, pyridone 5-H), 6.35 (1H, s, CHPh₂), 7.40 (12H, m, arom.). Secondary ion mass spectrometry (SI-MS) *m/z*: 402 (M+H)⁺.

3-(3-Diphenylmethoxy-4-pyridon-1-yl)-2-hydroxypropionic Acid (7a) Using the procedure described for the preparation of **6a**, the sodium salt

of **7a** was prepared from **1** and DL-isoserine. A white powder. IR (Nujol): 3200–3300, 1640 cm⁻¹. ¹H-NMR (90 MHz, D₂O, DOH at 4.82) δ: 4.10 (2H, m, CH₂), 4.20 (2H, m, CH), 6.42 (1H, s, CHPh₂), 6.60 (1H, d, *J*=7 Hz, pyridone 5-H), 7.30–7.70 (12H, m, arom.). SI-MS *m/z*: 388 (M+H)⁺.

1-(2-Hydroxyethyl)-3-diphenylmethoxy-4-pyridone (8a) A solution of **1** (1 g) in methanol (20 ml) was treated with ethanolamine (2.6 g), and the mixture was stirred for 3 h at room temperature. Evaporation of the solvent *in vacuo* gave a crystalline residue which was triturated in ethyl acetate to give pale yellow crystals (**8a**, 620 mg). mp 185–186°C (CHCl₃-CH₃OH). IR (Nujol): 1640, 1560 cm⁻¹. ¹H-NMR (CDCl₃) δ: 3.15–3.70 (4H, m, OCH₂CH₂), 6.08 (1H, d, *J*=7 Hz, pyridone 5-H), 6.62 (1H, s, CHPh₂), 7.05–7.35 (12H, m, arom.). FD-MS *m/z*: 321 (M⁺). Anal. Calcd for C₂₀H₁₉NO₃: C, 74.75; H, 5.96; N, 4.36. Found: C, 74.96; H, 5.99; N, 4.50.

Diphenylmethyl 2-(3-Diphenylmethoxy-4-pyridon-1-yl)-4-hydroxybutyrate (6b) Compound **6a** (500 mg) was dissolved in water (10 ml) and adjusted to pH 2.8–3.2 with 5% HCl at 5°C. A solution of diphenyldiazomethane in CH₂Cl₂ (10 ml) was added and the mixture was stirred for 1 h. After the mixture was adjusted to pH 7.0 with NaHCO₃, the organic layer was washed with water and brine, dried and evaporated *in vacuo*. The remaining residue was purified by chromatography on silica gel using chloroform–methanol (20:1) as an eluent to give a white powder, which was triturated in ethyl acetate to give colorless crystals (**6b**, 700 mg). mp 178–179°C (EtOAc). IR (Nujol): 3200, 1760, 1640 cm⁻¹. ¹H-NMR (90 MHz, CDCl₃) δ: 2.01–2.55 (2H, m, CH₂), 2.70–3.60 (2H, m, OCH₂), 4.45–4.80 (1H, m, CHCOOCHPh₂), 6.00 (1H, d, *J*=6 Hz, pyridone 5-H), 6.30 (1H, s, OCHPh₂), 6.82 (1H, s, OCHPh₂), 6.80–7.40 (22H, m, arom.). FD-MS *m/z*: 545 (M⁺). Anal. Calcd for C₃₅H₃₁NO₅: C, 77.04; H, 5.73; N, 2.57. Found: C, 76.95; H, 5.60; N, 2.41.

Diphenylmethyl 3-(3-Diphenylmethoxy-4-pyridon-1-yl)-2-hydroxypropionate (7b) Using the procedure described for the preparation of **6b**, this compound was prepared from **7a** and diphenyldiazomethane. A white powder, mp 91–92°C. IR (Nujol): 3200, 1740, 1640 cm⁻¹. ¹H-NMR (90 MHz, CDCl₃) δ: 3.55–3.70 (2H, m, CH₂), 4.15–4.20 (1H, m, CH), 6.05 (1H, d, *J*=7 Hz, pyridone 5-H), 6.20 (1H, s, CHPh₂), 6.85 (1H, s, CHPh₂), 6.90–7.30 (22H, m, arom.). FD-MS *m/z*: 530 (M+H)⁺. Anal. Calcd for C₃₄H₂₉NO₅: C, 76.82; H, 5.50; N, 2.63. Found: C, 76.81; H, 5.38; N, 2.46.

Diphenylmethyl 2-(3-Diphenylmethoxy-4-pyridon-1-yl)-4-phthalimidoxybutyrate (6c) A solution of *N*-hydroxyphthalimide (220 mg), triphenylphosphine (433 mg) and **6b** (600 mg) in tetrahydrofuran (THF) (30 ml) was treated with diethyl azodicarboxylate (288 mg) in THF (5 ml) at 5°C. The reaction mixture was stirred for 1 h at the same temperature, and evaporated *in vacuo*. The remaining residue was purified by column chromatography on silica gel using chloroform–methanol (20:1) as an eluent to give a pale yellow powder (**6c**, 624 mg). mp 89–90°C. IR (Nujol): 1795, 1740, 1640 cm⁻¹. ¹H-NMR (90 MHz, CDCl₃) δ: 2.20–2.60 (2H, m, CH₂), 3.30–4.20 (2H, m, OCH₂), 5.00–5.15 (1H, m, CH), 6.35 (1H, d, *J*=6 Hz, pyridone 5-H), 6.40 (1H, s, CHPh₂), 6.75 (1H, s, CHPh₂), 6.90–7.70 (26H, m, arom.). FD-MS *m/z*: 690 (M)⁺. Anal. Calcd for C₄₃H₃₄N₂O₇: C, 74.77; H, 4.96; N, 4.06. Found: C, 74.51; H, 4.81; N, 3.93.

Diphenylmethyl 3-(3-Diphenylmethoxy-4-pyridon-1-yl)-2-phthalimidoxypropionate (7c) Using the procedure described for the preparation of **6c**, this compound was prepared from **7b** and *N*-hydroxyphthalimide. A white powder, mp 85–86°C. IR (Nujol): 1795, 1740, 1640 cm⁻¹. ¹H-NMR (90 MHz, CDCl₃) δ: 4.10–4.20 (2H, m, CH₂), 4.75–4.85 (2H, m, CH), 6.20 (1H, d, *J*=7 Hz, pyridone 5-H), 6.42 (1H, s, CHPh₂), 6.80 (1H, s, CHPh₂), 6.90–7.70 (26H, m, arom.). FD-MS *m/z*: 676 (M⁺).

1-(2-Phthalimidoxyethyl)-3-diphenylmethoxy-4-pyridone (8b) Using the procedure described for the preparation of **6c**, this compound was prepared from **8a** and *N*-hydroxyphthalimide. A white powder. mp 92–94°C. IR (Nujol): 1795, 1740, 1640 cm⁻¹. ¹H-NMR (90 MHz, CDCl₃) δ: 3.85–4.05 (2H, m, CH₂), 4.06–4.30 (2H, m, CH₂), 6.35 (1H, d, *J*=7 Hz, pyridone 5-H), 6.58 (1H, s, CHPh₂), 7.10–7.75 (16H, m, arom.). FD-MS *m/z*: 467 (M+H)⁺.

(*Z*)-2-(2-Tritylaminothiazol-4-yl)-2-[3-(3-diphenylmethoxy-4-pyridon-1-yl)-3-diphenylmethoxycarbonylpropoxyimino]acetic Acid (10a) A solution of **6c** (780 mg) in CH₂Cl₂ (20 ml) was treated with hydrazine monohydrate (70 mg) at 5°C, and the mixture was stirred for 1 h at 5°C. The insoluble material was removed by filtration, and the filtrate was washed with water, dried and evaporated *in vacuo* to yield crude **6d** as a powder. The powder was dissolved in ethanol (5 ml), and the solution was added to a solution of **9** (380 mg), which was prepared in a usual manner *via* tritylation with tritylchloride followed by hydrolysis with 1N NaOH in methanol from commercially available ethyl 2-oxo-2-(2-aminothiazol-

4-yl)acetate, in chloroform (10 ml) at room temperature. The mixture was stirred at room temperature for 17 h and evaporated *in vacuo*. The remaining residue was purified by column chromatography on Sephadex LH-20 using chloroform-methanol (1:1) as an eluent to give a pale yellow powder (**10a**, 580 mg), mp 145–146 °C (dec.). IR (Nujol): 3400, 1750, 1640 cm⁻¹. ¹H-NMR (90 MHz, CDCl₃) δ: 2.60–2.95 (2H, m, CH₂), 4.05–4.30 (2H, m, OCH₂), 5.05–5.20 (1H, m, CH), 6.25 (1H, s, CHPh₂), 6.70 (1H, s, CHPh₂), 6.80 (1H, d, *J* = 6 Hz, pyridone 5-H), 7.00–7.40 (39H, m, NH, arom.). FD-MS *m/z*: 957 (M + H)⁺.

(Z)-2-(2-Tritylaminothiazol-4-yl)-2-[2-(3-diphenylmethoxy-4-pyridon-1-yl)-1-diphenylmethoxycarbonylthioxyimino]acetic Acid (10b) Using the procedure described for the preparation of **10a**, this compound was prepared from **7d** and **9**. mp 144–146 °C (dec.). IR (Nujol): 1740, 1640 cm⁻¹. ¹H-NMR (90 MHz, CDCl₃) δ: 4.10–4.20 (2H, m, CH₂), 4.95–5.05 (1H, m, CH), 6.20 (1H, s, CHPh₂), 6.60 (1H, d, *J* = 7 Hz, pyridone 5-H), 6.70 (1H, s, CHPh₂), 6.80 (1H, s, thiazole 5-H), 7.10–7.70 (38H, m, arom., NH). SI-MS *m/z*: 943 (M + H)⁺.

(Z)-2-(2-Tritylaminothiazol-4-yl)-2-[2-(3-diphenylmethoxy-4-pyridon-1-yl)ethoxyimino]acetic Acid (10c) Using the procedure described for the preparation of **10a**, this compound was prepared from **8c** and **9**. mp 159–161 °C (dec.). IR (Nujol): 3450, 1640 cm⁻¹. ¹H-NMR (90 MHz, CDCl₃) δ: 3.80–3.95 (2H, m, CH₂), 4.10–4.30 (2H, m, CH₂), 6.40 (1H, s, CHPh₂), 6.60 (1H, d, *J* = 7 Hz, pyridone 5-H), 6.80 (1H, s, thiazole 5-H), 7.05–7.40 (28H, m, arom., NH). FD-MS *m/z*: 733 (M + H)⁺.

p-Methoxybenzyl 7-[(Z)-2-(2-Tritylaminothiazol-4-yl)-2-(3-diphenylmethoxy-4-pyridon-1-yl)-3-(3-hydroxy-4-pyridon-1-yl)acetamido]-3-(1,2,3-thiadiazol-5-yl)thiomethyl-3-cephem-4-carboxylate (4) To a solution of **3** (223 mg) and **2** (160 mg) in dimethylformamide (DMF) (5 ml), *N,N*-dicyclohexylcarbodiimide (113 mg) was added at 0 °C and the mixture was stirred for 3 h under ice-cooling. The solid was filtered off, and the filtrate was diluted with ethyl acetate (30 ml), washed with water and brine, and then evaporated *in vacuo*. The remaining residue was purified by column chromatography on silica gel using chloroform-methanol (20:1) as an eluent to give a pale yellow powder (**4**, 253 mg). IR (Nujol): 1770, 1760 cm⁻¹. ¹H-NMR (90 MHz, CDCl₃) δ: 3.46 (2H, AB system δ_A 3.356, δ_B 3.55, *J* = 13 Hz, 2-H), 3.82 (3H, s, OCH₃), 4.07 (2H, AB system δ_A 4.03, δ_B 4.12, *J* = 11 Hz, 3'-H), 4.43 (2H, AB system δ_A 4.35, δ_B 4.52, *J* = 14 Hz, NCH₂), 4.85 (1H, d, *J* = 5 Hz, 6-H), 5.10 (2H, br s, CH₂Ph), 5.60 (1H, dd, *J* = 5, 8 Hz, 7-H), 6.38 (1H, s, CHPh₂), 6.50 (1H, d, *J* = 7 Hz, pyridone 5-H), 6.85 (2H, d, *J* = 12 Hz, C₆H₄-OCH₃), 7.23 (2H, d, *J* = 12 Hz, C₆H₄-OMe), 7.15–7.40 (12H, m, arom.), 8.40 (1H, s, thiadiazole 4-H), 9.42 (1H, d, *J* = 8 Hz, CONH).

p-Methoxybenzyl 7-[(Z)-2-(2-Tritylaminothiazol-4-yl)-2-(3-(3-diphenylmethoxy-4-pyridon-1-yl)-3-diphenylmethoxycarbonylpropoxyimino)acetamido]-3-(1,2,3-thiadiazol-5-yl)thiomethyl-3-cephem-4-carboxylate (11a) A solution of POCl₃ (120 mg) in CH₂Cl₂ (3 ml) was added dropwise to a solution of **3** (310 mg) and **10a** (500 mg) in CH₂Cl₂ (30 ml) containing pyridine (0.20 ml) at -20 °C. After stirring for 2 h at -20 to -10 °C, the reaction mixture was poured into water (10 ml). The organic layer was washed with water and brine, dried, and evaporated *in vacuo*. The remaining residue was purified by column chromatography on silica gel using chloroform-methanol (30:1) as an eluent to give a pale yellow powder (**11a**, 520 mg). IR (Nujol): 1770, 1760 cm⁻¹. ¹H-NMR (90 MHz, CDCl₃) δ: 2.25–2.75 (2H, m, CH₂), 3.20–4.40 (6H, m, 2-H, 3-H, OCH₂), 3.80 (3H, s, OCH₃), 4.50–4.70 (1H, m, CH), 4.85 (1H, bd, *J* = 5 Hz, 6-H), 5.05–5.15 (2H, m, CH₂Ph), 5.70 (1H, m, 7-H), 6.25–7.45 (46H, m, arom., NH, CHPh₂, CHPh₂), 7.60 (1H, d, *J* = 8 Hz, CONH), 8.38 (1H, br s, thiadiazole 4-H).

p-Methoxybenzyl 7-[(Z)-2-(2-Tritylaminothiazol-4-yl)-2-(2-(3-diphenylmethoxy-4-pyridon-1-yl)-1-diphenylmethoxycarbonylthioxyimino)acetamido]-3-(1,2,3-thiadiazol-5-yl)thiomethyl-3-cephem-4-carboxylate (11b) Using the procedure described for the preparation of **11a**, this compound was prepared from **10b** and **3**. A white powder. IR (Nujol): 1770, 1760 cm⁻¹. ¹H-NMR (90 MHz, CDCl₃) δ: 3.40 (2H, br s, 2-H), 3.75 (3H, s, OCH₃), 3.90–4.18 (4H, m, CH₂, 3'-H), 4.82 (1H, d, *J* = 5 Hz, 6-H), 5.10 (3H, m, CH, CH₂Ph), 5.70 (1H, dd, *J* = 5, 8 Hz, 7-H), 6.50–7.30 (46H, m, arom., CHPh₂, CHPh₂, NH), 8.30 (1H, s, thiadiazole 4-H).

p-Methoxybenzyl 7-[(Z)-2-(2-Tritylaminothiazol-4-yl)-2-(2-(3-diphenylmethoxy-4-pyridon-1-yl)ethoxyimino)acetamido]-3-(1,2,3-thiadiazol-5-yl)-

thiomethyl-3-cephem-4-carboxylate (11c) Using the procedure described for the preparation of **11a**, this compound was prepared from **10c** and **3**. A white powder. IR (Nujol): 1770, 1760 cm⁻¹. ¹H-NMR (90 MHz, CDCl₃) δ: 3.40 (2H, br s, 2-H), 3.72 (3H, s, OCH₃), 3.80–4.05 (4H, m, CH₂, 3'-H), 4.25–4.45 (2H, m, CH₂), 4.80 (1H, d, *J* = 5 Hz, 6-H), 5.05 (2H, br s, CH₂Ph), 5.65 (1H, dd, *J* = 5, 8 Hz, 7-H), 6.45–7.30 (35H, m, arom., thiazole 5-H, CHPh₂, NH), 8.30 (1H, br s, thiadiazole 4-H).

7-(3-Hydroxy-4-pyridon-1-ylacetamido)-3-(1,2,3-thiadiazol-5-yl)thiomethyl-3-cephem-4-carboxylic Acid (5) Compound **4** (200 mg) was treated with anisole (0.5 ml) and CF₃COOH (2 ml) at 0 °C for 1 h. The solution was diluted with isopropyl ether and the precipitate was triturated in isopropyl ether (100 ml). The resulting powder was dissolved in a mixture of water (1 ml) and ethyl acetate (3 ml) and the mixture was adjusted to pH 7.2 with NaHCO₃. The aqueous layer was chromatographed on a column of Diaion HP-20 using water as an eluent. The fractions were collected and lyophilized to give the sodium salt (80 mg) of **5** as an amorphous powder. IR (Nujol): 3150–3350, 1770, 1690 cm⁻¹. ¹H-NMR (400 MHz, D₂O DOH at 4.82) δ: 3.61 (2H, AB system, δ_A 3.45, δ_B 3.77, *J* = 17 Hz, 2-H), 4.16 (2H, AB system, δ_A 3.93, δ_B 4.40, *H* = 13.6 Hz, 3'-H), 4.95 (2H, s, CH₂), 5.12 (1H, d, *J* = 5 Hz, 6-H), 5.62 (1H, d, *J* = 5 Hz, 7-H), 6.60 (1H, d, *J* = 7 Hz, pyridone 5-H), 7.62 (1H, s, pyridone 2-H), 7.63 (1H, d, *J* = 7 Hz, pyridone 6-H), 8.72 (1H, s, thiadiazole 4-H). SI-MS *m/z*: 504 (M + H)⁺.

7-[(Z)-2-(2-Aminothiazol-4-yl)-2-(3-(3-hydroxy-4-pyridon-1-yl)-3-carboxypropoxyimino)acetamido]-3-(1,2,3-thiadiazol-5-yl)thiomethyl-3-cephem-4-carboxylic Acid (12a) Using the procedure described for the preparation of **5**, the disodium salt of **12a** was prepared from **11a**. A white powder. IR (Nujol): 3150–3350, 1760 cm⁻¹. ¹H-NMR (400 MHz, D₂O DOH at 4.82) δ: 2.53 (1H, m, CH₂), 2.86 (1H, m, CH₂), 3.66 (1H, AB system, δ_A 3.47, δ_B 3.83, *J* = 17 Hz, 2-H), 3.69 (1H, AB system, δ_A 3.50, δ_B 3.87, *J* = 18 Hz, 2-H), 3.90–4.60 (5H, m, 3'-H, OCH₂, CH), 5.27 (1/2H, d, *J* = 5 Hz, 6-H), 5.29 (1/2H, d, *J* = 5 Hz, 6-H), 5.88 (1/2H, d, *J* = 5 Hz, 7-H), 5.89 (1/2H, d, *J* = 5 Hz, 7-H), 6.68 (1/2H, d, *J* = 7 Hz, pyridone 5-H), 6.70 (1/2H, d, *J* = 7 Hz, pyridone 5-H), 7.10 (1H, br s, thiazole 5-H), 7.70 (1H, s, pyridone 2-H), 7.72 (1H, d, *J* = 7 Hz, pyridone 6-H), 8.80 (1H, s, thiadiazole 4-H). SI-MS *m/z*: 739 (M + H)⁺.

7-[(Z)-2-(2-Aminothiazol-4-yl)-2-(2-(3-hydroxy-4-pyridon-1-yl)-1-carboxyethoxyimino)acetamido]-3-(1,2,3-thiadiazol-5-yl)thiomethyl-3-cephem-4-carboxylic Acid (12b) Using the procedure described for the preparation of **5**, the disodium salt of **12b** was prepared from **11b**. A white powder. IR (Nujol): 3200–3350, 1770, 1620–1610 cm⁻¹. ¹H-NMR (400 MHz, D₂O DOH at 4.82) δ: 3.63 (2H, AB system, δ_A 3.46, δ_B 3.80, *J* = 16 Hz, 2-H), 4.22 (2H, AB system, δ_A 3.98, δ_B 4.46, *J* = 13 Hz, 3'-H), 4.58–5.15 (3H, m, CH₂-CH), 5.21 (1H, m, 6-H), 5.81 (1H, m, 7-H), 6.60 (1H, d, *J* = 7 Hz, pyridone 5-H), 7.11 (1H, s, thiazole 5-H), 7.70 (2H, m, pyridone 2-H, 6-H), 8.77 (1H, s, thiadiazole 4-H). SI-MS *m/z*: 725 (M + H)⁺.

7-[(Z)-2-(2-Aminothiazol-4-yl)-2-(3-hydroxy-4-pyridon-1-yl)ethoxyimino]acetamido]-3-(1,2,3-thiadiazol-5-yl)thiomethyl-3-cephem-4-carboxylic Acid (12c) Using the procedure described for the preparation of **5**, the sodium salt of **12c** was prepared from **11c**. A white powder. IR (Nujol): 3150–3300, 1760 cm⁻¹. ¹H-NMR (400 MHz, D₂O DOH at 4.82) δ: 3.50 (2H, AB system, δ_A 3.31, δ_B 3.70, *J* = 16 Hz, 2-H), 4.18 (2H, AB system, δ_A 3.95, δ_B 4.41, *J* = 13 Hz, 3'-H), 4.42 (2H, m, CH₂), 4.75 (2H, m, CH₂), 5.08 (1H, d, *J* = 5 Hz, 6-H), 5.70 (1H, *J* = 5 Hz, 7-H), 6.62 (1H, d, *J* = 7 Hz, pyridone 5-H), 7.12 (1H, s, thiazole 5-H), 7.70 (1H, s, pyridone 2-H), 7.72 (1H, d, *J* = 7 Hz, pyridone 6-H), 8.82 (1H, s, thiadiazole 4-H). SI-MS *m/z*: 659 (M + H)⁺.

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