Structure-Activity Relationships of the MEPicides: *N*-acyl and *O*-linked Analogs of FR900098 as Inhibitors of Dxr from *Mycobacterium tuberculosis* and *Yersinia pestis*

SUPPLEMENTARY INFORMATION

Géraldine San Jose, Emily R. Jackson, Amanda Haymond, Chinchu Johny, Rachel L. Edwards, Xu Wang, R. Carl Brothers, Emma K. Edelstein, Audrey R. Odom, Helena I. Boshoff, Robin D. Couch, Cynthia S. Dowd

Diethyl 3-[N-(benzyloxy)pentanamido]propyl phosphonate (6a): To a stirred solution of **5** (0.203 g, 0.66 mmol) and triethylamine (0.2 mL, 0.14 g, 1.3 mmol) in CH_2Cl_2 (3 mL) at room temperature and under argon, was added valeryl chloride (0.1 mL, 0.097 g, 0.8 mmol) dropwise. The reaction mixture was stirred at room temperature overnight. The reaction mixture was extracted with water and brine. The aqueous layer was back extracted with CH_2Cl_2 (x3) and dried over anhydrous magnesium sulfate. The magnesium sulfate was filtered from the organic layer and the solvent was removed under reduced pressure. The crude residue was purified using an Isolera Flash Chromatography (EtOAc/CH_2Cl_2 100% EtOAc) to give **6a** (0.207 g, 0.54 mmol, 81.4%) as a yellow oil. ^{1}H NMR ($CDCl_3$, 200MHz), δ (ppm): 1.24 - 1.37 (m, 2H), 1.30 (t, J = 6.2 Hz, 6H), 1.60 - 1.75 (m, 2H), 1.48 - 2.03 (m, 6H), 2.39 (t, J = 7.6, 2H), 3.71 (t, J = 6.8 Hz, 2H), 4.08 (quin, J = 7.3 Hz, 4H), 4.81 (s, 2H), 7.38 (s, $5H_{arom}$). LCMS (ESI^+) *m/z* 486.2 (M + H).

Diethyl 3-[N-(benzyloxy)heptanamido]propyl phosphonate (6b): To a stirred solution of **5** (0.10 g, 0.34 mmol) and triethylamine (0.07 mL, 0.05 g, 0.47 mmol) in CH_2Cl_2 (3 mL) at room temperature and under argon, was added heptanoyl chloride (0.06 mL, 0.06 g, 0.4 mmol) dropwise. The reaction mixture stirred at room temperature for 4 h. The reaction mixture was extracted with water and brine. The aqueous layer was back extracted with CH_2Cl_2 (x3) and dried over anhydrous magnesium sulfate. The magnesium sulfate was filtered from the organic layer and the solvent was removed under reduced pressure. The crude residue was purified using an Isolera Flash Chromatography System (EtOAc) to give **6b** (0.072 g, 0.17 mmol, 52.1%) as a light yellow oil. ^{1}H NMR ($CDCl_3$, 200MHz), δ (ppm): 1.30 (t, J = 7.0 Hz, 10H), 1.48 - 1.83 (m, 6H), 1.83 - 2.06 (m, 2H), 2.39 (t, 2H, J = 7.6 Hz), 3.71 (t, J = 6.8 Hz, 2H), 4.08 (quin, J = 7.2 Hz, 4H), 4.81 (s, 2H), 7.38 (s, $5H_{arom}$). LCMS (ESI^+) *m/z* 414.2 (M + H).

Diethyl 3-[N-(benzyloxy)-2,2-dimethylpropanamido]propyl phosphonate (6c): To a stirred solution of **5** (0.149 g, 0.5 mmol) and triethylamine (0.15 mL, 0.01 g, 1 mmol) in CH_2Cl_2 (3 mL) at room temperature and under argon, was added trimethyl acetyl chloride (0.074 mL, 0.072 g, 0.59 mmol) dropwise. The reaction mixture was stirred at room temperature overnight. The reaction mixture was extracted with water and brine. The aqueous layer was back extracted with CH_2Cl_2 (x3) and dried over anhydrous magnesium sulfate. The magnesium sulfate was filtered from the organic layer and the solvent was removed under reduced pressure. The crude residue was purified using an Isolera Flash Chromatography System (96 CH_2Cl_2: 4 MeOH) to give **6c** (0.188 g, 0.49 mmol, 98.7%) as a yellow oil. ^{1}H NMR ($CDCl_3$, 200MHz), δ (ppm): 1.23 - 1.34 (m, 9H), 1.23 - 1.34 (m, 6H), 3.83 (t, J = 6.8 Hz, 2H), 4.09 (quin, J = 7.3 Hz, 4H), 4.64 (s, 2H), 7.0 - 7.1 (m, $2H_{arom}$), 7.19 - 7.34 (m, $2H_{arom}$), 7.34 - 7.49 (m, $4H_{arom}$), 7.38 (s, $5H_{arom}$). LCMS (ESI^+) *m/z* 386.2 (M + H).

Diethyl 3-[N-(benzyloxy)-3-cyclohexylpropanamido]propyl phosphonate (6d): To a stirred solution of **5** (0.10 g, 0.34 mmol) and triethylamine (0.07 mL, 0.05 g, 0.47 mmol) in CH_2Cl_2 (3 mL) at room temperature and under argon, was added 3-cyclohexylpropionyl chloride (0.069 g, 0.39 mmol) dropwise. The reaction mixture was stirred at room temperature for 4 h. The reaction mixture was extracted with water and brine. The aqueous layer was back extracted with CH_2Cl_2 (x3) and dried over anhydrous

magnesium sulfate. The magnesium sulfate was filtered from the organic layer and the solvent was removed under reduced pressure. The crude residue was purified using an Isolera Flash Chromatography System (EtOAc) to give **6d** (0.074 g, 0.17 mmol, 50.5%) as a light yellow oil. ^{1}H NMR ($CDCl_3$, 200MHz), δ (ppm): 0.76 - 1.07 (m, 2H), 1.07 - 1.21 (m, 2H), 1.31 (t, *J* = 7.0 Hz, 6H), 1.4 - 1.84 (m, 10H), 1.84 - 2.04 (m, 2H), 2.39 (t, *J* = 7.8 Hz, 2H), 3.71 (t, *J* = 6.8 Hz, 2H), 4.08 (quin, *J* = 7.0 Hz, 4H), 4.81 (s, 2H), 7.38 (s, $5H_{arom}$). LCMS (ESI^+) *m/z* 440.2 (M + H).

Diethyl 3-[N-(benzyloxy)-1-phenylformamido]propyl phosphonate (6e): To a stirred solution of **5** (0.153 g, 0.5 mmol) and triethylamine (0.15 mL, 0.11 g, 0.6 mmol) in CH_2Cl_2 (3 mL) was added benzoyl chloride (0.15 mL, 0.085 g, 0.6 mmol) dropwise under argon and at room temperature. The reaction mixture was stirred at room temperature overnight. The reaction mixture was extracted with water and brine. The aqueous layer was back extracted with CH_2Cl_2 (x3) and dried over anhydrous magnesium sulfate. The magnesium sulfate was filtered from the organic layer and the solvent was removed under reduced pressure. The crude residue was purified using an Isolera Flash Chromatography System (98 EtOAc: 2 MeOH) to give **6e** (0.194 g, 0.48 mmol, 95.7%) as a yellow oil. ^{1}H NMR ($CDCl_3$, 200MHz), δ(ppm): 1.30 (t, *J* = 7.0 Hz, 6H), 1.66 - 1.94 (m, 2H), 1.94 - 2.15 (m, 2H), 3.83 (t, *J* = 6.8 Hz, 2H), 4.09 (quin, *J* = 7.3 Hz, 4H), 4.64 (s, 2H), 7.0 - 7.1 (m, $2H_{arom}$), 7.19 - 7.34 (m, $2H_{arom}$), 7.34 - 7.49 (m, $4H_{arom}$), 7.63 (d, *J* = 7.8 Hz, $2H_{arom}$). LCMS (ESI^+) *m/z* 406.1 (M + H).

Diethyl 3-[N-(benzyloxy)-1-(4-methylphenyl)formamido]propyl phosphonate (6f): To a stirred solution of **5** (0.197 g, 0.66 mmol) and triethylamine (0.2 mL, 0.14 g, 1.3 mmol) in CH_2Cl_2 (3 mL) was added toluoyl chloride (0.11 mL, 0.123 g, 0.8 mmol) dropwise under argon at room temperature. The reaction mixture was stirred at room temperature overnight. The reaction mixture was washed successively with water and brine. The aqueous layer was back extracted with CH_2Cl_2. The organic fractions were separated, dried over anhydrous magnesium sulfate and filtered. The solvent was removed under reduced pressure. The crude residue was purified by silica gel column chromatography (75 EtOAc: 25 CH_2Cl_2) to give **6f** (0.178 g, 0.42 mmol, 64.3%) as a yellow oil. ^{1}H NMR ($CDCl_3$, 200MHz), δ (ppm): 1.29 (t, *J* = 7.0 Hz, 6H), 1.68 - 1.91 (m, 2H), 1.91 - 2.13 (m, 2H), 2.40 (s, 3H), 3.80 (t, *J* = 6.8 Hz, 2H), 4.07 (quin, *J* = 7.3 Hz, 4H), 4.65 (s, $2H_{arom}$), 7.07 - 7.34 (m, $7H_{arom}$), 7.57 (d, *J* = 8.2 Hz, $2H_{arom}$). LCMS (ESI^+) *m/z* 420.1 (M + H).

Diethyl 3-(N-(benzyloxy)-3-phenylpropanamido)propyl phosphonate (6g): To a stirred solution of **5** (1.01 g, 3.36 mmol) and triethylamine (0.37 g, 3.70 mmol) in CH_2Cl_2 (15 mL) and under argon, was added hydrocinnamoyl chloride (0.63 g, 3.76 mmol) dropwise at 0°C. The resulting mixture was warmed to room temperature and stirred overnight. The reaction was monitored by TLC. The reaction mixture was washed successively with water, saturated $NaHCO_3$ (aq) and water. The organic fractions were separated, dried over anhydrous magnesium sulfate and filtered. The solvent was removed under reduced pressure. The crude product was purified using an Isolera Flash Chromatography System (EtOAc/MeOH 1-5% MeOH) to give **6g** (yield not calculated; ~69 – 89%) as an oil. ^{1}H NMR ($CDCl_3$, 200MHz), δ (ppm): 1.31 (t, *J* = 7.1 Hz, 6H),

1.64-1.93 (m, 4H), 2.71 (t, J = 7.8 Hz, 2H), 2.93 (t, J = 7.4 Hz, 2H), 3.71 (t, J = 6.8 Hz, 2H), 4.0 - 4.18 (m, 4H), 4.72 (s, 2H), 7.16 - 7.40 (m, $5H_{arom}$). LCMS (ESI^+) *m/z* 434.2 (M + H).

Diethyl 3-(N-hydroxy-3-phenylpropanamido)propyl phosphonate (6h): To a stirred solution of **5** (0.62 g, 2.00 mmol) and triethylamine (0.22 g, 2.14 mmol) in CH_2Cl_2 (15 mL) and under argon, was added 4-phenylbutryl chloride (0.4 mL, 0.41 g, 2.25 mmol) dropwise at 0°C. The resulting mixture was warmed to room temperature and stirred overnight. The reaction was monitored by TLC. The reaction mixture was washed successively with water, saturated $NaHCO_3$ (aq) and water. The organic fractions were separated, dried over anhydrous magnesium sulfate and filtered. The solvent was removed under reduced pressure. The crude product was purified using an Isolera Flash Chromatography System (EtOAc/MeOH; 1-5% MeOH) to give **6h** (0.69 g, 1.50 mmol, 75%) as a light yellow oil. ^1H NMR ($CDCl_3$, 200MHz), δ (ppm): 1.30 (t, J = 7.0 Hz, 6H), 1.67 - 2.04 (m, 6H), 2.41 (t, J = 7.4 Hz, 2H), 2.65 (t, J = 7.5 Hz, 2H), 3.72 (t, J = 7.0 Hz, 2H), 4.00 - 4.19 (m, 4H), 4.74 (s, 2H), 7.16 - 7.40 (s, $5H_{arom}$). LCMS (ESI^+) *m/z* 448.1 (M + H).

Diethyl 3-[N-(benzyloxy)-3-(4-methoxyphenyl)propanamido]propyl phosphonate (6i): To a stirred solution of **5** (0.25 g, 0.83 mmol) and triethylamine (0.24 mL, 0.18 g, 1.6 mmol) in CH_2Cl_2 (3 mL) at room temperature and under argon, was added 3-(4-methoxyphenyl)propionyl chloride (0.198 g, 1.0 mmol) dropwise. The reaction mixture was stirred at room temperature for 4 h. The reaction mixture was extracted with water and brine. The aqueous layer was back extracted with CH_2Cl_2 (x3) and dried over anhydrous magnesium sulfate. The magnesium sulfate was filtered from the organic layer and the solvent was removed under reduced pressure. The crude residue was purified using an Isolera Flash Chromatography System (EtOAc) to give **6i** (0.281 g, 0.61 mmol, 72.9%) as a light yellow oil. ^1H NMR ($CDCl_3$, 200MHz), δ (ppm): 1.30 (t, J = 7.0 Hz, 6H), 1.65 - 1.81 (m, 2H), 1.81 - 2.01 (m, 2H), 2.67 (t, J = 7.0 Hz, 2H), 2.87 (t, J = 7.2 Hz, 2H), 3.70 (t, J = 6.6 Hz, 2H), 3.78 (s, 3H), 4.07 (quin, J = 7.2 Hz, 4H), 6.82 (d, J = 8.6, 2H), 4.72 (s, 2H), 7.09 (d, J = 9Hz, 2H), 7.29 - 7.41 (m, $5H_{arom}$). LCMS (ESI^+) *m/z* 464.2 (M + H).

Diethyl 3-[(2)-N-(benzyloxy)-3-[3-(trifluoromethyl)phenyl]prop-2-enamido]propyl phosphonate (6j): To a stirred solution of **5** (0.2 g, 0.66 mmol) and triethylamine (0.14 mL, 0.1 g, 0.95 mmol) in CH_2Cl_2 (5 mL) at room temperature and under argon, was added trans-3-(trifluoromethyl)cinnamoyl chloride (0.185 g, 0.79 mmol) dropwise. The reaction mixture was stirred at room temperature overnight. The reaction mixture was extracted with water and brine. The aqueous layer was back extracted with CH_2Cl_2 (x3) and dried over anhydrous magnesium sulfate. The magnesium sulfate was filtered from the organic layer and the solvent was removed under reduced pressure. The crude residue was purified using an Isolera Flash Chromatography System (20 CH_2Cl_2: 80 EtOAc) to give **6j** (0.114 g, 0.21 mmol, 32%) as a light yellow oil. ^1H NMR ($CDCl_3$, 200MHz), δ (ppm): 1.32 (t, J = 7.1 Hz, 6H), 1.64 - 1.89 (m, 2H), 1.89 - 2.11 (m, 2H), 4.09 (quin, J = 7.2 Hz, 4H), 4.89 (s, 2H), 6.97 (d, J = 15.8 Hz, 1H), 7.29 - 7.69 (m, $10H_{arom}$). LCMS (ESI^+) *m/z* 500.2 (M + H).

Diethyl 3-[(2)-N-(benzyloxy)-3-(4-nitrophenyl)prop-2-enamido]propyl phosphonate (6k): To a stirred solution of **5** (0.205 g, 0.66 mmol) and triethylamine (0.19 mL, 0.14 g, 1.3 mmol) in CH_2Cl_2 (5 mL) at room temperature and under argon, was added trans-4-nitrocinnamoyl chloride (0.167 g, 0.79 mmol) dropwise. The reaction mixture was stirred at room temperature overnight. The reaction mixture was extracted with water and brine. The aqueous layer was back extracted with CH_2Cl_2 (x3) and dried over anhydrous magnesium sulfate. The magnesium sulfate was filtered from the organic layer and the solvent was removed under reduced pressure. The crude residue was purified using an Isolera Flash Chromatography System (EtOAc) to give **6k** (0.106 g, 0.22 mmol, 33.8%) as a yellow oil. ^{1}H NMR ($CDCl_3$, 200MHz), δ (ppm): 1.31 (t, J = 7.0 Hz, 6H), 1.51 - 1.67 (m, 2H), 1.67 - 1.94 (m, 2H), 3.87 (t, J = 7.0 Hz, 2H), 4.09 (quin, J = 7.1 Hz, 4H), 7.01 (d, J = 15.6 Hz, 2H), 4.9 (s, 2H), 7.37 (s, 5H_{arom}), 7.52 - 7.86 (m, 3H_{arom}), 8.21 (d, J = 8.6 Hz, 2H_{arom}). LCMS (ESI$^+$) *m/z* 477.1 (M + H).

Diethyl 3-[N-(benzyloxy)-2-(4-chlorophenoxy)acetamido]propyl phosphonate (6l): To a stirred solution of **5** (0.254 g, 0.83 mmol) and triethylamine (0.24 mL, 0.18 g, 1.6 mmol) in CH_2Cl_2 (3 mL) at room temperature and under argon, was added 2-(4-chlorophenoxy) acetyl chloride (0.15 mL, 0.204 g, 1 mmol) dropwise. The reaction mixture was stirred at room temperature overnight. The reaction mixture was extracted with water and brine. The aqueous layer was back extracted with CH_2Cl_2 (x3) and dried over anhydrous magnesium sulfate. The magnesium sulfate was filtered from the organic layer and the solvent was removed under reduced pressure. The crude residue was purified using an Isolera Flash Chromatography System (98 EtOAc: 2 MeOH) to give **6l** (0.199 g, 0.42 mmol, 61.7%) as an orange oil. ^{1}H NMR ($CDCl_3$, 200MHz), δ (ppm): 1.2 - 1.37 (m, 6H), 1.49 - 1.86 (m, 4H), 3.79 (t, J = 6.8 Hz, 2H), 4.09 (quin, J = 7.4 Hz, 4H), 4.57 (s, 2H), 4.86 (s, 2H), 6.64 (d, J = 9.0 Hz, 2H_{arom}), 7.17 (d, J = 6.6 Hz, 2H_{arom}), 7.41 (s, 5H_{arom}). LCMS (ESI$^+$) *m/z* 470.1 (M + H).

Diethyl 3-(N-(benzyloxy)biphenyl-4-ylcarboxamido)propylphosphonate (6m): To a stirred solution of **5** (0.22 g, 0.73 mmol) and triethylamine (0.13 mL, 0.095 g, 0.94 mmol) in CH_2Cl_2 (5 mL) was added biphenyl acid chloride (0.239 g,1.10 mmol) dropwise under argon at room temperature. The reaction mixture was stirred at room temperature overnight. The starting material remained and a second equivalent of triethylamine (0.10 mL, 0.073 g, 0.72 mmol) in CH_2Cl_2 (5 mL) and biphenyl acid chloride (0.155 g, 0.71 mmol) was added to the reaction mixture and continued to stir for 2 d. The reaction mixture was extracted with water and brine. The aqueous layer was back extracted with CH_2Cl_2 (x3). The organic fractions were separated, dried over anhydrous magnesium sulfate and filtered. The solvent was removed under reduced pressure to give the crude product, which was purified using an Isolera Flash Chromatography System (EtOAc) to give **6m** (0.332 g, 0.67 mmol, 94.5%) as a yellow oil. ^{1}H NMR ($CDCl_3$, 200MHz), δ (ppm): 1.31 (t, J = 7.1 Hz, 6H), 1.72 – 1.91 (m, 2H), 1.93 – 2.21 (m, 2H), 3.86 (t, J = 6.5 Hz, 2H), 4.09 (quin, J = 7.3 Hz, 4H), 4.68 (s, 2H), 7.01 – 7.11 (m, 2H_{arom}), 7.24 – 7.31 (m, 2H_{arom}), 7.36 – 7.53 (m, 4H_{arom}), 7.59 -7.65 (m, 4H_{arom}), 7.74 (d, J = 8.6 Hz, 2H_{arom}). LCMS (ESI$^+$) *m/z* 482.2 (M + H).

Diethyl {3-[(benzyloxy)(diphenylcarbamoyl)amino]propyl}phosphonate (6n): To a stirred solution of **5** (0.10 g, 0.34 mmol) and triethylamine (0.07 mL, 0.05 g, 0.47 mmol) in CH_2Cl_2 (3 mL) at room temperature and under argon, was added diphenylcarbamoyl chloride (0.094 g, 0.40 mmol) dropwise. The reaction mixture was stirred at room temperature for 4 h. The reaction mixture was extracted with water and brine. The aqueous layer was back extracted with CH_2Cl_2 (x3) and dried over anhydrous magnesium sulfate. The magnesium sulfate was filtered from the organic layer and the solvent was removed under reduced pressure. The crude residue was purified using an Isolera Flash Chromatography System (EtOAc) to give **6n** (0.041 g, 0.08 mmol, 36%) as a light yellow oil. ^{1}H NMR ($CDCl_3$, 200MHz), δ (ppm): 1.30 (t, *J* = 7.0 Hz, 6H), 1.47 - 1.99 (m, 4H), 3.52 (t, *J* = 7.1 Hz, 2H), 4.06 (quin, *J* = 7.3 Hz, 4H), 4.53 (s, 2H), 6.98 - 7.35 (m, $15H_{arom}$). LCMS (ESI^+) *m/z* 497.2 (M + H).

Diethyl 3-(N-hydroxypentanamido)propyl phosphonate (7a): A solution of **6a** (0.208 g, 0.54 mmol) in dry CH_2Cl_2 (10.0 mL) was cooled to -50°C and a 1M solution of BCl_3 in CH_2Cl_2 (3.5 mL, 3.5 mmol) was added dropwise. After stirring for 4 h at -50°C, the reaction was quenched with saturated $NaHCO_3$ (aq, 16 mL) and warmed to room temperature. The aqueous reaction mixture was extracted with CH_2Cl_2 (x3). The organic fractions were combined, dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The resulting crude mixture was purified using an Isolera Flash Chromatography System (EtOAc/MeOH; 5 – 10% MeOH) to yield **7a** (0.125 g, 0.42 mmol, 78.5 %) as a yellow oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm): 0.91 (t, *J* = 7.3 Hz, 3H), 1.32 (t, *J* = 7.1 Hz, 7H), 1.36 – 1.47 (m, 2H), 1.61 (quin, *J* = 7.4 Hz, 2H), 1.71 – 1.88 (m, 2H), 1.90 – 2.10 (m, 2H), 2.51 (t, *J* = 7.7 Hz, 2H), 3.74 (t, *J* = 5.6 Hz, 2H), 4.06 (quin, *J* = 6.9 Hz, 4H), 9.53 (s, 1H). ^{13}C NMR (50 MHz, CDCl3) δ (ppm): 13.92, 16.42 (dd, *J* = 3.2 Hz), 19.34, 22.66, 23.72, 26.89, 32.30, 47.81, 62.16 (d, *J* = 7.2 Hz), 175.31. LCMS (ESI^+) *m/z* 296.2 (M+H).

Diethyl 3-(N-hydroxyheptanamido)propyl phosphonate (7b): A solution of **6b** in dry CH_2Cl_2 (8 mL) was cooled to -50°C and a 1M solution of BCl_3 in CH_2Cl_2 (5.0 mL, 5.0 mmol) was added dropwise. After having been stirred for 4 h at -50°C, the reaction was quenched with saturated $NaHCO_3$ (aq, 12 mL) and warmed to room temperature. The aqueous reaction mixture was extracted with CH_2Cl_2 (x3). The organic fractions were combined, dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The resulting crude mixture was purified using an Isolera Flash Chromatography System (97 EtOAc: 3 MeOH) to yield **7b** (0.130 g, 0.40 mmol, 85%) as a yellow oil. ^{1}H NMR ($CDCl_3$, 200MHz), δ (ppm): 0.88 (t, *J* = 6.4 Hz, 3H), 1.32 (t, *J* = 6.8 Hz, 6H), 1.70-1.81 (m, 2H), 1.83-1.92 (m, 2H), 1.94-2.11 (m, 2H), 2.50 (t, *J* = 7.4 Hz, 2H), 3.75 (t, *J* = 5.6 Hz, 2H), 4.06 (quin, J =7.2 Hz, 4H), 9.51 (s, 1H). ^{13}C NMR (50 MHz, CDCl3) δ (ppm): 14.10, 16.43 (dd, *J* = 6.1, 2.9 Hz), 19.24, 22.61, 23.69, 24.72, 29.26, 31.71, 32.64, 47.75 (d, *J* = 12.6 Hz), 62.20 (d, *J* = 8.0 Hz), 175.46. LCMS (ESI^+) *m/z* 324.2 (M+H).

Diethyl 3-(N-hydroxypivalamido)propyl phosphonate (7c): A solution of **6c** in dry CH_2Cl_2 (6 mL) was cooled to -50°C and a 1M solution of BCl_3 in dichloromethane (3.2 mL, 3.2 mmol) was added dropwise. After stirring for 2 h at -50°C, the reaction was

quenched with saturated $NaHCO_3$ (aq, 9 mL) and warmed to room temperature. The aqueous reaction mixture was extracted with CH_2Cl_2 (x3). The organic fractions were combined, dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The resulting crude mixture was purified using an Isolera Flash Chromatography System (99 EtOAc: 1 MeOH) to yield **7c** (0.024 g, 0.081 mmol, 26%) as a light yellow oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm): 1.20 – 1.40 (m, 16H), 1.67 – 1.85 (m, 2H), 1.94 – 2.14 (m, 2H), 3.74 (t, *J* = 6.2 Hz, 2H), 4.07 (quin, *J* = 7.2 Hz, 4H). ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm): 16.51 (dd, *J* = 5.9, 3.1 Hz), 19.22 (d, *J* = 5.3 Hz), 26.07 – 28.21 (m), 39.18, 49.92 (d, *J* = 6.8 Hz), 62.30 (d, *J* = 6.8 Hz), 178.93. LCMS (ESI^+) *m/z* 296.0 (M+H).

Diethyl 3-(3-cyclohexyl-N-hydroxypropanamido)propyl phosphonate (7d): A solution of **6d** (0.156 g, 0.34 mmol) in dry CH_2Cl_2 (6.0 mL) was cooled to -50°C and a 1M solution of BCl_3 in CH_2Cl_2 (3.4 mL, 3.4 mmol) was added dropwise. After stirring for 4 h at -50°C, the reaction was quenched with saturated $NaHCO_3$ (aq, 12 mL) and warmed to room temperature. The aqueous reaction mixture was extracted with CH_2Cl_2 (x3). The organic fractions were combined, dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The resulting crude mixture was purified using an Isolera Flash Chromatography System (96 EtOAc: 4 MeOH) to yield **7d** (0.064 g, 0.18 mmol, 54%) as a light yellow oil. ^{1}H NMR ($CDCl_3$, 200MHz), δ (ppm): 1.06 - 1.26 (m, 4H), 1.31 (t, *J* = 7.0 Hz, 6H), 1.43 - 1.81 (m, 8H), 1.85 - 1.93 (m, 2H), 1.94 – 2.09 (m, 2H), 2.51 (t, *J* = 7.8 Hz, 2H), 3.74 (t, *J* = 5.4 Hz, 2H), 4.06 (quin, J =7.1 Hz, 4H), 9.53 (s, 1H). ^{13}C NMR (50 MHz, CDCl3) δ (ppm): 16.35, 19.19, 23.64, 26.53 (d, *J* = 16.6 Hz), 30.16, 32.14, 33.20, 37.63, 47.74 (d, *J* = 12.7 Hz), 62.20 (d, *J* = 7.6 Hz), 175.73. LCMS (ESI^+) *m/z* 350.2 (M+H).

Diethyl 3-(N-hydroxybenzamido)propyl phosphonate (7e): A solution of **6e** (0.085 g, 0.21 mmol) in dry CH_2Cl_2 (5 mL) was cooled to -50°C and a 1M solution of BCl_3 in CH_2Cl_2 (0.84 mL, 0.84 mmol) was added dropwise. After having been stirred for 6 h at -50°C, the reaction was quenched with saturated $NaHCO_3$ (aq, 10 mL) and warmed to room temperature. The aqueous reaction mixture was extracted with CH_2Cl_2 (x3). The organic fractions were combined, dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The resulting crude mixture was purified using an Isolera Flash Chromatography System (99 EtOAc: 1 MeOH) to yield **7e** (0.036 g, 0.11 mmol, 55%) as a light yellow oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm): 1.26 (t, 6H, *J* = 7.0 Hz), 1.66 - 1.91 (m, 2H), 1.91 - 2.14 (m, 2H), 3.79 (t, 2H, *J* = 5.6 Hz), 4.02 (quin, 4H, *J* = 7.6 Hz), 7.27 - 7.41 (m, $3H_{arom}$), 7.53 - 7.73 (m, $2H_{arom}$). ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm): 16.46 (dd, *J* = 5.9, 2.5 Hz), 19.88, 23.98, 49.76, 62.12 (d, *J* = 6.7 Hz), 128.28 (d, *J* = 13.7 Hz), 130.58, 133.87, 169.86. LCMS (ESI^+) *m/z* 316.1 (M+H).

Diethyl 3-(N-hydroxy-4-methylbenzamido)propyl phosphonate (7f): A solution of **6f** (0.17 g, 0.42 mmol) in dry CH_2Cl_2 (7.0 mL) was cooled to -50°C and a 1M solution of BCl_3 in CH_2Cl_2 (3.6 mL, 3.6 mmol) was added dropwise. After having been stirred for 2 h at -50 °C, the reaction was quenched with saturated $NaHCO_3$ (aq, 12 mL) and warmed to room temperature. The aqueous reaction mixture was extracted with CH_2Cl_2 (x3). The organic fractions were combined, dried over $MgSO_4$, filtered and the solvent was

removed under reduced pressure. The resulting crude mixture was purified using an Isolera Flash Chromatography System (97 EtOAc: 3 MeOH) to yield **7f** (0.11 g, 0.33 mmol, 78%) as a light yellow oil. ^{1}H NMR ($CDCl_3$, 200MHz), δ (ppm): 1.29 (t, *J* = 7.0 Hz, 6H), 1.71 - 1.91 (m, 2H), 1.93 – 2.18 (m, 2H), 2.73 (s, 3H), 3.82 (t, *J* = 7.0 Hz, 2H), 4.07 (quin, J =7.4 Hz, 4H), 7.17 – 7.28 (m, $2H_{arom}$), 7.51 - 7.61 (m, $2H_{arom}$). ^{13}C NMR (50 MHz, CDCl3) δ (ppm): 16.43 (d, *J* = 4.9 Hz), 20.03, 21.36 (d, *J* = 16.0 Hz), 24.02, 49.88 (d, *J* = 14.9 Hz), 62.09 (d, *J* = 7.2 Hz), 128.64 (d, *J* = 15.6 Hz), 130.55, 140.92, 169.92. LCMS (ESI^+) *m/z* 330.1 (M+H).

Diethyl 3-(N-hydroxy-3-phenylpropanamido)propyl phosphonate (7g): **6g** was dissolved in MeOH (30 mL) and hydrogenated at atmospheric pressure in the presence of 10% Pd/C (cat. amount). The resulting mixture was stirred at room temperature overnight. The reaction mixture was filtered to remove the catalyst. The solvent was removed under reduced pressure. The crude residue was purified using an Isolera Flash Chromatography System (EtOAc/MeOH; 1-10% MeOH) to give **7g** [0.625 g, 1.82 mmol, 54.4% (from **5**)] as an oil. ^{1}H NMR ($CDCl_3$, 200 MHz), δ (ppm): 1.32 (t, *J* = 6.2 Hz, 6H), 1.73 - 2.05 (m, 4H), 2.78 – 2.89 (m, 2H), 2.90 – 3.07 (m, 2H), 3.52 – 3.84 (m, 2H), 3.97 - 4.15 (m, 4H), 7.28 ($5H_{arom}$, s), 9.62 (1H, s). ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm): 16.50, 19.02, 22.90, 26.50, 32.23, 47.64, 62.36 (d, *J* = 6.2 Hz), 125.84, 128.60, 142.26, 175.09. LCMS (ESI^+) *m/z* 344.2 (M + H).

Diethyl 3-(N-hydroxy-4-phenylbutanamido)propylphosphonate (7h): 6h (0.69g, 1.5 mmol) was dissolved in MeOH (20 mL) and hydrogenated at atmospheric pressure in the presence of 10% Pd/C (cat. amount). The resulting mixture was stirred at room temperature overnight. The reaction mixture was filtered to remove the catalyst. The solvent was removed under reduced pressure. The crude residue was purified using an Isolera Flash Chromatography System (EtOAc/MeOH; 1-10% MeOH) to give **7h** (0.31g, 0.86mmol, 57%) as a light yellow oil. ^{1}H NMR ($CDCl_3$, 200MHz), δ (ppm): 1.30 (t, *J* = 6.8 Hz, 6H), 1.74 - 2.04 (m, 6H), 2.56 (t, *J* = 7.6 Hz, 2H), 2.68 (t, *J* = 7.6 Hz, 2H), 3.39 – 4.15 (m, 4H), 3.75 (m, 2H), 7.18 - 7.31 (m, $5H_{arom}$), 9.58 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm): 16.53, 18.79, 22.60, 34.16, 47.47, 62.09, 126.61, 125.70, 128.15, 141.49, 174.14. LCMS (ESI^+) *m/z* 358.1 (M + H).

Diethyl 3-(N-hydroxy-3-(4-methoxyphenyl)propanamido)propyl phosphonate (7i): A solution of **6i** (0.175 g, 0.377 mmol) in dry CH_2Cl_2 was cooled to -50°C and a 1M solution of BCl_3 in CH_2Cl_2 (4.0 mL, 4.0 mmol) was added dropwise. After stirring for 3 hours at -50°C, the reaction was quenched with saturated $NaHCO_3$ (aq, 12 mL) and warmed to room temperature. The aqueous reaction mixture was extracted with CH_2Cl_2 (x3). The organic fractions were combined, dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The resulting crude mixture was purified using an Isolera Flash Chromatography System (47 EtOAc: 3 MeOH) to yield **7i** (0.099 g, 0.26 mmol, 71%) as a light yellow oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm): 1.30 (t, *J* = 7.1 Hz, 6H), 1.70 – 1.86 (m, 2H), 1.96 – 2.14 (m, 2H), 2.73 – 2.85 (m, 2H), 2.85 – 2.96 (m, 2H), 3.71 – 3.78 (m, 2H), 3.78 (s, 3H), 4.03 (quin, *J* = 7.2 Hz, 4H), 6.81 (d, *J* = 8.6 Hz, 2H), 7.16 (d, *J* = 8.4 Hz, 2H), 9.59 (s, 1H). ^{13}C NMR (50 MHz, CDCl3) δ (ppm): 16.44

(d, J = 7.0 Hz), 19.16, 23.69, 29.92, 34.72, 47.77 (d, J = 12.1 Hz), 55.35, 62.30 (d, J = 7.8 Hz), 113.87, 129.45, 133.86, 157.91, 174.42, 210.78. LCMS (ESI^+) *m/z* 374.2 (M+H).

Diethyl 3-(N-hydroxy-3-(3-(trifluoromethyl)phenyl)acrylamido)propyl phosphonate (7j): A solution of **6j** (0.114 g, 0.213 mmol) in dry CH_2Cl_2 (5 mL) was cooled to -50°C and a 1M solution of BCl_3 in CH_2Cl_2 (1.3 mL, 1.3 mmol) was added dropwise. After stirring for 3 h at -50°C, the reaction was quenched with saturated $NaHCO_3$ (aq, 8 mL) and warmed to room temperature. The aqueous reaction mixture was extracted with CH_2Cl_2 (x3). The organic fractions were combined, dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The resulting crude mixture was purified using an Isolera Flash Chromatography System (CH_2Cl_2/EtOAc; 20 – 10% CH_2Cl_2) to yield **7j** (0.054 g, 0.133 mmol, 62%) as a light yellow oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm): 1.27 (t, J = 7.0 Hz, 6H), 1.70 – 2.36 (m, 4H), 3.74 – 3.93 (m, 2H), 4.03 (quin, J = 7.3 Hz, 4H), 7.30 – 7.91 (m, 6H), 10.01 (bs, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm): 16.41 (dd, J = 5.7, 3.0 Hz), 19.35, 23.78, 48.37 (d, J = 8.4 Hz), 62.38 (d, J = 6.5 Hz), 119.07, 124.43, 126.05, 129.38, 131.35, 136.33, 140.63, 167.09. LCMS (ESI^+) *m/z* 410.0 (M+H).

Diethyl 3-(N-hydroxy-3-(4-nitrophenyl)acrylamido)propyl phosphonate (7k): A solution of **6k** in dry CH_2Cl_2 (7.0 mL) was cooled to -50°C and a 1M solution of BCl_3 in CH_2Cl_2 (3.7 mL, 3.7 mmol) was added dropwise. After stirring for 6 h at -50°C, the reaction was quenched with saturated $NaHCO_3$ (aq, 12.0 mL) and warmed to room temperature. The aqueous reaction mixture was extracted with CH_2Cl_2 (x3). The organic fractions were combined, dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The resulting crude mixture was purified using an Isolera Flash Chromatography System (19 EtOAc: 1 MeOH) to yield **7k** (0.071 g, 0.18 mmol, 50 %) as a light yellow oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm): 1.29 (t, J = 7.1 Hz, 6H), 1.78 – 1.97 (m, 2H), 1.97 – 2.22 (m, 2H), 3.90 (t, J = 6.0, 2H), 4.04 (quin, J = 7.1 Hz, 4H), 7.45 (d, J = 16.6 Hz, 1H), 7.61 – 7.77 (m, 3H), 8.22 (d, J = 8.8 Hz, 2H), 10.11 (s, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm): 16.42, 19.16, 23.74, 48.07, 62.42 (d, J = 6.1Hz), 121.55, 124.14, 128.60, 139.32, 141.80, 148.62, 166.55. LCMS (ESI^+) *m/z* 387.0 (M+H).

Diethyl 3-(2-(4-chlorophenoxy)-N-hydroxyacetamido)propyl phosphonate (7l): A solution of **6l** in dry CH_2Cl_2 (8.0 mL) was cooled to -50°C and a 1M solution of BCl_3 in CH_2Cl_2 (4.0 mL, 4.0 mmol) was added dropwise. After stirring for 4.5 h at -50°C, the reaction was quenched with saturated $NaHCO_3$ (aq, 13 mL) and warmed to room temperature. The aqueous reaction mixture was extracted with CH_2Cl_2 (x3). The organic fractions were combined, dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The resulting crude mixture was purified using an Isolera Flash Chromatography System (47 EtOAc: 3 MeOH) to yield **7l** (0.102 g, 0.27 mmol, 63%) as a light yellow oil. ^{1}H NMR ($CDCl_3$, 200MHz), δ (ppm): 1.33 (t, J = 7.0 Hz, 6H), 1.77 – 1.85 (m, 2H), 1.98 – 2.14 (m, 2H), 3.79 (t, J = 5.6 Hz, 2H), 4.07 (quin, J =7.4 Hz, 4H), 4.89 (s, 2H), 6.89 (dt, J = 2.4, 9.0 Hz, 2H), 7.17 – 7.23 (m, 2H), 9.86 (s, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm): 16.43 (d, J = 9.1 Hz), 19.00, 23.56, 48.04,

62.50 (d, J = 6.8 Hz), 65.74, 116.26, 126.17, 129.34, 157.16, 169.29. LCMS (ESI^+) *m/z* 380.1 (M+H).

Diethyl 3-(N-hydroxybiphenyl-4-ylcarboxamido)propyl phosphonate (7m): A stirred solution of **6m** (0.265 g, 0.55 mmol) in MeOH (10 mL) was hydrogenated at atmospheric pressure in the presence of 10% Pd/C (cat. amount). The resulting mixture stirred at room temperature overnight. The reaction was monitored by TLC. The reaction mixture was filtered to remove the catalyst. The solvent was removed under reduced pressure and the crude residue was purified using an Isolera Flash Chromatography System (EtOAc) to give **7m** (0.111 g, 0.28 mmol, 52%) as a light yellow oil. ^{1}H NMR ($CDCl_3$, 200MHz), δ (ppm): 1.31 (t, J = 7.1 Hz, 6H), 1.78 – 2.18 (m, 4H), 3.89 (t, J = 6.0 Hz, 2H), 4.08 (quin, J = 7.2 Hz, 4H), 7.33 – 7.50 (m, $4H_{arom}$), 7.59 – 7.65 (m, $3H_{arom}$), 7.66 – 7.83 (m, $2H_{arom}$). ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm): 16.46 (dd, J = 3.0 Hz), 19.89, 24.02, 49.76, 62.16 (d, J = 6.8 Hz), 132.58, 140.33, 143.39, 169.65. LCMS (ESI^+) *m/z* 392.2 (M+H).

Diethyl 3-(1-hydroxy-3,3-diphenylureido)propyl phosphonate (7n): A solution of **6n** in dry CH_2Cl_2 (5 mL) was cooled to -50°C and a 1M solution of BCl_3 in CH_2Cl_2 (2.0 mL, 2.0 mmol) was added dropwise. After stirring for 5 hours at -50°C, the reaction was quenched with saturated $NaHCO_3$ (aq, 12 mL) and warmed to room temperature. The aqueous reaction mixture was extracted with CH_2Cl_2 (x3). The organic fractions were combined, dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The resulting crude mixture was purified using an Isolera Flash Chromatography System (EtOAc) to yield **7n** (0.087 g, 0.21 mmol, 87%) as a yellow oily solid. ^{1}H NMR ($CDCl_3$, 200MHz), δ (ppm): 1.29 (t, J = 6.8 Hz, 6H), 1.58 – 1.98 (m, 4H), 3.53 (t, J = 6.3 Hz, 2H), 4.07 (quin, J = 7.1 Hz, 4H), 7.04 – 7.23 (m, $2H_{arom}$), 7.21 – 7.47 (m, $6H_{arom}$). ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm): 16.46 (dd, J = 5.8, 3.0 Hz), 19.49 (d, J = 4.4 Hz), 23.81, 51.69 (d, J = 14.7 Hz), 61.81 (d, J = 6.5 Hz), 125.36, 125.94, 129.12, 144.45, 161.49. LCMS (ESI^+) *m/z* 407.2 (M+H).

Sodium hydrogen-3-(N-hydroxypentanamido)propyl phosphonate (8a): *N,O*-Bis(trimethylsilyl)trifluoroacetamide (0.15 mL, 0.145 g, 0.56 mmol) was added under nitrogen to **7a** (0.050 g, 0.17 mmol) in CH_2Cl_2 (0.75 mL) and stirred at room temperature for 20 min. The reaction mixture was cooled to 0°C and bromotrimethylsilane (0.22 mL, 0.255 g, 1.67 mmol) was added dropwise to the reaction. The reaction was warmed to room temperature and stirred overnight under nitrogen. Ethyl bromide and excess silylating agent were removed under reduced pressure and the residue was dissolved in aqueouse NaOH (0.86 mL, 7.8 mg/mL) and stirred for a second night. The reaction mixture was partitioned between H_2O and CH_2Cl_2 to remove any residual impurities/organics. The aqueous fractions were combined and the solvent was removed by lyophilization to give **8a** (0.049 g, 0.18 mmol, Quantitative) as a pale yellow solid. ^{1}H NMR (200 MHz, Acetone-d_6/D_2O) δ (ppm): 0.95 (t, J = 7.4 Hz, 3H), 1.39 (sex, J = 13.8, 7.1 Hz, 2H), 1.61 (quin, J = 8.3, 7.8 Hz, 4H), 1.77 – 2.07 (m, 2H), 2.55 (t, J = 7.7 Hz, 2H), 3.62 – 3.72 (m, 2H). ^{13}C NMR (50 MHz, Acetone-d_6/D_2O) δ (ppm): 13.52, 21.09, 22.30, 24.11, 27.02, 32.01, 49.00 (d, J = 18.8 Hz), 176.33, 214.78. LCMS (ESI^+) *m/z* 240.1 (M+H). HRMS (ESI) *m/z* calcd for $C_8H_{17}NO_5P$ (M-Na): 238.0838, found: 238.0833.

Sodium hydrogen-3-(N-hydroxyheptanamido)propyl phosphonate (8b): *N,O*-Bis(trimethylsilyl)trifluoroacetamide (0.14 mL, 0.134 g, 0.52 mmol) was added to **7b** (0.052 g, 0.16 mmol) in dry CH_2Cl_2 (0.70 mL) and was stirred at room temperature for 20 min. The reaction mixture was cooled to 0°C and bromotrimethylsilane (0.20 mL, 0.232 g, 1.51 mmol) was added dropwise to the reaction. The reaction was warmed to room temperature and was stirred overnight under nitrogen. Ethyl bromide and excess silylating agent were removed under reduced pressure and the residue was dissolved in aqueous NaOH (0.82 mL, 7.8 mg/mL) and stirred for a second night. The reaction mixture was partitioned between H_2O and CH_2Cl_2 to remove any residual impurities/organics. The aqueous fractions were combined and the solvent was removed by lyophilization to give **8b** (0.054 g, 0.18 mmol, quantitative) as a pale yellow solid. ^{1}H NMR (200 MHz, Aceton-d_6/D_2O) δ (ppm): 1.25 (t, J = 6.2 Hz, 3H), 1.58 – 1.82 (m, 6H), 1.82 – 2.08 (m, 4H), 2.12 – 2.39 (m, 2H), 2.86 (t, J = 7.6 Hz, 2H), 4.04 (t, J = 6.7 Hz, 2H). ^{13}C NMR (50 MHz, Acetone-d_6/D_2O) δ (ppm): 13.86, 21.26, 22.46, 24.24, 24.85, 26.91, 31.47, 32.39, 49.03 (d, J = 20.4 Hz), 175.82, 213.84. LCMS (ESI$^+$) *m/z* 268.0 (M+H). HRMS (ESI) *m/z* calcd for $C_{10}H_{21}NO_5P$ (M-Na): 266.1151, found: 266.1147.

Sodium hydrogen-3-(N-hydroxypivalamido)propyl phosphonate (8c): *N, O*-Bis(trimethylsilyl)trifluoroacetamide (0.06 mL, 0.058 g, 0.23 mmol) was added under Nitrogen to **7c** (0.023 g, 0.08 mmol) in CH_2Cl_2 (0.35 mL) and stirred at room temperature for 20 min. The reaction mixture was cooled to 0°C and bromotrimethylsilane (0.08 mL, 0.093 g, 0.60 mmol) was added dropwise to the reaction. The reaction was warmed room temperature and stirred overnight under nitrogen. Ethyl bromide and excess silylating agent were removed under reduced pressure and the residue was dissolved in aqueous NaOH (0.40 mL, 7.8 mg/mL) and stirred for a second night. The reaction mixture was partitioned between H_2O and CH_2Cl_2 to remove any residual impurities/organics. The aqueous fractions were combined and the solvent was removed by lyophilization to give **8c** (0.022 g, 0.08 mmol, quantitative) as a pale yellow solid. ^{1}H NMR (200 MHz, Acetone-d_6/D_2O) δ (ppm): (80/20 mixture of two conformers) 1.12 – 1.34 (m, 9H), 1.42 – 1.67 (m, 2H), 1.73 – 1.95 (m, 2H), 3.10 (t, J = 6.8 Hz, 20/100 of 2H), 3.68 (t, J = 6.8 Hz, 80/100 of 2H). ^{13}C NMR (50 MHz, Acetone-d_6/D_2O) δ (ppm): 23.98, 26.62 (d, J = 8.4 Hz), 39.07, 50.90 (d, J = 18.7 Hz), 180.66 (d, J = 14.8 Hz). LCMS (ESI$^+$) *m/z* 240.1 (M+H). HRMS (ESI) *m/z* calcd for $C_8H_{17}NO_5P$ (M-Na): 238.0838, found: 238.0833.

Sodium hydrogen-3-(3-cyclohexyl-N-hydroxypropanamido)propyl phosphonate (8d): Bromotrimethylsilane (0.15 mL, 0.175 g, 1.14 mmol) was added dropwise under nitrogen to **7d** (0.040 g, 0.11 mmol) in CH_2Cl_2 (0.62 mL) and stirred at 0°C. The reaction was warmed to room temperature and stirred overnight under nitrogen. Ethyl bromide and excess silylating agent were removed under reduced pressure and the residue was dissolved in aqueous NaOH (0.6 mL, 7.8 mg/mL) and stirred for a second night. The reaction mixture was partitioned between H_2O and CH_2Cl_2 to remove any residual impurities/organics. The aqueous fractions were combined and the solvent was removed by lyophilization to give **8d** (0.046 g, quantitative) as a white solid. ^{1}H NMR (400 MHz, D_2O) δ (ppm): (80/20 mixture of two conformers) 0.91 (q, J = 13.6, 12.9 Hz, 2H), 1.10 –

1.29 (m, 4H), 1.49 (q, J = 7.0 Hz, 2H), 1.62 – 1.77 (m, 5H), 1.81 – 1.95 (m, 2H), 2.54 (t, J = 8.0 Hz, 2H), 3.39 (t, J = 6.0 Hz, 20/100 of 2H), 3.70 (t, J = 6.8 Hz, 80/100 of 2H). ^{13}C NMR (101 MHz, D_2O) δ (ppm): 19.95, 25.78, 26.10, 29.44, 31.97, 32.49, 36.85, 48.30, 162.54. LCMS (ESI^+) *m/z* 294.1 (M+H). HRMS (ESI) *m/z* calcd for $C_{12}H_{23}NO_5P$ (M-Na): 292.1308, found: 292.1303.

Sodium hydrogen-3-(N-hydroxybenzamido)propyl phosphonate (8e): Bromotrimethylsilane (0.13 mL, 0.151 g, 0.99 mmol) was added dropwise under nitrogen to **7e** (0.34 g, 0.11 mmol) in CH_2Cl_2 (0.45 mL) and stirred at 0°C. The reaction was warmed to room temperature and stirred overnight under nitrogen. Ethyl bromide and excess silylating agent were removed under reduced pressure and the residue was dissolved in aqueous NaOH (0.56 mL, 7.8 mg/mL) and stirred for a second night. The reaction mixture was partitioned between H_2O and CH_2Cl_2 to remove any residual impurities/organics. The aqueous fractions were combined and the solvent was removed by lyophilization to give **8e** (0.031 g, 0.11 mmol, quantitative) as a pale yellow solid. ^{1}H NMR (200 MHz, D_2O/Acetone) δ (ppm): 1.44 – 1.87 (m, 2H), 1.87 – 2.15 (m, 2H), 3.59 – 3.99 (m, 2H),7.55 (s, 4H). ^{13}C NMR (50 MHz, D_2O/Acetone) δ (ppm): 20.74, 23.16, 25.92, 50.56, 127.51, 128.89, 131.14, 133.83, 171.84. LCMS (ESI^+) *m/z* 259.9 (M+H). HRMS (ESI) *m/z* calcd for $C_{10}H_{13}NO_5P$ (M-Na): 258.0525, found: 258.0520.

Sodium hydrogen-3-(N-hydroxy-4-methylbenzamido)propyl phosphonate (8f): Bromotrimethylsilane (0.16 mL, 0.185 g, 1.21 mmol) was added dropwise under nitrogen to **7f** (0.051 g, 0.15 mmol) in CH_2Cl_2 (0.65 mL) and stirred at 0°C. The reaction was warmed to room temperature and stirred overnight under argon. Ethyl bromide and excess silylating agent were removed under reduced pressure and the residue was dissolved in aqueous NaOH (0.78 mL, 7.8 mg/mL) and stirred for a second night. The reaction mixture was partitioned between H_2O and CH_2Cl_2 to remove any residual impurities/organics. The aqueous fractions were combined and the solvent was removed by lyophilization to give **8f** (0.035 g, 0.12 mmol, 76%) as a pale yellow solid. ^{1}H NMR ($CDCl_3$, 200MHz), δ (ppm): 1.37 – 1.73 (m, 2H), 1.79 – 2.06 (m, 2H), 2.37 (s, 3H), 3.55 – 3.86 (m, 2H), 7.25 – 7.54 (m, $4H_{arom}$). ^{13}C NMR (50 MHz, D_2O) δ (ppm): 20.93 (d, J = 16.7 Hz), 23.64, 26.34, 53.60, 127.51, 129.31, 130.63, 141.89, 171.60. LCMS (ESI^+) *m/z* 274.0 (M+H). HRMS (ESI) *m/z* calcd for $C_{11}H_{15}NO_5P$ (M-Na): 272.0682, found: 272.0684.

Sodium hydrogen-3-(N-hydroxy-3-phenylpropanamido)propyl phosphonate (8g): To a solution of **7g** (0.05 g, 0.146 mmol) in CH_2Cl_2 (0.25 mL) at 0°C was added dropwise bromotrimethylsilane (0.18 g, 0.21 mL, 1.17 mmol). The reaction mixture was stirred overnight at room temperature. Ethyl bromide and excess silylating agent were removed by rotary evaporation at room temperature. The concentrate was dissolved in dry CH_2Cl_2 and evaporated again (×2). Then H_2O was added to the residue and the mixture was stirred overnight at room temperature. The solution was filtered over cotton to remove the yellow oil and concentrated *in vacuo* at 50°C. The crude acid was rapidly neutralized with aqueous NaOH and the mixture was stirred overnight at room temperature. The reaction mixture was concentrated *in vacuo* at 50°C to yield **8g** (0.053g, quantitative yield) as a white solid. ^{1}H NMR (200 MHz, D_2O) δ (ppm): 1.39 - 2.09 (m,

4H), 2.76 - 2.98 (m, 4H), 3.62 (t, J = 6.7 Hz, 2H), 7.19 - 7.41 (m, 5H). ^{13}C NMR (101 MHz, D2O) δ (ppm): 20.19 (d, J = 3.8 Hz), 25.04, 30.31, 33.24, 48.52 (d, J = 19.2 Hz), 126.36, 128.36 (d, J = 7.5 Hz), 128.65, 140.88, 175.22. LCMS (ESI$^+$) *m/z* 288.1 (M+H). HRMS (ESI) *m/z* calcd for $C_{12}H_{18}NNaO_5P$ (M+H): 310.0814, found: 310.0813.

Sodium hydrogen-3-(N-hydroxy-4-phenylbutanamido)propyl phosphonate (8h): To a solution of **7h** (0.05 g, 0.140 mmol) in CH_2Cl_2 (0.24 mL) at 0°C was added bromotrimethylsilane (0.15 mL, 0.17 g, 1.12 mmol) dropwise. The reaction mixture was stirred overnight at room temperature. Ethyl bromide and excess silylating agent were removed by rotary evaporation at room temperature. The concentrate was dissolved in dry CH_2Cl_2 and evaporated again (×2). Then H_2O was added to the residue and the mixture was stirred overnight at room temperature. The solution was filtered over cotton to remove the yellow oil and concentrated *in vacuo* at 50°C. The crude acid was rapidly neutralized with aqueous NaOH and the mixture was stirred overnight at room temperature. The reaction mixture was concentrated *in vacuo* at 50°C to yield **8h** (0.052g, quantitative yield) as a white solid. ^{1}H NMR (200 MHz, D_2O) δ (ppm): (58:42 mixture of two conformers) 1.42 - 2.06 (m, 6H), 2.34 (t, 42/100 of 2H, J = 7.4 Hz), 2.48 (t, 58/100 of 2H, J = 7.4 Hz), 2.64 (t, 2H, J = 7.5 Hz), 3.34 (t, 42/100 of 2H, J = 7.3 Hz), 3.62 (t, 58/100 of 2H, J = 6.7 Hz), 7.18 - 7.42 (m, 5H). ^{13}C NMR (50 MHz, D2O) δ (ppm): 21.0, 25.1 (d, J = 134.4 Hz), 26.7, 31.9, 35.2, 49.2 (d, J = 19.0 Hz), 126.8, 129.3, 142.8, 176.8. LCMS (ESI$^+$) *m/z* 302.0 (M+H). HRMS (ESI) *m/z* calcd for $C_{13}H_{20}NNaO_5P$ (M+H): 324.0971, found: 324.0970.

Sodium hydrogen-3-(N-hydroxy-3-(4-methoxyphenyl)propanamido)propyl phosphonate (8i): Bromotrimethylsilane (0.14 mL, 0.162 g, 1.06 mmol) was added dropwise under nitrogen to **7i** (0.05 g, 0.13 mmol) in CH_2Cl_2 (0.58 mL) and stirred at 0 ^{o}C. The reaction was warmed to room temperature and stirred overnight under nitrogen. Ethyl bromide and excess silylating agent were removed under reduced pressure and the residue was dissolved in aqueous NaOH (0.69 mL, 7.8 mg/mL) and stirred for a second night. The reaction mixture was partitioned between H_2O and CH_2Cl_2 to remove any residual impurities/organics. The aqueous fractions were combined and the solvent was removed by lyophilization to give **8i** (0.05 g, 0.15 mmol, Quantitative) as a white solid. ^{1}H NMR (200 MHz, D_2O/Acetone-d_6) δ (ppm): 1.67 – 1.92 (m, 2H), 1.91 – 2.16 (m, 2H), 2.80 – 2.91 (m, 2H), 2.91 – 3.02 (m, 2H), 3.79 (t, J = 6.6 Hz, 2H), 3.88 (s, 3H), 6.98 (d, J = 8.7 Hz, 2H), 7.29 (d, J = 8.7 Hz, 2H). ^{13}C NMR (50 MHz, D_2O/Acetone-d_6) δ (ppm): 20.34, 34.26, 48.68 (d, J = 17.9 Hz), 55.42 (d, J = 3.8 Hz), 114.27, 129.77, 133.79, 157.82, 174.83. LCMS (ESI$^+$) *m/z* 318.0 (M+H). HRMS (ESI) *m/z* calcd for $C_{13}H_{19}NO_5P$ (M-Na): 316.0944, found: 316.0946.

Sodium hydrogen3-(N-hydroxy-3-(3-(trifluoromethyl)phenyl)acrylamido)propyl phosphonate (8j): Bromotrimethylsilane (0.06 mL, 0.070 g, 0.46 mmol) was added dropwise under nitrogen to **7j** (0.019 g, 0.050 mmol) in CH_2Cl_2 (0.4 mL) and stirred at 0 ^{o}C. The reaction was warned to room temperature and stirred overnight under nitrogen. Ethyl bromide and excess silylating agent were removed under reduced pressure and the residue was dissolved in aqueous NaOH (0.23 mL, 7.8 mg/mL) and stirred for a second night. The reaction mixture was partitioned between H_2O and CH_2Cl_2 to remove any

residual impurities/organics. The aqueous fractions were combined and the solvent was removed by lyophilization to give **8j** (0.16 g, 0.04 mmol, 87%) as a pale yellow solid. ^{1}H NMR (400 MHz, D_2O) δ (ppm): (80:20 mixture of two conformers) 1.60 – 1.65 (m, 2H), 1.87– 1.92 (m, 2H), 3.09 – 3.19 (m, 20/100 of 2H), 3.76 – 3.81 (m, 80/100 of 2H), 7.33 – 7.38 (m, 1H), 7.57 – 7.63 (m, 2H), 7.70 – 7.75 (m, 1H), 7.83 – 7.88 (m, 1H), 7.95 – 8.00 (m, 1H). ^{13}C NMR (101 MHz, D_2O) δ (ppm): 16.28, 25.77, 45.69, 110.81, 117.62, 124.57, 126.44, 129.53, 131.56, 141.83, 144.93, 152.92, 163.34. LCMS (ESI^+) *m/z* 354.0 (M+H). HRMS (ESI) *m/z* calcd for $C_{13}H_{14}F_3NO_5P$ (M-Na): 352.0556, found: 352.0558.

Sodium (E)-hydrogen3-(N-hydroxy-3-(4-nitrophenyl)acrylamido)propyl phosphonate (8k): Bromotrimethylsilane (0.11 mL, 0.127 g, 0.83 mmol) was added dropwise under nitrogen to **7k** (0.042 g, 0.11 mmol) in CH_2Cl_2 (0.45 mL) and stirred at 0 ^{o}C. The reaction was warmed to room temperature and stirred overnight under nitrogen. Ethyl bromide and excess silylating agent were removed under reduced pressure and the residue was dissolved in aqueous NaOH (0.56 mL, 7.8 mg/mL) and stirred for a second night. The reaction mixture was partitioned between H_2O and CH_2Cl_2 to remove any residual impurities/organics. The aqueous fractions were combined and the solvent was removed by lyophilization to give **8k** (0.035 g, 0.10 mmol, 92%) as a pale yellow solid. ^{1}H NMR (400 MHz, Acetone-d_6/D_2O) δ (ppm): 1.73 – 1.91 (m, 2H), 1.96 – 2.27 (m, 2H), 3.85 – 4.10 (m, 2H), 7.58 (d, J = 16.1 Hz, 1H), 7.78 (d, J = 15.1 Hz, 1H), 7.98 (d, J = 6.3 Hz, 2H), 8.42 (d, J = 7.5 Hz, 2H). ^{13}C NMR (101 MHz, Acetone-d_6/D_2O) δ (ppm): 20.63, 49.45, 120.35, 124.39, 129.22, 140.85, 148.19, 167.40. HRMS (ESI) *m/z* calcd for $C_{12}H_{14}N_2O_7P$ (M-Na): 329.0533, found: 329.0532.

Sodium hydrogen-3-(2-(4-chlorophenoxy)-N-hydroxyacetamido)propyl phosphonate (8l): Bromotrimethylsilane (0.17 mL, 0.197 g, 1.29 mmol) was added dropwise under nitrogen to **7l** (0.051 g, 0.134 mmol) in CH_2Cl_2 (0.60 mL) and stirred at 0^{o}C. The reaction was warmed to room temperature and stirred overnight under nitrogen. Ethyl bromide and excess silylating agent were removed under reduced pressure and the residue was dissolved in aqueous NaOH (0.68 mL, 7.8 mg/mL) and stirred for a second night. The reaction mixture was partitioned between H_2O and CH_2Cl_2 to remove any residual impurities/organics. The aqueous fractions were combined and the solvent was removed by lyophilization to give **8l** (0.043 g, 0.12 mmol, Quantitative) as a white solid. ^{1}H NMR (400 MHz, Acetone/D2O) δ (ppm): (80:20 mixture of two conformers) 1.65 – 1.89 (m, 2H), 1.89 – 2.10 (m, 2H), 3.42 (t, J = 7.6 Hz, 20/100 of 2H), 3.77 (t, J = 6.8 Hz, 80/100 of 2H), 5.02 (s, 2H), 7.02 (d, J = 9.0 Hz, 2H), 7.36 (d, J = 9.4 Hz, 2H). ^{13}C NMR (101 MHz, D_2O/Acetone-*d*) δ (ppm): 20.44, 23.31, 26.02, 49.01 (d, J = 21.1 Hz), 65.33, 116.60, 125.92, 129.66, 157.11, 169.68. LCMS (ESI^+) *m/z* 324.0 (M+H). HRMS (ESI) *m/z* calcd for $C_{11}H_{14}ClNO_6P$ (M-Na): 322.0241, found: 322.0244.

Sodium hydrogen-3-(N-hydroxybiphenyl-4-ylcarboxamido)propyl phosphonate (8m): Bromotrimethylsilane (0.14 mL, 0.159 g, 1.04 mmol) was added dropwise under nitrogen to **7m** (0.042 g, 0.11 mmol) in CH_2Cl_2 (0.55 mL) and stirred at 0^{o}C. The reaction was warmed to room temperature and stirred overnight under argon. Ethyl bromide and excess silylating agent were removed under reduced pressure and the residue was dissolved in aqueous NaOH (0.56 mL, 7.8 mg/mL) and stirred for a second

night. The reaction mixture was partitioned between H_2O and CH_2Cl_2 to remove any residual impurities/organics. The aqueous fractions were combined and the solvent was removed by lyophilization to give **8m** (0.021 g, 0.058 mmol, 53.8%) as a pale yellow solid. ^{1}H NMR (200 MHz, CD_3OD) δ (ppm): 1.64 – 1.86 (m, 2H), 1.91 – 2.16 (m, 2H), 3.83 (t, *J* = 6.0 Hz, 2H), 7.28 – 7.51 (m, 3H), 7.60 – 7.78 (m, 6H). ^{13}C NMR (50 MHz, CD_3OD) δ (ppm): 21.89, 27.10, 127.52, 128.07, 128.93, 129.97, 134.52, 141.44, 144.56, 171.48. Peak at 50ppm is masked by solvent. LCMS (ESI^+) *m/z* 336.0 (M+H). HRMS (ESI) *m/z* calcd for $C_{16}H_{17}NO_5P$ (M-Na): 334.0838, found: 334.0840.

Sodium hydrogen-3-(1-hydroxy-3,3-diphenylureido)propyl phosphonate (8n): Bromotrimethylsilane (0.13 mL, 0.150 g, 0.98 mmol) was added dropwise under nitrogen to **7n** (0.042 g, 0.10 mmol) in CH_2Cl_2 (0.45 mL) and stirred at 0^{o}C. The reaction was warmed to room temperature and stirred overnight under nitrogen. Ethyl bromide and excess silylating agent were removed under reduced pressure and the residue was dissolved in aqueous NaOH (0.53 mL, 7.8 mg/mL) and stirred for a second night. The reaction mixture was partitioned between H_2O and CH_2Cl_2 to remove any residual impurities/organics. The aqueous fractions were combined and the solvent was removed by lyophilization to give **8n** (0.037 g, 0.09 mmol, 95%) as an off white solid. ^{1}H NMR (200 MHz, Acetone-d_6/D_2O) δ (ppm): 1.92 – 2.15 (m, 2H), 2.17 – 2.39 (m, 2H), 3.99 (t, *J* = 6.1 Hz, 3H), 7.57 (dd, *J* = 17.7, 7.9 Hz, 6H), 7.77 (t, *J* = 7.5 Hz, 4H). ^{13}C NMR (50 MHz, Acetone-d_6/D_2O) δ (ppm): 24.13, 26.83, 52.36 (d, *J* = 18.1 Hz), 125.72, 126.38, 129.60, 145.39, 161.44. LCMS (ESI^+) *m/z* 351.0 [M+H]. HRMS (ESI) *m/z* calcd for $C_{16}H_{18}N_2O_5P$ (M-Na): 349.0947, found: 359.0951.

((3-(*N*-benzyloxy-3-phenylpropanamido)propyl) phosphoryl)bis(oxy) bis(methylene) bis(2,2-dimethylpropanoate) (9): Triethylamine (0.18 mL, 0.130 g, 1.29 mmol) was added to a stirred solution of **6g** (0.243 g, 0.644 mmol) in DMF (4 mL) under argon. Chloromethyl pivalate was added dropwise to the reaction mixture and was stirred overnight at 60°C and under argon. The reaction was monitored by TLC. The solvent was removed under reduced pressure at 60°C. The crude residue was partitioned between saturated $NaHCO_3$ (aq) and CH_2Cl_2. The organic fractions were separated, dried over $MgSO_4$ and filtered. The solvents were removed under reduced pressure. The resulting crude mixture was purified by silica gel column chromatography (5 Toluene: 1 Acetone) to yield **9** (0.20 g, 0.34 mmol, 53%) as a yellow oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm): 1.21 (s, 18H), 1.70 – 1.80 (m, 2H), 1.81 – 1.96 (m, 2H), 2.67 (t, *J* = 7.3 Hz, 2H), 2.90 (t, *J* = 7.3 Hz, 2H), 3.68 (t, *J* = 7.0 Hz, 2H), 4.96 (s, 2H), 5.64 (d, *J* = 13.2 Hz, 4H), 7.12 – 7.42 (m, 10H). LCMS (ESI^+) *m/z* 606.2 (M+H).

((3-(*N*-benzyloxy-4-phenylbutanamido)propyl)phosphoryl) bis(oxy)bis(methylene) bis(2,2-dimethylpropanoate) (10): Triethylamine (0.18 mL, 0.130 g, 1.29 mmol) was added to a stirred solution of **6h** (0.250 g, 0.638 mmol) in DMF (4 mL) under argon. Chloromethyl pivalate was added dropwise to the reaction mixture and stirred overnight at 65°C and under argon. The reaction was monitored by TLC. The solvent was removed under reduced pressure at 60°C. The crude residue was partitioned into saturated $NaHCO_3$(aq) and CH_2Cl_2. The organic fractions were combined, dried over $MgSO_4$ and filtered. The solvents were removed under reduced pressure. The resulting crude

mixture was purified by silica gel column chromatography (5 Toluene: 1 Acetone) to yield **10** (0.203 g, 0.33 mmol, 52%) as a yellow oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm): 1.20 (s, 18H), 1.71 – 2.01 (m, 6H), 2.38 (t, *J* = 7.6 Hz, 2H), 2.63 (t, *J* = 7.9 Hz, 2H), 3.60 – 3.74 (m, 2H), 4.71 (s, 2H), 5.65 (d, *J* = 13.0 Hz, 4H), 7.11 – 7.41 (m, 10H). LCMS (ESI^+) *m/z* 620.2 (M+H).

((3-(*N*-hydroxy-3-phenylpropanamido)propyl)phosphoryl) bis(oxy)bis(methylene) bis(2,2-dimethylpropanoate) (11): A solution of **9** (0.101 g, 0.17 mmol) in dry CH_2Cl_2 (5.0 mL) was cooled to -50°C and a 1M solution of BCl_3 in CH_2Cl_2 (1.4 mL, 1.4 mmol) was added dropwise. After having been stirred for 3 h at -50°C, the reaction was quenched with saturated $NaHCO_3$ (aq, 12 mL) and warmed to room temperature. The aqueous reaction mixture was extracted with CH_2Cl_2 (x3). The organic fractions were separated, dried over $MgSO_4$ and filtered. The solvents were removed under reduced pressure. The resulting crude mixture was purified by silica gel preparative thin layer chromatography (21% Acetone: 79% Toluene) to yield **11** (0.53 g, 1.02 mmol, 60%) as a light yellow oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm): 1.23 (s, 18H), 1.78 – 2.00 (m, 4H), 2.77 – 2.89 (m, 2H), 2.91 – 3.03 (m, 2H), 3.65 – 3.83 (m, 2H), 5.60 (d, *J* = 12.6 Hz, 4H), 7.16 – 7.39 (m, $5H_{arom}$), 8.83 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm): 18.85, 26.97, 29.82, 30.79, 34.45, 38.88, 47.60, 81.62, 126.07, 128.57, 141.69, 174.63, 177.05. LCMS (ESI^+) *m/z* 516.1 (M+H).

((3-(*N*-hydroxy-4-phenylbutanamido)propyl) phosphoryl)bis(oxy)bis(methylene) bis(2,2-dimethylpropanoate) (12): To a stirred solution of **10** (0.04 g, 0.065 mmol) in THF (6 mL) was added Na_2CO_3 (0.036 g, 0.34 mmol) and a catalytic amount of 10% Pd/C at room temperature and under a nitrogen atmosphere. Hydrogen was added to the reaction vessel and the reaction was stirred at room temperature for 4 h. The reaction was monitored by TLC. The reaction mixture was filtered to remove the catalyst and Na_2CO_3. The solvent was removed under reduced pressure. The crude product was purified by silica gel preparative thin layer chromatography (1 CH_2Cl_2: 1 EtOAc) to give **12** (0.006 g, 0.011 mmol, 17.6%) as a light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.20 – 1.38 (m, 18H), 1.65 – 1.70 (m, 2H), 1.97 – 2.07 (m, 4H), 2.58 – 2.63 (m, 2H), 2.73 (t, *J* = 7.3 Hz, 2H), 3.77 – 3.82 (m, 2H), 5.64 – 5.69 (m, 4H), 7.21 – 7.39 (m, $5H_{arom}$), 8.81 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm): 18.69, 22.85, 26.42, 27.00, 29.86, 32.21, 35.67, 38.91, 47.48, 81.66, 125.90, 128.44, 128.63, 142.20, 175.45, 177.08. LCMS (ESI^+) *m/z* 530.0 (M+H).

General Method for preparation of compounds 15a-m. To a solution of diethyl [3-(*N*-acetyl-*N*-hydroxyamino)propyl] phosphonate **14** (1 eq) in THF (3.9 mL/mmol of **14**) at 0°C was added sodium hydride (1.1 eq) in suspension in THF. The reaction mixture was allowed to room temperature and the desired arylbromide (1.1-2.0 eq) was added. Then, the mixture was heated at 70°C for 2-24 h. NaH was neutralized with water at 0°C, the organic layer was washed with H_2O and the aqueous phase was extracted three times with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography on silica gel (EtOAc/MeOH) gave the expected ether.

Diethyl 3-[*N*-(4-bromo-benzyloxy)acetamido]propyl phosphonate (15a): NaH (120 mg, 60 % dispersion in oil) was added to a solution of **14** (500 mg, 1.97 mmol) in THF (6 mL) at 0 ^{o}C. An additional 4 mL THF was added. The Solution was allowed to come to rt. 4-Bromo-benzyl bromide (543 mg, 2.17 mmol) was added as a solid. The mixture was heated overnight at 70^{o}C. The THF was removed under reduced pressure and the NaH was neutralized with water at 0^{o}C. The mixture was diluted with brine and extracted with CH2Cl2 (3 x 20 mL), dried over $MgSO_4$, filtered and evaporated to give 887 mg of a crude oil. Purification via column chromatography using EtOAc then EtOAc/MeOH (40/1, 33/1, 20/1 and 10/1) gave 691.7 mg (83%) the pure compound as a light yellow oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.31 (t, *J* = 7.0 Hz, 6H), 1.64-2.04 (m, 4H), 2.10 (s, 3H), 3.71 (t, *J* = 7.0 Hz, 2H), 4.01-4.16 (m, 4H), 4.78 (s, 2H), 7.22-7.28 (m, 2H), 7.49-7.56 (m, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.5, 16.6, 20.3, 20.4, 20.6, 22.4, 23.8, 45.7, 46.0, 61.7, 61.8, 75.7, 123.3, 130.8, 132.0, 133.5, 172.5. LCMS (ESI^{+}): m/z = 422.0 and 424.0 (isotopes) $[M+H]^{+}$.

Diethyl 3-(*N*-((4-(trifluoromethoxy)benzyl)oxy)acetamido)propyl phosphonate (15b). ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm): 1.29 (t, 6H, *J* = 7.0 Hz, C*H*$_3$-CH_2 ×2), 1.53-2.06 (m, 4H, C*H*$_2$-P and C*H*$_2$-CH_2P), 2.10 (s, 3H, C*H*$_3$-CO), 3.72 (t, 2H, *J* = 7.0 Hz, C*H*$_2$-N), 3.98-4.17 (m, 4H, C*H*$_2$-CH_3 ×2), 4.82 (s, 2H, C*H*$_2$-O-N), 7.23 (d, 2H, *J* = 8.6 Hz, Har), 7.41 (d, 2H, *J* = 8.6 Hz, Har). ^{13}C NMR (50 MHz, $CDCl_3$) δ 16.4, 16.5, 20.3, 20.4, 20.6, 21.6, 24.4, 45.6, 46.1, 61.6, 61.8, 75.4, 113.0, 117.9, 121.2, 123.0, 128.1, 130.6, 132.0, 133.2, 149.6, 172.4. LCMS (ESI^{+}): *m/z* = 428.1 $[M+H]^{+}$.

Diethyl 3-(*N*-((3,4-dichlorobenzyl)oxy)acetamido)propyl phosphonate (15c): ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm): 1.31 (t, 6H, *J* = 7.1 Hz, C*H*$_3$-CH_2 ×2), 1.54-2.08 (m, 4H, C*H*$_2$-P and C*H*$_2$-CH_2P), 2.12 (s, 3H, C*H*$_3$-CO), 3.72 (t, 2H, *J* = 6.8 Hz, C*H*$_2$-N), 3.99-4.19 (m, 4H, C*H*$_2$-CH_3 ×2), 4.79 (s, 2H, C*H*$_2$-O-N), 7.19-7.26 (m, 1H, H_{ar}), 7.44-7.52 (m, 2H, H_{ar}). ^{13}C NMR (50 MHz, $CDCl_3$) δ 16.5, 16.6, 20.3, 20.4, 20.7, 21.6, 24.5, 45.7, 46.0, 61.7, 61.8, 75.0, 128.2, 130.8, 130.9, 133.0, 133.3, 134.6, 172.4. LCMS (ESI^{+}): *m/z* = 412.0 $[M+H]^{+}$, 434.1 $[M+Na]^{+}$.

Diethyl 3-(*N*-((4-isopropylbenzyl)oxy)acetamido)propyl phosphonate (15d): ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm): 1.20-1.38 (m, 12H, C*H*$_3$-CH_2 ×2 and C*H*$_3$-CH ×2), 1.58-2.06 (m, 4H, C*H*$_2$-P and C*H*$_2$-CH_2P), 2.10 (s, 3H, C*H*$_3$-CO), 2.82-3.03 (m, 1H, C*H*-Ar), 3.72 (t, 2H, *J* = 6.4 Hz, C*H*$_2$-N), 4.07 (qt, 4H, *J* = 7.0 Hz, C*H*$_2$-CH_3 ×2), 4.78 (s, 2H, C*H*$_2$-O-N), 7.19-7.47 (m, 4H, H_{ar}). ^{13}C-NMR (400 MHz, $CDCl_3$) δ (ppm): 16.4, 16.5, 20.3, 20.3, 20.5, 22.4, 23.9, 31.0, 45.3, 61.6, 61.6, 76.3, 126.8, 129.4, 131.6, 150.0, 172.4. LCMS (ESI^{+}): *m/z* = 386.2 $[M+H]^{+}$.

Diethyl 3-(*N*-(1-phenylethoxy)acetamido)propyl phosphonate (15e): ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm): 1.24 (t, 6H, *J* = 7.1 Hz, C*H*$_3$-CH_2 ×2), 1.52 (d, 3H, *J* = 6.6 Hz, C*H*$_3$-CH), 1.45-1.85 (m, 4H, C*H*$_2$-P and C*H*$_2$-CH_2P), 1.95 (s, 3H, C*H*$_3$-CO), 3.10 (qt, 1H, *J* = 6.9 Hz, C*H*$_2$-N), 3.63 (qt, 1H, *J* = 6.9 Hz, C*H*$_2$-N), 4.00 (qt, 4H, *J* = 7.1 Hz, C*H*$_2$-CH_3 ×2), 4.78 (q, 1H, *J* = 6.6 Hz, C*H*-O), 7.19-7.43 (m, 5H, H_{ar}). ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm): 16.2 (d, $^{3}J_{C,P}$ = 5.9 Hz, *C*H_3-CH_2 ×2), 19.6 (*C*H_2-CH_2P), 20.2 (*C*H_3-CO), 20.4 (*C*H_3-CH), 22.7 (d, $^{1}J_{C,P}$ = 142.5 Hz, *C*H_2-P), 46.3 (d, *J* = 18.5 Hz, *C*H_2-N), 61.3 (d, $^{2}J_{C,P}$

= 6.5 Hz, *C*H_2-CH_3 ×2), 82.2 (*C*H-O-N), 127.0 (6C, C_{ar}), 128.5, 128.3, 139.9, 172.9 (*C*=O). LCMS (ESI^+): m/z = 358.2 $[M+H]^+$.

Diethyl 3-(*N*-(4-methoxyphenethoxy)acetamido)propyl phosphonate (15f): ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm): 1.25 (t, 6H, *J* = 7.0 Hz , C*H*$_3$-CH_2 ×2), 1.52-1.85 (m, 4H, C*H*$_2$-P and C*H*$_2$-CH_2P), 1.91 (s, 3H, C*H*$_3$-CO), 2.79 (t, 2H, *J* = 6.6 Hz, C*H*$_2$-Ar), 3.53 (t, 2H, *J* = 6.7 Hz, C*H*$_2$-N), 3.72 (s, 3H, C*H*$_3$-O), 3.93 (t, 2H, *J* = 6.6 Hz, C*H*$_2$-O-N), 4.05 (qt, 4H, *J* = 7.0 Hz, C*H*$_2$-CH_3 ×2), 6.78 (d, 2H, *J* = 8.6 Hz, H_{ar}), 7.07 (d, 2H, *J* = 8.6 Hz, H_{ar}). ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm): 16.2 (d, $^3J_{C,P}$ = 6.0 Hz, *C*H_3-CH_2), 16.3 (d, $^3J_{C,P}$ = 6.0 Hz, *C*H_3-CH_2), 19.9 (*C*H_3-CO), 20.1 (d, $^2J_{C,P}$ = 4.6 Hz, *C*H_2-CH_2P), 22.8 (d, $^1J_{C,P}$ = 142.6 Hz, *C*H_2-P), 33.6 (*C*H_2-Ar), 45.0 (d, $^3J_{C,P}$ = 18.5 Hz, *C*H_2-N), 55.0 (*C*H_3-O), 61.4 (d, $^2J_{C,P}$ = 6.6 Hz, *C*H_2-CH_3 ×2), 75.0 (*C*H_2-O-N), 113.7 (6C, C_{ar}), 129.4, 129.6, 158.2, 171.9 (*C*=O). LCMS (ESI^+): *m/z* = 388.2 $[M+H]^+$.

Diethyl 3-(*N*-(4-hydroxyphenethoxy)acetamido)propyl phosphonate (15g): ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm): (72:28 mixture of two conformers) 1.29 (t, 6H, *J* = 7.0 Hz, C*H*$_3$-CH_2 ×2), 1.52-1.92 (m, 4H, C*H*$_2$-P and C*H*$_2$-CH_2P), 1.96 (s, 3H, C*H*$_3$-CO), 2.78 (t, 72/100 of 2H, *J* = 6.5 Hz, C*H*$_2$-Ar), 2.96 (t, 28/100 of 2H, *J* = 7.0 Hz, C*H*$_2$-Ar), 3.46-3.67 (m, 2H, C*H*$_2$-N), 3.87-4.21 (m, 6H, C*H*$_2$-CH_3 ×2 and C*H*$_2$-O-N), 6.73-6.91 (m, 2H, H_{ar}), 6.93-7.18 (m, 2H, H_{ar}), 8.31 (bs, 1H, O*H*). ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm): 16.4 (d, $^3J_{C,P}$ = 5.7 Hz, *C*H_3-CH_2), 16.5 (d, $^3J_{C,P}$ = 5.7 Hz, *C*H_3-CH_2), 20.2 (*C*H_2-CH_2P and *C*H_3-CO), 22.9 (d, $^1J_{C,P}$ = 141.7 Hz, *C*H_2-P), 33.9 (*C*H_2-Ar), 45.3 (d, *J* = 18.1 Hz, *C*H_2-N), 62.0 (d, $^2J_{C,P}$ = 6.9 Hz, *C*H_2-CH_3 ×2), 75.5 (*C*H_2-O-N), 115.7 (6C, C_{ar}), 128.5, 129.9, 155.9, 172.4 (*C*=O). LCMS (ESI^+): *m/z* = 374.1 $[M+H]^+$.

Diethyl 3-(*N*-(4-phenylbutoxy)acetamido)propyl phosphonate (15h): ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm): 1.30 (t, 6H, *J* = 7.0 Hz, C*H*$_3$-CH_2 ×2), 1.59-2.03 (m, 8H, C*H*$_2$-P and C*H*$_2$-CH_2P and C*H*$_2$-CH_2O and C*H*$_2$-CH_2Ph), 2.11 (s, 3H, C*H*$_3$-CO), 2.65 (t, 2H, *J* = 7.0 Hz, C*H*$_2$-Ph), 3.66 (t, 2H, *J* = 6.7 Hz, C*H*$_2$-N), 3.81 (t, 2H, *J* = 5.9 Hz, C*H*$_2$-O-N), 4.07 (qt, 4H, *J* = 7.0 Hz, C*H*$_2$-CH_3 ×2), 7.10-7.34 (m, 5H, H_{ar}). ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm): 16.2 (2d, $^3J_{C,P}$ = 5.9 Hz, *C*H_3-CH_2 ×2), 20.0 (*C*H_3-CO), 20.1 (d, $^2J_{C,P}$ = 5.1 Hz, *C*H_2-CH_2P), 22.8 (d, $^1J_{C,P}$ = 142.6 Hz, *C*H_2-P), 27.4 (*C*H_2-$CH_2$$CH_2$Ph), 27.6 (*C*$H_2$-$CH_2$Ph), 35.4 (*C*$H_2$-Ph), 44.8 (d, $^3J_{C,P}$ = 18.0 Hz, *C*H_2-N), 61.3 (d, $^2J_{C,P}$ = 6.5 Hz, *C*H_2-CH_3 ×2), 73.7 (*C*H_2-O-N), 125.7 (6C, C_{ar}), 128.1, 141.5, 171.6 (*C*=O). LCMS (ESI^+): *m/z* = 386.3 $[M+H]^+$.

Diethyl 3-(*N*-(naphthalen-1-ylmethoxy)acetamido)propyl phosphonate (15i): ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.27 (t, *J* = 7 Hz, 6H), 1.58-1.75 (m, 2H), 1.86-1.94 (m, 2H), 2.04 (s, 3H), 3.67 (t, *J* = 6.8, 6.2 Hz, 2H), 3.97-4.12 (m, 4H), 5.29 (s, 2H), 7.44-7.64 (m, 4H), 7.86-7.91 (m, 2H), 8.09-8.13 (m, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 16.4, 16.6, 20.4, 20.6, 21.7, 24.5, 46.0, 46.4, 61.6, 61.7, 74.6, 123.5, 125.3, 126.2, 126.9, 127.7, 128.5, 128.9, 130.0, 130.6, 133.8, 172.8. LCMS (ESI^+): *m/z* = 394.1 $[M+H]^+$.

Diethyl 3-(*N*-(naphthalen-2-ylmethoxy)acetamido)propyl phosphonate (15j): ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm): 1.29 (t, 6H, *J* = 7.1 Hz, C*H*$_3$-CH_2 ×2), 1.50-2.09 (m, 4H, C*H*$_2$-P and C*H*$_2$-CH_2P), 2.14 (s, 3H, C*H*$_3$-CO), 3.73 (t, 2H, *J* = 6.8 Hz, C*H*$_2$-N), 4.07

(qt, 4H, J = 7.1 Hz, CH_2-CH_3 ×2), 4.99 (s, 2H, CH_2-O-N), 7.45-7.58 (m, 3H, H_{ar}), 7.80-7.93 (m, 4H, H_{ar}). ^{13}C NMR (50 MHz, $CDCl_3$) δ 16.4, 16.6, 20.3, 20.4, 20.6, 21.7, 24.5, 45.7, 46.0, 61.6, 61.8, 76.7, 126.5, 126.6, 126.8, 127.8, 128.1, 128.6, 131.9, 133.2, 133.5, 172.5. LCMS (ESI^+): m/z = 394.2 $[M+H]^+$.

Diethyl 3-(*N*-([1,1'-biphenyl]-4-ylmethoxy)acetamido)propyl phosphonate (15k): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.3 (t, J = 7.2, 6.8 Hz, 6H), 1.71-1.79 (m, 2H), 1.94-2.02 (m, 2H), 2.13 (s, 3H), 3.74 (t, J = 7.2, 6.8 Hz, 2H), 4.04-4.14 (m, 4H), 4.87 (s, 3H), 7.34-7.39 (m, 1H), 7.43-7.47 (m, 4H), 7.58-7.63 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.4, 16.5, 20.3, 20.3, 20.5, 22.3, 23.8, 45.5, 45.7, 61.6, 61.7, 127.1, 127.5, 127.6, 128.9, 129.7, 133.2, 140.4, 142.0, 172.5. LCMS (ESI^+): m/z = 420.2 $[M+H]^+$.

Diethyl 3-(*N*-([1,1'-biphenyl]-3-ylmethoxy)acetamido)propyl phosphonate (15l): ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm): 1.29 (t, 6H, J = 7.0 Hz, CH_3-CH_2 ×2), 1.64-2.08 (m, 4H, CH_2-P and CH_2-CH_2P), 2.14 (s, 3H, CH_3-CO), 3.75 (t, 2H, J = 6.8 Hz, CH_2-N), 3.96-4.17 (m, 4H, CH_2-CH_3 ×2), 4.89 (s, 2H, CH_2-O-N), 7.32-7.65 (m, 9H, Har). ^{13}C NMR (50 MHz, $CDCl_3$) δ 16.4, 16.6, 20.3, 20.4, 20.6, 21.7, 24.5, 45.5, 45.9, 61.6, 61.8, 76.5, 127.2, 127.7, 127.9, 128.0, 128.0, 128.9, 129.3, 134.9, 140.6, 141.9, 172.4. LCMS (ESI^+): m/z = 420.6 $[M+H]^+$.

Diethyl 3-(*N*-([1,1'-biphenyl]-2-ylmethoxy)acetamido)propyl phosphonate (15m): ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm): 1.30 (t, 6H, J = 7.1 Hz , CH_3-CH_2 ×2), 1.52-1.90 (m, 4H, CH_2-P and CH_2-CH_2P), 1.94 (s, 3H, CH_3-CO), 3.46 (t, 2H, J = 6.8 Hz, CH_2-N), 3.97-4.17 (m, 4H, CH_2-CH_3 ×2), 4.75 (s, 2H, CH_2-O-N), 7.28-7.55 (m, 9H, Har). ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm): 16.6 (2d, $^3J_{C,P}$ = 6.0 Hz, CH$_3$-CH_2 ×2), 20.4 (CH$_3$-CO), 20.4 (d, $^2J_{C,P}$ = 4.5 Hz, CH$_2$-CH_2P), 23.2 (d, $^1J_{C,P}$ = 142.4 Hz, CH$_2$-P), 45.5 (d, J = 24.0 Hz, CH$_2$-N), 61.7 (d, $^2J_{C,P}$ = 6.5 Hz, CH$_2$-CH_3 ×2), 74.0 (CH$_2$-O-N), 127.7 (12C, C_{ar}), 127.9, 128.5, 129.3, 129.4, 130.5, 131.2, 172.9 (C=O). LCMS (ESI^+): m/z = 420.6 $[M+H]^+$.

Method for the preparation of the biaryl ligands 15n-r by Suzuki reaction:
To a solution of **15a** (100 mg, 237 mmol, 1 eq) in DME (5.7 mL) was added $Pd(PPh_3)_4$ (28 mg, 24 mmol, 0.1 eq), and the mixture was stirred for 15 min. A solution of the boronic acid (1.2 mmol, 5 eq) in EtOH (1.41 mL) was added and the mixture was stirred for 15 min. Then 2M aqueous Na_2CO_3 (0.35 mL) was added and the mixture was heated at 75°C for 17-45 h. The solvents were evaporated, CH_2Cl_2 was added to the residue and the resulting suspension was filtered over cotton. The organic layer was washed with H_2O and the aqueous phase was extracted three times with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography on silica gel (EtOAc then EtOAc/MeOH 50/1 then 20/1 then 10/1) gave the expected biaryl compounds as light yellow oils in yields ranging from 86%-95%.

Diethyl 3-(*N*-((4'-methyl-[1,1'-biphenyl]-4-yl)methoxy)acetamido)propyl phosphonate (15n): ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.30 (t, J = 7 Hz, 3H), 1.66-2.03 (m, 4H), 2.39 (s, 3H), 2.13 (s, 3H), 3.74 (t, J = 7, 6.6 Hz, 2H), 4.01-4.16 (m, 4H), 4.85 (s, 2H), 7.23-7.29 (m, 2H), 7.38-7.54 (m, 4H), 7.58-7.62 (m, 2H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 16.4, 16.5, 20.3, 20.5, 21.1, 21.6, 24.4, 45.5, 45.8, 61.5, 61.6, 76.1, 126.9,

127.2, 129.5, 129.6, 130.7, 133.0, 137.4, 141.9, 172.3. LCMS (ESI^+): *m/z* = 434.2 $[M+H]^+$.

Diethyl 3-(*N*-((4'-methoxy-[1,1'-biphenyl]-4-yl)methoxy)acetamido)propyl phosphonate (15o): ^1H NMR (200 MHz, $CDCl_3$) δ 1.30 (t, *J* = 7 Hz, 6H), 1.63-2.06 (m, 4H), 2.13 (s, 3H), 3.74 (t, *J* = 7, 6.6 Hz, 2H), 3.84 (s, 3H), 3.97-4.20 (m, 4H), 4.85 (s, 2H), 6.98 (d, *J* = 8.6 Hz, 2H), 7.42 (d, *J* = 8.2 Hz, 2H), 7.47-7.64 (m, 4H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 16.3, 16.4, 20.2, 20.4, 21.5, 24.3, 45.4, 45.7, 55.3, 61.5, 61.6, 76.1, 114.2, 126.8, 128.0, 129.6, 130.7, 131.8, 141.5, 159.4, 172.3. LCMS (ESI^+): *m/z* = 450.2 $[M+H]^+$.

Diethyl 3-(*N*-((4'-isopropyl-[1,1'-biphenyl]-4-yl)methoxy)acetamido)propyl phosphonate (15p): ^1H NMR (200 MHz, $CDCl_3$) δ 1.30 (t, *J* = 6.6 Hz, 12H), 1.69-1.83 (m, 2H), 1.93-2.03 (m, 2H), 2.12 (s, 3H), 2.85-3.06 (m, 1H), 3.74 (t, *J* = 7, 6.2 Hz, 2H), 4.01-4.16 (m, 4H), 4.85 (s, 2H), 7.28-7.62 (m, 8H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 16.4, 16.5, 20.3, 20.5, 21.6, 23.9, 24.4, 33.7, 33.8, 45.5, 45.8, 61.5, 61.6, 76.1, 126.9, 127.0, 127.2, 129.6, 132.9, 137.8, 141.9, 148.4, 172.3. LCMS (ESI^+): *m/z* = 462.2 $[M+H]^+$.

Diethyl 3-(*N*-((4'-(hydroxymethyl)-[1,1'-biphenyl]-4-yl)methoxy)acetamido)propyl phosphonate (15q): ^1H NMR (400 MHz, $CDCl_3$) δ 1.30 (t, *J* = 7.0 Hz, 6H), 1.70-1.79 (m, 2H), 1.91-2.02 (m, 2H), 2.13 (s, 3H), 3.74 (t, *J* = 6.8 Hz, 2H), 4.03-4.13 (m, 4H), 4.74 (s, 2H), 4.86 (s, 2H), 7.43-7.46 (m, 4H), 7.57-7.62 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.42, 16.48, 20.26, 20.31, 20.52, 22.29, 23.71, 45.63, 61.66, 61.72, 64.71, 76.13, 127.19, 127.36, 127.45, 129.68, 133.22, 139.50, 140.77, 141.67, 172.50. LCMS (ESI^+): *m/z* = 450.2 $[M+H]^+$, 921.2 $[2M+Na]^+$.

Diethyl 3-(*N*-((4'-(trifluoromethyl)-[1,1'-biphenyl]-4-yl)methoxy)acetamido)propyl phosphonate (15r): ^1H NMR (400 MHz, $CDCl_3$) δ 1.31 (t, *J* = 7.2 Hz, 6H), 1.71-1.80 (m, 2H), 1.92-2.00 (m, 2H), 2.14 (s, 3H), 3.75 (t, *J* = 7.2, 6.4 Hz, 2H), 4.04-4.14 (m, 4H), 4.89 (s, 2H), 7.48-7.50 (m, 2H), 7.61-7.64 (m, 2H), 7.68-7.73 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.4, 16.5, 20.3, 20.3, 20.5, 22.3, 23.7, 45.8, 61.6, 61.7, 76.0, 120.2, 122.9, 125.6, 125.8, 127.4, 127.6, 128.3, 129.8, 134.4, 140.4, 143.9, 172.4. LCMS (ESI^+): *m/z* = 488.2 $[M+H]^+$, 997.2 $[2M+Na]^+$.

Protein Expression. Cloning of the Yp *ispC* and Mtb *ispC* genes into the pET101/D-TOPO vector was conducted as described previously [1]. The plasmid was transformed into chemically competent *E. coli* BL21 CodonPlus (DE3)-RIL cells (Stratagene, LA Jolla, CA) for protein expression. A 10 mL overnight seed culture of *E. coli* BL21 CodonPlus (DE3)-RIL + pYpIspC (or MtbIspC) was added to 1 L of LB media and incubated with shaking at 37°C and 250 rpm. Once an OD_{600} of 1.8 was achieved, protein expression was induced using 0.5 mM isopropyl β-D-thiogalactopyranoside (IPTG) and culture was allowed to incubate for an additional 18 h. Cells were harvested via centrifugation (4650×g, 20 min) and stored at −80°C. Protein was isolated and purified from the cells via chemical lysis and affinity chromatography. Cell lysis was achieved using Lysis Buffer A (100 mM Tris pH 8, 0.032% lysozyme, 3 mL per mg cell pellet), followed by Lysis Buffer B (0.1 M $CaCl_2$, 0.1M $MgCl_2$, 0.1M NaCl, 0.020% DNASE, 3

mL per mg cell pellet). Centrifugation (48,000×g, 20 min) yielded the clarified cell lysate that was passed through a TALON immobilized metal affinity column (Clontech Laboratories, Mountain View, CA). The column was washed with 20 column volumes of 1× equilibrium buffer (50 mM HEPES pH 7.5, 300 mM NaCl), 10 column volumes of 1× wash buffer (50 mM HEPES pH 7.5, 300 mM NaCl, 10 mM imidazole), and 15 column volumes of 2× wash buffer (100 mM HEPES pH 7.5, 600 mM NaCl, 20 mM imidazole). The protein was then eluted with 5 column volumes of 1× elution buffer (150 mM imidazole pH 7.0, 300 mM NaCl). Buffer was exchanged with 0.1 M Tris pH 7.5, 1 mM NaCl, 5 mM DTT during concentration by ultrafiltration. Protein concentration was determined using Advanced Protein Assay Reagent (Cytoskeleton, Denver CO) with γ-globulins (Sigma-Aldrich) as the standard. Purified protein was visualized via Coomassie stained SDS-PAGE. The yield of YpIspC averaged 30 mg per 1 L shake flask, and the yield of MtbIspC averaged 5 mg per 1 L shake flask.

***Yersinia pestis* growth inhibition assay.** Overnight cultures of *Yersinia pestis* subs. A1122 grown in Tryptic Soy Broth (TSB) + 0.1% cysteine at 37°C and 250 rpm were diluted to an OD_{600} of 0.2. 40 µL aliquots of the culture were used to inoculate 1.5 mL foam-capped microcentrifuge tubes containing 400 µL fresh TSB +0.1% cysteine and the appropriate antibiotic. Growth was monitored over 24 h, and final OD_{600} readings of treated versus untreated samples were used to determine the percentage growth. All growth assays were conducted in triplicate.

***Mycobacterium tuberculosis* growth inhibition assay.** Compounds were evaluated for their ability to inhibit growth of Mtb as described [4]. Briefly, Mtb H37Rv ATCC27294 was grown in Middlebrook 7H9 broth supplemented with 0.2% glycerol, 0.4% glucose, 0.5% BSA fraction V, 0.08% NaCl and 0.5% Tween or in GAST/Fe medium (PMID 10655517) to an OD_{650} of 0.2. Cells were then diluted to 100,000 cells/mL in their respective medium. An equal volume (50 uL/well) of cell dilution was added to clear polystyrene round-bottom 96-well plates containing 50 uL/well of the respective medium and drug as a 2-fold 12 point dilution series in duplicate. Plates were incubated at 37°C for 1 and 2 weeks after which growth was visualized using an enlarging mirror. The minimum inhibitory concentration (MIC) is scored as the lowest concentration that completely inhibits growth.

***Escherichia coli* growth inhibition assay.** Overnight cultures of *E. coli* wild-type (WT) MG1655, WT BW25113, and BW25113 Δ*bamB* Δ*tolC* [(gift from Gerard Wright, McMaster University, Ontario, Canada), see ref. 5], were diluted 1:500 into fresh Luria-Bertani (LB) broth and grown to the logarithmic phase (OD_{600} = 0.4-0.8). Bacteria were diluted to 10^5 cfu/mL in 100 µL/well of a 96-well plate containing compounds at concentrations between 0.49 - 250 µg/mL. Bacteria were cultured at 37ºC for 16 h in a FLUOstar Optima microplate reader (BMG Labtech) while shaking. GraphPad Prism software was used to calculate inhibitory constants (IC_{50} values) during exponential growth.

Table S1. Percent Residual Activity Values from Yp and Mtb Dxr Inhibition

Compound	Yp Trial 1	Yp Trial 2	Yp Average	(+/-) Yp 95% C. I.	Mtb Trial 1	Mtb Trial 2	Mtb Average	(+/-) Mtb 95% C.I.
DMSO (standardized)	100.00	100.00	100.00	0.00	100.00	100.00	100.00	0.00
Fos (1)	4.67	1.99	3.33	2.62	5.14	4.29	4.71	0.83
FR900098 (2)	2.03	0.79	1.41	1.22	6.10	7.10	6.60	0.98
8a	36.14	37.18	36.66	1.02	43.67	50.61	47.14	6.80
8b	25.30	28.07	26.68	2.71	43.64	42.59	43.12	1.03
8c	84.91	82.62	83.77	2.25	80.15	73.17	76.66	6.85
8d	44.49	44.40	44.45	0.08	50.75	56.02	53.39	5.16
8e	1.77	2.08	1.93	0.31	72.69	67.38	70.04	5.20
8f	13.93	12.53	13.23	1.37	74.74	75.77	75.26	1.01
8g	89.25	82.12	85.69	6.98	49.57	47.64	48.61	1.89
8h	25.34	20.41	22.87	4.83	36.00	31.00	33.50	4.90
8i	73.34	72.34	72.84	0.98	58.49	56.10	57.30	2.35
8j	93.45	93.75	93.60	0.29	88.35	95.49	91.92	7.00
8k	69.06	71.31	70.18	2.20	79.33	62.27	70.80	16.72
8l	69.81	73.34	71.57	3.46	57.51	56.24	56.88	1.24
8m	49.41	49.44	49.43	0.03	58.06	63.15	60.60	4.99
8n	57.05	58.47	57.76	1.39	92.19	98.62	95.41	6.29
16a	88.88	88.77	88.82	0.11	98.26	108.99	103.62	10.52
16b	70.97	73.50	72.24	2.48	74.17	75.82	74.99	1.61
16c	89.54	84.11	86.83	5.32	76.47	77.93	77.20	1.43
16d	9.60	11.44	10.52	1.80	27.07	27.00	27.04	0.07
16e	20.32	17.72	19.02	2.54	36.21	39.97	38.09	3.68
16f	64.77	72.67	68.72	7.74	60.12	68.25	64.19	7.96
16g	23.05	21.01	22.03	2.00	57.85	61.96	59.91	4.03
16h	104.27	101.17	102.72	3.04	61.98	71.78	66.88	9.60
16i	15.60	14.42	15.01	1.16	30.47	27.20	28.83	3.20
16j	5.31	5.50	5.40	0.19	17.18	15.86	16.52	1.30
16k	13.99	11.91	12.95	2.04	35.22	38.34	36.78	3.06
16l	46.31	45.56	45.93	0.74	72.95	72.69	72.82	0.25
16m	40.29	39.73	40.01	0.54	65.60	66.42	66.01	0.81
16n	72.06	71.63	71.85	0.42	84.92	95.80	90.36	10.66
16o	47.53	52.32	49.93	4.69	78.13	83.52	80.83	5.28
16p	70.06	67.73	68.90	2.28	70.32	72.38	71.35	2.02
16q	31.88	38.39	35.14	6.38	40.38	42.81	41.59	2.38
16r	20.33	19.14	19.73	1.17	69.88	69.57	69.72	0.30

Table S2. MIC and IC_{50} values for *N*-acyl compounds against Mtb and *E. coli*

Compound	7H9 Mtb MIC (ug/mL)	GAST-Fe Mtb MIC (ug/mL)	*E. coli* IC_{50} (ug/mL)
Isoniazid (INH)	0.01	0.02	N/A
Fosmidomycin (1)	>500	>500	
FR900098 (2)	>500	>500	
8a	>200	150	
7a	>200	150	
8b	>200	100	
7b	>200	50	
8c	>200	150	
7c	ND	ND	
8d	>200	25	>250
7d	200	37	>250
8e	>200	150	180.7
7e	>200	150	>250
8f	>200	150	
7f	>200	150	
8g	>200	150	
7g	400	≥400	
8h	>200	>200	>250
7h	200	200	
8i	>200	75	
7i	>200	150	
8j	>200	50	
7j	≥200	37	
8k	>200	150	
7k	>200	150	
8l	>200	150	>250
7l	>200	25	213.6
8m	>200	50	
7m	>200	75	
8n	>200	150	
7n	≥200	75	
11	200	50	
12	150	150	>250

Table S3. MIC and IC_{50} values for *O*-linked compounds against Mtb and *E. coli*

Compound	7H9 Mtb MIC (ug/mL)	GAST-Fe Mtb MIC (ug/mL)	*E. coli* IC_{50} (ug/mL)
Isoniazid (INH)	0.01	0.02	N/A
Fosmidomycin (1)	>500	>500	
FR900098 (2)	>500	>500	
14	>200	>200	
16b	>400	>400	
15b	400	200-400	
16c	>400	200-400	
15c	200	100	
16d	200	25	197.5
15d	400	200	
16e	>200	>200	>250
15e	200-400	N/A	>250
16f	>200	>200	
15f	200-400	N/A	
16g	>400	400	>250
15g	200-400	100	>250
16h	≥200	200	
15h	100-200	N/A	
16i	>400	200-400	
15i	400	100-200	
16j	≥200	≥200	191
15j	200	100	243.8
16k	25-50	25-50	>250
15k	200	100	169.7
16l	200-400	25-50	
15l	100	50	
16m	200-400	50	
15m	200-400	100	
16n	100-200	25-50	
15n	200-400	100-200	
16o	200-400	50-100	
15o	≥400	200-400	
16p	100	6.25-12.5	
15p	200-400	200	
16q	200	200	
15q	100	100	
16r	75	12.5	
15r	100	100	
17	12.5	6.25-12.5	119.1
18	12.5	6.25-12.5	
19	12.5	3.13-6.25	>250
20	18.75	4.7	
21	25	25	

References:

1. Haymond A, Johny C, Dowdy T, Schweibenz B, Villarroel K, Young R, et al. Kinetic Characterization and Allosteric Inhibition of the *Yersinia pestis* 1-Deoxy-D-Xylulose 5-Phosphate Reductoisomerase (MEP Synthase). PLOS ONE. 2014;9: e106243. doi:10.1371/journal.pone.0106243

2. Takahashi S, Kuzuyama T, Watanabe H, Seto H. A 1-deoxy-d-xylulose 5-phosphate reductoisomerase catalyzing the formation of 2-C-methyl-d-erythritol 4-phosphate in an alternative nonmevalonate pathway for terpenoid biosynthesis. Proc Natl Acad Sci. 1998;95: 9879–9884. doi:10.1073/pnas.95.17.9879

3. Dhiman RK, Schaeffer ML, Bailey AM, Testa CA, Scherman H, Crick DC. 1-Deoxy-d-Xylulose 5-Phosphate Reductoisomerase (IspC) from *Mycobacterium tuberculosis*: towards Understanding Mycobacterial Resistance to Fosmidomycin. J Bacteriol. 2005;187: 8395–8402. doi:10.1128/JB.187.24.8395-8402.2005

4. Duckworth BP, Wilson DJ, Nelson KM, Boshoff HI, Barry CE 3rd, Aldrich CC. Development of a selective activity-based probe for adenylating enzymes: profiling MbtA involved in siderophore biosynthesis from *Mycobacterium tuberculosis*. ACS Chem. Biol. 2012;7: 1653-1658. doi: 10.1021/cb300112x.

5. Stogios PJ, Spanogiannopoulos P, Evdokimova E, Egorova O, Shakya T, Todorovic N, Capretta A, Wright GD, Savchenko A 2013. Structure-guided optimization of protein kinase inhibitors reverses aminoglycoside antibiotic resistance. Biochem J 454:191–200. doi:.10.1042/BJ20130317