Supplementary Informaton

Exploring the SAR of the β-ketoacyl-ACP synthase inhibitor GSK3011724A and optimization around a genotoxic metabolite

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Additional experimental information:

General Information. Laboratory reagent grade solvents were used unless mentioned otherwise. Reagents were purchased from Sigma-Aldrich, Acros Organics, Fluorochem, TCI, Apollo Scientific or Enamine and were used without further purification unless otherwise stated. Reactions were monitored by TLC on silica gel and/or by HPLC-MS. Silica gel TLC analysis was performed using Polygram® precoated silica gel TLC sheets SIL G/UV254 with detection by UV light (254 nm).

Characterization of all compounds was done using ^{1}H NMR spectroscopy and mass spectrometry. ^{1}H NMR (400 MHz) spectra were recorded on Bruker 400 Ultrashield DPX spectrometers. The chemical shift (δ) values are expressed in parts per million (ppm) and coupling constants are in Hertz (Hz). The chemical shifts δ were given relative to the residual ^{1}H and ^{13}C signals of the solvent peak as an internal standard: in ^{1}H NMR (400 MHz) δ 2.50 ppm (quin, C_2D_5HOS) for DMSO-*d*$_6$, δ 2.05 ppm (quin, C_3D_5HO) for Acetone-*d*$_6$, δ 3.31 ppm (pent, CD_2HOD) for Methanol-*d*$_4$; in ^{13}C NMR (101 MHz) δ 39.51 ppm (sept) for DMSO-*d*$_6$, δ 29.84 ppm (sept), δ 206.26 ppm (s) for Acetone-*d*$_6$, δ 49.00 ppm (sept) for Methanol-*d*$_4$. Legend: s = singlet, d = doublet, t = triplet, q = quartet, quin = quintet, sept = septet, m = multiplet (denotes complex pattern), br = broad signal, dd = doublet of doublets, dt = doublet of triplets, td = triplet of doublets, etc.

UPLC-MS analysis was performed according to the following methods A, B and C. Method A involved the Waters Acquity UPLC system coupled to a Waters SQ detector. A Waters Acquity UPLC BEH C18 1.7 µm, 3 mm × 50 mm column was used. The concentration of the measured samples was 0.1 mg/ml and the flow was 0.8 mL/min. Solvent A consisted of aqueous ammonium acetate 25mM and 10% acetonitrile at pH 6.6 and Solvent B was acetonitrile. The method was as follows: 0.0-0.2 min A:B 99.9:0.1, 0.2-1.0 min 10:90, 1.0-1.8 min 10:90, 1.9-2.0 min 99.9:0.1 at temperature 40ºC. The UV detection was an averaged signal from wavelength of 210 nm to 400 nm. In methods B and C ESI mass spectra were obtained with an Esquire 3000plus ion trap mass spectrometer (Bruker Daltonics), using the direct infusion mode. A Waters acquity H-class UPLC system coupled to a waters TQD ESI mass spectrometer and a Waters TUV detector was used with a Waters acquity UPLC BEH C18 1.7µm 2.1´50 mm column. Solvent A consisted of water with 0.1% formic acid. Solvent B consisted of acetonitrile with 0.1% formic acid. Method B involved the following: flow 0.7 mL/min, 0.15 min isocratic elution (A:B = 95:5), then gradient elution during 1.85 min (A:B = from 95:5 to 0:100), followed by 0.25min of isocratic elution (A:B = 0:100), then 0.75 min of isocratic elution (A:B = 95:5). Method C involved the following: flow 0.4 mL/min, 0.15 min isocratic elution (A:B = 95:5), then gradient elution during 4.85 min (A:B = from 95:5 to 0:100), followed by 0.25min of isocratic elution (A:B = 0:100), then 0.75 min of isocratic elution (A:B = 95:5). In methods B and C, the wavelength for UV detection was 254 nm unless stated otherwise.

Where necessary, flash purification was performed on a Biotage ® ISOLERA One or Four flash systems equipped with an internal variable dual-wavelength diode array detector (200-400nm). For normal phase purifications Biotage SNAP (10-340g), Sylicicle SiliaSep (4-120g) or Götec-Labortechnik EasyVarioFlash (5-100g) cartridges were used (flow rates 10-100mL/min). Reversed phase purifications were performed with Biotage KP-C18 containing cartridges. Gradients used varied for each purification. However, typical gradients used for normal phase were gradient of 0−100% ethyl acetate in *n*-heptane or cyclohexane, or 0-

15% methanol in ethyl acetate. For reverse phase typically a gradient of 5% ACN in water to 50% ACN in water was used.

The preparative HPLC purification was conducted on the Agilent 1200 or Agilent 1100 instrument, employing either on an X-Bridge C_{18} column (19 mm x 150 mm, i.d 5 µm packing diameter or 30 mm x 150 mm, i.d. 5 µm packing diameter) or a SunFire C_{18} column (19 mm x 150 mm or 30 mm x 250 mm) at room temperature. The solvents employed were: A = 10 mM ammonium bicarbonate in water; B = acetonitrile ("basic" method) or A = 0.1 M formic acid in water; B = 0.1 M formic acid in acetonitrile ("acidic" method) respectively. The purification was run as a gradient (A:B) typically from 40 to 100% over either 20 min or 25 min, with a flow rate of 17 mL/min (19 mm column) or 35 mL/min (30 mm column). The UV detection wavelengths were 210 nm and 254 nm.

Microwave radiation-assisted reactions were performed in a Biotage Initiator instrument. The initial absorption was set as 'high' and 2 min of pre-stirring was applied before heating commenced.

The isolated yields are reported. The purity of all final compounds, tested on *in vitro* and in vivo assays, was 95% or higher (unless stated otherwise), verified by UPLC-MS and ^{1}H NMR data. All products were obtained as amorphous solids, and melting points were not measured.

The following section reports general methods for the synthesis of compounds within this paper and analytical data for some representative examples of final compounds, the remainder of which are in the supplementary data.

Synthesis:

General procedure A for sulphonamide synthesis.

The corresponding amine precursor (1.0 eq.) and base were dissolved in DCM and the corresponding sulfonyl chloride was added. The resulting suspension/solution was stirred until the reaction had completed. Methanol and sodium hydroxide (aq., 2 M) were added and the resulting 2 phase mixture stirred at room temperature until the hydrolysis was complete. Work up varied between compounds and series and is described for each compound, all final compounds had purity of > 90% by LCMS and NMR.

Any deviation from the above procedure is highlighted in the compound descriptions.

4,4,4-trifluoro-*N*-(1H-indazol-5-yl)butane-1-sulfonamide (3). The title compound was prepared following General Procedure A, using as base triethylamine (3 eq.). Work up: The aqueous phase was extracted with TBME and the crude product triturated in TBME/Cyclohexane to afford the title compound. Yield 55% (109 mg, 0.355 mmol). ^{1}H NMR (400 MHz, METHANOL-d4) δ 8.02 (s, 1 H) 7.67 (d, *J* = 1.5 Hz, 1H) 7.53 (d, *J* = 8.8 Hz, 1H) 7.33 (dd, *J* = 8.8, 2.0 Hz, 1H) 3.14 (t, *J* = 7.5 Hz, 2H) 2.40-2.26 (m, 2 H) 2.09-2.00 (m, 2 H). LCMS: $[M+H]^+$ 308.

3,3,3-trifluoro-*N*-(1H-indazol-5-yl)propane-1-sulfonamide (5). The title compound was prepared following General Procedure A, using as base triethylamine (5 eq.). Work up: The aqueous phase was washed with DCM then neutralized to pH 7 with HCl (aq., 2 N) and extracted with EtOAc the combined organic phases dried over $MgSO_4$ and evaporated in vacuo. The resulting powder was triturated in DCM:EtOAc (2:1) and the filtrate dissolved in EtOAc and washed with sodium carbonate solution (10%) and dried over magnesium sulfate. Yield 15% (74.8 mg, 0.23 mmol). ^{1}H NMR (400 MHz, METHANOL-d4) δ 8.04 (s, 1H), 7.69 (dd, *J* = 2.0, 0.8 Hz, 1H), 7.55 (d, *J* = 8.8 Hz, 1H), 7.33 (dd, *J* = 8.8, 2.0 Hz, 1H), 3.29-3.24 (m, 2H), 2.77-2.56 (m, 2H). LCMS: $[M+H]^+$ 394.

***N*-(1H-indazol-5-yl)-2-methylpropane-1-sulfonamide (6).** The title compound was prepared following General Procedure A, using as base triethylamine (5 eq.). Work up: The aqueous phase was washed with DCM then acidified to pH 5 with HCl (aq., 2N) before being extracted with EtOAc. The combined organic

phase was dried over $MgSO_4$ and evaporated in vacuo. The resulting crude was then triturated in DCM (with a few drops of EtOAc) to yield the title compound. Yield 18% (69.3 mg, 0.274 mmol). ^{1}H NMR (400 MHz, METHANOL-d4) δ 8.02 (s, 1H), 7.66 (dd, *J* = 2.0, 0.8 Hz, 1H), 7.52 (d, *J* = 9.1 Hz, 1H), 7.32 (dd, *J* = 9.0, 1.9 Hz, 1H), 2.93 (d, *J* = 6.6 Hz, 2H), 2.29-2.16 (m, 1 H), 1.08-1.03 (m, 6 H). LCMS: $[M+H]^+$ 254.

1-cyclopropyl-*N*-(1H-indazol-5-yl)methanesulfonamide (7). The title compound was prepared following General Procedure A, using as base triethylamine (5 eq.). Work up: The aqueous phase was washed with DCM and neutralised with HCl (aq., 2 N) then extracted with EtOAc. The combined organic phase were dried over $MgSO_4$ and evaporated in vacuo. The resulting crude was dissolved in EtOAc, washed with sodium bicarbonate solution and dried over $MgSO_4$ evaporated in vacuo to yield the title compound. Yield 62% (245.6 mg, 0.928 mmol). ^{1}H NMR (400 MHz, METHANOL-d4) δ 8.00 (s, 1H), 7.67 (dd, *J* = 2.0, 0.8 Hz, 1H), 7.51 (d, *J* = 9.1 Hz, 1H), 7.34 (dd, *J* = 9.0, 1.9 Hz, 1H), 2.99-3.00 (m, 2H), 1.16-1.06 (m, 1H), 0.67-0.55 (m, 2H), 0.33-0.22 (m, 2H). LCMS: $[M+H]^+$ 252.

***N*-(1H-indazol-5-yl)pentane-2-sulfonamide (8).** The title compound was prepared following General Procedure A, using as base triethylamine (1 eq.) with a second equivalent of base added to push reaction to completion. Work up: The aqueous phase was neutralized with HCl (aq., 2 N) and extracted with EtOAc, the combined organic phases were dried over $MgSO_4$ and evaporated in vacuo. The resulting crude was purified by HPLC (Xbridge 19, ACN/:aqNH_4HCO_3 (10 mM), 40-100%). Yield 9% (8.73 mg, 0.045 mmol). ^{1}H NMR (400 MHz, DMSO-d6) δ 13.04 (br s, 1H), 9.62 (s, 1H), 8.04 (s, 1H), 7.58 (d, *J* = 2.0 Hz, 1H), 7.50 (d, *J* = 8.6 Hz, 1H), 7.26 (dd, *J* = 8.8, 1.8 Hz, 1H), 3.03-2.96 (m, 1H), 1.88-1.78 (m, 1H), 1.46-1.35 (m, 2H), 1.23-1.22 (m, 3H), 0.82-0.72 (m, 3H). LCMS: $[M+H]^+$ 268.

***N*-(1H-indazol-5-yl)hexane-1-sulfonamide (9).** The title compound was prepared following General Procedure A, using as base triethylamine (5 eq.). Work up: the aqueous phase was washed with DCM and acidified to pH 7 with HCl (aq., 2 N) and the resulting precipitate was collected via vacuum filtration to give the title compound as a light colorless solid. Yield 57% (266.4 mg, 0.852 mmol). ^{1}H NMR (400 MHz, METHANOL-d4) δ 8.02 (s, 1H), 7.66 (dd, *J* = 2.0, 0.8 Hz, 1H), 7.52 (d, *J* = 9.1 Hz, 1H), 7.33 (dd, *J* = 8.8, 2.0 Hz, 1H), 3.05-2.99 (m, 2H), 1.82-1.74 (m, 2H), 1.411.20 (m, 6H), 0.91-0.81 (m, 3H). LCMS: $[M+H]^+$ 282.

***N*-(1H-indazol-5-yl)propane-1-sulfonamide (10).** The title compound was prepared following General Procedure A, using as base triethylamine (5 eq.). DCM was evaporated prior to hydrolysis step. Work up: the aqueous phase was washed with DCM and neutralised with HCl (aq., 2 N) then extracted with DCM. The organic phase was dried over $MgSO_4$ and evaporated in vacuo. The crude produce was triturated in DCM and the precipitate collected to give the title compound. Yield 34% (74 mg, 0.294 mmol). ^{1}H NMR (400 MHz, METHANOL-d4) δ 8.02 (s, 1H), 7.66 (dd, *J* = 2.0, 0.8 Hz, 1H), 7.52 (d, *J* = 8.8 Hz, 1H), 7.33 (dd, *J* =8.8, 2.0 Hz, 1H), 3.04-2.97 (m, 2H), 1.87-1.77 (m, 2H), 1.00 (t, *J* = 7.5 Hz, 3H). LCMS: $[M+H]^+$ 240.

***N*-(1H-indazol-5-yl)-2-methoxyethane-1-sulfonamide (11).** The title compound was prepared following General Procedure A, using as base triethylamine (3 eq.). The solvent was evapoarted prior to the hydrolysis step. Work up: The reaction was concentrated in vacuo and diluted with HCl (aq. 2N, 2 ml) and stirred for 1 hour. The solution was neutralized to pH 7 with NaOH (2N) and extracted with DCM/MeOH (95/5). The organic phase was dried over Na_2SO_4 and evaporated in vacuo to give the title compound. Yield 47% (115 mg, 0.41 mmol). ^{1}H NMR (400 MHz, DMSO-d6) δ 13.06 (br s, 1H), 9.59 (s, 1H), 8.05 (s, 1H), 7.58-7.59 (m, 1H), 7.51 (d, *J* = 8.9, 1H), 7.24 (dd, *J* = 8.8, 1.8, 1H), 3.67-3.64 (m, 2H), 3.27-3.24 (m, 2H), 3.19 (s, 3H). LCMS: $[M+H]^+$ 256.

***N*-(6-fluoro-1H-indazol-5-yl)butane-1-sulfonamide (23).** The title compound was prepared following General Procedure A, using as base triethylamine (2 eq.). Solvent was evaporated in vacuo and crude dissolved in EtOAc and washed with sodium bicarbonated solution prior to the hydrolysis step. Work up: The organic phase was separated, and aqueous phase extracted with EtOAc, before the combined organic phases dried over $MgSO_4$ and evaporated in vacuo. The compound was dissolved in the minimum amount of EtOAc and precipitate via the addition of ^{c}hexane. Yield 35% (147.1 mg, 0.515 mmol). ^{1}H NMR (400 MHz, METHANOL-d_4) δ ppm 8.06 (br s, 1 H) 7.88-7.86 (m, 1 H) 7.36-7.34 (m, 1 H) 3.09-3.05 (m, 2 H) 1.85-1.77 (m, 2 H) 1.49-1.40 (m, 2 H) 0.93 (br t, *J*=7.3 Hz, 3 H). LCMS: $[M+H]^+$ 272.

***N*-(6-methyl-1H-indazol-5-yl)butane-1-sulfonamide (24).** The title compound was prepared following General Procedure A, using as base triethylamine (1 eq.). Work up: The mixture was concentrated in vacuo and remaining aqueous phase was neutralized to pH 7 with HCl (2N, aq.) solution and wash with DCM before being extracted with EtOAc. The organic phase was dried over MgSO4 and evaporated in vacuo and the resulting crude product purified by flash column chromatography on silica gel (EtOAc in ^{c}hexane 0 – 50%). Yield 26% (82.1 mg, 0.307 mmol). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 12.95 (s, 1 H) 8.97 (s, 1 H) 8.01 (s, 1 H) 7.61 (s, 1 H) 7.38 (s, 1 H) 3.09-3.05 (m, 2 H) 2.43 (s, 3 H) 1.76-1.66 (m, 2 H) 1.41 (sxt, *J*=7.4 Hz, 2 H) 0.89 (t, *J*=7.3 Hz, 3 H). LCMS: $[M+H]^+$ 268.

***N*-(6-chloro-1H-indazol-5-yl)butane-1-sulfonamide (25).** The title compound was prepared following General Procedure A, using as base triethylamine (1 eq.). Work up: The mixture was concentrated in vacuo and resulting solution neutralized to pH 7 by HCl (2N, aq.) and extracted with EtOAc. The organic phase was dried over $MgSO_4$ and evaporated in vacuo. The crude product was purified by HPLC (Xbridge 30, ACN/:aqNH_4HCO_3 (10 mM), 40-100%). Yield 13% (44.0 mg, 0.153 mmol). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 13.22 (br s, 1 H) 9.39 (s, 1 H) 8.13 (s, 1 H) 7.83 (s, 1 H) 7.72 (s, 1 H) 3.09-3.05 (m, 2 H) 1.76-1.69 (m, 2 H) 1.44-1.34 (m, 2 H) 0.87 (t, *J*=7.3 Hz, 3 H). LCMS: $[M+H]^+$ 288.

***N*-(6-(trifluoromethyl)-1H-indazol-5-yl)butane-1-sulfonamide (26).** The title compound was prepared following General Procedure A, in acetonitrile and using as base triethylamine (3 eq.). Solvent was evaporated prior to the hydrolysis step. Work up: EtOAc and sodium bicarbonate (sat. aq.) solution were added and the phases separated. The aqueous phase was extracted with EtOAc and the combined organic phases dried over Na_2SO_4 and evaporated in vacuo. The crude product was purified by HPLC (Xbridge 30, ACN/:aqNH_4HCO_3 (10 mM), 40-100%). Yield 34% (18.0 mg, 0.056 mmol). ^{1}H NMR (400 MHz, METHANOL-d_4) δ ppm 8.19 (s, 1 H) 7.93 (s, 1 H) 7.65 (dd, *J*=1.8, 0.8 Hz, 1 H) 3.09-3.04 (m, 2 H) 1.82-1.73 (m, 2 H) 1.42 (sxt, *J*=7.5 Hz, 2 H) 0.90 (t, *J*=7.3 Hz, 3 H). LCMS: $[M+H]^+$ 322.

***N*-(7-chloro-1H-indazol-5-yl)butane-1-sulfonamide (27).** The title compound was prepared following General Procedure A, using DMF as the solvent and triethylamine (2.5 eq.) as the base. Work up: The mixture was concentrated in vacuo and partitioned between DCM and ammonium chloride (sat. aq.) solution. The organic phase was separated and dried over Na_2SO_4 and concentrated. The crude product was purified by flash column chromatography on silica gel (EtOAc in ^{c}hexane 0-40%) to give the title compound. Yield 49% (55.0 mg, 0.191 mmol). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 13.60 (br s, 1 H) 9.77 (s, 1 H) 8.18 (s, 1 H) 7.57 (d, *J*=1.3 Hz, 1 H) 7.32 (d, *J*=1.5 Hz, 1 H) 3.09-2.99 (m, 2 H) 1.69-1.59 (m, 2 H) 1.38-1.28 (m, 2 H) 0.82 (t, *J*=7.5 Hz, 3 H). LCMS: $[M+H]^+$ 288.

***N*-(7-methyl-1H-indazol-5-yl)butane-1-sulfonamide (28).** The title compound was prepared following General Procedure A, using triethylamine (4 eq.) as the base. Solvent was evaporated, crude was dissolved in EtOAc and washed with sodium bicarbonate before being dried over $MgSO_4$. The crude oil was dissolved in DCM before hydrolysis step. Work up: The organic phase was separated, and the aqueous phase extracted with DCM before being neutralized to pH 7 with HCl (aq. 2N) and extracted with EtOAc. The combined organic phases were dried over $MgSO_4$ and evaporated. The crude product was purified by HPLC (Sunfire 19, 0.1 M Formic acid in ACN/aq. formic acid (0.1 M), 40-100%). Yield 3% (9.7 mg, 0.031 mmol). ^{1}H NMR (400 MHz, METHANOL-d_4) δ ppm 8.00 (s, 1 H) 7.48 (s, 1 H) 7.10 (s, 1 H) 3.04-3.00 (m, 2 H) 2.55 (s, 3 H) 1.82-1.72 (m, 2 H) 1.40 (sxt, *J*=7.5 Hz, 2 H) 0.89 (t, *J*=7.5 Hz, 3 H). LCMS: $[M+H]^+$ 267.

***N*-(4-chloro-1H-indazol-5-yl)butane-1-sulfonamide (29).** The title compound was prepared following General Procedure A, using DCE as the solvent and triethylamine (3 eq.) as base. Solvent was evaporated prior to the hydrolysis step. Work up: The solution was neutralized to pH 7 with HCl (aq. 2N) and diluted in water (10 ml) before being extracted with EtOAc. The organic phase was Na_2SO_4 and evaporated. The crude product was purified by 2 rounds of flash column chromatography on silica gel (EtOAc in ^{c}hexane 0-50% twice). Yield 35% (166.8 mg, 0.522 mmol). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 13.46 (br s, 1 H) 9.48 (s, 1 H) 8.13 (s, 1 H) 7.54-7.52 (m, 1 H) 7.38-7.41 (m, 1 H) 3.09-3.05 (m, 2 H) 1.78-1.69 (m, 2 H) 1.45-1.34 (m, 2 H) 0.93-0.84 (m, 3 H). LCMS: $[M+H]^+$ 288.

***N*-(4-methyl-1H-indazol-5-yl)butane-1-sulfonamide (30).** The title compound was prepared following General Procedure A, with DCE as the solvent and triethylamine (3 eq.) as base. Solvent was evaporated prior to the hydrolysis step. Work up: The solution was neutralized to pH 7 with HCl (aq. 2N) and diluted in water (10 ml) before being extracted with EtOAc. The organic phase was Na_2SO_4 and evaporated. The crude was semi-purified by flash column chromatography on silica gel (EtOAc in ^{c}hexane 0-50%) before

being triturated in DCM. Yield 19% (89.2 mg, 0.113 mmol). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 13.07 (br s, 1 H) 9.01 (s, 1 H) 8.13 (s, 1 H) 7.34 (d, *J*=8.6 Hz, 1 H) 7.21 (d, *J*=8.6 Hz, 1 H) 3.05-2.96 (m, 2 H) 2.54 (s, 3 H) 1.76-1.66 (m, 2 H) 1.40 (sxt, *J*=7.4 Hz, 2 H) 0.88 (t, *J*=7.3 Hz, 3 H). LCMS: $[M+H]^+$ 268.

***N*-(4-fluoro-1H-indazol-5-yl)butane-1-sulfonamide (31).** The title compound was prepared following General Procedure A, with triethylamine (1.5 eq.) as base. Work up: The volume was reduced in vacuo and the resulting solution neutralized to pH 7 with HCl (aq. 1N) and extracted with EtOAc. The organic phase was dried over $MgSO_4$ and evaporated. The crude was semi-purified by flash column chromatography on silica gel (EtOAc in ^{c}hexane) before being dissolved in EtOAc and washed with NaOH solution (aq. 2N). The Aqueous layer was acidified to pH 5 and extracted with EtOAc. The combined organic phases (pre and post neutralization) were dried over $MgSO_4$ and evaporated to give the title compound. Yield 45% (53.0 mg, 0.195 mmol). ^{1}H NMR (400 MHz, METHANOL-d_4) δ ppm 8.13 (s, 1 H) 7.26-7.23 (m, 1 H) 6.85-6.78 (m, 1 H) 3.15-3.09 (m, 2 H) 1.85-1.75 (m, 2 H) 1.48-1.39 (m, 3 H) 0.92 (t, *J*=7.3 Hz, 3 H). LCMS: $[M+H]^+$ 272.

***N*-(1H-pyrazolo[3,4-b]pyridin-5-yl)butane-1-sulfonamide (33).** The title compound was prepared following General Procedure A, using as base triethylamine (2.5 eq.). Work up: The organic phase was separated, and the aqueous layer was neutralized with HCl (1 N, aq.) and extracted with EtOAc. The organic phases were combined and dried over $MgSO_4$ and concentrated in vacuo. The crude product was purified by flash column chromatography on silica gel (EtOAc in ^{c}hexane 0-33%). Yield 79% (237.0 mg, 0.932 mmol). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 13.67 (s, 1 H) 9.82 (s, 1 H) 8.39-8.38 (m, 1 H) 8.13 (d, *J*=1.5 Hz, 1 H) 8.04 (d, *J*=1.8 Hz, 1 H) 3.07-3.04 (m, 2 H) 1.71-1.62 (m, 2 H) 1.35 (sxt, *J*=7.4 Hz, 2 H) 0.84 (t, *J*=7.5 Hz, 3 H). LCMS: $[M+H]^+$ 255.

***N*-(1H-pyrazolo[3,4-c]pyridin-5-yl)butane-1-sulfonamide (34).** The title compound was prepared following General Procedure A, using as base triethylamine (8 eq.). Work up: DCM and water were added, and the aqueous phase was acidified to pH 3 with HCl (aq. 2N) and the resulting brown precipitate was extracted into DCM. The organic phase was then dried over Na_2SO_4 and evaporated in vacuo. The crude was dissolved in EtOAc, washed with sodium bicarbonate (sat. aq.), dried over Na_2SO_4, decolorized with activated charcoal. Yield 14% (47.9 mg, 0.170 mmol). ^{1}H NMR (400 MHz, METHANOL-d_4) δ ppm 8.79 (s, 1 H) 8.11 (s, 1 H) 7.49 (s, 1 H) 3.35-3.33 (m, 2 H) 1.86-1.7 (m, 2 H) 1.49-1.39 (m, 2 H) 0.91 (t, *J*=7.5 Hz, 3 H). LCMS: $[M+H]^+$ 255.

***N*-(4,5,6,7-tetrahydro-1H-indazol-5-yl)butane-1-sulfonamide (35).** The title compound was prepared following General Procedure A, using DMF as the solvent and triethylamine (2.5 eq.) as the base. The reaction was concentrated in vacuo and diluted with DCM and ammonium chloride (aq. Sat.). The organic phase was then dried over Na_2SO_4 and evaporated in vacuo. The crude product was purified by flash chromatography on silica gel (EtOAc in ^{c}hexane 0-40%). Yield 48% (180.0 mg, 0.699 mmol). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 12.30 (br d, *J*=8.6 Hz, 1 H) 7.38-7.18 (m, 2 H) 3.46 (br s, 1 H) 3.04-2.91 (m, 2 H) 2.83-2.63 (m, 3 H) 2.44-2.33 (m, 1 H) 1.98 (br s, 1 H) 1.74-1.60 (m, 3 H) 1.44-1.35 (m, 2 H) 0.89 (t, *J*=7.3 Hz, 3 H). LCMS: $[M+H]^+$ 258.

5-(butylsulfonyl)-4,5,6,7-tetrahydro-1H-pyrazolo[4,3-c]pyridine (36). The title compound was prepared following General Procedure A, using acetonitrile as a solvent and triethylamine (15.7 eq.) as the base. The reaction mixture was heated to reflux to 5 hours after stirring at room temperature for 16 hours. Once cool the mixture was concentrated in vacuo and the crude partitioned between EtOAc and water. The aqueous phase was extracted with EtoAc and the combined organic phases dried over Na_2SO_4 and evaporated in vacuo prior to the hydrolysis. Work up: the solution was extracted with DCM and the organic phase dried over Na_2SO_4 and evaporated to give the title compound. Yield 18% (55.6 mg, 0.229 mmol). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 12.56 (br s, 1 H) 4.32-4.25 (m, 2 H) 3.52-3.49 (m, 2 H) 3.08-3.04 (m, 2 H) 2.74-2.71 (m, 2 H) 1.67-1.58 (m, 2 H) 1.42-1.33 (m, 4 H) 0.90-0.85 (m, 6 H). LCMS: $[M+H]^+$ 244.

***N*-(1H-indol-5-yl)butane-1-sulfonamide (37).** The title compound was prepared following General Procedure A, using as base triethylamine (1.5 eq.). Prior to the hydrolysis step: The solvent was evaporated in vacuo and the resulting brown powder dissolved in EtOAc precipitating triethylamonium chloride which was filtered and discarded. The organic phase was then washed with sodium bicarbonate solution (aq. Sat.) dried and evaporated in vacuo. The crude was purified by flash column chromatography on silica gel (EtOAc in ^{c}hexane 0-50%). Work up: The solution was neutralized to pH 7 with HCl (aq. 0.5 N) and the volume reduced in vacuo. The remaining solution was diluted with water and extracted with EtOAc. The

organic phase was dried and evaporated in vacuo. Yield 34% (109.9 mg, 0.414 mmol). ^{1}H NMR (400 MHz, METHANOL-d_4) δ ppm 7.46 (d, *J*=2.0 Hz, 1 H) 7.34 (d, *J*=8.8 Hz, 1 H) 7.25 (d, *J*=3.0 Hz, 1 H) 7.04 (dd, *J*=8.6, 2.0 Hz, 1 H) 6.44-6.39 (m, 1 H) 3.00-2.96 (m, 2 H) 1.81-1.73 (m, 2 H) 1.44-1.39 (m, 2 H) 0.89 (t, *J*=7.5 Hz, 3 H). LCMS: $[M+H]^+$ 253.

***N*-(1-methyl-1H-indol-5-yl)butane-1-sulfonamide (38).** The title compound was prepared following General Procedure A, using as base triethylamine (1 eq.). An additional 0.5 equivalents of sulphonyl chloride and triethylamine were added to push the reaction to completion. No hydrolysis step was performed. Work up: the solvent was evaporated in vacuo and the crude material partition between EtOAc and Water. The aqueous phase was separated and the remaining organic phase washed with water, sodium bicarbonate (sat. aq.) solution, and a 1:1 solution of sodium bicarbonate (sat. aq.) and brine. The organic phase was dried and evaporated and the crude product purified via flash chromatography on silica gel (EtOAc - Cyclohexane 0-40 %), the combined fractions were decolourised with activated charcoal to yield the title compound. Yield 51% (99.4 mg, 0.355 mmol). ^{1}H NMR (400 MHz, METHANOL-d_4) δ ppm 7.47 (d, *J*=1.8 Hz, 1 H) 7.35 (d, *J*=8.8 Hz, 1 H) 7.19 (d, *J*=3.0 Hz, 1 H) 7.11 (dd, *J*=8.6, 2.0 Hz, 1 H) 6.41 (d, *J*=3.0 Hz, 1 H) 3.81 (s, 3 H) 3.00-2.96 (m, 2 H) 1.82-1.74 (m, 2 H) 1.44-1.35 (m, 2 H) 0.91 (t, *J*=7.5 Hz, 3 H). LCMS: $[M+H]^+$ 267.

***N*-(2,3-dihydro-1H-inden-5-yl)butane-1-sulfonamide (39).** The title compound was prepared following General Procedure A, using as base triethylamine (3 eq.). Work up: Reaction was concentrated under vacuum and then, diluted with DCM and ammonium chloride. The organic phase was extracted with ammonium chloride (sat. aq.), dried and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (0-40% EtOAc in chexane). Yield 93% (353.0 mg, 1.393 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.74 (d, *J*=8.1 Hz, 1 H) 7.12 (m, 1 H) 6.96 (dd, *J*=1.7, 7.8 Hz, 1 H) 6.30 (s, 1 H) 3.09-3.05 (m, 2 H) 2.93-2.86 (m, 4 H) 2.13-2.06 (m, 2 H) 1.85-1.78 (m, 2 H) 1.47-1.38 (m, 2 H) 0.92 (t, *J*=7.3 Hz, 3 H). LCMS: $[M+H]^+$ 254.

***N*-(benzo[d]isoxazol-5-yl)butane-1-sulfonamide (41).** The title compound was prepared following General Procedure A, using as base triethylamine (1.2 eq.). Work up: The reaction mixture was diluted with EtOAc and the resulting organic phase washed with ammonium chloride (aq., sat.), dried over $MgSO_4$, and concentrated in vacuo. The crude product was purified by flash column chromatography on silica gel (33% EtOAc in ^{c}hexane). Yield 33% (83.0 mg, 0.261 mmol). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.99 (br s, 1 H) 9.28 (d, *J*=1.3 Hz, 1 H) 7.85-7.77 (m, 2 H) 7.58-7.55 (m, 2 H) 3.16-3.12 (m, 2 H) 1.74-1.68 (m, 2 H) 1.44-1.38 (m, 2 H) 0.93-0.87 (m, 3 H). LCMS: $[M+H]^+$ 253.

***N*-(benzo[d]thiazol-6-yl)butane-1-sulfonamide (42).** The title compound was prepared following General Procedure A, using as base triethylamine (2 eq.). Work up: The organic phase was separated, and the aqueous phase neutralized with HCl (1 N, aq.) and extracted with EtOAc. The combined organic phases were dried over $MgSO_4$ and concentrated. The crude product was purified by flash column chromatography on silica gel (0 – 33% EtOAc in ^{c}hexane) followed by HPLC (Xbridge 30, ACN/:aqNH_4HCO_3 (10 mM), 40-100%). Yield 10% (54.0 mg, 0.200 mmol). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.04 (s, 1 H) 9.28 (s, 1 H) 8.03 (d, *J*=9.1 Hz, 1 H) 7.96 (d, *J*=2.0 Hz, 1 H) 7.37 (dd, *J*=8.8, 2.3 Hz, 1 H) 3.15-3.11 (m, 2 H) 1.70-1.60 (m, 2 H) 1.34 (sxt, *J*=7.4 Hz, 2 H) 0.82 (t, *J*=7.5 Hz, 3 H). LCMS: $[M+H]^+$ 271.

***N*-(benzo[d]oxazol-6-yl)butane-1-sulfonamide (43).** The title compound was prepared following General Procedure A, using as base triethylamine (1.2 eq.). No hydrolysis step was performed after the reaction had reached completion. Work up: The solvent was evaporated in vacuo and the crude product purified by flash chromatography on silica gel (33% EtOAc in ^{c}hexane). Yield 7% (30.0 mg, 0.118 mmol). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.02 (br s, 1 H) 8.66 (s, 1 H) 7.73 (d, *J*=8.6 Hz, 1 H) 7.55 (d, *J*=1.8 Hz, 1 H) 7.22 (dd, *J*=8.6, 2.0 Hz, 1 H) 3.12-3.08 (m, 2 H) 1.68-1.60 (m, 2 H) 1.33 (sxt, *J*=7.4 Hz, 2 H) 0.81 (t, *J*=7.5 Hz, 3 H). LCMS: $[M+H]^+$ 255.

***N*-(benzo[d]thiazol-5-yl)butane-1-sulfonamide (44).** The title compound was prepared following General Procedure A, using as base triethylamine (2 eq.). A second equivalent of base and sulphonyl chloride were added to help the reaction reach completion. Work up: The organic phase was separated, and the aqueous phase neutralized with HCl (1 N, aq.) and extracted with EtOAc. The combined organic phases were dried over $MgSO_4$ and concentrated. The crude product was purified by flash column chromatography on silica gel (0 – 33% EtOAc in ^{c}hexane) followed by HPLC (Xbridge 30, ACN/:aqNH_4HCO_3 (10 mM), 40-100%). Yield 10% (56.0 mg, 0.207 mmol). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.01 (s, 1 H) 9.40 (s, 1 H) 8.10

(d, *J*=8.6 Hz, 1 H) 7.90 (d, *J*=1.8 Hz, 1 H) 7.36 (dd, *J*=8.7, 2.1 Hz, 1 H) 3.13-3.09 (m, 2 H) 1.70-1.61 (m, 2 H) 1.39-1.29 (m, 2 H) 0.81 (t, *J*=7.5 Hz, 3 H).). LCMS: $[M+H]^+$ 271.

***N*-(2-methyl-1H-benzo[d]imidazol-5-yl)butane-1-sulfonamide (45).** The title compound was prepared following General Procedure A, using as base triethylamine (8 eq.). Work up: The organic phase was separated, and the aqueous phase neutralized with HCl (aq. 2N) extracted with EtOAc. The combined organic phases were washed with sodium bicarbonate (sat. aq.) and dried over $MgSO_4$ and evaporated in vacuo. The crude product was purified by HPLC (Xbridge 19, ACN/:aqNH_4HCO_3 (10 mM), 40-100%). Yield 13% (48.6 mg, 0.091 mmol). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 6.60-6.63 (m, 2 H) 6.28 (dd, *J*=8.6, 1.8 Hz, 1 H) 2.24-2.16 (m, 2 H) 1.74 (s, 3 H) 0.99-0.90 (m, 2 H) 0.67-0.54 (m, 2H) 0.08 (t, *J*=7.5 Hz, 3 H). LCMS: $[M+H]^+$ 268.

***N*-([1,2,4]triazolo[1,5-a]pyridin-6-yl)butane-1-sulfonamide (46).** The title compound was prepared following General Procedure A, using as base triethylamine (2.5 eq.). Work up: The aqueous phase was neutralized with HCl (aq. 2N) and extracted with DCM and EtOAc. The combined organic phases were washed with sodium bicarbonate (aq. Sat.) solution and then dried over $MgSO_4$ and evaporated to give the title compound as yellow microcrystals. Yield 43% (127.1 mg, 0.475 mmol). ^{1}H NMR (400 MHz, METHANOL-d_4) δ ppm 8.75-8.76 (m, 1 H) 8.39 (s, 1 H) 7.77 (d, *J*=9.5 Hz, 1 H) 7.64-7.62 (m, 1 H) 3.19-3.15 (m, 2 H) 1.83-1.75 (m, 2 H) 1.45 (sxt, *J*=7.4 Hz, 2 H) 0.93 (t, *J*=7.3 Hz, 3 H). LCMS: $[M+H]^+$ 255.

***N*-(benzo[c][1,2,5]thiadiazol-5-yl)butane-1-sulfonamide (47).** The title compound was prepared following General Procedure A, using as base triethylamine (3 eq.). Work up: The mixture was concentrated in vacuo and neutralized with HCl (1N, aq.) and extracted with EtOAc. The organic phase was dried over $MgSO_4$ and evaporated in vacuo. The crude was purified by flash chromatography on silica gel (EtOAc in ^{c}hexane). Yield 38% (127.1 mg, 0.468 mmol). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.44 (s, 1 H) 8.07 (d, *J*=9.3 Hz, 1 H) 7.73 (d, *J*=2.0 Hz, 1 H) 7.58 (dd, *J*=9.3, 2.3 Hz, 1 H) 3.30-3.26 (m, 2 H) 1.71-1.63 (m, 2 H) 1.40-1.31 (m, 2 H) 0.82 (t, *J*=7.3 Hz, 3 H). LCMS: $[M+H]^+$ 272.

***N*-(2-methylbenzo[d]oxazol-5-yl)butane-1-sulfonamide (48).** The title compound was prepared following General Procedure A, using acetonitrile as the solvent and triethylamine (1 eq.) as base. No hydrolysis step was performed. Work up: the solvent was evaporated and the crude dissolved in MeOH and purified by HPLC (Xbridge 19, ACN/:aqNH_4HCO_3 (10 mM), 25-100%). Yield 58% (60.0 mg, 0.224 mmol). ^{1}H NMR (400 MHz, $CDCL_3$) δ ppm 7.54 (d, *J*=2.0 Hz, 1 H) 7.45 (d, *J*=8.6 Hz, 1 H) 7.23 (dd, *J*=2.2, 8.6 Hz, 1 H) 6.63 (s, 1 H) 3.09-3.05 (m, 2 H) 2.65 (s, 3 H) 2.93-2.86 (m, 4 H) 1.85-1.78 (m, 2 H) 1.46-1.37 (m, 2 H) 0.91 (t, *J*=7.3 Hz, 3 H). LCMS: $[M+H]^+$ 269.

***N*-(imidazo[1,2-a]pyridin-6-yl)butane-1-sulfonamide (49).** The title compound was prepared following General Procedure A, using as base triethylamine (2 eq.). Work up: The organic phase was separated and the aqueous neutralized with HCl (1 N, aq.) and extracted with EtOAc. The combined organic phases were dried over $MgSO_4$ and evaporated in vacuo. The crude was purified by HPLC (Xbridge 30, ACN/:aqNH_4HCO_3 (10 mM), 40-100%). Yield 12% (58.0 mg, 0.229 mmol). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.71 (s, 1 H) 8.47-8.46 (m, 1 H) 8.00 (s, 1 H) 7.58-7.54 (m, 2 H) 7.14-7.11 (m, 1 H) 3.12-3.08 (m, 2 H) 1.72-1.63 (m, 2 H) 1.41-1.32 (m, 3 H) 0.85 (t, *J*=7.5 Hz, 3 H). LCMS: $[M+H]^+$ 254.

***N*-(1-methyl-1H-indazol-5-yl)butane-1-sulfonamide (50).** The title compound was prepared following General Procedure A, with triethylamine (3 eq.) as base. Work up: reaction was concentrated under vacuum and diluted with DCM and washed with ammonium chloride (sat. aq.). The aqueous phase was extracted with DCM and the combined organic phases were dried and concentrated. The crude compound was purified by flash chromatography on silica gel (0-10% MeOH in DCM). Yield 63% (7.18 g, 26.9 mmol). ^{1}H NMR (400 MHz, $CDCL_3$) δ ppm 7.97 (d, *J*=0.7 Hz, 1 H) 7.63 (d, *J*=1.7Hz, 1 H) 7.39 (m, 1 H) 7.31 (dd, *J*=2.0, 8.8 Hz, 1 H) 6.54 (s, 1 H) 4.09 (s, 3 H) 3.08-3.04 (m, 2 H) 1.87-1.80 (m, 2 H) 1.46-1.37 (m, 2 H) 0.91 (t, *J*=7.3 Hz, 3 H). LCMS: $[M+H]^+$ 268.

***N*-(2-methyl-3-oxoisoindolin-5-yl)butane-1-sulfonamide (51).** The title compound was prepared following General Procedure A, using as base triethylamine (1.5 eq.). Work up: the reaction mixture was concentrated in vacuo and the mixture neutralised with HCl (2N, aq.) and extracted with EtOAc. The combined organic phases were dried and concentrated in vacuo. The crude was purified by flash chromatography on silica gel (0-50% EtOAc in ^{c}hexane). Yield 55% (286.0 mg, 1.013 mmol). ^{1}H NMR (400 MHz, DMSO-d6) δ ppm 7.60 (d, *J*=8.0 Hz, 1 H) 7.55 (d, *J*= 1.7 Hz, 1 H) 7.47 (dd, *J*=2.7, 8.1 Hz, 1

H) 4.48 (s, 1 H) 3.16-3.13 (m, 5 H) 1.74-1.66 (m, 2 H) 1.43-1.36 (m, 2 H) 0.88 (t, *J*=7.3 Hz, 3 H). LCMS: $[M+H]^+$ 283.

***N*-(1-methyl-1H-benzo[d]imidazol-6-yl)butane-1-sulfonamide (52).** The title compound was prepared following General Procedure A, using as base triethylamine (6 eq.). Work up: the organic layer was separated and the aqueous phase neutralised with HCl (1N, aq.) and extracted with EtOAc. The combined organic phases were dried and concentrated and the crude residue purified by flash chromatography on silica gel (0- 50% Isopropyl alcohol in ^{c}hexane. Yield 80% (581.0 mg, 2.173 mmol). ^{1}H NMR (400 MHz, DMSO-d6) δ ppm 9.78 (s, 1 H) 8.20 (s, 1 H) 7.66 (d, *J*=8.5 Hz, 1 H) 7.44 (d, *J*=1.7 Hz, 1 H) 7.16 (dd, *J*=2.0, 8.6 Hz, 1 H) 3.40 (s, 3 H) 3.13-3.09 (m, 2H) 1.76-1.69 (m, 2 H) 1.45-1.36 (m, 2 H) 0.89 (t, *J*=7.3 Hz, 3 H). LCMS: $[M+H]^+$ 268.

***N*-([1,2,4]triazolo[4,3-a]pyridin-6-yl)butane-1-sulfonamide (53).** The title compound was prepared following General Procedure A, with heating to 50 °C using DCE as solvent and triethylamine (3 eq.) as base with no hydrolysis step performed. Work up: the solvent was evaporated, and the resulting powder partitioned between DCM and water. The resulting emulsion was left standing overnight before the mixture was concentrated in vacuo and the resulting black suspension neutralized to pH 7 with NaOH (aq. 1N). DCM was added, and the phases separated. The aqueous phase was extracted with DCM and EtOAc and the organic phases combined, washed with brine, dried and evaporated to yield a brown powder which was adsorbed on a SCX column, washed with MeOH and the title compound liberated with ammonia in methanol (7N). Yield 14% (56.1 mg, 0.199 mmol). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.96 (br s, 1 H) 9.26 (s, 1 H) 8.46-8.45 (m, 1 H) 7.80-7.78 (m, 1 H) 7.26-7.23 (m, 1 H) 3.21-3.14 (m, 2 H) 1.70-1.60 (m, 2 H) 1.41-1.32 (m, 2 H) 0.85 (t, *J*=7.3 Hz, 3 H). LCMS: $[M+H]^+$ 255.

***N*-(3-methylbenzo[d]isothiazol-5-yl)butane-1-sulfonamide (54).** The title compound was prepared following General Procedure A, without base addition. A few drops of methanol were required to fully dissolve the starting materials. A second equivalent of sulfonylchloride was added and the reaction heated to reflux overnight. No hydrolysis step was performed. Work up: the reaction was cooled to room temperature and evaporated to dryness in vacuo. The resulting orange solid was dissolved in water and neutralised with NaOH (1N, aq.). The aqueous phase was extracted with EtOAc and the organic phase back washed with water, dried and evaporate in vacuo. The crude material was triturated in diethylether and the filtrate evaporated in vacuo. The crude oil was purified by flash chromatography on silica gel (0-50% EtOAc in ^{c}hexane) selected fractions were combined and evaporated and the resulting solid decolourised with activated charcoal. Yield 18% (82.0 mg, 0.274 mmol). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.04 (s, 1 H) 8.11 (d, *J*=8.6 Hz, 1 H) 7.82 (d, *J*=1.8 Hz, 1 H) 7.46 (dd, *J*=8.8, 2.0 Hz, 1 H) 3.17-3.11 (m, 2 H) 2.65 (s, 3 H) 1.66 (quin, *J*=7.6 Hz, 2 H) 1.39-1.29 (m, 2 H) 0.82 (t, *J*=7.3 Hz, 3 H). LCMS: $[M+H]^+$ 285.

***N*-(1-methyl-1H-indol-6-yl)butane-1-sulfonamide (55).** The title compound was prepared following General Procedure A, using as base triethylamine (3.03 eq.). Work up: the reaction was concentrated in vacuo and diluted with EtOAc and water. The organic phase was washed with ammonium chloride (sat. aq.), dried and evaporated in vacuo. The crude product was purified by flash chromatography on silica gel (0-60% EtOAc in ^{c}hexane) followed by HPLC (Sunfire 30, 0.1 M Formic acid in ACN/aq. formic acid (0.1 M), 50-100%). Yield 46% (110.0 mg, 0.392 mmol). ^{1}H NMR (400 MHz, DMSO-d6) δ ppm 7.43 (d, *J*=8.3 Hz, 1 H) 7.23 (d, *J*=3.2 Hz, 1 H) 7.21-7.20 (m, 1H) 6.89 (dd, *J*=1.7, 8.3 Hz, 1 H) 6.37 (dd, *J*=0.7, 3.8 Hz, 1 H) 3.75 (s, 3H) 2.99-2.95 (m, 2 H) 1.76-1.69 (m, 2 H) 1.45-1.36 (m, 2H) 0.89 (t, *J*=7.3 Hz, 3 H). LCMS: $[M+H]^+$ 267.

***N*-(1H-benzo[d]imidazol-6-yl)butane-1-sulfonamide (56).** The title compound was prepared following General Procedure A, using as base triethylamine (4 eq.). Work up: the organic phase was separated and the aqueous layer neutralised with HCl (1N, aq.) and extracted with EtOAc. The combined organic phase was dried and concentrated in vacuo. The crude material was purified by flash chromatography (0-60% IPA in ^{c}hexane). Yield 62% (780.0 mg, 3.080 mmol). ^{1}H NMR (400 MHz, DMSO-d6) δ ppm 12.44 (m, 1 H) 9.69 (m, 1 H) 8.25 (s, 1 H) 7.69-7.49 (m, 2 H) 7.23 (d, *J*=3.2 Hz, 1 H) 7.20-7.14 (m, 1 H) 1.76-1.69 (m, 2 H) 1.45-1.36 (m, 2 H) 0.89 (t, *J*=7.3 Hz, 3 H). LCMS: $[M+H]^+$ 254.

***N*-(2-methyl-2H-indazol-6-yl)propane-1-sulfonamide (57).** The title compound was prepared following General Procedure A, using as base triethylamine (2 eq.). Work up: solvents were removed in vacuo and diluted with DCM and ammonium chloride (sat. aq.). The organic phase was separated and the aqueous phase extracted with DCM. The combined organic phases were dried, and evaporated in vacuo. The crude

material was purified by flash chromatography on silica gel (0-10% MeOH in DCM). Yield 50% (90.0 mg, 0.338 mmol). ^{1}H NMR (400 MHz, $CDCL_3$) δ ppm 7.86 (s, 1 H) 7.62-7.58 (m, 2 H) 7.55-7.54 (m, 1 H) 7.01 (dd, *J*=1.7, 8.8 Hz, 1 H) 4.18 (s, 3 H) 3.11-3.07 (m, 2 H) 1.87-1.80 (m, 2 H) 0.96 (t, *J*=7.3 Hz, 3 H). LCMS: $[M+H]^+$ 254.

***N*-(2-methylisoindolin-5-yl)butane-1-sulfonamide (58).** The title compound was prepared following General Procedure A, using as base triethylamine (3.03 eq.). Work up: the reaction mixture was concentrated in vacuo and diluted with DCM and ammonium chloride (sat. aq.). The organic phase was separated and the aqueous phase extracted with DCM. The combined organic phases were dried and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel (0-50% isopropyl alcohol in ^{c}hexane). Yield 20% (71.8 mg, 0.268 mmol). ^{1}H NMR (400 MHz, $CDCL_3$) δ ppm 7.14 (d, 8.1 Hz, 1 H) 7.06-7.04 (m, 1 H) 6.99 (dd, *J*=2.2, 8.1 Hz, 1 H) 3.11-3.05 (m, 2 H) 2.60 (s 3 H) 1.81-1.74 (m, 2 H) 1.43-1.36 (m, 2 H) 0.90 (t, *J*=7.3 Hz, 3 H). LCMS: $[M+H]^+$ 269.

***N*-(1,3-dimethyl-1H-indazol-6-yl)butane-1-sulfonamide (59).** The title compound was prepared following General Procedure A, using as base triethylamine (3.5 eq.). Work up: the reaction mixture was concentrated in vacuo and DCM added. The organic phase was separated and washed with ammonium bicarbonate (sat. aq.) solution then dried and evaporated in vacuo. The crude residue was purified by flash chromatography on silica gel (0-5% MeOH in DCM). Yield 25% (94.0 mg, 0.334 mmol). ^{1}H NMR (400 MHz, DMSO-d6) δ ppm 9.98 (s, 1 H) 7.70 (d, *J*=8.8 Hz, 1 H) 7.33 (d, *J*=1.3 Hz, 1 H) 7.03 (dd, *J*= 1.7, 8.6 Hz, 1 H) 3.95 (s, 3 H) 3.21-3.17 (m, 2 H) 2.49 (s, 3 H) 1.76-1.68 (m, 2 H) 1.45-1.36 (m, 2 H) 0.89 (t, *J*=7.3 Hz, 3 H). LCMS: $[M+H]^+$ 280.

***N*-(3-chloro-1-methyl-1H-indazol-6-yl)butane-1-sulfonamide (60).** The title compound was prepared following General Procedure A, using as base triethylamine (6 eq.). Work up: the organic phase was separated and the aqueous neutralized with HCl (1N, aq) and extracted with EtOAc. The combined organic phases were dried and concentrated in vacuo. The crude residue was purified by flash chromatography on silica gel (0-50% EtOAc in ^{c}hexanes). Yield 67% (46.0 mg, 0.152 mmol). ^{1}H NMR (400 MHz, DMSO-d6) δ ppm 10.21 (s, 1 H) 7.67 (d, *J*=8.8 Hz, 1 H) 7.43 (d, *J*=1.2 Hz, 1 H) 7.15 (dd, *J*= 1.2, 8.6 Hz, 1 H) 4.02 (s, 3 H) 3.29-3.24 (m, 2 H) 1.76-1.70 (m, 2 H) 1.47-1.39 (m, 2 H) 0.89 (t, *J*=7.3 Hz, 3 H). LCMS: $[M+H]^+$ 302.

***N*-(quinolin-6-yl)butane-1-sulfonamide (61).** The title compound was prepared following General Procedure A, using as base triethylamine (3 eq.). Work up: the reaction mixture was concentrated in vacuo and the resulting solution neutralized with HCl (aq. 1N) and extracted with EtOAc. The organic layers were dried over $MgSO_4$ and evaporated. The crude product was purified by flash chromatography on silica gel (EtOAc in ^{c}hexane 0-50%). Yield 72% (263.0 mg, 0.995 mmol). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.17 (br s, 1 H) 8.78-8.80 (m, 1 H) 8.30 (d, *J*=7.8 Hz, 1 H) 7.98 (d, *J*=9.1 Hz, 1 H) 7.71 (d, *J*=2.3 Hz, 1 H) 7.60 (dd, *J*=9.1, 2.5 Hz, 1 H) 7.50-7.47 (m, 1 H) 3.23-3.15 (m, 2 H) 1.72-1.61 (m, 2 H) 1.42-1.26 (m, 2 H) 0.81 (t, *J*=7.3 Hz, 3 H). LCMS: $[M+H]^+$ 265.

***N*-(4-oxo-3,4-dihydroquinazolin-6-yl)butane-1-sulfonamide (62).** 6-aminoquinazolin-4-(3*H*)-one (100 mg, 0.620 mmol, 1.0 eq.) was dissolved in DMF (5 ml) and 1-Butanesulfonyl chloride (0.080 mL, 0.620 mmol, 1.0 eq.) was added. A light-yellow suspension rapidly formed in the resulting orange solution which was left stirring for 16 hours. Water was added, and the resulting solution extracted with EtOAc. The combined organic phases were washed with sodium bicarbonate (sat., aq.) and ammonium chloride (aq., Sat.) solution . The organic phase was then dried over Na_2SO_4 and evaporated to yield a light-yellow oil which was triturated in a small amount of EtOAc. The title compound was collected via vacuum filtration. 2% yield (3.3 mg, 0.011 mmol). ^{1}H NMR (400 MHz, METHANOL-d_4) δ ppm 8.07-8.02 (m, 2 H) 7.77-7.67 (m, 2 H) 3.18-3.14 (m, 2 H) 1.81-1.71 (m, 2 H) 1.47-1.38 (m, 2 H) 0.90 (t, *J*=7.3 Hz, 3 H). LCMS: $[M+H]^+$ 282.

***N*-(quinoxalin-6-yl)butane-1-sulfonamide (63).** The title compound was prepared following General Procedure A, using as base triethylamine (1.5 eq.). Work up: the reaction mixture was diluted with EtOAc and washed with ammonium chloride (aq., sat.). The organic phase was dried and concentrated in vacuo. The crude material was purified by flash chromatography on silica gel (33% EtOAc in ^{c}hexane). Yield 13% (16.0 mg, 0.065 mmol). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.51 (s, 1 H) 8.89 (d, *J*=2.0 Hz, 1 H) 8.83 (d, *J*=1.8 Hz, 1 H) 8.07 (d, *J*=8.8 Hz, 1 H) 7.81 (d, *J*=2.5 Hz, 1 H) 7.70 (dd, *J*=9.1, 2.5 Hz, 1 H) 3.26-3.24 (m, 2 H) 1.72-1.62 (m, 2 H) 1.39-1.30 (m, 2 H) 0.81 (t, *J*=7.3 Hz, 3 H). LCMS: $[M+H]^+$ 266.

***N*-(5-(butylsulfonamido)-2-hydroxyphenyl)acetamide (64).** The title compound was prepared following General Procedure A, using acetonitrile as the solvent and triethylamine (1 eq.) as base. No hydrolysis step was performed. Work up: the solvent was evaporated in vacuo and the crude material purified by HPLC (Xbridge 19, ACN/:aqNH_4HCO_3 (10 mM), 25-100%). Yield 10% (11.0 mg, 0.038 mmol). ^{1}H NMR (400 MHz, METHANOL-d_4) δ ppm 7.70 (d, *J*=2.5 Hz, 1 H) 6.92 (dd, *J*=2.5, 8.6 Hz, 1 H) 6.81 (d, *J*=8.6 Hz, 1 H) 3.03-2.98 (m, 2 H) 2.07 (s, 3 H) 1.79-1.71 (m, 2 H) 1.44-1.36 (m, 2 H) 0.91 (t, *J*=7.3 Hz, 3 H). LCMS: $[M+H]^+$ 287.

***N*-(6-(butylsulfonamido)-2-methylpyridin-3-yl)acetamide (65).** The title compound was prepared following General Procedure A, using acetic anhydride as the electrophile and no base was used. No hydrolysis step was performed. Work up: the reaction was concentrated under vacuum and then the crude product was triturated in cyclohexane. Yield 86% (300.0 mg, 1.051 mmol). ^{1}H NMR (400 MHz, DMSO-d6) δ ppm 9.49 (s, 1 H) 7.71 (d, *J*=8.6 Hz, 1 H) 6.89 (d, *J*=8.6 Hz, 1 H) 7.03 (dd, *J*= 1.7, 8.6 Hz, 1 H) 3.95 (s, 3 H) 3.21-3.17 (m, 2 H) 2.49 (s, 3 H) 1.76-1.68 (m, 2 H) 1.45-1.36 (m, 2 H) 0.89 (t, *J*=7.3 Hz, 3 H). LCMS: $[M+H]^+$ 286.

***N*-(6-(butylsulfonamido)-4-methylpyridin-3-yl)acetamide (66).** The title compound was prepared following General Procedure A, with no base and acetic anhydride (1.3 eq.) as the electrophile. Work up: the solvent was evaporated and solid triturated in cyclohexane. The in soluble fraction was purified by flash chromatography on silica gel (25-100% EtOAc in ^{c}hexane). Yield 25% (23.0 mg, 0.081 mmol). ^{1}H NMR (400 MHz, METHANOL-d_4) δ ppm 8.13 (s, 1 H) 6.96 (s, 1 H) 3.43-3.39 (m, 2 H) 2.26 (s, 3 H) 2.17 (s, 3 H) 1.83-1.74 (m, 2 H) 1.49-1.40 (m, 2 H) 0.94 (t, *J*=7.3 Hz, 3 H). LCMS: $[M+H]^+$ 286.

4-(butylsulfonamido)-N,*N*-dimethylbenzamide (67). The title compound was prepared following General Procedure A, using as base triethylamine (3 eq.). Work up: the reaction was concentrated in vacuo then diluted with EtOAc and water. The organic phase was washed with ammonium chloride (sat. aq.), dried and evaporated in vacuo. The aqueous phase was extracted with EtOAc with 1% MeOH and the combined organic phases dried and evaporated in vacuo. The combined crudes were purified by flash chromatography on silica gel (0-80% EtOAc in ^{c}hexane). Yield 43% (75.0 mg, 0.264 mmol). ^{1}H NMR (400 MHz, METHANOL-d_4) δ ppm 7.43 (d, *J*=8.6 Hz, 1 H) 7.32 (d, *J*=8.6 Hz, 1 H) 3.17-3.13 (m, 2 H) 3.10 (s, 3 H) 3.04 (s, 3 H) 1.81-1.72 (m, 2 H) 1.49-1.40 (m, 2 H) 0.91 (t, *J*=7.3 Hz, 3 H). LCMS: $[M+H]^+$ 285.

***N*-(2-(3,5-dimethyl-1H-pyrazol-4-yl)ethyl)butane-1-sulfonamide (68).** The title compound was prepared following General Procedure A, with acetonitrile as the solvent and triethylamine (3 eq.) as base. Prior to the hydrolysis step the solvent was evaporated in vacuo and the resulting oil passed through an SCX column. The filtrate was evaporated the resulting oil used in the hydrolysis step. Work up: the mixture neutralised with HCl (1N, aq.) and evaporated in vacuo. The crude powder was triturated in refluxing DCM. The filtrate was evaporated in vacuo and the crude oil purified by HPLC (Xbridge 19, ACN/:aqNH_4HCO_3 (10 mM), 40-100%). Yield 40% (38.7 mg, 0.142 mmol). ^{1}H NMR (400 MHz, DMSO-d6) δ ppm 11.99 (s, 1 H) 7.13 (s, 1 H) 3.01-2.95 (m, 4 H) 2.49 (s, 3 H) 2.55-2.51 (m, 2 H) 2.15 (s, 6 H) 1.68-1.62 (m, 2 H) 1.46-1.40 (m, 2 H) 0.94 (t, *J*=7.3 Hz, 3 H). LCMS: $[M+H]^+$ 260.

***N*-(3-(pyrrolidine-1-carbonyl)phenyl)butane-1-sulfonamide (69).** The title compound was prepared following General Procedure A, using as base triethylamine (3 eq.). Work up: the reaction mixture was concentrated in vacuo then diluted with EtOAc and water. The organic phase was washed with ammonium chloride (sat. aq.), dried and evaporated in vacuo. The crude material was purified by flash chromatography on silica gel (0-90% EtOAc in ^{c}hexane). Yield 58% (100.0 mg, 0.322 mmol). ^{1}H NMR (400 MHz, METHANOL-d_4) δ ppm 7.44-7.41 (m, 2 H) 7.35-7.32 (m, 1 H) 7.28-7.26 (m, 1 H) 3.62-3.58 (m, 2 H) 3.48-3.45 (m, 2 H) 3.15-3.11 (m, 2 H) 2.04-1.89 (m, 4 H) 1.81-1.72 (m, 2 H) 1.47-1.39 (m, 2 H) 0.91 (t, *J*=7.3 Hz, 3 H). LCMS: $[M+H]^+$ 311.

***N*-(3-(4-methylthiazol-2-yl)phenyl)butane-1-sulfonamide (70).** The title compound was prepared following General Procedure A, using as base triethylamine (1.3 eq.). Work up: the reaction mixture was diluted with EtOAc and washed with ammonium chloride (aq., sat.). The aqueous phase was neutralised with HCl (1N, aq.) and extracted with EtOAc. The combined organic phases were dried and evaporated in vacuo. The crude product was purified by flash chromatography on silica gel (EtOAc-^{c}hexane 1:1). Yield 74% (175.0 mg, 0.564 mmol). ^{1}H NMR (400 MHz, DMSO-d6) δ ppm 10.05 (s, 1 H) 7.88-7.87 (m, 1 H) 7.68-7.65 (m, 1 H) 7.52-7.48 (m, 1 H) 7.68-7.65 (m, 1 H) 7.41 (d, *J*= 0.7 Hz, 1 H) 7.38-7.35 (m, 1 H) 3.21-

3.17 (m, 2 H) 2.49 (s, 3 H) 1.74-1.69 (m, 2 H) 1.46-1.39 (m, 2 H) 0.89 (t, *J*=7.3 Hz, 3 H). LCMS: $[M+H]^+$ 311.

***N*-(4-(1H-pyrazol-3-yl)phenyl)butane-1-sulfonamide (71).** The title compound was prepared following General Procedure A, using as base triethylamine (1.3 eq.). Work up: the reaction mixture was diluted with EtOAc and washed with ammonium chloride (sat. aq.). The aqueous phase was neutralised with HCl (1N, aq.) and extracted with EtOAc. The combined organic phases were dried and evaporated in vacuo. The crude product was purified by flash chromatography on silica gel (EtOAc-^{c}hexane 1:1). Yield 39% (100.0 mg, 0.358 mmol). ^{1}H NMR (400 MHz, DMSO-d6) δ ppm 12.88 (s, 1 H) 9.90 (s, 1 H) 7.83-7.81 (m, 2 H) 7.30-7.28 (m, 2 H) 6.71 (s, 1 H) 3.16-3.12 (m, 2 H) 1.67-1.65 (m, 2 H) 1.44-1.38 (m, 2 H) 0.89 (t, *J*=7.3 Hz, 3 H). LCMS: $[M+H]^+$ 280.

***N*-(3-(5-methyl-1H-imidazol-4-yl)phenyl)butane-1-sulfonamide (72).** The title compound was prepared following General Procedure A, using as base triethylamine (1.3 eq.). Work up: the reaction mixture was diluted with EtOAc and washed with ammonium chloride (sat. aq.). The aqueous phase was neutralised with HCl (1N, aq.) and extracted with EtOAc. The combined organic phases were dried and evaporated in vacuo. The crude product was purified by flash chromatography on silica gel (EtOAc-^{c}hexane 1:1). Yield 30% (155.0 mg, 0.528 mmol). ^{1}H NMR (400 MHz, DMSO-d6) δ ppm 12.06 (s, 1 H) 9.83 (s, 1 H) 7.64-7.62 (m, 2 H) 7.44-7.42 (m, 1 H) 7.38-7.34 (m, 1 H) 7.11-7.09 (m, 1 H) 3.15-3.11 (m, 2 H) 2.45 (s, 3 H) 1.76-1.68 (m, 2 H) 1.44-1.38 (m, 2 H) 0.88 (t, *J*=7.3 Hz, 3 H). LCMS: $[M+H]^+$ 294.

***N*-(3-(pyridin-2-yl)phenyl)butane-1-sulfonamide (73).** The title compound was prepared following General Procedure A, using as base triethylamine (3 eq.). Work up: the reaction mixture was diluted with EtOAc and washed with ammonium chloride (sat. aq.). The aqueous phase was neutralised with HCl (1N, aq.) and extracted with EtOAc. The combined organic phases were dried and evaporated in vacuo. The crude product was purified by flash chromatography on silica gel (EtOAc-^{c}hexane 1:1) and once selected fractions were combined HPLC (Xbridge 30, ACN/:aqNH_4HCO_3 (10 mM), 40-100%). Yield 24% (40.0 mg, 0.138 mmol). ^{1}H NMR (400 MHz, DMSO-d6) δ ppm 9.98 (s, 1 H) 8.75-8.73 (m, 1 H) 8.04-8.03 (m, 1 H) 7.97-7.96 (m, 2 H) 7.84-7.82 (m, 1 H) 7.53-7.49 (m, 1 H) 7.46-7.43 (m, 1 H) 7.36-7.34 (m, 1 H) 3.19-3.15 (m, 2 H) 1.76-1.68 (m, 2 H) 1.44-1.38 (m, 2 H) 0.88 (t, *J*=7.3 Hz, 3 H). LCMS: $[M+H]^+$ 291.

***N*-(4-(4-methylthiazol-2-yl)phenyl)butane-1-sulfonamide (74).** The title compound was prepared following General Procedure A, using as base triethylamine (2.5 eq.). Work up: the reaction mixture was diluted with EtOAc and washed with ammonium chloride (sat. aq.). The aqueous phase was neutralised with HCl (1N, aq.) and extracted with EtOAc. The combined organic phases were dried and evaporated in vacuo. The crude product was purified by flash chromatography on silica gel (EtOAc-^{c}hexane 1:2) Yield 43% (88.0 mg, 0.283 mmol). ^{1}H NMR (400 MHz, DMSO-d6) δ ppm 10.19 (s, 1 H) 7.93 (d, *J*= 8.8 Hz, 2 H) 7.35 (d, *J*= 8.8 Hz, 2 H) 7.33 (m, 1 H) 3.24-3.20 (m, 2 H) 2.47 (s, 3 H) 1.76-1.68 (m, 2 H) 1.44-1.38 (m, 2 H) 0.89 (t, *J*=7.3 Hz, 3 H). LCMS: $[M+H]^+$ 311.

***N*-(3-(1H-pyrazol-3-yl)phenyl)butane-1-sulfonamide (75).** The title compound was prepared following General Procedure A, using as base triethylamine (1.3 eq.). Work up: the reaction mixture was diluted with EtOAc and washed with ammonium chloride (sat. aq.). The aqueous phase was neutralised with HCl (1N, aq.) and extracted with EtOAc. The combined organic phases were dried and evaporated in vacuo. The crude product was purified by flash chromatography on silica gel (EtOAc-^{c}hexane 1:1) and once selected fractions were combined HPLC (Xbridge 30, ACN/:aqNH_4HCO_3 (10 mM), 40-100%). Yield 20% (68.0 mg, 0.243 mmol). ^{1}H NMR (400 MHz, DMSO-d6) δ ppm 12.98 (s, 1 H) 9.89 (s, 1 H) 7.86-7.78 (m, 2 H) 7.56-7.55 (m, 1 H) 7.42-7.38 (m, 1 H) 7.22-7.20 (m, 1 H) 6.71 (s, 1 H) 3.17-3.14 (m, 2 H) 1.76-1.68 (m, 2 H) 1.44-1.38 (m, 2 H) 0.88 (t, *J*=7.3 Hz, 3 H). LCMS: $[M+H]^+$ 280.

***N*-(3-(3,5-dimethylisoxazol-4-yl)phenyl)butane-1-sulfonamide (76).** The title compound was prepared following General Procedure A, using as base triethylamine (2 eq.). Work up: the mixture was concentrated in vacuo and neutralised with HCl (1N, aq.) and diluted with EtOAc. The aqueous phase was extracted with EtOAc and the combined organic phases washed with water and brine. The organic phase was then dried, evaporated in vacuo and the crude material purified via flash chromatography on silica gel (0-35% EtOAc in ^{c}hexanes). Yield 59% (255.0 mg, 0.786 mmol). ^{1}H NMR (400 MHz, DMSO-d6) δ ppm 9.89 (s, 1 H) 7.44-7.40 (m, 1 H) 7.22-7.20 (m, 2 H) 7.12-7.10 (m, 1 H) 3.14-3.10 (m, 2 H) 2.41 (s, 3 H) 2.23, (s, 3 H) 1.69-1.61 (m, 2 H) 1.40-1.32 (m, 2 H) 0.82 (t, *J*=7.3 Hz, 3 H). LCMS: $[M+H]^+$ 309.

***N*-(3-(thiophen-3-yl)phenyl)butane-1-sulfonamide (77).** The title compound was prepared following General Procedure A, using as base triethylamine (1.3 eq.). Work up: the reaction mixture was diluted with EtOAc and washed with ammonium chloride (sat. aq.). The aqueous phase was neutralised with HCl (1N, aq.) and extracted with EtOAc. The combined organic phases were dried and evaporated in vacuo. The crude product was purified by flash chromatography on silica gel (EtOAc-^{c}hexane 1:1) and once selected fractions were combined HPLC (Xbridge 30, ACN/:aqNH_4HCO_3 (10 mM), 40-100%). Yield 49% (82.0 mg, 0.278 mmol). ^{1}H NMR (400 MHz, DMSO-d6) δ ppm 9.90 (s, 1 H) 7.86 (dd, *J*=2.9, 1.4 Hz, 1 H) 7.72 (dd, *J*=4.9, 2.9 Hz, 1 H) 7.55-7.47 (m, 3 H) 7.44-7.40 (m, 1 H) 7.22-7.19 (m, 1 H) 3.19-3.15 (m, 2 H) 1.74-1.69 (m, 2 H) 1.46-1.38 (m, 2 H) 0.89 (t, *J*=7.3 Hz, 3 H). LCMS: $[M+H]^+$ 294.

***N*-(3-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl)butane-1-sulfonamide (78).** The title compound was prepared following General Procedure A, using as base triethylamine (1 eq.). Work up: the reaction mixture was diluted with EtOAc and washed with ammonium chloride (sat. aq.). The aqueous phase was neutralised with HCl (1N, aq.) and extracted with EtOAc. The combined organic phases were dried and evaporated in vacuo. The crude product was purified by flash chromatography on silica gel (EtOAc-^{c}hexane 1:2). Yield 62% (256.0 mg, 0.857 mmol). 1H NMR (400 MHz, DMSO-d6) δ ppm 10.15 (s, 1 H) 7.95 (m, 1 H) 7.78-7.75 (m, 1 H) 7.60-7.56 (m, 1 H) 7.48-7.45 (m, 1 H) 3.21-3.17 (m, 2 H) 2.74 (s, 3 H) 1.74-1.69 (m, 2 H) 1.46-1.38 (m, 2 H) 0.88 (t, *J*=7.3 Hz, 3 H). LCMS: $[M+H]^+$ 296.

4,4,4-trifluoro-*N*-(1-methyl-1H-benzo[d]imidazol-6-yl)butane-1-sulfonamide (79). The title compound was prepared following General Procedure A, using acetonitrile as solvent and no base, or hydrolysis step were needed. The reaction had to be heated to 50 °C to proceed. Work up: the solvent was evaporated and the crude was compound purified by HPLC (Xbridge 19, ACN/:aqNH_4HCO_3 (10 mM), 20-60%). Yield 32% (35.0 mg, 0.109 mmol). ^{1}H NMR (400 MHz, METHANOL-d_4) δ ppm 8.12 (s, 1 H) 7.64 (d, *J*= 8.6 Hz, 1 H) 7.50 (d, *J*=2.0 Hz, 1 H) 7.17 (dd, *J*= 8.6, 2.0 Hz, 1 H) 3.89 (s, 3 H) 3.21-3.17 (m, 2 H) 2.37-2.31 (m, 2 H) 2.07-2.03 (m, 2 H). LCMS: $[M+H]^+$ 322.

4,4,4-trifluoro-*N*-(isoquinolin-6-yl)butane-1-sulfonamide (80). The title compound was prepared following General Procedure A, using DCE as a solvent and triethylamine (1.3 eq.) as base. Work up: The reaction mixture was diluted with EtOAc and the organic phase separated and washed with sat. ammonium chloride solution (sat. aq.) while the aqueous phase was neutralized with HCl (aq. 1 N) and extracted with EtOAc. The combined organic phases were dried over $MgSO_4$ and concentrated in vacuo. The crude product was semi-purified by flash column chromatography on silica gel (EtOAc: ^{c}hexane) before being purified by HPLC (Xbridge 19, ACN/:aqNH_4HCO_3 (10 mM), 40-100%). Yield 32% (65.0 mg, 0.204 mmol). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.54 (br s, 1 H) 9.17 (s, 1 H) 8.42 (d, *J*=5.8 Hz, 1 H) 8.08 (d, *J*=9.1 Hz, 1 H) 7.73 (d, *J*=6.1 Hz, 1 H) 7.64 (s, 1 H) 7.47 (dd, *J*=8.8, 2.0 Hz, 1 H) 3.40-3.34 (m, 2 H) 2.45 - 2.37 (m, 2 H) 1.94 - 1.85 (m, 2 H).). LCMS: $[M+H]^+$ 319.

***N*-(3-methyl-1H-indazol-5-yl)butane-1-sulfonamide (81).** The title compound was prepared following General Procedure A, using as base triethylamine (3 eq.). An additional equivalent of sulphonyl chloride and triethylamine were added to help push the reaction to completion. Work up: the aqueous phase was washed with DCM before being acidified to pH 5 with HCl (aq. 2N) and extracted with EtOAc. The combined organic phases were dried over $MgSO_4$ and the solvent removed in vacuo. The crude was triturated in DCM and the precipitate collected via vacuum filtration then decolorized with activated charcoal. Yield 10% (77.8 mg, 0.276 mmol). ^{1}H NMR (400 MHz, METHANOL-d_4) δ ppm 7.60-7.59 (m, 1 H) 7.44 (dd, *J*=8.8, 0.8 Hz, 1 H) 7.31 (dd, *J*=8.8, 2.0 Hz, 1 H) 3.06-2.98 (m, 2 H) 2.58-2.48 (m, 3 H) 1.82-1.72 (m, 2 H) 1.47-1.38 (m, 2 H) 0.90 (t, *J*=7.5 Hz, 3 H). LCMS: $[M+H]^+$ 268.

***N*-(3-fluoro-1H-indazol-5-yl)butane-1-sulfonamide (82).** The title compound was prepared following General Procedure A, using as base triethylamine (2 eq.). Work up: the reaction was concentrated in vacuo and partitioned between EtOAc and water, the organic phase was washed with ammonium chloride (sat. aq.) and dried over Na_2SO_4 and evaporated in vacuo. The crude product was purified by flash column chromatography on silica gel (EtOAc in ^{c}hexane 0-60%), yield 11% (37.0 mg, 0.136 mmol). ^{1}H NMR (400 MHz, METHANOL-d_4) δ ppm 7.52 (d, *J*=1.8 Hz, 1 H) 7.46-7.35 (m, 2 H) 3.07-3.01 (m, 2 H) 1.81-1.72 (m, 2 H) 1.49-1.34 (m, 2 H) 0.90 (t, *J*=7.3 Hz, 3 H). LCMS: $[M+H]^+$ 272.

***N*-(3-chloro-1H-indazol-5-yl)butane-1-sulfonamide (83).** The title compound was prepared following General Procedure A, using as base triethylamine (2.5 eq.). Work up: the volume reduced in vacuo and solution partitioned between DCM and ammonium chloride (sat. aq.) solution . The organic phase was dried

over Na_2SO_4 and evaporated in vacuo. The crude product was purified by flash column chromatography on silica gel (MeOH:DCM 0-10%) to give two batches. Batch 1 was recrystallized in DCM/cyclohexane and the second by HPLC (Xbridge 30, ACN/:aqNH_4HCO_3 (10 mM), 40-100%). Both batches were combined for analysis. Yield 35% (120.0 mg, 0.417 mmol). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 13.30 (br s, 1 H) 9.77 (br s, 1 H) 7.56 (d, *J*=8.9 Hz, 1 H) 7.43-7-42 (m, 1 H) 7.34 (dd, *J*=9.1, 2.0 Hz, 1 H) 3.07-2.99 (m, 2 H) 1.69-1.59 (m, 2 H) 1.36-1.28 (m, 2 H) 0.81 (t, *J*=7.5 Hz, 3 H). LCMS: $[M+H]^+$ 288.

***N*-(3-bromo-1H-indazol-5-yl)butane-1-sulfonamide (84).** The title compound was prepared following General Procedure A, using DMF as solvent and triethylamine (2.5 eq.) as base. Work up: The volume was reduced in vacuo and solution partitioned between DCM and ammonium chloride solution. The organic phase was dried over Na_2SO_4 and evaporated in vacuo. The crude product was purified by flash column chromatography on silica gel (EtOAc: ^{c}hexane 0:1 – 3:2). Yield 46% (150.0 mg, 0.452 mmol). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 13.44 (br s, 1 H) 9.79 (br s, 1 H) 7.57 (dd, *J*=8.7, 0.9 Hz, 1 H) 7.37-7.32 (m, 2 H) 3.07-2.97 (m, 2 H) 1.69-1.59 (m, 2 H) 1.40-1.26 (m, 2 H) 0.81 (t, *J*=7.5 Hz, 3 H). LCMS: $[M+H]^+$ 334.

***N*-(3-ethyl-1H-indazol-5-yl)butane-1-sulfonamide (86).** The title compound was prepared following General Procedure A, using as base triethylamine (1.3 eq.). Work up: glacial acetic was added dropwise and the reaction stirred at 50 °C for 3 hours before cooling to 30 °C and stirred for 16 hours. EtOAc was added and the phases separated. The aqueous phase was extracted with EtOAc and the combined organic phases were washed with ammonium chloride (aq. sat.), dried over $MgSO_4$ and evaporated in vacuo. The crude product was purified by flash chromatography on silica gel (EtOAc in ^{c}hexane 1:1). Yield 17% (12.0 mg, 0.043 mmol). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 12.64 (s, 1 H) 9.53 (s, 1 H) 7.50 (d, *J*=1.8 Hz, 1 H) 7.43 (d, *J*=8.8 Hz, 1 H) 7.21 (dd, *J*=8.8, 2.0 Hz, 1 H) 3.02-2.93 (m, 2 H) 2.90-2.85 (m, 2 H) 1.70-1.60 (m, 2 H) 1.37-1.27 (m, 5 H) 0.81 (t, *J*=7.5 Hz, 3 H). LCMS: $[M+H]^+$ 282.

***N*-(3-(trifluoromethyl)-1H-indazol-5-yl)butane-1-sulfonamide (87).** The title compound was prepared following General Procedure A, using as base triethylamine (4 eq.). Work up: sat. bicarbonate solution and EtOAc were added. The phases were separated, and aqueous phase extracted with EtOAc. The combined organic phases were dried over Na_2SO_4 and evaporated. The crude product was purified by flash column chromatography on silica gel (EtOAc: ^{c}hexane 0:1 – 1:1), then HPLC (Xbridge 30, ACN/:aqNH_4HCO_3 (10 mM), 40-100%). Yield 20% (16.0 mg, 0.050 mmol). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 14.02 (br s, 1 H) 9.87 (br s, 1 H) 7.72-7.68 (m, 1 H) 7.59 (s, 1 H) 7.43-7.42 (m, 1 H) 3.08-3.00 (m, 2 H) 1.69-1.59 (m, 2 H) 1.37-1.28 (m, 2 H) 0.80 (t, *J*=7.3 Hz, 3 H). LCMS: $[M+H]^+$ 322.

***N*-(3-methoxy-1H-indazol-5-yl)butane-1-sulfonamide (88).** The title compound was prepared following General Procedure A, using as acetonitrile as the solvent and triethylamine (4 eq.) as the base. Work up: saturated sodium bicarbonate and EtOAc were added and phases separated. The aqueous phase was extracted with EtOAc and the combined organic phased dried over Na2SO4 and evaporated. The crude product was purified via flash chromotography on silica gel (0 - 50% EtOAc in ^{c}hexane) then (Xbridge 30, ACN/:aqNH_4HCO_3 (10 mM), 40-100%). Yield 43% (12.0 mg, 0.042 mmol). ^{1}H NMR (400 MHz, METHANOL-d_4) δ ppm 7.49 (s, 1 H) 7.35-7.27 (m, 2 H) 4.05 (s, 3 H) 3.02-2.98 (m, 2 H) 1.80-1.72 (m, 2 H) 1.45-1.36 (m, 2 H) 0.92-0.84 (m, 3 H). LCMS: $[M+H]^+$ 284.

***N*-(3-cyclopropyl-1H-indazol-5-yl)butane-1-sulfonamide (89).** The title compound was prepared following General Procedure A, using as base triethylamine (2.5 eq.). For hydrolysis to proceed the reaction was heated to 50 °C. Work up: EtOAc was added and the organic phase washed with sat. ammonium chloride solution. The aqueous layer was acidified to pH 5 with HCl (aq. 2N) and extracted with EtOAc. Both organic phases were combined and dried over Na_2SO_4 and evaporated in vacuo. The crude product was purified by flash column chromatography on silica gel (EtOAc: ^{c}hexane). Yield 20% (32.0 mg, 0.109 mmol). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 12.56 (s, 1 H) 9.52 (s, 1 H) 7.55 (d, *J*=1.8 Hz, 1 H) 7.41 (d, *J*=8.8 Hz, 1 H) 7.21 (dd, *J*=8.8, 2.0 Hz, 1 H) 3.03-2.93 (m, 2 H) 2.22-2.15 (m, 1 H) 1.71-1.61 (m, 2 H) 1.40-1.23 (m, 2 H) 1.00-0.79 (m, 7 H). LCMS: $[M+H]^+$ 294.

***N*-(3-isopropyl-1H-indazol-5-yl)butane-1-sulfonamide (90).** The title compound was prepared following General Procedure A, using as base triethylamine (1.3 eq.). Work up: EtOAc was added and the organic phase washed with sat. ammonium chloride solution. The organic phase was dried over $MgSO_4$ and evaporated in vacuo and the crude product was purified by flash column chromatography on silica gel (EtOAc: ^{c}hexane 1:1). Yield 27% (15.0 mg, 0.051 mmol). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 12.59 (s,

1 H) 9.50 (s, 1 H) 7.55 (d, *J*=1.8 Hz, 1 H) 7.43 (d, *J*=8.8 Hz, 1 H) 7.21 (dd, *J*=8.8, 2.0 Hz, 1 H) 2.99-2.95 (m, 2 H) 1.69-1.62 (m, 2 H) 1.37-1.30 (m, 8 H) 0.79 (t, *J*=7.3 Hz, 4 H). LCMS: $[M+H]^+$ 296.

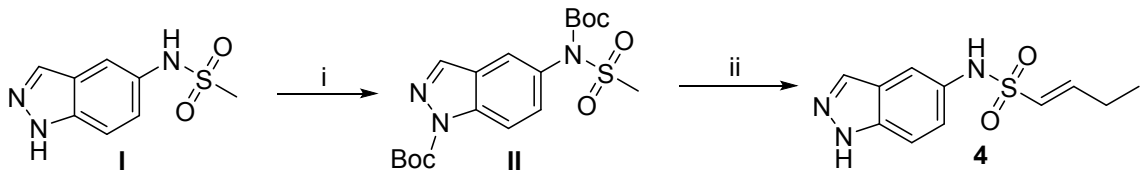
***N*-(3-cyano-1H-indazol-5-yl)butane-1-sulfonamide (91).** The title compound was prepared following General Procedure A, using acetonitrile as the solvent and no base. The reaction required heating to reflux in order to proceed. Work up: the solvent was evaporated in vacuo and the crude compound triturated with diethyl ether. The filtrate was evaporated in vacuo and the title compound precipitated from DCM by addition of chexane. Yield 22% (28.9 mg, 0.104 mmol). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 14.38 (br s, 1 H) 9.99 (s, 1 H) 7.77-7.75 (m, 1 H) 7.60 (s, 1 H) 7.44-7.41 (m, 1 H) 3.13-3.09 (m, 2 H) 1.65-1.63 (m, 2 H) 1.51-1.27 (m, 2 H) 0.83-0.79 (m, 3 H). LCMS: $[M+H]^+$ 279.

***N*-(3-propyl-1H-indazol-5-yl)butane-1-sulfonamide (94).** The title compound was prepared following General Procedure A, using as base triethylamine (1.3 eq.). Work up: acetic acid (glacial) was added and the resulting solution stirred for 2 hours before mixture was concentrated in vacuo. The crude was resuspended in acetic acid (glacial) and stirred for 16 hours before being heated to 40 °C for 30 minutes. The solution was diluted with EtOAc and washed with ammonium chloride (sat. aq.). The organic phase was then dried over $MgSO_4$ and evaporated in vacuo and the resulting crude product was purified by flash column chromatography on silica gel (EtOAc: ^{c}hexane 1:3). Yield 32% (12.0 mg, 0.051 mmol). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.36 (s, 1 H) 7.27-7.21 (m, 2 H) 6.76 (d, *J*=9.1 Hz, 1 H) 6.07 (t, *J*=5.8 Hz, 1 H) 3.12-3.07 (m, 2 H) 2.98-2.94 (m, 2 H) 1.66-1.49 (m, 4 H) 1.39-1.29 (m, 4 H) 0.91-0.82 (m, 6H). LCMS: $[M+H]^+$ 296.

***N*-(3-hydroxy-1H-indazol-5-yl)butane-1-sulfonamide (96).** The title compound was prepared following General Procedure A, using DCE as a solvent and triethylamine (1.5 eq.) as the base. The solvent was evaporated, and the crude dissolved in EtOAc and on standing a precipitate was formed filtered and discarded. The solvent was evaporated in vacuo and the crude was purified by flash column chromatography on silica gel (EtOAc: ^{c}hexane) prior to the hydrolysis step. Due to no hydrolysis being observed with 2N NaOH, the mixture was concentrated in vacuo and dissolved in NaOH (6N, aq., 10 ml) and stirred for 16 hours. Work up: the mixture was concentrated in vacuo and the aqueous phase extracted with EtOAc. The organic phase was dried over Na_2SO_4 and evaporated to give the title compound. Yield 2% (11.0 mg, 0.041 mmol). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 13.05 (br s, 1 H) 9.99 (s, 1 H) 7.80 (s, 1 H) 7.69-7.60 (m, 1 H) 7.47-7.42 (m, 2 H) 3.14-3.03 (m, 2 H) 1.70-1.49 (m, 2 H) 1.39-1.29 (m, 2 H) 0.81 (t, *J*=7.3 Hz, 3 H). LCMS: $[M+H]^+$ 270.

***N*-(3-(hydroxymethyl)-1H-indazol-5-yl)butane-1-sulfonamide (97).** The title compound was prepared following General Procedure A, using acetonitrile as the solvent and no base. The reaction required heating to reflux in order to proceed. Work up: the reaction solvent was evaporated in vacuo and the crude product purified by HPLC (Xbridge 19, ACN/:aqNH_4HCO_3 (10 mM), 20-100%). Yield 9% (5.2 mg, 0.021 mmol). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 12.79 (s, 1 H) 9.55 (s, 1 H) 7.66 (d, *J*=2.0 Hz, 1 H) 7.45 (d, *J*=8.8 Hz, 1 H) 7.23 (dd, *J*=8.8, 2.0 Hz, 1 H) 5.21 (t, *J*=5.6 Hz, 1 H) 4.74 (d, *J*=5.6 Hz, 2 H) 3.03-2.93 (m, 2 H) 1.70-1.61 (m, 2 H) 1.33 (sxt, *J*=7.4 Hz, 2 H) 0.82 (t, *J*=7.3 Hz, 3 H). LCMS: $[M+H]^+$ 284.

Synthesis of (*E*)-*N*-(1H-indazol-5-yl)but-1-ene-1-sulfonamide (4).



Scheme S1: Synthesis of compound 4. (i) **100** (2.5 eq.), (DMAP (cat. 0.1 eq.), DCM, 0 °C – RT, 72 hours, 52%. (ii) propionaldehyde (1.0 eq.), potassium *tert*-butoxide (2.1 eq.), 156 (1.0 eq.), THF, -78 °C – 0 °C, 16 hours, 12%.

***N*-(1H-indazol-5-yl)methanesulfonamide (I).** The title compound was prepared from 1H-indazol-5-amine (500 mg, 3.76 mmol, 1 eq.), and mesyl chloride (0.32 ml, 4.13 mmol, 1.1 eq.) in ACN (15 ml) with no base following general method A with stirring at 60 °C for 21 hours. Before MeOH (5 ml) and NaOH (5 ml) were added for the hydrolysis step. The mixture was stirred at RT for 4 hours before the solvents were

evaporated in vacuo and the crude was purified by flash column chromatography on silica gel (10 – 100% EtOAc in chexane) to give the title compound as a colorless solid, 54% yield (448 mg, 2.02 mmol). ^{1}H NMR (400 MHz, METHANOL-d4) δ 8.14 (s, 1H), 7.77-7.68 (m, 1H), 7.58 (d, *J*= 8.84 Hz, 1H), 7.39 (dd, *J*= 2.02, 8.84 Hz, 1H), 2.95 (s, 3H), 2.75 (br. s., 1H)

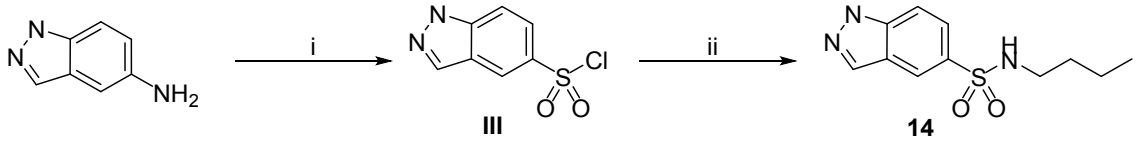
***Tert*-butyl 5-(*N*-(*tert*-butoxycarbonyl)methylsulfonamido)-1H-indazole-1-carboxylate (II).** Boc anhydride (**100**, 1149 mg, 5.27 mmol, 2.5 eq.) was added to a suspension of *N*-(1H-indazol-5-yl)methanesulfonamide (**I**) (445 mg, 2.11 mmol, 1.0 eq.), in DCM (20 mL) stirring under argon at 0°C. DMAP (25.7 mg, 0.21 mmol, 0.1 eq.) was added to the mixture and the reaction stirred for 30 min at 0 °C and then over a weekend at RT. The solvents were evaporated, and the crude product was purified by flash chromatography on silica gel (10 – 50% EtOAc in chexane) to isolate the title compound as a colorless oil, 52% (471 mg, 1.087 mmol). 1H NMR (400 MHz, METHANOL-d4) δ 8.36 (s, 1H), 8.20 (d, *J*= 9.09 Hz, 1H), 7.84 (d, *J*= 1.52 Hz, 1H), 7.52 (dd, *J*= 2.02, 8.84 Hz, 1H), 3.54 (s, 3H), 1.75 (s, 9H), 1.47 (s, 12H).

(*E*)-*N*-(1*H*-indazol-5-yl)but-1-ene-1-sulfonamide (4). A solution tBuOK (1N, THF, 0.77 mL, 0.77 mmol, 2.1 eq.) in THF was added dropwise to a stirring solution of *tert*-butyl 5-(*N*-(*tert*-butoxycarbonyl)methylsulfonamido)-1*H*-indazole-1-carboxylate (150 mg, 0.37 mmol, 1.0 eq.) in dry THF (4mL) under argon at -78°C. The reaction mixture was stirred at -78 °C for 1 h and them a solution of propanol (21.17 mg, 0.37 mmol, 1.0 eq.) in dry THF was added. The reaction mixture was warmed to RT and stirred for 16 hours. The solvents were evaporated in vacuo and the crude purified by flash chromatography on silica gel (EtOAc in ^{c}hexane 10-100%) and a subsequent HPLC (Xbridge 19, ACN/:aqNH_4HCO_3 (10 mM), 40-100%) to give the title compound as a colorless oil, 12% yield (11 mg, 0.04 mmol). ^{1}H NMR (400 MHz, METHANOL-d4) δ 8.00 (s, 1H), 7.44 - 7.59 (m, 2H), 7.25-7.28 (m, 1H), 6.58 - 6.67 (m, 1H), 6.26 - 6.30 (m, 1H), 2.10 - 2.18 (m, 2H), 0.93 (t, *J*= 7.5 Hz, 2H). LCMS: $[M+H]^+$ 252.

5-(pentylthio)-1H-indazole (12). 5-(chloromethyl)-1H-indazole (441.7 mg, 2.65 mmol, 1.0 eq.) and potassium carbonate (440 mg, 3.18 mmol, 1.2 eq.) were suspended in DMF (2 mL). Butane-1-thiol (0.285 mL, 2.65 mmol, 1.0 eq.) was added and the resulting colourless suspension was left stirring at room temperature for 16 hours. An additional equivalent of butane-1-thiol (0.285 mL, 2.65 mmol, 1.0 eq.) was added and the reaction left stirring for an additional 24 hours before the reaction mixture was heated to 50 °C for 1 hour. The reaction was allowed to cool to room temperature and ammonium chloride (sat., 1 N, aq.) was added and the resulting aqueous phase extracted with EtOAc. The combined organic phases were then dried over Na2SO4 and evaporated to yield a brown oil which was purified via flash chromatography on silica gel (0-50% EtOAc in chexane). The title compound was isolated as colourless microcrystals, 30% yield (172.9 mg, 0.79 mmol). ^{1}H NMR (400 MHz, DMSO-d6) δ 13.01 (br s, 1H), 8.01 (s, 1H), 7.64-7.63 (m, 1H), 7.49 (d, *J*= 8.3 Hz, 1H), 7.32 (dd, *J*= 8.6, 1.5 Hz, 1H), 3.81 (s, 2H), 3.32-3.30 (m, 1H), 2.40-2.34 (m, 2H), 1.51-1.44 (m, 2H), 1.35-1.26 (m, 2H), 0.82 (t, J = 7.3 Hz, 3H). LCMS: $[M+H]^+$ 221.

1H-indazol-5-yl butane-1-sulfonate (13). 1H-indazol-5-ol (200 mg, 1.49 mmol, 1.0 eq.) was suspended in dry THF (6 mL) at 0 °C and sodium hydride (42.9 mg, 1.789 mmol, 1.2 eq.) added portion wise over the course of 1 minute. The resulting colourless suspension was allowed to warm to room temperature and butane-1-sulfonyl chloride **98** (0.193 mL, 1.491 mmol, 1.0 eq.) was added dropwise. The light brown suspension was left stirring for 16 hours before sodium hydride (17.9 mg, 0.74 mmol, 0.5 eq.) was added and the mixture stirred for 5 mins before butane-1-sulfonyl chloride **98** (0.048 mL, 0.37 mmol, 0.25 eq.) was added. The resulting mixture was stirred for a further 3 hours and then the solvent was evaporated in vacuo. The resulting orange solid was suspended in EtOAc and water, the organic phase was separated, and the aqueous phase extracted EtOAc. The combined organic phases were dried over Na2SO4 and evaporate to yield a light orange oil which was purified by flash chromatography on silica gel (0-25% EtOAc in chexane) to give the title compounds as a colourless crystalline solid, 26% yield (102.1 mg, 0.38 mmol). ^{1}H NMR (400 MHz, DMSO-d6) δ 13.30 (br s, 1H), 8.15 (s, 1H), 7.74 (d, *J*= 2.4 Hz, 1H), 7.62 (d, *J*= 9.1 Hz, 1H), 7.30 (dd, *J*= 8.8, 2.3 Hz, 1H), 3.54-3.47 (m, 2H), 1.85-1.76 (m, 2H), 1.50-1.41 (m, 2H), 0.91 (t, J = 7.3 Hz, 3H). LCMS: $[M+H]^+$ 255.

Synthesis of *N*-butyl-1H-indazole-5-sulfonamide (14).

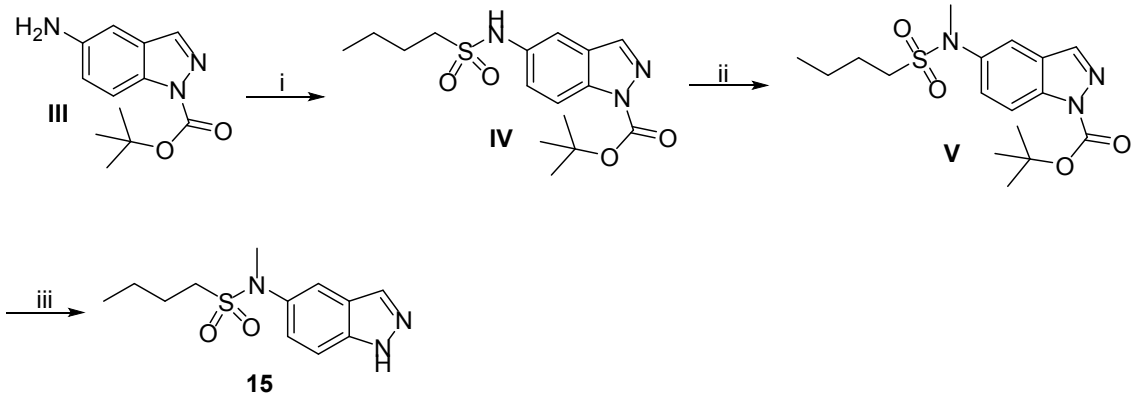


Scheme S2: (i) 1H-indazol-5-amine (1.0 eq.), Sodium nitrite (1.2 eq.), HCl (concentrated): water 1:1, 0 °C, SO2 (bubbled gas) and copper chloride (1.2 eq.), was added at 0 °C and the reaction allowed to warm to RT, overnight, 71% (ii) **III** (1.0 eq.), butylamine (1.0 eq), Et3N, DCM, 0 °C-RT, 15 minutes, 23%.

1H-indazole-5-sulfonyl chloride (III). A solution of sodium nitrite (311 mg, 4.51 mmol, 1.2 eq.) in Water (3 mL) was added to a solution of 1H-indazol-5-amine (500 mg, 3.76 mmol, 1.0 eq.) in concentrated hydrochloric acid (15.00 mL) at 0 ºC and the mixture was stirred at 0 °C for 45 min. In a 2-neck flask, sulphur dioxide gas was bubbled through a mixture of glacial acetic acid (15.00 mL) and acetonitrile (15.00 mL) for 60 mins. Copper (II) chloride (555 mg, 4.13 mmol, 1.1 eq.) was added to the sulphur dioxide solution, and the resulting mixture was poured carefully onto the diazonium mixture at 0 ºC. The resulting mixture was stirred at RT overnight. The mixture was diluted with ice water and extracted with ethyl acetate. The combined organic layers were washed with water and brine and dried over Na_2SO_4. Solvents were evaporated in vacuo to give the title compound, 71% yield (580 mg, 2.68 mmol). Compound was used in next step without further purifications.

***N*-butyl-1H-indazole-5-sulfonamide (14).** 1H-indazole-5-sulfonyl chloride (**III**) (300 mg, 1.39 mmol) was dissolved in DCM (10 mL) under an atmosphere of N2 (g) and the solution cooled to 0ºC. DIPEA (0.363 mL, 2.077 mmol, 1.5 eq.) was added and after a further 15 minutes butyl-1-amine (0.14 mL, 1.39 mmol, 1.0 eq.) was added to the mixture. The reaction mixture was stirred at room temperature for 15 minutes before being diluted with DCM and washed with ammonium chloride solution (aq. sat.). The organic layer was dried over MgSO4, filtered and concentrated in vacuo. The crude compound was purified by flash chromatography on silica gel (0-5% MeOH in DCM) to give the title compound, 23% yield (82 mg, 0.32 mmol). ^{1}H NMR (400 MHz, DMSO-d6) δ 13.49 (br s, 1H), 8.28 (d, *J*= 8.1 Hz, 2H), 7.72 (s, 2H), 7.49-7.46 (m, 1H), 2.72-2.67 (m, 2H), 1.36-1.13 (m, 4H), 0.76 (t, *J*= 7.3 Hz, 3H). LCMS: $[M+H]^+$ 254.

Synthesis of *N*-(1H-indazol-5-yl)-N-methylbutane-1-sulfonamide (15).



Scheme S3: (i) *tert*-butyl 5-amino-1H-indazole-1-carboxylate (1.0 eq.), triethylamine (1.0 eq.), buane-1-sulfonyl chloride **98** (1.1 eq.), DCM, 0 °C – RT, 19 hours, 58% (ii) **IV** (1.0 eq), Sodium hydride (1.1 eq), methyl iodide (1.1 eq.), 0 °C – RT, Overnight, 98%. (ii) **V** (1.0 eq.), 2N HCl in diethyl ether, 16 h, 56%

***Tert*-butyl 5-(butylsulfonamido)-1H-indazole-1-carboxylate (IV).** Triethylamine (0.18 mL, 1.29 mmol, 1.0 eq.) was added to a stirring solution of *tert*-butyl 5-amino-1H-indazole-1-carboxylate (300 mg, 1.29 mmol, 1.0 eq.) in DCM (10 mL) at 0ºC and stirred for 15 mins. Butane-1-sulfonyl chloride **98** (0.18 mL, 1.42 mmol, 1.1 eq.) was added and the reaction was stirred at room temperature for 19 hours. The solvents were evaporated in vacuo and the crude product dissolved in EtOAc and washed with brine before the solution was dried over MgSO4 and evaporated. The crude product was purified by flash chromatography

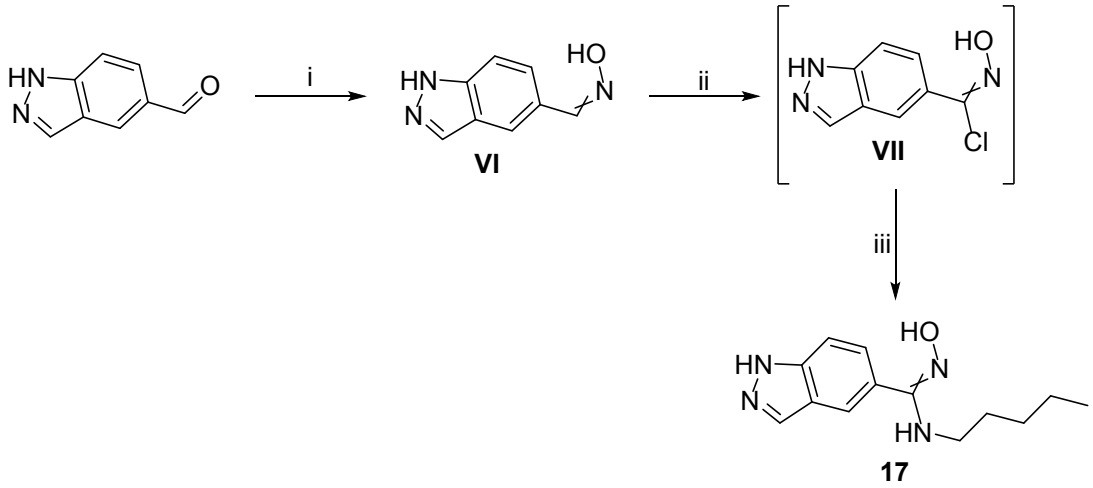
on silica gel (0 – 50% EtOAc in chexane) to give the title compound as a colourless solid, 58% yield (262 mg, 0.74 mmol). 1H NMR (400 MHz, DMSO-d6) δ 9.93 (s, 1H), 8.40 (s, 1H), 8.02 (d, *J*= 8.84 Hz, 1H), 7.68 (d, *J*= 1.77 Hz, 1H), 7.45 (dd, *J*= 2.02, 8.84 Hz, 1H), 3.11-3.02 (m, 2H), 1.64 (s, 11H), 1.33 (apparent sxt, J =7.40 Hz, 2H), 0.81 (t, *J*= 7.33 Hz, 3H).

***Tert*-butyl 5-(N-methylbutylsulfonamido)-1H-indazole-1-carboxylate (V).** *Tert*-butyl 5-(butylsulfonamido)-1H-indazole-1-carboxylate IV (255 mg, 0.72 mmol, 1.0 eq.) was dissolved in DMF (5 mL) and cooled to 0 °C. Sodium hydride (19.05 mg, 0.79 mmol, 1.1 eq.) was added to the solution at 0ºC and stirred for 10 min. After that time iodomethane (49.0 µL, 0.79 mmol, 1.1 eq.) was added dropwise and reaction was stirred for 2h 30 min. Solution was diluted with EtOAc and washed with ammonium chloride (1N, aq.), the organic phase was dried over MgSO4 and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel (0 – 50% EtOAc in chexane) to obtain the title compound, as a colourless oil 98% yield (260 mg, 0.71 mmol). 1H NMR (400 MHz, DMSO-d6) δ 8.44 (s, 1H), 8.07 (d, *J*= 9.09 Hz, 1H), 7.93 (d, *J*= 1.77 Hz, 1H), 7.67 (dd, *J*= 2.15, 8.97 Hz, 1H), 3.32 (br s, 3H), 3.33-3.03 (m, 2H), 1.75-1.52 (m, 1H), 1.65 (s, 10H), 1.47-1.27 (m, 2H), 0.86 (t, J = 7.33 Hz, 3H).

***N*-(1H-indazol-5-yl)-N-methylbutane-1-sulfonamide (15).** *Tert*-butyl 5-(N-methylbutylsulfonamido)-1H-indazole-1-carboxylate **V** (255 mg, 0.694 mmol, 1.0 eq.) was dissolved in DCM (10 mL) and HCl in ether (1N, 5 mL, 0.69 mmol, 1.0 eq.) was added and the mixture stirred for 16 hours. The solvents were evaporated in vacuo and the crude compound purified by flash chromatography on silica gel (0 – 50% EtOAc in chexane) to give the target compound, 56% yield (103 mg, 0.39 mmol). 1H NMR (400 MHz, DMSO-d6) δ 13.17 (br s, 1H), 8.10 (s, 1H), 7.81 (d, *J*= 1.8 Hz, 1H), 7.55 (d, *J*= 8.8 Hz, 1H), 7.38 (dd, *J*= 8.8, 1.8 Hz, 1H), 3.30-3.27 (m, 3H), 3.18-3.05 (m, 2H), 2.33 (s, 1H), 1.69-1.59 (m, 2H), 1.43-1.33 (m, 2H), 0.86 (t, *J*= 7.3 Hz, 3H). LCMS: $[M+H]^+$ 268.

***N*-((1H-indazol-5-yl)methyl)butane-1-sulfonamide (16).** Sodium hydride, 60% dispersion in mineral oil (33.5 mg, 0.84 mmol, 2.2 eq.) was added to a solution of butane-1-sulfonamide **98** (104 mg, 0.76 mmol, 2.0 eq.) in DMF (4 mL) and the resulting mixture stirred at RT for 30 mins. A solution of 5-(chloromethyl)-1H-indazole (63.4 mg, 0.38 mmol, 1.0 eq.) in DMF (4 mL) was then added and the resulting mixture left stirring for 16 hours. Water was added, and the suspension extracted with EtOAc and the combined organic phases were washed with ammonium chloride solution (aq. sat.), dried over Na2SO4 and evaporated to yield a yellow oil. The oil was dissolved in MeOH and loaded on to a SCX column and washed with MeOH and then the crude product was liberated with ammonia in MeOH (7 N). The solvent was evaporated, and yellow glass dissolved in methanol, filtered through a canular syringe, and purified by preparative HPLC (Sunfire 19, 0.1 M Formic acid in ACN/aq. formic acid (0.1 M), 40-100%) to give the title compound as a colourless amorphous solid, 4% yield (4.2 mg, 0.01 mmol). 1H NMR (400 MHz, DMSO-d6) δ 13.03 (br s, 1H), 8.05 (t, *J*= 1.3 Hz, 1H), 7.69 (s, 1H), 7.59 (t, *J*= 6.2 Hz, 1H), 7.52 (d, *J*= 8.7 Hz, 1H), 7.34 (dd, *J*= 8.6, 1.5 Hz, 1H), 4.22 (d, *J*= 6.3 Hz, 2H), 2.90-2.81 (m, 2H), 1.60-1.51 (m, 2H), 1.30-1.20 (m, 2H), 0.78 (t, *J*= 7.3 Hz, 3H). LCMS: $[M+H]^+$ 268.

Synthesis of (*E*)-*N*'-hydroxy-N-pentyl-1H-indazole-5-carboximidamide (17).



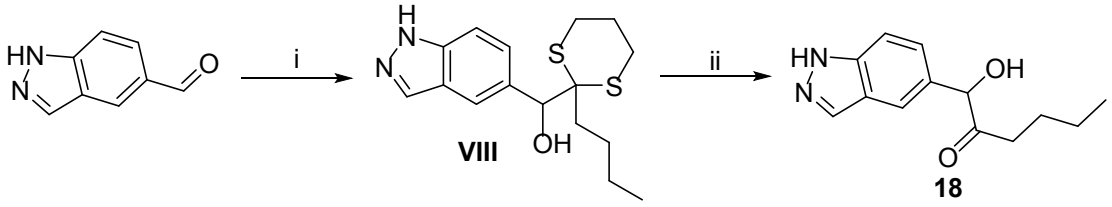
Scheme S4: (i) 1H-indazole-5-carbaldehyde (1.0 eq.), hydroxylamine (1.5 eq.), pyridine (2.0 eq.), ethanol, reflux, 18 hours, quant. (ii) **VI** (1.0 eq), NCS (1.1 eq), DMF, 70 °C, 3 h, (ii) **VII** (1.0 eq.), pentyl-1-amine (2.0 eq.), DMF, 0 °C – RT, 16 h, 26%

1H-indazole-5-carbaldehyde oxime (VI). Hydroxylamine hydrochloride (143 mg, 2.05 mmol, 1.0 eq.) was added to a stirring solution of 1H-indazole-5-carbaldehyde (200 mg, 1.37 mmol, 1.5 eq.) and pyridine (0.221 mL, 2.74 mmol, 2.0 eq.) in Ethanol (4 mL). The resulting mixture was heated to reflux for 18 hours before the solvent was evaporated and the residue partitioned between water and EtOAc. The organic phase was washed with water, dried over Mg_2SO_4 and evaporated to yield the title compound as a colourless solid, in quantitative yield (275.6 mg, 1.71 mmol). ^{1}H NMR (400 MHz, DMSO-d6) δ 13.18 (br. s., 1H), 11.00 (s, 1H), 8.22 (s, 1H), 8.11 (s, 1H), 7.89 (s, 1H), 7.70 (dd, *J*= 1.39, 8.72 Hz, 1H), 7.55 (d, *J*= 8.59 Hz, 1H).

***N*-hydroxy-1H-indazole-5-carbimidoyl chloride (VII).** H-indazole-5-carbaldehyde oxime **VI** (275.6 mg, 1.71 mmol, 1.0 eq.) and N-chlorosuccinimide (251 mg, 1.88 mmol, 1.1 eq.) were dissolved in DMF (8.55 ml) and heated to 70 °C for 3 hours before being cooled to room temperature. The solvent was evaporated in vacuo and the residue dissolved in EtOAc. The organic phase was washed with water and brine, dried over Na_2SO_4 and the solvent evaporated to give the crude product which was used without further purification.

(*E*)-*N*'-hydroxy-N-pentyl-1H-indazole-5-carboximidamide (17). Pentan-1-amine (0.43 mL, 3.69 mmol, 2.0 eq.) was added to N-hydroxy-1H-indazole-5-carbimidoyl chloride **VII** (360.8 mg, 1.85 mmol, 1.0 eq.) in DMF (2.4 mL) at 0 °C. The resulting mixture was allowed to warm to room temperature and left stirring for 16 hours. The solvent was evaporated in vacuo and the resulting yellow oil partitioned between water and EtOAc. The organic phase was separated and washed with brine, dried over Na2SO4 and evaporated to yield a free-flowing yellow oil which was purified via flash chromatography on silica gel (0- 50% EtOAc in chexane). ^{1}H NMR (400 MHz, DMSO-d6) δ 13.15 (br s, 1H), 9.61 (s, 1H), 8.11 (s, 1H), 7.79-7.78 (m, 1H), 7.56-7.54 (m, 1H), 7.38-7.36 (m, 1H), 5.63 (t, *J*= 6.6 Hz, 1H), 2.94-2.87 (m, 2H), 1.37-1.30 (m, 2H), 1.19-1.09 (m, 4H), 0.79-0.73 (m, 3H). LCMS: $[M+H]^+$ 247.

Synthesis of 1-Hydroxy-1-(1H-indazol-5-yl)hexan-2-one (18).

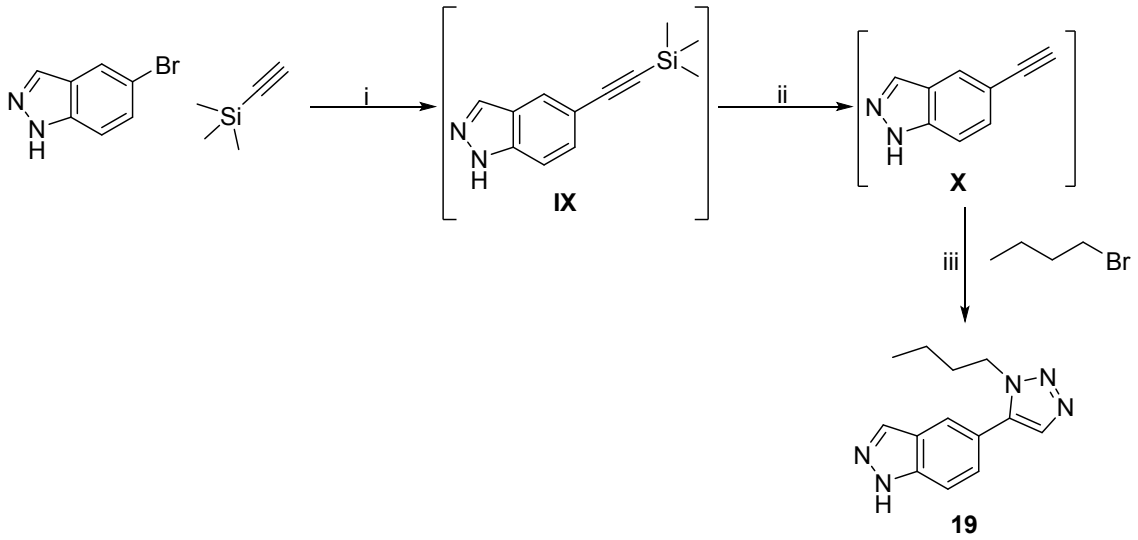


Scheme S5: (i) n-Butyllithium (1.0 eq.), 2-butyl-1,3-dithiane (1.0 eq.), 1H-indazole-5-carbaldehyde (1.5 eq.), THF, RT (ii) Silver nitrate (8.3 eq.), **VIII** (1.0 eq.), N-chlorosuccinimide (8.3 eq.) water, 45%.

(2-butyl-1,3-dithian-2-yl)(1H-indazol-5-yl)methanol (VIII). n-Butyllithium (0.71 mL, 1.13 mmol, 1.0 eq.) was added dropwise to a solution of 2-butyl-1,3-dithiane (200 mg, 1.13 mmol, 1.0 eq.) in THF (3.5 mL) at -78 ºC. The mixture was stirred and warmed to 0ºC over 3 hours before being cooled to -78ºC. A solution of 1H-indazole-5-carbaldehyde 157 (249 mg, 1.70 mmol, 1.5 eq.) in THF (2 mL) was then added dropwise. The reaction was allowed to slowly reach r.t. stirring for 21 hours. The reaction mixture was quenched with ammonium chloride (sat. aq.) and the resulting aqueous phase extracted with EtOAc. The combined organic phases were washed with brine, dried over Na2SO4, and concentrated in vacuo. The crude material was triturated with DCM-cyclohexane, the filtrate was concentrated in vacuo and the crude material purified by flash chromatography on silica gel (0-20% EtOAc in chexane) to give the title compound at 60% purity (by NMR) which was used without further purification. ^{1}H NMR (400 MHz, DMSO-d6) δ 13.05 (s, 4H), 8.52 (s, 2H), 8.42 (s, 2H), 8.12 (s, 4H), 7.85 (s, 4H), 7.57 (dd, *J*= 1.14, 8.72 Hz, 4H), 7.50 (d, *J*= 8.59 Hz, 4H), 5.60 (d, *J*= 4.29 Hz, 4H), 5.12 (d, *J*= 4.29 Hz, 4H), 3.20-3.06 (m, 4H), 3.04-2.89 (m, 4H), 2.81-2.61 (m, 8H), 1.98-1.71 (m, 13H), 1.71-1.49 (m, 13H), 1.47 (s, 4H), 1.36-1.20 (m, 10H), 0.91 (t, *J*= 7.33 Hz, 12H).

1-Hydroxy-1-(1H-indazol-5-yl)hexan-2-one (18). Silver nitrate (216 mg, 1.27 mmol, 8.3 eq.) in water (3 ml) was added to a solution of (2-butyl-1,3-dithian-2-yl)(1H-indazol-5-yl)methanol **VIII** (82.1 mg, 0.15 mmol, 1.0 eq.) in Acetonitrile (5 mL) at -10ºC. N-chlorosuccinimide (170 mg, 1.27 mmol, 8.3 eq.) was added and a white precipitated appeared. The mixture was allowed to stir for 5 minutes before the reaction mixture was quenched with sodium bicarbonate solution (aq. sat.) extracted with EtOAc, dried over Na_2SO_4, and concentrated in vacuo. The crude was purified by preparative HPLC (Xbridge 30, ACN/:aqNH4HCO3 (10 mM), 40-100%) to obtain the title compound as a colorless solid, 45% yield (15.9 mg, 0.07 mmol). 1H NMR (400 MHz, DMSO-d6) δ 13.05 (s, 1H), 8.06-8.07 (m, 1H), 7.78 (s, 1H), 7.50 (d, *J*= 8.6 Hz, 1H), 7.30 (dd, *J*= 8.6, 1.5 Hz, 1H), 5.92 (d, *J*= 4.5 Hz, 1H), 5.16 (d, *J*= 4.5 Hz, 1H) 2.48-2.42 (m, 2H), 1.37-1.29 (m, 2H), 1.16-1.03 (m, 2H), 0.75-0.70 (m, 3H). LCMS: $[M+H]^+$ 233.

Synthesis of 5-(1-butyl-1H-1,2,3-triazol-5-yl)-1H-indazole (19).



Scheme S6: (i) 5-bromo-1H-indazole (1.0 eq.), (trimethylsilyl)acetylene (1.2 eq.), Dichloro[bis(2-(diphenylphosphino)phenyl)ether]palladium(II) (0.05 eq.), triethylamine (5 eq.), Copper (I) iodide (0.05 eq.), DMF, 60 °C 2 h, 24%. (ii) **IX** (1.0 eq.), potassium hydroxide (2N, aq. 1.0 eq), MeOH, RT, 16 hours, quant.. (iii) **X** (1.0 eq.), 1-bromobutane (0.95 eq.), sodium azide (0.95 eq.), Copper (II) sulphate (1.3 eq.), Copper (3.0 eq.), *tert*-butanol, 125 °C, 100 minutes, 10%.

((trimethylsilyl)ethynyl)-1H-indazole (IX). 5-bromo-1H-indazole (200 mg, 1.02 mmol, 1.0 eq.), triethylamine (0.71 mL, 5.08 mmol, 5.0 eq.) and CuI (9.67 mg, 0.05 mmol, 0.05 eq.) in DMF (10 mL) were placed in a MW vial and the mixture degassed with bubbling N2 (g). Dichloro[bis(2-(diphenylphosphino) phenyl)ether]palladium(II) (36.3 mg, 0.05 mmol, 0.05 eq.) and (trimethylsilyl)acetylene (0.17 mL, 1.22 mmol, 1.2 eq.), were added and the resulting mixture was stirred at room temperature overnight , before being heated to 60ºC for 18 hours before being cooled to RT and diluted with ethyl acetate. The organic phases were washed with water dried over Na_2SO_4 and concentrated under in vacuo. The crude was purified by sequential flash chromatography on silica gel (0-20% EtOAc in chexane) then (0-15% EtOAc in chexane) to afford intermediate **IX**, 24% yield (52.9 mg, 0.25 mmol).

5-Ethynyl-1H-indazole (X). Intermediate **IX** (52.9 mg, 0.25 mmol) was dissolved in Methanol (2 mL) before a solution of potassium hydroxide (aq. 1N, 494 µL, 0.25 mmol) was added, and the mixture stirred at room temperature overnight , before the solvent was removed in vacuo and the resulting residue was diluted with ethyl acetate and the organic phase washed with water and brine, dried over Na_2SO_4 and concentrated in vacuo to afford 5-Ethynyl-1H-indazole **X** (35 mg, 0.25 mmol, 1.0 eq.) in quantitative yield.

5-(1-butyl-1H-1,2,3-triazol-5-yl)-1H-indazole (19). 5-Ethynyl-1H-indazole **X** (35 mg, 0.25 mmol, 1.0 eq.) was added to a microwave reaction tube with 600 µL water and sodium azide (aq. 15.21 mg, 0.23 mmol, 0.95 eq.). 1-bromobutane (25 µL, 0.23 mmol, 0.95 eq.), *tert*-butanol (0.6 mL), copper (46.9 mg, 0.739 mmol, 3.0 eq.) and copper sulfate pentahydrate solution (aq. 0.5 M, 100 µL). The reaction was heated under microwave irradiation at 125º C for 100 minutes and allowed to cool. The reaction mixture was diluted with HCI (aq. 0.5 N) and the aqueous suspension was extracted with DCM. The organic layers were washed with water and brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The crude product was triturated with DCM, and the resulting precipitate filtered to obtain the title compound as a colorless solid, 10% yield (6.1 mg, 25.0 µM). 1H NMR (400 MHz, METHANOL-d4) δ 8.33 (s, 1H), 8.32-8.23 (m, 1H), 8.10 (br s, 1H), 7.89-7.87 (m, 1H), 7.62 (d, *J*= 8.6 Hz, 1H), 4.47 (t, *J*= 7.2 Hz, 2H), 2.00-1.92 (m, 2H), 1.46-1.36 (m, 3H), 1.00 (t, *J*= 7.5 Hz, 3H). LCMS: $[M+H]^+$ 242.

5-((butylsulfonyl)methyl)-1H-indazole (20). mCPBA (336 mg, 1.36 mmol, 2.0 eq.) was added to an ice-cold solution (0 °C) of 5-((butylthio)methyl)-1H-indazole **12** (150 mg, 0.68 mmol, 1.0 eq.) in DCM (4.97 ml) and the resulting suspension left stirring for 1 h before being allowed to warm to RT. Sodium bicarbonate (sat. aq.) and DCM were added, and the aqueous phase separated. The aqueous phase was

extracted with EtOAc and the combined organic phases washed with sodium bicarbonate (aq. sat.), dried over Na_2SO_4 and evaporated in vacuo. The crude compound was triturated in DCM and the insoluble fraction collected via vacuum filtration to give the title compound as a colourless solid, 38% yield (68.7 mg, 0.26 mmol). 1H NMR (400 MHz, DMSO-d6) δ 13.14 (br s, 1H), 8.11 (s, 1H), 7.79 (s, 1H), 7.55 (d, *J*= 8.6 Hz, 1H), 7.37 (dd, *J*= 8.6, 1.5 Hz, 1H), 4.54 (s, 2H), 3.05- 2.95 (m, 2H), 1.70-1.60 (m, 2H), 1.41-1.32 (m, 2H), 0.86 (t, *J*= 7.3 Hz, 3H). LCMS: $[M+H]^+$ 253.

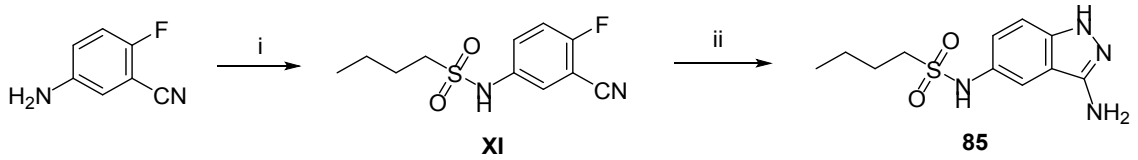
***N*-(1H-indazol-5-yl)pentanamide (21).** The title compound was prepared from *tert*-butyl 5-amino-1H-indazole-1-carboxylate (500 mg, 2.14 mmol, 1 eq.), triethylamine (1.49 ml, 10.72 mmol, 5 eq.) and pentanoyl chloride (1.03 ml, 8.57 mmol, 4 eq.) in DCM (15 ml) following general method A with stirring at RT for 18 hours. MeOH (3.5 ml) and NaOH (3.5 ml) were added for the hydrolysis and stirred for 20 hours. The organic phase was separated and aqueous phased extracted with EtOAc and the combined organic phases dried over MgSO4 and evaporated in vacuo. The crude product was triturated in EtOAc and the precipitate collected via vacuum filtration to yield the title compound as colourless oil, 32% yield (156.9 mg, 0.69 mmol). 1H NMR (400 MHz, METHANOL-d4) δ 8.04 (s, 1H), 7.99 (s, 1H), 7.52-7.40 (m, 2H), 2.39 (t, *J*= 7.6 Hz, 2H), 1.75-1.66 (m, 2H), 1.48-1.39 (m, 2H), 1.30 (t, *J*= 7.3 Hz, 1H), 0.98 (t, *J*= 7.5 Hz, 3H). LCMS: $[M+H]^+$ 218.

***N*-(1H-indazol-5-yl)butane-1-sulfinamide (22).** 1H-indazol-5-amine (600 mg, 4.51 mmol) was added to a stirring suspension of butane-1-sulfinic chloride (824 mg, 5.86 mmol) in Acetonitrile (20mL). The reaction was stirred at RT for 16h before being cooled to 0 ºC triethylamine (1.884 mL, 13.52 mmol) added dropwise and the resulting solution stirred for 5 h at RT. The solvent was evaporated, and the crude product partitioned between $NaHCO_3$ (sat., aq.) and EtOAc. Phases were separated, and the aqueous phase was extracted with EtOAc the combined organic fractions were dried over Na_2SO_4, filtered and evaporated. The crude product was purified by flash column chromatography on silica gel (50% - 100% EtOAc in chexane), then HPLC (Xbridge 30, ACN/:aq NH_4HCO_3 (10 mM), 40-100%) to yield the title compound as a pale pink solid, 23% (245 mg, 1.03 mmol). ^{1}H NMR (400 MHz, DMSO-d6) δ 12.94 (br s, 1H), 8.60 (s, 1H), 7.97-7.96 (m, 1H), 7.47 (d, *J*= 8.8 Hz, 1H), 7.35 (d, *J*= 2.0 Hz, 1H), 7.10 (dd, *J*= 8.7, 2.1 Hz, 1H), 3.03-2.86 (m, 2H), 1.69-1.54 (m, 2H), 1.50-1.37 (m, 2H), 0.92 (t, *J*= 7.3 Hz, 3H). LCMS: $[M+H]^+$ 238.

***N*-(1*H*-pyrazolo[4,3-*b*]pyridin-5-yl)butane-1-sulfonamide (32).** N-(6-(butylsulfonamido)-2-methylpyridin-3-yl)acetamide (100 mg, 0.350 mmol), potassium acetate (20.64 mg, 0.210 mmol) and Acetic anhydride (0.083 mL, 0.876 mmol) were dissolved in THF (15 mL). The resulting solution was heated to 70ºC before isopentyl nitrite (90 mg, 0.771 mmol) was added, the temperature increased to 100ºC and the reaction was stirred overnight. The reaction was cooled, filtered and evaporated and the resulting crude was dissolved in ammonia in methanol solution (7 N, 0.05 mL, 0.35 mmol, 1eq.). The reaction was stirred at RT overnight and then concentrated under vacuum. The crude was purified by flash column chromatography on silica gel (EtOAc in ^{c}hexane 0-50%) to give the title compound as a pale yellow solid 28% yield (25 mg, 0.10 mmol). ^{1}H NMR (400 MHz, DMSO-d6) δ 13.24 (br s, 1H), 10.52 (br s, 1H), 8.09 (s, 1H), 7.99 (m, *J* = 8.8 Hz, 1H), 7.00 (m, *J* = 8.8 Hz, 1H), 3.46 - 3.60 (m, 2H), 1.62 - 1.72 (m, 2H), 1.22 - 1.43 (m, 2H), 0.84 (t, *J* = 7.3 Hz, 2H). LC-MS = $[M+H]^+$ 255.

N-(1H-benzo[d][1,2,3]triazol-5-yl)butane-1-sulfonamide (40). 1H-benzo[d][1,2,3]-triazol-5-amine (500 mg, 3.73 mmol 1 eq.) was suspended in DMF (15 mL) at 0 °C and butane-1-sulfonyl chloride **98** (0.48 mL, 3.73 mmol, 1 eq.) added dropwise over the course of 1 minute. The resulting orange solution was allowed to warm to room temperature slowly over night with stirring. Water and EtOAc were added and the organic phase separated. The aqueous phase extracted with EtOAc. Salt (1 g) was added and the aqueous phase before extraction with EtOAc. The combined organic phases were dried over Na2SO4 and evaporate in vacuo. The crude was purified by flash chromatography on silica gel (EtOAc in chexane 0-50%) before additional purification by HPLC (Xbridge 19, ACN/:aqNH4HCO3 (10 mM), 40-100%). 5% yield (55 mg, 0.21 mmol)). 1H NMR (400 MHz, DMSO-d6) δ 7.91 (d, J = 8.8 Hz, 1H), 7.60 (d, J = 1.5 Hz, 1H), 7.26 (dd, J = 8.8, 1.8 Hz, 1H), 3.10 - 3.14 (m, 2H), 1.60 - 1.68 (m, 2H), 1.28 - 1.37 (m, 2H), 0.80 (t, J = 7.5 Hz, 3H). LCMS: $[M+H]^+$ 255

Synthesis of *N*-(3-amino-1H-indazol-5-yl)butane-1-sulfonamide (85).

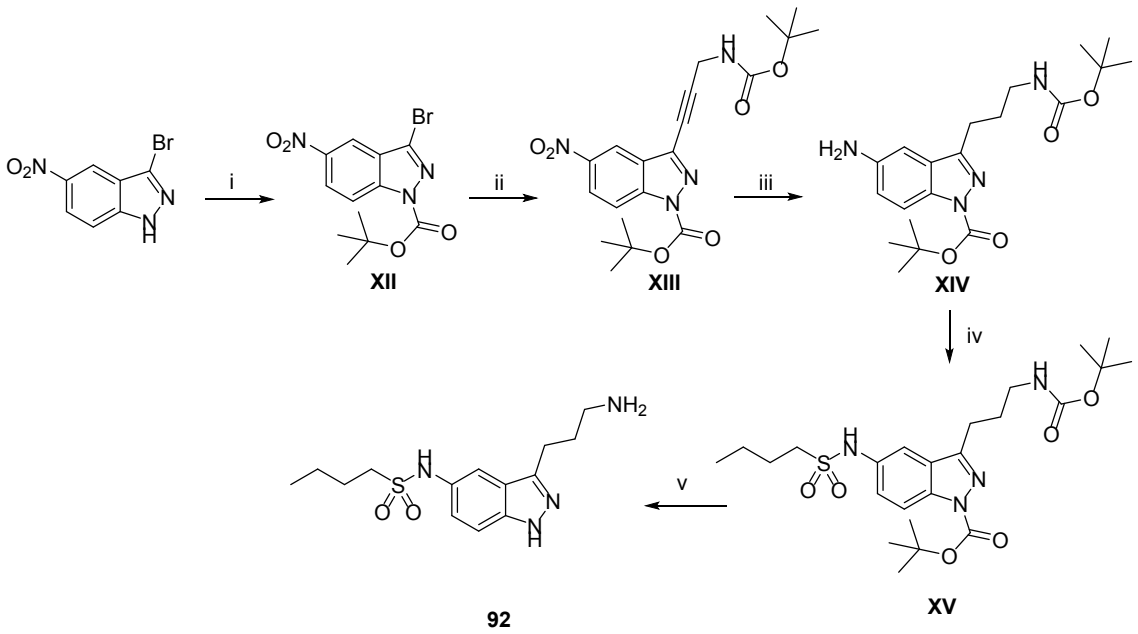


Scheme S7: (i) 5-Amino-2-fluorobenzonitrile (1.0 eq.), $BuSO_2Cl$ (1.0 eq.), DIPEA (1 eq.), ACN, RT, 1 h, 12%. (ii) **XI** (1.0 eq.), Hydrazine (2.0 eq), EtOH, 130ºC, 2 hours, 36%.

***N*-(3-cyano-4-fluorophenyl)butane-1-sulfonamide XI.** To a solution of 5-Amino-2-fluorobenzonitrile (500 mg, 3.67 mmol) in Acetonitrile (10 mL) at 0ºC was added butane-1-sulfonyl chloride **98** (575 mg, 3.67 mmol). The reaction mixture was stirred 5 min and then DIPEA (475 mg, 3.67 mmol) was added. The reaction was stirred 5 min at 0ºC and then was allow to reach RT and stirred 1 h. Solvent was evaporated and the crude was purified by prepHPLC (Xbridge 30x150, basic, 40-100%), 3 runs. Fractions were collected and evaporated to yield **XI**, 11% yield (107 mg, 0.42 mmol) ^{1}H NMR (400 MHz, $CDCl_3$-d) δ 7.50-7.54 (m, 1H), 7.48 (ddd, *J* = 2.27, 4.42, 6.69 Hz, 1H), 7.24 (appt. t, *J* = 8.46 Hz, 1H), 6.67 (br. s., 1H), 3.07-3.16 (m, 2H), 1.77-1.89 (m, 2H), 1.47 (appt. sxt, *J* = 7.43 Hz, 2H), 0.96 (t, *J* = 7.45 Hz, 3H). LCMS: $[M+H]^+$ 255

***N*-(3-amino-1H-indazol-5-yl)butane-1-sulfonamide (85).** Hydrazine (41.8 mg, 0.84 mmol, 2.0 eq.) was added to a solution of N-(3-cyano-4-fluorophenyl)butane-1-sulfonamide **XI** (107 mg, 0.42 mmol, 1.0 eq.) in Ethanol (1.15 ml) at 50ºC. The reaction mixture was stirred at reflux for 3h before being transferred to a microwave vial and heated under microwave irradiation at 130ºC for 2 hours. A precipitate was collected and triturated with MeOH the filtrated was evaporated in vacuo to give the title compound as a colorless solid 36% yield (40 mg, 0.15 mmol). ^{1}H NMR (400 MHz, DMSO-d6) δ 11.37 (s, 1H), 7.54 (d, *J*= 2.0 Hz, 1H), 7.19 (d, *J*= 8.6 Hz, 1H), 7.09 (dd, *J*= 8.8, 2.0 Hz, 1H), 5.32 (s, 2H), 2.97-2.94 (m, 2H), 1.71-1.62 (m, 2H), 1.40-1.30 (m, 2H), 0.84 (t, *J*= 7.3 Hz, 3H). LCMS: $[M+H]^+$ 269.

Synthesis of *N*-(3-(3-aminopropyl)-2H-indazol-5-yl)butane-1-sulfonamide (92).



Scheme S8: (i) di-*tert*-butyl dicarbonate **100** (1.3 eq.), DMAP (0.2 eq.), room temperature, overnight, 66% (ii) *tert*-butyl prop-2-yn-1-ylcarbamate (2.5 eq.), CuI (0.05 eq.), Pd(PPh3)2 (0.05eq.), Et3N (0.6 eq.), 50ºC overnight, 36% (iii) Pd/C (0.09 eq.), H2 (1 atm), room temperature 5h., 63% (iv) butane-1-sulfonyl chloride **98** (1 eq.), Et3N (2.0 eq.), 50ºC overnight, 51% (v) TFA (20 eq.) room temperature, 1.5 h. 53%.

***Tert*-butyl 3-bromo-5-nitro-1H-indazole-1-carboxylate (XII).** 3-bromo-5-nitro-1H-indazole (2.0 g, 8.26 mmol) and DMAP (0.151 g, 1.240 mmol) were dissolved in dry Acetonitrile (50 mL) under an atmosphere of N_2 and stirred for 15 mins. di-*tert*-butyl dicarbonate (2.278 mL, 9.92 mmol) was added and the resulting clear light yellow solution stirred at room temperature for 16 hours. The colourless solution was evaporated and the resulting colourless powder, partitioned between EtOAc (25 ml) and 1N HCl (25 ml). The aqueous phase was removed and the organic phased washed with Water (25 ml) and brine 25 ml). The organic phase was dried over MgSO4 and evaporated to yield *tert*-butyl 3-bromo-5-nitro-1H-indazole-1-carboxylate **XII** (1.9541 g, 5.43 mmol, 66% yield) as colourless solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.52-8.68 (m, 2H), 8.28-8.43 (m, 1H), 1.74 (s, 9H). LCMS: [M-COO^{t}Bu]$^-$ 240

***Tert*-butyl-3-(3-((*tert*-butoxycarbonyl)amino)prop-1-yn-1-yl)-5-nitro-1H-indazole-1-carboxylate (XIII).** *Tert*-butyl 3-bromo-5-nitro-1H-indazole-1-carboxylate **XII** (500 mg, 1.461 mmol) was dissolved in dry N,N-Dimethylformamide (DMF) (8 mL) under nitrogen and triethylamine (0.122 mL, 0.877 mmol) was added. Copper(I) Iodide (13.92 mg, 0.073 mmol), propargyl (567 mg, 3.65 mmol), bis(triphenylphosphine)palladium(II) chloride (51.3 mg, 0.073 mmol) and a further equivalent of triethylamine (0.122 mL, 0.877 mmol) were subsequently added and the resulting mixture heated to 50 °C overnight. The reaction was stopped any way and the black suspension was filtered through a celite (2.5 g) plug and the resulting solution partitioned EtOAc (25 ml) and water (25 ml), the organic phase was separated and washed with water (50 ml) and brine (50 ml). The organic phase was then dried over Na_2SO_4 and evaporated to yield a yellow oil. The oil was purified via column chromotography (40 g merk silica column, 0-50% EtOAc in cHexanes over 30 CV's). Selected fractions were combined and evaporated to yield a yellow foam that is used in the next step without further purifications, 36% (216.4 mg, 0.52 mmol). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.66 (d, J = 2.02 Hz, 1H), 8.50 (dd, J = 2.15, 9.22 Hz, 1H), 8.30 (d, J = 9.09 Hz, 1H), 7.57 (br. s., 1H), 4.16 (d, J = 5.56 Hz, 2H), 1.67 (s, 9H), 1.44 (s, 9H). LCMS: [M-COO^{t}Bu, ^{t}Bu) 261

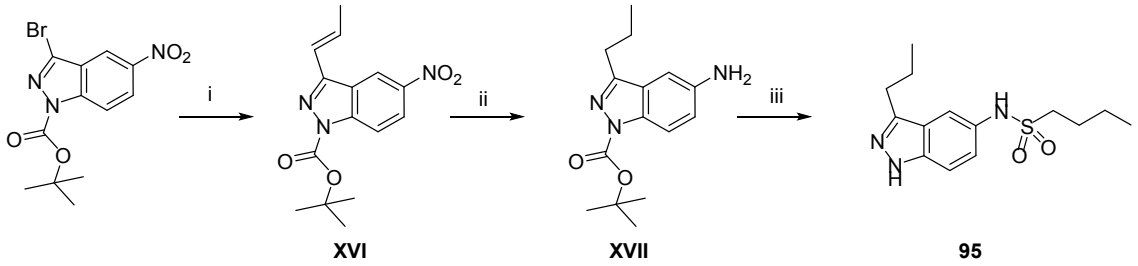
***Tert*-butyl-3-(3-((*tert*-butoxycarbonyl)amino)prop-1-yn-1-yl)-5-nitro-1H-indazole-1-carboxylate (XIV).** *Tert*-butyl-3-(3-((*tert*-butoxycarbonyl)amino)prop-1-yn-1-yl)-5-nitro-1H-indazole-1-carboxylate **XIII** (216.4 mg, 0.520 mmol) was dissolved in Methanol (25 mL) and put under an atmosphere of nitrogen. Pd/C (5.0 mg, 0.047 mmol) was added and the resulting suspension put under an atmosphere of hydrogen gas and stirred at room temperature for 5 hours. The palladium was removed when the suspension was filtered through a syringe filter and the resulting colourless solution evaporated to yield a dark orange oil. The oil was dissolved in around 15 ml of Methanol and passed through a 1g SCX column, resulting in a deep orange filtrate, the column was then washed with Methanol (10 ml) and the combined methanol phases evaporated to yield a red crystalline material. The desired compound was liberated by passing ammonia in methanol (7 N) through the column (25 ml). The resulting methanol phase was then evaporated to yield an orange glass 61% yield (127 mg, 0.33 mmol). ^{1}H NMR (400 MHz, CD_3OD-d_4) δ 7.85 (d, J = 8.59 Hz, 1H), 6.92 (dd, J = 2.27, 8.84 Hz, 1H), 6.85 (d, J = 2.02 Hz, 1H), 4.77 (br. s., 1H), 3.75 (br. s., 2H), 3.22 (d, J = 6.32 Hz, 1H), 3.22 (d, J = 18.95 Hz, 1H), 2.93 (t, J = 7.58 Hz, 2H), 2.00 (quin, J = 6.80 Hz, 2H), 1.70 (s, 9H), 1.43 (s, 9H).

***N*-(3-(3-aminopropyl)-2H-indazol-5-yl)butane-1-sulfonamide (92).** *Tert*-butyl-5-amino-3-(3-((*tert*-butoxycarbonyl)amino)propyl)-1H-indazole-1-carboxylate **XIV** (127.1 mg, 0.325 mmol) and triethylamine (0.091 mL, 0.651 mmol) were dissolved in Dichloromethane (DCM) (1.5 mL) and after stirring at room temperature for 5 minutes butane-1-sulfonyl chloride **98** (0.042 mL, 0.325 mmol) was added and the resulting solution stirred over the weekend. The solvent was evaporated to yield a suspension of a colourless solid in a yellow oil. The oil was then dissolved in a small amount of EtOAc and washed with water (15 ml), ammonium chloride solution (15 ml) and brine (15 ml). The organic phase was then dried over Na_2SO_4 and evaporated to yield a dark orange oil which was purified via column chromatography (Merk 20g, EtOAc in cHexanes Over 30 CV's) affording *tert*-butyl-3-(3-((*tert*-butoxycarbonyl)amino)propyl)-5-(N-(butylsulfonyl)butylsulfonamido)-1H-indazole-1-carboxylate (**XV**) 103.4 mg, 53% yield. *tert*-butyl-3-(3-((*tert*-butoxycarbonyl)amino)propyl)-5-(butylsulfonamido)-1H-indazole-1-carboxylate **XV** (57.0 mg, 0.112 mmol) was dissolved in Dichloromethane (DCM) (6 mL) and TFA (1mL, 12.98 mmol) added. The resulting solution was stirred at room temperature for 1.5 hours. The solvents were evaporated and the resulting colourless oil. The resulting yellow oils were dissolved in MeOH and loaded into a SCX (1 g) pre-packed column. The column was then washed with ammonia in MeOH (7N) and this organic fraction was then evaporated to yield a yellow oil. The compound was pushed to the protonated state by the addition of HCl (3N) in methanol and the evaporation of the resulting solution to

yield a red semi solid (23.1 mg, 0.060 mmol) 53% yield. ^{1}H NMR (400 MHz, DMSO-d6) δ ppm 9.57 (s, 1 H) 7.83 (bs, 2 H) 7.53 (d, *J*=1.5 Hz, 1 H) 7.46 (d, *J*=8.6 Hz, 1 H) 7.22 (dd, *J*=8.6, 1.5 Hz, 1 H) 3.0.1-2.88 (m, 2 H) 2.05-2.00 (m, 2 H) 1.68-1.62 (m, 2 H) 1.37-1.31 (m, 2 H) 0.83 (t, *J*=7.3 Hz, 3 H). LCMS: $[M+H]^+$ 311.

Methyl 5-(butylsulfonamido)-1H-indazole-3-carboxylate (93). To a solution of **87** in Acetonitrile (3mL) was added 1-Butanesulfonyl chloride **98** (0.173 mL, 1.333 mmol). The reaction mixture was stirred at room temperature for 5 min and then was cooled down to 0°C and triethylamine (0.212 mL, 1.523 mmol) 4 equiv. dissolved in 1 mL of Acetonitrile was added. The reaction was stirred at RT for 4h. Solvent was evaporated and 2 ml of MeOH and 1 ml of NaOH (2M) were added. The mixture was stirred at rt 1.5h. The crude was purified by prepHPLC, Xbridge column 30x150mm, 40-100%, TFA 0.1%, to yield a white solid, 12 mg, it is the 3-methyl ester derivative (12.0 mg, 0.028 mmol) 7% yield. ^{1}H NMR (400 MHz, METHANOL-d_4) δ ppm 8.02 (s, 1 H) 7.61 (d, *J*=9.3 Hz, 1 H) 7.42 (dd, *J*=9.1, 2.0 Hz, 1 H) 4.00 (s, 3 H) 3.10-3.04 (m, 2 H) 1.82-1.74 (m, 2 H) 1.41 (sxt, *J*=7.4 Hz, 2 H) 0.89 (t, *J*=7.5 Hz, 3 H). LCMS: $[M+H]^+$ 312.

***N*-(3-propyl-1H-indazol-5-yl)butane-1-sulfonamide (94).**



Scheme S9: (i) TetrakisPalladium (0.08 eq.), allyltributylstannane (1 eq.), Toluene, 100 °C, 1.5 h, 31% (ii) Pd/C (0.09 eq.), H2 (1 atm), room temperature, overnight, 85% (iii) butane-1-sulfonyl chloride **98** (1 eq.), Et3N (1.3 eq.), room temperature, overnight, 32%.

***Tert*-butyl 3-allyl-5-nitro-1H-indazole-1-carboxylate (XVI).** To a solution of *tert*-butyl 3-bromo-5-nitro-1H-indazole-1-carboxylate (250 mg, 0.731 mmol) in Toluene (4 mL) were added allyltributylstannane (0.226 mL, 0.731 mmol) and Tetrakis(triphenylphosphine)palladium (67.5 mg, 0.058 mmol) and the mixture was heated at 100 ºC in a microwave vial in an atmosphere of nitrogen gas for 1h 30 min. The reaction mixture was cooled to room temperature, and the solvent was evaporated. The residue was purified and separated by silica gel column chromatography (ethyl acetate:hexane = 1:4) to give *tert*-butyl 3-allyl-5-nitro-1H-indazole-1-carboxylate **XVI** 30 % yield (68 mg, 0.224 mmol). ^{1}H NMR (400 MHz, DMSO-d6) δ ppm 8.85 (d, *J*=2.5 Hz, 1 H) 8.60 (dd, *J*=8.8, 2.8 Hz, 1 H) 8.07 (d, *J*=8.8 Hz, 1 H) 5.94-5.83 (m, 1 H) 5.25-5.20 (m, 2 H) 4.44 (d, *J*= 4.8 Hz) 1.47 (s, 9 H). LCMS: $[M+H]^+$ 304

***N*-(3-propyl-1H-indazol-5-yl)butane-1-sulfonamide (94).** *Tert*-butyl 3-allyl-5-nitro-1H-indazole-1-carboxylate (224 mg, 0.739 mmol), was dissolved in dry Methanol (15 mL). Pd/C (12 mg, 0.113 mmol) was added to the mixture under N_2 atmosphere. Reaction was degassed using H_2 (g) (balloon) and left under stirring at room temperature overnight. After that time reaction was finished. Pd/C was filtered through a nylon filter and residue was concentrated to give *tert*-butyl 5-amino-3-propyl-1H-indazole-1-carboxylate **XVII** (168 mg, 0.610 mmol, 83 % yield) as an orange syrup. The product was used in the next step without further purifications.

Tert-butyl.5-amino-3-propyl-1H-indazole-1-carboxylate **XVII** (35 mg, 0.127 mmol) was dissolved in Dichloromethane (DCM) (5 mL), triethylamine (0.023 mL, 0.165 mmol) was added. Mixture was stirred at 0ºC for 15 min. After that time butane-1-sulfonyl chloride **98** (0.041 mL, 0.318 mmol) was added and reaction was stirred at room temperature overnight. Then 8 mL of NaOH (2M, aq) and 8 mL of MeOH were added to the mixture and reaction was stirred 12 h. Organic solvents were evaporated and acetic acid (8 mL) was added and mixture was heated to 40ºC during 30 min. Reaction mixture was diluted with EtOAc (15 ml) and washed with NH_4Cl (aq, sat) (20 mL x2). The organic phase was then dried over $MgSO_4$ and evaporated in vacuo and the resulting crude product was purified by flash column chromatography on silica gel (EtOAc: cHexane 1:3). Yield 32% (12.0 mg, 0.051 mmol). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.36

(s, 1 H) 7.27-7.21 (m, 2 H) 6.76 (d, *J*=9.1 Hz, 1 H) 6.07 (t, *J*=5.8 Hz, 1 H) 3.12-3.07 (m, 2 H) 2.98-2.94 (m, 2 H) 1.66-1.49 (m, 4 H) 1.39-1.29 (m, 4 H) 0.91-0.82 (m, 6H). LCMS: $[M+H]^+$ 296.

Cross Reactivity panel assay Results

Assay	Mode	pXC50
α1 nicotinic AChR	Opener	<4.3 (2)
α1 nicotinic AChR	Blocker	4.4 (2)
Acetylcholinesterase	Inhibition	<4 (2)
Adenosine A2a	Agonist	<4 (2)
Adrenergic α1B	Antagonist	<4.6 (2)
Adrenergic α2C	Agonist	<4 (2)
Adrenergic β2	Agonist	<4 (2)
Adrenergic β2	Antagonist	<4 (2)
AhR	Agonist	<4 (2)
Aurora B (STK12)	Antagonist	5.6 (2)
Cannabinoid CB2	Agonist	<4 (2)
COX-2	Blocker	<4 (2)
Dopamine D1	Antagonist	<4 (2)
Dopamine D2	Agonist	<4 (2)
Dopamine D2	Antagonist	<4 (2)
Histamine H1	Antagonist	<4.6 (2)
KCNQ1/minK	Blocker	<4.6 (2)
Kv1.5	Blocker	<4.3 (1)
LCK	Antagonist	<4.5 (2)
L-type Ca channel (CaV1.2)	Blocker	<4 (2)
Muscarine M1	Agonist	<4.3 (2)
Muscarine M1	Antagonist	<4.3 (2)
Muscarine M2	Agonist	<4.3 (2)
Muscarine M2	Antagonist	<4.3 (2)
NaV1.5	Blocker	<4 (2)
Neurokinin NK1	Antagonist	<4.6 (2)
NMDA Channel (NR2B)	Blocker	<4.3 (2)

Norepinephrine	Antagonist	<4 (2)
OATP1B1	Inhibition	<4.3 (2)
Opioid μ	Agonist	<4 (2)
Opioid κ	Agonist	<4 (2)
PDE3A	Inhibition	<4 (2)
PI3Kγ	Antagonist	<4.5 (1)
PXR	Agonist	<4.3 (2)
Serotonin 5HT1B	Agonist	<4 (2)
Serotonin 5HT1B	Antagonist	<4 (2)
Serotonin 5HT2A	Agonist	<4.6 (2)
Serotonin 5HT2A	Antagonist	<4.6 (2)
Serotonin 5HT2C	Agonist	<4.6 (2)
Serotonin 5HT2C	Antagonist	<4.6 (2)
Serotonin 5HT3	Opener	<4.3 (2)
Serotonin 5HT3	Blocker	<4.3 (2)
Vasopressin V1a	Antagonist	<4.3 (2)

Supplementary Table 1: Off-target selectivity data for **2**

Methodology for the detection of aniline metabolites in mice.

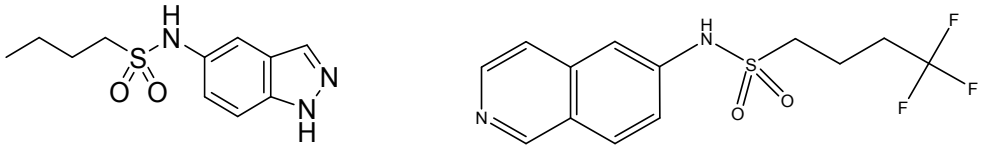
A male Sprague Dawley rat (n=1) was dosed orally at a target dose of 300 mg/kg. Following discrete oral gavage dosing from a suspension of 1% methyl cellulose of parent compound at 5 mL/kg, urine samples were taken at intervals over 48 hours after the administration and stored at -80ºC until analysis. Urine samples were analyzed for metabolite using a method based on protein precipitation followed by UPLC-MSMS detection.

Chromatographic separation was carried out on a reverse-phase Acquity UPLC HSS T3 column (2.1×50 mm, 1.8 μm). The UPLC was operated with a gradient mobile phase system comprising water containing 0.1% formic acid and ammonium formate 10 mM (phase A) and acetonitrile (phase B) at a flow rate of 0.4 ml/min and maintained at 40°C. A 5-μl sample was injected into the system with the autosampler conditioned at 7°C. The mass spectrometer was operated in positive ion mode. Multiple reaction monitoring (MRM) was used, and the fragmentation transitions were m/z 134/107.

All animal studies were ethically reviewed and carried out in accordance with European Directive 2010/63/EEC and the GSK Policy on the Care, Welfare and Treatment of Animals.

Additional Information X-ray Crystallography

Compounds in Paper



Supplementary Figure S1: Compound **2** in paper = **2** Compound **80** in paper = **80**

KasA Cocrystallisation and Structure determination

KasA / **2** was crystallised using protein at 10.6mg/ml and ligand at a nominal concentration of 30mM in 100nl+100nl sitting drops at 20°C. The well solution was 16% w/v PEG3350, 0.2M sodium citrate, 1.5mM TCEP. Crystals were cryoprotected using well with 30% ethylene glycol prior to flash freezing in liquid nitrogen. Data from a single crystal was collected at the Diamond Synchrotron Radiation Facility (i04) and processed in $P3_1$ to 1.53 Å using XDS (within AUTOPROC [Global Phasing Limited]) (1) and AIMLESS (2). A molecular replacement solution was determined with a previously collected in house structure using Phaser (3). The $P3_1$ cell (α=β= 90˚, γ=120˚, a=b=75.314Å, c=149.230Å) has two molecules in the ASU that form a dimer. Model building and refinement of the KasA structures was carried out using alternating rounds of COOT (4) for manual model building and REFMAC (5) for maximum likelihood refinement via CCP4(6). As the data was merohedrally twinned, TWIN refinement within REFMAC was used, with the refined twin fraction being 16%. Clear difference density for **2** and also for a PEG like chain were present in both chains in the dimer.

KasA / **80** The well solution was 20% w/v PEG3350, 0.2M sodium potassium tartrate, 1.5mM TCEP. Crystals were cryoprotected using well with 30% ethylene glycol prior to flash freezing in liquid nitrogen. Data from a single crystal was collected at the Europeon Synchortron Radiation Facility (ESRF, id23-1) and processed in $P3_1$ to 2.89 Å using XDS (within AUTOPROC [Global Phasing Limited]) (1) and AIMLESS (2). A molecular replacement solution was determined with a previously collected in house structure using Phaser (3). The $P3_1$ cell (α=β= 90˚, γ=120˚, a=b=151.242Å, c=147.886Å) has eight molecules in the ASU composed of four dimers. Model building and refinement of the KasA structures was carried out using alternating rounds of COOT (4) for manual model building and REFMAC (5) for maximum likelihood refinement via CCP4(6). As the data was merohedrally twinned, TWIN refinement within REFMAC was used, with the refined twin fraction being 39%. Clear difference density for **80** and also for a PEG like chain were present in both chains in the dimer.

OMIT maps, statistics for the data collection and refined co-ordinates are given in Tables S2 – S4. The final crystal structures are deposited in the Protein Data Bank under the accession codes 6Y2I and 6Y2J.

References

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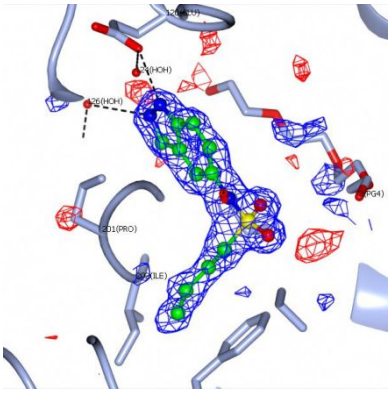
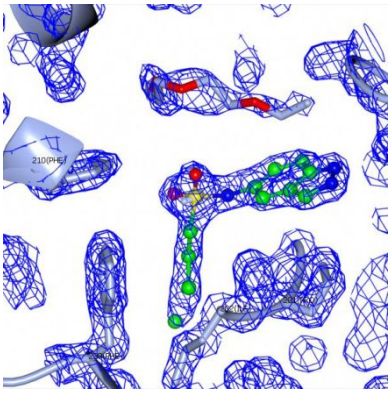
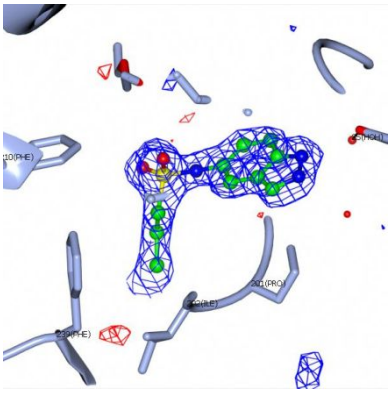
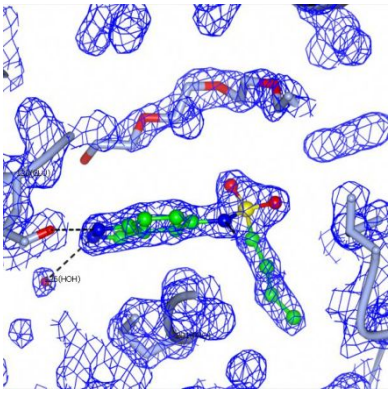
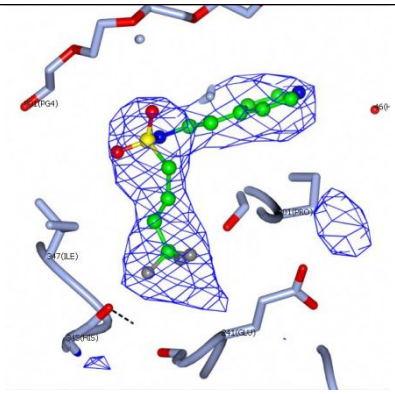
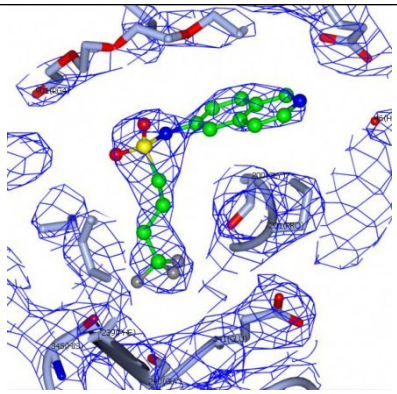
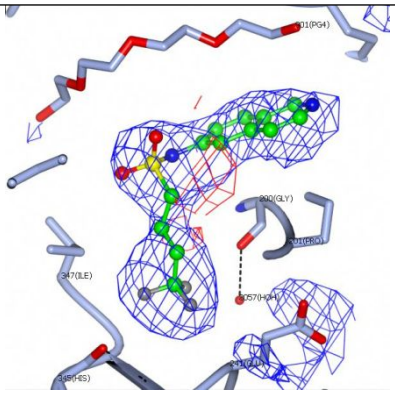
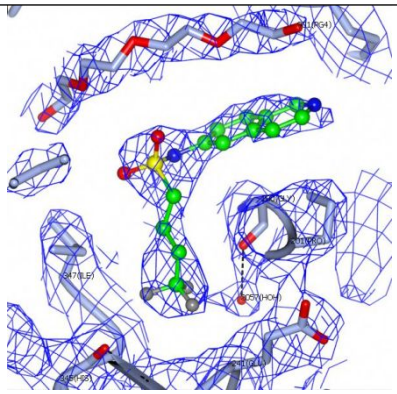
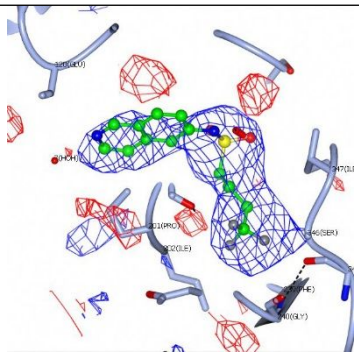
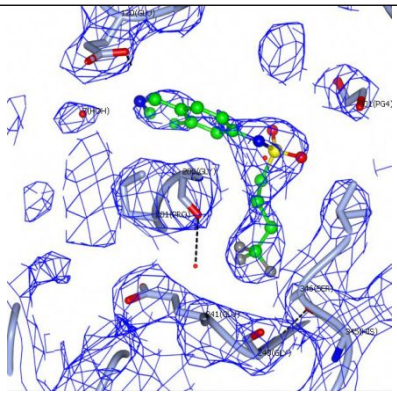
Crystallography Difference Maps around ligand

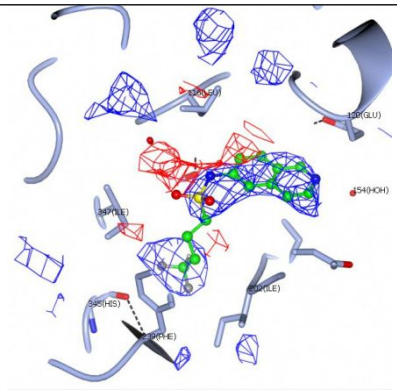
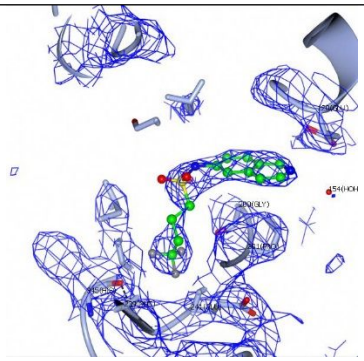
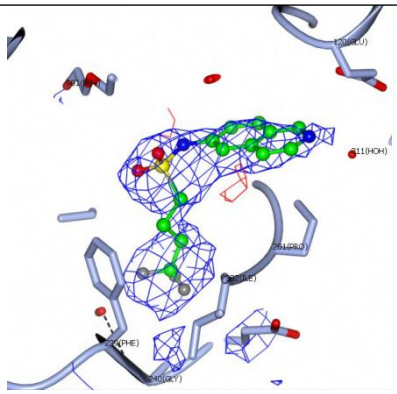
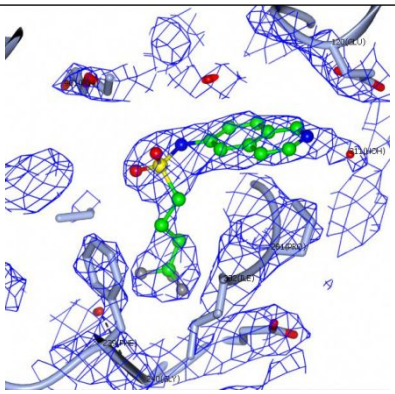
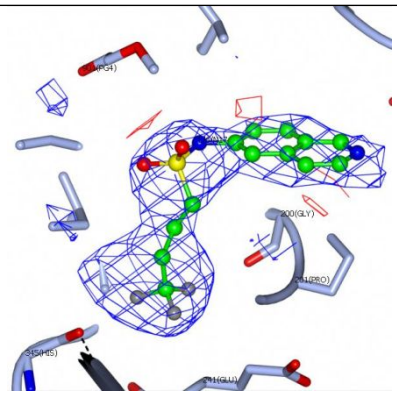
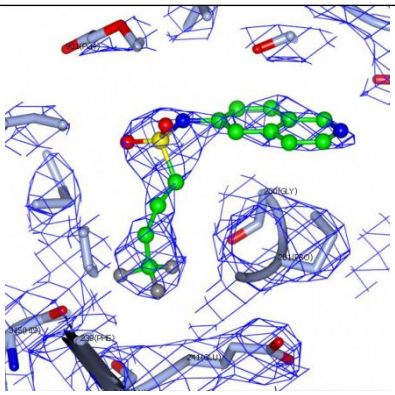
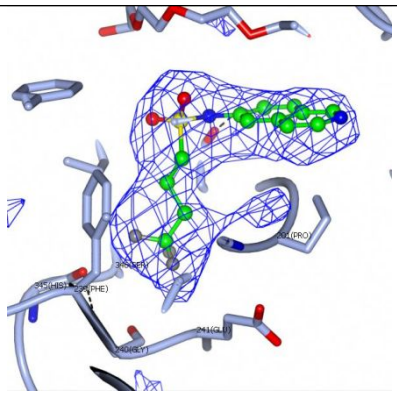
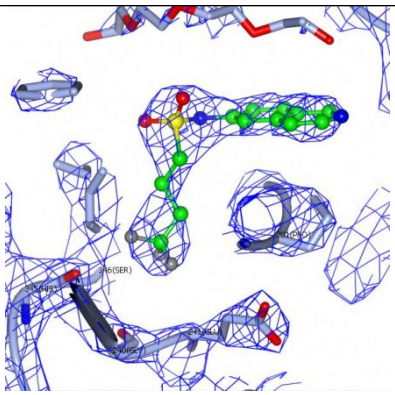
KASA / **2**

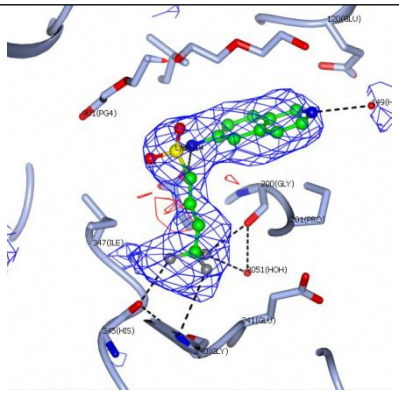
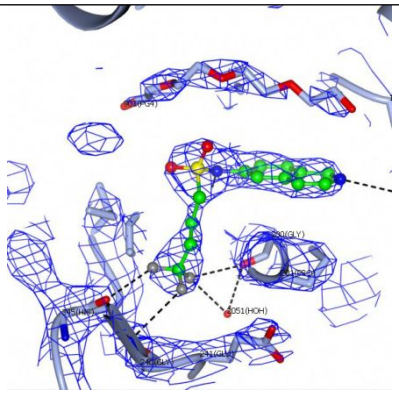
Chain	**OMIT (Fo-Fc) map ±3sigma (blue/red)**	**OMIT (2Fo-Fc) map +1.5sigma (blue)**
A		
B		

Supplementary Table 2: Crystallography Difference Map for KasA / **2**

KASA / 80

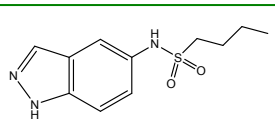
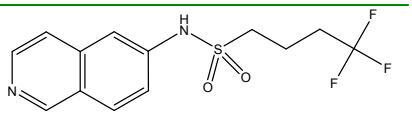
Chain	**OMIT (Fo-Fc) map** **±2sigma (blue/red)**	**OMIT (2Fo-Fc) map** **+1.0sigma (blue)**
A		
B		
C		

D		
E		
F		
G		

H		

Supplementary Table 3: Crystallography Difference Map for KasA / **80**

Table S4: Data collection and refinement statistics

(collection on a single crystal)	KASA / **2**	KASA / **80**
Compound		
Data collection		
Wavelength	0.91742	0.97242
Space Group	$P3_1$	$P3_1$
Cell Dimensions		
a,b,c (Å)	75.314, 75.314 , 149.230	151.242, 151.242 , 147.886
α,β,γ (°)	90.000, 90.000, 120.000	90.000, 90.000, 120.000
Resolution* (Å)	74.61-1.53(2.38-1.53)	130.98-2.89 (3.53-2.89)
R_{merge}*	0.040 (0.389)	0.085 (0.235)
CC(1/2)	0.999 (0.882)	0.994 (0.929)
Average $I/\sigma I$	16.8 (2.8)	12.2 (4.2)
Completeness (%)	99.4 (99.6)	98.3 (99.7)
Redundancy	4.2(4.0)	3.6 (3.7)
Wilson B-factor	21.0	51.84
Refinement		
Resolution (Å)	74.61-1.53	130.98-2.89
No. Reflections*	595983 (91527)	301081 (140228)
No. Unique Reflections*	141366 (22883)	83652 (38306)
R_{work}/R_{free}	0.123/0.136	0.118/0.165
No. atoms	7243	25455
Protein	6268	24277
Ligand/ion	34/68	168/112
Water	873	898
B-factors	23.55	56.10
Protein	21.39	56.28
Ligand/ion	19.38/32.74	62.27/69.52
Water	38.2	47.2
R.m.s deviations		
Bond lengths (Å)	0.0034	0.0038
Bond angles (°)	1.1843	1.2025
Twin fraction	0.16	0.388

*Values in parentheses are for highest-resolution shell.