

# Supporting Information

## Discovery of Potent, Selective and Orally Bioavailable Alkynyl-Phenoxyacetic Acids CRTH2 (DP2) Receptor Antagonists for the Treatment of Allergic Inflammatory Diseases

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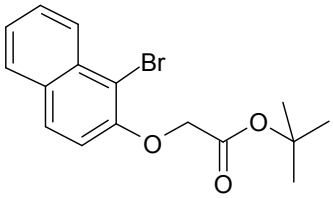
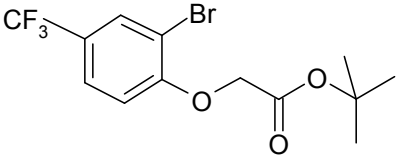
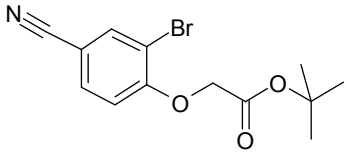
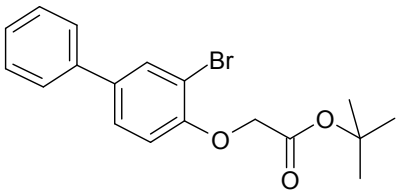
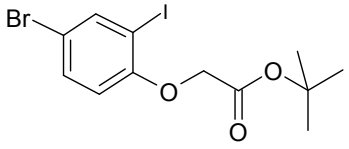
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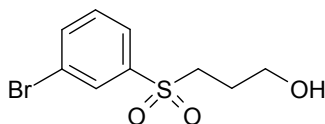
## A- Synthesis and characterization of intermediates

The following *tert*-butyl (2-halophenoxy)acetates were prepared as described for 10a

Cpd	Structure	Chemical name	<sup>1</sup> H NMR (400MHz) $\delta$ [ppm]
10b		<i>tert</i> -butyl (2-iodophenoxy)acetate	7.80 (1H, dd, $J$ = 7.6, $J$ = 1.6 Hz), 7.35 (1H, m), 6.88 (1H, dd, $J$ = 8.3, $J$ = 1.3 Hz), 6.79 (1H, dd, $J$ = 7.6, $J$ = 1.3 Hz), 4.77 (2H, s), 1.44 (9H, s).
10c		<i>tert</i> -butyl (2-bromo-4-methylphenoxy)acetate	8.18 (1H, d, $J$ = 2.1 Hz), 7.84 (1H, dd, $J$ = 8.7, 2.1 Hz), 7.17 (1H, d, $J$ = 8.7 Hz), 4.95 (2H, s), 2.23 (3H, s), 1.42 (9H, s).
10d		<i>tert</i> -butyl (2-bromo-4-fluorophenoxy)acetate	7.56 (1H, dd, $J$ = 8.2 Hz, $J$ = 3.1 Hz), 7.21 (1H, ddd, $J$ = 9.2 Hz, $J$ = 8.2 Hz, $J$ = 3.1 Hz), 7.02 (1H, dd, $J$ = 9.2 Hz, $J$ = 4.8 Hz), 4.77 (2H, s), 1.41 (9H, s).
10e		<i>tert</i> -butyl (2-bromo-5-fluorophenoxy)acetate	7.62 (1H, dd, $J$ = 6.3, $J$ = 8.8 Hz), 6.98 (1H, dd, $J$ = 2.7, $J$ = 11.0 Hz), 6.80 (1H, ddd, $J$ = 2.7; $J$ = 8.3, $J$ = 8.8 Hz), 4.83 (2H, s), 1.42 (9H, s).
10f		<i>tert</i> -butyl (3-chloro-2-iodophenoxy)acetate	7.34-7.30 (1H, m), 7.18-7.16 (1H, m), 6.80-6.77 (2H, d), 4.78 (2H, s), 1.40 (9H, s).

<b>10g</b>		<i>tert</i> -Butyl [(1-bromo-2-naphthyl)oxy]acetate	8.10 (1H, d), 7.94 (2H, m), 7.61 (1H, m), 7.45 (1H, m), 7.38 (1H, d), 4.94 (2H, s), 1.42 (9H, s).
<b>10h</b>		<i>tert</i> -butyl [2-bromo-4-(trifluoromethyl)phenoxy]acetate	7.99 (1H, dd, $J = 0.6$ , $J = 2.2$ Hz), 7.74 (1H, ddd, $J = 0.6$ , $J = 2.2$ , $J = 8.6$ Hz), 7.19 (1H, d, $J = 8.6$ Hz), 4.94 (2H, s), 1.44 (9H, s).
<b>10i</b>		<i>tert</i> -butyl (2-bromo-4-cyanophenoxy)acetate	8.18 (1H, d, $J = 2.0$ Hz), 7.84 (1H, dd, $J = 8.7$ , $J = 2.0$ Hz), 7.17 (1H, d, $J = 8.7$ Hz), 4.95 (2H, s), 1.42 (9H, s).
<b>10j</b>		<i>tert</i> -butyl [(3-bromobiphenyl-4-yl)oxy]acetate	7.88 (1H, d, $J = 2.3$ Hz), 7.61-7.66 (3H, m), 7.41-7.47 (2H, m), 7.34 (1H, m), 7.06 (1H, d, $J = 8.7$ Hz), 4.83 (2H, s), 1.44 (9H, s).
<b>10k</b>		<i>tert</i> -Butyl (4-bromo-2-iodophenoxy)acetate	7.92 (1H, t), 7.51 (1H, p), 6.83 (1H, d), 4.76 (2H, s), 1.40 (9H, s).

### 3-[(3-Bromophenyl)sulfonyl]propan-1-ol (12b)

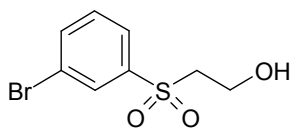


A solution of 3-bromobenzenethiol (5.00 g, 26.4 mmol) in anhydrous DMF (30 mL) was treated with  $\text{Cs}_2\text{CO}_3$  (17.2 g, 52.9 mmol) followed by 3-bromopropan-1-ol (4.40 g, 31.6 mmol). The mixture was heated to 50 °C under nitrogen for 12h. DMF was distilled out

completely, and the residue was dissolved in DCM and washed with water, brine and dried over Na<sub>2</sub>SO<sub>4</sub>. The solvent was evaporated to afford 6.4 g (98%) of 3-[(3-bromophenyl)thio]propan-1-ol as pale yellow liquid. <sup>1</sup>H NMR (400MHz, CDCl<sub>3</sub>) δ [ppm] 7.46 (1H, s), 7.30-7.25 (2H, m), 7.16-7.12 (1H, m), 3.78 (2H, t), 3.07-2.99 (2H, m) 1.93-1.87 (2H, m). MS (ESI<sup>+</sup>): 247.1. HPLC (Condition E): Rt 3.36 min.

A solution of 3-[(3-bromophenyl) thio] propan-1-ol (7.00 g, 49.2 mmol) in DCM (75 mL) was treated with *m*-chloroperbenzoic acid (25.4 g, 148 mmol) and stirred at RT for 5 h. The solid formed was removed by filtration and the filtrate was washed with sodium-bicarbonate solution, water and brine. Organic layer was dried over Na<sub>2</sub>SO<sub>4</sub> and evaporated to afford 6.7 g (93%) of the title compound as yellow semi-solid. <sup>1</sup>H NMR (400MHz, CDCl<sub>3</sub>) δ [ppm] 8.06 (1H, s), 7.85 (1H, dd), 7.79 (1H, dd), 7.46 (1H, dd), 3.76-3.73 (2H, m), 3.27-3.23 (2H, m), 2.02-1.97 (2H, m). MS (ESI<sup>+</sup>): 281.1. HPLC (Condition E): Rt 3.15 min (HPLC purity 99.3%).

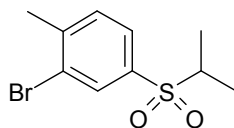
### 2-[(3-Bromophenyl)sulfonyl]ethanol (12c)



A solution of 3-bromobenzenethiol (5.00 g, 26.4 mmol) in anhydrous DMF (30 mL) was treated with Cs<sub>2</sub>CO<sub>3</sub> (17.2 g, 52.8 mmol) and 2-bromoethanol (3.90 g, 31.7mol) and heated to about 50 °C under nitrogen for 12h. DMF was distilled out completely and the residue was dissolved in DCM and washed with water and brine. Organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, evaporated and purified by column chromatography (silica) to afford 5.5 g (90%) of 2-[(3-bromophenyl)thio]ethanol as pale yellow solid. <sup>1</sup>H NMR (400MHz, CDCl<sub>3</sub>) δ [ppm] 7.53 (1H, s), 7.36(1H, m), 7.34 (1H, m), 7.16 (1H, t), 3.78 (2H, t), 3.14 (2H, t). MS (ESI<sup>+</sup>): 217.1. HPLC (Condition F): Rt 3.87 min (HPLC purity 99.8%).

A solution of 2-[(3-bromophenyl) thio] ethanol (5.50 g, 23.5 mmol) in DCM (75 mL) was treated with *m*-chloroperbenzoic acid (12.2 g, 70.7 mmol) and stirred at RT for 5h. The solid formed was filtered and washed with cold DCM and the filtrate was washed with 10% sodium hydroxide, water and brine. Organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, evaporated and passed through column chromatography using silica gel (60-120 mesh) to afford the title compound as off white solid (3.70 g; 59%). <sup>1</sup>H NMR (400MHz, CDCl<sub>3</sub>) δ [ppm] 8.04 (1H, s), 7.94-7.88 (2H, m), 7.61-7.53 (1H, m), 4.89 (1H, t), 3.70-3.66 (2H, m), 3.52 (2H, t). MS (ESI<sup>+</sup>): 310.6. HPLC (Condition F): Rt 2.04 min (HPLC purity 95.6%).

**2-Bromo-4-(isopropylsulfonyl)-1-methylbenzene (12d).**

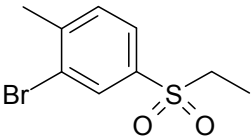


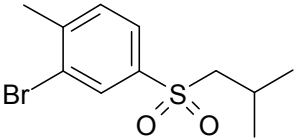
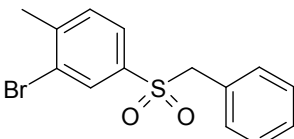
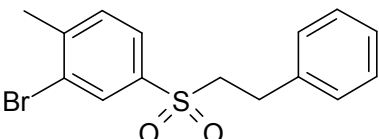
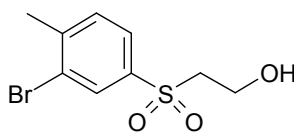
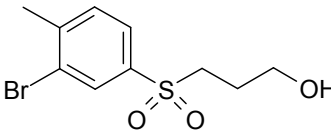
A cooled (-15 °C) solution of 3-bromo-4-methylaniline (2.00 g) in a 6N solution of HCl in water (30 mL) was treated drop-wise with a solution of sodium nitrite (1.78 g) in water (10 mL). The reaction mixture was stirred for 30 mins. The resulting clear solution was added dropwise to a stirred solution of *O*-ethyl xanthic acid potassium salt (6.10 g) in water (25 mL). The mixture was then heated to 80 °C for 15 minutes. The mixture was then cooled and extracted with diethyl ether twice. The solvents were evaporated under reduced pressure to give a residue, which was treated with a solution of KOH (6.1 g) in 95% ethanol (55 mL) and heated to reflux for 10 h. The reaction mixture was diluted with water and acidified with conc. HCl to pH 3 and extracted with diethyl ether. The organic layer was washed with water, brine and concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel), eluting with petroleum ether. This product obtained was triturated with hexane to give 2-bromo-4-(isopropylthio)-1-methylbenzene (1.5g, 70%) as an off-white solid.

A stirred suspension of NaH (40 mg) in anhydrous DMF (5 mL) was treated with a solution of 3-bromo-4-methylbenzenethiol (200 mg) in anhydrous DMF (3 ml). The reaction mixture was stirred for 30 minutes at RT, then 2-iodo propane (0.14 ml) was added to the reaction mixture and the reaction mixture was heated to 55 °C for 3 hours. The reaction mixture was quenched with ice and extracted with diethylether. The organic layer was dried over sodium sulfate and concentrated under reduced pressure. The crude product was purified by flash chromatography (Silica gel), eluting with hexane, to give 2-bromo-4-(isopropylthio)-1-methylbenzene (123 mg, 45%).

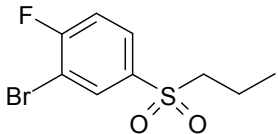
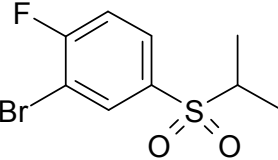
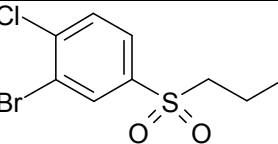
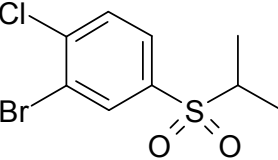
A cooled (0 °C) solution of 2-bromo-4-(isopropylthio)-1-methylbenzene (123 mg) in THF (10 ml) was treated with a solution of oxone (580 mg) in water (6 ml). The reaction mixture was stirred at RT for 16 hours. The reaction mixture was diluted with ethyl acetate and washed with water. The organic layer was dried over sodium sulfate and concentrated to give the title compound (120 mg, 92%). <sup>1</sup>H NMR (300MHz, DMSO-d<sub>6</sub>) δ [ppm] 7.55 (1H, dd, *J*= 8.4 Hz, *J*= 2.8 Hz), 7.18 (1H, dd, *J*= 8.4 Hz, *J*= 5.8 Hz), 7.09-7.04 (1H, m), 2.86-2.83 (1H, m), 2.49 (3H, s), 1.34 (3H, d, *J*= 7.0 Hz), 1.13 (3H, d, *J*= 6.8 Hz). MS (ESI<sup>+</sup>): 294.3 [M+NH<sub>4</sub>]<sup>+</sup>. HPLC (Condition A) Purity 93.0%; Rt 5.42 min.

The compounds in the table below were all prepared following the general method as outlined for **12d**:

Cpd	Structure	Chemical name	<sup>1</sup> H NMR (400MHz) δ [ppm]
<b>12e</b>		2-bromo-4-(ethylsulfonyl)-1-methylbenzene	8.07 (1H, d, <i>J</i> = 1.7 Hz), 7.74 (1H, dd, <i>J</i> = 7.9 Hz, <i>J</i> = 1.9 Hz), 7.44 (1H, d, <i>J</i> = 7.9 Hz), 3.76 (2H, q, <i>J</i> = 7.4 Hz), 2.50 (3H, s), 1.29 (3H, t, <i>J</i> = 7.4 Hz).

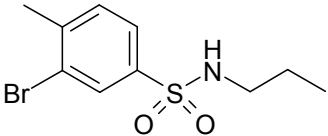
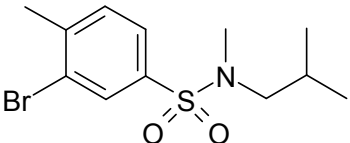
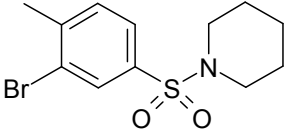
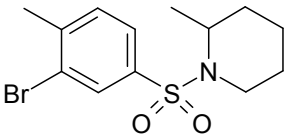
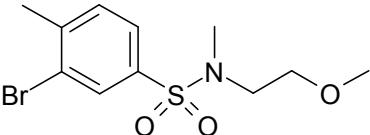
<b>12f</b>		2-bromo-4-(isobutylsulfonyl)-1-methylbenzene	8.07 (1H, d, $J = 1.7$ Hz), 7.54 (1H, dd, $J = 7.9$ Hz, $J = 1.8$ Hz), 7.42 (1H, d, $J = 7.9$ Hz), 2.98 (2H, d, $J = 6.4$ Hz), 2.49 (3H, s), 2.28-2.21 (1H, m), 1.08 (6H, d, $J = 6.7$ Hz).
<b>12g</b>		4-(benzylsulfonyl)-2-bromo-1-methylbenzene	7.78 (1H, d, $J = 1.8$ Hz), 7.43-7.40 (2H, m), 7.36-7.28 (3H, m), 7.13-7.10 (2H, m), 4.31 (2H, s), 2.46 (3H, s).
<b>12h</b>		2-bromo-1-methyl-4-[(2-phenylethyl)sulfonyl]benzene	$\delta$ 8.08 (1H, d, $J = 1.8$ Hz), 7.75 (1H, dd, $J = 7.9$ Hz, $J = 1.8$ Hz), 7.43 (1H, d, $J = 8.0$ Hz), 7.30-7.20 (2H, m), 7.14-7.11 (2H, m), 3.39-3.35 (2H, m), 3.08-3.04 (2H, m), 2.50 (3H, s).
<b>12i</b>		2-[(3-bromo-4-methylphenyl)sulfonyl]ethanol	8.03 (1H, d, $J = 1.8$ Hz), 7.79 (1H, dd, $J = 8.0$ Hz, $J = 1.8$ Hz), 7.61 (1H, d, $J = 8$ Hz), 4.88 (1H, t, $J = 5.4$ Hz), 3.67 (2H, m), 3.49 (2H, t, $J = 6.0$ Hz), 2.43 (3H, s).
<b>12j</b>		3-[(3-bromo-4-methylphenyl)sulfonyl]propan-1-ol	8.08 (1H, d, $J = 1.7$ Hz), 7.75 (1H, dd, $J = 7.9$ Hz, $J = 1.8$ Hz), 7.44 (1H, d, $J = 7.9$ Hz), 3.12 (2H, q, $J = 5.5$ Hz), 3.27-3.22 (2H, m), 2.50 (3H, s), 2.03-1.96 (2H, m), 1.60 (1H, bs).

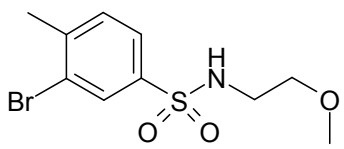
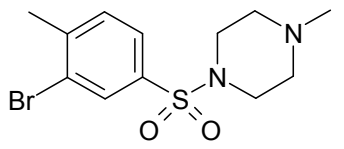
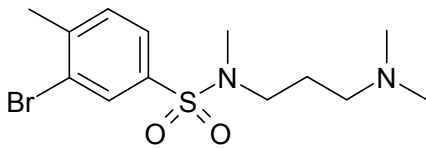
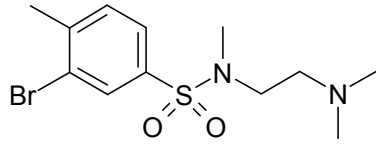
The compounds in the table below were all prepared following the general method outlined for **12k**:

Cpd	Structure	Chemical name	<sup>1</sup> H NMR (DMSO-d <sub>6</sub> ; 400MHz) δ [ppm]
<b>12l</b>		2-bromo-1-fluoro-4-(propylsulfonyl)benzene	8.22 (1H, dd, <i>J</i> = 6.3 Hz, <i>J</i> = 2.3 Hz), 7.99 (1H, ddd, <i>J</i> = 8.6 Hz, <i>J</i> = 4.6 Hz, <i>J</i> = 2.3 Hz), 7.67 (1H, t, <i>J</i> = 8.6 Hz), 3.38 (2H, m), 1.56 (2H, m), 0.93 (3H, t, <i>J</i> = 7.5 Hz).
<b>12m</b>		2-bromo-1-fluoro-4-(isopropylsulfonyl)benzene	8.17 (1H, dd, <i>J</i> = 6.4 Hz, <i>J</i> = 2.2 Hz), 7.93 (1H, ddd, <i>J</i> = 8.7 Hz, <i>J</i> = 4.8 Hz, <i>J</i> = 2.3 Hz), 7.68 (1H, d, <i>J</i> = 8.7 Hz), 3.55 (1H, septet, <i>J</i> = 6.8 Hz), 1.17 (6H, d, <i>J</i> = 6.8 Hz)
<b>12n</b>		2-bromo-1-chloro-4-(propylsulfonyl)benzene	8.22 (1H, d, <i>J</i> = 1.8 Hz), 7.95-7.87 (2H, m), 3.39 (2H, m), 1.57 (2H, m), 0.93 (3H, m)
<b>12o</b>		2-bromo-1-chloro-4-(isopropylsulfonyl)benzene	8.18 (1H, d, <i>J</i> = 2.1 Hz), 7.95 (1H, d, <i>J</i> = 8.4 Hz), 7.86 (1H, dd, <i>J</i> = 8.4 Hz, <i>J</i> = 2.1 Hz), 3.58 (1H, septet, <i>J</i> = 6.8 Hz), 1.17 (6H, d, <i>J</i> = 6.8 Hz).

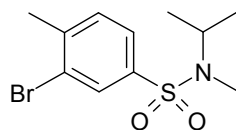
The compounds in the table below were all prepared following the general method as outlined for **12p** (Method 3, Scheme 4):



Cpd	Structure	Chemical name	<sup>1</sup> H NMR (CDCl <sub>3</sub> , 400MHz), δ [ppm]
12q		3-bromo-4-methyl-N-propylbenzenesulfonamide	8.04 (1H, s), 7.70 (1H, d, <i>J</i> = 9.8 Hz), 7.38 (1H, d, <i>J</i> = 8.0 Hz), 4.53-4.50 (1H, m), 2.96-2.91 (2H, m), 2.47 (3H, s), 1.54-1.48 (2H, m), 0.91-0.87 (3H, m)
12r		3-bromo-N-isobutyl-N,4-dimethylbenzenesulfonamide	7.95-7.94 (1H, s), 7.62-7.60 (1H, d, <i>J</i> = 8.0 Hz), 7.39-7.37 (1H, d, <i>J</i> = 8 Hz), 2.77-2.75 (2H, d, <i>J</i> = 7.5 Hz), 2.72 (3H, s), 2.47 (3H, s), 1.90-1.83 (1H, m), 0.96-0.94 (6H, d, <i>J</i> = 6.6 Hz)
12s		1-[(3-bromo-4-methylphenyl)sulfonyl]piperidine	7.84 (1H, s), 7.64-7.63 (2H, m), 2.89 (1H, t, <i>J</i> = 5.5 Hz), 2.44 (3H, s), 1.54 (4H, m), 1.37 (2H, m).
12t		1-[(3-bromo-4-methylphenyl)sulfonyl]-2-methylpiperidine	7.98 (1H, s), 7.66-7.64 (1H, d, <i>J</i> = 8Hz), 7.35-7.33 (1H, d, <i>J</i> = 8Hz), 4.25-4.24 (1H, s), 3.73-3.70 (1H, m), 3.0-2.9 (1H, t), 2.46 (3H, s), 1.62-1.37 (7H, m), 1.10-1.08 (3H, m)
12u		3-bromo-N-(2-methoxyethyl)-N,4-dimethylbenzenesulfonamide	7.97-7.96 (1H, s), 7.63-7.61 (1H, d, <i>J</i> = 9.8 Hz), 7.38-7.36 (1H, d, <i>J</i> = 8.0 Hz), 3.56-3.53 (2H, t), 3.33 (3H, s), 3.26-3.23 (2H, t), 2.85 (3H, s), 2.47 (3H, s)

12v		3-bromo- <i>N</i> -(2-methoxyethyl)-4-methylbenzenesulfonamide	8.02 (1H, s), 7.7 (1H, d, <i>J</i> = 9.8 Hz), 7.37 (1H, d, <i>J</i> = 8.0 Hz), 4.9 (1H, bs), 3.43-3.41 (2H, t), 3.29 (3H, s), 3.15-3.11 (2H, t), 2.47 (3H, s)
12w		1-[(3-bromo-4-methylphenyl)sulfonyl]-4-methylpiperazine	7.89 (1H, s), 7.58 (1H, d, <i>J</i> = 9.7 Hz), 7.39 (1H, d, <i>J</i> = 7.9 Hz), 3.04 (4H, m), 2.50-2.47 (7H, m), 2.28 (3H, s)
12x		3-bromo- <i>N</i> -[3-(dimethylamino)propyl]- <i>N</i> ,4-dimethylbenzenesulfonamide	7.92 (1H, s), 7.62 (1H, d, <i>J</i> = 9.8 Hz), 7.41 (1H, d, <i>J</i> = 8.0 Hz), 3.16-3.10 (4H, m), 2.8 (3H, s), 2.78 (6H, s), 2.48 (3H, s), 2.19-2.15 (2H, m)
12y		bromo- <i>N</i> -[2-(dimethylamino)ethyl]- <i>N</i> ,4-dimethylbenzenesulfonamide	7.98 (1H, s), 7.62 (1H, d, <i>J</i> = 9.8 Hz), 7.38 (1H, d, <i>J</i> = 8 Hz), 3.15-3.12 (2H, t), 2.8 (3H, s), 2.51-2.47 (2H, t), 2.26 (6H, s)

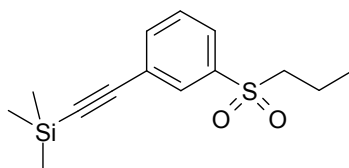
### 3-bromo-*N*-isopropyl-*N*,4-dimethylbenzenesulfonamide (12z)



A solution of *N*-isopropyl 3-bromo-4-methylbenzenesulfonamide (Combiblocks; 200 mg; 0.68 mmol) in anhydrous DMF (4 mL) was treated with NaH (33 mg; 0.82 mmol) and stirred at RT for five minutes. The resulting mixture was treated with iodomethane (43  $\mu$ L; 0.68 mmol) and the reaction mixture was stirred for 16 hours. The mixture was treated again with

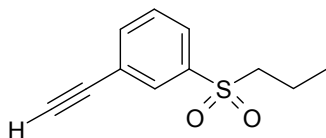
iodomethane (21  $\mu$ l; 0.34 mmol) and the reaction mixture was stirred at RT for 24 hours. The mixture was quenched with an aqueous (5 N) solution of NaOH and extracted with EtOAc. The organic phase was washed with water and brine, dried over MgSO<sub>4</sub>, concentrated and purified flash column chromatography (silica), eluting with cyclohexane containing increasing amounts of EtOAc affording the title compound (112 mg; 53%) as a colorless sticky solid. <sup>1</sup>H NMR (300MHz, DMSO-d<sub>6</sub>)  $\delta$  [ppm] 7.89 (1H, d,  $J$ = 1.9 Hz), 7.70 (1H, d,  $J$ = 8.0Hz,  $J$ = 1.9 Hz), 7.59 (1H, d,  $J$ = 8.0 Hz), 4.08 (1H, sept.,  $J$ = 6.7 Hz), 2.64 (3H, s), 2.43 (3H, s), 0.90 (6H, d,  $J$ = 6.7 Hz). HPLC (Condition A) Purity 98.3%; Rt 4.4 min.

**1-(2-Trimethylsilyl-1-ethynyl)-3-(propylsulfonyl)benzene (13a).**



A solution of 1-bromo-3-(propylsulfonyl) benzene (**12a**; 23 g, 88 mmol) in THF (450 ml) was treated with Pd(dppf)Cl<sub>2</sub> (3.9 g, 5.3 mmol), triethylamine (13.4 g, 132 mmol) and trimethylsilyl acetylene (8.64 g, 88 mmol). The reaction mixture was stirred at RT for 10 minutes, then cuprous iodide (1.0 g, 5.3 mmol) was added, the reaction mixture was heated at 60 °C for 24 h. The reaction mixture was filtered to remove the solid and the filtrate was concentrated under reduced pressure. The crude material was purified by column chromatography using petroleum ether and ethyl acetate (98:2) as a eluent to afford the title compound (9 g, 75%) as a brown oil. <sup>1</sup>H NMR (300MHz, DMSO-d<sub>6</sub>)  $\delta$  [ppm] 7.88 (2H, m), 7.79 (1H, t), 7.66 (1H, q), 3.34 (2H, m), 1.53 (2H, m), 0.92 (3H, t), 0.22 (9H, s).

**1-Ethynyl-3-(propylsulfonyl)benzene (14a).**

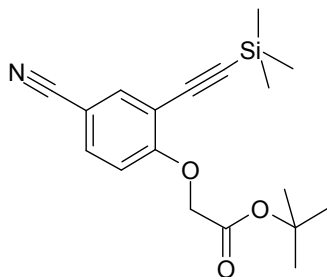


Following the general method as outlined for **16a**, starting from 1-(2-trimethylsilyl-1-ethynyl)-3-(propylsulfonyl)benzene (**13a**), the title compound was obtained as a brown liquid in 70% yield after purification by column chromatography (silica) eluting with petroleum ether and ethyl acetate. <sup>1</sup>H NMR (300MHz, DMSO-d<sub>6</sub>) δ [ppm] 7.89 (1H, t), 7.84 (1H, m), 7.67 (1H, t), 4.45 (1H, s), 3.33 (2H, m), 1.53 (2H, m), 0.90 (3H, t). MS (ESI<sup>+</sup>): 208.8. HPLC (Condition A) Purity 98.6%; Rt 3.89 min.

The (2-sulfonylphenyl)acetylenes in the table below were all prepared following the 2-steps general method as outlined for **14a**:

Cpd	Structure	Chemical name	<sup>1</sup> H NMR (CDCl <sub>3</sub> , 400MHz), δ [ppm]
<b>14b</b>		2-ethynyl-1-methyl-4-(propylsulfonyl)benzene	7.86 (1H, s), 7.78 (1H, d, <i>J</i> = 8.1 Hz), 7.57 (1H, d, <i>J</i> = 8.1 Hz), 4.63 (1H, s), 3.29 (2H, t, <i>J</i> = 8 Hz), 2.48 (3H, s), 1.56-1.54 (2H, m), 1.51 (3H, t, <i>J</i> = 7.6 Hz).
<b>14c</b>		2-ethynyl-1-fluoro-4-(propylsulfonyl)benzene	8.03 (1H, dd, <i>J</i> = 2.3 Hz, <i>J</i> = 8.8 Hz), 7.98-7.94 (1H, m), 7.60 (1H, t, <i>J</i> = 8.0 Hz), 4.74 (1H, s), 3.34 (2H, t, <i>J</i> = 8.0 Hz), 1.56-1.49 (2H, m), 0.90 (3H, t, <i>J</i> = 7.4 Hz).

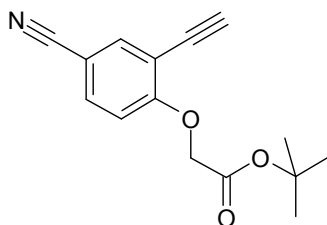
***tert*-Butyl {4-cyano-2-[(trimethylsilyl)ethynyl]phenoxy}acetate (**15b**)**



Following the general method as outlined for **15a**, starting from *tert*-butyl (2-bromo-4-cyanophenoxy)acetate (**10i**) and (trimethylsilyl)acetylene, the title compound was obtained as a dark brown sticky solid in 87% yield.

<sup>1</sup>H NMR (300MHz, DMSO-*d*<sub>6</sub>) δ [ppm] 7.89 (1H, d, *J*= 2.1 Hz), 7.81 (1H, dd, *J*= 2.1 Hz, *J*= 8.8 Hz), 7.09 (1H, d, *J*=8.8 Hz), 4.88 (2H, s), 1.42 (9H, s), 0.22 (9H, s).

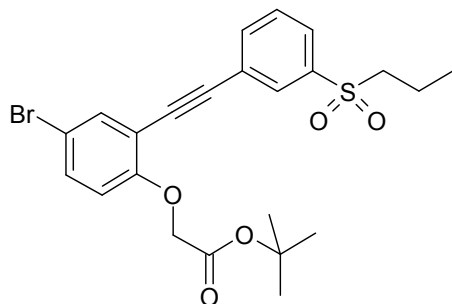
***tert*-Butyl (4-cyano-2-ethynylphenoxy)acetate (16b)**



Following the general method as outlined for **15a**, starting from *tert*-butyl {4-cyano-2-[(trimethylsilyl)ethynyl]phenoxy}acetate (**15b**), the title compound was obtained as an oil in 72% yield.

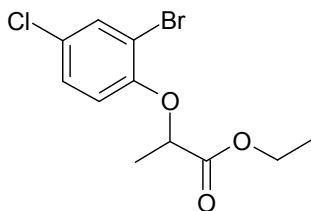
<sup>1</sup>H NMR (300MHz, DMSO-*d*<sub>6</sub>) δ [ppm] 7.93 (1H, d, *J*=2.1 Hz), 7.82 (1H, dd, *J*=2.1 Hz, *J*=8.8 Hz), 7.11 (1H, d, *J*=8.8 Hz), 4.89 (2H, s), 4.46(1H, s), 1.41 (9H, s). MS (ESI<sup>+</sup>): 199.7. HPLC (Condition A) Purity 98.0 %; Rt 4.82 min.

***tert*-Butyl (4-bromo-2-{[3-(propylsulfonyl)phenyl]ethynyl}phenoxy)acetate (26).**



Prepared according to Sonogashira general method 3, starting from (4-bromo-2-iodophenoxy)-acetic acid *tert*-butyl ester (**10k**; 3.0 g; 7.25 mmol) and 1-ethynyl-3-(propane-1-sulfonyl)-benzene (**14a**; 1.50 g; 7.25 mmol), the title compound was obtained as a yellow sticky solid (1.82 g; 51%) after purification by flash column chromatography (cyclohexane/EtOAc gradient).  $^1\text{H}$  NMR (300MHz, DMSO- $\text{d}_6$ )  $\delta$  [ppm] 8.02 (1H, t,  $J$  = 1.6 Hz), 7.94-7.84 (2H, m), 7.77 (1H, d,  $J$  = 2.5 Hz), 7.73 (1H, t,  $J$  = 7.8 Hz), 7.57 (1H, dd,  $J$  = 9.0 Hz,  $J$  = 2.5 Hz), 6.96 (1H, d,  $J$  = 9.0 Hz), 4.82 (2H, s), 3.36 (2H, m); 1.57 (2H, sext.,  $J$  = 7.6 Hz), 1.73 (9H, s), 0.92 (3H, t,  $J$  = 7.6 Hz). HPLC (Condition A) Purity 100.0%; Rt 5.4 min.

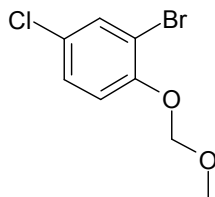
**Ethyl 2-(2-bromo-4-chlorophenoxy)-2-methylpropanoate (28b).**



A mixture of 2-bromo-4-chlorophenol (250 mg; 1.21 mmol) and ethyl-2-bromoisobutyrate (450  $\mu\text{L}$ ; 3.0 mmol) in DMF (5 mL) was treated with  $\text{K}_2\text{CO}_3$  (250 mg, 1.81 mmol) and heated at 120  $^\circ\text{C}$  for 4.5 hours. Water was added and the reaction mixture was extracted 3 times with EtOAc. The combined organic phases were dried over  $\text{MgSO}_4$ , filtered, concentrated and purified by flash column chromatography (silica), eluting with heptane containing increasing amounts of EtOAc. The title compound was obtained as a yellow sticky solid (320 mg; 83%).  $^1\text{H}$  NMR (300MHz, DMSO- $\text{d}_6$ )  $\delta$  [ppm] 7.73 (1H, d,  $J$  = 2.6 Hz), 7.37 (1H, dd,  $J$  = 9.0 Hz,  $J$  =

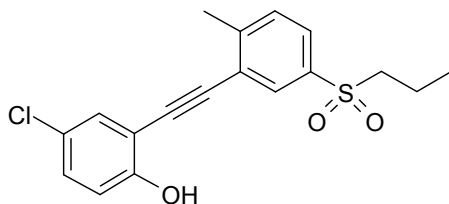
2.6 Hz), 6.85 (1H, d,  $J$  = 9.0 Hz), 4.18 (2H, q,  $J$  = 7.1 Hz), 1.55 (6H, s), 1.17 (3H, t,  $J$  = 7.1 Hz). HPLC (Condition A) Purity 99.4%; Rt 5.3 min.

**2-Bromo-4-chloro-1-(methoxymethoxy)benzene (30).**



A solution of 2-bromo-4-chlorophenol (3.00 g; 14.5 mmol) in DCM (20 ml) was treated with chloromethyl methyl ether (1.3 ml; 17 mmol) and DIEA (3.3 ml; 19 mmol) for 18 hours. The solvents were evaporated, the residue was taken up in EtOAc, washed with sat.  $\text{NH}_4\text{Cl}$  solution and brine, dried over  $\text{MgSO}_4$ , filtered and the solvent removed under reduced pressure to afford the title compound as a colorless oil (3.27 g, 90%).  $^1\text{H}$  NMR (300MHz,  $\text{DMSO-d}_6$ )  $\delta$  [ppm] 7.70 (1H, d,  $J$  = 2.6 Hz), 7.41 (1H, dd,  $J$  = 9.0 Hz,  $J$  = 2.6 Hz), 7.23 (1H, d,  $J$  = 9.0 Hz), 5.29 (2H, s), 3.40 (3H, s).

**4-Chloro-2-{{2-methyl-5-(propylsulfonyl)phenyl}ethynyl}phenol (31).**

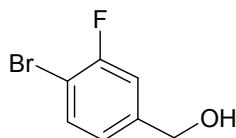


3-{{5-Chloro-2-(methoxymethoxy)phenyl}ethynyl}-4-methylphenyl propyl sulfone was prepared according to the protocol described for the preparation of **29a**, starting from 2-bromo-4-chloro-1-(methoxymethoxy)benzene (**30**) and 2-ethynyl-1-methyl-4-(propane-1-sulfonyl)-benzene (**14b**), and obtained as a white solid in 70% yield after purification by flash column chromatography (cyclohexane/EtOAc gradient).  $^1\text{H}$  NMR (300MHz,  $\text{DMSO-d}_6$ )  $\delta$

[ppm] 7.94 (1H, d,  $J$  = 2.0 Hz), 7.80 (1H, dd,  $J$  = 8.0 Hz,  $J$  = 2.0 Hz), 7.67 (1H, d,  $J$  = 2.7 Hz), 7.63 (1H, d,  $J$  = 8.0 Hz), 7.47 (1H, dd,  $J$  = 9.0 Hz,  $J$  = 2.7 Hz), 7.24 (1H, d,  $J$  = 9.0 Hz), 5.34 (2H, s), 3.43 (3H, s), 3.31 (2H, m), 2.58 (3H, s), 1.55 (2H, sext.,  $J$  = 7.5 Hz), 0.92 (3H, t,  $J$  = 7.5 Hz). HPLC (Condition A) Purity 100.0%; Rt 5.3 min.

3-{[5-Chloro-2-(methoxymethoxy)phenyl]ethynyl}-4-methylphenyl propyl sulfone (1.09 g; 2.77 mmol) was treated with a 4 N solution HCl in 1,4-dioxane (21 ml) and stirred at RT for 7 hours. The reaction mixture was concentrated to dryness under reduced pressure to afford the title compound as a beige solid (884 mg; 91%).  $^1\text{H}$  NMR (300MHz, DMSO- $\text{d}_6$ )  $\delta$  [ppm] 10.48 (1H, s), 7.94 (1H, d,  $J$  = 2.0 Hz), 7.78 (1H, dd,  $J$  = 8.0 Hz,  $J$  = 2.0 Hz), 7.61 (1H, d,  $J$  = 8.0 Hz), 7.51 (1H, d,  $J$  = 2.7 Hz), 7.30 (1H, dd,  $J$  = 9.0 Hz,  $J$  = 2.7 Hz), 6.94 (1H, d,  $J$  = 9.0 Hz), 3.32 (2H, m), 2.57 (3H, s), 1.55 (2H, sext.,  $J$  = 7.5 Hz), 0.91 (3H, t,  $J$  = 7.5 Hz). HPLC (Condition A) Purity 99.8%; Rt 4.8 min.

#### (4-Bromo-3-fluorophenyl)methanol (34a)

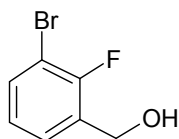


A cooled (0 °C) suspension of lithium aluminum hydride (88 mg; 2.3 mmol) in anhydrous THF (10 mL) was treated dropwise with a solution of methyl 4-bromo-3-fluorobenzoate (300 mg; 1.29 mmol) dissolved in anhydrous Et<sub>2</sub>O (10 mL), and the reaction mixture was stirred at RT for 2 days. The reaction mixture was treated with a saturated aqueous solution of sodium thiosulfate. The organic phase was separated, dried over MgSO<sub>4</sub>, filtered and concentrated to dryness affording the title compound as a yellow liquid (247 mg, 94%).

$^1\text{H}$  NMR (300MHz, DMSO- $\text{d}_6$ )  $\delta$  [ppm] 7.64 (1H, dd,  $J$  = 8.1,  $J$  = 7.5 Hz), 7.28 (1H, m), 7.11 (1H, m), 5.40 (1H, t,  $J$  = 5.8 Hz), 4.48 (2H, d,  $J$  = 5.8 Hz). HPLC (Condition A): Rt 2.78 min (HPLC purity 90.2%).



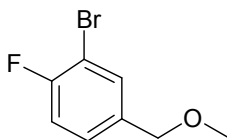
**(3-Bromo-2-fluorophenyl)methanol (34b)**



A cooled (0 °C) solution of 3-bromo-2-fluorobenzoic acid (500 mg; 2.28 mmol) in anhydrous THF (4 mL) was slowly treated with borane-tetrahydrofuran complex (3.42 mL; 1.00 M; 3.42 mmol) and the resulting solution was stirred at RT for 2 days. Borane-tetrahydrofuran complex (3.42 mL; 1.00 M; 3.42 mmol) was added and the reaction mixture was stirred at RT for a further 3 hours. The reaction was carefully quenched with water and the mixture was concentrated. The residue was dissolved in Et<sub>2</sub>O, and the aqueous phase was saturated with K<sub>2</sub>CO<sub>3</sub>. The organic layer was separated and the aqueous phase was extracted with Et<sub>2</sub>O. The combined organic phases were washed with water and brine, dried over MgSO<sub>4</sub> and concentrated to dryness affording the title compound as a colorless oil (388 mg, 83%).

<sup>1</sup>H NMR (300MHz, DMSO-d<sub>6</sub>) δ [ppm] 7.60 (1H, m), 7.45 (1H, m), 7.15 (1H, t, *J* = 7.1 Hz), 5.42 (1H, s), 4.57 (2H, s). HPLC (Condition A): Rt 2.67 min (HPLC purity 97.6%).

**2-Bromo-1-fluoro-4-(methoxymethyl)benzene (35a)**

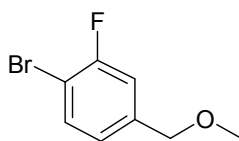


A cooled (-20 °C) solution of 3-bromo-4-fluorobenzyl alcohol (500 mg; 2.44 mmol) and methanesulfonyl chloride (123 μL; 1.59 mmol) in DCM (5 mL) was treated with a solution of triethylamine (255 μL; 1.83 mmol) in DCM (2.5 mL). The reaction mixture was allowed to warm to RT and stirred for 30 minutes before being quenched with water. The phases were

separated and the organic phase was washed with HCl (0.1N in water) and brine, dried over MgSO<sub>4</sub>, filtered and concentrated to dryness affording a residue, which was purified by flash column chromatography), eluting with cyclohexane containing increasing amounts of EtOAc, to give 3-bromo-4-fluorobenzyl methanesulfonate as a colorless liquid (330 mg, 48%). <sup>1</sup>H NMR (300MHz, DMSO-d<sub>6</sub>) δ [ppm] 7.84 (1H, dd, *J* = 6.7, *J* = 2.1 Hz), 7.54 (1H, ddd, *J* = 8.7, *J* = 4.9, *J* = 2.1 Hz), 7.45 (1H, d, *J* = 8.7 Hz), 5.25 (2H, s), 3.27 (3H, s).

A solution of 3-bromo-4-fluorobenzyl methanesulfonate (330 mg; 1.17 mmol) and 2,6-lutidine (176 μL; 1.52 mmol) in methanol (4 mL) was stirred for 16 hours at RT. Additional aliquots of 2,6-lutidine (176 μL; 1.52 mmol each) were added once a day for a total of three days, during which stirring was continued at RT. The mixture was taken up in Et<sub>2</sub>O, washed with water, HCl (0.1N in water) and brine. The organic phase was dried over MgSO<sub>4</sub>, filtered and concentrated with moderate vacuum and without heating affording the title compound as a pale yellow liquid (131 mg, 51%). <sup>1</sup>H NMR (300MHz, DMSO-d<sub>6</sub>) δ [ppm] 7.66 (1H, d, *J* = 7.3 Hz), 7.38 (2H, m), 4.41 (2H, s), 3.30 (3H, s).

#### 1-Bromo-2-fluoro-4-(methoxymethyl)benzene (35b)

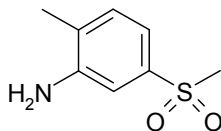


A cooled (0 °C) solution of (4-bromo-3-fluorophenyl)methanol (**34a**; 299 mg; 1.46 mmol) and methanesulfonyl chloride (147 μL; 1.90 mmol) in DCM (3 mL) was treated slowly with a solution of triethylamine (305 μL; 2.19 mmol) in DCM (1.5 mL). The reaction mixture was allowed to warm to RT and stirred for 45 minutes before being quenched by addition of water. The organic phase was washed with HCl (0.1N in water) and brine, dried over MgSO<sub>4</sub>, filtered and concentrated to dryness affording a residue, which was purified by flash column chromatography, eluting with cyclohexane containing increasing amounts of EtOAc to give 4-

bromo-3-fluorobenzyl methanesulfonate as a colourless liquid (286 mg, 69%).  $^1\text{H}$  NMR (300MHz, DMSO- $\text{d}_6$ )  $\delta$  [ppm] 7.77 (1H, dd,  $J= 8.2, J= 7.5$  Hz), 7.48 (1H, dd,  $J= 9.7, J= 2.0$  Hz), 7.26 (1H, dd,  $J= 8.2, J= 2.0$  Hz), 5.26 (2H, s), 3.27 (3H, s).

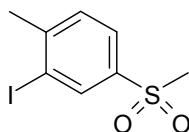
A solution of 4-bromo-3-fluorobenzyl methanesulfonate (286 mg; 1.01 mmol) and 2,6-lutidine (234  $\mu\text{L}$ ; 2.0 mmol) in methanol (4 mL) was stirred for 16 hours at RT. Additional aliquots of 2,6-lutidine (234  $\mu\text{L}$ ; 2.0 mmol each) were added once a day for a total of three days, during which stirring was continued at RT. The mixture was taken up in  $\text{Et}_2\text{O}$ , washed with water, HCl (0.1N in water) and brine. The organic phase was dried over  $\text{MgSO}_4$ , filtered and concentrated with moderate vacuum and without heating affording the title compound in a mixture with ethyl ether, which was directly used for the next step.

#### 2-Methyl-5-(methylsulfonyl)aniline (37a).



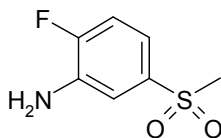
A mixture of 4-methylsulfonyl-2-nitrotoluene (4.00 g; 18.6 mmol) and platinum oxide (120 mg; 0.53 mmol) in EtOAc (200 mL) was hydrogenated in a PARR apparatus at 5 atm for 75 minutes. The mixture was filtered through a pad of celite and the solvent was evaporated to afford the title compound as a colorless oil (3.41 g, 99%).  $^1\text{H}$  NMR (300MHz, DMSO- $\text{d}_6$ )  $\delta$  [ppm] 7.16 (1H, d,  $J= 7.8$  Hz), 7.11 (1H, d,  $J= 1.9$  Hz), 6.95 (1H, dd,  $J= 7.7, 1.9$  Hz), 5.42 (2H, bs), 3.07 (3H, s), 2.12 (3H, s). MS ( $\text{ESI}^+$ ): 186.1.

#### 2-Iodo-1-methyl-4-(methylsulfonyl)benzene (38a).



A cooled (0 °C) solution of 2-methyl-5-(methylsulfonyl)aniline (**37a**; 556 mg; 3.00 mmol) in aqueous hydrogen chloride (5 M, 10 mL; 50 mmol) was treated with sodium nitrite (248 mg; 3.60 mmol) and the resulting mixture was stirred at 0 °C for 30 minutes, before being treated with a solution of potassium iodide (4.98 g; 30 mmol) in water (8 mL). The resulting mixture was stirred at RT for 1 hour, the EtOAc was added and the phases separated. The organic layer was washed twice with an aqueous, saturated sodium thiosulfate solution, then with brine, dried over MgSO<sub>4</sub> and concentrated to afford a residue which was purified by column chromatography, eluting with cyclohexane containing increasing amounts of EtOAc to afford the title compound (649 mg, 73%) as a colorless liquid. <sup>1</sup>H NMR (300MHz, DMSO-d<sub>6</sub>) δ [ppm] 8.28 (1H, d, *J*= 2.0 Hz), 7.85 (1H, dd, *J*= 8.0, *J*= 2.0 Hz), 7.60 (1H, d, *J*= 8.0 Hz), 3.24 (3H, s), 2.47 (3H, s). HPLC (Condition A): Rt 3.23 min (HPLC purity 100%).

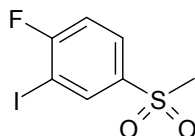
#### 2-Fluoro-5-(methylsulfonyl)aniline (**37b**)



A mixture of 4-fluoro-3-nitrophenyl methyl sulfone (1.50 g; 6.84 mmol) and 10% Pd/C (100 mg) in MeOH (30 ml) was placed in a PARR reactor and treated with a pressure of 15 atm of hydrogen for 2 hours. The reaction mixture was filtered through Celite and the filtrate was concentrated to dryness affording the title compound (1.04 g, 80%).

<sup>1</sup>H NMR (300MHz, DMSO-d<sub>6</sub>) δ [ppm] 7.31 (1H, dd, *J*= 2.4, *J*= 8.4 Hz), 7.26 (1H, dd, *J*= 8.4, *J*= 11.4 Hz), 7.05 (1H, ddd, *J*= 2.4, *J*= 4.2, *J*= 8.4 Hz), 5.75 (2H, s), 3.14 (3H, s).

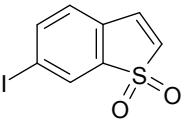
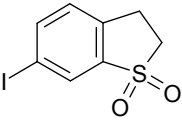
#### 1-Fluoro-2-iodo-4-(methylsulfonyl)benzene (**38b**)



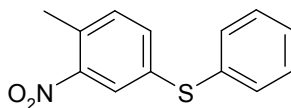
2-Fluoro-5-(methylsulfonyl)aniline (**37b**; 500 mg; 2.64 mmol) was treated with a 5 N solution of hydrochloric acid in water (8.98 ml; 44.92 mmol) and the solution cooled to 0 °C. The solution was treated with sodium nitrite (219 mg; 3.17 mmol) and stirred at 0 °C for 30 minutes, then treated with a solution of potassium iodide (4.39 g; 26.43 mmol) in water (8 mL) and stirred at RT for 1 hour. EtOAc was added, the phases were separated and the organic phase was washed with a saturated sodium thiosulfate solution twice, then with brine. The organic phase was dried on MgSO<sub>4</sub>, filtered and concentrated under reduced pressure to give a residue which was purified by by flash column chromatography, eluting with cyclohexane containing increasing amounts of EtOAc. The title compound was obtained as a white solid (212 mg; 27%). <sup>1</sup>H NMR (300MHz, DMSO-d<sub>6</sub>) δ [ppm] 8.37 (1H, dd, *J*= 5.8, *J*= 2.3 Hz), 8.00 (1H, ddd, *J*= 2.3, *J*= 4.8, *J*= 8.6 Hz), 7.56 (1H, dd, *J*= 0.4, *J*= 8.1 Hz), 3.30 (3H, s).

**The following iodoaryl compounds 38 were prepared according to the same general protocol**

Cpd	Structure	Chemical name	<sup>1</sup> H NMR (400MHz) δ [ppm]
<b>38c</b>		<b>1-chloro-2-iodo-4-(methylsulfonyl)benzene</b>	8.39 (1H, d, <i>J</i> = 2.1 Hz), 7.93 (1H, dd, <i>J</i> = 2.1, <i>J</i> = 8.3 Hz), 7.85 (1H, d, <i>J</i> = 8.3 Hz), 3.29 (3H, s)
<b>38d</b>		<b>3-iododibenzo[b,d]thiophene 5,5-dioxide</b>	8.40 (1H, d, <i>J</i> = 1.5 Hz), 8.21 (1H, d, <i>J</i> = 7.6 hz), 8.18 (1H, dd, <i>J</i> = 8.3 Hz, <i>J</i> = 1.5 Hz), 7.97-8.01 (2H, m), 7.81 (1H,

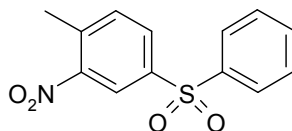
			dt, $J = 7.6$ Hz, $J = 1.0$ Hz), 7.69 (1H, dt, $J = 7.6$ Hz, $J = 1.0$ Hz).
<b>38e</b>		<b>6-iodo-1-benzothiophene 1,1-dioxide</b>	8.25 (1H, m), 8.07 (1H, dd, $J = 7.9$ Hz, $J = 1.6$ Hz), 7.601 (1H, dd, $J = 6.9$ Hz, $J = 1.0$ Hz), 7.38 (1H, d, $J = 7.9$ Hz), 7.34 (1H, d, $J = 6.9$ Hz).
<b>38f</b>		<b>6-iodo-2,3-dihydro-1-benzothiophene 1,1-dioxide</b>	8.08 (1H, d, $J = 1.5$ Hz), 7.99 (1H, dd, $J = 8.1$ Hz, $J = 1.5$ Hz), 7.36 (1H, d, $J = 8.1$ Hz), 3.60 (2H, t, $J = 6.9$ Hz), 3.29 (2H, t, $J = 6.9$ Hz).

**1-Methyl-2-nitro-4-(phenylthio)benzene (48).**



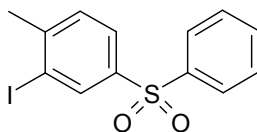
A mixture of 4-fluoro-2-nitrotoluene (800  $\mu$ l; 6.5 mmol), thiophenol (800  $\mu$ l; 7.8 mmol) and  $K_2CO_3$  (1780 mg; 12.9 mmol) in DMSO (16 ml) was placed in a microwave vial and submitted to microwave irradiation at 150 °C for 20 minutes. The reaction mixture was filtered, taken up in EtOAc and washed with water and brine. The organic phase was dried over  $MgSO_4$ , filtered, concentrated and purified by flash column chromatography (silica), eluting with cyclohexane containing 5% of DCM affording the title compound (745 mg; 47%) as a yellow solid.  $^1H$  NMR (300MHz, DMSO- $d_6$ )  $\delta$  [ppm] 7.80 (1H, d,  $J = 1.4$  Hz), 7.51-7.50 (2H, m), 7.45-7.43 (5H, m), 2.47 (3H, s). HPLC (Condition A) Purity 91.6%; Rt 5.2 min.

**1-Methyl-2-nitro-4-(phenylsulfonyl)benzene (49).**



A solution of 1-methyl-2-nitro-4-(phenylthio)benzene (**48**; 745 mg; 3.04 mmol) in MeOH (11 ml) and water (11 ml) was treated with Oxone® (5.60 g; 9.11 mmol) and the reaction mixture was stirred at RT for 6 hours. Water was added and the reaction mixture was extracted 2 times with DCM. The combined organic extracts were dried over MgSO<sub>4</sub>, filtered and concentrated to dryness affording the title compound as a beige solid (690 mg, 82%). <sup>1</sup>H NMR (300MHz, DMSO-d<sub>6</sub>) δ [ppm] 8.48 (1H, d, *J* = 2.0 Hz), 8.18 (1H, dd, *J* = 8.1 Hz, *J* = 2.0 Hz), 8.05-8.01 (2H, m), 7.77-7.62 (4H, m), 2.56 (3H, s). HPLC (Condition A) Purity 91.3%; Rt 3.9 min.

**2-Iodo-1-methyl-4-(phenylsulfonyl)benzene (50).**

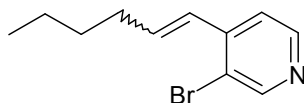


Following the general method as outlined for **37a** using MeOH and EtOAc as solvents, starting from 1-methyl-2-nitro-4-(phenylsulfonyl)benzene (**49**) and 4-bromophenyl methyl sulfone, 2-methyl-5-(phenylsulfonyl)aniline was obtained as a beige solid in 94% yield. <sup>1</sup>H NMR (300MHz, DMSO-d<sub>6</sub>) δ [ppm] 7.86-7.83 (2H, m), 7.63-7.56 (3H, m), 7.13-7.10 (2H, m), 6.97 (1H, dd, *J* = 7.8 Hz, *J* = 2.0 Hz), 5.42 (2H, s), 2.06 (3H, s). HPLC (Condition A) Rt 2.8 min.

Following the general method as outlined for **38a**, starting from 2-methyl-5-(phenylsulfonyl)aniline, 2-iodo-1-methyl-4-(phenylsulfonyl)benzene was obtained as a white solid after purification by flash column chromatography (silica), eluting with cyclohexane containing increasing amounts of EtOAc affording the title compound as a yellow solid in

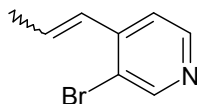
57% yield.  $^1\text{H}$  NMR (300MHz, DMSO- $\text{d}_6$ )  $\delta$  [ppm] 8.28 (1H, d,  $J$  = 2.0 Hz), 7.99-7.96 (2H, m), 7.88 (1H, dd,  $J$  = 8.0 Hz,  $J$  = 2.0 Hz), 7.73-7.54 (4H, m), 2.41 (3H, s).

**3-Bromo-4-(hex-1-en-1-yl)pyridine (54c).**



A cooled (0 °C) suspension of *n*-pentyl-triphenylphosphonium bromide (1.20 g; 2.90 mmol) in anhydrous THF (20 mL) was slowly treated with a solution (1.6 M) of butyllithium in hexane (2 700  $\mu\text{L}$ ; 4.35 mmol). The mixture was stirred for 1 hour, then a solution of 3-bromo-4-pyridinecarboxaldehyde (567 mg; 3.05 mmol) in anhydrous THF (10 mL) was added. After stirring for one hour, the reaction was quenched by addition of a saturated aqueous solution of ammonium chloride. After addition of EtOAc the phases were separated and the organic phase washed with brine, dried over  $\text{MgSO}_4$  and concentrated under vacuum to afford a crude product, which was purified by column chromatography, eluting with cyclohexane containing increasing amounts of EtOAc to afford the title compound as a mixture of *cis* and *trans* isomers (435 mg; 62%). MS (ESI): 240.1.

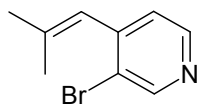
**3-Bromo-4-[prop-1-en-1-yl]pyridine (54a)**



Following the general method as outlined for **54c**, starting from 3-bromo-4-pyridinecarboxaldehyde and ethyltriphenylphosphonium bromide, the title compound (mixture of *cis* and *trans* isomers) was obtained as a colorless liquid after purification by flash column chromatography, eluting with cyclohexane containing increasing amounts of EtOAc (492; 46%). MS (ESI): 198.0

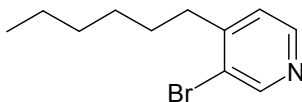


### 3-Bromo-4-(2-methylprop-1-en-1-yl)pyridine (**54b**)



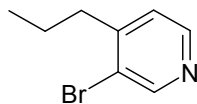
Following the general method as outlined for **54c**, starting from 3-bromo-4-pyridinecarboxaldehyde and isopropyltriphenylphosphonium iodide, the title compound was obtained as a yellow liquid after purification by flash column chromatography, eluting with cyclohexane containing increasing amounts of EtOAc (1.14 g, 50%). <sup>1</sup>H NMR (300MHz, DMSO-d<sub>6</sub>) δ [ppm] 8.73 (1H, s), 8.50 (1H, d, *J* = 5.0 Hz), 7.36 (1H, d, *J* = 5.0 Hz), 6.21 (1H, s), 1.96 (3H, d, *J* = 1.3 Hz), 1.80 (3H, d, *J* = 1.3 Hz). HPLC (Condition A) Purity 100.0%; Rt 1.9 min.

### 3-Bromo-4-hexylpyridine (**55c**).



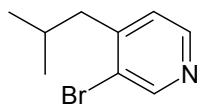
A mixture of 3-bromo-4-(hex-1-en-1-yl)pyridine (**54c**; 360 mg; 1.50 mmol) and platinum dioxide (34 mg; 0.15 mmol) in EtOAc (35 mL) was hydrogenated at 7 atm for 1 hour in a PARR apparatus. The reaction mixture was filtered, evaporated and purified by flash column chromatography, eluting with cyclohexane containing increasing amounts of EtOAc, affording the title compound (150 mg, 41%) as a colorless liquid. <sup>1</sup>H NMR (300MHz, DMSO-d<sub>6</sub>) δ [ppm] 8.67 (1H, s), 8.45 (1H, d, *J* = 5.0 Hz), 7.40 (1H, d, *J* = 5.0 Hz), 2.70 (2H, t, *J* = 7.8 Hz), 1.62-1.52 (2H, m), 1.34-1.28 (6H, m), 0.87 (3H, t, *J* = 7.0 Hz). MS (ESI<sup>+</sup>): 242.1. HPLC (Condition A): Rt 3.79 min (HPLC purity 98.0%).

### 3-Bromo-4-propylpyridine (**55a**)



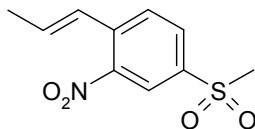
Following the general method as outlined for **55c**, starting from 3-bromo-4-(prop-1-en-1-yl)pyridine (**54a**), the title compound was obtained as a dark orange sticky solid in 79% yield after purification by flash column chromatography, eluting with cyclohexane containing increasing amounts of EtOAc. <sup>1</sup>H NMR (300MHz, DMSO-d<sub>6</sub>) δ [ppm] 8.68 (1H, s), 8.46 (1H, d, *J*= 4.9 Hz), 7.40 (1H, d, *J*= 4.9 Hz), 2.69 (2H, m), 1.62 (2H, sext., *J*= 7.5 Hz), 0.95 (3H, t, *J*= 7.5 Hz). HPLC (Condition A) Rt 1.8 min.

### 3-Bromo-4-isobutylpyridine (**55b**)



Following the general method as outlined for **55c**, starting from 3-bromo-4-(2-methylprop-1-en-1-yl)pyridine (**54c**), the title compound was obtained as a colorless liquid after purification by flash column chromatography, eluting with cyclohexane containing increasing amounts of EtOAc (214 mg, 19%). <sup>1</sup>H NMR (300MHz, DMSO-d<sub>6</sub>) δ [ppm] 8.69 (1H, s), 8.46 (1H, d, *J*= 4.9 Hz), 7.37 (1H, d, *J*= 4.9 Hz), 2.61 (1H, d, *J*= 7.3 Hz), 1.96 (1H, m), 0.91 (6H, d, *J*= 6.6 Hz). HPLC (Condition A) Rt 2.3 min.

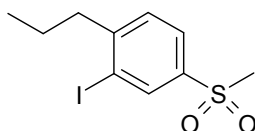
### 4-(Methylsulfonyl)-2-nitro-1-[(1*E*)-prop-1-en-1-yl]benzene (**57a**).



A mixture of 2-bromo-5-methylsulfonylnitrobenzene (1.50 g; 5.36 mmol), *trans*-propenylboronic acid (690 mg; 8.03 mmol), CsF (2.44 g; 16.1 mmol) and Pd(PPh<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub> (376 mg; 0.54 mmol) was degassed with nitrogen, then treated with dioxane (30 ml) and water (15

ml). The resulting reaction mixture was heated at 80 °C for 2 hours, taken up in EtOAc and washed with water and brine. The organic phase was dried on MgSO<sub>4</sub>, filtered and concentrated under reduced pressure to give a residue which was purified by flash column chromatography, eluting with cyclohexane containing increasing amounts of EtOAc. The title compound was obtained as an off-white solid (1.10 g, 85%). <sup>1</sup>H NMR (300MHz, DMSO-d<sub>6</sub>) δ [ppm] 8.40 (1H, d, *J*= 1.9 Hz), 8.14 (1H, dd, *J*= 8.3 Hz, *J*= 1.9 Hz), 8.05 (1H, d, *J*= 8.3 Hz), 6.68-6.59 (2H, m), 3.32 (3H, s), 1.95 (1H, dd, *J*= 6.1 Hz, *J*= 0.9 Hz).

**2-Iodo-4-(methylsulfonyl)-1-propylbenzene (58a).**



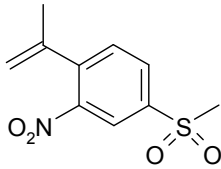
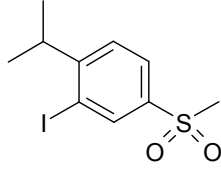
A solution of 4-(methylsulfonyl)-2-nitro-1-[(1*E*)-prop-1-en-1-yl]benzene (**57a**; 1.10 g; 4.56 mmol) in AcOH (7 ml) was treated with powdered iron (3.82 g; 68.4 mmol) and the reaction mixture was stirred at 90 °C for 25 min. Further AcOH was added (20 mL), the solid was filtered off and rinsed with EtOAc. The solvents were removed under reduced pressure, the residue was taken up in EtOAc and washed with saturated NaHCO<sub>3</sub> solution twice then with brine. The organic phase was dried on MgSO<sub>4</sub>, filtered and concentrated under reduced pressure to give 5-(methylsulfonyl)-2-[(1*E*)-prop-1-en-1-yl]aniline as a brown oil (784 mg, 81%). <sup>1</sup>H NMR (300MHz, DMSO-d<sub>6</sub>) δ [ppm] 7.40 (1H, d, *J*= 8.0 Hz), 7.13 (1H, d, *J*= 2.0 Hz), 6.96 (1H, dd, *J*= 8.0 Hz, *J*= 2.0 Hz), 6.58 (1H, dd, *J*= 5.5 Hz, *J*= 1.6 Hz), 6.20 (1H, m), 5.60 (2H, s), 3.09 (3H, s), 1.88 (1H, dd, *J*= 6.6 Hz, *J*= 1.5 Hz).

A mixture of 5-(methylsulfonyl)-2-[(1*E*)-prop-1-en-1-yl]aniline (1.50 g; 6.84 mmol) and 10% Pd/C (196 mg) in MeOH (39 ml) was placed in a PARR reactor and treated with a pressure of 20 atm of hydrogen for 3 hours. The reaction mixture was filtered through Celite and the filtrate was concentrated to dryness affording 5-(methylsulfonyl)-2-propylaniline (600

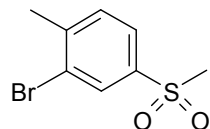
g, 76%).  $^1\text{H}$  NMR (300MHz, DMSO- $\text{d}_6$ )  $\delta$  [ppm] 7.14-7.11 (2H, m), 6.96 (1H, dd,  $J$ = 8.0 Hz,  $J$ = 2.0 Hz), 5.42 (2H, s), 3.08 (3H, s), 2.50-2.40 (2H, m), 1.60-1.48 (2H, m), 0.93 (1H, t,  $J$ = 7.3 Hz).

The conversion of the aniline to aromatic iodide **58a** was accomplished following the same general method as outlined for **38a**: 2-iodo-4-(methylsulfonyl)-1-propylbenzene was obtained in 61% yield as a yellow liquid after purification by flash column chromatography (cyclohexane/EtOAc gradient)  $^1\text{H}$  NMR (300MHz, DMSO- $\text{d}_6$ )  $\delta$  [ppm] 8.27 (1H, d,  $J$ = 2.0 Hz), 7.87 (1H, dd,  $J$ = 8.0 Hz,  $J$ = 2.0 Hz), 7.55 (1H, d,  $J$ = 8.0 Hz), 3.25 (3H, s), 2.74 (2H, m), 1.58 (2H, m), 0.96 (1H, t,  $J$ = 7.3 Hz).

The compounds **57b** and **58b** in the table below were all prepared following the 2-steps general method as outlined for **57a** and **58a**:

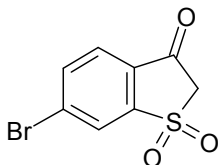
Cpd	Structure	Chemical name	$^1\text{H}$ NMR ( $\text{CDCl}_3$ , 400MHz), $\delta$ [ppm]
<b>57b</b>		<b>1-isopropenyl-4-(methylsulfonyl)-2-nitrobenzene</b>	8.44 (1H, d, $J$ = 1.8 Hz) 8.20 (1H, dd, $J$ = 8.1 Hz, $J$ = 1.8 Hz), 7.78 (1H, d, $J$ = 8.1 Hz), 5.30 (1H, t, $J$ = 1.3 Hz), 5.30 (1H, m), 5.00 (1H, s), 3.36 (3H, s), 2.08 (3H, s).
<b>58b</b>		<b>2-iodo-1-isopropyl-4-(methylsulfonyl)benzene</b>	8.28 (1H, d, $J$ = 1.9 Hz), 7.90 (1H dd, $J$ = 8.2 Hz, $J$ = 1.9 Hz), 7.59 (1H d, $J$ = 8.2 Hz), 3.25 (3H, s), 3.18 (1H, sept., $J$ = 6.8 Hz), 1.21 (6H, d, $J$ = 6.8 Hz)

**Methyl 4-bromo-2-(methylsulfonyl)benzoate (60).**



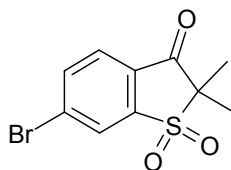
A suspension of 4-bromo-2-(methylsulfonyl)benzoic acid (5.00 g; 17.9 mmol) in MeOH (100 ml) was treated with conc. sulphuric acid and the resulting mixture was heated at reflux for 5 days. The mixture was concentrated under reduced pressure, the residue was dissolved in EtOAc then washed with water, twice with NaHCO<sub>3</sub> (sat) then with brine, dried on MgSO<sub>4</sub>, filtered and concentrated to give the title compound as a yellow solid (4.00 g, 72%). <sup>1</sup>H NMR (300MHz, DMSO-d<sub>6</sub>) δ [ppm] 8.14 (1H, d, *J*= 1.9 Hz), 8.08 (1H, d, *J*= 1.9 Hz, 8.1 Hz), 7.73 (1H, d, *J*= 8.1 Hz), 3.86 (3H, s), 3.42 (3H, s). HPLC (Condition A): Rt 3.54 min (HPLC purity 95.5%).

**6-Bromo-1-benzothiophen-3(2*H*)-one 1,1-dioxide (61).**



A solution of methyl 4-bromo-2-(methylsulfonyl)benzoate (**60**; 4.00 g; 13.6 mmol) in anhydrous THF (60 ml) was treated with NaH (595 mg; 13.6 mmol) and stirred at RT for 1.5 h. The reaction was quenched with water. AcOEt and a 1N solution of HCl in water were added and the phases were separated. The organic phase was washed with brine, dried on MgSO<sub>4</sub>, filtered and concentrated to give the title compound as a yellow solid (3.63 g, quant). <sup>1</sup>H NMR (300MHz, DMSO-d<sub>6</sub>) δ [ppm] 8.55 (1H, d, *J*= 1.7 Hz), 8.15 (1H, d, *J*= 8.2 Hz, *J*= 1.7 Hz), 7.93 (1H, d, *J*= 8.2 Hz), 4.62 (2H, s). MS (ESI<sup>+</sup>): 261.0. HPLC (Condition A): Rt 2.56 min.

**6-Bromo-2,2-dimethyl-1-benzothiophen-3(2*H*)-one 1,1-dioxide (62).**

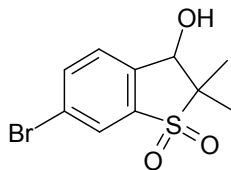


A solution of 6-bromo-1-benzothiophen-3(2*H*)-one 1,1-dioxide (**61**; 1.00 g; 3.83 mmol) in anhydrous DMF (4 mL) was treated with sodium hydride (337 mg; 8.43 mmol) and stirred for 1 h. The resulting mixture was treated with iodomethane (715  $\mu$ L; 11.5 mmol) and stirred for 15 min. The reaction was quenched with water, then partitioned between AcOEt and brine. The organic phase was washed with brine, dried on  $\text{MgSO}_4$ , filtered and concentrated to give a residue which was purified by flash column chromatography (cyclohexane/EtOAc gradient). The title compound was obtained as an orange oil in 52% yield. Methyl 4-bromo-2-(isopropylsulfonyl)benzoate **63** was also isolated from the crude mixture.

**62**  $^1\text{H}$  NMR (300MHz,  $\text{DMSO-d}_6$ )  $\delta$  [ppm] 8.64-8.58 (1H, m), 8.22-8.12 (1H, m), 8.00-7.94 (1H, m), 1.50 (6H, s). HPLC (Condition A): Rt 3.65 min (HPLC purity 100%).

**63**  $^1\text{H}$  NMR (300MHz,  $\text{DMSO-d}_6$ )  $\delta$  [ppm] 8.12-8.04 (2H, m), 7.74 (1H, d,  $J = 8$  Hz), 3.85 (3H, s), 3.81 (1H, m), 1.24 (3H, s), 1.22 (3H, s). MS ( $\text{ESI}^+$ ): 321.0. HPLC (Condition A): Rt 3.78 min.

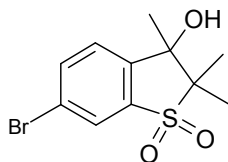
**6-Bromo-2,2-dimethyl-2,3-dihydro-1-benzothiophene-3-ol 1,1-dioxide (64).**



A cooled (0  $^\circ\text{C}$ ) solution of 6-bromo-2,2-dimethyl-1-benzothiophen-3(2*H*)-one 1,1-dioxide (**62**; 652 mg; 2.25 mmol) in MeOH (15 mL) and DCM (7 mL) was treated with  $\text{NaBH}_4$  (43 mg; 1.13 mmol) portionwise. The resulting solution was stirred at RT for 1.5 h, before being cooled to 0  $^\circ\text{C}$  and carefully quenched with water. The mixture was concentrated under

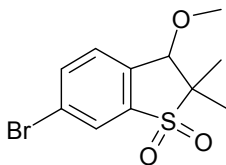
reduced pressure, water was added to the residue and the aqueous phase was extracted three times with DCM. The combined organic phases were washed with brine, dried with  $\text{MgSO}_4$ , filtered and concentrated to dryness to give the title compound as a white solid (637 mg, 97%).  $^1\text{H}$  NMR (300MHz,  $\text{DMSO-d}_6$ )  $\delta$  [ppm] 8.12 (1H, d,  $J=1.8$  Hz), 7.99 (1H, dd,  $J=8.1$  Hz,  $J=1.8$  Hz), 7.65 (1H, d,  $J=8.1$  Hz), 6.62 (1H, s), 4.95 (1H, s), 1.47 (3H, s), 1.19 (3H, s). MS ( $\text{ESI}^+$ ): 308.0  $[\text{M}+\text{NH}_4]^+$ . HPLC (Condition A): Rt 3.30 min (purity 97%).

**6-Bromo-2,2,3-trimethyl-2,3-dihydro-1-benzothiophene-3-ol 1,1-dioxide (65).**



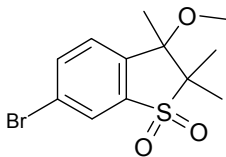
A cooled (0 °C) solution of 6-bromo-2,2-dimethyl-1-benzothiophen-3(2*H*)-one 1,1-dioxide (**62**; 750 mg; 2.59 mmol) in anhydrous  $\text{Et}_2\text{O}$  (22.5 ml) was treated carefully with a 3 M solution of methylmagnesium bromide in  $\text{Et}_2\text{O}$  (2.6 ml; 7.8 mmol). The white solution was stirred at RT for 1.5 before being quenched with a saturated solution of  $\text{NH}_4\text{Cl}$  in water. The phases were separated and the aqueous phase was extracted with  $\text{Et}_2\text{O}$ . The combined organic phases were washed with water and brine, dried over anhydrous magnesium sulfate and concentrated to dryness to afford the title compound as a white solid (767 mg, 97%).  $^1\text{H}$  NMR (300MHz,  $\text{DMSO-d}_6$ )  $\delta$  [ppm] 8.02 (1H, d,  $J=1.9$  Hz), 7.93 (1H, dd,  $J=8.1$  Hz,  $J=1.9$  Hz), 7.64 (1H, d,  $J=8.1$  Hz), 6.11 (1H, s), 1.45 (3H, s), 1.32 (3H, s), 1.19 (3H, s). MS ( $\text{ESI}^-$ ): 305.1. HPLC (Condition A): Rt 3.07 min (HPLC purity 99.1%).

**6-Bromo-2,2-dimethyl-1,1-dioxido-2,3-dihydro-1-benzothien-3-yl methyl ether (66).**



A cooled (0 °C) suspension of NaH (20.61 mg; 0.52 mmol; 1.00 eq.) in dry DMF was carefully treated with solution of 6-bromo-2,2-dimethyl-2,3-dihydro-1-benzothiophene-3-ol 1,1-dioxide (**64**; 150 mg; 0.52 mmol) in anhydrous DMF. The reaction mixture was stirred at RT for 4 min then treated with a 3 M solution of iodomethane (240  $\mu$ l; 0.72 mmol). The mixture was stirred at RT for 2.5h, then quenched with water. EtOAc was added, the phases were separated and the aqueous phase was extracted with EtOAc. The combined organic phases were washed with brine, dried over anhydrous magnesium sulfate and concentrated to dryness to afford a residue, which was purified by flash column chromatography (cyclohexane/EtOAc gradient). The title compound was obtained as a white solid in 60% yield.  $^1\text{H}$  NMR (300MHz, DMSO- $d_6$ )  $\delta$  [ppm] 8.11 (1H, d,  $J$ = 1.8 Hz), 7.94 (1H, dd,  $J$ = 8.0 Hz,  $J$ = 1.8 Hz), 7.65 (1H, d,  $J$ = 8.0 Hz), 4.69 (1H, s), 3.52 (3H, s), 1.40 (3H, s) 1.27 (3H, s). HPLC (Condition A): Rt 3.64 min.

**6-Bromo-2,2,3-trimethyl-1,1-dioxido-2,3-dihydro-1-benzothien-3-yl methyl ether (67).**



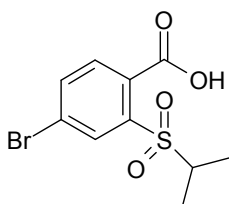
Following the general method as outlined for **66**, starting from 6-bromo-2,2,3-trimethyl-2,3-dihydro-1-benzothiophene-3-ol 1,1-dioxide (**65**), the title compound was obtained in 07% yield.  $^1\text{H}$  NMR (300MHz, DMSO- $d_6$ )  $\delta$  [ppm] 8.10 (1H, d,  $J$ = 1.9 Hz), 7.95 (1H, dd,  $J$ = 8.1



Hz, 1.9 Hz), 7.72 (1H, d,  $J$  = 8.1 Hz), 3.95 (3H, s), 1.53 (3H, s), 1.35 (3H, s), 1.24 (3H, s).

HPLC (Condition A): Rt 3.64 min.

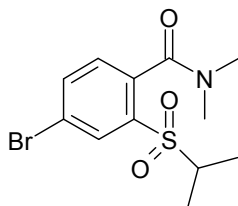
#### 4-Bromo-2-(isopropylsulfonyl)benzoic acid **68**



A solution of methyl 4-bromo-2-(isopropylsulfonyl)benzoate (**63**, 6 mg; 1.61 mmol) in THF (10 ml) was treated with a 5 N solution of NaOH in water (4 mL) and the reaction mixture was heated at 60°C for 1 day. The reaction mixture was acidified with aqueous HCl and the reaction mixture was extracted 3 times with EtOAc. The combined organic phases were dried over MgSO<sub>4</sub>, filtered and concentrated to dryness affording the title compound as a pale yellow solid (386 mg; 78%).

<sup>1</sup>H NMR (300MHz, DMSO-*d*<sub>6</sub>)  $\delta$  [ppm] 12.50 (1H, bs), 8.05 (1H, dd,  $J$  = 8.1 Hz,  $J$  = 2.0 Hz), 8.01 (1H, d,  $J$  = 2.0 Hz), 7.73 (1H, dd,  $J$  = 8.1 Hz), 3.96 (1H, sext.,  $J$  = 6.9 Hz), 1.22 (6H, d,  $J$  = 6.9 Hz). HPLC (Condition A) Purity 97.8%; Rt 3.1 min.

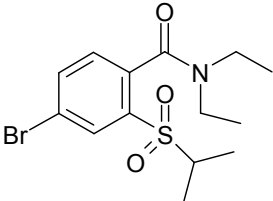
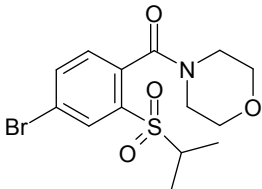
#### 4-Bromo-2-(isopropylsulfonyl)-*N,N*-dimethylbenzamide **69a**



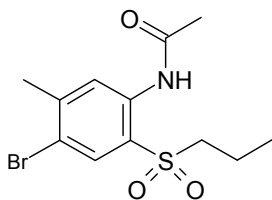
A solution of 4-bromo-2-(isopropylsulfonyl)benzoic acid (**68**, 250 mg; 0.81 mmol), dimethylamine (610  $\mu$ l; 2.00 M in THF; 1.22 mmol) and TEA (340  $\mu$ l; 2.44 mmol) in DMF (10 ml) was treated with polymer-supported Mukaiyama reagent (1.30 g; 1.63 mmol) and the

reaction mixture was stirred for 20 hours. The reaction mixture was filtered and the polymer was washed twice with EtOAc. The filtrate was washed twice with a sat. NaHCO<sub>3</sub> solution and twice with brine. The organic phase was dried over MgSO<sub>4</sub>, filtered and concentrated to dryness affording the title compound (128 mg; 47%) as a pink solid. <sup>1</sup>H NMR (300MHz, DMSO-d<sub>6</sub>) δ [ppm] 8.04 (1H, dd, *J* = 8.0 Hz, *J* = 2.0 Hz), 7.99 (1H, d, *J* = 2.0 Hz), 7.48 (1H, d, *J* = 8.0 Hz), 3.71 (1H, sept., *J* = 7.0 Hz), 2.96 (3H, s), 2.71 (3H, s), 1.27 (3H, m), 1.04 (3H, m). HPLC (Condition A) Purity 99.4%; Rt 3.0 min.

The following 4-bromo-2-(isopropylsulfonyl)-benzamides **69** were prepared according to the general protocol described for **69a**

Cpd	Structure	Chemical name	<sup>1</sup> H NMR (400MHz) δ [ppm]
<b>69b</b>		<b>4-bromo-N,N-diethyl-2-(isopropylsulfonyl)benzamide</b>	8.02 (1H, dd, <i>J</i> = 8.0 Hz, <i>J</i> = 2.0 Hz), 7.98 (1H, d, <i>J</i> = 2.0 Hz), 7.48 (1H, d, <i>J</i> = 8.0 Hz), 3.74 (1H, sept., <i>J</i> = 6.9 Hz), 3.57 (1H, m), 3.25 (1H, m), 2.92-3.09 (2H, m), 1.28 (3H, d, <i>J</i> = 6.9 Hz), 1.12 (3H, t, <i>J</i> = 7.1 Hz), 1.03 (3H, d, <i>J</i> = 6.9 Hz), 1.01 (3H, t, <i>J</i> = 7.1 Hz).
<b>69c</b>		<b>4-[4-bromo-2-(isopropylsulfonyl)benzoyl]morpholine</b>	8.04 (1H, dd, <i>J</i> = 8.0 Hz, <i>J</i> = 2.0 Hz), 8.01 (1H, d, <i>J</i> = 2.0 Hz), 7.52 (1H, d, <i>J</i> = 8.0 Hz), 3.46-3.76 (7H, m), 2.98-3.18 (2H, m), 1.28 (3H, d, <i>J</i> = 6.8 Hz), 1.05 (3H, d, <i>J</i> = 6.8 Hz).

**N-[4-Bromo-5-methyl-2-(propylsulfonyl)phenyl]acetamide (73).**



A solution of 4-chloro-3-nitro-toluene (25 g, 145 mmol) in anhydrous DMF (200 ml) was treated with  $K_2CO_3$  (40.29 g, 291 mmol) and 1-propane thiol (12.2 g, 160 mmol). The reaction mixture was heated to 70 °C for 12 h. The reaction mixture was filtered, the filtrate was concentrated under reduced pressure, diluted water and extracted with ethyl acetate (200 ml). The organic layer was washed with brine, dried over sodium sulphate and evaporated under reduced pressure, to give a crude which was purified by column chromatography (silica) using petroleum ether/ethyl acetate as eluent to afford 4-methyl-2-nitro-1-(propylthio)benzene (28 g, 91%) as a pale yellow solid.  $^1H$  NMR (300MHz,  $DMSO-d_6$ )  $\delta$  [ppm] 8.01 (1H, s), 7.37-7.35 (2H, m), 7.28 (1H, m), 2.96-2.89 (2H, m), 2.40 (3H, s), 1.81-1.17 (2H, m), 1.11 (1H, s).

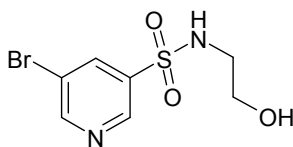
A cooled (0 °C) solution of 4-methyl-2-nitro-1-(propylthio)benzene (15 g, 70 mmol) in anhydrous DCM (200 ml) was treated with a solution of 3-chloroperbenzoic acid (60%) (51.0 g, 177 mol) in DCM (300 ml). The reaction mixture was stirred at 0 °C for 3 h, then at RT for 16 h. The reaction mixture was filtered and the filtrate was extracted with ethyl acetate. The organic layer was washed with 1N NaOH (200 ml), water (200 ml), brine and dried over sodium sulphate and evaporated under reduced pressure. The crude product was purified by column chromatography (silica) using petroleum ether / ethyl acetate as eluent to afford 4-methyl-2-nitro-1-(propylsulfonyl)benzene as a pale yellow liquid (11 g, 64%).  $^1H$  NMR (300MHz,  $CDCl_3$ )  $\delta$  [ppm] 8.01-7.99 (1H, dd), 7.62 (1H, s), 7.56-7.54 (1H, dd), 3.53-3.49 (2H, m), 2.53 (3H, s), 1.89-1.80 (2H, m), 1.09 (3H, s).

A solution of 4-methyl-2-nitro-1-(propylsulfonyl)benzene (11 g, 45 mmol) in methanol (150 ml) was treated with Pd/C (1.1 g) and the reaction mixture was stirred under 3 Kg/cm<sup>2</sup>

pressure of hydrogen at RT for 5 h. The catalyst was filtered through celite and the solvent was removed under reduced pressure to afford 5-methyl-2-(propylsulfonyl) aniline (9 g, 94 %) as pale yellow liquid. <sup>1</sup>H NMR (300MHz, DMSO-d<sub>6</sub>) δ [ppm] 7.35-7.33 (1H, dd), 6.65 (1H, s), 6.51-6.49 (1H, dd), 5.94 (2H, bs), 3.13-3.10 (2H, m), 2.20 (3H, s), 1.55-1.49 (2H, m), 0.90-0.85 (3H, t). MS (ESI<sup>+</sup>): 214.2. HPLC (Method D) Purity 99.8%; Rt 3.34 min.

A solution of 5-methyl-2-(propylsulfonyl) aniline (6.0 g, 28 mmol) in DCM (100 ml) was added *N*-methyl morpholine (4.3 g, 42.1 mmol) and Acetyl chloride (2.4 g, 31 mmol). The reaction mixture was stirred at RT for 12 h. The reaction mixture was diluted with water (200 ml), the organic layer was washed with brine solution and dried over sodium sulphate and evaporated. The crude product was purified by column chromatography (silica) using petroleum ether/ethyl acetate as eluent to afford *N*-[5-methyl-2-(propylsulfonyl)phenyl]acetamide (5.0 g, 70%) as a white solid. <sup>1</sup>H NMR (300MHz, DMSO-d<sub>6</sub>) δ [ppm] 9.53 (1H, bs), 7.84 (1H, s), 7.72-7.70 (1H, dd, *J* = 8.0 Hz), 7.20 (1H, dd, *J* = 8.0 Hz), 3.28-3.24 (2H, m), 2.36 (3H, s), 2.10 (3H, s), 1.54-1.48 (2H, m), 0.9-0.86 (3H, t, *J* = 7.4 Hz). MS (ESI<sup>+</sup>): 256. HPLC (Condition A) Purity 99.1%; Rt 3.36 min.

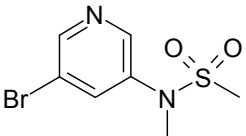
A mixture of *N*-[5-methyl-2-(propylsulfonyl)phenyl]acetamide (5.0 g, 20 mmol) in conc. sulphuric acid (25 ml) was treated in portions with *N*-bromosuccinamide (3.8 g, 22 mmol). Reaction mixture was stirred at RT for 18 hrs, carefully quenched on ice and extracted to DCM (100 ml). The organic layer was washed with water and brine, dried over sodium sulphate and concentrated. The crude product was purified by column chromatography (silica) eluting with petroleum ether/ethyl acetate to afford the title compound (4.1 g, 62%) as a white solid. <sup>1</sup>H NMR (300MHz, DMSO-d<sub>6</sub>) δ [ppm] 9.54 (1H, bs), 7.98 (1H, s), 7.91 (1H, s), 3.37-3.33 (2H, m), 2.40 (3H, s), 2.10 (3H, s), 1.59-1.50 (2H, m), 0.91 (3H, t, *J* = 7.5 Hz). MS (ESI<sup>+</sup>): 334. HPLC (Condition A) Purity 97%; Rt 4.35 min.

**5-bromo-*N*-(2-hydroxyethyl)pyridine-3-sulfonamide (75a)**

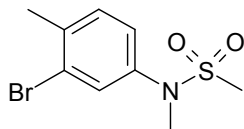
A cooled (0 °C) solution of 5-bromopyridine-3-sulfonyl chloride hydrochloride (3.00 g, 10.2 mmol) in DCM (50 ml) was slowly treated with triethylamine (4.3 ml) and stirred until a clear solution was obtained. This solution was treated dropwise with 2-hydroxyethylamine (0.68 g, 0.68 mL) and stirred at RT for 16 hours. The reaction mixture was washed successively with water and brine, the organic layer was dried with sodium sulfate and evaporated under reduced pressure. The crude product was purified by column chromatography (silica) eluting with 20% ethyl acetate in petroleum ether, to give the title compound (1.43 g; 50%). <sup>1</sup>H NMR (400MHz, DMSO-*d*<sub>6</sub>) δ [ppm] 8.97 (1H, d, *J*= 2.1 Hz), 8.91 (1H, d, *J*= 1.9 Hz), 8.37 (1H, t, *J*= 2.1 Hz), 7.99 (1H, bs), 4.73 (1H, t, *J*= 5.4 Hz), 3.39-3.32 (2H, m), 2.90-2.86 (2H, m). HPLC (Condition A), Rt: 2.07 (purity: 93.7%). MS (ESI<sup>+</sup>): 280.8.

The compounds in the table below were all prepared following the general method as outlined for **75a**:

Cpd	Structure	Chemical name	<sup>1</sup> H NMR 300MHz, DMSO- <i>d</i> <sub>6</sub> ) δ [ppm]
<b>75b</b>		5-bromo-pyridine-3-sulfonic acid dimethylamide	9.05 (1H, d, <i>J</i> = 2.0 Hz), 8.90 (1H, d, <i>J</i> = 2.0 Hz), 8.39 (1H, t, <i>J</i> = 2.0 Hz), 2.69 (6H, s)

<b>75c</b>		<i>N</i> -(5-bromopyridin-3-yl)- <i>N</i> -methylmethanesulfonamide	8.62-8.60 (2H, m), 8.16 (1H, t, <i>J</i> = 2.1 Hz), 3.28 (3H, s), 3.05 (3H, s)
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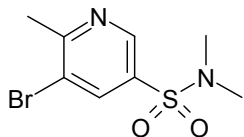
***N*-(3-Bromo-4-methylphenyl)-*N*-methylmethanesulfonamide 75d**



A solution of *N*-(3-bromo-4-methylphenyl)methanesulfonamide (710 mg; 2.69 mmol) in anhydrous DMF (14 mL) was treated with NaH (129 mg; 3.23 mmol) followed after 5 minutes by treatment with iodomethane (200  $\mu$ l; 3.23 mmol). The reaction mixture was stirred for 16 hours, then quenched with a 5 N solution of NaOH in water. The reaction mixture was stirred for few minutes and extracted with EtOAc. The organic phase was washed with water and brine, dried over MgSO<sub>4</sub> and concentrated to dryness affording the title compound as a brown sticky solid (730 mg, 98%).

<sup>1</sup>H NMR (300MHz, DMSO-*d*<sub>6</sub>)  $\delta$  [ppm] 7.63 (1H, d, *J* = 2.1 Hz), 7.39 (1H, d, *J* = 8.3 Hz), 7.33 (1H, dd, *J* = 8.3 Hz, *J* = 2.1 Hz), 3.22 (3H, s), 2.95 (3H, s), 2.33 (3H, s). HPLC (Condition A) Purity 98.9%; Rt 3.8 min.

**5-Bromo-*N,N*,6-trimethylpyridine-3-sulfonamide (75e)**



A cooled (0 °C) solution of 6-amino-5-bromopyridine-3-sulfonic acid (12.65 g; 50.00 mmol) in HCl (60 ml; 5 N solution in water) was treated carefully with a solution of sodium nitrite (3.80 g; 55.0 mmol) in water (15 ml) and stirred at 0 °C for 1 hour. The solvents were

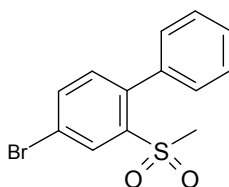
evaporated and the residue was dried under high vacuum for 2 days, then treated with phosphorus pentachloride (15.00 g; 72 mmol) and phosphorus oxide chloride (0.50 ml; 5.5 mmol). The solid mixture was heated at 125 °C to give a refluxing solution. After heating at 75 °C for 3 hours, the solution was cooled and carefully poured on crushed ice. EtOAc was added and the phases separated. The organic phase was washed with brine, dried on MgSO<sub>4</sub>, filtered and concentrated under reduced pressure to give 5-bromo-6-chloropyridine-3-sulfonyl chloride as a brown oil (14.91 g, quantitative yield), which was used without purification.

A cooled (0 °C) solution of 5-bromo-6-chloropyridine-3-sulfonyl chloride (2.00 g; 6.87 mmol) in DCM (20 mL) was treated first with triethylamine (1.06 ml; 7.56 mmol) then with a 5.6 M solution of dimethylamine in EtOH (1.35 ml; 7.56 mmol). The reaction was stirred at 0 °C for 1.5 hours then brine was added and the phases separated. The organic phase was washed with brine, dried on MgSO<sub>4</sub>, filtered and concentrated under reduced pressure to give a residue which was purified by flash column chromatography (silica), eluting with cyclohexane containing increasing amounts of EtOAc to give 5-bromo-6-chloro-*N,N*-dimethylpyridine-3-sulfonamide (247 mg; 12%) as a colorless oil.

A solution of 5-bromo-6-chloro-*N,N*-dimethylpyridine-3-sulfonamide (400 mg; 1.34 mmol) and diethyl malonate (204 µl; 1.34 mmol) in anhydrous THF (2 ml) was added to a suspension of sodium hydride (53 mg; 1.34 mmol) in anhydrous THF (2 ml). The resulting mixture was stirred for 48 hours, then quenched by careful addition of a saturated solution of NH<sub>4</sub>Cl in water. EtOAc was added and the phases separated. The organic phase was washed with brine, dried on MgSO<sub>4</sub>, filtered and concentrated under reduced pressure to give a residue which was purified by flash column chromatography (silica), eluting with cyclohexane containing increasing amounts of EtOAc to give diethyl {3-bromo-5-[(dimethylamino)sulfonyl]pyridin-2-yl}malonate (341 mg; 60%) as a colorless oil.

Diethyl {3-bromo-5-[(dimethylamino)sulfonyl]pyridin-2-yl} malonate (222 mg; 0.52 mmol) was treated with a 5 N solution of HCl in water (11 ml) and the resulting solution was refluxed for 6 h. The solvent was removed under reduced pressure, and the solid residue was carefully quenched with a saturated Na<sub>2</sub>CO<sub>3</sub> solution in water. The resulting suspension was extracted with AcOEt. The organic phase was washed with brine, dried on MgSO<sub>4</sub>, filtered and concentrated under reduced pressure to give 5-bromo-*N,N*,6-trimethylpyridine-3-sulfonamide **75e** as a white solid (125 mg; 86% yield). <sup>1</sup>H NMR (300MHz, DMSO-*d*<sub>6</sub>) δ [ppm] 8.78 (1H, d, *J*= 2.0 Hz), 8.31 (1H, d, *J*= 2.0 Hz), 2.70 (3H, s), 2.69 (6H, s).

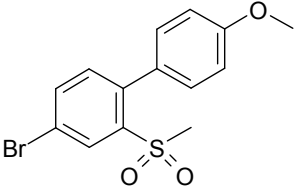
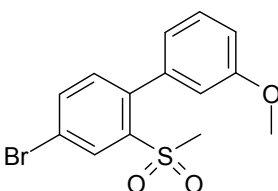
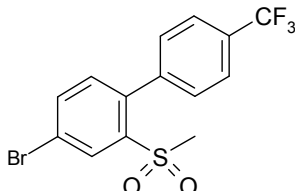
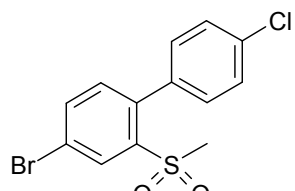
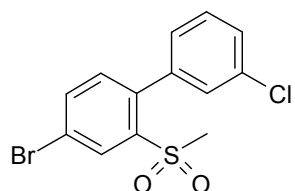
#### 4-Bromo-2-(methylsulfonyl)biphenyl **79a**

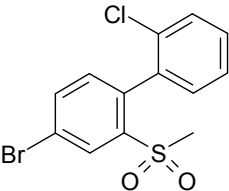


A solution of 4-bromo-1-iodo-2-(methylsulfonyl)benzene (200 mg; 0.55 mmol), phenylboronic acid (68 mg; 0.55 mmol;) was placed in a microwave vial and treated with caesium fluoride (252 mg; 1.66 mmol) and bis(triphenylphosphine)palladium(II) chloride (39 mg; 0.06 mmol). The tube was sealed and degased with N<sub>2</sub> before adding dioxane (3 ml) and water (1.5 ml). The resulting reaction mixture was irradiated in a microwave reactor at 110 °C for 20 minutes. The reaction mixture was taken up in EtOAc and washed with water and brine. The organic phase was dried over MgSO<sub>4</sub>, filtered, concentrated and purified by flash column chromatography (silica), eluting with cyclohexane containing increasing amounts of EtOAc affording the title compound (100 mg; 58%) as an orange sticky solid. <sup>1</sup>H NMR (300MHz, DMSO-*d*<sub>6</sub>) δ [ppm] 8.17 (1H, dd, *J*= 2.2 Hz), 7.98 (1H, dd, *J*= 8.2 Hz, *J*= 2.2 Hz), 7.36-7.47 (6H, m), 2.86 (3H, s). HPLC (Condition A) Purity 90.7%; Rt 4.2 min.



The following 4-bromo-2-biphenyls **79** were prepared according to the general protocol described for **79a**

Cpd	Structure	Chemical name	<sup>1</sup> H NMR (400MHz) δ [ppm]
<b>79b</b>		4-bromo-4'-methoxy-2-(methylsulfonyl)biphenyl	8.14 (1H, dd, <i>J</i> = 2.1 Hz), 7.95 (1H, dd, <i>J</i> = 8.1 Hz, <i>J</i> = 2.1 Hz), 7.32-7.36 (3H, m), 7.02 (2H, d, <i>J</i> = 8.8 Hz), 3.81 (3H, s), 2.83 (3H, s).
<b>79c</b>		4-bromo-3'-methoxy-2-(methylsulfonyl)biphenyl	8.16 (1H, dd, <i>J</i> = 2.1 Hz), 7.97 (1H, dd, <i>J</i> = 8.1 Hz, <i>J</i> = 2.1 Hz), 7.34-7.40 (2H, m), 6.95-7.05 (3H, m), 3.77 (3H, s), 2.88 (3H, s).
<b>79d</b>		4-bromo-2-(methylsulfonyl)-4'-(trifluoromethyl)biphenyl	8.20 (1H, dd, <i>J</i> = 2.1 Hz), 8.02 (1H, dd, <i>J</i> = 8.1 Hz, <i>J</i> = 2.1 Hz), 7.81 (2H, d, <i>J</i> = 8.1 Hz), 7.62 (2H, d, <i>J</i> = 8.1 Hz), 7.40 (1H, d, <i>J</i> = 8.1 Hz), 3.02 (3H, s).
<b>79e</b>		4-bromo-4'-chloro-2-(methylsulfonyl)biphenyl	8.17 (1H, dd, <i>J</i> = 2.1 Hz), 7.99 (1H, dd, <i>J</i> = 8.2 Hz, <i>J</i> = 2.1 Hz), 7.52 (2H, d, <i>J</i> = 8.6 Hz), 7.42 (2H, d, <i>J</i> = 8.6 Hz), 7.37 (1H, d, <i>J</i> = 8.2 Hz), 2.96 (3H, s).
<b>79f</b>		4-bromo-3'-chloro-2-(methylsulfonyl)biphenyl	8.18 (1H, dd, <i>J</i> = 2.0 Hz), 7.99 (1H, dd, <i>J</i> = 8.0 Hz, <i>J</i> = 2.0 Hz), 7.45-7.55 (3H, m), 7.34-7.40 (2H, m), 2.98 (3H, s).

79g		4-bromo-2'-chloro-2-(methylsulfonyl)biphenyl	8.20 (1H, dd, $J = 2.2$ Hz), 8.01 (1H, dd, $J = 8.2$ Hz, $J = 2.2$ Hz), 7.56 (1H, m), 7.38-7.50 (3H, m), 7.34 (1H, d, $J = 8.2$ Hz), 3.04 (3H, s).
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## B- Synthesis and characterization of all final compounds

**[4-Chloro-2-(phenylethynyl)phenoxy]acetic acid (8a).** Prepared according to Sonogashira general method 1, starting from *tert*-butyl (2-bromo-4-chlorophenoxy)acetate (**10a**) and phenylacetylene, without purification of the intermediate ester and deprotecting using TFA (20%) in DCM. After purification by preparative HPLC the title compound was obtained as a brown solid. <sup>1</sup>H NMR (300MHz, DMSO-d<sub>6</sub>) δ [ppm] 13.17 (1H, s), 7.57-7.52 (3H, m), 7.46-7.38 (4 H, m), 6.99 (1H, d, *J* = 9.0 Hz), 4.82 (2H, s). MS (ESI<sup>-</sup>): 285.1. HPLC (Condition A): Rt 4.61 min (HPLC purity 98.3%).

**{4-Chloro-2-[(2-chlorophenyl)ethynyl]phenoxy}acetic acid (8b).** Prepared according to Sonogashira general method 1, starting from *tert*-butyl (2-bromo-4-chlorophenoxy)acetate (**10a**) and 2'-chlorophenyl acetylene, without purification of the intermediate ester and deprotecting using TFA (20%) in DCM. After purification by preparative HPLC the title compound was obtained as a beige solid. <sup>1</sup>H NMR (300MHz, DMSO-d<sub>6</sub>) δ [ppm] 13.21 (1H, s), 7.66 (1H, dd, *J* = 7.3, *J* = 2.5 Hz), 7.60 (1H, dd, *J* = 7.3, *J* = 1.5 Hz), 7.55 (1H, d, *J* = 2.5 Hz), 7.37-7.48 (3H, m), 7.02 (1H, d, *J* = 9.0 Hz), 4.83 (2H, s). MS (ESI<sup>-</sup>): 319.0. HPLC (Condition A): Rt 4.54 min (HPLC purity 99.8%).

**{4-Chloro-2-[(4-chlorophenyl)ethynyl]phenoxy}acetic acid (8d).** Prepared according to Sonogashira general method 1, starting from *tert*-butyl (2-bromo-4-chlorophenoxy)acetate (**10a**) and 4'-chlorophenyl acetylene, without purification of the intermediate ester and deprotecting using TFA (20%) in DCM. After purification by preparative HPLC the title compound was obtained as a beige solid. <sup>1</sup>H NMR (300MHz, DMSO-d<sub>6</sub>) δ [ppm] 13.17 (1H,

bs), 7.59-7.48 (5H, m), 7.42 (1H, dd,  $J = 9.0$ ,  $J = 2.7$  Hz), 7.00 (1H, d,  $J = 9.0$  Hz), 4.83 (2H, s). MS (ESI<sup>-</sup>): 319.0. HPLC (Condition A): Rt 4.79 min (HPLC purity 98.7%).

**{4-Chloro-2-[(2-methoxyphenyl)ethynyl]phenoxy}acetic acid (8e).** Prepared according to Sonogashira general method 1, starting from non-protected (2-bromo-4-chlorophenoxy)acetic acid and 2'-methoxy acetylene. After purification by preparative HPLC the title compound was obtained as a brown oil. MS (ESI<sup>-</sup>): 315.1. HPLC (Condition A): Rt 4.27 min (HPLC purity 100%).

**{4-Chloro-2-[(2-fluorophenyl)ethynyl]phenoxy}acetic acid (8f).** Prepared according to Sonogashira general method 1, starting from *tert*-butyl (2-bromo-4-chlorophenoxy)acetate (**10a**) and 2'-fluoro acetylene, the intermediate ester was purified by column chromatography and deprotected using HCl (4 N) in dioxane. After purification by preparative HPLC the title compound was obtained as a light brown solid. <sup>1</sup>H NMR (300MHz, DMSO-d<sub>6</sub>) δ [ppm] 7.63 (1H, td,  $J = 7.5$ , 1.8 Hz), 7.57 (1H, d,  $J = 2.6$  Hz), 7.55-7.23 (4 H, m), 7.01 (1H, d,  $J = 9.0$  Hz), 4.83 (2H, s). MS (ESI<sup>-</sup>): 303.1. HPLC (Condition A): Rt 4.42 min (HPLC purity 98.3%).

**(4-Chloro-2-{[2-(trifluoromethyl)phenyl]ethynyl}phenoxy)acetic acid (8g).** Prepared according to Sonogashira general method 1, starting from *tert*-butyl (2-bromo-4-chlorophenoxy)acetate (**10a**) and 2'-trifluoromethyl acetylene, the intermediate ester was purified by column chromatography and deprotected using HCl (4 N) in dioxane. After purification by preparative HPLC the title compound was obtained as a beige solid. <sup>1</sup>H NMR (300MHz, DMSO-d<sub>6</sub>) δ [ppm] 13.2 (1H, bs), 7.86-7.69 (3H, m), 7.63 (1H, t,  $J = 7.5$  Hz), 7.49-7.42 (2H, m), 7.03 (1H, d,  $J = 8.8$  Hz), 4.82 (2H, s). MS (ESI<sup>-</sup>): 353.1. HPLC (Condition A): Rt 4.75 min (HPLC purity 95.9%).

**(4-Chloro-2-{{3-(trifluoromethyl)phenyl}ethynyl}phenoxy)acetic acid (8h).** Prepared according to Sonogashira general method 1, starting from non-protected (2-bromo-4-chlorophenoxy)acetic acid and 3'-trifluoromethyl acetylene. After purification by preparative HPLC the title compound was obtained as a brown sticky solid. <sup>1</sup>H NMR (300MHz, DMSO-d<sub>6</sub>) δ [ppm] 13.16 (1H, bs), 7.91 (1H, s), 7.85 (1H, d, *J*= 7.8 Hz), 7.80 (1H, d, *J*= 7.8 Hz), 7.69 (1H, t, *J*= 7.8 Hz), 7.63 (1H, d, *J*= 2.7 Hz), 7.44 (1H, dd, *J*= 9.0, 2.7 Hz), 7.02 (1H, d, *J*= 9.0 Hz), 4.84 (2H, s). MS (ESI<sup>+</sup>): 353.1. HPLC (Condition A): Rt 5.12 min (HPLC purity 96.1%).

**{4-Chloro-2-[(2,4-difluorophenyl)ethynyl]phenoxy}acetic acid (8i).** Prepared according to Sonogashira general method 1, starting from *tert*-butyl (2-bromo-4-chlorophenoxy)acetate (**10a**) and 2',4'-difluoro acetylene, the intermediate ester was purified by column chromatography and deprotected using HCl (4 N) in dioxane. After purification by preparative HPLC the title compound was obtained as an off-white solid. <sup>1</sup>H NMR (300MHz, DMSO-d<sub>6</sub>) δ [ppm] 13.17 (1H, s), 7.70 (1H, td, *J*= 8.5, *J*= 6.5 Hz), 7.57 (1H, d, *J*= 2.7 Hz), 7.49-7.40 (2H, m), 7.24-7.16 (1H, m), 7.01 (1H, d, *J*= 9.0 Hz), 4.83 (2H, s). MS (ESI<sup>+</sup>): 321.1. HPLC (Condition A): Rt 4.50 min (HPLC purity 100%).

**{4-Chloro-2-[(5-chloro-2-thienyl)ethynyl]phenoxy}acetic acid (8j).** Prepared according to Sonogashira general method 2, starting from *tert*-butyl (4-chloro-2-ethynylphenoxy)acetate (**16a**) and 2-bromo-5-chlorothiophene, without purification of the intermediate ester and deprotecting using HCl (4 N) in dioxane. After purification by preparative HPLC the title compound was obtained as a brown sticky solid. <sup>1</sup>H NMR (300MHz, DMSO-d<sub>6</sub>) δ [ppm] 13.2 (1H, bs), 7.57 (1H, d, *J*= 2.7 Hz), 7.43 (1H, dd, *J*= 9.0, *J*= 2.7 Hz), 7.31 (1H, d, *J*= 4.0 Hz),

7.19 (1H, d,  $J$  = 4.0 Hz), 7.00 (1H, d,  $J$  = 9.0 Hz), 4.82 (2H, s). MS (ESI<sup>+</sup>): 325.0. HPLC (Condition A): Rt 5.35 min (HPLC purity 96.4%).

**{4-Chloro-2-[(1-methyl-1H-imidazol-2-yl)ethynyl]phenoxy}acetic acid (8k).** Prepared according to Sonogashira general method 2, starting from *tert*-butyl (4-chloro-2-ethynylphenoxy)acetate (**16a**) and 2-bromo-1-methyl-1*H*-imidazole, without purification of the intermediate ester and deprotecting using HCl (4 N) in dioxane. After purification by preparative HPLC the title compound was obtained as an off-white solid. <sup>1</sup>H NMR (300MHz, DMSO-*d*<sub>6</sub>)  $\delta$  [ppm] 13.2 (1H, bs), 7.73 (1H, d,  $J$  = 2.7 Hz), 7.68 (1H, d,  $J$  = 1.6 Hz), 7.55 (1H, dd,  $J$  = 9.0,  $J$  = 2.7 Hz), 7.49 (1H, d,  $J$  = 1.6 Hz), 7.12 (1H, d,  $J$  = 9.0 Hz), 4.89 (2H, s), 3.92-3.89 (3H, s). MS (ESI<sup>+</sup>): 291.1. HPLC (Condition A): Rt 2.16 min (HPLC purity 98.2%).

**(4-Chloro-2-{[2-fluoro-5-(hydroxymethyl)phenyl]ethynyl}phenoxy)acetic acid (17a).** Prepared according to Sonogashira general method 2, starting from *tert*-butyl (4-chloro-2-ethynylphenoxy)acetate (**16a**) and 3-bromo-4-fluorobenzyl alcohol, the intermediate ester was purified by column chromatography and deprotected using HCl (4 N) in dioxane. After purification by preparative HPLC the title compound was obtained as a beige solid. <sup>1</sup>H NMR (300MHz, DMSO-*d*<sub>6</sub>)  $\delta$  [ppm] 13.2 (1H, s), 7.55 (1H, d,  $J$  = 2.6 Hz), 7.54 (1H, dd,  $J$  = 5.1,  $J$  = 2.2 Hz), 7.42 (1H, dd,  $J$  = 9.0,  $J$  = 2.6 Hz), 7.40 (1H, ddd,  $J$  = 8.7,  $J$  = 5.1,  $J$  = 2.2 Hz), 7.29 (1H, t,  $J$  = 5.7 Hz), 6.99 (1H, d,  $J$  = 9.0 Hz), 5.31 (1H, bs), 4.81 (2H, s), 4.50 (2H, s). MS (ESI<sup>+</sup>): 333.2. HPLC (Condition A): Rt 3.83 min (HPLC purity 99.2%).

**(4-Chloro-2-{[2-fluoro-4-(hydroxymethyl)phenyl]ethynyl}phenoxy)acetic acid (17b).** Prepared according to Sonogashira general method 2, starting from *tert*-butyl (4-chloro-2-ethynylphenoxy)acetate (**16a**) and (4-bromo-3-fluorophenyl)methanol (**34a**), the intermediate

ester was purified by column chromatography and deprotected using HCl (4 N) in dioxane. After purification by preparative HPLC the title compound was obtained as a white solid. <sup>1</sup>H NMR (300MHz, DMSO-d<sub>6</sub>) δ [ppm] 13.2 (1H, s), 7.57 (1H, d, *J*= 7.8 Hz), 7.54 (1H, d, *J*= 2.6 Hz), 7.42 (1H, dd, *J*= 9.0, *J*= 2.6 Hz), 7.24 (1H, d, *J*= 10.7 Hz), 7.20 (1H, d, *J*= 7.8 Hz), 6.98 (1H, d, *J*= 9.0 Hz), 5.43 (1H, s), 4.80 (2H, s), 4.55 (2H, s). MS (ESI<sup>+</sup>): 333.2. HPLC (Condition A): Rt 3.73 min (HPLC purity 99.7%).

**(4-Chloro-2-{{2-fluoro-3-(hydroxymethyl)phenyl}ethynyl}phenoxy)acetic acid (17c).**

Prepared according to Sonogashira general method 2, starting from *tert*-butyl (4-chloro-2-ethynylphenoxy)acetate (**16a**) and (3-bromo-2-fluorophenyl)methanol (**34b**), the intermediate ester was purified by column chromatography and deprotected using HCl (4 N) in dioxane. After purification by preparative HPLC the title compound was obtained as a white solid. <sup>1</sup>H NMR (300MHz, DMSO-d<sub>6</sub>) δ [ppm] 7.47-7.54 (3H, m), 7.41 (1H, dd, *J*= 9.0, *J*= 2.7 Hz), 7.25 (1H, t, *J*= 7.6 Hz), 6.97 (1H, d, *J*= 9.0 Hz), 5.37 (1H, bs), 4.75 (2H, s), 4.58 (2H, s). MS (ESI<sup>+</sup>): 333.1. HPLC (Condition A): Rt 3.70 min (HPLC purity 98.8%).

**(4-Chloro-2-{{2-fluoro-5-(methoxymethyl)phenyl}ethynyl}phenoxy)acetic acid (17d).**

Prepared according to Sonogashira general method 2, starting from *tert*-butyl (4-chloro-2-ethynylphenoxy)acetate (**16a**) and 2-bromo-1-fluoro-4-(methoxymethyl)benzene (**35a**), the intermediate ester was purified by column chromatography and deprotected using HCl (4 N) in dioxane. After purification by preparative HPLC the title compound was obtained as a beige solid. <sup>1</sup>H NMR (300MHz, DMSO-d<sub>6</sub>) δ [ppm] 13.2 (1H, bs), 7.56-7.59 (2H, m), 7.41-7.47 (2H, m), 7.34 (1H, m), 7.01 (1H, d, *J*= 9.0 Hz), 4.84 (2H, s), 4.43 (2H, s), 3.32 (3H, s). MS (ESI<sup>+</sup>): 347.2. HPLC (Condition A): Rt 4.37 min (HPLC purity 96.0%).

**(4-Chloro-2-{[2-fluoro-4-(methoxymethyl)phenyl]ethynyl}phenoxy)acetic acid (17e).**

Prepared according to Sonogashira general method 2, starting from *tert*-butyl (4-chloro-2-ethynylphenoxy)acetate (**16a**) and 1-bromo-2-fluoro-4-(methoxymethyl)benzene (**35b**), the intermediate ester was purified by column chromatography and deprotected using HCl (4 N) in dioxane. After purification by preparative HPLC the title compound was obtained as a beige solid. <sup>1</sup>H NMR (300MHz, DMSO-d<sub>6</sub>) δ [ppm] 13.25 (1H, s), 7.62 (1H, t, *J* = 7.6 Hz), 7.58 (1H, d, *J* = 2.7 Hz), 7.44 (1H, dd, *J* = 9.0, *J* = 2.7 Hz), 7.29 (1H, d, *J* = 10.5 Hz), 7.24 (1H, m), 7.02 (1H, d, *J* = 9.0 Hz), 4.83 (2H, s), 4.49 (2H, s), 3.3 (3H, s). MS (ESI<sup>+</sup>): 347.2. HPLC (Condition A): Rt 4.40 min (HPLC purity 99.9%).

**[4-Chloro-2-(pyridin-2-ylethynyl)phenoxy]acetic acid (18a).** Prepared according to Sonogashira general method 2, starting from *tert*-butyl (4-chloro-2-ethynylphenoxy)acetate (**16a**) and 2-bromopyridine, without purification of the intermediate ester and deprotecting using HCl (4 N) in dioxane. The title compound was obtained as a beige powder after purification by precipitation in acetonitrile. <sup>1</sup>H NMR (300MHz, DMSO-d<sub>6</sub>) δ [ppm] 13.18 (1H, s), 8.62 (1H, ddd, *J* = 4.9, *J* = 1.8, *J* = 1.0 Hz), 7.87 (1H, td, *J* = 7.7, *J* = 1.8 Hz), 7.66-7.61 (2H, m), 7.48-7.39 (2H, m), 7.02 (1H, d, *J* = 9.0 Hz), 4.86 (2H, s). MS (ESI<sup>+</sup>): 288.1. HPLC (Condition A): Rt 2.53 min (HPLC purity 98.4%).

**[4-Chloro-2-(pyridin-4-ylethynyl)phenoxy]acetic acid (18c).** Prepared according to Sonogashira general method 2, starting from *tert*-butyl (4-chloro-2-ethynylphenoxy)acetate (**16a**) and 4-bromopyridine, without purification of the intermediate ester and deprotecting using HCl (4 N) in dioxane. The title compound was obtained as a yellow solid after purification by precipitation in dioxane. <sup>1</sup>H NMR (300MHz, DMSO-d<sub>6</sub>) δ [ppm] 13.2 (1H,



bs), 8.66-8.62 (2H, m), 7.64 (1H, d,  $J$  = 2.7 Hz), 7.53-7.44 (3H, m), 7.04 (1H, d,  $J$  = 9.0 Hz), 4.86 (2H, s). MS (ESI<sup>+</sup>): 288.0. HPLC (Condition A): Rt 2.37 min (HPLC purity 97.5%).

**{4-Chloro-2-[(2-methylpyridin-3-yl)ethynyl]phenoxy}acetic acid (18d).** Prepared according to Sonogashira general method 2, starting from *tert*-butyl (4-chloro-2-ethynylphenoxy)acetate (**16a**) and 3-bromo-2-methylpyridine, the intermediate ester was purified by column chromatography and deprotected using HCl (4 N) in dioxane. After purification by preparative HPLC the title compound was obtained as a dark brown solid. <sup>1</sup>H NMR (300MHz, DMSO-d<sub>6</sub>)  $\delta$  [ppm] 13.32 (1H, s), 8.65 (1H, d,  $J$  = 5.1 Hz), 8.29 (1H, d,  $J$  = 7.9 Hz), 7.70-7.65 (2H, m), 7.48 (1H, dd,  $J$  = 9.0,  $J$  = 2.8 Hz), 7.07 (1H, d,  $J$  = 9.0 Hz), 4.85 (2H, s), 2.81 (3H, s). MS (ESI<sup>+</sup>): 302.1. HPLC (Condition A): Rt 2.56 min (HPLC purity 93.4%).

**{4-Chloro-2-[(4-methylpyridin-3-yl)ethynyl]phenoxy}acetic acid (18e).** Prepared according to Sonogashira general method 2, starting from *tert*-butyl (4-chloro-2-ethynylphenoxy)acetate (**16a**) and 3-bromo-4-methylpyridine, the intermediate ester was purified by column chromatography and deprotected using HCl (4 N) in dioxane. After purification by preparative HPLC the title compound was obtained as a beige solid. <sup>1</sup>H NMR (300MHz, DMSO-d<sub>6</sub>)  $\delta$  [ppm] 8.91 (1H, s), 8.68 (1H, s), 7.86-7.72 (1H, m), 7.65 (1H, d,  $J$  = 2.7 Hz), 7.49 (1H, dd,  $J$  = 9.0,  $J$  = 2.7 Hz), 7.08 (1H, d,  $J$  = 9.0 Hz), 4.86 (2H, s), 2.64 (3H, s). MS (ESI<sup>+</sup>): 302.2. HPLC (Condition A): Rt 2.53 min (HPLC purity 99.6%).

**{4-Chloro-2-[(4-propylpyridin-3-yl)ethynyl]phenoxy}acetic acid (18f).** Prepared according to Sonogashira general method 2, starting from *tert*-butyl (4-chloro-2-ethynylphenoxy)acetate (**16a**) and 3-bromo-4-propylpyridine (**55a**), the intermediate ester was

purified by column chromatography and deprotected using HCl (4 N) in dioxane. After purification by preparative HPLC the title compound was obtained as a white solid. <sup>1</sup>H NMR (300MHz, DMSO-d<sub>6</sub>) δ [ppm] 8.66 (1H, s), 8.48 (1H, d, *J*= 5.1 Hz), 7.59 (1H, d, *J*= 2.7 Hz), 7.45 (1H, dd, *J*= 2.7, *J*= 9.0 Hz), 7.38 (1H, d, *J*= 5.1 Hz), 7.05 (1H, d, *J*= 9.0 Hz), 4.82 (2H, s), 2.83 (2H, t, *J*= 7.5 Hz), 1.69 (2H, sext. *J*= 7.5 Hz), 0.94 (3H, t, *J*= 7.5 Hz). MS (ESI): 328.2. HPLC (Condition A): Rt 3.06 min (HPLC purity 97.2%).

**{4-Chloro-2-[(4-isobutylpyridin-3-yl)ethynyl]phenoxy}acetic acid (18g).** Prepared according to Sonogashira general method 2, starting from *tert*-butyl (4-chloro-2-ethynylphenoxy)acetate (**16a**) and 3-bromo-4-isobutylpyridine (**55b**), the intermediate ester was purified by column chromatography and deprotected using HCl (4 N) in dioxane. After purification by preparative HPLC the title compound was obtained as a beige solid. <sup>1</sup>H NMR (300MHz, DMSO-d<sub>6</sub>) δ [ppm] 8.68 (1H, s), 8.48 (1H, d, *J*= 5.1 Hz), 7.58 (1H, d, *J*= 2.7 Hz), 7.45 (1H, dd, *J*= 2.7, *J*= 9.0 Hz), 7.34 (1H, d, *J*= 5.1 Hz), 7.05 (1H, d, *J*= 9.0 Hz), 4.83 (2H, s), 2.74 (2H, d, *J*= 6.8 Hz), 2.05 (1H, sept., *J*= 6.8 Hz), 0.91 (6H, d, *J*= 6.8 Hz). MS (ESI): 342.2. HPLC (Condition A): Rt 3.84 min (HPLC purity 99.7%).

**{4-Chloro-2-[(4-hexylpyridin-3-yl)ethynyl]phenoxy}acetic acid (18h).** Prepared according to Sonogashira general method 2, starting from *tert*-butyl (4-chloro-2-ethynylphenoxy)acetate (**16a**) and 3-bromo-4-hexylpyridine (**55c**), without purification of the intermediate ester and deprotecting using HCl (4 N) in dioxane. The title compound was obtained as a beige solid after purification by preparative HPLC. <sup>1</sup>H NMR (300MHz, DMSO-d<sub>6</sub>) δ [ppm] 13.2 (1H, bs), 8.64 (1H, s), 8.46 (1H, d, *J*= 5.1 Hz), 7.56 (1H, d, *J*= 2.7 Hz), 7.44 (1H, d, *J*= 9.0, *J*= 2.7 Hz), 7.36 (1H, d, *J*= 5.1 Hz), 7.03 (1H, d, *J*= 9.0 Hz), 4.81 (2H, s),

2.83 (2H, m), 1.62 (2H, m), 1.27 (6H, m), 0.82 (3H, t,  $J = 7.2$  Hz). MS (ESI<sup>+</sup>): 372.3. HPLC (Condition A): Rt 3.85 min (HPLC purity 96.7%).

**{4-Chloro-2-[(4-methyl-1-oxidopyridin-3-yl)ethynyl]phenoxy}acetic acid (18i).** A solution of *tert*-butyl {4-chloro-2-[(4-methylpyridin-3-yl)ethynyl]phenoxy}acetate (**18e**; 110 mg; 0.31 mmol) in DCM (5 mL) was treated with 3-chloroperbenzoic acid (91 mg; 0.37 mmol) and stirred at RT for 2 hours. The solvents were removed under vacuum, the residue was taken up in EtOAc and the organic phase washed with a saturated bicarbonate solution twice, then with brine. The organic layer was then dried over MgSO<sub>4</sub> and concentrated under vacuum to afford the *tert*-butyl intermediate (110 mg, 96%). Deprotection using HCl (4 N) in dioxane afforded the title compound as a beige solid after purification by preparative HPLC. <sup>1</sup>H NMR (300MHz, DMSO-d<sub>6</sub>)  $\delta$  [ppm] 8.57 (1H, d,  $J = 2.0$  Hz), 8.37 (1H, dd,  $J = 6.6$ ,  $J = 2.0$  Hz), 7.64 (1H, d,  $J = 2.7$  Hz), 7.56 (1H, d,  $J = 6.6$  Hz), 7.49 (1H, dd,  $J = 9.0$ ,  $J = 2.7$  Hz), 7.08 (1 H, d,  $J = 9.0$  Hz), 4.85 (2H, s), 2.50 (3H, s). MS (ESI<sup>+</sup>): 318.1. HPLC (Condition A): Rt 2.96 min (HPLC purity 97.7%).

**(4-Chloro-2-{[3-(methylsulfonyl)phenyl]ethynyl}phenoxy)acetic acid (19a).** Prepared according to Sonogashira general method 2, starting from *tert*-butyl (4-chloro-2-ethynylphenoxy)acetate (**16a**) and 3-bromophenylmethylsulfone, without purification of the intermediate ester and deprotecting using HCl (4 N) in dioxane. The title compound was obtained as a beige solid after purification by preparative HPLC. <sup>1</sup>H NMR (300MHz, DMSO-d<sub>6</sub>)  $\delta$  [ppm] 13.21 (1H, s), 8.06 (1H, t,  $J = 1.6$  Hz), 7.96 (1H, dt,  $J = 7.8$ ,  $J = 1.6$  Hz), 7.88 (1H, dt,  $J = 7.8$ ,  $J = 1.6$  Hz), 7.72 (1H, t,  $J = 7.8$ Hz), 7.63 (1H, d,  $J = 2.6$  Hz), 7.44 (1H, dd,  $J = 9.0$ ,  $J = 2.6$  Hz), 7.01 (1H, d,  $J = 9.0$  Hz), 4.84 (2H, s), 3.29 (1H, s). MS (ESI<sup>+</sup>): 363.2. HPLC (Condition A): Rt 3.81 min (HPLC purity 99.2%).

**[4-Chloro-2-({3-[(3-hydroxypropyl)sulfonyl]phenyl}ethynyl)phenoxy]acetic acid (19c).**

Prepared according to Sonogashira general method 2, starting from *tert*-butyl (4-chloro-2-ethynylphenoxy)acetate (**16a**) and 3-[(3-bromophenyl)sulfonyl]propan-1-ol (**12b**), without purification of the intermediate ester and deprotecting using HCl (4 N) in dioxane. The title compound was obtained as a brown solid after purification by preparative HPLC. <sup>1</sup>H NMR (300MHz, DMSO-d<sub>6</sub>) δ [ppm] 13.21 (1H, s), 8.01 (1H, t, *J*= 1.6 Hz), 7.92 (2H, m), 7.74 (1H, t, *J*= 7.8 Hz), 7.65 (1H, d, *J*= 2.6 Hz), 7.44 (1H, dd, *J*= 9.0, *J*= 2.6 Hz), 7.01 (1H, d, *J*= 9.0 Hz); 4.85 (2H, s), 4.66 (1H, s), 3.43-3.36 (4H, m), 1.68 (2H, m). MS (ESI<sup>+</sup>): 409.2. HPLC (Condition A): Rt 3.60 min (HPLC purity 93.7%).

**[4-Chloro-2-({3-[(2-hydroxyethyl)sulfonyl]phenyl}ethynyl)phenoxy]acetic acid (19d).**

Prepared according to Sonogashira general method 2, starting from *tert*-butyl (4-chloro-2-ethynylphenoxy)acetate (**16a**) and 2-[(3-Bromophenyl)sulfonyl]ethanol (**12c**), without purification of the intermediate ester and deprotecting using HCl (4 N) in dioxane. The title compound was obtained as a beige solid after purification by preparative HPLC. <sup>1</sup>H NMR (300MHz, DMSO-d<sub>6</sub>) δ [ppm] 13.28 (1H, s), 8.00 (1H, t, *J*= 1.6 Hz), 7.90 (1H, dt, *J*= 7.8, *J*= 1.6 Hz), 7.85 (1H, dt, *J*= 7.8, *J*= 1.6 Hz), 7.68 (1H, t, *J*= 7.8 Hz), 7.61 (1H, d, *J*= 2.7 Hz), 7.41 (1H, dd, *J*= 9.0, *J*= 2.7 Hz), 6.99 (1H, d, *J*= 9.0 Hz), 4.85 (1H, bs), 4.83 (2H, s), 3.67 (2H, t, *J*= 6.1 Hz), 3.51 (2H, t, *J*= 6.1 Hz). MS (ESI<sup>-</sup>): 393.2. HPLC (Condition A): Rt 3.46 min (HPLC purity 97.9%).

**(4-Chloro-2-{[2-methyl-5-(methylsulfonyl)phenyl]ethynyl}phenoxy)acetic acid (19e).**

Prepared according to Sonogashira general method 3, starting from *tert*-butyl (4-chloro-2-ethynylphenoxy)acetate (**16a**) and 2-iodo-1-methyl-4-(methylsulfonyl)benzene (**38a**), the title

compound was obtained as a brown solid.  $^1\text{H}$  NMR (300MHz,  $\text{DMSO-d}_6$ )  $\delta$  [ppm] 13.2 (1H, bs), 8.00 (1H, d,  $J = 2.0$  Hz), 7.84 (1H, dd,  $J = 8.0$ ,  $J = 2.0$  Hz), 7.65 (1H, d,  $J = 2.7$  Hz), 7.62 (1H, d,  $J = 8.0$  Hz), 7.45 (1H, dd,  $J = 9.0$ ,  $J = 2.7$  Hz), 7.05 (1H, d,  $J = 9.0$  Hz), 4.85 (2H, s), 3.25 (3H, s), 2.58 (3H, s). MS (ESI $^-$ ): 377.2. HPLC (Condition A): Rt 4.00 min (HPLC purity 93.4%).

**(4-Chloro-2-{[2-fluoro-5-(methylsulfonyl)phenyl]ethynyl}phenoxy)acetic acid (19f).**

Prepared according to Sonogashira general method 2, starting from *tert*-butyl (4-chloro-2-ethynylphenoxy)acetate (**16a**) and 1-fluoro-2-iodo-4-(methylsulfonyl)benzene (**38b**), without purification of the intermediate ester and deprotecting using HCl (4 N) in dioxane. The title compound was obtained as a brown solid after purification by preparative HPLC.  $^1\text{H}$  NMR (300MHz,  $\text{DMSO-d}_6$ )  $\delta$  [ppm] 13.25 (1H, bs), 8.18 (1H, dd,  $J = 2.4$ ,  $J = 6.5$  Hz), 8.03 (1H, m), 7.69-7.63 (2H, m), 7.47 (1H, dd,  $J = 2.7$ ,  $J = 9.0$  Hz), 7.03 (1H, d,  $J = 9.0$  Hz), 4.85 (2H, s), 3.31 (3H, s). MS (ESI $^-$ ): 381.2. HPLC (Condition A): Rt 3.89 min (HPLC purity 96.7%).

**(4-Chloro-2-{[2-chloro-5-(methylsulfonyl)phenyl]ethynyl}phenoxy)acetic acid (19g).**

Prepared according to Sonogashira general method 2, starting from *tert*-butyl (4-chloro-2-ethynylphenoxy)acetate (**16a**) and 1-chloro-2-iodo-4-(methylsulfonyl)benzene (**38c**), without purification of the intermediate ester and deprotecting using HCl (4 N) in dioxane. The title compound was obtained as a beige solid after purification by preparative HPLC.  $^1\text{H}$  NMR (300MHz,  $\text{DMSO-d}_6$ )  $\delta$  [ppm] 13.17 (1H, s), 8.17 (1H, d,  $J = 2.0$  Hz), 7.94 (1H, dd,  $J = 8.4$ ,  $J = 2.0$ ), 7.90 (1H, d,  $J = 8.4$  Hz), 7.64 (1H, d,  $J = 2.7$  Hz), 7.47 (1H, dd,  $J = 9.0$ ,  $J = 2.7$  Hz), 7.05 (1H, d,  $J = 9.0$  Hz), 4.85 (2H, s) (3 remaining protons, probably hidden under the signal of water). MS (ESI $^-$ ): 397.2. HPLC (Condition A): Rt 4.10 min (HPLC purity 96.8%).

**(4-Chloro-2-{{5-(methylsulfonyl)-2-propylphenyl}ethynyl}phenoxy)acetic acid (19h).**

Prepared according to Sonogashira general method 3, starting from *tert*-butyl (4-chloro-2-ethynylphenoxy)acetate (**16a**) and 2-iodo-4-(methylsulfonyl)-1-propylbenzene (**58a**), the title compound was obtained as a white solid after slurrying in diethyl ether. <sup>1</sup>H NMR (300MHz, DMSO-d<sub>6</sub>) δ [ppm] 13.18 (1H, bs), 8.01 (1H, d, *J*= 1.5 Hz), 7.86 (1H, dd, *J*= 8.0 Hz, *J*= 1.5 Hz), 7.62-7.59 (2H, m), 7.45 (1H, dd, *J*= 8.8 Hz, *J*= 2.0 Hz), 7.05 (1H, d, *J*= 8.8 Hz), 4.85 (2H, s), 3.26 (3H, s), 2.91 (2H, t, *J*= 7.5 Hz), 1.68 (2H, sextet, *J*= 7.5 Hz), 0.94 (3H, t, *J*= 7.5 Hz). MS (ESI<sup>+</sup>): 405.3. HPLC (Condition A): Rt 4.60 min (HPLC purity 98.8%).

**(4-Chloro-2-{{2-isopropyl-5-(methylsulfonyl)phenyl}ethynyl}phenoxy)acetic acid (19i).**

Prepared according to Sonogashira general method 3, starting from *tert*-butyl (4-chloro-2-ethynylphenoxy)acetate (**16a**) and 2-iodo-1-isopropyl-4-(methylsulfonyl)benzene (**58b**), the title compound was obtained as a white solid after purification by preparative HPLC. <sup>1</sup>H NMR (300MHz, DMSO-d<sub>6</sub>) δ [ppm] 13.18 (1H, bs), 8.01 (1H, d, *J*= 2.0 Hz), 7.90 (1H, dd, *J*= 8.3 Hz, *J*= 2.0 Hz), 7.67 (1H, d, *J*= 8.3 Hz), 7.63 (1H, d, *J*= 2.7 Hz), 7.44 (1H, dd, *J*= 9.0 Hz, *J*= 2.7 Hz), 7.05 (1H, d, *J*= 9.0 Hz), 4.83 (2H, s), 3.65 (1H, sept., *J*= 6.9 Hz), 3.26 (3H, s), 1.28 (6H, d, *J*= 6.9 Hz). MS (ESI<sup>+</sup>): 405.2. HPLC (Condition A): Rt 4.43 min (HPLC purity 99.8%).

**(4-Chloro-2-{{5-(ethylsulfonyl)-2-methylphenyl}ethynyl}phenoxy)acetic acid (19j).**

Prepared according to Sonogashira general method 3, starting from *tert*-butyl (4-chloro-2-ethynylphenoxy)acetate (**16a**) and 2-bromo-4-(ethylsulfonyl)-1-methylbenzene (**12e**), the title compound was obtained as a brown oil after purification by preparative HPLC. <sup>1</sup>H NMR (300MHz, DMSO-d<sub>6</sub>) δ [ppm] 7.93 (1H, s), 7.92-7.76 (1H, m), 7.62-7.58 (2H, m), 7.38 (1H, dd, *J*= 9.0 Hz, *J*= 2.4 Hz), 6.91 (1H, d, *J*= 9.0 Hz), 4.53 (2H, s), 3.34 (2H, m), 2.57 (3H, s),

1.08 (3H, t,  $J = 7.3$  Hz). MS ( $\text{ESI}^+$ ): 392.8. HPLC (Condition A): Rt 4.77 min (HPLC purity 96.0%).

**(4-Chloro-2-{{5-(isopropylsulfonyl)-2-methylphenyl}ethynyl}phenoxy)acetic acid (19l).**

Prepared according to Sonogashira general method 3, starting from *tert*-butyl (4-chloro-2-ethynylphenoxy)acetate (**16a**) and 2-bromo-4-(isopropylsulfonyl)-1-methylbenzene (**12d**), the title compound was obtained as a yellow solid after purification by preparative HPLC.  $^1\text{H}$  NMR (300MHz,  $\text{DMSO-d}_6$ )  $\delta$  [ppm] 13.15 (1H; s), 7.89 (1H, d,  $J = 1.8$  Hz), 7.60 (1H, dd,  $J = 8.0$  Hz,  $J = 1.8$  Hz), 7.65-7.61 (2H, m), 7.43 (1H, dd,  $J = 9.0$  Hz,  $J = 2.6$  Hz), 7.03 (1H, d,  $J = 9.0$  Hz), 4.83 (2H, s), 3.46 (1H, septet,  $J = 6.8$  Hz), 2.57 (3H, s), 1.12 (6H, d,  $J = 6.8$  Hz). MS ( $\text{ESI}^+$ ): 407.0. HPLC (Condition A): Rt 4.98 min (HPLC purity 92.3%).

**(4-Chloro-2-{{5-(isobutylsulfonyl)-2-methylphenyl}ethynyl}phenoxy)acetic acid (19m).**

Prepared according to Sonogashira general method 3, starting from *tert*-butyl (4-chloro-2-ethynylphenoxy)acetate (**16a**) and 2-bromo-4-(isobutylsulfonyl)-1-methylbenzene (**12f**), the title compound was obtained as a yellow solid after purification by preparative HPLC.  $^1\text{H}$  NMR (300MHz,  $\text{DMSO-d}_6$ )  $\delta$  [ppm] 7.95 (1H, s), 7.80 (1H, d,  $J = 8.0$  Hz), 7.63-7.60 (2H, m), 7.43 (1H, dd,  $J = 9.0$  Hz,  $J = 2.6$  Hz), 7.01 (1H, d,  $J = 9.0$  Hz), 4.79 (2H, s), 3.25 (2H, d,  $J = 6.4$  Hz), 2.57 (3H, s), 2.03-1.96 (1H, m), 0.96 (6H, d,  $J = 6.7$  Hz). MS ( $\text{ESI}^+$ ): 420.0. HPLC (Condition A): Rt 5.33 min (HPLC purity 97.6%).

**(2-{{5-(Benzylsulfonyl)-2-methylphenyl}ethynyl}-4-chlorophenoxy)acetic acid (19n).**

Prepared according to Sonogashira general method 3, starting from *tert*-butyl (4-chloro-2-ethynylphenoxy)acetate (**16a**) and 4-(benzylsulfonyl)-2-bromo-1-methylbenzene (**12g**), the title compound was obtained as a yellow solid after purification by preparative HPLC.  $^1\text{H}$

NMR (300MHz, DMSO- $d_6$ )  $\delta$  [ppm] 13.15 (1H, bs), 7.80 (1H, s), 7.62 (1H, d,  $J$  = 2.6 Hz), 7.54-7.53 (2H, m), 7.45 (1H, s), 7.31-7.30 (3H, m), 7.18 (2H, d,  $J$  = 5.0 Hz), 7.03 (1H, d,  $J$  = 9.2 Hz), 4.83 (2H, s), 4.71 (2H, s), 2.55 (3H, s). MS (ESI<sup>+</sup>): 455.0. HPLC (Condition A): Rt 5.29 min (HPLC purity 97.2%).

**[4-Chloro-2-({2-methyl-5-[(2-phenylethyl)sulfonyl]phenyl}ethynyl)phenoxy]acetic acid (19o).** Prepared according to Sonogashira general method 3, starting from *tert*-butyl (4-chloro-2-ethynylphenoxy)acetate (**16a**) and 2-bromo-1-methyl-4-[(2-phenylethyl)sulfonyl]benzene (**12h**), the title compound was obtained as a yellow solid after purification by preparative HPLC. <sup>1</sup>H NMR (300MHz, DMSO- $d_6$ )  $\delta$  [ppm] 13.16 (1H, s), 7.97 (1H, s), 7.82 (1H, d,  $J$  = 8.0 Hz), 7.61 (1H, t,  $J$  = 9.1 Hz), 7.44 (1H, d,  $J$  = 8.4 Hz), 7.24-7.17 (5H, m), 7.04 (1H, d,  $J$  = 9.0 Hz), 4.84 (2H, s), 3.68 (2H, t,  $J$  = 8.0 Hz), 2.88 (2H, t,  $J$  = 8.0 Hz), 2.57 (3H, s). MS (ESI<sup>+</sup>): 467.0. HPLC (Condition A): Rt 5.53 min (HPLC purity 97.0%).

**(4-Chloro-2-{{2-methyl-5-(phenylsulfonyl)phenyl}ethynyl}phenoxy)acetic acid (19p).** Prepared according to Sonogashira general method 3, starting from *tert*-butyl (4-chloro-2-ethynylphenoxy)acetate (**16a**) and 2-iodo-1-methyl-4-(phenylsulfonyl)benzene (**50**), the title compound was obtained as a brown solid after purification by preparative HPLC. <sup>1</sup>H NMR (300MHz, DMSO- $d_6$ )  $\delta$  [ppm] 13.26 (1H, bs), 8.02-7.97 (3H, m), 7.87 (1H, dd,  $J$  = 8.0 Hz,  $J$  = 2.0 Hz), 7.73-7.56 (5H, m), 7.43 (1H, dd,  $J$  = 9.0 Hz,  $J$  = 2.7 Hz), 7.03 (1H, d,  $J$  = 9.0 Hz), 4.79 (2H, s), 2.52 (3H, s). MS (ESI<sup>+</sup>): 439.2. HPLC (Condition A): Rt 4.90 min (HPLC purity 98.4%).

**[4-Chloro-2-({5-[(2-hydroxyethyl)sulfonyl]-2-methylphenyl}ethynyl)phenoxy]acetic acid (19q).** Prepared according to Sonogashira general method 3, starting from *tert*-butyl (4-



chloro-2-ethynylphenoxy)acetate (**16a**) and 2-[(3-bromo-4-methylphenyl)sulfonyl]ethanol (**12i**), the title compound was obtained as a yellow solid after purification by preparative HPLC. <sup>1</sup>H NMR (300MHz, DMSO-d<sub>6</sub>) δ [ppm] 13.15 (1H, s), 7.94 (1H, d, *J*= 2.0 Hz), 7.79 (1H, dd, *J*= 8.0 Hz, *J*= 2.0 Hz), 7.64 (1H, d, *J*= 2.6 Hz), 7.59 (1H, d, *J*= 8.0 Hz), 7.43 (1H, dd, *J*= 9.0 Hz, *J*= 2.6 Hz), 7.03 (1H, d, *J*= 9.0 Hz), 4.83 (2H, s), 3.67 (2H, m), 3.48 (2H, t, *J*= 6.0 Hz), 2.56 (3H, s). MS (ESI<sup>+</sup>): 408.8. HPLC (Condition A): Rt 4.17 min (HPLC purity 96.4%).

**[4-Chloro-2-({5-[(3-hydroxypropyl)sulfonyl]-2-methylphenyl}ethynyl)phenoxy]acetic acid (19r).** Prepared according to Sonogashira general method 3, starting from *tert*-butyl (4-chloro-2-ethynylphenoxy)acetate (**16a**) and 3-[(3-bromo-4-methylphenyl)sulfonyl]propan-1-ol (**12j**), the title compound was obtained as a yellow solid after purification by preparative HPLC. <sup>1</sup>H NMR (300MHz, DMSO-d<sub>6</sub>) δ [ppm] 7.93 (1H, d, *J*= 2.0 Hz), 7.79 (1H, dd, *J*= 8.0 Hz, *J*= 2.0 Hz), 7.64-7.61 (2H, m), 7.43 (1H, dd, *J*= 9.0 Hz, *J*= 2.6 Hz), 7.02 (1H, d, *J*= 9.0 Hz), 4.80 (2H, s), 3.39 (2H, t, *J*= 6.2 Hz), 3.35-3.31 (2H, m), 2.57 (3H, s), 1.65 (2H, d, *J*= 7.9 Hz). MS (ESI<sup>-</sup>): 422.0. HPLC (Condition A): Rt 4.27 min (HPLC purity 97.2%).

**(4-Chloro-2-{[2-fluoro-5-(isopropylsulfonyl)phenyl]ethynyl}phenoxy)acetic acid (19t).** Prepared according to Sonogashira general method 4, starting from *tert*-butyl (4-chloro-2-ethynylphenoxy)acetate (**16a**) and 2-bromo-1-fluoro-4-(isopropylsulfonyl)benzene (**12m**), the title compound was obtained as a white solid after purification by preparative HPLC. <sup>1</sup>H NMR (300MHz, DMSO-d<sub>6</sub>) δ [ppm] 13.20 (1H, bs), 8.08 (1H, dd, *J*= 6.5 Hz, *J*= 2.4 Hz), 7.95 (1H, ddd, *J*= 8.7 Hz, *J*= 4.6 Hz, *J*= 2.4 Hz), 7.70-7.64 (2H, m), 7.47 (1H, dd, *J*= 9.0 Hz, *J*= 2.7 Hz), 7.03 (1H, d, *J*= 9.0 Hz), 4.85 (2H, s), 3.55 (2H, septet, *J*= 6.8 Hz), 1.18 (6H, d, *J*= 6.8 Hz). MS (ESI<sup>-</sup>): 409.0. HPLC (Condition A): Rt 4.34 min (HPLC purity 98.3%).

**(4-Chloro-2-{{2-chloro-5-(propylsulfonyl)phenyl}ethynyl}phenoxy)acetic acid (19u).**

Prepared according to Sonogashira general method 4, starting from *tert*-butyl (4-chloro-2-ethynylphenoxy)acetate (**16a**) and 2-bromo-1-chloro-4-(propylsulfonyl)benzene (**12n**), the title compound was obtained as a white solid after purification by preparative HPLC. <sup>1</sup>H NMR (300MHz, DMSO-d<sub>6</sub>) δ [ppm] 13.20 (1H, bs), 8.12 (1H, t, *J*= 1.3 Hz), 7.90 (2H, d, *J*= 1.3 Hz), 7.65 (1H, d, *J*= 2.7 Hz), 7.48 (1H, dd, *J*= 9.0 Hz, *J*= 2.7 Hz), 7.05 (1H, d, *J*= 9.0 Hz), 4.85 (2H, s), 3.40 (2H, m), 1.58 (2H, m), 0.93 (3H, t, *J*= 7.5 Hz). MS (ESI<sup>+</sup>): 425.0. HPLC (Condition A): Rt 4.51 min (HPLC purity 100%).

**(4-Chloro-2-{{2-chloro-5-(isopropylsulfonyl)phenyl}ethynyl}phenoxy)acetic acid (19v).**

Prepared according to Sonogashira general method 4, starting from *tert*-butyl (4-chloro-2-ethynylphenoxy)acetate (**16a**) and 2-bromo-1-chloro-4-(isopropylsulfonyl)benzene (**12o**), the title compound was obtained as a white solid after purification by preparative HPLC. <sup>1</sup>H NMR (300MHz, DMSO-d<sub>6</sub>) δ [ppm] 13.19 (1H, bs), 8.07 (1H, d, *J*= 1.9 Hz), 7.93-7.85 (2H, m), 7.66 (1H, d, *J*= 2.7 Hz), 7.48 (1H, dd, *J*= 9.0 Hz, *J*= 2.7 Hz), 7.05 (1H, d, *J*= 9.0 Hz), 4.85 (2H, s), 3.57 (2H, septet, *J*= 6.8 Hz), 1.19 (6H, d, *J*= 6.8 Hz). MS (ESI<sup>+</sup>): 424.9. HPLC (Condition A): Rt 4.57 min (HPLC purity 99.6%).

**[4-Chloro-2-({3-[(dimethylamino)sulfonyl]phenyl}ethynyl)phenoxy]acetic acid (20a).**

Prepared according to Sonogashira general method 3, starting from *tert*-butyl (4-chloro-2-ethynylphenoxy)acetate (**16a**) and *N,N*-dimethyl 3-bromobenzenesulfonamide, the title compound was obtained as an off-white solid. <sup>1</sup>H NMR (300MHz, DMSO-d<sub>6</sub>) δ [ppm] 13.16 (1H, bs), 7.89-7.60 (4H, m), 7.66 (1H, d, *J*= 2.7 Hz), 7.44 (1H, dd, *J*= 9.0 Hz, *J*= 2.7 Hz),

7.03 (1H, d,  $J$  = 9.0 Hz), 4.85 (2H, s), 2.66 (6H, s). MS (ESI<sup>+</sup>): 392.1. HPLC (Condition A): Rt 4.40 min (HPLC purity 96.5%).

**[4-Chloro-2-({5-[(dimethylamino)sulfonyl]-2-methylphenyl}ethynyl)phenoxy]acetic acid (20b).** Prepared according to Sonogashira general method 3, starting from *tert*-butyl (4-chloro-2-ethynylphenoxy)acetate (**16a**) and *N,N*-dimethyl 3-bromo-4-methylbenzenesulfonamide, the title compound was obtained as a white solid after purification by preparative HPLC. <sup>1</sup>H NMR (300MHz, DMSO-*d*<sub>6</sub>)  $\delta$  [ppm] 13.15 (1H, bs), 7.80 (1H, d,  $J$  = 1.8 Hz), 7.69-7.60 (3H, m), 7.44 (1H, dd,  $J$  = 9.0 Hz,  $J$  = 2.7 Hz), 7.04 (1H, d,  $J$  = 9.0 Hz), 4.83 (2H, s), 2.63 (6H, s), 2.58 (3H, s). MS (ESI<sup>+</sup>): 406.1. HPLC (Condition A): Rt 4.55 min (HPLC purity 97.1%).

**[4-Chloro-2-({5-[(diethylamino)sulfonyl]-2-methylphenyl}ethynyl)phenoxy]acetic acid (20d).** Prepared according to Sonogashira general method 3, starting from *tert*-butyl (4-chloro-2-ethynylphenoxy)acetate (**16a**) and *N,N*-diethyl 3-bromobenzenesulfonamide, the title compound was obtained as a white solid after purification by preparative HPLC. <sup>1</sup>H NMR (300MHz, DMSO-*d*<sub>6</sub>)  $\delta$  [ppm] 13.16 (1H, bs), 7.84 (1H, d,  $J$  = 2.0 Hz), 7.71 (1H, dd,  $J$  = 8.1 Hz,  $J$  = 2.0 Hz), 7.66 (1H, d,  $J$  = 2.7 Hz), 7.57 (1H, d,  $J$  = 8.1 Hz), 7.44 (1H, dd,  $J$  = 9.0 Hz,  $J$  = 2.7 Hz), 7.04 (1H, d,  $J$  = 9.0 Hz), 4.82 (2H, s), 3.17 (4H, q,  $J$  = 7.1 Hz), 2.56 (3H, s), 1.05 (6H, t,  $J$  = 7.1 Hz). MS (ESI<sup>+</sup>): 434.1. HPLC (Condition A): Rt 4.80 min (HPLC purity 99.2%).

**[2-({5-[(*tert*-Butylamino)sulfonyl]-2-methylphenyl}ethynyl)-4-chlorophenoxy]acetic acid (20e).** Prepared according to Sonogashira general method 3, starting from *tert*-butyl (4-chloro-2-ethynylphenoxy)acetate (**16a**) and *N-tert*-butyl 3-bromo-4-methylbenzenesulfonamide, the title compound was obtained as a beige solid after purification

by preparative HPLC. <sup>1</sup>H NMR (300MHz, DMSO-d<sub>6</sub>) δ [ppm] 13.17 (1H, bs), 7.90 (1H, d, *J*= 2.0 Hz), 7.74 (1H, dd, *J*= 8.0 Hz, *J*= 2.0 Hz), 7.64 (1H, d, *J*= 2.7 Hz), 7.57 (1H, s), 7.53 (1H, d, *J*= 8.0 Hz), 7.43 (1H, dd, *J*= 9.0 Hz, *J*= 2.7 Hz), 7.03 (1H, d, *J*= 9.0 Hz), 4.82 (2H, s), 2.54 (3H, s); 1.10 (9H, s). MS (ESI<sup>-</sup>): 434.2. HPLC (Condition A): Rt 4.86 min (HPLC purity 96.7%).

**[4-Chloro-2-({2-methyl-5-[(methylamino)sulfonyl]phenyl}ethynyl)phenoxy]acetic acid (20f).** Prepared according to Sonogashira general method 3, starting from *tert*-butyl (4-chloro-2-ethynylphenoxy)acetate (**16a**) and 3-bromo-*N*,4-dimethylbenzenesulfonamide, the title compound was obtained as a beige solid after purification by preparative HPLC. <sup>1</sup>H NMR (300MHz, DMSO-d<sub>6</sub>) δ [ppm] 13.19 (1H, bs), 7.85 (1H, d, *J*= 2.0 Hz), 7.68 (1H, dd, *J*= 8.0 Hz, *J*= 2.0 Hz), 7.64 (1H, d, *J*= 2.7 Hz), 7.57 (1H, d, *J*= 8.0 Hz), 7.45 (1H, dd, *J*= 9.0 Hz, *J*= 2.7 Hz), 7.03 (1H, d, *J*= 9.0 Hz), 4.82 (2H, s), 2.55 (3H, s), 2.41 (3H, d, *J*= 5.0 Hz). MS (ESI<sup>-</sup>): 392.1. HPLC (Condition A): Rt 4.05 min (HPLC purity 99.3%).

**[4-Chloro-2-({5-[(ethylamino)sulfonyl]-2-methylphenyl}ethynyl)phenoxy]acetic acid (20g).** Prepared according to Sonogashira general method 3, starting from *tert*-butyl (4-chloro-2-ethynylphenoxy)acetate (**16a**) and *N*-ethyl 3-bromo-4-methylbenzenesulfonamide, the title compound was obtained as a beige solid after purification by preparative HPLC. <sup>1</sup>H NMR (300MHz, DMSO-d<sub>6</sub>) δ [ppm] 13.15 (1H, s), 7.85 (1H, d, *J*= 2.0 Hz), 7.69 (1H, dd, *J*= 8.0, *J*= 2.0 Hz), 7.63 (1H, d, *J*= 2.7 Hz), 7.60-7.54 (2H, m), 7.44 (1H, dd, *J*= 9.0, *J*= 2.7 Hz), 7.04 (1H, d, *J*= 9.0 Hz), 4.84 (2H, s), 2.78 (2H, qd, *J*= 7.1, *J*= 5.7 Hz), 2.55 (3H, s), 0.97 (3H, t, *J*= 7.1 Hz). MS (ESI<sup>+</sup>): 408.2. HPLC (Condition A): Rt 4.31 min (HPLC purity 99.6%).

**[4-Chloro-2-({5-[(isopropylamino)sulfonyl]-2-methylphenyl}ethynyl)phenoxy]acetic acid (20h).** Prepared according to Sonogashira general method 3, starting from *tert*-butyl (4-chloro-2-ethynylphenoxy)acetate (**16a**) and *N*-isopropyl 3-bromo-4-methylbenzenesulfonamide, the title compound was obtained as a beige solid after purification by preparative HPLC. <sup>1</sup>H NMR (300MHz, DMSO-d<sub>6</sub>) δ [ppm] 13.17 (1H, bs), 7.87 (1H, d, *J*= 2.0 Hz), 7.71 (1H, dd, *J*= 8.0 Hz, *J*= 2.0 Hz), 7.64 (1H, d, *J*= 2.7 Hz), 7.61 (1H, d, *J*= 7.0 Hz), 7.54 (1H, d, *J*= 8.0 Hz), 7.43 (1H, dd, *J*= 9.0 Hz, *J*= 2.7 Hz), 7.03 (1H, d, *J*= 9.0 Hz), 4.83 (2H, s), 3.25 (1H, m), 2.55 (3H, s), 0.95 (6H, d, *J*= 6.6 Hz). MS (ESI): 420.2. HPLC (Condition A): Rt 4.64 min (HPLC purity 98.4%).

**{4-Chloro-2-[(5-{isopropyl(methyl)amino}sulfonyl)-2-methylphenyl]ethynyl}phenoxy}acetic acid (20i).** Prepared according to Sonogashira general method 3, starting from *tert*-butyl (4-chloro-2-ethynylphenoxy)acetate (**16a**) and 3-bromo-*N*-isopropyl-*N*,4-dimethylbenzenesulfonamide (**12z**), the title compound was obtained as a beige solid after purification by preparative HPLC. <sup>1</sup>H NMR (300MHz, DMSO-d<sub>6</sub>) δ [ppm] 13.16 (1H, bs), 7.83 (1H, d, *J*= 2.0 Hz), 7.71 (1H, dd, *J*= 8.1 Hz, *J*= 2.0 Hz), 7.66 (1H, d, *J*= 2.7 Hz), 7.57 (1H, d, *J*= 8.1 Hz), 7.44 (1H, dd, *J*= 9.0 Hz, *J*= 2.7 Hz), 7.04 (1H, d, *J*= 9.0 Hz), 4.83 (2H, s), 4.09 (1H, septet, *J*= 6.7 Hz), 2.66 (3H, s); 2.56 (3H, s), 0.91 (6H, d, *J*= 6.7 Hz). MS (ESI): 434.1. HPLC (Condition A): Rt 4.99 min (HPLC purity 98.6%).

**{4-Chloro-2-[(5-{isobutyl(methyl)amino}sulfonyl)-2-methylphenyl]ethynyl}phenoxy}acetic acid (20j).** Prepared according to Sonogashira general method 3, starting from *tert*-butyl (4-chloro-2-ethynylphenoxy)acetate (**16a**) and 3-bromo-*N*-isobutyl-*N*,4-dimethylbenzenesulfonamide (**12r**), the title compound was obtained as a beige solid after after tituration in pentane/diethyl ether. <sup>1</sup>H NMR (300MHz, DMSO-d<sub>6</sub>) δ

[ppm] 13.14 (1H, bs), 7.81 (1H, d,  $J$  = 2.0 Hz), 7.69 (1H, dd,  $J$  = 8.0 Hz,  $J$  = 2.0 Hz), 7.66 (1H, d,  $J$  = 2.7 Hz), 7.58 (1H, d,  $J$  = 8.0 Hz), 7.44 (1H, dd,  $J$  = 9.0 Hz,  $J$  = 2.7 Hz), 7.04 (1H, d,  $J$  = 9.0 Hz), 4.83 (2H, s), 2.71 (2H, d,  $J$  = 7.4 Hz), 2.66 (3H, s), 2.56 (3H, s), 1.83 (1H, m), 0.87 (6H, d,  $J$  = 6.7 Hz). MS (ESI<sup>-</sup>): 448.1. HPLC (Condition A): Rt 5.03 min (HPLC purity 92.2%).

**(4-Chloro-2-{{2-methyl-5-(piperidin-1-ylsulfonyl)phenyl}ethynyl}phenoxy)acetic acid (20k).** Prepared according to Sonogashira general method 3, starting from *tert*-butyl (4-chloro-2-ethynylphenoxy)acetate (**16a**) and 1-[(3-bromo-4-methylphenyl)sulfonyl]piperidine (**12s**), the title compound was obtained as an off-white solid. <sup>1</sup>H NMR (300MHz, DMSO-d<sub>6</sub>) δ [ppm] 13.06 (1H, bs), 7.68 (1H, d,  $J$  = 1.8 Hz), 7.59-7.50 (3H, m), 7.35 (1H, dd,  $J$  = 9.0 Hz,  $J$  = 2.7 Hz), 6.96 (1H, d,  $J$  = 9.0 Hz), 4.75 (2H, s), 2.81 (4H, m), 2.49 (3H, s); 1.46 (4H, m), 1.28 (2H, m). MS (ESI<sup>-</sup>): 446.1. HPLC (Condition A): Rt 4.88 min (HPLC purity 96.8%).

**(4-Chloro-2-{{2-methyl-5-(morpholin-4-ylsulfonyl)phenyl}ethynyl}phenoxy)acetic acid (20l).** Prepared according to Sonogashira general method 3, starting from *tert*-butyl (4-chloro-2-ethynylphenoxy)acetate (**16a**) and 1-(3-bromo-4-methylphenylsulfonyl)morpholine, the title compound was obtained as a beige solid after purification by preparative HPLC. <sup>1</sup>H NMR (300MHz, DMSO-d<sub>6</sub>) δ [ppm] 13.16 (1H, bs), 7.79 (1H, d,  $J$  = 1.5 Hz), 7.68-7.61 (3H, m), 7.44 (1H, dd,  $J$  = 9.0 Hz,  $J$  = 2.7 Hz), 7.04 (1H, d,  $J$  = 9.0 Hz), 4.83 (2H, s), 3.64 (4H, m), 2.89 (4H, m), 2.59 (3H, s). MS (ESI<sup>-</sup>): 448.1. HPLC (Condition A): Rt 4.46 min (HPLC purity 98.9%).

**[4-Chloro-2-{{2-methyl-5-[(2-methylpiperidin-1-yl)sulfonyl]phenyl}ethynyl}phenoxy]acetic acid (20m).** Prepared according to Sonogashira

general method 3, starting from *tert*-butyl (4-chloro-2-ethynylphenoxy)acetate (**16a**) and 1-[(3-bromo-4-methylphenyl)sulfonyl]-2-methylpiperidine (**12t**), the title compound was obtained as a white solid after purification by preparative HPLC. <sup>1</sup>H NMR (300MHz, DMSO-*d*<sub>6</sub>) δ [ppm] 13.17 (1H, bs), 7.84 (1H, d, *J*= 2.0 Hz), 7.71 (1H, dd, *J*= 8.1 Hz, *J*= 2.0 Hz), 7.66 (1H, d, *J*= 2.7 Hz), 7.56 (1H, d, *J*= 8.1 Hz), 7.44 (1H, dd, *J*= 9.0 Hz, *J*= 2.7 Hz), 7.03 (1H, d, *J*= 9.0 Hz), 4.82 (2H, s), 4.13 (1H, m), 3.63 (1H, m), 2.98 (1H, dt, *J*= 13.0 Hz, *J*= 2.0 Hz), 2.55 (3H, s), 1.56-1.40 (5H, m), 1.20 (1H, m), 1.00 (3H, d, *J*= 6.9 Hz). MS (ESI<sup>+</sup>): 460.1. HPLC (Condition A): Rt 5.19 min (HPLC purity 99.6%).

**{4-Chloro-2-[(5-[(2-methoxyethyl)(methyl)amino]sulfonyl}-2-methylphenyl)ethynyl]phenoxy}acetic acid (20n)**. Prepared according to Sonogashira general method 3, starting from *tert*-butyl (4-chloro-2-ethynylphenoxy)acetate (**16a**) and 3-bromo-*N*-(2-methoxyethyl)-*N*,4-dimethylbenzenesulfonamide (**12u**), the title compound was obtained as a pink solid after purification by preparative HPLC. <sup>1</sup>H NMR (300MHz, DMSO-*d*<sub>6</sub>) δ [ppm] 13.17 (1H, bs), 7.83 (1H, d, *J*= 2.0 Hz), 7.70 (1H, dd, *J*= 8.1 Hz, *J*= 2.0 Hz), 7.66 (1H, d, *J*= 2.7 Hz), 7.58 (1H, d, *J*= 8.1 Hz), 7.44 (1H, dd, *J*= 9.0 Hz, *J*= 2.7 Hz), 7.04 (1H, d, *J*= 9.0 Hz), 4.83 (2H, s), 3.45 (2H, t, *J*= 5.5 Hz), 3.22 (3H, s), 3.17 (2H, t, *J*= 5.5 Hz), 2.73 (3H, s), 2.56 (3H, s). MS (ESI<sup>+</sup>): 450.1. HPLC (Condition A): Rt 4.39 min (HPLC purity 100%).

**{4-Chloro-2-[(5-[(2-methoxyethyl)amino]sulfonyl}-2-methylphenyl)ethynyl]phenoxy}acetic acid (20o)**. Prepared according to Sonogashira general method 3, starting from *tert*-butyl (4-chloro-2-ethynylphenoxy)acetate (**16a**) and 3-bromo-*N*-(2-methoxyethyl)-4-methylbenzenesulfonamide (**12v**), the title compound was obtained as a white solid after purification by preparative HPLC. <sup>1</sup>H NMR (300MHz, DMSO-

$\delta$  [ppm] 13.17 (1H, bs), 7.87 (1H, d,  $J$  = 2.0 Hz), 7.77 (1H, t,  $J$  = 5.9 Hz), 7.70 (1H, dd,  $J$  = 8.1 Hz,  $J$  = 2.0 Hz), 7.63 (1H, d,  $J$  = 2.7 Hz), 7.55 (1H, d,  $J$  = 8.1 Hz), 7.44 (1H, d,  $J$  = 9.0 Hz,  $J$  = 2.7 Hz), 7.03 (1H, d,  $J$  = 9.0 Hz), 4.83 (2H, s), 3.30 (2H, t,  $J$  = 5.7 Hz), 3.16 (3H, s), 2.91 (2H, q,  $J$  = 5.7 Hz), 2.55 (3H, s). MS (ESI<sup>-</sup>): 436.0.

**[4-Chloro-2-({2-methyl-5-[(4-methylpiperazin-1-yl)sulfonyl]phenyl}ethynyl)phenoxy]acetic acid (20p).** Prepared according to Sonogashira general method 3, starting from *tert*-butyl (4-chloro-2-ethynylphenoxy)acetate (**16a**) and 1-[(3-bromo-4-methylphenyl)sulfonyl]-4-methylpiperazine (**12w**), the title compound was obtained as a white solid after filtration from the reaction mixture. <sup>1</sup>H NMR (300MHz, DMSO- $d_6$ )  $\delta$  [ppm] 7.84 (1H, d,  $J$  = 1.7 Hz), 7.73-7.65 (3H, m), 7.45 (1H, dd,  $J$  = 9.0 Hz,  $J$  = 2.7 Hz), 7.05 (1H, d,  $J$  = 9.0 Hz), 4.84 (2H, s), 3.79 (2H, bs), 3.36 (4H, bs), 3.19 (2H, bs), 2.74 (3H, s), 2.60 (3H, s). MS (ESI<sup>-</sup>): 461.0. HPLC (Condition A): Rt 3.31 min (HPLC purity 99.7%).

**{4-Chloro-2-[(5-{[3-(dimethylamino)propyl](methyl)amino}sulfonyl]-2-methylphenyl}ethynyl)phenoxy}acetic acid (20q).** Prepared according to Sonogashira general method 3, starting from *tert*-butyl (4-chloro-2-ethynylphenoxy)acetate (**16a**) and 3-bromo-*N*-[3-(dimethylamino)propyl]-*N*,4-dimethylbenzenesulfonamide (**12x**), the title compound was obtained as a white solid. <sup>1</sup>H NMR (300MHz, DMSO- $d_6$ )  $\delta$  [ppm] 7.83 (1H, d,  $J$  = 1.9 Hz), 7.71 (1H, dd,  $J$  = 8.0 Hz,  $J$  = 1.9 Hz), 7.65 (1H, d,  $J$  = 2.7 Hz), 7.61 (1H, d,  $J$  = 8.0 Hz), 7.45 (1H, dd,  $J$  = 9.0 Hz,  $J$  = 2.7 Hz), 7.04 (1H, d,  $J$  = 9.0 Hz), 4.83 (2H, s), 3.04 (4H, m), 2.75 (6H, s), 2.70 (3H, s), 2.57 (3H, s), 1.89 (2H, m). MS (ESI<sup>-</sup>): 477.2. HPLC (Condition A): Rt 3.57 min (HPLC purity 98.8%).



**{4-Chloro-2-[(5-{[2-(dimethylamino)ethyl](methylamino)sulfonyl}-2-methylphenyl)ethynyl]phenoxy}acetic acid (20r).** Prepared according to Sonogashira general method 3, starting from *tert*-butyl (4-chloro-2-ethynylphenoxy)acetate (**16a**) and bromo-*N*-[2-(dimethylamino)ethyl]-*N*,4-dimethylbenzenesulfonamide (**12y**), the title compound was obtained as a beige solid after purification by preparative HPLC. <sup>1</sup>H NMR (300MHz, DMSO-*d*<sub>6</sub>) δ [ppm] 7.95 (1H, t, *J*= 2.0 Hz), 7.69 (1H, dd, *J*= 8.0 Hz, *J*= 2.0 Hz), 7.61-7.58 (2H, m), 7.42 (1H, dd, *J*= 9.0 Hz, *J*= 2.7 Hz), 7.05 (1H, d, *J*= 9.0 Hz), 4.54 (2H, s), 3.23 (2H, m), 2.83 (2H, m), 2.69 (3H, s), 2.56 (3H, s), 2.43 (6H, s). MS (ESI<sup>+</sup>): 463.0. HPLC (Condition A): Rt 3.47 min (HPLC purity 99.1%).

**(4-Chloro-2-{[4-(methylsulfonyl)phenyl]ethynyl}phenoxy)acetic acid (21a).** Prepared according to Sonogashira general method 3, starting from *tert*-butyl (4-chloro-2-ethynylphenoxy)acetate (**16a**) and 4-bromophenyl methyl sulfone, the title compound was obtained as a white solid after purification by preparative HPLC. <sup>1</sup>H NMR (300MHz, DMSO-*d*<sub>6</sub>) δ [ppm] 13.20 (1H, bs), 7.98 (2H, d, *J*= 8.5 Hz), 7.80 (2H, d, *J*= 8.5 Hz), 7.63 (1H, d, *J*= 2.7 Hz), 7.45 (1H, dd, *J*= 9.0 Hz, *J*= 2.7 Hz), 7.02 (1H, d, *J*= 9.0 Hz), 4.84 (2H, s), 3.27 (3H, s). MS (ESI<sup>+</sup>): 363.0. HPLC (Condition A): Rt 3.91 min (HPLC purity 100%).

**[4-Chloro-2-({4-[(dimethylamino)carbonyl]phenyl}ethynyl)phenoxy]acetic acid (21b).** Prepared according to Sonogashira general method 3, starting from *tert*-butyl (4-chloro-2-ethynylphenoxy)acetate (**16a**) and 4-bromo-*N,N*-dimethylbenzamide, the title compound was obtained as a beige solid after purification by preparative HPLC. <sup>1</sup>H NMR (300MHz, DMSO-*d*<sub>6</sub>) δ [ppm] 13.15 (1H, bs), 7.61-7.58 (3H, m), 7.47-7.40 (3H, m), 7.01 (1H, d, *J*= 9.0 Hz), 4.84 (2H, s), 2.99 (3H, s), 2.92 (3H, s). MS (ESI<sup>+</sup>): 356.1. HPLC (Condition A): Rt 4.21 min (HPLC purity 95.8%).

**[4-Chloro-2-({3-[(dimethylamino)carbonyl]phenyl}ethynyl)phenoxy]acetic acid (21c).**

Prepared according to Sonogashira general method 3, starting from *tert*-butyl (4-chloro-2-ethynylphenoxy)acetate (**16a**) and 3-bromo-*N,N*-dimethylbenzamide, the title compound was obtained as a white solid after purification by preparative HPLC. <sup>1</sup>H NMR (300MHz, DMSO-*d*<sub>6</sub>) δ [ppm] 13.17 (1H, bs), 7.62-7.39 (6H, m), 6.99 (1H, d, *J*= 9.0 Hz), 4.82 (2H, s), 2.99 (3H, s), 2.92 (3H, s). MS (ESI<sup>+</sup>): 356.0. HPLC (Condition A): Rt 3.78 min (HPLC purity 100%).

**[4-Chloro-2-({3-[(methylsulfonyl)methyl]phenyl}ethynyl)phenoxy]acetic acid (21d).**

Prepared according to Sonogashira general method 5, starting from *tert*-butyl (4-chloro-2-ethynylphenoxy)acetate (**16a**) and 3-bromobenzylmethylsulfone, the title compound was obtained as a white solid after purification by preparative HPLC. <sup>1</sup>H NMR (300MHz, DMSO-*d*<sub>6</sub>) δ [ppm] 13.16 (1H, bs), 7.59-7.55 (3H, m), 7.48-7.46 (2H, m), 7.41 (1H, dd, *J*= 9.0 Hz, *J*= 2.7 Hz), 7.00 (1H, d, *J*= 9.0 Hz), 4.84 (2H, s), 4.54 (2H, s), 2.93 (3H, s). MS (ESI<sup>+</sup>): 377.0. HPLC (Condition A): Rt 3.82 min (HPLC purity 94.8%).

**(4-Chloro-2-{[2-methyl-5-(propylsulfinyl)phenyl]ethynyl}phenoxy)acetic acid (21e). A**

solution of 3-bromo-4-methyl-benzenethiol (1.27 g; 6.25 mmol) in anhydrous DMF (12.5 ml) was treated with sodium hydride (300 mg; 7.5 mmol). Then reaction mixture was stirred at RT for 15 minutes, then the treated with 1-iodopropane (0.73 ml; 7.5 mmol). The reaction was stirred for 24 hours, before being quenched by dropwise addition of water. EtOAc was added and the layers separated. The organic layer was washed with brine, dried on MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. The residue was dissolved in MeOH (13 mL), cooled to 0 °C and treated with a 0.5 M solution of sodium (meta)periodate in water (12.5 ml;

6.24 mmol). After stirring for 24 hours at RT, EtOAc and water were added and the phases separated and the organic phase was dried over MgSO<sub>4</sub> and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (silica), eluting with cyclohexane containing increasing amounts of EtOAc to give 2-bromo-1-methyl-4-(propylsulfinyl)benzene **51** (771 mg, 47%) as a yellow sticky solid. <sup>1</sup>H NMR (300MHz, DMSO-d<sub>6</sub>) δ [ppm] 8.28 (1H, s), 8.00 (2H, m), 3.40-3.15 (2H, m), 2.91 (3H, s), 2.28-1.96 (2H, m), 1.48 (3H, t, *J* = 7.4 Hz).

A solution of (4-chloro-2-ethynyl-phenoxy)-acetic acid *tert*-butyl ester (**16a**; 500 mg; 1.87 mmol) in MeOH (10 ml) was treated with a 1.25 N solution of HCl in methanol (1.5 ml). The solution was heated at 60 °C for 24 hours. The solvents were removed under reduced pressure to give methyl (4-chloro-2-ethynylphenoxy)acetate compound as an oil which solidifies upon standing (445 mg, quant.). <sup>1</sup>H NMR (300MHz, DMSO-d<sub>6</sub>) δ [ppm] 7.47 (1H, d, *J* = 2.7 Hz), 7.38 (1H, dd, *J* = 9.0 Hz, *J* = 2.7 Hz), 6.98 (1H, d, *J* = 9.0 Hz), 4.91 (2H, s), 4.40 (1H, s), 3.68 (3H, s).

Following the Sonogashira general method 4, starting from methyl (4-chloro-2-ethynylphenoxy)acetate and 2-bromo-1-methyl-4-(propylsulfinyl)benzene, methyl (4-chloro-2-{[2-methyl-5-(propylsulfinyl)phenyl]ethynyl}phenoxy)acetate was obtained as a yellow oil (128 mg, 24%) after purification by flash column chromatography (silica). <sup>1</sup>H NMR (300MHz, DMSO-d<sub>6</sub>) δ [ppm] 7.75 (1H, d, *J* = 1.6 Hz), 7.63-7.52 (3H, m), 7.43 (1H, dd, *J* = 9.0 Hz, *J* = 2.7 Hz), 7.08 (1H, d, *J* = 9.0 Hz), 4.96 (2H, s), 3.72 (3H, s), 2.94 (1H, m), 2.78 (1H, m), 2.54 (3H, s), 1.64 (1H, m), 1.47 (1H, m), 0.97 (3H, t, *J* = 7.4 Hz).

A solution of methyl (4-chloro-2-{[2-methyl-5-(propylsulfinyl)phenyl]ethynyl}phenoxy)acetate (**52**, 125 mg; 0.31 mmol) in MeOH (5 ml) was treated with a 1M solution of sodium hydroxide in water (0.93 ml; 0.93 mmol). After stirring for 3 hours, the solvent was removed under reduced pressure, the residue was taken up in AcOEt and extracted with 0.1N HCl. The

organic phase was dried on  $\text{MgSO}_4$  and concentrated to give a residue which was triturated in diethyl ether, to afford 4-chloro-2-([2-methyl-5-(propylsulfinyl)phenyl]ethynyl)phenoxy)acetic acid **21e** as a pale yellow solid (101 mg, 83%).  $^1\text{H}$  NMR (300MHz,  $\text{DMSO-d}_6$ )  $\delta$  [ppm] 13.2 (1H, bs), 7.73 (1H, d,  $J = 1.6$  Hz), 7.62-7.52 (3H, m), 7.43 (1H, dd,  $J = 9.0$  Hz,  $J = 2.7$  Hz), 7.03 (1H, d,  $J = 9.0$  Hz), 4.83 (2H, s), 2.96 (1H, m), 2.77 (1H, m), 2.54 (3H, s), 1.65 (1H, m), 1.46 (1H, m), 0.97 (3H, t,  $J = 7.4$  Hz). MS (ESI $^-$ ): 389.1. HPLC (Condition A): Rt 4.15 min (HPLC purity 98.8%).

**[4-Chloro-2-([2-methyl-5-[(methylsulfonyl)amino]phenyl]ethynyl)phenoxy]acetic acid (21f)**. Prepared according to Sonogashira general method 3, starting from *tert*-butyl (4-chloro-2-ethynylphenoxy)acetate (**16a**) and *N*-(3-bromo-4-methylphenyl)methanesulfonamide, the title compound was obtained as a pink solid after purification by preparative HPLC.  $^1\text{H}$  NMR (300MHz,  $\text{DMSO-d}_6$ )  $\delta$  [ppm] 13.18 (1H, bs), 9.73 (1H, s), 7.58 (1H, d,  $J = 2.7$  Hz), 7.40 (1H, dd,  $J = 9.0$  Hz,  $J = 2.7$  Hz), 7.30-7.28 (2H, m), 7.16 (1H, dd,  $J = 8.2$ ,  $J = 2.3$  Hz), 7.00 (1H, d,  $J = 9.0$  Hz), 4.81 (2H, s), 2.98 (3H, s), 2.42 (3H, s). MS (ESI $^-$ ): 392.0. HPLC (Condition A): Rt 4.17 min (HPLC purity 99.9%).

**[4-Chloro-2-([2-methyl-5-[methyl(methylsulfonyl)amino]phenyl]ethynyl)phenoxy]acetic acid (21g)**. Prepared according to Sonogashira general method 3, starting from *tert*-butyl (4-chloro-2-ethynylphenoxy)acetate (**16a**) and *N*-(3-bromo-4-methylphenyl)-*N*-methylmethanesulfonamide (**75d**), the title compound was obtained as a white solid after purification by preparative HPLC.  $^1\text{H}$  NMR (300MHz,  $\text{DMSO-d}_6$ )  $\delta$  [ppm] 13.17 (1H, bs), 7.58 (1H, d,  $J = 2.7$  Hz), 7.52 (1H, m), 7.42 (1H, dd,  $J = 9.0$  Hz,  $J = 2.7$  Hz), 7.36 (2H, m),

7.02 (1H, d,  $J$  = 9.0 Hz), 4.82 (2H, s), 3.24 (3H, s), 2.95 (3H, s), 2.46 (3H, s). MS (ESI<sup>+</sup>): 406.0. HPLC (Condition A): Rt 4.23 min (HPLC purity 99.8%).

**(4-Chloro-2-{{5-(methylsulfonyl)pyridin-3-yl}ethynyl}phenoxy)acetic acid (21h).**

Prepared according to Sonogashira general method 5, starting from *tert*-butyl (4-chloro-2-ethynylphenoxy)acetate (**16a**) and 5-bromo-3-methylsulfonylpyridine, the title compound was obtained as a white solid after purification by flash column chromatography (silica). <sup>1</sup>H NMR (300MHz, DMSO-*d*<sub>6</sub>)  $\delta$  [ppm] 9.06-9.04 (2H, m) 8.45 (1H, t,  $J$  = 2.0 Hz), 7.66 (1H, d,  $J$  = 2.7 Hz), 7.47 (1H, dd,  $J$  = 9.0 Hz,  $J$  = 2.7 Hz), 7.04 (1H, d,  $J$  = 9.0 Hz), 4.85 (2H, s) 3.39 (3H, s). MS (ESI<sup>+</sup>): 363.9. HPLC (Condition A): Rt 3.93 min (HPLC purity 98.9%).

**[4-Chloro-2-{{5-[(dimethylamino)sulfonyl]pyridin-3-yl}ethynyl}phenoxy]acetic acid (21i).**

Prepared according to Sonogashira general method 5, starting from *tert*-butyl (4-chloro-2-ethynylphenoxy)acetate (**16a**) and 5-bromo-pyridine-3-sulfonic acid dimethylamide (**75b**), the title compound was obtained as a white solid after precipitation from the reaction mixture. <sup>1</sup>H NMR (300MHz, DMSO-*d*<sub>6</sub>)  $\delta$  [ppm] 13.17 (1H, bs), 9.01 (1H, d,  $J$  = 1.9 Hz), 8.91 (1H, d,  $J$  = 2.1 Hz), 8.26 (1H, d,  $J$  = 2.1 Hz), 7.67 (1H, d,  $J$  = 2.6 Hz), 7.47 (1H, dd,  $J$  = 8.9 Hz,  $J$  = 2.6 Hz), 7.04 (1H, d,  $J$  = 9.0 Hz), 4.85 (2H, s), 2.70 (6H, s). MS (ESI<sup>+</sup>): 393.0. HPLC (Condition A): Rt 4.40 min (HPLC purity 98.2%).

**[4-Chloro-2-{{5-[(methylsulfonyl)amino]pyridin-3-yl}ethynyl}phenoxy]acetic acid (21j).**

Prepared according to Sonogashira general method 5, starting from *tert*-butyl (4-chloro-2-ethynylphenoxy)acetate (**16a**) and *N*-(5-bromopyridin-3-yl)methanesulfonamide, the title compound was obtained as a beige solid after after purification by preparative HPLC. <sup>1</sup>H NMR (300MHz, DMSO-*d*<sub>6</sub>)  $\delta$  [ppm] 10.24 (1H, s), 8.47 (1H, d,  $J$  = 1.6 Hz), 8.43-8.40 (1H,

m), 7.70 (1H, d,  $J$  = 2.3 Hz), 7.63 (1H, d,  $J$  = 2.6 Hz), 7.44 (1H, dd,  $J$  = 8.9 Hz,  $J$  = 2.6 Hz), 7.00 (1H, d,  $J$  = 9.0 Hz), 4.84 (2H, s), 3.12 (3H, s). MS (ESI<sup>+</sup>): 381.0. HPLC (Condition A): Rt 3.66 min (HPLC purity 95.4%).

**[4-Chloro-2-({5-[methyl(methylsulfonyl)amino]pyridin-3-yl}ethynyl)phenoxy]acetic acid (21k).** Prepared according to Sonogashira general method 3, starting from *tert*-butyl (4-chloro-2-ethynylphenoxy)acetate (**16a**) and *N*-(5-bromopyridin-3-yl)-*N*-methylmethanesulfonamide (**75c**), the title compound was obtained as a white solid after purification by preparative HPLC. <sup>1</sup>H NMR (300MHz, DMSO-d<sub>6</sub>) δ [ppm] 8.64-8.62 (2H, m), 8.03 (1H, t,  $J$  = 6.9 Hz), 7.61 (1H, d,  $J$  = 2.6 Hz), 7.44 (1H, dd,  $J$  = 8.9 Hz,  $J$  = 2.6 Hz), 7.01 (1H, d,  $J$  = 9.0 Hz), 4.83 (2H, s), 3.32 (3H, s), 3.05 (3H, s). MS (ESI<sup>+</sup>): 395.0. HPLC (Condition A): Rt 4.93 min (HPLC purity 99.0%).

**{4-Chloro-2-[(5-[(2-hydroxyethyl)amino]sulfonyl)pyridin-3-yl]ethynyl}phenoxy}acetic acid (21l).** Prepared according to Sonogashira general method 3, starting from *tert*-butyl (4-chloro-2-ethynylphenoxy)acetate (**16a**) and 5-bromo-*N*-(2-hydroxyethyl)pyridine-3-sulfonamide (**75a**), the title compound was obtained as an off-white solid. <sup>1</sup>H NMR (300MHz, DMSO-d<sub>6</sub>) δ [ppm] 8.95 (1H, d,  $J$  = 2.2 Hz), 8.91 (1H, d,  $J$  = 2.0 Hz), 8.31 (1H, d,  $J$  = 1.8 Hz), 8.02 (1H, bs), 7.64 (1H, d,  $J$  = 2.6 Hz), 7.44 (1H, dd,  $J$  = 9.0 Hz,  $J$  = 2.6 Hz), 6.98 (1H, d,  $J$  = 9.0 Hz), 4.71 (2H, s), 3.39-3.36 (2H, m), 2.99 (1H, bs), 2.90-2.88 (2H, m). MS (ESI<sup>+</sup>): 410.8. HPLC (Condition A): Rt 3.73 min (HPLC purity 93.5%).

**(4-Chloro-2-{[5-(morpholin-4-ylsulfonyl)pyridin-3-yl]ethynyl}phenoxy)acetic acid (21m).** Prepared according to Sonogashira general method 5, starting from *tert*-butyl (4-chloro-2-ethynylphenoxy)acetate (**16a**) and 4-[(5-bromopyridin-3-yl)sulfonyl]morpholine, the

title compound was obtained as an off-white solid. <sup>1</sup>H NMR (300MHz, DMSO-d<sub>6</sub>) δ [ppm] 9.04 (1H, d, *J*= 2.0 Hz), 8.90 (1H, d, *J*= 2.0 Hz), 8.25 (1H, t, *J*= 2.0 Hz), 7.67 (1H, d, *J*= 2.6 Hz), 7.47 (1H, dd, *J*= 9.0 Hz, *J*= 2.6 Hz), 7.04 (1H, d, *J*= 9.0 Hz), 4.85 (2H, s), 3.64 (4H, t, *J*= 4.7 Hz), 3.00 (4H, t, *J*= 4.7 Hz). MS (ESI<sup>+</sup>): 435.0. HPLC (Condition A): Rt 4.36 min (HPLC purity 98.4%).

**[4-Chloro-2-({5-[(dimethylamino)sulfonyl]-2-methylpyridin-3-yl}ethynyl)phenoxy]acetic acid (21n).** Prepared according to Sonogashira general method 5, starting from *tert*-butyl (4-chloro-2-ethynylphenoxy)acetate (**16a**) and 5-bromo-*N,N*,6-trimethylpyridine-3-sulfonamide (**75e**), the title compound was obtained as an off-white solid after precipitation from the reaction mixture. <sup>1</sup>H NMR (300MHz, DMSO-d<sub>6</sub>) δ [ppm] 13.4 (1H, bs), 8.77 (1H, d, *J*= 2.2 Hz), 8.18 (1H, d, *J*= 2.2 Hz), 7.70 (1H, d, *J*= 2.7 Hz), 7.48 (1H, dd, *J*= 9.0 Hz, *J*= 2.7 Hz), 7.08 (1H, d, *J*= 9.0 Hz), 4.85 (2H, s), 2.79 (3H, s), 2.69 (6H, s). MS (ESI<sup>-</sup>): 407.1. HPLC (Condition A): Rt 3.93 min (HPLC purity 99.1%).

**{4-Chloro-2-[(1,1-dioxido-1-benzothien-6-yl)ethynyl]phenoxy}acetic acid (21p).** Prepared according to Sonogashira general method 4, starting from *tert*-butyl (4-chloro-2-ethynylphenoxy)acetate (**16a**) and 6-iodo-1-benzothiophene 1,1-dioxide (**38d**), the title compound was obtained as a beige solid. <sup>1</sup>H NMR (300MHz, DMSO-d<sub>6</sub>) δ [ppm] 13.19 (1H, bs), 8.04 (1H, m), 7.83 (1H, dd, *J*= 7.9 Hz, *J*= 1.4 Hz), 7.70-7.65 (2H, m), 7.63 (1H, d, *J*= 2.7 Hz), 7.49 (1H, d, *J*= 7.0 Hz), 7.45 (1H, dd, *J*= 9.0 Hz, *J*= 2.7 Hz), 7.03 (1H, d, *J*= 9.0 Hz), 4.85 (2H, s). MS (ESI<sup>-</sup>): 373.0. HPLC (Condition A): Rt 4.03 min (HPLC purity 94.8%).

**[4-Chloro-2-[(1,1-dioxido-2,3-dihydro-1-benzothien-6-yl)ethynyl]phenoxy]acetic acid (21q).** Prepared according to Sonogashira general method 3, starting from *tert*-butyl (4-

chloro-2-ethynylphenoxy)acetate (**16a**) and 6-iodo-2,3-dihydro-1-benzothiophene 1,1-dioxide (**38f**), the title compound was obtained as a beige solid after trituration in DCM / pentane. <sup>1</sup>H NMR (300MHz, DMSO-d<sub>6</sub>) δ [ppm] 13.17 (1H, bs), 7.90 (1H,m), 7.80 (1H, dd, *J*= 8.0 Hz, *J*= 1.5 Hz), 7.63-7.60 (2H, m), 7.43 (1H, dd, *J*= 9.0 Hz, *J*= 2.7 Hz), 7.02 (1H, d, *J*= 9.0 Hz), 4.84 (2H, s), 3.65 (2H, t, *J*= 6.8 Hz), 3.40 (2H, t, *J*= 6.8 Hz). MS (ESI): 375.0. HPLC (Condition A): Rt 3.89 min (HPLC purity 97.8%).

**{2-[(2-*tert*-Butyl-1,1-dioxido-3-oxo-2,3-dihydro-1,2-benzisothiazol-6-yl)ethynyl]-4-chlorophenoxy}acetic acid (21r)**. A mixture of (4-chloro-2-ethynylphenoxy)acetic acid (**16a**; 211 mg; 1.00 mmol), 6-bromo-2-*tert*-butyl-1,2-benzisothiazol-3(2*H*)-one-1,1-dioxide (382 mg; 1.20 mmol, prepared according to Xu, L.; Shu, H.; Liu, Y.; Zhang, S.; Trudell, M.L. *Tetrahedron* **2006**, 62, 7902-7910), Pd(PPh<sub>3</sub>)Cl<sub>2</sub> (70 mg; 0.10 mmol) and CuI (9.5 mg; 0.05 mmol) in anhydrous THF (4 ml) was degassed for 10 minutes then treated with triethylamine (1.00 ml; 7.21 mmol) and the mixture stirred at 60 °C for 16 h. EtOAc was added and the organic phase washed with a sat. NH<sub>4</sub>Cl solution then brine. The organic phase was dried on MgSO<sub>4</sub>, filtered and concentrated under reduced pressure to give a residue which was purified by preparative HPLC to afford the title compound (24 mg, 6%) as a white solid. <sup>1</sup>H NMR (300MHz, DMSO-d<sub>6</sub>) δ [ppm] 13.2 (1H, bs), 8.42 (1H, t, *J*= 0.9 Hz), 8.09-8.02 (2H, m), 7.67 (1H, d, *J*= 2.7 Hz), 7.48 (1H, dd, *J*= 9.0 Hz, *J*= 2.7 Hz), 7.06 (1H, d, *J*= 9.0 Hz), 4.87 (2H, s), 1.70 (9H, s). MS (ESI): 446.1. HPLC (Condition A): Rt 4.86 min (HPLC purity 96.6%).

**{4-Chloro-2-[(2,2-dimethyl-1,1-dioxido-3-oxo-2,3-dihydro-1-benzothien-6-yl)ethynyl]phenoxy}acetic acid (21s)**. Prepared according to Sonogashira general method 4, starting from *tert*-butyl (4-chloro-2-ethynylphenoxy)acetate (**16a**) and 6-bromo-2,2-dimethyl-1-benzothiophen-3(2*H*)-one 1,1-dioxide (**62**), the title compound was obtained as a yellow



solid.  $^1\text{H}$  NMR (300MHz, DMSO- $\text{d}_6$ )  $\delta$  [ppm] 13.2 (1H, bs), 8.38 (1H, m), 8.11-8.03 (2H, m), 7.69 (1H, d,  $J$  = 2.7 Hz), 7.49 (1H, dd,  $J$  = 9.0 Hz;  $J$  = 2.7 Hz), 7.06 (1H, d,  $J$  = 9.0 Hz), 4.87 (2H, s), 1.52 (6H, s). MS (ESI $^-$ ): 417.1. HPLC (Condition A): Rt 4.53 min (HPLC purity 95.6%).

**{4-Chloro-2-[(3-hydroxy-2,2-dimethyl-1,1-dioxido-2,3-dihydro-1-benzothien-6-yl)ethynyl]phenoxy}acetic acid (21t)**. Prepared according to Sonogashira general method 4, starting from *tert*-butyl (4-chloro-2-ethynylphenoxy)acetate (**16a**) and 6-bromo-2,2-dimethyl-2,3-dihydro-1-benzothiophene-3-ol 1,1-dioxide (**64**), the title compound was obtained as a yellow solid after purification by preparative HPLC.  $^1\text{H}$  NMR (300MHz, DMSO- $\text{d}_6$ )  $\delta$  [ppm] 13.2 (1H, bs), 7.94 (1H, m), 7.86 (1H, dd,  $J$  = 8.0;  $J$  = 1.5 Hz), 7.69 (1H, d,  $J$  = 8.0 Hz), 7.62 (1H, d,  $J$  = 2.7 Hz), 7.44 (1H, dd,  $J$  = 9;  $J$  = 2.7 Hz), 7.01 (1H, d,  $J$  = 9 Hz), 6.58 (1H, bs), 4.96 (1H, s), 4.82 (2H, s), 1.42 (3H, s), 1.13 (3H, s). MS (ESI $^-$ ): 419.2. HPLC (Condition A): Rt 3.89 min (HPLC purity 99.8%).

**{4-Chloro-2-[(3-hydroxy-2,2,3-trimethyl-1,1-dioxido-2,3-dihydro-1-benzothien-6-yl)ethynyl]phenoxy}acetic acid (21u)**. Prepared according to Sonogashira general method 4, starting from *tert*-butyl (4-chloro-2-ethynylphenoxy)acetate (**16a**) and 6-bromo-2,2,3-trimethyl-2,3-dihydro-1-benzothiophene-3-ol 1,1-dioxide (**65**), the title compound was obtained as a yellow solid after purification by preparative HPLC and precipitation from pentane.  $^1\text{H}$  NMR (300MHz, DMSO- $\text{d}_6$ )  $\delta$  [ppm] 13.24 – 13.18 (1H, bs), 7.95 – 7.82 (2H, m), 7.75 (1H, d,  $J$  = 8.0), 7.62 (1H, d,  $J$  = 2.7), 7.44 (1H dd,  $J$  = 9.0, 2.7), 7.02 (1H, d,  $J$  = 9.0), 6.12 (1H, bs), 4.83 (2H, s), 1.48 (3H, s), 1.34 (3H, s), 1.21 (3H, s). MS (ESI $^-$ ): 433.2. HPLC (Condition A): Rt 3.98 min (HPLC purity 100%).

**{4-Chloro-2-[(3-methoxy-2,2-dimethyl-1,1-dioxido-2,3-dihydro-1-benzothien-6-yl)ethynyl]phenoxy}acetic acid (21v).** Prepared according to Sonogashira general method 4, starting from *tert*-butyl (4-chloro-2-ethynylphenoxy)acetate (**16a**) and 6-bromo-2,2-dimethyl-1,1-dioxido-2,3-dihydro-1-benzothien-3-yl methyl ether (**66**), the title compound was obtained as a yellow solid after purification by preparative HPLC. <sup>1</sup>H NMR (300MHz, DMSO-d<sub>6</sub>) δ [ppm] 7.97 (1H, bs), 7.87 (1H, dd, *J* = 7.8 Hz, *J* = 1.8 Hz), 7.74 (1H, d, *J* = 8.1 Hz), 7.61 (1H, d, *J* = 2.8 Hz), 7.43 (1H, dd, *J* = 8.9, 2.8 Hz), 7.00 (1H, d, *J* = 8.9 Hz), 4.80 (2H, s), 4.76 (1H, s), 3.56 (3H, s), 1.42 (3H, s), 1.27 (3H, s). MS (ESI<sup>+</sup>): 433.2. HPLC (Condition A): Rt 4.84 min (HPLC purity 100%).

**{4-Chloro-2-[(3-methoxy-2,2,3-trimethyl-1,1-dioxido-2,3-dihydro-1-benzothien-6-yl)ethynyl]phenoxy}acetic acid (21w).** Prepared according to Sonogashira general method 4, starting from *tert*-butyl (4-chloro-2-ethynylphenoxy)acetate (**16a**) and 6-bromo-2,2,3-trimethyl-1,1-dioxido-2,3-dihydro-1-benzothien-3-yl methyl ether (**67**), the title compound was obtained as a yellow solid after purification by preparative HPLC. <sup>1</sup>H NMR (300MHz, DMSO-d<sub>6</sub>) δ [ppm] 13.01 (1H, bs), 7.97 (1H, d, *J* = 1.2 Hz), 7.87 (1H, dd, *J* = 8.0, *J* = 1.4 Hz), 7.82 (1H, d, *J* = 8.1 Hz), 7.62 (1H, d, *J* = 2.6 Hz), 7.43 (1H, dd, *J* = 8.9, *J* = 2.6 Hz), 7.02 (1H, d, *J* = 9.1 Hz), 4.84 (2H, s), 3.06 (3H, s), 1.55 (3H, s), 1.34 (3H, s), 1.24 (3H, s). MS (ESI<sup>+</sup>): 447.2. HPLC (Condition A): Rt 4.91 min (HPLC purity 99.7%).

**(4-Chloro-2-{[2-(methylsulfonyl)biphenyl-4-yl]ethynyl}phenoxy)acetic acid (22a)**

Prepared according to Sonogashira general method 4, starting from *tert*-butyl (4-chloro-2-ethynylphenoxy)acetate (**16a**) and 4-bromo-2-(methylsulfonyl)biphenyl (**79a**), the title compound was obtained as a white solid after purification by preparative HPLC. <sup>1</sup>H NMR (300MHz, DMSO-d<sub>6</sub>) δ [ppm] 13.23 (1H, bs), 8.18 (1H, d, *J* = 1.8 Hz), 7.89 (1H, dd, *J* = 7.9

Hz,  $J = 1.8$  Hz), 7.68 (1H, d,  $J = 2.7$  Hz), 7.43 (7H, m), 7.02 (1H, d,  $J = 9.0$  Hz), 4.84 (2H, s), 2.88 (3H, s). MS (ESI<sup>-</sup>): 439.2. HPLC (Condition A): Rt 4.78 min (HPLC purity 98.8%).

**(4-Chloro-2-{{4'-methoxy-2-(methylsulfonyl)biphenyl-4-yl}ethynyl}phenoxy)acetic acid (22b).** Prepared according to Sonogashira general method 4, starting from *tert*-butyl (4-chloro-2-ethynylphenoxy)acetate (**16a**) and 4-bromo-4'-methoxy-2-(methylsulfonyl)biphenyl (**79b**), the title compound was obtained as a beige solid after purification by preparative HPLC. <sup>1</sup>H NMR (300MHz, DMSO-*d*<sub>6</sub>)  $\delta$  [ppm] 13.21 (1H, bs), 8.17 (1H, d,  $J = 1.8$  Hz), 7.87 (1H, dd,  $J = 8.0$  Hz,  $J = 1.8$  Hz), 7.67 (1H, d,  $J = 2.7$  Hz), 7.47-7.43 (2H, m), 7.38 (2H, d,  $J = 8.7$  Hz), 7.05-7.00 (3H, m), 4.85 (2H, s), 3.82 (3H, s), 2.85 (3H, s). MS (ESI<sup>-</sup>): 469.1. HPLC (Condition A): Rt 4.76 min (HPLC purity 95.7%).

**(4-Chloro-2-{{3'-methoxy-2-(methylsulfonyl)biphenyl-4-yl}ethynyl}phenoxy)acetic acid (22c).** Prepared according to Sonogashira general method 4, starting from *tert*-butyl (4-chloro-2-ethynylphenoxy)acetate (**16a**) and 4-bromo-3'-methoxy-2-(methylsulfonyl)biphenyl (**79c**), the title compound was obtained as a white solid after purification by preparative HPLC. <sup>1</sup>H NMR (300MHz, DMSO-*d*<sub>6</sub>)  $\delta$  [ppm] 8.17 (1H, d,  $J = 1.8$  Hz), 7.89 (1H, dd,  $J = 8.0$  Hz,  $J = 1.8$  Hz), 7.66 (1H, d,  $J = 2.7$  Hz), 7.48 (1H, d,  $J = 8.0$  Hz), 7.45-7.36 (2H, m), 7.06-6.96 (4H, m), 4.74 (2H, s), 3.79 (3H, s), 2.90 (3H, s). MS (ESI<sup>-</sup>): 469.2. HPLC (Condition A): Rt 4.78 min (HPLC purity 99.0%).

**(4-Chloro-2-{{2-(methylsulfonyl)-4'-(trifluoromethyl)biphenyl-4-yl}ethynyl}phenoxy)acetic acid (22d).** Prepared according to Sonogashira general method 4, starting from *tert*-butyl (4-chloro-2-ethynylphenoxy)acetate (**16a**) and 4-bromo-2-(methylsulfonyl)-4'-(trifluoromethyl)biphenyl (**79d**), the title compound was obtained as a

beige solid after purification by preparative HPLC.  $^1\text{H}$  NMR (300MHz, DMSO- $\text{d}_6$ )  $\delta$  [ppm] 13.21 (1H, bs), 8.21 (1H, d,  $J$  = 1.7 Hz), 7.93 (1H, dd,  $J$  = 7.9 Hz,  $J$  = 1.7 Hz), 7.83 (2H, d,  $J$  = 8.1 Hz), 7.68-7.65 (3H, m), 7.51 (1H, d,  $J$  = 7.9 Hz), 7.46 (1H, dd,  $J$  = 9.0 Hz,  $J$  = 2.7 Hz), 7.02 (1H, d,  $J$  = 9.0 Hz), 4.85 (2H, s), 3.03 (3H, s). MS (ESI $^-$ ): 507.2. HPLC (Condition A): Rt 5.23 min (HPLC purity 98.2%).

**(4-Chloro-2-{{4'-chloro-2-(methylsulfonyl)biphenyl-4-yl}ethynyl}phenoxy)acetic acid (22e).** Prepared according to Sonogashira general method 4, starting from *tert*-butyl (4-chloro-2-ethynylphenoxy)acetate (**16a**) and 4-bromo-4'-chloro-2-(methylsulfonyl)biphenyl (**79e**), the title compound was obtained as a beige solid after purification by preparative HPLC.  $^1\text{H}$  NMR (300MHz, DMSO- $\text{d}_6$ )  $\delta$  [ppm] 13.22 (1H, bs), 8.18 (1H, d,  $J$  = 1.7 Hz), 7.90 (1H, dd,  $J$  = 7.9 Hz,  $J$  = 1.7 Hz), 7.67 (1H, d,  $J$  = 2.7 Hz), 7.531 (2H, d,  $J$  = 8.6 Hz), 7.49-7.43 (4H, m), 7.02 (1H, d,  $J$  = 9.0 Hz), 4.85 (2H, s), 2.97 (3H, s). MS (ESI $^-$ ): 473.1. HPLC (Condition A): Rt 5.07 min (HPLC purity 97.7%).

**(4-Chloro-2-{{3'-chloro-2-(methylsulfonyl)biphenyl-4-yl}ethynyl}phenoxy)acetic acid (22f).** Prepared according to Sonogashira general method 4, starting from *tert*-butyl (4-chloro-2-ethynylphenoxy)acetate (**16a**) and 4-bromo-3'-chloro-2-(methylsulfonyl)biphenyl (**79f**), the title compound was obtained as a beige solid after purification by preparative HPLC.  $^1\text{H}$  NMR (300MHz, DMSO- $\text{d}_6$ )  $\delta$  [ppm] 13.21 (1H, bs), 8.18 (1H, d,  $J$  = 1.8 Hz), 7.90 (1H, dd,  $J$  = 7.9 Hz,  $J$  = 1.8 Hz), 7.68 (1H, d,  $J$  = 2.7 Hz), 7.56-7.44 (5H, m), 7.40 (1H, dt,  $J$  = 7.1 Hz,  $J$  = 1.6 Hz), 7.03 (1H, d,  $J$  = 9.0 Hz), 4.85 (2H, s), 2.99 (3H, s). MS (ESI $^-$ ): 473.2. HPLC (Condition A): Rt 5.04 min (HPLC purity 100%).

**(4-Chloro-2-{[2'-chloro-2-(methylsulfonyl)biphenyl-4-yl]ethynyl}phenoxy)acetic acid (22g).** Prepared according to Sonogashira general method 4, starting from *tert*-butyl (4-chloro-2-ethynylphenoxy)acetate (**16a**) and 4-bromo-2'-chloro-2-(methylsulfonyl)biphenyl (**79g**), the title compound was obtained as a white solid after purification by preparative HPLC. <sup>1</sup>H NMR (300MHz, DMSO-d<sub>6</sub>) δ [ppm] 13.22 (1H, bs), 8.20 (1H, d, *J* = 1.6 Hz), 7.92 (1H, dd, *J* = 7.9 Hz, *J* = 1.6 Hz), 7.67 (1H, d, *J* = 2.7 Hz), 7.57 (1H, m), 7.50-7.39 (5H, m), 7.03 (1H, d, *J* = 9.0 Hz), 4.86 (2H, s), 3.04 (3H, s). MS (ESI): 473.1 HPLC (Condition A): Rt 4.89 min (HPLC purity 100%).

**(2-{[4-(Acetylamino)-2-methyl-5-(propylsulfonyl)phenyl]ethynyl}-4-chlorophenoxy)acetic acid (22h).** Prepared according to Sonogashira general method 4, starting from *tert*-butyl (4-chloro-2-ethynylphenoxy)acetate (**16a**) and *N*-[4-Bromo-5-methyl-2-(propylsulfonyl)phenyl]acetamide (**73**), the title compound was obtained as a white solid after purification by preparative HPLC. <sup>1</sup>H NMR (300MHz, DMSO-d<sub>6</sub>) δ [ppm] 13.20 (1H, bs), 9.62 (1H, s), 8.12 (1H, s), 7.89 (1H, s), 7.64 (1H, d, *J* = 2.7 Hz), 7.42 (1H, dd, *J* = 9.0 Hz, *J* = 2.7 Hz), 7.02 (1H, d, *J* = 9.0 Hz), 4.823 (2H, s), 3.37 (2H, m), 2.54 (3H, s), 2.15 (3H, s), 1.57 (2H, sext., *J* = 7.5 Hz), 0.93 (3H, t, *J* = 7.5 Hz). MS (ESI): 462.2. HPLC (Condition A): Rt 4.51 min (HPLC purity 97.9%).

**(4-Chloro-2-{[4-[(dimethylamino)carbonyl]-3-(isopropylsulfonyl)phenyl]ethynyl}phenoxy)acetic acid (22i).** Prepared according to Sonogashira general method 4, starting from *tert*-butyl (4-chloro-2-ethynylphenoxy)acetate (**16a**) and 3-bromo-2-(isopropylsulfonyl)-*N,N*-dimethylbenzamide (**69a**), the title compound was obtained as a beige solid after purification by preparative HPLC. <sup>1</sup>H NMR (300MHz, DMSO-d<sub>6</sub>) δ [ppm] 13.20 (1H, bs), 7.98 (1H, d, *J* = 1.6 Hz), 7.93 (1H, dd, *J* = 7.8 Hz; *J* = 1.6

Hz), 7.68 (1H, d,  $J$  = 2.7 Hz), 7.57 (1H, d,  $J$  = 7.8 Hz), 7.45 (1H, dd,  $J$  = 9.0 Hz,  $J$  = 2.7 Hz), 7.01 (1H, d,  $J$  = 9.0 Hz), 4.83 (2H, s), 3.72 (1H, sept.,  $J$  = 6.9 Hz), 2.98 (3H, s), 2.73 (3H, s), 1.29 (3H, m), 1.05 (3H, m). MS (ESI<sup>+</sup>): 432.2. HPLC (Condition A): Rt 3.95 min (HPLC purity 100%).

**(4-Chloro-2-{[4-[(diethylamino)carbonyl]-3-(isopropylsulfonyl)phenyl]ethynyl}phenoxy)acetic acid (22j).** Prepared according to Sonogashira general method 4, starting from *tert*-butyl (4-chloro-2-ethynylphenoxy)acetate (**16a**) and 4-bromo-*N,N*-diethyl-2-(isopropylsulfonyl)benzamide (**69b**), the title compound was obtained as a white solid after purification by preparative HPLC. <sup>1</sup>H NMR (300MHz, DMSO-*d*<sub>6</sub>)  $\delta$  [ppm] 13.19 (1H, bs), 7.97 (1H, d,  $J$  = 1.6 Hz), 7.92 (1H, dd,  $J$  = 7.8 Hz,  $J$  = 1.6 Hz), 7.68 (1H, d,  $J$  = 2.7 Hz), 7.57 (1H, d,  $J$  = 7.8 Hz), 7.45 (1H, dd,  $J$  = 9.0 Hz,  $J$  = 2.7 Hz), 7.02 (1H, d,  $J$  = 9.0 Hz), 4.84 (2H, s), 3.75 (1H, sept.,  $J$  = 6.9 Hz), 3.58 (1H, m), 3.30 (1H, m), 3.12-2.94 (2H, m), 1.29 (3H, d,  $J$  = 6.9 Hz), 1.14 (3H, t,  $J$  = 7.1 Hz), 1.05 (3H, d,  $J$  = 6.9 Hz), 1.03 (3H, t,  $J$  = 7.1 Hz). MS (ESI<sup>+</sup>): 490.3. HPLC (Condition A): Rt 4.88 min (HPLC purity 99.9%). CHN analysis: [C<sub>24</sub>H<sub>26</sub>NO<sub>6</sub>ClS + 0.5 H<sub>2</sub>O] Calculated: C 57.31%, H 5.43%, N 2.77%; Found: C 57.27%, H 5.32%, N 3.00%.

**(4-Chloro-2-{[4-{[ethyl(propyl)amino]carbonyl}-3-(isopropylsulfonyl)phenyl]ethynyl}phenoxy)acetic acid (22k).** Prepared according to Sonogashira general method 4, starting from *tert*-butyl (4-chloro-2-ethynylphenoxy)acetate (**16a**) and 4-[4-bromo-2-(isopropylsulfonyl)benzoyl]morpholine (**69c**), the title compound was obtained as a beige solid after purification by preparative HPLC. <sup>1</sup>H NMR (300MHz, DMSO-*d*<sub>6</sub>)  $\delta$  [ppm] 13.27 (1H, bs), 7.97 (1H, m), 7.94 (1H, dd,  $J$  = 7.8 Hz,  $J$  = 1.6 Hz), 7.68 (1H, d,  $J$  = 2.7 Hz), 7.56 (1H, m), 7.45 (1H, dd,  $J$  = 9.0 Hz,  $J$  = 2.7 Hz), 7.01 (1H, d,  $J$  = 9.0

Hz), 4.85 (2H, s), 3.73 (1H, m), 3.59 (0.5H, m), 3.44 (0.5H, m), 3.26 (1H, m), 3.13-2.79 (2H, m), 1.65-1.40 (2H, m), 1.28 (3H, d,  $J = 7.0$  Hz), 1.13 (1.5H, t,  $J = 7.0$  Hz), 1.04 (3H, d,  $J = 7.0$  Hz), 1.02 (1.5H, t,  $J = 7.0$  Hz), 0.93 (1.5H, t,  $J = 7.0$  Hz), 0.69 (1.5H, t,  $J = 7.0$  Hz). (high-temperature NMR experiment gave evidence of presence of rotamers) MS (ESI<sup>-</sup>): 504.3. HPLC (Condition A): Rt 4.72 min (HPLC purity 99.3%). CHN analysis: [C<sub>25</sub>H<sub>28</sub>NO<sub>6</sub>ClS + 0.2 H<sub>2</sub>O] Calculated: C 58.70%, H 5.60%, N 2.76%; Found: C 58.49%, H 5.35%, N 2.85%.

**{2-[(2-Chlorophenyl)ethynyl]phenoxy}acetic acid (23a).** Prepared according to Sonogashira general method 1, starting from *tert*-butyl (2-iodophenoxy)acetate (**10b**) and 2'-chlorophenyl acetylene, the intermediate ester was purified by column chromatography and deprotected using HCl (4 N) in dioxane. After purification by preparative HPLC the title compound was obtained as a white solid. <sup>1</sup>H NMR (300MHz, DMSO-d<sub>6</sub>) δ [ppm] 13.14 (1H, bs), 7.67 (1H, m), 7.61 (1H, m), 7.53 (1H, dd,  $J = 7.5$ ,  $J = 1.6$  Hz), 7.48-7.37 (3H, m), 7.06-6.97 (2H, m), 4.82 (2H, s). MS (ESI<sup>-</sup>): 285.1. HPLC (Condition A): Rt 4.18 min (HPLC purity 98.8%).

**{2-[(2-Chlorophenyl)ethynyl]-4-methylphenoxy}acetic acid (23b).** Prepared according to Sonogashira general method 1, starting from *tert*-butyl (2-bromo-4-methylphenoxy)acetate (**10c**) and 2'-chlorophenyl acetylene, the intermediate ester was purified by column chromatography and deprotected using HCl (4 N) in dioxane. After purification by preparative HPLC the title compound was obtained as a brown solid. MS (ESI<sup>-</sup>): 299.1. HPLC (Condition B): Rt 1.31 min (HPLC purity 97.5%).

**(4-Fluoro-2-{[3-(propylsulfonyl)phenyl]ethynyl}phenoxy)acetic acid (23c).** Prepared according to Sonogashira general method 4, starting from (4-fluoro-2-bromo-phenoxy)-acetic

acid *tert*-butyl ester (**10d**) and 1-ethynyl-3-(propane-1-sulfonyl)-benzene (**14a**),. After purification by preparative HPLC the title compound was obtained as an orange. <sup>1</sup>H NMR (300MHz, DMSO-d<sub>6</sub>) δ [ppm] 13.12 (1H, bs), 8.00 (1H, t, *J*= 1.5 Hz), 7.91 (2H, m), 7.73 (1H, t, *J*= 7.8 Hz), 7.45 (1H, dd, *J*= 8.7 Hz, *J*= 3.1 Hz), 7.26 (1H, m), 7.00 (1H, dd, *J*= 9.3 Hz, *J*= 4.4 Hz), 4.82 (2H, s), 3.37 (2H, m), 1.57 (2H, sext., *J*= 7.5 Hz), 0.92 (3H, t, *J*= 7.5 Hz). MS (ESI): 375.1. HPLC (Condition A): Rt 3.95 min (HPLC purity 95.4%).

**{2-[(2-Chlorophenyl)ethynyl]-5-fluorophenoxy}acetic acid (23d)**. Prepared according to Sonogashira general method 4, starting from *tert*-butyl (2-bromo-5-fluorophenoxy)acetate (**10e**) and 2'-chlorophenyl acetylene, the title compound was obtained as a red oil after purification by preparative HPLC. MS (ESI): 303.2. HPLC (Condition A): Rt 4.48 min.

**(3-Chloro-2-{[3-(propylsulfonyl)phenyl]ethynyl}phenoxy)acetic acid (23e)**. Prepared according to Sonogashira general method 5, starting from (3-chloro-2-iodo-phenoxy)-acetic acid *tert*-butyl ester (**10f**) and 1-ethynyl-3-(propane-1-sulfonyl)-benzene (**14a**), the title compound was obtained as a dark brown sticky solid after purification by preparative HPLC. <sup>1</sup>H NMR (300MHz, DMSO-d<sub>6</sub>) δ [ppm] 13.28 (1H, bs), 7.97-7.89 (3H, m), 7.74 (1H, t, *J*= 7.8 Hz), 7.39 (1H, t, *J*= 8.3 Hz), 7.20 (1H, d, 7.8 Hz), 6.99 (1H, d, *J*= 8.3 Hz), 4.86 (2H, s), 3.38 (2H, m), 1.56 (2H, sext., *J*= 7.5 Hz), 0.93 (3H, t, *J*= 7.5 Hz). MS (ESI): 391.1. HPLC (Condition A): Rt 4.29 min (HPLC purity 98.8%).

**[(1-{[3-(Propylsulfonyl)phenyl]ethynyl}-2-naphthyl)oxy]acetic acid (23f)**. A mixture of (1-bromo-naphthalen-2-yloxy)-acetic acid *tert*-butyl ester (**10g**; 500 mg; 1.48 mmol), 1-ethynyl-3-(propane-1-sulfonyl)-benzene (**14a**; 618 mg; 2.97 mmol) and PPh<sub>3</sub> (39 mg; 0.15 mmol) in water (4.40 ml) and Acetone (5.6 ml) was treated with PdCl<sub>2</sub> (13 mg; 0.07 mmol)



and piperidine (295  $\mu$ l; 2.97 mmol) and heated at 60 °C for 2 days. The reaction mixture was extracted with EtOAc, the organic phase was dried over MgSO<sub>4</sub> and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (cyclohexane/EtOAc gradient) to give *tert*-butyl [(1-{[3-(propylsulfonyl)phenyl]ethynyl}-2-naphthyl)oxy]acetate (65 mg, 10%) as a yellow sticky solid. <sup>1</sup>H NMR (300MHz, DMSO-d<sub>6</sub>)  $\delta$  [ppm] 8.29 (1H, d, *J*= 8.2 Hz), 8.12 (1H, t, *J*= 1.5 Hz), 8.04-8.01 (2H, m), 7.96-7.92 (2H, m), 7.76 (1H, t, *J*= 7.7 Hz), 7.66 (1H, ddd, *J*= 8.2 Hz, *J*= 7.0 Hz, *J*= 1.5 Hz), 7.48 (1H, ddd, *J*= 8.2 Hz, *J*= 7.0 Hz, *J*= 1.5 Hz), 7.36 (1H, d, *J*= 9.2 Hz), 4.99 (2H, s), 3.40 (2H, m), 1.60 (2H, sext., *J*= 7.5 Hz), 1.44 (9H, s), 0.94 (3H, t, *J*= 7.5 Hz). HPLC (Condition A) Purity 94.7%; Rt 5.4 min.

A solution of *tert*-butyl [(1-{[3-(propylsulfonyl)phenyl]ethynyl}-2-naphthyl)oxy]acetate (60 mg; 0.13 mmol) in DCM (1.2 mL) was treated with TFA (98  $\mu$ l; 0.65 mmol). After stirring for 1 hour, the solvents were removed under vacuum to afford a residue, which was purified by preparative HPLC to give [(1-{[3-(propylsulfonyl)phenyl]ethynyl}-2-naphthyl)oxy]acetic acid as a beige solid in 34% yield. <sup>1</sup>H NMR (300MHz, DMSO-d<sub>6</sub>)  $\delta$  [ppm] 13.18 (1H, bs), 8.29 (1H, d, *J*= 8.0 Hz), 8.10 (1H, t, *J*= 1.5 Hz), 8.04-8.00 (2H, m), 7.96-7.91 (2H, m), 7.76 (1H, t, *J*= 8.0 Hz), 7.68-7.63 (1H, m), 7.50-7.45 (1H, m), 7.39 (1H, d, *J*= 9.2 Hz), 5.01 (2H, s), 3.40 (2H, m), 1.60 (2H, sext., *J*= 7.6 Hz), 0.94 (3H, t, *J*= 7.6 Hz). MS (ESI<sup>+</sup>): 407.1. HPLC (Condition A): Rt 4.88 min.

**[2-[(2-Chlorophenyl)ethynyl]-4-(trifluoromethyl)phenoxy]acetic acid (23g).** Prepared according to Sonogashira general method 5, starting from *tert*-butyl [2-bromo-4-(trifluoromethyl)phenoxy]acetate (**10h**) and 2'-chlorophenyl acetylene, the title compound was obtained as a white solid after purification by preparative HPLC. <sup>1</sup>H NMR (300MHz, DMSO-d<sub>6</sub>)  $\delta$  [ppm] 13.2 (1H, bs), 7.84 (1H, d, *J*= 2.0 Hz), 7.77 (1H, dd, *J*= 9.0 Hz, *J*= 2.0

Hz), 7.07 (1H, m), 7.61 (1H, m), 7.50-7.39 (2H, m), 7.20 (1H, d,  $J$  = 8.8 Hz), 4.94 (2H, s). MS (ESI<sup>+</sup>): 353.2. HPLC (Condition A): Rt 4.80 min (HPLC purity 98.3%).

**[2-{{3-(Propylsulfonyl)phenyl}ethynyl}-4-(trifluoromethyl)phenoxy]acetic acid (23h).**

Prepared according to Sonogashira general method 3, starting from *tert*-butyl [2-bromo-4-(trifluoromethyl)phenoxy]acetate (**10h**) and 1-ethynyl-3-(propane-1-sulfonyl)-benzene (**14a**), the title compound was obtained as a yellow solid after slurrying in diethyl ether. <sup>1</sup>H NMR (300MHz, DMSO-*d*<sub>6</sub>)  $\delta$  [ppm] 13.2 (1H, bs), 8.05 (1H, m), 7.96-7.91 (3H, m), 7.78-7.71 (2H, m), 7.20 (1H, d,  $J$  = 8.8 Hz), 4.97 (2H, s), 3.40-3.34 (2H, m), 1.57 (2H, m), 0.93 (3H, t,  $J$  = 7.5 Hz). MS (ESI<sup>+</sup>): 425.2. HPLC (Condition A): Rt 4.45 min (HPLC purity 96.2%).

**{2-[(2-Chlorophenyl)ethynyl]-4-cyanophenoxy}acetic acid (23i).** Prepared according to Sonogashira general method 1, starting from *tert*-butyl (2-bromo-4-cyanophenoxy)acetate (**10i**) and 2'-chlorophenyl acetylene, without purification of the intermediate ester and deprotecting using HCl (4 N) in dioxane. After purification by preparative HPLC the title compound was obtained as a white solid. <sup>1</sup>H NMR (300MHz, DMSO-*d*<sub>6</sub>)  $\delta$  [ppm] 13.3 (1H, bs), 8.02 (1H, d,  $J$  = 2.2 Hz), 7.87 (1H, dd,  $J$  = 8.8, 2.2 Hz), 7.68 (1H, dd,  $J$  = 7.3, 2.1 Hz), 7.61 (1H, dd,  $J$  = 7.7, 1.6 Hz), 7.51-7.39 (2H, m), 7.19 (1H, d,  $J$  = 8.8 Hz), 4.95 (2H, s). MS (ESI<sup>+</sup>): 310.1. HPLC (Condition A): Rt 4.19 min (HPLC purity 98.0%).

**(4-Cyano-2-{{3-(propylsulfonyl)phenyl}ethynyl}phenoxy)acetic acid (23j).** Prepared according to Sonogashira general method 3, starting from *tert*-butyl (2-bromo-4-cyanophenoxy)acetate (**10i**) and 1-ethynyl-3-(propane-1-sulfonyl)-benzene (**14a**), the title compound was obtained as a yellow solid after purification by preparative HPLC. <sup>1</sup>H NMR (300MHz, DMSO-*d*<sub>6</sub>)  $\delta$  [ppm] 13.3 (1H, bs), 8.10 (1H, d,  $J$  = 2.2 Hz), 8.03 (1H, t,  $J$  = 1.7 Hz),

7.96-7.85 (3H, m), 7.75 (1H, t,  $J = 7.8$  Hz), 7.19 (1H, d,  $J = 8.9$  Hz), 4.96 (2H, s), 3.41-3.33 (2H, m), 1.62-1.51 (2H, m), 0.97-0.89 (3H, t,  $J = 7.4$ ). MS (ESI<sup>-</sup>): 382.3. HPLC (Condition A): Rt 3.75 min (HPLC purity 99.5%).

**(4-Cyano-2-{[2-methyl-5-(propylsulfonyl)phenyl]ethynyl}phenoxy)acetic acid (23k).**

Prepared according to Sonogashira general method 3, starting from 2-bromo-1-methyl-4-(propylsulfonyl)benzene (**12b**) and *tert*-butyl (4-cyano-2-ethynylphenoxy)acetate (**16b**), the title compound was obtained as a white solid after purification by preparative HPLC. <sup>1</sup>H NMR (300MHz, DMSO-d<sub>6</sub>) δ [ppm] 13.2 (1H, bs), 8.11 (1H, d,  $J = 2.0$  Hz), 7.95 (1H, d,  $J = 2.0$  Hz), 7.87 (1H, dd,  $J = 8.8$  Hz,  $J = 2.0$  Hz), 7.81 (1H, dd,  $J = 8.0$  Hz,  $J = 2.0$  Hz), 7.61 (1H, d,  $J = 8.0$  Hz), 7.21 (1H, d,  $J = 8.8$  Hz), 4.96 (2H, s), 3.32 (2H, m), 2.59 (3H, s), 1.55 (2H, m), 0.94 (3H, t,  $J = 7.5$  Hz). MS (ESI<sup>-</sup>): 396.3. HPLC (Condition A): Rt 4.04 min (HPLC purity 99.7%).

**(4-Cyano-2-{[2-isopropyl-5-(methylsulfonyl)phenyl]ethynyl}phenoxy)acetic acid (23l).**

Prepared according to Sonogashira general method 3, starting from *tert*-butyl (4-cyano-2-ethynylphenoxy)acetate (**16b**) and 2-iodo-1-isopropyl-4-(methylsulfonyl)benzene (**58b**), the title compound was obtained as a beige solid after purification by preparative HPLC. <sup>1</sup>H NMR (300MHz, DMSO-d<sub>6</sub>) δ [ppm] 13.31 (1H, bs), 8.10 (1H, d,  $J = 2.1$  Hz), 8.01 (1H, d,  $J = 2.0$  Hz), 7.91 (1H, dd,  $J = 8.3$  Hz,  $J = 2.0$  Hz), 7.87 (1H, dd,  $J = 8.7$  Hz,  $J = 2.1$  Hz), 7.68 (1H, d,  $J = 8.3$  Hz), 7.21 (1H, d,  $J = 8.7$  Hz), 4.95 (2H, s), 3.65 (1H, sept.,  $J = 6.9$  Hz), 3.26 (3H, s), 1.28 (6H, d,  $J = 6.9$  Hz). MS (ESI<sup>-</sup>): 396.3. HPLC (Condition A): Rt 3.93 min (HPLC purity 97.3%).

**(4-(2,4-Dimethyl-1,3-thiazol-5-yl)-2-{[3-(propylsulfonyl)phenyl]ethynyl}phenoxy)acetic acid (27b).** A solution of *tert*-butyl (4-bromo-2-{[3-(propylsulfonyl)phenyl]ethynyl}phenoxy)acetate (**26**; 100 mg; 0.20 mmol), 2,4-dimethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3-thiazole (73 mg; 0.30 mmol) was placed in a microwave vial and treated with CsF (93 mg; 0.61 mmol) and Pd(PPh<sub>3</sub>)Cl<sub>2</sub> (14 mg; 0.02 mmol). The tube was sealed and degassed with N<sub>2</sub> before adding dioxane (2 ml) and water (1 ml). The resulting reaction mixture was irradiated in a microwave reactor at 120 °C for 10 minutes. The reaction mixture was taken up in EtOAc and washed with water and brine. The organic phase was dried over MgSO<sub>4</sub>, filtered, concentrated and purified by flash column chromatography (silica), eluting with cyclohexane containing increasing amounts of EtOAc affording the *tert*-butyl ester intermediate as a brown sticky solid (78 mg, 73%). The intermediate was dissolved in a minimum of DCM and treated with HCl (4 N) in dioxane (3 mL) for 18 h. After evaporation of the solvents, the residue was purified by preparative HPLC to give the title compound as a white solid (38 mg, 55%). <sup>1</sup>H NMR (300MHz, DMSO-d<sub>6</sub>) δ [ppm] 13.34 (1H, bs), 8.01 (1H, t, *J*= 1.5 Hz), 7.93-7.89 (2H, m), 7.72 (1H, t, *J*= 7.8 Hz), 7.60 (1H, d, *J*= 2.3 Hz), 7.45 (1H, dd, *J*= 8.8 Hz, *J*= 2.3 Hz), 7.06 (1H, d, *J*= 8.8 Hz), 4.86 (2H, s), 3.37 (2H, m), 2.62 (3H, s), 2.36 (3H, s), 1.57 (2H, sext., *J*= 7.6 Hz), 0.93 (3H, t, *J*= 7.6 Hz). MS (ESI): 468.0. HPLC (Condition A): Rt 3.43 min (HPLC purity 100%).

The following compounds were prepared using the same procedure as for compound **27b**:

**[(3-{[3-(Propylsulfonyl)phenyl]ethynyl}biphenyl-4-yl)oxy]acetic acid (27a).** The title compound was obtained as a beige solid after purification by preparative HPLC. <sup>1</sup>H NMR (300MHz, DMSO-d<sub>6</sub>) δ [ppm] 13.20 (1H, bs), 8.02 (1H, t, *J*= 1.6 Hz), 7.92 (1H, m), 7.90 (1H, d, *J*= 1.6 Hz), 7.86 (1H, d, *J*= 2.3 Hz), 7.75-7.66 (4H, m), 7.48-7.43 (2H, m), 7.35 (1H, dt, *J*= 7.3 Hz, *J*= 2.3 Hz), 7.06 (1H, d, *J*= 8.8 Hz), 4.86 (2H, s), 3.40-3.36 (2H, m), 1.57 (2H,

sext.,  $J = 7.6$  Hz), 0.93 (3H, t,  $J = 7.6$  Hz). MS (ESI<sup>-</sup>): 433.1. HPLC (Condition A): Rt 5.20 min (HPLC purity 91.8%).

**[2-{{3-(Propylsulfonyl)phenyl}ethynyl}-4-(3-thienyl)phenoxy]acetic acid (27c).** The title compound was obtained as a white solid after purification by preparative HPLC. <sup>1</sup>H NMR (300MHz, DMSO-d<sub>6</sub>)  $\delta$  [ppm] 13.17 (1H, bs), 8.01 (1H, t,  $J = 1.5$  Hz), 7.93-7.86 (4H, m), 7.77-7.70 (2H, m), 7.64 (1H, dd,  $J = 5.0$  Hz,  $J = 2.9$  Hz), 7.58 (1H, dd,  $J = 5.0$  Hz,  $J = 1.0$  Hz), 7.02 (1H, d,  $J = 8.6$  Hz), 4.85 (2H, s), 3.37 (2H, m), 1.57 (2H, sext.,  $J = 7.5$  Hz), 0.93 (3H, t,  $J = 7.5$  Hz). MS (ESI<sup>-</sup>): 439.0. HPLC (Condition A): Rt 4.66 min (HPLC purity 97.3%).

**[2-{{3-(Propylsulfonyl)phenyl}ethynyl}-4-(2-thienyl)phenoxy]acetic acid (27d).** The title compound was obtained as a white solid after purification by preparative HPLC. <sup>1</sup>H NMR (300MHz, DMSO-d<sub>6</sub>)  $\delta$  [ppm] 13.19 (1H, bs), 8.03 (1H, t,  $J = 1.5$  Hz), 7.92 (2H, dd,  $J = 7.8$  Hz,  $J = 1.5$  Hz), 7.84 (1H, d,  $J = 8.7$  Hz,  $J = 2.4$  Hz), 7.73 (1H, t,  $J = 7.8$  Hz), 7.67 (1H, dd,  $J = 2.4$  Hz), 7.52 (1H, dd,  $J = 5.1$  Hz,  $J = 1.1$  Hz), 7.50 (1H, dd,  $J = 3.6$  Hz,  $J = 1.1$  Hz), 7.13 (1H, dd,  $J = 5.1$  Hz,  $J = 3.6$  Hz), 7.04 (1H, d,  $J = 8.7$  Hz), 4.87 (2H, s), 3.37 (2H, m), 1.57 (2H, sext.,  $J = 7.5$  Hz), 0.93 (3H, t,  $J = 7.5$  Hz). MS (ESI<sup>-</sup>): 439.0. HPLC (Condition A): Rt 4.66 min (HPLC purity 99.7%).

**2-(4-Chloro-2-{{2-fluoro-5-(propylsulfonyl)phenyl}ethynyl}phenoxy)-2-methylpropanoic acid (29b).** Following the general method as outlined for **29a**, starting from 2-(2-bromo-4-chlorophenoxy)-2-methylpropanoate (**28b**), and 2-ethynyl-1-fluoro-4-(propane-1-sulfonyl)-benzene (**14c**) the title compound was obtained as a brown sticky solid after purification by preparative HPLC. <sup>1</sup>H NMR (300MHz, DMSO-d<sub>6</sub>)  $\delta$  [ppm] 13.41 (1H, bs), 8.11 (1H, dd,  $J = 6.5$  Hz,  $J = 2.4$  Hz), 7.98 (1H, ddd,  $J = 8.8$  Hz,  $J = 4.7$  Hz,  $J = 2.4$  Hz), 7.69-

7.63 (2H, m), 7.46 (1H, dd,  $J = 9.0$  Hz,  $J = 2.7$  Hz), 6.91 (1H, d,  $J = 9.0$  Hz), 3.37 (2H, m), 1.60-1.51 (8H, m), 0.93 (3H, t,  $J = 7.4$  Hz). MS (ESI<sup>+</sup>): 437.1. HPLC (Condition A): Rt 4.81 min (HPLC purity 98.9%).

**2-(4-Chloro-2-{[2-methyl-5-(propylsulfonyl)phenyl]ethynyl}phenoxy)propanoic acid (32a).** A solution of 4-chloro-2-{[2-methyl-5-(propylsulfonyl)phenyl]ethynyl}phenol (**31**, 150 mg; 0.43 mmol) and methyl-2-bromopropionate (53  $\mu$ l; 0.47 mmol) in DME (3 ml) was treated with K<sub>2</sub>CO<sub>3</sub> (89 mg, 69 mmol) and heated at 70 °C for 4.5 hours. The reaction mixture was filtered and the filtrate was concentrated affording a sticky solid, which was dissolved in MeOH (1.5 ml) and treated with a 1 N solution of NaOH in water (129  $\mu$ l) and the mixture heated for 1 hour at 70 °C. A 5 N solution of HCl in water (52  $\mu$ l) was added and the solvents removed under reduced pressure, to give a residue which was purified by preparative HPLC to give the title compound (40 mg; 22%) as a white solid. <sup>1</sup>H NMR (300MHz, DMSO-d<sub>6</sub>)  $\delta$  [ppm] 13.26 (1H, bs), 7.95 (1H, d,  $J = 2.0$  Hz), 7.80 (1H, dd,  $J = 8.0$  Hz,  $J = 2.0$  Hz), 7.65 (1H, d,  $J = 2.7$  Hz), 7.63 (1H, d,  $J = 8.0$  Hz), 7.44 (1H, dd,  $J = 9.0$  Hz,  $J = 2.7$  Hz), 6.95 (1H, d,  $J = 9.0$  Hz), 4.98 (1H, q,  $J = 6.7$  Hz), 3.32 (2H, m), 2.59 (3H, s), 1.62-1.49 (5H, m), 0.92 (3H, t,  $J = 7.5$  Hz). MS (ESI<sup>+</sup>): 418.9. HPLC (Condition A): Rt 5.23 min (HPLC purity 98.6%).

**2-(4-Chloro-2-{[2-methyl-5-(propylsulfonyl)phenyl]ethynyl}phenoxy)butanoic acid (32b).** A mixture of 4-chloro-2-{[2-methyl-5-(propylsulfonyl)phenyl]ethynyl}phenol (**31**, 110 mg; 0.32 mmol) and ethyl 2-bromobutyrate (50  $\mu$ l; 0.35 mmol) in DME (2 mL) was treated with K<sub>2</sub>CO<sub>3</sub> (250 mg, 1.81 mmol) and refluxed for 18 hours. Water was added and the reaction mixture was extracted with EtOAc. The organic phase was dried over MgSO<sub>4</sub>, filtered, concentrated and purified by flash column chromatography (silica), eluting with heptane containing increasing amounts of EtOAc. The intermediate ethyl ester (100 mg; 0.11

mmol) in EtOH (1 ml) was treated with a 1 M solution of sodium hydroxide in water (0.16 ml; 0.16 mmol). After stirring at 70 °C for 45 minutes, a 1 N solution of HCl in water (65 µl) was added, the solvents removed under reduced pressure and the residue purified by preparative HPLC to afford the title compound (88 mg; 45%) as a beige solid. <sup>1</sup>H NMR (300MHz, DMSO-d<sub>6</sub>) δ [ppm] 7.94 (1H, d, *J*= 2.0 Hz), 7.80 (1H, dd, *J*= 8.0 Hz, *J*= 2.0 Hz), 7.65 (1H, d, *J*= 2.7 Hz), 7.62 (1H, d, *J*= 8.0 Hz), 7.42 (1H, dd, *J*= 9.0 Hz, *J*= 2.0 Hz), 6.92 (1H, d, *J*= 9.0 Hz), 4.78 (1H, t, *J*= 5.7 Hz), 2.58 (3H, s), 1.94 (2H, m), 1.54 (2H, sext., *J*= 7.5 Hz), 1.04 (3H, t, *J*= 7.5 Hz), 0.91 (3H, t, *J*= 7.5 Hz) (2 remaining protons, probably hidden under the peak of water). MS (ESI<sup>+</sup>): 433.2. HPLC (Condition A): Rt 4.98 min (HPLC purity 98.4%).

The following compounds were prepared using the same procedure as for compound **32b**:

**2-(4-Chloro-2-{[2-methyl-5-(propylsulfonyl)phenyl]ethynyl}phenoxy)pentanoic acid (32c).** The title compound was obtained as a white solid after purification by preparative HPLC. <sup>1</sup>H NMR (300MHz, DMSO-d<sub>6</sub>) δ [ppm] 13.28 (1H, bs), 7.94 (1H, d, *J*= 2.0 Hz), 7.80 (1H, dd, *J*= 8.0 Hz, *J*= 2.0 Hz), 7.65 (1H, d, *J*= 2.7 Hz), 7.63 (1H, d, *J*= 8.0 Hz), 7.43 (1H, dd, *J*= 9.0 Hz, *J*= 2.7 Hz), 6.92 (1H, d, *J*= 9.0 Hz), 4.85 (1H, t, *J*= 5.8 Hz), 3.30 (2H, m), 2.58 (3H, s), 1.94-1.86 (2H, m), 1.63-1.49 (4H, m), 0.95-0.89 (6H, m). MS (ESI<sup>+</sup>): 447.2. HPLC (Condition A): Rt 5.69 min (HPLC purity 99.7%).

**2-(4-Chloro-2-{[2-methyl-5-(propylsulfonyl)phenyl]ethynyl}phenoxy)-4-methylpentanoic acid (32d).** The title compound was obtained as a beige solid after purification by preparative HPLC. <sup>1</sup>H NMR (300MHz, DMSO-d<sub>6</sub>) δ [ppm] 13.25 (1H, bs), 7.93 (1H, d, *J*= 2.0 Hz), 7.80 (1H, dd, *J*= 8.0 Hz, *J*= 2.0 Hz), 7.66 (1H, d, *J*= 2.7 Hz), 7.63 (1H, d, *J*= 8.0 Hz), 7.44 (1H, dd, *J*= 9.0 Hz, *J*= 2.7 Hz), 6.96 (1H, d, *J*= 9.0 Hz), 4.86 (1H,

dd,  $J = 9.0$  Hz,  $J = 3.7$  Hz), 3.29 (2H, m), 2.58 (3H, s), 1.99-1.84 (2H, m), 1.77-1.66 (1H, m), 1.54 (2H, sext.,  $J = 7.5$  Hz), 0.97-0.89 (9H, m). MS (ESI<sup>+</sup>): 461.2. HPLC (Condition A): Rt 5.42 min (HPLC purity 98.5%).



### C- Protocols for the ADME assays

**Oxidative metabolism.** Rat and human liver microsomes were used to screen the metabolic instability resulting from phase I oxidation. Microsomes (final concentration 0.5 mg/mL), 50 mM phosphate buffer pH 7.4, NADPH (final concentration 1.5 mM) and compound (final concentration 1  $\mu$ M,) were added to the assay plate. The microsomes suspension was added to initiate the reaction and the plate was incubated at 37°C.. The reaction was stopped by the addition of cold acetonitrile at the appropriate time points (time 0, 5, 15 and 45 minutes). The samples were centrifuged at 4000 rpm for 30 minutes at 4 °C to precipitate the proteins. Samples were analyzed by LC-MS/MS. The *in vitro* intrinsic clearance was calculated from the rate of compound disappearance.

**Cytochrome P450 inhibition.** Seven human recombinant cytochrome P450 isoenzymes were tested (CYP 1A2, CYP 2C9, CYP 2C19, CYP2C08, CYP2B6, CYP 2D6 and CYP 3A4). The aim of this method is to determine the concentration of a compound required to obtain 50% inhibition of the recombinant human cytochrome P450. The assay is based on the Promega P450-Glo™ Screening System, which includes, a luminogenic substrate, an NADPH regeneration system and a Luciferin Detection Reagent.

Upon CYP450 activity, the substrate e.g. Luciferin-ME EGE for 2B6 assay is converted to luciferin EGE, which is converted to D-luciferin by the Luciferin Detection Reagent. The D-luciferin reacts in turn with the Luciferin Detection Reagent to produce light.

The CYP membranes are prepared from baculovirus-infected insect cells and contain human CYP450 and P450 reductase. In order not to be depleted in NADPH cofactor during the course of the reaction, the assay includes a NADPH Regeneration System.

Test compounds are pre-incubated for 15 min at room temperature with the CYP450 enzyme

(and appropriate cofactors), in the absence of substrate. Then the enzymatic reaction is initiated by the addition of the substrate, followed by 30 min of incubation at 37°C. As controls, BLANK and NEUTRAL values are tested on each plate. In the NEUTRAL control, DMSO is added in place of the test compound: it defines the maximum achievable substrate conversion, reflected by the strongest luminescence signal. In the BLANK control, a membrane fraction devoid of cytochrome P450 activity (control membranes prepared from wild type baculovirus-infected cells), substitutes the membranes from CYP450 expressing cells: consequently, no substrate conversion is observed. The amount of control membranes in BLANK controls is calculated to match the amount of membranes proteins brought by the CYP450 positive membranes in the rest of the assay plate. The measured signal in BLANK wells describes the background value. The percentage of inhibition is determined for each inhibitor concentration and the corresponding IC<sub>50</sub> value is calculated by non-linear curve fitting. The IC<sub>50</sub> value is determined in triplicate, using 10 different concentrations of test compound. As additional control, the IC<sub>50</sub> value of one well-characterized CYP inhibitor (called reference control) is determined.

**Caco-2 permeability.** Caco-2 cells were obtained from Advancell (Barcelona, Spain). The cells were seeded onto 24-well polycarbonate filter membrane (Transwell inserts, surface area: 0.33 cm<sup>2</sup>) and grown in Dulbecco's modified Eagle's medium supplemented with 10% fetal bovine serum, 1% L-glutamine. Permeability studies were performed with the monolayers cultured for 21 days. Prior to all experiments, the cell monolayer integrity was evaluated by trans epithelial electrical resistance (TEER), values greater than 1000 ohm-per well were used. The permeability studies were initiated by adding an appropriate volume of Hank's balanced salt solution buffer containing 1 µM test compound to either the apical (for apical to basolateral transport; A to B) or basolateral (for basolateral to apical transport; B to

A) side of the monolayer. The monolayers were then placed in an incubator at 37 °C. At the end of the incubation time (2 hours) samples were taken from both the apical and basolateral compartments. The concentrations of test compound were analyzed by LC/MS-MS.

Permeability coefficient ( $P_{app}$ ,  $10^{-6}$  cm/s) was calculated according to the following equation:  $P_{app} = dA/(dt \cdot S \cdot C_0)$ , where  $dA/dt$  is the flux of the test compound across the monolayer (nmol/s);  $S$  is the surface area of the cell monolayer ( $cm^2$ ); and  $C_0$  is the initial concentration ( $\mu M$ ) in the donor compartment.

**In vivo Pharmacokinetic Evaluation in Rat and Mouse.** In order to study the pharmacokinetic (PK) profile of test compounds in vivo, Sprague Dawley male rats or balb/c female mice were dosed intravenously or after oral gavage. For both species, test compounds were dosed in solution at 1 mg/kg for i.v. route (10% ethanol, 10% *N, N*-dimethylacetamide, 30% propylene glycol, 50% water, v/v) and in suspension at 5 mg/kg (0.5% carboxymethylcellulose suspension, containing 0.25% Tween 20 in water) for oral gavage. PK profile in rat was obtained from 3 animals per dosing route and mouse PK profile was determined from 3 animals for each time points. The volume of administration was 2 mL/kg for i.v. dosing in both species and either 5 mL/kg (rat) or 10 mL/kg (mouse) for oral gavage. Blood samples (100  $\mu L$ /time point) were collected at 0.083 (5 min), 0.25, 0.5, 1, 4, 7 and 24 hours post-dose for i.v. dosing, and at 0.5, 1, 4, 7 and 24 h for oral dosing, into heparin-Li<sup>+</sup> containing tubes. For rats, all blood samples were collected through a catheter in the carotid artery (placed in the artery the day before the experiment), under light isoflurane anesthesia, and stored on ice until centrifugation and plasma isolation. For mouse, blood samples were collected from intracardiac puncture at sacrifice at each time point and processed as described above for the rat. Plasma samples were stored frozen until analysis (-20 °C to -70 °C). For bioanalysis, samples were processed by protein precipitation (acetonitrile, formic acid 0.1%,

addition of 3 volumes) after addition of one internal standard and analysed using a sensitive and selective LC-MS/MS method. An aliquot of the resulting supernatant was subject to LC-MS/MS analysis using a reverse phase column (Waters Xterra, C8, (3.5  $\mu$ m particle size, 2.1 x 50 mm) and a short gradient (1.1 min) from 100% Solvent A (ammonium hydroxide 0.1%) to 90% Solvent B (acetonitrile + 0.1% formic acid) followed by isocratic conditions of 90% Solvent B for 3.5 min at 0.4 mL/min. The total run time was 10 minutes. Column effluent was monitored using a Sciex API 4000 triple quadrupole mass spectrometer with a Turbo V electrospray ion source in negative mode.