

# Supporting Information

## Potent and Orally Bioavailable Inverse Agonists of ROR $\gamma$ t Resulting from Structure-Based Design

Frank Narjes,<sup>\*,†</sup> Yafeng Xue,<sup>§</sup> Stefan von Berg,<sup>†</sup> Jesper Malmberg,<sup>†</sup> Antonio Llinas,<sup>‡</sup> Roine I. Olsson,<sup>†</sup> Johan Jirholt,<sup>†</sup> Hanna Grindebacke,<sup>†</sup> Agnes Leffler,<sup>†</sup> Nafizal Hossain,<sup>†</sup> Matti Lepistö,<sup>†</sup> Linda Thunberg,<sup>≠</sup> Hanna Leek,<sup>≠</sup> Anna Aagaard,<sup>§</sup> Jane McPheat,<sup>¶</sup> Eva L. Hansson,<sup>¶</sup> Elisabeth Bäck,<sup>¶</sup> Stefan Tängefjord,<sup>§</sup> Rongfeng Chen,<sup>^</sup> Yao Xiong,<sup>^</sup> Hongbin Ge,<sup>^</sup> Thomas G. Hansson<sup>†</sup>

<sup>†</sup>Medicinal Chemistry, <sup>‡</sup>DMPK and <sup>†</sup>Bioscience, Respiratory, Inflammation and Autoimmunity, IMED Biotech Unit, AstraZeneca, Gothenburg, SE-43183 Mölndal, Sweden.

<sup>§</sup>Structure, Biophysics & FBLG and <sup>¶</sup>Mechanistic Biology and Profiling, Discovery Sciences, IMED Biotech Unit, AstraZeneca, Gothenburg, SE-43183 Mölndal, Sweden.

<sup>≠</sup>Early Product Development, Pharmaceutical Sciences, IMED Biotech Unit, AstraZeneca, Gothenburg, SE-43183 Mölndal, Sweden.

<sup>^</sup>Pharmaron Beijing Co., Ltd., Taihe Road BDA, Beijing, 100176, P.R. China

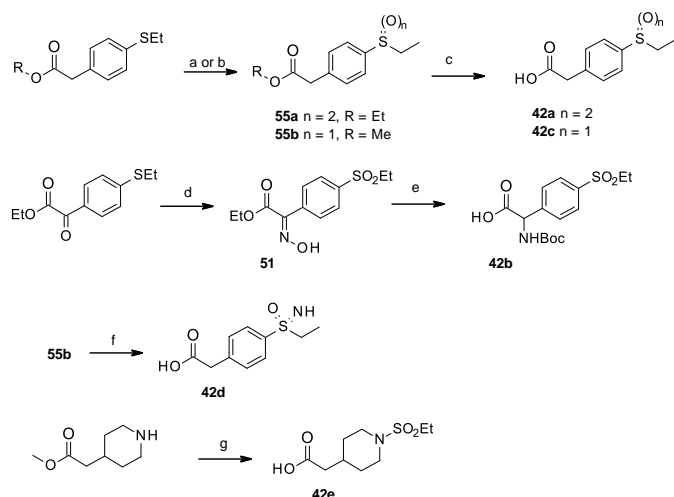
E-mail: [Frank.Narjes@astrazeneca.com](mailto:Frank.Narjes@astrazeneca.com)

## Table of Contents

Page number:

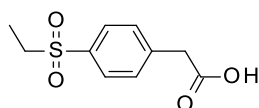
S2 – S23	Synthesis and characterization of compounds <b>5</b> , <b>6</b> , <b>8</b> , <b>9-11</b> , <b>13 - 21</b> , <b>23 - 25</b> , <b>31</b> , <b>34</b> , <b>36</b> and <b>37</b> .
S27	Table S1. X-ray data collection and refinement statistics
S29	Assay conditions
S1	

**Scheme 1. Synthesis of phenylacetic acid derivatives 42a-e<sup>a</sup>**



<sup>a</sup>Reagents and conditions: (a) *m*-CPBA, DCM, RT for **55a**; (b) H<sub>2</sub>O<sub>2</sub>, AcOH, RT for **55b**; (c) THF, NaOH, RT; (d) *m*-CPBA, DCM 0 °C to RT, 88%; H<sub>2</sub>NOH·HCl, EtOH, 80 °C, quantitative; (e) Pd/C (10% Pd), H<sub>2</sub>, EtOH, RT; Boc<sub>2</sub>O, TEA, DCM, 57%; LiOH, THF, H<sub>2</sub>O, RT, 86%; (f) CF<sub>3</sub>C(O)NH<sub>2</sub>, Rh(OAc)<sub>2</sub>, PhI(OAc)<sub>2</sub>, MgO, DCM; (g) EtSO<sub>2</sub>Cl, DIEA, DCM, RT; LiOH, THF, RT.

**2-(4-(Ethylsulfonyl)phenyl)acetic acid (42a).**

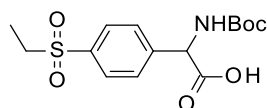


*Step 1:* Ethyl 2-(4-(ethylsulfonyl)phenyl)acetate **55a**. To a solution of ethyl 2-(4-(ethylthio)phenyl)acetate (6.0 g, 26.80 mmol) in DCM (100 mL) was added *m*-CPBA (14.6 g, 84.6 mmol) at 0 °C. The resulting mixture was stirred at RT for 12 h. The solids were removed by filtration and the filtrate was washed with saturated Na<sub>2</sub>CO<sub>3</sub> (2×50 mL) and brine (1×50 mL), dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under vacuum. The residue was applied onto a silica gel column and eluted with EtOAc/petroleum ether (1/3). This resulted in 6.0 g (89%) of **55a** as an off-white solid. LCMS ES<sup>+</sup> *m/z* = 298 [M+H+CH<sub>3</sub>CN]<sup>+</sup>. <sup>1</sup>HNMR (400 MHz, CDCl<sub>3</sub>) δ 1.25-1.30 (m, 6H), 3.11 (q, *J* = 7.6 Hz, 2H), 3.72 (s, 2H), 4.17 (q, *J* = 7.2 Hz, 2H), 7.50 (d, *J* = 8.0

Hz, 2H), 7.87 (d,  $J = 8.0$  Hz, 2H).

*Step 2:* 2-(4-(Ethylsulfonyl)phenyl)acetic acid **42a**. To a solution of **55a** (6.0 g, 23.43 mmol) in ethanol (45 mL) was added aqueous NaOH (41 mL, 2 M). The resulting solution was stirred for 12 h at RT and concentrated under vacuum. The residue was then diluted with water and washed with EtOAc (2×75 mL). The pH value of the solution was adjusted to 1 by the addition of aqueous HCl (6 M) and the resulting mixture was extracted with EtOAc (2×100 mL). The organic layer was washed with brine (2×50 mL), dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under vacuum. This resulted in 4.6 g (86%) of **42a** as an off-white solid, which was used without further purification. LCMS ES<sup>+</sup>  $m/z = 229$  [M+H]<sup>+</sup>. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  1.10 (t,  $J = 7.2$  Hz, 3H), 3.28 (q,  $J = 7.2$  Hz, 2H), 3.74 (s, 2H), 7.55 (d,  $J = 8.0$  Hz, 2H), 7.83 (d,  $J = 8.0$  Hz, 2H).

**2-(tert-Butoxycarbonylamino)-2-(4-(ethylsulfonyl)phenyl)acetic acid (42b).**



*Step 1:* Ethyl 2-(4-ethylthio)phenyl)-2-oxoacetate (**50**). Ethyl 2-chloro-2-oxoacetate (14.8 g, 108.5 mmol) was added dropwise to a mixture of ethyl(phenyl)sulfane (5.0 g, 36.17 mmol) and aluminum trichloride (14.5 g, 108.51 mmol) in CHCl<sub>3</sub> (100 mL) at 0 °C over a period of 30 minutes under nitrogen. The resulting mixture was stirred at 0 °C for 3 hours. The reaction mixture was poured into ice/water (400 ml) and extracted with DCM (3 × 200 mL). The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and evaporated to afford yellow oil. The crude product was purified by flash silica chromatography, elution gradient 0 to 20% EtOAc in petroleum ether to afford **50** (6.2 g, 73%) as a yellow oil. LCMS ES<sup>+</sup>  $m/z = 239$  [M+H]<sup>+</sup>. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  1.38 - 1.46 (m, 6H), 3.06 (q,  $J = 7.2$  Hz, 2H), 4.46 (q,  $J = 7.2$  Hz, 2H), 7.33 (d,  $J = 8.8$  Hz, 2H), 7.93 (d,  $J = 8.8$  Hz, 2H).

*Step 2:* (Z,E)-Ethyl 2-(4-(ethylsulfonyl)phenyl)-2-(hydroxyimino)acetate (**51**). *m*-CPBA (9.1 g, 52.45 mmol) was added portionwise to **50** (5.0 g, 20.98 mmol) in DCM (200 mL) under nitrogen at 0 °C over a period of 10 minutes. The resulting mixture was stirred at RT for 16 hours. The reaction mixture was quenched with water (200 mL) and extracted with DCM (3×500 mL). The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and evaporated to afford a colorless solid, which was purified by crystallization from EtOAc/petroleum ether to afford 2-(4-(ethylsulfonyl)phenyl)-2-oxoacetate (5.0 g, 88%) as a colorless solid. LCMS ES<sup>+</sup> *m/z* = 271 [M+H]<sup>+</sup>. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 1.19-1.34 (m, 6H), 3.17 (q, *J* = 7.2 Hz, 2H), 4.49 (q, *J* = 7.2 Hz, 2H), 8.07 (d, *J* = 8.0 Hz, 2H), 8.24 (d, *J* = 8.0 Hz, 2H).

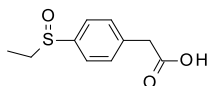
Hydroxylamine hydrochloride (1.7 g, 24.1 mmol) was added to ethyl 2-(4-(ethylsulfonyl)phenyl)-2-oxoacetate (5.0 g, 18.50 mmol) in EtOH (130 mL) at RT under nitrogen. The resulting solution was stirred at 80 °C for 2 hours. The reaction mixture was concentrated, diluted with water (50 mL), and extracted with EtOAc (3× 40 mL). The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and evaporated to afford **51** (5.5 g, 104%) as a colorless solid. LCMS ES<sup>+</sup> *m/z* = 286 [M+H]<sup>+</sup>.

*Step 3:* 2-(*tert*-Butoxycarbonylamino)-2-(4-(ethylsulfonyl)phenyl)acetic acid (**42b**). Pd/C (7.1 g, 66.59 mmol, 10% Pd) was added to **51** (19.0 g, 66.59 mmol) in EtOH (400 mL) under nitrogen. The mixture was stirred under hydrogen at RT for 16 hours. The reaction mixture was filtered and concentrated to afford a crude product, which was dissolved in DCM (200 mL). TEA (10.1 g, 99.9 mmol) and Boc<sub>2</sub>O (21.8 g, 99.9 mmol) were added. The resulting solution was stirred at RT for 5 hours. The reaction mixture diluted with water (200 mL), and extracted with EtOAc (3×100 mL). The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and evaporated to afford crude product, which was purified by flash chromatography on silica gel (0 to 60% EtOAc in petroleum ether) to afford ethyl 2-((*tert*-butoxycarbonyl)amino)-2-(4-(ethylsulfonyl)phenyl)acetate (14 g, 57%) as a yellow oil. LCMS ES<sup>+</sup> *m/z* = 372 [M+H]<sup>+</sup>.

$^1\text{H}$ NMR (400 MHz,  $\text{DMSO}-d_6$ )  $\delta$  1.08 - 1.18 (m, 6H), 1.40 (s, 9H), 3.31 (q,  $J = 7.6$  Hz, 2H), 4.12 (q,  $J = 6.8$  Hz, 2H), 5.37 (d,  $J = 8.4$  Hz, 1H), 7.68 (d,  $J = 8.0$  Hz, 2H), 7.88 (d,  $J = 8.0$  Hz, 2H), 7.94 (d,  $J = 8.0$  Hz, 1H).

LiOH (0.2 g, 7.00 mmol) was added to ethyl 2-((*tert*-butoxycarbonyl)amino)-2-(4-(ethylsulfonyl)phenyl)acetate (1.3 g, 3.50 mmol) in THF (10 mL) and water (10 mL). The resulting solution was stirred at RT for 2 hours. The reaction mixture was adjusted to pH = 1-2 with HCl (1M) and extracted with EtOAc (2 $\times$  50 mL). The organic layer was dried over  $\text{Na}_2\text{SO}_4$ , filtered and evaporated to dryness to afford **42b** (1.0 g, 86%) as a colorless solid. LCMS  $\text{ES}^+$   $m/z = 344$   $[\text{M}+\text{H}]^+$ .  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ )  $\delta$  1.10 (t,  $J = 7.2$  Hz, 3H), 1.39 (s, 9H), 3.29 (q,  $J = 7.2$  Hz, 2H), 5.29 (d,  $J = 8.4$  Hz, 1H), 7.68 (d,  $J = 8.4$  Hz, 2H), 7.78 (d,  $J = 8.4$  Hz, 1H), 7.87 (d,  $J = 8.4$  Hz, 1H), 13.05 (s, 1H).

### 2-(4-(Ethylsulfinyl)phenyl)acetic acid (**42c**)

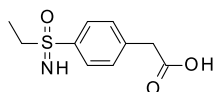


*Step 1:* Methyl 2-(4-(ethylsulfinyl)phenyl)acetate (**55b**). Methyl 2-(4-(ethylthio)phenyl)acetate (1.5 g, 7.13 mmol) was dissolved in acetic acid (4 mL) and aqueous  $\text{H}_2\text{O}_2$  (0.729 mL, 7.13 mmol) was added. The mixture was stirred at RT for 6 h. The reaction mixture was partitioned between EtOAc (250 mL) and water (50 mL). The organic layer was washed with water (2 x 50 mL) and sat. aq.  $\text{NaHCO}_3$  (2 x 50 mL), dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated to give crude **55b** (1.3g, 81%) as an oil.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  1.20 (t,  $J = 7.4$  Hz, 3H), 2.72 – 2.8 (m, 1H), 2.85 – 2.95 (m, 1H), 3.69 (s, 2H), 3.71 (s, 3H), 7.42 – 7.46 (m, 2H), 7.55 – 7.59 (m, 2H).

*Step 2:* Preparation of **42c**. To a solution of **55b** (72 mg, 0.32 mmol) in THF (0.4 mL) an aqueous solution of NaOH (25.5 mg, 0.64 mmol in 0.4 mL water) was added and the reaction

mixture was stirred at RT for 4 h and then cooled in an ice-water bath. The pH was adjusted to 3 by addition of diluted aqueous HCl, and the resulting mixture extracted with EtOAc (50 mL). The organic layer was washed with water (2 x 10 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and the filtrate was concentrated *in vacuo* to give **42c** (65 mg, 96%) as an oil, which solidified on standing. <sup>1</sup>H-NMR (500 MHz, CD<sub>3</sub>OD); δ 1.18 (t, *J* = 7.4 Hz, 3H), 2.87 (dq, *J* = 13.5, 7.4 Hz, 1H), 3.02 (dq, *J* = 13.5, 7.4 Hz, 1H), 3.72 (s, 2H), 7.52 – 7.54 (m, 2H, m), 7.61 – 7.64 (m, 2H).

**2-(4-(Ethylsulfonimidoyl)phenyl)acetic acid (42d).**

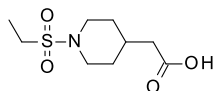


*Step 1:* 2-(4-(Ethylsulfonimidoyl)phenyl)acetic acid (**42d**). To a mixture of **55b** (0.535 g, 2.36 mmol), 2,2,2-trifluoroacetamide (0.401 g, 3.55 mmol), magnesium oxide (0.381 g, 9.46 mmol) and diacetoxyrhodium (0.026 g, 0.06 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (15 mL), iodobenzene diacetate (1.142 g, 3.55 mmol) was added under nitrogen. The reaction mixture was stirred at RT for 24 h. The reaction mixture was filtered and concentrated to give a crude, which was purified by column chromatography on silica (0-50% EtOAc in heptane). The fractions containing the desired product were collected and concentrated *in vacuo* to give methyl 2-(4-(*N*-(2,2,2-trifluoroacetyl)ethylsulfonimidoyl)phenyl)acetate (329 mg, 41%) as an oil. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 1.33 (t, *J* = 7.4 Hz, 3H), 3.49 – 3.65 (m, 2H), 3.74 (s, 3H), 3.76 (s, 2H), 7.56 – 7.6 (m, 2H), 7.88 – 7.93 (m, 2H).

To a solution of methyl 2-(4-(*N*-(2,2,2-trifluoroacetyl)ethylsulfonimidoyl)phenyl)acetate (225 mg, 0.67 mmol) in THF (1.5 mL), water (0.4 mL) was added, followed by aqueous NaOH (2 M, 1.0 mL, 2.0 mmol) and the reaction mixture was stirred at RT for 2 h. The reaction mixture was cooled in an ice-water bath, pH was adjusted to 2 by addition HCl (2 M) and extracted with

EtOAc (2 x 200 mL). The combined organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated to give **42d** (105 mg, 69%) as a gum, which was used without further purification.

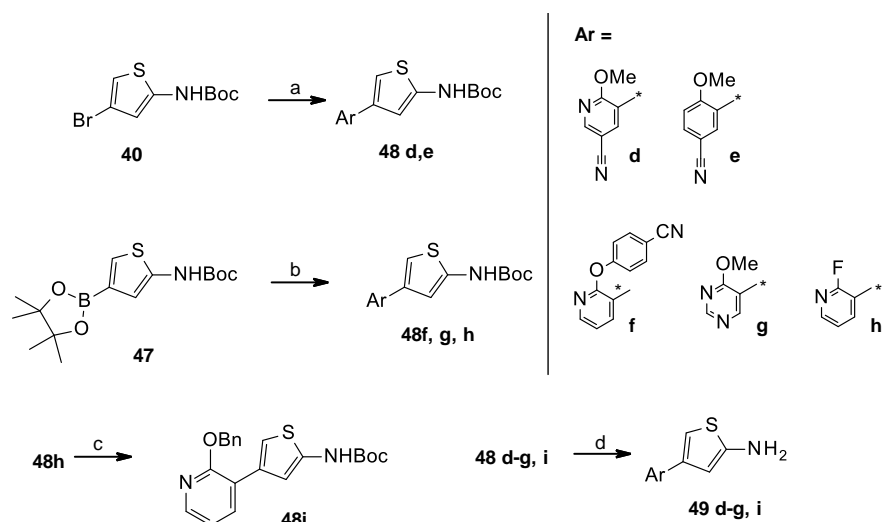
**2-(1-(Ethylsulfonyl)piperidin-4-yl)acetic acid (**42e**).**



*Step 1:* Methyl 2-(1-(ethylsulfonyl)piperidin-4-yl)acetate. Ethanesulfonyl chloride (1.963 g, 15.3 mmol) was added to methyl 2-(piperidin-4-yl)acetate (2.0 g, 12.72 mmol), DIEA (6.67 mL, 38.17 mmol) in DCM (40 mL) cooled to 0 °C under nitrogen. The resulting mixture was stirred at RT for 12 hours. The reaction mixture was diluted with DCM (50 mL), and washed sequentially with 0.1 M HCl (50 mL), water (75 mL), and saturated brine (50 mL). The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and evaporated. The residue was purified by flash chromatography (EtOAc/petroleum ether 1:1), to afford methyl 2-(1-(ethylsulfonyl)piperidin-4-yl)acetate (2.2 g, 69%) as a colorless solid.

*Step 2:* 2-(1-(Ethylsulfonyl)piperidin-4-yl)acetic acid (**42e**). A mixture of lithium hydroxide (0.317 g, 13.24 mmol) in water (15 mL) was added to a stirred mixture of methyl 2-(1-(ethylsulfonyl)piperidin-4-yl)acetate (2.2 g, 8.82 mmol) in THF (15 mL). The resulting mixture was stirred at RT for 12 hours, then THF was removed under reduced pressure. The mixture was acidified with 0.5 M HCl to pH for 3-4. The precipitated solid was isolated by filtration and dried under vacuum to afford **42e** (1.7 g, 82%) as a white solid. <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ 1.12-1.19 (m, 2H), 1.20 (t, *J* = 7.4 Hz, 3H), 1.73 (d, *J* = 12.4, 2H), 1.74 – 1.83 (m, 1H), 2.19 (d, *J* = 6.8 Hz, 2H), 2.79 (dt, *J* = 2.0, 12.0 Hz, 2H), 3.02 (q, *J* = 7.4 Hz, 2H), 3.56 (d, *J* = 12.1, 2H), 12.14 (s, 1H).

**Scheme 2.** Synthesis of 4-aryl-substituted 2-aminothiophenes<sup>a</sup>



<sup>a</sup>Reagents and conditions: (a) PdCl<sub>2</sub>(dppf), solvent, base; (b) PdCl<sub>2</sub>(dppf), solvent, base; (c) BnOH, KOtBu; (d) TBSOTf or TFA, DCM.

### 3-(5-Amino-3-thienyl)-4-methoxy-benzonitrile (49e)

**Step 1:** *tert*-Butyl *N*-[4-(5-cyano-2-methoxy-phenyl)-2-thienyl]carbamate (**48e**). To a mixture of (5-cyano-2-methoxyphenyl)boronic acid (100 mg, 0.57 mmol) and **40** (157 mg, 0.57 mmol) in acetonitrile (2.5 mL) was added aqueous Na<sub>2</sub>CO<sub>3</sub> (0.38 mL, 1.13 mmol). The reaction mixture was purged with nitrogen and Pd(dppf)Cl<sub>2</sub> (19.85 mg, 0.03 mmol) was added. The mixture was stirred at 95 °C for 4h. The reaction mixture was cooled to RT, partitioned between EtOAc (200 mL) and water (25 mL). The layers were separated and the organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated. The residue was purified by column chromatography on silica (0-30% EtOAc in heptane) to give **48e** (129 mg, 69%) as gum. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 1.55 (s, 9H), 3.94 (s, 3H), 6.83 (d, *J* = 1.6 Hz, 1H), 7.00 (d, *J* = 8.6 Hz, 1H), 7.03 (bs, 1H), 7.15 (d, *J* = 1.3 Hz, 1H), 7.57 (dd, *J* = 8.6, 2.1 Hz, 1H), 7.71 (d, *J* = 2.1 Hz, 1H). LCMS ES<sup>-</sup> *m/z* = 329 [M-H]<sup>-</sup>.

**Step 2:** 3-(5-Amino-3-thienyl)-4-methoxy-benzonitrile (**49e**). To a solution of **48e** (126 mg, 0.38 mmol) in DCM (6 mL), TFA (1.5 μl, 0.02 mmol) was added and the reaction mixture was stirred at RT for 1.5 h, and then concentrated. The residue was dissolved in EtOAc (250 mL)



and washed with aqueous Na<sub>2</sub>CO<sub>3</sub>. The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated to give crude **49e** (75 mg, 85%) as gum, which was used without further purification. LCMS ES<sup>+</sup>  $m/z$  = 231 [M+H]<sup>+</sup>.

#### **5-(5-Aminothiophen-3-yl)-6-methoxynicotinonitrile (49d)**

*Step 1:* *tert*-Butyl (4-(5-cyano-2-methoxypyridin-3-yl)thiophen-2-yl)carbamate (**48d**).

Following the procedure for **48e**, compound **48d** (600 mg, 40.3%) was obtained from (5-cyano-2-methoxypyridin-3-yl)boronic acid (800 mg, 4.50 mmol) and **40** (1.63 g, 5.84 mmol) conducting the reaction in DME (20 mL) and water (4 mL) under nitrogen at 100 °C for 12 hours. LCMS ES<sup>+</sup>  $m/z$  = 332 [M+H]<sup>+</sup>.

*Step 2:* 5-(5-Aminothiophen-3-yl)-6-methoxynicotinonitrile (**49d**). TFA (2 ml, 26 mmol) was added to **48g** (600 mg, 1.81 mmol) in dioxane (4 mL). The resulting mixture was stirred at RT for 3 hours. The solvent was removed under reduced pressure to give the trifluoroacetic acid salt of **49g** (400 mg, 64%) as a dark solid. The product was used directly in the next step without further purification. LCMS ES<sup>+</sup>  $m/z$  = 232 [M+H]<sup>+</sup>.

#### **4-((3-(5-Aminothiophen-3-yl)pyridin-2-yl)oxy)benzonitrile (49f)**

*Step 1:* *tert*-Butyl (4-(2-(4-cyanophenoxy)pyridin-3-yl)thiophen-2-yl)carbamate (**48f**).

PdCl<sub>2</sub>(dppf) (40.7 mg, 0.05 mmol) was added to a mixture of **46b** (274 mg, 1.00 mmol) and **47** (389 mg, 1.20 mmol) and NaHCO<sub>3</sub> (167 mg, 1.99 mmol) in dioxane (12 mL) and water (3 mL) at 25 °C under nitrogen. The resulting solution was stirred at 80 °C for 12 hours. The reaction mixture was quenched with water (100 mL), extracted with EtOAc (2 x 50 mL), the organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and evaporated to afford yellow residue, which was purified by flash silica chromatography (0 to 100% EtOAc in petroleum ether) to afford **48f** (140 mg, 36%) as a solid. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 1.49 (s, 9H), 6.99 (s, 1H), 7.27 –

7.41 (m, 4H), 7.90 (d,  $J = 8.6$  Hz, 2H), 8.06 – 8.14 (m, 2H), 10.50 (s, 1H). LCMS ES<sup>-</sup>  $m/z = 394$  [M+H]<sup>+</sup>.

*Step 2:* 4-((3-(5-Aminothiophen-3-yl)pyridin-2-yl)oxy)benzonitrile (**49f**). TBSOTf (376 mg, 1.42 mmol) was added to **48f** (140 mg, 0.36 mmol) in DCM (10 mL) cooled to 0 °C under nitrogen. The resulting solution was stirred at RT for 12 hours. The reaction mixture was quenched with saturated NaHCO<sub>3</sub> (50 mL), extracted with DCM (2 x 50 mL), the organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and evaporated to afford **49f** (100 mg, 96%) as yellow solid. LCMS ES<sup>+</sup>  $m/z = 294$  [M+H]<sup>+</sup>.

#### **4-(4-Methoxypyrimidin-5-yl)thiophen-2-amine (49g)**

*Step1:* *tert*-Butyl (4-(4-methoxypyrimidin-5-yl)thiophen-2-yl)carbamate (**48g**). PdCl<sub>2</sub>(dppf) (33.7 mg, 0.04 mmol) was added to 5-bromo-4-methoxypyrimidine (156 mg, 0.83 mmol), **47** (295 mg, 0.91 mmol) and K<sub>2</sub>CO<sub>3</sub> (228 mg, 1.65 mmol) in 1,4-dioxane (4 mL) and water (1 mL) under nitrogen. The resulting mixture was stirred at 100 °C for 2 hours. The reaction mixture was diluted with water (20 mL) and extracted with EtOAc (50 mL). The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 30% EtOAc in petroleum ether. Pure fractions were evaporated to dryness to afford **48g** (170 mg, 67%) as a yellow solid. LCMS ES<sup>+</sup>  $m/z = 308$  [M+H]<sup>+</sup>.

*Step2:* 4-(4-Methoxypyrimidin-5-yl)thiophen-2-amine (**49g**). Compound **48g** (170 mg, 0.55 mmol) was dissolved in DCM (2 mL) and treated with TFA (1 mL, 12.98 mmol) at RT. The resulting solution was stirred for 3 hours at RT and then concentrated under vacuum to afford crude trifluoroacetate of **49d** (180 mg, quantitative) as brown oil. LCMS ES<sup>+</sup>  $m/z = 208$  [M+H]<sup>+</sup>.

#### 4-(2-(Benzyloxy)pyridin-3-yl)thiophen-2-amine (**49i**)

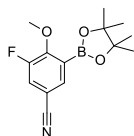
*Step 1:* *tert*-Butyl 4-(2-fluoropyridin-3-yl)thiophen-2-ylcarbamate (**48h**). PdCl<sub>2</sub>(dppf) (226 mg, 0.28 mmol) was added to NaHCO<sub>3</sub> (581 mg, 6.92 mmol), **47** (900 mg, 2.77 mmol) and 2-fluoro-3-iodopyridine (740 mg, 3.32 mmol) in water (1 mL) and 1,4-dioxane (4 mL) at 25 °C under nitrogen. The resulting solution was stirred at 90 °C for 3 hours. The reaction mixture was diluted with EtOAc (100 mL), and washed sequentially with saturated brine (100 mL x 3). The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and evaporated to afford crude product, which was purified by flash silica chromatography (0 - 15% EtOAc in petroleum ether) to afford **48i** (600 mg, 74%) as a grey solid. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 1.55 (s, 9H), 6.90 (s, 1H), 7.20 (s, 1H), 7.21 – 7.27 (m, 1H), 7.89 – 7.97 (m, 1H), 8.12 (dt, *J* = 1.5, 4.9 Hz, 1H). LCMS ES<sup>+</sup> *m/z* = 295 [M+H]<sup>+</sup>.

*Step 2:* *tert*-Butyl 4-(2-(benzyloxy)pyridin-3-yl)thiophen-2-ylcarbamate (**48i**). Benzyl alcohol (184 mg, 1.70 mmol) was added to KOtBu (229 mg, 2.04 mmol), and **48h** (200 mg, 0.68 mmol) in THF (20 mL) at 25 °C. The resulting solution was stirred at 95 °C for 12 hours. The reaction mixture was diluted with EtOAc (100 mL), and washed with brine (100 mL x 3). The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and evaporated to afford the crude product, which was purified by flash silica chromatography (0 – 10% EtOAc in petroleum ether) to afford **48i** (200 mg, 77%) as a yellow oil. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 1.53 (s, 9H), 5.56 (s, 2H), 6.92 (s, 1H), 6.91 – 7.00 (bs, 1H), 6.99 (dd, *J* = 5.0, 7.4 Hz, 1H), 7.26 (m, 1H), 7.29 – 7.42 (m, 3H), 7.47 (d, *J* = 6.9 Hz, 2H), 7.80 (dd, *J* = 1.8, 7.4 Hz, 1H), 8.12 (dd, *J* = 1.8, 5.0, 1H). LCMS ES<sup>+</sup> *m/z* = 383 [M+H]<sup>+</sup>.

*Step 3:* 4-(2-(Benzyloxy)pyridin-3-yl)thiophen-2-amine (**49i**). TBSOTf (346 mg, 1.31 mmol) was added to **48i** (200 mg, 0.52 mmol) in DCM (50 mL) at 25 °C. The resulting solution was stirred at 25 °C for 3 hours. The reaction mixture was diluted with EtOAc (50 mL), and washed sequentially with saturated NaHCO<sub>3</sub> (100 mL) and brine (100 mL). The organic layer was dried

over Na<sub>2</sub>SO<sub>4</sub>, filtered and evaporated to afford crude product **49i** (130 mg, 88%) as yellow solid. LCMS ES<sup>+</sup>  $m/z$  = 283 [M+H]<sup>+</sup>.

### 3-Fluoro-4-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzonitrile (**52**)

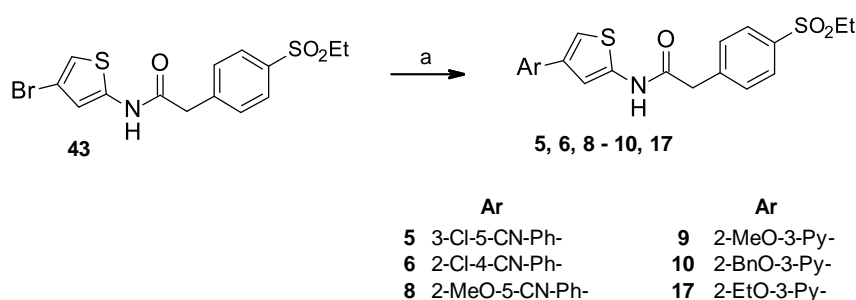


*Step 1: 3-bromo-5-fluoro-4-hydroxybenzonitrile.* NBS (3.1 g, 17.50 mmol) was added to 3-fluoro-4-hydroxybenzonitrile (2.0 g, 14.59 mmol) in THF (40 mL) under nitrogen. The resulting mixture was stirred at RT for 12 hours. The reaction mixture was diluted with EtOAc (75 mL), and washed sequentially with water (75 mL) and brine (2 × 75 mL). The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, (20 - 50% EtOAc in petroleum ether). Pure fractions were evaporated to dryness to afford 3-bromo-5-fluoro-4-hydroxybenzonitrile (3.0 g, 95%) as a pale yellow solid. <sup>1</sup>HNMR (400 MHz, CDCl<sub>3</sub>) δ 6.19 (s, 1H), 7.39 (dd,  $J$  = 1.6, 9.6 Hz, 1H), 7.63 (d,  $J$  = 1.6 Hz, 1H).

*Step 2: 3-bromo-5-fluoro-4-methoxybenzonitrile.* Iodomethane (26.3 g, 185.18 mmol) was added to 3-bromo-5-fluoro-4-hydroxybenzonitrile (20.0 g, 92.59 mmol) and K<sub>2</sub>CO<sub>3</sub> (25.6 g, 185.2 mmol) in acetone (300 mL) under nitrogen. The resulting mixture was stirred at 40 °C for 3 h. The reaction mixture was diluted with EtOAc (300 mL), and washed sequentially with water (2 × 100 mL) and brine (2 × 100 mL). The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography (10 - 30% EtOAc in petroleum ether). Pure fractions were evaporated to dryness to afford 3-bromo-5-fluoro-4-methoxybenzonitrile (19.0 g, 89%) as a pale yellow solid. <sup>1</sup>HNMR (400 MHz, CDCl<sub>3</sub>) δ 4.11 (s, 3H), 7.39 (dd,  $J$  = 1.6, 10.8 Hz, 1H), 7.67 (d,  $J$  = 1.6 Hz, 1H).

**Step 3: Synthesis of 52.** Pd(dppf)Cl<sub>2</sub> (1.1 g, 1.56 mmol) was added to 3-bromo-5-fluoro-4-methoxybenzonitrile (3.6 g, 15.65 mmol), (PinB)<sub>2</sub> (5.6 g, 21.91 mmol) and KOAc (3.1 g, 31.30 mmol) in dioxane (30 mL) under nitrogen. The resulting mixture was stirred at 120 °C for 6 h. The reaction mixture was quenched with water (20 mL), extracted with EtOAc (2 × 100 mL). The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and evaporated to afford brown residue. The crude product was purified by flash silica chromatography (0 - 10% EtOAc in petroleum ether). Pure fractions were evaporated to dryness to afford **52** (2.5 g, 58%) as a white solid. <sup>1</sup>HNMR (300 MHz, DMSO-d<sub>6</sub>) δ 1.31 (s, 12H), 3.93 (s, 3H), 7.70 (d, *J* = 2.1 Hz, 1H), 8.02 (dd, *J* = 2.1, 11.7 Hz, 1H). LCMS ES<sup>+</sup> *m/z* = 278 [M+H]<sup>+</sup>.

**Scheme 3.** Compounds prepared from intermediate **43**<sup>a</sup>



<sup>a</sup>Reagents and conditions: (a) ArB(OH)<sub>2</sub> or Arpin, PdCl<sub>2</sub>(dppf), K<sub>2</sub>CO<sub>3</sub>, dioxane/H<sub>2</sub>O (4:1), 80 °C.

**N-[4-(2-Chloro-5-cyano-phenyl)-2-thienyl]-2-(4-ethylsulfonylphenyl)acetamide (5).** 22 mg (15%). <sup>1</sup>H NMR (400MHz, DMSO-d<sub>6</sub>) δ 1.10 (t, *J* = 7.3 Hz, 3H), 3.27 (q, *J* = 7.3 Hz, 2H), 3.86 (s, 2H), 6.97 (d, *J* = 1.5 Hz, 1H), 7.27 (d, *J* = 1.5 Hz, 1H), 7.61 (d, *J* = 8.2 Hz, 2H), 7.77 (d, *J* = 8.3 Hz, 1H), 7.83 (dd, *J* = 1.9, 8.3 Hz, 1H), 7.86 (d, *J* = 8.2 Hz, 2H), 7.98 (d, *J* = 1.9 Hz, 1H), 11.63 (s, 1H). LCMS ES<sup>+</sup> *m/z* = 445 [M+H]<sup>+</sup>, purity 97%. HRMS (ES<sup>+</sup>) for C<sub>21</sub>H<sub>18</sub>ClN<sub>2</sub>O<sub>3</sub>S<sub>2</sub> [M+H]<sup>+</sup> calculated 445.0447, found 445.0464.

***N*-[4-(2-Chloro-4-cyano-phenyl)-2-thienyl]-2-(4-ethylsulfonylphenyl)acetamide (6).** 20 mg (13%). <sup>1</sup>H NMR (400MHz, DMSO-d<sub>6</sub>) δ 1.10 (t, *J* = 7.4 Hz, 3H), 3.28 (q, *J* = 7.4 Hz, 2H), 3.86 (s, 2H), 6.99 (d, *J* = 1.7 Hz, 1H), 7.31 (d, *J* = 1.7 Hz, 1H), 7.61 (d, *J* = 8.2 Hz, 2H), 7.68 (d, *J* = 8.0 Hz, 1H), 7.83 (dd, *J* = 1.9, 8.3 Hz, 1H), 7.85 (m, 1H), 7.86 (d, *J* = 8.2 Hz, 2H), 8.14 (d, *J* = 1.5 Hz, 1H), 11.64 (s, 1H). LCMS ES<sup>+</sup> *m/z* = 443 [M-H]<sup>+</sup>, purity 99%. HRMS (ES<sup>+</sup>) for C<sub>21</sub>H<sub>18</sub>ClN<sub>2</sub>O<sub>3</sub>S<sub>2</sub> [M+H]<sup>+</sup> calculated 445.0477, found 445.0464.

***N*-[4-(5-Cyano-2-methoxy-phenyl)-2-thienyl]-2-(4-ethylsulfonylphenyl)acetamide (8).** 24 mg (11%). <sup>1</sup>H NMR (300MHz, DMSO-d<sub>6</sub>) δ 1.10 (t, *J* = 7.4 Hz, 3H), 3.28 (q, *J* = 7.4 Hz, 2H), 3.85 (s, 2H), 3.92 (s, 3H), 7.08 (d, *J* = 1.7 Hz, 1H), 7.27 (d, *J* = 8.7 Hz, 1H), 7.33 (d, *J* = 1.5 Hz, 1H), 7.61 (d, *J* = 8.3 Hz, 2H), 7.78 (dd, *J* = 8.6, 2.1 Hz, 1H), 7.86 (d, *J* = 8.3 Hz, 2H), 7.90 (d, *J* = 2.1 Hz, 1H), 11.53 (s, 1H). LCMS ES<sup>+</sup> *m/z* = 439 [M-H]<sup>+</sup>, purity 98%. HRMS (ES<sup>+</sup>) for C<sub>22</sub>H<sub>21</sub>N<sub>2</sub>O<sub>4</sub>S<sub>2</sub> [M+NH<sub>4</sub>]<sup>+</sup> calculated 458.1208, found 458.1214.

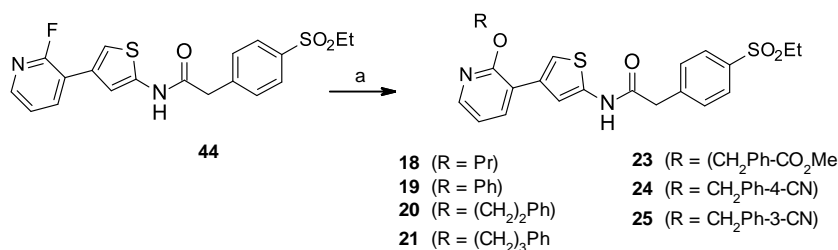
**2-(4-Ethylsulfonylphenyl)-*N*-[4-(2-methoxy-3-pyridyl)-2-thienyl]acetamide (9).** 61 mg (29%). <sup>1</sup>H NMR (400MHz, DMSO-d<sub>6</sub>) δ 1.10 (t, *J* = 7.4 Hz, 3H), 3.28 (q, *J* = 7.4 Hz, 2H), 3.85 (s, 2H), 3.94 (s, 3H), 7.06 (dd, *J* = 4.9, 7.4 Hz, 1H), 7.13 (d, *J* = 1.6 Hz, 1H), 7.35 (d, *J* = 1.6 Hz, 1H), 7.61 (d, *J* = 8.3 Hz, 2H), 7.86 (d, *J* = 8.3 Hz, 2H), 7.90 (dd, *J* = 1.7, 7.4 Hz, 1H), 8.11 (dd, *J* = 1.7, 4.9 Hz, 1H), 11.55 (s, 1H). <sup>13</sup>C NMR (126 MHz, DMSO) δ 7.2, 41.6, 49.2, 53.3, 111.4, 115.8, 117.4, 118.6, 127.9, 130.2, 132.4, 136.9, 137.1, 139.1, 140.8, 141.6, 145.0, 159.7, 166.5. LCMS ES<sup>+</sup> *m/z* = 417 [M+H]<sup>+</sup>, purity 98%. HRMS (ES<sup>+</sup>) for C<sub>20</sub>H<sub>21</sub>N<sub>2</sub>O<sub>4</sub>S<sub>2</sub> [M+H]<sup>+</sup> calculated 417.0943, found 417.0949.

***N*-{4-[2-(Benzyloxy)-3-pyridinyl]-2-thienyl}-2-[4-(ethylsulfonyl)phenyl]acetamide (10).** 41 mg (87%). <sup>1</sup>H NMR (300MHz, DMSO-d<sub>6</sub>) δ 1.10 (t, *J* = 7.4 Hz, 3H), 3.28 (q, *J* = 7.4 Hz, 2H),

3.85 (s, 2H), 5.49 (s, 2H), 7.08 (dd,  $J = 4.9, 7.4$  Hz, 1H), 7.16 (d,  $J = 1.6$  Hz, 1H), 7.24 – 7.42 (m, 4H), 7.46 (d,  $J = 7.0$  Hz, 2H), 7.61 (d,  $J = 8.3$  Hz, 2H), 7.86 (d,  $J = 8.3$  Hz, 2H), 7.92 (dd,  $J = 1.7, 7.4$  Hz, 1H), 8.10 (dd,  $J = 1.7, 4.9$  Hz, 1H), 11.55 (s, 1H). LCMS ES<sup>+</sup>  $m/z = 493$  [M+H]<sup>+</sup>, purity 97%. HRMS (ES<sup>+</sup>) for C<sub>26</sub>H<sub>25</sub>N<sub>2</sub>O<sub>4</sub>S<sub>2</sub> [M+H]<sup>+</sup> calculated 493.1255, found 493.1244.

***N*-[4-(2-Ethoxy-3-pyridyl)-2-thienyl]-2-(4-ethylsulfonylphenyl)acetamide (17).** 88 mg (41%). <sup>1</sup>H NMR (300MHz, DMSO-d<sub>6</sub>) δ 1.10 (t,  $J = 7.4$  Hz, 3H), 1.38 (t,  $J = 7.0$  Hz, 3H), 3.28 (q,  $J = 7.4$  Hz, 2H), 3.86 (s, 2H), 4.41 (q,  $J = 7.0$  Hz, 2H), 7.03 (dd,  $J = 7.5, 4.9$  Hz, 1H), 7.16 (d,  $J = 1.7$  Hz, 1H), 7.38 (d,  $J = 1.7$  Hz, 1H), 7.61 (d,  $J = 8.4$  Hz, 2H), 7.86 (d,  $J = 8.4$  Hz, 2H), 7.90 (dd,  $J = 7.5, 1.9$  Hz, 1H), 8.08 (dd,  $J = 4.9, 1.8$  Hz, 1H), 11.54 (s, 1H). <sup>13</sup>C NMR (126 MHz, DMSO) δ 7.2, 14.6, 41.6, 49.2, 61.4, 111.4, 115.7, 117.2, 118.4, 127.9, 130.3, 132.5, 136.9, 137.0, 139.1, 141.6, 145.0, 159.4, 166.5. LCMS ES<sup>+</sup>  $m/z = 431$  [M+H]<sup>+</sup>, purity 99%. HRMS (ES<sup>+</sup>) for C<sub>21</sub>H<sub>23</sub>N<sub>2</sub>O<sub>4</sub>S<sub>2</sub> [M+H]<sup>+</sup> calculated 431.1099, found 431.1076.

**Scheme 4.** Synthesis of compounds **18–21** and **23–25** from intermediate **44**<sup>a</sup>



<sup>a</sup>Reagent and conditions: (a) ROH, KO<sup>t</sup>Bu, THF, 80 °C.

**2-(4-Ethylsulfonylphenyl)-*N*-[4-(2-propoxy-3-pyridyl)-2-thienyl]acetamide (18).** To a solution of **44** (100 mg, 0.25 mmol) and *n*-propanol (59.4 mg, 0.99 mmol) in THF (10 mL) KO<sup>t</sup>Bu (55.5 mg, 0.49 mmol) was added to under nitrogen. The resulting mixture was stirred at 80 °C for 70 hours. The reaction mixture was diluted with EtOAc (50 mL), and washed

sequentially with saturated NaHCO<sub>3</sub> (25 mL), saturated brine (100 mL). The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and evaporated to afford the crude product, which was purified by flash silica chromatography (25 - 50% EtOAc in petroleum ether) to afford **18** (60 mg, 54%) as a white solid. <sup>1</sup>H NMR (300MHz, DMSO-d<sub>6</sub>) δ 1.00 (t, *J* = 7.4 Hz, 3H), 1.10 (t, *J* = 7.4 Hz, 3H), 1.79 (h, *J* = 7.1 Hz, 2H), 3.28 (q, *J* = 7.3 Hz, 2H), 3.86 (s, 2H), 4.32 (t, *J* = 6.6 Hz, 2H), 7.03 (dd, *J* = 7.5, 4.9 Hz, 1H), 7.15 (d, *J* = 1.7 Hz, 1H), 7.36 (d, *J* = 1.5 Hz, 1H), 7.61 (d, *J* = 8.3 Hz, 2H), 7.86 (d, *J* = 8.3 Hz, 2H), 7.90 (dd, *J* = 1.8, 7.5 Hz, 1H), 8.08 (dd, *J* = 4.9, 1.8 Hz, 1H), 11.54 (s, 1H). LCMS ES<sup>+</sup> *m/z* = 445 [M+H]<sup>+</sup>. HRMS (ES<sup>+</sup>) for C<sub>22</sub>H<sub>25</sub>N<sub>2</sub>O<sub>4</sub>S<sub>2</sub> [M+H]<sup>+</sup> calculated 445.1255, found 445.1233.

**2-(4-Ethylsulfonylphenyl)-N-[4-(2-phenoxy-3-pyridyl)-2-thienyl]acetamide (19).** The same procedure as for **18** was applied; scale: 0.37 mmol **44**; yield: 14 mg (8%). <sup>1</sup>H NMR (300MHz, DMSO-d<sub>6</sub>) δ 1.09 (t, *J* = 7.3 Hz, 3H), 3.27 (q, *J* = 7.4 Hz, 2H), 3.83 (s, 2H), 7.14 (d, *J* = 7.5 Hz, 2H), 7.17 – 7.26 (m, 3H), 7.38 – 7.48 (m, 3H), 7.59 (d, *J* = 8.3 Hz, 2H), 7.85 (d, *J* = 8.3 Hz, 2H), 8.04 (dd, *J* = 1.8, 4.8 Hz, 1H), 8.7 (dd, *J* = 1.8, 7.5 Hz, 1H), 11.58 (s, 1H). LCMS ES<sup>+</sup> *m/z* = 479 [M+H]<sup>+</sup>. HRMS (ES<sup>+</sup>) for C<sub>25</sub>H<sub>23</sub>N<sub>2</sub>O<sub>4</sub>S<sub>2</sub> [M+H]<sup>+</sup> calculated 479.1099, found 479.1111.

**2-(4-Ethylsulfonylphenyl)-N-[4-[2-(2-phenylethoxy)-3-pyridyl]-2-thienyl]acetamide (20).** The same procedure as for **18** was applied; scale: 0.3 mmol **44**; yield: 50 mg (33%). <sup>1</sup>H NMR (300MHz, DMSO-d<sub>6</sub>) δ 1.09 (t, *J* = 7.4 Hz, 3H), 3.10 (t, *J* = 6.8 Hz, 2H), 3.27 (q, *J* = 7.4 Hz, 2H), 3.86 (s, 2H), 4.58 (t, *J* = 6.8 Hz, 2H), 7.03 (dd, *J* = 7.4, 4.9 Hz, 1H), 7.10 (d, *J* = 1.7 Hz, 1H), 7.15 – 7.36 (m, 6H), 7.61 (d, *J* = 8.3 Hz, 2H), 7.82 – 7.93 (m, 3H), 8.08 (dd, *J* = 4.9, 1.8 Hz, 1H), 11.50 (s, 1H). LCMS ES<sup>+</sup> *m/z* = 507 [M+H]<sup>+</sup>. HRMS (ES<sup>+</sup>) for C<sub>27</sub>H<sub>27</sub>N<sub>2</sub>O<sub>4</sub>S<sub>2</sub> [M+H]<sup>+</sup> calculated 507.1412, found 507.1396.



**2-(4-Ethylsulfonylphenyl)-N-[4-[2-(3-phenylpropoxy)-3-pyridyl]-2-thienyl]acetamide**

**(21).** The same procedure as for **18** was applied; scale: 0.25 mmol **44**, yield: 50 mg (39%). <sup>1</sup>H NMR (400MHz, DMSO-d<sub>6</sub>) δ 1.10 (t, *J* = 7.4 Hz, 3H), 2.09 (p, *J* = 6.7 Hz, 2H), 2.72 – 2.79 (m, 2H), 3.28 (q, *J* = 7.4 Hz, 2H), 3.86 (s, 2H), 4.34 (t, *J* = 6.6 Hz, 2H), 7.05 (dd, *J* = 7.4, 4.9 Hz, 1H), 7.16 – 7.32 (m, 6H), 7.38 (d, *J* = 1.5 Hz, 1H), 7.61 (d, *J* = 8.3 Hz, 2H), 7.86 (d, *J* = 8.3 Hz, 2H), 7.91 (dd, *J* = 7.4, 1.8 Hz, 1H), 8.08 (dd, *J* = 4.9, 1.8 Hz, 1H), 11.56 (s, 1H). LCMS ES<sup>+</sup> *m/z* = 521 [M+H]<sup>+</sup>. HRMS (ES<sup>+</sup>) for C<sub>28</sub>H<sub>29</sub>N<sub>2</sub>O<sub>4</sub>S<sub>2</sub> [M+H]<sup>+</sup> calculated 521.1569, found 521.1588.

**Methyl 4-[[3-[5-[[2-(4-ethylsulfonylphenyl)acetyl]amino]-3-thienyl]-2-pyridyl]oxymethyl]**

**benzoate (23).** Reaction of **44** (56 mg, 0.49 mmol) and methyl 4-hydroxymethylbenzoate (82 mg, 0.49 mmol) under the same conditions as described for **18**. After 4 h at 90 °C, the mixture was quenched with water, the pH was adjusted to 3 using 2 M HCl, and the resulting mixture extracted with EtOAc. Drying over Na<sub>2</sub>SO<sub>4</sub> and evaporation afforded 4-(((3-(5-(2-(4-ethylsulfonylphenyl)-acetamido)thiophen-3-yl)pyridin-2-yl)oxy)methyl)benzoic acid (100 mg, 75%); LCMS ES<sup>+</sup> *m/z* = 537 [M+H]<sup>+</sup>. The acid was esterified using TMS-diazomethane: 90 mg acid (0.17 mmol) was dissolved in a mixture of DCM (3 mL) and MeOH (1 mL). TMS diazomethane (2 M in hexanes, 1.5 eq., 0.17 mmol) was added and the resulting mixture stirred at RT for 2 h. Evaporation and C18-flash chromatography (0 to 100% MeCN in water) afforded **23** (13 mg, 14%) as a solid. <sup>1</sup>H NMR (400MHz, DMSO-d<sub>6</sub>) δ 1.10 (t, *J* = 7.3 Hz, 3H), 3.28 (q, *J* = 7.3 Hz, 2H), 3.86 (s, 5H), 5.58 (s, 2H), 7.10 (dd, *J* = 7.4, 4.9 Hz, 1H), 7.19 (s, 1H), 7.38 (s, 1H), 7.60 (d, *J* = 7.8 Hz, 2H), 7.63 (d, *J* = 7.8 Hz, 2H), 7.86 (d, *J* = 8.2 Hz, 2H), 7.97 (dd, *J* = 11.6, 7.9 Hz, 3H), 8.10 (d, *J* = 3.5 Hz, 1H), 11.58 (s, 1H). LCMS ES<sup>+</sup> *m/z* = 551 [M+H]<sup>+</sup>. HRMS (ES<sup>+</sup>) for C<sub>28</sub>H<sub>27</sub>N<sub>2</sub>O<sub>6</sub>S<sub>2</sub> [M+H]<sup>+</sup> calculated 551.1310, found 551.1307.

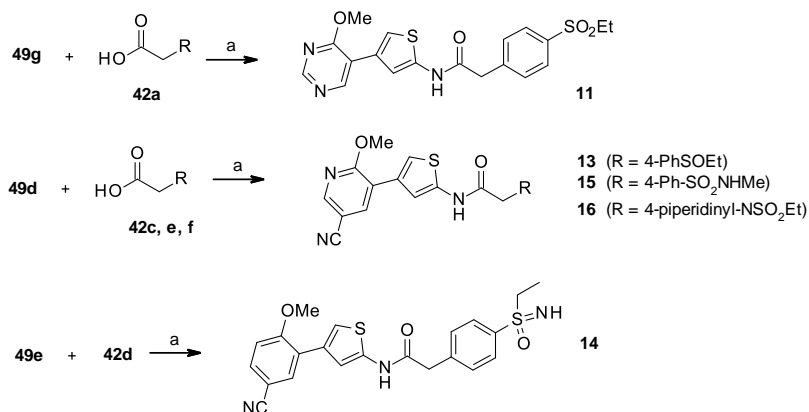
***N*-[4-[2-[(4-Cyanophenyl)methoxy]-3-pyridyl]-2-thienyl]-2-(4-ethylsulfonylphenyl)**

**acetamide (24).** The same procedure as for **18** was applied; scale: 0.37 mmol **44**; yield: 92 mg, 48%. <sup>1</sup>H NMR (300MHz, DMSO-d<sub>6</sub>) δ 1.09 (t, *J* = 7.4 Hz, 3H), 3.27 (q, *J* = 7.4 Hz, 2H), 3.86 (s, 2H), 5.59 (s, 2H), 7.09 (dd, *J* = 7.4, 4.9 Hz, 1H), 7.17 (d, *J* = 1.7 Hz, 1H), 7.39 (s, 1H), 7.61 (d, *J* = 8.2 Hz, 2H), 7.63 (d, *J* = 8.0 Hz, 2H), 7.85 (d, *J* = 8.0, 2H), 7.86 (d, *J* = 8.2, 2H), 7.95 (dd, *J* = 1.7, 7.4 Hz, 1H), 8.10 (dd, *J* = 4.8, 1.8 Hz, 1H), 11.56 (s, 1H). <sup>13</sup>C NMR (126 MHz, DMSO) δ 7.2, 41.6, 49.2, 66.2, 110.2, 111.4, 115.9, 118.0, 118.8, 118.9, 127.8, 127.9, 130.2, 132.3, 132.4, 136.9, 137.6, 139.3, 141.6, 143.5, 145.0, 158.7, 166.6. LCMS ES<sup>+</sup> *m/z* = 518 [M+H]<sup>+</sup>. HRMS (ES<sup>+</sup>) for C<sub>27</sub>H<sub>24</sub>N<sub>3</sub>O<sub>4</sub>S<sub>2</sub> [M+H]<sup>+</sup> calculated 518.1208, found 518.1190.

***N*-[4-[2-[(3-Cyanophenyl)methoxy]-3-pyridyl]-2-thienyl]-2-(4-ethylsulfonylphenyl)**

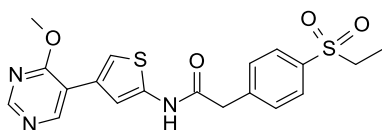
**acetamide (25).** The same procedure as for **18** was applied; scale: 0.37 mmol **44**; yield: 67 mg, 35%. <sup>1</sup>H NMR (300MHz, DMSO-d<sub>6</sub>) δ 1.10 (t, *J* = 7.3 Hz, 3H), 3.28 (d, *J* = 7.3 Hz, 2H), 3.85 (s, 2H), 5.53 (s, 2H), 7.10 (dd, *J* = 7.5, 4.9 Hz, 1H), 7.16 (d, *J* = 1.7 Hz, 1H), 7.37 (d, *J* = 1.6 Hz, 1H), 7.60 (d, *J* = 8.3 Hz, 2H), 7.57 – 7.63 (m, 1H), 7.77 – 7.83 (m, 2H), 7.86 (d, *J* = 8.3 Hz, 2H), 7.91 (s, 1H), 7.94 (dd, *J* = 7.5, 1.8 Hz, 1H), 8.11 (dd, *J* = 4.8, 1.7 Hz, 1H), 11.56 (s, 1H). <sup>13</sup>C NMR (126 MHz, DMSO-*d*<sub>6</sub>) δ 7.2, 41.6, 49.2, 66.0, 111.4, 111.44, 115.9, 118.0, 118.7, 118.8, 127.7, 129.7, 130.2, 130.8, 131.4, 132.2, 132.3, 136.9, 137.6, 139.3, 139.34, 141.6, 145.0, 158.8, 166.6. LCMS ES<sup>+</sup> *m/z* = 518 [M+H]<sup>+</sup>. HRMS (ES<sup>+</sup>) for C<sub>27</sub>H<sub>24</sub>N<sub>3</sub>O<sub>4</sub>S<sub>2</sub> [M+H]<sup>+</sup> calculated 518.1208, found 518.1214.

**Scheme 5.** Synthesis of compounds **11**, **13-16**<sup>a</sup>



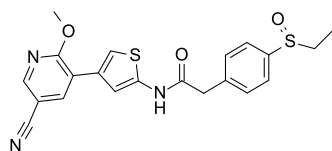
<sup>a</sup>Reagents and conditions: (a) for **11** and **16**: EDC, DMAP, THF; for **13** and **14**: HBTU, DCM, NEt<sub>3</sub>, RT; for **15**: TBTU, DCM, NEt<sub>3</sub>, RT.

## 2-[4-(Ethylsulfonyl)phenyl]-N-[4-(4-methoxy-5-pyrimidinyl)-2-thienyl]acetamide (**11**)



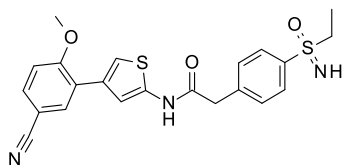
Compound **49g** (340 mg, 1.06 mmol) was added to a solution of **42a** (266 mg, 1.16 mmol), DMAP (259 mg, 2.12 mmol) and EDC (304 mg, 1.59 mmol) in THF (10 mL) under nitrogen. The resulting mixture was stirred at RT for 4 hours. The reaction mixture was diluted with EtOAc (20 mL), and washed with brine (20 mL). The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and evaporated to afford the crude product, which was purified by flash silica chromatography (0 - 75% EtOAc in petroleum ether). The product was further purified by crystallisation from EtOAc/MeOH to afford **11** (70 mg, 16%) as a pale yellow solid. <sup>1</sup>H NMR (300 MHz, DMSO) δ 1.10 (t, *J* = 7.4 Hz, 3H), 3.27 (q, *J* = 7.4 Hz, 2H), 3.86 (s, 2H), 4.03 (s, 3H), 7.14 (d, *J* = 1.7 Hz, 1H), 7.46 (d, *J* = 1.7 Hz, 1H), 7.61 (d, *J* = 8.3 Hz, 2H), 7.86 (d, *J* = 8.3 Hz, 2H), 8.72 (s, 1H), 8.77 (s, 1H), 11.61 (s, 1H). LCMS ES<sup>+</sup> *m/z* = 418 [M+H]<sup>+</sup>. HRMS (ES<sup>+</sup>) for C<sub>19</sub>H<sub>20</sub>N<sub>3</sub>O<sub>4</sub>S<sub>2</sub> [M+H]<sup>+</sup> calculated 418.0895, found 418.0893.

## N-[4-(5-Cyano-2-methoxy-3-pyridyl)-2-thienyl]-2-[4-[ethylsulfinyl]phenyl]acetamide (**13**)



To a mixture of **42a** (7.93 mg, 0.04 mmol) and HBTU (18.41 mg, 0.05 mmol) in DCM (0.2 mL), was added Et<sub>3</sub>N (0.016 mL, 0.11 mmol) and the reaction mixture stirred at RT for 10 min. To this mixture **49d** (10 mg, 0.04 mmol) was added and the reaction mixture was stirred at RT overnight. The volatiles were removed *in vacuo*, the residue was dissolved in DMSO (1.5 mL), filtered and the filtrate was purified by RP-HPLC (gradient 5-95% ACN in 0.1 M HCO<sub>2</sub>H, pH 3; Column: Waters Sunfire C18 ODB 5μ 19x150mm) to afford **13** (6 mg, 37%). <sup>1</sup>H NMR (300MHz, DMSO-d<sub>6</sub>) δ 1.02 (t, *J* = 7.3 Hz, 3H), 2.74 (dq, *J* = 14.5, 7.3 Hz, 1H), 2.99 (dd, *J* = 14.1, 7.3 Hz, 1H), 3.79 (s, 2H), 4.03 (s, 3H), 7.15 (d, *J* = 1.7 Hz, 1H), 7.49 (d, *J* = 1.7 Hz, 1H), 7.52 (d, *J* = 8.2 Hz, 2H), 7.60 (d, *J* = 8.2 Hz, 2H), 8.36 (d, *J* = 2.2 Hz, 1H), 8.62 (d, *J* = 2.1 Hz, 1H), 11.58 (s, 1H). LCMS ES<sup>+</sup> *m/z* = 426 [M+H]<sup>+</sup>. HRMS (ES<sup>+</sup>) for C<sub>21</sub>H<sub>20</sub>N<sub>3</sub>O<sub>3</sub>S<sub>2</sub> [M+H]<sup>+</sup> calculated 426.0946, found 426.0912.

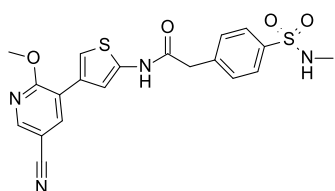
***N*-[4-(5-Cyano-2-methoxy-phenyl)-2-thienyl]-2-[4-(ethylsulfonimidoyl)phenyl]acetamide (14)**



To a mixture of **42d** (40 mg, 0.18 mmol), **49e** (40.5 mg, 0.18 mmol) and HBTU (85 mg, 0.26 mmol) in DCM (0.5 mL) Et<sub>3</sub>N (0.074 mL, 0.53 mmol) was added and the reaction mixture stirred at RT for 6h, and then concentrated. The residue was dissolved in DMSO (2 mL) and purified on a Waters Viridis 2-EP 5μ 30x250mm column, using MeOH/NH<sub>3</sub> (20 mM) to give **14** (8 mg, 10%). <sup>1</sup>H NMR (600 MHz, DMSO) δ 1.06 (t, *J* = 7.4 Hz, 3H), 3.11 (q, *J* = 7.4 Hz,

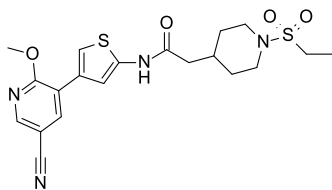
2H), 3.81 (s, 2H), 3.92 (s, 3H), 4.14 (s, 1H), 7.08 (d,  $J = 1.7$  Hz, 1H), 7.27 (d,  $J = 8.7$  Hz, 1H), 7.33 (d,  $J = 1.7$  Hz, 1H), 7.54 (d,  $J = 8.4$  Hz, 2H), 7.77 (dd,  $J = 8.6, 2.2$  Hz, 1H), 7.83 – 7.85 (m, 2H), 7.89 (d,  $J = 2.2$  Hz, 1H), 11.51 (s, 1H). LCMS ES<sup>+</sup>  $m/z = 440$  [M+H]<sup>+</sup>. HRMS (ES<sup>+</sup>) for C<sub>22</sub>H<sub>22</sub>N<sub>3</sub>O<sub>3</sub>S<sub>2</sub> [M+H]<sup>+</sup> calculated 440.1103, found 440.1112.

***N*-[4-(5-Cyano-2-methoxy-3-pyridyl)-2-thienyl]-2-[4-(methylsulfonyl)phenyl]acetamide  
(15)**



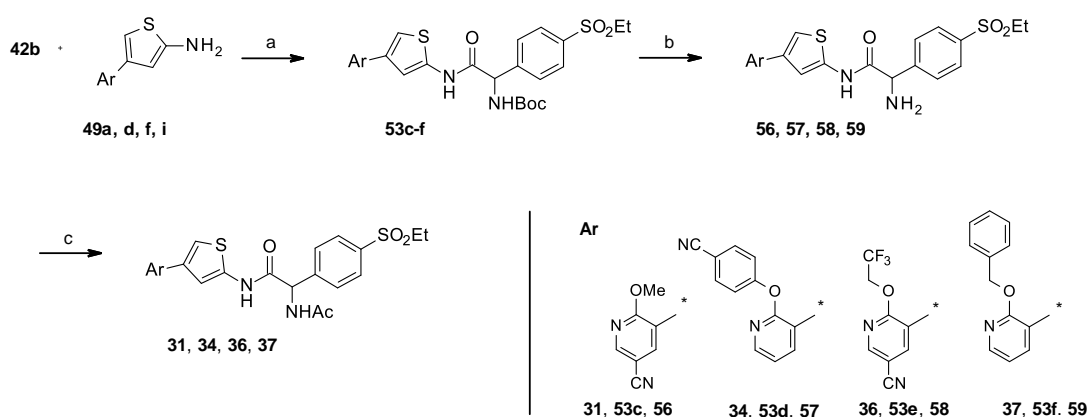
Compound **49d** (0.015 g, 0.06 mmol) was mixed with commercially available **42f** (0.015 g, 0.06 mmol) and diluted in DCM (1 mL) and Et<sub>3</sub>N (0.027 mL, 0.19 mmol). TBTU (0.025 g, 0.08 mmol) was added and the resulting mixture was stirred at ambient temperature for 16 h. The reaction mixture was partitioned between DCM (5 mL) and sat. NaHCO<sub>3</sub> (1 mL). The layers were separated in a phase separator and the organic layer was concentrated under reduced pressure. The residue was dissolved in DMSO (1 mL), filtered and purified by RP-HPLC (gradient 5-95% ACN in 0.1 M HCO<sub>2</sub>H, pH 3; Column: Waters Sunfire C18 ODB 5μ 19x150mm) to give **15** (91 mg, 32%). <sup>1</sup>H NMR (300MHz, DMSO-d<sub>6</sub>) δ 2.41 (d,  $J = 3.8$  Hz, 3H), 3.82 (s, 2H), 4.03 (s, 3H), 7.15 (d,  $J = 1.8$  Hz, 1H), 7.40 – 7.45 (m, 1H), 7.49 (d,  $J = 1.8$  Hz, 1H), 7.54 (d,  $J = 8.4$  Hz, 2H), 7.74 (d,  $J = 8.4$  Hz, 2H), 8.37 (d,  $J = 2.2$  Hz, 1H), 8.62 (d,  $J = 2.2$  Hz, 1H), 11.60 (s, 1H). LCMS ES<sup>+</sup>  $m/z = 443$  [M+H]<sup>+</sup>. HRMS (ES<sup>+</sup>) for C<sub>20</sub>H<sub>19</sub>N<sub>4</sub>O<sub>4</sub>S<sub>2</sub> [M+H]<sup>+</sup> calculated 443.0847, found 443.0862.

***N*-[4-(5-Cyano-2-methoxy-3-pyridyl)-2-thienyl]-2-(1-ethylsulfonyl-4-piperidyl)acetamide  
(16)**



Compound **49d** (100 mg, 0.43 mmol) was added to **42e** (153 mg, 0.65 mmol), EDC (99 mg, 0.52 mmol) and DMAP (158 mg, 1.30 mmol) in THF (8 mL). The resulting mixture was stirred at RT for 12 hours. The reaction mixture was diluted with EtOAc (25 mL), and washed sequentially with water (25 mL x 3) and brine (20 mL x 2). The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and evaporated to afford crude product which was purified by flash silica chromatography (10 to 50% EtOAc in petroleum ether). Pure fractions were evaporated to dryness to afford **16** (20 mg, 10%) as a solid. <sup>1</sup>H NMR (300MHz, DMSO-d<sub>6</sub>) δ 1.20 (t, *J* = 7.4 Hz, 3H), 1.23 – 1.33 (m, 2H), 1.74 (d, *J* = 11.4 Hz, 2H), 1.83 – 1.98 (m, 1H), 2.33 (d, *J* = 7.0 Hz, 2H), 2.71 – 2.96 (m, 2H), 3.02 (q, *J* = 7.4 Hz, 2H), 3.58 (d, *J* = 11.3 Hz, 2H), 4.03 (s, 3H), 7.11 (d, *J* = 1.6 Hz, 1H), 7.48 (d, *J* = 1.6 Hz, 1H), 8.36 (d, *J* = 2.1 Hz, 1H), 8.62 (d, *J* = 2.1 Hz, 1H), 11.29 (s, 1H). LCMS ES<sup>+</sup> *m/z* = 449 [M+H]<sup>+</sup>. HRMS (ES<sup>+</sup>) for C<sub>20</sub>H<sub>25</sub>N<sub>4</sub>O<sub>4</sub>S<sub>2</sub> [M+H]<sup>+</sup> calculated 449.1317, found 449.1330.

**Scheme 6. Synthesis of compounds 31, 34, 36 and 37<sup>a</sup>**



<sup>a</sup>Reagents and conditions: (a) EDC, HOBt, DIPEA, DCM, RT; (b) TBSOTf, DCM; (c) DCM, Ac<sub>2</sub>O, Et<sub>3</sub>N.

**2-Acetamido-*N*-[4-(5-cyano-2-methoxy-3-pyridyl)-2-thienyl]-2-(4-ethylsulfonylphenyl)acetamide (31).**

*Step 1:* *tert*-Butyl (2-((4-(5-cyano-2-methoxypyridin-3-yl)thiophen-2-yl)amino)-1-(4-(ethylsulfonyl)phenyl)-2-oxoethyl)carbamate (**53c**). DIPEA (0.121 mL, 0.69 mmol) was added to a mixture of HOBt (106 mg, 0.69 mmol), EDC (133 mg, 0.69 mmol), **49d** (160 mg, 0.69 mmol) and **42b** (238 mg, 0.69 mmol) in DCM (50 mL) at 25°C. The resulting solution was stirred at 25°C for 6 hours. The reaction mixture was diluted with EtOAc (125 mL), and washed with brine (125 mL). The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and evaporated to afford crude product, which was purified by flash silica chromatography (0 to 50% EtOAc in petroleum ether) to afford **53c** (320 mg, 83%) as a white solid. <sup>1</sup>H NMR (300MHz, CDCl<sub>3</sub>) δ 1.28 (t, *J* = 7.3 Hz, 3H), 1.46 (s, 9H), 3.11 (q, *J* = 7.4 Hz, 2H), 4.07 (s, 3H), 5.93 (s, 1H), 5.58 (s, 1H), 7.00 (s, 1H), 7.33 (s, 1H), 7.67 (d, *J* = 7.8 Hz, 2H), 7.83 – 7.90 (m, 3H), 8.38 (d, *J* = 1.8 Hz, 1H), 9.37 (s, 1H). LCMS ES<sup>+</sup> *m/z* = 557 [M+H]<sup>+</sup>.

*Step 2:* 2-Amino-*N*-(4-(5-cyano-2-methoxypyridin-3-yl)thiophen-2-yl)-2-(4-(ethylsulfonyl)phenyl)acetamide (**56**). TBSOTf (142 mg, 0.54 mmol) was added to **53c** (300mg, 0.54 mmol) in DCM (50 mL) at 0 °C. The resulting solution was stirred at 0 °C for 1 hour. The reaction mixture was diluted with EtOAc (125 mL), and washed sequentially with saturated brine (125 mL). The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and evaporated to afford crude product, which was purified by crystallisation from EtOAc and petroleum ether (1:1) to afford **56** (150 mg, 61%) as a yellow solid. <sup>1</sup>H NMR (300MHz, DMSO-*d*<sub>6</sub>) δ 1.09 (t, *J* = 7.4 Hz, 3H), 3.27 (q, *J* = 7.4 Hz, 2H), 4.03 (s, 3H), 4.74 (s, 1H), 5.34 – 5.95 (bs, 2H), 7.28 (d, *J* = 1.7 Hz, 1H), 7.50 (d, *J* = 1.7 Hz, 1H), 7.75 (d, *J* = 8.3 Hz, 2H), 7.88 (d, *J* = 8.3 Hz, 2H), 8.35 (d, *J* = 2.2 Hz, 1H), 8.62 (d, *J* = 2.2 Hz, 1H). LCMS ES<sup>+</sup> *m/z* = 457 [M+H]<sup>+</sup>.

*Step 3: Synthesis of 31.* Acetic anhydride (29.1 mg, 0.28 mmol) was added to a solution of Et<sub>3</sub>N (0.040 mL, 0.28 mmol) and **56** (130 mg, 0.28 mmol) in DCM (50 mL) at 25°C. The resulting solution was stirred at 25°C for 3 hours. The reaction mixture was diluted with EtOAc (75 mL), and washed with saturated brine (75 mL). The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and evaporated to afford crude product, which was purified by flash silica chromatography (0 to 100% EtOAc in petroleum ether) to afford **31** (100 mg, 70%) as a yellow solid. <sup>1</sup>H NMR (300MHz, DMSO-d<sub>6</sub>) δ 1.10 (t, *J* = 7.4 Hz, 3H), 1.96 (s, 3H), 3.29 (q, *J* = 7.4 Hz, 2H), 4.03 (s, 3H), 5.78 (d, *J* = 7.6 Hz, 1H), 7.19 (s, *J* = 1.2 Hz, 1H), 7.53 (d, *J* = 1.2 Hz, 1H), 7.73 (d, *J* = 8.3 Hz, 2H), 7.93 (d, *J* = 8.3 Hz, 2H), 8.38 (d, *J* = 2.1 Hz, 1H), 8.63 (d, *J* = 2.1 Hz, 1H), 8.93 (d, *J* = 7.5 Hz, 1H), 11.80 (s, 1H). <sup>13</sup>C NMR (126 MHz, DMSO) δ 7.1, 22.3, 49.1, 54.5, 56.1, 102.4, 112.1, 117.3, 117.8, 119.3, 128.2, 128.4, 130.6, 138.2, 138.9, 139.5, 143.4, 149.7, 161.8, 166.5, 169.5. LCMS ES<sup>+</sup> *m/z* = 499 [M+H]<sup>+</sup>. HRMS (ES<sup>+</sup>) for C<sub>23</sub>H<sub>23</sub>N<sub>4</sub>O<sub>5</sub>S<sub>2</sub> [M+H]<sup>+</sup> calculated 499.1110, found 499.1091.

**2-Acetamido-*N*-[4-[2-(4-cyanophenoxy)-3-pyridyl]-2-thienyl]-2-(4-ethylsulfonylphenyl)acetamide (34)**

*Step 1:* *tert*-Butyl (2-((4-(2-(4-cyanophenoxy)pyridin-3-yl)thiophen-2-yl)amino)-1-(4-(ethylsulfonyl)phenyl)-2-oxoethyl)carbamate (**53d**). Following the procedure for compound **31**, **49f** (188 mg, 0.64 mmol) was reacted with **42b** (200 mg, 0.58 mmol) to afford **53d** (200 mg, 56%) as a solid. <sup>1</sup>H NMR (300MHz, CDCl<sub>3</sub>) δ 1.29 (t, *J* = 7.4 Hz, 3H), 1.46 (s, 9H), 3.12 (q, *J* = 7.4 Hz, 2H), 5.57 (s, 1H), 5.95 (s, 1H), 7.09 (s, 1H), 7.14 – 7.20 (m, 1H), 7.23 (d, *J* = 8.3 Hz, 2H), 7.26 – 7.30 (m, 2H), 7.62 – 7.74 (m, 3H), 7.82 – 7.96 (m, 3H), 8.12 (d, *J* = 3.4 Hz, 1H), 9.37 (s, 1H). LCMS ES<sup>+</sup> *m/z* = 619 [M+H]<sup>+</sup>.



*Step 2:* 2-Amino-*N*-(4-(2-(4-cyanophenoxy)pyridin-3-yl)thiophen-2-yl)-2-(4-(ethylsulfonyl)phenyl)acetamide (**57**). Following the procedure for compound **31**, deprotection of **53d** (190 mg, 0.31 mmol) afforded **57** (130 mg, 82%) as a solid. LCMS ES<sup>+</sup>  $m/z$  = 519 [M+H]<sup>+</sup>.

*Step 3:* Synthesis of **34**. Acetylation of **57** (120 mg, 0.23 mmol), according to the procedure described for compound **31**, afforded **34** (90 mg, 69%). <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  1.09 (t,  $J$  = 7.4 Hz, 3H), 1.94 (s, 3H), 3.28 (q,  $J$  = 7.4 Hz, 2H), 5.74 (d,  $J$  = 7.6 Hz, 1H), 7.18 (d,  $J$  = 1.7 Hz, 1H), 7.28 (dd,  $J$  = 4.8, 7.5 Hz, 1H), 7.35 (d,  $J$  = 8.6 Hz, 2H), 7.47 (d,  $J$  = 1.6 Hz, 1H), 7.70 (d,  $J$  = 8.4 Hz, 2H), 7.90 (d,  $J$  = 8.5 Hz, 2H), 7.91 (d,  $J$  = 8.3 Hz, 2H), 8.10 (dd,  $J$  = 1.8, 4.7 Hz, 1H), 8.12 (dd,  $J$  = 1.6, 7.5 Hz, 1H), 8.82 (d,  $J$  = 7.6 Hz, 1H), 11.79 (s, 1H). <sup>13</sup>C NMR (126 MHz, DMSO)  $\delta$  7.1, 22.3, 49.1, 56.1, 106.8, 112.1, 116.8, 118.7, 120.3, 120.7, 122.1, 128.2, 128.4, 131.8, 134.2, 138.2, 139.0, 139.1, 143.4, 145.7, 157.9, 158.0, 166.4, 169.4. LCMS ES<sup>+</sup>  $m/z$  = 561 [M+H]<sup>+</sup>. HRMS (ES<sup>+</sup>) for C<sub>28</sub>H<sub>25</sub>N<sub>4</sub>O<sub>5</sub>S<sub>2</sub> [M+H]<sup>+</sup> calculated 561.1266, found 561.1285.

**2-Acetamido-*N*-[4-[5-cyano-2-(2,2,2-trifluoroethoxy)-3-pyridyl]-2-thienyl]-2-(4-ethylsulfonylphenyl)acetamide (36)**

*Step 1:* *tert*-Butyl (2-((4-(5-cyano-2-(2,2,2-trifluoroethoxy)pyridin-3-yl)thiophen-2-yl)amino)-1-(4-(ethylsulfonyl)phenyl)-2-oxoethyl)carbamate (**53e**). Following the procedure for compound **31**, **49a** (145 mg, 0.49 mmol) was reacted with **42b** (200 mg, 0.58 mmol) to afford **53e** (120 mg, 40%) as a solid. <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  1.09 (t,  $J$  = 7.3 Hz, 3H), 1.40 (s, 9H), 3.27 (q,  $J$  = 7.3 Hz, 2H), 5.17 (q,  $J$  = 8.8 Hz, 2H), 5.53 (s, 1H), 7.16 (d,  $J$  = 1.5 Hz, 1H), 7.48 (d,  $J$  = 1.5 Hz, 1H), 7.74 (d,  $J$  = 8.3 Hz, 2H), 7.90 (d,  $J$  = 8.3 Hz, 2H), 7.92 – 7.97 (m, 1H), 8.50 (d,  $J$  = 2.1 Hz, 1H), 8.67 (d,  $J$  = 2.1 Hz, 1H), 11.75 (s, 1H). LCMS ES<sup>+</sup>  $m/z$  = 625 [M+H]<sup>+</sup>.

*Step 2:* 2-Amino-*N*-{4-[5-cyano-2-(2,2,2-trifluoroethoxy)-3-pyridinyl]-2-thienyl}-2-[4-(ethylsulfonyl)phenyl]acetamide (**58**). Following the procedure for compound **31**, deprotection of

**53e** (110 mg, 0.18 mmol) afforded **58** (80 mg, 87%) as a solid.  $^1\text{H}$  NMR (300MHz, DMSO- $d_6$ )  $\delta$  1.09 (t,  $J$  = 7.4 Hz, 3H), 3.26 (q,  $J$  = 7.4 Hz, 2H), 4.75 (s, 1H), 5.18 (q,  $J$  = 8.9 Hz, 2H), 5.41 – 5.81 (bs, 3H), 7.24 (d,  $J$  = 1.7 Hz, 1H), 7.46 (d,  $J$  = 1.7 Hz, 1H), 7.74 (d,  $J$  = 8.4 Hz, 2H), 7.87 (d,  $J$  = 8.4 Hz, 2H), 8.48 (d,  $J$  = 2.1 Hz, 1H), 8.67 (d,  $J$  = 2.1 Hz, 1H). LCMS ES $^+$   $m/z$  = 525 [M+H] $^+$ .

*Step 3: Synthesis of 36.* Acetylation of **58** (110 mg, 0.21 mmol), according to the procedure described for compound **31**, afforded **36** (80 mg, 67%).  $^1\text{H}$  NMR (500MHz, DMSO- $d_6$ )  $\delta$  1.10 (t,  $J$  = 7.4 Hz, 3H), 1.95 (s, 3H), 3.26 (q,  $J$  = 7.4 Hz, 2H), 5.17 (q,  $J$  = 8.9 Hz, 2H), 5.82 (d,  $J$  = 7.7 Hz, 1H), 7.16 (d,  $J$  = 1.6 Hz, 1H), 7.49 (d,  $J$  = 1.6 Hz, 1H), 7.73 (d,  $J$  = 8.3 Hz, 2H), 7.92 (d,  $J$  = 8.3 Hz, 2H), 8.50 (d,  $J$  = 2.0 Hz, 1H), 8.67 (d,  $J$  = 2.0 Hz, 1H), 8.95 (d,  $J$  = 7.7 Hz, 1H), 11.86 (s, 1H).  $^{13}\text{C}$  NMR (126 MHz, DMSO)  $\delta$  7.1, 22.3, 49.1, 56.0, 62.4 (q,  $J$  = 34.9 Hz), 104.2, 111.8, 116.9, 118.0, 119.3, 123.8 (q,  $J$  = 277.9 Hz), 128.2, 128.4, 130.0, 138.2, 139.3, 140.8, 143.4, 149.3, 159.3, 166.7, 169.5. LCMS ES $^+$   $m/z$  = 567 [M+H] $^+$ . HRMS (ES $^+$ ) for C<sub>24</sub>H<sub>22</sub>F<sub>3</sub>N<sub>4</sub>O<sub>5</sub>S<sub>2</sub> [M+H] $^+$  calculated 567.0984, found 567.0985.

## **2-Acetamido-*N*-[4-(2-benzyloxy-3-pyridyl)-2-thienyl]-2-(4-ethylsulfonylphenyl)acetamide (37)**

*Step 1: tert*-Butyl (2-((4-(2-(benzyloxy)pyridin-3-yl)thiophen-2-yl)amino)-1-(4-(ethylsulfonyl)phenyl)-2-oxoethyl)carbamate (**53f**). Following the procedure for compound **31**, **49i** (156 mg, 0.55 mmol) was reacted with **42b** (190 mg, 0.55 mmol) to afford **53f** (150 mg, 45%) as a solid. LCMS ES $^+$   $m/z$  = 608 [M+H] $^+$ .

*Step 2:* 2-Amino-*N*-(4-(2-(benzyloxy)pyridin-3-yl)thiophen-2-yl)-2-(4-(ethylsulfonyl)phenyl)acetamide (**57**). Following the procedure for compound **31**, deprotection of **53f** (140 mg, 0.23 mmol) afforded **59** (120 mg, quantitative) as a solid. LCMS ES $^+$   $m/z$  = 508 [M+H] $^+$ .

*Step 3: Synthesis of 37.* Acetylation of **59** (90 mg, 0.18 mmol), according to the procedure described for compound **31**, afforded **37** (67 mg, 69%). <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ 1.10 (t, *J* = 7.4 Hz, 3H), 1.95 (s, 3H), 3.29 (q, *J* = 7.4 Hz, 2H), 5.43 – 5.55 (m, 2H), 5.77 (d, *J* = 7.6 Hz, 1H), 7.04 – 7.12 (m, 1H), 7.19 (s, 1H), 7.28 – 7.41 (m, 4H), 7.45 (d, *J* = 7.5 Hz, 2H), 7.73 (d, *J* = 8.2 Hz, 2H), 7.92 (d, *J* = 8.0 Hz, 3H), 8.11 (d, *J* = 4.8 Hz, 1H), 8.93 (d, *J* = 7.5 Hz, 1H), 11.76 (s, 1H). LCMS ES<sup>+</sup> *m/z* = 550 [M+H]<sup>+</sup>. HRMS (ES<sup>+</sup>) for C<sub>28</sub>H<sub>28</sub>N<sub>3</sub>O<sub>5</sub>S<sub>2</sub> [M+H]<sup>+</sup> calculated 550.1470, found 550.1469.

### **X-ray analysis of ligand complexes**

Complete data were collected at the European Synchrotron Radiation Facility (ESRF, Grenoble, France) for all the crystals. The data were processed with XDS or MOSFLM.<sup>1,2</sup> The structures of RORγ complexes were determined by molecular replacement (Phaser<sup>3</sup>) using the RORγ-25-hydroxylcholesterol complex structure (PDB: 3L0L) as the search model. Programs Autobuster<sup>4</sup> and Coot<sup>5</sup> were used for refinement and model (re)building. The final refined structures have R (R<sub>free</sub>) values ranging from 0.192 to 0.236 (0.227 to 0.265) and showed excellent geometry in the Ramachandran plot. See Table S1 in the supporting information for details of the data collection and structure refinement. The atomic coordinates and the structure factors of the RORγ complexes have been deposited in the protein data bank ([www.pdb.org](http://www.pdb.org)) with PDB ID's 5NI5, 5NI7, 5NI8, 6FGQ, 5NIB and 6ESN.

1. W. Kabsch, Acta Crystallogr. D Biol. Crystallogr. 2010, 66, 125-132.
2. A.G.W. Leslie and H.R. Powell (2007), Processing Diffraction Data with Mosflm, Evolving Methods for Macromolecular Crystallography, 245, 41-51 ISBN 978-1-4020-6314-5
3. Collaborative Computational Project, Number 4, Acta Crystallogr. D Biol. Crystallogr. 1994, 50, 760-763.

4. G. Bricogne, E. Blanc, M. Brandl, C. Flensburg, P. Keller, W. Paciorek, P. Roversi, O.S. Smart, C. Vonnrhein, T.O. Womack, 2009, 2.11.1.
5. P. Emsley, K. Cowtan, Acta Crystallogr. D Biol. Crystallogr. 2004, 60, 2126-2132.

**Table S1. X-ray data collection and refinement statistics**

<b>Data collection</b> (complex with) / PDB code	<b>1 / 5NI5</b>	<b>8 / 5NI7</b>	<b>10 / 5NI8</b>	<b>23 / 6FGQ</b>	<b>25 / 5NIB</b>	<b>32 / 6ESN</b>
Wavelength ( Å ) (Beamline at ESRF)	0.979 (ID23-1)	0.984 (ID23-1)	0.984 (ID23-1)	0.972 (ID23-1)	0.976 (ID23-1)	0.976 (ID29)
Space group	P41212	P41212	P41212	P61	P41212	P41212
Cell parameter ( Å )	62.31 62.31 158.64	62.62 62.62 157.3	62.15 62.15 158.3	99.55 99.55 129.5	62.14 62.14 158.25	62.25 62.25 157.3
Resolution ( Å ) (last shell)	2.30 (2.30-2.36)	2.45 (2.45-2.54)	1.94 (1.94-2.01)	2.37 (2.37-2.45)	1.82 (1.82-1.92)	1.84 (1.84-1.90)
Unique reflections	14115	12226	23286	29472	28799	26861
Rmerge (%) (all/last shell)	0.127/0.882	0.131/1.370	0.242/1.457	0.094/1.233	0.127/2.352	0.096/4.711
I/ $\sigma$ (all/last shell)	7.0/2.7	12.9/1.9	8.7/1.7	14.0/1.8	14.7/1.2	15.3/0.6
Completeness (%) (all/last shell)	96.6/91.3	100.0/100.0	98.1/97.0	99.8/97.8	100.0/99.9	96.8/95.8
Redundancy (all/last shell)	6.5/5.8	12.4/13.4	12.4/13.1	10.1/10.2	12.7/13.3	12.7/13.1
<b>Structure refinement</b>						
Resolution (last shell) ( Å )	33.85-2.30 (2.30-2.48)	48.99-2.45 (2.45-2.68)	43.95-1.94 (1.94-2.03)	40.64-2.37 (2.37-2.45)	43.94-1.82 (1.82-1.89)	42.39-1.84 (1.84-1.92)
Number of reflections used (all/last shell)	14078/2700	12168/ 2817	23269/2727	29420/2764	28720/ 2961	25959/2147
Fraction of test set for calculating $R_{\text{free}}$ (%)	4.98	4.78	5.11	5.07	5.09	5.05
No. of reflections in the test set (all/last shell)	701/147	582/137	1190/156	1492/128	1462/149	1312/93
R factor: $R_{\text{work}}/R_{\text{free}}$ (last shell)	0.222/0.265 (0.337/0.370)	0.212/0.258 (0.230/0.298)	0.236/0.262 (0.283/0.266)	0.212/0.242 (0.247/0.256)	0.192/0.227 (0.284/0.329)	0.212/0.261 (0.316/0.325)
R.m.s.d. bond lengths ( Å ) / bond angles ( ° )	0.010/1.02	0.010/0.98	0.010/1.02	0.010/1.14	0.010/0.94	0.010/0.99
Estimated error (Luzzati plot / DPI by free $R^*$ ) ( Å )	0.395/0.247	0.320/0.273	0.353/0.162	0.340/0.206	0.241/0.118	0.301/0.150
B values ( Wilson plot / mean B value) ( Å <sup>2</sup> )	45.37/55.25	65.59/56.14	34.43/31.24	70.61/65.16	37.89/39.05	40.21/43.87
Number of atoms -- final model (Protein/ Waters/Ligand)	2151/79/36	2159/94/34	2140/117/34	3610/141/76	2140/176/40	2169/258/35

\* Cruickshank, D.W.J. (1999) Acta Cryst. D55, 583-601

## Assays

### ROR $\gamma$ Radioligand Competition Binding Assay

The scintillation proximity assay (SPA) was run in white polystyrene flat-bottom 384-well plates (Greiner, cat. No. 781075). Assays were carried out in 40  $\mu$ l reaction volumes. Various concentrations of test ligands in 0.4  $\mu$ L of DMSO were added to assay plates using an acoustic liquid dispenser. Purified N-(HN)6-GST-TCS-hROR $\gamma$  (258-518, 4 nM) was mixed with 40  $\mu$ g Yttrium oxide (YOx), glutathione SPA imaging beads in assay buffer (20 mM Tris, 150 mM NaCl, 10% Glycerol, 0.25% CHAPS, 1 mM TCEP) prior to adding 30  $\mu$ L to test ligands. Assay plates were incubated for 1 h at RT before adding 10  $\mu$ L tritiated 2-(4-(ethylsulfonyl)phenyl)-N-(4-(2-(methoxymethyl)phenyl)thiophen-2-yl)acetamide to test plates in assay buffer (final concentration, 25 nM). Test plates were incubated for 16 h and read using a LEADseeker Multimodality imaging instrument.

The raw data was analysed and IC<sub>50</sub> values for the compounds were calculated using Genedata Screener software. Raw data was transformed to % effect using equation 1:

$$\text{Compound \% effect} = 100 * [(X - \text{min}) / (\text{max} - \text{min})],$$

Where X represents the normalized value for the compound based on the Min (vehicle) and Max (reference compound) inhibition controls. The concentration of test ligand that inhibited radioligand binding by 50% (*i.e.*, the IC<sub>50</sub>) was calculated by plotting the % effect versus test ligand concentration and fitting the data using the Genedata Screener Smart fit algorithm.

### ROR $\gamma$ co-factor recruitment assay

The assay was run in black 384 well plates (Greiner cat no: 784900). Various concentrations of test ligands in 0.1  $\mu$ L DMSO were dispensed to assay plates using an Echo acoustic dispenser. Two pre-mixes were prepared and incubated for 1 h at room temp in the dark. Pre-mix 1 comprised 100 nM protein (biotinylated HN-Avi-MBP-TCS-hROR $\gamma$  (258-518)) and 60 nM Streptavidin APC in assay buffer, 50 mM MOPS pH 7.4, 50 mM KF, 0.003% (w/v) CHAPS, 10 mM DTT and 0.01% (w/v) BSA. Pre-mix 2 comprised 160 nM biotinylated SRC-1 peptide

(NCOA1-677-700) and 20 nM Europium-W8044 labelled Streptavidin in assay buffer. Five  $\mu\text{L}$  of pre-mix 2 was dispensed to assay plates containing 0.1  $\mu\text{L}$  of test compound and was incubated for 15 min prior to adding five  $\mu\text{L}$  of pre-mix 1. Plates were incubated at RT for 1 hour in the dark, prior to reading in a Pherastar multi-mode plate reader using HTRF filter set (ex 320, em 612 and 665). The FRET signal at 665 nm was divided by the signal at 612 nm and multiplied by 10,000 to generate a signal ratio value for each well. The raw data was transformed to % effect using the equation:

$$\text{Compound \% effect} = 100 * [(X - \text{min}) / (\text{max} - \text{min})],$$

where X represents the normalized value for the compound based on the Min (vehicle) and Max (reference compound) inhibition control. The concentration of test ligand that inhibited the activity by 50% (*i.e.*, the  $\text{IC}_{50}$ ) was calculated by plotting the % effect versus test ligand concentration and fitting the data using the Genedata Screener Smart fit algorithm.

### **ROR $\alpha$ co-factor recruitment assay**

The assay was run in black 384 well plates (Greiner: 784900). 0.2 microlitres of a fixed concentration range of test ligands dissolved in DMSO were added to assay plates using an acoustic liquid dispenser. Two pre-mixes were prepared in falcon tubes. Pre-mix 1 comprised 180 nM Protein (His6-tcs-hROR $\alpha$ LBD) and 8 nM Lance Eu-W1024-anti 6xHis in assay buffer, 50 mM Hepes pH 7.4, 100 mM NaCl, 0.1% (w/v) BSA, 1 mM TCEP which was incubated for 30 minutes at RT before dispensing 10 microlitres to assay plates. Then pre-mix 2 comprising 200 nM biotinylated PGC1 $\alpha$  peptide and 50 nM Streptavidin APC in assay buffer was prepared and incubated for 30 minutes at RT before adding 10 microlitres to assay plates containing test compound and premix 1. Plates were incubated at RT for 1 hour in the dark, prior to reading in a Pherastar multi-mode plate reader using HTRF filter set (ex 320, em

612 and 665). The FRET signal at 665 nM was divided by the signal at 612 nM and multiplied by 10,000 to generate a signal ratio value for each well.

Data analysis was carried out as described in the ROR $\gamma$  co-factor recruitment assay.

### **ROR $\beta$ radioligand binding assay**

The scintillation proximity assay (SPA) was run in white/clear polystyrene flat-bottom 384-well plates (Greiner, cat. No. 781095). Assays were carried out in 50  $\mu$ l reaction volumes. 0.5 microlitres of a fixed concentration range of test ligands dissolved in DMSO were added to assay plates using an acoustic liquid dispenser. 150nM 6H-AVI-GST-TEV-hROR $\beta$ (T221-K470) was mixed with 0.8 mgml<sup>-1</sup> Yttrium silicate (YSi) copper SPA beads in assay buffer (50mM Tris pH 7.5, 150mM NaCl, 10% Glycerol, 0.1% Triton X-100, 1mM TCEP) prior to adding 40 microlitres to test ligands. Assay plates were incubated for 30 minutes at room temperature before adding 10 microlitres tritiated ATRA to test plates in assay buffer (final concentration, 30nM). Test plates were incubated for 18-23 hours and read using a Wallac 1450 MicroBeta TriLux Liquid Scintillation Counter.

Data analysis was carried out as described in the ROR $\gamma$  binding assay.