# SYNTHESIS AND ANTIBACTERIAL ACTIVITY OF C-3′ ISOTHIAZOLYL AND RELATED CEPHALOSPORINS

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The synthesis of C-3′ isothiazolyl and related cephalosporins is presented. The compounds exhibit activity against a variety of Gram-positive and Gram-negative organisms.

Chemical manipulation of the C-3′ position in the cephalosporin molecule has resulted in the discovery of numerous important antibiotics.[1~4] Several groups have attempted to define a consistent structure-activity pattern and recent reports have developed a correlation between C-3′ substituent leaving group ability and electron withdrawing potential with improved antimicrobial action.[5~8] In order to further explore this relationship we have undertaken a limited, systematic study focusing on the synthesis and microbiological evaluation of a series of unique C-3′ isothiazolyl and benzothiadiazinyl cephalosporin derivatives, which appear to embody the aforesaid nucleofugic and inductive properties.

Scheme 1.

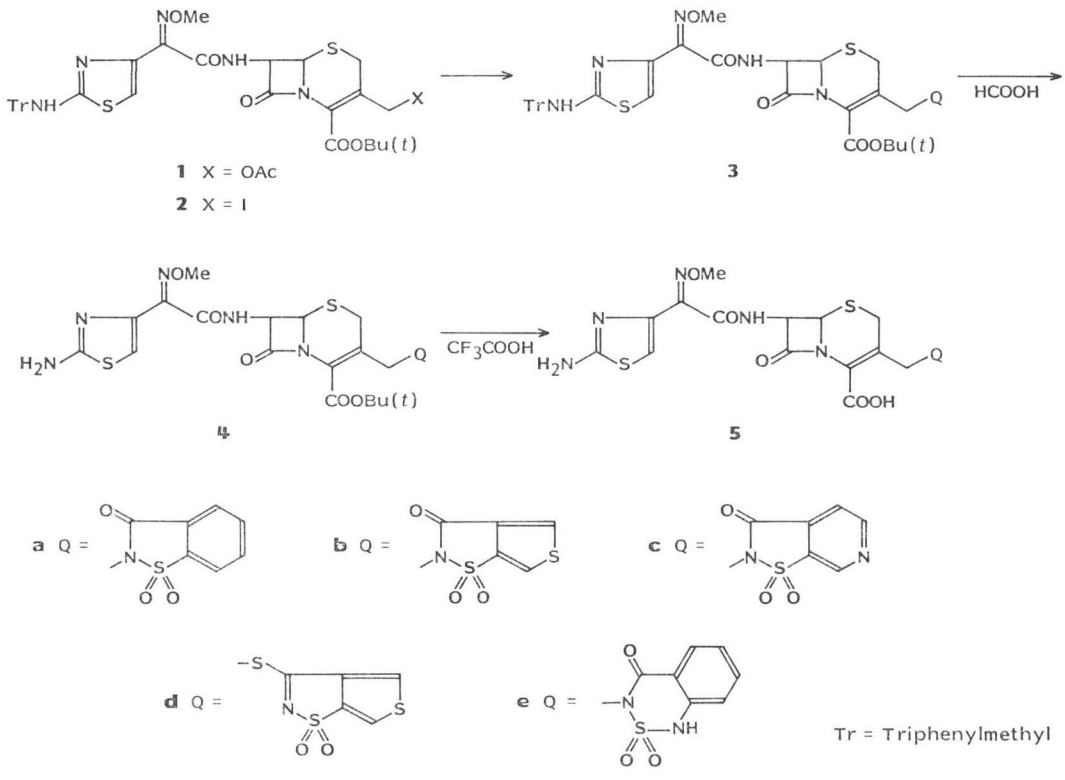
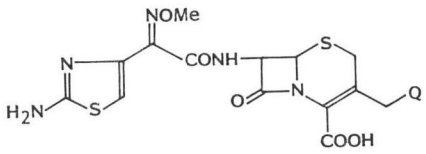
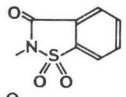
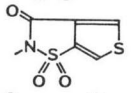
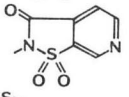
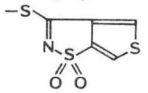
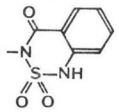


Table 1. *In vitro* antibacterial screening results (MIC $\mu$g/ml).




| Compound | Q | *Sa** | *Ef* | *Ecl* | *Ec* | *Kp* | *Pv* | *Pa* | *Sm* |
|---|---|---|---|---|---|---|---|---|---|
| **5a** |  | 4 | 8 | 8 | 1 | 0.5 | 0.5 | 32 | 4 |
| **5b** |  | 4 | 8 | 4 | 2 | 1 | 0.5 | 64 | 2 |
| **5c** |  | 32 | 128 | 16 | 2 | 1 | 2 | 128 | 2 |
| **5d** |  | 32 | 256 | 32 | 2 | <1 | <1 | >256 | 2 |
| **5e** |  | 32 | 128 | 64 | 4 | 2 | 0.25 | 128 | 16 |
| Cefotaxime | | 1 | 128 | 0.125 | 0.015 | 0.03 | 0.06 | 8 | 0.25 |
| Cefpiramide | | 1 | 4 | 32 | 1 | 2 | 8 | 2 | 16 |

* *Sa*; *Staphylococcus aureus* ATCC 29213, *Ef*; *Enterococcus faecalis* ATCC 29212, *Ecl*; *Enterobacter cloacae* ATCC 13047, *Ec*; *Escherichia coli* ATCC 25922, *Kp*; *Klebsiella pneumoniae* KL-1, *Pv*; *Proteus vulgaris* A84354 1, *Pa*; *Pseudomonas aeruginosa* ATCC 27853, *Sm*; *Serratia marcescens* ATCC 13880.

The facile preparation of the title compounds is depicted in Scheme 1. Treatment of cephalosporanic acid derivative **1** with trimethylsilyl iodide by the reported procedure[9] gave a complex mixture. Careful high performance liquid chromatographic purification afforded C-3 iodomethylcephalosporin (**2**) as a homogeneous solid in 40% yield.

Displacement of the iodide was smoothly effected using sodium saccharin in dimethylformamide at ambient temperature to give **3a** in 80% yield. Removal of the trityl protecting group was accomplished using aqueous formic acid at 25°C to furnish **4a** (82%). Deprotection of the acid function by the reaction of **4a** with trifluoroacetic acid in the presence of anisole at 0°C provided **5a** (79%). Cephalosporin derivatives **5b, c, e** were prepared analogously.

Utilization of **2** and thieno[3,4-*d*]isothiazol-3(2*H*)-thione 1,1-dioxide in the above sequence, followed by removal of the trityl and *tert*-butyl protecting groups, yielded related cephalosporin **5d**.

The *in vitro* antibacterial evaluation of cephalosporin analogs **5a**~**e** is summarized in Table 1. It is evident from the data presented that incorporation of the aryl fused isothiazolyl and thiadiazinyl units at C-3′ in the cephalosporin molecule is consistent with potent antibacterial action.

The most interesting compound of this series, thiophene saccharin derivative **5b**, exhibits a profile similar to cefpiramide displaying good activity against a variety of Gram-negative (with the exception of *Pseudomonas aeruginosa*) and Gram-positive organisms. By contrast, in juxtaposition with cefotaxime, **5b** is less potent.

In view of the high activity associated with C-3′ heterocyclic thiomethyl substitution, it is surprising that the related thiomethyl derivative **5d** did not demonstrate improved activity.

## Experimental

IR spectra were recorded on a Perkin-Elmer 299 infrared spectrophotometer. NMR spectra were obtained on a Varian XL-300 NMR spectrometer in the indicated solvents with $Me_4Si$ as the internal standard. HPLC purifications were performed using a Waters Prep-500 unit.

(6*R*,7*R*)-3-(Iodomethyl)-7-[[(*Z*)-methoxyimino-[4-[(triphenylmethyl)amino]-2-thiazolyl]acetyl]-amino]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic Acid *tert*-Butyl Ester (**2**)

To a solution of 8.4 g (0.0111 mol) of **1** and 100 ml of $CH_2Cl_2$ at ambient temperature under a nitrogen atmosphere was added dropwise 3.35 ml (4.71 g, 0.0235 mmol) of trimethylsilyl iodide. The reaction mixture was stirred for 2 hours, then washed successively with cold 10% $Na_2S_2O_3$ solution, satd $NaHCO_3$ solution, and brine, dried over $Na_2SO_4$, and concentrated *in vacuo*. The many component residue was purified by high performance liquid chromatography (EtOAc - $CH_2Cl_2$, 2: 98) to afford 3.62 g (40%) of **2**: IR (KBr) 3280, 1785, 1715, 1675, 1520, 1365, 1300, 1150, 1035 $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 7.34 (s, 15H), 6.94~6.86 (m, 1H), 6.76 (s, 1H), 5.96~5.88 (m, 1H), 5.06 (d, 1H), 4.45 (d, 1H), 4.32 (d, 1H), 4.12 (s, 3H), 3.76 (d, 1H), 3.52 (d, 1H), 2.06 (s, 3H), and 1.56 (s, 9H).

(6*R*,7*R*)-7-[[(*Z*)-Methoxyimino-[2-[(triphenylmethyl)amino]-4-thiazolyl]acetyl]amino]-3-[(3-oxo-1,2-benzisothiazol-2(3*H*)-yl)methyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic Acid *tert*-Butyl Ester $S^3$,$S^3$-Dioxide (**3a**)

To a solution of 400 mg (0.49 mmol) of cephalosporin **2** and 2 ml of DMF at ambient temperature was added portionwise 100 mg (0.49 mmol) of saccharin sodium salt. After 4 hours, the reaction mixture was diluted with EtOAc and washed copiously with water, then brine. The organic phase was dried over $Na_2SO_4$, and concentrated under reduced pressure to give a waxy solid. Trituration with $Et_2O$ furnished 345 mg (80%) of **3a**: IR (KBr) 3300, 1785, 1725, 1675, 1520, 1365, 1250, 1180, 1150, 1035 $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 8.16~7.88 (m, 4H), 7.26 (s, 15H), 6.82 (s, 1H), 6.04~5.92 (m, 1H), 5.13 (d, 1H), 4.71 (d, 1H), 5.09 (d, 1H), 4.12 (s, 3H), 3.63 (d, 1H), 3.39 (d, 1H), and 1.62 (s, 9H).

(6*R*,7*R*)-7-[[(*Z*)-(2-Amino-4-thiazolyl)(methoxyimino)acetyl]amino]-3-[(3-oxo-1,2-benzisothiazol-2(3*H*)-yl)methyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic Acid *tert*-Butyl Ester $S^3$,$S^3$-Dioxide (**4a**)

A solution of 300 mg (0.34 mmol) of **3a** and 3 ml of HCOOH (88%) was stirred at ambient temperature for 3 hours, then filtered. The filtrate was concentrated *in vacuo*. The resulting waxy solid was triturated with $Et_2O$ to afford 179 mg (82%) of **4a**: IR (KBr) 3300 (br), 1785, 1720, 1670 (br), 1530, 1250, 1180, 1150, 1030 $cm^{-1}$; NMR (DMSO-$d_6$) $\delta$ 9.67 (d, 1H), 8.19~8.0 (m, 4H), 6.76 (s, 1H), 5.88~5.78 (m, 1H), 5.15 (d, 1H), 5.03 (d, 1H), 4.67 (d, 1H), 3.86 (s, 3H), 3.65 (d, 1H), 3.47 (d, 1H), and 1.54 (s, 9H).

(6*R*,7*R*)-7-[[(*Z*)-(2-Amino-4-thiazolyl)(methoxyimino)acetyl]amino]-3-[(3-oxo-1,2-benzisothiazol-2(3*H*)-yl)methyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic Acid $S^3$,$S^3$-Dioxide, Trifluoroacetate Salt (**5a**)

A solution of 115 mg (0.18 mmol) of **4a**, 0.4 ml of anisole, and 4 ml of $CF_3COOH$ was stirred at 0°C for 3 hours. The reaction mixture was concentrated under high vacuum to give a brown oil. Trituration with $Et_2O$ provided 98 mg (79%) of **5a**: IR (KBr) 3300 (br), 1785, 1730, 1670 (br), 1250, 1180, 1140, 1045 $cm^{-1}$; NMR (DMSO-$d_6$) $\delta$ 9.71 (d, 1H), 8.2~8.0 (m, 4H), 6.84 (s, 1H), 5.88~5.78 (m, 1H), 5.13 (d, 1H), 5.07 (d, 1H), 4.75 (d, 1H), 3.89 (s, 3H), and 3.65~3.45 (m, 2H).

Compounds **5b**~e were prepared analogously.

(6*R*,7*R*)-7-[[(*Z*)-(2-Amino-4-thiazolyl)(methoxyimino)acetyl]amino]-8-oxo-3-[(3-oxothieno[3,4-*d*]-isothiazol-2(3*H*)-yl)methyl]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic Acid $S^3$,$S^3$-Dioxide, Trifluoroacetate Salt (**5b**)

IR (KBr) 3350 (br), 1775, 1720, 1675 (br), 1330, 1240, 1175, 1130, 1035 $cm^{-1}$; NMR (DMSO-$d_6$) $\delta$ 9.90 (d, 1H), 8.85 (d, 1H), 8.69 (d, 1H), 6.82 (s, 1H), 5.88~5.76 (m, 1H), 5.13 (d, 1H), 5.03 (d, 1H), 4.67 (d, 1H), 3.87 (s, 3H), 3.61 (d, 1H), and 3.43 (d, 1H).

(6*R*,7*R*)-7-[[(*Z*)-(2-Amino-4-thiazolyl)(methoxyimino)acetyl]amino]-8-oxo-3-[(3-oxoisothiazolo-[5,4-*b*]pyridin-2(3*H*)-yl)methyl]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic Acid $S^3$,$S^3$-Dioxide, Trifluoroacetate Salt (**5c**)

IR (KBr) 3350 (br), 1780, 1665 (br), 1310, 1260, 1175, 1130, 1040 $cm^{-1}$; NMR (DMSO-$d_6$) $\delta$ 9.68 (s, 1H), 9.26 (d, 1H), 8.14 (d, 1H), 6.82 (s, 1H), 5.98~5.88 (m, 1H), 5.12 (d, 1H), 5.08 (d, 1H), 4.78 (d, 1H), 3.88 (s, 3H), and 3.70~3.44 (m, 2H).

(6*R*,7*R*)-7-[[(*Z*)-(2-Amino-4-thiazolyl)(methoxyimino)acetyl]amino]-8-oxo-3-[(thieno-[3,4-*d*]iso-thiazol-3-ylthio)methyl]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic Acid $S^3$,$S^3$-Dioxide, Trifluoroacetate Salt (**5d**)

IR (KBr) 3350 (br), 1780, 1710, 1670 (br), 1460, 1330, 1200, 1170, 1040, 935 $cm^{-1}$; NMR (DMSO-$d_6$) $\delta$ 9.71 (d, 1H), 8.57 (d, 1H), 8.43 (d, 1H), 6.86 (s, 1H), 5.92~5.8 (m, 1H), 5.21 (d, 1H), 4.67 (d, 1H), 4.23 (d, 1H), 3.88 (s, 3H), and 3.66~3.38 (m, 2H).

(6*R*,7*R*)-7-[[(*Z*)-(2-Amino-4-thiazolyl)(methoxyimino)acetyl]amino]-3-[(1,4-dihydro-4-oxo-3*H*-2,1,3-benzothiadiazin-3-yl)methyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic Acid $S^3$,$S^3$-Dioxide, Trifluoroacetate Salt (**5e**)

IR (KBr) 3280 (br), 3100 (br), 1780, 1670 (br), 1530 (br), 1360 (br), 1180, 1135, 1040 $cm^{-1}$; NMR (DMSO-$d_6$) $\delta$ 9.66 (d, 1H, exchangeable), 8.08~7.96 (m, 1H), 7.36~7.20 (m, 1H), 7.00~6.94 (m, 1H), 6.86~6.76 (m, 1H), 6.80 (s, 1H), 5.84~5.74 (m, 1H), 5.16 (d, 1H), 5.06~4.82 (m, 2H), and 3.54~3.32 (m, 2H, partially obscured by $H_2O$).

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