약학회지 제42권 제 1 호 12~24(1998)
Yakhak Hoeji Vol. 42, No. 1

3-(치환) 테트라조일메칠세파로스포린의 합성과 생리활성

고옥현# · 김영수 · 고봉석 · 이재영 · 하재천 · 방희재 · 유진철 · 강형룡
조선대학교 약학대학

(Received October 29, 1997)

Synthesis and Biological Activity of 3-(Substituted) Tetrazolylmethyl Cephalosporins

Ok-Hyun Ko#, Young-Soo Kim, Bong-Suk Ko, Jae-Young Lee, Jai-Chun Ha, Hee-Jae Bang, Jin-Cheol Yoo and Hyung-Ryong Kang
College of Pharmacy, Chosun University, Kwangju, 501-759 Korea

Abstract—For the developement of new cephalosporin antibiotics with aminothiazolcarboxymethylethoxyimino moiety on the C-7 position and tetrazolymethyl moiety on the C-3 position of cephem ring, 7β-[(Z)-2-(2-aminothiazol-4-yl)-2-(1-carboxy-1-methylethoxyimino)acetamido]-3-[5-(substituted)tetrazol-2-yl]methyl-3-cephem-4-carboxylic acids(**28~35**) were synthesized. These compounds were tested for antimicrobial activity *in vitro* against Gram(+) and Gram(-) bacteria. They showed remarkable antibacterial activity against *Escherichia coli* AB 1157, *Escherichia coli* AB 0111, *Escherichia coli* BE 1186, *Micrococcus luteus* ATCC 9341, *Salmonella typhimurium* TV 119, *Salmonella typhimurium* SL 1102, *Staphylococcus aureus* IFO 12732, *Staphylococcus aureus* R-209, but these compounds were not active against *Pseudomonas aeruginosa* N-10.

Keywords □ Formylation, ACLE, tetrazole, HOBT-DCC method, Vilsmeyer reagent, sillylation, deformylation, hydrolysis, antibacterial activity.

지금까지의 cephalosporin계 항생제는 cephem핵의 C-7, C-3, C-4 위치를 변형시킨 화합물들이다. C-7위치에는 항균력과 G(-)균의 외막투과성을 증가시켜 광범위 항균 spectrum을 갖게 하는 aminothiazole기와 β-lactamase에 안정성을 증가시키고 penicillin binding protein(PBP)에 대한 결합친화성을 증가시키는 alkoxyimimo기가 *syn*체로 결합된 aminothiazolealkoxyimino moiety을 가진 화합물들이 주류를 이루고 있다. 특히 alkoxyimino부위에 methoxyimino기를 가진 ceftixozime[1-3], cefotaxime[4-5], cefmenoxime[6] 그리고 ceftriaxone[7] 등이 보고 되었으며 carboxymethoxyimino기와 carboxymethylethoxyimino기를 각각 가진 cefixime[8]과 ceftazidime[9]들이 우수한 광범위 항균력이 있다고 보고되었다. C-3위치는 항균력, 흡수, 대사를 결정짓는 중요한 부위이다. *Pseudomonas*와 같은 G(-)균에 강력한 항균력을 가지며 β-lactamase에 대한 저항성을 향상시킬 목적으로 C-3위치에 heterocyclic-thiomethyl[10-14]기와 quarternary ammonium salt[15-23], vinyl[24-29], catechol[30-37]들을 도입시킨 세파로스포린계 항생제들이 보고되어 있다. C-4위치

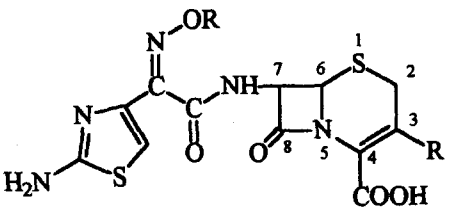


Fig. 1—General structure of aminothiazole-alkoxyiminocephalosporin.

본 논문에 관한 문의는 이 저자에게로
(전화) 062-220-3748 (팩스) 062-234-3016

의 carboxy기에 ester를 도입시켜 흡수율을 개선하고 생체이용율을 높일 목적으로 prodrug형태의 cephalosporin계 항생제[38-40]도 보고되었다.

본 저자등은 C-7위치에 aminothiazole-carboxymethylethoxyimino기를 도입시키고 C-3위치에 약리활성이 기대되는 tetrazole을 도입시킨 cephalosporin계 항생제를 합성하여 G(+) 및 G(-)균에 대하여 항균력을 기존의 항생제와 비교 실험한 결과를 보고하려고 한다.

실 험

시약 및 기기

본 실험에 사용된 시약들은 Aldrich Co., Sigma Co., Tokyo Kasei., Fluka Co.에서 구입한 일급 시약을 사용하였으며 *p*-methoxybenzyl 7-amino-3-chloromethyl-3-cephem-4-carboxylate hydrochloride (ACLE)는 Otsuka사 제품을, (Z)-2-(2-aminothiazol-4-yl)-2-(1-*tert*-butoxycarbonyl-1-methylethoxy imino)acetic acid는 Lonza사 제품을, silica gel(230~400 mesh)은 Sigma사 제품을 사용하였고 용매는 필요에 따라 정제하여 사용하였다. Mueller-Hinton broth는 Difco co., 제품을 사용하였다. Thin layer chromatography(TLC)는 Kieselgel F_{254}(0.25 mm)를 바른 유리판을 잘라 이용하였으며 tlc spot는 자외선램프 UVGL-58을 사용하였다. 융점 측정은 Gallen- Kamp 융점측정기를 사용하였으며 이에 대한 보정은 하지 않았다. Column chromatography는 silica gel(230~400 mesh, 60Å, Merck)을 사용하였다. IR spectra는 Bruker IFS 66을 사용하여 KBr pellet으로 측정하였다. NMR spectra는 tetramethylsilane(TMS)를 내부 표준 물질로 하여 Bruker FT-80 MHz, FT-300 MHz를 사용하였다.

(Z)-2-(2-Formamidothiazol-4-yl)-2-(1-*tert*-butoxycarbonyl-1-methylethoxyimino)acetic acid(2)

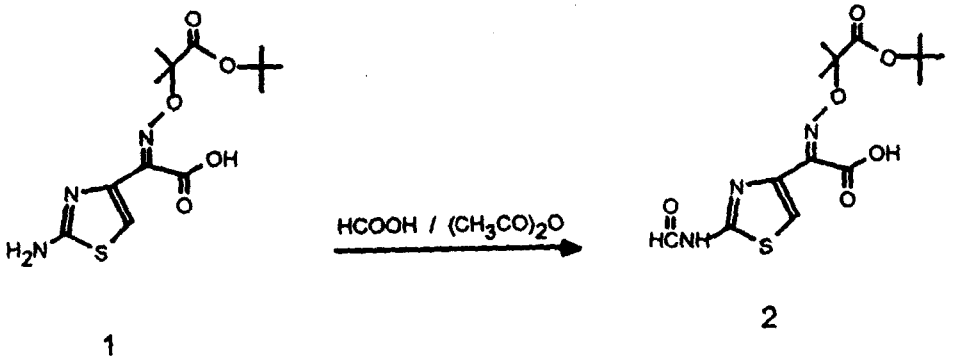
$(CH_3CO)_2O$ 12.4 g(0.12 mol)과 HCOOH 5.6 g(0.12 mol)을 55~60°C에서 1시간 교반하고 어름물로 냉각하여 15°C에서 (Z)-2-(2-aminothiazol-4-yl)-2-(1-*tert*-butoxycarbonyl-1-methylethoxyimino)acetic acid (**1**) 10.00 g(0.03 mol)을 가하여 상온에서 2시간 교반하였다. 반응물에 EtOAc 300 m*l*을 가하여 30분간 교반하고 EtOc층을 분리하여 감압 농축하였다. 잔유물을 *iso*-propylether(iPE) 300 m*l*에 교반하면서 분산시켰다. 생성된 침전을 여과하고 iPE로 수회 세척하였다. P_2O_5로 건조하여 백색결정 8.93 g(82%)을 얻었다.

IR (KBr) cm^{-1} : 3347, 1725, 1638.

^{1}H-NMR (DMSO-d_6) δ : 1.39(9H, s, $C(CH_3)_3$), 1.44(6H, s, $C(CH_3)_2$), 7.41(1H, s , thiazole-H), 8.52 (1H, s, HCO), 12.76(1H, br.s, HCONH)

***p*-Methoxybenzyl 7β-[(Z)-2-(2-formamidothiazol-4-yl)-2-(1-*tert*-butoxycarbonyl-1-methylethoxyimino) acetamido]-3-chloromethyl-3-cephem-4-carboxylate (3)**

(Method A) : 화합물(**2**) 3 g(8.74 mmol), 1-hydroxybenzotriazole hydrate(HOBT) 1.38 g(8.95 mmol)을 DMF 20 m*l*에 용해시키고 *N,N*-dicyclohexylcarbodiimde(DCC) 1.85 g(8.95 mmol)을 가하여 상온에서 3시간 교반후 냉장고에 24시간 방치하였다. 생성된 결정을 여과하여 제거하고 여액을 보관하였다. 한편 ACLE 3.54 g(8.74 mmol), EtOAc 100 m*l*, H_2O 20 m*l*, $NaHCO_3$ 0.74 g(8.8 mmol)을 0~5°C에



1 2

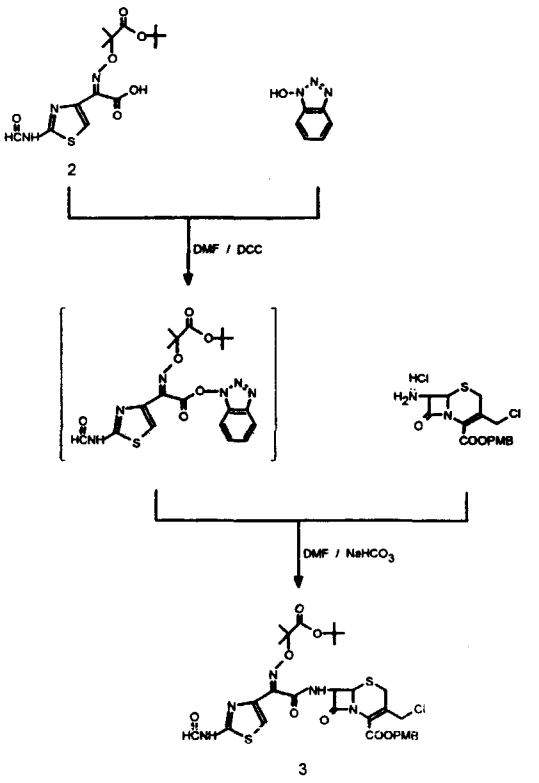
Scheme I — Synthesis of Compound (2).

서 30분간 교반후 EtOAc층을 분리하여 20%식염수 20 m*l*로 세척한후 $MgSO_4$로 건조하였다. 이 EtOAc액에 상기 보관한 반응액을 가하여 상온에서 3시간 교반하였다. EtOAc층을 취하고 여액을 다시 EtOAc 100 m*l*로 추출하여 EtOAc층을 합하여 0.5N-HCl 수용액(50 m*l*), 5% $Na_2S_2O_3$(50 m*l*), brine의 순으로 세척하고 $MgSO_4$로 건조하여 감압농축하였다. 잔유물은 *n*-hexane에 분산시켜 생성된 침전물을 여과하여 백색결정 5.13 g을 얻었다. 이 결정을 column chromatography(EtOAc/cyclohexane=1:1)로 정제하여 백색결정 4.5 g(68.7%)을 얻었다.

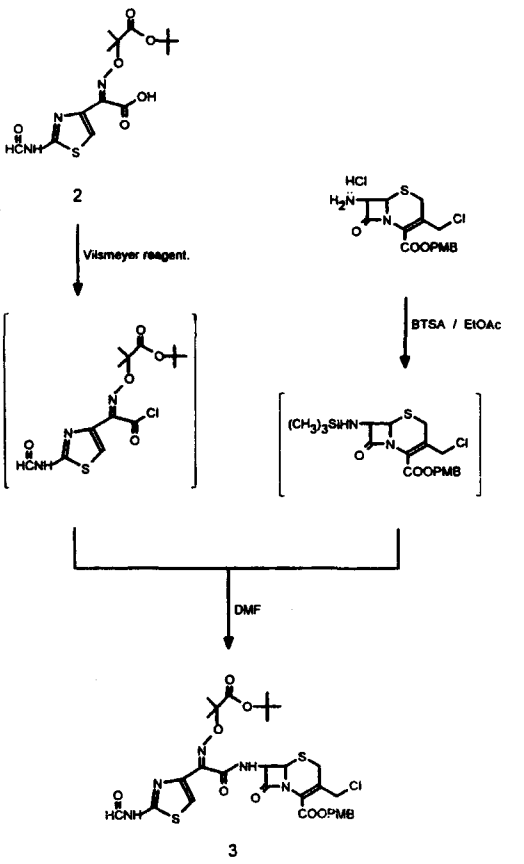
(Method B) : DMF 2.3 m*l*와 THF 31.2 m*l*의 혼합 용액에 $POCl_3$ 3.1 m*l*(33.6 mmol)를 가하여 -10~0°C에서 30분 동안 교반시킨 Vilsmeyer reagent를 만든 용액에 화합물(**2**) 10.00 g(30 mmol)을 가하여 같은 온도에서 1시간동안 교반하였다. 한편 ACLE 11.34 g(28 mmol)을 EtOAc 120 m*l*에 현탁시키고 *N,O*-bis(trimethylsilyl)acetamide(BTSA) 17.3 m*l*(70 mmol)를 가하여 용해시킨 용액을 -20°C에서 위의 용액에 가하여 같은 온도에서 1.5시간동안 교반하였다. 이 용액에 EtOAc와 H_2O(1:2)의 혼합용매 300 m*l*를 가하고 교반시킨 후 유기층을 분리하여 포화 중조액 20 m*l*, brine 20 m*l*순으로 세척하고 무수 $MgSO_4$로 건조하였다. 이를 감압 농축하여 이 잔유물을 *n*-hexane에 분산시킨 후 생성된 결정을 여과하였다. 이것을 col- um chromatography(EtOAc/cyclohexane=1:1)로 정제하여 백색결정 13.8 g(67.2%)을 얻었다.

IR (KBr) cm^{-1} : 1788, 1723, 1685

^{1}H-NMR (DMSO-d_6) δ : 1.38(9H, s, $C(CH_3)_3$), 1.45(6H, s, $C(CH_3)_2$), 3.52(2H, d, C_2-2H), 3.85(3H, s, OCH_3), 4.54(2H, d, CH_2Cl), 5.19(1H, d, C_6-H), 5.25(2H, s, OCH_2), 5.83(1H, dd, C_7-H), 6.50(1H, s, thiazole-H), 6.84~7.32(4H, m, ArH), 8.81(1H, s, HCO), 9.65(1H, d, CONH), 12.65(1H, br.s, HCONH)



Scheme II — Synthesis of Compound **3**, Method A.



Scheme III — Synthesis of Compound **3**, Method B.

5-(Thiophen-2-yl)-2H-tetrazole(4)

2-Thiophenecarbonitrile 10 g(91.6 mmol), sodium azide 6.58 g(100 mmol), NH_4Cl 5.44 g(100 mmol)을 증류한 DMF 90 m*l*에 가하고 130~140°C에서 17시간 동안 가열 반응시킨 반응물을 빙수 중에 저으면서 가하고 2N-HCl로 pH 2.0가 되도록 산성화시켰다. 생성된 결정을 여과하고 얼음물로 세척한 후, 95%-EtOH로 재결정하여 백색 결정 10.25 g(73.53 %)을 얻었다.

mp : 197~200°C

^{1}H-NMR (DMSO-d_6) δ : 7.10(1H, m, thiophene-H), 7.83~7.95(2H, m, thiophene-H)

5-Diphenylmethyl-2H-tetrazole(5)

Diphenylacetonitrile 3.00 g(15.2 mmol), sodium azide 1.1 g(16.7 mmol), NH_4Cl 0.91 g(16.7 mmol)을 증류한 DMF 15 m*l*에 가하고 (**4**)와 같은 방법으로 합성하였다.

수득율 : 49.9%

mp : 170~174°C

^{1}H-NMR (DMSO-d_6) δ : 5.95(1H, s, CH), 7.01~7.54(10H, m, ArH)

5-(4-Chlorophenyl)-2H-tetrazole(6)

p-Chlorobenzonitrile 3.00 g(21.6 mmol), sodium azide 1.56 g(24 mmol), NH_4Cl 1.3 g(24 mmol), 증류한 DMF 20 m*l*을 (**4**)와 같은 방법으로 합성하였다.

수득율 : 60.9%

mp : 274~275°C

^{1}H-NMR (DMSO-d_6) δ : 7.64~7.74(2H, m, ArH), 8.02~8.13(2H, m, ArH)

5-(4-Methylthiophenyl)-2H-tetrazole(7)

4-(Methylthio)benzonitrile 5.10 g(34 mmol), sodium azide 2.45 g(37.4 mmol), NH_4Cl 2.03 g(37.4 mmol), 증류한 DMF 30 m*l*을 (**4**)와 같은 방법으로 합성하였다.

수득율 : 94.4%

mp : 220~223°C

^{1}H-NMR (DMSO-d_6) δ : 2.56(3H, s, CH_3), 7.42~7.53(2H, m, ArH), 7.94~8.05(2H, m, ArH)

5-(4-Hydroxyphenyl)-2H-tetrazole(8)

4-Cyanophenol 10.00 g(84 mmol), sodium azide 5.17 g(92 mmol), NH_4Cl 4.49 g(92 mmol), 증류한 DMF 60 m*l*을 (**4**)와 같은 방법으로 합성하였다.

수득율 : 62%

mp : 185°C

^{1}H-NMR (DMSO-d_6) δ : 6.97~7.08(2H, m, ArH), 7.89~8.00(2H, m, ArH)

5-(2-Methoxybenzyl)-2H-tetrazole(9)

2-Methoxybenzylcyanide 12.20 g(83 mmol), sodium azide 5.17 g(92 mmol), NH_4Cl 4.49 g(92 mmol), 증류한 DMF 60 m*l*을 (**4**)와 같은 방법으로 합성하였다.

수득율 : 61.9%

mp : 175~178°C

^{1}H-NMR (DMSO-d_6) δ : 3.74(2H, s, CH_2), 3.78 (3H, s, OCH_3), 7.37(4H, m, ArH)

5-(1,5-Dimethyl-2-pyrrole)-2H-tetrazole(10)

1,5-Dimethyl-2-pyrrolecarbonitrile 5.00 g(42 mmol), sodium azide 3.02 g(46 mmol), NH_4Cl 2.5 g(46 mmol), 증류한 DMF 40 m*l*을 (**4**)와 같은 방법으로 합성하였다.

수율 : 50.8%

mp : 198°C

^{1}H-NMR (DMSO-d_6) δ : 2.27(3H, s, $ArCH_3$), 3.89(3H, s, $N-CH_3$), 6.00~6.05(1H, m, ArH), 6.72~6.77(1H, m, ArH)

5-Naphthyl-2H-tetrazole(11)

1-Cyanonaphthalene 10.00 g(65.2 mmol), sodium azide 4.66 g(71.7 mmol), NH_4Cl 3.83 g(71.7 mmol), 증류한 DMF 60 m*l*을 화합물 (**4**)와 같은 방법으로 합성하였다.

수득율 : 82.4%

mp : 167~169°C

^{1}H-NMR (DMSO-d_6) δ : 7.58~8.69(7H, m, ArH)

***p*-Methoxybenzyl 7β-[(Z)-2-(2-formamidothiazol-4-yl)-2-(1-*tert*-butoxycarbonyl-1-methylethoxyimino)aceta-**

mido]-3-[5-(thiophen-2-yl)tetrazol-2-yl]methyl-3-cephem-4-carboxylate(12)

Me_2CO 10 ml에 화합물(**3**) 1.00 g(1.27 mmol)을 녹인 후 NaI 0.23 g(1.52 mmol)을 가하여 상온에서 1.5시간 동안 반응시킨 용액에 화합물(**4**) 0.21 g(1.40 mmol)과 K_2CO_3 0.21 g(1.53 mmol)을 넣어 45~50°C에서 5시간 동안 교반시켰다. 반응물을 여과하고 여액을 감압농축하여 잔사를 소량의 Me_2CO에 용해시키고 이것을 H_2O/EtOH(2:1)의 혼합용매 120 ml에 분산하여 10분간 교반하고 d-HCl로 pH 2.0로 산성화하여 생성된 결정을 여과하여 황색 결정 0.75 g을 얻었다. 이 결정을 silica gel(230~400 mesh)을 사용하여 column chromatography (CH_3CN/Toluene=1:5)로 정제하여 백색 결정 0.43 g(42.3%)을 얻었다.

IR (KBr) cm^{-1} : 1787, 1733, 1615.

^{1}H-NMR (DMSO-d_6) δ : 1.38(9H, s, $C(CH_3)_3$), 1.43(6H, s, $C(CH_3)_2$), 3.75(3H, s, OCH_3), 5.04~5.27(6H, m, C_2-2H, C_3'-CH_2, OCH_2), 5.41~5.80 (2H, m, C_6-H, C_7-H), 6.88~7.82(8H, m, thiazole-H, ArH), 8.49(1H, s, HCO), 9.60(1H, d, CONH), 12.68(1H, br.s, HCONH)

***p*-Methoxybenzyl 7β-[(Z)-2-(2-formamidothiazol-4-yl)-2-(1-*tert*-butoxycarbonyl-1-methylethoxyimino)acetamido]-3-(5-diphenylmethyltetrazol-2-yl)methyl-3-cephem-4-carboxylate(13)**

화합물**13~19**은 화합물**12**와 같은 방법으로 합성하였다.

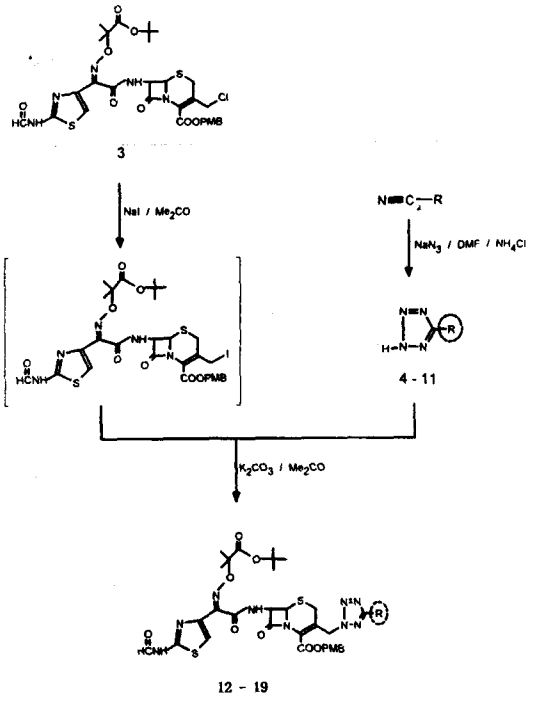
수득율 : 27.2%

IR (KBr) cm^{-1} : 1787, 1733, 1610.

^{1}H-NMR (DMSO-d_6) δ : 1.38(9H, s, $C(CH_3)_3$), 1.44(6H, s, $C(CH_3)_2$), 3.75(3H, s, OCH_3), 4.90~5.25(6H, m, C_2-2H, C_3'-CH_2, OCH_2), 5.38~5.65 (2H, m, C_6-H, C_7-H), 6.87~7.40(15H, m, thiazole-H, ArH), 8.49(1H, s, HCO), 9.62(1H, d, CONH), 12.67(1H, br.s, HCONH)

***p*-Methoxybenzyl 7β-[(Z)-2-(2-formamidothiazol-4-yl)-2-(1-*tert*-butoxycarbonyl-1-methylethoxyimino)acetamido]-3-[5-(4-chlorophenyl)tetrazol-2-yl]methyl-3-cephem-4-carboxylate(14)**

수득율 : 51%



Scheme IV — Synthesis of Compounds **12-19**.

IR (KBr) cm^{-1} : 1785, 1730, 1612.

^{1}H-NMR (DMSO-d_6) δ : 1.38(9H, s, $C(CH_3)_3$), 1.44(6H, s, $C(CH_3)_2$), 3.74(3H, s, OCH_3), 4.98~5.31(6H, m, C_2-2H, C_3'-CH_2, OCH_2), 5.47~5.73 (2H, m, C_6-H, C_7-H), 6.87~8.03(9H, m, thiazole-H, ArH), 8.49(1H, s, HCO), 9.62(1H, d, CONH), 12.66(1H, br.s, HCONH)

***p*-Methoxybenzyl 7β-[(Z)-2-(2-formamidothiazol-4-yl)-2-(1-*tert*-butoxycarbonyl-1-methylethoxyimino)acetamido]-3-[5-(4-methylthiophenyl)tetrazol-2-yl]methyl-3-cephem-4-carboxylate(15)**

수득율 : 41.6%

IR (KBr) cm^{-1} : 1787, 1733, 1610.

^{1}H-NMR (DMSO-d_6) δ : 1.38(9H, s, $C(CH_3)_3$), 1.44(6H, s, $C(CH_3)_2$), 2.53(3H, s, SCH_3), 3.75(3H, s, OCH_3), 5.04~5.46(6H, m, C_2-2H, C_3'-CH_2, OCH_2), 5.53(1H, dd, C_6-H), 5.66~5.73(1H, m, C_7-H), 6.88~8.18(9H, m, thiazole-H, ArH), 8.49(1H, s, HCO), 9.62(1H, d, CONH), 12.68(1H, br.s, HCONH)

p-Methoxybenzyl 7β-[(Z)-2-(2-formamidothiazol-4-yl)-2-(1-*tert*-butoxycarbonyl-1-methylethoxyimino)acetamido]-3-[5-(4-hydroxyphenyl)tetrazol-2-yl]methyl-3-cephem-4-carboxylate(16)

수득율 : 37%

IR (KBr) cm^{-1} : 1785, 1733, 1612.

^{1}H-NMR (DMSO-d_6) δ : 1.38(9H, s, $C(CH_3)_3$), 1.45(6H, s, $C(CH_3)_2$), 3.76(3H, s, OCH_3), 5.99~5.28(6H, m, C_2-2H, C_3'-CH_2, OCH_2), 5.52(1H, dd, C_6-H), 5.58~5.71(1H, m, C_7-H), 6.89~7.87 (9H, m, thiazole-H, ArH), 8.50(1H, s, HCO), 9.63(1H, d, CONH), 12.69(1H, br.s, HCONH)

p-Methoxybenzyl 7β-[(Z)-2-(2-formamidothiazol-4-yl)-2-(1-*tert*-butoxycar-bonyl-1-methylethoxyimino)acetamido]-3-[5-(2-methoxybenzyl)tetrazol-2-yl]methyl-3-cephem-4-carboxylate(17)

수득율 : 55%

IR (KBr) cm^{-1} : 1787, 1731, 1612.

^{1}H-NMR (DMSO-d_6) δ : 1.38(9H, s, $C(CH_3)_3$), 1.44(6H, s, $C(CH_3)_2$), 3.57(2H, s, $-CH_2Ar$), 3.76 (6H, s, $2\times OCH_3$), 5.04~5.28(6H, m, C_2-2H, C_3'-CH_2, OCH_2), 5.47~5.70(2H, m, C_6-H, C_7-H), 6.89~7.86(9H, m, thiazole-H, ArH), 8.49 (1H, s, HCO), 9.62(1H, d, CONH), 12.63(1H, br.s, HCONH)

p-Methoxybenzyl 7β-[(Z)-2-(2-formamidothiazol-4-yl)-2-(1-*tert*-butoxycarbonylmethylethoxyimino)acetamido]-3-[5-(1,5-dimethyl-2-pyrrole)tetrazol-2-yl]methyl-3-cephem-4-carboxylate(18)

수득율 : 47%

IR (KBr) cm^{-1} : 1787, 1733, 1594.

^{1}H-NMR (DMSO-d_6) δ : 1.38(9H, s, $C(CH_3)_3$), 1.44(6H, s, $C(CH_3)_2$), 2.25(3H, s, CH_3-Ar), 3.74~3.76(6H, m, OCH_3, N-CH_3), 5.01~5.28(6H, m, C_2-2H, C_3'-CH_2, OCH_2), 5.44(1H, dd, C_6-H), 5.67 ~5.70(1H, m, C_7-H), 6.64(1H, s, thiazole-H), 6.89~7.40(6H, m, ArH), 8.49(1H, s, HCO), 9.61 (1H, d, CONH), 12.68(1H, s, HCONH)

p-Methoxybenzyl 7β-[(Z)-2-(2-formamidothiazol-4-yl)-2-(1-*tert*-butoxycarbonylmethylethoxyimino)acetamido]-3-(5-naphthyltetrazol-2-yl)methyl-3-cephem-4-carboxylate(19)

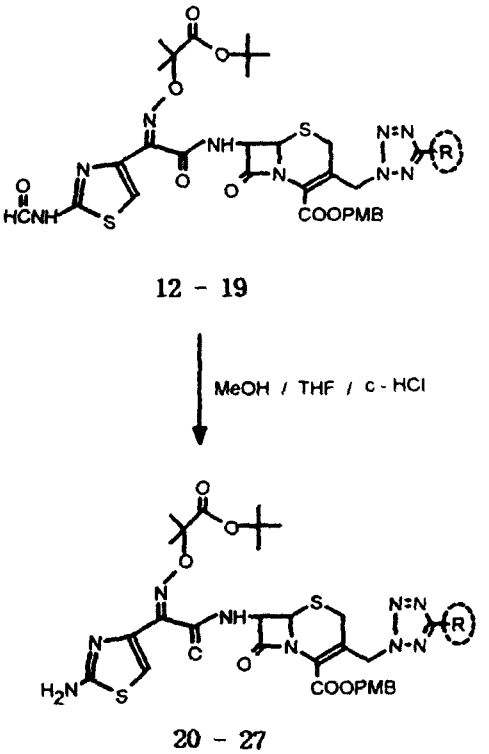
수득율 : 43%

IR (KBr) cm^{-1} : 1787, 1733, 1620.

^{1}H-NMR (DMSO-d_6) δ : 1.37(9H, s, $C(CH_3)_3$), 1.44(6H, s, $C(CH_3)_2$), 3.69~3.72(6H, m, OCH_3), 5.05~5.29(6H, m, C_2-2H, C_3'-CH_2, OCH_2), 5.48~5.72(2H, m, C_6-H, C_7-H), 6.85~8.78(12H, m, thiazole-H, ArH), 8.50(1H, s, HCO) 9.62(1H, d, CONH), 12.69(1H, s, HCONH)

p-Methoxybenzyl 7β-[(Z)-2-(2-aminothiazol-4-yl)-2-(1-*tert*-butoxycarbonyl-1-methylethoxyimino)acetamido]-3-[5-(thiophen-2-yl)tetrazol-2-yl]methyl-3-cephem-4-carboxylate(20)

화합물(**12**) 0.50 g(0.63 mmol)에 MeOH 10 m*l*, THF 5 m*l*, c-HCl 0.2 m*l*을 가하여 2.5시간동안 상온에서 교반하였다. 5% $NaHCO_3$ 용액으로 중화시키고 감압농축한 후 다시 10% HCl로 pH 2.0으로 산성



Scheme V — Synthesis of Compounds **20-27**.

화시켰다. EtOAc 100 m*l*, H_20 50 m*l*를 가하여 유기층을 취하여 brine 100 m*l*(50 m*l*×2)로 세척한후 무수 $MgSO_4$로 건조하였다. 감압농축하여 잔유물을 *n*-hexane에 분산하고 생성된 결정을 여과하였다. 황색결정 0.31 g을 얻었다. 이 결정을 silica gel(230~400 mesh)을 사용하여 column chromatography(CH_3-CN/Toluene=1:7)로 정제하여 백색결정 0.15 g(48.4 %)을 얻었다.

IR (KBr) cm^{-1} : 1787, 1733, 1618.

^{1}H-NMR (DMSO-d_6) δ : 1.39(15H, br.s, $C(CH_3)_3$, $C(CH_3)_2$), 3.75(3H, s, OCH_3), 4.99~5.54(6H, m, C_2-2H, C_3'-CH_2, OCH_2), 5.45~5.72(2H, m, C_6-H, C_7-H), 6.70~7.82(10H, m, thiazole-H, NH_2, ArH), 9.60(1H, d, CONH)

***p*-Methoxybenzyl 7β-[(Z)-2-(2-aminothiazol-4-yl)-2-(1-*tert*-butoxycarbonyl-1-methylethoxyimino)acetamido]-3-(5-diphenylmethyltetrazol-2-yl)methyl-3-cephem-4-carboxylate(21)**

화합물**21~27**은 화합물**20**의 방법으로 각각 합성하였다.

수득율 : 37%

IR (KBr) cm^{-1} : 1787, 1731, 1615.

^{1}H-NMR (DMSO-d_6) δ : 1.37(15H, br.s, $C(CH_3)_3$, $C(CH_3)_2$), 3.74(3H, s, OCH_3), 4.93~5.25(6H, m, C_2-2H, C_3'-CH_2, OCH_2), 5.43~5.64(2H, m, C_6-H, C_7-H), 6.69~7.33(17H, m, thiazole-H, NH_2, ArH), 9.47(1H, d, CONH)

***p*-Methoxybenzyl 7β-[(Z)-2-(2-aminothiazol-4-yl)-2-(1-*tert*-butoxycarbonyl-1-methylethoxyimino)acetamido]-3-[5-(4-chlorophenyl)tetrazol-2-yl]methyl-3-cephem-4-carboxylate(22)**

수득율 : 50%

IR (KBr) cm^{-1} : 1787, 1735, 1687.

^{1}H-NMR (DMSO-d_6) δ : 1.38(15H, br.s, $C(CH_3)_3$, $C(CH_3)_2$), 3.74(3H, s, OCH_3), 4.98~5.32(6H, m, C_2-2H, C_3'-CH_2, OCH_2), 5.47~5.62(1H, m, C_6-H), 5.73(1H, br.s, C_7-H), 6.70~8.04(10H, m, thiazole-H, NH_2, ArH), 9.46(1H, d, CONH)

***p*-Methoxybenzyl 7β-[(Z)-2-(2-aminothiazol-4-yl)-2-(1-*tert*-butoxycarbonyl-1-methylethoxyimino)acetamido]-3-[5-(4-methylthiophenyl)tetrazol-2-yl]methyl-3-cephem-4-carboxylate(23)**

수득율 : 48.3%

IR (KBr) cm^{-1} : 1787, 1731, 1615.

^{1}H-NMR (DMSO-d_6) δ : 1.38(9H, s, $C(CH_3)_3$), 1.42(6H, s, $C(CH_3)_2$), 2.53(3H, s, SCH_3), 3.75(3H, s, OCH_3), 4.99~5.33(6H, m, C_2-2H, C_3'-CH_2, OCH_2), 5.51~5.74(2H, m, C_6-H, C_7-H), 6.71~7.96(11H, m, thiazole-H, NH_2, ArH), 9.47(1H, d, CONH)

***p*-Methoxybenzyl 7β-[(Z)-2-(2-aminothiazol-4-yl)-2-(1-*tert*-butoxycarbonyl-1-methylethoxyimino)acetamido]-3-[5-(4-hydroxyphenyl)tetrazol-2-yl]methyl-3-cephem-4-carboxylate(24)**

수득율 : 62.5%

IR (KBr) cm^{-1} : 1785, 1731, 1615.

^{1}H-NMR (DMSO-d_6) δ : 1.38(15H, br.s, $C(CH_3)_3$, $C(CH_3)_2$), 3.75(3H, s, OCH_3), 4.99~5.33(6H, m, C_2-2H, C_3'-CH_2, OCH_2), 5.54(1H, dd, C_6-H), 5.68~5.70(1H, m, C_7-H), 6.70~7.86(11H, m, thiazole-H, NH_2, ArH), 9.46(1H, d, CONH)

***p*-Methoxybenzyl 7β-[(Z)-2-(2-aminothiazol-4-yl)-2-(1-*tert*-butoxycarbonyl-1-methylethoxyimino)acetamido]-3-[5-(2-methoxybenzyl)tetrazol-2-yl]methyl-3-cephem-4-carboxylate(25)**

수득율 : 24%

IR (KBr) cm^{-1} : 1785, 1730, 1684.

^{1}H-NMR (DMSO-d_6) δ : 1.38(15H, br.s, $C(CH_3)_3$, $C(CH_3)_2$), 3.56(2H, s, CH_2-Ar), 3.74(6H, s, OCH_3, Ar-OCH_3), 5.03~5.32(6H, m, C_2-2H, C_3'-CH_2, OCH_2), 5.41~5.70(2H, m, C_6-H, C_7-H), 6.69~7.85(11H, m, thiazole-H, NH_2, Ar-H), 9.62(1H, d, CONH)

***p*-Methoxybenzyl 7β-[(Z)-2-(2-aminothiazol-4-yl)-2-(1-*tert*-butoxycarbonyl-1-methylethoxyimino)acetamido]-3-[5-(1,5-dimethyl-2-pyrrole)tetrazol-2-yl]methyl-3-cephem-4-carboxylate(26)**

수득율 : 42%

IR (KBr) cm^{-1} : 1785, 1733, 1602.

^{1}H-NMR (DMSO-d_6) δ : 1.35(15H, brs, $C(CH_3)_3$, $C(CH_3)_2$), 2.23(3H, s, Ar-CH_3), 3.73(3H, s, OCH_3), 3.88(3H, s, N-CH_3), 5.02~5.29(6H, m, C_2-2H, C_3'-CH_2, OCH_2), 5.37~5.67(2H, m, C_6-H, C_7-H), 6.62~7.55(9H, m, thiazole-H, NH_2, ArH), 9.43(1H, d, CONH)

_p_-Methoxybenzyl 7β-[(Z)-2-(2-aminothiazol-4-yl)-2-(1-*tert*-butoxycarbonyl-1-methylethoxyimino)acetamido]-3-(5-naphthyltetrazol-2-yl)methyl-3-cephem-4-carboxylate(27)

수득율 : 46%

IR (KBr) cm^{-1} : 1787, 1731, 1618.

^{1}H-NMR (DMSO-d_6) δ : 1.34(9H, s, $C(CH_3)_3$), 1.39(6H, s, $C(CH_3)_2$), 3.70(3H, s, OCH_3), 4.98~5.27(6H, m, C_2-2H, C_3'-CH_2, OCH_2), 5.55~5.71(2H, m, C_6-H, C_7-H), 6.69~8.76(14H, m, thiazole-H, NH_2, ArH), 9.46(1H, d, CONH)

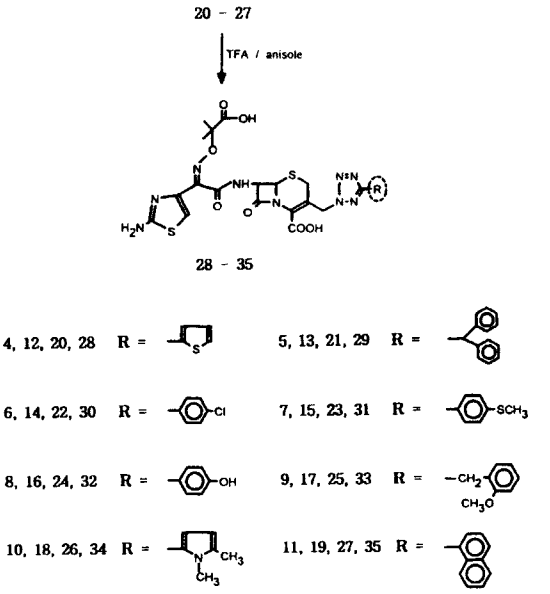
7β-[(Z)-2-(2-Aminothiazol-4-yl)-2-(1-carboxy-1-methylethoxyimino)acetamido]-3-[5-(2-thiophen-2-yl)tetrazol-2-yl]methyl-3-cephem-4-carboxylic acid(28)

화합물(**20**) 0.50 g(0.64 mmole)에 CH_2Cl_2 2 m*l*와 anisole 2 m*l*, TFA 4 m*l*를 0~5°C에서 가하여 1.5시간 동안 교반시키고 iPE 50 m*l*에 분산하여 생성된 결정을 여과하였다. 이 결정을 5%-$NaHCO_3$ 용액에 녹이고 EtOAc 20 m*l*로 세척한 후 수층을 취해 5°C 이하에서 10%-HCl로 pH 2.0로 산성화하여 생성된 결정을 여과하여 흑갈색 결정 0.34 g을 얻었다. 이 결정을 silica gel(230~400 mesh)을 사용하여 column chromatography(CH_3CN/H_2O=8:1)로 정제하고 냉동건조하여 황색 결정 0.14 g(41.2%)을 얻었다.

IR (KBr) cm^{-1} : 3341, 1772, 1674, 1636.

^{1}H-NMR (DMSO-d_6) δ : 1.45(6H, s, $C(CH_3)_2$), 4.94~5.28(4H, m, C_2-H, C_3'-H), 5.51(1H, dd, C_6-H), 5.63(1H, m, C_7-H), 6.76~7.87(6H, m, thiazole-H, NH_2, ArH), 9.63(1H, d, CONH)

7β-[(Z)-2-(2-Aminothiazol-4-yl)-2-(1-carboxy-1-methylethoxyimino)acetamido]-3-(5-diphenylmethyltetrazol-2-yl)methyl-3-cephem-4-carboxylic acid(29)



Scheme VI — Synthesis of Compounds **28-35**.

화합물**29-35**는 화합물**28**의 방법에 따라 합성하였다.

수득율 :34%

IR (KBr) cm^{-1} : 3338, 1772, 1633.

^{1}H-NMR (DMSO-d_6) δ : 1.44(6H, s, $C(CH_3)_2$), 4.77~5.15(4H, m, C_2-H, C_3'-H), 5.39(1H, dd, C_6-H), 5.67(1H, s, C_7-H), 5.95(1H, s, -$CHPh_2$), 6.80(1H, s, thiazole-H), 6.89~7.45(12H, m, NH_2, ArH), 9.62(1H, d, CONH)

7β-[(Z)-2-(2-Aminothiazol-4-yl)-2-(1-carboxy-1-methylethoxyimino)acetamido]-3-[5-(4-chlorophenyl)tetrazol-2-yl]methyl-3-cephem-4-carboxylic acid(30)

수득율 : 51.6%

IR (KBr) cm^{-1} : 3323, 1772, 1635.

^{1}H-NMR (DMSO-d_6) δ : 1.44(6H, s, $C(CH_3)_2$), 3.99(2H, s, C_2-H), 5.01~5.32(2H, m, C_3'-H), 5.5(1H, dd, C_6-H), 5.62~5.8(1H, m, C_7-H), 6.78(1H, s, thiazole-H), 7.59~7.61(2H, m, ArH), 7.89~8.03(2H, m, ArH), 9.62(1H, d, CONH)

7β-[(Z)-2-(2-Aminothiazol-4-yl)-2-(1-carboxy-1-methylethoxyimino)acetamido]-3-[5-(4-methylthiophenyl)tetrazol-2-yl]methyl-3-cephem-4-carboxylic acid(31)

수득율 : 47.8%

IR (KBr) cm^{-1} : 3307, 1777, 1731.

^{1}H-NMR (DMSO-d_6) δ : 1.49(6H, s, $C(CH_3)_2$), 2.54(3H, s, SCH_3), 5.03~5.31(2H, m, C_3'-H), 5.29~5.93(2H, m, C_6-H, C_7-H), 6.89~8.00(5H, m, thiazole-H, ArH), 9.69(1H, d, CONH)

7β-[(Z)-2-(2-Aminothiazol-4-yl)-2-(1-carboxy-1-methylethoxyimino)acetamido]-3-[5-(4-hydroxyphenyl)tetrazol-2-yl]methyl-3-cephem-4-carboxylic acid(32)

수득율 : 32%

IR (KBr) cm^{-1} : 3307, 1767, 1672.

^{1}H-NMR (DMSO-d_6) δ : 1.40(6H, s, $C(CH_3)_2$), 4.98~5.32(2H, m, C_3'-H), 5.54~5.90(2H, m, C_6-H, C_7-H), 6.86~7.89(7H, m, thiazole-H, NH_2, ArH), 9.68(1H, d, CONH)

7β-[(Z)-2-(2-Aminothiazol-4-yl)-2-(1-carboxy-1-methylethoxyimino)acetamido]-3-[5-(2-methoxybenzyl)tetrazol-2-yl]methyl-3-cephem-4-carboxylic acid(33)

수득율 : 43%

IR (KBr) cm^{-1} : 3330, 1774, 1677.

^{1}H-NMR (DMSO-d_6) δ : 1.48(6H, s, $C(CH_3)_2$), 3.56(2H, s, CH_2-Ar), 3.73(3H, s, $-OCH_3$), 5.02~5.32(4H, m, C_2-CH_2, C_3-CH_2), 5.50(1H, dd, C_6-H), 5.69(1H, s, C_7-H), 6.78(1H, s, thiazole-H), 7.18~7.42(4H, m, ArH, NH_2), 7.81~7.89(2H, m, ArH), 9.62(1H, d, CONH)

7β-[(Z)-2-(2-Aminothiazol-4-yl)-2-(1-carboxy-1-methylethoxyimino)acetamido]-3-[5-(1,5-dimethyl-2-pyrrole)tetrazol-2-yl]methyl-3-cephem-4-carboxylic acid(34)

수득율 : 30%

IR (KBr) cm^{-1} : 3305, 1777, 1679.

^{1}H-NMR (DMSO-d_6) δ : 1.40(6H, s, $C(CH_3)_2$), 2.25(3H, s, Ar-CH_3), 3.74(3H, s, N-CH_3), 5.03~5.29(4H, m, C_2-2H, C_3-CH_2), 5.44(1H, dd, C_6-H), 5.68(1H, m, ArH), 6.64(1H, s, thiazole-H), 6.88~6.94(1H, m, ArH), 7.29~7.41(3H, m, ArH), 9.62 (1H, d, CONH)

7β-[(Z)-2-(2-Aminothiazol-4-yl)-2-(1-carboxy-1-methylethoxyimino)acetamido]-3-(5-naphthyltetrazol-2-yl)methyl-3-cephem-4-carboxylic acid(35)

수득율 : 42%

IR (KBr) cm^{-1} : 3320, 1772, 1728.

^{1}H-NMR (DMSO-d_6) δ : 1.40(6H, s, $C(CH_3)_2$), 5.01~5.37(4H, m, C_2-CH_2, C_3-CH_2), 5.62~5.85 (2H, m, C_6-H, C_7-H), 6.85~8.79(10H, m, thiazole-H, ArH), 9.63(1H, d, CONH)

항균력 실험

시험 균주

Alcaligenes faecalis KCTC 1004, *Bacillus subtilis* ATCC 6633, *Escherichia coli* AB 1157, *Escherichia coli* AB 0111, *Escherichia coli* BE 1186, *Micrococcus luteus* ATCC 9341, *Mycobacterium phlei* IFO 3158, *Pseudomonas aeruginosa* N-10, *Salmonella typhimurium* TV 119, *Salmonella typhimurium* SL 1102, *Staphylococcus aureus* IFO 12732, *Staphylococcus aureus* R-209

배지

시험 균주의 전배양 및 검정 plate의 제조 목적으로 Mueller Hinton broth(DIF Co.)를 사용하였다.

항균 활성 측정법

시험균의 전배양 - *Alcaligenes faecalis* KCTC 1004 외 11개의 균은 액체 배지에서 37°C, 24시간 진탕 배양하여 사용하였다.

검정 plate의 제조 - 화합물 **28, 29, 30, 31, 31, 32, 33, 34, 35**를 소량의 DMSO에 각각 녹인 후 증류수를 가하여 최종 DMSO의 농도가 2%(V/V)가 되도록 하였다. 각각의 시료 1 m*l*를 2단계 희석법으로 14차례 희석하여 영양 한천 배지 14 m*l*와 섞었을 때, 최종 배지의 화합물 **28, 29, 30, 31, 31, 32, 33, 34, 35** 및 대조 물질(cefotaxime, cefazolin)의 농도가 각각 40, 20, 10, 5, 2.5, 1.25, 0.63, 0.31, 0.16, 0.08, 0.04, 0.02, 0.01, 0.005 g/ m*l*이 되도록 제조하였다.

항균력 판정 - 각각의 시험 균주들을 검정 plate에 접종한 것을 37±2°C에서 18시간 배양 후 육안으로 관찰하여 성장이 억제되는 항균제의 최소 발육 저지 농도(Minimum Inhibitory Concentration, MIC)를 조

Table I—MIC(μg/l) of synthetic compounds and commercial antibiotics against representative microorganisms

Strains \ Compounds	**28**	**29**	**30**	**31**	**32**	**33**	**34**	**35**	**S-1**	**S-2**
Alcaligense faecalis KCTC 1004	>40	>40	>40	>40	>40	>40	>40	>40	>40	10
Bacillus subtilis ATCC 6633	0.32	0.64	1.25	0.32	2.5	0.64	0.16	2.5	0.16	0.64
Escherichia coli AB 1157	5	5	2.5	1.25	0.32	1.25	5	1.25	2.5	0.16
Escherichia coli AB 0111	2.5	1.25	5	0.63	2.5	5	4	2.5	2.5	0.32
Escherichia coli BE 1186	1.25	0.64	2.5	1.25	0.16	1.25	2.5	0.32	2.5	0.08
Micrococcus luteus ATCC 9341	2.5	0.64	1.25	2.5	0.32	2.5	0.16	0.64	2.5	0.04
Mycobacterium phlei IFO 3158	40	40	40	20	40	10	40	40	5	1.25
Pseudomonas aeruginosa N-10	>40	>40	>40	>40	>40	>40	>40	>40	>40	>40
Staphylococcus aureus IFO 12732	10	5	10	5	20	10	20	5	1.25	5
Staphylococcus aureus R-209	5	10	20	2.5	20	5	10	10	0.32	2.5
Salmonella typhimurium SL 1102	5	2.5	10	2.5	5	0.64	10	5	5	0.32
Salmonella typhimurium TV 119	2.5	1.25	2.5	0.64	1.25	0.32	2.5	2.5	2.5	0.04

S-1 : Cefazoline, **S-2** : Cefotaxime

사하여 **Table I**과 같은 결과를 얻었다.

결 론

화합물 **1**을 acetic anhydride와 formic acid를 반응시켜 amino기를 formylation 한 **2**를 82% 수율로 합성하였다. 화합물 **2**를 HOBT와 DCC를 사용하여 active ester을 만든 다음 ACLE을 반응시켜 **3**을, 또한 **2**를 Vilsmeyer reagent를 사용하여 acyl chloride을 만들고 여기에 BTSA를 사용하여 amino기를 sillylation한 ACLE을 반응시켜 각각 68.7%, 67.2%의 수율로 합성하였다. 5-(Substituted)phenyl-2H-tetrazole유도체 **4~11**은 cyano기를 갖는 다양한 화합물로 NaN_3, NH_4Cl을 사용하여 DMF 용매 중에서 반응시켜 47.6~94.4%의 수율로 용이하게 합성할 수 있었다. *p*-methoxy 7β-[(Z)-2-(2-formamidothiazole-4-yl)-2-(*tert*-buthoxycarbonylisoproroxyimino)acetamido]-3-[5-(substituted)tetrazole-2-yl]methyl-3-cephem-4-carboxylate **12~19**는 **3**을 NaI를 가하여 Cl을 I로 치환시키고 tetrazole **4~11**을 acetone과 K_2CO_3 중에서 반응시켜 얻는 물질을 column chromatography로 정제하여 27.2%~60%의 수율로 얻었다. Formamido기를 가진 화합물 **12~19**를 MeOH/THF 용매 중에서 c-HCl을 반응시켜 deformylation시킨 화합물 **20~27**을 얻었고 화합물 **20~27**을 anisole용매 중에서 TFA와 반응시켜 t-butyl ester와 *p*-methoxybenzyl(PMB)ester를 유리 -COOH기로 변환시킨 7β-[(Z-2-(2-aminothiazole-4-yl)-2-(1-carboxy-1-methylethoxyimino) acetamido]-3-[5-(substituted)tetrazole-2-yl]methyl-3-cephem-4-carboxylic acid **28~35**을 얻은후 이것을 CH_3CN/H_2O(8:1)의 용매로 column chromatography로 정제한 후 냉동건조하여 34~51.6%의 수율로 얻을 수 있었다.

화합물 **28~35**를 *Alcaligenes faecalis* KCTC 1004, *Bacillus subtilis* ATCC 6633, *Escherichia coli* AB 1157, *Escherichia coli* AB 0111, *Escherichia coli* BE 1186, *Micrococcus luteus* ATCC 9341, *Mycobacterium phlei* IFO 3158, *Pseudomonas aeruginosa* N-10, *Salmonella typhimurium* TV 119, *Salmonella typhimurium* SL 1102, *Staphylococcus aureus* IFO 12732, *Staphylococcus aureus* R-209 균에 대하여 항균력 실험을 하여 기존의 cephalosporin계 항생제인 cefazolin, cefotaxime과 비교, 검토하였던 바 *Micrococcus luteus* ATCC 9341, *Escherichia coli* AB 1157, *Escherichia coli* AB 0111, *Escherichia coli* BE 1186, 및 *Salmonella typhimurium* TV 119, *Salmonella typhimurium* SL 1102에 대해서는 항균력이 우수하였으나 기대하였던 penicillin 내성균주인 *Pseudomonas aeruginosa* N-10균에 대해서는 효과를 발현하지 않았다.

감사의 말씀

본 연구는 서울대학교 신의약품 개발연구센터의 지원에 의하여 수행되었으므로 이에 감사드립니다.

문 헌

1) Takaya, T., Kamimura, T., Kojo, H., Mine, Y., Nishida, S., Goto, S. and Kuwahara, S. : Ceft-

izoxime (FK 749), a new paranteral cephalosporin : *in vitro* and *in vivo* antibacterial activities. Current chemotheraphy and infectious disease, Vol. I. pp. 255. The American Society of Microbiology, Washington, DC (1980).

2) Takaya, T., Takasugi, H., Masugi, T., Chiba, T., Kochi, H., Takano, T. and Nakano, H. : Structure-activity relationships of sodium 7β-[(Z)-2-(2-amino -4-thiazolyl)-2-(methoxyimino)acetamido]-3-cephem-4-carboxylate(ceftizoxime) and its related compounds. *Nippon Kagaku Kaishi* **1981**, 785~804 (1981).

3) Takaya, T., Takasugi, H., Masugi, T., Kochi, H. and Nakano, H. : Studies on β-lactam antibiotics. IV. Structure-activity relationships of 7β-[(2)-2-alkoxyimino-2-(2-amino-4-thiazolyl) acetamido]-3-cephem-4-carboxylic acids. *J. Antibiotics* **34**, 1357~1359 (1981).

4) Bucourt, R., Heymes, R., Lutz, A., Penasse, L. and Perronnet, J. : Proprietes antibiotiques inattendues dans le domains des cephalosporins. C. R. Acad. Sci. Paris, Serie D. 284 : 1847~1849 (1977).

5) Heymes, R., Lutz, A. and Schrinner : Experimental evaluation of HR 756, a new cephalosporin derivative : Pre-clinical study. *Infection* **5**, 259~260 (1977).

6) Ochiai, M., Aki, O., Morimoto, A., Okada, T. and Matsushita, Y. : New cephalosporin derivatives with high antibacterial activities. *Chem. Pharm. Bull.* **25**, 3115~3117 (1977).

7) Reiner, R., Welss, U., Brombacher, U., Lanz, P., Montavon, M., Furlenmeier, A., Angehrn, P. and Probst, P. J. : Ro 13-99041001, a novel potent and long-acting parenteral cephalosporin. *J. Antibiotics* **33**, 783~786 (1980).

8) Yamanaka, H., Chiba, T., Kawabata, K., Takasugi, H., Masugi, T. and Takaya, T. : Synthesis and biological activity of a new orally active cephalosporin, Cefixime (FK 027). *J. Antibiotics* **38**, 1738~1751 (1985).

9) Ocallaghan, C. H., Acred, P., Harper, P. B., Ryan, D. M., Kirby, S. M. and Harding, S. M., A new aminothiazoyl cephalosporin with high activity against *Pseudomonas* and *Enterobacteriaceae*. *Antimicrob. Agents Chemother.* **17**, 876~883 (1980).

10) Saryan, L. A., Ankel, E., Krishnamurti, C., Petering, D. H. and Elford, H. : Comparative cytotoxic and biochemical effects of ligands and metal comlexes of α-N-heterocyclic carboxaldehyde thiosemicarbazones. *J. Med. Chem.* **22**(10), 1216 (1979).

11) Lewis G. S. and Nelson P. H. : 3-[(1,2,3-thiadiazol-5-ylthio)methyl] cephalosporins. *J. Med. Chem.* **22**(10), 1214 (1979).

12) Arimoto, M., Hayano, K., Soga, T., Yoshioka, T., Tagwa, H. and Furukawa, M. : Semisynthetic β-lactam antibiotics III. Synthesis and antibacterial activity of 7β-[2-(2-aminothiazol-4-yl)-2-(substituted carbamoyl methoxyimino) acetamido]cephalosporins. *J. Antibiotics* **39**(9), 1243 (1986).

13) Hara, R., Nakai, E. I., Hiasmichi, H. and Nagano, N. : Studies on β-lactam antibiotics IV. An improved synthesis of 3-(isothiazolyl- thiomethyl) cephalosporins and its application to new derivatives. *J. Antibiotics* **47**(4), 477 (1994).

14) Adams, R. G., Brain, E. G., Branch, C. L., Guest, A. W., Harrigton, F. P., Mizen, L., Neale, J. E., Pearson, M. J., Simson, I. N., Smulders, H. and Zomaya I. I. : Structure-activity relationships within a series of C(7)-substituted doxyiminocephalosporins containing the C(3)-methyl aminopyridiniumthiomethyl substituent. Synthesis and biological properties of BRL 57342 and some close analogues. *J. Antibiotics* **48**(5), 417 (1995).

15) Arimoto, M., Yokohama, S., Sudov, M., Ichikawa, Y., Hayano, T., Tagawa, H. and Furukawa, M. : Semisynthetic β-lactam antibiotics IV. Synthesis and antibacterial activity of 7β-[2-(heteroaromatic methoxyimino)-2-(2-aminothiazol-4-yl)acetamido]cephalosporins. *J. Antibiotics* **XLI**(12), 1795 (1988).

16) Lattrell, R., Blumbach, J., Ckheimer, W., Schmann, K. F., Kirrstetter, R., Klesel, N., Mencke, B., Scheunemann, K. H., Schwab, W., Seliger, H., Stache, U. and Winkler, I. : Synthesis and structure-activity realationships in the cefpirome series II. Analogues of cefpirome

with different 7-heteroaryl-acetamido and 3′-ammonium substituents. *J. Antibiotics* **XLI**(10), 1395 (1988).

17) Yoshimura, Y., Miyake, A., Nishimura, T., Kawai, T. and Yamaoka, M. : Studies on condensed-heterocyclic azolium cephalosporins II. Synthesis and antibacterial activity of 7β-[2-(2-aminothiazole-4-yl)-2(Z)-alkoxyiminoacetamido]-3-(condensed-heterocyclicazolium)methyl-3-cephem-4-carboxylates. *J. antibiotics*. **44**(12), 1394 (1991).

18) Nishimura, T., Yoshimura, Y. and Miyake, A. : Studies on condensed heterocyclic azolium cephalosporins III. Synthesis and antibacterial activity of 7β-[2-(2-amino-5-substituted-thiazole-4-yl)-2(Z)-alkoxyiminoacetamido]-3-(condensed-heterocyclic azolium)methyl-3-cephem-4-carboxylates. *J. antibiotics* **45**(4), 485 (1992).

19) Cho, S. K., Lee, K. H. and An, S. H. : Synthesis and biological activities of 3-(dihydroxycinnamamidoalkyl)pyridiniummethyl cephalosporins. *Korean J. Med. Chem.* **3**(1) 14 (1993).

20) Ohki, H., Kawabata, K., Okuda, S., Kamimura T. and Sakane, K. : FK037, A new parenteral cephalosporin with a broad antibacterial spectrum : Synthesis and antibacterial activity. *J. Antibiotics* **46**(2), 359 (1993).

21) Hanaki, H., Akagi, H., Yasui, M. and Otani, T. : Structure-activity realtionships of 2-thiosocephem against methicillin resistant *Staphylococcus aureus*. *J. Antibiotics* **48**(8) 901 (1995).

22) Ohki, H., Kawabata, K., Okuda, S., Kamimura, T. and Sakane, K. : Studies on 3′-quaternary ammonium cephalosporins II. Synthesis and antibacterial activity of 7β-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido] cephalosporin derivatives bearing various quaternary ammonium methyl groups at the 3 position. *J. Antibiotics* **48**(9), 1049 (1995).

23) Lee, J. Y., Lee, Y. S., Suk, D. W., Woo, E. R., Chung, B. Y. and Park, H. K. : Synthesis and biological activity of quaternary ammoniopropenylcephalosporins with hydroxylated alicyclic or aliphatic amines. *J. Antibiotics* **49**(12), 1286 (1996).

24) Yamanaka, H., Chiba, T., Kawabata, K., Takasugi, H., Masugi, T. and Takaya, T. : Studies on β-lactam antibiotics IX. Synthesis and biological activity of a new orally active cephalosporin, cefixime (FK 027). *J. Antibiotics* **38**(12), 1738 (1985).

25) Kawabata, K., Masugi, T. and Takaya, T. : Studies on β-lactam antibiotics XI. Synthesis and structure-activity realationships of new 3-(2,2-dihalovinyl) cephalosporins. *J. Antibiotics* **39**(3), 384 (1986).

26) Kawabata, K., Yamanaka, H., Takasugi, H. and Takaya, T. : Studies on β-lactam antibiotics XIII. Synthesis and structure-activity relationships of 7β-[(Z)-2-aryl-2-carboxymethoxyiminoacetamido]-3-vinylcephalosporins. *J. Antibiotics* **39**(3), 404 (1986).

27) Smith, P. W., Chamiec, A. J., Chung, G., Cobley, K. N., Duncan, K., Howes, P. D., Whittigton, A. R. and Wood, M. R. : Synthesis and biological activity of novel cephalosporins containing a (Z)-vinyl dimethylphosphonate group. *J. Antibiotics* **48**(1), 73 (1995).

28) Hara, R., Sakamoto, K., Hisamichi, H. and Nagano, N. : Structure-activity relationships of cephalosporins having a (dimethylisoxazoli- dinio)vinyl moiety at their 3-position. *J. Antibiotics* **49**(11), 1162 (1996).

29) Hara, R., Itahana, H., Sakamoto, K., Hisamichi, H. and Nagano, N. : Cycloaddition reactions of a 3-(1,3-butadienyl)cephalosporin and antibacterial activity of new cephem derivatives. *J. Antibiotics* **49**(11), 1182 (1996).

30) Naito, T., Aburaki, S., Kamachi, H., Narita, Y., Okumura, J. and Kawaguchi, H. : Synthesis and structure-activity relationships of a new series of cephalosporins, BMY-28142 and related compounds. *J. Antibiotics* **39**(8), 1092 (1986).

31) Arnould, J. C., Bertrandie, A., Bird, T. G. C., Boucherot, D., Jung, F., Lohmann, J. J., Oliver, A., Bailey, J. P., Bell, W. and Davies, G. M. : Synthesis and structure-activity relationships of cephlosporins with C-3′ catechol-containing residues. *J. Med. Chem.* **35**(14), 2631 (1992).

32) Cho, S. K., Lee, K. H. and An, S. H. : Syn-

thesis and biological activities of 3-(dihydroxycinnamamidoalkyl)pyridiniummethyl cephalosporins. *Korean J. Med. Chem.* **3**(1), 14 (1993).

33) Cho, S. K., Yoon, Y. H., Lee, K. H., An, S. H. and Kim, C. S. : Synthesis and biological activity of 3-(dioxopiperazinylcarboxyamido) pyridinium methyl cephalosporins. *Korean J. Med. Chem.* **3**(1), 20 (1993).

34) Obi, K., Saito, T., Kojima, A., Fukuda, H., Hirai, K. and Suzue, S : Novel cephalosporins having a benzothiopyran group 2. Synthesis and biological activity of catecholic benzothiopyran group at the C-3 side chain. *J. Antibiotics* **48**(3), 278 (1995).

35) Kim, Y. Z., Lim, J. C., Yeo, J. H., Bang, C. S., Kim, S. S., Lee, T. H., Oh, S. H., Moon, Y. C. and Lee, C. S. : Synthesis and antibacterial activities of novel C(7)-catechol-substituted cephalosporins(II). *J. Antibiotics* **49**(5), 499 (1996).

36) Hara, R., Itahana, H., Hisamichi, H., Fukuoka, S. and Nagano, N. : Synthesis and biological activity of new cephem compounds with a 3-(2-butenyl) and a 3-(1,3-butadienyl)group at their 3-position. *J. Antibiotics* **49**(11), 1179 (1996).

37) Choi, K. I., Cha, J. H., Pae, A. N., cho, Y. S., Koh, H. Y., Chang, M. H., Kang, H. Y. and Chung, B. Y. : Studies on new catechol containing cephalosporins having a pyridone moiety at the C-7 position. *J. Antibiotics* **50**(3), 279 (1997).

38) Kim, W. J., Ko, K. Y., Jung, M. H., Kim, M. H., Lee, K. Y. and Kim, J. H. : Synthesis and biological activity of novel 3-(2-propenyl)cephalosporin II. Preparation of prodrugs. *J. Antibiotics* **44**(10), 1083 (1991).

39) La, S. B., Jung, M. H., Kim, W. J. and Jee, U. K. : Synthesis and antibacterial activities of new oral cephalosporins. *Yakhak Hoeji* **37**(3), 295 (1993).

40) Suh, K. H. and Park, J. W. : Synthesis and antibacterial activity of new cephalosporins with lactonyloxyimino moiety. *Arch. Pharm. Res.* **17**(2), 87 (1994).