

## Supporting Information for:

### 3-(3,4-Dihydroisoquinolin-2(1*H*)-ylsulfonyl)benzoic acids; Highly Potent and Selective Inhibitors of the Type 5 17- $\beta$ -hydroxysteroid Dehydrogenase AKR1C3

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### 3-(3,4-Dihydroisoquinolin-2(1*H*)-ylsulfonyl)benzoic acids; a New Class of Highly

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## Compounds of Table 2 (Scheme 1A)

**3-({3,4-Dihydroisoquinolin-2[1H]-yl}sulfonyl)benzoic acid (17).**<sup>S1</sup> Reaction of 3-(chlorosulfonyl)benzoic acid (**95**) and 1,2,3,4-tetrahydroisoquinoline with (**96a**) by method A, followed by re-precipitation of the crude product from EtOAc:hexanes, afforded **17** (yield 50%, unoptimized) as an amorphous white solid; mp 276-280 °C; <sup>1</sup>H NMR [(CD<sub>3</sub>)<sub>2</sub>SO]: δ 13.53 (br s, 1H), 8.27 (t, *J* = 1.6 Hz, 1H), 8.21 (d, *J* = 7.8 Hz, 1H), 8.07 (dt, *J* = 7.8, 1.5 Hz, 1H), 7.76 (t, *J* = 7.8 Hz, 1H), 7.13 (m, 4H), 4.24 (s, 2H), 3.35 (t<sub>overlapping water peak</sub>, *J* = 6.0 Hz, 2H), 2.84 (t, *J* = 6.0 Hz, 2H); HRESIMS calcd. for C<sub>16</sub>H<sub>15</sub>NO<sub>4</sub>S *m/z* [M + H]<sup>+</sup> 318.0795, found 318.0794; HPLC purity: 99.8%.

**3-({5,6-Dihydropyridin-1[2H]-yl}sulfonyl)benzoic acid (18).** Reaction of 3-(chlorosulfonyl)benzoic acid (**95**) and 1,2,3,6-tetrahydropyridine by method A, followed by recrystallization of the crude product from EtOAc:hexanes, afforded **18** (58%, unoptimized) as cream flakey crystals; mp 166-168 °C; <sup>1</sup>H NMR [(CD<sub>3</sub>)<sub>2</sub>SO]: δ 13.54 (br s, 1H), 8.23 (m, 2H), 8.01 (dt, *J* = 7.9, 1.5 Hz, 1H), 7.78 (m, 1H), 5.73 (m, 1H), 5.65 (m, 1H), 3.53 (m, 2H), 3.14 (t, *J* = 5.7 Hz, 2H), 2.12 (m, 2H); HRESIMS calcd. for C<sub>12</sub>H<sub>14</sub>NO<sub>4</sub>S *m/z* [M + H]<sup>+</sup> 268.0638, found 268.0641; HPLC purity: 98.9%.

**3-({6,7-Dihydrothieno[3,2-c]pyridin-5(4H)-yl}sulfonyl)benzoic acid (19).** Reaction of 3-(chlorosulfonyl)benzoic acid (**95**) and 4,5,6,7-tetrahydrothieno[3,2-c]pyridine hydrochloride by method A (omitting DMF), followed by reprecipitation of the crude product from EtOAc:hexanes, afforded **19** (31%) as an amorphous white solid; mp 221-223 °C; <sup>1</sup>H NMR [(CD<sub>3</sub>)<sub>2</sub>SO]: δ 13.50 (br s, 1H), 8.26 (d, *J* = 1.6 Hz, 1H), 8.21 (dt, *J* = 8.0, 1.4 Hz, 1H), 8.05 (ddd, *J* = 7.9, 1.9, 1.2 Hz, 1H), 7.75 (t, *J* = 7.8 Hz, 1H), 7.31 (d, *J* = 5.2 Hz, 1H), 6.86 (d, *J* = 5.2 Hz, 1H), 4.20 (s, 2H), 3.43 (t<sub>overlapping water peak</sub>, *J* = 5.8 Hz, 2H), 2.83 (t, *J* = 5.6 Hz, 2H); HRESIMS calcd. for C<sub>14</sub>H<sub>14</sub>NO<sub>4</sub>S<sub>2</sub> *m/z* [M + H]<sup>+</sup> 324.0359, found 324.0358; HPLC purity: 100%.

**3-(Indolin-1-ylsulfonyl)benzoic acid (20).** Reaction of 3-(chlorosulfonyl)benzoic acid (**95**) with indoline by method A (omitting DMF), followed by re-precipitation of the crude product from EtOAc:hexanes, afforded **20** (12%, unoptimized) as an amorphous off-white solid; mp 171-172 °C; <sup>1</sup>H NMR [(CD<sub>3</sub>)<sub>2</sub>SO]: δ 13.55 (br s, 1H), 8.23 (t, *J* = 1.6 Hz, 1H), 8.19 (d, *J* = 7.9 Hz, 1H), 8.05 (dt, *J* = 7.9, 1.5 Hz, 1H), 7.71 (t, *J* = 7.9 Hz, 1H), 7.49 (d, *J* = 7.9 Hz, 1H), 7.22 (m, 1H), 7.16 (dd *J* = 7.4, 0.6 Hz, 1H), 7.00 (td, *J* = 7.4, 0.9 Hz, 1H), 3.92 (m, 2H), 2.89 (t, *J* = 8.4 Hz, 2H); HRESIMS calcd. for C<sub>16</sub>H<sub>13</sub>NNaO<sub>4</sub>S *m/z* [M + Na]<sup>+</sup> 326.0457, found 326.0467; HPLC purity: 99.9%.

**3-(Isoindolin-2-ylsulfonyl)benzoic acid (21).** Reaction of 3-(chlorosulfonyl)benzoic acid (**95**) and isoindoline by method A was followed by a modified work-up. Following completion of the reaction (~1.5 h), the resulting suspension was diluted with acetone and filtered. The

resulting solid was re-suspended in 1M NaOH, filtered, and the filtrate re-acidified with 1M HCl gave a crude product, which was-precipitated from EtOAc:hexanes to furnish **21** (4%, unoptimized) as an amorphous off-white solid; mp 219-221 °C; <sup>1</sup>H NMR [(CD<sub>3</sub>)<sub>2</sub>SO]: δ 13.49 (br s, 1H), 8.31 (t, *J* = 1.6 Hz, 1H), 8.19 (d, *J* = 7.8 Hz, 1H), 8.11 (d, *J* = 7.9, 1H), 7.75 (t, *J* = 7.8 Hz, 1H), 7.24 (m, 4H), 4.60 (s, 4H); HRESIMS calcd. for C<sub>15</sub>H<sub>14</sub>NO<sub>4</sub>S *m/z* [M + H]<sup>+</sup> 304.0638, found 304.0638; HPLC purity: 99.4%.

**3-({3,4-Dihydroquinolin-1[2*H*]-yl)sulfonyl)benzoic acid (22).** Reaction of 3-(chlorosulfonyl)benzoic acid (**95**) with 1,2,3,4-tetrahydroquinoline by method A (omitting DMF), followed by re-precipitation of the resulting dark brown tarry mixture from EtOAc:hexanes, afforded **22** (2%, unoptimized) as an amorphous off-white solid; mp 140-141 °C; <sup>1</sup>H NMR [(CD<sub>3</sub>)<sub>2</sub>SO]: δ 13.46 (br s, 1H), 8.17 (d, *J* = 7.8 Hz, 1H), 8.06 (d, *J* = 1.6 Hz, 1H), 7.81 (dt, *J* = 7.8, 1.5 Hz, 1H), 7.68 (t, *J* = 7.8 Hz, 1H), 7.61 (d, *J* = 8.1 Hz, 1H), 7.21 (m, 1H), 7.09 (m, 2H), 3.78 (m, 2H), 2.40 (t, *J* = 6.7 Hz, 2H), 1.60 (m, 2H); HRESIMS calcd. for C<sub>16</sub>H<sub>16</sub>NO<sub>4</sub>S *m/z* [M + H]<sup>+</sup> 318.0795, found 318.0801; HPLC purity: 99.5%.

**3-(*N*-Naphthalen-2-ylsulfamoyl)benzoic acid (23).** A solution of 3-(chlorosulfonyl)benzoic acid (**95**) (1 eq.) in dry CH<sub>2</sub>Cl<sub>2</sub> was treated with TEA (1.5 eq.) and 3-naphthylamine (1.2 eq.) and stirred at 20 °C until completion. Solvent was removed under reduced pressure and the crude was purified by flash-column chromatography (EtOAc/petroleum ether 1:4) on silica to give **23** (20% yield); mp 215-217 °C. <sup>1</sup>H NMR [(CD<sub>3</sub>)<sub>2</sub>SO]: δ 13.43 (s, 1 H), 10.60 (s, 1 H), 8.35 (s, 1 H), 8.10 (d, *J* = 8.40 Hz, 1 H), 8.00 (d, *J* = 7.2 Hz, 1 H), 7.81 - 7.76 (m, 3 H), 7.65 (t, *J* = 7.6 Hz, 1 H), 7.57 (s, 1 H), 7.42 (m<sub>c</sub>, 2 H), 7.28 (d, *J* = 8.8 Hz, 1 H) ppm. HRMS (ESI): *m/z* = [M-H]<sup>-</sup> calculated: 326.0493; found: 326.0484; HPLC purity: 98.7 %. Anal. Calcd for C<sub>17</sub>H<sub>13</sub>NO<sub>4</sub>S.0.25H<sub>2</sub>O: C, H, N.

### Compounds of Table 3 (Schemes 1B-1C)

**3-((1-Methyl-3,4-dihydroisoquinolin-2(1H)-yl)sulfonyl)benzoic acid (25).** Reaction of 3-(chlorosulfonyl)benzoic acid (**95**) and 1-methyl-1,2,3,4-tetrahydroisoquinoline<sup>S2</sup> (**96b**) by method A, followed by re-precipitation of the crude product from EtOAc:hexanes, afforded **25** (16%, unoptimized) as an off-white solid; mp 153-155°C; <sup>1</sup>H NMR [(CD<sub>3</sub>)<sub>2</sub>SO]: δ 7.90 (d, *J* = 7.3 Hz, 1H), 7.77 (s, app. 0.2H), 7.72 (s, app. 0.8H), 7.66-7.46 (m, 2H), 7.35-6.87 (m, 8H), 5.52 (app. br d, *J* = 7.0 Hz, 1H), 5.13 (app. br dd, *J* = 30.0, 6.8 Hz, 1H), 4.52 (br s, app. 0.5H), 3.86 (m, 1H), 3.49 (m, 1H), 3.29-3.04 (m, 2H), 2.80 (m, app. 1.5H), 2.62 (m, 2H), 1.57-1.20 (m, 6H); HRESIMS calcd. for C<sub>17</sub>H<sub>17</sub>NNaO<sub>4</sub>S *m/z* (M + Na)<sup>+</sup> 354.0770, found 354.0771; calcd. for C<sub>17</sub>H<sub>18</sub>NO<sub>4</sub>S *m/z* (M + H)<sup>+</sup> 332.0951, found 332.0953; HPLC purity: 98.2%.

**3-(3-Methyl-3,4-dihydroisoquinolin-2(1H)-ylsulfonyl)benzoic acid (26).** Reaction of 3-(chlorosulfonyl)benzoic acid (**95**) with 3-methyl-1,2,3,4-tetrahydroisoquinoline (**96c**) by method A gave acid **26** (yield 49 %); mp 182-184 °C. <sup>1</sup>H NMR [(CD<sub>3</sub>)<sub>2</sub>SO]: δ 13.45 (br s, 1H), 8.24 (d, *J* = 1.6 Hz, 1H), 8.10 (dt, *J* = 7.8, 1.3 Hz, 1H), 8.03 (ddd, *J* = 7.9, 1.9, 1.2 Hz, 1H), 7.63 (t, *J* = 7.8 Hz, 1H), 7.18 (d, *J* = 7.4 Hz, 1H), 7.09 (m, 2H), 6.98 (d, *J* = 7.2 Hz, 1H), 5.09 (q, *J* = 13.4, 6.7 Hz, 1H), 3.83 (m, 1H), 3.46 (m, 1H), 2.72-2.52 (m<sub>overlapping</sub> DMSO peak, 2H), 1.37 (d, *J* = 6.8 Hz, 3H).

HRESIMS calcd for  $C_{17}H_{16}NO_4S$   $m/z$   $[M-H]^-$  330.0806; found: 330.0803; HPLC purity: 97%.  
Anal. Calcd for  $C_{17}H_{17}NO_4S$ : C,H,N.

**3-({5-Amino-3,4-dihydroisoquinolin-2[1H]-yl)sulfonyl}benzoic acid (27).** Reaction of 3-(chlorosulfonyl)benzoic acid (**95**) with 5-amino-1,2,3,4-tetrahydroisoquinoline (**96d**) by method A (omitting DMF), followed by re-precipitation of the crude product from MeOH:EtOAc, afforded **27** (2%, unoptimized) as an amorphous white solid; mp 276-280 °C;  $^1H$  NMR  $[(CD_3)_2SO]$ :  $\delta$  8.27 (t,  $J$  = 1.6 Hz, 1H), 8.13 (dd,  $J$  = 7.7, 1.2 Hz, 1H), 7.72 (dt,  $J$  = 7.7, 1.6 Hz, 1H), 7.53 (t,  $J$  = 7.7 Hz, 1H), 6.84 (d,  $J$  = 7.7 Hz, 1H), 6.47 (d,  $J$  = 7.4 Hz, 1H), 6.34 (d,  $J$  = 7.4 Hz, 1H), 4.85 (s, 2H), 4.01 (s, 2H), 3.24 (t,  $J$  = 6.1 Hz, 2H), 2.53 (t<sub>overlapping DMSO peak</sub>,  $J$  = 6.1 Hz, 2H) [-CO<sub>2</sub>H *not visible*]; HRESIMS calcd. for  $C_{16}H_{17}N_2O_4S$   $m/z$   $[M+H]^+$  333.0904, found 333.0899; HPLC purity: 96.8%.

**3-((5-Nitro-3,4-dihydroisoquinolin-2(1H)-yl)sulfonyl)benzoic acid (28).** Reaction of 3-(chlorosulfonyl)benzoic acid (**95**) and 5-nitro-1,2,3,4-tetrahydroisoquinoline<sup>S1</sup> (**96e**) by method A, followed by re-precipitation of the crude product from EtOAc/hexanes, afforded **28** (22%, unoptimized) as an amorphous white solid; mp 249-251 °C;  $^1H$  NMR  $[(CD_3)_2SO]$ :  $\delta$  13.62 (br s, 1H), 8.28 (t,  $J$  = 1.6 Hz, 1H), 8.21 (dt,  $J$  = 7.9, 1.3 Hz, 1H), 8.06 (ddd,  $J$  = 7.9, 1.8, 1.2 Hz, 1H), 7.83 (dd,  $J$  = 8.0, 1.0 Hz, 1H), 7.75 (t,  $J$  = 7.8 Hz, 1H), 7.59 (d,  $J$  = 7.4 Hz, 1H), 7.43 (t,  $J$  = 7.9 Hz, 1H), 4.38 (s, 2H), 3.38 (t<sub>overlapping water peak</sub>,  $J$  = 6.0 Hz, 2H), 3.03 (t,  $J$  = 6.0 Hz, 2H); HRESIMS calcd. for  $C_{16}H_{14}N_2NaO_6S$   $m/z$   $(M+Na)^+$  385.0465; found 385.0477; calc. for  $C_{16}H_{15}N_2O_6S$   $m/z$   $(M+H)^+$  363.0645, found 363.0653; HPLC purity: 100%.

**3-(5-Chloro-3,4-dihydroisoquinolin-2(1H)-ylsulfonyl)benzoic acid (29).** Reaction of 3-(chlorosulfonyl)benzoic acid (**95**) with 5-chloro-1,2,3,4-tetrahydroisoquinoline (**96f**) by method A gave acid **29** (yield 16%); mp 258-260 °C.  $^1H$  NMR  $[(CD_3)_2SO]$ :  $\delta$  13.52 (s, 1 H), 8.26 (s, 1 H), 8.20 (d,  $J$  = 7.85 Hz, 1 H), 8.03 (d,  $J$  = 7.48 Hz, 1 H), 7.73 (t,  $J$  = 7.77 Hz, 1 H), 7.32 - 7.26 (m, 1 H), 7.22 - 7.16 (m, 1 H), 4.27 (s, 2 H), 3.41 (t,  $J$  = 6.01 Hz, 2 H), 2.75 (t,  $J$  = 6.08 Hz, 2 H) ppm. HRESIMS calcd. for  $C_{16}H_{13}ClNO_4S$   $m/z$   $[M-H]^-$  350.0259; found: 350.0256; HPLC purity: 96%. Anal. Calcd. for  $C_{16}H_{14}ClNO_4S$ : C,H,N.

**3-(5-Bromo-3,4-dihydroisoquinolin-2(1H)-ylsulfonyl)benzoic acid (30).** Reaction of 3-(chlorosulfonyl)benzoic acid (**95**) with 5-bromo-1,2,3,4-tetrahydroisoquinoline (**96g**) by method A gave **30** (yield 43%); mp 267-269 °C.  $^1H$  NMR  $[(CD_3)_2SO]$ :  $\delta$  13.54 (s, 1 H), 8.26 (s, 1 H), 8.20 (d,  $J$  = 7.81 Hz, 1 H), 8.03 (d,  $J$  = 7.89 Hz, 1 H), 7.73 (t,  $J$  = 7.73 Hz, 1 H), 7.45 (d,  $J$  = 7.88 Hz, 1 H), 7.24 (d,  $J$  = 7.12 Hz, 1 H), 7.11 (t,  $J$  = 7.81 Hz, 1 H), 4.28 (s, 2 H), 3.41 (t,  $J$  = 6.09 Hz, 2 H), 2.75 (t,  $J$  = 6.09 Hz, 2 H) ppm. HRESIMS calcd. for  $C_{16}H_{14}BrNO_4S$   $m/z$   $[M-H]^-$  393.9754; found: 393.9744/395.9726; HPLC purity: 96.2%. Anal. Calcd for  $C_{16}H_{14}BrNO_4S$ : C,H,N.

**3-(5-Iodo-3,4-dihydroisoquinolin-2(1H)-ylsulfonyl)benzoic acid (31).** Reaction of 3-(chlorosulfonyl)benzoic acid (**95**) with 5-iodo-1,2,3,4-tetrahydroisoquinoline (**96h**) by method A gave acid **31** (yield: 68 %); mp 257-260 °C.  $^1H$  NMR  $[(CD_3)_2SO]$ :  $\delta$  13.53 (s, 1 H), 8.26 (s, 1 H), 8.19 (d,  $J$  = 7.89 Hz, 1 H), 8.04 (d,  $J$  = 8.45 Hz, 1 H), 7.73 (t,  $J$  = 7.88 Hz, 1 H), 7.69 (d,  $J$  = 7.00 Hz, 1 H), 7.24 (d,  $J$  = 7.08 Hz, 1 H), 6.94 (t,  $J$  = 7.76 Hz, 1 H), 4.26 (s, 2 H), 3.40 (t,  $J$  = 6.12 Hz, 2 H), 2.66 (t,  $J$  = 6.12 Hz, 2 H) ppm. HRMS (ESI):  $m/z$  =  $[M+H]^+$  calculated: 443.9761;

found: 443.9768;  $[M+Na]^+$  calculated: 465.9580; found: 465.9591; HPLC purity: 99.7%. Anal Calcd for  $C_{16}H_{14}INO_4S$ : C,H,N.

**3-(5-Hydroxy-3,4-dihydroisoquinolin-2(1H)-ylsulfonyl)benzoic acid (32).** Reaction of 3-(chlorosulfonyl)benzoic acid (**95**) with 1,2,3,4-tetrahydroisoquinolin-5-ol (**96i**) by method A gave **32** (yield 40%); mp 241-244 °C.  $^1H$  NMR  $[(CD_3)_2SO]$ :  $\delta$  13.53 (s, 1 H), 9.45 (s, 1 H), 8.26 (s, 1 H), 8.21 (d,  $J = 7.84$  Hz, 1 H), 8.05 (d,  $J = 8.40$  Hz, 1H), 7.76 (t,  $J = 7.80$  Hz, 1 H), 6.96 (t,  $J = 7.81$  Hz, 1 H), 6.61 (t,  $J = 7.96$  Hz, 1 H), 4.16 (s, 2 H), 3.33 (t<sub>under water peak</sub>,  $J = 6.01$  Hz, 2 H), 2.64 (t,  $J = 6.01$  Hz, 2 H) ppm. HRMS (ESI):  $m/z = [M-H]^-$  calculated: 332.0598; found: 332.0589; HPLC purity: 94.9%. Anal. Calcd for  $C_{16}H_{15}NO_5S$ : C,H,N.

**3-(5-Methoxy-3,4-dihydroisoquinolin-2(1H)-ylsulfonyl)benzoic acid (33).** Reaction of 3-(chlorosulfonyl)benzoic acid (**95**) and 5-methoxy-1,2,3,4-tetrahydroisoquinoline (**96j**) by method A gave **33** (yield 11%); mp 208-211 °C.  $^1H$  NMR  $[(CD_3)_2SO]$ :  $\delta$  13.55 (s<sub>br</sub>, 1 H), 8.27 (t,  $J = 1.56$  Hz, 1 H), 8.21 (td,  $J = 7.80$  Hz,  $J = 1.20$  Hz, 1 H), 8.05 (td,  $J = 7.80$  Hz,  $J = 1.20$  Hz, 1 H), 7.75 (t,  $J = 7.76$  Hz, 1 H), 7.13 (t,  $J = 7.96$  Hz, 1 H), 6.77 (t,  $J = 8.24$  Hz, 1 H), 4.19 (s, 2 H), 3.74 (s, 3 H), 3.33 (t<sub>under water peak</sub>,  $J = 5.92$  Hz, 2 H), 2.67 (t,  $J = 5.92$  Hz, 2 H) ppm. HRMS (ESI):  $m/z = [M-H]^-$  calculated: 348.0900; found: 348.0890;  $[M+Na]^+$  calculated: 370.0720; found: 370.0709;  $[M+K]^+$  calculated: 386.0459; found: 386.0479. HPLC purity: 97.1%. Anal. Calcd for  $C_{17}H_{17}NO_5S \cdot H_2O$ : C,H,N.

**3-({6-Methyl-3,4-dihydroisoquinolin-2[1H]-yl}sulfonyl)benzoic acid (34).** Reaction of sulfonamide **58** with methanesulfonic acid and *s*-trioxan by method B, followed by column chromatography (eluting with 0-50% EtOAc:hexanes + 0.5% v/v  $CH_3CO_2H$ ), and then re-precipitation of the crude product from EtOAc:hexanes, afforded **34** (1%, unoptimized) as an amorphous off-white solid; mp 196-198 °C;  $^1H$  NMR  $[(CD_3)_2SO]$ :  $\delta$  13.51 (br s, 1H), 8.26 (t,  $J = 1.6$  Hz, 1H), 8.21 (d,  $J = 7.9$  Hz, 1H), 8.05 (dt,  $J = 7.9, 1.5$  Hz, 1H), 7.76 (t,  $J = 7.9$  Hz, 1H), 7.04 (d,  $J = 7.8$  Hz, 1H), 6.95 (d,  $J = 7.8$  Hz, 1H), 6.91 (s, 1H), 4.19 (s, 2H), 3.33 (t<sub>overlapping water peak</sub>,  $J = 6.0$  Hz, 2H), 2.80 (t,  $J = 6.0$  Hz, 2H), 2.21 (s, 3H); HRESIMS calcd. for  $C_{17}H_{18}NO_4S$   $m/z [M + H]^+$  332.0951, found 332.0944; HPLC purity: 96.0%.

**3-({6-Nitro-3,4-dihydroisoquinolin-2[1H]-yl}sulfonyl)benzoic acid (35).** Reaction of 3-(chlorosulfonyl)benzoic acid (**95**) and 6-nitro-1,2,3,4-tetrahydroisoquinoline hydrochloride<sup>S3</sup> (**96k**) by method A, followed by re-precipitation of the crude product from EtOAc:hexanes, afforded **35** (37%, unoptimized) as an amorphous brown solid; mp 201-203 °C;  $^1H$  NMR  $[(CD_3)_2SO]$ :  $\delta$  13.53 (v br s, 1H), 8.28 (t,  $J = 1.6$  Hz, 1H), 8.20 (d,  $J = 7.8$  Hz, 1H), 8.03 (dt,  $J = 7.8, 1.4$  Hz, 1H), 7.75 (t,  $J = 7.8$  Hz, 1H), 6.99 (d,  $J = 8.4$  Hz, 1H), 6.78 (d,  $J = 2.7$  Hz, 1H), 6.71 (dd,  $J = 8.4, 2.7$  Hz, 1H), 4.21 (s, 2H), 3.69 (s, 3H), 3.21 (t,  $J = 6.0$  Hz, 2H), 2.75 (t,  $J = 6.0$  Hz, 2H); HRESIMS calcd. for  $C_{16}H_{13}N_2O_6S$   $m/z [M - H]^+$  361.0500 found 361.490; HPLC purity: 96.7%.

**3-(6-Cyano-3,4-dihydroisoquinolin-2(1H)-ylsulfonyl)benzoic acid (36).** Reaction of 3-(chlorosulfonyl)benzoic acid (**95**) and 1,2,3,4-tetrahydroisoquinoline-6-carbonitrile (**96l**) with by method A gave acid **36** (40%); mp 243-245 °C.  $^1H$  NMR  $[(CD_3)_2SO]$ :  $\delta$  13.52 (s<sub>br</sub>, 1 H), 8.26 (t,  $J = 1.60$  Hz, 1 H), 8.21 (td,  $J = 7.76$  Hz,  $J = 1.24$  Hz, 1 H), 8.07 (td,  $J = 7.88$  Hz,  $J = 1.16$  Hz, 1 H), 7.77 (t,  $J = 7.84$  Hz, 1 H), 7.63 - 7.57 (m, 2 H), 7.41 (d,  $J = 8.36$  Hz, 1 H), 4.35 (s, 2 H), 3.39

(t,  $J = 6.04$  Hz, 2 H), 2.88 (t,  $J = 5.93$  Hz, 2 H) ppm. HRMS (ESI):  $m/z = [M+H]^+$  calculated: 343.0747; found: 343.0749;  $[M+Na]^+$  calculated: 365.0566; found: 365.0575;  $[M+K]^+$  calculated: 381.0306; found: 381.0310; HPLC purity: 99.4%. Anal. Calcd for  $C_{17}H_{14}N_2O_4S$ : C, H, N.

**3-({6-Chloro-3,4-dihydroisoquinolin-2[1H]-yl}sulfonyl)benzoic acid (37).** Reaction of sulfonamide **63** with methanesulfonic acid and *s*-trioxan by method B, followed by re-precipitation of the crude product from EtOAc:hexanes, and then column chromatography on silica gel (eluting with 0-40% EtOAc:hexanes + 0.5% v/v  $CH_3CO_2H$ ), afforded **37** (35%, unoptimized) as an amorphous white solid; mp 202-203 °C;  $^1H$  NMR [ $(CD_3)_2SO$ ]:  $\delta$  13.51 (br s, 1H), 8.27 (t,  $J = 1.6$  Hz, 1H), 8.21 (dt,  $J = 7.8, 1.3$  Hz, 1H), 8.06 (d,  $J = 8.2$  Hz, 1H), 7.76 (t,  $J = 7.8$  Hz, 1H), 7.21 (m, 3H), 4.25 (s, 2H), 3.35 ( $t_{\text{overlapping water peak}}$ ,  $J = 6.0$  Hz, 2H), 2.84 (t,  $J = 6.0$  Hz, 2H); HRESIMS calcd. for  $C_{16}H_{15}ClNO_4S$   $m/z [M + H]^+$  354.0376, 352.0405, found 354.0385, 352.0407; HPLC purity: 97.1%.

**3-(6-Bromo-3,4-dihydroisoquinolin-2(1H)-ylsulfonyl)benzoic acid (38).** Reaction of 3-(chlorosulfonyl)benzoic acid (**95**) and 6-bromo-1,2,3,4-tetrahydroisoquinoline (**96m**) by method A gave acid **38** (yield 27%); mp 204-206 °C.  $^1H$  NMR [ $(CD_3)_2SO$ ]:  $\delta$  13.52 ( $s_{br}$ , 1 H), 8.27 (t,  $J = 1.64$  Hz, 1 H), 8.21 (td,  $J = 7.92$  Hz,  $J = 1.20$  Hz, 1 H), 8.06 (td,  $J = 7.92$  Hz,  $J = 1.20$  Hz, 1 H), 7.77 (t,  $J = 7.76$  Hz, 1 H), 7.35 - 7.30 (m, 2 H), 7.15 (d,  $J = 8.88$  Hz, 1 H), 4.22 (s, 2 H), 3.34 ( $t_{\text{under water peak}}$ ,  $J = 6.05$  Hz, 2 H), 2.84 (t,  $J = 5.92$  Hz, 2 H) ppm. HRMS (ESI):  $m/z = [M+H]^+$  calculated: 395.9900; found: 395.9891/397.9872;  $[M+Na]^+$  calculated: 417.9719; found: 417.9712/417.9688;  $[M+K]^+$  calculated: 433.9458; found: 433.9462/435.9460; HPLC purity: 98.6%. Anal Calcd for  $C_{16}H_{14}BrNO_4S$ : C, H, N.

**3-(6-Iodo-3,4-dihydroisoquinolin-2(1H)-ylsulfonyl)benzoic acid (39).** Reaction of 3-(chlorosulfonyl)benzoic acid (**95**) with 6-iodo-1,2,3,4-tetrahydroisoquinoline (**96n**) by method A gave **39** (yield 56%); mp 202-205 °C.  $^1H$  NMR [ $(CD_3)_2SO$ ]:  $\delta$  13.56 ( $s_{br}$ , 1 H), 8.26 (t,  $J = 1.56$  Hz, 1 H), 8.21 (td,  $J = 7.76$  Hz,  $J = 1.24$  Hz, 1 H), 8.05 (td,  $J = 7.92$  Hz,  $J = 1.08$  Hz, 1 H), 7.76 (t,  $J = 7.80$  Hz, 1 H), 7.51 - 7.46 (m, 2 H), 6.99 (d,  $J = 8.48$  Hz, 1 H), 4.20 (s, 2 H), 3.32 ( $t_{\text{under water peak}}$ ,  $J = 5.96$  Hz, 2 H), 2.82 (t,  $J = 5.88$  Hz, 2 H) ppm. HRMS (ESI):  $m/z = [M+H]^+$  calculated: 443.9761; found: 443.9772;  $[M+Na]^+$  calculated: 465.9580; found: 465.9587; HPLC purity: 97.2%. Anal. Calcd for  $C_{16}H_{14}INO_4S$ : C, H, N.

**3-({6-Hydroxy-3,4-dihydroisoquinolin-2[1H]-yl}sulfonyl)benzoic acid (40).** Reaction of 3-(chlorosulfonyl)benzoic acid (**95**) and 1,2,3,4-tetrahydroisoquinolin-6-ol hydrobromide<sup>S4</sup> (**96o**) by method A, followed by re-precipitation of the crude product from MeOH:EtOAc:hexanes, afforded **40** (26%, unoptimized) as an amorphous white solid; mp 218-221 °C;  $^1H$  NMR [ $(CD_3)_2SO$ ]:  $\delta$  13.50 (v br s, 1H), 9.21 (br s, 1H), 8.26 (t,  $J = 1.6$  Hz, 1H), 8.21 (d,  $J = 7.8$  Hz, 1H), 8.04 (dt,  $J = 7.8, 1.5$  Hz, 1H), 7.76 (t,  $J = 7.8$  Hz, 1H), 6.94 (d,  $J = 8.4$  Hz, 1H), 6.55 (dd,  $J = 8.4, 2.5$  Hz, 1H), 6.47 (d,  $J = 2.5$  Hz, 1H), 4.12 (s, 2H), 3.29 ( $t_{\text{overlapping water peak}}$ ,  $J = 6.0$  Hz, 2H), 2.75 (t,  $J = 6.0$  Hz, 2H); HRESIMS calcd. for  $C_{16}H_{16}NO_5S$   $m/z [M + H]^+$  337.0744, found 334.0741; HPLC purity: 96.4%.

**3-({6-Methoxy-3,4-dihydroisoquinolin-2[1H]-yl}sulfonyl)benzoic acid (41).** Reaction of 3-(chlorosulfonyl)benzoic acid (**95**) and 6-methoxy-1,2,3,4-tetrahydroisoquinoline hydrochloride<sup>S5</sup>

**(96p)** by method A, followed by re-precipitation of the crude product from EtOAc:hexanes, afforded **41** (45%, unoptimized) as an amorphous white solid; mp 210-212 °C; <sup>1</sup>H NMR [(CD<sub>3</sub>)<sub>2</sub>SO]: δ 13.50 (v br s, 1H), 8.27 (t, *J* = 1.5 Hz, 1H), 8.21 (d, *J* = 7.8 Hz, 1H), 8.04 (d, *J* = 7.8 Hz, 1H), 7.75 (t, *J* = 7.8 Hz, 1H), 7.08 (d, *J* = 8.5 Hz, 1H), 6.72 (dd, *J* = 8.5, 2.6 Hz, 1H), 6.66 (d, *J* = 2.6 Hz, 1H), 4.16 (s, 2H), 3.69 (s, 3H), 3.32 (t, *J* = 5.9 Hz, 2H), 2.82 (t, *J* = 5.9 Hz, 2H); HRESIMS calcd. for C<sub>17</sub>H<sub>18</sub>NO<sub>5</sub>S *m/z* [M + H]<sup>+</sup> 348.9000, found 348.0904; HPLC purity: 98.3%.

**3-((7-Methyl-3,4-dihydroisoquinolin-2(1H)-yl)sulfonyl)benzoic acid (42).** Reaction of sulfonamide **64** with methanesulfonic acid and *s*-trioxan by method B, followed by re-precipitation of the crude product from EtOAc/hexanes, and then column chromatography on silica gel (eluting with 0-50% EtOAc:hexanes + 0.5% v/v CH<sub>3</sub>CO<sub>2</sub>H), afforded **42** (18%, unoptimized) as an amorphous white solid; mp 225-227 °C; <sup>1</sup>H NMR [(CD<sub>3</sub>)<sub>2</sub>SO]: δ 13.52 (br s, 1H), 8.26 (t, *J* = 1.6 Hz, 1H), 8.20 (d, *J* = 7.8 Hz, 1H), 8.05 (d, *J* = 8.2 Hz, 1H), 7.75 (t, *J* = 7.8 Hz, 1H), 6.95 (m, 3H), 4.21 (s, 2H), 3.33 (t<sub>overlapping water peak</sub>, *J* = 6.0 Hz, 2H), 2.78 (t, *J* = 6.0 Hz, 2H), 2.21 (s, 3H); HRESIMS calcd. for C<sub>17</sub>H<sub>17</sub>NNaO<sub>4</sub>S *m/z* [M + Na]<sup>+</sup> 354.0770, found 354.0773; HPLC purity: 100%.

**3-((7-Ethynyl-3,4-dihydroisoquinolin-2(1H)-yl)sulfonyl)benzoic acid (43).** A solution of iodide **50** (0.43g, 0.96 mmol, 1.00 equiv.) in CH<sub>3</sub>CN (10 mL) and DMF (15 mL) was treated sequentially with Pd(PPh<sub>3</sub>)<sub>4</sub> (60 mg, 0.05 mmol, 0.05 equiv.), CuI (11 mg, 0.06 mmol, 0.06 equiv), (trimethylsilyl)acetylene (**97**) (0.23 mL, 1.63 mmol, 1.70 equiv.) and N,N-diisopropylethylamine (0.28 mL, 1.63 g, 1.70 equiv.).<sup>S6,S7</sup> The resulting mixture was deoxygenated by five N<sub>2</sub>-flush-evacuate cycles, and then stirred at 20 °C for 48 h. The reaction mixture was then diluted with water and saturated aqueous NH<sub>4</sub>Cl, and then extracted with CH<sub>2</sub>Cl<sub>2</sub> (x 4). The combined organic layers were washed with brine, dried (MgSO<sub>4</sub>), and evaporated under reduced pressure. The resulting crude products from two equal runs were combined and chromatographed on silica gel, eluting with 0–50% EtOAc:hexanes + 0.5% v/v AcOH to afford 3-((7-((trimethylsilyl)ethynyl)-3,4-dihydroisoquinolin-2(1H)-yl)sulfonyl)benzoic acid (**98**) (0.27 g, 37% combined yield) as an amorphous off-white solid (APCI–): *m/z* 413.1; TLC R<sub>f</sub> 0.47 (50% EtOAc:hexanes + 3 drops AcOH)), which was used without further purification.

A solution of the TMS ethyne **98** (78 mg, 0.19 mmol, 1.00 equiv.) in MeOH (4 mL) was treated with anhydrous Cs<sub>2</sub>CO<sub>3</sub> (0.19 g, 0.59 mmol, 3.12 equiv.), and the resulting dark brown solution was stirred at 20 °C for 100 min, then diluted with saturated aqueous NH<sub>4</sub>Cl, and extracted with EtOAc (x 4).<sup>S6,S8</sup> The combined organic extracts were washed with brine, dried (MgSO<sub>4</sub>) and evaporated under reduced pressure to afford crude product. This was combined with a second run from 161 mg of **x** and by chromatography on silica gel, eluting with 0–50% EtOAc:hexanes + 0.5% v/v AcOH followed by re-precipitation from EtOAc:hexanes, to yield **43** (21 mg, 11%, unoptimized) as an amorphous pale pink solid: mp 224-227 °C; <sup>1</sup>H NMR [(CD<sub>3</sub>)<sub>2</sub>SO]: δ 13.54 (v br s, 1H), 8.27 (t, *J* = 1.6 Hz, 1H), 8.21 (dt, *J* = 7.8, 1.3 Hz, 1H), 8.06 (d, *J* = 8.0 Hz, 1H), 7.76 (t, *J* = 7.8 Hz, 1H), 7.32 (s, 1H), 7.23 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.11 (d, *J* = 8.0 Hz, 1H), 4.25 (s, 2H), 4.11 (s, 1H), 3.35 (t, *J* = 6.0 Hz, 2H), 2.84 (t, *J* = 5.9 Hz, 2H); HRESIMS calcd. for C<sub>18</sub>H<sub>16</sub>NO<sub>4</sub>S *m/z* [M + H]<sup>+</sup> 342.0795, found 342.0792; HPLC purity: 96.7%.

**3-((7-((4-(Trifluoromethoxy)phenyl)ethynyl)-3,4-dihydroisoquinolin-2(1H)-yl)sulfonyl)benzoic acid (44).** Based on the procedures described by Gu *et al.*,<sup>e18</sup> 1-ethynyl-4-(trifluoromethoxy)benzene (**99**) (0.035 mL, 0.23 mmol, 1.00 equiv.) was added to a mixture of iodide **50** (100 mg, 0.23 mmol, 1.00 equiv.), Pd(PPh<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub> (6 mg, 0.009 mmol, 0.04 equiv.) in piperidine (1.00 mL, 2.26 mmol, 45 equiv.) at 20 °C. The resulting semi-solid yellow-white mixture was heated to 85 °C to form an orange solution, and was then stirred at this temperature for a further 12 h. The reaction mixture was cooled to 20 °C, diluted with H<sub>2</sub>O and 15% HCl, and then extracted with Et<sub>2</sub>O (x 4). The combined organic layers were washed with water until neutral, and then dried (MgSO<sub>4</sub>) and concentrated to dryness under reduced pressure. The residue was re-precipitated from EtOAc:hexanes to furnish **44** (21 mg, 20%, unoptimized) as an amorphous off-white solid; mp 235-238 °C; <sup>1</sup>H NMR [(CD<sub>3</sub>)<sub>2</sub>SO]: δ 13.62 (v br s, 1H), 8.28 (t, *J* = 1.6 Hz, 1H), 8.21 (dt, *J* = 7.8, 1.4 Hz, 1H), 8.05 (d, *J* = 8.0 Hz, 1H), 7.75 (t, *J* = 7.8 Hz, 1H), 7.66 (ddd, *J* = 9.4, 4.8, 2.7 Hz, 2H), 7.42 (m, 3H), 7.33 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.16 (d, *J* = 8.0 Hz, 1H), 4.29 (s, 2H), 3.38 (t, *J* = 6.0 Hz, 2H), 2.87 (t, *J* = 5.8 Hz, 2H); HRESIMS calcd. for C<sub>25</sub>H<sub>18</sub>F<sub>3</sub>NO<sub>5</sub>S *m/z* [M + H]<sup>+</sup> 502.0931, found 502.0940; HPLC purity: 98.7%.

**3-((7-(2H-Tetrazol-5-yl)-3,4-dihydroisoquinolin-2(1H)-yl)sulfonyl)benzoic acid (45) [SN 34166].** Following the method of Nakamura *et al.*,<sup>S9</sup> sodium azide (102 mg, 1.57 mmol, 1.25 equiv.) was added to a mixture of nitrile **51** (430 mg, 1.27 mmol, 1.00 equiv.) and NH<sub>4</sub>Cl (84 mg, 1.57 mmol, 1.25 equiv.) in DMF and the resulting mixture was stirred at 120 °C for 171 h. After this time, the reaction mixture was cooled to 20 °C, and then concentrated to dryness under reduced pressure. Trituration of the resulting brown gum in an ultrasonic bath afforded a glutinous tan solid, which was re-precipitated from MeOH:EtOAc:hexanes to furnish **45** (327 mg, 68%) as an amorphous white solid; mp: 246 °C (dec.); <sup>1</sup>H NMR [(CD<sub>3</sub>)<sub>2</sub>SO]: δ 14.77 (br s, 1H), 8.28 (t, *J* = 1.6 Hz, 1H), 8.21 (dt, *J* = 7.9, 1.3 Hz, 1H), 8.09 (dd, *J* = 7.9, 1.8, 1.2 Hz, 1H), 7.86 (s, 1H), 7.77 (m, 2H), 7.31 (d, *J* = 8.0 Hz, 1H), 4.37 (s, 2H), 3.41 (t, *J* = 6.0 Hz, 2H), 2.91 (t, *J* = 6.0 Hz, 2H) {tetrazole -NH- not visible}; HRESIMS calcd. for C<sub>17</sub>H<sub>15</sub>N<sub>5</sub>NaSO<sub>4</sub>Cl *m/z* [M + Na]<sup>+</sup> 408.0737, found 408.0748; HPLC purity: 96.9%.

**3-((7-Nitro-3,4-dihydroisoquinolin-2(1H)-yl)sulfonyl)benzoic acid (46).** Reaction of 3-(chlorosulfonyl)benzoic acid (**95**) and 7-nitro-1,2,3,4-tetrahydroisoquinoline<sup>S10</sup> (**96q**) by method A, followed by re-precipitation of the crude product from EtOAc:hexanes, afforded **46** (73%) as an off-white amorphous solid; mp 230-231 °C; <sup>1</sup>H NMR [(CD<sub>3</sub>)<sub>2</sub>SO]: δ 13.58 (br s, 1H), 8.26 (t, *J* = 1.6 Hz, 1H), 8.20 (dt, *J* = 7.9, 1.3 Hz, 1H), 8.17 (d, *J* = 2.4 Hz, 1H), 8.06 (ddd, *J* = 7.8, 1.8, 1.1 Hz, 1H), 7.99 (dd, *J* = 8.5, 2.5 Hz, 1H), 7.75 (t, *J* = 7.7 Hz, 1H), 7.36 (d, *J* = 8.5 Hz, 1H), 4.43 (s, 2H), 3.42 (t<sub>overlapping water peak</sub>, *J* = 6.0 Hz, 2H), 2.94 (t, *J* = 6.0 Hz, 2H); HRESIMS calcd. for C<sub>16</sub>H<sub>14</sub>N<sub>2</sub>NaO<sub>6</sub>S *m/z* [M + Na]<sup>+</sup> 385.0465; found 385.0459; calcd. for C<sub>16</sub>H<sub>15</sub>N<sub>2</sub>O<sub>6</sub>S *m/z* [M + H]<sup>+</sup> 363.0645, found 363.0636; HPLC purity: 98.1%.

**3-((7-Fluoro-3,4-dihydroisoquinolin-2(1H)-yl)sulfonyl)benzoic acid (47).** Reaction of 3-(chlorosulfonyl)benzoic acid (**95**) and 7-fluoro-1,2,3,4-tetrahydroisoquinoline hydrochloride (**96r**) by method A, followed by re-precipitation of the crude product from EtOAc:hexanes, afforded **47** (4%, unoptimized) as an amorphous white solid; mp 213-216 °C; <sup>1</sup>H NMR [(CD<sub>3</sub>)<sub>2</sub>SO]: δ 13.59 (br s, 1H), 8.26 (d, *J* = 1.6 Hz, 1H), 8.21 (dt, *J* = 7.7, 1.3 Hz, 1H), 8.05 (app. dd, *J* = 6.7, 1.4 Hz, 1H), 7.75 (t, *J* = 7.8 Hz, 1H), 7.10 (m, 2H), 6.97 (td, *J* = 8.7, 2.7 Hz, 1H),

4.27 (s, 2H), 3.36 (t,  $J = 6.0$  Hz, 2H), 2.80 (t,  $J = 5.8$  Hz, 2H); HRESIMS calcd. for  $C_{16}H_{15}FNO_4S$   $m/z$  (M + H)<sup>+</sup> 336.0700, found 336.0695; HPLC purity: 96.2%.

**3-((7-Chloro-3,4-dihydroisoquinolin-2(1H)-yl)sulfonyl)benzoic acid (48).** Reaction of sulfonamide **59** with methanesulfonic acid and *s*-trioxan by method B, followed by re-precipitation of the crude product from EtOAc:hexanes, afforded **48** (68%) as an amorphous white solid; mp 238-240 °C; <sup>1</sup>H NMR [(CD<sub>3</sub>)<sub>2</sub>SO]: δ 13.51 (br s, 1H), 8.27 (t,  $J = 1.6$  Hz, 1H), 8.21 (dt,  $J = 7.8, 1.3$  Hz, 1H), 8.05 (ddd,  $J = 7.8, 1.7, 1.2$  Hz, 1H), 7.76 (t,  $J = 7.8$  Hz, 1H), 7.30 (d,  $J = 2.0$  Hz, 1H), 7.19 (dd,  $J = 8.3, 2.2$  Hz, 1H), 7.11 (d,  $J = 8.3$  Hz, 1H), 4.28 (s, 2H), 3.37 (t<sub>overlapping water peak</sub>,  $J = 6.0$  Hz, 2H), 2.80 (t,  $J = 6.0$  Hz, 2H); HRESIMS calcd. for  $C_{16}H_{14}ClNNO_4S$   $m/z$  [M + Na]<sup>+</sup> 376.0196, 374.0224, found 376.0203, 374.0225; calcd. for  $C_{16}H_{15}ClNO_4S$   $m/z$  [M + H]<sup>+</sup> 354.0376, 352.0405, found 354.0374, 352.0396; HPLC purity: 100%.

**3-((7-Bromo-3,4-dihydroisoquinolin-2(1H)-yl)sulfonyl)benzoic acid (49).** A solution of 7-bromo-1,2,3,4-tetrahydroisoquinoline (**96s**) (0.914 g, 4.308 mmol, 2.50 equiv.) in dry pyridine (5 mL) was treated slowly at 0°C with a solution of 3-(chlorosulfonyl)benzoic acid (**95**) (0.380 g, 1.723 mmol, 1.00 equiv.) in dry dioxane (8 mL), and the resulting mixture allowed to warm to 20°C. After analysis (TLC, LRMS) showed the reaction was complete, the reaction mixture was poured into a solution of 1M HCl (50 mL), and the resulting suspension filtered. The resulting solid was re-precipitated from EtOAc:hexanes to afford **49** (333 mg, 49%, unoptimized) as an amorphous white solid; mp 239-241 °C; <sup>1</sup>H NMR [(CD<sub>3</sub>)<sub>2</sub>SO]: δ 13.59 (br s, 1H), 8.27 (t,  $J = 1.6$  Hz, 1H), 8.20 (dt,  $J = 7.8, 1.3$  Hz, 1H), 8.01 (ddd,  $J = 7., 1.7, 1.1$  Hz, 1H), 7.73 (t,  $J = 7.8$  Hz, 1H), 7.44 (d,  $J = 2.0$  Hz, 1H), 7.31 (dd,  $J = 8.2, 2.1$  Hz, 1H), 7.05 (t,  $J = 8.2$  Hz, 1H), 4.27 (s, 2H), 3.35 (t<sub>overlapping water peak</sub>,  $J = 6.2$  Hz, 2H), 2.79 (t,  $J = 5.9$  Hz, 2H); HRESIMS calcd. for  $C_{16}H_{15}BrNO_4S$   $m/z$  (M + H)<sup>+</sup> 397.9880, 395.9900, found 397.9874, 395.9892; HPLC purity: 100%.

**3-((7-Iodo-3,4-dihydroisoquinolin-2(1H)-yl)sulfonyl)benzoic acid (50).** Reaction of 3-(chlorosulfonyl)benzoic acid (**95**) and 7-iodo-1,2,3,4-tetrahydroisoquinoline by the transhalogenation method of Klapars & Buchwald<sup>S11</sup> (**96t**) by general method A, followed by re-precipitation of the crude product from EtOAc:hexanes, afforded **50**, a small amount of which was purified for characterisation (30 mg, 2%, unoptimized); mp 242-243 °C; <sup>1</sup>H NMR [(CD<sub>3</sub>)<sub>2</sub>SO]: δ 13.48 (br s, 1H), 8.26 (t,  $J = 1.6$  Hz, 1H), 8.21 (dt,  $J = 7.9, 1.4$  Hz, 1H), 8.05 (dt,  $J = 8.2, 1.5$  Hz, 1H), 7.76 (t,  $J = 7.8$  Hz, 1H), 7.58 (d,  $J = 1.5$  Hz, 1H), 7.47 (dd,  $J = 8.1, 1.8$  Hz, 1H), 6.90 (d,  $J = 8.1$  Hz, 1H), 4.25 (s, 2H), 3.35 (dd<sub>overlapping water peak</sub>,  $J = 6.0$  Hz, 2H), 2.78 (t,  $J = 5.9$  Hz, 2H); HRESIMS calcd. for  $C_{16}H_{14}INNaSO_4$   $m/z$  (M + Na)<sup>+</sup> 465.9580, found 465.9579; HPLC purity: 99.3%.

**3-((7-Cyano-3,4-dihydroisoquinolin-2(1H)-yl)sulfonyl)benzoic acid (51).** Reaction of 3-(chlorosulfonyl)benzoic acid (**95**) and 1,2,3,4-tetrahydroisoquinoline-7-carbonitrile (**96u**) by method A, followed by re-precipitation of the crude product mixture from MeOH:EtOAc, gave **51** (46%) as an amorphous off-white solid; mp 219-222 °C; <sup>1</sup>H NMR [(CD<sub>3</sub>)<sub>2</sub>SO]: δ 13.70 (v br s, 1H), 8.27 (s, 1H), 8.20 (d,  $J = 7.8$  Hz, 1H), 8.01 (d,  $J = 7.9$  Hz, 1H), 7.73 (m, 2H), 7.57 (dd,  $J = 8.0, 1.5$  Hz, 1H), 7.30 (d,  $J = 8.0$  Hz, 1H), 4.32 (s, 2H), 3.39 (t,  $J = 6.0$  Hz, 2H), 2.91 (t,  $J = 6.0$

Hz, 2H); HRESIMS calcd. for C<sub>17</sub>H<sub>14</sub>N<sub>2</sub>O<sub>3</sub>S *m/z* [M + H]<sup>+</sup> 343.0747, found 343.0739; HPLC purity: 95.7%.

**3-({7-Methoxy-3,4-dihydroisoquinolin-2[1H]-yl)sulfonylbenzoic acid (52).** Reaction of 3-(chlorosulfonyl)benzoic acid (**95**) and 7-methoxy-1,2,3,4-tetrahydroisoquinoline<sup>S12</sup> (**96v**) by method A, followed by re-precipitation of the crude product from EtOAc:hexanes, afforded **52** (22%, unoptimized) as an amorphous white solid; mp 180-181 °C; <sup>1</sup>H NMR [(CD<sub>3</sub>)<sub>2</sub>SO]: δ 13.67 (v br s, 1H), 8.28 (t, *J* = 1.6 Hz, 1H), 8.21 (dt, *J* = 7.8, 1.4 Hz, 1H), 8.08 (dt, *J* = 7.8, 1.5 Hz, 1H), 8.00 (m, 2H), 7.76 (t, *J* = 7.8 Hz, 1H), 7.49 (d, *J* = 8.6 Hz, 1H), 4.41 (s, 2H), 3.42 (t, *J* = 6.0 Hz, 2H), 2.97 (t, *J* = 6.0 Hz, 2H); HRESIMS calcd. for C<sub>17</sub>H<sub>18</sub>NO<sub>5</sub>S *m/z* [M + H]<sup>+</sup> 348.9000, found 348.0903; HPLC purity: 97.4%.

**3-((8-Chloro-3,4-dihydroisoquinolin-2(1H)-yl)sulfonylbenzoic acid (53).** Reaction of 3-(chlorosulfonyl)benzoic acid (**95**) and 8-chloro-1,2,3,4-tetrahydroisoquinoline<sup>S13</sup> (**96w**) by method A, followed by re-precipitation of the crude product from EtOAc:hexanes, column chromatography on silica gel (eluting with 0–50% EtOAc:hexanes + 0.5% v/v CH<sub>3</sub>CO<sub>2</sub>H), and finally re-precipitation from EtOAc:hexanes, afforded **53** (31 mg, 20%, unoptimized) as an off-white amorphous solid; mp 209-210 °C; <sup>1</sup>H NMR [(CD<sub>3</sub>)<sub>2</sub>SO]: δ 13.55 (br s, 1H), 8.26 (t, *J* = 1.6 Hz, 1H), 8.21 (dt, *J* = 7.8, 1.3 Hz, 1H), 8.07 (m, 1H), 7.77 (t, *J* = 7.8 Hz, 1H), 7.29 (d, *J* = 7.0 Hz, 1H), 7.20 (t, *J* = 7.8 Hz, 1H), 7.11 (d, *J* = 7.5 Hz, 1H), 4.25 (s, 2H), 3.40 (t<sub>overlapping water peak</sub>, *J* = 6.0 Hz, 2H), 2.87 (t, *J* = 5.9 Hz, 2H); HRESIMS calcd. for C<sub>16</sub>H<sub>14</sub>ClNNaO<sub>4</sub>S *m/z* [M + Na]<sup>+</sup> 376.0196, 374.0224, found 376.0194, 374.0218; HPLC purity: 98.4%.

**3-({6,7-Dimethoxy-3,4-dihydroisoquinolin-2[1H]-yl)sulfonylbenzoic acid (54).** Reaction of 3-(chlorosulfonyl)benzoic acid (**95**) and 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline hydrochloride<sup>S14</sup> (**96x**) by method A, followed by re-precipitation of the crude product from MeOH:EtOAc, or trituration with MeOH, afforded **54** (77%, unoptimized) as an amorphous white solid; mp 217-219 °C; <sup>1</sup>H NMR [(CD<sub>3</sub>)<sub>2</sub>SO]: δ 13.51 (br s, 1H), 8.26 (t, *J* = 1.6 Hz, 1H), 8.05 (m, 1H), 8.21 (dt, *J* = 7.8, 1.5 Hz, 1H), 7.77 (t, *J* = 7.8 Hz, 1H), 6.78 (s, 1H), 6.65 (s, 1H), 4.15 (s, 2H), 3.68 (m, 6H), 3.31 (t, *J* = 5.9 Hz, 2H), 2.75 (t, *J* = 5.9 Hz, 2H); HRESIMS calcd. for C<sub>18</sub>H<sub>20</sub>NO<sub>6</sub>S *m/z* [M + H]<sup>+</sup> 378.1006, found 378.1005; HPLC purity: 100%.

**5-((3,4-Dihydroisoquinolin-2(1H)-yl)sulfonyl)nicotinic acid (55).** 2,4-Dichloro-5,5-dimethylhydantoin (2.42 g, 12.27 mmol, 1.61 equiv) was added portionwise to a solution of methyl 5-mercaptonicotinate<sup>S15</sup> (**100**) in MeCN/AcOH/water (40:1.5:1.0, 128 mL) cooled to at 0 °C that the reaction temperature remained <10 °C. Once the addition was complete, the reaction mixture was allowed to warm to and stir at 20 °C for 110 min, then almost all solvent was removed under reduced pressure (<30 °C), and the resulting concentrated solution was diluted with CH<sub>2</sub>Cl<sub>2</sub> (8 mL) and cooled to 0 °C. This solution was treated with 5% NaHCO<sub>3</sub> (53 mL), at such a rate that the temperature remained <10 °C. The resulting mixture was stirred at 0–5 °C for 15 min., and then separated. The organic layer was washed with a cooled (<10 °C) solution of 10% brine, and then dried (MgSO<sub>4</sub>) and filtered. Solvent was removed under reduced pressure (bath temperature 30 °C) to afford methyl 5-(chlorosulfonyl)nicotinate (**101**) as a yellow viscous oil (1.18 g), which was used without further purification, as soon as possible.

Reaction of **101** (0.066 g, 0.28 mmol, 1.00 equiv) with 1,2,3,4-tetrahydroisoquinoline (**96a**) (0.42 mL, 0.34 mmol, 1.20 equiv) by method A, and the resulting crude ester (39 mg, 0.12 mmol, 1.00 equiv.) was dissolved in MeOH (5.8 mL) and water (3.9 mL) and treated with anhydrous LiOH (9 mg, 0.40 mmol, 3.38 equiv.) with stirring at 20 °C for 80 min, when all starting material was consumed (TLC). Solvent was removed under reduced pressure, and the residue was re-dissolved in H<sub>2</sub>O (50 mL), acidified to pH 1 by addition of 1M HCl (~1 mL) and the product was collected by filtration, washed with hexanes, and dried to afford crude **55** as an amorphous pale yellow solid. The product from two reactions was combined and re-precipitated from EtOAc:hexanes to give pure **41** (87 mg, 30%) as an amorphous tan solid; mp 233-237 °C; <sup>1</sup>H NMR [(CD<sub>3</sub>)<sub>2</sub>SO]: δ 14.06 (br s, 1H), 9.26 (d, *J* = 1.9 Hz, 1H), 9.17 (d, *J* = 2.2 Hz, 1H), 8.48 (d, *J* = 2.1 Hz, 1H), 7.22-7.05 (m, 4H), 4.33 (s, 2H), 3.44 (t<sub>overlapping water peak</sub>, *J* = 6.0 Hz, 2H), 2.84 (t, *J* = 6.0 Hz, 2H); HRESIMS calcd. for C<sub>15</sub>H<sub>15</sub>N<sub>2</sub>O<sub>4</sub>S *m/z* (M + H)<sup>+</sup> 319.0747, found 319.0747; HPLC purity: 98.6%.

### Compounds of Table 5 (Scheme 2)

**3-(*N*-Phenethylsulfamoyl)benzoic acid (**56**).** Reaction of 3-(chlorosulfonyl)benzoic acid (**96**) and 2-phenylethanamine (**102a**) (5.00 equiv.), under the conditions used to prepare acid **49**, gave **56** (53%) as an amorphous white solid; mp 188-190 °C; <sup>1</sup>H NMR [(CD<sub>3</sub>)<sub>2</sub>SO]: δ = 13.44 (br s, 1H), 8.31 (t, *J* = 1.6 Hz, 1H), 8.16 (d, *J* = 7.8 Hz, 1H), 7.99 (d, *J* = 8.1 Hz, 1H), 7.85 (t, *J* = 5.7 Hz, 1H), 7.71 (dd, *J* = 7.8, 7.7 Hz, 1H), 7.25 (m, 2H), 7.18 (m, 1H), 7.14 (m, 2H), 2.99 (m, 2H), 2.81 (dd, *J* = 7.6, 7.2 Hz, 2H); HRESIMS calcd. for C<sub>15</sub>H<sub>15</sub>NNaO<sub>4</sub>S *m/z* [M + Na]<sup>+</sup> 328.0614, found 328.0610; TLC; HPLC purity: 98.8%.

**3-(*N*-(2-Fluorophenethyl)sulfamoyl)benzoic acid (**57**).** Reaction of 3-(chlorosulfonyl)benzoic acid (**95**) and 2-(2-fluorophenyl)ethanamine (**102b**) by method A gave acid **57** (yield 57%); mp 174-177 °C. <sup>1</sup>H NMR [(CD<sub>3</sub>)<sub>2</sub>SO]: δ 13.45 (s<sub>br</sub>, 1 H), 8.30 (t, *J* = 1.60 Hz, 1 H), 8.16 (td, *J* = 7.80 Hz, *J* = 1.28 Hz, 1 H), 7.99 (td, *J* = 7.84 Hz, *J* = 1.20 Hz, 1 H), 7.93 (t, *J* = 5.84 Hz, 1 H), 7.72 (t, *J* = 7.89, 1 H), 7.28 - 7.21 (m, 2 H), 7.13 - 7.06 (m, 2 H), 2.98 (dd, *J* = 13.04 Hz, *J* = 7.00 Hz, 2 H), 2.71 (t, *J* = 7.37 Hz, 2 H) ppm. HRMS (ESI): *m/z* = [M+H]<sup>+</sup> calculated: 324.0700; found: 324.0695; [M+Na]<sup>+</sup> calculated: 346.0520; found: 346.0512. HPLC purity: 97.2%. Anal. Calcd for C<sub>15</sub>H<sub>14</sub>FNO<sub>4</sub>S: C,H,N.

**3-(*N*-{4-Chlorophenethyl}sulfamoyl)benzoic acid (**58**).** Reaction of 3-(chlorosulfonyl)benzoic acid (**95**) and 2-(3-chlorophenyl)ethanamine (**102c**) by method A yielded **58** (20%, unoptimized) as an amorphous white solid; mp 201-204 °C; <sup>1</sup>H NMR [(CD<sub>3</sub>)<sub>2</sub>SO]: δ 13.35 (br s, 1H), 8.28 (t, *J* = 1.6 Hz, 1H), 8.16 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.97 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.83 (t, *J* = 5.8 Hz, 1H), 7.70 (t, *J* = 7.9 Hz, 1H), 7.28 (d, *J* = 8.4 Hz, 2H), 7.16 (d, *J* = 8.4 Hz, 2H), 3.00 (q, *J* = 13.0, 7.1 Hz, 2H), 2.67 (t, *J* = 7.1 Hz, 2H); HRESIMS calcd. for C<sub>15</sub>H<sub>15</sub>ClNO<sub>4</sub>S *m/z* [M + H]<sup>+</sup> 342.0376, 340.0405, found 342.0387, 340.0398; HPLC purity: 97.4%.

**3-(*N*-(4-Chlorophenethyl)sulfamoyl)benzoic acid (**59**).** Reaction of 3-(chlorosulfonyl)benzoic acid (**95**) and 2-(4-chlorophenyl)ethanamine (**102d**) by method A gave acid **59** (yield 50%); mp 203-204 °C. <sup>1</sup>H NMR [(CD<sub>3</sub>)<sub>2</sub>SO]: δ 13.45 (s<sub>br</sub>, 1 H), 8.28 (t, *J* = 1.64 Hz, 1 H), 8.16 (td, *J* = 7.80 Hz, *J* = 1.28 Hz, 1 H), 7.97 (td, *J* = 7.76 Hz, *J* = 1.24 Hz, 1 H), 7.86 (t, *J* = 5.76 Hz, 1 H), 7.70

(t,  $J = 7.76$  Hz, 1 H), 7.28 (d,  $J = 8.44$  Hz, 1 H), 7.17 (d,  $J = 8.48$  Hz, 1 H), 2.99 (dd,  $J = 13.00$  Hz,  $J = 7.04$  Hz, 2 H), 2.68 (t,  $J = 7.08$  Hz, 2 H) ppm. HRMS (ESI):  $m/z = [M+Na]^+$  calculated: 362.0224; found: 362.0218/364.0195;  $[M+K]^+$  calculated: 377.9964; found: 377.9967/379.9942. HPLC purity: 99.2%. Anal. Calcd for  $C_{15}H_{14}ClNO_4S$ : C,H,N.

**3-(*N*-{3-Methoxyphenethyl}sulfamoyl)benzoic acid (60).** Reaction of 3-(chlorosulfonyl)benzoic acid (**95**) and 2-(3-methoxyphenyl)ethamine (**102e**) by method A yielded **60** (13%, unoptimized) as an amorphous off-white solid; mp 145-147 °C;  $^1H$  NMR  $[(CD_3)_2SO]$ :  $\delta$  13.39 (br s, 1H), 8.30 (t,  $J = 1.6$  Hz, 1H), 8.15 (d,  $J = 7.8$  Hz, 1H), 7.99 (d,  $J = 7.9$  Hz, 1H), 7.84 (t,  $J = 5.7$  Hz, 1H), 7.71 (dd,  $J = 7.9, 7.7$  Hz, 1H), 7.15 (dd,  $J = 8.0, 8.2$  Hz, 1H), 6.72 (m, 3H), 3.70 (s, 3H), 3.00 (m, 2H), 2.81 (dd,  $J = 7.5, 7.2$  Hz, 2H); HRESIMS calcd. for  $C_{16}H_{17}NNaO_5S$   $m/z [M + Na]^+$  358.0720, found 358.0725; HPLC purity: 97.5%.

**3-(*N*-(4-Methoxyphenethyl)sulfamoyl)benzoic acid (61).** Reaction of 3-(chlorosulfonyl)benzoic acid (**95**) and 2-(4-methoxyphenyl)ethanamine (**102f**) by method A gave acid **61** (yield 28%); mp 197-200 °C.  $^1H$  NMR  $[(CD_3)_2SO]$ :  $\delta$  13.44 (s<sub>br</sub>, 1 H), 8.29 (s, 1 H), 8.15 (d,  $J = 7.24$  Hz, 1 H), 7.98 (d,  $J = 7.80$  Hz, 1 H), 7.83 (t,  $J = 5.60$  Hz, 1 H), 7.70 (t,  $J = 7.64$  Hz, 1 H), 7.04 (d,  $J = 8.61$  Hz, 1 H), 6.79 (d,  $J = 6.72$  Hz, 1 H), 3.70 (s, 3 H), 2.93 (dd,  $J = 13.08$  Hz,  $J = 7.00$  Hz, 2 H), 2.60 (t,  $J = 7.48$  Hz, 2 H) ppm. HRMS (ESI):  $m/z = [M+H]^+$  calculated: 336.0900; found: 336.0900;  $[M+Na]^+$  calculated: 358.0720; found: 358.0714;  $[M+K]^+$  calculated: 374.0459; found: 374.0462; HPLC purity: 96%. Anal. Calcd for  $C_{16}H_{17}NO_5S \cdot H_2O$ : C,H,N.

**3-(*N*-(3-Phenoxyphenethyl)sulfamoyl)benzoic acid (62).** Reaction of 3-(chlorosulfonyl)benzoic acid (**95**) and 2-(3-phenoxyphenyl)ethanamine (**102g**) by method A gave acid **62** (yield 26%); mp 152-154 °C.  $^1H$  NMR  $[(CD_3)_2SO]$ :  $\delta$  13.45 (s<sub>br</sub>, 1 H), 8.30 (t,  $J = 1.56$  Hz, 1 H), 8.16 (td,  $J = 7.80$  Hz,  $J = 1.20$  Hz, 1 H), 7.98 (td,  $J = 8.36$  Hz,  $J = 1.16$  Hz, 1 H), 7.85 (t,  $J = 5.72$  Hz, 1 H), 7.70 (t,  $J = 7.80$ , 1 H), 7.37 (dt,  $J = 7.44$  Hz,  $J = 2.00$  Hz, 1 H), 7.25 (t, 7.77 Hz, 1 H), 7.13 (t,  $J = 7.40$  Hz, 1 H), 7.12 - 6.95 (m, 2 H), 6.92 (d,  $J = 7.68$  Hz, 1 H), 6.85 — 6.76 (m, 2 H), 2.98 (dd,  $J = 13.12$  Hz,  $J = 7.04$  Hz, 2 H), 2.66 (t,  $J = 7.12$  Hz, 2 H) ppm. HRMS (ESI):  $m/z = [M+H]^+$  calculated: 398.1057; found: 398.1056;  $[M+Na]^+$  calculated: 420.0876; found: 420.0872, HPLC purity: 99%.

**3-(*N*-(3-Methylphenethyl)sulfamoyl)benzoic acid (63).** Reaction of 3-(chlorosulfonyl)benzoic acid (**95**) and 2-(3-methylphenyl)ethanamine (**102h**) by method A gave acid **63** (yield 48%); mp 163-164 °C.  $^1H$  NMR  $[(CD_3)_2SO]$ :  $\delta$  13.45 (s<sub>br</sub>, 1 H), 8.30 (t,  $J = 1.64$  Hz, 1 H), 8.16 (td,  $J = 8.84$  Hz,  $J = 1.28$  Hz, 1 H), 7.99 (td,  $J = 7.88$  Hz,  $J = 1.12$  Hz, 1 H), 7.87 (t,  $J = 5.76$  Hz, 1 H), 7.71 (t,  $J = 7.81$ , 1 H), 7.12 (t,  $J = 7.84$  Hz, 1 H), 6.97 (d,  $J = 7.56$  Hz, 1 H), 6.94 — 6.88 (m, 2 H), 2.97 (dd,  $J = 12.96$  Hz,  $J = 7.04$  Hz, 2 H), 2.62 (t,  $J = 7.56$  Hz, 2 H), 2.23 (s, 3 H) ppm. HRMS (ESI):  $m/z = [M+H]^+$  calculated: 320.0951; found: 320.0945;  $[M+Na]^+$  calculated: 342.0770; found: 342.0761;  $[M+K]^+$  calculated: 358.0510; found: 358.0497. HPLC purity: 99.3%. Anal. Calcd for  $C_{16}H_{17}NO_4S$ : C,H,N.

**3-(*N*-{4-Methylphenethyl}sulfamoyl)benzoic acid (64).** Reaction of 3-(chlorosulfonyl)benzoic acid (**95**) and 2-(4-methylphenyl)ethanamine (**104i**) by method A yielded **64** (7%, unoptimized) as an amorphous off-white solid; mp 198-201 °C;  $^1H$  NMR  $[(CD_3)_2SO]$ :  $\delta$  13.48 (br s, 1H), 8.29

(t,  $J = 1.6$  Hz, 1H), 8.15 (d,  $J = 7.8$  Hz, 1H), 7.97 (d,  $J = 8.1$  Hz, 1H), 7.82 (t,  $J = 5.7$  Hz, 1H), 7.69 (d,  $J = 7.8$  Hz, 1H), 7.02 (m, 4H), 2.96 (m, 2H), 2.62 (dd,  $J = 7.5, 7.3$  Hz, 2H), 2.24 (s, 3H); HRESIMS calcd. for  $C_{16}H_{18}NO_4S$   $m/z$   $[M + H]^+$  320.0951, found 320.0943; HPLC purity: 99.5%.

### Compounds of Table 6 (Scheme 3)

**3-((3,4-Dihydroisoquinolin-2(1H)-yl)sulfonyl)benzonitrile (65).** A suspension of 1,2,3,4-tetrahydroisoquinoline (**96a**) (0.76 mL, 6.05 mmol, 1.00 equiv.) and 3-cyanobenzene-1-sulfonyl chloride (**103a**) (1.22 g, 6.05 mmol, 1.00 equiv.) in acetone (17 mL), was treated with  $Et_3N$  (0.84 mL, 6.05 mmol, 1.00 equiv.), and the resulting viscous suspension was stirred vigorously for 3 d at 20 °C. The mixture was then filtered and the crude product was collected and re-precipitated to give **65** (247 mg, 14%, unoptimized) as an amorphous white solid; mp 192-194 °C;  $^1H$  NMR  $[(CD_3)_2SO]$ :  $\delta$  8.25 (t,  $J = 1.6$  Hz, 1H), 8.14 (m, 2H), 7.81 (t,  $J = 7.9$  Hz, 1H), 7.21-7.12 (m, 3H), 7.12-7.06 (m, 1H), 4.29 (s, 2H), 3.39 (t,  $J = 6.0$  Hz, 2H), 2.83 (t,  $J = 6.0$  Hz, 2H); HRESIMS calcd. for  $C_{16}H_{14}N_2NaO_2S$   $m/z$   $[M + Na]^+$  321.0668, found 321.0661; calcd. for  $C_{16}H_{15}N_2O_2S$   $m/z$   $[M + H]^+$  299.0849, found 299.0842; HPLC purity: 99.5%.

**2-(3-Nitrophenylsulfonyl)-1,2,3,4-tetrahydroisoquinoline (66).** A solution of 1,2,3,4-tetrahydroisoquinoline (**96a**) (1.5g, 11.3 mmol) in pyridine (10 mL) at 0 °C was slowly treated with a solution of 3-nitrobenzenesulfonyl chloride (**103b**) (1.66 g, 7.49 mmol) in dioxane (10 mL). After stirring at 20 °C for 2 h, the mixture was diluted with excess dilute HCl and the resulting solid was recrystallised from EtOAc/petroleum ether to give **66** (2.19 g, 92%); mp 178-180 °C;  $^1H$  NMR  $[(CD_3)_2SO]$   $\delta$  8.50 (ddd,  $J = 8.2, 2.3, 1.0$  Hz, 1H), 8.45 (t,  $J = 1.9$  Hz, 1H), 8.26 (ddd,  $J = 7.8, 1.7, 1.0$  Hz, 1H), 7.91 (t,  $J = 8.1$  Hz, 1H), 7.19-7.06 (m, 4H), 4.32 (s, 2H), 3.42 (t,  $J = 6.1$  Hz, 2H), 2.84 (t,  $J = 6.0$  Hz, 2H); HRESIMS calcd for  $C_{15}H_{14}NaN_2O_4S$   $m/z$   $[M + Na]^+$  3421.0566, found 341.0557; HPLC purity 98.2%.

**3-(3,4-Dihydroisoquinolin-2(1H)-ylsulfonyl)aniline (67).** A solution of **19** (1.00 g, 3.14 mmol) in a mixture of AcOH (1 mL), DMF (15 mL), EtOH (20 mL) and water (2 mL) was treated at reflux with Fe powder (2.0g, excess). The mixture was heated for a further hour, then treated with conc.  $NH_4OH$  (2 mL), filtered through Celite and concentrated to small volume. Dilution with water gave a solid that was recrystallised from EtOAc/petroleum ether to give **67** (0.81g, 89%); mp 208-209 °C;  $^1H$  NMR  $[(CD_3)_2SO]$   $\delta$  7.23 (t,  $J = 7.9$  Hz, 1H), 7.19-7.07 (m, 4 H), 7.00 (t,  $J = 1.9$  Hz, 1H), 6.89 (d,  $J = 7.7$  Hz, 1H), 6.81 (dd,  $J = 1.5, 1.0$  Hz, 1H), 5.60 (s, 2H), 4.15 (s, 2H), 3.25 (t,  $J = 5.9$  Hz, 2H), 2.86 (t,  $J = 5.8$  Hz, 2H); HRESIMS calcd for  $C_{15}H_{16}NaN_2O_2S$   $m/z$   $[M + Na]^+$  311.0825, found 311.0845; HPLC purity 99.9%.

**2-({3-[Trifluoromethyl]phenyl}sulfonyl)-1,2,3,4-tetrahydroisoquinoline (68).** Reaction of 1,2,3,4-tetrahydroisoquinoline (**96a**) and 3-(trifluoromethyl)benzene-1-sulfonyl chloride (**103c**) using method A (omitting DMF) for 46 h, followed by filtration through Celite,<sup>®</sup> and evaporation of the filtrate to dryness under reduced pressure gave crude product. This was recrystallized from EtOAc:hexanes to give **68** (27%, unoptimized) as a fine off-white crystalline solid; mp 119-120 °C;  $^1H$  NMR  $[(CD_3)_2SO]$   $\delta$  8.15 (d,  $J = 7.9$  Hz, 1H), 8.07 (d,  $J = 7.9$  Hz, 1H), 8.03 (s, 1H), 7.86 (t,  $J = 7.9$  Hz, 1H), 7.15 (m, 3H), 7.07 (m, 1H), 4.32 (s, 2H), 3.42 (t,  $J = 6.1$

Hz, 2H), 2.82 (t,  $J = 6.1$  Hz, 2H); HRESIMS calcd. for  $C_{16}H_{15}F_3NO_2S$   $m/z$   $[M + H]^+$  342.0770, found 342.0762; HPLC purity: 100%.

**2-((3-Bromophenyl)sulfonyl)-1,2,3,4-tetrahydroisoquinoline (69).** Reaction of 1,2,3,4-tetrahydroisoquinoline (**96a**) (2.43 g, 19.42 mmol, 1.20 equiv.) and 3-bromobenzene-1-sulfonyl chloride (**103d**) (4.14 g, 16.18 mmol, 1.00 equiv.) by general method A gave a crude product that was re-precipitated from EtOAc:hexanes, further purified by trituration with 5% EtOAc:hexanes, and finally recrystallized from EtOAc:hexanes to yield **69** (447 mg, 8%, unoptimized) as a white flaky crystalline solid; mp 149-150 °C;  $^1H$  NMR  $[(CD_3)_2SO]$ :  $\delta$  7.94 (t,  $J = 1.8$  Hz, 1H), 7.91 (ddd,  $J = 8.0, 1.9, 1.0$  Hz, 1H), 7.84 (ddd,  $J = 7.9, 1.6, 1.0$  Hz, 1H), 7.58 (t,  $J = 7.9$  Hz, 1H), 7.16 (m, 3H), 7.10 (m, 1H), 4.26 (s, 2H), 3.36 (t,  $J = 6.0$  Hz, 2H), 2.84 (t,  $J = 6.0$  Hz, 2H); HRESIMS calcd. for  $C_{15}H_{15}BrNO_2S$   $m/z$   $[M + H]^+$  353.9981, 352.0001, found 353.9989, 352.0005; HPLC purity: 99.9%.

**2-({3-[Trifluoromethoxy]phenyl}sulfonyl)-1,2,3,4-tetrahydroisoquinoline (70).** Reaction of 1,2,3,4-tetrahydroisoquinoline (**96a**) and 3-(trifluoromethoxy)benzene-1-sulfonyl chloride (**103e**) by method A (omitting DMF) for 93 h, then filtering through a pad of Celite,<sup>®</sup> and evaporation of the filtrate to dryness under reduced pressure, gave a crude product. This was re-dissolved in MeOH, and treated with EtOAc to afford a suspension, which was filtered. The filtrate was evaporated and the resulting yellow solid was triturated with a minimum quantity of MeOH to give **70** (3%, unoptimized) as a fine white crystalline solid; mp 119-120 °C;  $^1H$  NMR  $[(CD_3)_2SO]$ :  $\delta$  7.86 (d,  $J = 7.6$  Hz, 1H), 7.75 (m, 3H), 7.15 (m, 3H), 7.09 (m, 1H), 4.29 (s, 2H), 3.39 (t,  $J = 6.0$  Hz, 2H), 2.83 (t,  $J = 6.0$  Hz, 2H); HRESIMS calcd. for  $C_{16}H_{15}F_3NO_3S$   $m/z$   $[M + H]^+$  358.0719, found 358.0714; HPLC purity: 100%.

**4-({3,4-Dihydroisoquinolin-2[1H]-yl}sulfonyl)benzoic acid (71).** Reaction of 1,2,3,4-tetrahydroisoquinoline (**96a**) with 4-(chlorosulfonyl)benzoic acid (**103f**) by method A for 2 h, followed by filtration, gave a crude product that was re-precipitated from EtOAc:hexanes and then chromatographed (eluting with 0-50% EtOAc:hexanes + 0.5% v/v  $CH_3CO_2H$ ) to give **71** (8%, unoptimized) as an amorphous white solid; mp 260-263 °C;  $^1H$  NMR  $[(CD_3)_2SO]$ :  $\delta$  13.43 (br s, 1H), 8.13 (dt,  $J = 8.6$  Hz, 2H), 7.94 (d,  $J = 8.6$  Hz, 2H), 7.19-7.17 (m, 4H), 4.25 (s, 2H), 3.39 (t, overlapping water peak,  $J = 6.0$  Hz, 2H), 2.85 (t,  $J = 6.0$  Hz, 2H); HRESIMS calcd. for  $C_{16}H_{15}NNaO_4S$   $m/z$   $[M + H]^+$  340.0614, found 340.0622; HPLC purity: 100%.

**2-(3-(3,4-Dihydroisoquinolin-2(1H)-ylsulfonyl)phenylamino)-2-oxoacetic acid (72).** A stirred suspension of **67** (400 mg, 1.39 mmol) in a mixture of THF (30 mL) and pyridine (5 mL) was treated dropwise with ethyl 2-chloro-2-oxoacetate (0.20 mL, 179 mmol) at 10 °C. The mixture was stirred at 20 °C for 1 h, then diluted with water (200 mL) and stirred for a further 30 min. The resulting solid was collected and washed with hexane to give ethyl 2-(3-(3,4-dihydroisoquinolin-2(1H)-ylsulfonyl)phenylamino)-2-oxoacetate (**104**) (513 mg, 95%): mp (EtOAc/petroleum ether) 156-158 °C, which was used directly.  $^1H$  NMR  $[(CD_3)_2SO]$ :  $\delta$  11.09 (s, 1H), 8.29 (s, 1H), 8.04 (d,  $J = 7.1$  Hz, 1H), 7.68-7.53 (m, 2H), 7.14 (br s, 4H), 4.33 (q,  $J = 6.8$  Hz, 2H), 4.21 (s, 2H), 3.29 (after  $D_2O$  exchange, s, 2H), 2.87 (s, 2H), 1.32 (t,  $J = 6.8$  Hz, 3H).

A stirred suspension of **104** (0.25 g, 0.64 mmol) in THF (6 mL) was treated dropwise with a solution of  $Cs_2CO_3$  (0.23 g, 0.71 mmol) in water (3 mL). The mixture was stirred at 20 °C for 3h,

then diluted with 0.1 M HCl (80 mL). The resulting solid was extracted with dilute NH<sub>4</sub>OH and the filtrate was acidified to give a solid. Recrystallisation of this from MeOH/water gave **72** (176 mg, 76%); mp 194 °C; <sup>1</sup>H NMR [(CD<sub>3</sub>)<sub>2</sub>SO]: δ 14.33 (v br s, 1H), 11.06 (s, 1H), 8.33 (t, *J* = 7.0 Hz, 1H), 8.04 (dt, *J* = 7.8, 1.7 Hz, 1H), 7.61 (t, *J* = 7.8 Hz, 1H), 7.57 (dt, *J* = 7.9, 1.5 Hz, 1H), 7.17-7.08 (m, 4H), 4.20 (2, 2H), 3.28 (after D<sub>2</sub>O exchange, t, *J* = 6.0 Hz, 2H), 2.87 (t, *J* = 5.9 Hz, 2H); HRESIMS calcd for C<sub>17</sub>H<sub>15</sub>N<sub>2</sub>O<sub>5</sub> *m/z* [M-1]<sup>-</sup> 359.0707, found 359.0715; HPLC purity 99.7%.

**3-((3,4-Dihydroisoquinolin-2(1H)-yl)sulfonyl)-N-sulfamoylbenzamide (73)**. A solution of acid **17** (1.80g, 5.67 mmol, 1.00 equiv.) in THF (15 mL) was treated with CDI (2.00 g, 12.33 mmol, 2.17 equiv.) and the resulting mixture was stirred for 70 min at 60 °C to give the intermediate imidazolide. The mixture was cooled to 20 °C, treated with sulfamide (1.105 g, 11.502 mmol, 2.028 equiv.) for 30 min at 20 °C, then a solution of DBU (1.72 mL, 11.50 mmol, 2.03 equiv.) was added dropwise. After the exotherm the mixture was stirred at 20 °C for 2.5 h and then diluted with EtOAc (56 mL) and CH<sub>2</sub>Cl<sub>2</sub> (68 mL), and washed with 1M HCl (68 mL x 2). The combined aqueous layers were extracted with CH<sub>2</sub>Cl<sub>2</sub> (38 mL x 2), and remaining aqueous suspension was filtered through a pad of Celite to afford an amorphous yellow solid. Re-precipitation of this from EtOAc:hexanes:MeOH furnished **73** (82 mg, unoptimized) as an amorphous white solid; mp 188-189 °C; <sup>1</sup>H NMR [(CD<sub>3</sub>)<sub>2</sub>SO]: δ 12.25 (s, 1H), 8.36 (t, *J* = 1.6 Hz, 1H), 8.20 (dt, *J* = 8.0, 1.3 Hz, 1H), 8.02 (d, *J* = 7.8 Hz, 1H), 7.74 (t, *J* = 7.8 Hz, 1H), 7.37 (br s, 2H), 7.18-7.09 (m, 4H), 4.25 (s, 2H), 3.35 (t, *J* = 6.0 Hz, 2H), 2.85 (t, *J* = 5.9 Hz, 2H); HRESIMS calcd. for C<sub>16</sub>H<sub>17</sub>N<sub>3</sub>NaO<sub>5</sub>S<sub>2</sub> *m/z* [M + Na]<sup>+</sup> 418.0502, found 418.0503; HPLC purity: 98.7%.

**2-((3-(2H-Tetrazol-5-yl)phenyl)sulfonyl)-1,2,3,4-tetrahydroisoquinoline (74)**. Nitrile **65** (269 mg, 0.90 mmol, 1.00 equiv.) and NH<sub>4</sub>Cl (60 mg, 1.13 mmol, 1.25 equiv.) in DMF (14 mL) was treated with solid sodium azide (73 mg, 1.13 mmol, 1.25 equiv.), and the resulting mixture was stirred at 120 °C for 69 h (method of Nakamura *et al.*<sup>S16</sup>). The reaction mixture was cooled to 20 °C and concentrated to dryness under reduced pressure. Trituration of the resulting orange-brown residue in an ultrasonic bath afforded a pale orange-brown solid, which was re-precipitated from EtOAc:hexanes to give tetrazole **74** (107 mg, 35%) as an amorphous off-white solid; mp 250-251 °C; <sup>1</sup>H NMR [(CD<sub>3</sub>)<sub>2</sub>SO]: δ 17.07 (br s, 1H), 8.45 (t, *J* = 1.6 Hz, 1H), 8.33 (dt, *J* = 7.9, 1.4 Hz, 1H), 8.00 (dt, *J* = 7.9, 1.4 Hz, 1H), 7.84 (t, *J* = 7.8 Hz, 1H), 7.12 (m, 4H), 4.29 (s, 2H), 3.39 (t, *J* = 6.0 Hz, 2H), 2.86 (t, *J* = 6.0 Hz, 2H); HRESIMS calcd. for C<sub>16</sub>H<sub>16</sub>N<sub>5</sub>O<sub>2</sub>S *m/z* [M + H]<sup>+</sup> 342.1019, found 342.1027; HPLC purity: 99.5%.

**3-((3,4-Dihydroisoquinolin-2[1H]-yl)sulfonyl)benzamide (75)**. The acid chloride of **17** was prepared and treated with aqueous ammonia (25% w/w) by method A. The resulting white suspension was filtered to yield a first batch of crude product. The filtrate was diluted with H<sub>2</sub>O, back-extracted with CH<sub>2</sub>Cl<sub>2</sub> (x 4), and the combined organic extracts were dried (MgSO<sub>4</sub>) and evaporated to give a second batch. Both batches were combined and recrystallized from EtOAc:hexanes to give **75** (42%) as a white crystalline solid; mp 182-184 °C; <sup>1</sup>H NMR [(CD<sub>3</sub>)<sub>2</sub>SO]: δ 8.29 (t, *J* = 1.6 Hz, 1H), 8.26 (br s, 1H), 8.16 (dt, *J* = 8.0, 1.4 Hz, 1H), 7.97 (dt, *J* = 8.0, 1.4 Hz, 1H), 7.72 (t, *J* = 7.9 Hz, 1H), 7.63 (br s, 1H), 7.18-7.06 (m, 4H), 4.23 (s, 2H), 3.34 (t, *J* = 6.0 Hz, 2H), 2.85 (t, *J* = 6.0 Hz, 2H); HRESIMS calcd. for C<sub>16</sub>H<sub>16</sub>N<sub>2</sub>NaO<sub>3</sub>S *m/z* [M + Na]<sup>+</sup> 339.0774, found 339.0767; HPLC purity: 99.7%.

**3-({3,4-Dihydroisoquinolin-2(1H)-yl}sulfonyl)phenyl(morpholino)methanone (76)**. The acid chloride of **17** (1.00 equiv.) was prepared and treated with morpholine (3.07 equiv.) by method A to give, after re-precipitation of the crude product, **76** (35%) as an amorphous white solid; mp 131-133 °C; <sup>1</sup>H NMR [(CD<sub>3</sub>)<sub>2</sub>SO]: δ 7.91 (dt, *J* = 6.5, 2.2 Hz, 1H), 7.80 (m, 1H), 7.70 (m, 2H), 7.13 (m, 3H), 7.09 (m, 1H), 4.26 (s, 2H), 3.77-3.41 (br m, 6H), 3.37 (t, *J* = 6.0 Hz, 2H), 3.30-3.11 (br m, 2H), 2.83 (t, *J* = 6.0 Hz, 2H); HRESIMS calcd. for C<sub>20</sub>H<sub>23</sub>N<sub>2</sub>O<sub>4</sub>S *m/z* [M + H]<sup>+</sup> 383.1373, found 387.1371; TLC *R<sub>f</sub>* 0.27 (50% EtOAc:hexanes + 3 drops CH<sub>3</sub>CO<sub>2</sub>H; HPLC purity: 100%.

**3-({3,4-Dihydroisoquinolin-2(1H)-yl}sulfonyl)phenyl(thiomorpholino)methanone (77)**. The acid chloride of **17** (1.00 equiv.) was prepared and treated with thiomorpholine by method A, with column chromatography (eluting with 0–50% EtOAc:hexanes) and re-precipitation of the crude product residue from EtOAc:hexanes furnishing **77** (13%, unoptimized) as an amorphous white solid; mp 138-140 °C; <sup>1</sup>H NMR [(CD<sub>3</sub>)<sub>2</sub>SO]: δ 7.88 (m, 1H), 7.81 (m, 1H), 7.70 (m, 2H), 7.17-7.08 (m, 4H), 4.24 (s, 2H), 3.87 (br s, 2H), 3.43 (br s, 2H), 3.35 (t, *J* = 6.0 Hz, 2H), 2.84 (t, *J* = 6.0 Hz, 2H), 2.71 (br s, 2H), 2.57 (br s, 2H); HRESIMS calcd. for C<sub>20</sub>H<sub>22</sub>N<sub>2</sub>NaO<sub>3</sub>S<sub>2</sub> *m/z* [M + Na]<sup>+</sup> 425.0964, found 425.0979; HPLC purity: 97.3%.

**3-({3,4-Dihydroisoquinolin-2[1H]-yl}sulfonyl)-*N*-(2-{dimethylamino}ethyl)benzamide (78)**. The acid chloride of **17** (1.00 equiv.) was prepared and treated with *N,N*-(dimethylamino)ethylamine by method A, with column chromatography (eluting with 0–10% MeOH:CH<sub>2</sub>Cl<sub>2</sub>) and re-precipitation of the crude product furnishing **78** (16%, unoptimized) as an amorphous white solid; mp 190-191 °C; <sup>1</sup>H NMR [(CD<sub>3</sub>)<sub>2</sub>SO]: δ 10.05 (br s, 1H), 9.07 (t, *J* = 5.08 Hz, 1H), 8.30 (t, *J* = 1.6 Hz, 1H), 8.21 (dt, *J* = 7.9, 1.4 Hz, 1H), 7.99 (dt, *J* = 7.9, 1.4 Hz, 1H), 7.75 (t, *J* = 7.9 Hz, 1H), 7.14 (m, 4H), 4.25 (s, 2H), 3.61 (q, *J* = 11.7, 5.9 Hz, 2H), 3.35 (t, *J* = 5.9 Hz, 2H), 3.14 (m, 2H), 2.85 (t, *J* = 5.9 Hz, 2H), 2.73 (s, 6H); HRESIMS calcd. for C<sub>20</sub>H<sub>26</sub>N<sub>3</sub>O<sub>3</sub>S *m/z* [M + H]<sup>+</sup> 388.1689, found 388.1684; HPLC purity: 97.2%.

**3-({3,4-Dihydroisoquinolin-2[1H]-yl}sulfonyl)-*N*-methylbenzamide (79)**. The acid chloride of **17** (1.00 equiv.) was prepared and treated with methylamine (2M in THF, 1.00 equiv.) by method A, with another portion of methylamine (2M in THF, 1.59 equiv.) being added to the reaction mixture after 12 h. The reaction was complete after a further 2 h, and re-precipitation of the crude product residue gave **79** (51%) as an amorphous white solid; mp 190-191 °C; <sup>1</sup>H NMR [(CD<sub>3</sub>)<sub>2</sub>SO]: δ 8.73 (d, *J* = 4.5 Hz, 1H), 8.26 (t, *J* = 1.6 Hz, 1H), 8.12 (dt, *J* = 7.9, 1.4 Hz, 1H), 7.96 (dt, *J* = 7.9, 1.4 Hz, 1H), 7.72 (t, *J* = 7.9 Hz, 1H), 7.19-7.05 (m, 4H), 4.23 (s, 2H), 3.32 (t<sub>under water peak</sub>, *J* = 6.1 Hz, 2H), 2.85 (t, *J* = 6.06 Hz, 2H), 2.81 (d, *J* = 4.5 Hz, 3H); HRESIMS calcd. for C<sub>17</sub>H<sub>19</sub>N<sub>2</sub>O<sub>3</sub>S *m/z* [M + H]<sup>+</sup> 331.1111, found 331.1108; HPLC purity: 99.1%.

**3-({3,4-Dihydroisoquinolin-2[1H]-yl}sulfonyl)-*N,N*-dimethylbenzamide (80)**. The acid chloride of **17** (1.00 equiv.) was prepared and treated with *N,N*-dimethylamine (2M in THF, 1.52 equiv.) by method A. Re-precipitation of the crude product residue furnished **80** (30%) as an amorphous white solid; mp 159-160 °C; <sup>1</sup>H NMR [(CD<sub>3</sub>)<sub>2</sub>SO]: δ 7.89 (dt, *J* = 7.1, 1.9 Hz, 1H), 7.78 (m, 1H), 7.69 (m, 2H), 7.18-7.05 (m, 4H), 4.25 (s, 2H), 3.35 (t, *J* = 6.0 Hz, 2H), 2.99 (s, 3H), 2.84 (m, 5H); HRESIMS calcd. for C<sub>18</sub>H<sub>21</sub>N<sub>2</sub>O<sub>3</sub>S *m/z* [M + H]<sup>+</sup> 345.1267, found 345.1261; HPLC purity: 99.6%.

**(3-((3,4-Dihydroisoquinolin-2(1H)-yl)sulfonyl)phenyl)(2-oxa-6-azaspiro[3.3]heptan-6-yl)methanone (81).** The acid chloride of **17** (1.00 equiv.) was prepared and treated with a solution of bis(2-oxa-6-azaspiro[3.3]heptane) oxalate<sup>S17</sup> (1.05 equiv.) in CH<sub>2</sub>Cl<sub>2</sub>:DMF (1.0:0.8) by method A to afford a crude product. This was purified by re-precipitation from EtOAc:hexanes, column chromatography on silica gel (eluting with 0–5% MeOH:CH<sub>2</sub>Cl<sub>2</sub>), preparative TLC on silica (eluting with 5% MeOH:CH<sub>2</sub>Cl<sub>2</sub>), and finally a further re-precipitation from EtOAc:hexanes, to furnish **81** (28 mg, 6%, unoptimized), as an amorphous white solid; mp 160-162 °C; <sup>1</sup>H NMR [(CD<sub>3</sub>)<sub>2</sub>SO]: δ 7.96 (m, 2H), 7.88 (dt, *J* = 8.0, 1.3 Hz, 1H), 7.71 (td, *J* = 7.7, 0.5 Hz, 1H), 7.19-7.09 (m, 4H), 4.67 (s, 4H), 4.41 (s, 2H), 4.24 (pseudo-d, *J* = 11.0 Hz, 4H), 3.36 (t, *J* = 6.0 Hz, 2H), 2.83 (t, *J* = 5.9 Hz, 2H); HRESIMS calcd. for C<sub>21</sub>H<sub>22</sub>N<sub>2</sub>NaO<sub>4</sub>S *m/z* (M + Na)<sup>+</sup> 421.1192, found 421.1193; HPLC purity: 94.8%.

**3-({3,4-Dihydroisoquinolin-2[1H]-yl}sulfonyl)-N-(pyridin-4-ylmethyl)benzamide (82).** The acid chloride of **17** (1.00 equiv.) was prepared and reacted with 4-(aminomethyl)pyridine (1.05 equiv.) by method A. Recrystallization of the crude product furnished **82** (68%) as a crystalline creamy white solid; mp 177-181 °C; <sup>1</sup>H NMR [(CD<sub>3</sub>)<sub>2</sub>SO]: δ = 9.42 (t, *J* = 5.9 Hz, 1H), 8.51 (dd, *J* = 4.4, 1.6 Hz, 2H), 8.33 (t, *J* = 1.6 Hz, 1H), 8.21 (m, 1H), 8.00 (m, 1H), 7.75 (t, *J* = 7.8 Hz, 1H), 7.32 (d, *J* = 6.0 Hz, 2H); 7.19-7.04 (m, 4H), 4.53 (d, *J* = 5.9 Hz, 2H), 4.26 (s, 2H), 3.36 (t, *J* = 6.0 Hz, 2H), 2.85 (t, *J* = 6.0 Hz, 2H); HRESIMS calcd. for C<sub>22</sub>H<sub>22</sub>N<sub>3</sub>O<sub>3</sub>S *m/z* [M + H]<sup>+</sup> 408.1376, found 408.1373; HPLC purity: 99.7%.

**1-(4-(3,4-Dihydroisoquinolin-2(1H)-ylsulfonyl)phenyl)pyrrolidin-2-one (83).** 2-((4-Iodophenyl)sulfonyl)-1,2,3,4-tetrahydroisoquinoline (42 mg, 105 μmol), Pd<sub>2</sub>dba<sub>3</sub> (25 mg, 27 μmol, 0.2 eq.), Xantphos (30 mg, 52 μmol, 0.4 eq.), 2-pyrrolidinone (11 mg, 126 μmol, 1.2 eq) and Cs<sub>2</sub>CO<sub>3</sub> (52 mg, 160 μmol, 1.5 eq.) were dissolved in dry dioxane (1 ml, 0.1 M) and heated at 100 °C for 18 h. The reaction mixture was cooled to 20 °C and solvent was removed under reduced pressure. The residue was purified by column flash-chromatography on silica to give **83** (71 %); mp 180-181 °C. <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 7.85 - 7.80 (m, 4 H), 7.16 - 7.14 (m, 2 H), 7.17 - 7.14 (m, 2 H), 7.14 - 7.06 (m, 1 H), 7.03 - 7.01 (m, 1 H), 4.26 (s, 2 H), 3.89 (t, *J* = 7.20 Hz, 2 H), 3.37 (t, *J* = 6.00 Hz, 2 H), 2.92 (t, *J* = 6.00 Hz, 2 H), 2.65 (t, *J* = 8.00 Hz, 2 H), 2.22 (hept, *J* = 3.20 Hz, 2 H). HRESIMS calcd for C<sub>19</sub>H<sub>21</sub>N<sub>2</sub>O<sub>3</sub>S; *m/z* [M+H]<sup>+</sup> 357.1267; found: 357.1258; [M+Na]<sup>+</sup> calculated: 379.1087; found: 379.1088; HPLC purity: 99.8%. Anal. Calcd for C<sub>19</sub>H<sub>20</sub>N<sub>2</sub>O<sub>3</sub>S.0.5H<sub>2</sub>O: C, H, N.

#### Compounds of Table 7 (Scheme 4)

**(S)-1-(naphthalen-2-ylsulfonyl)piperidine-3-carboxylic acid (84).** Reaction of naphthalene-2-sulfonyl chloride (**107**) and (*S*)-piperidine-3-carboxylic acid (**107a**) by method A gave acid **84** (yield 53%); mp 103-105 °C. <sup>1</sup>H NMR [(CD<sub>3</sub>)<sub>2</sub>SO]: δ 12.49 (s<sub>br</sub>, 1 H), 8.45 (d, *J* = 1.44 Hz, 1 H), 8.23 (d, *J* = 7.96 Hz, 1 H), 8.17 (d, *J* = 8.72 Hz, 1 H), 8.08 (d, *J* = 14.04 Hz, 1 H), 7.78 - 7.66 (m, 3 H), 3.60 (dd, *J* = 8.20 Hz, *J* = 2.84 Hz, 1 H), 3.44 - 3.36 (m, 1 H), 2.60 (t, *J* = 9.88 Hz, 1 H), 2.55 - 2.45 (m, 2 H), 1.8 - 1.65 (m, 2 H), 1.57 - 1.43 (m, 1 H), 1.40 - 1.28 (m, 1 H) ppm. HRMS (ESI): *m/z* = [M+H]<sup>+</sup> calculated: 320.0951; found: 320.0955; [M+Na]<sup>+</sup> calculated:

342.0770; found: 342.0777;  $[M+K]^+$  calculated: 358.0510; found: 358.0508; HPLC purity: 99.6%. Anal. Calcd for  $C_{16}H_{17}NO_4S$ : C,H,N.

**(R)-1-(naphthalen-2-ylsulfonyl)piperidine-3-carboxylic acid (85).** Reaction of naphthalene-2-sulfonyl chloride (**107**) and (*R*)-piperidine-3-carboxylic acid (**107b**) by method A gave acid **86** (yield 59%); 104-106 °C.  $^1H$  NMR  $[(CD_3)_2SO]$ :  $\delta$  12.49 (s<sub>br</sub>, 1 H), 8.45 (d,  $J = 1.44$  Hz, 1 H), 8.23 (d,  $J = 7.96$  Hz, 1 H), 8.17 (d,  $J = 8.72$  Hz, 1 H), 8.08 (d,  $J = 14.04$  Hz, 1 H), 7.78 - 7.66 (m, 3 H), 3.60 (dd,  $J = 8.20$  Hz,  $J = 2.84$  Hz, 1 H), 3.44 - 3.36 (m, 1 H), 2.60 (t,  $J = 9.88$  Hz, 1 H), 2.55 - 2.45 (m, 2 H), 1.8 - 1.65 (m, 2 H), 1.57 - 1.43 (m, 1 H), 1.40 - 1.28 (m, 1 H) ppm. HRMS (ESI):  $m/z = [M+H]^+$  calculated: 320.0951; found: 320.0953;  $[M+Na]^+$  calculated: 342.0770; found: 342.0773;  $[M+K]^+$  calculated: 358.0496; found: 358.0505; HPLC purity: 99.8%. Anal. Calcd for  $C_{16}H_{17}NO_4S$ : C,H,N.

**1-(Naphthalen-2-ylsulfonyl)pyrrolidine-3-carboxylic acid (86).** Reaction of naphthalene-2-sulfonyl chloride (**107**) and pyrrolidine-3-carboxylic acid (**107c**) by method A gave acid **86** (yield 42%); mp 167-169 °C.  $^1H$  NMR  $[(CD_3)_2SO]$ :  $\delta$  12.47 (s<sub>br</sub>, 1 H), 8.49 (d,  $J = 1.36$  Hz, 1 H), 8.22 (d,  $J = 7.92$  Hz, 1 H), 8.16 (d,  $J = 8.72$  Hz, 1 H), 8.08 (d,  $J = 8.00$  Hz, 1 H), 7.83 (dd,  $J = 8.64$  Hz,  $J = 1.88$  Hz, 1 H), 7.73 (dt,  $J = 6.92$  Hz,  $J = 1.44$  Hz, 1 H), 7.69 (dt,  $J = 6.92$  Hz,  $J = 1.36$  Hz, 1 H), 3.44 (d,  $J = 8.12$  Hz, 1 H), 8.09 Hz, 1H), 3.36 (d,  $J = 6.32$  Hz, 1H), 3.34 (d,  $J = 6.36$  Hz, 1 H), 3.30—3.19 (m, 2 H), 2.93 (m<sub>c</sub>, 1 H) ppm. HRMS (ESI):  $m/z = [M+H]^+$  calculated: 306.0795; found: 306.0792;  $[M+Na]^+$  calculated: 328.0614; found: 328.0615;  $[M+K]^+$  calculated: 344.0353; found: 344.0355; HPLC purity: 100%. Anal. Calcd for  $C_{15}H_{15}NO_4S$ : C,H,N.

**1-(Naphthalen-2-ylsulfonyl)azetidine-3-carboxylic acid (87).** Reaction of naphthalene-2-sulfonyl chloride (**106**) and azetidine-3-carboxylic acid (**107d**) by method A gave acid **87** (68% yield); mp 169-170 °C.  $^1H$  NMR  $[(CD_3)_2SO]$ :  $\delta$  12.61 (s<sub>br</sub>, 1 H), 8.53 (d,  $J = 2.21$  Hz, 1 H), 8.26 (d,  $J = 8.01$  Hz, 1 H), 8.21 (d,  $J = 8.72$  Hz, 1 H), 8.11 (d,  $J = 7.97$  Hz, 1 H), 7.83 (dd,  $J = 8.60$  Hz,  $J = 1.88$  Hz, 1 H), 7.76 (dt,  $J = 6.84$  Hz,  $J = 1.28$  Hz, 1 H), 7.71 (dt,  $J = 6.80$  Hz,  $J = 1.32$  Hz, 1 H), 3.95 (dd,  $J = 8.65$  Hz,  $J = 8.65$  Hz, 2 H), 3.79 (dd,  $J = 8.05$  Hz,  $J = 6.53$  Hz, 2 H), 3.28 - 3.20 (m, 1 H) ppm. HRMS (ESI):  $m/z = [M+H]^+$  calculated: 292.0625; found: 292.0634;  $[M+Na]^+$  calculated: 314.0457; found: 314.0452;  $[M+K]^+$  calculated: 330.0197; found: 330.0192; HPLC purity: 100%. Anal. Calcd for  $C_{14}H_{13}NO_4S$ : C,H,N.

**1-(Naphthalen-2-ylsulfonyl)-1H-pyrazole-3-carboxylic acid (88).** Reaction of naphthalene-2-sulfonyl chloride (**106**) and 1H-pyrazole-3-carboxylic acid (**107e**) by method A gave acid **88** (yield 6%); mp 165-168 °C.  $^1H$  NMR  $(CD_3OD)$ :  $\delta$  8.78 (d,  $J = 1.72$  Hz, 1 H), 8.45 (d,  $J = 2.80$  Hz, 1 H), 8.13 (d,  $J = 8.04$  Hz, 1 H), 8.10 (d,  $J = 8.88$  Hz, 1 H), 8.00 (d,  $J = 8.16$  Hz, 1 H), 8.80 Hz,  $J = 2.00$  Hz, 1 H), 7.73 (dt,  $J = 6.96$  Hz,  $J = 1.28$  Hz, 1 H), 7.70 (dt,  $J = 8.24$  Hz,  $J = 1.36$  Hz, 1 H), 6.91 (d,  $J = 2.76$  Hz, 1 H). HRMS (ESI):  $m/z = [M+H]^+$  calculated: 303.0434; found: 303.0437;  $[M+Na]^+$  calculated: 325.0253; found: 325.0256;  $[M+K]^+$  calculated: 340.9993; found: 340.9991; HPLC purity: 98.3 %.

**1-(4'-Chlorobiphenyl-4-ylsulfonyl)piperidine-3-carboxylic acid (89).** Reaction of piperidine-3-carboxylic acid (**108**) and 4'-chlorobiphenyl-4-sulfonyl chloride (**109a**) by method A gave acid **89** (yield 56%); mp 257-260 °C.  $^1H$  NMR  $[(CD_3)_2SO]$ :  $\delta$  12.51 (s<sub>br</sub>, 1 H), 7.95 (dd,  $J = 6.73$  Hz,  $J$

= 1.81 Hz, 2 H), 7.84 - 7.76 (m, 4 H), 7.58 (m<sub>c</sub>, 2 H), 3.49 (d, *J* = 8.93 Hz, 1 H), 3.29 (d, *J* = 11.24 Hz, 1 H), 2.60 - 2.40 (m, 3 H), 1.85 - 1.78 (m, 1 H), 1.78 - 1.68 (m, 1 H), 1.58—1.43 (m, 1 H), 1.42—1.30 (m, 1 H) ppm. HRMS (ESI): *m/z* = [M+H]<sup>+</sup> calculated: 380.0718; found: 380.0707; [M+Na]<sup>+</sup> calculated: 402.0537; found: 402.0529; [M+K]<sup>+</sup> calculated: 418.0277; found: 418.0260; HPLC purity: 96.5%. Anal. Calcd for C<sub>18</sub>H<sub>18</sub>ClNO<sub>4</sub>S: C,H,N.

**1-(2'-Chlorobiphenyl-4-ylsulfonyl)piperidine-3-carboxylic acid (90).** Reaction of piperidine-3-carboxylic acid (**108**) and 2'-chlorobiphenyl-4-sulfonyl chloride (**109b**) by method A gave acid **90** (yield 68%); mp 193-195 °C. <sup>1</sup>H NMR [(CD<sub>3</sub>)<sub>2</sub>SO]: δ 7.83 (d, *J* = 8.00 Hz, 2 H), 7.61 (d, *J* = 8.00 Hz, 2 H), 7.51 - 7.48 (m, 1 H), 7.40 - 7.30 (m, 3 H), 3.88 (d, *J* = 6.80 Hz, 1 H), 3.64 (d, *J* = 12.00 Hz, 1 H), 2.90 - 2.60 (m, 2 H), 2.60 - 2.40 (m, 1 H), 2.20 - 1.95 (m, 1 H), 1.95 - 1.80 (m, 1 H), 1.80 - 1.60 (m, 1 H), 1.60 - 1.30 (m, 1 H) ppm. HRMS (ESI): *m/z* = [M+H]<sup>+</sup> calculated: 378.0567; found: 378.0567; HPLC purity: 95.6%. Anal. Calcd for C<sub>18</sub>H<sub>18</sub>ClNO<sub>4</sub>S: C,H,N.

**1-(2'-Chlorobiphenyl-3-ylsulfonyl)piperidine-3-carboxylic acid (91).** Reaction of piperidine-3-carboxylic acid (**108**) and 2'-chlorobiphenyl-3-sulfonyl chloride (**109c**) by method A gave acid **91** (yield 79%); mp 140-142 °C. <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 10.55 (s<sub>br</sub>, 1 H), 7.88 (t, *J* = 1.52 Hz, 1 H), 7.78 (tt, *J* = 7.64 Hz, *J* = 1.40 Hz, 1 H), 7.68 (td, *J* = 7.80 Hz, *J* = 1.36 Hz, 1 H), 7.61 (t, *J* = 7.72 Hz, 1 H), 7.57 - 7.52 (m, 0.5 H), 7.51 - 7.47 (m, 1 H), 7.38 - 7.30 (m, 1.5 H), 7.27 - 7.21 (m, 0.5 H), 7.18 - 7.14 (m, 0.5 H), 3.93 - 3.80 (m, 1 H), 3.69 - 3.56 (m, 1 H), 2.73 - 2.61 (m, 2 H), 2.53 - 2.44 (m, 1 H), 2.07—1.96 (m, 1 H), 1.87 - 1.75 (m, 1 H), 1.74 - 1.59 (m, 1 H), 1.52 - 1.37 (m, 1 H) ppm. HRMS (ESI): *m/z* = [M-H]<sup>-</sup> calculated: 378.0572; found: 378.0564; [M+Na]<sup>+</sup> calculated: 402.0537; found: 402.0536; HPLC purity: 97.7 %.

**1-(2'-Chlorobiphenyl-2-ylsulfonyl)piperidine-3-carboxylic acid (92).** Reaction of piperidine-3-carboxylic acid (**109**) and 2'-chlorobiphenyl-2-sulfonyl chloride (**109d**) by method A gave acid **92** (yield 45%). <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 9.30 (s<sub>br</sub>, 1 H), 8.11 (dd, *J* = 7.81 Hz, *J* = 1.80 Hz, 1 H), 7.80 - 7.75 (m, 1 H), 7.73 (dd, *J* = 7.73 Hz, *J* = 1.32 Hz, 1 H), 7.65 - 7.58 (m, 1 H), 7.58 - 7.52 (m, 1 H), 7.46 (tt, *J* = 7.48 Hz, *J* = 1.28 Hz, 1 H), 7.42 - 7.35 (m, 2 H), 3.93 - 3.79 (m, 1 H), 3.73 - 3.64 (m, 0.75 H), 3.64 - 3.55 (m, 0.25 H), 3.03 (d, *J* = 9.89 Hz, 0.25 H), 3.00 (d, *J* = 9.88 Hz, 0.25 H), 2.98 - 2.88 (m, 0.5 H), 2.72 - 2.61 (m, 1 H), 2.61 - 2.53 (m, 0.5 H), 2.46 - 2.36 (m, 0.5 H), 2.12 - 1.96 (m, 1 H), 1.87 - 1.75 (m, 1 H), 1.73 - 1.55 (m, 1.5 H), 1.49 - 1.36 (m, 0.5 H) ppm. HRMS (ESI): *m/z* = [M+H]<sup>+</sup> calculated: 402.0537; found: 402.0535; HPLC purity: 96.0 %.

**1-(Anthracen-2-ylsulfonyl)piperidine-3-carboxylic acid (93).** Reaction of piperidine-3-carboxylic acid (**108**) and anthracene-2-sulfonyl chloride (**109e**) by method A gave acid **93** (yield 41%); mp 214-217 °C. <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 8.60 (s, 1 H), 8.55 (s, 1 H), 8.50 (s, 1 H), 8.12 (d, *J* = 9.20 Hz, 1 H), 8.10 - 8.00 (m, 2 H), 7.68 (dd, *J* = 8.80 Hz, *J* = 1.60 Hz, 1 H), 7.60 - 7.50 (m, 2 H), 3.95 (d, *J* = 8.00 Hz, 1 H), 3.71 (d, *J* = 11.60 Hz, 1 H), 2.80 - 2.65 (m, 2 H), 2.56 (t, *J* = 10.80 Hz, 1 H), 2.10 - 1.30 (m, 4 H) ppm. HRMS (ESI): *m/z* = [M+H]<sup>+</sup> calculated: 474.1370; found: 474.1379; HPLC purity: 97.0%. Anal. Calcd for C<sub>20</sub>H<sub>19</sub>NO<sub>4</sub>S: C,H,N.

**1-(1,1':3',1''-Terphenyl-4-sulfonyl)piperidine-3-carboxylic acid (94).** Reaction of piperidine-3-carboxylic acid (**108**) 1,1':3',1''-terphenyl-4-sulfonyl chloride (**109f**) (made from the acid) by method A gave acid **94** (yield 19%); mp 168-171 °C. <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 7.86 (d, *J* = 8.40 Hz, 2 H), 7.83 - 7.76 (m, 2 H), 7.65 (d, *J* = 7.05 Hz, 3 H), 7.61 - 7.53 (m, 2 H), 7.47 (t, *J* = 7.36 Hz, 2

H), 7.43 - 7.36 (m, 2 H), 3.89 (d,  $J = 9.93$  Hz, 1 H), 3.65 (d,  $J = 12.01$  Hz, 1 H), 2.78 - 2.60 (m, 2 H), 2.48 (dt,  $J = 11.17$  Hz,  $J = 2.84$  Hz, 1 H), 2.10 - 1.98 (m, 1 H), 1.90 - 1.20 (m, 3 H) ppm. HRMS (ESI):  $m/z = [M-H]^-$  calculated: 420.1275; found: 420.1265; HPLC purity: 97.9 %.

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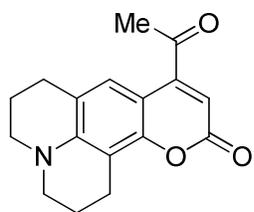
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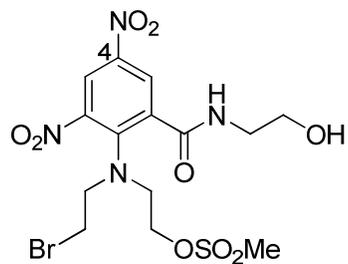
Combustion Analysis Data

No	molecular formula	Calculated				Found	
		C	H	N	C	H	N
23	C <sub>17</sub> H <sub>13</sub> NO <sub>4</sub> S.0.25H <sub>2</sub> O	61.53	4.10	4.22	61.40	4.02	4.22
24	C <sub>15</sub> H <sub>10</sub> BrNO <sub>4</sub> S	47.38	2.65	3.68	47.63	2.64	3.74
26	C <sub>17</sub> H <sub>17</sub> NO <sub>4</sub> S	61.61	5.17	4.23	61.34	5.18	4.22
29	C <sub>16</sub> H <sub>14</sub> ClNO <sub>4</sub> S	54.62	4.01	3.98	54.59	4.37	3.54
30	C <sub>16</sub> H <sub>14</sub> BrNO <sub>4</sub> S	48.50	3.56	3.53	49.62	3.77	3.34
31	C <sub>16</sub> H <sub>14</sub> INO <sub>4</sub> S	43.35	3.18	3.16	43.62	3.25	3.21
32	C <sub>16</sub> H <sub>15</sub> NO <sub>5</sub> S	57.65	4.54	4.20	57.31	4.55	4.05
33	C <sub>17</sub> H <sub>17</sub> NO <sub>5</sub> S.H <sub>2</sub> O	55.88	5.24	3.83	56.26	5.28	3.88
36	C <sub>17</sub> H <sub>14</sub> N <sub>2</sub> O <sub>4</sub> S	59.64	4.12	8.18	59.32	4.04	7.87
38	C <sub>16</sub> H <sub>14</sub> BrNO <sub>4</sub> S	48.50	3.56	3.53	48.94	3.49	3.53
39	C <sub>16</sub> H <sub>14</sub> INO <sub>4</sub> S	43.35	3.18	3.16	43.58	3.25	3.03
57	C <sub>15</sub> H <sub>14</sub> FNO <sub>4</sub> S	55.72	4.36	4.33	55.49	4.3	4.27
59	C <sub>15</sub> H <sub>14</sub> ClNO <sub>4</sub> S	53.02	4.15	4.12	53.11	4.06	4.11
61	C <sub>16</sub> H <sub>17</sub> NO <sub>5</sub> S.H <sub>2</sub> O	5.80	5.27	4.27	55.17	5.15	4.01
61	C <sub>21</sub> H <sub>19</sub> NO <sub>5</sub> S	63.46	4.82	3.52	63.42	4.89	3.52
63	C <sub>16</sub> H <sub>17</sub> NO <sub>4</sub> S	60.17	5.37	4.39	60.12	5.39	4.45
83	C <sub>19</sub> H <sub>20</sub> N <sub>2</sub> O <sub>3</sub> S.0.5H <sub>2</sub> O	62.45	5.79	7.67	62.36	5.64	7.66
84	C <sub>16</sub> H <sub>17</sub> NO <sub>4</sub> S	60.17	5.37	4.39	59.50	5.29	4.19
85	C <sub>16</sub> H <sub>17</sub> NO <sub>4</sub> S	60.17	5.37	4.39	60.45	5.39	4.29
85	C <sub>15</sub> H <sub>15</sub> NO <sub>4</sub> S	59.00	4.95	4.59	59.11	4.89	4.58
85	C <sub>14</sub> H <sub>13</sub> NO <sub>4</sub> S	57.72	4.50	4.81	57.89	4.36	4.74
89	C <sub>18</sub> H <sub>18</sub> ClNO <sub>4</sub> S	56.91	4.78	3.69	56.87	4.61	2.91
90	C <sub>18</sub> H <sub>18</sub> ClNO <sub>4</sub> S	56.91	4.78	3.69	56.67	4.81	3.72
93	C <sub>20</sub> H <sub>19</sub> NO <sub>4</sub> S	65.02	5.18	3.79	64.85	5.19	3.85

Structures of probe A and PR-104A



**probe 5**  
J. Amer. Chem. Soc.  
2004, 126, 2282-2283



**PR-104A**  
Cancer Res. 2010,  
70, 1573-1584

Table S2. X-ray data collection and refinement statistics

	17	79	85
<b>Data:</b>			
Wavelength (Å)	1.54182	1.54182	1.54182
Space group	P2 <sub>1</sub>	P2 <sub>1</sub> 2 <sub>1</sub> 2 <sub>1</sub>	P2 <sub>1</sub> 2 <sub>1</sub> 2 <sub>1</sub>
Unit cell parameters (Å ; °)	48.72, 106.76, 74.88; β=103.11	58.69, 64.70, 96.65	57.13, 63.47, 96.44
Resolution (Å)	20.03 - 2.00 (2.07 - 2.00)	18.65 - 2.00 (2.07 - 2.00)	18.68 - 2.20 (2.28 - 2.20)
Number of molecules/AU	2	1	1
Total number of reflections	139694 (8737)	88047 (5495)	51579 (3956)
Unique reflections	49665 (4646)	24949 (2378)	17915 (1656)
Multiplicity	2.8 (1.9)	3.5 (2.3)	2.9 (2.4)
Completeness (%)	98.7 (92.8)	97.9 (95.2)	97.6 (93.5)
<I/σI>	16.5 (3.4)	18.6 (3.0)	7.0 (1.9)
R <sub>merge</sub>	0.047 (0.206)	0.044 (0.257)	0.096 (0.342)
Wilson B (Å <sup>2</sup> )	22.0	29.4	35.1
<b>Refinement:</b>			
Resolution	20.03-2.00 (2.05-2.00)	18.65 - 2.00 (2.05- 2.00)	18.68 - 2.20 (2.26 - 2.20)
R <sub>work</sub> <sup>a</sup>	0.168 (0.251)	0.182 (0.264)	0.208 (0.247)
R <sub>free</sub> <sup>b</sup>	0.218 (0.294)	0.221 (0.326)	0.278 (0.250)
No. of working reflections	47140 (3250)	23672 (1654)	17000 (1161)

No. of free reflections	2524 (171)	1275 (80)	915 (72)
Average B factor protein	18.7/20.0	26.9/28.8	28.3/29.5
main-chain/side-chain (Å <sup>2</sup> )			
Average B factor ligands (Å <sup>2</sup> )	17.8	29.2	27.3
Average B factor water (Å <sup>2</sup> )	29.7	35.3	33.7
RMSD bond (Å)	0.0233	0.0233	0.0222
RMSD angles (°)	1.920	1.915	1.848
Ramachandran most	97.8/0.2	97.4/0.0	97.3/0.0
favoured/outliers (%)			
Molprobit all-atom clash	6.5	3.0	6.2
score			

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#### Footnotes for Table S2.

Numbers in parentheses represent data in the highest resolution shell.

$R_{\text{work}}^{\text{a}} = \frac{\sum |F(\text{obs}) - |F(\text{calc})||}{\sum |F(\text{obs})|}$  for the 95% of the reflection data used in refinement.

$R_{\text{free}}^{\text{b}} = \frac{\sum |F(\text{obs}) - |F(\text{calc})||}{\sum |F(\text{obs})|}$  for the remaining 5%