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트리아조릴 티오메칠피로리딘을 3번 측쇄에 가진 세파로스포린 유도체의 합성

고옥현# · 홍준희
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Synthesis of Cephalosporin Derivatives with Triazolylthiomethylpyrrolidines at the C-3 Side Chain

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Abstract — Synthesis of 7β-[(Z)-2-(2-aminothiazol-4-yl)-2-(1-carboxy-1-methylethoxyimino)acetamido]-3-[[(3S,5S)-5-[4-phenyl-5-(4-methylphenyl or 2-thiophenyl)-4*H*-1,2,4- triazol-3-yl]thiomethylpyrrolidin-3-yl]]thiomethyl-3-cephem-4-carboxylic acids (**7a,7b**) were described. (2S,4S)-4-acethylthio-2-[4-phenyl-5-(4-methylphenyl or 2-thiophenyl)-4 *H*-1,2,4-triazol-3-yl]thiomethyl-1-*tert*-butoxycarbonylpyrrolidines (**4a,4b**) were prepared from *trans*-4-hydroxy-*L*-proline with (2S,4R)-absolute configuration as starting material. 4-Phenyl-5-(4-methylphenyl or 2-thiophenyl)-4 *H*-1,2,4-triazol-3-thiols (**2a,2b**) were prepared from *p*-toluic anhydride and 2-thiophene carboxylic acid hydrazide, respectively. *p*-Methoxybenzyl 7β-(Z)-2-(2-formamidothiazol-4-yl)-2-(1-tert-butoxycarbonylisopropylimino]acetamido-3-[[(3S,5S)-5-[4-phenyl-5-(4-methylphenyl or 2-thiophenyl)-4*H*-1,2,3-triazol-3-yl]thiomethyl-1-*tert*-butoxycarbonylpyrrolidin-3-yl]]thiomethyl-3-cephem-4-carboxylates (**6a,6b**) were achieved by using *p*-methoxybenzyl 7β-(Z)-2-(2-formamidothiazol-4-yl)-2-(*tert*-butoxycarbonylisopropylimino] acetamido-3-chloromethyl-3-cephem-4-carboxylate (5) and (2S,4S)-4-acethylthio-2-[4-phenyl-5-(4-methyl phenyl or 2-thiophenyl)-4*H*-1,2,4-triazol-3-yl]thiomethyl-1-tert-butoxycarbonyl pyrrolidines (**4a,4b**). Removal of formyl, Boc, and p-methoxybenzyl protecting groups were carried out by triflu oroacetic acid and anisole to give the target compounds.

Keywords □ pyrrolidine, cephalosporin, antibacterial activity

Cephalosporin항생제의 cephem핵의 7번위치에 aminothiazole-alkoxyimino기의 도입은 β-lactamase에 대한 안정성과 광범위 항균spectrum을 갖게하고 3번위치에 heterocycle의 도입은 항균력을 증가시킨다. Alkoxyimino부위는 methoxyimino기를 가진 ceftizoxime,[1-3] cefotaxime,[4-15] cefmenoxime,[6] 그리고 ceftriaxone[7] 등이 보고 되었으며 carboxymethoxyimino기와 carboxymethyl ethoxyimino기를 가진 cefixime[8]와 ceftazidine[9] 등이 보고되었다. 3번위치에 heterocyclic-thiomethyl,[10-14] quaternary ammonium salt,[15-23] vinyl[24-29] 및 catechol[30-37]등을 도입시킨 cephalosporin계 항생제들은 항균력, 흡수, 대사를 결정짓는 중요한 부위로서 *pseudomonase*균과 같은 G(−)균에 강력한 항균력을 가지면서 β-lactamase에 대한 저항성을 향상시키는 것으로 보고되어 있다. 또한 4번위치의 carboxy기를 ester로 전환시킨 화합물들은 흡수율을 개선하고 생체이용율을 높일 목적으로 prodrug형태의 세파로스포린계[38-40]항생제가 보고되어 있다. 본 저자는 cephem ring의 7번위치에는 aminothiazole-carboxymethylethoxyimino기를 도입시키고, 3번위치에는 carbapenem 항생제의 thiomethylpyrrolidine기가 광범위 항균spectrum을 가질 뿐만아니라, *pseudomonas*균에 대한 항균력도 증가시킨다는 보고[41-44]에 착안하여 약리활성이 기대되는 triazolylthiomethylpyrrolidine 유도체을 도입한 새로운 cephalospolin계 항생물질을 합성하였다.

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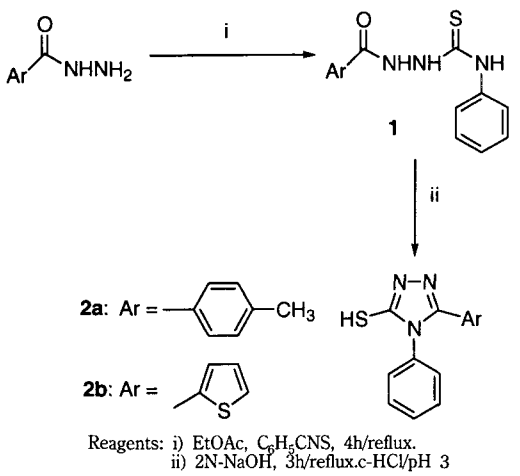
실 험

시약 및 기기 – 본 실험에 사용된 시약들은 Aldrich Co., Sigma Co., Tokyo Kasei., 및 Fluka Co. 에서 구입한 특급과 일급시약을 사용하였으며 (Z)-(2-aminothiazol-4-yl)-2-(*tert*-butoxycar-



Reagents: i) EtOAc, C_6H_5CNS, 4h/reflux.
ii) 2N-NaOH, 3h/reflux.c-HCl/pH 3

Scheme 1 – Synthesis of compound **2a** and **2b**.

bonylisopropoxyiminoacetic acid는 Lonz사 제품을 *p*-methoxybenzy7-amino-3-chloromethyl-3-cephem-4-carboxylate hydrochloride(ACLE)는 Otsuka사 제품을, silica gel (70~230 mesh)은 Sigma사 제품을 사용하였고 용매는 필요에 따라 정제하여 사용하였다. Thin layer chromatography (tlc)는 Kieselgel F_{254}(0.25 mm)를 바른 유리판을 잘라 이용하였으며 tlc spot은 자외선램프 UVGL-58와 $KMnO_4$ 발색시약을 사용하였다. 융점 측정은 Gallen-Kamp melting point apparatus를 사용하였으며, 이에 대한 보정은 하지 않았다. NMR spectra는 tetramethylsilane (TMS)를 내부 표준물질로 하여 Bruker FT-80 MHz, FT-300 MHz를 사용하였다.

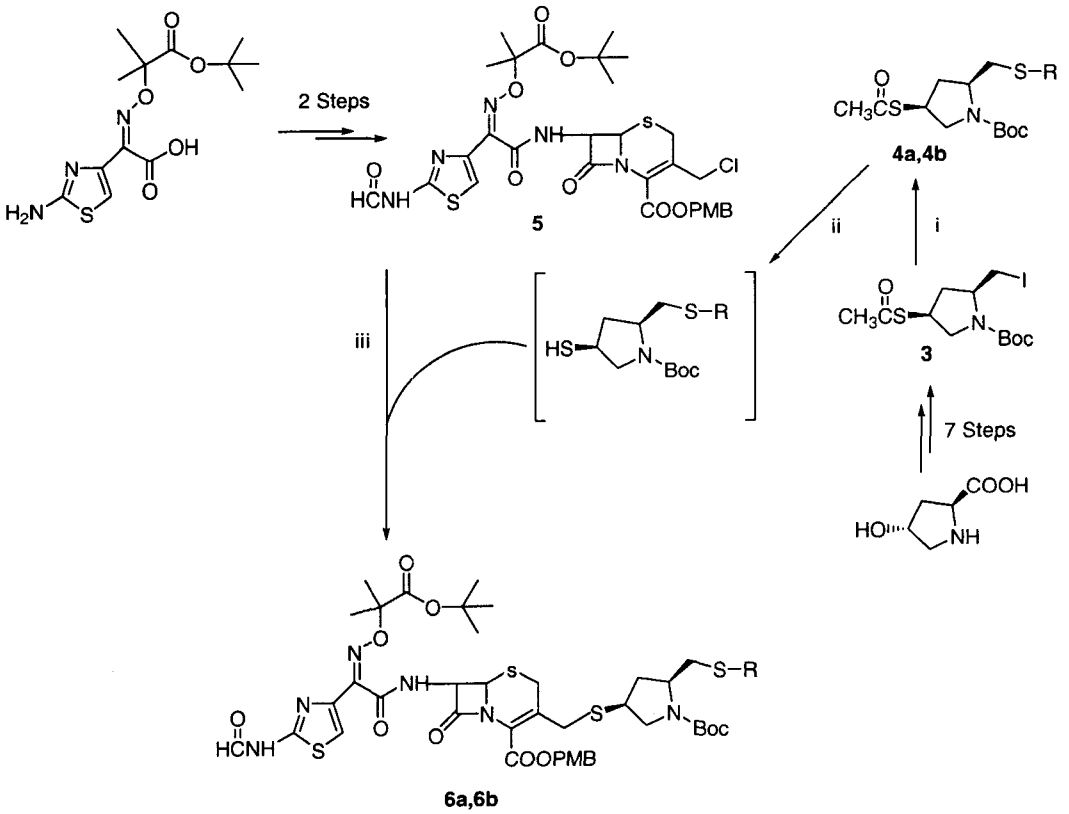
1-(4-Methylbenzoyl)-4-phenyl-3-thiosemicarbazide (1a)

p-Toluic hydrazide 5 g(0.033 mol)을 EtOH 50 m*l*에 녹인 뒤 phenylisothio cyanate 4.51 g (0.033 mol)을 가해 4시간 동안 가열반응 시킨 다음, 감압농축하여생성된 결정을 여과하였다. 95% EtOH로 재결정하여 흰색 결정 8.4 g(87%)을 얻었다. mp : 182°C

^{1}H-NMR(DMSO-d_6) δ : 2.37(3H, s, CH3), 7.12~7.86(7H, m, ArH) 7.86(2H, d, *J*=8.1Hz, ArH), 9.71(2H, d, *J*=11.0Hz, CONH), 10.43(2H, brs, NHCSNH)

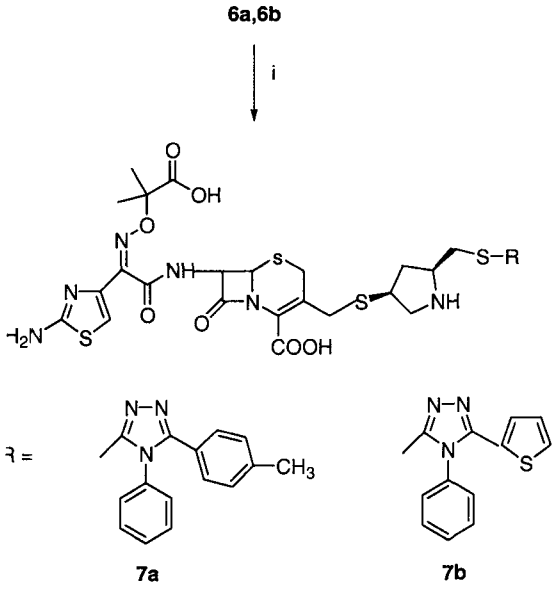
1-(2-Thiophenecarbonyl)-4-phenyl-3-thiosemicarbazide (1b)

2-Thiophenecaboxylic hydrazide 14.7 g(0.1 mol), phenylisothiocyanate 13.7 g(0.1 mol), EtOH 125 m*l*을 화합물 1a와



Reagents : i) a) MeOH/5.2*N*-methanolic CH_3ONa, Het-SH (**2a,2b**), 30 min. b) Me_2CO, 4h. rt.
ii) MeOH, 1*N*-NaOH EtOAc, 30 min./rt.
iii) DMF, Me_2CO, NaI, K_2CO_3, 40°C/4h, EtOAc

Scheme 2 – Synthesis of Compound **6a** and **6b**.



Reagents: i) a) MeOH, THF, C-HCl, 2h/rt. b) CH_2Cl_2, anisole, TFA

Scheme 3 – Synthesis of compounds (**7a,7b**).

같은 방법으로 합성하여 흰색 결정 24.7 g(87.9%)을 얻었다. mp: 193-195°C

^{1}H-NMR(DMSO-d_6) δ: 6.69~6.76(1H, m, thienyl-βH), 6.69~7.04 2H, m, thi enyl-αH), 7.45~7.86(5H, m, ArH). 9.67(1H, d, CONH), 10.43(2H, brs, NHCS NH)

4-phenyl-5-(4-methylphenyl)-4*H*-1,2,3-triazol-3-thiol(2a)

화합물 **1a** 3 g(0.01 mol)을 2N-NaOH 100 m*l*에 가하고 4시간 동안 환류교반시킨 다음 냉각하고 c-HCl로 pH 2로 산성화하였다. 생성된 결정을 여과하고 냉수로 세척한후 EtOH로 재결정하여 흰색 결정 2.8 g(98%)을 얻었다. mp : 269-270°C ^{1}H-NMR(DMSO-d_6) δ: 2.36(3H, s, CH_3), 7.16(5H, s, ArH), 7.27~7.53 4H, m, ArH), 14.02(1H, brs, SH)

4-phenyl-5-(2-thiophenyl)-4*H*-1,2,3-triazol-3-thiol(2b)

화합물 **1b** 2 g(0.007 mol), 2N-NaOH 80 m*l*을 사용하여 화합물 **2a**와 같은 방법으로 합성하여 흰색 결정1.5 g(81%)을 얻었다. mp : 264~267°C

^{1}H-NMR(DMSO-d_6) δ : 6.71~6.77(1H, thienyl-βH), 6.90-7.07 2H, m, thi enyl-αH), 7.50~7.78(5H, m, ArH), 14.18(1H, brs. SH)

(2S,4S)-4-Acetylthio-2-[4-phenyl-5-(4-methylphenyl)-4*H*-1,2,3-triazol-3-yl]thiomethyl-1-*tert*-butoxycarbonylpyrrolidine (4a)

화합물 **2a** 0.38 g(1.42 mmol)을 MeOH 10 m*l*에 녹이고 -20°C에서 5.2N-methanolic sodium methoxide 0.2 m*l*을 가하고 30분동안 교반하였다. 반응물을 감압 농축시킨 후 무수 Me_2CO 10 m*l*을 가하였다. 화합물 **3** 0.5 g (1.3 mmol)을 Me_2CO 20 m*l*에 녹인 용액에 위의 화합물을 가한 뒤 실온에서 4시간 교반하였다. 반응물을 감압농축한 후 EtOAc 200 m*l*로 추출하고 증류수, sat. $NaHCO_3$ 용액, brine 순으로 세척한 후 유기층을 취하여 무수 $MgSO_4$로 건조시키고 감압 농축하였다. Column chromatography(EtOAc/hexane=1:4)로 정제하여 미황색 고체 0.41 g(60.3%)을 얻었다. mp : 167~168°C

Rf : 0.44 (EtOAc/hexane=1:2)

^{1}H-NMR(DMSO-d_6) δ: 1.42(9H, s, $CH_3\times3$), 2.18 (1H, m, Pyrr.-H), 2.30 (3H, s, CH_3CO), 2.35(3H, s, CH_3) 2.75(1H, m, Pyrr.-H), 2.52(1H, m, Pyrr.-H), 2.75(1H, m, Pyrr.-H), 2.80 (2H, m, CH_2), 4.14(2H, m, Pyrr.-H), 7.13 (2H, m, ArH), 7.24~7.56(7H, m, ArH),

(2S,4S)-4-Acetylthio-2-[4-phenyl-5-(2-thiophenyl)-4*H*-1,2,4,-triazol-3-yl]thiomethyl-1-*tert*-butoxycarbonylpyrrolidine (4b)

화합물 **4a**와 같은 방법으로 합성하여 미황색결정 0.5 g(72%)을 얻었다. mp : 182~184°C, Rf: 0.54(EtOAc/hexane=1:2) ^{1}H-NMR(DMSO-d_6) δ: 1.40(9H, s, $CH_3\times3$), 2.15(1H, m, Pyrr.-H), 2.30(3H, s, CH_3CO), 2.78(1H, m, Pyrr.-H), 3.50 (1H, m, Pyrr.-H), 2.78(1H, m, Pyrr.-H) 2.80(2H, s, CH_2), 4.12(2H, m, Pyrr.-H), 6.78(1H, m, thienyl-H), 6.98(2H, m, thienyl-H), 7.33(5H, m, ArH)

***p*-Methoxybenzyl7β-[(Z)-2-(2-formamidothiazol-4-yl)-2-(tert-butoxycarbonylisopropylimino]acetamido-3-[[(3S,5S)-5-[4-phenyl-5-(4-methylphenyl)-4*H*-1,2,3-triazol-3-yl]thiomethyl-1-*tert*-butoxycarbonylpyrrolidin-3-ylthio]methyl-3-cephem-4-carboxylate (6a)**

화합물 **4a** 0.5 g(0.95 mmol)을 MeOH 20 m*l*에 녹이고 ice-bath상에서 1*N*-NaOH 1 m*l*를 가한 후 30분 동안 교반하였다. 반응물을 EtOAc로 추출하고 1*N*-HCl, sat. $NaHCO_3$, brine순으로 세척하였다. 유기층을 취하여 무수 $MgSO_4$로 건조시킨 후 감압 농축하여 미황색 액체를 얻었다. 얻어진 화합물을 정제하지 않고 바로 다음 반응에 사용하였다. 한편 화합물 **5** (0.5 g, 0.7 mmol)에 DMF 10 m*l*, Me_2CO 20 m*l*, NaI 0.12 g(0.8 mmol), K_2CO_3 0.17 g(1.2 mmol)을 가하고 4시간 동안 40~45°C에서 가열 교반한 후 여과하고 여액을 감압 농축하고 EtOAc 100 m*l*로 추출 후 증류수, sat. $NaHCO_3$, brine순으로 세척하였다. 유기층을 취하여 무수 $MgSO_4$로 건조시킨 후 감압 농축한 잔유물에 위의 화합물을 Me_2CO 20 m*l*에녹인 용액을 가하여 40~45°C에서

4시간 동안 가열 교반하였다. 반응물을 감압 농축시킨후 EtOAc 200 ml로 추출하고 증류수, sat. $NaHCO_3$ 용액, brine순으로 세척한 후 유기층을 취하여 무수 $MgSO_4$로 건조시키고 감압 농축한 후 column chromatography (EtOAc/hexane=1:2)로 정제하여 미황색 고체 0.29 g(38%)을 얻었다. mp : 93~96°C

Rf : 0.42 (EtOAc/hexane=1:2)

^{1}H-NMR(DMSO-d_6), δ: 1.40(9H, s, CH_3×3), 1.42(9H, s, CH_3×3), 1.45(6H, s, CH_3×2), 1.85(1H, m, Pyrr.-H), 2.35(3H, s, CH_3), 2.45(1H, m, Pyrr.-H), 3.14, 3.20(5H, m, CH_2S×2, Pyrr.-H), 3.35~3.64(2H, m, Pyrr.-H,), 3.76 (3H, s, OCH_3), 4.20(2H q, C-2), 5.18(1H, d, *J*=5.0Hz, C_6-H), 5.40(2H, s, OCH_2), 5.75(1H, dd, *J*=5.8Hz, C_7-H), 6.76(1H, s, thiazole-H), 7.18(5H, s, ArH), 7.25~7.54(4H, m, ArH), 8.26(1H, s, HCO), 9.64(1H, d, *J*=8.0Hz, CONH)

***p*-Methoxybenzyl7β-[(Z)-2-(2-formamidothiazol-4-yl)-2-(*tert*-butoxycarbonylisopropoxyimino]acetamido-3-[[(3S, 5S)-5-[4-phenyl-(2-thiophenyl)-4*H*-1,2,4,-triazol-3-yl]]thiomethyl-1-*tert*-butoxycarbonylpyrrolidin-3-ylthio]] methyl-3-cephem-4-carboxylate (6b)**

화합물 **4b** 0.5 g(0.97 mmol), MeOH 20 ml, 1*N*-NaOH 1 ml, 화합물 **5** 0.5 g(0.7 mmole), NaI 0.22 g(1.5 mmol), K_2CO_3 0.25 g(1.8 mmol)을 사용하여 화합물 **6a**와같이 합성한 후 column chromatography (EtOAc/hexane=1:2)로 정제하여 황색 고체 0.6 g(38%)을 얻었다.

Rf : 0.55 (EtOAc/hexane=1:2)

^{1}H-NMR(DMSO-d_6) δ: 1.41(9H, s, CH_3×3), 1.43(9H, s, CH_3×3), 1.48(6H, s, CH_3×2), 1.90~1.93(1H, m, Pyrr.-H), 2.47(1H, m, Pyrr.-H), 3.18~3.76(5H, m, Pyrr.-H, CH_2S), 3.79(2H, q, CH_2), 3.82(3H, s, OCH_3), 3.93~4.16(3H, m, Pyrr.-H, CH_2), 5.06~5.27(3H, m, C6-H, OCH2), 5.80(1H, dd, *J*=5.8Hz, C7-H), 6.70~6.76(1H, thienyl-βH), 6.79~6.95(5H, m, ArH, thiazole-H), 6.89~7.02(2H, m, thienyl-αH), 7.31~7.40 (5H, m, ArH), 8.25(1H, s, HCO), 9.59(1H, d, *J*=8Hz, CONH)

7β-[(Z)-2-(2-Aminothiazol-4-yl)-2-(1-carboxy-1-methylethoxyimino]acetamido-3-[[(3S,5S)-5-[4-phenyl-5-(4-methylphenyl)-4*H*-1,2,3-triazol-3-yl]thiomethylpy-rrolidin-3-yl]]thiomethyl-3-cephem-4-carboxylic acid (7a)

화합물 **6a** 0.5 g(0.44 mmol)을 MeOH 15 ml와 THF 5 ml에 녹이고 c-HCl 0.1 g(0.88 mmol)을 가하여 실온에서 2시간 동안 교반하였다. 반응물을 EtOAc 100 ml와 물 5.0 ml의 혼합 용매에 가하여 sat. $NaHCO_3$용액으로 pH 7.5로 조절 하였다. 유기층을 brine으로 세척하여 $MgSO_4$로 건조한 후 감압 농축하였다. 전자의 화합물을 ice-bath상에서 CH_2Cl_2 20 ml에 녹이고 여기에 anisole 2.0 ml과 TFA 3.5 ml(46 mmol)를 서서히 가해준다. 실온에서 2시간 동안 교반한 후 감압 농축시키고 isopropylether (IPE)로 결정화 하였다. 이것을 중조용액에 녹힌후 EtOAc, CH_2Cl_2으로세척한후 물층을 냉동건조하였다. Column chromatography (H_2O/AcCN=1:5)로 정제하여 미백색의 고체 0.09 g(25%)을 얻었다. mp : 203~205°C

Rf: 0.42(CH_3CN/H_2O=3:1) ^{1}H-NMR(DMSO-d_6) δ: 1.45 and 1.47(6H, s, CH_3×2), 2.02(2H, m, Pyrr.-H) 2.36(3H, s, CH_3), 2.65(1H, m, Pyrr.-H), 3.03(3H, m, CH_2S, Pyrr.-H), 3.08(2H, m Pyrr.-H), 3.68(2H, q, C_2-H). 4.15(2H, s, CH_2), 5.18(1H, d, 5.0Hz, C6-H). 5.85(1H, *J*=5.8Hz, C_7-H), 6.78~7.05(5H, m, ArH, thiazole-H), 7.32~7.40(5H, m, ArH) 9.53(1H, d, *J*= 8.0Hz, CONH)

7β-[(Z)-2-(2-Aminothiazol-4-yl)-2-(1-carboxy-1-methylethoxyiminoacetamido-3-[[(3S,5S)-5-[4-phenyl-5-(2-thiophenyl)-4*H*-1,2,4,-triazol-3-yl]thiomethylpyrrolidin-3-yl]] thiomethyl-3-cephem-4-carboxylic acid (7b)

화합물 **6b** 0.5 g(0.44 mmol)을 6a와 같은 방법으로 합성한 후 column chromatography(H_2O/AcCN=1:5)로 정제하여 미백색의 고체 0.1 g(26.6%)을 얻었다. mp : 209~211°C

Rf : 0.42 (CH_3CN/H_2O=3:1)

^{1}H-NMR(DMSO-d_6) δ: 1.44 and 1.47(6H, s, CH_3×2), 1.98 (1H, m, Pyrr.-H), 2.65(4H, m, Pyrr.-H), 3.12(2H, m, Prr.-H), 3.67(2H, q, C_2-H), 4.15(2H, q, CH_2 S), 5.15(1H, d, C_6-H), 5.83(1H, dd, *J*=5.8Hz, C_7-H), 6.73(1H, s, thiazole-H), 6.67~ 6.75(1H, m, thienyl-H), 6.92~7.11(2H, m, thienyl-H), 7.31 (5H, brs, ArH), 7.12, 7.36(4H, m, ArH), 9.55(1H, d, *J*= 8.0Hz, CONH)

결 론

Cephalosporin의 7위치에는 (*Z*)-2-(2-aminothiazol-4-yl)-2-(1-carboxy-1-methylethoxyimino) acetyl group을, 3위치에는 triazolylpyrrolidine moiety를 합성하여 도입시킨 7β-[(*Z*)-2-(2-aminothiazol-4-yl)-2-(1-carboxy-1-methylethoxyimino]acetamido-3-[[(3S,5S)-5-[4-phenyl-5-(4-methylphenyl)-4*H*-1,2,3-triazol-3-yl]thiomethylpyrrolidin-3-yl]]thiomethyl-3-cephem-4-carboxylic acid (7a)와 7β-[(*Z*)-2-(2-aminothiazol-4-yl)-2-(1-carboxy-1-methylethoxyimino]acetamido-3-[[(3S,5S)-5-[4-phenyl-5-(2-thiophenyl)-4*H*-1,2,4-triazol-3-yl]thiomethylpyrrolidin-3-yl]] thiomethyl-3-cephem-4-carboxylic acid (**7b**)을 합성하였다. (2S,4S)-4-Acetylthio-2-[4-phenyl-5-(4-methylphenyl or 2-thio-

phenyl)-4*H*-1,2,4-triazol-3-yl-thiomethyl-1-*tert*-butoxycarbonylpyrrolidine(**4a,4b**)는(2S,4R) absolute configuration을 가진 trans-4-hydroxy-L-proline을 출발물질로 합성 하여 사용하였다. 4-Phenyl-5-(4-methylphenyl or 2-thiophenyl)-4*H*-1,2,4-triazol-3-thiol(**2a,2b**)는 p-toluic anhydride 와 2-thiophenecarboxylic acid hydrazide 로부터 높은 수율로 합성하여 사용하였다. p-Methoxybenzyl7β-[(Z)-2-(2-formamidothiazol-4-yl)-2-(1-*tert*-butoxycarbonylisopropylimino] acetamido-3-[(3S,5S)-5-[4-phenyl-5-(4-methylphenyl or 2-thiophenyl)-4*H*-1,2,3-triazol-3-yl]thiomethyl-1-*tert*-butoxycarbonylpyrrolidin-3-yl]] thiomethyl-3-cephem-4-carboxylate(**6a,6b**)는 *p*-methoxybenzyl 7β-(Z)-2-(2-formamidothiazol-4-yl)-2-(*tert*-butoxycarbonylisopropylimino] acetamido-3-chloromethyl-3-ceph em-4-carboxylate (**5**)와 (2S,4S)-4-acethylthio-2-[4-phenyl-5-(4-methylphenyl or 2-thiophenyl)-4H-1,2,4-triazol-3-yl]thiomethyl-1-*tert*-butoxycarbonylpyrrolidine(**4a,4b**)로 부터 합성하였다. Protecting groups인 formyl, Boc, p-methoxybenzyl 은 TFA와 anisole를 사용하여 제거하였다.

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