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Synthesis and Antibacterial Activity of New Cephalosporins with Lactonyloxyimino Moiety

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A series of 7-{2-(2-aminothiazol-4-yl)-2-Z-(γ-lacton-3-yl)oxyiminoacetamido} cephalosporins with various substituents at the 3-position in cephem nucleus were synthesized and evaluated microbiologically. The tested compounds showed potent activities but were somewhat less active than cefotaxime or cefixime against a wide variety of Gram-positive and Gram-negative bacteria.

Key words: Cephalosporin, Lactonyloxyimino moiety, Benzotriazole ester, Antibacterial activity

INTRODUCTION

During the past decade, cephalosporins bearing 2-aminothiazol-alkoxyimino acetyl moiety at the C-7 position of cephem nucleus have been developed successively. Among a number of these so-called third-generation antibiotics, a lot of cephalosporin including cefotaxime, **A** (Bucourt *et al.*, 1977; Heymes *et al.*, 1977) has a methoxy imino group at the α-position of 2-aminothiazol-4-ylacetyl moiety, and on the other hand, ceftazidime, **B** (O'callaghan *et al.*, 1980) and cefixime, **C** (Yamanaka *et al.*, 1985) have 2,2-dimethylacetic acid and acetic acid, respectively, in place of methyl group at the oxyimino moiety, as shown in Fig. 1.

It has been known that these substituted alkoxyimino groups were responsible for high antibacterial activity and marked resistance to β-lactamase (Newall, 1985). Recently Oine *et al.* (1985, 1986) developed new cephalosporins having potent activity such as structure **D** through the introduction of 2-pyrrolidon-3-yl moiety as a substituent of oxyimino group. Accordingly, as a part of our research program on the development of novel cephalosporin antibiotics we became interested in the synthesis of γ-lacton-3-yl moiety as a substitutent of the mentioned oxyimino group. We describe herein the synthesis of α-(2-aminothiazol-4-yl)-α-(γ-lacton-3-yl)oxyiminoacetic acid derivatives, their conversion to cephalosporin antibiotics and the antimicrobial activity of new derivatives with general structure **1**.

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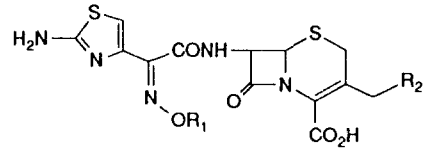
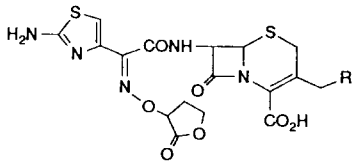
MATERIALS AND METHODS

Melting points were determined using a Thomas Hoover melting point apparatus and uncorrected. IR spectra were taken on an Analect 6160 spectrophotometer. NMR spectra were recorded at 60 MHz on an Varian 60-T spectrometer and 200 MHz on a Varian XL-200 spectrometer using tetramethylsilane or sodium 3-trimethylsilylpropane sulfonate as an internal stan-



		R_1	R_2
A	Cefotaxime	$-CH_3$	-OAc
B	Ceftazidime	$-CH(CH_3)CO_2H$	$-N^+$
C	Cefixime	$-CH_2CO_2H$	$-CH=CH_2$
D		R_1 =	R_2 = acceptable groups

Fig. 1. Structure of several antibiotics



Structure 1

dard. High performance liquid chromatography (HPLC) was done a Waters μ-bondapark C_{18} (3.9×300 mm), using a Waters pump (model 600E) and a Water detector (model 484 spectrometer set at 254 nm).

Ethyl 3-oxo-2-{(tetrahydro-2-furanon)-3-yl}oxyiminobutyrate (2)

To a solution of ethyl α-hydroxyiminoacetoacetate (5.09 g, 32 mmol) and α-bromo-γ-butyrolactone (5.45 g, 33 mmol) in DMF (10 ml) and EtOAc (10 ml) was added potassium carbonate (4.56 g, 33 mmol) at room temperature and the resulting solution was stirred for 2.5 hr at the same temperature. The mixture was poured into water (50 ml) and extracted with EtOAc three times. The org. layer was washed with water three times and brine, dried over $MgSO_4$, and concentrated to afford a yellowish oil (7.22 g, 93%) of **2**; IR (neat, cm^{-1}) 1792, 1745, 1701, 1240, 1181, 1058; ^{1}H-NMR ($CDCl_3$) δ 1.30 (t, 3H, CH_3), 2.19-2.83 (m, 2H, lactone CH_2), 2.37 (s, 3H, CH_3), 4.06-4.60 (m, 2H, lactone CH2 O), 4.29 (q, 2H, CH_2), 5.04 (t, 1H, lactone CHO-).

Ethyl 4-bromo-3-oxo-2-{(tetrahydro-2-furanon)-3-yl}oxyiminobutyrate (3)

A solution of **2** (2.65 g, 11 mmol) and bromine (2.10 g, 13 mmol) in dried dichloromethane (15 ml) was refluxed along with irradiation of W-lamp until the bromine color disappeared (ca. 8 hr) and cooled to room temperature. The reaction mixture was diluted with dichloromethane, washed with dil. $Na_2S_2O_3$ solution and water, and dried over $MgSO_4$. Evaporation of solvent gave a greenish oil, which was subjected to flash chromatography on silica gel using hexane-EtOAc (3 : 2) as an eluent to afford a pale yellowish oil (3.3 g, 94%) of **3**; IR (neat, cm $^{-1}$) 1791, 1745, 1717, 1256, 1182, 1086, 1020, 909; ^{1}H-NMR ($CDCl_3$) δ 1.31(t, 3H, CH_3), 2.18-2.84 (m, 2H, lactone CH_2), 4.06-4.60 (m, 2H, lactone CH_2O), 4.30 (q, 2H, CH_2), 4.61 (s, 2H, $BrCH_2$), 5.05 (t, 1H, lactone CHO-).

Ethyl 2-(2-aminothiazol-4-yl)-2-Z-{(tetrahydro-2-furanon)-3-yl}oxyiminoacetate (4)

To a solution of **3** (3.22 g, 10 mmol) in abs. ethanol (20 ml) were added N,N-dimethylaniline (1.21 g, 10 mmol) and thiourea (0.84 g, 11 mmol), and the resulting mixture was stirred for 2.5 hr at room temperature and concentrated under reduced pressure. The residue was dissolved in chloroform and washed with water twice and then brine. The dried ($MgSO_4$) org. layer was evaporated to give an orange oil (2.6 g), which was crystallized from isopropyl alcohol (10 ml) to give **4** (Z-isomer, 1.20 g, 40%) as a pale yellowish crystalline powder; mp 128-9℃; IR (KBr, cm^{-1}) 3431, 1775, 1747, 1623, 1544, 1187, 1034; ^{1}H-NMR ($CDCl_3$/DMSO-d^6) δ 1.32 (t, 3H, CH_3), 2.13-2.78 (m, 2H, lactone CH_2), 4.12-4.59 (m, 2H, lactone CH_2O), 4.37 (q, 2H, CH_2), 5.04 (t, 1H, lactone CHO-), 6.71 (s, 1H, thiazole H), 6.98 (br.s, 2H, NH_2).

Ethyl 2-Z-{(tetrahydro-2-furanon)-3-yl}oxyimino-2-{(2-tritylaminothiazol)-4-yl}acetate (5)

Method I: Triethylamine (1.0 ml, 7 mmol) was dropwise added to a cooled (−20℃) mixture of **4** (1.50 g, 5.0 mmol) and triphenylmethyl chloride (1.53 g, 5.5 mmol) in dichloromethane (30 ml) and DMF (3 ml). The resulting mixture was stirred at −15~−20℃ for 30 min and at room temperature overnight, and washed with water three times and then brine. The dried ($MgSO_4$) org. layer was concentrated in vacuo to give a reddish residue which was dissolved in hot abs. ethanol (12 ml). On cooling to room temperature with stirring a off-white powder (2.0g , 74%) of **5** was adducted; mp 157-8℃; ^{1}H-NMR ($CDCl_3$) δ 1.30 (t, 3H, CH_3), 2.30-2.81 (m, 2H, lactone CH_2), 4.12-4.58 (m, 2H, lactone CH_2O), 4.36 (q, 2H, CH_2), 5.07 (t, 1H, lactone CHO-), 6.64 (s, 1H, thiazole H), 6.86 (s, 1H, NH), 7.35 (s, 15H, 3 phenyl).

Method II: To a solution of **7** (2.75 g, 6.01 mmol) in DMSO (15 ml) was added powdered potassium carbonate (1.66 g, 12.01 mmol), and the mixture was stirred for 20 min at room temperature then α-bromo-γ-butyrolactone (1.09 g, 6.61 mmol) was added at room temperature, and the resulting mixture was stirred overnight. After acetic acid (5 ml) was added, the mixture was partitionized between EtOAc (60 ml) and ice-water (30 ml). The separated org. layer was washed with water twice and brine. The dried ($MgSO_4$) solution was decolorized over charcoal and concentrated to a yellowish oil which was crystallized from isopropyl alcohol-EtOAc (10 : 1) to afford a white powder (2.66 g, 82%) of **5**. Tlc, mp, and nmr spectra were identical to those adducted in method I.

Sodium 2-Z-{(3-hydroxy-1-sodiocarboxyprop)-1-yl}oxyimino-2-{(2-tritylaminothiazol)-4-yl}acetate (6)

To a suspension of ester (**5**, 14.1 g, 26 mmol) in abs. ethanol (200 ml) was added 4N-sodium hydroxide (13 ml, 52 mmol) at room temperature. After stirred for 4hr at the same temperature, the precipitated solid was filtered and washed with cold ethanol to give

a white crystalline (13.5 g, 90%) of **7**; mp 213-4℃.

2-Z-{(Tetrahydro-2-furanon)-3-yl}oxyimino-2-{(2-tritylaminothiazol)-4-yl}acetic acid 1-hydroxy-benzotriazole active ester (8)

To a cooled (0℃) solution of 1-hydroxybenzotriazole (7.05 g, 52.2 mmol) and triethylamine (8.7 ml, 62.7 mmol) in N,N-dimethylacetamide (DMAc, 75 ml) was dropwise added a solution of methanesulfonyl chloride (4.5 ml, 57.3 mmol) in DMAc (15 ml). The resulting mixture was stirred for 1.5 hr at 0-5℃. Disodium salt (**6**, 15.3 g, 26.1 mmol) was portionwise added to the in situ prepared solution of 1-hydroxybenzotriazole methanesulfonate at 0-5℃, and the mixture was stirred for 2hr at 0-5℃ and then for 4 hr at room temperature. The reaction mixture was partitionized between water (80 ml) and EtOAc (120 ml), and the separated org. layer was washed with 5% $NaHCO_3$ solution. Further washing with water three times, decolorization over active charcoal, drying over $MgSO_4$ and evaporation of the solvent gave a foam-like solid, which was redissolved in small amount of EtOAc. The solution was dispersed into isopropyl ether to afford a pale brown solid (13.39 g, 81%) of **8**; mp 161-2℃; IR (KBr, cm^{-1}) 1733 (carbonyl of active ester).

General procedure for the acylation of 7-aminocephems with 1-hydroxybenzotriazole active ester and deprotection of protecting groups

Diphenylmethyl 7β-[2-Z-{(tetrahydro-2-furanon)-3-yl}oxyimino-2-{(2-tritylaminothiazol)-4-yl}]acetamido-3-acetoxymethyl-3-cephem-4-carboxylic acid benzhydryl ester (11a): A solution of active ester (**8**, 1.89 g, 3 mmol) and benzhydryl 7-ACA (**10a**, 1.32 g, 3 mmol) in dichloromethane (30 ml) was stirred for 40 hr at room temperature (20℃) and concentrated under reduced pressure. The residue was dissolved in EtOAc, washed with dil. HCl solution, dil. $NaHCO_3$ solution and brine, dried over $MgSO_4$, and concentrated to leave a brown foam, which was chromatographed by flash method on silica gel using hexane-EtOAc (1 : 1) to give a yellowish solid (1.50 g, 54%) of **11a**; ^{1}H-NMR ($CDCl_3$) δ 2.03 (s, 3H, $OCOCH_3$), 2.30-2.81 (m, 2H, lactone CH_2), 3.47 (br.s, 2H, $2C_2$-H), 3.99-4.45 (m, 2H, lactone CH_2O), 4.87 (ABq, 2H, $2C_3$-H), 5.05 (d, 1H, C_6-H, J=5 Hz), 5.08 (t, 1H, lactone CHO-), 5.68 (dd, 1H, C_7-H, J=5 Hz, 8 Hz), 6.69 (s, 1H, thiazole H), 6.88 (s, 1H, $NHCPh_3$), 6.95 (s, 1H, $CHPh_2$), 7.35 (25H, 5 phenyl), 9.13 (d, 1H, NH-C_7, J=8 Hz).

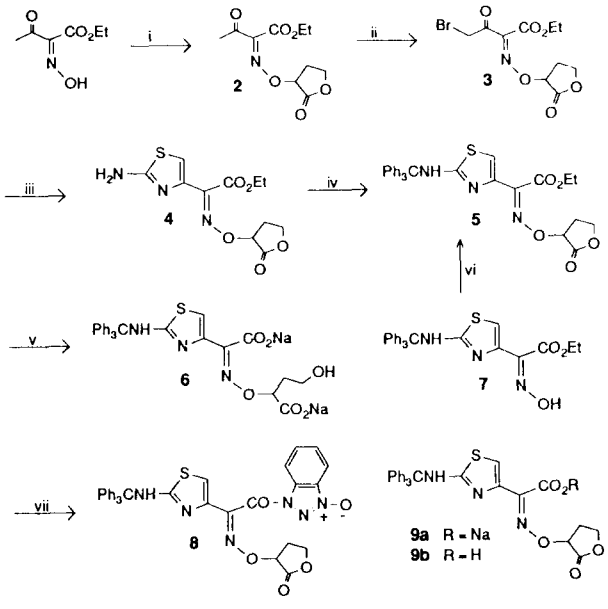
7β-{(2-Aminothiazol)-4-yl}-2-Z-{(tetrahydro-2-furanon)-3-yl}oxyiminoacetamido-3-acetoxymethyl-3-cephem-4-carboxylic acid (1a): A mixture of protected cephem (**11a**, 1.11 g, 1.19 mmol) in anisole (2 ml) and THF (20 ml) was stirred for 4 hr at room temperature and concentrated under reduced pressure. The residue was dissolved in small amount of EtOAc and the solution diluted with ethyl ether. The precipitated solid was collected by filtration and washed with ether to give a yellowish solid (0.36g, 47%) of **1a**, which was purified by column chromatography on silica gel using EtOAc-EtOH-water (10 : 4 : 1) as an eluent. The product fractions were collected and lyophilized to afford a pure yellowish powder; ^{1}H-NMR (DMSO-d^6) δ 2.01 (s, 3H, $OCOCH_3$), 2.33 (m, 2H, lactone CH_2), 3.45 (ABq, 2H, $2C_2$-H), 3.97-3.47 (m, 2H, lactone CH_2 O), 4.85 (ABq, 2H, $2C_3$-H), 5.05 (d, 1H, C_6-H, J=5 Hz), 5.09 (t, 1H, lactone CHO-), 5.79 (dd, 1H, C_7-H, J=5 Hz, 8 Hz), 6.71 (s, 1H, thiazole H).

Another acylation compounds (**11b** or **11c**) and deprotected cephalosporins (**1b** or **1c**) were prepared from **10b** or **10c** according to the same procedure as described for the synthesis of **11a** and **1a**, respectively.

Diphenylmethyl 7β-[2-Z-{(tetrahydro-2-furanon)-3-yl}oxyimino-2-{(2-tritylaminothiazol)-4-yl}] acetamido-3-vinyl-3-cephem-4-carboxylic acid benzhydryl ester (11b): Yield 63%; ^{1}H-NMR ($CDCl_3$) δ 2.32-2.81 (m, 2H, lactone CH_2), 3.70 (br.s, 2H, $2C_2$-H), 3.97-4.40 (m, 2H, lactone CH_2O), 5.05 (d, 1H, C_6-H, J=5 Hz), 5.10 (t, 1H, lactone CHO-), 5.32 (d, 1H, vinyl H, J=11 Hz), 5.68 (dd, 1H, C_7-H, J=5 Hz, 8 Hz), 5.73 (d, 1H, vinyl H, J=16 Hz), 6.51 (dd, 1H, vinyl H, J=11 Hz, 16 Hz), 6.65 (s, 1H, thiazole H), 6.90 (s, 1H, $CHPh_2$), 7.30 (25H, 5 phenyl), 9.35 (d, 1H, NH-C7, J=8 Hz).

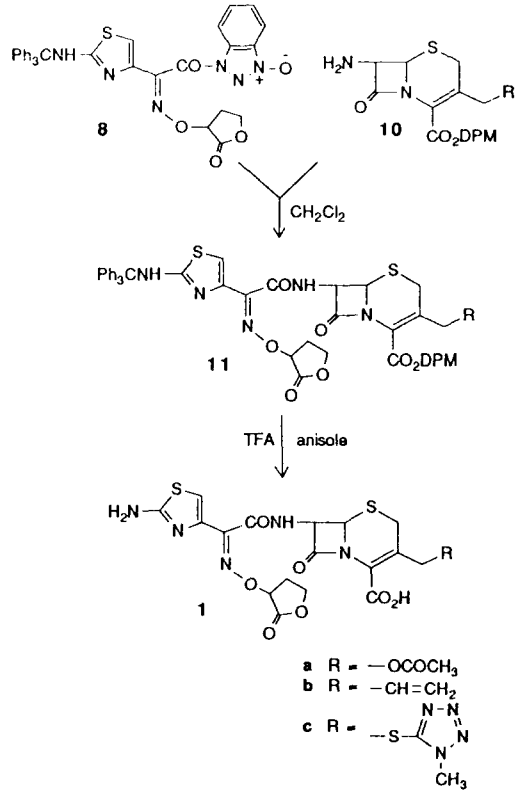
7β-{(2-Aminothiazol)-4-yl}-2-Z-{(tetrahydro-2-furanon)-3-yl}oxyiminoacetamido-3-vinyl-3-cephem-4-carboxylic acid (1b): Yield 69% (crude); ^{1}H-NMR (DMSO-d^6) δ 2.32-2.79 (m, 2H, lactone CH_2), 3.68 (br.s, 2H, C_2-H), 3.95-4.37 (m, 2H, lactone CH_2O), 5.10 (d, 1H, C_6-H, J=5 Hz), 5.13 (t, 1H, lactone CHO-), 5.37 (d, 1H, vinyl H, J=11 Hz), 5.65 (dd, 1H, C_7-H, J=5 Hz, 8 Hz), 5.76 (d, 1H, vinyl H, J=16 Hz), 6.57 (dd, 1H, vinyl H, J=11 Hz, 16 Hz), 6.69 (s, 1H, thiazole H), 6.90 (s, 1H, $CHPh_2$), 7.30 (25H, 5 phenyl) 9.28 (d, 1H, NH-C_7, J=8 Hz).

Diphenylmethyl 7β-[2-Z-{(tetrahydro-2-furanon)-3-yl}oxyimino-2-{(2-tritylaminothiazol)-4-yl}]acetamido-3-(1-methyltetrazol-5-yl)thiomethyl-3-cephem-4-carboxylic acid benzhydryl ester (11c): Yield 62%; ^{1}H-NMR ($CDCl_3$) δ 2.30-2.81 (m, 2H, lactone CH_2), 3.65 (br.s, 2H, $2C_2$-H), 3.78 (s, 3H, NCH_3), 3.99-4.45 (m, 2H, lactone CH_2O), 4.33 (ABq, 2H, $2C_3$-H), 5.08 (t, 1H, lactone CHO-), 5.13 (d, 1H, C_6-H, J=5 Hz), 5.83 (dd, 1H, C_7-H, J=5 Hz, 8 Hz), 6.70 (s, 1H, thiazole H), 6.83 (s, 1H, $NHCPh_3$), 6.92 (s, 1H, $CHPh_2$), 7.36 (25H, 5 phenyl), 9.20 (d, 1H, NH-C_7, J=8 Hz).



Reagents : i) α -bromo-γ -butyrolactone, K_2CO_3, DMF ; ii) bromine, CH_2Cl_2 ; iii) thiourea, DMA, EtOH ; iv) triphenylmethylchloride, TEA, CH_2Cl_2 / DMF ; v) 4N-NaOH, EtOH ; vi) α -bromo-γ -butyrolactone, powdered K_2CO_3, DMSO ; vii) HOBt, MsCl, TEA, DMAc

Scheme 1



Scheme 2

7β-{(2-Aminothiazol)-4-yl}-2-Z-{(tetrahydro-2-furanon)-3-yl}oxyiminoacetamido-3-(1-methyl-tetrazol-5-yl)thiomethyl-3-cephem-4-carboxylic acid (1c): Yield 83%; ^{1}H-NMR (DMSO-d^6) δ 2.33-2.84 (m, 2H, lactone CH_2), 3.68 (br.s, 2H, $2C_2$-H), 3.81 (s, 3H, NC-H_3), 3.99-4.41 (m, 2H, lactone CH_2O), 4.38 (ABq, 2H, $2C_3$-H), 5.08 (t, 1H, lactone CHO-), 5.20 (d, 1H, C_6-H, J=5 Hz), 5.87 (dd, 1H, C_7-H, J=5 Hz, 8 Hz), 6.71 (s, 1H, thiazole H), 9.229 (d, 1H, NH-C_7, J=8 Hz).

Determination of *in vitro* Antibacterial Activity

All the in vitro antibacterial activities which are given as MIC (minimum inhibitory concentration) in μg/ml required to prevent growth of the bacterial culture, were determined by the standard 2-fold agar dilution method (Japan Society of Chemotherapy, 1975) using Muller-Hinton agar (Difco) after at 36℃ for 18hr with an inoculum size of 10^6 cfu/ml.

RESULTS AND DISCUSSION

Chemistry

Our synthetic target was α-(2-aminothiazol-4-yl)-α-(γ-lacton-3-yl)acetic acid derivatives or it's activated ester, considered to be an intermediate in the preparation of the desired cephalosporin antibiotics, and the synthetic method is described in Scheme 1.

Ethyl α-hydroxyiminoacetoacetate was transformed to **2** via O-alkylation with α-bromo-γ-butyrolactone using K_2CO_3 in DMF in good yield. Compound **2** was brominated at α-position of keto group with bromine in dichloromethane to give **3**, which was reacted with thiourea in the presence of N,N-dimethylaniline in ethanol to afford a pure Z-isomer **4**, after crystallization from isopropyl alcohol. Amino group of thiazole moiety of **4** was protected with triphenylmethyl(trityl) group in order to easily manipulate the isolation of products in the next steps. Selective hydrolysis of ethyl ester in compound **5** without causing lactone ring opening was failed. But the treatment of two equivalent of sodium hydroxide to the ethyl ester in absolute ethanol precipitated the crystal of di-sodium salt such as structure **6**, the product derived from the concomitant lactone ring opening, which was relatively stable to moisture in the air. Also **5** could be synthesized from α-(2-tritylaminothiazol-4-yl)-α-hydroxyiminoacetic acid ethyl ester **7** (Bucourt *et al.*, 1978; Ochiai *et al.*, 1981) by the use of powdered K_2CO_3 in DMSO.

When the di-sodium salt **6** was treated with two equivalent of 1-methanesulfonyloxy-benzotriazole (MsOBt) prepared *in situ* by the reaction of 1-hydroxybenzotriazole (HOBt) with methanesulfonyl chloride and triethylamine in N,N-dimethylacetamide (DMAc), the active ester **8** could be synthesized together with lactone ring closure via the intermediate **9a**. In fact, the treatment of di-acid adducted after acidification of di-sodium salt with one equivalent of N,N-dicyclo-

Table I. Antibacterial activity (MIC, μg/ml) of new cephalosporins, **1**

NO	Strains	**1a**	**1b**	**1c**	CTX	CFX
1	*Streptococcus pyogenes* 308A	0.025	0.098	0.025	0.013	0.013
2	*Streptoccus pyogenes* 77A	0.025	0.049	0.013	0.007	0.025
3	*Streptoccus faecium* MD8b	25	50	12.5	50	50
4	*Staphylococcus aureus* SG511	0.781	3.125	1.563	0.781	1.563
5	*Staphylococcus aureus* 285	1.563	3.125	1.563	3.125	6.25
6	*Staphylococcus aureus* 503	0.781	1.563	0.196	1.563	6.25
7	*Escherichia coli* O78	0.781	1.563	0.391	0.049	0.098
8	*Escherichia coli* DC0	0.098	0.196	0.098	0.049	0.098
9	*Escherichia coli* DC2	0.098	0.391	0.049	0.025	0.098
10	*Escherichia coli* TEM	0.049	0.781	0.098	0.025	0.098
11	*Escherichia coli* 1507E	0.049	0.196	0.025	0.013	0.049
12	*Pseudomonas aeruginosa* 9027	50	50	25	25	25
13	*Pseudomonas aeruginosa* 1592E	25	50	25	12.5	25
14	*Pseudomonas aeruginosa* 1771	3.125	6.25	3.125	6.25	25
15	*Pseudomonas aeruginosa* 1771M	0.195	0.781	0.391	0.098	0.196
16	*Salmonella typhimurium*	0.195	0.391	0.195	0.049	0.098
17	*Klebsiella oxytoca* 1082E	1.563	0.781	0.781	3.125	0.391
18	*Klebsiella aerogenes* 1522E	0.781	0.781	0.391	0.098	0.195
19	*Enterobacter cloacae* P99	100	100	100	100	100
20	*Enterobacter cloacae* 1321E	0.049	0.195	0.049	0.013	0.049

CTX: cefotaxime, CFX: cefixime

hexylcarbodiimide (DCCD) gave the desired acid derivatives **9b** as a result of only the closure of lactone ring.

Acylation of HOBt can potentially occur at either nitrogen or oxygen of HOBt. Horiki (1977) showed that though isomerization of the resulting N-acyl and O-acyl products occurred in solution and the ratio of these isomers was dependent upon the nature of the solvents used, one rigioisomer could be exclusively obtained as several different amino acids were reacted with HOBt. Because the IR stretching of the carbonyl group of the N-acyl product occurs at ~1735 cm^{-1}, the acylation site with HOBt can be identified from the IR spectra of the acylated product. The product in the reaction of the di-sodium salt **6** with MsOBt was only the N-acylated product **8** (carbonyl 1733 cm^{-1}).

New cephalosporins were prepared by coupling benzotriazole active ester with 7β-amino-3-cephem-4-carboxylic acid diphenylmethyl(DPM) esters, **10a**, **10b** and **10c** as depicted in Scheme 2.

That is, 7-aminocephem esters were coupled with ester **8** in dichloromethane in reasonable yields, followed by removal of protective groups(trityl and DPM) using anisole and trifluoroacetic acid to afford desired cephalosporin derivatives **1a**, **1b**, and **1c**. The HPLC analysis showed that each of new cephalosporins **1a**, **1b** and **1c** consisted of a 1 : 1 mixture of diastereomers due to the stereocenter at α-position of the lactone moiety.

Antibacterial Activity

The *in vitro* antibacterial activities of new 7-{α-(2-aminothazol-4-yl)-α-(γ-lacton-3-yl)oxyiminoacetamido} cephems against selected Gram-positve and Gram-negative organisms are shown in Table I. In general, their (γ-lacton-3-yl)oxyimino derivatives (**1a**, **1b**, and **1c**) were less active against most of organisms than selected reference antibiotics, cefotaxime or cefixime. Although **1a** and **1c** showed the activities slightly more potent against *Staph. aureus* strains than, and equivant against *E. coli*, *Ps. aeruginosa* or *Strep. pyogens* strains to cefixime, they are less active than cefotaxime against most of strains. Accordingly, these present activities could not force us to proceed further research in field of these lactonyl moieties as oxyimino substituents.

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