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Synthetic Cephalosporin Derivatives

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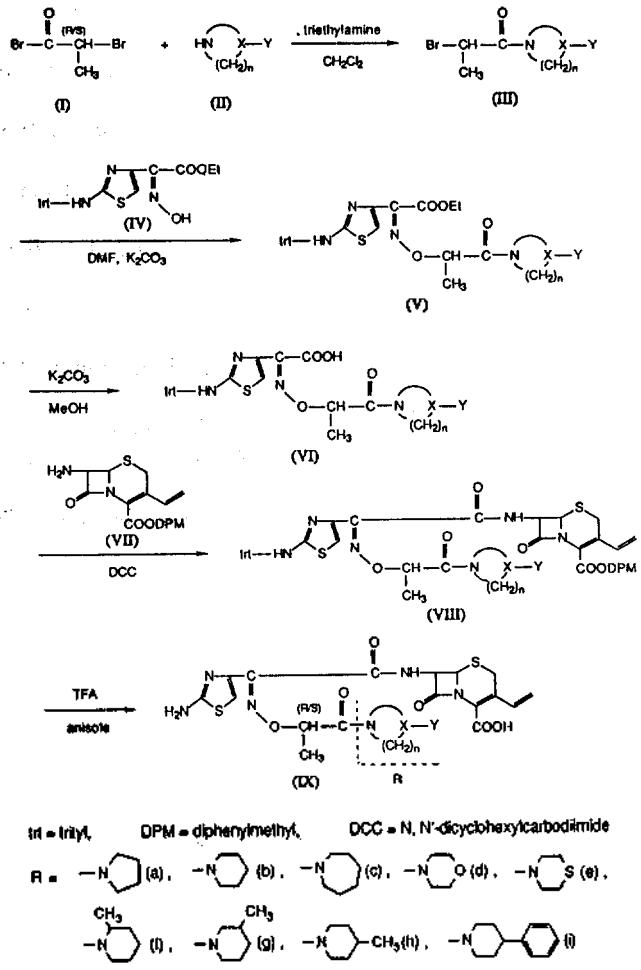
The synthesis and some biological properties of 7β-[2-(Z)-(2-aminothiazole-4-yl)-2-(N-substitutedcarbonyl)ethoxyimino-acetamido]-3-vinyl-3-cephem-4-carboxylic acid are described. The effect of substituents on the carbamoyl group in the 7-side chain were investigated in order to improve antibacterial activities. Two of these new orally active β-lactam derivatives showed wide expanded antimicrobial activities against Gram-positive and Gram-negative bacteria, including *Pseudomonas aeruginosa*, as well as good stability to β-lactamases.

Introduction

Since the discovery of penicillins more than sixty years ago[1], the β-lactam family has grown enormously to include a wide variety of structural types[2]. In 1945, a sardinian bacteriologist, Brotzu found a strain of *Cephalosporium acremonium* which produced antibiotic material with a broader spectrum of activity[3]. But the early developed compounds possessed a relatively narrow spectrum of activity and the weakness of resistance caused by β-lactamase appeared to be a serious problem. However the use of 6-aminopenicillanic acid(6-APA) and 7-aminocephalosporanic acid(7-ACA) as a synthetic intermediate enabled a large scale production and afforded a wide range of compounds with a broad spectrum of activity. In spite of their high antibacterial acitivity and their broad antimicrobial spectrum, some bacteral species or strains are not inhibited at concentrations sufficient of successful chemotherapy. They are usually not effective against some clinically important bacteria, including *Pseudomonas* and some *Proteus* species[4]. It was not until 1980 when cefotaxime, a semisynthetic cephalosporin prepared by direct acylation of 7-ACA by 2-(2-aminothiazone-4-yl)-2-syn-methoxyiminoacetic acid, was available for clinical use[5]. It has a high antibacterial activity against all tested strains of Gram-positive and Gram-negative aerobic and facultatively anaerobic bacteria. The syn-methoxyimino(generally alkoxyimino) group is known to play an important role in the stability to the β-lactamase-releasing Gram-negative bacteria. In contrast to the remarkable improvements of the injectable β-lactam antibiotics, progress has been less evident among the oral β-lactam antibiotics such as the cephalosporins. Cefixime, developed by Fujisawa, would be the most potent antibiotics and is characterized by displacement of the 3-acetoxymethyl group in cefotaxime with vinyl moiety. It shows also a relatively high antibacterial activity against Gram-positive and Gram-negative bacteria[6].

Results and Discussion

Recently many new β-lactam antibiotics modified with 7β-[2-(2-aminothiazole-4-yl)-2-(substituted carbamoylmethoxyimino)acetamido]group at the C-7 position and with various heteroaromatics at the C-3 position are reported[7]. In the course of our extensive research on the modification of cephalosporin, efforts has been focused on synthesizing new



Scheme 1

oral cephalosporins with improved antibacterial activity against a variety of Gram-positive and Gram-negative bacteria including *Pseudomonas aeruginosa*. We studied cephalosporins bearing a basic carbamoyl alkoxyimino group instead of a acidic carboxymethoxyimino group in the 7-side chain of cefixime. Most 7β-[2-[2-aminothiazole-4-yl)-2-(N-substituted carbonylethoxyimino)acetamido]-3-vinyl-3-cephem-4-carboxylic acids were prepared according to the synthetic route shown in Scheme 1. Acylation of the appropriate cyclic amines(II) with (R/S)-2-bromopropionyl bromides(I)[8], followed by alkylation with 2-(Z)-(2-tritylaminothiazol-4-yl)hydroxyimino acetic acid ethyl ester(IV) in the presence of base such as K_2CO_3, afforded the 2-aminothiazole derivatives(V). The acid compounds(VI) were made by hydrolysis of these corresponding esters(V) with K_2CO_3 and the coupling of the α-oxyiminoacetic acid derivatives with protected 7-amino cephalosporin compounds(VII) was accomplished *via* the DCC(N,N'-dicyclohexylcarbodiimide) method to give the protected final compounds(VIII). The protecting groups of these compounds were generally removed with trifluoroacetic acid and anisole to afford the desired final β-lactam compounds(IX). The MIC(minimum inhibitory concentration) values of this series of new cephalosporins were shown in Table 1 and determined by the standard serial agar dilution method against selected strains of Gram-positive and Gramnegative bacteria including *Pseudomonas aeruginosa*[9].

Table 1. MIC(Minimum Inhibitory Concentration) Values of the Selected Cephalosporins

No.	Strains	IXc	IXe	Cefixime
1	*Streptococcus pyogenes* 308	0.025	0.013	0.098
2	*Streptococcus pyogenes* 77	0.013	25	50
3	*Streptococcus faecium* MD 8b	100	>100	>100
4	*Staphylococcus aureus* SG 511	6.25	6.25	25
5	*Staphylococcus aureus* 285	6.25	6.25	25
6	*Staphylococcus aureus* 503	6.25	6.25	25
7	*Escherichia coli* O 55	0.781	0.781	0.195
8	*Escherichia coli* DC 0	3.125	3.125	0.781
9	*Escherichia coli* DC 2	0.098	0.098	0.195
10	*Escherichia coli* TEM	3.125	3.125	0.391
11	*Escherichia coli* 1507E	6.25	3.125	0.931
12	*Pseudomonas aeruginosa* 9027	100	100	100
13	*Pseudomonas aeruginosa* 1592E	100	>100	100
14	*Pseudomonas aeruginosa* 1771	50	50	50
15	*Pseudomonas aeruginosa* 1771M	0.781	0.781	0.195
16	*Salmonella typhimirium*	6.25	3.125	0.195
17	*Klebsiella oxytoca* 1082E	6.25	6.25	0.195
18	*Klebsiella aerogenes* 1522E	6.25	6.25	0.049
19	*Enterobacter cloacae* P 99	>100	>100	>100
20	*Enterobacter cloacae* 1321E	1.563	1.563	0.025

Most cephalosporins prepared showed excellent activities against Gram-positive bacteria, especially *Staphylococcus aureus* and good activities against Gram-negative strains.

Among them, compound IXc and IXe, which bears homopiperidine and thiomorpholine group respectively, showed much higher antibacterial activities against Gram-positive bacteria and similiar or in some extent inferior results against Gram-negative strains than cefixime. Because of the excellent antibacterial activities of this series of compounds, further modifications with respect to cyclic amino or alkoxyimino substituent will be continued in order to improve antimicrobial activity.

Experimental

Melting Points were measured on Thomas Hoover Capillary Melting Point Appartus and uncorrected. ^{1}H-NMR data was obtained by recording the spectra on a Bruker AM-200 or JEOL JNM-PMX 60SI spectrometer using TMS as an internal standard. Column chromatography was performed, if necessary, using Merck silica gel 60(70-230 mesh). 7-ACA was purchased from Lark Chem. Co. Italy and 3-vinyl derivative was prepared according to the literature.[6]

General Procedure for the Preparation of Amides (III). 0.02 Mole of cyclic(or heterocyclic) amine and the same equivalent of triethylamine were dissolved in 50 m*l* methylene chloride and coold to −10 °C. 0.02 mole of 2-bromopropionyl bromide was dropped slowly to the above solution and the solution was stirred for an hour at room temperature. Reaction mixture was washed with water several times and after the evaporation of solvent was obtained the oily product.

General Procedure for the Preparation of V. 0.01 Mole of ethyl-(Z)-2-(2-tritylaminothiazole-4-yl)-hydroxy-

imino acetate(IV) and 0.012 mole of K_2CO_3 were dissolved in 20 m*l* DMF. After the mixture was stirred for 10 minutes at room temperature, 0.01 mole of above synthesized amide(III) was dropped slowly to this solution. After being stirred for 5 hours, 200 m*l* water water was added drop by drop and the whole reaction mixture was extracted with 100 m*l* methylene chloride and the organic layer was washed with 10% K_2CO_3 solution. Solvent was removed by rotary evaporator and was obtained the product as a pale yellow solid.

General Procedure for the Hydrolysis of (V)(synthesis of VI). 0.0086 Mole of the above prepared ester(IV) was dissolved in 150 m*l* of 80% methanol. After the addition of 0.03 mole K_2CO_3, the reaction mixture was refluxed for 5 hours. Methanol was removed at reduced pressure and was added 50 m*l* of water and 10 m*l* of ethyl acetate to this solution.

The solution was acidified to pH 2 with dilute HCl. Organic phase was washed with water several times and dried over anhydrous $MgSO_4$. Evaporation of solvent afforded the corresponding acid as a pale yellow solid.

General Procedure for the Coupling Between VI and VII(3-vinyl cephem). 0.002 Mole of IV and the same equivalent of VII was added in 20 m*l* dried methylene chloride. The solution was cooled to 0 °C and 0.002 mole of DCC (N,N'-dicyclohexylcarbodiimide) was added slowly. The mixture was stirred for half an hours at 0 °C and for 2 hours at room temperature. Dicyclohexylurea was removed by filtration and the residue was concentrated to furnish the crude product, which was purified by column chromatography(hexane: ethylacetate = 1:1).

General Procedure for the Deprotection of VIII(synthesis of IX). To the solution of 0.001 mole of VIII in 5 m*l* methylene chloride was added 3 m*l* anisole and 40 m*l* of trifluoroacetic acid with constant ice-cooling. The mixture was agitated for an hour with cooling and the stirring was continued for 5 hours at room temperature. Trifluoroacetic acid was removed by concentration and the addition of 50 m*l* isopropyl ether induced precipitation which was dissolved in 30 m*l* of 5% $NaHCO_3$ solution. After washing with ethyl acetate, the aqueous layer was acidified to pH 2 with 5% HCl solution.

The mixture was again extracted with 20 m*l* ethyl acetate and the organic phase was washed with NaCl solution and water. Evaporation of ethyl acetate provided the product as a white solid.

Amides

N-(2-Bromopropionyl)-pyrrolidine(IIIa). Yield: 85%, ^{1}H-NMR: δ($CDCl_3$); 1.65(br, 4H), 1.75)d, 3H, $-CH_3$), 3.55(br, 4H), 4.70(q, 1H, -CH).

N-(2-Bromopropionyl)-piperidine(IIIb). Yield: 87%, ^{1}H-NMR: δ($CDCl_3$); 1.70(br, 6H), 1.85(d, 3H, $-CH_3$), 3.50(br, 4H), 4.70(q, 1H, -CH).

N-(2-Bromopropionyl)-homopiperidine(IIIc). Yield: 90%, ^{1}H-NMR: δ($CDCl_3$); 1.68(br, 8H), 1.80(d, 3H, $-CH_3$), 3.55(br, 4H), 4.75(q, 1H, -CH).

N-(2-Bromopropionyl)-morpholine(IIId). Yield: 86%, ^{1}H-NMR: δ($CDCl_3$); 1.78(d, 3H, $-CH_3$), 3.63(br, 8H), 4.65(q, 1H, -CH).

N-(2-Bromopropionyl)-thiomorpholine(IIIe). Yield: 85%, ^{1}H-NMR: δ($CDCl_3$); 1.75(d, 3H, $-CH_3$), 2.70(br, 4H), 3.70(br, 4H), 4.70(q, 1H, -CH).

N-(2-Bromopropionyl)-2-methylpiperidine(IIIf). Yield: 87%, ^{1}H-NMR: δ($CDCl_3$); 1.15(d, 3H, $-CH_3$), 1.50(br, 6H), 1.80(d, 3H, $-CH_3$), 2.25(br, 3H), 4.70(q, 1H, -CH).

N-(2-Bromopropionyl)-3-methylpiperidine(IIIg). Yield: 82%, ^{1}H-NMR: δ($CDCl_3$); 1.16(d, 3H, $-CH_3$), 1.51(br, 6H), 1.82(d, 3H, $-CH_3$), 2.3(br, 3H), 4.70(q, 1H, -CH).

N-(2-Bromopropionyl)-4-methylpiperidine(IIIh). Yield: 87%, ^{1}H-NMR: δ($CDCl_3$); 1.08(d, 3H, $-CH_3$), 1.48(br, 6H), 1.79(d, 3H, $-CH_3$), 2.20(br, 3H), 4.70(q, 1H, -CH).

N-(2-Bromopropionyl)-N(4)-phenylpiperazine(IIIi). Yield: 86%, ^{1}H-NMR: δ($CDCl_3$); 1.80(d, 3H, $-CH_3$), 2.15(s, 3H, $-CH_3$), 2.30(br, 6H), 3.55(br, 4H), 4.70(q, 1H, -CH).

ATZ-Ester

Ethyl 2-(Z)-(2-tritylaminothiazole-4-yl)-2-(N-pyrrolidinylcarbonyl)ethoxyimino Acetate(Va). Yield: 90%, ^{1}H-NMR: δ($CDCl_3$ + DMSO-d_6); 1.35(t, 3H), 1.48(d, 3H), 1.60(br, 4H), 3.60(br, 4H), 4.30(q, 2H), 5.10(q, 1H), 6.70(s, 1H), 7.40(br, 15H).

Ethyl 2-(Z)-(2-tritylaminothiazole-4-yl)-2-(N-piperidinylcarbonyl)ethoxyimino Acetate(Vb). Yield: 93.3%, m.p.: 170-71 °C, ^{1}H-NMR: δ($CDCl_3$ + DMSO-d_6); 1.35(t, 3H), 1.45(d, 3H), 1.55(br, 6H), 3.50(br, 4H), 4.35(q, 2H), 5.15(q, 1H), 6.55(s, 1H), 7.27(s, 15H).

Ethyl 2-(Z)-(2-tritylaminothiazole-4-yl)-2-(N-homopiperidinylcarbonyl)ethoxyimino Acetate(Vc). Yield: 87%, ^{1}H-NMR: δ($CDCl_3$ + DMSO-d_6); 1.36(t, 3H) 1.46(d, 3H), 1.55(br, 8H), 3.50(br, 4H), 4.32(q, 2H), 5.10(q, 1H), 6.75(s, 1H), 7.28(br, 15H).

Ethyl 2-(Z)-(2-tritylaminothiazole-4-yl)-2-(N-morpholinylcarbonyl)ethoxyimino Acetate(Vd). Yield: 85%, ^{1}H-NMR: δ($CDCl_3$ + DMSO-d_6); 1.34(t, 3H), 1.50(d, 3H), 3.60(br, 8H), 4.30(q, 2H), 5.10(q, 1H), 6.70(s, 1H), 7.30(br, 15H).

Ethyl 2-(Z)-(2-tritylaminothiazole-4-yl)± - (N-tiomorpholinylcarbonyl)ethoxyimino Acetate(Ve). Yield: 76%, ^{1}H-NMR: δ($CDCl_3$ + DMSO-d_6); 1.36(t, 3H), 1.45(d, 3H), 2.60(br, 4H), 3.75(br, 4H), 4.31(q, 2H), 5.10(q, 1H), 6.86(s, 1H), 7.36(br, 15H).

Ethyl 2-(Z)-(2-tritylaminothiazole-4-yl)-2-[(N-(2-methylpiperidinyl)carbonyl]ethoxyimino Acetate (Vf). Yield: 72%, ^{1}H-NMR: δ($CDCl_3$ + DMSO-d_6); 1.15(t, 3H), 1.35(t, 3H), 1.50(d, 3H), 1.83(br, 6H), 3.50(br, 3H), 4.30(q, 2H), 4.95(q, 1H,), 6.80(s, 1H), 7.30(br, 15H).

Ethyl 2-(Z)-(2-tritylaminothiazole- 4 -yl)-2-[N-(3-methylpiperidinyl)carbonyl]ethoxyimino Acetate (Vg). Yield: 80%, ^{1}H-NMR: δ($CDCl_3$ + DMSO-d_6); 1.11(t, 3H), 1.36(t, 3H), 1.46(d, 3H), 1.80(br, 5H), 3.50(br, 4H), 4.30(q, 2H), 5.10(q, 1H), 6.80(s, 1H), 7.30(br, 15H).

Ethyl 2-(Z)-(2-tritylaminothiazole-4-yl)-2-[N-(4-methylpiperidinyl)carbonyl]ethoxyimino Acetate(Vh). Yield: 82%, ^{1}H-NMR: δ($CDCl_3$ + DMSO-d_6); 1.14(d, 3H), 1.35(t, 3H), 1.45(d, 3H), 1.80(br, 5H), 3.50(br, 4H), 4.30(q, 2H), 5.00(q, 1H), 6.80(s, 1H), 7.30(br, 15H).

Ethyl 2-(Z)-(2-tritylaminothiazole-4-yl)-2-[N-(4-phenylpiperazinyl)carbonyl]ethoxyimino Acetate(Vi). Yield: 85%, ^{1}H-NMR: δ($CDCl_3$ + DMSO-d_6); 1.36(t, 3H), 1.42(d, 3H), 3.11(br, 4H), 3.60(br, 4H), 4.30(q, 2H), 5.10(q,

1H), 6.54(s, 1H), 7.25(br, 15H).

ATZ-Acid

2-(Z)-(2-Tritylaminothiazole-4-yl)-2-(N-pyrrolidinylcarbonyl)ethoxyiminoacetic Acid(VIa). Yield: 89%, m.p.: 186-89 °C, ^{1}H-NMR: δ (DMSO-d_6); 1.48(d, 3H), 1.60(br, 4H), 5.10(q, 1H), 6.85(s, 1H), 7.35(br, 15H).

2-(Z)-(2-Tritylaminothiazole-4-yl)-2-(N-piperidinylcarbonyl) ethoxyiminoacetic acid(VIb). Yield: 90%, m.p.: 190-92 °C, ^{1}H-NMR: δ (DMSO-d_6); 1.40(d, 3H), 1.55(br, 6H), 3.50(br, 4H), 5.15(q, 1H), 6.55(s, 1H), 7.25(br, 15H).

2-(Z)-(2-Tritylaminothiazole-4-yl)-2-(N-homopiperidinylcarbonyl)ethoxyiminoacetic Acid(VIc). Yield: 88%, m.p.: 190-92 °C, ^{1}H-NMR: δ(DMSO-d_6); 1.45(d, 3H), 1.55(br, 8H), 3.50(br, 4H), 5.08(q, 1H), 6.80(s, 1H), 7.30(br, 15H).

2-(Z)-(2-Tritylaminothiazole-4-yl)-2-(N-morpholinylcarbonyl)ethoxyiminoacetic Acid(VId). Yield: 82%, m.p.: 150-53 °C, ^{1}H-NMR: δ (DMSO-d_6); 1.50(d, 3H), 3.65(br, 8H), 5.10(q, 1H), 6.65(s, 1H), 7.28(br, 15H).

2-(Z)-(2-Tritylaminothiazole-4-yl)-2-(N-thiomorpholinylcarbonyl)ethoxyiminoacetic Acid(VIe). Yield: 85%, m.p.: 168-70 °C, ^{1}H-NMR: δ(DMSO-d_6); 1.45(d, 3H), 2.60(br, 4H), 3.75(br, 4H), 5.10(q, 1H), 6.85(s, 1H), 7.30(br, 15H).

2-(Z)-(2-Tritylaminothiazole-4-yl)-2-[N-(2-methylpiperidinyl)carbonyl]ethoxyiminoacetic Acid (VIf). Yield: 89%, ^{1}H-NMR: δ (DMSO-d_6); 1.15(d, 3H), 1.48(d, 3H), 1.90(br, 6H), 3.50(br, 3H), 4.95(q, 1H), 6.80(s, 1H), 7.30(br, 15H).

2-(Z)-(2-Tritylaminothiazole-4-yl)-2-[N-(3-methylpiperidinyl)carbonyl]ethoxyiminoacetic Acid (VIg). Yield: 85%, ^{1}H-NMR: δ (DMSO-d_6); 1.10(d, 3H), 1.45(d, 3H), 1.80(br, 5H), 3.50(br, 4H), 5.05(q, 1H), 6.80(s, 1H), 7.30(br, 15H).

2-(Z)-(2-Tritylaminothiazole-4-yl)-2-[N-(4-methylpiperidinyl)carbonyl]ethoxyiminoacetic Acid(VIh). Yield: 90%, ^{1}H-NMR: δ (DMSO-d_6); 1.15(d, 3H), 1.45(d, 3H), 1.80(br, 5H), 3.50(br, 4H), 4.95(q, 1H), 6.80(s, 1H), 7.30(br, 15H).

2-(Z)-(2-Tritylaminothiazole-4-yl)-2-[N-(4-phenylpiperazinly)carbonyl]ethoxyiminoacetic Acid(VIi). Yield: 92%, ^{1}H-NMR: δ(DMSO-d_6); 1.41(d, 3H), 3.11(br, 4H), 3.60(br, 4H), 5.10(q, 1H), 6.55(s, 1H), 7.25(br, 15H).

Blocked Cepha

Diphenylmethyl 7β-[(Z)-2-(2-tritylaminothiazole-4-yl)-2-(N-pyrrolidinylcarbonyl)ethoxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylate(VIIIa). Yield: 60%, ^{1}H-NMR: δ(CDCl$_3$); 1.50(d, 3H), 1.60(br, 6H), 3.55(br, 4H), 5.05(d, 1H), 5.30(d, 1H), 5.65(d, 1H), 5.90(dxd, 1H), 6.95(s, 1H), 7.35(br, 25H), 9.80(d, 1H).

Diphenylmethyl 7β-[(Z)-2-(2-tritylaminothiazole-4-yl)-2-(N-piperidinylcarbonyl)ethoxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylate(VIIIb). Yield: 68%, ^{1}H-NMR: δ(CDCl$_3$); 1.55(d, 3H), 1.65(br, 6H), 3.55(br, 4H), 5.10(d, 1H), 5.30(d, 1H), 5.65(d, 1H), 5.95(dxd, 1H), 6.90(s, 1H), 7.35(br, 25H), 9.80(d, 1H).

Diphenylmethyl 7β-[(Z)-2-(2-tritylaminothiazole-4-yl]-2-(N-homopiperidinylcarbonyl)ethoxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylate(VIIIc). Yield: 69%, ^{1}H-NMR: δ(CDCl$_3$); 1.50(d, 3H), 1.58(br, 8H), 3.50(br, 4H), 5.05(d, 1H), 5.28(d, 1H), 5.95(dxd, 1H), 6.90(s, 1H), 7.35(br, 25H), 9.95(d, 1H).

Diphenylmethyl 7β-[(Z)-2-(2-tritylaminothiazole-4-yl)-2-(N-morpholinylcarbonyl)ethoxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylate(VIIId). Yield: 52%, ^{1}H-NMR: δ(CDCl$_3$); 1.45(t, 3H), 3.55(br, 8H), 5.15(d, 1H), 5.30(d, 1H), 5.60(d, 1H), 6.05(dxd, 1H), 7.35(br, 25H), 9.80(d, 1H).

Diphenylmethyl 7β-[(Z)-2-(2-tritylaminothiazole-4-yl)-2-(N-thiomorpholinylcarbonyl)ethoxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylate(VIIIe). Yield: 67%, ^{1}H-NMR: δ(CDCl$_3$); 1.45(d, 3H), 2.75(br, 4H), 3.90(br, 4H), 5.09(d, 1H), 5.20(d, 1H), 5.65(d, 1H), 5.90(dxd, 1H), 6.90(s, 1H), 7.35(br, 25H), 9.85(d, 1H).

Diphenylmethyl 7β-[(Z)-2-(2-tritylaminothiazole-4-yl)-2-{N-(2-methylpiperidinyl)carbonyl}ethoxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylate(VIIIf). Yield: 54%, ^{1}H-NMR: δ(CDCl$_3$); 1.10(d, 3H), 1.50(d, 3H), 1.70(br, 6H), 2.05(s, 3H), 3.30-3.60(br, 3H), 5.05(d, 1H), 5.90(dxd, 1H), 6.95(s, 1H), 7.35(br, 25H), 10.10(d, 1H).

Diphenylmethyl 7β-[(Z)-2-(2-tritylaminothiazole-4-yl)-2-{N-(3-methylpiperidinyl)carbonyl}ethoxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylate (VIIIg). Yield: 51%, ^{1}H-NMR: δ(CDCl$_3$); 1.10(d, 3H), 1.50(d, 3H), 1.70-2.00(br, 5H), 2.05(s,3H), 3.55(br, 4H), 5.90(dxd, 1H), 6.95(s, 1H), 7.35(br, 25H), 9.80(d, 1H).

Diphenylmethyl 7β-[(Z)-2-(2-tritylaminothiazole-4-yl)-2-{N-(4-methylpiperidinyl)carbonyl}ethoxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylate-(VIIIh). Yield: 58%, ^{1}H-NMR: δ(CDCl$_3$); 1.10(d, 3H), 1.50(d, 3H), 1.70-2.00(br, 5H), 2.05(s, 3H), 3.55(br, 4H), 5.05(d, 1H), 5.90(dxd, 1H), 6.95(s, 1H), 7.35(br, 25H), 9.80(d, 1H).

Diphenylmethyl 7β-[(Z)-2-(2-tritylaminothiazole-4-yl)-2-{N-(4-phenylpiperazinyl)carbonyl}ethoxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylate(VIIIi). Yield: 57%, ^{1}H-NMR: δ(CDCl$_3$); 1.15(d, 3H), 3.11(br, 4H), 3.60(br, 4H), 5.05(d, 1H), 5.30(d, 1H), 5.65(d, 1H), 5.90(dxd, 1H), 6.95(s, 1H), 7.35(br, 30H), 9.95(d, 1H).

Cepha

7β-[(Z)-2-(2-Aminothiazole-4-yl)-2-(N-pyrrolidinylcarbonyl)ethoxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylic Acid(IXa). Yield: 24%, m.p.>300 °C (dec.), ^{1}H-NMR: δ (DMSO-d_6); 1.4(d, 3H), 1.50(br, 4H), 3.55(br, 4H), 5.08(d, 1H), 5.20(d, 1H), 5.85(dxd, 1H), 6.90(s, 1H), 7.00(s, 1H), 9.95(d, 1H).

7β-[(Z)-2-(2-Aminothiazole-4-yl)-2-(N-piperidinylcarbonyl)ethoxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylic Acid(IXb). Yield: 56%, m.p.>300 °C (dec.), ^{1}H-NMR: δ(DMSO-d_6); 1.40(d, 3H), 1.50(br, 6H) 3.65(br, 4H), 5.15(d, 1H), 5.25(d, 1H), 5.85(dxd, 1H), 6.85(s, 1H), 7.01(s, 1H), 9.85(d, 1H).

7β-[(Z)-2-(2-Aminothiazole-4-yl)-2-(N-homopiperidinylcarbonyl)ethoxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylic Acid(IXc). Yield: 56%, m.p.>300 °C (dec.), ^{1}H-NMR: δ(DMSO-d_6); 1.40(d, 3H),

1.50(br, 8H), 3.65(br, 4H), 5.15(d, 1H), 5.30(d, 1H), 5.85(dxd, 1H), 6.90(s, 1H), 7.10(s, 1H), 9.90(d, 1H).

7β-[(Z)-2-(2-Aminothiazole-4-yl)-2-(N-morpholinylcarbonyl)ethoxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylic Acid(IXd). Yield: 25%, m.p.=284 °C (dec.), ^{1}H-NMR: δ(DMSO-d_6); 1.40(d, 3H), 3.55(br, 8H), 5.15(d, 1H), 5.35(d, 1H), 5.65(d, 1H), 6.00(dxd, 1H), 6.88(s, 1H), 6.99(s, 1H), 9.85(d, 1H).

7β-[(Z)-2-(2-Aminothiazole-4-yl)-2-(N-thiomorpholinylcarbonyl)ethoxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylic Acid(IXe). Yield: 60%, m.p.>300 °C (dec.), ^{1}H-NMR: δ(DMSO-d_6); 1.40(d, 3H), 2.55(br, 4H), 3.90(br, 4H), 5.09(d, 1H), 5.25(d, 1H), 5.85(dxd, 1H), 6.90(s, 1H), 7.00(s, 1H), 9.85(d, 1H).

7β-[(Z)-2-(2-Aminothiazole-4-yl)-2-{N-(2-methylpiperidinyl)carbonyl}ethoxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylic Acid(IXf). Yield: 16%, m.p. =181-85 °C(dec.), ^{1}H-NMR: δ(DMSO-d_6); 1.15(d, 3H), 1.40(br, 3H), 1.70(br, 6H), 3.35-3.60(br, 3H), 5.15(d, 1H), 5.25(d, 1H), 6.00(dxd, 1H), 6.87(s, 1H), 7.08(s, 1H), 9.85(d, 1H).

7β-[(Z)-2-(2-Aminothiazole-4-yl)-2-{N-(3-methylpiperidinyl)carbonyl}ethoxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylic Acid(IXg). Yield: 20%, m.p. =165-67 °C(dec.), ^{1}H-NMR: δ(DMSO-d_6); 1.10(d, 3H), 1.40(br, 3H), 1.70-2.00(br, 5H), 3.35(br, 4H), 5.15(d, 1H), 5.27(d, 1H), 6.00(dxd, 1H), 6.85(s, 1H), 7.10(s, 1H), 9.85(d, 1H).

7β-[(Z)-2-(2-Aminothiazole-4-yl)-2-{N-(4-methylpiperidinyl)carbonyl}ethoxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylic Acid(IXh). Yield: 11%, m.p. =154-57 °C(dec.), ^{1}H-NMR: δ(DMSO-d_6); 1.15(d, 3H), 1.40 (br, 3H), 3.60(br, 4H), 5.15(d, 1H), 5.20(d, 1H), 5.30(d, 1H), 6.00(dxd, 1H), 6.88(s, 1H), 7.15(s, 1H), 9.85(d, 1H).

7β-[(Z)-2-(2-Aminothiazole-4-yl)-2-{N-(4-phenylpiperazinyl)carbonyl}ethoxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylic Acid(IXi). Yield: 19%, ^{1}H-NMR: δ(DMSO-d_6); 1.40(d, 3H), 3.15(br, 4H), 3.60(br, 4H), 5.15(d, 1H), 5.35(d, 1H), 5.65(d, 1H), 6.00(dxd, 1H), 6.90(s, 1H), 7.35(br, 5H), 9.82(d, 1H).

(R)-2-Chloropropionyl Chloride. 0.5Mole of thionyl chloride was added to 0.2 mole L-(+)-lactic acid and the mixture was stirred at 95 °C for 3 hours and the agitation was continued for 8 hours at 113 °C. After evaporation of residual thionyl chloride was obtained the acid chloride.

Yield: 56%, ^{1}H-NMR: 1.95-2.00(d, 3H), 4.60-4.85(q, 1H).

(S)-2-Chloropropionyl Chloride. 0.2 Mole of L-(+)-lactic acid was dissolved in 0.2 mole dioxane and to this solution was added 0.5 mole of thionyl chloride. The mixture was agitated at 95 °C for 3 hours and the stirring was continued for 8 hours at 113 °C. Excess thionyl chloride was evaporated to give the product as a pale yellow liquid.

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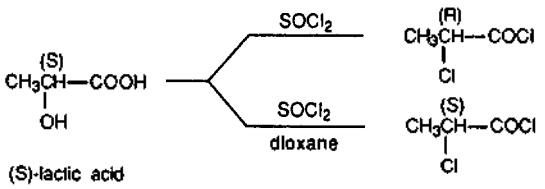
8. In order to prepare the optically pure cephem derivatives and to investigate the influence on the MIC value, (R)- or (S)-2-chloropropionyl chloride was synthesized as follows(see experimental part):



Above obtained optically pure acid chloride was reacted again with thiomorpholine and homopiperazine to afford the corresponding (R)- or (S)-amide, which proceeded to give the final cephalosporins. But the results of antibacterial test exhibited no significant difference between optically pure and diastereomeric compounds.

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