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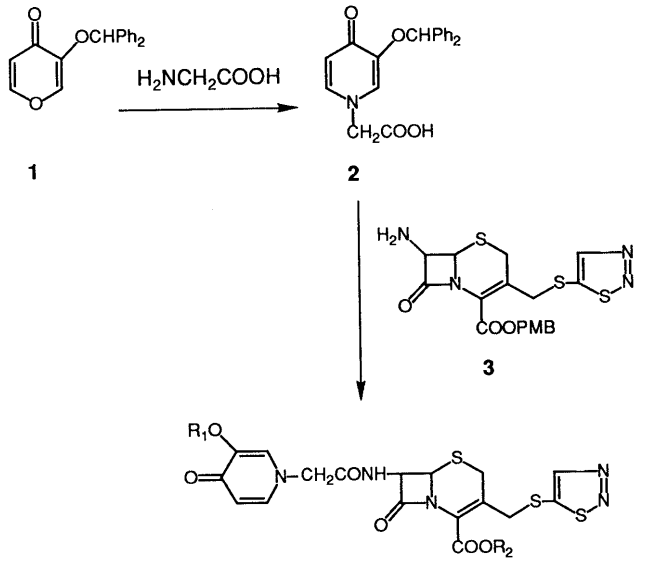
Synthesis and antibacterial activity of 7-[(*Z*)-2-(2-aminothiazol-4-yl)-2-(3-(3-hydroxy-4-pyridon-1-yl)-3-carboxypropoxyimino)acetamido]-3-(1,2,3-thiadiazol-5-yl)thiomethyl-3-cephem-4-carboxylic acid (12a) and its related compounds are described. Compound 12a exhibited excellent antibacterial activity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

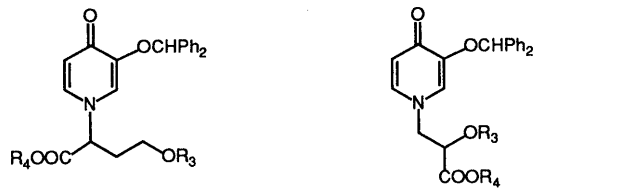


1 2 3

4: R_1=$CHPh_2$, R_2=PMB
5: R_1= H, R_2= H

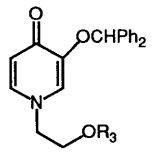
PMB = *p*-methoxybenzyl

Chart 1

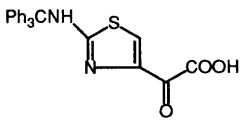


6a : R_3= H, R_4= H
6b : R_3= H, R_4=$CHPh_2$
6c : R_3=Phth, R_4=$CHPh_2$
6d : R_3=NH_2, R_4=$CHPh_2$

7a : R_3= H, R_4= H
7b : R_3= H, R_4=$CHPh_2$
7c : R_3=Phth, R_4=$CHPh_2$
7d : R_3=NH_2, R_4=$CHPh_2$



8a : R_3= H
8b : R_3=Phth
8c : R_3=NH_2



9

Phth=phthalimide

Chart 2

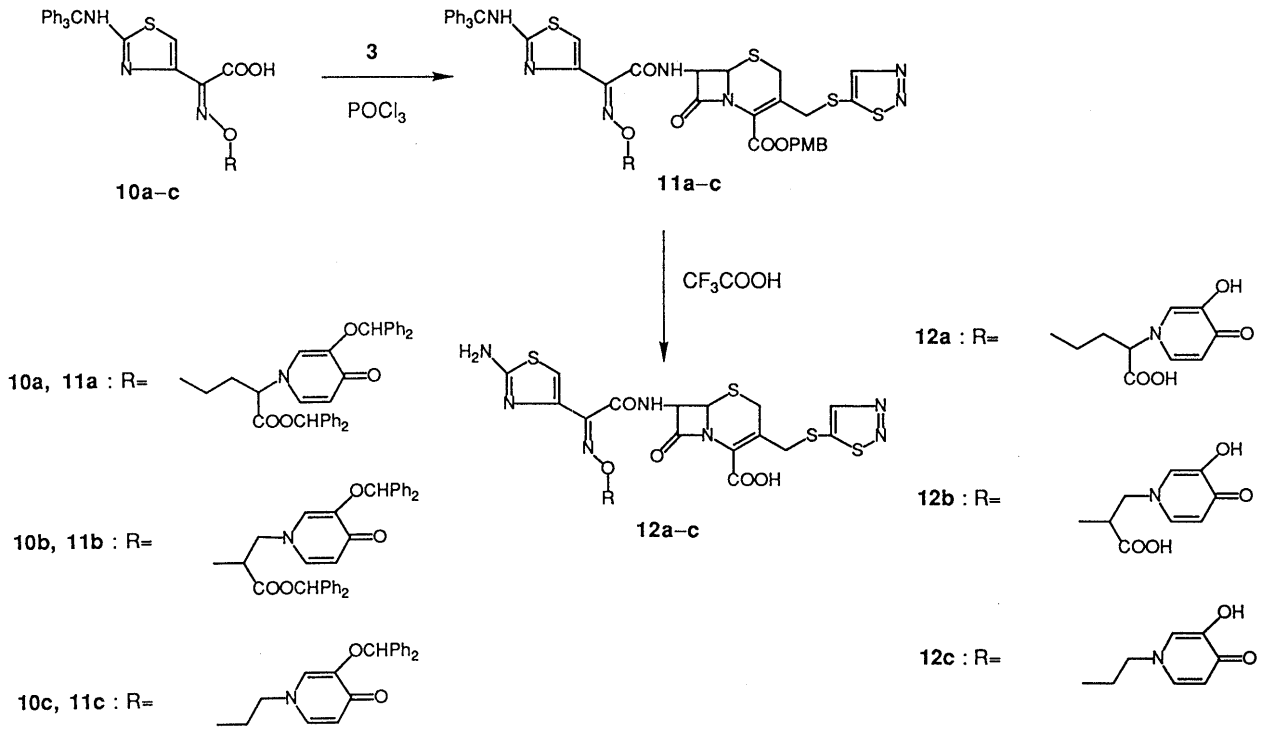


Chart 3

TABLE I. *in Vitro* MICs (μg/ml)

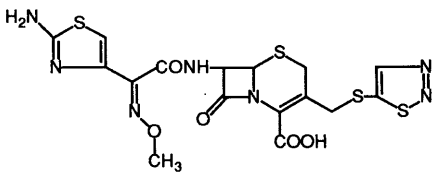
Test organisms	5	12a	12b	12c	CZON	CAZ
Staphylococcus aureus 606	0.78	12.5	25	3.13	0.39	6.25
S. aureus SMITH (1)	0.39	12.5	25	1.56	0.39	3.13
S. epidermidis ATCC14990	0.39	12.5	25	0.78	0.39	6.25
Bacillus subtilis ATCC6633	0.20	3.13	50	0.78	0.39	3.13
Escherichia coli W3630 RGN823	50	0.78	1.56	1.56	0.10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

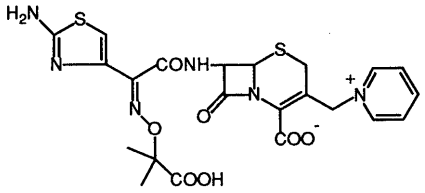
A Mitsunobu reaction of **6b**, **7b** and **8a** with *N*-hydroxyphthalimide, and subsequent removal of the phthaloyl groups of **6c**, **7c** and **8b** produced the alkoxyamines **6b**, **7d** and **8c** in good yields. The alkoxyamines were allowed to react with 2-oxo-2-(2-tritylaminothiazol-4-yl)-acetic 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}H-NMR) spectra.

Antibacterial Activity The minimum inhibitory concentrations (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.



cefuzonam (CZON)



ceftazidime (CAZ)

Chart 4

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. ^{1}H-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] (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 CH_2Cl_2. 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}. ^{1}H-NMR (90 MHz, $CDCl_3$–DMSO-d_6) δ: 4.38 (2H, s, CH_2), 6.30 (1H, d, J=7 Hz, pyridone 5-H), 6.60 (1H, s, C<u>H</u>Ph$_2$), 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-hydroxybutylic 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}. ^{1}H-NMR (90 MHz, D_2O, DOH at 4.82) δ: 1.8—3.4 (4H, m, OC<u>H</u>$_2$C<u>H</u>$_2$), 4.55—4.75 (1H, m, CH), 6.15 (1H, d, J=7 Hz, pyridone 5-H), 6.35 (1H, s, C<u>H</u>Ph$_2$), 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}. ^{1}H-NMR (90 MHz, D_2O, DOH at 4.82) δ: 4.10 (2H, m, CH_2), 4.20 (2H, m, CH), 6.42 (1H, s, C<u>H</u>Ph$_2$), 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 ($CHCl_3$–CH_3OH). IR (Nujol): 1640, 1560 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.15—3.70 (4H, m, OCH_2CH_2), 6.08 (1H, d, J=7 Hz, pyridone 5-H), 6.62 (1H, s, C<u>H</u>Ph$_2$), 7.05—7.35 (12H, m, arom.). FD-MS *m/z*: 321 (M$^+$). *Anal.* Calcd for $C_{20}H_{19}NO_3$: 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-hydroxybutylate (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 CH_2Cl_2 (10 ml) was added and the mixture was stirred for 1 h. After the mixture was adjusted to pH 7.0 with $NaHCO_3$, 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}. ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 2.01—2.55 (2H, m, CH_2), 2.70—3.60 (2H, m, OCH_2), 4.45—4.80 (1H, m, C<u>H</u>COOCHPh$_2$), 6.00 (1H, d, J=6 Hz, pyridone 5-H), 6.30 (1H, s, OC<u>H</u>Ph$_2$), 6.82 (1H, s, OC<u>H</u>Ph$_2$), 6.80—7.40 (22H, m, arom.). FD-MS *m/z*: 545 (M$^+$). *Anal.* Calcd for $C_{35}H_{31}NO_5$: 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}. ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 3.55—3.70 (2H, m, CH_2), 4.15—4.20 (1H, m, CH), 6.05 (1H, d, J=7 Hz, pyridone 5-H), 6.20 (1H, s, C<u>H</u>Ph$_2$), 6.85 (1H, s, C<u>H</u>Ph$_2$), 6.90—7.30 (22H, m, arom.). FD-MS *m/z*: 530 (M−H)$^+$. *Anal.* Calcd for $C_{34}H_{29}NO_5$: 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-phthalimidooxybutylate (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}. ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 2.20—2.60 (2H, m, CH_2), 3.30—4.20 (2H, m, OCH_2), 5.00—5.15 (1H, m, CH), 6.35 (1H, d, J=6 Hz, pyridone 5-H), 6.40 (1H, s, $CHPh_2$), 6.75 (1H, s, C<u>H</u>Ph$_2$), 6.90—7.70 (26H, m, arom.). FD-MS *m/z*: 690 (M)$^+$. *Anal.* Calcd for $C_{43}H_{34}N_2O_7$: 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-phthalimidooxypropionate (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}. ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 4.10—4.20 (2H, m, CH_2), 4.75—4.85 (2H, m, CH), 6.20 (1H, d, J=7 Hz, pyridone 5-H), 6.42 (1H, s, C<u>H</u>Ph$_2$), 6.80 (1H, s, C<u>H</u>Ph$_2$), 6.90—7.70 (26H, m, arom.). FD-MS *m/z*: 676 (M$^+$).

1-(2-Phthalimidooxyethyl)-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}. ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 3.85—4.05 (2H, m, CH_2), 4.06—4.30 (2H, m, CH_2), 6.35 (1H, d, J=7 Hz, pyridone 5H), 6.58 (1H, s, C<u>H</u>Ph$_2$), 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 CH_2Cl_2 (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 fitration, 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 1 N 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}. ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 2.60—2.95 (2H, m, CH_2), 4.05—4.30 (2H, m, OCH_2), 5.05—5.20 (1H, m, CH), 6.25 (1H, s, $C\underline{H}Ph_2$), 6.70 (1H, s, $C\underline{H}Ph_2$), 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-diphenylmethoxycarbonylethoxyimino]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}. ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 4.10—4.20 (2H, m, CH_2), 4.95—5.05 (1H, m, CH), 6.20 (1H, s, $C\underline{H}Ph_2$), 6.60 (1H, d, J=7 Hz, pyridone 5-H), 6.70 (1H, s, $C\underline{H}Ph_2$), 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}. ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 3.80—3.95 (2H, m, CH_2), 4.10—4.30 (2H, m, CH_2), 6.40 (1H, s, $C\underline{H}Ph_2$), 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-(3-Diphenylmethoxy-4-pyridon-1-ylacetamido)-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}. ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 3.46 (2H, AB system δ_A 3.356, δ_B 3.55, J=13 Hz, 2-H), 3.82 (3H, s, OCH_3), 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, NCH_2), 4.85 (1H, d, J=5 Hz, 6-H), 5.10 (2H, br s, $C\underline{H}_2Ph$), 5.60 (1H, dd, J=5, 8 Hz, 7-H), 6.38 (1H, s, $C\underline{H}Ph_2$), 6.50 (1H, d, J=7 Hz, pyridone 5-H), 6.85 (2H, d, J=12 Hz, C_6H_4–OCH_3), 7.23 (2H, d, J=12 Hz, C_6H_4–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 $POCl_3$ (120 mg) in CH_2Cl_2 (3 ml) was added dropwise to a solution of **3** (310 mg) and **10a** (500 mg) in CH_2Cl_2 (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}. ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 2.25—2.75 (2H, m, CH_2), 3.20—4.40 (6H, m, 2-H, 3-H, OCH_2), 3.80 (3H, s, OCH_3), 4.50—4.70 (1H, m, CH), 4.85 (1H, bd, J=5 Hz, 6-H), 5.05—5.15 (2H, m, $C\underline{H}_2Ph$), 5.70 (1H, m, 7-H), 6.25—7.45 (46H, m, arom., NH, $C\underline{H}Ph_2$, $C\underline{H}Ph_2$), 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-diphenylmethoxycarbonylethoxyimino)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}. ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 3.40 (2H, br s, 2-H), 3.75 (3H, s, OCH_3), 3.90—4.18 (4H, m, CH_2, 3′-H), 4.82 (1H, d, J=5 Hz, 6-H), 5.10 (3H, m, CH, $C\underline{H}_2Ph$), 5.70 (1H, dd, J=5, 8 Hz, 7-H), 6.50—7.30 (46H, m, arom., $C\underline{H}Ph_2$, $C\underline{H}Ph_2$, 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}. ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 3.40 (2H, br s, 2-H), 3.72 (3H, s, OCH_3), 3.80—4.05 (4H, m, CH_2, 3′-H), 4.25—4.45 (2H, m, CH_2), 4.80 (1H, d, J=5 Hz, 6-H), 5.05 (2H, br s, $C\underline{H}_2Ph$), 5.65 (1H, dd, J=5, 8 Hz, 7-H), 6.45—7.30 (35H, m, arom., thiazole 5-H, $C\underline{H}Ph_2$, 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 CF_3COOH (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 $NaHCO_3$. 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}. ^{1}H-NMR (400 MHz, D_2O 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, CH_2), 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}. ^{1}H-NMR (400 MHz, D_2O DOH at 4.82) δ: 2.53 (1H, m, CH_2), 2.86 (1H, m, CH_2), 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, OCH_2, 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}. ^{1}H-NMR (400 MHz, D_2, 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, CH_2–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}. ^{1}H-NMR (400 MHz, D_2O, 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, CH_2), 4.75 (2H, m, CH_2), 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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