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Regioselective Epimerisation of *cis*-3-Amino-4-oxo-azetidine-2-sulphonic acid and Synthesis of Monocyclic β-Lactams☆

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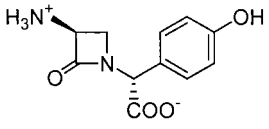
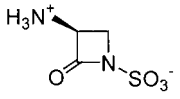
Abstract—A novel procedure for the regioselective epimerisation of *cis*-3-amino-4-oxo-azetidine-2-sulphonic acid (3-AAA) into the *trans*-isomer is described. It was found that a complete inversion of C-3 configuration of the *cis*-3-AAA takes place during the formation of a Schiff base. The cleavage of the imine bond of the Schiff base in methanol resulted in the generation of *trans*-3-AAA in good yield. Here is also described a preparation of novel *cis*- and *trans*-monobactams with an amidosulphonic acid group on azetidinone nitrogen.

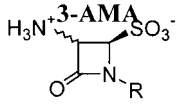
Introduction

The preparation of monobactams is mostly based on derivatisation of 3-amino-nocardicinic acid (3-ANA) as well as 3-amino-monobactamic acid (3-AMA). Recently, we reported the novel monocyclic β-lactam synthons *cis*- and *trans*-3-amino-4-oxo-azetidine-2-sulphonic acids (3-AAA) that could be very useful for further transformations into potential monobactam antibiotics.[1,2]



3-ANA





3-AAA

The synthons *cis*-3-AAA and *trans*-3-AAA were previously generated in situ by hydrolysis of 2-sulphonic acid methyl ester group and 3-phenoxyacetamido side chain of the (2*R*,3*R*)- and (2*R*,3*S*)-3-phenoxyacetamido-4-oxo-azetidine-2-sulphonic acid methyl ester, respectively.[3,4] The 3-β-methyl analogue of *cis*-3-AAA has also been prepared by total synthesis.[5]

Here we report a novel procedure for the generation of *trans*-3-AAA by epimerisation of *cis*-3-AAA. The new route enabled us to avoid the previously mentioned multistep procedure for the preparation of *trans*-3-AAA and synthesise a series of novel *cis*- and *trans*-monobactams as potential antibacterial agents.

Results and Discussion

Starting from the β-lactam synthon *cis*-1[1,2] and aromatic sydnonyl aldehyde[6,7] we prepared Schiff base **3x** (Scheme 1). The coupling constant of the vicinal C_2–H and C_3–H protons from ^{1}H NMR spectra of imine **3x** confirmed the *trans*- geometry of the azetidinone ring, due to complete inversion of configuration at the C_3 position. Epimerisation is explained by the existence of the more acidic proton in the Schiff base, which gives the enolate with the traces of triethylamine (TEA) and subsequently the more stable *trans*-isomer. Similar epimerisation was observed earlier with the Schiff base of 6-aminopenicillins in the presence of diisopropylethylamine,[8] and also in the case of 3-amino-β-lactams in the presence of lithium hexamethyldisilazide (LHMDS).[9] Schiff base **3x** was hydrolysed

☆ The authors wish to dedicate this paper to Dr Branimir Gašpert for his 70th birthday.

Keywords: azetidinones; epimerisation; imines; sydnones.
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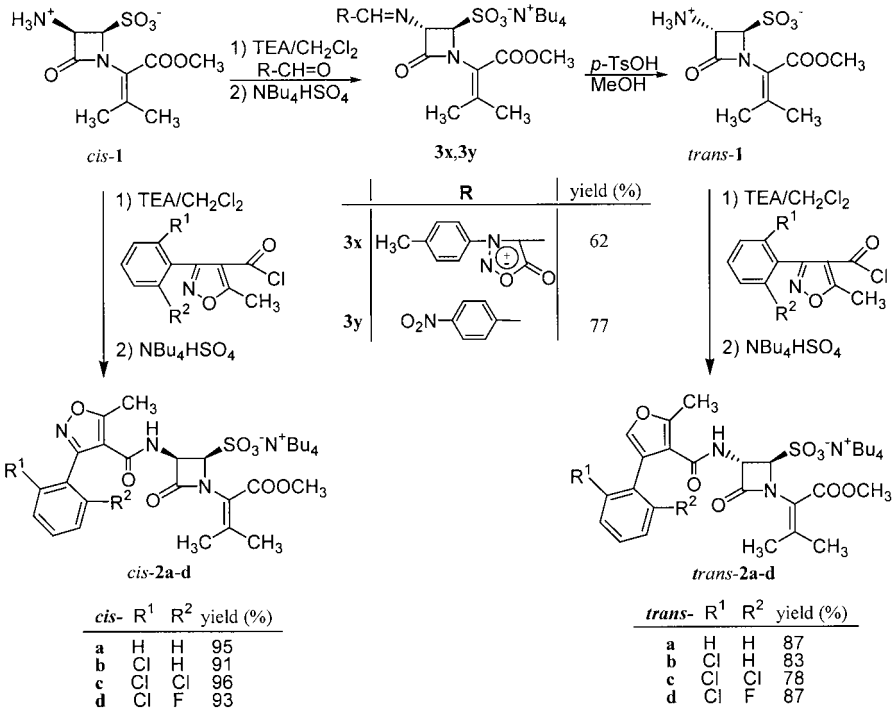


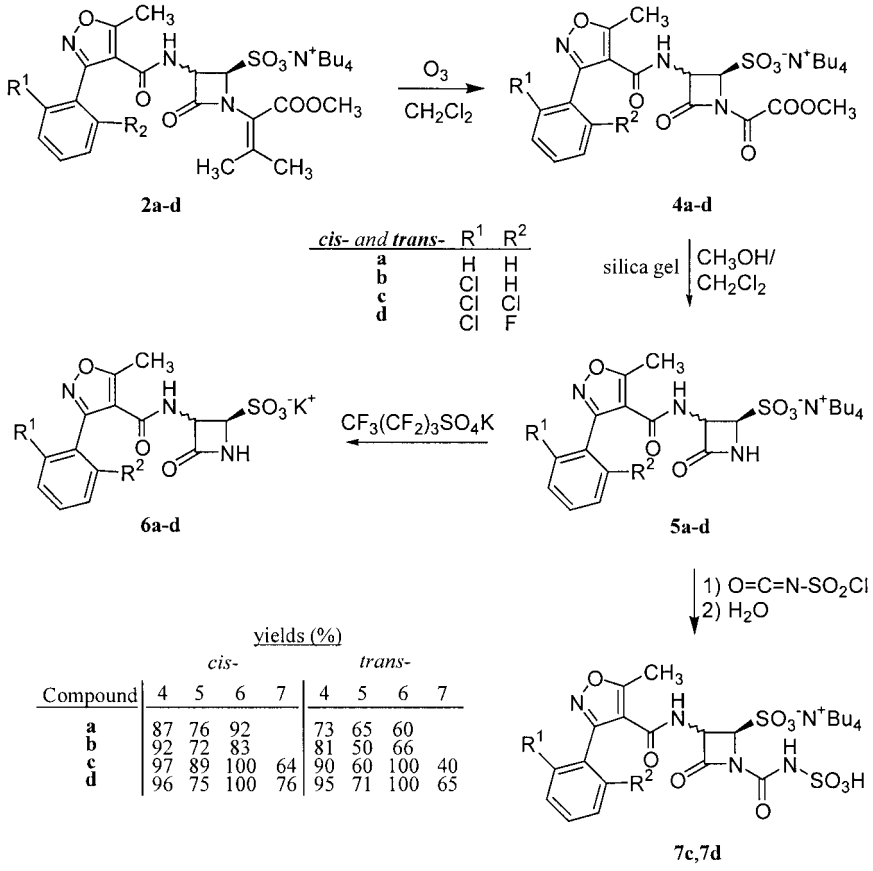
cis-	R^1	R^2	yield (%)
a	H	H	95
b	Cl	H	91
c	Cl	Cl	96
d	Cl	F	93

trans-	R^1	R^2	yield (%)
a	H	H	87
b	Cl	H	83
c	Cl	Cl	78
d	Cl	F	87

Scheme 1.

with *p*-toluenesulphonic acid in methanol and *trans*-**1** was isolated by crystallisation. This procedure was improved using the more available *p*-nitrobenzaldehyde instead of sydnonyl aldehyde, which resulted in the preparation of imine **3y** and subsequent hydrolysis into *trans*-**1** in better yield.

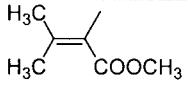
Monocyclic β-lactam synthons *cis*-**1** and *trans*-**1** were

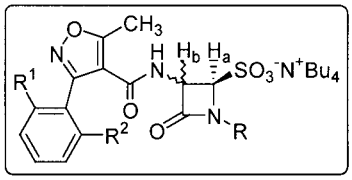


	yields (%)							
	cis-				*trans-*			
Compound	4	5	6	7	4	5	6	7
a	87	76	92		73	65	60	
b	92	72	83		81	50	66	
c	97	89	100	64	90	60	100	40
d	96	75	100	76	95	71	100	65

Scheme 2.

Table 1. ^{1}H and ^{13}C NMR data (δ/ppm, J/Hz) of compounds **2**, **5** and **7**

Compound	R
2	
5	—H
7	—CONH-SO_3H



Compound	R^1	R^2
a	H	H
b	Cl	H
c	Cl	Cl
d	Cl	F

Compound	^{1}H NMR			^{13}C NMR			
	H_a	H_b	NH	C-2	C-3	Amid C=O	
cis-							
2a	4.95 (d), J=5.4	5.82 (dd), J=5.4; 10.1	8.10 (d), J=10.1	69.5	56.0	166.9	171.0
2b	4.86 (d), J=5.4	5.73 (dd), J=5.4; 10.0	7.91 (d), J=10.0	69.5	55.9	166.8	170.8
2c	4.83 (d), J=5.5	5.73 (dd), J=5.5; 10.0	7.95 (d), J=10.0	69.6	55.9	167.0	171.2
2d	4.85 (d), J=5.5	5.73 (dd), J=5.5; 10.0	8.04 (d), J=10.0	69.4	55.8	167.0	171.0
5a	4.65 (d), J=5.1	5.77 (dd), J=5.1; 10.1	8.00 (d), J=10.1	64.6	57.2	168.6	170.8
5b	4.51 (d), J=5.1	5.63 (dd), J=5.1; 10.0	7.77 (d), J=10.0	64.7	57.0	168.7	170.6
5c	4.53 (d), J=5.0	5.63 (dd), J=5.0; 10.0	7.80 (d), J=10.0	64.7	57.0	168.8	171.1
5d	4.55 (d), J=5.0	5.64 (dd), J=5.0; 10.0	7.88 (d), J=10.0	64.6	55.8	168.8	170.8
7c	4.99 (d), J=6.3	5.82(dd), J=6.3; 9.9	7.74 (d), J=9.9	67.6	56.5	166.4	171.7 175.3
7d	4.98 (d), J=6.3	5.82(dd), J=6.3; 9.9	7.68 (d), J=9.9	67.5	56.4	166.4	171.6 177.2
trans-							
2a	4.70 (d), J=2.3	5.24 (dd), J=2.3, 9.0	6.18 (d), J=9.0	71.3	59.1	165.1	174.1
2b	4.70 (d), J=2.3	5.02 (dd), J=2.3; 8.5	6.10 (d), J=8.5	71.5	59.3	164.8	173.7
2c	4.74 (d), J=2.1	5.06 (dd), J=2.1; 8.3	6.03 (d), J=8.3	71.5	59.5	164.9	173.3
2d	4.71 (d), J=2.2	5.11 (dd), J=2.2; 8.5	6.15 (d), J=8.5	71.6	59.3	164.0	173.7
5a	4.69 (d), J=2.1	4.78 (dd), J=2.1; 7.8	6.74 (bs); 6.26 (bs)	64.6	57.2	168.6	170.8
5b	4.63 (d), J=2.3	4.71 (dd), J=2.3; 7.5	7.08 (bs); 6.34 (bs)	64.7	57.0	168.7	170.6
5c	4.47 (bs)	4.64 (bs)	6.43 (bs)	64.7	57.0	168.8	171.1
5d	4.62 (d), J=2.3	4.78 (dd), J=2.3; 7.5	5.25 (bs)	64.6	55.8	168.8	170.8
7c	4.98 (d), J=3.2	4.92 (dd), J=3.2; 6.8	5.05 (bs)	69.4	62.6	165.3	173.5 176.1
7d	5.03 (d), J=3.4	4.85 (dd), J=3.4; 6.8	6.94 (bs)	68.9	63.7	165.5	173.7 176.1

acylated with phenylisoxazolyl carboxylic acid chlorides to give compounds *cis*-**2a**–**d** and *trans*-**2a**–**d** (Scheme 1), which have been transformed into monobactams **6** and **7** via intermediates **4** and **5** (Scheme 2). The cleavage of the double bond on the azetidinone nitrogen of compounds **2a**–**d** was performed by ozonolysis and compounds **4a**–**d** were obtained. Compounds **4a**–**d** were found to be highly unstable and decompose at room temperature. During purification of compounds **4a**–**d** on silica gel (eluent CH_2Cl_2/CH_3OH), methanolysis of the methoxyoxalyl moiety occurred and compounds **5a**–**d** were isolated. In order to obtain water soluble salts, tetrabutylammonium ion was exchanged with potassium in reaction of compounds **5a**–**d** with potassium nonafluorobutanesulphonate and compounds **6a**–**d** were obtained. Incorporation of the sulphonic group on the azetidinone nitrogen of compounds **5a**–**d** was not possible using published protocols.[10,11] However, the introduction of the carbonylamino sulphonic group on the azetidinone nitrogen was successfully performed with chlorosulphonyl isocyanate and compounds **7c** and **7d** were produced.

All compounds were identified by spectroscopic methods. Some characteristic ^{1}H and ^{13}C NMR data are given in Table 1. Hydrogens H_a and H_b on the β-lactam ring appear as a doublet at 4.51–5.03 ppm and a doublet of doublets at 4.70–5.82 ppm, respectively. From their vicinal coupling constants, J_{Ha-Hb}=5.0–6.3 Hz and J_{Ha-Hb}=2.1–3.4 Hz, *cis*- or *trans*- configuration of the azetidinone ring can be unambiguously estimated. Assignment of C-2 and C-3 was made by 2D NMR using HETCOR technique.

Experimental

General

IR spectra were obtained with a Nicolet Magna-IR 760 FT-IR spectrometer with KBr optic and DTGS-KBr detector. ^{1}H NMR and ^{13}C NMR spectra were recorded on JEOL FX-90Q and VARIAN GEMINI 300 using $CDCl_3$ or DMSO as a solvent at room temperature and tetramethylsilane (TMS) as an internal standard. Mass spectra were recorded on Auto Spec Q (VG Analytical Manchester, GB) spectrometer using FAB technique. Elemental analysis was obtained using PERKIN ELMER 2400 Series II CHNS/O analyser. Column chromatography was performed on silica gel Merck Kieselgel 60 (70–230 mesh ASTM).

General procedure for preparation of compounds 3x and 3y

(2*R*,3*R*)-3-Amino-1-(1′-methoxycarbonyl-2′-methyl-propenyl)-4-oxo-azetidine-2-sulphonic acid *cis*-1 (1.40 g; 5.0 mmol) was dissolved in 20 ml CH_2Cl_2 with addition of TEA (0.70 ml; 5.0 mmol). Corresponding aldehyde (5.5 mmol) was dissolved in 20 ml CH_2Cl_2 and added to the solution (sydnonyl carboxaldehyde was previously prepared by a known procedure[10,11]). The mixture was stirred on magnetic stirrer with reflux for 5 h. Tetrabutylammonium hydrogensulphate (1.7 g; 5.0 mmol) was dissolved in 30 ml dist. H_2O, added to reaction and the mixture was stirred for 1/2 h at room temperature. Layers were separated, organic layer was washed with 20 ml dist. H_2O, dried (Na_2SO_4) and solvent was evaporated. After column chromatography on silica gel (gradient elution with CH_2Cl_2/CH_3OH, 10–50%) compound **3x** or **3y** was isolated.

(2*R*,3*S*)-1-(1′-Methoxycarbonyl-2′-methyl-propenyl)-4-oxo-3-[(5-oxo-3-*p*-tolyl-[1,2,3]-oxadiazolydin-4-yl-methylene)-amino]-azetidine-2-sulphonic acid tetrabutylammonium salt (3x). Yield 62%; Yellow oil; IR ($CHCl_3$, cm^{-1}): 3444, 2963, 1769, 1715, 1682, 1230, 1039; ^1H NMR ($CDCl_3$): 0.99 (t, 12H, J=7.2 Hz), 1.38–1.48 (m, 8H), 1.59–1.69 (m, 8H), 2.08 (s, 3H), 2.22 (s, 3H), 2.47 (s, 3H), 3.22–3.28 (m, 8H), 3.68 (s, 3H), 4.83 (d, 1H, J_{Ha-Hb}= 1.7 Hz), 4.96 (bs, 1H), 7.40 (d, 2H, J=8.4 Hz), 7.49 (d, 2H, J=8.4 Hz), 8.21 (s, 1H); ^{13}C NMR: 13.3 (q), 19.3 (t), 21.1 (q), 21.8 (q), 23.6 (t), 51.2 (q), 58.5 (t), 72.1 (d), 77.2 (d), 105.1 (s), 119.8 (s), 124.6 (d), 130.3 (d), 130.9 (s), 143.3 (s), 148.9 (d), 152.9 (s), 163.9 (s), 164.8 (s), 165.3 (s); Anal. Calcd for $C_{35}H_{55}N_5O_8S$: C 59.55, H 7.85, N 9.92, O 18.13, S 4.54; Found: C 59.58, H 7.96, N 9.86, S 4.41; MS: m/z=707 $(M+H)^+$.

(2*R*,3*S*)-1-(1′-Methoxycarbonyl-2′-methyl-propenyl)-3-[(4-nitro-benzylidene)-amino]-4-oxoazetidine-2-sulphonic acid tetrabutylammonium salt (3y). Yield 77%; Yellow oil; IR ($CHCl_3$, cm^{-1}): 3432, 2962, 1763, 1719, 1636, 1345, 1225,; ^1H NMR ($CDCl_3$): 0.99 (t, 12H, J=7.4 Hz), 1.39–1.46 (m, 8H), 1.59–1.69 (m, 8H), 2.17 (s, 3H), 2.26 (s, 3H), 3.22–3.27 (m, 8H), 3.76 (s, 3H), 5.05 (bs, 1H), 5.19 (bs, 1H), 7.97 (d, 2H, J=8.4 Hz), 8.25 (d, 2H, J=8.4 Hz), 8.60 (s, 1H); ^{13}C NMR: 13.2 (q), 19.4 (t), 21.9 (q), 23.6 (t), 23.8 (q), 51.4 (q), 58.6 (t), 72.3 (d), 77.1 (d), 119.9 (s), 123.6 (d), 129.2 (d), 149.0 (s), 153.2 (s), 162.1 (s), 164.0 (s), 165.0 (s); Anal. Calcd for $C_{32}H_{52}N_4O_8S_2$: C 48.46, H 6.17, N 9.12, O 19.61, S 8.35; Found: C 48.31, H 6.98, N 9.26, S 8.41.

(2*R*,3*S*)-3-Amino-1-(1′-methoxycarbonyl-2′-methyl-propenyl)-4-oxo-azetidine-2-sulphonic acid (*trans*-1). Compound **3x** or **3y** (3.1 mmol) was dissolved in 20 ml CH_3OH, and *p*-toluenesulphonic acid (0.59 g; 3.1 mmol) was added to the solution. The mixture was stirred for 1.5 h at room temperature. Methanol was evaporated and acetone (10 ml) was added to the residue. After 1/2 h amino-sulphonic acid *trans*-**1** crystallised by stirring. Yield 63%; White crystals, mp=260–263°C; IR (KBr, cm^{-1}): 3445, 1780, 1713, 1235; ^1H NMR (DMSO): 1.87 (s, 3H), 2.11 (s, 3H), 3.67 (s, 3H), 3.98 (d, 1H, J=2.2 Hz), 4.14 (d, 1H, J=2.2 Hz); ^{13}C NMR (DMSO): 21.8 (q), 23.4 (q), 52.0 (q), 56.9 (d), 69.1 (d), 119.7 (s), 151.6 (s), 160.7 (s), 163.5 (s); MS: m/z=279 $(M+H)^+$; Anal. Calcd for $C_9H_{14}N_2O_6S$: C 38.85, H 5.07, N 10.07; Found: C 39.05, H 5.26, N 10.23.

General procedure for preparation of compounds 2a–d

3-Amino-1-(1′-methoxycarbonyl-2′-methyl-propenyl)-4-oxo-azetidine-2-sulphonic acid *cis*-**1** or *trans*-**1** (200 mg; 0.72 mmol) was dissolved in 20 ml CH_2Cl_2 with addition of TEA (0.2 ml; 1.44 mmol). Corresponding carboxylic acid chloride (5.5 mmol) was dissolved in 20 ml CH_2Cl_2 and added to the solution. The reaction mixture was stirred for 1.5 h at 0°C and 40 min at room temperature. Tetrabutylammonium hydrogensulphate (240 mg; 0.72 mmol) was dissolved in 10 ml dist. water, added to the reaction mixture and stirred for 1 h at room temperature. Layers were separated, organic layer was washed with 20 ml dist. H_2O, dried (Na_2SO_4) and evaporated. After column chromatography on silica gel (gradient elution with CH_2Cl_2/CH_3OH, 10–50%) compounds **2a**–**d** were isolated.

(2*R*,3*R*)-3-[(5-Methyl-3-phenyl-isoxazole-4-carbonyl)-amino]-1-(1′-methoxycarbonyl-2′-methyl-propenyl)-4-oxo-azetidine-2-sulphonic acid tetrabutylammonium salt (*cis*-2a). Yield 95%; Colourless oil; IR (CH_2Cl_2, cm^{-1}): 3336, 2964, 1768, 1721, 1672, 1230; ^1H NMR ($CDCl_3$): 0.94 (t, 12H, J=7.2 Hz), 1.26–1.38 (m, 8H), 1.40–1.60 (m, 8H), 2.11 (s, 3H), 2.23 (s, 3H), 2.71 (s, 3H), 3.05–3.10 (m, 8H), 3.69 (s, 3H), 4.95 (d, 1H, J_{Ha-Hb}= 5.4 Hz), 5.82 (dd, 1H, J_{Hb-Ha}=5.4, J_{Hb-NH}=10.1 Hz), 7.33–7.44 (m, 1H), 7.62–7.65 (m, 2H), 7.73–7.75 (m, 2H), 8.10 (d, 1H, J_{Hb-NH}=10.1 Hz); ^{13}C NMR ($CDCl_3$): 12.4 (q), 13.2 (q), 19.3 (t), 21.8 (q), 23.5 (t), 23.8 (q), 51.4 (q), 56.0 (d), 58.4 (t), 69.5 (d), 111.9 (s), 119.2 (s), 127.9 (s), 128.4 (d), 128.7 (d), 129.3 (d), 129.6 (d), 129.7 (d), 155.6 (s), 161.4 (s), 161.5 (s), 163.8 (s), 166.9 (s), 171.0 (s); Anal. Calcd for $C_{36}H_{56}N_4O_8S$: C 61.34, H 8.01, N 7.95, O 18.16, S 4.55; Found: C 61.50, H 7.89, N 7.80, S 4.36; MS: m/z=705 $(M+H)^+$.

(2*R*,3*R*)-3-{[3-(2-Chloro-phenyl)-5-methyl-isoxazole-4-carbonyl]-amino}-1-(1′-methoxycarbonyl-2′-methyl-propenyl)-4-oxo-azetidine-2-sulphonic acid tetrabutylammonium salt (*cis*-2b). Yield 91%; Colourless oil; IR (CH_2Cl_2, cm^{-1}): 3390, 2964, 1767, 1723, 1672, 1230, 1033; ^1H NMR ($CDCl_3$): 0.96 (t, 12H, J=7.2 Hz), 1.30–1.42 (m, 8H), 1.51–1.62 (m, 8H), 2.07 (s, 3H), 2.22 (s, 3H), 2.78 (s, 3H), 3.11–3.16 (m, 8H), 3.67 (s, 3H), 4.86 (d, 1H, J_{Ha-Hb}=5.4 Hz), 5.73 (dd, 1H, J_{Hb-Ha}=5.4, J_{Hb-NH}= 10.0 Hz), 7.31–7.50 (m, 4H), 7.91 (d, 1H, J_{Hb-NH}= 10.0 Hz); ^{13}C NMR ($CDCl_3$): 12.6 (q), 13.3 (q), 19.3 (t), 21.7 (q), 23.6 (t), 23.8 (q), 51.4 (q), 55.9 (d), 58.4 (t), 69.5 (d), 112.9 (s), 119.2 (s), 126.7 (d), 127.7 (s), 129.6 (d), 130.7 (d), 131.4 (d), 133.8 (s), 155.6 (s), 160.5 (s), 160.7 (s), 163.8 (s), 166.8 (s), 170.8 (s); Anal. Calcd for $C_{36}H_{55}N_4O_8SCl$: C 58.48, H 7.50, N 7.58, O 17.31, S 4.34, Cl 4.80; Found: C 58.60, H 7.59, N 7.50, S 4.20; MS: m/z=739 $(M+H)^+$.

(2*R*,3*R*)-3-{[3-(2,6-Dichloro-phenyl)-5-methyl-isoxazole-4-carbonyl]-amino}-1-(1′-methoxycarbonyl-2′-methyl-propenyl)-4-oxo-azetidine-2-sulphonic acid tetrabutyl-

ammonium salt (*cis*-2c). Yield 96%; Colourless oil; IR (CH_2Cl_2, cm^{-1}): 3350, 2964, 1765, 1720, 1665, 1225; ^1H NMR ($CDCl_3$): 0.96 (t, 12H, J=7.2 Hz), 1.31–1.47 (m, 8H), 1.49–1.63 (m, 8H), 2.10 (s, 3H), 2.21 (s, 3H), 2.85 (s, 3H), 3.07–3.24 (m, 8H), 3.66 (s, 3H), 4.83 (d, 1H, J_{Ha-Hb}= 5.5 Hz), 5.73 (dd, 1H, J_{Hb-Ha}=5.5, J_{Hb-NH}=10.0 Hz), 7.24–7.40 (m, 3H), 7.95 (d, 1H, J_{Hb-NH}=10.0 Hz); ^{13}C NMR ($CDCl_3$): 12.9 (q), 13.3 (q), 19.4 (t), 21.7 (q), 23.6 (t), 23.8 (q), 51.4 (q), 55.9 (d), 58.5 (t), 69.6 (d), 112.5 (s), 119.3 (s), 127.8 (s), 127.8 (d), 128.0 (d), 131.0 (d), 135.4 (s), 135.6 (s), 155.4 (s), 158.8 (s), 160.0 (s), 164.0 (s), 167.0 (s), 171.2 (s); Anal. Calcd for $C_{36}H_{54}N_4O_8SCl_2$: C 55.88, H 7.03, N 7.24, O 16.54, S 4.14, Cl 9.16; Found: C 55.97, H 7.09, N 7.30, S 4.06; MS: m/z=773 $(M+H)^+$.

(2*R*,3*R*)-3-{[3-(2-Chloro-6-fluoro-phenyl)-5-methyl-isoxazole-4-carbonyl]-amino}-1-(1′-methoxycarbonyl-2′-methyl-propenyl)-4-oxo-azetidine-2-sulphonic acid tetrabutylammonium salt (*cis*-2d). Yield 93%; Colourless oil; IR (CH_2Cl_2, cm^{-1}): 3350, 2960, 1770, 1720, 1670, 1225, 785; ^1H NMR ($CDCl_3$): 0.96 (t, 12H, J=7.2 Hz), 1.27–1.45 (m, 8H), 1.51–1.62 (m, 8H), 2.10 (s, 3H), 2.22 (s, 3H), 2.83 (s, 3H), 3.11–3.17 (m, 8H), 3.66 (s, 3H), 4.85 (d, 1H, J_{Ha-Hb}=5.5 Hz), 5.73 (dd, 1H, J_{Hb-Ha}=5.5, J_{Hb-NH}= 10.0 Hz), 7.04–7.43 (m, 3H), 8.04 (d, 1H, J_{Hb-NH}= 10.0 Hz); ^{13}C NMR ($CDCl_3$): 12.9 (q), 13.2 (q), 19.3 (t), 21.7 (q), 23.5 (t), 23.8 (q), 51.3 (q), 55.8 (d), 58.4 (t), 69.4 (d), 112.9 (s), 114.2 (d), 117.2 (s), 119.3 (s), 125.2 (d), 131.4 (d), 135.2 (s), 155.4 (s), 155.6 (s), 160.0 (s), 162.4 (s), 163.9 (s), 167.0 (s), 171.0 (s); Anal. Calcd for $C_{36}H_{54}N_4O_8SClF$: C 57.09, H 7.19, N 7.40, O 16.90, S 4.23, Cl 4.68, F 2.51; Found: C 57.27, H 7.01, N 7.55, S 4.34; MS: m/z=757 $(M+H)^+$.

(2*R*,3*S*)-3-[(5-Methyl-3-phenyl-isoxazole-4-carbonyl)-amino]-1-(1′-methoxycarbonyl-2′-methyl-propenyl)-4-oxo-azetidine-2-sulphonic acid tetrabutylammonium salt (*trans*-2a). Yield 87%; Colourless oil; IR (CH_2Cl_2, cm^{-1}): 3250, 2963, 1768, 1720, 1228, 641; ^1H NMR ($CDCl_3$): 0.97 (t, 12H, J=7.2 Hz), 1.34–1.46 (m, 8H), 1.57–1.67 (m, 8H), 2.08 (s, 3H), 2.21 (s, 3H), 2.69 (s, 3H), 3.22–3.27 (m, 8H), 3.62 (s, 3H), 4.70 (d, 1H, J_{Ha-Hb}= 2.3 Hz), 5.24 (dd, 1H, J_{Hb-Ha}=2.3, J_{Hb-NH}=9.0 Hz), 6.18 (d, 1H, J_{Hb-NH}=9.0 Hz), 7.67 (dd, 2H, J=1.5; 7.2 Hz), 7.52–7.56 (m, 3H); ^{13}C NMR ($CDCl_3$): 12.5 (q), 13.3 (q), 19.36 (t), 21.8 (q), 23.5 (q), 23.6 (t), 51.3 (q), 58.4 (t), 59.1 (d), 71.3 (d), 110.5 (s), 119.8 (s), 127.5 (s), 128.2 (d), 129.0 (d), 129.0 (d), 130.1 (d), 130.4 (d), 152.9 (s), 160.1 (s), 161.1 (s), 164.0 (s), 165.1 (s), 174.1 (s); Anal. Calcd for $C_{36}H_{56}N_4O_8S$: C 61.34, H 8.01, N 7.95, O 18.16, S 4.55; Found: C 61.52, H 7.97, N 8.11, S 4.44; MS: m/z=705 $(M+H)^+$.

(2*R*,3*S*)-3-{[3-(2-Chloro-phenyl)-5-methyl-isoxazole-4-carbonyl]-amino}-1-(1′-methoxycarbonyl-2′-methyl-propenyl)-4-oxo-azetidine-2-sulphonic acid tetrabutylammonium salt (*trans*-2b). Yield 83%; Colourless oil; IR (CH_2Cl_2, cm^{-1}): 3380, 2964, 1790, 1724, 1675, 1036; ^1H NMR ($CDCl_3$): 0.90 (t, 12H, J=7.2 Hz), 1.28–1.37 (m, 8H), 1.47–1.58 (m, 8H), 1.96 (s, 3H), 2.12 (s, 3H), 2.68 (s, 3H), 3.11–3.17 (m, 8H), 3.59 (s, 3H), 4.70 (d, 1H, J_{Ha-Hb}= 2.3 Hz), 5.02 (dd, 1H, J_{Hb-Ha}=2.3, J_{Hb-NH}=8.5 Hz), 6.10 (d, 1H, J_{Hb-NH}=8.5 Hz), 7.18–7.48 (m, 4H); ^{13}C NMR ($CDCl_3$): 12.6 (q), 13.3 (q), 19.3 (t), 21.8 (q), 23.5 (q), 23.6 (t), 51.3 (q), 58.4 (t), 59.3 (d), 71.5 (d), 111.7 (s), 119.8 (s), 126.6 (d), 127.2 (s), 129.5 (d), 131.0 (d), 131.2 (d), 133.8 (s), 152.7 (s), 160.2 (s), 160.9 (s), 164.0 (s), 164.8 (s), 173.7 (s); Anal. Calcd for $C_{36}H_{55}N_4O_8SCl$: C 58.48, H 7.50, N 7.58, O 17.31, S 4.34, Cl 4.80; Found: C 58.40, H 7.32, N 7.61, S 4.45; MS: m/z=739 $(M+H)^+$.

(2*R*,3*S*)-3-{[3-(2,6-Dichloro-phenyl)-5-methyl-isoxazole-4-carbonyl]-amino}-1-(1′-methoxycarbonyl-2′-methyl-propenyl)-4-oxo-azetidine-2-sulphonic acid tetrabutylammonium salt (*trans*-2c). Yield 78%; Colourless oil; IR (CH_2Cl_2, cm^{-1}): 3424, 2965, 1789, 1725, 1700, 1430, 781; ^1H NMR ($CDCl_3$): 0.97 (t, 12H, J=7.2 Hz), 1.33–1.45 (m, 8H), 1.56–1.66 (m, 8H), 2.03 (s, 3H), 2.19 (s, 3H), 2.76 (s, 3H), 3.20–3.26 (m, 8H), 3.68 (s, 3H), 4.74 (d, 1H, J_{Ha-Hb}=2.1 Hz), 5.06 (dd, 1H, J_{Hb-Ha}=2.1, J_{Hb-NH}= 8.3 Hz), 6.03 (d, 1H, J_{Hb-NH}=8.3 Hz), 7.21–7.48 (m, 3H); ^{13}C NMR ($CDCl_3$): 12.8 (q), 13.3 (q), 19.31 (t), 21.7 (q), 23.4 (q), 23.5 (t), 51.4 (q), 58.4 (t), 59.5 (d), 71.5 (d), 111.8 (s), 119.7 (s), 127.7 (d), 127.8 (s), 128.0 (d), 131.0 (d), 135.2 (s), 152.9 (s), 158.8 (s), 160.6 (s), 164.0 (s), 164.9 (s), 173.3 (s); Anal. Calcd for $C_{36}H_{54}N_4O_8SCl_2$: C 55.88, H 7.03, N 7.24, O 16.54, S 4.14, Cl 9.16; Found: C 56.02, H 7.19, N 7.10, S 4.33; MS: m/z=773 $(M+H)^+$.

(2*R*,3*S*)-3-{[3-(2-Chloro-6-fluoro-phenyl)-5-methyl-isoxazole-4-carbonyl]-amino}-1-(1′-methoxycarbonyl-2′-methyl-propenyl)-4-oxo-azetidine-2-sulphonic acid tetrabutylammonium salt (*trans*-2d). Yield 87%; Colourless oil; IR (CH_2Cl_2, cm^{-1}): 3427, 2965, 1791, 1720, 1671, 1459, 899; ^1H NMR ($CDCl_3$): 0.97 (t, 12H, J=7.2 Hz), 1.33–1.45 (m, 8H), 1.56–1.66 (m, 8H), 2.03 (s, 3H), 2.19 (s, 3H), 2.76 (s, 3H), 3.20–3.26 (m, 8H), 3.68 (s, 3H), 4.71 (d, 1H, J_{Ha-Hb}=2.2 Hz), 5.06 (dd, 1H, J_{Hb-Ha}=2.2, J_{Hb-NH}= 8.5 Hz), 6.15 (d, 1H, J_{Hb-NH}=8.5 Hz), 7.05–7.49 (m, 3H); ^{13}C NMR ($CDCl_3$): 12.7 (q), 13.3 (q), 19.3 (t), 21.7 (q), 23.5 (q), 23.6 (t), 51.3 (q), 58.4 (t), 59.3 (d), 71.6 (d), 112.1 (s), 114.3 (d), 117.2 (s), 119.9 (s), 125.3 (d), 131.9 (d), 134.9 (s), 152.6 (s), 155.7 (s), 159.1 (s), 162.2 (s), 164.0 (s), 164.0 (s), 173.7 (s); Anal. Calcd for $C_{36}H_{54}N_4O_8SClF$: C 57.09, H 7.19, N 7.40, O 16.90, S 4.23, Cl 4.68, F 2.51; Found: C 56.91, H 7.31, N 7.58, S 4.10; MS: m/z=757 $(M+H)^+$.

General procedure for preparation of compounds 4a–d and 5a–d

Corresponding compound **2a–d** (1.0 mmol) was dissolved in 30 ml CH_2Cl_2. The solution was cooled at −15°C and ozone was introduced for ~15 min (until pale blue colour) and followed by oxygen (99.5%) for ~20 min (until the solvent turned colourless). The solvent was evaporated to obtain compounds **4a–d**. After column chromatography of compounds **4a–d** on silica gel (gradient elution with CH_2Cl_2/CH_3OH, 10–50%) compounds **5a–d** were isolated.

(2*R*,3*R*)-3-[(5-Methyl-3-phenyl-isoxazole-4-carbonyl)-amino]-1-methoxyoxalyl-4-oxo-azetidine-2-sulphonic acid tetrabutylammonium salt (*cis*-4a). Yield 87%; Colourless oil; IR (CH_2Cl_2, cm^{-1}): 3329, 2963, 1825, 1753, 1706; ^1H NMR ($CDCl_3$): 0.97 (t, 12H, J=7.4 Hz), 1.35–1.46 (m, 8H), 1.53–1.64 (m, 8H), 2.75 (s, 1H), 3.11–3.17 (m, 8H), 3.87 (s, 3H), 5.45 (d, 1H, J_{Ha-Hb}=6.5 Hz), 6.09 (dd, 1H, J_{Hb-Ha}=6.5, J_{Hb-NH}=10.0 Hz), 7.35–7.71 (m, 5H), 7.88 (d, 1H,

J_{Hb-NH}=10.0 Hz); ^{13}C NMR: 12.4 (q), 13.3 (q), 19.3 (t), 23.5 (t), 53.2 (q), 57.4 (d), 58.3 (t), 68.6 (d), 111.3 (s), 127.8 (s), 128–130 (d), 159.0 (s), 161.6 (s), 165.1 (s), 166.1 (s), 171.7 (s), 177.0 (s); Anal. Calcd for $C_{33}H_{50}N_4O_9S$: C 58.39, H 7.42, N 8.25, O 21.21, S 4.72; Found: C 58.45, H 7.16, N 8.06, S 4.58.

(2*R*,3*R*)-3-{[3-(2-Chloro-phenyl)-5-methyl-isoxazole-4-carbonyl]-amino}-1-methoxyoxalyl-4-oxo-azetidine-2-sulphonic acid tetrabutylammonium salt (*cis*-4b). Yield 92%; Colourless oil; IR (CH_2Cl_2, cm^{-1}): 3349, 2964, 1826, 1753, 1709, 1662, 1259; ^{1}H NMR ($CDCl_3$): 0.97 (t, 12H, *J*=7.2 Hz), 1.34–1.41 (m, 8H), 1.52–1.62 (m, 8H),), 2.74 (s, 1H), 3.10–3.15 (m, 8H), 3.85 (s, 3H), 5.40 (d, 1H, J_{Ha-Hb}=6.4 Hz), 5.99 (dd, 1H, J_{Hb-Ha}=6.4, J_{Hb-NH}= 9.9 Hz), 7.30–7.48 (m, 4H), 7.79 (d, 1H, J_{Hb-NH}=9.9 Hz); ^{13}C NMR: 12.6 (q), 13.3 (q), 19.3 (t), 23.5 (t), 53.1 (q), 57.3 (d), 58.4 (t), 68.5 (d), 112.4 (s), 126.4 (d), 127.4 (s), 129.4 (d), 130.8 (d), 130.9 (s), 133.7 (s), 160.4 (s), 160.8 (s), 164.8 (s), 166.0 (s), 171.3 (s), 176.2 (s); Anal. Calcd for $C_{33}H_{49}N_4O_9SCl$: C 55.57, H 6.92, N 7.85, O 20.19, S 4.49, Cl 4.97; Found: C 55.44, H 7.07, N 7.69, 4.30.

(2*R*,3*R*)-3-{[3-(2,6-Dichloro-phenyl)-5-methyl-isoxazole-4-carbonyl]-amino}-1-methoxyoxalyl-4-oxo-azetidine -2-sulphonic acid tetrabutylammonium salt (*cis*-4c). Yield 97%; Colourless oil; IR (CH_2Cl_2, cm^{-1}): 3369, 2966, 1826, 1753, 1709, 1677, 1257; ^{1}H NMR ($CDCl_3$): 0.98 (t, 12H, *J*=7.2 Hz), 1.35–1.45 (m, 8H), 1.51–1.64 (m, 8H),), 2.82 (s, 1H), 3.11–3.16 (m, 8H), 3.86 (s, 3H), 5.39 (d, 1H, J_{Ha-Hb}=6.4 Hz), 5.98 (dd, 1H, J_{Hb-Ha}=6.4, J_{Hb-NH}= 10.0 Hz), 7.29–7.41 (m, 3H), 7.80 (d, 1H, J_{Hb-NH}= 10.0 Hz); ^{13}C NMR: 13.0 (q), 13.3 (q), 19.3 (t), 23.5 (t), 53.2 (q), 57.2 (d), 58.3 (t), 68.5 (d), 112.0 (s), 127.3 (s), 128.0 (d), 128.4 (d), 131.2 (d), 135.3 (s), 135.6 (s), 158.4 (s), 160.0 (s), 163.5 (s), 166.0 (s), 171.7 (s), 176.6 (s); Anal. Calcd for $C_{33}H_{48}N_4O_9SCl_2$: C 53.01, H 6.47, N 7.49, O 19.26, S 4.29, Cl 9.48; Found: C 53.14, H 6.50, N 7.69, S 4.15.

(2*R*,3*R*)-3-{[3-(2-Chloro-6-fluoro-phenyl)-5-methyl-isoxazole-4-carbonyl]-amino}-1-methoxyoxalyl-4-oxo-azetidine-2-sulphonic acid tetrabutylammonium salt (*cis*-4d). Yield 96%; Colourless oil; IR (CH_2Cl_2, cm^{-1}): 3448, 2964, 1828, 1752, 1709, 1674, 1253; ^{1}H NMR ($CDCl_3$): 0.99 (t, 12H, *J*=7.2 Hz), 1.37–1.44 (m, 8H), 1.51–1.64 (m, 8H),), 2.83 (s, 1H), 3.12–3.17 (m, 8H), 3.87 (s, 3H), 5.40 (d, 1H, J_{Ha-Hb}=6.3 Hz), 5.99 (dd, 1H, J_{Hb-Ha}=6.3, J_{Hb-NH}=9.9 Hz), 7.06–7.38 (m, 3H), 7.86 (d, 1H, J_{Hb-NH}=9.9 Hz); ^{13}C NMR: 12.7 (q), 13.4 (q), 19.3 (t), 23.5 (t), 53.3 (q), 57.3 (d), 58.4 (t), 68.5 (d), 112.4 (s), 114.4 (d), 116.2 (s), 125.7 (d), 132.2 (d), 135.0 (s), 155.8 (s), 160.1 (s), 162.4 (s), 163.5 (s), 166.2 (s), 171.4 (s), 176.4 (s); Anal. Calcd for $C_{33}H_{48}N_4O_9SClF$: C 54.20, H 6.62, N 7.66, O 19.69, S 4.38, Cl 4.85, F 2.60; Found: C 54.15, H 6.52, N 7.57, S 4.17.

(2*R*,3*S*)-3-[(5-Methyl-3-phenyl-isoxazole-4-carbonyl)-amino]-1-methoxyoxalyl-4-oxo-azetidine-2-sulphonic acid tetrabutylammonium salt (*trans*-4a). Yield 73%; Colourless oil; IR (CH_2Cl_2, cm^{-1}): 3251, 2964, 1825, 1756, 1715, 1239; ^{1}H NMR ($CDCl_3$): 0.95 (bs, 12H), 1.26–1.43 (m, 8H), 1.45–1.67 (m, 8H),), 2.73 (s, 1H), 3.10–3.18 (m, 8H), 3.88 (s, 3H), 5.00 (bs, 1H), 5.46 (bs, 1H), 6.91 (bs, 1H), 7.43–7.67 (m, 5H); ^{13}C NMR: 12.5 (q), 13.3 (q), 19.3 (t), 23.5 (t), 53.0 (q), 58.4 (t), 63.0 (d), 69.3 (d), 109.9 (s), 128.1 (s), 128–130 (d), 160.4 (s), 162.7 (s), 163.9 (s), 165.4 (s), 174.1 (s), 177.0 (s); Anal. Calcd for $C_{33}H_{50}N_4O_9S$: C 58.39, H 7.42, N 8.25, O 21.21, S 4.72; Found: C 58.51, H 7.50, N 8.14, S 4.89.

(2*R*,3*S*)-3-{[3-(2-Chloro-phenyl)-5-methyl-isoxazole-4-carbonyl]-amino}-1-methoxyoxalyl-4-oxo-azetidine-2-sulphonic acid tetrabutylammonium salt (*trans*-4b). Yield 81%; Colourless oil; IR (CH_2Cl_2, cm^{-1}): 3385, 2964, 1825, 1756, 1714, 1670, 1241; ^{1}H NMR ($CDCl_3$): 0.95 (t, 12H, *J*=7.2 Hz), 1.30–1.42 (m, 8H), 1.52–1.61 (m, 8H),), 2.74 (s, 1H), 3.10–3.16 (m, 8H), 3.86 (s, 3H), 4.87 (dd, 1H, J_{Hb-Ha}=3.9, J_{Hb-NH}=7.5 Hz), 5.37 (bs, 1H), 6.83 (bs, 1H), 7.30–7.51 (m, 4H); ^{13}C NMR: 12.6 (q), 13.3 (q), 19.3 (t), 23.5 (t), 53.1 (q), 58.4 (t), 62.9 (d), 69.0 (d), 109.3 (s), 128.2 (s), 126.5 (d), 129.4 (d), 130.8 (d), 130.9 (d), 133.9 (s), 158.9 (s), 161.0 (s), 164.6 (s), 166.2 (s), 173.7 (s), 176.1 (s); Anal. Calcd for $C_{33}H_{49}N_4O_9SCl$: C 55.57, H 6.92, N 7.85, O 20.19, S 4.49, Cl 4.97; Found: C 55.69, H 6.80, N 7.99, S 4.61.

(2*R*,3*S*)-3-{[3-(2,6-Dichloro-phenyl)-5-methyl-isoxazole-4-carbonyl]-amino}-1-methoxyoxalyl-4-oxo-azetidine -2-sulphonic acid tetrabutylammonium salt (*trans*-4c). Yield 90%; Colourless oil; IR (CH_2Cl_2, cm^{-1}): 2964, 1827, 1756, 1720, 1690, 1432, 784; ^{1}H NMR ($CDCl_3$): 0.94 (t, 12H, *J*=6.9 Hz), 1.28–1.40 (m, 8H), 1.52–1.60 (m, 8H),), 2.67 (s, 1H), 3.08–3.16 (m, 8H), 3.84 (s, 3H), 4.91 (dd, 1H, J_{Hb-Ha}=3.6, J_{Hb-NH}=6.8 Hz), 5.31 (bs, 1H), 6.58 (d, 1H, J_{Hb-NH}=6.8 Hz), 7.29–7.43 (m, 3H); ^{13}C NMR: 12.8 (q), 13.3 (q), 19.3 (t), 23.6 (t), 53.0 (q), 58.4 (t), 63.0 (d), 69.1 (d), 108.9 (s), 126.3 (s), 128.4 (d), 128.8 (d), 131.1 (d), 135.3 (s), 158.7 (s), 161.5 (s), 163.5 (s), 165.4 (s), 173.8 (s), 177.0 (s); Anal. Calcd for $C_{33}H_{48}N_4O_9SCl_2$: C 53.01, H 6.47, N 7.49, O 19.26, S 4.29, Cl 9.48; Found: C 52.94, H 6.30, N 7.36, S 4.34.

(2*R*,3*S*)-3-{[3-(2-Chloro-6-fluoro-phenyl)-5-methyl-isoxazole-4-carbonyl]-amino}-1-methoxyoxalyl-4-oxo-azetidine-2-sulphonic acid tetrabutylammonium salt (*trans*-4d). Yield 95%; Colourless oil; IR (CH_2Cl_2, cm^{-1}): 2965, 1825, 1757, 1701, 1672, 1458; ^{1}H NMR ($CDCl_3$): 0.93 (t, 12H, *J*=7.2 Hz), 1.28–1.40 (m, 8H), 1.48–1.62 (m, 8H),), 2.65 (s, 1H), 3.09–3.15 (m, 8H), 3.85 (s, 3H), 4.95 (dd, 1H, J_{Hb-Ha}=3.5, J_{Hb-NH}=6.9 Hz), 5.33 (bs, 1H), 6.91 (d, 1H, J_{Hb-NH}=6.9 Hz), 7.08 (t, 1H, *J*=8.1 Hz), 7.26–7.42 (m, 2H); ^{13}C NMR: 12.6 (q), 13.2 (q), 19.3 (t), 23.5 (t), 53.0 (q), 58.4 (t), 63.0 (d), 69.4 (d), 109.3 (s), 116.9 (s), 114.1 (d), 125.1 (d), 131.5 (d), 135.0 (s), 155.6 (s), 159.0 (s), 162.4 (s), 163.6 (s), 165.3 (s), 173.2 (s), 176.9 (s); Anal. Calcd for $C_{33}H_{48}N_4O_9SClF$: C 54.20, H 6.62, N 7.66, O 19.69, S 4.38, Cl 4.85, F 2.60; Found: C 54.37, H 6.74, N 7.48, S 4.50.

(2*R*,3*R*)-3-[(5-Methyl-3-phenyl-isoxazole-4-carbonyl)-amino]-4-oxo-azetidine-2-sulphonic acid tetrabutylammonium salt (*cis*-5a). Yield 76%; Colourless oil; IR (CH_2Cl_2, cm^{-1}): 3221, 2963, 1779, 1697, 1180; ^{1}H NMR ($CDCl_3$): 0.98 (t, 12H, *J*=7.2 Hz), 1.35–1.45 (m, 8H), 1.54–1.64 (m, 8H), 2.74 (s, 3H), 3.15–3.20 (m, 8H), 4.65 (d, 1H,

J_{Ha-Hb}=5.1 Hz), 5.77 (dd, 1H, J_{Hb-Ha}=5.1, J_{Hb-NH}= 10.1 Hz), 7.42–7.44 (m, 1H), 7.68–7.70 (m, 2H), 7.76–7.79 (m, 2H), 8.00 (d, 1H, J_{Hb-NH}=10.1 Hz); ^{13}C NMR: 12.4 (q), 13.3 (q), 19.3 (t), 23.5 (t), 57.2 (d), 58.4 (t), 64.6 (d), 112.0 (s), 128.0 (s), 128–130 (d), 161.4 (s), 168.6 (s), 170.8 (s); Anal. Calcd for $C_{30}H_{48}N_4O_6S$: C 60.79, H 8.16, N 9.45, O 16.19, S 5.41; Found: C 60.67, H 8.01, N 9.55, S 5.34.

(2*R*,3*R*)-3-{[3-(2-Chloro-phenyl)-5-methyl-isoxazole-4-carbonyl]-amino}-4-oxo-azetidine-2-sulphonic acid tetrabutylammonium salt (*cis*-5b). Yield 72%; Colourless oil; IR (CH_2Cl_2, cm^{-1}): 3350, 2963, 2876, 1775, 1672, 1607, 1524, 1452, 1225, 1059, 1009, 763; ^{1}H NMR ($CDCl_3$): 0.94 (t, 12H, *J*=7.2 Hz), 1.31–1.41 (m, 8H), 1.51–1.62 (m, 8H), 2.75 (s, 3H), 3.12–3.17 (m, 8H), 4.51 (d, 1H, J_{Ha-Hb}= 5.1 Hz), 5.63 (dd, 1H, J_{Hb-Ha}=5.1, J_{Hb-NH}=10.0 Hz), 7.30–7.47 (m, 4H), 7.77 (d, 1H, J_{Hb-NH}=10.0 Hz); ^{13}C NMR: 12.6 (q), 13.3 (q), 19.3 (t), 23.6 (t), 57.0 (d), 58.4 (t), 64.7 (d), 113.0 (s), 126.7 (d), 127.8 (s), 129.6 (d), 130.8 (d), 131.3 (d), 133.7 (s), 160.6 (s), 160.7 (s), 168.7 (s), 170.6 (s); Anal. Calcd for $C_{30}H_{47}N_4O_6SCl$: C 57.45, H 7.55, N 8.93, O 15.30, S 5.11, Cl 5.65; Found: C 57.64, H 7.41, N 9.05, S 5.24; MS: *m*/*z*=627 (M+H)$^+$.

(2*R*,3*R*)-3-{[3-(2,6-Dichloro-phenyl)-5-methyl-isoxazole-4-carbonyl]-amino}-4-oxo-azetidine-2-sulphonic acid tetrabutylammonium salt (*cis*-5c). Yield 89%; Colourless oil; IR (CH_2Cl_2, cm^{-1}): 3226, 2964, 1775, 1671, 1432, 1195; ^{1}H NMR ($CDCl_3$): 0.95 (t, 12H, *J*=7.2 Hz), 1.31–1.42 (m, 8H), 1.52–1.63 (m, 8H), 2.83 (s, 3H), 3.13–3.18 (m, 8H), 4.53 (d, 1H, J_{Ha-Hb}=5.0 Hz), 5.63 (dd, 1H, J_{Hb-Ha}=5.0, J_{Hb-NH}= 10.0 Hz), 7.32–7.40 (m, 3H), 7.80 (d, 1H, J_{Hb-NH}= 10.0 Hz); ^{13}C NMR: 13.0 (q), 13.3 (q), 19.3 (t), 23.5 (t), 57.0 (d), 58.4 (t), 64.7 (d), 112.5 (s), 127.7 (s), 127.8 (d), 127.9 (d), 131.0 (d), 135.2 (s), 135.7 (s), 158.8 (s), 159.8 (s), 168.8 (s), 171.1 (s); Anal. Calcd for $C_{30}H_{46}N_4O_6SCl_2$: C 54.46, H 7.01, N 8.47, O 14.51, S 4.85, Cl 10.72; Found: C 54.40, H 6.89, N 8.50, S 4.80; MS: *m*/*z*=661 (M–H)$^-$.

(2*R*,3*R*)-3-{[3-(2-Chloro-6-fluoro-phenyl)-5-methyl-isoxazole-4-carbonyl]-amino}-4-oxo-azetidine-2-sulphonic acid tetrabutylammonium salt (*cis*-5d). Yield 75%; Colourless oil; IR (CH_2Cl_2, cm^{-1}): 3217, 2966, 1776, 1670, 1458, 1223; ^{1}H NMR ($CDCl_3$): 0.96 (t, 12H, *J*=7.2 Hz), 1.32–1.43 (m, 8H), 1.52–1.64 (m, 8H), 2.83 (s, 3H), 3.15–3.20 (m, 8H), 4.55 (d, 1H, J_{Ha-Hb}=5.0 Hz), 5.64 (dd, 1H, J_{Hb-Ha}=5.0, J_{Hb-NH}=10.0 Hz), 7.08–7.42 (m, 3H), 7.88 (d, 1H, J_{Hb-NH}=10.0 Hz); ^{13}C NMR: 12.8 (q), 13.2 (q), 19.2 (t), 23.5 (t), 56.9 (d), 58.3 (t), 64.6 (d), 112.8 (s), 114.2 (d), 117.1 (s), 125.2 (d), 131.4 (d), 135.0 (s), 155.6 (s), 159.8 (s), 162.3 (s), 168.8 (s), 170.8 (s); Anal. Calcd for $C_{30}H_{46}N_4O_6SClF$: C 55.85, H 7.19, N 8.68, O 14.88, S 4.97; Cl 5.49, F 2.94; Found: C 55.91, H 7.12, N 8.70, S 5.02; MS: *m*/*z*=645 (M+H)$^+$.

(2*R*,3*S*)-3-[(5-Methyl-3-phenyl-isoxazole-4-carbonyl)-amino]-4-oxo-azetidine-2-sulphonic acid tetrabutylammonium salt (*trans*-5a). Yield 65%; Colourless oil; IR (CH_2Cl_2, cm^{-1}): 3239, 2962, 1765, 1664, 1465, 1192; ^{1}H NMR ($CDCl_3$): 0.96 (t, 12H, *J*=7.2 Hz), 1.32–1.45 (m, 8H), 1.54–1.65 (m, 8H), 2.67 (s, 3H), 3.22–3.28 (m, 8H), 4.69 (d, 1H, J_{Ha-Hb}=2.1 Hz), 4.78 (dd, 1H, J_{Hb-Ha}=2.1, J_{Hb-NH}= 7.8 Hz), 6.26 (bs, 1H), 6.74 (bs, 1H), 7.26–7.77 (m, 5H); ^{13}C NMR: 12.8 (q), 13.3 (q), 19.4 (t), 23.6 (t), 58.4 (t), 61.7 (d), 66.1 (d), 112.0 (s), 127.7 (s), 129.5 (d), 130.4 (d), 160.0 (s), 161.7 (s), 166.3 (s), 173.0 (s); Anal. Calcd for $C_{30}H_{48}N_4O_6S$: C 60.79, H 8.16, N 9.45, O 16.19, S 5.41; Found: C 60.98, H 7.99, N 9.63, S 5.25; MS: *m*/*z*=591 (M–H)$^-$.

(2*R*,3*S*)-3-{[3-(2-Chloro-phenyl)-5-methyl-isoxazole-4-carbonyl]-amino}-4-oxo-azetidine-2-sulphonic acid tetrabutylammonium salt (*trans*-5b). Yield 50%; Colourless oil; IR (CH_2Cl_2, cm^{-1}): 3239, 2963, 1764, 1670, 1193; ^{1}H NMR ($CDCl_3$): 0.95 (t, 12H, *J*=7.2 Hz), 1.34–1.41 (m, 8H), 1.51–1.64 (m, 8H), 2.70 (s, 3H), 3.18–3.23 (m, 8H), 4.63 (d, 1H, J_{Ha-Hb}=2.3 Hz), 4.71 (dd, 1H, J_{Hb-Ha}=2.3, J_{Hb-NH}= 7.5 Hz), 6.34 (bs, 1H), 7.35–7.52 (m, 4H), 7.08 (bs, 1H); ^{13}C NMR: 12.8 (q), 13.3 (q), 19.4 (t), 23.6 (t), 58.4 (t), 61.7 (d), 66.2 (d), 111.6 (s), 127.2 (s), 127.3 (d), 129.1 (d), 130.3 (d), 131.5 (d), 133.9 (s), 158.8 (s), 161.5 (s), 166.3 (s), 173.7 (s); Anal. Calcd for $C_{30}H_{47}N_4O_6SCl$: C 57.45, H 7.55, N 8.93, O 15.30, S 5.11, Cl 5.65; Found: C 57.59, H 7.67, N 9.10, S 5.00; MS: *m*/*z*=625 (M–H)$^-$.

(2*R*,3*S*)-3-{[3-(2,6-Dichloro-phenyl)-5-methyl-isoxazole-4-carbonyl]-amino}-4-oxo-azetidine-2-sulphonic acid tetrabutylammonium salt (*trans*-5c). Yield 60%; Colourless oil; IR (CH_2Cl_2, cm^{-1}): 3258, 2963, 1767, 1669, 1194; ^{1}H NMR ($CDCl_3$): 0.79 (t, 12H, *J*=7.2 Hz), 1.15–1.27 (m, 8H), 1.38–1.48 (m, 8H), 2.57 (s, 3H), 3.02–3.07 (m, 8H), 4.47 (bs, 1H), 4.64 (bs, 1H), 6.43 (bs, 1H), 7.09–7.25 (m, 3H); ^{13}C NMR: 12.9 (q), 13.3 (q), 19.3 (t), 23.6 (t), 58.4 (t), 61.5 (d), 66.3 (d), 111.9 (s), 127.0 (s), 128.3 (d), 128.4 (d), 130.4 (d), 135.2 (s), 135.6 (s), 159.2 (s), 160.9 (s), 166.5 (s), 175.0 (s); Anal. Calcd for $C_{30}H_{46}N_4O_6SCl_2$: C 54.46, H 7.01, N 8.47, O 14.51, S 4.85, Cl 10.72; Found: C 54.55, H 7.19, N 8.60, S 4.98; MS: *m*/*z*=659 (M–H)$^-$.

(2*R*,3*S*)-3-{[3-(2-Chloro-6-fluoro-phenyl)-5-methyl-isoxazole-4-carbonyl]-amino}-4-oxo-azetidine-2-sulphonic acid tetrabutylammonium salt (*trans*-5d). Yield 71%; Colourless oil; IR (CH_2Cl_2, cm^{-1}): 3423, 2964, 1775, 1671, 1616, 1458, 1250; ^{1}H NMR ($CDCl_3$): 0.92 (t, 12H, *J*=7.2 Hz), 1.26–1.38 (m, 8H), 1.49–1.60 (m, 8H), 2.68 (s, 3H), 3.11–3.17 (m, 8H), 4.62 (d, 1H, J_{Ha-Hb}=2.3 Hz), 4.78 (dd, 1H, J_{Hb-Ha}=2.3, J_{Hb-NH}=7.5 Hz), 5.25 (bs, 1H), 7.00 (t, 1H, *J*=8.1; 8.7 Hz), 7.19–7.45 (m, 2H), 7.21 (d, 1H, *J*=8.1 Hz); ^{13}C NMR: 12.6 (q), 13.2 (q), 19.3 (t), 23.5 (t), 58.4 (t), 61.4 (d), 66.3 (d), 112.4 (s), 113.8 (d), 118.2 (s), 124.8 (d), 130.9 (d), 135.0 (s), 159.0 (s), 160.7 (s), 160.9 (s), 166.8 (s), 175.0 (s); Anal. Calcd for $C_{30}H_{46}N_4O_6SClF$: C 55.85, H 7.19, N 8.68, O 14.88, S 4.97; Cl 5.49, F 2.94; Found: C 55.72, H 7.08, N 8.49, S 5.11; MS: *m*/*z*=643 (M–H)$^-$.

General procedure for preparation of compounds 6a–d

Corresponding compound **5a–d** (0.56 mmol) was dissolved in 20 ml CH_2Cl_2. Potassium nonafluorobutanesulphonate (190 mg; 0.56 mmol) was dissolved in 20 ml dist. H_2O and added to the previous solution. The reaction mixture was stirred for 1 h at room temperature. The layers were separated and water was lyophilised to give compounds **6a–d** as white crystals.

(2*R*,3*R*)-3-[(5-Methyl-3-phenyl-isoxazole-4-carbonyl)-amino]-4-oxo-azetidine-2-sulphonic acid potassium salt (*cis*-6a). Yield 92%; White crystals, decomposition >150°C; IR (KBr, cm^{-1}): 3413, 1772, 1664, 1219; ^1H NMR (DMSO): 2.66 (s, 3H), 4.39 (d, 1H, J_{Ha-Hb}=5.1 Hz), 5.47 (dd, 1H, J_{Hb-Ha}=5.1, J_{Hb-NH}=10.1 Hz), 7.47–7.67 (m, 5H), 8.21 (d, 1H, J=10.1 Hz), 8.88 (s, 1H); ^{13}C NMR: 12.2 (q), 56.9 (d), 64.3 (d), 112.2 (s), 128.2 (s), 128.6 (d), 128.9 (d), 130.2 (d), 160.8 (s), 161.1 (s), 168.4 (s), 170.8 (s); Anal. Calcd for $C_{14}H_{12}N_3O_6SK$: C 43.18, H 3.11, N 10.79, O 24.65, S 8.23, K 10.04; Found: C 43.30, H 3.13, N 10.70, S 8.03.

(2*R*,3*R*)-3-{[3-(2-Chloro-phenyl)-5-methyl-isoxazole-4-carbonyl]-amino}-4-oxo-azetidine-2-sulphonic acid potassium salt (*cis*-6b). Yield 83%; White crystals, decomposition>150°C; IR (KBr, cm^{-1}): 3400, 1773, 1664, 1218; ^1H NMR (DMSO): 2.74 (s, 3H), 4.33 (d, 1H, J_{Ha-Hb}= 5.1 Hz), 5.37 (dd, 1H, J_{Hb-Ha}=5.1, J_{Hb-NH}=10.0 Hz), 7.37–7.57 (m, 4H), 8.05 (d, 1H, J=10.0 Hz), 8.86 (s, 1H); ^{13}C NMR: 12.8 (q), 56.6 (d), 64.2 (d), 112.5 (s), 127.8 (s), 128.1 (d), 128.4 (d), 132.3 (d), 134.5 (s), 135.0 (s), 159.0 (s), 159.0 (s), 168.7 (s), 170.8 (s); Anal. Calcd for $C_{14}H_{11}N_3O_6SClK$: C 39.67, H 2.62, N 9.91, O 22.65, S 7.56, Cl 8.36, K 9.22; Found: C 39.49, H 2.51, N 9.74, S 7.43.

(2*R*,3*R*)-3-{[3-(2,6-Dichloro-phenyl)-5-methyl-isoxazole-4-carbonyl]-amino}-4-oxo-azetidine-2-sulphonic acid potassium salt (*cis*-6c). Yield 100%; White crystals, decomposition>150°C; IR (KBr, cm^{-1}): 3388, 1774, 1665, 1218; ^1H NMR (DMSO): 2.82 (s, 3H), 4.34 (d, 1H, J_{Ha-Hb}=5.0 Hz), 5.36 (dd, 1H, J_{Hb-Ha}=5.0, J_{Hb-NH}= 10.1 Hz), 7.09–7.25 (m, 3H), 8.01 (d, 1H, J=10.1 Hz), 8.83 (s, 1H); ^{13}C NMR: 11.9 (q), 56.1 (d), 63.6 (d), 112.6 (s), 126.8 (d), 127.5 (s), 129.2 (d), 131.0 (d), 132.6 (d), 159.2 (s), 160.1 (s), 168.0 (s), 169.8 (s); Anal. Calcd for $C_{14}H_{10}N_3O_6SCl_2K$: C 36.69, H 2.20, N 9.17, O 20.95, S 7.00, Cl 15.47, K 8.53; Found: C 36.49, H 2.36, N 9.25, S 7.03.

(2*R*,3*R*)-3-{[3-(2-Chloro-6-fluoro-phenyl)-5-methyl-isoxazole-4-carbonyl]-amino}-4-oxo-azetidine-2-sulphonic acid potassium salt (*cis*-6d). Yield 100%; White crystals, decomposition>150°C; IR (KBr, cm^{-1}): 3421, 1774, 1664, 1217; ^1H NMR (DMSO): 2.74 (s, 3H), 4.33 (d, 1H, J_{Ha-Hb}=5.1 Hz), 5.37 (dd, 1H, J_{Hb-Ha}=5.1, J_{Hb-NH}= 10.0 Hz), 7.33–7.62 (m, 3H), 8.06 (d, 1H, J=10.0 Hz), 8.81 (s, 1H); ^{13}C NMR: 12.7 (q), 56.6 (d), 64.2 (d), 112.8 (s), 115.0 (d), 117.2 (s), 125.7 (d), 132.7 (d), 134.3 (s), 155.7 (s), 159.2 (s), 162.1 (s), 168.6 (s), 171.1 (s); Anal. Calcd for $C_{14}H_{10}N_3O_6SClFK$: C 38.06, H 2.28, N 9.51, O 21.73, S 7.26, Cl 8.02, F 4.30, K 8.85; Found: C 38.19, H 2.36, N 9.39, S 7.13.

(2*R*,3*S*)-3-[(5-Methyl-3-phenyl-isoxazole-4-carbonyl)-amino]-4-oxo-azetidine-2-sulphonic acid potassium salt (*trans*-6a). Yield 60%; White crystals, decomposition >150°C; IR (KBr, cm^{-1}): 3435, 1781, 1658, 1257; ^1H NMR (DMSO): 3.17 (s, 3H), 4.18 (bs, 1H), 4.77 (bs, 1H), 7.69–7.71 (m, 5H), 8.77 (s, 1H), 9.04 (d, 1H, J=8.1 Hz); ^{13}C NMR: 12.7 (q), 61.6 (d), 66.6 (d), 113.1 (s), 128.7 (s), 128.9 (d), 129.7 (d), 130.9 (d), 160.8 (s), 162.3 (s), 167.5 (s), 170.8 (s); Anal. Calcd for $C_{14}H_{12}N_3O_6SK$: C 43.18, H 3.11, N 10.79, O 24.65, S 8.23, K 10.04; Found: C 43.05, H 3.30, N 10.65, S 8.32.

(2*R*,3*S*)-3-{[3-(2-Chloro-phenyl)-5-methyl-isoxazole-4-carbonyl]-amino}-4-oxo-azetidine-2-sulphonic acid potassium salt (*trans*-6b). Yield 66%; White crystals, decomposition>150°C; IR (KBr, cm^{-1}): 3429, 1754, 1664, 1257; ^1H NMR (DMSO): 2.61 (s, 3H), 4.20 (d, 1H, J_{Ha-Hb}=1.8 Hz), 4.64 (dd, 1H, J_{Hb-Ha}=1.8, J_{Hb-NH}=8.1 Hz), 7.36–7.60 (m, 4H), 8.66 (s, 1H), 8.79 (d, 1H, J=8.1 Hz); ^{13}C NMR: 12.4 (q), 61.0 (d), 65.9 (d), 113.8 (s), 127.5 (d), 127.8 (s), 130.0 (d), 130.5 (d), 131.9 (d), 132.9 (s), 160.4 (s), 161.1 (s), 167.1 (s), 170.0 (s); Anal. Calcd for $C_{14}H_{11}N_3O_6SClK$: C 39.67, H 2.62, N 9.91, O 22.65, S 7.56, Cl 8.36, K 9.22; Found: C 39.52, H 2.74, N 9.76, S 7.53.

(2*R*,3*S*)-3-{[3-(2,6-Dichloro-phenyl)-5-methyl-isoxazole-4-carbonyl]-amino}-4-oxo-azetidine-2-sulphonic acid potassium salt (*trans*-6c). Yield 100%; White crystals, decomposition>150°C; IR (KBr, cm^{-1}): 3414, 1778, 1668, 1605, 1541, 1194; ^1H NMR (DMSO): 2.68 (s, 3H), 4.17 (d, 1H, J=1.9 Hz), 4.64 (dd, 1H, J_{Hb-Ha}=1.9, J_{Hb-NH}=8.1 Hz), 7.43–7.64 (m, 3H), 8.67 (s, 1H), 8.71 (d, 1H, J_{Ha-Hb}=8.1 Hz); ^{13}C NMR: 12.8 (q), 60.9 (d), 65.9 (d), 113.4 (s), 127.5 (s), 128.5 (d), 128.6 (d), 132.4 (d), 134.6 (s), 134.7 (s), 158.6 (s), 160.2 (s), 167.1 (s), 170.3 (s); Anal. Calcd for $C_{14}H_{10}N_3O_6SCl_2K$: C 36.69, H 2.20, N 9.17, O 20.95, S 7.00, Cl 15.47, K 8.53; Found: C 36.49, H 2.36, N 9.25, S 7.03; Anal. Calcd for $C_{14}H_{10}N_3O_6SCl_2K$: C 36.69, H 2.20, N 9.17, O 20.95, S 7.00, Cl 15.47, K 8.53; Found: C 36.78, H 2.38, N 9.04, S 6.83.

(2*R*,3*S*)-3-{[3-(2-Chloro-6-fluoro-phenyl)-5-methyl-isoxazole-4-carbonyl]-amino}-4-oxo-azetidine-2-sulphonic acid potassium salt (*trans*-6d). Yield 100%; White crystals, decomposition>150°C; IR (KBr, cm^{-1}): 3416, 1781, 1665, 1615, 1255; ^1H NMR (DMSO): 2.66 (s, 3H), 4.17 (bs, 1H), 4.64 (dd, 1H, J_{Hb-Ha}=1.9, J_{Hb-NH}=8.1 Hz), 7.26–7.63 (m, 3H), 8.67 (s, 1H), 8.77 (d, 1H, J=8.1 Hz); ^{13}C NMR: 12.6 (q), 60.9 (d), 66.0 (d), 113.8 (s), 115.1 (d), 116.9 (s), 125.9 (d), 132.9 (d), 134.2 (s), 155.2 (s), 160.4 (s), 162.2 (s), 167.0 (s), 170.5 (s); Anal. Calcd for $C_{14}H_{10}N_3O_6SClFK$: C 38.06, H 2.28, N 9.51, O 21.73, S 7.26, Cl 8.02, F 4.30, K 8.85; Found: C 38.17, H 2.09, N 9.68, S 7.30.

General procedure for preparation of compounds 7c and 7d

Corresponding compound **5c** or **5d** (0.1 mmol) was dissolved in 20 ml CH_2Cl_2 and cooled at −15°C. Chlorosulphonyl isocyanate (0.02 ml; 0.24 mmol) was added and the reaction mixture was stirred for 1 h at −15°C and for 3 h at room temperature. Water was added and the reaction mixture was stirred for 1 h, layers were separated and organic layer was washed with dist. water, dried (Na_2SO_4) and evaporated to give compound **7c** or **7d**.

(2*R*,3*R*)-3-{[3-(2,6-Dichloro-phenyl)-5-methyl-isoxazole-4-carbonyl]-amino}-4-oxo-1-sulphoaminocarbonyl-azetidine-2-sulphonic acid tetrabutylammonium salt (*cis*-7c). Yield 64%; Yellow oil; IR (CH_2Cl_2, cm^{-1}): 3422, 2963,

1812, 1785, 1728, 1677, 1238; ^{1}H NMR ($CDCl_3$): 0.97 (t, 12H, J=7.2 Hz), 1.36–1.43 (m, 8H), 1.56–1.66 (m, 8H), 2.86 (s, 1H), 3.18–3.23 (m, 8H), 4.99 (d, 1H, J_{Ha-Hb}= 6.3 Hz), 5.82 (dd, 1H, J_{Hb-Ha}=6.3, J_{Hb-NH}=9.9 Hz), 7.28–7.51 (m, 3H), 7.74 (d, 1H, J=9.9 Hz); ^{13}C NMR: 13.3 (q), 13.6 (q), 19.6 (t), 23.8 (t), 56.5 (d), 58.6 (t), 67.6 (d), 112.1 (s), 127.7 (s), 128.1 (d), 128.6 (d), 131.2 (d), 135.4 (s), 135.7 (s), 158.6 (s), 160.0 (s), 166.4 (s), 171.7 (s), 175.3 (s); Anal. Calcd for $C_{31}H_{47}N_5O_{10}S_2Cl_2$: C 47.45, H 6.04, N 8.92, O 20.39, S 8.17, Cl 9.04; Found: C 47.29, H 6.16, N 8.99, S 8.13.

(2*R*,3*R*)-3-{[3-(2-Chloro-6-fluoro-phenyl)-5-methyl-isoxazole-4-carbonyl]-amino}-4-oxo-1-sulphoaminocarbonyl-azetidine-2-sulphonic acid tetrabutylammonium salt (*cis*-7d). Yield 76%; Yellow oil; IR (CH_2Cl_2, cm^{-1}): 3360, 2964, 1813, 1784, 1677, 1457, 1249; ^{1}H NMR ($CDCl_3$): 0.96 (t, 12H, J=7.2 Hz), 1.34–1.42 (m, 8H), 1.49–1.60 (m, 8H), 2.84 (s, 3H), 3.16–3.21 (m, 8H), 4.98 (d, 1H, J_{Ha-Hb}= 6.3 Hz), 5.82 (dd, 1H, J_{Hb-Ha}=6.3, J_{Hb-NH}=9.9 Hz), 7.06–7.12 (t, 1H, J=8.1 Hz), 7.27–7.42 (m, 2H), 7.68 (d, 1H, J=9.9 Hz); ^{13}C NMR: 12.9 (q), 13.3 (q), 19.4 (t), 23.6 (t), 56.4 (d), 58.5 (t), 67.5 (d), 112.5 (s), 114.1 (d), 117.0 (s), 125.4 (d), 131.6 (d), 135.1 (s), 155.5 (s), 160.1 (s), 162.5 (s), 166.4 (s), 171.6 (s), 177.2 (s); Anal. Calcd for $C_{31}H_{47}N_5O_{10}S_2ClF$: C 48.46, H 6.17, N 9.12, O 20.82, S 8.35, Cl 4.61, F 2.47; Found: C 48.58, H 5.96, N 9.26, S 8.41.

(2*R*,3*S*)-3-{[3-(2,6-Dichloro-phenyl)-5-methyl-isoxazole-4-carbonyl]-amino}-4-oxo-1-sulphoaminocarbonyl-azetidine-2-sulphonic acid tetrabutylammonium salt (*trans*-7c). Yield 40%; Yellow oil; IR (CH_2Cl_2, cm^{-1}): 3440, 2963, 1812, 1785, 1732, 1464, 1259; ^{1}H NMR ($CDCl_3$): 0.93 (t, 12H, J=7.2 Hz), 1.30–1.42 (m, 8H), 1.55–1.60 (m, 8H), 2.75 (s, 1H), 3.16–3.21 (m, 8H), 4.92 (dd, 1H, J_{Hb-Ha}=3.2, J_{Hb-NH}=6.8 Hz), 4.98 (d, 1H, J_{Ha-Hb}=3.2 Hz), 5.05 (bs, 1H), 7.26–7.47 (m, 3H); ^{13}C NMR: 13.1 (q), 13.4 (q), 19.4 (t), 23.6 (t), 58.5 (t), 62.6 (d), 69.4 (d), 127.7 (s), 128.0 (d), 128.9 (d), 130.9 (d), 135.3 (s), 135.5 (s), 156.3 (s), 163.8 (s), 165.3 (s), 173.5 (s),176.1 (s); Anal. Calcd for $C_{31}H_{47}N_5O_{10}S_2Cl_2$: C 47.45, H 6.04, N 8.92, O 20.39, S 8.17, Cl 9.04; Found: C 47.48, H 5.98, N 9.10, S 8.05.

(2*R*,3*S*)-3-{[3-(2-Chloro-6-fluoro-phenyl)-5-methyl-isoxazole-4-carbonyl]-amino}-4-oxo-1-sulphoaminocarbonyl-azetidine-2-sulphonic acid tetrabutylammonium salt (*trans*-7d). Yield 65%; Yellow oil; IR (CH_2Cl_2, cm^{-1}): 3418, 2964, 1814, 1792, 1732, 1669, 1457, 1251; ^{1}H NMR ($CDCl_3$): 0.96 (t, 12H, J=7.2 Hz), 1.35–1.42 (m, 8H), 1.52–1.64 (m, 8H), 2.79 (s), 3.17–3.23 (m, 8H), 4.85 (dd, 1H, J_{Hb-Ha}=3.4, J_{Ha-NH}=6.8 Hz), 5.03 (d, 1H, J_{Ha-Hb}=3.4 Hz), 6.94 (bs, 1H), 7.18 (t, 1H, J=9.0 Hz), 7.31–7.48 (m, 2H); ^{13}C NMR: 12.8 (q), 13.2 (q), 19.4 (t), 23.7 (t), 58.6 (t), 63.7 (d), 68.9 (d), 113.2 (s), 115.3 (d), 117.0 (s), 125.5 (d), 132.3 (d), 135.2 (s), 155.6 (s), 160.0 (s), 161.9 (s), 165.5 (s), 173.7 (s), 176.1 (s); Anal. Calcd for $C_{31}H_{47}N_5O_{10}S_2ClF$: C 48.46, H 6.17, N 9.12, O 20.82, S 8.35, Cl 4.61, F 2.47; Found: C 48.30, H 5.99, N 9.01, S 8.21.

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