Electronic supplementary materials *Mendeleev Commun.*, 2021, **31**, 498–500

Synthesis of substituted-amidine derivatives of avibactam and synergistic antibacterial activity with meropenem

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Materials and Methods

All ^{1}H and ^{19}F NMR spectra were recorded on a Bruker AVANCE NEO 400 NMR operating at 400 MHz for ^{1}H, and 376 MHz for ^{19}F respectively. NMR data was recorded in chemical shifts relative to TMS as internal standard. NMR spectra were run either in $CDCl_3$ containing 0.05% TMS, CD_3OD containing 0.05% TMS, D_2O or DMSO-d_6 containing 0.03% TMS. Preparative HPLC was performed on an Agilent 1260 Infinity II System on Agilent 10 prep-C18 250×21.2 mm column, using an acetonitrile/aqueous 0.1% trifluoroacetic acid gradient, or an acetonitrile/aqueous 0.1% formic acid gradient, or an acetonitrile/water at 22 °C. Mass spectra were performed on an Agilent 1260II-6125 Separation Module using either ES^- or ES^+ ionization modes. Column chromatography was performed with using Qingdao Inc. Silica Gel: CC Grade (230 – 400 Mesh). Percentage purity was determined by an Agilent 1260 Infinity system equipped with Agilent Eclipse plus C18 3.5μm 2.1×100 mm column, using acetonitrile/water solvent at 22 ºC. Commercial solvents and reagents were generally used without further purification. All products were dried before characterization and use in subsequent synthetic steps.

Synthesis of compounds 2a-e

*Synthesis of tert-butyl (Z)-N-{(amino)[(2S,5R)-6-benzyloxy-7-oxo-1,6-diazabicyclo[3.2.1]octan-2-yl]methylidene)}carbamate (**2a**):* $AlMe_3$ in *n*-hexane (2 N, 9.00 mL, 18.0 mmol) and NH_4Cl (0.96 g, 18.0 mmol) were added to a solution of **1** (3.08 g, 15.0 mmol) in anhydrous CH_2Cl_2 (45 mL) at 0 ºC. The reaction mixture was stirred at room temperature overnight, cooled to 0 ºC, quenched by addition of silica gel (8 g) and methanol (8 mL). The resulting mixture was stirred at room temperature for 20 minutes, filtered off, rinsed with 10% MeOH in CH_2Cl_2 (2×30 mL). The filtrate was concentrated and purified by flash column chromatography using 2-5% MeOH in CH_2Cl_2 to give the title compound **3a** (1.81 g, 44%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.61 – 1.79 (m, 2 H), 1.80 – 1.92 (m, 2 H), 2.77 – 2.95 (m, 2 H), 3.12 – 3.21 (m, 1 H), 3.80 – 3.92 (m, 1 H), 4.09 – 4.15 (m, 1 H), 4.74 – 4.84 (m, 2 H), 6.52 – 6.66 (m, 2 H), 7.33 – 7.42 (m, 3 H), 7.45 – 7.54 (m, 2 H). LC-MS $[M+Na]^+$ *m/z* 297.1 (calcd for $C_{14}H_{18}N_4O_2$, 274.14). A mixture of this crude compound (0.5 g, 1.33 mmol), $(Boc)_2O$

(0.67 g, 4.0 mmol) and triethylamine (0.55 mL, 3.0 mmol) in CH_2Cl_2 (15 mL) was stirred at 20 ºC for 48 hours. The reaction mixture was concentrated under reduced pressure and the residue was purified by flash chromatography on silica gel, eluting with 30% EtOAc in petroleum ether to give the title compound **2a** (0.39 g, 76%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.49 (s, 9 H) , 1.81 – 1.91 (m, 1 H), 1.93 – 2.01 (m, 1 H), 2.04 – 2.17 (m, 2 H), 3.21 (t, *J* = 11.4 Hz, 1 H) , 4.09 – 4.18 (m, 2 H) , 4.89 (s, 2 H) , 5.26 – 5.44 (m, 3 H), 7.38 – 7.44 (m, 5 H). LC-MS $[M+H]^+$ *m/z* 375.2 (calcd for $C_{19}H_{26}N_4O_4$, 374.20).

*Synthesis of tert-butyl (Z)-N-{[(2S,5R)-6-benzyloxy-7-oxo-1,6-diazabicyclo[3.2.1]octan-2-yl](methylamino)methylidene}carbamate (**2b**):* Compound **2b** was prepared from compound **1** (0.61 g, 2.3 mmol) and methylamine hydrochloride (0.24 g, 3.5 mmol) by using the method described for **2a** to give the intermediate compound (0.40 g, 61%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.81 – 1.96 (m, 2 H), 1.97 – 2.14 (m, 2 H), 2.74 (d, *J* = 4.8 Hz, 3 H), 3.07 – 3.14 (m, 1 H), 3.22 (t, *J* = 10.9 Hz, 1 H), 4.06 – 4.08 (m, 1 H), 4.14 – 4.22 (m, 1 H), 4.81 (s, 2 H), 5.74 (br s, 1 H), 7.41 – 7.44 (m, 5H). LC-MS $[M+Na]^+$ *m/z* 311.2 (calcd for $C_{15}H_{20}N_4O_2$, 288.16), which was (0.5 g, 1.73 mmol) reacted with $(Boc)_2O$ (0.67 g, 4.0 mmol) to afford the title compound (0.4 g, 60%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.49 (s, 9 H), 1.79 – 1.95 (m, 2 H), 2.02 – 2.15 (m, 2 H), 2.76 (d, *J* = 4.4 Hz, 3 H), 3.19 (t, *J* = 11.1 Hz, 1 H), 4.06 – 4.16 (m, 2 H), 4.83 (s, 2 H), 5.76 (s, 1 H), 7.39 – 7.45 (m, 5 H). LC-MS $[M+Na]^+$ *m/z* 411.2 (calcd for $C_{20}H_{28}N_4O_4$, 388.21).

*Synthesis of tert-butyl ((Z)-(ethylamino)((2S,5R)-6-hydroxy-7-oxo-1,6-diazabicyclo[3.2.1]octan-2-yl)methylene)carbamate (**2c**)*: Compound **1** (0.60 g, 2.3 mmol) was reacted with ethylamine hydrochloride (0.29 g, 3.5 mmol) as described for the synthesis of compound **2a**. The crude compound (0.5 g) was obtained and directly used for next step without further purification. LC-MS $[M+Na]^+$ *m/z* 325.1 (calcd for $C_{16}H_{22}N_4O_2$, 302.17). A mixture of crude compound (0.5 g) was reacted with $(Boc)_2O$ (0.67 g, 4.0 mmol) and the crude product was purified with 30% EtOAc in petroleum ether to provide the title compound **2c** (0.41 g, 44% in two steps) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.00 (t, *J* = 7.1 Hz, 3 H), 1.45 (s, 9 H), 1.75 – 1.94 (m 2 H), 1.97 – 2.13 (m, 2 H), 3.10 – 3.22 (m, 3 H), 4.08 (q, *J* = 7.1 Hz, 2 H), 4.81 (s, 2 H), 5.21 (br s, 1 H), 5.62 – 5.95 (m, 1 H), 7.41 (s, 5 H). LC-MS $[M+H]^+$ *m/z* 403.1 (calcd for $C_{21}H_{30}N_4O_4$, 402.23).

*Synthesis of tert-butyl (Z)-N-{(2-acetamidoethylamino)[(2S,5R)-6-benzyloxy-7-oxo-1,6-diazabicyclo[3.2.1]octan-2-yl]methylidene}carbamate (**2d**):* Trimethylsilyl triflate (0.60 mL, 3.31 mmol) and *N*-(2-aminoethyl)acetamide (1.02 g, 10.00 mmol) were added to a solution of compound **1** (1.67 g, 6.50 mmol) in anhydrous THF (20 mL) at 0 ºC. The mixture was stirred at room temperature for 3.5 days, concentrated, diluted with CH_2Cl_2 (80 mL), washed with water (20 mL), brine (15 mL) and dried over Na_2SO_4. The filtrate was concentrated and purified by flash column chromatography using 2-5% MeOH in CH_2CH_2 to give the intermediate compound (1.11 g, 47%) as a white foam. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.77 – 1.86 (m, 2 H), 1.94 (s, 3 H). 1.92 – 2.01 (m, 1 H), 2.11–2.20 (m, 1

H), 2.79 – 2.88 (m, 1 H), 3.10 – 3.16 (m, 1 H), 3.19 – 3.29 (m, 4 H), 3.52 – 3.60 (m, 1 H), 3.96 – 4.06 (m, 1 H), 4.76 (s, 2 H), 6.06 (br s, 2 H), 7.32 – 7.45 (m, 5 H). LC-MS $[M+H]^+$ *m/z* 360.1 (calcd for $C_{18}H_{25}N_5O_3$, 359.20). The intermediate compound (1.10 g, 3.06 mmol) was then treated with $(Boc)_2O$ to give the title compound **2d** (0.98 g, 70%) as a white foam. ^1H NMR (400 MHz, $CDCl_3$): δ 1.36 (s, 9 H), 1.80 – 1.90 (m, 1 H), 1.95 (s, 3 H), 2.00 – 2.08 (m, 2 H), 2.30 – 2.3 (m, 1 H), 3.09 – 3.20 (m, 1 H), 3.21 – 3.42 (m, 4 H), 4.23 – 4.39 (m, 2 H), 4.69 – 4.79 (m, 2 H), 5.23 (s, 1 H), 6.00 – 6.10 (m, 1 H), 7.28 – 7.44 (m, 5 H). LC-MS $[M+H]^+$ *m/z* 460.1 (calcd for $C_{23}H_{33}N_5O_5$, 459.25).

*Synthesis of tert-butyl (E)-N-{[(2S,5R)-6-benzyloxy-7-oxo-1,6-diazabicyclo[3.2.1]octan-2-yl)][(tetrahydropyran-4-ylmethyl)amino]methylidene}carbamate (**2e**):* Compound **2e** was prepared from **1** (1.0 g, 3.60 mmol) and (tetrahydropyran-4-yl)methanamine (0.64 g, 5.40 mmol) as described for **2a** to get the title compound (0.35 g, in 54% in two steps) as a white solid. ^1H NMR (400 MHz, $CDCl_3$): δ 1.39 – 1.44 (m, 12 H) 1.49 – 1.61 (m, 2 H), 1.75 – 1.94 (m, 2 H), 1.99 – 2.14 (m, 2 H), 2.95 – 3.60 (m, 2 H), 3.13 – 3.22 (m, 1 H), 3.26 – 3.33 (m, 2 H), 3.89 – 3.95 (m, 2 H), 4.63 – 4.13 (m, 2 H), 4.81 (s, 2 H), 5.83 (s, 1 H), 7.36 – 7.41 (m, 5 H). LC-MS $[M+Na]^+$ *m/z* 495.1 (calcd for $C_{25}H_{36}N_4O_5$, 472.27).

Synthesis of compounds 3a-e

*Synthesis of sodium (2S,5R)-2-carbamimidoyl-7-oxo-1,6-diazabicyclo[3.2.1]octan-6-yl sulfate (**3a**):* A mixture of compound **2a** (0.7 g, 1.9 mmol) and 10% Pd/C, wetted with ca. 55% water, 0.2 g, 20% w/w) in MeOH (50 mL) was stirred at 5 ºC for 10 minutes. Then hydrogen gas was inserted into the system, the mixture was reacted at room temperature overnight. The mixture was then filtrated, and the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel, eluting with 70% EtOAc in petroleum ether to give the intermediate hydroxy compound (0.46 g, 71%) as a white solid. ^1H NMR (400 MHz, DMSO-d_6) δ 1.42 (s, 9 H), 1.66 – 1.72 (m, 1 H), 1.75 – 1.82 (m, 2 H), 1.96 – 2.01 (m, 1 H), 2.80 – 2.96 (m, 1 H), 3.79 – 3.93 (m, 2 H), 5.23 (br s, 1H), 6.49 (br s, 2 H), 9.24 (s, 1 H). LC-MS $[M+Na]^+$ *m/z* 307.2 (calcd for $C_{12}H_{20}N_4O_4$, 284.15). SO_3-pyridine complex (0.56 g, 3.50 mmol) was added to a solution of hydroxy compound (0.20 g, 0.70 mmol) in anhydrous pyridine (7 mL). The mixture was stirred at room temperature overnight, concentrated to dryness under reduced pressure. The residue was suspended with CH_2Cl_2 (10 mL), filtered off and rinsed with CH_2Cl_2 (2×3 mL). The filtrate was concentrated to give a residue, which was purified by flash column chromatography using 5-15% MeOH in CH_2Cl_2 to give the sulfonated compound (0.27 g, 87%) as a pale yellow foam. ^1H NMR (400 MHz, DMSO-d_6): δ 1.42 (s, 9 H), 1.65 – 1.91 (m, 3 H), 1.91 – 2.03 (m, 1 H), 2.94 – 3.03 (m, 1 H), 3.77 – 3.87 (m, 1 H), 3.92 – 4.00 (m, 1 H), 5.18 – 5.26 (m, 1 H), 6.44 (br s, 2 H), 7.98 – 8.06 (m, 2 H of pyridine), 8.50 – 8.56 (m, 1 H of pyridine), 8.88 – 8.94 (m, 2 H of pyridine) . LC-MS $[M\text{-}Pyr\text{-}H]^-$ *m/z* 363.1 (calcd for $C_{12}H_{20}N_4O_7S$, 364.11). Triflouroacetic acid (TFA, 1.5 mL) was added to a solution of sulfonated compound (0.27 g, 0.61 mmol) in anhydrous CH_2Cl_2 (8 mL) at 0 ºC. The mixture was stirred for 3.5

hours at 0 ºC, concentrated under reduced pressure to give a residue. The residue was dissolved with CH_2Cl_2 (20 mL) and extracted with water (2×10 mL). The aqueous layer was freeze-dried and purified by resin Dowex-50wx Na^+, using water as elution solvent to give **3a** (32 mg, 18%, 95.2% purity) as a white powder. ^{1}H NMR (400 MHz, D_2O): δ 1.70 – 2.05 (m, 4 H), 3.00 – 3.13 (m, 2 H), 3.77 – 3.87 (m, 1 H), 4.17 – 4.27 (m, 1 H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 23.8 (s), 27.9 (s), 44.5 (s), 44.8 (s), 55.7 (s), 119.9 (s), 161.9 (s). LC-MS $[M-Na]^-$ *m/z* 263.1 (calcd for $C_7H_{11}N_4NaO_5S$, 286.03).

*Synthesis of sodium (2S,5R)-2-(N-methylcarbamimidoyl)-7-oxo-1,6-diazabicyclo[3.2.1]octan-6-yl sulfate (**3b**):* Compound **2b** (0.78 g, 2.0 mmol) was hydrogenated over palladium to furnish the hydroxy compound (0.55 g, 66%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.42 (s, 9 H), 1.64 – 1.69 (m, 1 H), 1.74 – 1.82 (m, 2 H),1.95 – 2.01 (m, 1 H), 2.61 (d, J = 4.46 Hz, 3 H), 3.17(d, J = 5.09 Hz, 1 H), 3.77 – 3.91 (m, 2 H), 5.22 (br s, 1 H), 6.94 – 6.99 (m, 2 H), 9.15 (s, 1 H). LC-MS $[M+Na]^+$ *m/z* 321.2 (calcd for $C_{13}H_{22}N_4O_4$, 298.16). The hydroxy derivative (0.16 g, 0.53 mmol) was reacted with SO_3-pyridine complex in anhydrous pyridine (6 mL) overnight to give sulfonated compound (0.19 g, 79%) as a white foam. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.43 (s, 9 H), 1.64 – 1.89 (m, 3 H), 1.91 – 2.00 (m, 1 H), 2.63 (d, J = 4.50 Hz, 3 H), 2.96 – 3.13 (m, 1 H), 3.76 –3.86 (m, 1 H), 3.90 – 4.00 (m, 1 H), 5.18 – 5.26 (m, 1 H), 6.75 (d, J = 4.50 Hz, 1 H), 7.85 – 7.92 (m, 2 H of pyridine), 8.33 – 8.41 (m, 1 H of pyridine), 8.80 – 8.87 (m, 2 H of pyridine). LC-MS $[M-Pyr-H]^-$ *m/z* 377.1 (calcd for $C_{13}H_{22}N_4O_7S$, 378.12). Compound **3b** (26 mg, 26%, 95.3% purity) as a white powder was prepared from sulfonated intermediate (0.19 g, 0.42 mmol) by treating it with TFA and subsequent purification by ion exchange resin as described for **3a**. ^{1}H NMR (400 MHz, D_2O): δ 1.69 – 2.04 (m, 4 H), 2.63 (s, 3 H), 3.00 – 3.10 (m, 2 H), 3.83 – 3.93 (m, 1 H), 4.19 – 4.24 (m, 1 H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 23.7 (s), 27.0 (s), 27.9 (s), 44.5 (s), 44.8 (s), 56.3 (s), 119.8 (s), 161.2 (s). LC-MS $[M-Na]^-$ *m/z* 277.1 (calcd for $C_8H_{13}N_4NaO_5S$, 300.05).

*Synthesis of (2S,5R)-2-(N-ethylcarbamimidoyl)-7-oxo-1,6-diazabicyclo[3.2.1]octan-6-yl hydrogen sulfate (**3c**):*Compound **2c** (1.1 g, 2.7 mmol) was hydrogenated and purified by 70% EtOAc in petroleum ether to give the hydroxy intermediate (0.55 g, 66%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.01 (t, J = 7.1 Hz, 3H), 1.43 (s, 9H), 1.63 – 1.70 (m, 1 H), 1.74 – 1.82 (m, 2 H), 1.95 – 2.01 (m, 1 H), 2.79 – 2.94 (m, 1 H), 3.03 – 3.12 (m, 2H),3.78 – 3.91 (m, 2 H), 5.01 – 5.42 (m, 1 H), 7.11 (t, J = 5.9 Hz, 1 H), 9.19 (s, 1 H). LC-MS $[M+Na]^+$ *m/z* 335.1 (calcd for $C_{14}H_{24}N_4O_4$, 312.18). A mixture of hydroxy compound (0.35 g, 1.12 mmol), SO_3-NMe_3 complex (0.47 g, 3.36 mmol) and TEA (0.47 mL, 3.36 mmol) in MeOH (15 mL) was stirred at room temperature overnight. The reaction mixture was concentrated under reduced pressure to provide a residue, which was washed with a small amount of water to give a solid. The solid was collected and dried to give the crude sulfonated compound as triethylamine salt (0.41 g, 74%), which was used for next step without further purification. LC-MS $[M+H]^+$ *m/z* 393.1 (calcd for $C_{14}H_{24}N_4O_7S$, 392.14). The crude sulfonated compound (0.07 g, 0.14 mmol) was added into formic acid (3.0 mL, 88%) and was stirred at 0 ºC for 30 hours. The reaction mixture was concentrated under reduced pressure. The residue was dissolved

with water, and then neutralized with saturated $NaHCO_3$. The solution was lyophilized and then purified by preparative HPLC on an Agilent 10 prep-C18 250×21.2 mm column and lyophilized to give **3c** (15 mg, 36%, 96.0% purity) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.01 (t, J = 7.2 Hz, 3H), 1.71 – 1.96 (m, 2 H), 2.08 – 2.16 (m, 1 H), 2.22 – 2.34 (m, 1 H), 3.04 – 3.33 (m, 3 H), 4.22 (br s, 1 H), 4.85 (br s, 1 H), 6.82 – 6.89 (m, 1 H). ^{13}C NMR (100 MHz, DMSO-d_6 with 3 drops of D_2O): δ 15.1 (s), 18.5 (s), 34.9 (s), 35.0 (s), 44.8 (s), 56.5 (s), 57.0 (s), 120.7 (s), 160.8 (s). LC-MS $[M-H]^-$ *m/z* 291.1 (calcd for $C_9H_{16}N_4O_5S$, 292.08).

*Synthesis of sodium (2S,5R)-2-[N-(2-acetamidoethyl)carbamimidoyl]-7-oxo-1,6-diazabicyclo[3.2.1]octan-6-yl sulfate (**3d**):* Hydrogenation of compound **2d** (0.97 g, 2.11 mmol) was performed in EtOAc (10 mL) over palladium to get the hydroxy compound (0.71 g, 94%) as a white solid which was directly used for next step without further purification. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.41 (s, 9 H), 1.72 – 1.92 (m, 3 H), 1.80 (s, 3 H), 2.14 – 2.24 (m, 1 H), 3.04 – 3.14 (m, 4 H), 3.16 – 3.24 (m, 1 H), 3.79 – 3.90 (m, 1 H), 4.04 – 4.13 (m, 1 H), 5.05 – 5.12 (m, 1 H), 7.03 – 7.10 (m, 1 H), 7.81 – 7.92 (m, 1 H), 9.14 (s, 1 H). LC-MS $[M+H]^+$ *m/z* 370.1 (calcd for $C_{16}H_{27}N_5O_5$, 369.20).

The hydroxy compound (0.29 g, 0.79 mmol) was treated with SO_3-pyridine complex (0.64 g, 4.0 mmol) in anhydrous pyridine (7 mL) to obtain the sulfonated compound (0.37 g, 90%) as a pale yellow foam. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.41 (s, 9 H), 1.67 – 1.88 (m, 2 H), 1.78 (s, 3 H), 2.10 – 2.33 (m, 2 H) 3.03 – 3.15 (m, 4 H), 3.23 – 3.33 (m, 1 H), 3.72 – 3.83 (m, 1 H), 4.04 – 4.14 (m, 1 H), 4.94 – 5.05 (m, 1 H), 6.93 – 7.03 (m, 1 H), 7.69 – 7.79 (m, 1 H), 7.91 – 8.00 (m, 2 H of pyridine), 8.42 – 8.50 (m, 1 H of pyridine), 8.82 – 8.91 (m, 2 H of pyridine). LC-MS $[M-Pyr-H]^-$ *m/z* 448.2 (calcd for $C_{16}H_{27}N_5O_8S$, 449.16). The sulfonated compound was (0.37 g, 0.70 mmol) was treated with TFA to afford the final compound **3d** (40 mg, 15%, 99.0% purity) as a white powder. ^{1}H NMR (400 MHz, D_2O): δ 1.62 – 1.75 (m, 1 H), 1.82 (s, 3 H), 1.82 – 1.92 (m, 2 H), 2.16 – 2.26 (m, 1 H), 3.11 – 3.26 (m, 5 H), 3.33 – 3.45 (m, 1 H), 3.68 – 3.77 (m, 1 H), 4.09 – 4.21 (m, 1 H). ^{13}C NMR (100 MHz, D_2O): δ 21.8 (s), 26.0 (s), 27.4 (s), 38.6 (s), 39.3 (s), 55.3 (s), 56.6 (s), 161.1 (s), 171.4 (s), 174.2 (s). LC-MS $[M-Na]^-$ *m/z* 348.2 (calcd for $C_{11}H_{18}N_5NaO_6S$, 371.09).

*Synthesis of sodium (2S,5R)-2-{(Z)-N'-tert-butoxycarbonyl-N-[(tetrahydro-2H-pyran-4-ylmethyl)carbamimidoyl]}-7-oxo-1,6-diazabicyclo[3.2.1]octan-6-yl sulfate (**3e**):* Compound **2e** (0.30 g, 0.63 mmol) was hydrogenated to obtain the hydroxy compound (0.20 g, 82%) as a white solid, which was directly used for next step without further purification. LC-MS $[M+H]^+$ *m/z* 383.2 (calcd for $C_{18}H_{30}N_4O_5$, 382.22). Sulfonated compound (240 mg, as a NMe_3 salt) as a white powder was prepared from hydroxy compound (0.20 g, 0.52 mmol) following the procedure described for **3c.** The salt was further purified by resin Dowex-50wx Na^+, using water as elution solvent to give **3e** (198 mg, 78%, 95.4% purity). ^{1}H NMR (400 MHz, D_2O): δ 1.13 – 1.24 (m, 2 H), 1.38 (s, 9 H), 1.56 – 1.62 (m, 2 H), 1.70 – 1.81 (m, 2 H), 1.88 – 2.06 (m, 3 H), 2.99 – 3.15 (m, 3 H), 3.36 (t, J = 11.4 Hz, 2 H), 3.81 – 3.92 (m, 3 H), 4.03 – 4.11 (m, 1 H), 5.28 (s, 1 H). ^{13}C NMR (100 MHz, D_2O): δ 26.9 (s), 27.3 (s), 27.4 (s),

27.5 (s), 29.5 (s), 34.3 (s), 42.3 (s), 45.4 (s), 57.7 (s), 67.3 (s), 83.5 (s), 117.6 (s), 155.0 (s), 161.6 (s). LC-MS $[M-Na]^-$ *m/z* 461.2 (calcd for $C_{18}H_{29}N_4N_aO8S$, 484.1604).

Synthesis of compound 3f

*Synthesis of ethyl 4-((2S,5R)-6-benzyloxy-7-oxo-1,6-diazabicyclo[3.2.1]octane-2-carboximidamido)piperidine-1-caboxylate (**4**):* Compound **4** (0.56 g, 26%) as a white foam was synthesized from ethyl 4-aminopiperidine-1-carboxylate (1.40 mL, 8.17 mmol) and **1** (1.30 g, 5.00 mmol) by using TMSOTf as described for **2d**. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.02 – 1.07 (m, 2 H), 1.27 (t, *J* = 7.07 Hz, 3 H), 1.68 – 1.87 (m, 5 H), 1.95 – 2.08 (m, 1 H), 2.80 – 2.93 (m, 2 H), 3.22 – 3.32 (m, 2 H), 3.65 – 3.76 (m, 1 H), 3.81 – 4.03 (m, 3 H), 4.14 (q, *J* = 7.07 Hz, 2 H), 4.67 – 4.74 (m, 2 H), 4.82 (d, *J* = 7.10 Hz, 1 H), 5.40 – 5.60 (m, 2 H), 7.28 – 7.38 (m, 5 H). LC-MS $[M+H]^+$ *m/z* 430.2 (calcd for $C_{22}H_{31}N_5O_4$, 429.24).

*Synthesis of sodium (2S,5R)-2-(N-(1-ethoxycarbonylpiperidin-4-yl)carbamimidoyl)-7-oxo-1,6-diazabicyclo[3.2.1]octan-6-yl sulfate (**3f**):* Triethylamine (0.65 mL, 4.65 mmol) and trifluoroacetic anhydride (0.33 mL, 2.33 mmol) were added to a solution of compound **4** (0.80 g, 1.86 mmol) in CH_2Cl_2 (15 mL) at 0 ºC. The resulting mixture was stirred at room temperature for 4 hours. The mixture was concentrated to leave a residue, which was purified by flash column chromatography using 25% EtOAc in hexane to give the unprotected compound (0.35 g, 36%) as a white foam. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.07 – 1.30 (m, 2 H), 1.26 (t, *J* = 7.10 Hz, 3 H), 1.65 – 1.75 (m, 1 H), 1.83 – 1.97 (m, 2 H), 2.02 – 2.14 (m, 2 H), 2.32 – 2.42 (m, 1 H), 2.77 – 2.94 (m, 2 H), 3.41 –3.50 (m, 1 H), 3.63 – 3.76 (m, 1 H), 3.91 – 4.09 (m, 2 H), 4.12 (q, *J* = 7.10 Hz, 2 H), 4.27 – 4.41 (m, 2 H), 4.82 – 4.90 (m, 1 H), 4.95 (s, 2 H), 5.30 – 5.37 (m, 1 H), 7.30 – 7.45 (m, 5 H); ^{19}F NMR (376 MHz, $CDCl_3$): δ -70.98 (s, 3F). LC-MS $[M+H]^+$ *m/z* 526.2 (calcd for $C_{24}H_{30}F_3N_5O_5$, 525.22). The unprotected compound was then hydrogenated by Pd to get the hydroxy intermediate as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.18 (t, *J* = 7.10 Hz, 3 H), 1.22 – 1.34 (m, 2 H), 1.64 – 1.77 (m, 2 H), 1.79 – 1.92 (m, 2 H), 1.95 – 2.03 (m, 1 H), 2.10 – 2.20 (m, 1 H), 2.73 – 2.93 (m, 2 H), 3.18 – 3.28 (m, 1 H), 3.57 – 3.69 (m, 1 H), 3.84 – 3.96 (m, 3 H), 4.02 (q, *J* = 7.10 Hz, 2 H), 4.31 – 4.40 (m, 1 H), 5.20 – 5.27 (m, 1 H), 6.65 (d, *J* = 7.20 Hz, 1 H), 10.6 (s, 1 H); ^{19}F NMR (376 MHz, DMSO-d_6): δ -70.00 (s, 3F). LC-MS $[M-H]^-$ *m/z* 434.2 (calcd for $C_{17}H_{24}F_3N_5O_5$, 435.17). The hydroxy compound was treated with SO3-pyridine to obtain the sulfonated compound as a pyridine salt. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.18 (t, *J* = 7.10 Hz, 3 H), 1.21 – 1.34 (m, 4 H), 1.66 – 1.88 (m, 4 H), 2.78 – 2.96 (m, 2 H), 3.22 – 3.32 (m, 1 H), 3.54 – 3.66 (m, 1 H), 3.81 – 3.92 (m, 2 H), 4.02 (q, *J* = 7.10 Hz, 2 H), 4.23 – 4.33(m, 2 H), 5.04 – 5.09 (m, 1 H), 6.44 (d, *J* = 7.20 Hz, 1 H), 7.88 – 7.97 (m, 2 H of pyridine), 8.39 – 8.47 (m, 1 H of pyridine), 8.82 – 8.90 (m, 2 H of pyridine) (SO_3H missing); ^{19}F NMR (376 MHz, DMSO-d_6): δ -68.72 (s, 3F). LC-MS $[M-Pyr-H]^-$ *m/z* 514.2 (calcd for $C_{17}H_{24}F_3N_5O_8S$, 515.13). In next step, Na_2CO_3 (65.0 mg, 0.610 mmol) was added to a solution of sulfonated salt (0.19 g, 0.31 mmol) in MeOH (4

mL) and H_2O (3 mL). The mixture was stirred for 2 hours at room temperature. The mixture was concentrated to leave a residue which was purified by Diaion HP-20, using water and then 10% MeCN in water as eluting solvent to provide the title compound **3f** (13 mg, 10%, 95.4% purity) as a white powder. ^{1}H NMR (400 MHz, D_2O): δ 1.17 (t, J = 7.17 Hz, 3 H), 1.57 – 1.72 (m, 3 H), 1.76 – 1.88 (m, 1 H), 1.93 – 2.22 (m, 4 H), 2.69 – 2.92 (m, 3 H), 2.98 – 3.14 (m, 1 H), 3.92 – 4.20 (m, 5 H), 4.05 (q, J = 7.17 Hz, 2 H) (2 NH not shown). ^{13}C NMR (100 MHz, D_2O): δ 13.6 (s), 25.1 (s), 27.5 (s), 39.0 (s), 41.6 (s), 43.1 (s), 43.3 (s), 49.2 (s), 55.6 (s), 56.0 (s), 62.4 (s), 80.9 (s), 153.7 (s), 155.1 (s), 156.9 (s). LC-MS $[M\text{-}Na]^-$ *m/z* 418.2 (calcd for $C_{15}H_{24}N_5NaO_7S$, 441.13).

Synthesis of compounds 6a-c

Synthesis of (R)-1-(methylsulfonyl)pyrrolidine-3-carboxylic acid: This compound was prepared in two steps, the first, TEA was added to a solution of methyl (*R*)-pyrrolidine-3-carboxylate (0.78 g, 4.74 mmol) and methanesulfonic anhydride (1.64 g, 9.42 mmol) in CH_2Cl_2 (20 mL) at 0 ^{o}C, then stirred overnight at room temperature. The reaction was quenched with water and extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4 and filtered. The filtrate was concentrated to leave a residue, which was purified by silica gel column chromatography eluting with 50% ethyl acetate in petroleum ether to give the mesylated intermediate (0.88 g, 90%) as a brown oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.22-2.31 (m, 2H), 2.89 (s, 3H), 3.13-3.20 (m, 2H), 3.34-3.40 (m, 1H), 3.45-3.51 (m, 1H), 3.57-3.60 (m, 1H), 3.75 (s, 3H). LC-MS $[M+H]^+$ *m/z* 208.0 (calcd for $C_7H_{13}NO_4S$, 207.06). Next, NaOH (2 N, 4.83, 9.66 mmol) was added to a solution of the mesylated intermediate (1.0 g, 4.83 mmol) in THF (10 mL) at 0 ^{o}C, then this was stirred at room temperature for 4 h. The mixture was acidified with 1 N HCl to adjust pH to 3, extracted with CH_2Cl_2, the organic layer was washed with brine, dried over Na_2SO_4 and filtered. The filtrate was concentrated to give the title compound (0.88 g, 90%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.99-2.16 (m, 2H), 2.89 (s, 3H), 3.07-3.14 (m, 1H), 3.24-3.28 (m, 2H), 3.39-3.46 (m, 2H). LC-MS $[M+H]^+$ *m/z* 194.0 (calcd for $C_6H_{11}NO_4S$, 193.04).

Synthesis of (S)-1-acetylpiperidine-3-carboxylate: Acetic anhydride (1.4 g, 14.3 mmol) was added to a solution of ethyl (*S*)-piperidine-3-carboxylate (2.0 g, 12.7 mmol) in CH_2Cl_2 (20 mL), and this was stirred at room temperature for 24 h. The mixture was concentrated to leave a residue, which was purified by silica gel column chromatography eluting with 50% ethyl acetate in petroleum ether to give the *N*-acylated intermediate (2.51 g ,99%) as an oil. ^{1}H NMR (400 MHz, CD_3Cl): δ 1.25(t, J = 7.1 Hz, 1.5H), 1.28 (t, J = 7.1 Hz, 1.5H), 1.41-1.55 (m, 1H), 1.64-1.73 (m, 1H), 1.76-1.86 (m, 1H), 1.97-2.07 (m, 1H), 2.09 (s, 1.5H), 2.14 (s, 1.5H), 2.39-2.52 (m, 1H), 2.80-2.87 (m, 0.5H), 3.03-3.14 (m, 1H), 3.43-3.50 (m, 0.5H), 3.68-3.77 (m, 1H), 3.94-4.01 (m, 0.5H), 4.10-4.20 (m, 2H), 4.59-4.65 (m, 0.5H). In next step, NaOH (2 N, 6 mL, 12 mmol) was added to a solution of the above intermediate (1.2 g, 6.0 mmol) in THF (8 mL) at 0 ^{o}C, and this was stirred at room temperature for 2 hours. The mixture was concentrated to remove THF, water (5 mL) was added, the aqueous phase was separated

and some impurities were extracted into CH_2Cl_2 (10×2 mL). The aqueous layer was acidified to pH~4 with 3 N HCl at 0 °C, and this was lyophilized to give a residue, which was extracted with CH_2Cl_2. The CH_2Cl_2 layer was concentrated to give the title compound (0.88 g, 85%) as a solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.44-1.57(m, 1H),1.65-1.73 (m, 0.5H), 1.74-1.90 (m, 1.5H), 1.93-2.03 (m, 1H), 2.09 (s, 1.5H), 2.15 (s, 1.5H), 2.41-2.52 (m, 1H), 3.13-3.20 (m, 0.5H), 3.24-3.32 (m, 0.5H), 3.38-3.57 (m, 1.5H), 3.71-3.77 (m, 0.5H), 3.88-3.96 (m, 0.5H), 4.01-4.08 (m, 0.5H), 8.12 (brs, 1H). LC-MS $[M+H]^+$ *m/z* 172.1 (calcd for $C_8H_{13}NO_3$, 171.09).

*Synthesis of (3R)-N-[((2S,5R)-6-benzyloxy-7-oxo-1,6-diazabicyclo[3.2.1]octan-2-yl)(imino)methyl]-1-(methylsulfonyl)piperidine-3-carboxamide (**5a**):* (*R*)-1-(Methylsulfonyl)-piperidine-3-carboxylic acid (207 mg, 1.0 mmol) was added to a solution of compound **2a** (137 mg, 0.5 mmol), HATU (380 mg, 1.0 mmol) and DIPEA (259 μL, 1.5 mmol) in DMF (3 mL) at room temperature, and this was stirred at room temperature for 24 h. The reaction was quenched with saturated $NaHCO_3$ and water, extracted with EtOAc. The organic layer was washed with water, then brine, dried over Na_2SO_4 and filtered. The filtrate was concentrated to leave a residue, which was purified by silica gel column chromatography eluting with 50% ethyl acetate in petroleum ether to give the title compound **5a** (100 mg, 44%) as a red oil. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.32-1.44 (m, 1H), 1.56-1.69 (m, 1H), 1.71-2.10 (m, 6H), 2.68-2.91 (m, 3H), 2.94 (s, 3H), 3.25-3.35 (m, 1H), 3.55-3.66 (m, 2H), 3.83-4.03 (m, 2H), 4.90 (s, 2H), 5.71 (s, 1H), 6.81 (s, 2H), 7.40-7.47 (m, 3H), 7.53-7.60 (m, 2H). LC-MS $[M+Na]^+$ *m/z* 486.2 (calcd for $C_{21}H_{29}N_5O_5S$, 463.19).

*Synthesis of sodium (2S,5R)-2-[N-((R)-1-methylsulfonylpiperidine-3-carbonyl)carbamimidoyl]-7-oxo-1,6-diazabicyclo[3.2.1]octan-6-yl sulfate (**6a**):* Catalyst 10% Pd/C (wet, 55% water w/w, 70 mg) was added to a solution of compound **5a** (100 mg, 0.22 mmol) in THF (3 mL) with a few drops of TEA. The mixture was stirred under H_2 (~ 1 atm, balloon) at room temperature overnight, filtered through a pad of Celite and rinsed with EtOAc. The filtrate was concentrated to leave a residue, which was purified silica gel column chromatography eluting with 50% ethyl acetate in petroleum ether to give the intermediate hydroxy compound (70 mg, 85%) as a brown solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.45-1.63 (m, 2H), 1.68-2.03 (m, 6H), 2.64-2.69 (m, 1H), 2.77-2.86 (m, 2H), 2.89 (s, 3H), 3.02-3.13 (m, 1H), 3.50-3.60 (m, 2H), 3.75-3.96 (m, 2H), 5.66 (s, 1H), 6.45 (s, 2H), 9.25 (s, 1H). LC-MS $[M+Na]^+$ *m/z* 396.2 (calcd for $C_{14}H_{23}N_5O_5S$, 373.14). In next step, a mixture of the above hydroxy compound (70 mg, 0.19 mmol), SO_3-NMe_3 (53 mg, 0.38 mmol) and TEA (55 mg, 0.38 mmol) in THF/water (1.5/1.5 mL) was stirred at room temperature overnight. The mixture was concentrated under reduced pressure to leave a residue. The residue was purified by preparative HPLC on an Agilent 10 prep-C18 250×21.2 mm column and lyophilized, followed by resin Dowex-50wx Na^+ exchange using water as elution solvent to give product **6a** (23 mg, 25%, 95.0% purity) as a white solid. ^{1}H NMR (400 MHz, D_2O) δ 1.31-1.43 (m, 1H), 1.50-1.61 (m, 1H), 1.68-1.96 (m, 4H), 2.00-2.11 (m, 2H), 2.64-2.93 (m, 6H, containing Me), 3.41-3.58 (m, 3H), 3.87-4.05 (m, 2H), 5.62 (s, 1H).

^{13}C NMR (100 MHz, D_2O): δ 23.6 (s), 25.8 (s), 26.8 (s), 34.2 (s), 38.5 (s), 40.8 (s), 45.8 (s), 47.1 (s), 47.4 (s), 57.3 (s), 57.8 (s), 117.3 (s), 162.8 (s), 174.6 (s). LC-MS $[M\text{-}Na]^-$ *m/z* 452.1 (calcd for $C_{14}H_{22}N_5NaO_8S_2$, 475.08).

Synthesis of (3R)-N-[((2S,5R)-6-benzyloxy-7-oxo-1,6-diazabicyclo[3.2.1]octan-2-yl)(imino)methyl[-1-(methylsulfonyl)pyrrolidine-3-carboxamide (**5b**): Compound **5b** (90 mg, 40%) as an oil was prepared from (*R*)-1-(methylsulfonyl)pyrrolidine-3-carboxylic acid (193 mg, 1.0 mmol) and **2a** (137 mg, 0.5 mmol) by using the procedure described for **5a**. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.83-2.02 (m, 4H), 2.91 (s, 3H), 3.23-3.54 (m, 9H), 3.89-3.95 (m, 1H), 4.86 (s, 2H), 5.69 (s, 1H), 6.67 (s, 2H), 7.34-7.41 (m, 3H), 7.48-7.53 (m, 2H). LC-MS $[M+Na]^+$ *m/z* 472.2 (calcd for $C_{20}H_{27}N_5O_5S$, 449.17).

*Synthesis of sodium (2S,5R)-2-[N-((R)-1-methylsulfonylpyrrolidine-3-carbonyl)carbamimidoyl]-7-oxo-1,6-diazabicyclo[3.2.1]octan-6-yl sulfate (**6b**):* Hydrogenation of compound **5b** (90 mg, 0.2 mmol) in THF was performed. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.87-2.15 (m, 4H), 2.91 (s, 3H), 3.01-3.12 (m, 4H), 3.22-3.29 (m, 2H), 3.48-3.54 (m, 1H), 3.58-3.62 (m, 2H), 3.83-3.89 (m, 1H), 5.69 (s, 1H), 6.52 (s, 2H), 9.31 (s, 1H). LC-MS $[M+Na]^+$ *m/z* 382.1 (calcd for $C_{13}H_{21}N_5O_5S$, 359.13). The final compound **6b** (37 mg, 50%, 95.1% purity) as a white solid was obtained from hydroxy intermediate (60 mg, 0.16 mmol) and SO_3-pyridine (91 mg, 0.57 mmol) in pyridine (3 mL) by using the similar procedure described for **6a**. ^{1}H NMR (400 MHz, D_2O) δ 1.61-1.70 (m, 1H), 1.80-1.90 (m, 2H), 1.93-2.01 (m, 2H), 2.06-2.13 (m, 1H), 2.82 (s, 3H), 3.15-3.22 (m, 2H), 3.31-3.46 (m, 4H), 3.81-3.90 (m, 1H), 3.92-4.00 (m, 1), 5.54 (s, 1H). ^{13}C NMR (100 MHz, D_2O): δ 26.4 (s), 28.4 (s), 33.2 (s), 40.2 (s), 41.2 (s), 45.3 (s), 47.1 (s), 49.6 (s), 55.9 (s), 57.4 (s), 117.2 (s), 162.8 (s), 173.7 (s). LC-MS $[M\text{-}Na]^-$ *m/z* 438.1 (calcd for $C_{13}H_{20}N_5NaO_8S_2$, 461.07).

*Synthesis of (3S)-1-acetyl-N-[((2S,5R)-6-benzyloxy-7-oxo-1,6-diazabicyclo[3.2.1]octan-2-yl)(imino)methyl]piperidine-3-carboxamide (**5c**):* Compound **5c** (278 mg, 81%) as a pale yellow solid was prepared from (*S*)-1-acetylpiperidine-3-carboxylic acid (215 mg, 1.26 mmol) and **2a** (220 mg, 0.80 mmol) by using the procedure described for **5a**. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.38-1.55 (m, 2H), 1.57-1.77 (m, 3H), 1.79-1.99 (m, 3H), 2.01 (s, 3H), 2.50-2.61 (m, 1H), 2.71-2.89 (m, 1H), 2.96-3.26 (m, 2H), 3.67-4.03 (m, 3H), 4.16-4.32 (m, 1H), 4.74-4.92 (m, 2H), 5.57-5.71 (m, 1H), 6.64-6.86 (m, 2H), 7.31-7.42 (m, 3H), 7.44-7.56 (m, 2H). LC-MS $[M+H]^+$ *m/z* 428.3 (calcd for $C_{22}H_{29}N_5O_4$, 427.22).

*Synthesis of sodium (2S,5R)-2-[N-((S)-1-acetylpiperidine-3-carbonyl)carbamimidoyl]-7-oxo-1,6-diazabicyclo[3.2.1]octan-6-yl sulfate (**6c**)*: Compound **5c** (276 mg, 0.64 mmol) was subjected to hydrogenation in THF. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.43-1.55 (m, 2H), 1.57-1.65 (m, 1H), 1.67-1.93 (m, 4H), 1.94-2.02 (m, 1H), 2.02 (s, 3H), 2.57-2.73 (m, 1H), 2.80-2.90 (m, 1H), 2.99-3.23 (m, 2H), 3.66-3.90 (m, 2H), 4.00-4.12 (m, 1H), 4.18-4.32 (m, 1H), 5.61-5.70 (m, 1H), 6.42-6.48 (m, 2H), 9.26 (s, 1H). LC-MS $[M+H]^+$ *m/z* 338.2 (calcd for $C_{15}H_{23}N_5O_4$, 337.18). The intermediate hydroxy

compound (133 mg, 0.395 mmol) was treated with SO_3-NMe_3 (139 mg, 1.0 mmol) to get the final compound **6c** (160 mg, 97%, 95.2% purity) as white solid. ^{1}H NMR (400 MHz, D_2O): δ 1.45-1.64 (m, 2H), 1.75-1.87 (m, 2H), 1.91-2.03 (m, 1H), 2.08 (s, 1.5H), 2.09 (s, 1.5H), 2.09-2.21 (m, 2H), 2.81-3.10 (m, 3H), 3.29-3.39 (m, 1H), 3.53-3.64 (m, 1H), 3.72-3.84 (m, 1H), 4.04-4.15 (m, 2H), 5.68-5.73 (m, 1H). ^{13}C NMR (100 MHz, D_2O): δ 20.3 (s), 23.1 (s), 26.3 (s), 37.9 (s), 40.3 (s), 42.2 (s), 43.7 (s), 46.9 (s), 48.4 (s), 57.2 (s), 65.7 (s), 117.4 (s), 162.8 (s), 172.2 (s), 174.6 (s). LC-MS $[M\text{-}Na]^-$ *m/z* 416.2. (calcd for $C_{15}H_{22}NaN_5O_7S$, 439.11).

Antibacterial activity and synergistic activity

A number of bacterial species with different β-lactamases (see Table 1 of the main text), *i.e.*, *E. coli* clinical isolate; *E. coli* 8739; *K. pneumoniae* clinical isolate; *K. pneumoniae* 700603; *E. cloacae* clinical isolate; *E. cloacae* 700323; *A. baumannii* clinical isolate; *A. baumannii* 19606; *P. aeruginosa* clinical isolate and *P. aeruginosa* 9027, were used as test bacterial species. Meropenem (MER) alone and as a combination with avibactam as well as with synthesized compounds **3a-f, 6a-c** were analyzed for antimicrobial activity by determing minimum inhibitory concentration (MIC, mg/L). For comparison MIC values for avibactam and newly synthesized compounds **3a-f, 6a-c** without meropenem were also determined. A standard procedure was employed for these studies using the broth microdilution method according to the guidelines of the Clinical Laboratories and Stansards Insitute [M. A. Wikler, *Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically; Approved Standard*, Clinical and Laboratory Standards Institute Wayne, Pa., USA, **2009**]. In a typical experiment, meropenem as a test antibiotic compound was dissolved in DMSO and diluted in microbial growth medium (Mueller-Hinton Broth II, cation adjusted) to a final concention range of 0.125-64 mg/L in serial two-fold dilution. In all cases the final DMSO concentraion was less than 0.5%. Bacteria were added to 96-well microtitre plates containing the serial two-fold dilutions of the compoumds; the final cell density was appoximately 5×10^5 colony forming units/mL (CFU/mL). Plates were incubated at 37 ºC for 18-24 hours and read visually. The MIC of the test compound that inhibited visible growth of the bacteria was recorded. The same assay conditions were used when the compounds **3a-f, 6a-c** and avibactam (as control) alone and as a combination with test meropenem as an antibiotic compound were tested for MIC (mg/L). While meropenem was serially diluted as descrribed above, a constant concentration of inhibitor compounds **3a-f, 6a-c** of 4 mg/L was used.

NMR Spectra of key intermediates & final compounds

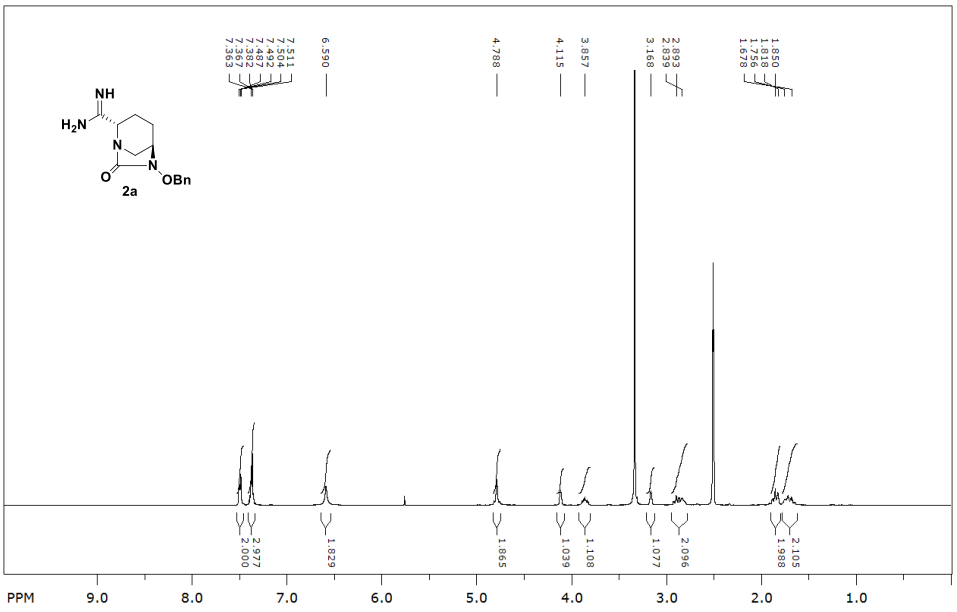

Figure S1. ^{1}H NMR spectrum of compound **2a** in DMSO-d_6

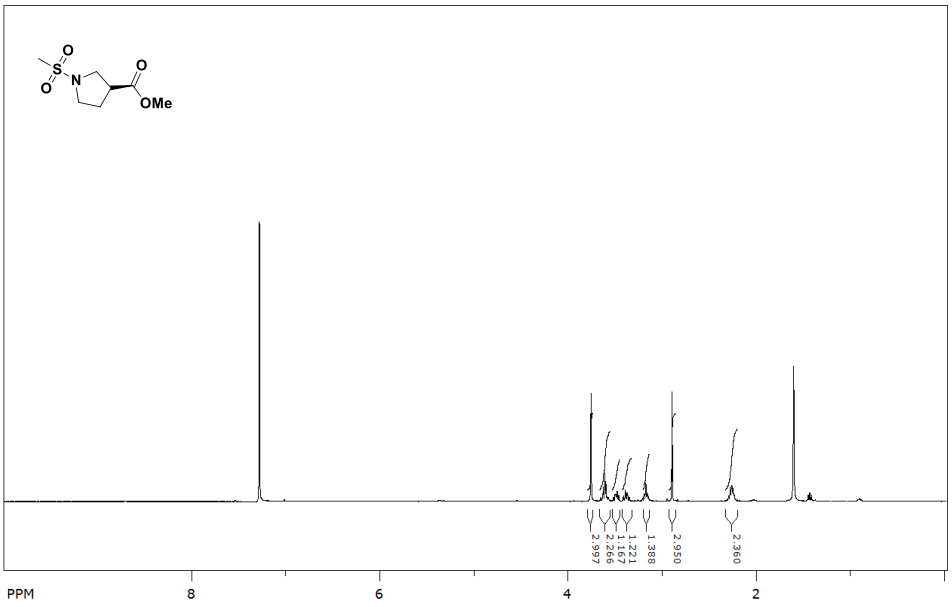

Figure S2. ^{1}H NMR spectrum of (R)-methyl 1-(methylsulfonyl)pyrrolidine-3-carboxylate $CDCl_3$

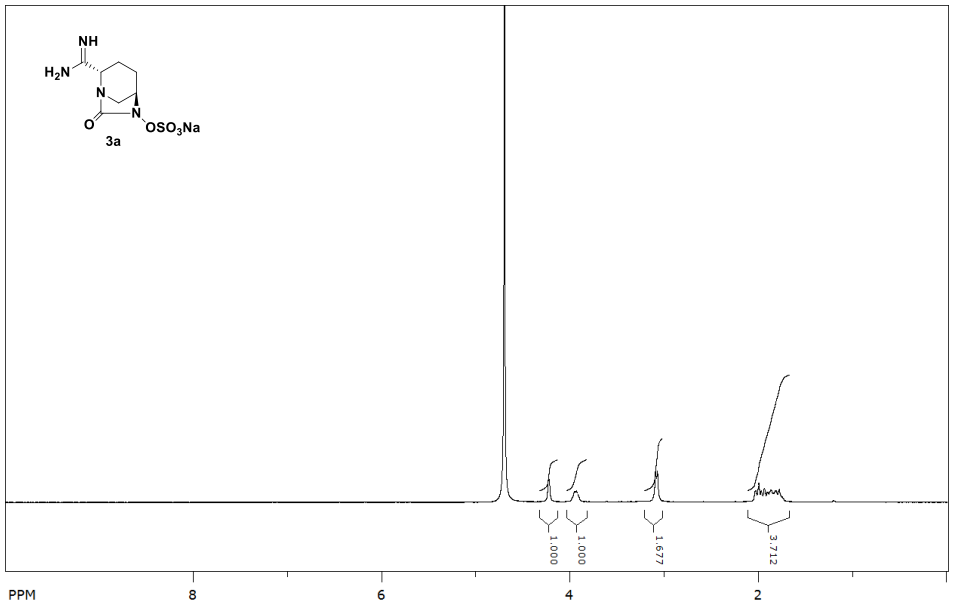

Figure S3-1. ^{1}H NMR spectrum of compound **7a** in D_2O

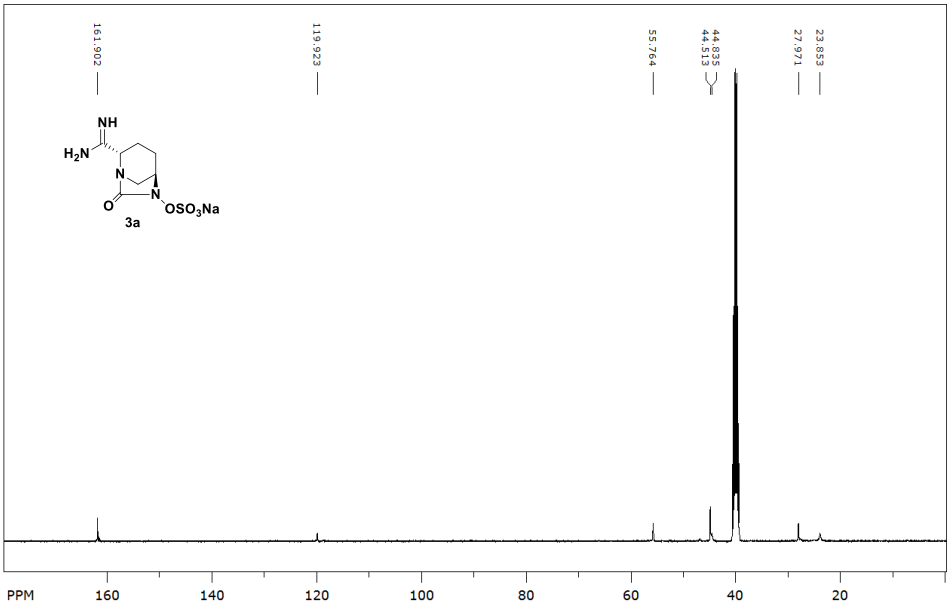

Figure S3-2. ^{13}C NMR spectrum of compound **7a** in DMSO-d_6

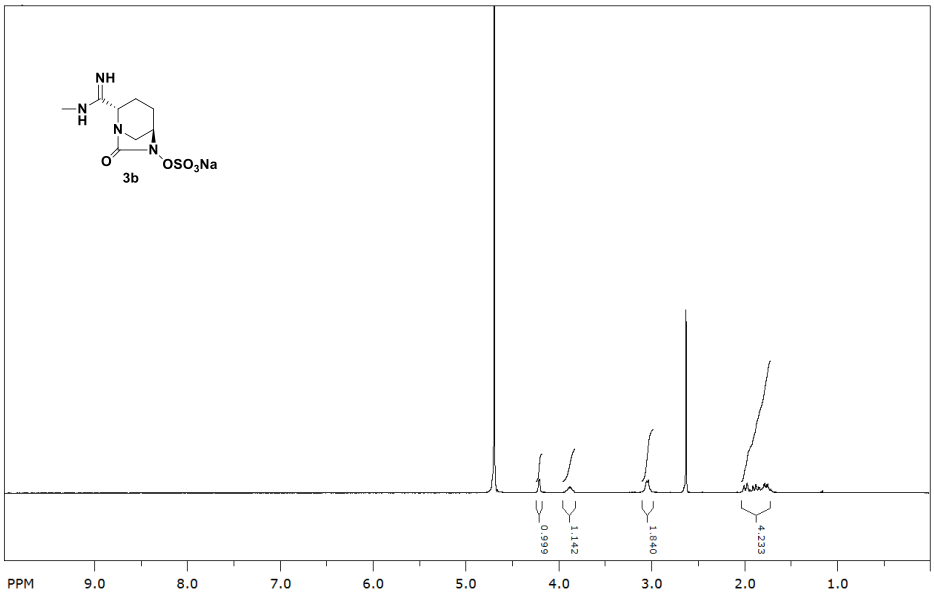

Figure S4-1. ^{1}H NMR spectrum of compound **7b** in D_2O

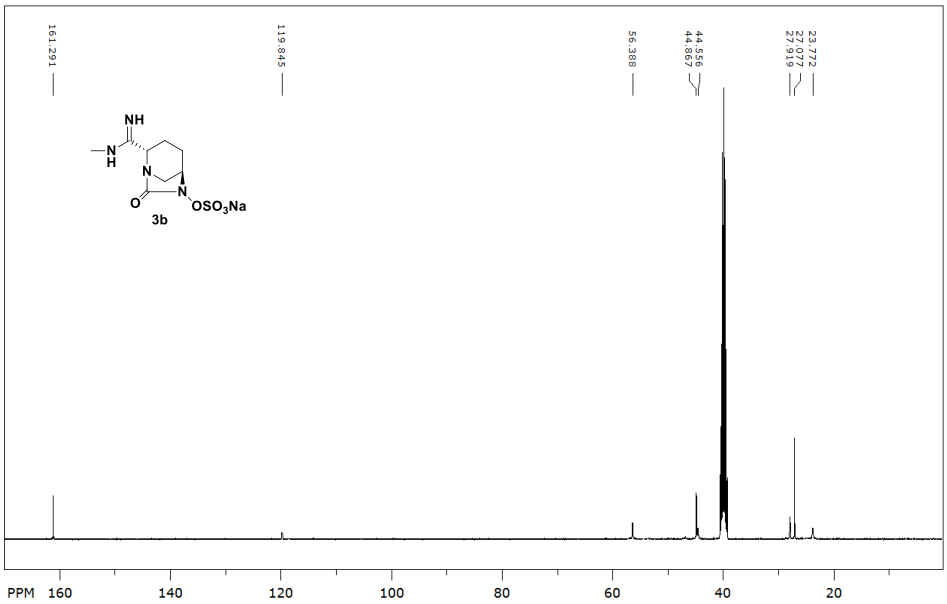

Figure S4-2. ^{13}C NMR spectrum of compound **7b** in DMSO-d_6

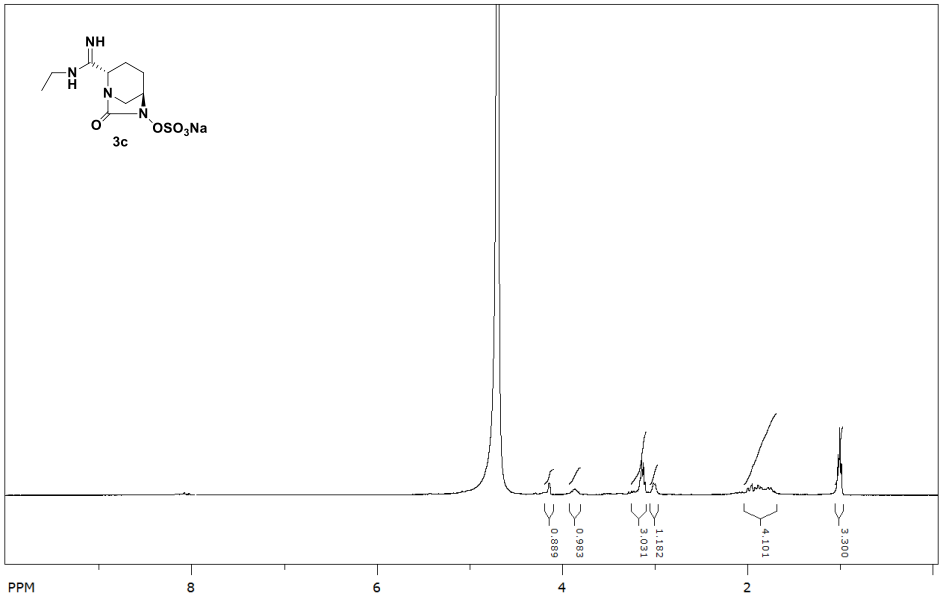

Figure S5-1. ^{1}H NMR spectrum of compound **7c** in D_2O

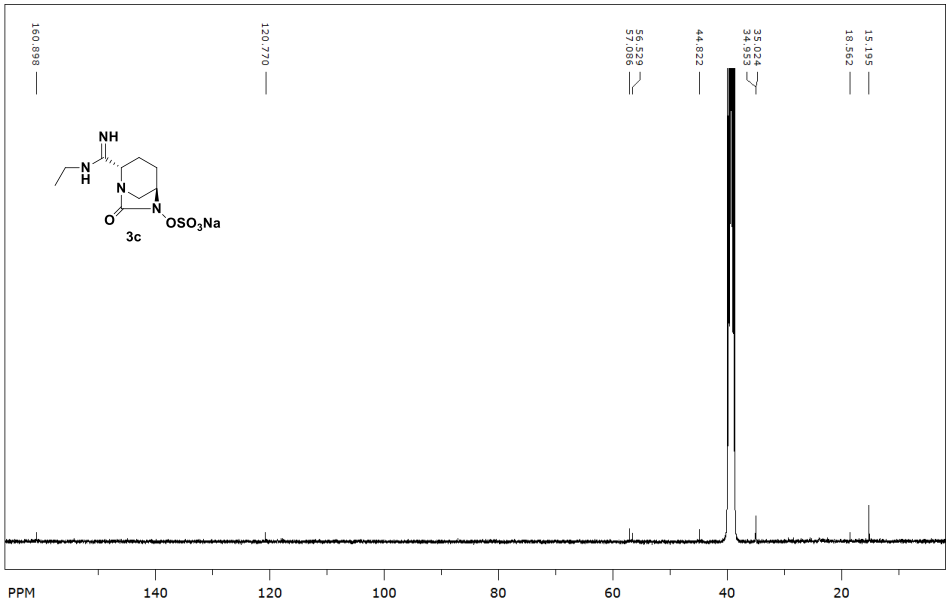

Figure S5-2. ^{13}C NMR spectrum of compound **7c** in DMSO-d_6 with 3 drops of D_2O

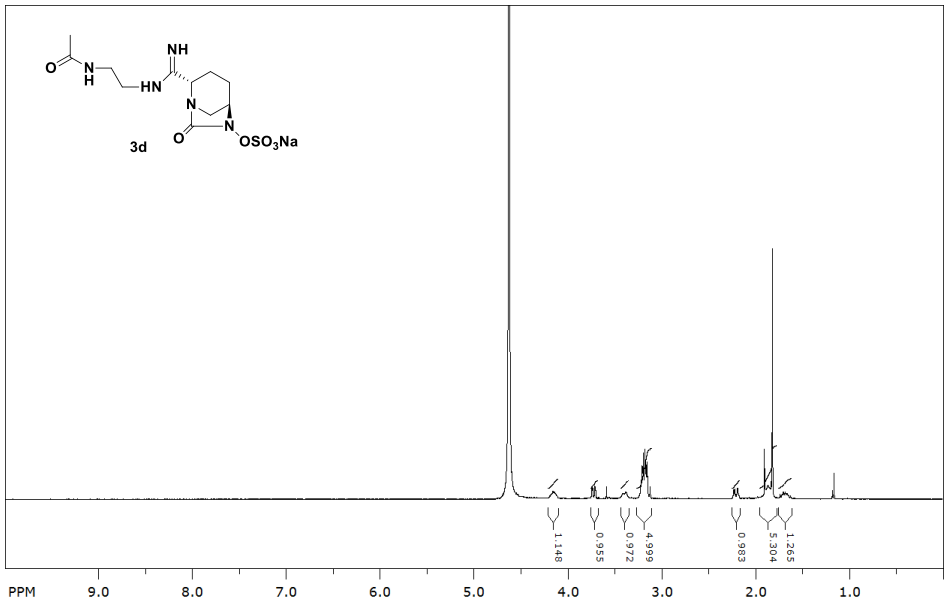

Figure S6-1. ^{1}H NMR spectrum of compound **7d** in D_2O

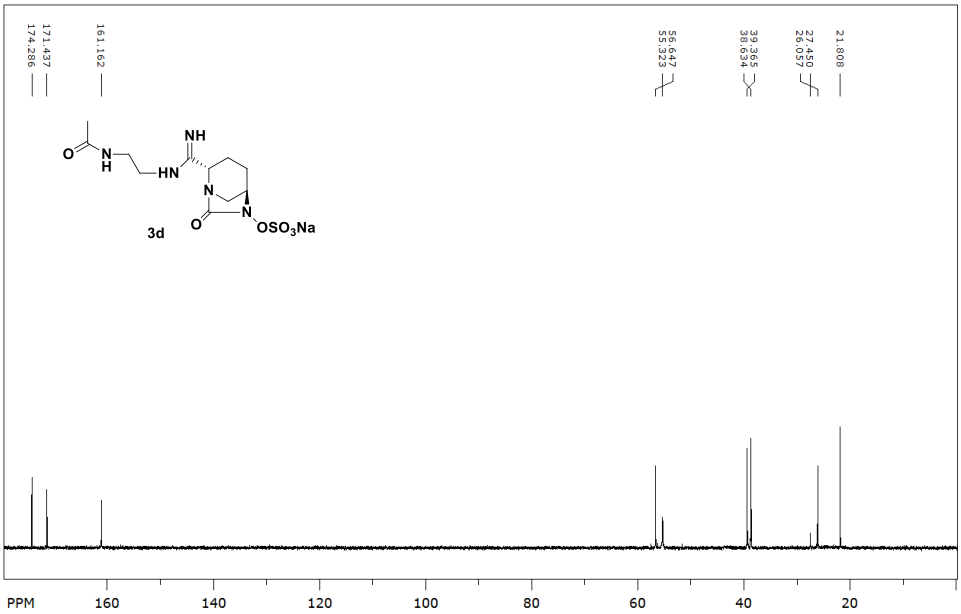

Figure S6-2. ^{13}C NMR spectrum of compound **7d** in D_2O

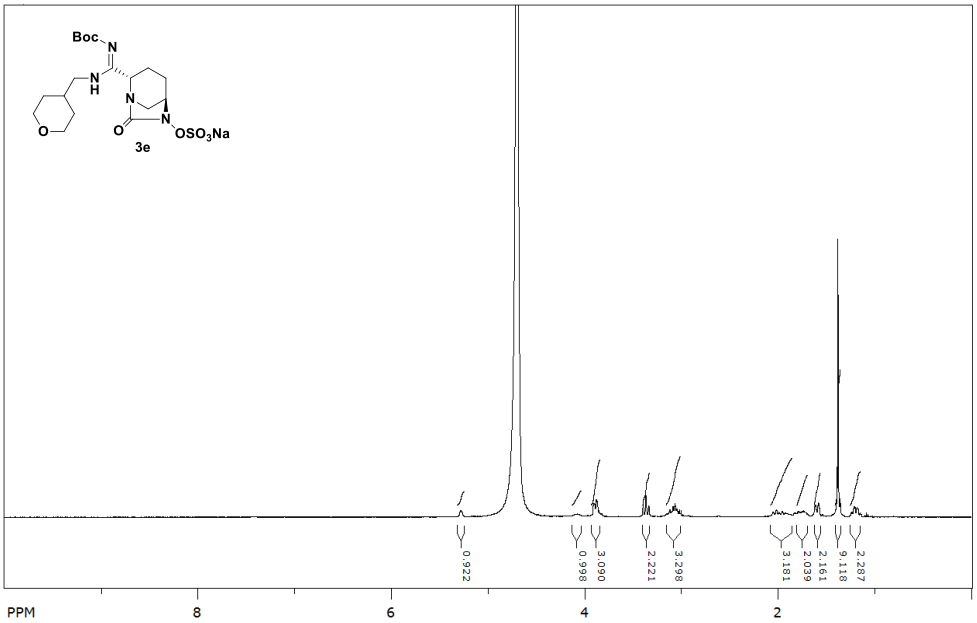

Figure S7-1. ^{1}H NMR spectrum of compound **7e** in D_2O

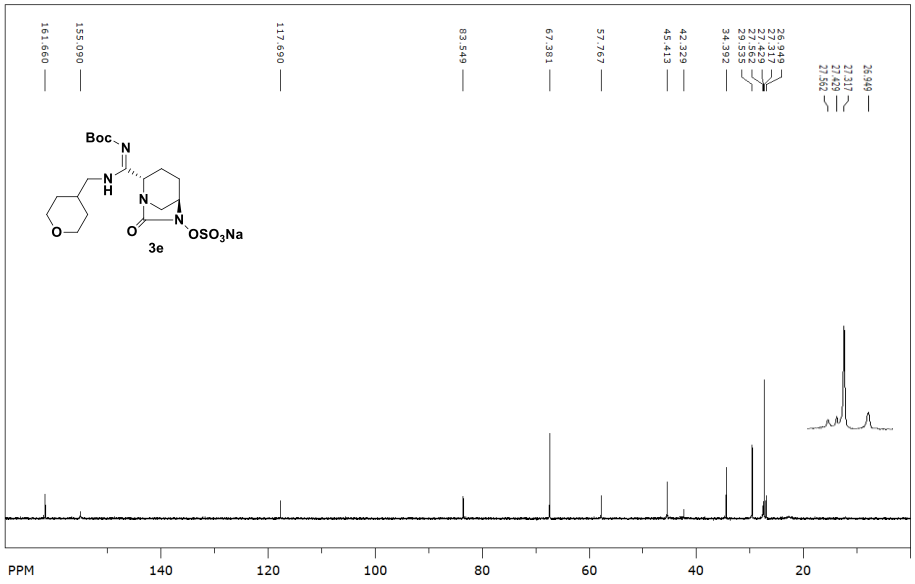

Figure S7-2. ^{13}C NMR spectrum of compound **7e** in D_2O

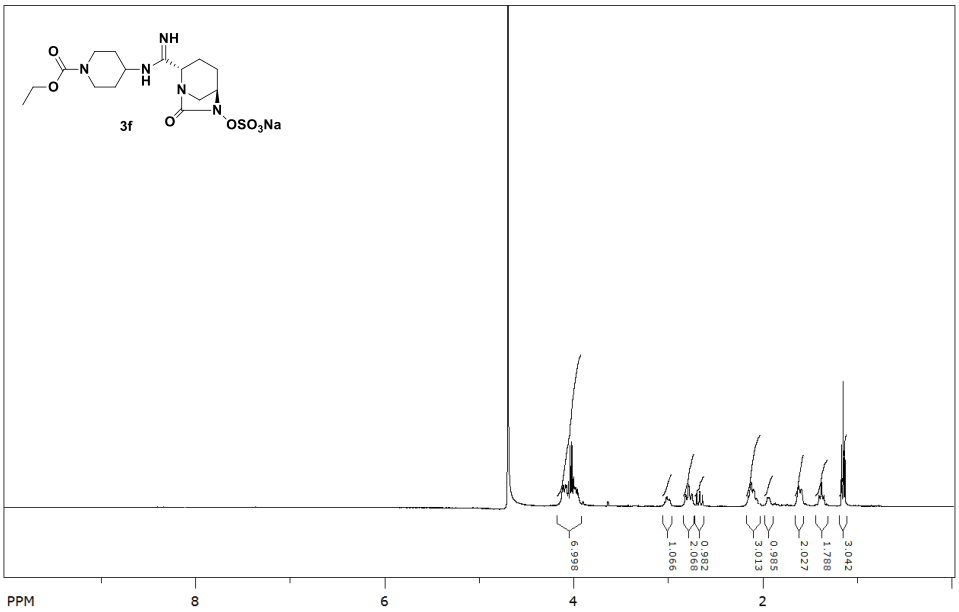

Figure S8-1. ^{1}H NMR spectrum of compound **7f** in D_2O

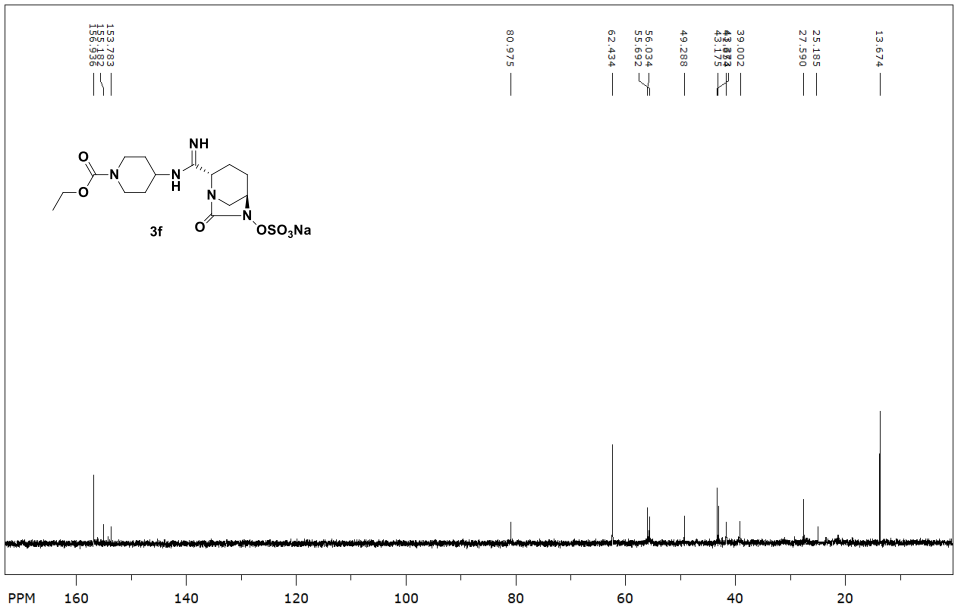

Figure S8-2. ^{13}C NMR spectrum of compound **7f** in D_2O

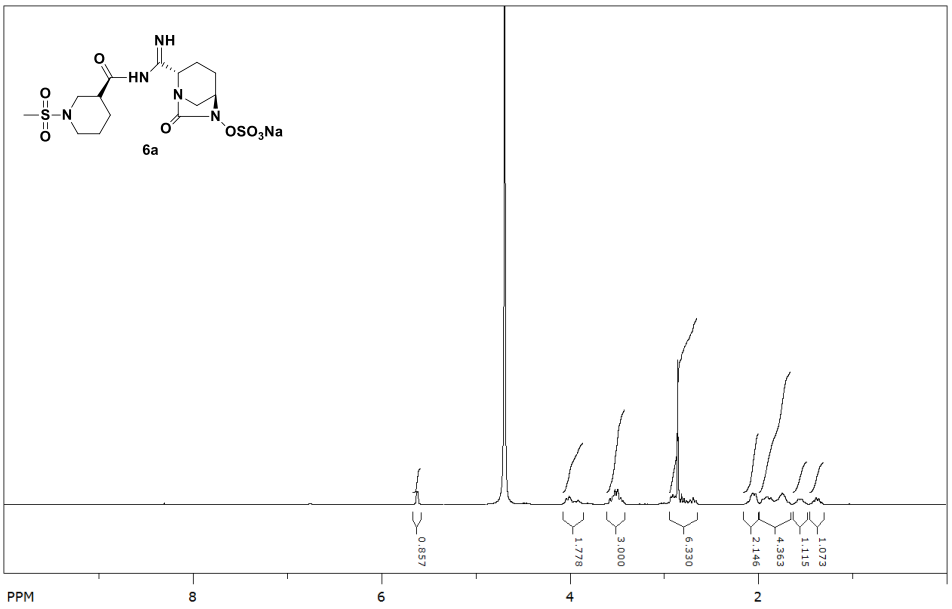

Figure S9-1. ^{1}H NMR spectrum of compound **7g** in DMSO-d_6

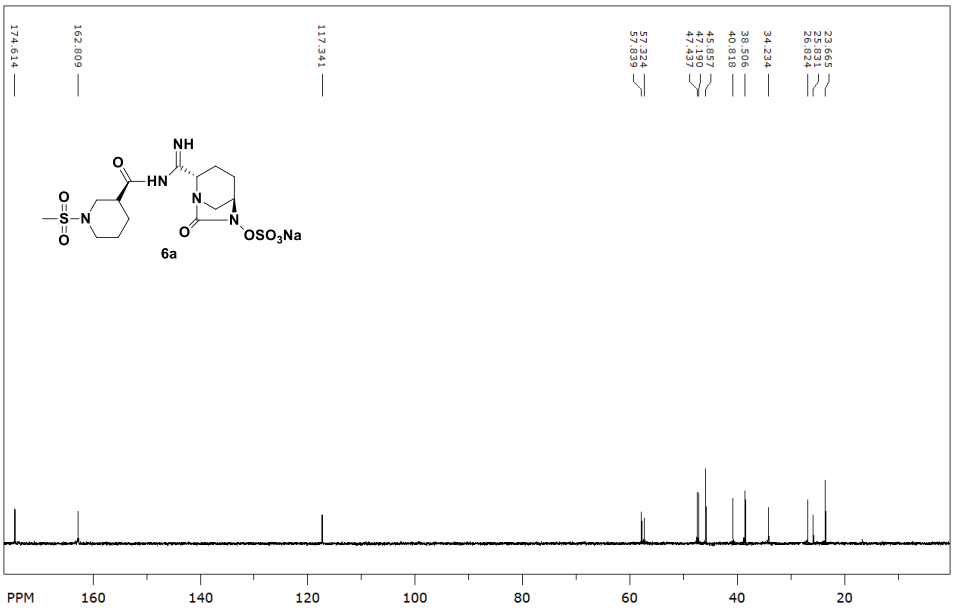

Figure S9-2. ^{13}C NMR spectrum of compound **7g** in D_2O

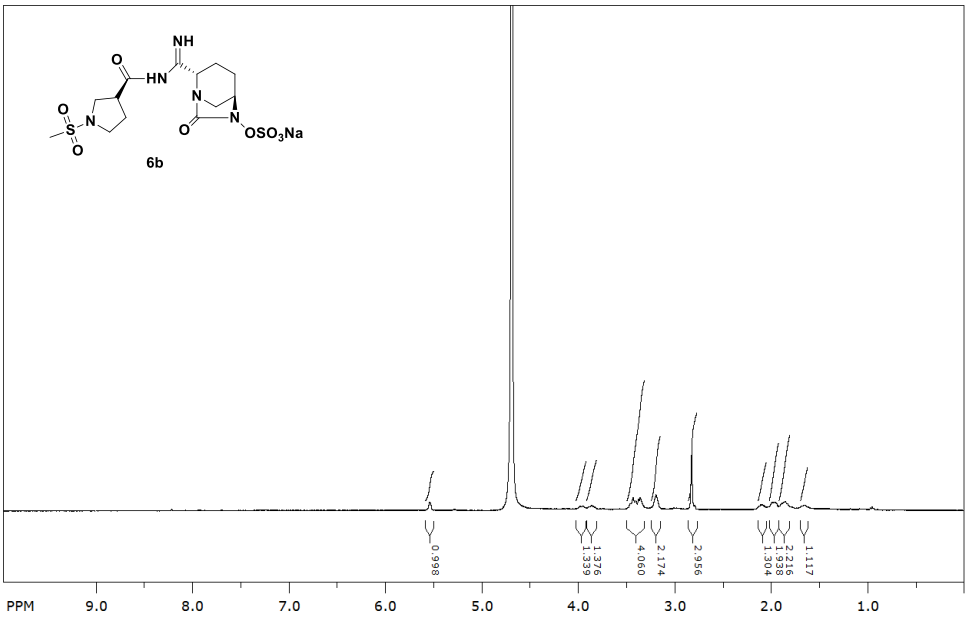

Figure S10-1. ^{1}H NMR spectrum of compound **7h** in DMSO-d_6

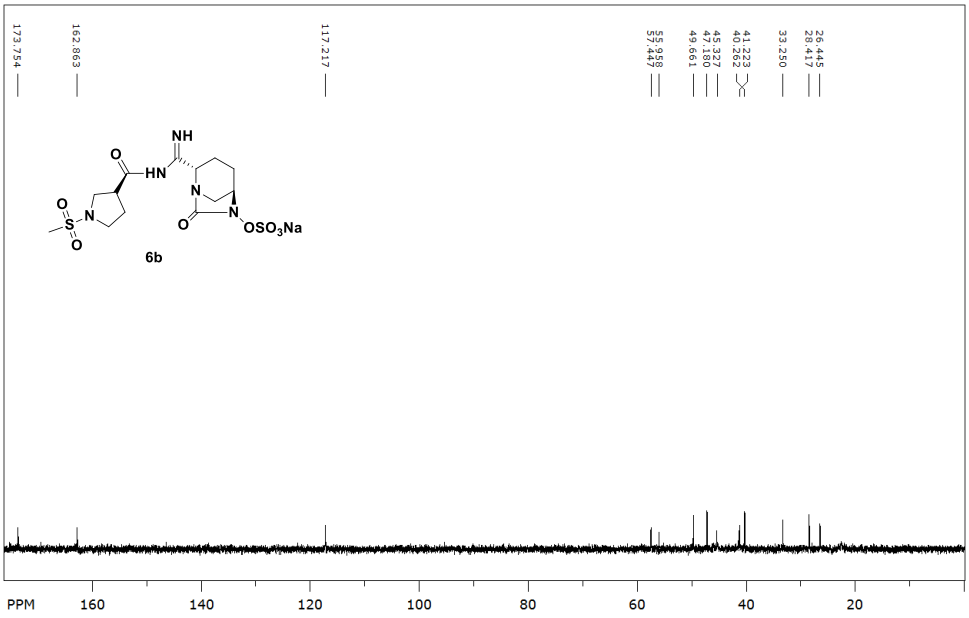

Figure S10-2. ^{13}C NMR spectrum of compound **7h** in D_2O

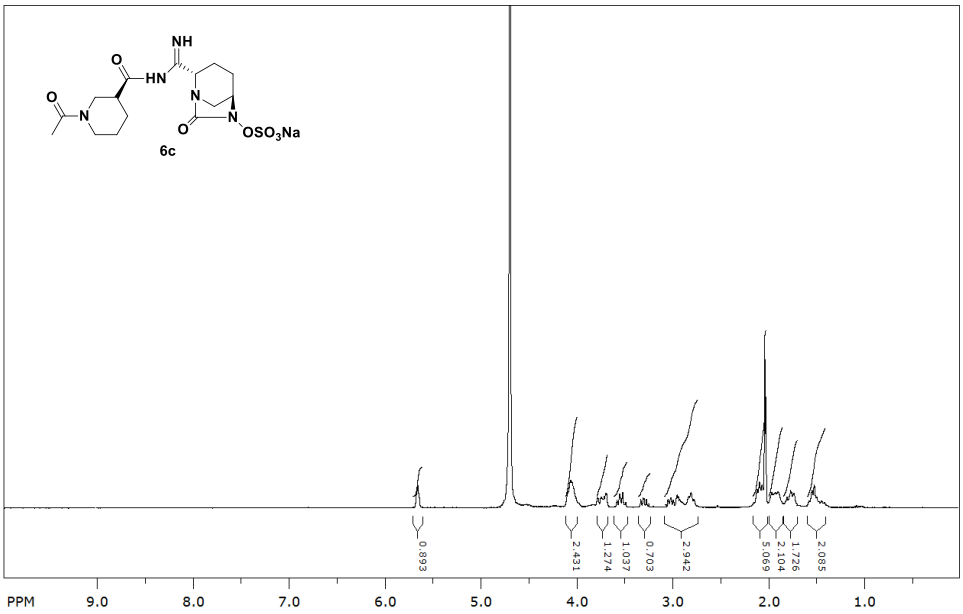

Figure S11-1. ^{1}H NMR spectrum of compound **7i** in D_2O

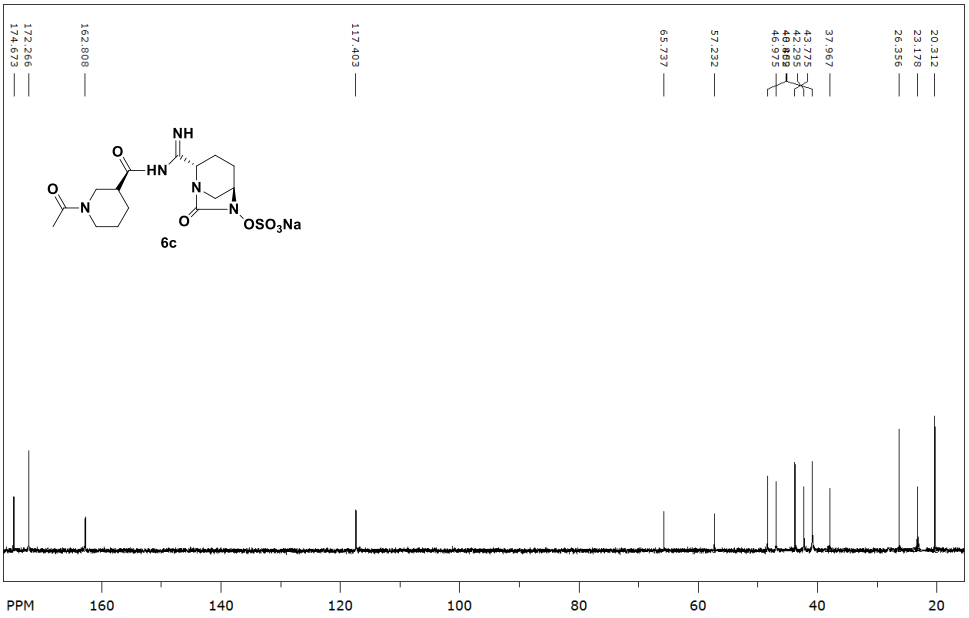

Figure S11-2. ^{13}C NMR spectrum of compound **7i** in D_2O

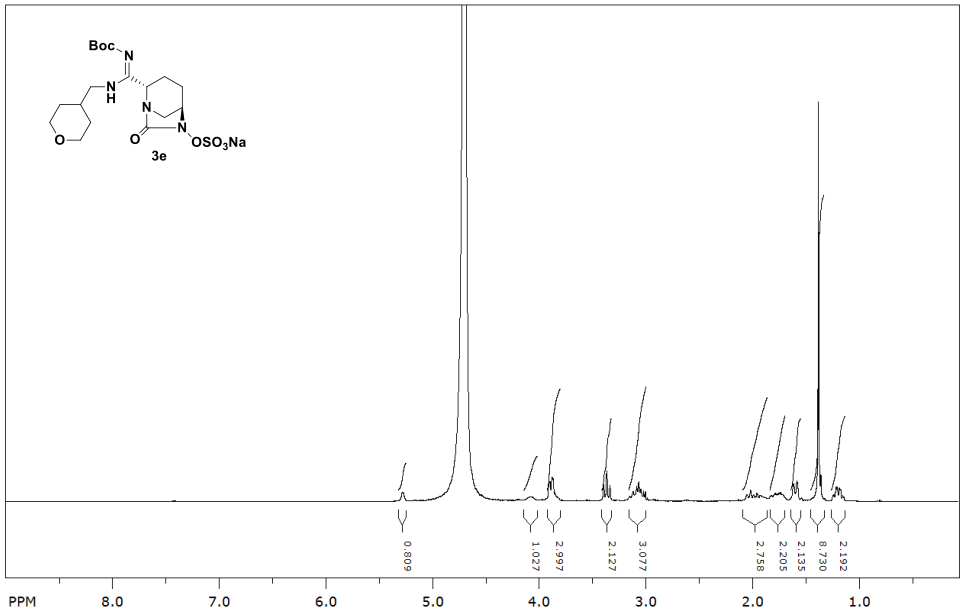

Figure S12-1. ^{1}H NMR spectrum of compound **7e** in D_2O

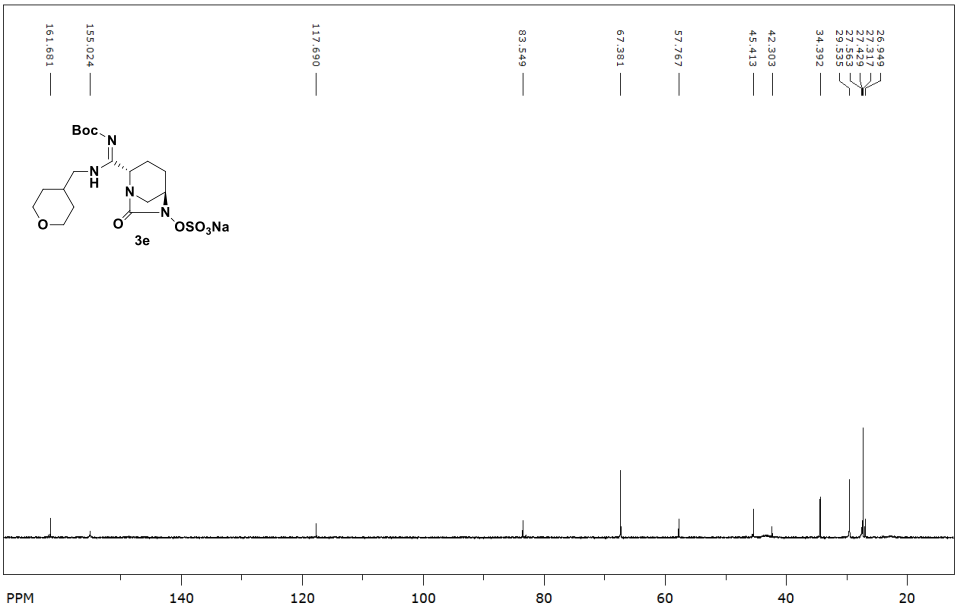

Figure S12-2. ^{13}C NMR spectrum of compound **7e** in D_2O