Supporting Information

Fragment-based discovery of 6-arylindazole JAK inhibitors

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Biology Experimental

JAK kinase assays

Human baculovirus-expressed Janus kinase (JAK) 1, 2, 3 and tyrosin kinase (TYK) 2 were purchased from Carna Biosciences, Inc (#08-144, -045, -046, -147 resp.). All four purified enzymes contain only the catalytic domain. JAK1 (aa 850-1154) and TYK2 (aa 871-1187) are expressed with an N-terminally fused GST-tag, and JAK2 and JAK3 with an N-terminally fused His-tag. Inhibition of phosphorylation of a synthetic peptide was measured in an HTRF-based assay (CisBio #62TK0PEC). First, 75 nL of test compound solution (100% DMSO) is added to a white shallow 384-well plate (NUNC #264706) using a Labcyte ECHO 550 liquid handler. Thereafter, 1 μ L of compound dilution buffer (50 mM HEPES, 0.05% bovine serum albumin) and 2 μ L of TK solution (TK substrate-biotin in kinase buffer [1x enzymatic buffer from HTRFKinEASE TK kit, 1 mM DTT]) is added. Then, 5 μ L kinase-ATP mix (prepared in kinase buffer) is added to the wells and the plates are incubated at RT for 20 (JAK2, 3 and TYK2) to 40 (JAK1) min. For all four kinases a concentration of ATP that corresponded to the K_m for ATP was used. The final concentrations of buffers, substrate, kinase and ATP were: JAK1: 50 mM Hepes buffer pH 7.0, 0.01% BSA, 10 mM $MgCl_2$, 1 mM DTT, 7 μ M ATP, 50 nM SEB, 1 μ M TK Substrate-Biotin and 5 ng JAK1; JAK2: 50mM Hepes buffer pH 7.0, 0.01% BSA, 5 mM $MgCl_2$, 1 mM DTT, 4 μ M ATP, 1 μ M TK Substrate-Biotin and 0.1 ng JAK2; JAK3: 50 mM Hepes buffer pH 7.0, 0.01% BSA, 5 mM $MgCl_2$, 1 mM DTT, 2 μ M ATP, 1 μ M TK Substrate-Biotin and 0.3 ng JAK3; TYK2: 50 mM Hepes buffer pH 7.0, 0.01% BSA, 5 mM $MgCl_2$, 1 mM DTT, 13 μ M ATP, 50 nM SEB, 1 μ M TK Substrate-Biotin and 0.8 ng TYK2. Thereafter, the kinase reaction is stopped by adding 4 μ L detection mix (final concentrations: 50mM Hepes buffer pH 7.0, 0.01% BSA, 0.8 M KF, 20 mM EDTA, 42 nM Streptavidin-XL665 and 1:400 STK Ab Cryptate) and the plates are incubated overnight in the dark. A PerkinElmer Envision reader is used to quantify the HTRF signal using the following filters; 320 nm excitation filter, 665 nm emission filter and a 615 nm 2nd emission filter. A ratio $((665/615) \times 10^4)$ is calculated for each well

STAT6 assay

Twenty-five μ L of a STAT6-bla-RA1 (Invitrogen #K1243) cell suspension is seeded with a density of 30-40,000 cells/well in 384-well Black View-plates (PerkinElmer #6007460) with clear bottom in assay medium (Opti-MEM (Invitrogen #11058-021) + 0.5% heat inactivated fetal bovine Serum (Invitrogen #10082-147) + 1% non-essential amino acids (Invitrogen #11140-050) + 1% sodium pyruvate (Invitrogen #11360-070) + 1% penicillin/streptomycin (Invitrogen #15140-122)); containing 550 ng/mL of CD40 ligand

(Invitrogen #PHP0025). The cell plates are incubated overnight in a humidified 37 °C air/CO₂ (95%/5%) incubator. The following day, 125 nL of solutions of test compounds and reference compounds are transferred to cell plates using the Labcyte Echo 550 liquid handler. The plates are then incubated for 1 h at RT. Hereafter recombinant human interleukin 4 (Invitrogen #PHC0045) are added to the plates also using the Labcyte Echo 550 to a final concentration of 5 ng/mL. The cells are then incubated for 4½-5 h in a humidified 37 °C air/CO₂ (95%/5%) incubator. 8 µL of LiveBLAzer substrate mixture (Invitrogen #K1095) are then added to the assay plates, which are then incubated overnight at RT. Fluorescence is then measured: Excitation: 405 nm; Emission: 460 nm (green channel), Emission: 535 nm (blue channel). Background is subtracted in both emission channels and the ratio 460/535 nm is calculated for each well.

Photostability test

Compounds were dissolved in acetonitrile:water 1:1 v/v at a concentration of 0.1 mg/mL. In some cases, residual DMSO (< 10% v/v) was present in the test solution. The solutions were irradiated with simulated outdoor sun light as defined in ISO 10977 using a Heraeus Suntest CPS instrument equipped with a Xenon lamp. The light intensity was approx. 22.5 W/m² and the temperature increased from 18.4 to 28.3 °C during the course of the experiment. The samples were analyzed using HPLC before the start of the irradiation and after 2, 4, and 6 h and the relative concentrations $C(t)/C_0$ at time t were determined as the ratio of the UV peak areas at time points t and 0. The half-life ($t_{1/2}$) was determined from linear regression of $\ln C(t)/C_0$ vs. time. A dark control sample was included to ascertain chemical stability in the absence of irradiation. None of the compounds tested showed any measurable degradation in the dark.

Chemistry Experimental

General. Reagents and solvents were commercially available and were used without purification unless otherwise noted. Chromatographic purification was performed using a Grace REVELERIS[®] system with pre-packed REVELERIS[®] Silica Flash Cartridges, or manually using silica gel 60. Mass spectra of intermediates were recorded using a Shimadzu LCMS2020 system equipped with a LCMS2020 mass spectrometer operating in positive electrospray ionisation mode. A Chromolith SpeedROD RP-18e column (50 × 4.6 mm, 2 µm particle size) at 40 °C was used (mobile phase: A = CH₃CN/H₂O/HCO₂H = 10/90/0.05 and B = CH₃CN/H₂O/ HCO₂H = 90/10/0.05; flow rate: 3.0 mL/min; gradient: 0.8 min @ 10% B, 2.7 min gradient (10-95% B), then 0.8min @ 95% B). Alternatively, UPLC-MS analyses of intermediates were performed using a Waters Acquity UPLC system with a 2.1 × 50 mm Acquity UPLC[®] HSS T3 1.8µm column and an Acquity SQ Detector operated in positive ionization electrospray mode. The mobile phases consisted of 0.1% formic acid in an aqueous 10 mM ammonium acetate solution for buffer A and 0.1% formic acid in acetonitrile for buffer B. A binary gradient (A:B 95:5→5:95) over 1.4 min was used with a flow rate of 1.2 mL/min and the column temperature was 60 °C. Purities and high resolution mass spectra of all compounds tested in biological assays were determined using a Waters Acquity UPLC system with UV detection at 254 nm and a Waters LCT Premier XE high resolution TOF mass spectrometer operated in positive ionization electrospray mode. The same column and mobile phases A and B as above were used, but with a slower gradient (A:B 99:1→1:99 over 4.8 min; 0.7 mL/min; column temp. 40 °C). ¹H NMR spectra were recorded on Bruker instruments at 300, 400, or 600 MHz with tetramethylsilane as reference.

6-Bromo-4-nitro-1-tetrahydropyran-2-yl-indazole (5)

A suspension of 6-bromo-4-nitro-1*H*-indazole (1.00 g, 4.13 mmol), 3,4-dihydro-2*H*-pyran (0.848 mL, 9.30 mmol) and PPTS (4.0 mg, 0.016 mmol) in DCM (15 mL) was heated at reflux for 2 h. A second portion of PPTS (52 mg, 0.21 mmol) was added and the mixture was heated at reflux for an additional 1 h 15 min. The resulting red-brown solution was cooled to rt, diluted with sat. aq. sodium bicarbonate solution (20 mL) and extracted with DCM (3 × 20 mL). The combined organic phases were sequentially washed with 5% aq. citric acid solution (20 mL) and brine (20 mL) and were dried over sodium sulfate. After filtration and evaporation of volatiles, the residue was purified by chromatography using a

GRACE system (24 g silica gel column, EtOAc:heptane 0:100 → 40:60) to afford **5** (1.04 g, 77%) as an orange solid. ¹H NMR (300 MHz, Chloroform-*d*) δ 8.78 (s, 1H), 8.26 (s, 2H), 5.73 (dd, *J* = 9.0, 3.1 Hz, 1H), 4.23 – 4.08 (m, 1H), 3.89 – 3.73 (m, 1H), 2.37 – 1.95 (m, 3H), 1.90 – 1.61 (m, 3H).

tert-Butyl-dimethyl-[4-(4-nitro-1-tetrahydropyran-2-yl-indazol-6-yl)phenoxy]silane (**6**)

To a 25 ml RBF was added DMF (2.8 mL) and water (0.7 mL). The flask was evacuated, filled with argon, and **5** (250 mg, 0.750 mmol), K₂CO₃ (259 mg, 1.88 mmol), [4-*tert*-butyl(dimethyl)silyl]oxyphenyl]boronic acid (236 mg, 0.938 mmol) and Pd(dppf)Cl₂ (55 mg, 0.075 mmol) were added. The red-brown reaction mixture was stirred at rt for 1 h. The resulting thick brown suspension was poured into water (30 mL) and extracted with EtOAc (2 × 30 mL). The combined organic phases were washed with brine, dried over sodium sulfate, filtered and concentrated to afford a brown oil. The crude product was purified by chromatography using a GRACE system (40 g silica gel column, EtOAc:heptane 0:100 → 30:70) to afford **6** (326 mg, 94%) as a yellow semi-solid that crystallized upon standing in the freezer overnight. ¹H NMR (300 MHz, Chloroform-*d*) δ 8.77 (d, *J* = 1.0 Hz, 1H), 8.45 (d, *J* = 1.3 Hz, 1H), 8.22 (t, *J* = 1.1 Hz, 1H), 7.60 – 7.51 (m, 2H), 7.00 – 6.91 (m, 2H), 5.81 – 5.68 (m, 1H), 4.25 – 4.12 (m, 1H), 3.89 – 3.76 (m, 1H), 2.35 – 2.19 (m, 2H), 2.16 – 2.03 (m, 1H), 1.90 – 1.64 (m, 3H), 1.02 (s, 9H), 0.25 (s, 6H). UPLC *t*_R = 1.12 min. MS Anal. Calcd. for [M+H]⁺ C₂₄H₃₂N₃O₄Si: 454.2; found 454.3.

tert-Butyl-dimethyl-[4-(4-amino-1-tetrahydropyran-2-yl-indazol-6-yl)phenoxy]silane (**7**)

To a solution of **6** (336 mg, 0.704 mmol) in EtOAc (8 mL) under argon was added 10% Pd/C (40 mg, 0.038 mmol). The mixture was hydrogenated at atmospheric pressure for 6 h at rt. after which the catalyst was removed by filtration through Hyflo® Super Cel®. The filter pad was washed with EtOAc and the combined filtrates were evaporated to afford a yellow foam (312 mg). The crude product was purified by chromatography using a GRACE

system (12 g silica gel column, EtOAc:heptane 0:100 → 80:20) to afford **7** (182 mg, 58%) as a yellow resin. ¹H NMR (300 MHz, Chloroform-*d*) δ 8.10 (s, 1H), 7.55 – 7.45 (m, 2H), 7.31 (s, 1H), 6.94 – 6.83 (m, 2H), 6.50 (s, 1H), 5.66 (dd, *J* = 8.8, 3.4 Hz, 1H), 4.17 – 4.10 (m, 1H), 3.99 (br s, 2H), 3.84 – 3.73 (m, 1H), 2.32 – 2.11 (m, 2H), 1.86 – 1.60 (m, 4H), 1.00 (s, 9H), 0.23 (s, 6H). UPLC *t*_R = 0.96 min. MS Anal. Calcd. for [M+H]⁺ C₂₄H₃₄N₃O₂Si: 424.2; found 424.4.

N-[6-[4-*tert*-Butyl(dimethyl)silyl]oxyphenyl]-1-tetrahydropyran-2-yl-indazol-4-yl]methanesulfonamide (**8**)

To a solution of **7** (176 mg, 0.395 mmol) in DCM (3 mL) and pyridine (48 μL, 0.59 mmol) was added methanesulfonyl chloride (38 μL, 0.49 mmol) and the mixture was stirred at rt. for 3 h 30 min. The resulting yellow solution was poured into sat. aq. sodium bicarbonate solution and the mixture was extracted twice with EtOAc. The organic phases were washed with brine, dried over sodium sulfate, filtered and concentrated. The residue was triturated with *tert*-butyl methyl ether (2 mL) with gentle warming and sonication and the remaining solids were collected by filtration, washed with *tert*-butyl methyl ether and dried to afford **8** (109 mg, 54%) as a yellow-brown solid. ¹H NMR (300 MHz, Chloroform-*d*) δ 8.35 (d, *J* = 1.0 Hz, 1H), 7.72 (t, *J* = 1.1 Hz, 1H), 7.55 – 7.47 (m, 2H), 7.27 (s, 1H), 6.96 – 6.88 (m, 2H), 6.80 (br s, 1H), 5.68 (dd, *J* = 8.3, 3.9 Hz, 1H), 4.20 – 4.09 (m, 1H), 3.85 – 3.74 (m, 1H), 3.07 (s, 3H), 2.32 – 2.15 (m, 2H), 2.14 – 1.98 (m, 1H), 1.86 – 1.63 (m, 3H), 1.01 (s, 9H), 0.24 (s, 6H). UPLC *t*_R = 0.97 min. MS Anal. Calcd. for [M+H]⁺ C₂₅H₃₆N₃O₄SSi: 502.2; found 502.4.

N-[6-(4-Hydroxyphenyl)-1*H*-indazol-4-yl]methanesulfonamide (**2**)

To a suspension of **8** (52.8 mg, 0.103 mmol) in methanol (1 mL) was added 4 M HCl in dioxane (1.0 mL, 4.0 mmol) at rt (*CAUTION! Exothermic!*). The resulting yellow solution was stirred at rt for 2 h after which volatiles were evaporated. To the red-brown solid residue was added sat. aq. sodium bicarbonate solution (0.5 mL) and the mixture was extracted once with EtOAc and once with DCM. The remaining solid was collected by filtration, washed with water, dissolved in EtOAc/methanol 8:2, and combined with the organic extracts. Solvents were evaporated and the residue was dissolved in EtOAc/methanol 95:5 (3 mL) and filtered. The filtrate was evaporated and the residue was co-evaporated with EtOAc. The resulting solid was triturated with *tert*-butyl methyl ether and the remaining solid was collected by filtration. Drying under high vacuum afforded **2** (23.3 mg, 71%) as a yellow solid. ¹H NMR (300 MHz, DMSO-*d*₆) δ 13.05 (br s, 1H), 10.05 (br s, 1H), 9.56 (br s, 1H), 8.27 (s, 1H), 7.53 – 7.44 (m, 2H), 7.34 (t, *J* = 1.1 Hz, 1H), 7.23 (d, *J* = 1.2 Hz, 1H), 6.92 – 6.83 (m, 2H), 3.05 (s, 3H). UPLC *t*_R = 1.80 min, Purity UV₂₅₄ > 98%. HRMS Anal. Calcd. for [M+H]⁺ C₁₄H₁₄N₃O₃S: 304.0750; found 304.0860.

N-[6-(4-Hydroxyphenyl)-1*H*-indazol-4-yl]ethanesulfonamide (**9**)

Step 1: 6-bromo-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-4-amine

To a mixture of **5** (1.0 g, 3.08 mmol) and Na₂S₂O₄ (2.14 g, 12.31 mmol) in EtOH was added aqueous NaOH (8.0 eq). The reaction mixture was stirred at room temperature for 2 h. Volatiles were evaporated and the residue was extracted with EtOAc. The organic layer was washed with brine, dried over Na₂SO₄, filtered and concentrated *in vacuo*. The residue was purified by silica gel column chromatography to give the title compound (180 mg, 20%). MS Anal. Calcd. for [M+H]⁺ C₁₂H₁₅BrN₃O: 296; found 296.

Step 2: *N*-(6-bromo-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-4-yl)ethanesulfonamide

To a stirred solution of the product of step 1 (180 mg, 0.61 mmol) and pyridine (241 mg, 3.05 mmol) in DCM (5 mL) was added ethanesulfonyl chloride (236 mg, 1.83 mmol) dropwise under N₂. The reaction mixture was stirred at room temperature for 16 h. The reaction mixture was diluted with water and extracted with EtOAc. The organic layer was washed with brine, dried over Na₂SO₄, filtered and concentrated *in vacuo*. The residue was purified by silica gel column chromatography to give the title compound (190 mg, 80%). MS Anal. Calcd. for [M+H]⁺ C₁₄H₁₉BrN₃O₃S: 388; found 388.

Step 3: *N*-(6-(4-hydroxyphenyl)-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-4-yl)ethanesulfonamide

A mixture of the product of step 2 (190 mg, 0.49 mmol), (4-hydroxyphenyl)boronic acid (75 mg, 0.54 mmol), Na₂CO₃ (159 mg, 1.5 mmol), and Pd(dppf)Cl₂ (37 mg, 0.05 mmol) in THF (10 mL) and H₂O (2 mL) was stirred at 85 °C for 1 h. The reaction mixture was filtered, the filtrate was diluted with water, and extracted with EtOAc. The organic layer was washed with brine, dried over Na₂SO₄, filtered and concentrated *in vacuo*. The residue was purified by silica gel column chromatography to give the title compound (160 mg, 80%). MS Anal. Calcd. for [M+H]⁺ C₂₀H₂₄N₃O₄S: 402; found 402.

Step 4: *N*-(6-(4-hydroxyphenyl)-1*H*-indazol-4-yl)ethanesulfonamide (9)

To a solution of the product of step 3 (160 mg, 0.40 mmol) in MeOH (2 mL) at 0 °C was added 7 M HCl in MeOH (2 mL). The reaction mixture was stirred at room temperature for 3 h. MeOH was removed under reduced pressure, and the residue was neutralized with 1 M aqueous NaOH solution to pH 10. The mixture was extracted with EtOAc and the organic layer was washed with brine, dried over Na₂SO₄, filtered and concentrated *in vacuo*. The residue was purified by silica gel column chromatography to give **9** (20 mg, 16%). ¹H

NMR (400 MHz, Methanol- d_4) δ 8.26 (s, 1H), 7.56 – 7.50 (m, 2H), 7.46 (s, 1H), 7.41 (d, J = 1.1 Hz, 1H), 6.94 – 6.88 (m, 2H), 3.19 (q, J = 7.4 Hz, 2H), 1.36 (t, J = 7.4 Hz, 3H). UPLC t_R = 1.85 min, Purity UV_{254} > 98%. HRMS Anal. Calcd. for $[M+H]^+$ $C_{15}H_{16}N_3O_3S$: 318.0907; found 318.0946.

N-(6-(4-Hydroxy-2-methylphenyl)-1*H*-indazol-4-yl)ethanesulfonamide (**10**)

Step 1: 4-nitro-1-(tetrahydro-2*H*-pyran-2-yl)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indazole

A mixture of **5** (8.00 g, 24.5 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (7.5 g, 30 mmol), KOAc (7.3 g, 74 mmol) and Pd(dppf)Cl₂ (1.8 g, 2.5 mmol) in 1,4-dioxane was stirred at 80 °C under N₂ for 2 h. The reaction mixture was filtered and the filtrate was concentrated. The residue was dissolved in EtOAc, washed with brine, dried over Na₂SO₄, filtered and concentrated *in vacuo*. The residue was purified by silica gel column chromatography to give the title compound (3.5 g, 38%). MS Anal. Calcd. for $[M+H]^+$ $C_{18}H_{25}BN_3O_5$: 374; found 374.

Step 2: 3-methyl-4-(4-nitro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-6-yl)phenol

A stirred mixture of the product of step 1 (500 mg, 1.34 mmol), 4-bromo-3-methylphenol (275 mg, 1.474 mmol), Na₂CO₃ (426 mg, 4.02 mmol), Pd(dppf)Cl₂ (98 mg, 0.134 mmol) and H₂O (2 mL) in THF (10 mL) was stirred at 85 °C under N₂ atmosphere for 1 h. The reaction mixture was filtered and the filtrate was concentrated. The residue was dissolved in EtOAc, washed with brine, dried over Na₂SO₄, filtered and concentrated *in vacuo*. The residue was purified by silica gel column chromatography to give the title compound (460 mg, 97%). MS Anal. Calcd. for $[M+H]^+$ $C_{19}H_{20}N_3O_4$: 354; found 354.

Step 3: 6-(4-((*tert*-butyldimethylsilyl)oxy)-2-methylphenyl)-4-nitro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazole

A solution of the product of step 2 (460 mg, 1.33 mmol), TBSCl (240 mg, 1.6 mmol), and Et₃N (270 mg, 2.66 mmol) in DCM (10 mL) was stirred at room temperature for 2 h. Volatiles were removed by evaporation and the residue was dissolved in EtOAc, washed with brine, dried over Na₂SO₄, filtered and concentrated. The residue was purified by silica gel column chromatography to give the title compound (450 mg, 72%). MS Anal. Calcd. for [M+H]⁺ C₂₅H₃₄N₃O₄Si: 468; found 468.

Step 4: 6-(4-((*tert*-butyldimethylsilyl)oxy)-2-methylphenyl)-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-4-amine

A stirred mixture of the product of step 3 (450 mg, 0.964 mmol) and 10% Pd/C (45 mg) in MeOH (10 mL) was stirred at room temperature under H₂ for 2 h. The reaction mixture was filtered and the filtrate was concentrated. The residue was dissolved in EtOAc, washed with brine, dried over Na₂SO₄, filtered and concentrated. The residue was purified by silica gel column chromatography to give the title compound (350 mg, 83%). MS Anal. Calcd. for [M+H]⁺ C₂₅H₃₆N₃O₂Si: 438; found 438.

Step 5: *N*-(6-(4-((*tert*-butyldimethylsilyl)oxy)-2-methylphenyl)-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-4-yl)ethanesulfonamide

To a solution of the product of step 4 (350 mg, 0.80 mmol) and pyridine (190 mg, 2.4 mmol) in DCM (5 mL) was added ethanesulfonyl chloride (124 mg, 0.96 mmol) dropwise under N₂. The reaction mixture was stirred at room temperature for 16 h. The reaction mixture was concentrated and the residue was dissolved in EtOAc, washed with brine, dried over Na₂SO₄, filtered and concentrated. The residue was purified by silica gel column chromatography to give the title compound (320 mg, 75%). MS Anal. Calcd. for [M+H]⁺ C₂₇H₄₀N₃O₄SSi: 530; found 530.

Step 6: *N*-(6-(4-hydroxy-2-methylphenyl)-1*H*-indazol-4-yl)ethanesulfonamide (**10**)

To a solution of the product of step 5 (320 mg, 0.605 mmol) in MeOH (5 mL) at 0 °C was added 7 M HCl in MeOH (5 mL). The reaction mixture was stirred at room temperature for 3 h after which volatiles were removed under reduced pressure. The residue was neutralized with 1 M aqueous NaOH solution to pH = 10. The mixture was extracted with EtOAc, and the organic layer was washed with brine, dried over Na₂SO₄, filtered and concentrated. The residue was purified by silica gel column chromatography to give **10** (240 mg, 99%). ¹H NMR (400 MHz, Methanol-*d*₄) δ 8.29 (d, *J* = 0.6 Hz, 1H), 7.19 (s, 1H), 7.11 (dd, *J* = 4.6, 3.6 Hz, 2H), 6.77 – 6.67 (m, 2H), 3.17 (q, *J* = 7.4 Hz, 2H), 2.24 (s, 3H), 1.35 (t, *J* = 7.4 Hz, 3H). UPLC t_R = 1.89 min, Purity UV₂₅₄ > 98%. HRMS Anal. Calcd. for [M+H]⁺ C₁₆H₁₈N₃O₃S: 332.1063; found 332.1072.

N-(6-(2-Ethyl-4-hydroxyphenyl)-1*H*-indazol-4-yl)ethanesulfonamide (**11**)

Step 1: 3-ethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol

A mixture of 3-ethyl-4-iodophenol (2.5 g, 10 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (3 g, 12 mmol), KOAc (3 g, 30 mmol) and Pd(dppf)Cl₂ (731 mg, 1.0 mmol) in 1,4-dioxane was stirred at 80 °C under N₂ for 2 h. The reaction mixture was

filtered and the filtrate was concentrated. The residue was diluted with water and extracted with EtOAc. The organic layer was washed with brine, dried over Na₂SO₄, filtered and concentrated *in vacuo*. The residue was purified by silica gel column chromatography to give the title compound (4 g, 98%). MS Anal. Calcd. for [M+H]⁺ C₁₄H₂₂BO₃: 249; found 249.

Step 2: 3-ethyl-4-(4-nitro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-6-yl)phenol

A mixture of the product of step 1 (500 mg, 2 mmol), compound **5** (650 mg, 2 mmol), Na₂CO₃ (640 mg, 6 mmol), Pd(dppf)Cl₂ (150 mg, 0.2 mmol) and H₂O (2 mL) in THF (10 mL) was stirred under nitrogen at 85 °C for 1 h. The reaction mixture was filtered. The filtrate was diluted with water and extracted with EtOAc. The organic layer was washed with brine, dried over Na₂SO₄, filtered and concentrated *in vacuo*. The residue was purified by silica gel column chromatography to give the title compound (160 mg, 22%). MS Anal. Calcd. for [M+H]⁺ C₂₀H₂₂N₃O₄: 368; found 368.

Step 3: 6-(4-(((tert-butyldimethylsilyl)oxy)-2-ethylphenyl)-4-nitro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole

A solution of the product of step 2 (160 mg, 0.44 mmol), TBSCl (132 mg, 0.88 mmol), and Et₃N (178 mg, 1.76 mmol) in DCM (10 mL) was stirred at room temperature for 2 h. The reaction mixture was diluted with water and extracted with EtOAc. The organic layer was washed with brine, dried over Na₂SO₄, filtered and concentrated *in vacuo*. The residue was purified by silica gel column chromatography to give the title compound (130 mg, 61%). MS Anal. Calcd. for [M+H]⁺ C₂₆H₃₆N₃O₄Si: 482; found 482.

Step 4: 6-(4-((*tert*-butyldimethylsilyl)oxy)-2-ethylphenyl)-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-4-amine

A mixture of the product of step 3 (130 mg, 0.27 mmol) and 10% Pd/C (20 mg) in MeOH (10 mL) was stirred at room temperature under H₂ (1 atm) for 2 h. The reaction mixture was filtered and the filtrate was concentrated. The residue was partitioned with EtOAc and water. The organic layer was washed with brine, dried over Na₂SO₄, filtered and concentrated *in vacuo*. The residue was purified by silica gel column chromatography to give the title compound (100 mg, 83%). MS Anal. Calcd. for [M+H]⁺ C₂₆H₃₈N₃O₂Si: 452; found 452.

Step 5: *N*-(6-(4-((*tert*-butyldimethylsilyl)oxy)-2-ethylphenyl)-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-4-yl)ethanesulfonamide

To a solution of the product of step 4 (100 mg, 0.22 mmol) and pyridine (46 mg, 0.66 mmol) in DCM (5 mL) was added ethanesulfonyl chloride (113 mg, 0.44 mmol) dropwise under N₂. The reaction mixture was stirred at room temperature for 16 h. The reaction mixture was diluted with water and extracted with EtOAc. The organic layer was washed with brine, dried over Na₂SO₄, filtered and concentrated *in vacuo*. The residue was purified by silica gel column chromatography to give the title compound (75 mg, 67%). MS Anal. Calcd. for [M+H]⁺ C₂₈H₄₂N₃O₄SSi: 544; found 544.

Step 6: *N*-(6-(2-ethyl-4-hydroxyphenyl)-1*H*-indazol-4-yl)ethanesulfonamide (11**)**

To a solution of the product of step 5 (75 mg, 0.138 mmol) in MeOH (2 mL) was added 7 M HCl in MeOH (2 mL) at 0 °C. The reaction mixture was stirred at room temperature for 3 h. Volatiles were removed under reduced pressure and the residue was neutralized with 1 M aqueous NaOH solution to pH 10. The mixture was extracted with EtOAc. The organic layer was washed with brine, dried over Na₂SO₄, filtered and concentrated *in vacuo*. The residue was purified by silica gel column chromatography to give the title compound (12 mg, 30%). ¹H NMR (400 MHz, Methanol-*d*₄) δ 8.29 (s, 1H), 7.19 (s, 1H), 7.13 – 7.05 (m, 2H), 6.78 (d, *J* = 2.4 Hz, 1H), 6.69 (dd, *J* = 8.3, 2.5 Hz, 1H), 3.17 (q, *J* = 7.4 Hz, 2H), 2.59 (q, *J* = 7.5 Hz, 2H), 1.34 (t, *J* = 7.4 Hz, 3H), 1.10 (t, *J* = 7.5 Hz, 3H). UPLC *t*_R = 1.95 min, Purity UV₂₅₄ = 96%. HRMS Anal. Calcd. for [M+H]⁺ C₁₇H₂₀N₃O₃S: 346.1220; found 346.1232.

***N*-[6-(2-Chloro-4-hydroxy-phenyl)-1*H*-indazol-4-yl]ethanesulfonamide (**12**)**

Prepared analogously to compound **10** starting from 4-bromo-3-chlorophenol. The nitro group was reduced using Na₂S₂O₄ (see compound **9**, step 1) to avoid dehalogenation. ¹H NMR (400 MHz, Methanol-*d*₄) δ 8.30 (s, 1H), 7.30 (s, 1H), 7.28 (d, *J* = 8.5 Hz, 1H), 7.21 (s, 1H), 6.96 (d, *J* = 2.4 Hz, 1H), 6.84 (dd, *J* = 8.4, 2.5 Hz, 1H), 3.20 (q, *J* = 7.4 Hz, 2H), 1.35 (t, *J* = 7.3 Hz, 3H). UPLC *t*_R = 1.94 min, Purity UV₂₅₄ > 98%. HRMS Anal. Calcd. for [M+H]⁺ C₁₅H₁₅ClN₃O₃S: 352.0517; found 352.0532.

N-[6-(4-Hydroxy-3-methyl-phenyl)-1*H*-indazol-4-yl]ethanesulfonamide (**13**)

Prepared analogously to compound **10** starting from 4-bromo-2-methylphenol. ^1H NMR (400 MHz, Methanol- d_4) δ 8.26 (s, 1H), 7.45 (s, 1H), 7.42 – 7.40 (m, 2H), 7.34 (dd, $J = 8.3$, 2.4 Hz, 1H), 6.85 (d, $J = 8.3$ Hz, 1H), 3.18 (q, $J = 7.3$ Hz, 2H), 2.29 (s, 3H), 1.35 (t, $J = 7.4$ Hz, 3H). UPLC $t_R = 1.93$ min, Purity $\text{UV}_{254} > 98\%$. HRMS Anal. Calcd. for $[\text{M}+\text{H}]^+$ $\text{C}_{16}\text{H}_{18}\text{N}_3\text{O}_3\text{S}$: 332.1063; found 332.1041.

N-[6-(3-Chloro-4-hydroxy-phenyl)-1*H*-indazol-4-yl]ethanesulfonamide (**14**)

Prepared analogously to compound **9** starting from 2-chloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol **36**. ^1H NMR (400 MHz, Methanol- d_4) δ 8.28 (s, 1H), 7.63 (d, $J = 2.4$ Hz, 1H), 7.44-7.48 (m, 2H), 7.39 (s, 1H), 7.03 (d, $J = 8.4$ Hz, 1H), 3.19 (q, $J = 7.4$ Hz, 2H), 1.36 (t, $J = 7.4$ Hz, 3H). UPLC $t_R = 1.96$ min, Purity $\text{UV}_{254} > 98\%$. HRMS Anal. Calcd. for $[\text{M}+\text{H}]^+$ $\text{C}_{15}\text{H}_{15}\text{ClN}_3\text{O}_3\text{S}$: 352.0517; found 352.0524.

N-[6-(3-Fluoro-4-hydroxy-phenyl)-1*H*-indazol-4-yl]ethanesulfonamide (**15**)

Prepared analogously to compound **10** starting from 4-bromo-2-fluorophenol. ¹H NMR (400 MHz, Methanol-*d*₄) δ 8.27 (s, 1H), 7.47 (s, 1H), 7.42 – 7.37 (m, 2H), 7.34 (d, *J* = 8.6 Hz, 1H), 7.03 (t, *J* = 8.7 Hz, 1H), 3.20 (q, *J* = 7.4 Hz, 2H), 1.36 (t, *J* = 7.4 Hz, 3H). UPLC *t*_R = 1.90 min, Purity UV₂₅₄ > 98%. HRMS Anal. Calcd. for [M+H]⁺ C₁₅H₁₅FN₃O₃S: 336.0813; found 336.0874.

N-[6-(4-Hydroxy-3-methoxy-phenyl)-1*H*-indazol-4-yl]ethanesulfonamide (**16**)

Prepared analogously to compound **10** starting from 4-bromo-2-methoxyphenol. ¹H NMR (400 MHz, DMSO-*d*₆) δ 13.10 (br s, 1H), 9.23 (br s, 1H), 8.37 (br s, 1H), 8.33 (s, 1H), 7.40 (s, 1H), 7.28 (s, 1H), 7.18 (d, *J* = 1.7 Hz, 1H), 7.07 (dd, *J* = 1.7, 8.1 Hz, 1H), 6.89 (d, *J* = 8.1 Hz, 1H), 3.86 (s, 3H), 3.16 (q, *J* = 7.3 Hz, 2H), 1.22 (t, *J* = 7.3 Hz, 3H). UPLC *t*_R = 1.87 min, Purity UV₂₅₄ = 97%. HRMS Anal. Calcd. for [M+H]⁺ C₁₆H₁₈N₃O₄S: 348.1013; found 348.1055.

N-(6-(4-Hydroxy-2,6-dimethylphenyl)-1*H*-indazol-4-yl)ethanesulfonamide (**17**)

Prepared analogously to compound **10** starting from 4-bromo-3,5-dimethylphenol. ¹H NMR (400 MHz, Methanol-*d*₄) δ 8.30 (s, 1H), 7.07 (s, 1H), 6.92 (s, 1H), 6.58 (s, 2H), 3.15 (q, *J* = 7.4 Hz, 2H), 1.99 (s, 6H), 1.34 (t, *J* = 7.4 Hz, 3H). UPLC *t*_R = 1.93 min, Purity UV₂₅₄ > 98%. HRMS Anal. Calcd. for [M+H]⁺ C₁₇H₂₀N₃O₃S: 346.1220; found 346.1217.

N-[6-(2-Ethyl-5-fluoro-4-hydroxy-phenyl)-1*H*-indazol-4-yl]methanesulfonamide (**18**)

Step 1: 6-bromo-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-4-amine

To a stirred solution of **5** (6.2 g, 18.6 mol) in MeOH (100 mL) was added NH₄Cl (10.8 g, 6.6 mmol) and Zn dust (13 g, 20.0 mmol) at 0 °C. After the addition, the reaction mixture was stirred at rt overnight. After the reaction was completed, the mixture was filtered. The filtrate was concentrated *in vacuo* and the residue was purified by silica gel column chromatography (PE/EtOAc 3/1) to give the title compound (2.2 g, 41%). MS Anal. Calcd. for [M+H]⁺ C₁₂H₁₅BrN₃O: 296; found 296.

Step 2: *N*-(6-bromo-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-4-yl)methanesulfonamide

To a stirred solution of the product of step 1 (1.5 g, 5.1 mmol) in DCM (15 mL) was added pyridine (1.23 mL, 15.3 mmol) and methanesulfonyl chloride (0.48 mL, 6.12 mmol) at 0 °C. After the addition, the reaction mixture was stirred at rt for 2h. After the reaction was completed, the reaction mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (PE/EtOAc 4/1) to give the title compound (1.7 g, 89%). MS Anal. Calcd. for [M+H]⁺ C₁₃H₁₇BrN₃O₃S: 374; found 374.

Step 3: *N*-(6-(2-ethyl-5-fluoro-4-hydroxyphenyl)-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-4-yl)methanesulfonamide

To a solution of the product of step 2 (100 mg, 0.26 mmol) in dioxane (5 mL) was added compound **37** (85 mg, 0.32 mmol), Na₂CO₃ (83 mg 0.80 mmol), H₂O (2 mL) and Pd(PPh₃)₂Cl₂ (44 mg, 0.06 mmol), and the mixture was stirred at 70 °C under N₂ atmosphere for 3 h. After the reaction was completed, the reaction mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (PE/EtOAc 1/1) to give the title compound (50 mg, 45%). MS Anal. Calcd. for [M+H]⁺ C₂₁H₂₅FN₃O₄S: 434; found 434.

Step 4: *N*-[6-(2-ethyl-5-fluoro-4-hydroxy-phenyl)-1*H*-indazol-4-yl]methanesulfonamide (**18**)

A solution of the product of step 3 (50 mg, 0.13 mmol) in 7 M MeOH in HCl (5 mL) was stirred at rt for 3 h. After the reaction was completed, the reaction mixture was concentrated under reduced pressure. The residue was neutralized with 1 M aqueous NaOH solution to pH 8 and the mixture was extracted with EtOAc. The organic layer was concentrated and the residue was purified by preparative HPLC to give the title compound (2 mg, 10%). ¹H NMR (400 MHz, Methanol-*d*₄) δ 8.28 (s, 1H), 7.22 (s, 1H), 7.10 (s, 1H), 6.97 (d, *J* = 11.8 Hz, 1H), 6.90 (d, *J* = 8.9 Hz, 1H), 3.05 (s, 3H), 2.56 (q, *J* = 7.5 Hz, 2H), 1.10 (t, *J* = 7.5 Hz, 3H). UPLC *t*_R = 1.94 min, Purity UV₂₅₄ > 98%. HRMS Anal. Calcd. for [M+H]⁺ C₁₆H₁₇FN₃O₃S: 350.0969; found 350.0998.

N-[6-(2-Ethyl-5-fluoro-4-hydroxy-phenyl)-1*H*-indazol-4-yl]ethanesulfonamide (**19**)

Step 1: 6-(4-(*tert*-butyldimethylsilyloxy)-2-ethyl-5-fluorophenyl)-4-nitro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazole

To a solution of compound **5** (5.00 g, 15.4 mmol) in dioxane (20 mL) was added compound **38** (6.44 g, 0.32 mmol), Na₂CO₃ (4.9 g 46 mmol), H₂O (5 mL) and Pd(PPh₃)₂Cl₂ (563 mg, 0.77 mmol), and the mixture was stirred at 90 °C under N₂ atmosphere for 3 h. The reaction mixture was concentrated under reduced pressure and the residue was purified by silica gel column chromatography (PE/EtOAc 100/1) to give the title compound (3.26 g, 42%). MS Anal. Calcd. for [M+H]⁺ C₂₆H₃₅FN₃O₄Si: 500; found 500.

Step 2: 6-[4-[*tert*-butyl(dimethyl)silyl]oxy-2-ethyl-5-fluoro-phenyl]-1-tetrahydropyran-2-yl-indazol-4-amine

To a solution of the product of step 1 (3.26 g, 6.53 mmol) in EtOAc (20 mL) was added 10% Pd/C (326 mg) at r.t. The reaction mixture was stirred under H₂ atmosphere (1 atm) at r.t. overnight. After the reaction was completed, the reaction mixture was filtrated through a pad of celite. The filtrate was concentrated under reduced pressure to give the title compound (2.8 g, 95%). MS Anal. Calcd. for [M+H]⁺ C₂₆H₃₇FN₃O₂Si: 470; found 470.

Step 3: *N*-(6-(4-(*tert*-butyldimethylsilyloxy)-2-ethyl-5-fluorophenyl)-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-4-yl)ethanesulfonamide

To a solution of the product of step 2 (130 mg, 0.277 mmol) in DCM (5 mL) was added pyridine (88 mg, 1.1 mmol) and ethanesulfonyl chloride (53 mg, 0.42 mmol) at 0 °C. After the addition, the reaction mixture was stirred at rt for 2h. After the reaction was completed, the mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (PE/EtOAc, 4/1) to give the title compound (110 mg, 71%). MS Anal. Calcd. for $[M+H]^+$ $C_{28}H_{41}FN_3O_4SSi$: 562; found 562.

Step 4: *N*-[6-(2-Ethyl-5-fluoro-4-hydroxy-phenyl)-1*H*-indazol-4-yl]ethanesulfonamide (**19**)

A solution of the product of step 3 (110 mg, 0.196 mmol) in 7 M MeOH in HCl (5 mL) was stirred at rt for 3 h. After the reaction was completed, the reaction mixture was concentrated under reduced pressure. The residue was neutralized with 1 M aqueous NaOH solution to pH 8 and the mixture was extracted with EtOAc. The organic layer was concentrated and the residue was purified by preparative HPLC to give the title compound (25 mg, 30%). 1H NMR (400 MHz, Methanol- d_4) δ 8.30 (s, 1H), 7.19 (s, 1H), 7.10 (s, 1H), 6.97 (d, J = 11.8 Hz, 1H), 6.90 (d, J = 8.9 Hz, 1H), 3.17 (q, J = 7.4 Hz, 2H), 2.56 (q, J = 7.5 Hz, 2H), 1.34 (t, J = 7.4 Hz, 3H), 1.09 (t, J = 7.5 Hz, 3H). UPLC t_R = 1.99 min, Purity UV_{254} > 98%. HRMS Anal. Calcd. for $[M+H]^+$ $C_{17}H_{19}FN_3O_3S$: 364.1126; found 364.1145.

N-[6-(2-Ethyl-5-fluoro-4-hydroxy-phenyl)-1*H*-indazol-4-yl]-*N*-methyl-methanesulfonamide (**20**)

Step 1: *N*-[6-bromo-1-(tetrahydro-pyran-2-yl)-1*H*-indazol-4-yl]-*N*-methyl-methanesulfonamide

To a mixture of *N*-(6-bromo-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-4-yl)methanesulfonamide, see compound **18**, step 2 (300 mg, 0.8 mmol) and potassium carbonate (330 mg, 2.4 mmol) in acetonitrile (10 mL) was added iodomethane (340 mg, 2.4 mmol) and the mixture was stirred at rt overnight. The reaction mixture was filtered, the filtrate was concentrated, and the residue was purified by silica gel column chromatography (PE:EtOAc 10:1) to give the title compound as a yellow solid (300 mg, 97%). MS Anal. Calcd. for $[M+H]^+$ $C_{14}H_{19}BrN_3O_3S$: 388; found 388.

Step 2: *N*-[6-[4-(*tert*-butyl-dimethyl-silanyloxy)-2-ethyl-5-fluoro-phenyl]-1-(tetrahydro-pyran-2-yl)-1*H*-indazol-4-yl]-*N*-methyl-methanesulfonamide

To a mixture of the product of step 1 (300 mg, 0.77 mmol) and compound **38** (350 mg, 0.92 mmol) in dioxane (10 mL) was added potassium acetate (300 mg, 3.06 mmol) and $Pd(dppf)Cl_2$ (60 mg, 0.08 mmol) under N_2 atmosphere. The resultant mixture was refluxed under N_2 overnight. The mixture was cooled to room temperature, filtered, and the filtrate was concentrated. The residue was purified by silica gel column chromatography (PE:EtOAc 2:1) to give the title compound as colorless oil (200 mg, 50%). MS Anal. Calcd. for $[M+H]^+$ $C_{28}H_{41}FN_3O_4SSi$: 562; found 562.

Step 3: *N*-[6-(2-ethyl-5-fluoro-4-hydroxy-phenyl)-1*H*-indazol-4-yl]-*N*-methyl-methanesulfonamide (20)

A mixture of the product of step 2 (200 mg, 0.36 mmol) in 7 M HCl in MeOH (5 mL) was stirred at room temperature for 5 h. The reaction mixture was adjusted to pH 9 with aqueous NaOH, and the aqueous layer was extracted with EtOAc (2 × 20 mL). The organic layers were washed with brine, dried over anhydrous Na₂SO₄, and concentrated *in vacuo*. The residue was purified by preparative TLC to afford the title compound as a white solid (80 mg, 61%). ¹H NMR (400 MHz, Chloroform-*d*) δ 8.26 (s, 1H), 7.36 (s, 1H), 7.07 (s, 1H), 6.98 (d, *J* = 3.0 Hz, 1H), 6.96 (d, *J* = 5.2 Hz, 1H), 3.47 (s, 3H), 2.97 (s, 3H), 2.51 (q, *J* = 7.6 Hz, 2H), 1.08 (t, *J* = 7.5 Hz, 3H). UPLC *t*_R = 2.03 min, Purity UV₂₅₄ > 98%. HRMS Anal. Calcd. for [M+H]⁺ C₁₇H₁₉FN₃O₃S: 364.1126; found 364.1111.

***N*-[6-(2-Ethyl-5-fluoro-4-hydroxy-phenyl)-1*H*-indazol-4-yl]propane-2-sulfonamide (21)**

Prepared analogously to compound **19** starting from propane-2-sulfonyl chloride. ¹H NMR (600 MHz, DMSO-*d*₆) δ 13.12 (br s, 1H), 10.13 (br s, 1H), 9.83 (br s, 1H), 8.40 (s, 1H), 7.08 (s, 1H), 7.00 (d, *J* = 1.2 Hz, 1H), 6.99 (d, *J* = 11.9 Hz, 1H), 6.89 (d, *J* = 9.1 Hz, 1H), 3.31 – 3.26 (m, 1H), 2.45 (q, *J* = 7.6 Hz, 2H), 1.24 (d, *J* = 6.8 Hz, 6H), 1.01 (t, *J* = 7.5 Hz, 3H). UPLC *t*_R = 2.04 min, Purity UV₂₅₄ = 90%. HRMS Anal. Calcd. for [M+H]⁺ C₁₈H₂₁FN₃O₃S: 378.1282; found 378.1307.

N-[6-(2-Ethyl-5-fluoro-4-hydroxy-phenyl)-1*H*-indazol-4-yl]cyclopropanesulfonamide (**22**)

Prepared analogously to compound **19** starting from cyclopropanesulfonyl chloride. ¹H NMR (400 MHz, Methanol-*d*₄) δ 8.29 (s, 1H), 7.23 (s, 1H), 7.12 (s, 1H), 6.97 – 6.87 (m, 2H), 2.61 – 2.53 (m, 3H), 1.12 – 0.90 (m, 7H). UPLC *t*_R = 2.01 min, Purity UV₂₅₄ > 98%. HRMS Anal. Calcd. for [M+H]⁺ C₁₈H₁₉FN₃O₃S: 376.1126; found 376.1097.

1-Cyclobutyl-*N*-[6-(2-ethyl-5-fluoro-4-hydroxy-phenyl)-1*H*-indazol-4-yl]methanesulfonamide (**23**)

Prepared analogously to compound **19** starting from cyclobutylmethanesulfonyl chloride. ¹H NMR (400 MHz, Methanol-*d*₄) δ 8.27 (s, 1H), 7.16 (s, 1H), 7.08 (s, 1H), 6.94 (d, *J* = 11.8 Hz, 1H), 6.88 (d, *J* = 8.9 Hz, 1H), 3.26 (d, *J* = 7.3 Hz, 2H), 2.90 – 2.76 (m, 1H), 2.54 (q, *J* = 7.5 Hz, 2H), 2.19 – 2.06 (m, 2H), 1.95 – 1.85 (m, 1H), 1.84 – 1.72 (m, 3H), 1.07 (t, *J* = 7.6 Hz, 3H). UPLC *t*_R = 2.16 min, Purity UV₂₅₄ = 96%. HRMS Anal. Calcd. for [M+H]⁺ C₂₀H₂₃FN₃O₃S: 404.1439; found 404.1484.

N-[6-(2-Ethyl-5-fluoro-4-hydroxy-phenyl)-1*H*-indazol-4-yl]cyclopentanesulfonamide (**24**)

Prepared analogously to compound **19** starting from cyclopentanesulfonyl chloride. UPLC $t_R = 2.13$ min, Purity $UV_{254} = 96\%$. HRMS Anal. Calcd. for $[M+H]^+$ $C_{20}H_{23}FN_3O_3S$: 404.1439; found 404.1468.

N-[6-(2-Ethyl-5-fluoro-4-hydroxy-phenyl)-1*H*-indazol-4-yl]-1,1,1-trifluoro-methanesulfonamide (**25**)

Prepared analogously to compound **19** starting from triflic anhydride. 1H NMR (400 MHz, Chloroform-*d*) δ 8.31 (s, 1H), 7.36 (s, 1H), 7.23 (s, 1H), 6.99 (d, $J = 1.1$ Hz, 1H), 6.96 (d, $J = 3.4$ Hz, 1H), 2.52 (q, $J = 7.5$ Hz, 2H), 1.08 (t, $J = 7.5$ Hz, 3H). UPLC $t_R = 2.12$ min, Purity $UV_{254} > 98\%$. HRMS Anal. Calcd. for $[M+H]^+$ $C_{16}H_{14}F_4N_3O_3S$: 404.0687; found 404.1012.

N-[6-(2-Ethyl-5-fluoro-4-hydroxy-phenyl)-1*H*-indazol-4-yl]-2-hydroxy-ethanesulfonamide (**26**)

Prepared analogously to compound **19** starting from methyl 3-chlorosulfonylpropanoate and reducing the methyl ester with LiAlH_4 in THF prior to deprotection. UPLC $t_R = 1.86$ min, Purity $\text{UV}_{254} = 86\%$. HRMS Anal. Calcd. for $[\text{M}+\text{H}]^+$ $\text{C}_{17}\text{H}_{19}\text{FN}_3\text{O}_4\text{S}$: 380.1075; found 380.1096.

N-[6-(2-Ethyl-5-fluoro-4-hydroxy-phenyl)-1*H*-indazol-4-yl]-2-methoxy-ethanesulfonamide (**27**)

Prepared analogously to compound **19** starting from methyl 3-chlorosulfonylpropanoate. Prior to deprotection, the methyl ester was reduced with LiAlH_4 in THF, the resulting alcohol was mesylated with MsCl and pyridine, and the mesylate was substituted with sodium methoxide. ^1H NMR (400 MHz, $\text{Methanol-}d_4$) δ 8.27 (s, 1H), 7.18 (s, 1H), 7.12 (d, $J = 1.1$ Hz, 1H), 6.94 (d, $J = 11.8$ Hz, 1H), 6.88 (d, $J = 8.9$ Hz, 1H), 3.77 (t, $J = 5.8$ Hz, 2H), 3.37 (t, $J = 5.8$ Hz, 2H), 3.23 (s, 3H), 2.54 (q, $J = 7.5$ Hz, 2H), 1.07 (t, $J = 7.5$ Hz, 3H). UPLC $t_R = 1.99$ min, Purity $\text{UV}_{254} = 96\%$. HRMS Anal. Calcd. for $[\text{M}+\text{H}]^+$ $\text{C}_{18}\text{H}_{21}\text{FN}_3\text{O}_4\text{S}$: 394.1231; found 394.1237.

Methyl 3-[[6-(2-ethyl-5-fluoro-4-hydroxy-phenyl)-1*H*-indazol-4-yl]sulfamoyl]-propanoate (**28**)

Prepared analogously to compound **19** starting from methyl 3-chlorosulfonylpropanoate. ¹H NMR (400 MHz, Methanol-*d*₄) δ 8.28 (s, 1H), 7.21 (s, 1H), 7.11 (s, 1H), 6.97 (d, *J* = 11.8 Hz, 1H), 6.90 (d, *J* = 8.9 Hz, 1H), 3.59 (s, 3H), 3.51 (t, *J* = 7.3 Hz, 2H), 2.83 (t, *J* = 7.2 Hz, 2H), 2.56 (q, *J* = 7.5 Hz, 2H), 1.10 (t, *J* = 7.5 Hz, 3H). UPLC *t*_R = 2.01 min, Purity UV₂₅₄ > 98%. HRMS Anal. Calcd. for [M+H]⁺ C₁₉H₂₁FN₃O₅S: 422.1180; found 422.1136.

N-[6-(2-Ethyl-5-fluoro-4-hydroxy-phenyl)-1*H*-indazol-4-yl]-2-(1-piperidyl)ethanesulfonamide (**29**)

Prepared analogously to compound **19** starting from methyl 3-chlorosulfonylpropanoate. Prior to deprotection, the methyl ester was reduced with LiAlH₄ in THF, the resulting alcohol was mesylated with MsCl and pyridine, and the mesylate was substituted with piperidine in DCM. ¹H NMR (400 MHz, Methanol-*d*₄) δ 8.28 (s, 1H), 7.24 (s, 1H), 7.10 (s, 1H), 6.94 (d, *J* = 11.8 Hz, 1H), 6.89 (d, *J* = 8.9 Hz, 1H), 3.67 – 3.58 (m, 2H), 3.40 – 3.33 (m, 2H), 3.06 – 2.94 (m, 4H), 2.54 (q, *J* = 7.6 Hz, 2H), 1.77 – 1.67 (m, 4H), 1.62 – 1.51 (m, 2H), 1.08 (t, *J* = 7.5 Hz, 3H). UPLC *t*_R = 1.79 min, Purity UV₂₅₄ > 98%. HRMS Anal. Calcd. for [M+H]⁺ C₂₂H₂₈FN₄O₃S: 447.1861; found 447.1861.

N-[6-(2-Ethyl-5-fluoro-4-hydroxy-phenyl)-1*H*-indazol-4-yl]-2-(4-methylpiperazin-1-yl)-ethanesulfonamide (**30**)

Prepared analogously to compound **19** starting from methyl 3-chlorosulfonylpropanoate. Prior to deprotection, the methyl ester was reduced with LiAlH_4 in THF, the resulting alcohol was mesylated with MsCl and pyridine, and the mesylate was substituted with 1-methylpiperazine in DCM. ^1H NMR (400 MHz, Methanol- d_4) δ 8.47 (br s, 1H), 8.33 (s, 1H), 7.22 (s, 1H), 7.13 (s, 1H), 6.96 (d, $J = 11.7$ Hz, 1H), 6.91 (d, $J = 9.0$ Hz, 1H), 3.41 (t, $J = 6.8$ Hz, 2H), 2.97 – 2.82 (m, 6H), 2.65 (s, 3H), 2.63 – 2.51 (m, 6H), 1.09 (t, $J = 7.5$ Hz, 3H). UPLC $t_R = 1.75$ min, Purity $\text{UV}_{254} > 98\%$. HRMS Anal. Calcd. for $[\text{M}+\text{H}]^+$ $\text{C}_{22}\text{H}_{29}\text{FN}_5\text{O}_3\text{S}$: 462.1970; found 462.1940.

2-Chloro-*N*-[6-(2-ethyl-5-fluoro-4-hydroxy-phenyl)-1*H*-indazol-4-yl]benzenesulfonamide (**31**)

Prepared analogously to compound **19** starting from 2-chlorobenzenesulfonyl chloride. UPLC $t_R = 2.16$ min, Purity $\text{UV}_{254} > 98\%$. HRMS Anal. Calcd. for $[\text{M}+\text{H}]^+$ $\text{C}_{21}\text{H}_{18}\text{ClFN}_3\text{O}_3\text{S}$: 446.0736; found 446.0721.

N-[6-(2-Ethyl-5-fluoro-4-hydroxy-phenyl)-1*H*-indazol-4-yl]pyridine-2-sulfonamide (**32**)

Prepared analogously to compound **19** starting from pyridine-2-sulfonyl chloride. ^1H NMR (400 MHz, DMSO- d_6) δ 13.08 (br s, 1H), 10.92 (br s, 1H), 9.87 (br s, 1H), 8.71 – 8.67 (m, 1H), 8.26 (s, 1H), 8.03 (td, J = 7.8, 1.7 Hz, 1H), 7.93 (d, J = 7.8 Hz, 1H), 7.66 – 7.60 (m, 1H), 7.02 (s, 1H), 6.86 (d, J = 1.8 Hz, 1H), 6.83 (s, 1H), 6.75 (d, J = 1.2 Hz, 1H), 2.22 (q, J = 7.6 Hz, 2H), 0.82 (t, J = 7.5 Hz, 3H). UPLC t_R = 2.00 min, Purity UV_{254} > 98%. HRMS Anal. Calcd. for $[\text{M}+\text{H}]^+$ $\text{C}_{20}\text{H}_{18}\text{FN}_4\text{O}_3\text{S}$: 413.1078; found 413.1071.

N-[6-(2-Ethyl-5-fluoro-4-hydroxy-phenyl)-1*H*-indazol-4-yl]pyridine-3-sulfonamide (**33**)

Prepared analogously to compound **19** starting from pyridine-3-sulfonyl chloride. ^1H NMR (400 MHz, Methanol- d_4) δ 8.82 (d, J = 2.0 Hz, 1H), 8.70 (dd, J = 4.9, 1.5 Hz, 1H), 8.17 – 8.13 (m, 1H), 8.06 (s, 1H), 7.54 (dd, J = 8.1, 4.9 Hz, 1H), 7.20 (s, 1H), 6.90 – 6.81 (m, 3H), 2.39 (q, J = 7.5 Hz, 2H), 0.99 (d, J = 7.5 Hz, 3H). UPLC t_R = 1.98 min, Purity UV_{254} > 98%. HRMS Anal. Calcd. for $[\text{M}+\text{H}]^+$ $\text{C}_{20}\text{H}_{18}\text{FN}_4\text{O}_3\text{S}$: 413.1078; found 413.1145.

4-(Dimethylsulfamoylamino)-6-(2-ethyl-5-fluoro-4-hydroxy-phenyl)-1*H*-indazole (34)

Prepared analogously to compound **19** starting from dimethylsulfamoyl chloride. ¹H NMR (400 MHz, Methanol-*d*₄) δ 8.31 (d, *J* = 1.0 Hz, 1H), 7.15 (t, *J* = 1.1 Hz, 1H), 7.10 (d, *J* = 1.2 Hz, 1H), 6.93 (d, *J* = 11.7 Hz, 1H), 6.90 (d, *J* = 9.0 Hz, 1H), 2.81 (s, 6H), 2.56 (q, *J* = 7.6 Hz, 2H), 1.08 (t, *J* = 7.5 Hz, 3H). UPLC *t*_R = 2.02 min, Purity UV₂₅₄ = 98%. HRMS Anal. Calcd. for [M+H]⁺ C₁₇H₂₀FN₄O₃S: 379.1235; found 379.1245.

4-[4-(Diethylphosphorylamino)-1*H*-indazol-6-yl]-5-ethyl-2-fluoro-phenol (35)

Prepared analogously to compound **19** starting from diethylphosphoryl chloride. ¹H NMR (400 MHz, Methanol-*d*₄) δ 8.14 (s, 1H), 7.30 (d, *J* = 8.0 Hz, 1H), 7.09 (d, *J* = 11.2 Hz, 1H), 6.66 (s, 1H), 6.24 (s, 1H), 2.61 (q, *J* = 7.5 Hz, 2H), 2.12 – 1.99 (m, 4H), 1.35 – 1.21 (m, 6H), 1.11 (t, *J* = 7.5 Hz, 3H). UPLC *t*_R = 2.01 min, Purity UV₂₅₄ > 98%. HRMS Anal. Calcd. for [M+H]⁺ C₁₉H₂₄FN₃O₂P: 376.1585; found 376.1572.

2-Chloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (36)

To a solution of 4-bromo-2-chloro-phenol (1 g, 4.85 mmol) in THF (20 mL) was added 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (1.5 g, 5.82 mmol), Pd(dppf)Cl₂ (396 mg, 0.485 mmol) and KOAc (1.9 g, 19.4 mmol). The reaction mixture was stirred at 80 °C under nitrogen overnight. The mixture was filtered and the filtrate was concentrated. The residue was purified by silica gel column chromatograph to give the title compound (600 mg, 57%). MS Anal. Calcd. for [M+H]⁺ C₁₂H₁₇BClO₃; 255; found 255.

5-Ethyl-2-fluoro-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenol (**37**)

To a stirred mixture of 4-bromo-5-ethyl-2-fluoro-phenol[†] (11 g, 50 mmol) and 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (25 g, 100 mmol) in dioxane (40 mL) was added potassium acetate (12.3 g, 125 mmol) and Pd(dppf)Cl₂ (818 mg, 1 mmol) under N₂ atmosphere. Then resultant mixture was stirred at 90 °C overnight. The reaction mixture was cooled to room temperature, filtered, the filtrate was concentrated, and the residue was purified by silica gel column chromatography (PE: EtOAc = 30:1) to give the title compound as a colorless oil (14 g, 93%).

2-[4-(*tert*-Butyl-dimethyl-silyloxy)-2-ethyl-5-fluoro-phenyl]-4,4,5,5-tetramethyl-[1,3,2]dioxaborolane (**38**)

To a solution of **37** (13 g, 48.9 mmol) and imidazole (6.6 g, 97.7 mmol) in DCM (50 mL) was added slowly a solution of TBSCl (13.2 g, 88 mmol) in DCM (30 mL). After the addition, the reaction mixture was stirred at room temperature for 1 h. The reaction mixture was washed with water and brine, dried over anhydrous Na₂SO₄, filtered, the filtrate was concentrated under reduced pressure and the residue was purified by silica gel column chromatography (PE:EtOAc = 30:1) to give the title compound as white solid (13 g, 70%).

[†] Coe, J. W.; Dehnhardt, C. M.; Jones, P.; Kortum, S. W.; Sabnis, Y. A.; Wakenhut, F. M.; Whitlock, G. A. Indazoles. PCT Pat. Appl. WO2013014567, Jan. 31, 2013.