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## STRUCTURE-BASED DESIGN OF A NOVEL SERIES OF NONPEPTIDE LIGANDS THAT BIND TO THE pp60<sup>src</sup> SH2 DOMAIN

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### Supporting Information

#### General Methods and Procedures

<sup>1</sup>H Nuclear Magnetic Resonance (NMR) spectra were recorded on either a Varian XL300 or XL400 spectrometers in d<sub>6</sub> DMSO (DMSO). Chemical shifts are reported in parts per million ( $\delta$ ) relative to an internal standard or appropriate solvent peak. Signals are described as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), bs (broad singlet) and dd (double doublet). Chemical ionization mass spectra (CI) were recorded on a Fisons (VG Biotech) Trio 2A using 1% ammonia in methane as the reagent gas. Electrospray mass spectra (ES) were obtained on a single quadrupole instrument (VG Fisons Trio-2000) in negative ion mode. Flash silica gel chromatography was performed using Keisegel 230-400 mesh. Thin layer chromatography (TLC) employed EM Science silica gel 60 F254 glass backed plate. Analytical HPLC chromatograms were obtained using a C18 analytical column (Vydac, 4.6x250 mm) eluting with a linear gradient of 0% to 66% acetonitrile containing 0.1% Trifluoroacetic acid (TFA) over 22 minutes unless otherwise indicated. Peaks were detected at 214 nm. Tetrahydrofuran (THF) was dried over sodium-benzophenone ketyl and distilled. All other commercially available solvents and reagents were used without further purification.

#### 5-Aminomethylsalicylic acid (4a)

(4a) was prepared according to literature procedure. *Chem. Pharm. Bull.* 1963, 11, 551.

#### 5-(tert-Butoxycarbonylamino-methyl)-2-hydroxy-benzoic acid (4b)

To a solution of 5-aminomethylsalicylic acid (8.30g, 49.70mmol) in 100mL water and 100mL of dioxane at 0°C was added 1N sodium hydroxide (54.67mL, 54.67mmol) followed by di-tert-butyl dicarbonate (11.92g, 54.76mmol). The reaction was allowed to warm slowly to room temperature and stirred overnight. The reaction was then concentrated under reduced pressure to 15mL. A layer of ethyl acetate was then added and the reaction was acidified to pH 2 with saturated potassium hydrogen sulfate. The aqueous layer was then extracted with ethyl acetate (3X150mL). The combined ethyl acetate layers

were combined and washed with saturated sodium chloride (1X150mL), dried over magnesium sulfate, filtered and concentrated under reduced pressure to yield a white powder. The powder was collected and washed with ether, followed by drying under reduced pressure to yield 11.5g (87%). <sup>1</sup>H NMR (400MHz, DMSO) 7.67(s,1H), 7.38(d, 2H), 6.91(d,1H), 4.04(d,2H), 1.41(s,9H). MS(CI+) *m/z* 268 (5), 212 (100), 194 (14), 179 (9), 167 (17), 151 (49), 139 (81), 102 (14); IR(KBr) 3364, 3223, 3061, 2982, 2935, 2876, 1670, 1620, 1593, 1527, 1491, 1448, 1365, 1300, 1222, 1163, 1051, 906, 842, 794, 675, 599, 511, 468 cm<sup>-1</sup>; Anal. Calcd. for C<sub>13</sub>H<sub>17</sub>NO<sub>5</sub> : C, 58.42; H, 6.41; N, 5.24. Found: C, 58.43; H, 6.45; N, 5.21.

### (3-Carbamoyl-4-hydroxy-benzyl)-carbamicacid tert-butyl ester (4c)

To a solution of 5-(tert-butoxycarbonylamino-methyl)-2-hydroxy-benzoicacid (20.0g, 74.90mmol) in 700mL tetrahydrofuran at 0°C was added 4-methyl morpholine ( 12.34mL, 112.35mmol), 1-hydroxybenzotriazole (15.17g, 112.35mmol), followed by 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (21.53g, 112.35mmol). The reaction was stirred for 1 hour at 0°C, then concentrated ammonium hydroxide was added (15.18mL, 112.35mmol). The reaction was allowed to warm slowly to room temperature and stirred overnight. The reaction was then diluted with ethyl acetate and washed with 5% citric acid (3X250mL), saturated sodium bicarbonate (3X250mL), and saturated sodium chloride (1X250mL), dried over magnesium sulfate, filtered and concentrated under reduced pressure to yield a pale yellow powder. The powder was collected and washed with ether, followed by drying under reduced pressure to yield 14.03g (71%). <sup>1</sup>H NMR (400MHz, DMSO) 12.77(bs,1H), 8.33(bs,1H), 7.72(d,1H), 7.28(d,2H), 6.84(d,1H), 4.05 (d,2H), 1.38(s,9H); MS(CI+) *m/z* 267 (2), 239 (0.2), 211 (100), 178 (1), 138 (14); IR(KBr) 1589, 1562, 1502, 1475, 1332, 1303, 1278, 1249, 1174, 1103,1043, 918, 852, 781, 758, 734, 704, 734, 688, 434 cm<sup>-1</sup>; Anal. Calcd. for C<sub>13</sub>H<sub>18</sub>N<sub>2</sub>O<sub>4</sub> : C, 58.64; H, 6.81; N, 10.52. Found: C, 58.71; H, 6.68; N, 9.82.

### (3-Carbamoyl-4-benzyloxy-benzyl)-carbamic acid tert-butyl ester (4d)

To a solution of (3-carbamoyl-4-hydroxy-benzyl)-carbamicacid tert-butyl ester (2.00g, 7.51mmol) in 15mL methanol at room temperature was added cesium carbonate (2.69g, 8.27mmol). The reaction was stirred overnight. The reaction was then concentrated under reduced pressure. N,N-dimethylformamide (50mL) was then added and the reaction was then reconcentrated under reduced pressure to chase off any remaining methanol. The residue was then suspended in N,N-dimethylformamide (15mL) and benzyl bromide (0.983mL, 8.27mmol) was then added and the reaction was heated at 65°C for 4 hours. The reaction was then concentrated under reduced pressure. The residue was diluted with ethyl acetate and 5% citric acid. The organic layer was washed with 5% citric acid (2X50mL), 1N sodium hydroxide (2X50mL), 5% citric acid (2X50mL), and saturated sodium chloride (1X50mL), dried over magnesium sulfate, filtered and concentrated under reduced pressure to yield a pale yellow powder. The powder was collected and washed with ether, followed by drying under reduced pressure to yield 2.50g (93%). <sup>1</sup>H NMR (400MHz, DMSO) 7.14(m,11H), 5.23(s,2H), 4.06(d,2H), 1.38(s,9H); MS(CI+) *m/z* 357 (2), 301 (39), 228 (71), 150 (15), 91 (100); IR(KBr) 3499, 3352, 3323, 2978, 2931, 1709, 1689, 1647, 1593, 1520, 1500, 1438, 1367, 1275, 1246, 1168, 1022, 731, 607 cm<sup>-1</sup>; Anal. Calcd. for C<sub>20</sub>H<sub>24</sub>N<sub>2</sub>O<sub>4</sub> : C, 67.75; H, 6.89; N, 7.81. Found: C, 67.40; H, 6.79; N, 7.86.

### Benzamide, 2-(benzyloxy)-5-[[[(4-hydroxyphenyl) carbonyl]amino] methyl] (16)

A solution of 4N hydrochloric acid in dioxane (15mL) was added to (3-carbamoyl-4-hydroxy-benzyl)-carbamicacid tert-butyl ester (1.00g, 2.80mmol). The reaction is stirred for 1 hour and then concentrated under reduced pressure to yield a solid. This solid of the amine hydrochloride was then used for the coupling without further purification. To a

solution of the amine hydrochloride was added *N,N*-dimethylformamide (27mL) and the reaction was cooled to 0°C. 4-methyl morpholine (0.75mL, 6.82mmol) was then added, followed by 1-hydroxybenzotriazole (554mg, 4.10mmol), 4-hydroxybenzoic acid (566mg, 4.10mmol), and 1-(3 dimethylaminopropyl)-3-ethyl carbodiimide hydrochloride (786mg, 4.10mmol). The reaction was allowed to warm slowly to room temperature and stirred overnight. The reaction was concentrated under reduced pressure in 10mL. The residue was then diluted with ethyl acetate and washed with 5% citric acid (3X250mL), saturated sodium bicarbonate (3X250mL), and saturated sodium chloride (1X250mL), dried over magnesium sulfate, filtered and concentrated under reduced pressure to yield an oil. Chromatography of the residue (40% acetone, 59% dichloromethane, 1% acetic acid) gave a solid which was collected, washed with dichloromethane, and dried under reduced pressure to yield 410mg (40%). <sup>1</sup>H NMR (400MHz, DMSO) 9.98(s,1H), 8.78(t,1H), 7.76(s,2H), 7.75(s,1H), 7.61(bs,1H), 7.53(bs,1H), 7.48(d,2H), 7.15 (d,1H), 6.80(d,2H), 5.24(s,2H), 4.38(d,2H); MS(CI+) *m/z* 377 (13), 274 (18), 228 (63), 165 (12), 150 (40), 138 (34), 105 (13), 91 (100); IR(KBr) 3445, 3254, 3178, 3036, 1655, 1608, 1585, 1502, 1437, 1377, 1278, 1240, 1174, 1095, 1004, 850, 744, 698 cm<sup>-1</sup>; Anal. Calcd. for C<sub>22</sub>H<sub>20</sub>N<sub>2</sub>O<sub>4</sub> : C, 70.20; H, 5.36; N, 7.44. Found: C, 69.57; H, 5.34; N, 7.27.

**Phosphoric acid mono-[4-(4-benzyloxy-3-carbamoyl-benzylcarbamoyl)-phenyl] ester (4) and Phosphoric acid mono-[4-(3-carbamoyl-4-hydroxy-benzylcarbamoyl)-phenyl] ester (8)**

To a dichloromethane (5mL) solution of benzamide, 2-(benzyloxy)-5-[[[(4-hydroxyphenyl) carbonyl]amino] methyl] (100mg, 0.26mmol) was added tetrazole (56mg, 0.39mmol) and di-*tert*-butyl diethylphosphoramidate (0.11mL, 0.39mmol). After 3 hours, thin layer analysis indicated that the reaction was completed and *tert*-butylhydroperoxide (1.0mL) was added. After 2 hours, ethyl acetate was added and the organic phase was washed with 5% citric acid (50mL), water, 1N sodium hydroxide (50mL) and then saturated sodium chloride (50mL). The solvent was removed under reduced pressure to give an oil (127mg, 84%). This oil was treated with trifluoroacetic acid (10mL) and water (1mL) for 1 hour. The solvent was removed under reduced pressure to give a colorless oil. The crude residue was purified by preparative HPLC using an acetonitrile/water gradient, 10% to 70% acetonitrile over 140 minutes to yield 2 colorless solids after lyophilization: Phosphoric acid mono-[4-(3-carbamoyl-4-hydroxy-benzylcarbamoyl)-phenyl] ester **4** (4.1mg, 5%). HPLC 100%, *rt*=10.57 min.; Electrospray MS (50/50 acetonitrile/water + 0.1% ammonium hydroxide) *m/z* 365.2 (M-H), and Phosphoric acid mono-[4-(4-benzyloxy-3-carbamoyl-benzylcarbamoyl)-phenyl] ester **8** (21.3mg, 26%). HPLC 100%, *rt*=14.84 min. <sup>1</sup>H NMR (400MHz, DMSO) 8.98(t,1H), 7.86(d,2H), 7.77(s,1H), 7.57(d,2H), 7.49(d,2H), 7.39(m,4H), 7.22(d,2H), 7.16(d,1H), 5.24(s,2H), 4.41(d,2H); Electrospray MS (50/50 acetonitrile/water + 0.1% ammonium hydroxide) *m/z* 455.2 (M-H).

**Phosphoric acid mono-[4-[3-carbamoyl-4-(3,5-dimethyl-benzyloxy)-benzylcarbamoyl]-phenyl] ester (5)**

**5** was synthesized in a manner similar to that described for **4** except that 3, 5-dimethyl benzyl bromide was used for alkylation in place of benzyl bromide. The product was obtained as a colorless powder (85.4 mg, 36%). HPLC 100%, *rt*=17.22 min. <sup>1</sup>H NMR (400MHz, DMSO) 9.01(t,1H), 7.87(d,2H), 7.78(s,1H), 7.39(d,2H), 7.37(d,1H), 7.23(d,2H), 7.15(d,1H), 7.08 (s,2H), 6.96(d,2H), 5.15(s,2H), 4.41(d,2H), 2.26(s,6H); Electrospray Mass Spec. (50/50 acetonitrile/water+0.1% ammonium hydroxide) *m/z* 483.4 (M-H).

**Phosphoric acid mono-[4-(3-carbamoyl-4-cyclohexylmethoxy-benzylcarbamoyl) phenyl] ester (6)**

**6** was synthesized in a manner similar to that described for **4** except that cyclohexylmethyl bromide was used for alkylation in place of benzyl bromide. The product was obtained as a colorless powder (50.0 mg, 21%). HPLC 92%, *rt*=17.23 min. <sup>1</sup>H NMR (400MHz, DMSO) 8.99(t,1H), 7.87(d,2H), 7.78(s,1H), 7.55(d,2H), 7.40(d,1H), 7.23(d,2H), 7.08(d,1H), 4.40(d,2H), 3.91(d,2H), 1.63-1.80(m,6H), 1.06(m,5H); Electrospray MS (50/50 acetonitrile/water+0.1% ammonium hydroxide) *m/z* 461.5 (M-H).

**Phosphoric acid mono-{4-[3-carbamoyl-4-(4-methyl-hexyloxy) benzylcarbamoyl]-phenyl} ester (7)**

**7** was synthesized in a manner similar to that described for **4** except that 1-bromo-4-methylhexane was used for alkylation in place of benzyl bromide. The product was obtained as a colorless powder (100.3 mg, 42%). HPLC 99%, *rt*=18.26 min. <sup>1</sup>H NMR (400MHz, DMSO) 9.00(t,1H), 7.87(d,2H), 7.80(s,1H), 7.57(d,2H), 7.40(d,1H), 7.22(d,2H), 7.09(d,1H), 4.41(d,2H), 4.08(t,2H), 1.72-1.82(m,2H), 1.10-1.45(m,5H), 0.84-0.87(m,6H); Electrospray MS (50/50 acetonitrile/water+0.1% ammonium hydroxide) *m/z* 463.4 (M-H).

**3-Cyano-benzamide (9a)**

To a solution of 3-cyanobenzoic acid (5.00g, 33.9mmol) in 350mL tetrahydrofuran at 0°C was added 4-methyl morpholine ( 9.31mL, 84.7mmol), 1-hydroxybenzotriazole (6.88g, 50.9mmol), followed by 1-(3 dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (9.7g, 50.9mmol). The reaction mixture was stirred for 1 hour at 0°C then concentrated ammonium hydroxide (6.8mL, 50.97mmol) was added. The reaction was allowed to warm slowly to room temperature and stirred overnight. The reaction was then diluted with ethyl acetate and washed with 5% citric acid (3X250mL), saturated sodium bicarbonate (3X250mL), and saturated sodium chloride (1X250mL), dried over magnesium sulfate, filtered and concentrated under reduced pressure to yield a pale yellow powder. The powder was collected and washed with ether, followed by drying under reduced pressure to yield 1.18g (24%). <sup>1</sup>H NMR (400MHz, DMSO) 8.29(s,1H), 8.20(d,2H), 8.18(d,1H), 7.70(m,2H); MS(Cl<sup>+</sup>) *m/z* 130 (100), 130 (20); IR(KBr) 3419, 3308, 3157, 3073, 2231, 1703, 1627, 1581, 1395, 1136, 1001, 906, 877, 786, 674, 548 cm<sup>-1</sup>; Anal. Calcd. for C<sub>8</sub>H<sub>6</sub>N<sub>2</sub>O : C, 65.75; H, 4.14; N, 19.17. Found: C, 65.72; H, 4.13; N, 19.13.

**3-Aminomethyl-benzamide, hydrochloride (9b)**

To a solution of 3-cyano-benzamide (1.00g, 6.8mmol) in 100mL of methanol that had been saturated with anhydrous ammonia was added Raney-Nickel (0.50g). The reaction was pressured to 50 psi and stirred for 18 hours. The solution was filtered through celite and concentrated under reduced pressure. The residue was dissolved in a 1:1 mixture of dichloromethane/diethyl ether (250mL) and anhydrous hydrochloric acid was bubbled through the solution. The solution was concentrated under reduced pressure. The solid was collected, washed with diethyl ether, and dried under reduced pressure to yield a white powder 1.18g (93%). <sup>1</sup>H NMR (400MHz, DMSO) 8.68(d,2H), 7.88(d,1H), 7.66(d,1H), 7.47(d,2H), 4.04(q,2H); MS(Cl<sup>+</sup>) *m/z* 151 (23), 134 (100), 122 (4), 106 (31); IR(KBr) 3387, 3105, 3034, 2994, 1665, 1599, 1479, 1270, 1214, 1120, 1066, 901, 768, 711, 620 cm<sup>-1</sup>. Anal. Calcd. for C<sub>8</sub>H<sub>10</sub>N<sub>2</sub>O·HCl : C, 51.48; H, 5.94; N, 15.01; Cl, 19.00. Found: C, 41.79; H, 5.19; N, 11.91.

**Phosphoric acid mono-[4-(3-carbamoyl-benzylcarbamoyl)-phenyl] ester (9)**

**9** was synthesized in a manner similar to that described for **4** except that 3-aminomethyl-benzamide was coupled to 4-hydroxybenzoic acid and subsequently phosphorylated. The product was obtained as a colorless powder (49.2 mg, 19%). HPLC 100%, *rt*=9.64 min.; <sup>1</sup>H NMR (400MHz, DMSO) 9.02(t,1H), 7.96(s,1H), 7.89(d,2H), 7.75(s,1H),

7.74(d,1H), 7.34-7.46(m,3H), 4.50(d,2H); Electrospray Mass Spec. (50/50 acetonitrile/water+0.1% ammonium hydroxide)  $m/z$  349.4 (M-H).

**(3-methylcarbamoyl-4-hydroxy-benzyl)-carbamic acid tert-butyl ester (10a)**

To a solution of 5-(tert-butoxycarbonylamino-methyl)-2-hydroxy-benzoic acid (2.0g, 7.49mmol) in 75mL tetrahydrofuran at 0°C was added 4-methyl morpholine (2.05mL, 18.72mmol), 1-hydroxybenzotriazole (1.51g, 11.21mmol), followed by 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (2.15g, 11.23mmol) and finally methylamine hydrochloride (0.61g, 8.98mmol). The reaction was allowed to warm slowly to room temperature and stirred overnight. The reaction was then diluted with ethyl acetate and washed with 5% citric acid (3X50mL), saturated sodium bicarbonate (3X50mL), and saturated sodium chloride (1X50mL), dried over magnesium sulfate, filtered and concentrated under reduced pressure to yield a white foam 1.5g (72%). <sup>1</sup>H NMR (400MHz, DMSO) 12.44(bs,1H), 8.76(bs,1H), 7.68(s,1H), 7.25(m,2H), 6.85(d,1H), 4.03 (d,2H), 2.81(d,3H), 1.38(s,9H); MS(CI+)  $m/z$  280 (4), 225 (100), 179 (23), 152 (24), 148 (11), 105 (3); IR(KBr) 3362, 2978, 2934, 1693, 1646, 1600, 1538, 1499, 1367, 1252, 1167, 1048, 942, 860, 815, 783, 677, 607, 504 cm<sup>-1</sup>; Anal. Calcd. for C<sub>14</sub>H<sub>20</sub>N<sub>2</sub>O<sub>4</sub> : C, 59.99; H, 7.19; N, 9.99. Found: C, 59.14; H, 6.90; N, 9.18.

**(4-Cyclohexylmethoxy-3-methylcarbamoyl-benzyl)-carbamic acid tert-butyl ester (10b)**

To a solution (3-methylcarbamoyl-4-hydroxy-benzyl)-carbamic acid tert-butyl ester (1.5g, 5.35mmol) in 10mL methanol at room temperature was added cesium carbonate (1.92g, 5.89mmol). The reaction was stirred overnight. The reaction was then concentrated under reduced pressure. N,N-dimethylformamide (25mL) was then added and the reaction was then reconcentrated under reduced pressure to chase off any remaining methanol. The residue was then suspended in N,N-dimethylformamide (10mL). Cyclohexylmethyl bromide (0.821mL, 5.89mmol) was then added and the reaction was heated at 65°C for 4 hours. The reaction was then concentrated under reduced pressure. The residue was diluted with ethyl acetate (100mL) and 5% citric acid (25mL). The organic layer was washed with 5% citric acid (2X150mL), 1N sodium hydroxide (2X25mL), 5% citric acid (2X25mL), and saturated sodium chloride (1X25mL), dried over magnesium sulfate, filtered and concentrated under reduced pressure to yield an oil. Purification by silica gel chromatography [ethyl acetate/hexane (50/50) yielded a clear oil, 0.74g (37%). <sup>1</sup>H NMR (400MHz, DMSO) 7.99(d,1H), 7.60(s,1H), 7.37(t,1H), 7.26(d,1H), 7.06 (d,1H), 4.03(d,2H), 3.90(d,2H), 2.79(d,3H), 1.64-1.79(m,6H), 1.38(s,9H), 1.03-1.34(m,5H); MS(CI+)  $m/z$  377 (13), 321 (100), 275 (29), 225 (11), 179 (37), 164 (13), 148 (11); IR(KBr) 3408, 3326, 2974, 2927, 2853, 1709, 1652, 1607, 1536, 1497, 1390, 1364, 1245, 1171, 1107, 1014, 946, 863, 816, 783cm<sup>-1</sup>; Anal. Calcd. for C<sub>21</sub>H<sub>32</sub>N<sub>2</sub>O<sub>4</sub> : C, 66.99; H, 8.57; N, 7.44. Found: C, 66.53; H, 8.65; N, 7.17.

**Phosphoric acid mono-[4-(4-cyclohexylmethoxy-3-methylcarbamoyl-benzyl)carbamoyl]-phenyl ester (10)**

**10** was synthesized in a manner similar to that described for **4** except that 4-cyclohexylmethoxy-3-methylcarbamoyl-benzylamine was used for the coupling and subsequently phosphorylated. The product was obtained as a colorless powder (79.3mg, 49%). HPLC 100%, *rt*=18.27 min.; <sup>1</sup>H NMR (400MHz, DMSO) 7.85(d,2H), 7.68(s,1H), 7.39(d,1H), 7.24(d,2H), 7.08(d,1H), 4.41(s,2H), 3.71(d,2H), 2.80(s,3H), 1.63-1.78(m,6H), 1.03-1.26(m,5H); Electrospray MS (50/50 acetonitrile/water+0.1% ammonium hydroxide)  $m/z$  475.5 (M-H).

**4-Cyclohexylmethoxy-benzonitrile (11a)**

To a solution of 4-cyanophenol (10.0g, 83.9mmol) in 170mL methanol at room temperature was added cesium carbonate (27.3g, 83.9mmol). The reaction was stirred

overnight. The reaction was then concentrated under reduced pressure. N,N-dimethylformamide (75mL) was then added and the reaction was then reconcentrated under reduced pressure to chase off any remaining methanol. The residue was then suspended in N,N-dimethylformamide (170mL). Cyclohexylmethyl bromide (11.6mL, 83.9mmol) was then added and the reaction was heated at 65°C for 4 hours. The reaction was then concentrated under reduced pressure. The residue was diluted with ethyl acetate (500mL) and 5% citric acid (150mL). The organic layer was washed with 5% citric acid (2X150mL), 1N sodium hydroxide (2X150mL), 5% citric acid (2X150mL), and saturated sodium chloride (1X150mL), dried over magnesium sulfate, filtered and concentrated under reduced pressure to yield a pale yellow powder. The powder was collected and washed with ether, followed by drying under reduced pressure to yield 13.9g (77%). <sup>1</sup>H NMR (400MHz, DMSO) 7.74(d,2H), 7.10(d,2H), 3.85(d,2H), 1.63-1.80(m,6H), 0.98-1.30(m,5H); MS(CI+) *m/z* 216 (100), 134 (7), 120 (15), 97 (16); IR(KBr) 2926, 2850, 2223, 1606, 1510, 1466, 1305, 1262, 1173, 1014, 895, 8333, 547cm<sup>-1</sup>; Anal. Calcd. for C<sub>14</sub>H<sub>17</sub>NO : C, 78.10; H, 7.96; N, 6.51. Found: C, 78.04; H, 7.90; N, 6.50.

#### 4-Cyclohexylmethoxy-benzylamine, hydrochloride (11b)

To a solution of 4-cyclohexylmethoxy-benzonitrile (3.0g, 13.95mmol) in 100mL of methanol that had been saturated with anhydrous ammonia was added Raney-Nickel (2.0g). The reaction was pressured to 50 psi and stirred for 20 hours. The solution was filtered through celite and concentrated under reduced pressure. The residue was dissolved in a 1:1 mixture of dichloromethane/diethyl ether (250mL) and anhydrous hydrochloric acid was bubbled through the solution. The solution was concentrated under reduced pressure. The solid was collected, washed with diethyl ether, and dried under reduced pressure to yield a white powder, 3.48g (97%). <sup>1</sup>H NMR (400MHz, DMSO) 7.39(d,2H), 7.95(d,2H), 3.91(s,2H), 3.77(d,2H), 1.63-1.69(m,6H), 1.29-0.97(m,5H); MS(CI+) *m/z* 219 (38), 203 (95), 165 (5), 123 (46), 107 (100), 97 (18); IR(KBr) 3001, 2924, 2853, 2569, 2340, 2050, 1616, 1517, 1464, 1296, 1250, 1138, 1077, 1035, 963, 874, 824, 754, 553 cm<sup>-1</sup>. Anal. Calcd. for C<sub>14</sub>H<sub>21</sub>NO·HCl : C, 65.74; H, 8.67; N, 5.48. Found: C, 64.43; H, 8.55; N, 5.35.

#### Phosphoric acid mono-[4-(4-cyclohexylmethoxy-benzylcarbamoyl)-phenyl] ester (11)

**11** was synthesized in a manner similar to that described for **4** except that 4-cyclohexylmethoxy-benzylamine was coupled to 4-hydroxybenzoic acid and subsequently phosphorylated. The product was obtained as a colorless powder (80.2mg, 44%). HPLC 100%, rt=20.65 min.; <sup>1</sup>H NMR (400MHz, DMSO) 8.90(t,1H), 7.88(d,2H), 7.22(m,4H), 6.86(d,2H), 4.38(d,2H), 1.62-1.80(m,6H), 0.96-1.28(m,5H); Electrospray Mass Spec. (50/50 acetonitrile/water+0.1% ammonium hydroxide) *m/z* 418.4 (M-H).

#### 5-Acetyl-2-cyclohexylmethoxy-benzamide (12a)

To a solution of 5-acetylsalicylamide (2.0g, 11.17mmol) in 25mL N,N-dimethylformamide is added potassium carbonate (2.31g, 16.75mmol) followed by cyclohexylmethyl bromide (1.71mL, 12.28mmol) The reaction is heated to 100°C overnight.. The reaction was then concentrated under reduced pressure. The residue was diluted with ethyl acetate and 5% citric acid. The organic layer was washed with 5% citric acid (2X50mL), 1N sodium hydroxide (2X50mL), 5% citric acid (2X50mL), and saturated sodium chloride (1X50mL), dried over magnesium sulfate, filtered and concentrated under reduced pressure to yield a pale yellow powder. The powder was collected and washed with ether, followed by drying under reduced pressure to yield 2.10g (68%). <sup>1</sup>H NMR (400MHz, DMSO) 8.82(s,1H), 8.07(d,1H), 7.20(d,1H), 4.04(d,2H), 1.64-1.82(m,6H), 1.02-1.20(m,5H); MS(CI+) *m/z* 357 (2), 301 (39), 228 (71), 150 (15), 91 (100); IR(KBr) 3455, 3202, 2934, 2853, 1672, 1538, 1495, 1455, 1365, 1253, 1178, 1105, 1004, 973, 829, 534 cm<sup>-1</sup>.

1; Anal. Calcd. for C<sub>16</sub>H<sub>21</sub>N<sub>1</sub>O<sub>3</sub> : C, 69.79; H, 7.69; N, 5.09. Found: C, 69.39; H, 7.69; N, 4.91.

**2-Cyclohexylmethoxy-5-(1-hydroxyimino-ethyl)-benzamide (12b)**

To a solution of 5-acetyl-2-cyclohexylmethoxy-benzamide (1.0 g, 3.63 mmol) in pyridine (25 mL) at room temperature was added hydroxylamine hydrochloride (0.38 g, 5.45 mmol). The reaction was stirred 48 hours. The reaction was then concentrated under reduced pressure, diluted with ethyl acetate and washed with 5% citric acid (3X100 mL), saturated sodium chloride (1X100 mL), dried over magnesium sulfate, filtered, and concentrated under reduced pressure to yield a foam. <sup>1</sup>H NMR (400 MHz, DMSO) 11.07(s,1H), 8.08(d,1H), 7.72(d,1H), 7.61(bs,1H), 7.53(bs,1H), 7.14(d,1H), 4.03(d,2H), 2.13(s,3H), 1.74(m,6H), 1.11(m,5H). Mass Spectrum (Chemical Ionization, 1% NH<sub>3</sub> in CH<sub>4</sub>) *m/z* 291 (M+H).

**5-(1-Amino-ethyl)-2-cyclohexylmethoxy-benzamide, hydrochloride (12c)**

To a solution of 2-cyclohexylmethoxy-5-(1-hydroxyimino-ethyl)-benzamide (0.50 g, 1.72 mmol) in methanol (20 mL) and triethylamine (5 mL) was added wet Raney Nickel (0.30 g). The reaction was then pressured under an atmosphere of hydrogen (45psi) for 16.5 hours. The reaction was then concentrated under reduced pressure to yield a white solid. <sup>1</sup>H NMR (400 MHz, DMSO) 7.86(s,1H), 7.59(d,2H), 7.47(d,1H), 7.10(d,1H), 4.03(q,1H), 3.97(d,2H), 1.83(m,6H), 1.23(m,8H). Mass Spectrum (Chemical Ionization, 1% NH<sub>3</sub> in CH<sub>4</sub>) *m/z* 277 (M+H).

**Phosphoric acid mono-{4-[1-(3-carbamoyl-4-cyclohexylmethoxy-phenyl)-ethylcarbamoyl]-phenyl} ester (12)**

**12** was synthesized in a manner similar to that described for **4** except that 5-(1-amino-ethyl)-2-cyclohexylmethoxy-benzamide was coupled to 4-hydroxybenzoic acid and subsequently phosphorylated. The product was obtained as a colorless powder (49.2 mg, 53%). HPLC 100%, *rt*=17.73 min.; <sup>1</sup>H NMR (400MHz, DMSO) 8.77(t,1H), 7.87(m,3H), 7.50(d,2H), 7.43(d,2H), 7.21(d,2H), 7.07(d,1H), 5.11(m,1H), 3.91(d,2H), 1.63-1.80(m,6H), 1.45(d,3H), 1.08-1.30(m,5H); Electrospray Mass Spec. (50/50 acetonitrile/water+0.1% ammonium hydroxide) *m/z* 475.4 (M-H).

**Phosphoric acid mono-[4-(3-carbamoyl-4-cyclohexylmethoxy-benzylcarbamoyl)-2,6-dimethyl phenyl] ester (13)**

**13** was synthesized in a manner similar to that described for **4** except that 3, 5-dimethyl-4-hydroxy benzoic acid was coupled. The product was obtained as a colorless powder (79.0 mg, 33%). HPLC 100%, *rt*=18.26 min. <sup>1</sup>H NMR (400MHz, DMSO) 8.89(t,1H), 7.77(s,1H), 7.55(m,4H), 7.38(d,1H), 7.08(d,1H), 4.37(d,2H), 3.91(d,2H), 2.30(s,6H), 1.63-1.82(m,6H), 1.03-1.29(m,5H); Electrospray MS (50/50 acetonitrile/water+0.1% ammonium hydroxide) *m/z* 489.4 (M-H).

**[Difluoro-(4-iodo-phenyl)-methyl]-phosphonic acid diethylester (14a)**

**14a** was prepared according to literature procedure. *J. Org. Chem.* **1993**, *58*, 1337.

**[Difluoro-(4-formyl-phenyl)-methyl]-phosphonic acid diethyl ester (14b)**

To a solution of [difluoro-(4-iodo-phenyl)-methyl]-phosphonic acid diethyl ester (1.6g, 4.10mmol) in anhydrous ether (40mL) at -78°C was added dropwise n-butyl lithium (2.5M in hexane, 2.46mL, 6.15mmol). The brown solution was stirred at -78°C for 2 minutes. Ethyl formate (0.66mL, 8.20mmol) was then added and the reaction was stirred for 10 minutes at -78°C. The mixture was then quenched with saturated ammonium chloride (10mL) and warmed to room temperature. The reaction was then diluted with ether. The organic layers were washed with saturated sodium chloride (20mL), dried over magnesium sulfate, filtered and concentrated under reduced pressure to yield a yellow oil. Purification

by silica gel chromatography [ethyl acetate/hexane (30/70) gradient to (50/50)] afforded the aldehyde 268mg (22%) as a clear oil. <sup>1</sup>H NMR (400MHz, DMSO) 10.28(s,1H), 8.25(d,2H), 7.97(d,2H), 4.42(m,4H), 1.40(t,6H).

**4-[(Diethoxy-phosphoryl)-difluoro-methyl]-benzoic acid (14c)**

To a solution of [difluoro-(4-formyl-phenyl)-methyl]-phosphonic acid diethyl ester (260mg,0.89mmol) in acetone (25mL) at room temperature was added Jones reagent (5mL). The reaction was quenched by addition of ethanol (5mL). The reaction was then concentrated under reduced pressure to 5mL. The residue was diluted with ethyl acetate and washed with water (2X20mL), saturated sodium chloride (20mL), dried over magnesium sulfate, filtered and concentrated under reduced pressure to yield a white crystalline solid 268mg (98%). <sup>1</sup>H NMR (400MHz, DMSO) 8.09(d,2H), 7.70(d,2H), 4.15(m,4H), 1.22(t,6H); MS(CI+) *m/z* 309 (100), 289 (21), 281 (22), 204 (68), 186 (16), 171 (22), 154 (87), 109 (30); IR(KBr) 3065, 2988, 2919, 2873, 2851, 1690, 1615, 1510, 1427, 1408, 1319, 1288, 1272, 1165, 1118, 1051, 1011, 945, 857, 759, 710, 556; Anal. Calcd. for C<sub>12</sub>H<sub>15</sub>F<sub>2</sub>O<sub>5</sub>P : C, 46.76; H, 4.91; Found: C, 47.89; H, 4.95.

**{[4-(3-Carbamoyl-4-cyclohexylmethoxy-benzylcarbamoyl)-phenyl]-difluoro-methyl}-phosphonic acid diethyl ester**

4-[(diethoxy-phosphoryl)-difluoro-methyl]-benzoic acid was coupled as described for compound **16**. The crude residue was purified by preparative HPLC using an acetonitrile/water gradient, 20% to 65% acetonitrile over 120 minutes to yield a colorless solid after lyophilization (79mg, 30%). HPLC 100%, *rt*=23.64 min. <sup>1</sup>H NMR (400MHz, DMSO) 9.21(t,1H), 8.01(d,2H), 7.80(s,1H), 7.66(d,2H), 7.53(d,2H), 7.40(d,1H), 7.09(d,1H), 4.43(d,2H), 4.13(m,4H), 3.90(d,2H), 1.63-1.80(m,6H), 1.00-1.29(m,11H); Atmospheric Pressure Chemical Ionization (20/80 methanol/acetonitrile) *m/z* 553.5.(M+H).

**{[4-(3-Carbamoyl-4-cyclohexylmethoxy-benzylcarbamoyl)-phenyl]-difluoro-methyl}-phosphonic acid (14)**

{[4-(3-carbamoyl-4-cyclohexylmethoxy-benzylcarbamoyl)-phenyl]-difluoro-methyl}-phosphonic acid diethyl ester (100mg, 0.181mmol) was cleaved with 5.0mL of the following solution (4.83mL trifluoromethanesulfonic anhydride and 3.67mL dimethyl sulfide diluted to 25.0mL with trifluoroacetic acid) for 2 hours at room temperature. The residue was purified by HPLC using an acetonitrile/water gradient, 10% to 55% acetonitrile over 140 minutes to yield a colorless solid after lyophilization (39.2 mg, 44%). HPLC 100%, *rt*=17.36 min. <sup>1</sup>H NMR (400MHz, DMSO) 9.17(t,1H), 7.96(d,2H), 7.79(s,1H), 7.61(m,3H), 7.53(s,1H), 7.40(d,1H), 7.09(d,1H), 4.44(d,2H), 3.90(d,2H), 1.64-1.80(m,6H), 1.00-1.29(m,5H); Electrospray Mass Spec. (50/50 acetonitrile/water+0.1% ammonium hydroxide) *m/z* 495.4 (M-H).

**4-[[[3-(aminocarbonyl)-4-(cyclohexylmethoxy)phenyl]methyl]amino]carbonyl]-1,2-benzenedicarboxylic acid (15)**

To a dichloromethane (5mL) solution of 4-cyclohexylmethoxy-3-carbamoyl-benzylamine at room temperature was added 4-methyl morpholine ( 0.164mL, 1.5mmol), followed by dropwise addition of trimellitic anhydride chloride ( 0.105mg, 1.5mmol). The reaction was stirred overnight. The reaction was then diluted with ethyl acetate and washed with 5% citric acid (3X50mL) and saturated sodium chloride (1X50mL), dried over magnesium sulfate, filtered and concentrated under reduced pressure to yield a white foam. The residue was purified by HPLC using an acetonitrile/water gradient, 10% to 45% acetonitrile over 140 minutes to yield a colorless solid after lyophilization (25.1 mg, 11%). HPLC 96%, *rt*= 19.16min. <sup>1</sup>H NMR (400MHz, DMSO) 9.29(t,1H), 8.22(bs,1H), 8.05(d,2H),

7.79(m,2H), 7.55(d,2H), 7.42(d,2H), 7.10(d,1H), 4.42(d,2H), 3.90(d, 2H), 1.64-1.80(m,6H), 1.03-1.26(m,5H); Electrospray Mass Spec. (50/50 acetonitrile/water+0.1% ammonium hydroxide)  $m/z$  453.4 (M-H).

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