SYNTHESIS AND ANTIBACTERIAL ACTIVITY OF C-4 SUBSTITUTED MONOBACTAMS

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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. Our interest in this area was in response to the excellent activity displayed from the monobactam antibiotic azithromycin and more recently carumonam. Herein is reported the results of our detailed study concerning the synthesis and antibacterial profile.

Scheme 1.

[Chemical structures and reactions are shown, but not transcribed due to the complexity and nature of the image.]
Table 1. Antibacterial screening results.

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<th>MIC (µg/ml)&lt;sup&gt;b&lt;/sup&gt;</th>
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<th>S.f.</th>
<th>E.cl.</th>
<th>E.c.</th>
<th>K.p.</th>
<th>P.v.</th>
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<sup>a</sup> Compounds were evaluated as a mixture of racemates.

<sup>b</sup> The MIC values reported were obtained by the microdilution broth method.

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 afforded alcohol 2 in 90% yield. Coupling of 2 with N-hydroxyphthalimide using the Mitsunobu procedure gave the 4-phthalimidooxymethyl compound 3 in 81% yield. Oxidative dearylation of 3 using ceric ammonium nitrate (CAN) afforded 4 in 75% yield. Treatment of 4 with hydrazine provided the requisite intermediate 5 in excellent yield. Treatment of 5 with acetic anhydride, 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 followed by treatment with tetrabutylammonium hydrogen sulfate gave compounds 7a~7f in good yield (Table 2). Removal of the N-ter/-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 nonafluorobutane-sulfonate 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. 1H NMR spectra were obtained on a Varian XL-300 spectrometer in the indicated solvents with Me4Si 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-Dimethyl ethyl 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 CH2Cl2 (250 ml) and acidified with 1 N HCl. The aqueous layer was washed with CH2Cl2 (4×80 ml) and the combined organic layers washed with 5% sodium bicarbonate (150 ml). The organic layer the dried (MgSO4) 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; 1H NMR (DMSO-d6) 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-2H-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$_2$Cl$_2$ and again the solvent evaporated to rid any residual THF. A solid precipitates and is washed with a solution of CH$_2$Cl$_2$ - ether (1 : 1). The filtrate is concentrated and the solid precipitate is again washed with a solution of CH$_2$Cl$_2$ - 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; $^1$H NMR (CDCl$_3$) $\delta$ 1.48 (9H, s), 3.74 (3H, s), 4.40 (1H, br d, $J$=12Hz), 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$_7$N$_3$: 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-2H-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 x200 ml). The organic layer was washed consecutively with 10% Na$_2$SO$_3$ (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$_2$Cl$_2$); IR (KBr) cm$^{-1}$ 3325, 2920, 1775, 1730, 1680, 1525, 1370; $^1$H NMR (DMSO-d$_6$) $\delta$ 1.36 (9H, s), 4.08 (1H, m), 4.30 (2H, m), 4.97 (1H, dd, $J$=9 and 6Hz), 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$_6$N$_3$Na: 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$_2$Cl$_2$ (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$_2$Cl$_2$. The filtrate was concentrated and the solid material was washed with a solution of MeOH - CH$_2$Cl$_2$ (1: 20). The filtrate was again concentrated and the solid material was washed with ether to afford 2.96 g of oxime 5 (91%): MP 158~ 159°C (CH$_2$Cl$_2$); IR (KBr) cm$^{-1}$ 3350, 3250, 1775, 1690, 1530, 1330, 1165; $^1$H NMR (DMSO-d$_6$) $\delta$ 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$_9$H$_{17}$O$_4$N$_3$: C 46.88, H 7.34, N 18.14. Found: C 46.60, H 7.61, N 17.98.

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

Oxime 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; $^1$H NMR (CDCl$_3$) $\delta$ 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$_4$N$_3$: 272.1610).

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

To oxime 5 (400 mg, 1.73 mmol) dissolved in a solution of CH$_2$Cl$_2$ - 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 CH₂Cl₂ to 10% MeOH in CH₂Cl₂) to afford amide 6b (418 mg, 88.6%). IR (KBr) cm⁻¹: 3290, 2980, 1760, 1690, 1365, 1160; ¹H NMR (80 MHz, DMSO-d₆) 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-MS m/z 274.1400 (M+H calcd for C₁₃H₁₉N₂O₅): 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 CH₂Cl₂ (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% NaHCO₃, 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 - CH₂Cl₂, 2:25) to afford sulfonamide 6c (414 mg, 64%): mp 157-158°C (CH₂Cl₂); IR (KBr) cm⁻¹: 3340, 3210, 2970, 1780, 1687, 1525, 1330, 1160; ¹H NMR (DMSO-d₆) 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).


[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 - CH₂Cl₂ (1:20) to afford oxime 6d (630 mg, 79%): IR (KBr) cm⁻¹: 3325, 2960, 1755, 1705, 1785, 1595, 1515, 1330, 1265, 1155; ¹H NMR (DMSO-d₆) 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-MS m/z 288.1194 (M+H calcd for C₁₂H₁₈O₆N₃: 288.1195).

[cis-3-[[[(1,1-Dimethylethoxy)carbonyl]amino]-2-oxo-2-azetidinyl]methoxy]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 CISO₂CH₂COOCH₃ 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 (isopropyl ether - CH₂Cl₂); IR (KBr) cm⁻¹: 3340, 2980, 1755, 1700, 1685, 1525, 1160; ¹H NMR (DMSO-d₆) 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 5 Hz), 6.98 (2H, d, J=10 Hz), 7.56 (2H, d, J=10 Hz), 7.66 (1H, d, J=9 Hz).


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 128-129°C (CH₂Cl₂); IR (KBr) cm⁻¹: 3340, 2980, 1755, 1700, 1685, 1525, 1160; ¹H NMR (DMSO-d₆) 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).


Found: C 39.19, H 5.86, N 11.66.
Table 2. Spectral data of sulfonates 7a~7f.

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<th>Yield (%)</th>
<th>1H NMR (solvent) δ (J=Hz)</th>
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<th>FAB-HRMS (m/z) (calcd for/found)</th>
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<td>3440, 2960, 2880, 1765, 1710, 1040</td>
<td>C₂₀H₂₅N₃O₇: 250.0497 C₂₀H₂₅N₃O₇: 250.0488</td>
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<td>3220, 2960, 1765, 1700, 1040</td>
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<td>3300, 2950, 1765, 1700, 1035</td>
<td>C₁₀H₁₅O₆N₃S: 388.0484 C₁₀H₁₅O₆N₃S: 388.0474</td>
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<td>90</td>
<td>(CDCl₃) 1.00 (12H, t, J=7), 1.36<del>1.52 (17H, m), 1.66 (8H, m), 3.24 (8H, m), 4.40</del>4.48 (2H, m), 5.10 (1H, d, J=12), 5.24 (1H, m), 7.55 (1H, s), 8.06 (1H, br s)</td>
<td>3300, 2960, 1775, 1710, 1670, 1050</td>
<td>C₁₁H₁₅O₆N₃S: 366.0607 C₁₁H₁₅O₆N₃S: 366.0591</td>
</tr>
<tr>
<td>7e</td>
<td>92</td>
<td>(CDCl₃) 1.40 (12H, t, J=7), 1.36<del>1.52 (17H, m), 1.66 (8H, m), 3.26 (8H, m), 3.84 (3H, s), 4.22</del>4.64 (5H, m), 4.60 (1H, dd, J=9, 6), 5.40 (1H, d, J=9, exchangeable), 9.08 (1H, s, exchangeable)</td>
<td>3300, 2960, 1760, 1745, 1710, 1040</td>
<td>a</td>
</tr>
<tr>
<td>7f</td>
<td>95</td>
<td>(DMSO-d₆) 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)</td>
<td>3320, 2960, 1770, 1715, 1040</td>
<td>C₁₂H₂₅O₆N₃S: 392.0764 C₁₂H₂₅O₆N₃S: 392.0761</td>
</tr>
</tbody>
</table>

a Not analyzed.

Analytical data for 7a: C₇H₁₂N₃O₅S: 250.0497 C₇H₁₂N₃O₅S: 250.0488

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 CH₂Cl₂ (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 CH₂Cl₂ (2 x 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 CH₂Cl₂ (2 x 10 ml) to afford the title compounds.
Table 3. Spectral data of salts 8a~8f.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Yield (%)</th>
<th>Methoda</th>
<th>&quot;H NMR (DMSO-d6) δ (J=Hz)</th>
<th>IR (KBr) (cm⁻¹)</th>
<th>FAB-HRMS (m/z) (calcd for/found)</th>
</tr>
</thead>
<tbody>
<tr>
<td>8a</td>
<td>75</td>
<td>A</td>
<td>1.84 (6H, s), 4.14~4.34 (2H, m), 4.52 (1H, m), 4.68 (1H, br d, J=6)</td>
<td>3100, 1755, 1500, 1040</td>
<td>b</td>
</tr>
<tr>
<td>8b</td>
<td>82</td>
<td>A</td>
<td>1.78 (3H, s), 4.16 (2H, m), 4.34 (1H, m), 4.60 (1H, d, J=6)</td>
<td>3180, 3000, 1780 (br), 1040</td>
<td>b</td>
</tr>
<tr>
<td>8c</td>
<td>84</td>
<td>A</td>
<td>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)</td>
<td>3560, 1765, 1710, 1040, C_{12}H_{20}O_{7}N_{3}S_{2}: 287.9960</td>
<td></td>
</tr>
<tr>
<td>8d</td>
<td>68</td>
<td>A</td>
<td>4.27 (1H, m), 4.54~4.80 (3H, m), 7.68 (1H, s), 8.78 (3H, br s)</td>
<td>3450 (br), 3000 (br), C_{6}H_{9}O_{7}N_{3}S: 266.0087</td>
<td></td>
</tr>
<tr>
<td>8e</td>
<td>90</td>
<td>B</td>
<td>3.74 (3H, s), 4.19~4.76 (6H, m), 8.72 (3H, br s), 10.40 (1H, br s)</td>
<td>3500, 3100, 1775, 1715, 1605, 1045, C_{12}H_{20}O_{7}N_{3}S_{2}: 346.0014</td>
<td></td>
</tr>
<tr>
<td>8f</td>
<td>94</td>
<td>B</td>
<td>2.64 (4H, s), 4.24 (1H, m), 4.48~4.74 (3H, m), 8.80 (3H, br s)</td>
<td>3560, 1765, 1710, 1040, C_{12}H_{20}O_{7}N_{3}S: 292.0239</td>
<td></td>
</tr>
</tbody>
</table>

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_{2}Cl_{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; "H NMR (DMSO-d6) 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_{7}N_{6}S_{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; "H NMR (DMSO-d6) 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 (9e)

47% yield: IR (KBr) cm⁻¹ 3440, 3320, 1765, 1665, 1610, 1530, 1160, 1045; "H NMR (DMSO-d6)
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_{9}N_{6}S_{3}: 471.0062).

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

28% yield: IR (KBr) cm\(^{-1}\) 3350, 1765, 1660, 1210, 1050; \(^1\)H 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_{6}O_{9}S_{2}K_{2}·H_{2}O: C 26.56, H 2.39, N 15.42.

Found: C 26.67, H 2.57, N 15.36.

[[3-[[2-Amino-4-thiazolyl](methoxylimino)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; \(^1\)H NMR (DMSO-d\(_6\)) δ 3.72 (3H, s), 3.84 (3H, s), 4.05~4.44 (5H, 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_{13}H_{17}N_{6}O_{11}S_{3}K: C 32.22, H 3.24, N 16.03.

Found: C 32.52, H 3.48, N 16.25.


53% yield: IR (KBr) cm\(^{-1}\) 3440, 3325, 2980, 1760, 1615, 1530, 1160, 1050; \(^1\)H NMR (DMSO-d\(_6\)) δ 1.44 (9H, s), 2.94 (3H, s), 4.08~4.45 (3H, m), 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_{15}H_{21}N_{6}O_{9}S_{2}K: C 32.32, H 3.48, N 12.52.

Found: C 32.52, H 3.48, N 12.75.


59% yield: IR (KBr) cm\(^{-1}\) 3420, 2985, 1760, 1615, 1520, 1045; \(^1\)H 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), 9.12 (1H, d, J=9 Hz, exchangeable).

Anal Calcd for C_{17}H_{25}N_{6}O_{11}S_{3}K_{2}·CH_{3}COOH: C 32.35, H 4.02, H 12.52.

Found: C 32.67, H 3.95, N 12.75.


45% yield: IR (KBr) cm\(^{-1}\) 3420, 1760, 1715, 1665, 1520, 1045; \(^1\)H 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).

Anal Calcd for C_{16}H_{23}N_{6}O_{11}S_{3}K: C 32.35, H 3.95, N 12.75.


65% yield: IR (KBr) cm\(^{-1}\) 3320, 1765, 1715, 1675, 1615, 1325, 1245, 1050; \(^1\)H 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).

Anal Calcd for C_{17}H_{25}N_{6}O_{11}S_{3}K: C 32.35, H 3.95, N 12.75.
2-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; \(^1\)H NMR (DMSO-\(d_6\)) \(\delta\) 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\(_{15}\)N\(_6\)O\(_3\)S\(_3\): 514.9961).

Found: C 25.60, H 2.99, N 12.27.


Followed method B in general procedure I.

74% yield: IR (KBr) cm\(^{-1}\) 3350, 1755, 1655, 1625, 1040; \(^1\)H NMR (DMSO-\(d_6\)) \(\delta\) 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; \(^1\)H NMR (DMSO-\(d_6\)) \(\delta\) 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).


Followed method B in general procedure I.

50% yield: IR (KBr) cm\(^{-1}\) 3200, 1775, 1725, 1675, 1050; \(^1\)H NMR (DMSO-\(d_6\)) \(\delta\) 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\(_3\)COOH calcd for C\(_{15}\)H\(_{17}\)N\(_6\)O\(_4\): 521.0397).

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References