SYNTHESIS AND ANTIBACTERIAL ACTIVITY OF C-4 SUBSTITUTED MONOBACTAMS

RICHARD E. MEWSHAW and THOMAS J. COMMONS

Medicinal Chemistry Department, Wyeth Laboratories, Inc.,
P.O. Box 8299, Philadelphia, Pennsylvania 19101, U.S.A.

(Received for publication May 12, 1987)

The synthesis and *in vitro* antibacterial profile of several novel C-4 substituted monobactam analogs are reported.

Continuing efforts in these laboratories have focused on the design and synthesis of novel 4-substituted monobactam derivatives.[1] Our interest in this area was in response to the excellent activity displayed from the monobactam antibiotic azthreonam,[2] and more recently carumonam.[3] Herein is reported the results of our detailed study concerning the synthesis and antibacterial profile

Scheme 1.

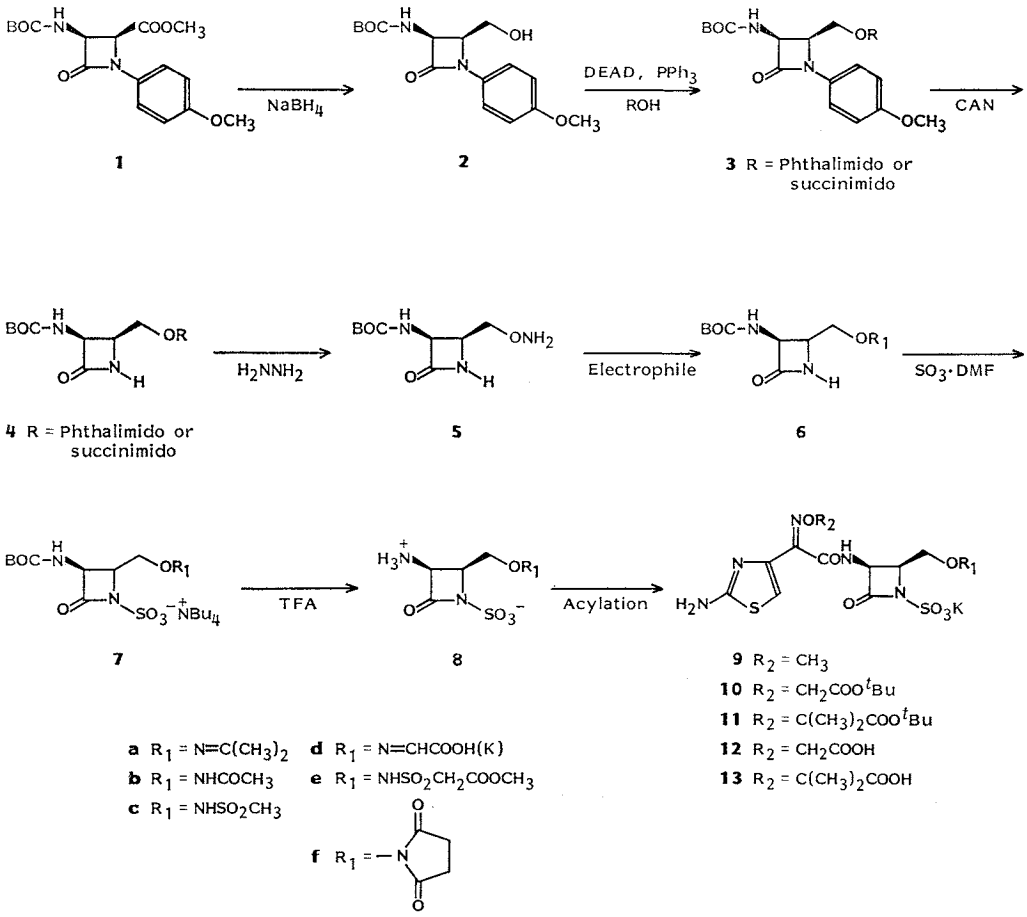
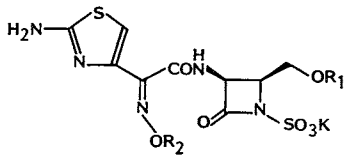


Table 1. Antibacterial screening results.



Compound[a]	R_2	R_1	MIC (μg/ml)[b]							
			S.a.	*S.f.*	*E.cl.*	*E.c.*	*K.p.*	*P.v.*	*P.a.*	*S.m.*
9a	CH_3	$N=C(CH_3)_2$	>256	>256	8	4	4	1	256	8
9b	CH_3	$NHCOCH_3$	>256	>256	16	8	4	2	>256	16
9c	CH_3	$NHSO_2CH_3$	256	>256	2	0.5	1	0.03	>256	4
9d	CH_3	N=CHCOOK	>256	>256	16	2	0.5	0.125	64	2
9e	CH_3	$NHSO_2CH_2COOCH_3$	>256	>256	32	16	8	1	>256	16
9f	CH_3	$N(COCH_3)_2$	>256	>256	8	4	1	0.125	>256	4
10c	CH_2COO^tBu	$NHSO_2CH_3$	>256	>256	128	64	32	16	>256	64
12c	CH_2COOH	$NHSO_2CH_3$	>256	>256	4	4	0.5	0.5	256	8
10d	CH_2COO^tBu	N=CHCOOK	>256	>256	128	32	16	1	128	32
12d	CH_2COOH	N=CHCOOH	>256	>256	16	16	2	0.06	8	8
10f	CH_2COO^tBu	$N(COCH_2)_2$	>256	>256	128	128	32	32	>256	64
12f	CH_2COOH	$N(COCH_2)_2$	>256	>256	8	8	2	0.5	>256	4
11d	$C(CH_3)_2COO^tBu$	N=CHCOOH	>256	>256	>256	256	128	4	>256	>256
13d	$C(CH_3)_2COOH$	N=CHCOOH	>256	>256	128	64	32	0.5	64	64

[a] Compounds were evaluated as a mixture of racemates.

[b] The MIC values reported were obtained by the microdilution broth method.

Test organisms and abbreviations: *S.a.*; *Staphylococcus aureus* ATCC 29213, *S.f.*; *Streptococcus faecalis* ATCC 29212, *E.cl.*; *Enterobacter cloacae* ATCC 13047, *E.c.*; *Escherichia coli* ATCC 25922, *K.p.*; *Klebsiella pneumoniae* KL-1, *P.v.*; *Proteus vulgaris* A84354 1, *P.a.*; *Pseudomonas aeruginosa* ATCC 27853, *S.m.*; *Serratia marcescens* ATCC 13880.

of a series of C-4 aminooxymethyl monobactam analogs.

The strategy for the preparation of the title compounds **9**~**13** involves the initial synthesis of key intermediate **5**. Elaboration to compounds **9**~**13** was effected conveniently and efficiently in four to five steps (Scheme 1).

Selective sodium borohydride reduction of known methyl ester **1**[4] afforded alcohol **2** in 90% yield. Coupling of **2** with *N*-hydroxyphthalimide using the MITSUNOBU procedure[5,6] gave the 4-phthalimidooxymethyl compound **3** in 81% yield. Oxidative dearylation of **3** using ceric ammonium nitrate[4] (CAN) afforded **4** in 75% yield. Treatment of **4** with hydrazine provided the requisite intermediate **5** in excellent yield. Treatment of **5** with acetone, acetyl chloride, methanesulfonyl chloride, glyoxylic acid and methyl chlorosulfonylacetate provided compounds **6a**~**6e**, respectively (54 to 97% yields). The 4-succinimidooxymethyl compound **6f** was prepared analogously, without hydrazinolysis. Sulfonation of **6a**~**6f** with sulfur trioxide dimethylformamide complex[7] (SO_3·DMF) followed by treatment with tetrabutylammonium hydrogen sulfate gave compounds **7a**~**7f** in good yield (Table 2). Removal of the *N-tert*-butoxycarbonyl (BOC) group by reaction with trifluoroacetic acid (TFA) in the presence of anisole at 0°C provided **8a**~**8f** (68 to 94%; Table 3). Coupling of **8a**~**8f** with the appropriate aminothiazoleacetic acid, followed by treatment with potassium nonafluorobutanesulfonate or ion exchange chromatography afforded **9a**~**9f**, **10c**, **10d**, **10f** and **11d**. Compounds **12c**, **12d**, **12f** and **13d** were prepared from the corresponding *tert*-butyl esters by the action of TFA at 0°C. Due to the synthetic expediency, the title compounds were tested as racemic mixtures.

The results of *in vitro* antibacterial evaluation are summarized in Table 1. The most active member in this series, against a variety of Gram-negative organisms was oxysulfonamide **9c**. Compound **12d** displays an interesting profile including good activity against *Pseudomonas aeruginosa*. It is evident from these data that the aminooxymethyl monobactams of this study are effective antibacterial agents. In particular, these compounds show good to moderate activity against a variety of Gram-negative organisms. However, they were essentially ineffective against Gram-positive bacteria at the concentrations tested, which is consistent with previous findings concerning monobactam derivatives.

Experimental

Elemental analyses were performed with a Perkin-Elmer model 240 elemental analyzer by the Analytical Section of these laboratories. IR spectra were recorded on a Perkin-Elmer 299 IR spectrophotometer. ^{1}H NMR spectra were obtained on a Varian XL-300 spectrometer in the indicated solvents with Me_4Si as the internal standard. Fast atom bombardment high resolution mass spectra (FAB-HRMS) were obtained on a Kratos MS 50-2C-HM system.

[*cis*-2-(Hydroxymethyl)-1-(4-methoxyphenyl)-4-oxo-3-azetidinyl]carbamic Acid 1,1-Dimethylethyl Ester (**2**)

Ester **1** (10.0 g, 0.028 mol) was dissolved in a solution of THF (250 ml) and water (250 ml). To this solution was added sodium borohydride (4.4 g, 0.12 mol) and stirred at room temp for 3.5 hours. The THF was evaporated *in vacuo* and the aqueous layer was poured into CH_2Cl_2 (250 ml) and acidified with 1 N HCl. The aqueous layer was washed with CH_2Cl_2 (4×80 ml) and the combined organic layers washed with 5% sodium bicarbonate (150 ml). The organic layer the dried ($MgSO_4$) and the solvent removed under reduced pressure to afford 8.1 g (90%) of a white solid: MP 166~167°C; IR (KBr) cm^{-1} 3490, 3420, 2980, 1745, 1660, 1505, 1245, 1160; ^{1}H NMR (DMSO-d_6) δ 1.40 (9H, s), 3.25 (3H, s), 4.25 (1H, m), 5.05 (2H, m), 6.90 (2H, d, J=8 Hz), 7.20 (1H, d, J=9 Hz, exchangeable), 7.45 (2H, d, J=8 Hz).

[*cis*-2-[[(1,3-Dihydro-1,3-dioxo-2*H*-isoindol-2-yl)oxy]methyl]-1-(4-methoxyphenyl)-4-oxo-3-azetidinyl]carbamic Acid 1,1-Dimethylethyl Ester (**3**)

To a mixture of alcohol **2** (5.8 g, 18 mmol), *N*-hydroxyphthalimide (3.0 g, 18 mmol) and triphenylphosphine (5.7 g, 22 mmol) in dry THF (100 ml) was added diethyl azodicarboxylate (DEAD) (3.7 g, 21 mmol.) The reaction was allowed to stir at room temp for 0.5 hour whereby the solvent was removed *in vacuo*. The reaction mixture was dissolved in CH_2Cl_2 and again the solvent evaporated to rid any residual THF. A solid precipitates and is washed with a solution of CH_2Cl_2 - ether (1 : 1). The filtrate is concentrated and the solid precipitate is again washed with a solution of CH_2Cl_2 - ether (1 : 1) and combined with the previously recovered material to afford 5.0 g of phthalimide **3** (59%); an additional 1.9 g (22.3%) of product could be recovered after concentration of the filtrate followed by flash chromatography (EtOAc - hexane, 1 : 9): MP 188~189°C; IR (KBr) cm^{-1} 3435, 2980, 2930, 1795, 1735, 1710, 1500, 1390, 1370, 1160, 1130; ^1H NMR ($CDCl_3$) δ 1.48 (9H, s), 3.74 (3H, s), 4.40 (1H, br d, J=12 Hz), 4.52 (1H, m), 4.98 (1H, br d, J=12 Hz), 5.44 (1H, m), 6.22 (1H, d, J=9 Hz, exchangeable), 6.82 (2H, d, J=8 Hz), 7.43 (2H, d, J=8 Hz), 7.78 (4H, m).

Anal Calcd for $C_{24}H_{25}O_7N_3$: C 61.79, H 5.34, N 8.97.
Found: C 61.84, H 5.36, N 8.88.

[*cis*-2-[[(1,3-Dihydro-1,3-dioxo-2*H*-isoindol-2-yl)oxy]methyl]-4-oxo-3-azetidinyl]carbamic Acid 1,1-Dimethylethyl Ester (**4**)

To a solution of **3** (5.1 g, 10.9 mmol) in acetonitrile (150 ml) at 0°C was slowly added a solution of CAN (17.9 g, 32.6 mmol) in water (125 ml). The reaction was allowed to stir for another 0.5 hour after addition was complete whereupon the reaction mixture was diluted with 200 ml of water and washed with EtOAc (3×200 ml). The organic layer was washed consecutively with 10% Na_2SO_3 (100 ml), 5% $NaHCO_3$ (100 ml), brine and dried over anhydrous magnesium sulfate. The solvent was evaporated *in vacuo* and the solid washed with ether to afford 2.96 g of the title compound **4** (75%): MP 218~219°C (CH_2Cl_2); IR (KBr) cm^{-1} 3325, 2920, 1775, 1730, 1680, 1525, 1370; ^1H NMR (DMSO-d_6) δ 1.36 (9H, s), 4.08 (1H, m), 4.30 (2H, m), 4.97 (1H, dd, J=9 and 6 Hz), 7.62 (1H, d, J=9 Hz, exchangeable), 7.90 (4H, s), 7.60 (1H, s, exchangeable); FAB-HRMS m/z 384.1208 (M+Na calcd for $C_{17}H_{19}O_6N_3Na$: 384.1172).

[*cis*-2-[(Aminooxy)methyl]-4-oxo-3-azetidinyl]carbamic Acid 1,1-Dimethylethyl Ester (**5**)

To phthalimide **4** (2.9 g, 8 mmol) in a solution of MeOH - CH_2Cl_2 (1 : 20) at 0°C was added hydrazine monohydrate (0.78 ml, 16 mmol). The reaction was stirred 1 hour then allowed to warm to room temp. The insoluble impurities were filtered and washed with CH_2Cl_2. The filtrate was concentrated and the solid material was washed with a solution of MeOH - CH_2Cl_2 (1 : 20). The filtrate was again concentrated and the solid material was washed with ether to afford 1.69 g of oxyamine **5** (91%): MP 158~159°C (CH_2Cl_2); IR (KBr) cm^{-1} 3350, 3250, 1775, 1690, 1530, 1330, 1165; ^1H NMR (DMSO-d_6) δ 1.40 (9H, s), 3.60 (2H, m), 3.82 (1H, m), 4.86 (1H, dd, J=9 and 5 Hz), 6.07 (2H, s, exchangeable), 7.58 (1H, d, J=9 Hz, exchangeable), 8.32 (1H, s, exchangeable).

Anal Calcd for $C_9H_{17}O_4N_3$: C 46.88, H 7.34, N 18.14.
Found: C 46.60, H 7.61, N 17.98.

[*cis*-2-[[[(1-Methylethylidene)amino]oxy]methyl]-4-oxo-3-azetidinyl]carbamic Acid 1,1-Dimethylethyl Ester (**6a**)

Oxyamine **5** (150 mg, 0.65 mmol) was dissolved in acetone (20 ml) and allowed to stir for 10 minutes. The solvent was then evaporated *in vacuo* and the solid washed with ether (40 ml) to afford oxime **6a** (171 mg, 97%): IR (KBr) cm^{-1} 3350, 3220, 2980, 1775, 1690, 1525, 1365, 1330; ^1H NMR ($CDCl_3$) δ 1.25 (9H, s), 1.86 (3H, s), 1.88 (3H, s), 4.04 (1H, m), 4.17 (1H, dd, J=12 and 6 Hz), 4.35 (1H, dd, J=12 and 4 Hz), 5.22 (1H, dd, J=9 and 6 Hz), 5.36 (1H, d, J=9 Hz, exchangeable), 5.90 (1H, s, exchangeable); FAB-HRMS m/z 272.1596 (M+H calcd for $C_{12}H_{22}O_4N_3$: 272.1610).

[*cis*-2-[[(Acetylamino)oxy]methyl]-4-oxo-3-azetidinyl]carbamic Acid 1,1-Dimethylethyl Ester (**6b**)

To oxyamine **5** (400 mg, 1.73 mmol) dissolved in a solution of CH_2Cl_2 - DMF (1 : 1) at 0°C was added pyridine (1.1 eq) followed by acetyl chloride (1.1 eq). The reaction was allowed to stir for

15 minutes followed by removal of the solvents under reduced pressure. The residue obtained was purified by flash chromatography (5% MeOH in CH_2Cl_2 to 10% MeOH in CH_2Cl_2) to afford amide **6b** (418 mg, 88.6%): IR (KBr) cm^{-1} 3290, 2980, 1760, 1690, 1365, 1160; ^1H NMR (80 MHz, DMSO-d_6) δ 1.40 (9H, s), 1.73 (3H, s), 3.83 (3H, m), 4.90 (1H, dd, J=9 and 5 Hz), 7.60 (1H, d, J=9 Hz, exchangeable), 8.55 (1H, s, exchangeable); FAB-HRMS m/z 274.1400 (M+H calcd for $C_{11}H_{20}O_5N_3$: 274.1403).

[*cis*-2-[[[(Methylsulfonyl)amino]oxy]methyl]-4-oxo-3-azetidinyl]carbamic Acid 1,1-Dimethylethyl Ester (**6c**)

To a solution of oxyamine **5** (485 mg, 2.1 mmol) in CH_2Cl_2 (40 ml) containing pyridine (4 ml) at 0°C was added methanesulfonyl chloride (1.2 eq). The reaction was allowed to stir for 1 hour whereupon it was poured into a solution of THF - EtOAc (1 : 1, 100 ml) and washed with 1 N HCl (30 ml). The aqueous layer was extracted with another solution of THF - EtOAc (1 : 1, 50 ml) and the combined organic layers washed with water, 5% $NaHCO_3$, and brine. The organic layer was dried over anhydrous magnesium sulfate and the solvent concentrated *in vacuo* to afford a yellow oil. The product was purified using flash chromatography (MeOH - CH_2Cl_2, 2 : 25) to afford sulfonamide **6c** (414 mg, 64%): MP 157~158°C (CH_2Cl_2); IR (KBr) cm^{-1} 3340, 3210, 2970, 1780, 1687, 1525, 1330, 1160; ^1H NMR (DMSO-d_6) δ 1.40 (9H, s), 3.03 (3H, s), 3.84~4.08 (3H, m), 4.94 (1H, dd, J=9 and 5 Hz), 7.68 (1H, d, J=9 Hz, exchangeable), 8.44 (1H, s, exchangeable).

Anal Calcd for $C_{10}H_{19}N_3O_6S$: C 38.95, H 6.14, N 13.57.
Found: C 39.09, H 6.26, N 13.28.

[[[*cis*-3-[[(1,1-Dimethylethoxy)carbonyl]amino]-4-oxo-2-azetidinyl]methoxy]imino]acetic Acid (**6d**)

A solution of oxyamine **5** (637 mg, 2.75 mmol) and glyoxylic acid monohydrate (295 mg, 3.20 mmol) in THF (25 ml) was allowed to stir for 1 hour. The solvent was removed under reduced pressure and the resulting solid triturated with a solution of MeOH - CH_2Cl_2 (1 : 20) to afford oxime **6d** (630 mg, 79%): IR (KBr) cm^{-1} 3325, 2960, 1755, 1705, 1685, 1595, 1515, 1330, 1265, 1155; ^1H NMR (DMSO-d_6) δ 1.40 (9H, s), 3.86 (1H, m), 4.25 (2H, m), 4.88 (1H, dd, J=9 and 5 Hz), 7.59 (1H, s), 7.65 (1H, d, J=9 Hz, exchangeable), 8.40 (1H, s, exchangeable); FAB-HRMS m/z 288.1194 (M+H calcd for $C_{11}H_{18}O_6N_3$: 288.1195).

[[[[*cis*-3-[[(1,1-Dimethylethoxy)carbonyl]amino]-4-oxo-2-azetidinyl]methoxy]amino]sulfonyl]acetic Acid Methyl Ester (**6e**)

To a solution of oxyamine **5** (495 mg, 2.1 mmol) in dry THF containing pyridine (1.1 eq) was added $ClSO_2CH_2COOCH_3$ and allowed to stir for 1 hour at 0°C. The reaction was diluted with EtOAc and washed with 1 N HCl, 5% sodium bicarbonate, brine and dried over anhydrous magnesium sulfate. The product was purified by flash chromatography (EtOAc - hexane, 1 : 2) to afford 426 mg (54%) of the title compound **6e**: MP 128~129°C (CH_2Cl_2); IR (KBr) cm^{-1} 3340, 3210, 2975, 1780, 1740, 1685, 1525, 1160; ^1H NMR (DMSO-d_6) δ 1.40 (9H, s), 3.75 (3H, s), 3.90 (1H, m), 4.00 (2H, m), 4.34 (1H, d, J=15 Hz), 4.42 (1H, d, J=15 Hz), 4.94 (1H, d, J=9 and 6 Hz), 7.68 (1H, d, J=9 Hz, exchangeable), 8.44 (1H, s, exchangeable).

Anal Calcd for $C_{12}H_{21}N_3O_8S$: C 39.36, H 5.71, N 11.42.
Found: C 39.19, H 5.86, N 11.66.

[*cis*-2-[[(2,5-Dioxo-1-pyrrolidinyl)oxy]methyl]-4-oxo-3-azetidinyl]carbamic Acid 1,1-Dimethylethyl Ester (**6f**)

To a mixture of alcohol **2** (1.0 g, 3.1 mmol), *N*-hydroxysuccinimide (392 mg, 3.4 mmol) and triphenylphosphine (977 mg, 3.7 mmol) in dry THF (25 ml) was added diethyl azodicarboxylate (650 mg, 3.7 mmol). The reaction was allowed to stir for 1 hour whereupon the solvent removed under reduced pressure. The remaining residue was purified by flash chromatography (benzene - EtOAc, 1 : 1) to afford succinimide **3** (R=succinimido, Scheme 1) (1.07 g, 82%): MP 168~169°C (isopropyl ether - CH_2Cl_2); IR (KBr) cm^{-1} 3340, 2980, 1755, 1720, 1510, 1380, 1340, 1245; ^1H NMR (DMSO-d_6) δ 1.42 (9H, s), 2.62 (4H, s), 3.76 (3H, s), 4.38 (2H, m), 4.64 (1H, m), 5.22 (1H, dd, J=9 and 6 Hz), 6.98 (2H, d, J=10 Hz), 7.56 (2H, d, J=10 Hz), 7.66 (1H, d, J=9 Hz).

Table 2. Spectral data of sulfonates **7a**~**7f**.

Compound	Yield (%)	^{1}H NMR (solvent) δ (J=Hz)	IR (film) (cm^{-1})	FAB-HRMS (m/z) (calcd for/found)
7a	84	($CDCl_3$) 1.00 (12H, t, J=7), 1.36~1.50, (17H, m), 1.64 (8H, m), 1.86 (3H, s), 1.88 (3H, s), 3.28 (8H, m), 4.42~4.58 (3H, m), 5.10 (1H, dd, J=9, 6), 5.62 (1H, d, J=9)	3440, 2960, 2880, 1765, 1710, 1040	$C_7H_{12}N_3O_5S$: 250.0497 250.0488
7b	82	($CDCl_3$) 1.00 (12H, t, J=7), 1.36~1.50 (17H, m), 1.64 (8H, m), 1.88 (3H, s), 3.28 (8H, m), 4.26 (1H, m), 4.42 (2H, m), 5.20 (1H, dd, J=9, 6), 5.74 (1H, d, J=9)	3220, 2960, 1765, 1700, 1040	[a]
7c	95	(DMSO-d_6) 0.94 (12H, t, J=7), 1.32 (8H, q, J=7), 1.40 (9H, s), 1.58 (8H, m), 2.98 (3H, s), 3.20 (8H, m), 4.04~4.16 (2H, m), 4.28 (1H, d, J=9), 4.84 (1H, dd, J=9, 6), 7.66 (1H, d, J=9), 9.96 (1H, br s)	3300, 2950, 1765, 1700, 1035	$C_{10}H_{10}O_9N_3S$: 388.0484 388.0474
7d	90	($CDCl_3$) 1.00 (12H, t, J=7), 1.36~1.52 (17H, m), 1.66 (8H, m), 3.24 (8H, m), 4.40~4.48 (2H, m), 5.10 (1H, d, J=12), 5.24 (1H, m), 7.55 (1H, s), 8.06 (1H, br s)	3300, 2960, 1775, 1710, 1670, 1050	$C_{11}H_{15}O_9N_3S$: 366.0607 366.0591
7e	92	($CDCl_3$) 1.40 (12H, t, J=7), 1.36~1.52 (17H, m), 1.66 (8H, m), 3.26 (8H, m), 3.84 (3H, s), 4.22~4.64 (5H, m), 4.60 (1H, dd, J=9, 6), 5.40 (1H, d, J=9, exchangeable), 9.08 (1H, s, exchangeable)	3300, 2960, 1760, 1745, 1710, 1040	[a]
7f	95	(DMSO-d_6) 0.94 (12H, t, J=7), 1.32 (8H, q, J=7), 1.40 (9H, s), 1.58 (8H, m), 2.60 (4H, s), 3.18 (8H, m), 4.14 (1H, m), 4.38 (2H, m), 4.78 (1H, dd, J=9, 6), 7.52 (1H, d, J=9)	3320, 2960, 1770, 1715, 1040	$C_{13}H_{18}O_9N_3S$: 392.0764 392.0761

[a] Not analyzed.

Anal Calcd for $C_{20}H_{25}N_3O_7$: C 57.40, H 5.95, N 10.00.
Found: C 57.20, H 5.96, N 9.55.

The succinimide prepared above was used to prepare the title compound following the same general procedure as in the preparation of **4**. Yield 87%: MP 206.5~208°C (dec, EtOAc); IR (KBr) cm^{-1} 3350, 2975, 1770, 1720, 1685, 1420; ^{1}H NMR (DMSO-d_6) δ 1.40 (9H, s), 2.62 (4H, s), 3.95 (1H, m), 4.10 (2H, m), 4.95 (1H, dd, J=9 and 6 Hz), 7.62 (1H, d, J=9 Hz, exchangeable), 8.55 (1H, s).

Anal Calcd for $C_{13}H_{19}N_3O_6$: C 49.96, H 6.06, N 13.39.
Found: C 50.04, H 6.05, N 13.43.

Preparation of Sulfonates **7a**~**7f**

To a solution of β-lactam **6** (1.5 mmol) in dry DMF (4 ml) was added sulfur trioxide - DMF complex (5 eq) and allowed to stir for 2 hours. The reaction was diluted with CH_2Cl_2 (30 ml) and 1 N potassium hydrogen phosphate (15 ml). The pH was adjusted to approximately 6, followed by the addition of tetrabutylammonium hydrogen sulfate (1.0 eq). The layers were separated and the aqueous layer extracted again with CH_2Cl_2 (2×20 ml). The combined organic layers dried over anhydrous magnesium sulfate. The solvent was evaporated *in vacuo* to afford **7a**~**7f** as a yellow oil or foam. Results of **7a**~**7f** are summarized in Table 2.

General Procedure I: Deprotection of *tert*-Butyl Esters (**8**, **12c**, **12d**, **12f** and **13d**)

Method A: The *tert*-BOC intermediates (**7a**~**7f**, **10c**, **10d**, **10f** and **11d**; 1.6 mmol) were added to a cold solution (0°C) of TFA (7 ml) containing anisole (1.5 ml). The reaction was allowed to stir for 3 hours whereupon cold toluene (10 ml) was added and the solvents removed under reduced pressure. Additional toluene was added and distilled to remove any residual TFA. The solid residue was washed with CH_2Cl_2 (2×10 ml) to afford the title compounds.

Table 3. Spectral data of salts **8a**~**8f**.

Compound	Yield (%)	Method[a]	^{1}H NMR (DMSO-d_6) δ (J=Hz)	IR (KBr) (cm^{-1})	FAB-HRMS (m/z) (calcd for/found)
8a	75	A	1.84 (6H, s), 4.14~4.34 (2H, m), 4.52 (1H, m), 4.68 (1H, br d, J=6)	3100, 1755, 1500, 1040	[b]
8b	82	A	1.78 (3H, s), 4.16 (2H, m), 4.34 (1H, m), 4.60 (1H, d, J=6)	3180, 3000, 1780 (br), 1040	[b]
8c	84	A	3.08 (3H, s), 4.20~4.48 (3H, m), 4.68 (1H, d, J=6), 8.70 (3H, br s), 10.07 (1H, s)	3560, 1765, 1710, 1040	$C_5H_{10}O_7N_3S_2$: 287.9960 288.0008
8d	68	A	4.27 (1H, m), 4.54~4.80 (3H, m), 7.68 (1H, s), 8.78 (3H, br s)	3450 (br), 3000 (br), 1775, 1715, 1605, 1045	$C_6H_9O_7N_3S$: 266.0087 266.0078
8e	90	B	3.74 (3H, s), 4.19~4.76 (6H, m), 8.72 (3H, br s), 10.40 (1H, br s)	3500, 3100, 1775, 1735	$C_7H_{12}O_9N_3S_2$: 346.0014 345.9974
8f	94	B	2.64 (4H, s), 4.24 (1H, m), 4.48~4.74 (3H, m), 8.80 (3H, br s)	3560, 1765, 1710, 1040	$C_8H_{10}O_7N_3S$: 292.0239 292.0245

[a] See Experimental section.
[b] Not analyzed.

Method B: Followed method A until reaction is complete after which time ether (30 ml) was added and the precipitate filtered and washed with CH_2Cl_2 (10 ml) to afford the title compounds. Results of **8** are summarized in Table 3.

General Procedure II: Acylation of 3-Amino-2-azetidinone-1-sulfonic Acids (**9**, **10** and **11**)

A solution of *N*-hydroxybenzotriazole hydrate (1 mmol) and the aminothiazoleacetic acid (1 mmol) in DMF (7 ml) was treated with diisopropylcarbodiimide (1.1 mmol) under nitrogen at ambient temp. The reaction mixture is stirred for 45 minutes at which time the (±)-3-amino-4-substituted-2-oxo-1-azetidinesulfonic acid derivative **8** (1 mmol) was added in a solution of DMF (2 ml) containing triethylamine (2 mmol). The reaction was stirred for 17 hours at which time the DMF was removed under high vacuum. The residue was taken up in acetone (8 ml) and any insoluble material was filtered. To this acetone solution was added potassium nonafluorobutanesulfonate (1 mmol) in acetone (previously filtered before addition). The precipitate was filtered and washed with acetone (10 ml) followed by ether (5 ml) to afford aminothiazoles **9**, **10** and **11**. If further purification was necessary, compounds were subjected to an ion exchange resin (Na^+ form) and lyophilized.

3-[[(*Z*)-(2-Amino-4-thiazolyl)(methoxyimino)acetyl]amino]-2-[[[(1-methylethylidene)amino]oxy]-methyl]-4-oxo-1-azetidine Sulfonic Acid, Potassium Salt (**9a**)

60% yield: IR (KBr) cm^{-1} 3400, 1765, 1670, 1530, 1050; ^{1}H NMR (DMSO-d_6) δ 1.74 (3H, s), 1.82 (3H, s), 3.84 (3H, s), 4.10 (2H, m), 4.42 (1H, m), 5.00 (1H, dd, J=9 and 5 Hz), 6.74 (1H, s), 7.25 (2H, br s, exchangeable), 9.34 (1H, d, J=9 Hz, exchangeable); FAB-HRMS m/z 433.0595 (M−K calcd for $C_{13}H_{17}O_7N_6S_2$: 433.0600).

2-[[(Acetylamino)oxy]methyl]-3-[[(2-amino-4-thiazolyl)(methoxyimino)acetyl]amino]-4-oxo-1-azetidine Sulfonic Acid, Potassium Salt (**9b**)

62% yield: IR (KBr) cm^{-1} 3400, 1765, 1660, 1525, 1045; ^{1}H NMR (DMSO-d_6) δ 1.70 (3H, s), 3.82 (3H, s), 3.88 (1H, m), 4.04~4.32 (2H, m), 5.32 (1H, dd, J=9 and 6 Hz), 6.80 (1H, s), 7.20 (2H, br s, exchangeable,) 9.44 (1H, d, J=9 Hz, exchangeable).

3-[[(2-Amino-4-thiazolyl)(methoxyimino)acetyl]amino]-2-[[[(methylsulfonyl)amino]oxy]methyl]-4-oxo-1-azetidine Sulfonic Acid, Potassium Salt (**9c**)

47% yield: IR (KBr) cm^{-1} 3440, 3320, 1765, 1665, 1610, 1530, 1160, 1045; ^{1}H NMR (DMSO-d_6)

δ 3.00 (3H, s), 3.87 (3H, s), 4.09~4.14 (3H, m), 5.27 (1H, dd, J=9 and 5 Hz), 6.81 (1H, s), 7.25 (2H, br s, exchangeable), 9.28 (1H, d, J=9 Hz, exchangeable), 9.97 (1H, br s, exchangeable); FAB-HRMS m/z 471.0063 (M−K calcd for $C_{11}H_{15}O_9N_6S_3$: 471.0062).

[[[3-[[(2-Amino-4-thiazolyl) (methoxyimino) acetyl] amino]-4-oxo-1-sulfo-2-azetidinyl] methoxy]-imino]acetic Acid, Dipotassium Salt (**9d**)

28% yield: IR (KBr) cm^{-1} 3350, 1765, 1660, 1620, 1210, 1050; ^1H NMR (DMSO-d_6) δ 3.84 (3H, s), 4.10~4.24 (2H, m), 4.42 (1H, m), 5.22 (1H, dd, J=9 and 5 Hz), 6.78 (1H, s), 7.27 (2H, br s, exchangeable), 7.32 (1H, s), 9.34 (1H, d, J=9 Hz, exchangeable).

Anal Calcd for $C_{12}H_{12}N_6O_9S_2K_2 \cdot H_2O$: C 26.56, H 2.39, N 15.42.
Found: C 26.67, H 2.57, N 15.36.

[[[3-[[(2-Amino-4-thiazolyl)(methoxyimino)acetyl]amino]-4-oxo-1-sulfo-2-azetidinyl]methoxy]-amino]sulfonyl]acetic Acid Methyl Ester, Potassium Salt (**9e**)

75% yield: IR (KBr) cm^{-1} 3320, 1755, 1665, 1525, 1045; ^1H NMR (DMSO-d_6) δ 3.72 (3H, s), 3.84 (3H, s), 4.05~4.44 (5H, m), 5.25 (1H, dd, J=9 and 5 Hz), 6.77 (1H, s), 7.24 (2H, br s, exchangeable), 9.26 (1H, d, J=9 Hz, exchangeable); FAB-HRMS m/z 529.0052 (M−K calcd for $C_{13}H_{17}N_6O_{11}S_3$: 529.0117.

3-[[(2-Amino-4-thiazolyl)(methoxyimino)acetyl]amino]-2-[[2,5-dioxo-1-pyrrolidinyl)oxy]methyl]-4-oxo-1-azetidine Sulfonic Acid, Potassium Salt (**9f**)

60% yield: IR (KBr) cm^{-1} 3420, 1765, 1715, 1665, 1525, 1045; ^1H NMR (DMSO-d_6) δ 2.60 (4H, s), 3.87 (3H, s), 4.27~4.44 (3H, m), 5.26 (1H, dd, J=9 and 5 Hz), 6.84 (1H, s), 7.23 (2H, br s, exchangeable), 9.12 (1H, d, J=9 Hz, exchangeable).

Anal Calcd for $C_{14}H_{15}N_6O_9SK \cdot \frac{1}{2}H_2O$: C 32.22, H 3.24, N 16.03.
Found: C 32.52, H 3.48, N 16.25.

[[[1-(2-Amino-4-thiazolyl)-2-[[2-[[[(methylsulfonyl)amino]oxy]methyl]-4-oxo-1-sulfo-3-azetidinyl]-amino]-2-oxoethylidene]amino]oxy]acetic Acid 1,1-Dimethylethyl Ester, Potassium Salt (**10c**)

53% yield: IR (KBr) cm^{-1} 3440, 3325, 2980, 1760, 1670, 1615, 1530, 1160, 1050; ^1H NMR (DMSO-d_6) δ 1.44 (9H, s), 2.94 (3H, s), 4.08~4.45 (3H, m), 4.56 (2H, s), 5.26 (1H, dd, J=9 and 5 Hz), 6.82 (1H, s), 7.24 (2H, br s, exchangeable), 9.28 (1H, d, J=9 Hz, exchangeable).

Anal Calcd for $C_{16}H_{23}N_6O_{11}S_3K \cdot CH_3COOH$: C 32.35, H 4.02, H 12.52.
Found: C 32.67, H 3.95, N 12.75.

[[[1-(2-Amino-4-thiazolyl)-2-[[2-[[[(carboxymethylene)amino]oxy]methyl]-4-oxo-1-sulfo-3-azetidinyl]amino]-2-oxoethylidene]amino]oxy]acetic Acid 1,1-Dimethylethyl Ester, Dipotassium Salt (**10d**)

59% yield: IR (KBr) cm^{-1} 3420, 2985, 1760, 1660, 1615, 1045; ^1H NMR (DMSO-d_6) δ 1.44 (9H, s), 4.10~4.64 (5H, m), 5.26 (1H, dd, J=9 and 5 Hz), 6.80 (1H, s), 7.20 (2H, br s, exchangeable), 7.40 (1H, s), 9.34 (1H, d, J=9 Hz).

[[[1-(2-Amino-4-thiazolyl)-2-[[2-[[(2,5-dioxo-1-pyrrolidinyl)oxy]methyl]-4-oxo-1-sulfo-3-azetidinyl]-amino]-2-oxoethylidene]amino]oxy]acetic Acid 1,1-Dimethylethyl Ester, Potassium Salt (**10f**)

45% yield: IR (KBr) cm^{-1} 3420, 1760, 1715, 1665, 1520, 1045; ^1H NMR (DMSO-d_6) δ 1.45 (9H, s), 2.60 (4H, s), 4.08~4.60 (5H, m), 5.26 (1H, dd, J=9 and 5 Hz), 6.85 (1H, s), 7.26 (2H, br s, exchangeable), 9.12 (1H, d, J=9 Hz, exchangeable).

2-[[[1-(2-Amino-4-thiazolyl)-2-[[2-[[[(carboxymethylene)amino]oxy]methyl]-4-oxo-1-sulfo-3-azetidinyl]amino]-2-oxoethylidene]amino]oxy]-2-methylpropanoic Acid, 1,1-Dimethylethyl Esters, Potassium Salt (**11d**)

65% yield: IR (KBr) cm^{-1} 3320, 1765, 1715, 1675, 1615, 1325, 1245, 1050; ^1H NMR (DMSO-d_6) δ 1.40 (15H, s), 4.12~5.60 (3H, m), 5.26 (1H, dd, J=9 and 5 Hz), 6.72 (1H, s), 7.30 (2H, br s, exchangeable), 7.45 (1H, s), 9.12 (1H, d, J=9 Hz, exchangeable).

[[[1-(2-Amino-4-thiazolyl)-2-[[2-[[[(methylsulfonyl)amino]oxy]methyl]-4-oxo-1-sulfo-3-azetidinyl]-

amino]-2-oxoethylidene]amino]oxy]acetic Acid, Potassium Salt, Trifluoroacetate (**12c**)

Followed method B in general procedure I.

20% yield: IR (KBr) cm^{-1} 3360, 1760, 1660, 1625, 1040; ^1H NMR (DMSO-d_6) δ 3.00 (3H, s), 3.78~4.38 (3H, m), 4.65 (2H, s), 5.28 (1H, dd, J=9 and 5 Hz), 6.90 (1H, s), 9.38 (1H, d, J=9 Hz, exchangeable), 9.98 (1H, s, exchangeable); FAB-HRMS m/z 514.9957 (M−K calcd for $C_{12}H_{15}O_{11}N_6S_3$: 514.9961).

Anal Calcd for $C_{12}H_{15}N_6O_{11}SK \cdot CF_3COOH$: C 25.24, H 2.39, N 12.56.
Found: C 25.60, H 2.99, N 12.27.

[[[1-(2-Amino-4-thiazolyl)-2-[[[(carboxymethylene)amino]oxy]methyl]-4-oxo-1-sulfo-3-azetidinyl]-amino]-2-oxoethylidene]amino]oxy]acetic Acid, Potassium Salt, Trifluoroacetate (**12d**)

Followed method B in general procedure I.

74% yield: IR (KBr) cm^{-1} 3350, 1755, 1655, 1625, 1040; ^1H NMR (DMSO-d_6) δ 4.12~4.80 (5H, m), 5.32 (1H, dd, J=9 and 5 Hz), 6.81 (1H, s), 7.58 (1H, s, exchangeable), 9.42 (1H, d, J=9 Hz).

[[[1-(2-Amino-4-thiazolyl)-2-[[2-[[(2,5-dioxo-1-pyrrolidinyl)oxy]methyl]-4-oxo-1-sulfo-3-azetidinyl]-amino]-2-oxoethylidene]amino]oxy]acetic Acid, Potassium Salt, Trifluoroacetate (**12f**)

Followed method B in general procedure I.

69% yield: IR (KBr) cm^{-1} 3300, 1765, 1715, 1670, 1045; ^1H NMR (DMSO-d_6) δ 2.60 (4H, s), 4.34 (1H, m), 4.46 (1H, m), 5.30 (1H, dd, J=9 and 5 Hz), 6.98 (1H, s), 9.12 (1H, d, J=9 Hz, exchangeable).

2-[[[1-(2-Amino-4-thiazolyl)-2-[[2-[[[(carboxymethylene)amino]oxy]methyl]-4-oxo-1-sulfo-3-azetidinyl]amino]-2-oxoethylidene]amino]oxy]-2-methylpropanoic Acid, Potassium Salt, Trifluoroacetate (**13d**)

Followed method B in general procedure I.

50% yield: IR (KBr) cm^{-1} 3200, 1775, 1725, 1675, 1050; ^1H NMR (DMSO-d_6) δ 1.42 (6H, s), 4.50~4.64 (3H, m), 5.30 (1H, dd, J=9 and 5 Hz), 6.76 (1H, s), 7.58 (1H, s), 9.22 (1H, d, J=9 Hz, exchangeable); FAB-HRMS m/z 521.0380 (M−K−CF_3COOH calcd for $C_{15}H_{17}O_{11}N_6S_2$: 521.0397).

Acknowledgments

The authors wish to thank Dr. JOHN L. SPETH for furnishing *in vitro* antibacterial data, Mr. BRUCE HOFMANN for the NMR spectral data and Dr. LEONARD R. SCHRONK for the high resolution mass spectral data. We are also grateful to the Analytical Section of these laboratories for providing other spectral data as well as the microanalytical analysis. Helpful discussions with Dr. JERAULD S. SKOTNICKI and Dr. DONALD P. STRIKE were appreciated very much.

References

1) SKOTNICKI, J. S.; T. J. COMMONS, R. W. REES & J. L. SPETH: Synthesis and biological evaluation of a 4-fluoromethyl monobactam analog. J. Antibiotics 36: 1201~1204, 1983
2) SYKES, R. B.; D. P. BONNER, K. BUSH & N. H. GEORGOPAPADAKOU: Azthreonam (SQ 26,776), a synthetic monobactam specifically active against aerobic gram-negative bacteria. Antimocrob. Agents Chemother. 21: 85~92, 1982
3) KISHIMOTO, S.; M. SENDAI, S. HASHIGUCHI, M. TOMIMOTO, Y. SATOH, T. MATSUO, M. KONDO & M. OCHIAI: Synthesis of sulfazecin-type 2-azetidinones with a carbon substituent at the 4-position. J. Antibiotics 36: 1421~1424, 1983
4) KRONENTHAL, D. R.; C. Y. HAN & M. K. TAYLOR: Oxidative *N*-dearylation of 2-azetidinones. J. Org. Chem. 47: 2765~2768, 1982
5) MITSUNOBU, O.: Review on the use of diethyl azodicarboxylate and triphenylphosphine in the synthesis of natural products. Synthesis 1981: 1~28, 1981
6) GROCHOWSKI, E. & J. JURCZAK: Synthesis of *N*-alkoxyphthalimides. Synthesis 1976: 682~684, 1976
7) FLOYD, D. M.; A. W. FRITZ, J. PLUSCEC, E. R. WEAVER & C. M. CIMARUSTI: Preparation of (*S*)-3-amino-2-oxoazetidine-1-sulfonic acids. J. Org. Chem. 47: 5160~5167, 1982