Supporting Information.

Pyrrolopyrazines as selective spleen tyrosine kinase inhibitors.

Fernando Padilla*†, Niala Bhagirath†, Shaoqing Chen†, Eric Chiao†, David M. Goldstein†, Johannes C. Hermann†, Jonathan Hsu†, Joshua J. Kennedy-Smith†, Andreas Kuglstatter†, Cheng Liao†, Wenjian Liu‡, Lee E. Lowrie Jr.†, Kin Chun Luk†, Stephen M. Lynch†, John Menke†, Linghao Niu†, Timothy D. Owens†, Counde O-Yang‡, Aruna Railkar†, Ryan C. Schoenfeld†, Michelle Slade†, Sandra Steiner†, Yun-Chou Tan†, Armando G. Villaseñor†, Ce Wang‡, Jutta Wanner†, Wenwei Xie‡, Daigen Xu†, Xiaohu Zhang‡, Mingyan Zhou†, and Matthew C. Lucas†*.

† Hoffmann-La Roche Inc., pRED, Pharma Research & Early Development, 340 Kingsland Street, Nutley, NJ, United States, 07110; ‡BioDuro Beijing Co. Ltd.; Building E, No.29, Life Science Park Road, Changping District, Beijing 102206, P.R. China

Table of Contents.

- Experimental Section S1
  - General methods S1
  - Commonly used abbreviations S2
  - Detailed procedures for all new compounds S2
- SYK Assay Information S80
  - Experimental Method S81

Experimental Section.

General Methods.

All reagents and solvents were purchased from commercial sources and used without further purification.

^{1}H NMR spectra were measured using a Bruker NMR Avance 400MHz or Bruker NMR Avance 300MHz spectrometer, and chemical shifts were expressed in δ (ppm) units using tetramethylsilane as an internal standard (in ^{1}H NMR description, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, and br = broad peak). Mass spectra were recorded on and Agilent AG1 Single Quad G6140A spectrometer.

Purity values for all tested compounds were found to be above 95% from the high-performance liquid chromatography (HPLC) analyses.

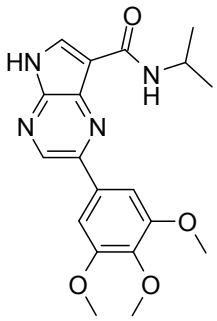
In general, the nomenclature used in this section is based on AUTONOMTM v.4.0, as noted above, or, alternatively, based on ChemDraw.

Protein crystal structures were determined as described previously (Villaseñor, A. G.; Kondru, R.; Ho, H.; Wang, S.; Papp, E.; Shaw, D.; Barnett, J. W.; Browner, M. F. and Kuglstatter, A. Structural Insights for Design of Potent Spleen Tyrosine Kinase Inhibitors from Crystallographic Analysis of Three Inhibitor Complexes. *Chem. Biol. Drug Des*. **2009**, *73*, 466-470).

Commonly used abbreviations:

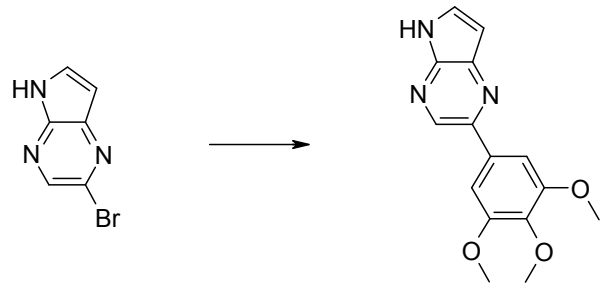
Acetyl (Ac), atmospheres (Atm), *tert*-butoxycarbonyl (Boc), benzyl (Bn), butyl (Bu), benzyloxycarbonyl (CBZ or Z), dibenzylideneacetone (dba), dichloromethane (DCM), di-*iso*-butylaluminumhydride (DIBAL or DIBAL-H), di-iso-propylethylamine (DIPEA), 4-*N,N*-dimethylaminopyridine (DMAP), *N,N*-dimethylformamide (DMF), dimethyl sulfoxide (DMSO), 1,1'-*bis*-(diphenylphosphino)ferrocene (dppf), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI), ethylenediaminetetraacetic acid (EDTA), ethyl (Et), ethyl acetate (EtOAc), ethanol (EtOH), diethyl ether (Et_2O), O-(7-azabenzotriazole-1-yl)-*N,N,N'N'*-tetramethyluronium hexafluorophosphate acetic acid (HATU), 1-*N*-hydroxybenzotriazole (HOBt), high pressure liquid chromatography (HPLC), liquid chromatography-mass spectrometry (LCMS), methanol (MeOH), melting point (mp or MP), methyl (Me), mass spectrum (ms or MS), *N*-methylmorpholine (NMM), *N*-methylpyrrolidone (NMP), phenyl (Ph), propyl (Pr), *iso*-propyl (*i*-Pr), pyridine (pyr), room temperature (rt or RT), triethylamine (TEA or Et_3N), trifluoroacetic acid (TFA), thin layer chromatography (TLC), tetrahydrofuran (THF).
Conventional nomenclature including the prefixes *normal* (*n*), *iso* (*i*-), *secondary* (*sec*-), *tertiary* (*tert*-) and *neo* have their customary meaning when used with an alkyl moiety. (J. Rigaudy and D. P. Klesney, *Nomenclature in Organic Chemistry,* IUPAC **1979** Pergamon Press, Oxford.).

2-(3,4,5-Trimethoxy-phenyl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxylic acid isopropylamide **6**



Step 1

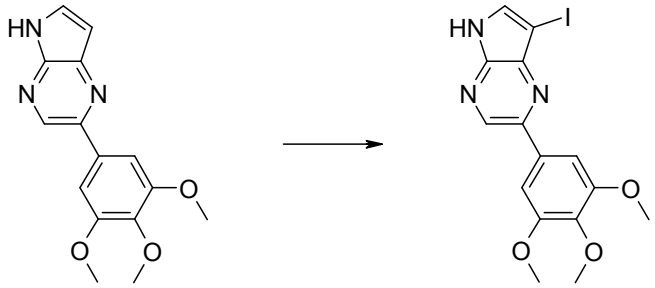
2-(3,4,5-Trimethoxy-phenyl)-5H-pyrrolo[2,3-b]pyrazine **44**



A round-bottomed flask was charged with 2-bromo-5H-pyrrolo[2,3-b]pyrazine (1.30 g, 6.56 mmol, available commercially from Ark Pharm, Inc.), 3,4,5-trimethoxyboronic acid (1.67 g, 7.87 mmol), K_2CO_3 (2.73 g, 19.7 mmol) and $Pd(dppf)Cl_2.CH_2Cl_2$ (0.16 g, 0.197 mmol) and a degassed mixture of 1,4-dioxane (20 mL) and water (5 mL). The reaction mixture was heated in an oil bath to 110 °C and stirred for 18 h. After cooling to room temperature the reaction mixture was filtered over celite, washed with EtOAc. The filtrate partitioned and the organic layer was washed with water and brine then dried over sodium sulfate, filtered and concentrated. The residue was purified by flash chromatography eluting with 10% to 100% ethyl acetate/hexanes to afford **44** (1.55 g, 83%) as a yellow solid. ^{1}H NMR (DMSO-d_6) δ: 12.09 (br. s., 1H), 8.92 (s, 1H), 7.91 (d, J = 3.4 Hz, 1H), 7.43 (s, 2H), 6.71 (d, J = 3.8 Hz, 1H), 3.91 (s, 6H), 3.73 (s, 3H).

Step 2

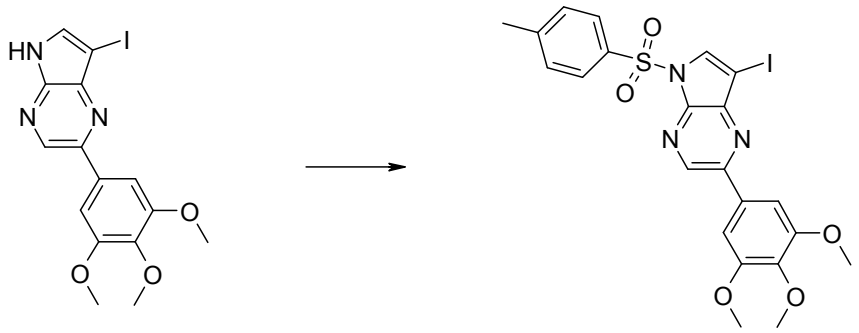
7-Iodo-2-(3,4,5-trimethoxy-phenyl)-5H-pyrrolo[2,3-b]pyrazine **45**



To a slurry of **44** (1.54 g, 5.40 mmol) in DMF (14 mL) was added KOH (1.08 g, 19.40 mmol) and the mixture stirred at room temperature for 40 min. Then the mixture was cooled in an ice bath and added iodine (1.37 g, 5.40 mmol), portion-wise over 5 min and then reaction continued for 30 min at that temperature. The reaction mixture was poured slowly onto a stirred solution of water (70 mL) and saturated solution of $Na_2S_2O_3$ (10 mL). A yellow solid precipitated and was collected by filtration, washed with water and then dried in a vacuum oven overnight to afford **45** (2.175 g, 98%) as a yellow solid. ^{1}H NMR (DMSO-d_6) δ: 8.94 (s, 1H), 8.13 (s, 1H), 7.46 (s, 2H), 3.92 (s, 6H), 3.74 (s, 3H).

Step 3

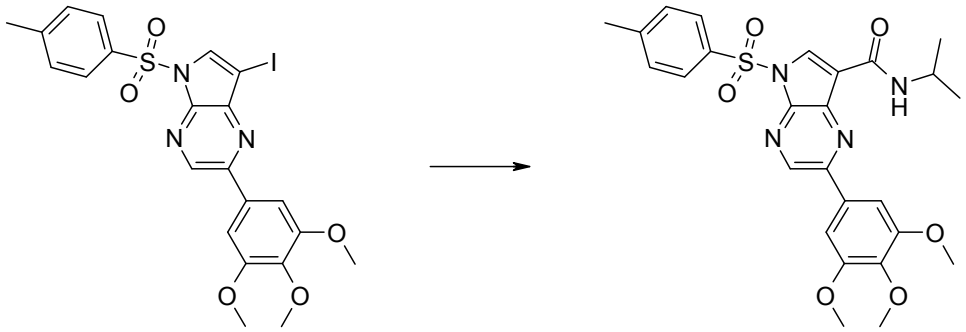
7-Iodo-5-(toluene-4-sulfonyl)-2-(3,4,5-trimethoxy-phenyl)-5H-pyrrolo[2,3-b]pyrazine **46**



To a slurry of **45** (160 mg, 0.389 mmol) in THF (3 mL) at room temperature was added NaH (60% in mineral oil, 18 mg, 0.45 mmol) with stirring. After 15 min it was added *p*-toluenesulfonyl chloride and reaction continued for 18 h. The mixture was quenched with water and extracted with EtOAc. The combined organic layers were washed with water and with brine then dried over sodium sulfate, filtered and concentrated. The residue was purified by flash chromatography eluting with 0-50% EtOAc/hexanes to give **46** (163 mg, 74.4%) as a white solid. ^{1}H NMR (CHLOROFORM-d) δ: 8.75 (s, 1H), 8.15 (s, 1H), 8.03 - 8.12 (m, 2H), 7.33 (d, J = 7.9 Hz, 2H), 3.97 (s, 6H), 3.91 (s, 3H), 2.40 (s, 3H).

Step 4

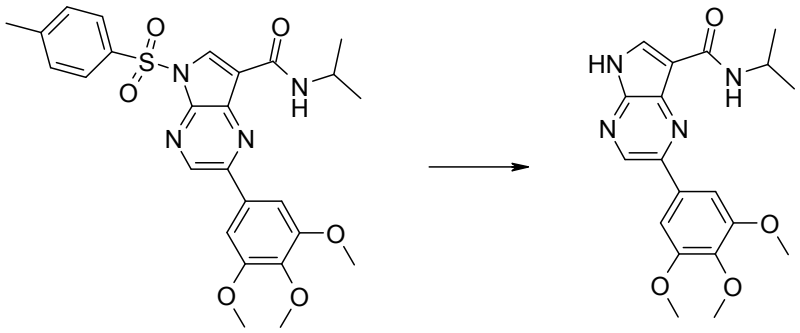
5-(Toluene-4-sulfonyl)-2-(3,4,5-trimethoxy-phenyl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxylic acid isopropylamide **47**



A round-bottomed flask charged with **46** (82 mg, 0.145 mmol), Pd(OAc) (1.8 mg), xantphos (8.2 mg) and K_2CO_3 in toluene (2 mL). The mixture was heated to 100 ^{o}C and CO was bubbled with stirring for 15 min, then isopropylamine (300 μL) was added and reaction continued overnight under a CO filled balloon. The mixture was diluted with EtOAc, filtered and concentrated. The residue was purified by flash chromatography eluting with 0-50% EtOAc/hexanes to give **47** (76 mg, 100%) as a tan solid. ^{1}H NMR (CHLOROFORM-d) δ: 8.84 (s, 1H), 8.69 (s, 1H), 8.26 (d, J = 7.5 Hz, 1H), 8.10 (d, J = 8.7 Hz, 2H), 7.33 (d, J = 8.7 Hz, 2H), 7.21 (s, 2H), 4.35 (td, J = 13.6, 6.8 Hz, 1H), 3.96 (s, 6H), 3.93 (s, 3H), 2.40 (s, 3H), 1.32 (d, J = 6.8 Hz, 6H).

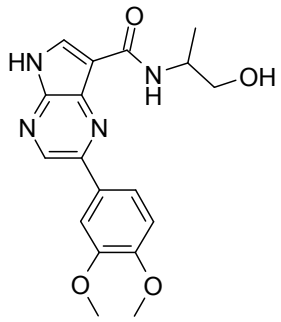
Step 5

2-(3,4,5-Trimethoxy-phenyl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxylic acid isopropylamide **6**



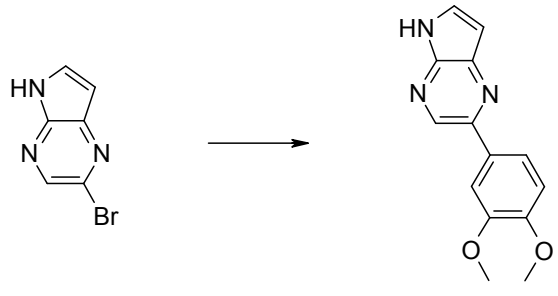
To a slurry of **47** (76 mg, 0.145 mmol) in methanol (2.1 mL) was added a 5M solution of NaOH (160 μL) and the mixture heated to 40 ^{o}C and reaction continued for 15 min. After cooling to room temperature, it was added HCl 1M solution (2 mL). The product was extracted with EtOAc, the combined organic layers were washed with water and with brine then dried over sodium sulfate, filtered and concentrated. The residue was purified by flash chromatography eluting with 50-100% EtOAc/hexanes to give **6** (24 mg, 53.6%) as an off-white solid. LCMS $(M+H)^{+}$ = 372; ^{1}H NMR (CHLOROFORM-d) δ: 9.56 (br. s., 1H), 8.78 (s, 1H), 8.39 (d, J = 7.9 Hz, 1H), 8.34 (d, J = 3.4 Hz, 1H), 7.31 (s, 2H), 4.27 - 4.50 (m, 1H), 4.00 (s, 6H), 3.95 (s, 3H), 1.36 (d, J = 6.4 Hz, 6H).

2-(3,4-Dimethoxy-phenyl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxylic acid (2-hydroxy-1-methyl-ethyl)-amide **7**



Step 1

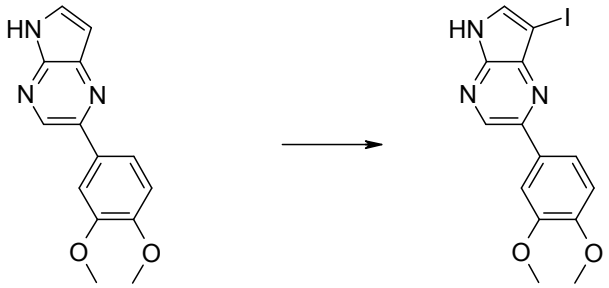
2-(3,4-Dimethoxy-phenyl)-5H-pyrrolo[2,3-b]pyrazine **48**



A round-bottomed flask was charged with 2-bromo-5H-pyrrolo[2,3-b]pyrazine (1.50 g, 8.0 mmol), 3,4-dimethoxyboronic acid (2.068 g, 11 mmol), K_2CO_3 (2.61 g, 19 mmol) and $Pd(dppf)Cl_2.CH_2Cl_2$ (0.495 g, 1 mmol) and a degassed mixture of 1,4-dioxane (24 mL) and water (6 mL). The reaction mixture was heated in an oil bath to 110 °C and stirred for 18 h. After cooling to room temperature the reaction mixture was filtered over celite, washed with dioxane and dichloromethane. The filtrate was concentrated the residue was triturated with a mixture of dichloromethane/EtOAc, the insoluble materials were separated by filtration to yield **48** (1.565 g, 76.9%) as a brown solid that was used into the next step without further purification. ^{1}H NMR (DMSO-d_6) δ: 12.03 (br. s., 1H), 8.83 (s, 1H), 7.83 - 7.93 (m, 1H), 7.64 - 7.76 (m, 2H), 7.07 (d, J = 8.5 Hz, 1H), 6.67 (dd, J = 3.6, 1.9 Hz, 1H), 3.88 (s, 3H), 3.82 (s, 3H).

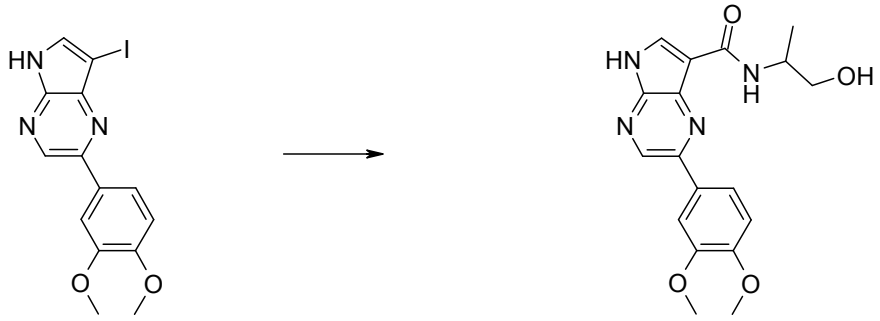
Step 2

7-Iodo-2-(3,4-dimethoxy-phenyl)-5H-pyrrolo[2,3-b]pyrazine **49**



To a solution of **48** (1.565 g, 6 mmol) in DMF (20 mL) was added KOH (0.98 g, 17 mmol) and the mixture stirred at room temperature for 10 min. Then the mixture was cooled in an ice bath and added iodine (1.478 g, 6 mmol), portion-wise over 2 min and the reaction continued for 30 min at that temperature. The reaction mixture was poured slowly onto a stirred solution of water (40 mL) and saturated solution of $Na_2S_2O_3$ (5 mL). A brown solid precipitated and was collected by filtration, washed with water and then dried in a vacuum oven overnight to afford **49** (1.68 g, 75.7%) as a brown solid. ^{1}H NMR (DMSO-d_6) δ: 8.87 (s, 1H), 8.09 (s, 1H), 7.66 - 7.84 (m, 2H), 7.11 (d, J = 8.7 Hz, 1H), 3.89 (s, 3H), 3.83 (s, 3H), 3.34 (br. s., 3H).

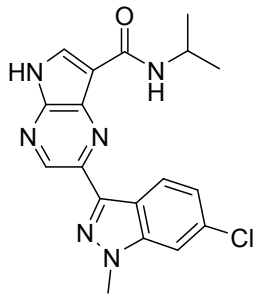
Step 3



2-(3,4-Dimethoxy-phenyl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxylic acid (2-hydroxy-1-methyl-ethyl)-amide **7**

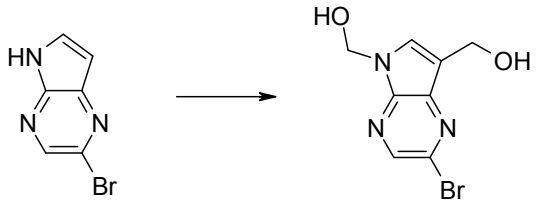
A round-bottomed flask charged with **49** (76 mg, 0.2 mmol), Pd(OAc) (4.3 mg, 0.020 mmol), xantphos (14 mg, 0.024 mmol) and K_2CO_3 (70 mg, 0.52 mmol) in toluene (1 mL). The mixture was heated to 60 ^oC and CO was bubbled with stirring for 15 min, then 2-amino-propan-1-ol (80 mg, 1.0 mmol) in toluene (1 mL) was added and reaction continued for 2 h under a CO filled balloon. The mixture was filtered over celite, washed with a solution of dichloromethane/methanol (4:1). The mixture was adsorbed on silica gel and purified by flash chromatography eluting with 0-8% methanol/dichloromethane to give **7** as an off-white solid. ^1H NMR (DMSO-d_6) δ: 12.68 (br. s., 1H), 9.01 (s, 1H), 8.57 (d, J = 7.9 Hz, 1H), 8.35 (s, 1H), 7.72 - 7.91 (m, 2H), 7.10 (d, J = 8.3 Hz, 1H), 4.99 (t, J = 5.2 Hz, 1H), 4.02 - 4.26 (m, 1H), 3.91 (s, 3H), 3.84 (s, 3H), 3.46 - 3.60 (m, 2H), 1.24 (d, J = 6.8 Hz, 3H)

2-(6-Chloro-1-methyl-1H-indazol-3-yl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxylic acid isopropylamide **8**



Step 1

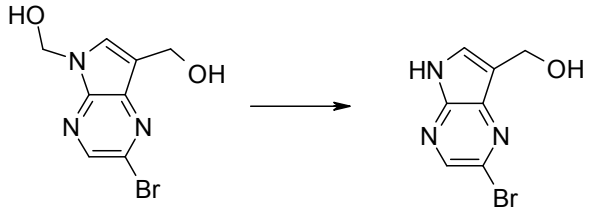
(2-Bromo-7-hydroxymethyl-pyrrolo[2,3-b]pyrazin-5-yl)-methanol **50**



To a suspension of 2-bromo-5H-pyrrolo[2,3-b]pyrazine (5.0 g, 25.2 mmol) in 1,4-dioxane (100 mL) was added 2.0 M aqueous NaOH (25 mL, 50.0 mmol) and 37% aqueous formaldehyde (19 mL, 252 mmol). The dark homogenous reaction mixture was stirred at room temperature overnight. The organics were evaporated under reduced pressure. The aqueous layer was neutralized with 1.0 M HCl and extracted with EtOAc (2x). The combined organics were concentrated to afford 2.6 g of an orange solid. Upon standing, a thick brown precipitate formed in the aqueous layer. The precipitate was collected by filtration and dried. The brown solid was extracted with hot 10% MeOH/EtOAc (3 x 200 mL). The extracts were combined and evaporated to provide an additional 3.05 g of orange solid, to yield **50** (5.65 g, 87%). LCMS $(M+H)^+$ = 258, 260; ^1H NMR (DMSO-d_6, 400 MHz) δ: 8.43 (s, 1H), 7.96 (s, 1H), 6.71 (t, J=7.3 Hz, 1H), 5.59 (d, J=7.6 Hz, 2H), 5.10 (t, J=5.3 Hz, 1H), 4.66 (d, J=5.6 Hz, 2H).

Step 2

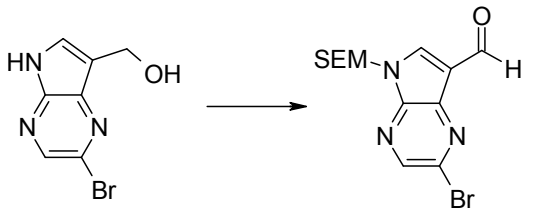
(2-Bromo-5H-pyrrolo[2,3-b]pyrazin-7-yl)-methanol **51**



To a suspension of **50** (5.65 g, 21.9 mmol) in THF (150 mL) was added a solution of 2.0 M aqueous NaOH (33 mL, 66 mmol). The homogeneous reaction mixture was stirred overnight then the organics were removed under reduced pressure. The aqueous residue was brought to pH 4 with 1.0 M aqueous HCl. The resulting precipitate was collected by filtration and rinsed with H_2O to afford 3.68 g of a yellow solid. The filtrate was extracted with EtOAc (2x) and the organics were concentrated under reduced pressure to provide an additional 0.92 g of yellow solid to yield **51** (4.60 g, 92%). ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 12.19 (br. s., 1H), 8.33 (s, 1H), 7.85 (s, 1H), 4.96 (t, *J*=5.3 Hz, 1H), 4.62 (d, *J*=4.9 Hz, 2H).

Step 3

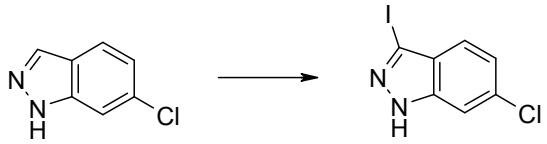
2-Bromo-5-(2-trimethylsilanyl-ethoxymethyl)-5H-pyrrolo[2,3-b]pyrazine-7-carbaldehyde **52**



A stock solution of Jones reagent (2.67 M) was prepared by carefully adding concentrated H_2SO_4 (2.3 mL) to CrO_3 (2.67 g) then diluting to 10 mL with H_2O. To a suspension of **51** (4.6 g, 20.1 mmol) in acetone (300 mL) was slowly added Jones reagent (9 mL, 24.0 mmol). During the addition the starting material gradually dissolved and a thick green solid was formed. The reaction mixture was stirred for 15 min then quenched with *i*-PrOH (2 mL) and filtered over celite, rinsing with acetone. The filtrate was concentrated to provide 4.76 g of 2-bromo-5H-pyrrolo[2,3-b]pyrazine-7-carbaldehyde as a yellow-orange solid that was used without further purification. To a solution of this solid in DMF (50 mL) at 0 °C was added NaH (60% in mineral oil, 1.2 g, 30.1 mmol). The reaction mixture was stirred at room temperature for 30 min then cooled back to 0 °C and 2-(trimethylsilyl)ethoxymethyl chloride (4.3 mL, 24.1 mmol) was slowly added. The reaction mixture was warmed to room temperature and stirred for 1 h then quenched with H_2O and extracted with EtOAc (3x). The combined organics were washed with H_2O (3x) and brine then dried over $MgSO_4$ and concentrated. The residue was purified by flash chromatography eluting with 20 to 30% EtOAc/hexanes to give **52** (3.82 g, 53%) as a yellow solid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 10.37 (s, 1H), 8.50 (s, 1H), 8.33 (s, 1H), 5.73 (s, 2H), 3.53 - 3.70 (m, 2H), 0.90 - 1.05 (m, 2H), 0.00 (s, 9H).

Step 4

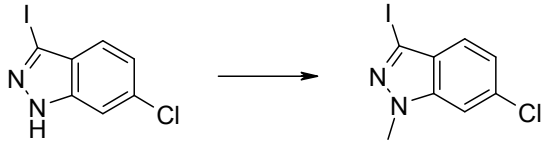
6-Chloro-3-iodo-1H-indazole **53**



In a round-bottomed flask, 6-chloro-1H-indazole (90 mg, 0.59 mmol, available commercially from Ark Pharm, Inc.) was dissolved in DMF (1.4 mL). Iodine (300 mg, 1.18 mmol) was added followed by potassium hydroxide (128 mg, 2.28 mmol). The dark reaction mixture was stirred at room temperature for 3 h, then was quenched with 10% aqueous $NaHSO_3$ and extracted with diethyl ether (2x). The combined organic layers were washed with water and brine then dried over sodium sulfate, filtered and concentrated to give **53** (169 mg, 98%) as an orange solid. ^{1}H NMR (CHLOROFORM-d) δ: 7.52 (d, J = 1.5 Hz, 1H), 7.46 (s, 1H), 7.44 (s, 1H), 7.23 (d, J = 1.5 Hz, 1H), 7.20 (d, J = 1.5 Hz, 1H)

Step 5

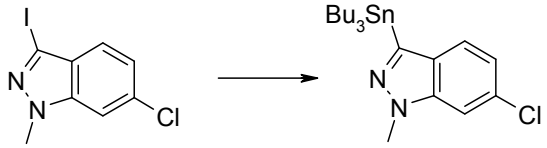
6-Chloro-3-iodo-1-methyl-1H-indazole **54**



In a round-bottomed flask, **53** (167 mg, 0.57 mmol) was dissolved in THF (2 mL) and the solution was cooled to 0 °C. Potassium *tert*-butoxide (90 mg, 0.80 mmol) was added and the reaction mixture was stirred at 0 °C for 1.25 h. Methyl iodide (0.045 mL, 0.72 mmol) was added drop-wise then the ice bath was removed and the reaction mixture was stirred at room temperature for 2 h. The reaction mixture was quenched with water and extracted with EtOAc (2x). The combined organic layers were washed with water and brine then dried over sodium sulfate, filtered and concentrated. The residue was purified by flash chromatography eluting with 0-5% EtOAc/Hexanes to afford **54** (110 mg, 63%) as a yellow solid. ^{1}H NMR (DMSO-d_6) δ: 7.91 (dd, J = 1.8, 0.5 Hz, 1H), 7.44 (dd, J = 8.7, 0.6 Hz, 1H), 7.22 (dd, J = 8.5, 1.8 Hz, 1H), 4.05 (s, 3H).

Step 6

6-Chloro-1-methyl-3-tributylstannanyl-1H-indazole **55**

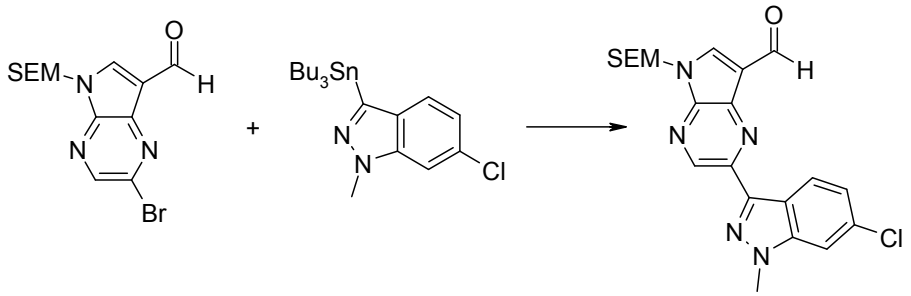


Compound **54** (108 mg, 0.35 mmol) was dissolved in THF (2 mL) and the solution was cooled to -16 °C using a NaCl/ice bath. Isopropylmagnesium chloride (2.0 M in THF, 0.20 mL, 0.40 mmol) was added drop-wise and the reaction mixture was stirred at -16 °C for 15 min. Tributylchlorostannane (0.11 mL, 0.40 mmol) was slowly added and the reaction mixture was allowed to warm to room temperature over 1.5 h. The reaction mixture was quenched with saturated NH_4Cl solution and extracted with EtOAc (2x). The combined organic layers were washed with water and brine then dried over sodium sulfate, filtered and

concentrated to afford **55** as a brown oil which was used immediately into the next step without further purification.

Step 7

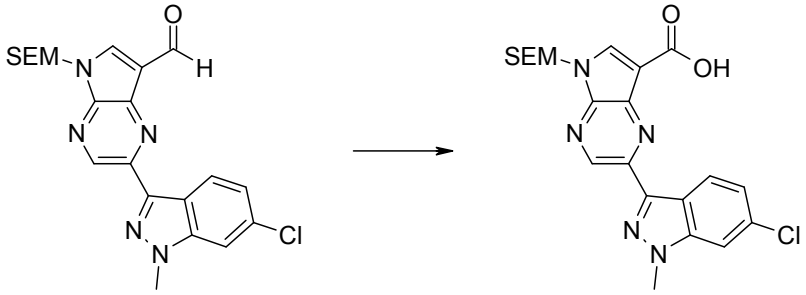
2-(6-Chloro-1-methyl-1H-indazol-3-yl)-5-(2-trimethylsilanyl-ethoxymethyl)-5H-pyrrolo[2,3-b]pyrazine-7-carbaldehyde **56**



In a round-bottomed flask, **52** (400 mg, 1.12 mmol) and **55** (1.11 g, 1.7 mmol) were dissolved in DMF (10 mL). The flask was evacuated and backfilled with argon then tetrakis(triphenylphosphine)palladium (0) (65 mg, 0.056 mmol) and copper (I) iodide (43 mg, 0.23 mmol) were added. The reaction mixture was stirred at 80 °C in an oil bath overnight then cooled to room temperature, quenched with water and extracted with diethyl ether (2x). The combined organic layers were washed twice with water and once with brine then dried over sodium sulfate, filtered and concentrated. The residue was adsorbed on silica gel and purified by flash chromatography eluting with 0-30% EtOAc/hexanes to give **56** (416 mg, 84%) as a yellow solid. ^{1}H NMR (CHLOROFORM-d) δ: 10.52 (s, 1H), 9.33 (s, 1H), 8.78 (d, J = 8.7 Hz, 1H), 8.33 (s, 1H), 7.49 (s, 1H), 7.34 (dd, J = 8.7, 1.5 Hz, 1H), 5.80 (s, 2H), 4.19 (s, 3H), 3.58 - 3.77 (m, 2H), 0.91 - 1.05 (m, 2H), 0.00 (s, 9H).

Step 8

2-(6-Chloro-1-methyl-1H-indazol-3-yl)-5-(2-trimethylsilanyl-ethoxymethyl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxylic acid **57**

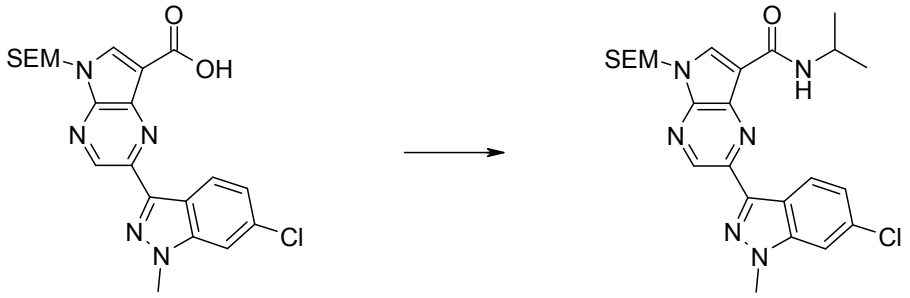


In a round-bottomed flask, **56** (412 mg, 0.93 mmol) was suspended in 1,4-dioxane (15 mL) and water (3 mL). The suspension was cooled to 0 °C and sulfamic acid (543 mg, 5.59 mmol) was added. Then, a solution of sodium chlorite (80%, 137 mg, 1.21 mmol) and potassium dihydrogen phosphate (1.52 g, 11.2 mmol) in water (9 mL) was added via dropping funnel over 20 min. After the addition was complete, the ice bath was removed and the reaction mixture was stirred at room temperature for 3 h. THF (15 mL) was added and the reaction mixture was stirred at room temperature for an additional 3 h. The reaction mixture was

diluted with water and extracted with EtOAc (2x). The combined organic layers were washed with water and brine then dried over sodium sulfate, filtered and concentrated. The residue was triturated with ethyl acetate/hexanes to afford **57** (358 mg, 84%) as a light yellow powder. ^{1}H NMR (CHLOROFORM-d) δ: 9.37 (s, 1H), 8.42 (t, J = 4.3 Hz, 2H), 7.52 (d, J = 1.5 Hz, 1H), 7.34 (dd, J = 8.5, 1.7 Hz, 1H), 5.79 (s, 2H), 4.20 (s, 3H), 3.52 - 3.75 (m, 2H), 0.93 - 1.06 (m, 2H), 0.00 (s, 9H).

Step 9

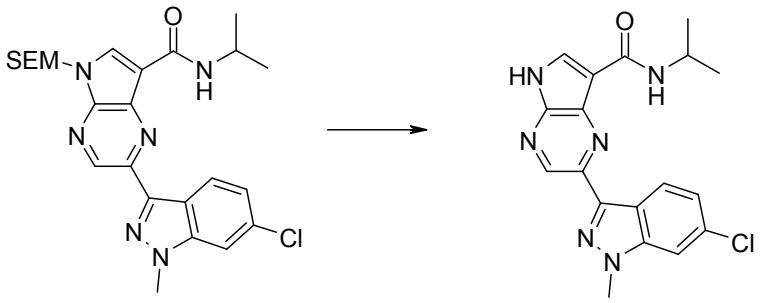
2-(6-Chloro-1-methyl-1H-indazol-3-yl)-5-(2-trimethylsilanyl-ethoxymethyl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxylic acid isopropylamide **58**



Compound **57** (80 mg, 0.175 mmol), O-benzotriazol-1-yl-*N,N,N',N'*-tetramethyluronium tetrafluoroborate (84 mg, 0.26 mmol) and *N,N*-diisopropylethylamine (0.076 mL, 0.44 mmol) were dissolved in acetonitrile (1.75 mL). Isopropylamine (0.018 mL, 0.21 mmol) was added and the mixture was stirred at room temperature overnight. Water and ethyl acetate were added, the layers were separated and the aqueous layer was extracted twice with ethyl acetate. The combined organic layers were washed with sodium chloride solution, dried over sodium sulfate and concentrated. The residue was purified by flash chromatography eluting with 50 % ethyl acetate/hexanes to give **58** (45 mg, 52%). LCMS $(M+H)^+$ = 500. ^{1}H NMR (CHLOROFORM-d) δ: 9.28 (s, 1H), 8.50 (d, J = 8.6 Hz, 1H), 8.41 (s, 1H), 8.23 (d, J = 8.1 Hz, 1H), 7.54 (d, J = 2.0 Hz, 1H), 7.22 - 7.30 (m, 1H), 5.76 (s, 2H), 4.51 (dq, J = 14.0, 6.8 Hz, 1H), 4.21 (s, 3H), 3.53 - 3.69 (m, 2H), 1.46 (d, J = 6.6 Hz, 6H), 0.85 - 1.10 (m, 2H), 0.00 (s, 9H).

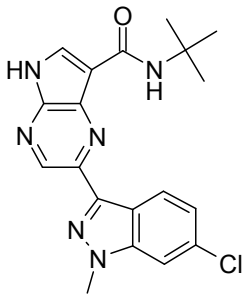
Step 10

2-(6-Chloro-1-methyl-1H-indazol-3-yl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxylic acid isopropylamide **8**

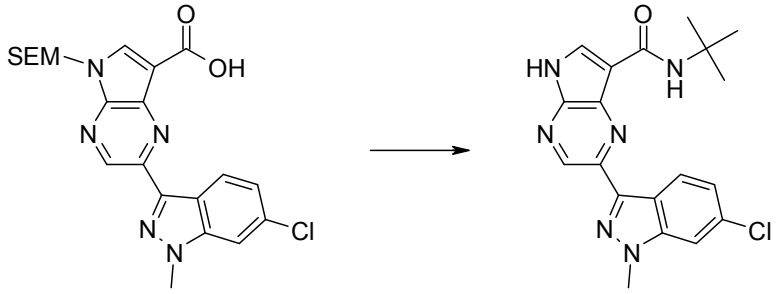


Compound **58** (45 mg, 0.09 mmol) was dissolved in dichloromethane (1 mL) and cooled in ice bath. Trifluoroacetic acid (0.3 mL) was added slowly and the reaction was stirred at room temperature for 3.5 h. The solvents were evaporated and the residue was dissolved in dichloromethane (2 mL). Ethylenediamine (0.36 mL, 5.4 mmol) was added and the mixture was stirred at room temperature for 18 h. Water and ethyl acetate were added to the mixture. The resulting precipitate was separated by filtration, the filter cake rinsed with water and dried under high vacuum to give **8** (21 mg, 81%). LCMS $(M+Na)^+$ = 391; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 12.79 - 12.90 (m, 1 H) 9.09 (s, 1 H) 8.44 (d, *J*=9.1 Hz, 1 H) 8.42 (s, 1 H) 8.02 (d, *J*=7.6 Hz, 1 H) 8.00 (d, *J*=1.5 Hz, 1 H) 7.30 (dd, *J*=8.8, 1.8 Hz, 1 H) 4.19 - 4.27 (m, 1 H) 4.17 (s, 3 H) 1.32 (d, *J*=6.6 Hz, 6 H).

N-*tert*-Butyl-2-(6-chloro-1-methyl-1H-indazol-3-yl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide **9**



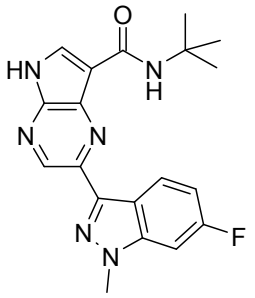
N-*tert*-Butyl-2-(6-chloro-1-methyl-1H-indazol-3-yl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide **9**



To a stirred suspension of **57** (111 mg, 242 µmol) in DMF (4 mL) was added EDC (107 mg, 557 µmol), HOBT (107 mg, 557 µmol) and 2-methylpropan-2-amine (78.6 mg, 0.113 mL, 1.08 mmol) at 20 °C. After 3 h, the reaction mixture was diluted with ethyl acetate, washed with 10% citric acid solution, saturated sodium bicarbonate and brine then dried (sodium sulfate), filtered and concentrated *in vacuo*. Crude *N*-*tert*-butyl-2-(6-chloro-1-methyl-1H-indazol-3-yl)-5-((2-(trimethylsilyl)ethoxy)methyl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide (140 mg, 273 µmol) was dissolved in dichloromethane (5 mL), to this solution was added trifluoroacetic acid (3.11 g, 2.1 mL, 27.3 mmol) at 20 °C. After 6 h, the mixture was concentrated *in vacuo*. The residue was suspended in dichloromethane (5 mL) and ethylenediamine (1.23 g, 1.38 mL, 20.5 mmol) added and the mixture stirred at room temperature for 15 h, and then concentrated *in vacuo*. The solid residue was triturated with water, separated by filtration, dried and then purified by flash chromatography eluting with 0-

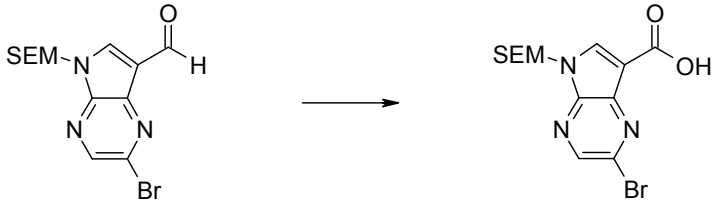
5% methanol in dichloromethane to give **9** (63 mg, 60%) as a pale yellow powder. LCMS $(M+Na)^+$ = 405; ^{1}H NMR ($CDCl_3$) δ: 11.84 (br. s., 1H), 9.05 (s, 1H), 8.38 (d, *J*=8.7 Hz, 1H), 8.14 (d, *J*=3.4 Hz, 1H), 7.96 (s, 1H), 7.39 (d, *J*=1.5 Hz, 1H), 7.08 (dd, *J*=8.5, 1.7 Hz, 1H), 4.04 (s, 3H), 1.48 (s, 9H).

2-(6-Fluoro-1-methyl-1H-indazol-3-yl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxylic acid *tert*-butylamide **10**



Step 1

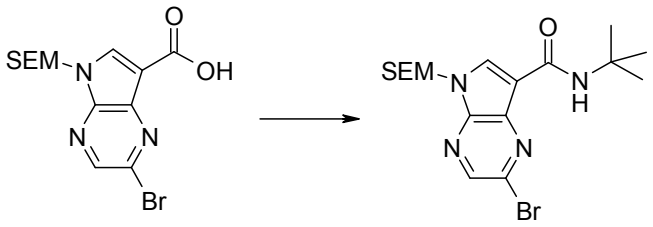
2-Bromo-5-(2-trimethylsilanylethoxymethyl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxylic acid **59**



Compound **52** (3.11 g, 8.74 mmol) was dissolved in dioxane (120 mL) and H_2O (30 mL) and the mixture cooled at 0 °C. Sulfamic acid (5.09 g, 52.4 mmol) was added, followed by the addition of a solution of sodium chlorite (1.28 g, 11.4 mmol) and potassium dihydrogen phosphate (14.3 g, 104.9 mmol) in H_2O (75 mL) via an addition funnel over 15 min. The mixture was allowed to warm to room temperature over 2 h. The resulting yellow solid was separated by filtration, washed with H_2O, hexanes and dried. The filtrate was extracted with EtOAc, the combined organics washed with brine, dried over $MgSO_4$ and concentrated to give additional product to yield **59** (3.25 g, 100%) as a yellow solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.52 (s, 1H), 8.42 (s, 1H), 5.73 (s, 2H), 3.56 - 3.65 (m, 2H), 0.90 - 1.02 (m, 2H), 0.00 (s, 9H).

Step 2

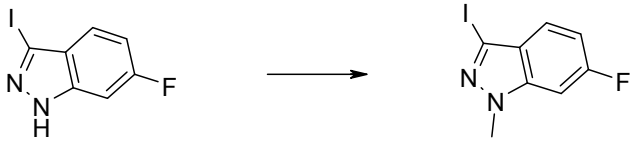
2-Bromo-5-(2-trimethylsilanyl-ethoxymethyl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxylic acid *tert*-butylamide **60**



In a 100 mL round-bottomed flask, **59** (1.0 g, 2.69 mmol) was dissolved in DMF (6 mL), to this solution was added *tert*-butylamine (1.7 mL, 16.2 mmol) followed by HATU (1.12 g, 2.95 mmol). The yellow suspension was stirred at room temperature for 72 h then quenched with water and extracted with a 1:1 mixture of diethyl ether and EtOAc. The combined organic layers were washed twice with water and once with brine, dried over sodium sulfate, filtered and concentrated. The solid residue was triturated with petroleum ether to afford **60** (989 mg, 86%) as an off-white powder. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 8.40 (s, 1H), 8.31 (s, 1H), 7.86 (s, 1H), 5.65 (s, 2H), 3.46 - 3.58 (m, 2H), 1.54 (s, 9H), 0.84 - 0.98 (m, 2H), -0.04 (s, 9H).

Step 3

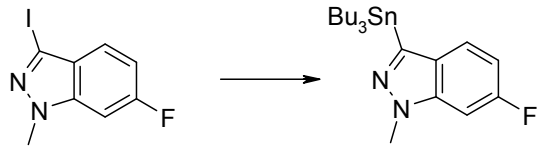
6-Fluoro-3-iodo-1-methyl-1H-indazole **61**



In a round-bottomed flask, 6-fluoro-3-iodo-1H-indazole (1.2 g, 4.58 mmol, available commercially from Beta Pharma Scientific, Inc.) was dissolved in THF (15 mL), the light yellow solution was cooled to 0 °C then potassium *tert*-butoxide (725 mg, 6.46 mmol) was added and the reaction mixture was stirred at 0 °C for 30 min. Methyl iodide (840 mg, 0.37 mL, 5.92 mmol) was added drop-wise at 0 °C. After the addition was complete, the ice bath was removed and the reaction mixture was stirred at room temperature for 5 h. The reaction mixture was quenched with water (20 mL) and extracted with EtOAc (2x120 mL). The combined organic layers were washed with water, brine, then dried over sodium sulfate, filtered and concentrated. The residue was separated by flash chromatography eluting with 0-10% EtOAc/hexanes to give **61** (858 mg, 68%) as a light yellow solid. ^{1}H NMR (CHLOROFORM-d) δ: 7.43 (dd, J = 8.9, 5.1 Hz, 1H), 6.93 - 7.07 (m, 2H), 4.06 (s, 3H).

Step 4

6-Fluoro-1-methyl-3-(tributylstannyl)-1H-indazole **62**

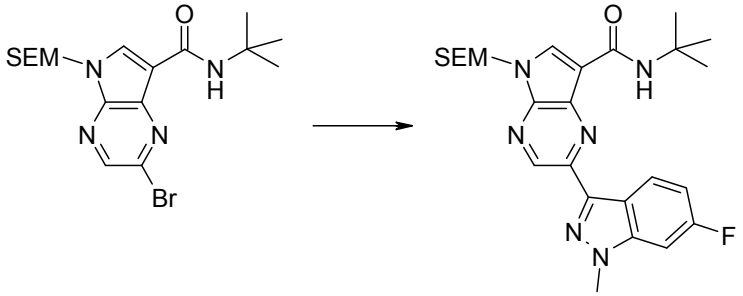


In a round-bottomed flask, **61** (130 mg, 471 µmol) was dissolved in THF (2.7 mL). The pale yellow solution was cooled to -16 °C (NaCl/ice bath) and isopropylmagnesium chloride 2.0M in THF (0.29 mL, 580 µmol) was added drop-wise at -16 °C. The reaction mixture was

stirred at -16 °C for 20 min. Then, tributylchlorostannane (180 mg, 0.15 mL, 553 μmol) was added slowly; the reaction mixture was allowed to warm to room temperature and stirred for 2.5 h. The reaction was quenched with saturated NH_4Cl-solution and extracted with EtOAc (2x40 mL). The combined organic layers were washed with 5 mL of water and 5 mL of brine then dried over sodium sulfate, filtered and concentrated to give crude **62**, which was used immediately into the next step without further purification.

Step 5

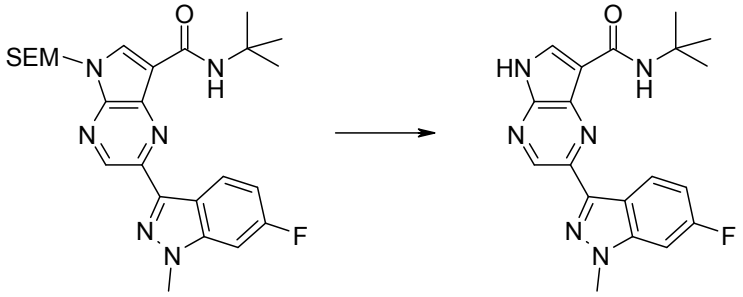
2-(6-Fluoro-1-methyl-1H-indazol-3-yl)-5-((2-(trimethylsilyl)ethoxy)methyl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxylic acid *tert*-butylamide **63**



Compound **60** (80 mg, 0.187 mmol) and **62** (0.1 g, 0.228 mmol) were dissolved in DMF (3 mL). The reaction mixture was evacuated and backfilled with nitrogen. Copper (I) iodide (6.71 mg, 0.075 mmol) and tetrakis(triphenylphosphine)palladium (0) (10.8 mg, 0.009 mmol) were added. The reaction mixture was heated at 90 °C for 2 h. The mixture was cooled to room temperature and partitioned between ethyl acetate and water, the organic phase washed with brine, then dried over magnesium sulfate and concentrated. The residue was purified by flash chromatography eluting with 25% ethyl acetate/hexanes to give **63** (35 mg, 38%). ^{1}H NMR (DMSO-d_6) δ: 9.22 (s, 1H), 8.68 (s, 1H), 8.51 - 8.61 (m, 1H), 7.99 (s, 1H), 7.72 - 7.84 (m, 1H), 7.11 - 7.30 (m, 1H), 5.81 (s, 2H), 4.24 (s, 3H), 3.66 (t, J = 8.0 Hz, 2H), 1.61 (s, 10H), 0.83 - 1.05 (m, 2H), 0.00 (s, 9H).

Step 6

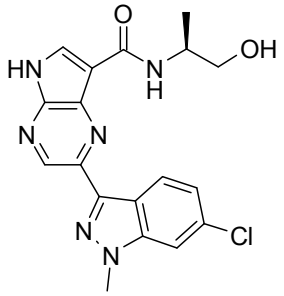
2-(6-Fluoro-1-methyl-1H-indazol-3-yl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxylic acid *tert*-butylamide **10**



To a solution of **63** (35 mg, 0.070 mmol) in dichloromethane (3.0 mL) was added trifluoroacetic acid (0.54 mL, 7.05 mmol) with stirring. After 3 h, the reaction mixture was concentrated and the residue redissolved in dichloromethane (3.0 mL). To this mixture was

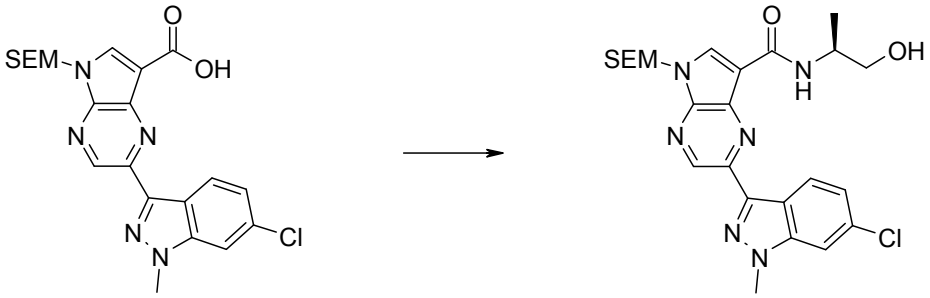
added ethylenediamine (0.476 mL, 7.05 mmol) with stirring. After 1 h, the mixture was concentrated and diluted with 2 mL water. The solid formed was separated by filtration and dried to yield **10** (9 mg, 35%) as an off white solid. LCMS $(M+H)^+ = 367$; ^{1}H NMR (DMSO-d_6) δ: 9.05 (s, 1H), 8.14 - 8.62 (m, 2H), 7.92 (s, 1H), 7.69 (dd, *J*=9.7, 1.9 Hz, 1H), 6.84 - 7.32 (m, 1H), 4.15 (s, 3H), 1.52 (s, 6H).

2-(6-Chloro-1-methyl-1H-indazol-3-yl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxylic acid ((S)-2-hydroxy-1-methyl-ethyl)-amide **11**



Step 1

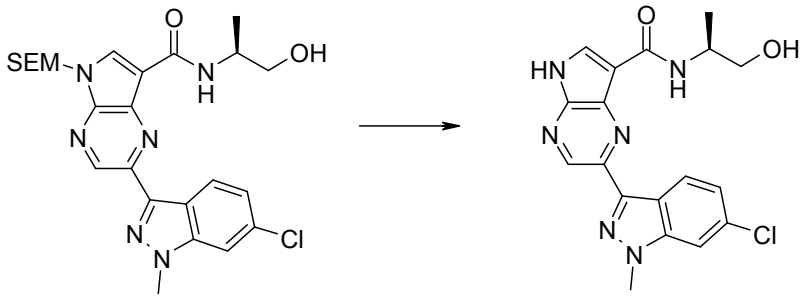
2-(6-Chloro-1-methyl-1H-indazol-3-yl)-5-(2-trimethylsilanyl-ethoxymethyl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxylic acid ((S)-2-hydroxy-1-methyl-ethyl)-amide **64**



A 25 mL round-bottomed flask was charged with **57** (0.20 g, 0.44 mmol), (S)-2-aminopropan-1-ol (0.10 mL, 1.31 mmol), HBTU (331 mg, 0.87 mmol), and HOBT (134 mg, 0.87 mmol). Then added DMF (1 mL) followed by *N,N*-diisopropylethylamine (0.31 mL, 1.75 mmol). The yellow reaction mixture was stirred at room temperature overnight then quenched with water and extracted with EtOAc (30 mL). The organic layer was washed once with saturated $NaHCO_3$ and water. The combined aqueous layers were back extracted with EtOAc (25 mL). The combined organic layers were dried over sodium sulfate, filtered and concentrated. The residue was purified by flash chromatography eluting with 0-100% EtOAc/hexanes to afford **64** (149 mg, 66%) as a white solid. ^{1}H NMR (CHLOROFORM-d) δ: 9.28 (s, 1H), 8.51 (d, J = 8.7 Hz, 1H), 8.34 - 8.46 (m, 2H), 7.52 (s, 1H), 7.21 - 7.29 (m, 1H), 5.74 (s, 2H), 4.39 - 4.58 (m, 1H), 4.20 (s, 3H), 3.88 - 4.03 (m, 1H), 3.74 - 3.85 (m, 1H), 3.50 - 3.69 (m, 2H), 1.49 (d, J = 6.8 Hz, 3H), 0.88 - 1.09 (m, 2H), 0.00 (s, 9H).

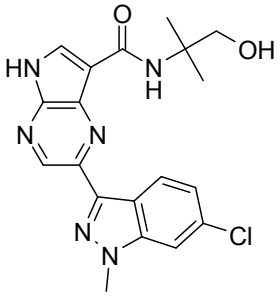
Step 2

2-(6-Chloro-1-methyl-1H-indazol-3-yl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxylic acid ((S)-2-hydroxy-1-methyl-ethyl)-amide **11**



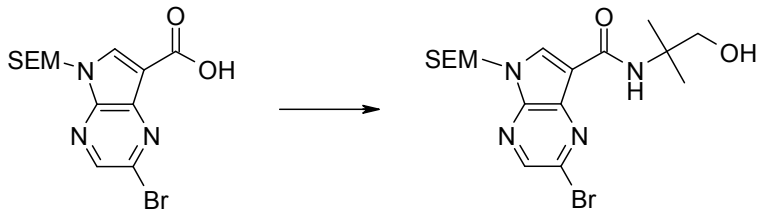
In a 25 mL round-bottom flask, a stirred solution of **64** (41 mg, 0.080 mmol) in dichloromethane (2 mL) was treated with TFA (0.6 mL, 7.8 mmol) to give an orange solution. The reaction mixture was stirred at room temperature for 2.5 h then was concentrated under reduced pressure. The residue was dissolved in dichloromethane (2 mL) and ethylenediamine (400 µl, 5.9 mmol) was added. The reaction mixture was stirred at room temperature for 18 h, and then was concentrated. The solid residue was suspended in water, the suspension was stirred for 1 h and the solid collected by filtration. The crude solid was triturated with dichloromethane:MeOH (9:1), separated by filtration and dried to afford **11** (11 mg, 36%) as an off-white solid. LCMS $(M+H)^+$ = 385; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 12.84 (br. s., 1H), 9.13 (s, 1H), 8.66 (d, *J* = 8.7 Hz, 1H), 8.43 (s, 1H), 8.21 (d, *J* = 8.3 Hz, 1H), 7.91 - 8.04 (m, 1H), 7.32 (dd, *J* = 8.7, 1.5 Hz, 1H), 5.09 (t, *J* = 5.1 Hz, 1H), 4.18 (s, 3H), 4.08 - 4.33 (m, 1H), 3.58 (t, *J* = 4.7 Hz, 2H), 1.28 (d, *J* = 6.8 Hz, 3H).

2-(6-Chloro-1-methyl-1H-indazol-3-yl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxylic acid (2-hydroxy-1,1-dimethyl-ethyl)-amide **12**



Step 1

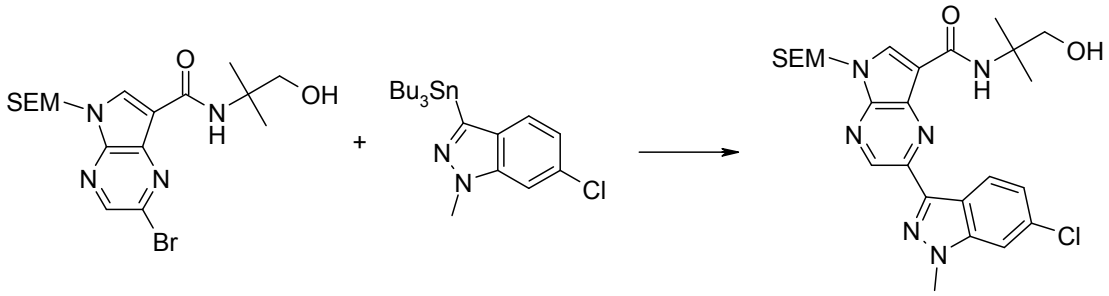
2-Bromo-*N*-(1-hydroxy-2-methylpropan-2-yl)-5-((2-(trimethylsilyl)ethoxy)methyl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide **65**



In a 50 mL round-bottomed flask, **59** (0.8 g, 2.15 mmol) was dissolved in DMF (7.6 mL), then 2-amino-2-methylpropan-1-ol (230 mg, 2.58 mmol) was added followed by HATU (899 mg, 2.36 mmol). The reaction mixture was stirred at room temperature for 18 h, then quenched with water and extracted with EtOAc (3x). The combined organic layers were washed with water (3x) and brine then dried over sodium sulfate, filtered and concentrated. The residue was purified by flash chromatography eluting with 0-35% EtOAc/hexanes to give **65** (880 mg, 41%) as a white powder. ^{1}H NMR (CHLOROFORM-d) δ: 8.46 (s, 1H), 8.34 (s, 1H), 8.12 (s, 1H), 5.69 (s, 2H), 3.78 (s, 2H), 3.52 - 3.67 (m, 2H), 1.52 (s, 6H), 0.88 - 1.03 (m, 2H), -0.04 - 0.06 (m, 9H).

Step 2

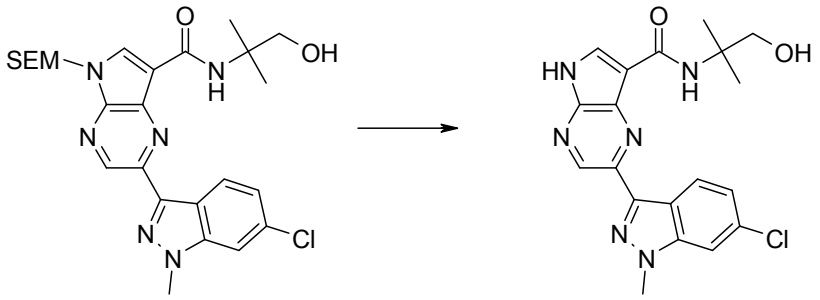
2-(6-Chloro-1-methyl-1H-indazol-3-yl)-5-trimethyl-silanyl-ethoxymethyl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxylic acid (2-hydroxy-1,1-dimethyl-ethyl)-amide **66**



Compound **65** (90 mg, 0.203 mmol) and **55** (0.148 g, 0.228 mmol) were dissolved in DMF (3 mL). The reaction mixture was evacuated and backfilled with nitrogen then copper (I) iodide (9 mg, 0.081 mmol) and tetrakis(triphenylphosphine)palladium (0) (46 mg, 0.046 mmol) were added. The reaction mixture was heated at 90 °C for 2 h and after cooling to room temperature, the reaction mixture was partitioned between ethyl acetate and water. The organic phase was washed with brine, dried over magnesium sulfate and concentrated. The residue was purified by flash chromatography eluting with 25% ethyl acetate/hexane to give **66** (40 mg, 37%). ^{1}H NMR (DMSO-d_6) δ: 9.24 (s, 1H), 8.60 - 8.79 (m, 2H), 8.08 (s, 1H), 7.96 (s, 1H), 7.39 (d, J = 9.0 Hz, 1H), 5.81 (s, 2H), 5.22 (br. s., 1H), 4.27 (s, 3H), 3.53 - 3.81 (m, 4H), 1.54 (s, 6H), 0.94 (t, J = 8.0 Hz, 2H), 0.00 (s, 9H).

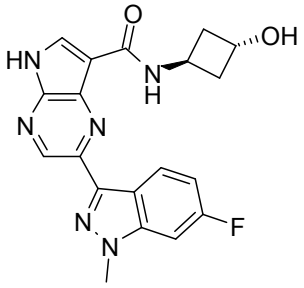
Step 3

2-(6-Chloro-1-methyl-1H-indazol-3-yl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxylic acid (2-hydroxy-1,1-dimethyl-ethyl)-amide **12**



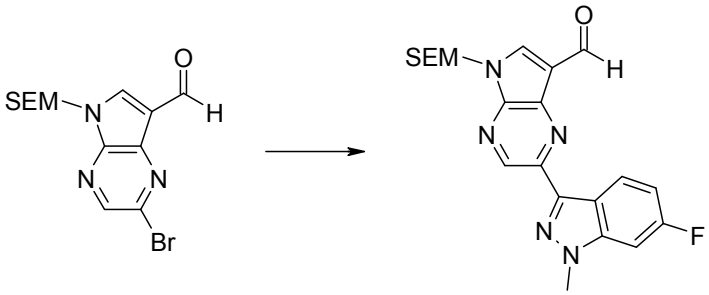
Compound **66** (0.04 g, 0.076 mmol) dissolved in dichloromethane (3.0 mL) was treated with trifluoroacetic acid (0.58 mL, 7.56 mmol) and the mixture stirred at room temperature for 3 h. The reaction mixture was concentrated and diluted with dichloromethane (3 mL), and then ethylenediamine (0.51 mL, 7.56 mmol) was added. After stirring at room temperature for 1 h, the mixture was concentrated. To the residue was added ice water (1 mL) and the solid formed was collected by filtration then triturated with ethyl acetate, the solid was separated by filtration and dried to give **12** (5 mg, 16%). LCMS $(M+H)^+ = 399$; ^1H NMR (DMSO-d_6) δ: 8.94 - 9.36 (m, 1H), 8.51 - 8.76 (m, 1H), 8.37 (s, 1H), 7.80 - 8.08 (m, 2H), 7.29 (t, *J*=8.8 Hz, 1H), 4.17 (d, *J*=5.8 Hz, 3H), 3.48 - 3.80 (m, 2H), 1.45 (d, *J*=3.3 Hz, 6H).

2-(6-Fluoro-1-methyl-1H-indazol-3-yl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxylic acid (trans-3-hydroxy-cyclobutyl)-amide **13**



Step 1

2-(6-Fluoro-1-methyl-1H-indazol-3-yl)-5-(2-trimethylsilanyl-ethoxymethyl)-5H-pyrrolo[2,3-b]pyrazine-7-carbaldehyde **67**

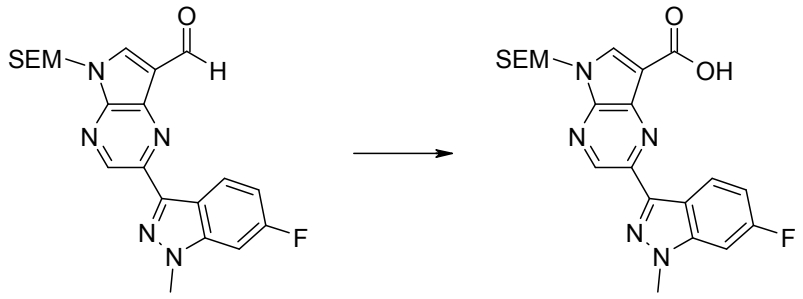


To a 350 mL pressure vial containing **52** (4.89 g, 13.7 mmol) was added a solution of **62** (6.63 g, 15.1 mmol) in DMF (150 mL). The vial was backfilled with N_2 and tetrakis(triphenylphosphine)palladium (0) (793 mg, 686 μmol) and copper (I) iodide (523 mg,

2.74 mmol) were added. The vial was backfilled again with N_2, then sealed and stirred in an oil bath at 80 °C for 4 h. The reaction mixture was cooled to room temperature, concentrated, diluted with a mixture of ethyl acetate/hexanes (120/80 mL) and washed with water (200 mL) and brine (150 mL). The organic layer was then dried over MgSO4, filtered, concentrated and the crude was purified by flash chromatography eluting with 0 to 40% ethyl acetate/hexanes to yield **67** (4.83 g, 82.7%) as a yellow solid. ^{1}H NMR (CHLOROFORM-d) δ: 10.50 (s, 1H), 9.29 (s, 1H), 8.77 (dd, J = 9.1, 5.3 Hz, 1H), 8.29 (s, 1H), 7.01 - 7.20 (m, 2H), 5.76 (s, 2H), 4.14 (s, 3H), 3.43 - 3.75 (m, 2H), 0.76 - 1.05 (m, 2H), -0.03 (s, 9H). LCMS $(M+H)^+$= 426.

Step 2

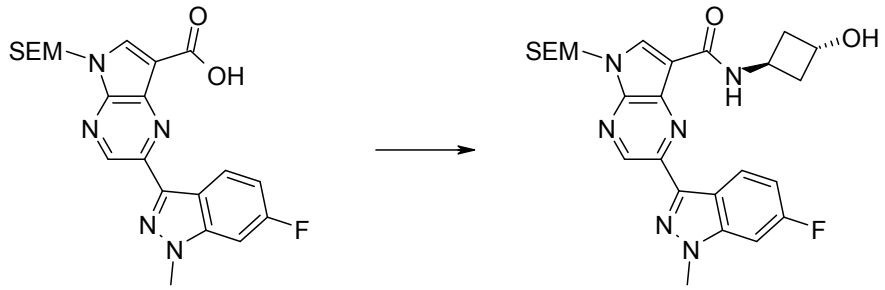
2-(6-Fluoro-1-methyl-1H-indazol-3-yl)-5-methyl-5H-pyrrolo[2,3-b]pyrazine-7-carboxylic acid **68**



A round bottom flask was charged with a solution of **67** (4.83 g, 11.4 mmol) in dioxane (250 mL). The solution was magnetically stirred then water (30 mL) was added. To the clear yellow solution was added sulfamic acid (6.61 g, 68.1 mmol) portion-wise and the mixture cooled in an ice bath. The reaction was stirred for 10 min, then a solution of sodium chlorite (1.76 g, 15.6 mmol) and potassium dihydrogen phosphate (18.5 g, 136 mmol) in water (150 mL) was added drop-wise via an addition funnel over 2 h. The reaction was stirred in the ice bath for 1 h and then was allowed to warm to room temperature and stirred for 18 h. The reaction mixture was diluted with ethyl acetate (300 mL) and water, the organic layer separated, the aqueous layer was extracted ethyl acetate (300 mL). The combined organics were washed with brine (200 mL), dried over MgSO4 and concentrated to a yellow solid that was triturated with a mixture of hexanes:Et_2O (2:1, 4 x 80 mL) to yield **68** (4.2 g, 83.8%) as a light yellow solid. ^{1}H NMR (CHLOROFORM-d) δ: 9.35 (s, 1H), 8.44 (dd, J = 9.6, 5.1 Hz, 1H), 8.40 (s, 1H), 7.01 - 7.19 (m, 2H), 5.77 (s, 2H), 4.16 (s, 3H), 3.44 - 3.74 (m, 2H), 0.80 - 1.09 (m, 2H), -0.03 (s, 9H).

Step 3

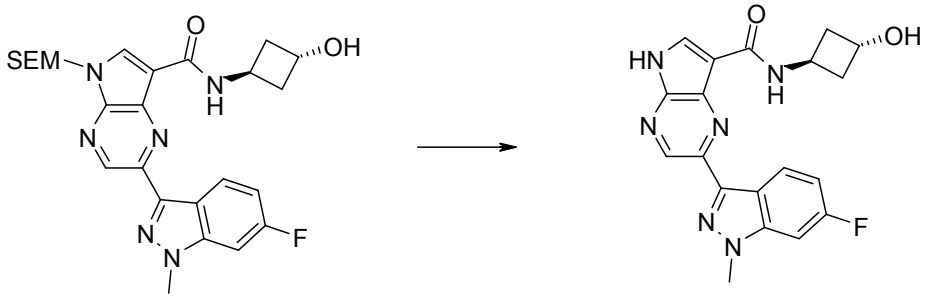
2-(6-Fluoro-1-methyl-1H-indazol-3-yl)-5-(2-trimethylsilanyl-ethoxymethyl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxylic acid (trans-3-hydroxy-cyclobutyl)-amide **69**



A 10 mL round-bottomed flask was charged with **68** (250 mg, 0.57 mmol), 3-aminocyclobutanol hydrochloride (98 mg, 0.79 mmol) and DMF (2.8 mL). *N,N*-diisopropylethylamine (266 mg, 0.36 mL, 2.06 mmol) was added followed by HATU (237 mg, 0.62 mmol). The yellow solution was stirred at room temperature overnight (a precipitate was formed). The reaction mixture was diluted with water and petroleum ether. The suspension was filtered. The filter cake was washed with water and petroleum ether. The resulting off-white powder was dried under high vacuum. The mixture of cis- and trans-product (265mg) was separated by SFC chromatography (KROMASIL OD 3x25cm, 25% MeOH/CO_2 +0.1% triethylamine) to afford 2-(6-fluoro-1-methyl-1H-indazol-3-yl)-5-(2-trimethylsilanyl-ethoxymethyl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxylic acid (cis-3-hydroxy-cyclobutyl)-amide (139 mg, 48%) as an off-white solid and **69** (102 mg, 35%) as an off-white solid. ^{1}H NMR (DMSO-d_6) δ: 9.10 (s, 1H), 8.52 (dd, J = 9.0, 5.2 Hz, 1H), 8.43 (s, 1H), 8.36 (d, J = 7.1 Hz, 1H), 7.72 (dd, J = 9.7, 2.1 Hz, 1H), 7.20 (td, J = 9.1, 2.3 Hz, 1H), 5.22 (br. s., 1H), 4.52 - 4.62 (m, 1H), 4.48 (br. s., 1H), 4.08 - 4.20 (m, 3H), 2.17 - 2.41 (m, 4H).

Step 4

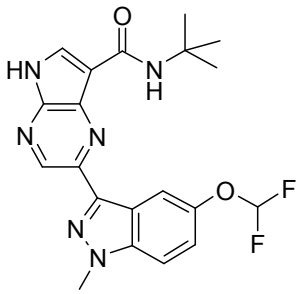
2-(6-Fluoro-1-methyl-1H-indazol-3-yl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxylic acid (trans-3-hydroxy-cyclobutyl)-amide **13**



In a 10 mL round-bottomed flask, **69** (100 mg, 0.20 mmol) was dissolved in dichloromethane (1.0 mL). Trifluoroacetic acid (0.61 mL, 7.92 mmol) was added and the orange solution was stirred at room temperature for 2 h. The reaction mixture was concentrated. The residue (light orange foam) was suspended in dichloromethane (1.0 mL) and ethylenediamine (0.80 mL, 11.8 mmol) was added. The light yellow suspension was stirred at room temperature for 1 h. The reaction mixture was diluted with water and ethyl acetate. The suspension was filtered and washed with hot water and ethyl acetate. The resulting off-white powder was dried under high vacuum to provide **13** (55 mg, 66%). LCMS $(M-H)^-$ = 379. ^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 12.31 - 12.64 (br. s., 1H), 9.10 (s, 1H), 8.52 (dd, *J*=9.0, 5.2 Hz, 1H), 8.43 (s,

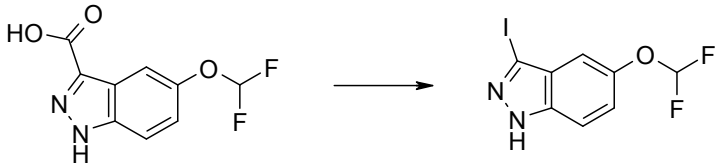
1H), 8.36 (d, *J*=7.1 Hz, 1H), 7.72 (dd, *J*=9.7, 2.1 Hz, 1H), 7.20 (td, *J*=9.1, 2.3 Hz, 1H), 5.19 - 5.26 (m, 1H), 4.52 - 4.61 (m, 1H), 4.44 - 4.61 (m, 1H), 4.16 (s, 3H), 2.25 - 2.40 (m, 4H).

2-(5-Difluoromethoxy-1-methyl-1H-indazol-3-yl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxylic acid *tert*-butylamide **14**



Step 1

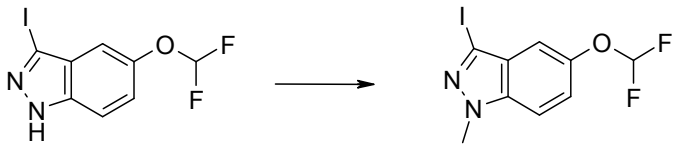
5-(Difluoromethoxy)-3-iodo-1H-indazole **70**



To a mixture of 5-(difluoromethoxy)-1H-indazole-3-carboxylic acid (1 g, 4.38 mmol), and sodium bicarbonate (1.22 g, 563 µL, 14.5 mmol) in dichloroethane (10.0 mL) and water (10.0 mL) were added in one portion sodium iodide (1.71 g, 11.4 mmol) and iodine (1.45 g, 5.7 mmol) and the mixture heated to 100 °C (oil bath temperature) with vigorous stirring for 45 minutes. After cooling to 25 °C the mixture was diluted with dichloromethane then washed with 10% $Na_2S_2O_3$ and saturated $NaHCO_3$. The organic layer was dried ($MgSO_4$) and concentrated to an off-white solid. The solid was dissolved in dichloromethane then hexanes were added to promote solid formation and allowed to stand for 18 h. The solid formed was separated by decanting the mother liquor and dried to give **70** (1.145 g, 84.3%) as a white fluffy solid. LCMS $(M-H)^-$ = 308.9; ^1H NMR ($CDCl_3$) δ: 7.52 (d, *J*=9.1 Hz, 1H), 7.28 - 7.36 (m, 1H), 6.57 (t, *J*=73.7 Hz, 1H).

Step 2

5-(Difluoromethoxy)-3-iodo-1-methyl-1H-indazole **71**

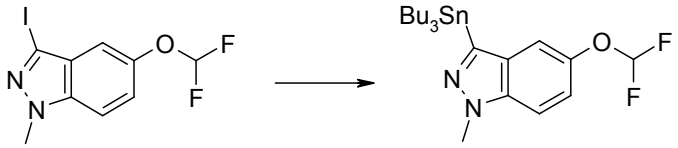


To a solution of **70** (562 mg, 1.81 mmol) in THF (10.0 mL) at 0 °C was added KO*t*-Bu (1M in THF, 2.54 mL, 2.54 mmol) and the mixture stirred at 0 °C for 30 min then MeI (360 mg, 159 µL, 2.54 mmol) was added drop-wise. The reaction mixture was stirred at 0 °C for 30

min then warmed to 25 °C and stirred for 1.5 h. The reaction mixture was quenched with saturated ammonium chloride in water and extracted with dichloromethane (3 x 30 mL), combined organics dried over $MgSO_4$ and concentrated to a clear oil. Purification by flash chromatography eluting with 0-20% EtOAc in hexanes gave **71** (465 mg, 79.2%) as a waxy off-white solid. LCMS $(M+H)^+$ = 324.9; ^1H NMR ($CDCl_3$) δ: 7.32 - 7.40 (m, 1H), 7.24 - 7.30 (m, 1H), 7.21 (d, *J*=2.3 Hz, 1H), 6.55 (t, *J*=73.7 Hz, 1H), 4.10 (s, 3H). Also obtained the regioisomeric product, 5-(difluoromethoxy)-3-iodo-2-methyl-2H-indazole (108 mg, 18%) as a white solid.

Step 3

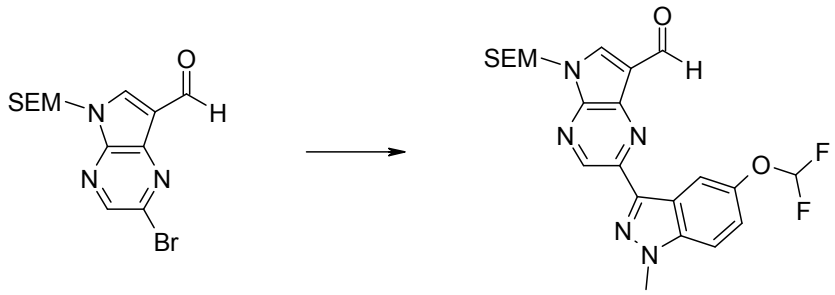
5-(Difluoromethoxy)-1-methyl-3-(tributylstannyl)-1H-indazole **72**



Compound **71** (0.265 g, 818 µmol) was dissolved in THF (3.0 mL). The colorless solution was cooled to -16 °C (NaCl/ice bath) then isopropylmagnesium chloride (2M in THF, 458 µL, 916 µmol) added drop-wise at -16 °C. The reaction mixture was stirred at -16 °C for 20 min then tributylchlorostannane (306 mg, 255 µL, 940 µmol) was added slowly. The reaction mixture was warmed to 25 °C and stirred for 1.5 h. The reaction mixture was quenched with saturated ammonium chloride solution, extracted with dichloromethane (3 x 30 mL), organics dried over $MgSO_4$ and concentrated to give **72** as a yellow oil which was taken immediately into the next step without further purification.

Step 4

2-(5-(Difluoromethoxy)-1-methyl-1H-indazol-3-yl)-5-((2-(trimethylsilyl)ethoxy)methyl)-5H-pyrrolo[2,3-b]pyrazine-7-carbaldehyde **73**

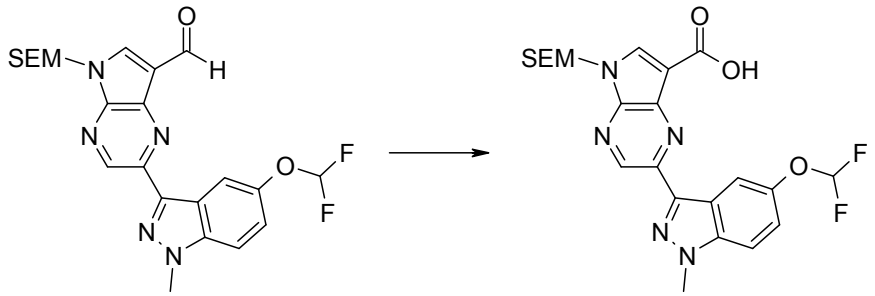


Compound **52** (224 mg, 629 µmol) and **72** (398 mg, 818 µmol) were dissolved in DMF (3 mL) under argon, tetrakis(triphenylphosphine)palladium (0) (36.3 mg, 31.4 µmol) and CuI (24.0 mg, 126 µmol) were added and the mixture sonicated for 5 min while bubbling argon through the solution. The reaction mixture was heated at 90 °C (oil bath temperature) with stirring for 2.5 h. After cooling to room temperature, the reaction mixture was concentrated under high vacuum and the residue was purified by flash chromatography eluting with 0-50% EtOAc in hexanes to give **73** (217 mg, 72.9%) as a light brown solid. LCMS $(M+H)^+$ = 474; ^1H NMR ($CDCl_3$) δ: 10.51 (br. s., 1H), 9.29 (s, 1H), 8.61 (s, 1H), 8.30 (s, 1H), 7.38 - 7.52 (m,

1H), 7.27 - 7.36 (m, 1H), 6.69 (t, *J*=74.8 Hz, 1H), 5.76 (s, 2H), 4.20 (s, 3H), 3.56 - 3.70 (m, 2H), 0.91 - 1.02 (m, 2H), -0.08 - 0.06 (m, 9H).

Step 5

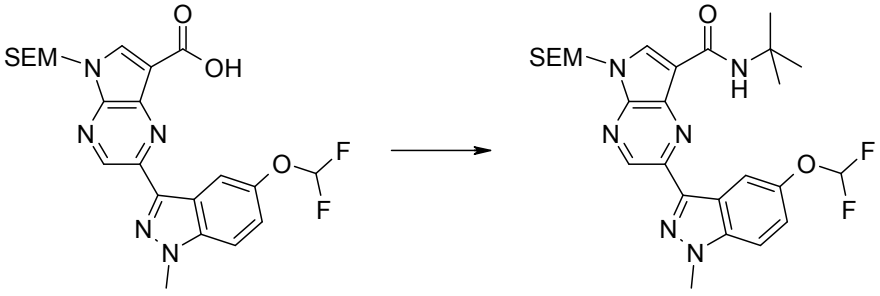
2-(5-(Difluoromethoxy)-1-methyl-1H-indazol-3-yl)-5-((2-(trimethylsilyl)ethoxy)methyl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxylic acid **74**



To a solution of **73** (217 mg, 458 µmol) in dioxane (6.5 mL) and water (2 mL) at 0 °C was added sulfamic acid (267 mg, 2.75 mmol), followed by drop-wise addition of a solution of sodium chlorite (67.3 mg, 596 µmol) and KH_2PO_4 (748 mg, 5.5 mmol) in water (4.5 mL) via dropping funnel over 15 min. The ice bath was removed and the light yellow suspension was stirred at 25 °C for 18 h. THF (6.5 mL) was added to the yellow suspension and the reaction continued at 25 °C for 2 h, then sulfamic acid (267 mg, 2.75 mmol) was added followed by drop-wise addition of sodium chlorite (67.3 mg, 596 µmol) and KH_2PO_4 (748 mg, 5.5 mmol) in water (5 mL). After 2 h the mixture was diluted with water (20 mL) and extracted with dichloromethane (3 x 30 mL). The combined organic layers were dried ($MgSO_4$) and evaporated. The light yellow solid residue was dissolved in dichloromethane/MeOH and the dichloromethane evaporated to promote solid formation and the formed solid separated by filtration, rinsed with MeOH and hexanes then dried to give **74** (127 mg, 57%) as a light yellow solid. LCMS $(M+H)^+$ = 490; ^{1}H NMR (DMSO-d_6) δ: 12.57 (br. s., 1H), 9.12 (s, 1H), 8.69 (s, 1H), 8.65 (d, *J*=2.3 Hz, 1H), 7.80 (d, *J*=9.1 Hz, 1H), 7.35 (dd, *J*=8.9, 2.5 Hz, 1H), 7.20 (t, *J*=74.8 Hz, 1H), 5.71 (s, 2H), 4.18 (s, 3H), 3.58 (t, *J*=7.9 Hz, 2H), 0.84 (t, *J*=7.9 Hz, 2H), -0.21 - -0.01 (s, 9H).

Step 6

N-*tert*-Butyl-2-(5-(difluoromethoxy)-1-methyl-1H-indazol-3-yl)-5-((2-(trimethylsilyl)ethoxy)methyl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide **75**

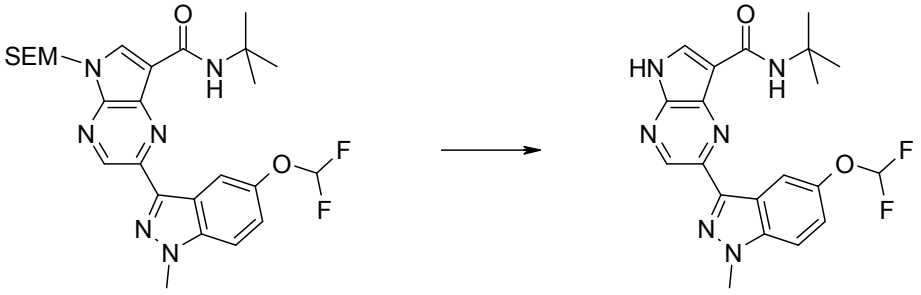


In a 16x100 mm screw cap test tube were added HATU (28.0 mg, 73.5 µmol) and 2-methylpropan-2-amine (17.9 mg, 245 µmol), then **74** (30 mg, 61.3 µmol) dissolved in DMF

(2.0 mL) was added to give a light yellow solution which immediately formed a white precipitated. The reaction mixture stirred at 25 °C overnight. Added additional 2-methylpropan-2-amine (17.9 mg, 245 µmol) and HATU (28.0 mg, 73.5 µmol.20) and the reaction continued at 25 °C for 3 h. Solvents evaporated and residue purified by flash chromatography eluting with 0 to 50% EtOAc in hexanes to yield **75** (33.4 mg, 100%) as an off-white solid. ^{1}H NMR ($CDCl_3$) δ: 9.21 (s, 1H), 8.35 (s, 1H), 8.29 (d, *J*=2.3 Hz, 1H), 8.04 (s, 1H), 7.44 - 7.53 (m, 1H), 7.30 - 7.38 (m, 1H), 7.27 (s, 2H), 6.39 (t, *J*=74.0 Hz, 1H), 5.72 (s, 2H), 4.21 (s, 3H), 3.50 - 3.65 (m, 2H), 1.61 (s, 9H), 0.86 - 1.07 (m, 2H), -0.04 (s, 9H).

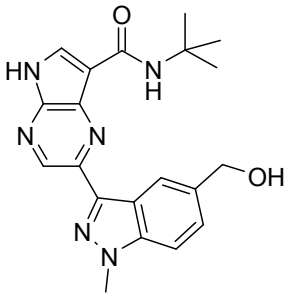
Step 7

2-(5-Difluoromethoxy-1-methyl-1H-indazol-3-yl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxylic acid *tert*-butylamide **14**



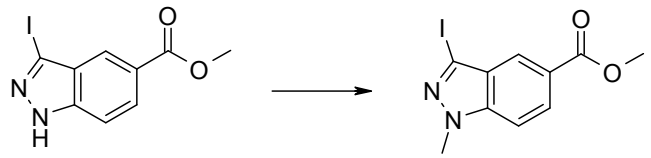
To a pale yellow solution of **75** (33.4 mg, 61.3 µmol) in dichloromethane (1.5 mL) was added TFA (426 mg, 288 µL, 3.74 mmol). The reaction mixture turned orange and was stirred at 25 °C overnight then concentrated. The residue was re-dissolved in a solution of (dichloromethane/MeOH/ammonium hydroxide; 60:10:1) (5 mL) and stirred at 25 °C for 3 h, then evaporated to a light yellow solid that was purified by flash chromatography eluting with 0 to 5% (MeOH containing 10% ammonium hydroxide)/dichloromethane to give **14** (23 mg, 90.5%) as an off-white solid. LCMS $(M+H)^+$ = 415; ^{1}H NMR (DMSO-d_6) δ: 12.80 (br. s., 1H), 9.06 (s, 1H), 8.37 (s, 1H), 8.20 (d, *J*=1.9 Hz, 1H), 7.85 (d, *J*=8.7 Hz, 2H), 7.40 (dd, *J*=8.9, 2.1 Hz, 1H), 7.19 (t, *J*=74.4 Hz,, 1H), 4.19 (s, 3H), 1.49 (s, 9H).

2-(5-Hydroxymethyl-1-methyl-1H-indazol-3-yl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxylic acid *tert*-butylamide **15**



Step 1

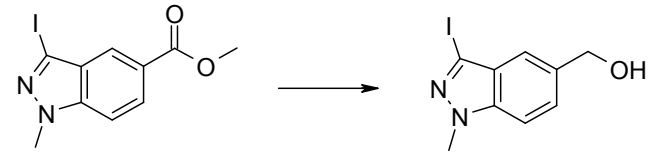
3-Iodo-1-methyl-1H-indazole-5-carboxylic acid methyl ester **76**



To a solution of 3-iodo-1H-indazole-5-carboxylic acid methyl ester (1.0 g, 3.31 mmol, commercially available from Advanced ChemBlocks Inc.) in THF (12 mL) at 0 °C was added KO*t*-Bu (520 mg, 4.63 mmol). The reaction mixture was stirred at 0 °C for 30 min, then added iodomethane (0.29 mL, 4.63 mmol) and stirred at 0 °C for 30 min then warmed to room temperature and stirred for 2 h. The reaction was quenched with water and extracted with EtOAc (2x) then with CH_2Cl_2 (2x). The combined organics were dried over $MgSO_4$ and concentrated to afford 950 mg of **76** as a pale yellow solid. NMR analysis revealed an 8:1 mixture of N1:N2 alkylated regioisomers. Major: ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 8.25 (s, 1H), 8.13 (dd, *J*=8.7, 1.5 Hz, 1H), 7.39 (d, *J*=8.7 Hz, 1H), 4.13 (s, 3H), 3.98 (s, 3H).

Step 2

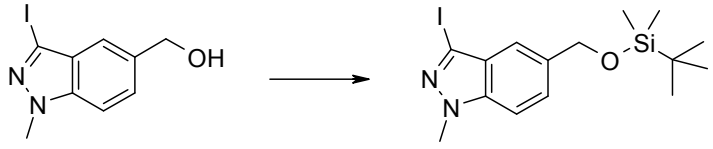
(3-Iodo-1-methyl-1H-indazol-5-yl)-methanol **77**



To a solution of **76** (0.95 g, 3.01 mmol) in CH_2Cl_2 (30 mL) at 0 °C was slowly added DIBAL-H (1.18 mL, 6.61 mmol). The reaction mixture was stirred at 0 °C for 1.5 h then carefully quenched with MeOH (1 mL), diluted with CH_2Cl_2 (20 mL) and added saturated aqueous solution of sodium and potassium tartrate (30 mL). The biphasic mixture was stirred vigorously at room temperature for 1 h. The layers were separated and the aqueous phase was extracted with CH_2Cl_2. The combined organic layers were washed with water, dried over $MgSO_4$ and concentrated to afford 810 mg of **77** as a yellow waxy solid. ^{1}H NMR (CHLOROFORM-d) δ: 7.46 - 7.55 (m, 1H), 7.39 (dd, J = 8.6, 0.8 Hz, 1H), 4.85 (s, 2H), 4.12 (s, 3H).

Step 3

5-(*tert*-Butyl-dimethylsilanyloxymethyl)-3-iodo-1-methyl-1H-indazole **78**

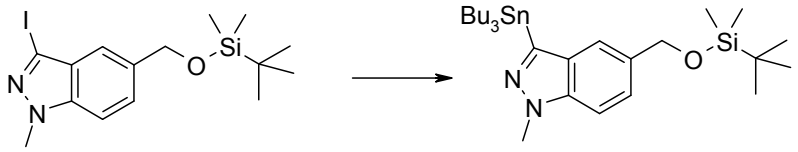


To a solution of **77** (810 mg, 2.81 mmol) in DMF (9 mL) was added imidazole (479 mg, 7.03 mmol) followed by *tert*-butyldimethylsilyl chloride (466 mg, 3.09 mmol). The reaction mixture was stirred at room temperature overnight then quenched with water and extracted with EtOAc (2x). The combined organics were washed with water (3x) then dried over $MgSO_4$ and concentrated. The residue was purified by flash chromatography eluting with 10% EtOAc/hexanes to afford **78** (732 mg, 65%) as a pale yellow solid. ^{1}H NMR ($CDCl_3$,

300 MHz) δ: 7.26 - 7.34 (m, 2H), 7.17 - 7.23 (m, 1H), 4.73 (s, 2H), 3.97 (s, 3H), 0.84 (s, 9H), 0.00 (s, 6H).

Step 4

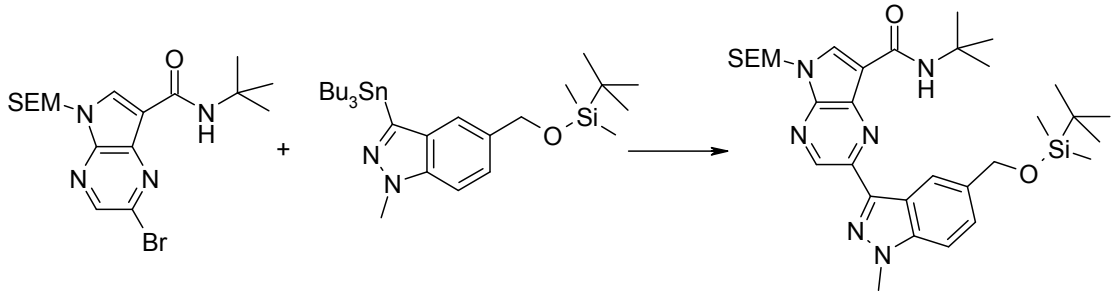
5-(*tert*-Butyl-dimethyl-silanyloxymethyl)-1-methyl-3-tributylstannanyl-1H-indazole **79**



To a solution of **78** (201 mg, 0.50 mmol) in THF (3 mL) at -10 °C (ice/acetone bath) was added isopropylmagnesium chloride 2.0 M in THF (0.30 mL, 0.60 mmol). The pale yellow reaction mixture was stirred at -10 °C for 20 min then tributylchlorostannane (0.16 mL, 0.60 mmol) was added. Stirring was continued at -10 °C for 30 min then at room temperature for 1 h. The reaction was quenched with water and extracted with EtOAc (2x). The combined organics were dried over $MgSO_4$ and concentrated to give **79** as a colorless oil which was used immediately into the next step without further purification.

Step 5

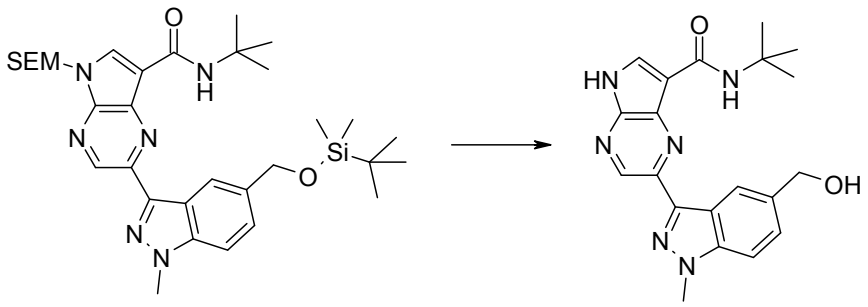
2-[5-(*tert*-Butyl-dimethyl-silanyloxymethyl)-1-methyl-1H-indazol-3-yl]-5-(2-trimethylsilanyl-ethoxymethyl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxylic acid *tert*-butylamide **80**



To a solution of **79** (265 mg, 0.47 mmol) and **60** (100 mg, 0.23 mmol) in DMF (2 mL) were added $Pd(PPh_3)_4$ (14 mg, 0.012 mmol) and copper (I) iodide (9 mg, 0.047 mmol). The reaction mixture was heated at 90 °C for 1 h then cooled to room temperature, quenched with water and extracted with EtOAc (2x). The combined organics were washed with water (3x), brine then dried over $MgSO_4$ and concentrated. The residue was adsorbed on silica gel and purified by flash chromatography eluting with 20 to 50% EtOAc/hexanes to give **80** (106 mg, 73%) as a beige solid. ^{1}H NMR (CHLOROFORM-d) δ: 9.22 (s, 1H), 8.40 (s, 1H), 8.35 (s, 1H), 8.25 (s, 1H), 7.41 - 7.68 (m, 2H), 7.29 (s, 1H), 5.76 (s, 2H), 4.92 (s, 2H), 4.23 (s, 3H), 3.40 - 3.86 (m, 2H), 1.64 (s, 9H), 0.77 - 1.09 (m, 11H), 0.15 (s, 6H), 0.00 (s, 9H).

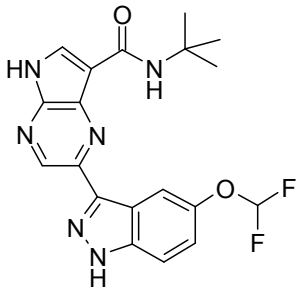
Step 6

2-(5-Hydroxymethyl-1-methyl-1H-indazol-3-yl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxylic acid *tert*-butylamide **15**



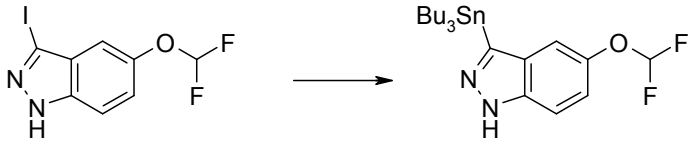
To a solution of **80** (106 mg, 0.17 mmol) in THF (2 mL) was added tetrabutylammonium fluoride (1.0 M in THF, 1.7 mL, 1.7 mmol). The reaction mixture was stirred at room temperature for 10 min then heated at reflux for 2 h. After cooling to room temperature, the reaction was quenched with water and extracted with EtOAc and then with 5% $MeOH/CH_2Cl_2$. The combined organic layers were dried over $MgSO_4$ and concentrated. The residue was triturated with EtOAc/MeOH and the solids collected via filtration and dried to afford **15** (30 mg, 47%) as a light yellow solid. LCMS $(M+Na)^+ = 401$; ^1H NMR (DMSO-d_6, 300 MHz) δ: 12.76 (br. s., 1H), 9.04 (s, 1H), 8.35 (s, 1H), 8.31 (s, 1H), 8.00 (s, 1H), 7.71 (d, *J*=8.7 Hz, 1H), 7.48 (d, *J*=8.7 Hz, 1H), 5.20 (t, *J*=5.5 Hz, 1H), 4.64 (d, *J*=5.3 Hz, 2H), 4.16 (s, 3H), 1.49 (s, 9H).

2-(5-Difluoromethoxy-1H-indazol-3-yl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxylic acid *tert*-butylamide **16**



Step 1

5-(Difluoromethoxy)-3-(tributylstannyl)-1H-indazole **81**

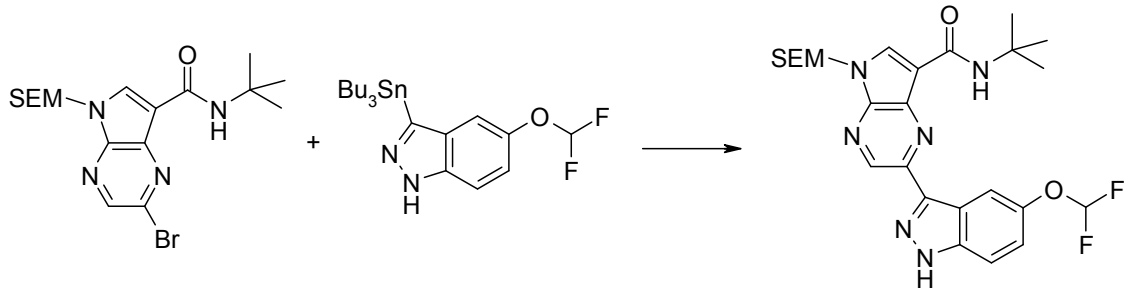


In a round-bottomed flask, a solution of **70** (1.2 g, 2.93 mmol) in THF (30 mL) was cooled to -25 ^oC. Isopropylmagnesium chloride 1M in THF (8.8 mL, 8.8 mmol) was added drop-wise at -25 ^oC. The reaction mixture was stirred at -25 ^oC for 20 min. Then chlorotributyltin (1.6 mL, 5.86 mmol) was added slowly. The reaction mixture was allowed to warm to room temperature and stirred for 1.5 h. The reaction mixture was quenched with saturated NH_4Cl solution and then extracted with EtOAc (3×20 mL), organics were washed with water (10

mL), brine (2×10 mL), dried over Na_2SO_4 and concentrated. The residue was purified by flash chromatography eluting with petroleum ether:EtOAc (8:1) to give **81** (1.1 g, 79%) as an oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.52 - 7.46 (m, 2H), 7.19 (d, 1H, *J*=7.9 Hz), 6.51 (t, 1H, *J*=88.6 Hz), 1.68 - 1.57 (m, 6H), 1.45 - 1.14 (m, 12H), 0.93 - 0.84 (m, 9H).

Step 2

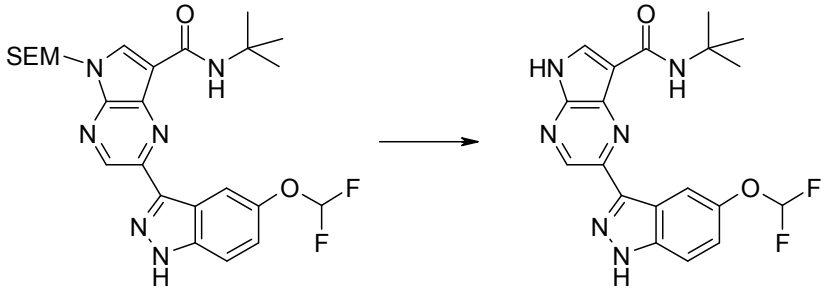
N-tert-Butyl-2-(5-(difluoromethoxy)-1H-indazol-3-yl)-5-((2-(trimethylsilyl)ethoxy)methyl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide **82**



In a 25 mL round-bottomed flask, **60** (220 mg, 515 µmol) and **81** (268 mg, 566 µmol) were dissolved in DMF (1.0 mL) under argon, tetrakis(triphenylphosphine)palladium (0) (29.7 mg, 25.7 µmol) and CuI (19.6 mg, 103 µmol) were added and the mixture sonicated for 5 min while bubbling argon through the solution. The reaction mixture was stirred at 90 °C (oil bath temperature) for 2.5 h. The reaction mixture was concentrated under high vacuum and the residue was purified by flash chromatography eluting with 0-50% EtOAc in hexanes to give **82** (159 mg, 58.2%) as an off-white solid. LCMS $(M+Na)^+$ = 553; ^{1}H NMR ($CDCl_3$) δ: 10.74 (br. s., 1H), 9.29 (s, 1H), 8.42 (s, 1H), 8.36 (d, *J*=2.3 Hz, 1H), 8.09 (s, 1H), 7.64 (d, *J*=9.1 Hz, 1H), 7.40 (dd, *J*=8.9, 2.1 Hz, 1H), 6.57 (t, *J*=74.0 Hz, 1H), 5.76 (s, 2H), 3.56 - 3.70 (m, 2H), 1.67 (s, 9H), 0.92 - 1.04 (m, 2H), 0.00 (s, 9H).

Step 3

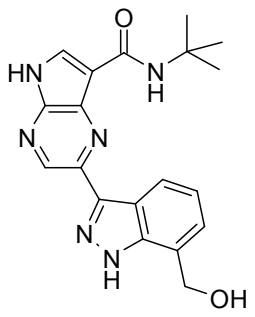
N-tert-Butyl-2-(5-(difluoromethoxy)-1H-indazol-3-yl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide **16**



To a pale yellow solution of **82** (55 mg, 104 µmol) in dichloromethane (3 mL) was added TFA (1 mL, 13.0 mmol), the reaction mixture turned orange and was stirred at 25 °C overnight then concentrated. The residue was re-dissolved in a solution of (dichloromethane/MeOH/ammonium hydroxide; 60:10:1) (5 mL) and stirred at 25 °C for 3 h, then evaporated to a light yellow solid. The solid was purified by flash chromatography eluting with 0 to 5% (MeOH containing 10% ammonium hydroxide)/dichloromethane to give

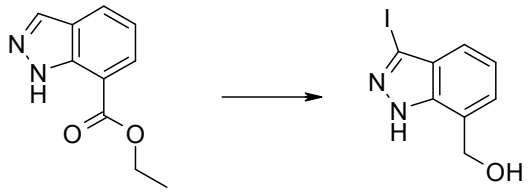
16 (26 mg, 62.7%) as a white solid. LCMS $(M+H)^+$ = 401.1; ^{1}H NMR (DMSO-d_6) δ: 9.12 (s, 1H), 8.36 (s, 1H), 8.21 (d, *J*=2.3 Hz, 1H), 7.88 (s, 1H), 7.72 (d, *J*=9.1 Hz, 1H), 7.35 (dd, *J*=9.1, 2.3 Hz, 1H), 7.17 (t, *J*=74.4 Hz,, 1H), 1.50 (s, 9H).

2-(7-Hydroxymethyl-1H-indazol-3-yl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxylic acid *tert*-butylamide **17**



Step 1

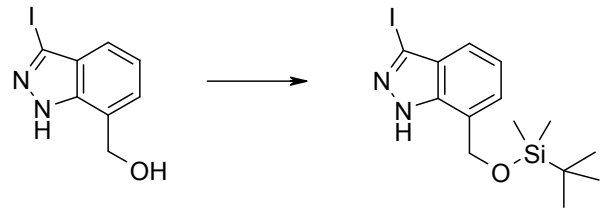
(3-Iodo-1H-indazol-7-yl)-methanol **83**



In a round-bottomed flask, ethyl 1H-indazole-7-carboxylate (600 mg, 3.15 mmol, available commercially from Chem-Impex International, Inc.) was dissolved in THF (16 mL). The light yellow solution was cooled to 0 °C and lithium aluminum hydride (1.0 M in THF, 3.8 mL, 3.8 mmol) was added drop-wise. The bright yellow reaction mixture was stirred at 0 °C for 1.25 h then sodium sulfate decahydrate was carefully added. When gas evolution had stopped, the ice bath was removed, sodium sulfate was added and the mixture was stirred for 30 min at room temperature. The suspension was filtered over celite and rinsed with ethyl acetate/methanol and the filtrate was concentrated. Crude (1H-indazol-7-yl)-methanol (572 mg, 3.09 mmol) dissolved in DMF (8 mL) was treated with potassium hydroxide (671 mg, 12.0 mmol) and iodine (1.57 g, 6.18 mmol. The dark brown suspension was stirred at room temperature overnight then quenched with aqueous 10% $Na_2S_2O_3$ and extracted with diethyl ether (2x). The combined organic layers were washed twice with water and once with brine then dried over sodium sulfate, filtered and concentrated to give **83** (433 mg, 50% for two steps) as a light yellow solid. ^{1}H NMR (CHLOROFORM-d) δ: 7.46 (d, J = 7.9 Hz, 1H), 7.09 - 7.26 (m, 2H), 5.11 (s, 2H).

Step 2

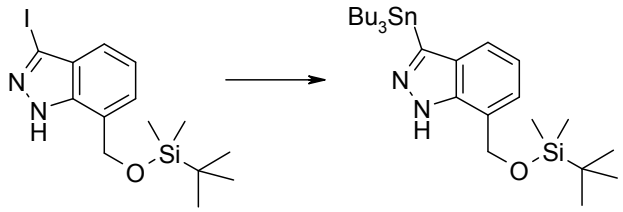
7-(*tert*-Butyl-dimethyl-silanyloxymethyl)-3-iodo-1H-indazole **84**



In a round-bottomed flask, **83** (317 mg, 1.16 mmol) was dissolved in DMF (3.6 mL) and imidazole (197 mg, 2.89 mmol) and *tert*-butyldimethylsilyl chloride (192 mg, 1.27 mmol) were added. The reaction mixture was stirred at room temperature for 72 h then quenched with water and extracted with diethyl ether (2x). The combined organic layers were washed twice with water and once with brine then dried over sodium sulfate, filtered and concentrated. The residue was purified by flash chromatography eluting with 0-5% EtOAc/hexanes to give **84** (357 mg, 80%) as an off-white solid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: (ppm) 10.76 (br. s., 1H), 7.42 (dd, *J*=6.8, 2.3 Hz, 1H), 7.15 - 7.20 (m, 2H), 5.09 (s, 2H), 0.95 (s, 9H), 0.13 (s, 6H).

Step 3

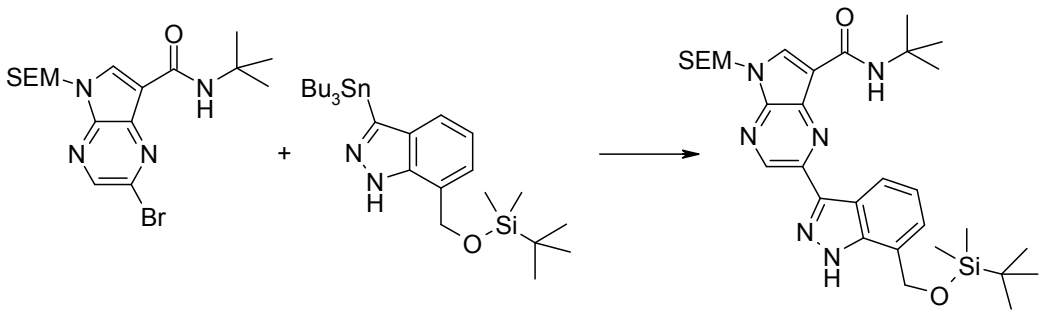
7-(*tert*-Butyl-dimethyl-silanyloxymethyl)-3-tributylstannanyl-1H-indazole **85**



In a round-bottomed flask, **84** (200 mg, 0.52 mmol) was dissolved in THF (2.8 mL) and sodium hydride (60% in mineral oil, 25 mg, 0.63 mmol) was added. The reaction mixture was stirred at room temperature for 10 min then cooled to -16 °C (NaCl/ice bath) and isopropylmagnesium chloride (2.0 M in THF, 0.36 mL, 0.72 mmol) was added drop-wise. The reaction mixture was stirred at -16 °C for 30 min then tributylchlorostannane (0.16 mL, 0.59 mmol) was slowly added. The reaction mixture was allowed to warm to room temperature and stirred for 2.5 h then quenched with saturated aqueous NH_4Cl and extracted with EtOAc (2x). The organic layers were washed with water and brine then dried over sodium sulfate, filtered and concentrated to give **85** as a yellow oil which was used immediately into the next step without further purification.

Step 4

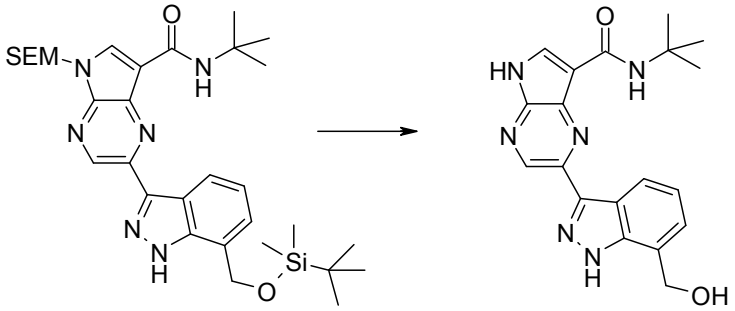
2-[7-(*tert*-Butyl-dimethyl-silanyloxymethyl)-1H-indazol-3-yl]-5-(2-trimethylsilanyl-ethoxymethyl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxylic acid *tert*-butylamide **86**



In a 25 mL round-bottomed flask, **60** (180 mg, 0.42 mmol) and **85** (462 mg, 0.50 mmol) were dissolved in DMF (2.8 mL). The reaction mixture was evacuated and backfilled with argon and tetrakis(triphenylphosphine)palladium (0) (25 mg, 0.022 mmol) and copper (I) iodide (16 mg, 0.084 mmol) were added. The reaction mixture was stirred at 80 °C overnight then cooled to room temperature, quenched with water and extracted with diethyl ether (2x). The combined organic layers were washed twice with water and once with brine then concentrated. The residue was purified by flash chromatography eluting with 0-30% EtOAc/hexanes to afford **86** (86 mg, 34%) as a light yellow solid. ^{1}H NMR (CHLOROFORM-d) δ: 9.33 (s, 1H), 8.54 (dd, J = 6.2, 2.9 Hz, 1H), 8.41 (s, 1H), 8.23 (s, 1H), 7.16 - 7.28 (m, 2H), 5.76 (s, 2H), 5.20 (s, 2H), 3.52 - 3.72 (m, 2H), 1.67 (s, 9H), 0.91 - 1.09 (m, 11H), 0.22 (s, 6H), 0.00 (s, 9H).

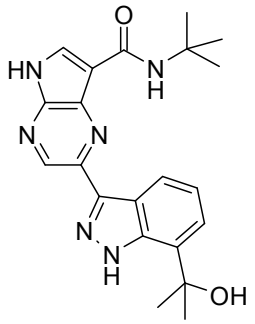
Step 5

2-(7-Hydroxymethyl-1H-indazol-3-yl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxylic acid *tert*-butylamide **17**



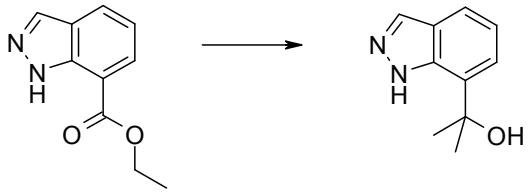
In a round-bottomed flask, **86** (85 mg, 0.14 mmol) was dissolved in THF (0.7 mL) and tetrabutylammonium fluoride (1.0 M in THF, 1.4 mL, 1.4 mmol) was added drop-wise. The light brown solution was stirred at room temperature for 10 min then heated at 70 °C for 2.5 h. The reaction mixture was cooled to room temperature, quenched with water and extracted with EtOAc (2x). The combined organic layers were washed with water and brine then dried over sodium sulfate, filtered and concentrated. The residue was adsorbed on silica gel and purified by flash chromatography eluting with 0 to 10% (MeOH containing 10% ammonium hydroxide)/dichloromethane to afford **17** (21 mg, 41%) as an off-white powder. LCMS $(M+Na)^+$ = 387; ^{1}H NMR (DMSO-d_6, 400 MHz) δ: (ppm) 13.49 (s, 1H), 12.77 (s, 1H), 9.15 (s, 1H), 8.39 (d, *J*=8.1 Hz, 1H), 8.36 (d, *J*=3.0 Hz, 1H), 8.01 (s, 1H), 7.38 - 7.46 (m, 1H), 7.16 - 7.25 (m, 1H), 5.37 (t, *J*=5.6 Hz, 1H), 4.88 (d, *J*=5.6 Hz, 2H), 1.53 (s, 9H).

2-[7-(1-Hydroxy-1-methyl-ethyl)-1H-indazol-3-yl]-5H-pyrrolo[2,3-b]pyrazine-7-carboxylic acid *tert*-butylamide **18**



Step 1

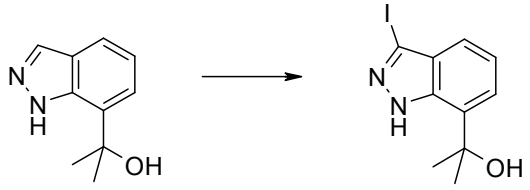
2-(1H-Indazol-7-yl)-propan-2-ol **87**



In a 50 mL round-bottomed flask, ethyl 1H-indazole-7-carboxylate (350 mg, 1.84 mmol) was dissolved in THF (10 mL). The yellow solution was cooled to 0 °C and methylmagnesium bromide (3.0 M in diethyl ether, 2.2 mL, 6.6 mmol) was added drop-wise. The reaction mixture was stirred at 0 °C for 1.5 h then quenched with saturated aqueous NH_4Cl and extracted with EtOAc (2x). The combined organic layers were washed with water and brine then dried over sodium sulfate, filtered and concentrated. The residue was purified by flash chromatography eluting with 0 to 50% EtOAc/hexanes to afford **87** (225 mg, 69%) as a yellow oil. ^{1}H NMR (CHLOROFORM-d) δ: 8.08 (s, 1H), 7.67 (dd, J = 7.7, 1.3 Hz, 1H), 7.06 - 7.21 (m, 2H), 1.75 (s, 6H).

Step 2

2-(3-Iodo-1H-indazol-7-yl)-propan-2-ol **88**

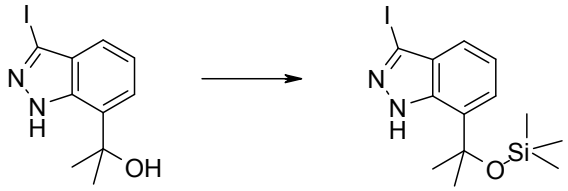


In a round-bottomed flask, **87** (204 mg, 1.16 mmol) was dissolved in DMF (3 mL) then iodine (588 mg, 2.32 mmol) and potassium hydroxide (251 mg, 4.48 mmol) were added. The dark brown suspension was stirred at room temperature for 5 h then quenched with 10% aqueous $NaHSO_3$ and extracted with a mixture of diethyl ether and EtOAc (2x). The combined organic layers were washed twice with water and once with brine then dried over sodium sulfate, filtered and concentrated to afford **88** (479mg, 95.7%) as a light yellow oil

which was used into the next step without further purification. ^{1}H NMR (CHLOROFORM-d) δ: 8.03 (s, 2H), 7.42 (dd, J = 7.6, 1.5 Hz, 1H), 7.09 - 7.24 (m, 2H), 1.91 (br. s., 2H), 1.73 (s, 6H).

Step 3

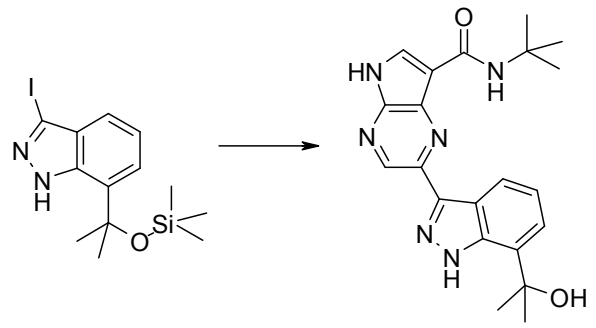
3-Iodo-7-(1-methyl-1-trimethylsilanyloxy-ethyl)-1H-indazole **89**



In a round-bottomed flask, **88** (479 mg, 1.11 mmol) was dissolved in DMF (3.2 mL) then imidazole (189 mg, 2.77 mmol) and trimethylsilyl chloride (0.17 mL, 1.33 mmol) were added. The reaction mixture was stirred at room temperature overnight then quenched with water and extracted with diethyl ether (2x). The combined organic layers were washed twice with water and once with brine then dried over sodium sulfate, filtered and concentrated to give **89** (383 mg, 88%) as a light yellow solid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: (ppm) 10.86 (br. s., 1H), 7.40 (dd, *J*=6.8, 2.3 Hz, 1H), 7.12 - 7.21 (m, 2H), 1.73 (s, 6H), 0.11 (s, 9H).

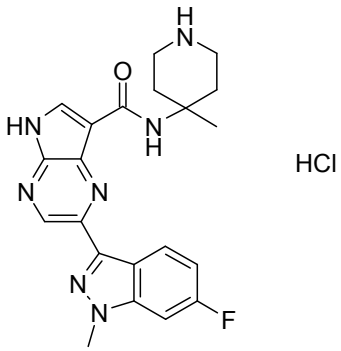
Step 4

2-[7-(1-Hydroxy-1-methyl-ethyl)-1H-indazol-3-yl]-5H-pyrrolo[2,3-b]pyrazine-7-carboxylic acid *tert*-butylamide **18**



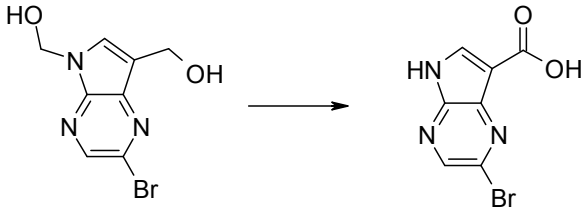
Prepared according to the procedure outlined for compound **17**, steps 3-5, substituting in step 3, **84** by **89** to ultimately produce **18**. LCMS $(M+Na)^+$ = 415; ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 13.08 (s, 1H), 12.78 (br. s., 1H), 9.14 (s, 1H), 8.39 (d, *J*=7.8 Hz, 1H), 8.35 (s, 1H), 8.03 (s, 1H), 7.35 (d, *J*=6.3 Hz, 1H), 7.16 (t, *J*=7.7 Hz, 1H), 5.49 (s, 1H), 1.64 (s, 6H), 1.53 (s, 9H).

2-(6-Fluoro-1-methyl-1H-indazol-3-yl)-*N*-(4-methylpiperidin-4-yl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide hydrochloride **19**



Step 1

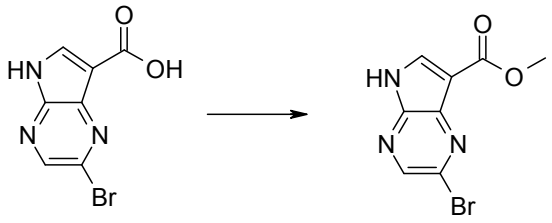
2-Bromo-5H-pyrrolo[2,3-b]pyrazine-7-carboxylic acid **90**



To a stirred solution of **50** (0.525 g, 2.03 mmol) in acetone (200 mL) at 40°C was added a solution of CrO_3 (0.832 g, 8.32 mmol) and H_2SO_4 (1.32 g, 13.4 mmol) in water (3 ml). The reaction was stirred at 40 °C for 16 h then filtered through celite. The filtrate was evaporated under reduced pressure to give **90** (0.492 g, 100 %) as an off-white solid. LCMS $(M+H)^+$ = 264; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 13.04 (s, 1H), 8.53 (s, 1H), 8.45 (s, 1H), 5.63 (s, 1H).

Step 2

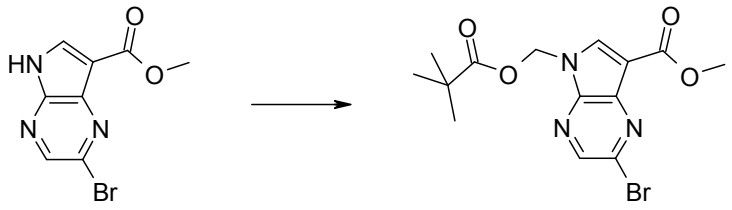
2-Bromo-5H-pyrrolo[2,3-b]pyrazine-7-carboxylic acid methyl ester **91**



To a stirred solution of **90** (0.527 g, 2.18 mmol) in methanol (50 mL) was added slowly at room temperature H_2SO_4 (1.5 mL). The reaction mixture was heated to reflux with stirring for 16 h. The solvents were evaporated under reduced pressure and the residue was suspended in water (5 mL) and neutralized (pH = 7) with solid $NaHCO_3$. The product was extracted with ethyl acetate (90 mL), the organic phase was washed with water (20 mL), brine (20 mL) and dried over anhydrous sodium sulfate and concentrated. The residue was purified by flash chromatography eluting with petroleum ether:ethyl acetate (1:1) to give **91** (0.24 g, 43 %) as a white solid. LCMS $(M+H)^+$ = 278; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 8.62 (s, 1H), 8.48 (s, 1H), 3.91 (s, 3H).

Step 3

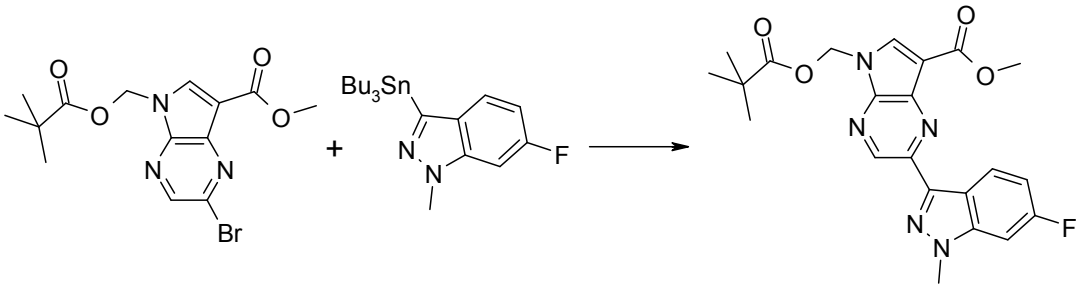
Methyl 2-bromo-5-(pivaloyloxymethyl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxylate **92**



To a stirred mixture of **91** (0.24 g, 0.94 mmol) and K_2CO_3 (0.156 g, 1.13 mmol) in DMF (10 mL) was added chloromethyl pivalate (0.17 g, 1.13 mmol) drop-wise at room temperature. The mixture was stirred at room temperature for 16 h and then the mixture was poured into water (30 mL), extracted with ethyl acetate (90 mL). The organic phase was washed with brine (10 mL), dried over Na_2SO_4 and concentrated. The residue was purified by flash chromatography eluting with ethyl acetate:petroleum ether (1:1) to give **92** (0.276 g, 79.5 %) as a pale yellow solid. LCMS $(M+H)^+ = 370$; ^1H NMR (300 MHz, $CDCl_3$): δ 8.42 (s, 1H), 8.38 (s, 1H), 6.21 (s, 2H), 3.96 (s, 3H), 1.15 (s, 9H).

Step 4

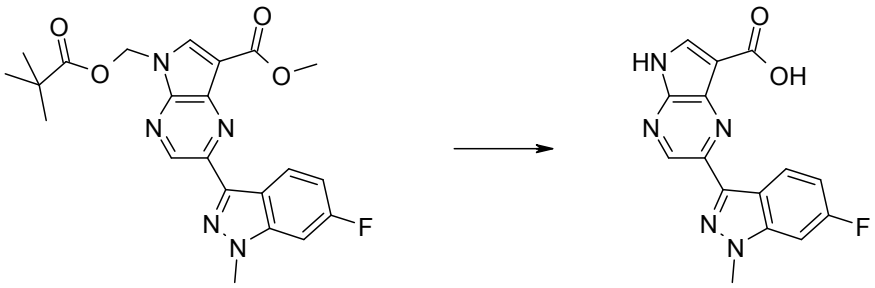
Methyl 2-(6-fluoro-1-methyl-1H-indazol-3-yl)-5-(pivaloyloxymethyl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxylate **93**



To a stirred solution of **62** (0.51 g, 0.616 mmol) and **92** (0.18 g, 0.486 mmol) in DMF (6 mL) were added CuI (0.04 g, 0.21 mmol) and $Pd(PPh_3)_4$ (0.057 g, 0.045 mmol) in one portion under nitrogen at room temperature. The reaction mixture was degassed by bubbling nitrogen for 10 minutes and then heated to 90 ^oC under nitrogen with stirring for 16 h. The solvent was evaporated under reduced pressure and the residue was purified by flash chromatography eluting with ethyl acetate:petroleum ether (1:1) to give **93** (0.182 g, 85.2 %) as a yellow solid. LCMS $(M+H)^+ = 440$; ^1H NMR (300 MHz, DMSO-d_6): δ 9.13 (s, 1H), 8.83 - 8.78 (m, 1H), 8.70 (s, 1H), 7.63 (dd, 1H, J1 = 9.6 Hz, J2 = 2.1 Hz), 7.23 (dt, 1H, J1 = 9.3 Hz, J2 = 2.1 Hz), 6.30 (s, 2H), 4.13 (s, 3H), 3.92 (s, 3H), 1.08 (s, 9H).

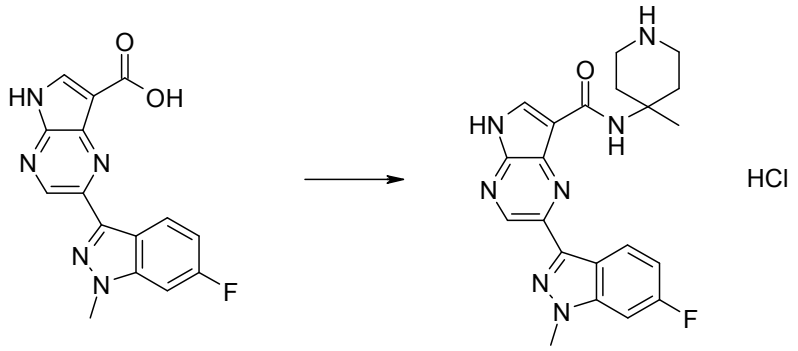
Step 5

2-(6-Fluoro-1-methyl-1H-indazol-3-yl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxylic acid **94**



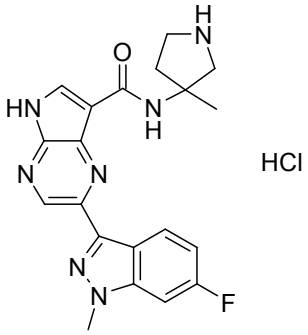
A mixture of **93** (0.24 g, 0.546 mmol), KOH (0.611 g, 10.9 mmol), water (4 mL) and dioxane (10 mL) was heated to 100 ^{o}C with stirring for 5 h. After cooling to room temperature the reaction mixture was acidified with 1N HCl to pH= 2. The solvent was evaporated under reduced pressure and the residue was triturated with water (10 mL), then decanted and dried under reduced pressure to give **94** (0.161 g, 94.8 %) as a yellow solid. LCMS $(M+H)^+$ = 312.0, $[M + Na]^+$ 334.0; ^{1}H NMR (300 MHz, DMSO-d_6): δ 12.87 (s, 1H), 12.28 (s, 1H), 9.05 (s, 1H), 8.82 (dd, 1H, J1 = 9.0 Hz, J2 = 5.7 Hz), 8.48 (d, 1H, J = 2.7 Hz), 7.61 (dd, 1H, J1 = 10.2 Hz, J2 = 2.7 Hz), 7.15 (t, 1H, J = 12.0 Hz), 4.12 (s, 3H).

2-(6-Fluoro-1-methyl-1H-indazol-3-yl)-*N*-(4-methylpiperidin-4-yl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide hydrochloride **19**

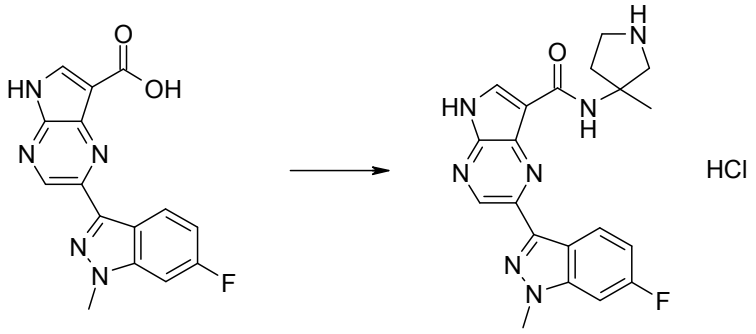


To a stirred solution of **94** (100 mg, 0.32 mmol) in DMF (10 mL) were added EDCI (122 mg, 0.64 mmol), *tert*-butyl 4-amino-4-methylpiperidine-1-carboxylate (103 mg, 0.48 mmol, available commercially from AstaTech, Inc) and DMAP (78 mg, 0.64 mmol) in one portion at room temperature. The reaction mixture was stirred for 16 hours, then was poured into 50 mL of water. The solid formed was separated by filtration, the filter cake was washed with water (10 mL) and passed through a pad of silica gel eluting with petroleum ether:ethyl acetate (1:2). The crude *tert*-butyl 4-(2-(6-fluoro-1-methyl-1H-indazol-3-yl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxamido)-4-methylpiperidine-1-carboxylate (100 mg, 0.20 mmol) was dissolved in a saturated solution of HCl (g) in dioxane (30 mL) and the mixture was stirred at room temperature for 16 hours. The solid formed during the reaction was separated by filtration, the filter cake washed with dichloromethane (20 mL), diethyl ether (30 mL) and dried to give **19** (29 mg, 20.4 % for two steps) as a white solid. LCMS $(M+H)^+$ = 408; ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.16 (s, 1H), 8.57 - 8.41 (m, 4H), 7.92 (s, 1H), 7.75 (d, 1H, *J*=10.5 Hz), 7.32 - 7.26 (m, 1H), 6.98 - 6.93 (m, 1H), 5.75 (d, 2H, *J*=6.9 Hz), 4.19 (s, 3H), 3.16 (brs, 5H), 1.96 (*br*s, 3H), 1.61 (s, 3H).

2-(6-Fluoro-1-methyl-1H-indazol-3-yl)-*N*-(3-methylpyrrolidin-3-yl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide hydrochloride **20**

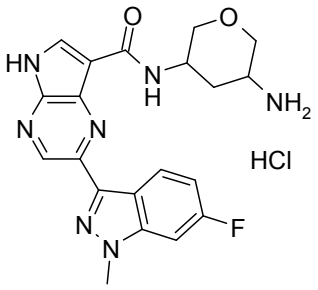


2-(6-Fluoro-1-methyl-1H-indazol-3-yl)-*N*-(3-methylpyrrolidin-3-yl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide hydrochloride **20**



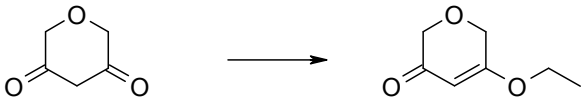
To a stirred solution of **94** (100 mg, 0.32 mmol) in DMF (6 mL) were added EDCI (123 mmol, 0.64 mmol), DMAP (110 mg, 0.90 mmol) and *tert*-butyl 3-amino-3-methylpyrrolidine-1-carboxylate (128 mg, 0.64 mmol, available commercially from Advanced ChemBlocks Inc.) in one portion at room temperature and the mixture stirred for 16 hours. The solvent was evaporated under reduced pressure, the residue was triturated with petroleum ether then decanted and dried. The crude *tert*-butyl 4-(2-(6-fluoro-1-methyl-1H-indazol-3-yl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxamido)-4-methylpiperidine-1-carboxylate (103 mg, 0.20 mmol) was dissolved in a saturated solution of HCl (g) in dioxane (20 mL) and the mixture was stirred at room temperature for 2 hours. The solvent was evaporated under reduced pressure and the residue was purified by preparative-HPLC (Gemini 5u C18 150×21.2 mm; inject volume: 3 mL/inj, flow rate: 20 mL/min; wavelength: 214 nm and 254 nm; gradient: 20% acetonitrile/80% water (0.1% trifluoroacetic acid) to 40% acetonitrile/60% water (0.1% trifluoroacetic acid) in a linear fashion over 9 min). The pure product was treated with concentrated HCl (1 mL), stirred for 5 min, filtered and dried to afford **20** (30 mg, 21.7 % for two steps) as a pale yellow solid. LCMS $(M+H)^+ = 408$; ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.16 (s, 1H), 8.57 - 8.41 (m, 4H), 7.92 (s, 1H), 7.75 (d, 1H, *J*=10.5 Hz), 7.32 - 7.26 (m, 1H), 6.98 - 6.93 (m, 1H), 5.75 (d, 2H, *J*=6.9 Hz), 4.19 (s, 3H), 3.16 (brs, 5H), 1.96 (brs, 3H), 1.61 (s, 3H).

N-(5-Amino-tetrahydro-2H-pyran-3-yl)-2-(6-fluoro-1-methyl-1H-indazol-3-yl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide hydrochloride **21**



Step 1

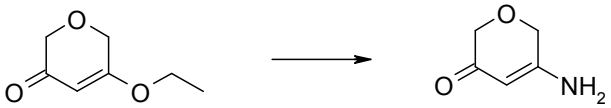
5-Ethoxy-2H-pyran-3(6H)-one **95**



To a solution of 2H-pyran-3,5(4H,6H)-dione, sodium salt (1.36 g, 10 mmol) in ethanol (50 mL) was added concentrated sulphuric acid (1.5 mL) and the reaction mixture was stirred at room temperature overnight. Most of the solution was evaporated under vacuum, the residue was neutralized with saturated sodium bicarbonate, product extracted with ethyl acetate (4 × 50 mL), organics combined dried with sodium sulfate, filtered and concentrated. The residue was purified by flash chromatography eluting with ethyl acetate:petroleum ether (1:1) to afford **95** (641 mg, 45%) as yellow solid. LCMS $(M+H)^+ = 143$; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 5.44 (s, 1H), 4.25 (s, 2H), 4.06 (s, 2H), 3.98 (*q*, 2H, *J* = 6.9 Hz), 1.38 (*t*, 3H, *J* = 6.9 Hz).

Step 2

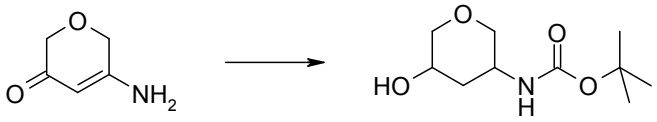
5-Amino-2H-pyran-3(6H)-one **96**



A solution of **95** (641 mg, 4.5 mmol) in 50 mL of ethanol was cooled in a dry ice bath, and then ammonia (g) was bubbled with stirring for 10 min. The reaction mixture was stirred at room temperature overnight, then concentrated to dryness and purified by flash chromatography eluting with 10% methanol in dichloromethane to afford **96** (290 mg, 57%) as pale yellow solid. LCMS $(M+H)^+ = 114$; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 4.99 (s, 1H), 4.17 (s, 2H), 3.79 (s, 2H).

Step 3

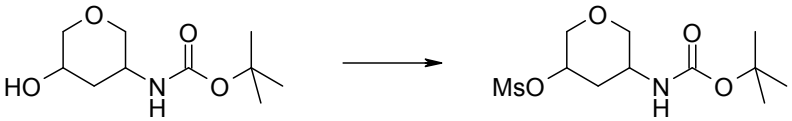
tert-Butyl 5-hydroxy-tetrahydro-2H-pyran-3-ylcarbamate **97**



A hydrogenation bottle was charged with a mixture of **96** (290 mg, 2.6 mmol) and 500 mg of wet Raney nickel in ethanol (20 mL). The mixture was shook for 6 hours under 4 atm hydrogen gas at 60 °C. The reaction mixture was cooled to room temperature, filtered over celite, the filtrate was concentrated to dryness. Crude 5-amino-tetrahydro-2H-pyran-3-ol (389 mg, about 3.3 mmol) was mixed with di-*tert*-butyl dicarbonate (700 mg, 3.3 mmol) and TEA (0.5 mL, 3.3 mmol) in THF (40 mL) and the mixture was stirred for 4 h at room temperature, then concentrated to dryness and the residue purified by flash chromatography eluting with ethyl acetate:petroleum ether (1:1) to afford **97** (400 mg, 56%) as pale yellow solid. LCMS $(M+H)^+ = 240$; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 4.78 - 4.72 (m, 1H), 3.94 - 3.85 (m, 2H), 3.77 - 3.59 (m, 3H), 3.47 - 3.33 (m, 2H), 1.92 - 1.85 (m, 2H), 1.42 (s, 9H).

Step 4

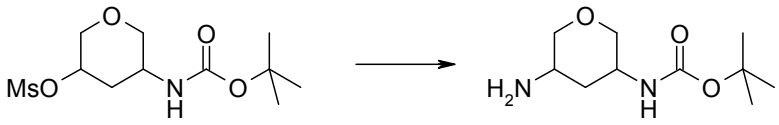
5-(*tert*-Butoxycarbonylamino)-tetrahydro-2H-pyran-3-yl methanesulfonate **98**



A solution of **97** (109 mg, 0.5 mmol) and DMAP (80 mg, 0.65 mmol) in dichloromethane (10 mL) was cooled in an ice bath, methanesulfonyl chloride (0.05 mL, 0.6 mmol) was added drop-wise. The reaction mixture was stirred overnight at room temperature, after that time was quenched with water (50 mL), and extracted with dichloromethane. The organic phase was dried with sodium sulfate filtered and concentrated. The residue was purified by flash chromatography eluting with ethyl acetate:petroleum ether (1:1) to afford **98** (100 mg, 67%) as white solid. LCMS $(M+H)^+ = 318$; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 4.89 - 4.83 (m, 1H), 3.99 - 3.62 (m, 5H), 3.06 (s, 3H), 2.26 - 2.20 (m, 2H), 1.45 (s, 9H).

Step 5

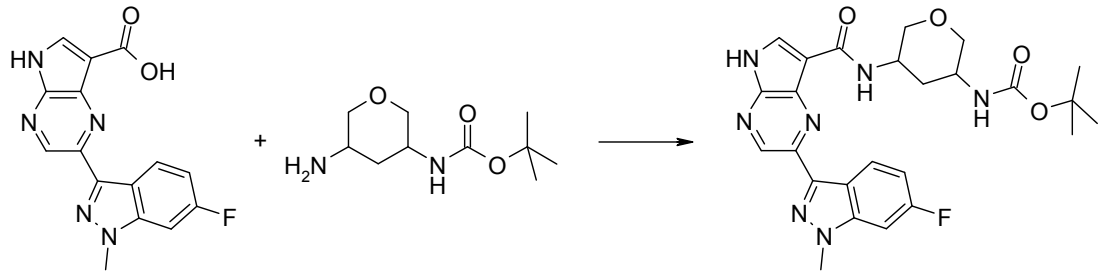
tert-Butyl 5-amino-tetrahydro-2H-pyran-3-ylcarbamate **99**



A solution of **98** (900 mg, 3 mmol) and sodium azide (300 mg, 5 mmol) in dry *N,N*-dimethylformamide (100 mL) was heated to 100 °C for 3h. The reaction mixture was cooled to room temperature, 400 mL of water were added, product extracted with ethyl acetate (2 × 500 mL), combined organics dried with sodium sulfate, filtered and concentrated. Crude *tert*-butyl 5-azido-tetrahydro-2H-pyran-3-ylcarbamate (1g, 4.13 mmol) dissolved in ethyl acetate (30 mL) was treated with Pd/C (10%, 1g), the reaction mixture was stirred overnight at room temperature under a hydrogen filled balloon. The reaction mixture was filtered over celite, the filtrate was concentrated to give **99** (188 mg, 21%) as white solid. LCMS $(M+H)^+ = 217$; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.84 - 3.57 (m, 4H), 3.19 - 3.05 (m, 2H), 2.21 - 1.65 (m, 2H), 1.44 (s, 9H).

Step 6

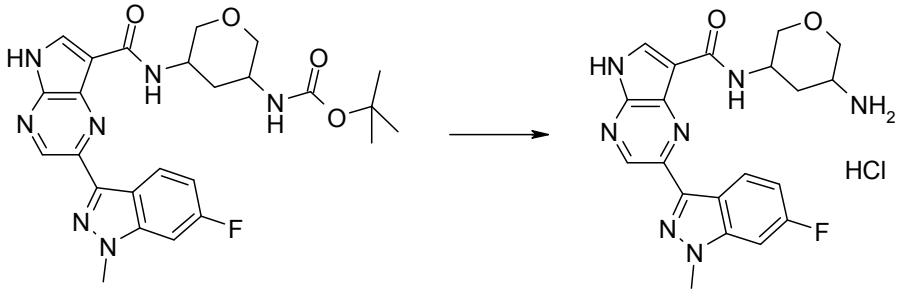
tert-Butyl 5-(2-(6-fluoro-1-methyl-1H-indazol-3-yl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxamido)-tetrahydro-2H-pyran-3-ylcarbamate **100**



A mixture of **99** (100 mg, 0.46 mmol), **94** (200 mg, 0.7 mmol), EDCI (134 mg, 0.7 mmol), DMAP (85 mg, 0.7 mmol), HOBt (95 mg, 0.7 mmol) and TEA (0.4 mL, 2.3 mmol) in dry DMF (10 mL) was stirred for 6 h at room temperature. The reaction mixture was concentrated to dryness and residue purified by flash chromatography eluting with ethyl acetate to afford **100** (120 mg, 51%) as yellow solid. LCMS $(M+H)^+ = 510$; $(M+Na)^+ = 532$; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 12.87 (s, 1H), 9.08 (d, 1H, *J* = 9.3Hz), 8.45 - 8.34 (m, 2H), 7.96 - 7.94 (m, 1H), 7.68-7.65 (m, 1H), 7.23 - 7.14 (m, 1H), 7.04 - 7.01 (m, 1H), 4.13 - 4.04 (m, 5H), 3.82 - 3.78 (m, 4H), 3.07 - 3.01 (m, 2H), 1.46 (s, 9H).

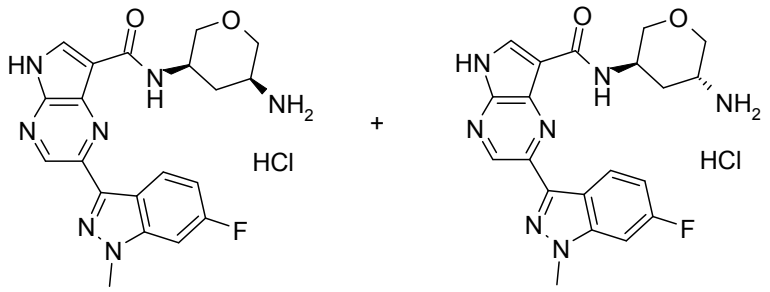
Step 7

N-(5-Amino-tetrahydro-2H-pyran-3-yl)-2-(6-fluoro-1-methyl-1H-indazol-3-yl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide hydrochloride **21**



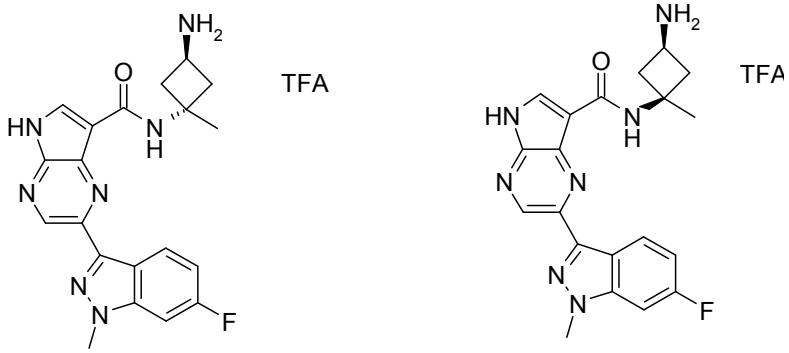
To a solution of **100** (120 mg, 0.24 mmol) in dioxane (10 mL) was bubbled HCl (g) for 3 h. Then the reaction mixture was stirred overnight at room temperature. The formed solid was separated by filtration and the filter cake washed with 10 mL of ether to give **21** (30 mg, 28.6%). LCMS $(M+H)^+ = 410$.

2-(6-Fluoro-1-methyl-1H-indazol-3-yl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxylic acid ((3R,5S)-5-amino-tetrahydro-pyran-3-yl)-amide **22**; 2-(6-Fluoro-1-methyl-1H-indazol-3-yl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxylic acid ((3R,5R)-5-amino-tetrahydro-pyran-3-yl)-amide **23**



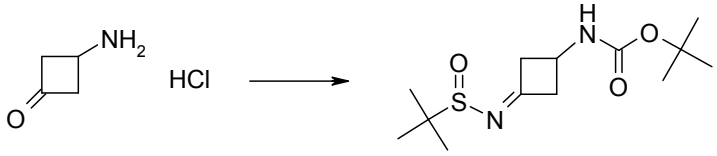
The filtrate from step 7 was concentrated to dryness and purified by preparative HPLC (Gemini 5u C18 150 × 21.2 mm; inject volume: 3 mL/inj, flow rate: 20 mL/min; wavelength: 214 nm and 254 nm; gradient: 40% acetonitrile/60% water (0.1% trifluoroacetic acid) to 10% acetonitrile/90% water (0.1% trifluoroacetic acid) in a linear fashion over 9 min) to give two diastereoisomers (10 mg each) the relative stereochemistry of which was arbitrarily assigned. The more polar diastereoisomer **22**, LCMS $(M+H)^+ = 410$; ^{1}H NMR (300 MHz, DMSO-d_6 + D_2O) δ: 9.02 (s, 1H), 8.34 - 8.28 (m, 2H), 7.51 (d, 1H, *J* = 9.6 Hz), 7.24 (*t*, 1H, *J* = 9.3 Hz), 4.14 - 4.04 (m, 8H), 3.37 - 3.12 (m, 3H). The less polar diastereoisomer **23**, LCMS $(M+H)^+ = 410$; ^{1}H NMR (300 MHz, DMSO-d_6 + D_2O) δ: 9.03 (s, 1H), 8.41 - 8.37 (m, 2H), 8.20 (d, 1H, *J* = 7.8 Hz), 7.49 (d, 1H, *J* = 9.3 Hz), 7.09 (*t*, 1H, *J* = 8.7 Hz), 4.38 (*br*s, 1H), 4.04 (s, 3H), 3.89 - 3.86 (m, 2H), 3.67 - 3.42 (m, 3H), 2.23 - 2.01 (m, 2H).

N-(cis-3-amino-1-methylcyclobutyl)-2-(6-fluoro-1-methyl-1H-indazol-3-yl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide 2,2,2-trifluoroacetate **24;** *N*-(trans-3-amino-1-methylcyclobutyl)-2-(6-fluoro-1-methyl-1H-indazol-3-yl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide 2,2,2-trifluoroacetate **25**



Step 1

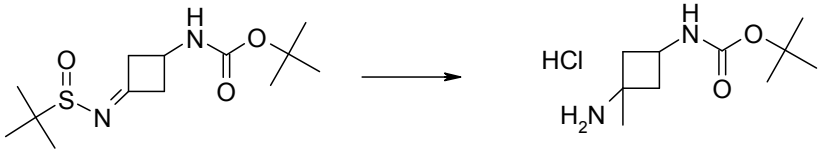
tert-Butyl 3-(*tert*-butylsulfinylimino)cyclobutylcarbamate **101**



A mixture of 3-aminocyclobutanone hydrochloride (2.0 g, 16.4 mmol, commercially available from Matrix Scientific), $(Boc)_2O$ (3.9 g, 18 mmol) and Na_2CO_3 (3.5 g, 33 mmol) in water (10 mL) and THF (50 mL) was stirred at room temperature overnight. The solvent was evaporated under reduced pressure and the residue was passed through a pad of silica gel eluting with a mixture of ethyl acetate:petroleum ether (1:3) and used immediately into the next step. Crude tert-butyl 3-oxocyclobutylcarbamate (2.2 g, 11.9 mmol) was mixed with 2-methylpropane-2-sulfinamide (1.6 g, 13.1 mmol) and $Ti(OEt)_4$ (5.5 g, 24 mmol) in THF (20 mL). The mixture was heated at 50-60 ^oC with stirring overnight. The mixture was cooled to room temperature and then quenched with saturated NH_4Cl solution. The formed solid was removed by filtration. The filtrate was evaporated to dryness and the crude residue was purified by flash chromatography eluting with petroleum ether:ethyl acetate (4:1) to give **101** (2 g, 41.9 % for two steps) as clear oil. LCMS $(M+H)^+$ = 289.1; ^1H NMR (300 MHz, $CDCl_3$) δ: 5.08 (m, 1H), 4.29 (s, 1H), 3.42-3.00 (m, 4H), 1.43 (s, 9H), 1.22 (s, 9H).

Step 2

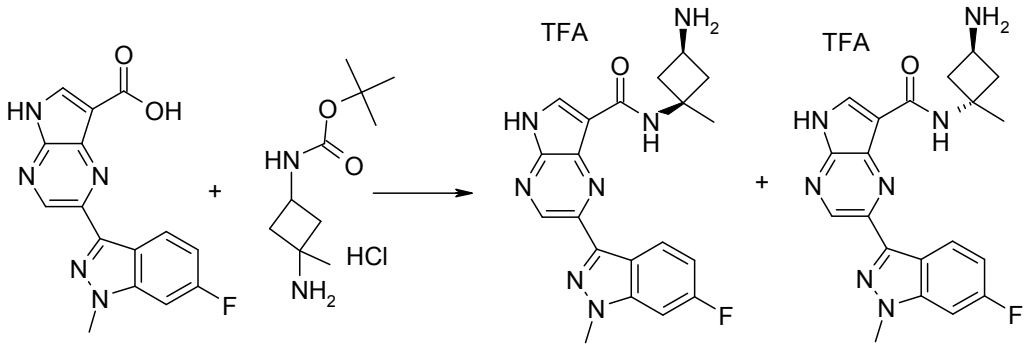
tert-Butyl 3-amino-3-methylcyclobutylcarbamate hydrochloride **102**



To a stirred solution of *tert*-butyl 3-(*tert*-butylsulfinylimino)cyclobutylcarbamate (0.8 g, 2.8 mmol) in toluene (60 mL) at -78 ^oC was added Me_3Al 2M in toluene (3.1 mL, 6.2 mmol). After stirring for 20 minutes at -78 ^oC, MeLi 3M in dimethoxymethane (4.1 mL, 12.3 mmol) was added slowly. The reaction mixture was stirred at -78 ^oC for additional 4 h and then quenched by adding 3 mL of water. The solvent was removed under reduced pressure and the residue was passed through a pad of silica gel eluting with a mixture of petroleum ether:ethyl acetate (4:1) and used immediately into the next step. Crude *tert*-butyl 3-(1,1-dimethylethylsulfinamido)-3-methylcyclobutylcarbamate (0.45 g, 1.48 mmol) was dissolved in MeOH (150 mL), to this solution was added 2N HCl in dioxane (1.8 mL). The solution was stirred at room temperature overnight. The solvent was removed under reduced pressure and the residue was triturated with EtOAc, then decanted and dried to give **102** (0.22 g, 33.8 % for two steps) as a white solid. LCMS $(M+H)^+$ = 201.2; ^1H NMR (300 MHz, DMSO-d_6) δ: 2.24 - 2.22 (m, 1H), 1.43 - 1.383 (m, 13H), 1.10 (s, 3H).

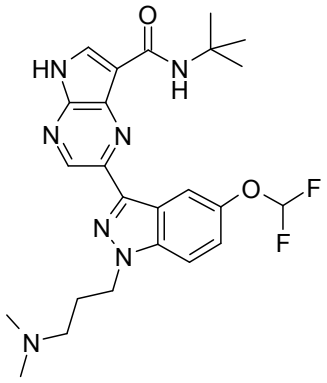
Step 3

N-(cis-3-Amino-1-methylcyclobutyl)-2-(6-fluoro-1-methyl-1H-indazol-3-yl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide 2,2,2-trifluoroacetate **24**; *N*-(trans-3-amino-1-methylcyclobutyl)-2-(6-fluoro-1-methyl-1H-indazol-3-yl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide 2,2,2-trifluoroacetate **25**



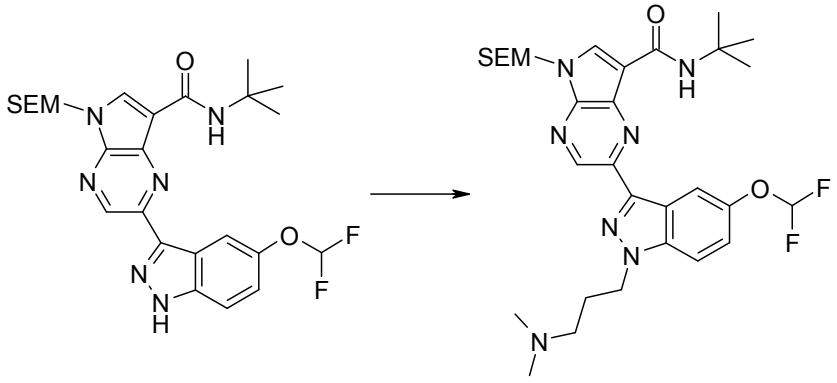
A mixture of **94** (0.1 g, 0.32 mmol), **102** (0.1 g, 0.42 mmol), EDCI (0.092 g, 0.48 mmol), DMAP (0.059 g, 0.48 mmol), HOBT (0.065 g, 0.48 mmol) and DIPEA (0.248 g, 1.92 mmol) in DMF (2.5 mL) was stirred at room temperature overnight. The solvent was removed under reduced pressure and the residue was passed through a pad of silica gel eluting with a mixture of petroleum ether:ethyl acetate (4:1) and used immediately into the next step. Crude *tert*-butyl 3-(2-(6-fluoro-1-methyl-1H-indazol-3-yl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxamido)-3-methylcyclobutylcarbamate hydrochloride (0.11 g, 0.22 mmol) was dissolved in a mixture of trifluoroacetic acid (1 mL) and dichloromethane (3 mL) and stirred at room temperature overnight. The solvents were removed under reduced pressure and the residue was purified by preparative-HPLC (Gemini 5u C18 150×21.2 mm; inject volume: 3 mL/inj, flow rate: 20 mL/min; wavelength: 214 nm and 254 nm; gradient: 23% acetonitrile/77% water (0.1% trifluoroacetic acid) to 32% acetonitrile/68% water (0.1% trifluoroacetic acid) in a linear fashion over 9 min) to give **24** (16 mg, 14 %), LCMS $(M+H)^+$ = 394; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 9.14 (s, 1H), 8.54 - 8.45 (m, 3H), 8.06 (brs, 2H), 7.75 (d, 1H, *J*=9.9 Hz), 7.25 (t, 1H, *J*=9.0 Hz), 4.18 (s, 3H), 3.76 (t, 1H, *J*=7.7 Hz), 2.61 (brs, 4H), 1.63 (s, 3H) and **25** (3 mg, 2.7 %), LCMS $(M+H)^+$ = 394; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 12.98 (brs, 1H), 9.12 (s, 1H), 8.54 - 8.47 (m, 2H), 8.26 (s, 1H), 7.75 (d, 1H, *J*=9.9 Hz), 8.04 (brs, 2H), 7.74 (d, 1H, *J*=9.6 Hz), 7.31 (t, 1H, *J*=8.8 Hz), 4.18 (s, 3H), 4.00 (brs, 1H), 2.85 - 2.78 (brs, 2H), 2.37 - 2.31 (m, 2H), 1.64 (s, 3H).

2-[5-Difluoromethoxy-1-(3-dimethylamino-propyl)-1H-indazol-3-yl]-5H-pyrrolo[2,3-b]pyrazine-7-carboxylic acid *tert*-butylamide **26**



Step 1

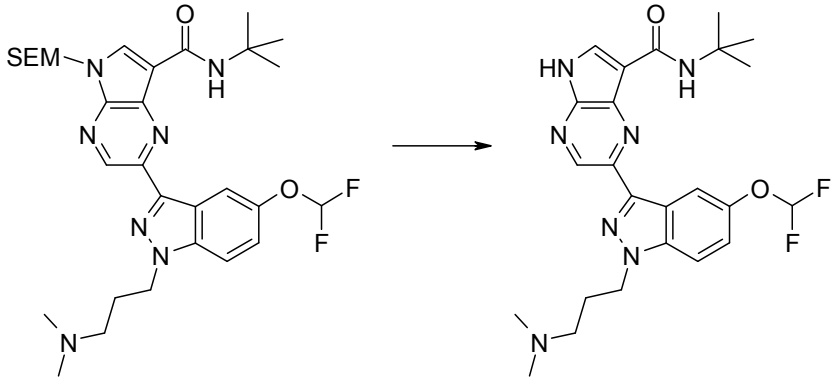
N-tert-butyl-2-(5-(difluoromethoxy)-1-(3-(dimethylamino)propyl)-1H-indazol-3-yl)-5-((2-(trimethylsilyl)ethoxy)methyl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide **103**



In a 2-5 mL Biotage microwave vial were mixed **82** (109 mg, 205 µmol), 3-chloro-*N,N*-dimethylpropan-1-aminium chloride (97.4 mg, 616 µmol) and Cs_2CO_3 (402 mg, 1.23 mmol) in DMF (2 mL). The mixture was stirred for 10 min at 25 °C then heated to 100 °C in the Biotage microwave reactor for 30 min. After cooling to room temperature the mixture was diluted with 10 mL of dichloromethane and filtered through a celite pad and the filtrate concentrated under high vacuum. The residue was purified by flash chromatography eluting with 0 to 5% (MeOH containing 10% ammonium hydroxide)/dichloromethane to give **103** (97 mg, 76.7%) as a light brown solid. LCMS $(M+H)^+$ = 616; ^{1}H NMR ($CDCl_3$) δ: 9.24 (s, 1H), 8.36 (s, 1H), 8.32 (d, *J*=2.3 Hz, 1H), 8.06 (s, 1H), 7.60 (d, *J*=8.7 Hz, 1H), 7.35 (dd, *J*=9.1, 2.3 Hz, 1H), 6.55 (t, *J*=74.8 Hz, 1H), 5.75 (s, 2H), 4.60 (t, *J*=6.6 Hz, 2H), 3.53 - 3.74 (m, 2H), 2.33 - 2.42 (m, 2H), 2.29 (s, 6H), 2.14 - 2.27 (m, 2H), 1.65 (s, 9H), 0.90 - 1.07 (m, 2H), 0.00 (s, 9H).

Step 3

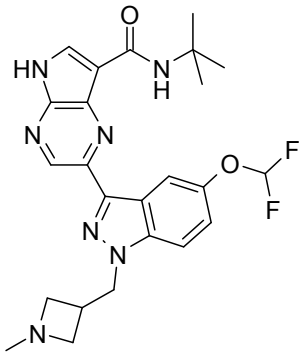
2-[5-Difluoromethoxy-1-(3-dimethylamino-propyl)-1H-indazol-3-yl]-5H-pyrrolo[2,3-b]pyrazine-7-carboxylic acid *tert*-butylamide **26**



To a pale yellow solution of **103** in dichloromethane (4 mL) was added TFA (1.48 g, 1 mL, 13.0 mmol), the reaction mixture turned orange and was stirred at 25 °C for 2 h, mixture concentrated and the residue was re-dissolved in 5 mL of a solution of (dichloromethane/MeOH/ammonium hydroxide; 60:10:1) and stirred at 25 °C for 1 h, then evaporated to a yellow solid, which was purified by flash chromatography eluting with 0 to

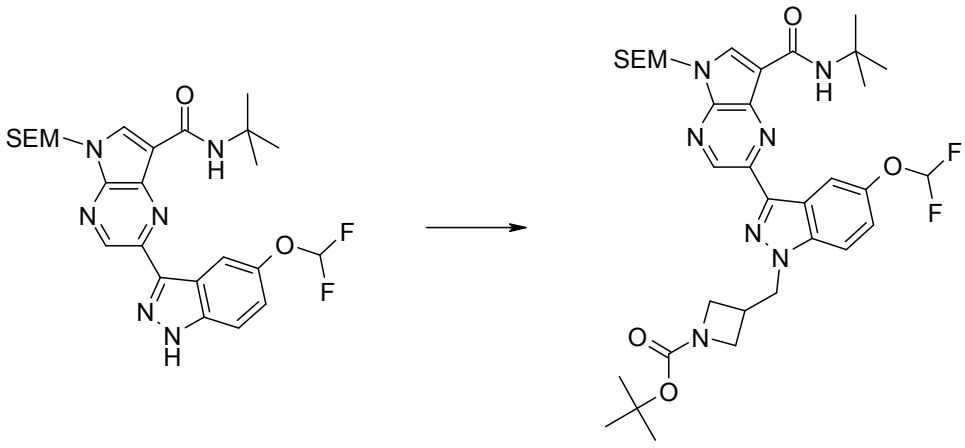
5% (MeOH containing 10% ammonium hydroxide)/dichloromethane to give **26** (62 mg, 81.1%) as an off-white solid. LCMS $(M+H)^+$ = 486; ^{1}H NMR (DMSO-d_6) δ: 9.07 (s, 1H), 8.37 (s, 1H), 8.20 (s, 1H), 7.78 - 7.95 (m, 2H), 7.39 (d, *J*=8.7 Hz, 1H), 7.19 (s, 1H), 4.55 (t, *J*=6.2 Hz, 2H), 2.17 - 2.30 (m, 2H), 2.12 (s, 7H), 1.99 - 2.07 (m, 2H), 1.49 (s, 10H).

2-[5-Difluoromethoxy-1-(1-methyl-azetidin-3-ylmethyl)-1H-indazol-3-yl]-5H-pyrrolo[2,3-b]pyrazine-7-carboxylic acid *tert*-butylamide **27**



Step 1

tert-Butyl 3-((3-(7-(*tert*-butylcarbamoyl)-5-((2-(trimethylsilyl)ethoxy)methyl)-5H-pyrrolo[2,3-b]pyrazin-2-yl)-5-(difluoromethoxy)-1H-indazol-1-yl)methyl)azetidine-1-carboxylate **104**

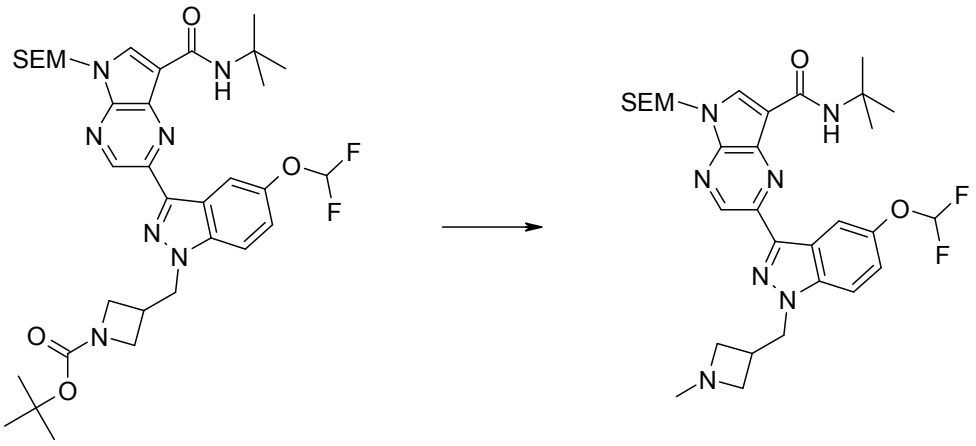


Compound **82** (100 mg, 188 µmol), *tert*-butyl 3-(iodomethyl)azetidine-1-carboxylate (56.0 mg, 188 µmol, available commercially from Advanced ChemBlocks Inc.) and cesium carbonate (184 mg, 565 µmol) in dimethylformamide (2 mL) were heated under microwaves at 150 °C for 30 min. The mixture was cooled, partitioned between ethyl acetate and water, and the organic phase washed with water 3 times then dried ($MgSO_4$) and concentrated. Purification by flash chromatography eluting with 0-40% ethyl acetate in hexanes gave **104** (108 mg, 82%). LCMS $(M+H)^+$ = 700; ^{1}H NMR ($CDCl_3$) δ: 9.18 (s, 1H), 8.34 (s, 1H), 8.30 (d, *J*=2.1 Hz, 1H), 8.00 (s, 1H), 7.50 (d, *J*=9.0 Hz, 1H), 7.35 (dd, *J*=9.0, 2.1 Hz, 1H), 6.24 - 6.81 (m, 1H), 5.72 (s, 3H), 5.30 (s, 2H), 4.66 (d, *J*=7.5 Hz, 2H), 3.89 (dd, *J*=8.9, 5.2 Hz, 2H),

3.58 (dd, *J*=8.8, 7.6 Hz, 2H), 3.21 - 3.33 (m, 1H), 1.61 (s, 9H), 1.45 (s, 9H), 0.88 - 1.00 (m, 2H), -0.08 - -0.01 (m, 9H).

Step 2

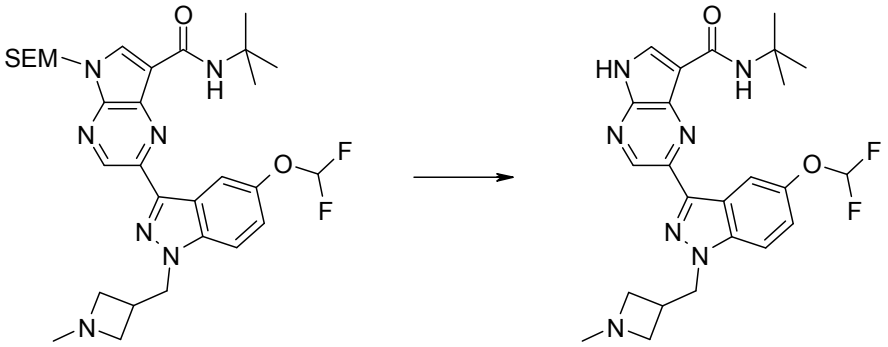
N-*tert*-Butyl-2-(5-(difluoromethoxy)-1-((1-methylazetidin-3-yl)methyl)-1H-indazol-3-yl)-5-((2-(trimethylsilyl)ethoxy)methyl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide **105**



A solution of **104** (180 mg, 257 µmol) in 2,2,2-trifluoroethanol (2 mL) was heated under microwaves at 150 °C for 6 h then cooled and concentrated. Crude 2-(1-(azetidin-3-ylmethyl)-5-(difluoromethoxy)-1H-indazol-3-yl)-*N*-*tert*-butyl-5-((2-(trimethylsilyl)ethoxy)methyl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide (37 mg, 61.7 µmol) was dissolved in methanol (4 mL) and cooled to 0 °C. Then was added aqueous formaldehyde (1 mL, 13.4 mmol), followed by the addition of sodium triacetoxyborohydride (29.4 mg, 139 µmol). The reaction mixture was stirred at room temperature for 15 h then concentrated and purified by flash chromatography eluting with 0-10% (methanol containing 10% ammonium hydroxide)/dichloromethane to give **105** (33 mg, 87%). LCMS $(M+H)^+$ = 614. ^{1}H NMR (CHLOROFORM-d) δ: 9.09 (s, 1H), 8.56 (s, 1H), 7.93 (s, 1H), 7.83 (d, J = 9.2 Hz, 1H), 7.69 (d, J = 9.2 Hz, 1H), 7.56 (s, 1H), 6.32 - 6.97 (m, 1H), 5.77 (s, 2H), 3.51 - 3.76 (m, 2H), 3.06 (br. s., 2H), 2.52 (br. s., 7H), 1.53 (s, 9H), 0.87 - 1.02 (m, 3H), 0.00 (s, 9H).

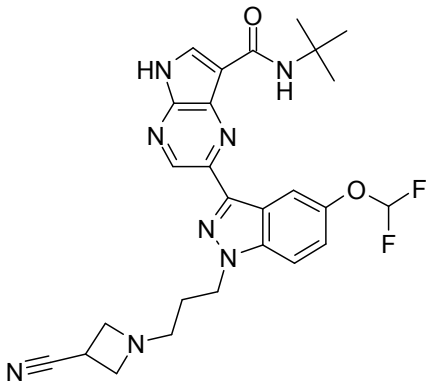
Step 3

2-[5-Difluoromethoxy-1-(1-methyl-azetidin-3-ylmethyl)-1H-indazol-3-yl]-5H-pyrrolo[2,3-b]pyrazine-7-carboxylic acid *tert*-butylamide **27**



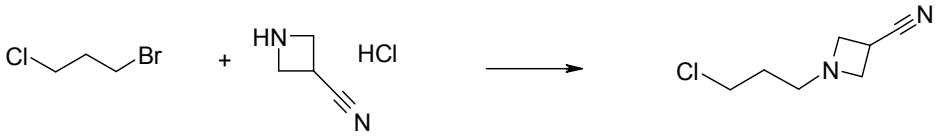
To a stirred solution of **105** (33 mg, 53.8 μmol) in dichloromethane (2 mL) was added trifluoroacetic acid (1 mL). After stirring at room temperature for 15 h the mixture was concentrated *in vacuo*, then dissolved in a solution of ammonium hydroxide/methanol/dichloromethane (1/10/60, 25 mL). After stirring at room temperature for 1 h, the mixture was concentrated *in vacuo*. Purification by flash chromatography eluting with 0-4% (methanol containing 10% ammonium hydroxide) /dichloromethane gave **27** (18 mg, 69%). LCMS $(M+H)^+$ = 484; ^{1}H NMR (DMSO-d_6) δ: 9.07 (s, 1H), 8.39 (s, 1H), 8.21 (d, *J*=2.3 Hz, 2H), 7.93 (d, *J*=9.0 Hz, 1H), 7.87 (s, 1H), 7.38 - 7.46 (m, 2H), 7.20 (s, 1H), 4.76 (d, *J*=7.3 Hz, 2H), 4.55 (s, 2H), 3.48 (t, *J*=8.0 Hz, 1H), 2.36 (s, 3H), 1.50 (s, 9H), 1.05 (t, *J*=7.3 Hz, 2H).

2-{1-[3-(3-Cyano-azetidin-1-yl)-propyl]-5-difluoromethoxy-1H-indazol-3-yl}-5H-pyrrolo[2,3-b]pyrazine-7-carboxylic acid *tert*-butylamide **28**



Step 1

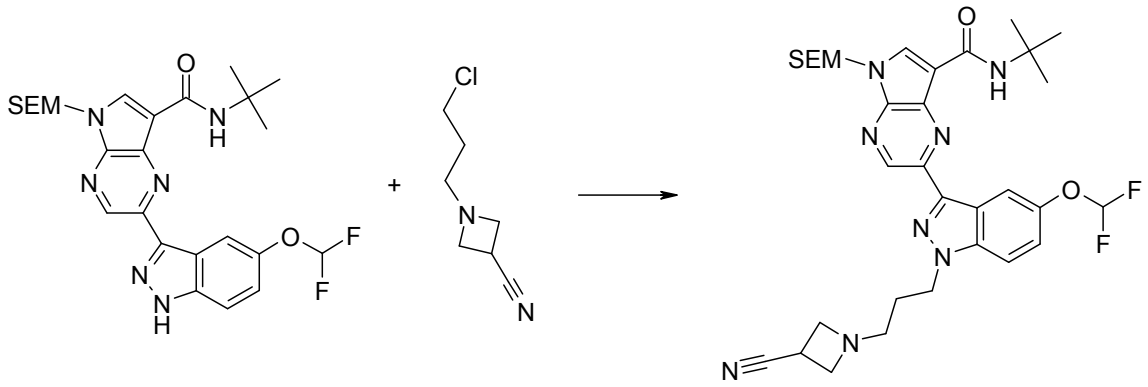
1-(3-Chloropropyl)azetidine-3-carbonitrile **106**



In a 25 mL round-bottomed flask were mixed with stirring azetidine-3-carbonitrile hydrochloride (250 mg, 2.11 mmol, available commercially from ASW MedChem Inc.) and 1-bromo-3-chloropropane (664 mg, 415 μL, 4.22 mmol) in acetonitrile (5 mL). To the suspension was added Cs_2CO_3 (2.06 g, 6.33 mmol) and the mixture was stirred at 25 °C for 18 h, then diluted with 15 mL of EtOAc and filtered to remove solids. Filtrate was evaporated and residue purified by flash chromatography eluting with 0 to 5% (MeOH containing 10% ammonium hydroxide)/dichloromethane (developing TLC in an iodine chamber) to give **106** (230 mg, 68.8%) as a clear dense liquid. ^{1}H NMR ($CDCl_3$) δ: 3.46 - 3.59 (m, 4H), 3.20 - 3.31 (m, 3H), 2.55 (t, *J*=6.8 Hz, 2H), 1.75 (quin, *J*=6.6 Hz, 2H).

Step 2

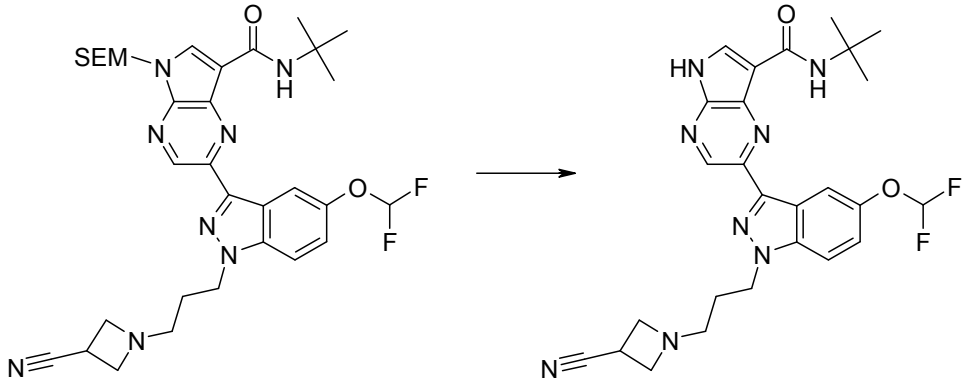
N-*tert*-Butyl-2-(1-(3-(3-cyanoazetidin-1-yl)propyl)-5-(difluoromethoxy)-1H-indazol-3-yl)-5-((2-(trimethylsilyl)ethoxy)methyl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide **107**



In a 2-5 mL Biotage microwave vial were mixed **82** (50 mg, 94.2 µmol), **106** (44.8 mg, 283 µmol) and Cs_2CO_3 (123 mg, 377 µmol) in DMF (2.0 mL). The mixture was stirred for 10 min at 25 °C then heated to 100 °C in the Biotage microwave reactor for 30 min. The mixture was diluted with 10 mL of dichloromethane and filtered through a celite pad, filtrate concentrated under high vacuum and residue purified by flash chromatography eluting with 0 to 5% (MeOH containing 10% ammonium hydroxide)/dichloromethane to give **107** (45 mg, 73.2%) as a white solid. LCMS $(M+H)^+$ = 653.1; ^{1}H NMR ($CDCl_3$) δ: 9.22 (s, 1H), 8.36 (s, 1H), 8.31 (d, *J*=2.3 Hz, 1H), 8.04 (s, 1H), 7.58 (d, *J*=9.1 Hz, 1H), 7.36 (dd, *J*=8.9, 2.1 Hz, 1H), 6.56 (t, *J*=73.7 Hz, 1H), 5.75 (s, 2H), 4.57 (t, *J*=6.6 Hz, 2H), 3.24 - 3.40 (m, 3H), 2.50 (t, *J*=6.6 Hz, 2H), 2.08 (quin, *J*=6.5 Hz, 2H), 1.65 (s, 9H), 0.91 - 1.03 (m, 2H), 0.00 (s, 9H).

Step 3

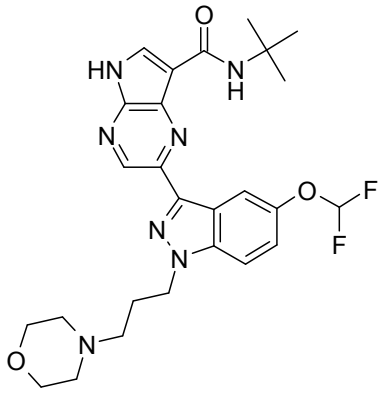
2-{1-[3-(3-Cyano-azetidin-1-yl)-propyl]-5-difluoromethoxy-1H-indazol-3-yl}-5H-pyrrolo[2,3-b]pyrazine-7-carboxylic acid *tert*-butylamide **28**



To a pale yellow solution of **107** (45 mg, 68.9 µmol) in dichloromethane (4.0 mL) was added TFA (740 mg, 0.5 mL, 6.49 mmol), the reaction mixture turned orange and was stirred at 25 °C for 18 h, mixture concentrated and the residue was re-dissolved in 5 mL of a solution of (dichloromethane:MeOH:ammonium hydroxide; 60:10:1) and stirred at 25 °C for 1 h, then evaporated to a yellow solid, which was purified by flash chromatography eluting with 0 to 5% over 20 min (MeOH containing 10% ammonium hydroxide)/dichloromethane to give **28** (33 mg, 91.6%) as a light yellow solid. LCMS $(M+H)^+$ = 523; ^{1}H NMR (DMSO-d_6) δ: 12.80 (br. s., 1H), 9.06 (s, 1H), 8.37 (s, 1H), 8.19 (d, *J*=2.3 Hz, 1H), 7.81 - 7.96 (m, 2H), 7.39 (dd,

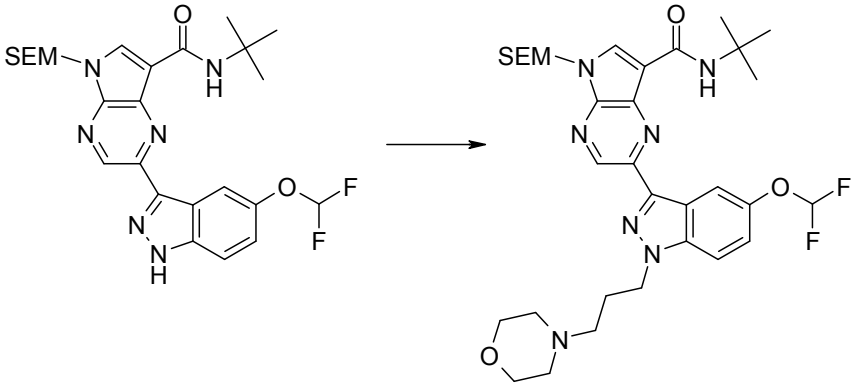
J=9.1, 2.3 Hz, 1H), 7.19 (t, *J*=74.4 Hz,, 1H), 4.53 (t, *J*=6.6 Hz, 2H), 3.35 - 3.57 (m, 3H), 3.16 - 3.25 (m, 2H), 2.38 (t, *J*=6.8 Hz, 2H), 1.78 - 2.02 (m, 2H), 1.49 (s, 9H).

2-[5-Difluoromethoxy-1-(3-morpholin-4-yl-propyl)-1H-indazol-3-yl]-5H-pyrrolo[2,3-b]pyrazine-7-carboxylic acid *tert*-butylamide **29**



Step 1

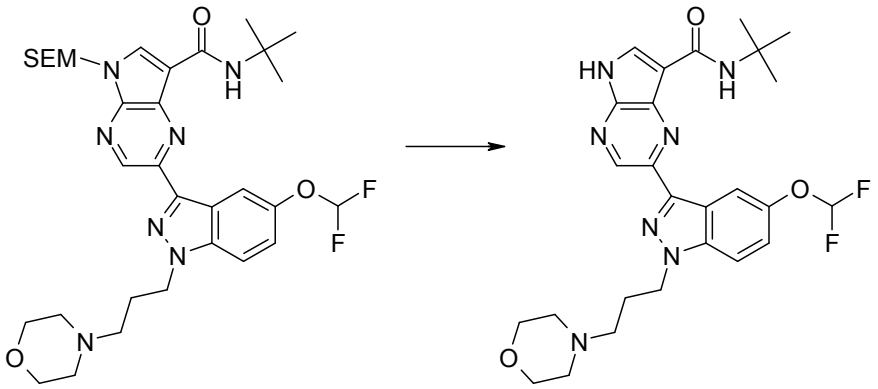
N-*tert*-Butyl-2-(5-(difluoromethoxy)-1-(3-morpholinopropyl)-1H-indazol-3-yl)-5-((2-(trimethylsilyl)ethoxy)methyl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide **108**



In a 2-5 mL Biotage microwave vial were mixed **82** (60 mg, 113 µmol), 4-(3-chloropropyl)morpholine (55.5 mg, 339 µmol) and Cs_2CO_3 (147 mg, 452 µmol) in DMF (2 mL). The mixture was stirred for 10 min at 25 °C then heated to 100 °C in a Biotage microwave reactor for 30 min. Then, diluted with 10 mL of dichloromethane and filtered through a celite pad, filtrate concentrated under high vacuum and residue purified by flash chromatography eluting with 0 to 5% (MeOH containing 10% ammonium hydroxide)/dichloromethane to give **108** (62 mg, 83.4%) as an off-white solid. LCMS $(M+Na)^+$ = 680; ^{1}H NMR ($CDCl_3$) δ: 9.23 (s, 1H), 8.36 (s, 1H), 8.32 (d, *J*=2.3 Hz, 1H), 8.05 (s, 1H), 7.59 (d, *J*=9.1 Hz, 1H), 7.35 (dd, *J*=8.9, 2.1 Hz, 1H), 6.55 (t, *J*=74.4 Hz, 1H), 5.75 (s, 2H), 4.61 (t, *J*=6.4 Hz, 2H), 3.75 (br. s., 4H), 3.55 - 3.66 (m, 2H), 2.45 (br. s., 6H), 2.25 (br. s., 2H), 1.65 (s, 9H), 0.90 - 1.06 (m, 2H), 0.00 (s, 9H).

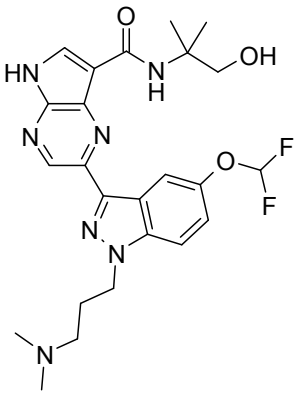
Step 2

2-[5-Difluoromethoxy-1-(3-morpholin-4-yl-propyl)-1H-indazol-3-yl]-5H-pyrrolo[2,3-b]pyrazine-7-carboxylic acid *tert*-butylamide **29**



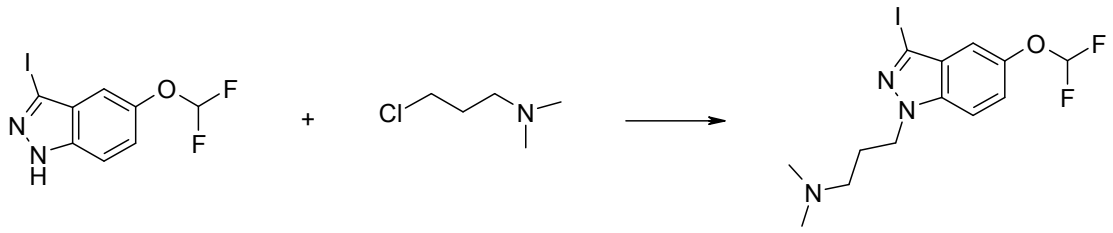
To a pale yellow solution of **108** (62 mg, 94.2 µmol) in dichloromethane (4.0 mL) was added TFA (1.48 g, 1.0 mL, 13.0 mmol), the reaction mixture turned orange and was stirred at 25 °C for 18 h, mixture concentrated and the residue was re-dissolved in 5 mL of a solution of (dichloromethane/MeOH/ammonium hydroxide; 60:10:1) and stirred at 25 °C for 1 h, then evaporated to a yellow solid, which was purified by flash chromatography eluting with 0 to 5% over 20 min (MeOH containing 10% ammonium hydroxide)/dichloromethane to give **29** (45 mg, 90.5%) as a light yellow solid. LCMS $(M+H)^+$ = 528; ^{1}H NMR (DMSO-d_6) δ: 12.80 (br. s., 1H), 9.06 (s, 1H), 8.37 (s, 1H), 8.19 (s, 1H), 7.77 - 7.98 (m, 2H), 7.38 (d, *J*=8.7 Hz, 1H), 7.18 (t, *J*=74.4 Hz,, 1H), 4.57 (t, *J*=5.7 Hz, 2H), 3.49 (br. s., 4H), 2.26 (br. s., 6H), 2.00 - 2.15 (m, 2H), 1.49 (s, 9H).

2-(5-(Difluoromethoxy)-1-(3-(dimethylamino)propyl)-1H-indazol-3-yl)-*N*-(1-hydroxy-2-methylpropan-2-yl)-5H-pyrrolo[3,2-b]pyrazine-7-carboxamide **30**



Step 1

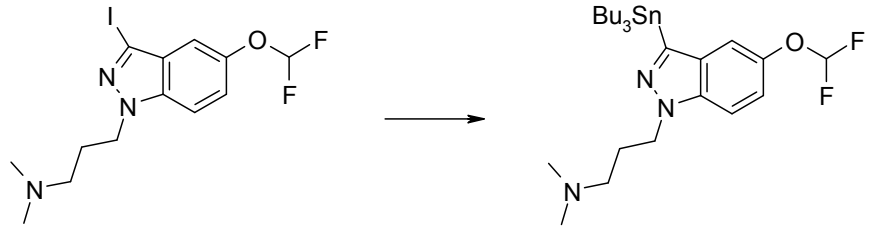
3-(5-(Difluoromethoxy)-3-iodo-1H-indazol-1-yl)-*N*,*N*-dimethylpropan-1-amine **109**



To a solution of **70** (1 g, 3.2 mmol) in DMF (25 mL) was added K_2CO_3 (1. 8 g, 12.8 mmol) and 3-chloro-*N*,*N*-dimethylpropan-1-amine (1.1 g, 6.4 mmol), after the addition, the reaction mixture was stirred at 80 ^oC for 4 hour. After cooling to room temperature, H_2O (25 mL) was added and product extracted with ethyl acetate (100 mL). The organic layer was washed with H_2O (100 mL), brine (100 mL), dried over Na_2SO_4 and concentrated under reduced pressure and the residue was purified by flash chromatography eluting with dichloromethane:CH_3OH (10:1) to give **109** (1.1 g, 78.5%) as yellow oil. LCMS $(M+H)^+$ = 396; ^1H NMR (300 MHz, $CDCl_3$) δ: 7.46 - 7.42 (m, 1H), 7.27 - 7.17 (m, 2H), 6.87 - 6.29 (*t*, 1H, *J* = 73.8 Hz), 4.47 - 4.41 (m, 2H), 2.24 - 2.18 (m, 8H), 2.08 - 2.03 (m, 2H).

Step 2

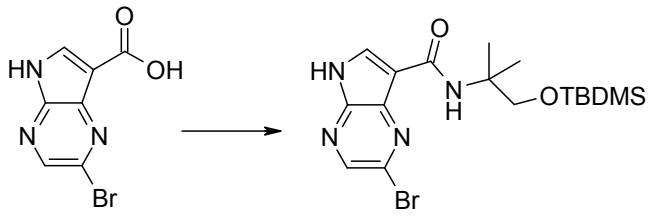
3-(5-(Difluoromethoxy)-3-(tributylstannyl)-1H-indazol-1-yl)-*N,N*-dimethylpropan-1-amine **110**



To a solution of **109** (1.2 g, 2.78 mmol) in dry THF (25 mL) was added isopropylmagnesium chloride (1.5 mL, 2M in THF, 3 mmol) drop-wise at -16 ^oC under nitrogen atmosphere with stirring, mixture stirred for 30 minutes and tributylchlorostannane (3.3 mL, 3.6 mmol) was added drop-wise at -16 ^oC under nitrogen, then the reaction mixture was warmed to room temperature slowly and stirred for 2 hours. The reaction mixture was quenched with a saturated solution of NH_4Cl (40 mL), extracted with EtOAc (3 × 30 mL), the combined organic layer were dried over Na_2SO_4, filtered and concentrated under reduced pressure to give **110** (1.1 g, 71 %) as an oil which was used immediately into the next step without purification.

Step 3

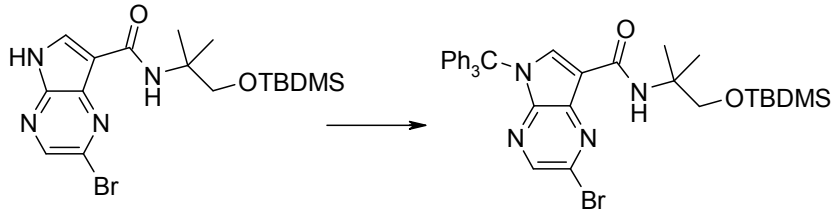
2-Bromo-*N*-(1-(*tert*-butyldimethylsilyloxy)-2-methylpropan-2-yl)-5H-pyrrolo[3,2-b]pyrazine-7-carboxamide **111**



A mixture of **90** (2.5 g, 10.33 mmol), 1-(*tert*-butyldimethylsilyloxy)-2-methylpropan-2-amine (2.52 g, 12.4 mmol), EDCI (1.97 g, 10.33 mmol), HOBt (2.8 g, 20.6 mmol) and DIPEA (2.7 g, 20.66 mmol) in dry DMF (30 mL) was heated to 30 °C for 16 hours. Then water (30 mL) was added, the formed precipitate was separated by filtration and the filter cake was washed with water (10 mL) and dried to afford **111** (2.7 g, 61 %) as a yellow solid which was used immediately into the next step. LCMS $(M+H)^+ = 427$.

Step 4

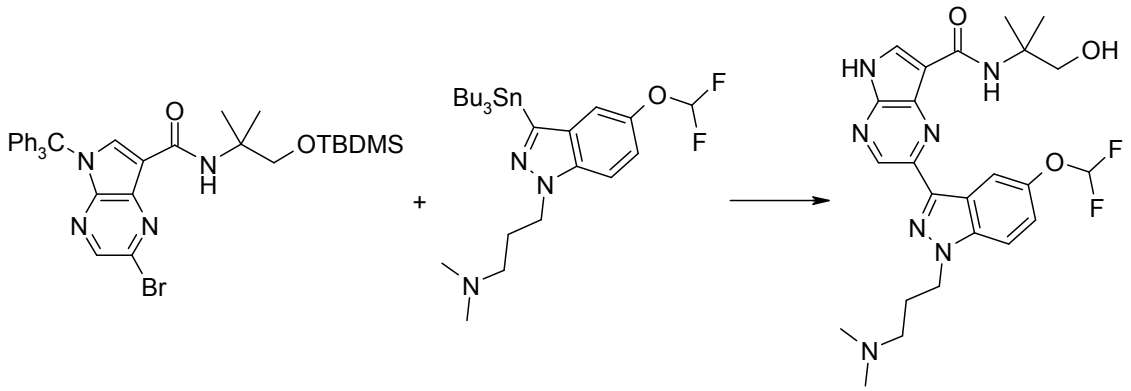
2-Bromo-*N*-(1-(*tert*-butyldimethylsilyloxy)-2-methylpropan-2-yl)-5-trityl-5H-pyrrolo[3,2-b]pyrazine-7-carboxamide **112**



A mixture of **111** (1.3 g, 3.04 mmol), chlorotriphenylmethane (1.0 g, 3.65 mmol) and triethylamine (0.46 g, 4.56 mmol) in dry DMF (20 mL) was heated to 90 °C for 5 h. After cooling down to room temperature water was added and the product was extracted with ethyl acetate (200 mL), organic phase washed with water (3 × 20 mL) and brine (2 × 20 mL). The organic layer was then dried over Na_2SO_4, filtered, concentrated and the residue was purified by flash chromatography eluting with ethyl acetate:petroleum ether (1:10) to afford **112** (1.73 g, 85%) as a yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.29 (s, 1H), 8.00 (s, 1H), 7.93 (s, 1H), 7.29 - 7.26 (m, 9H), 7.14 - 7.11 (m, 6H), 3.71 (s, 2H), 1.48 (s, 6H), 0.90 (s, 9H), 0.11 (s, 6H).

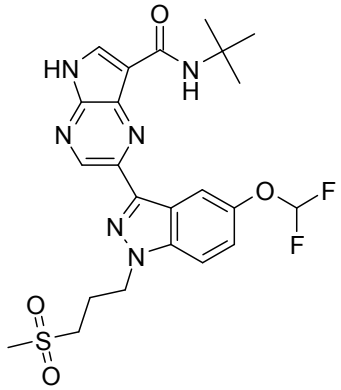
Step 5

2-(5-(Difluoromethoxy)-1-(3-(dimethylamino)propyl)-1H-indazol-3-yl)-*N*-(1-hydroxy-2-methylpropan-2-yl)-5H-pyrrolo[3,2-b]pyrazine-7-carboxamide **30**



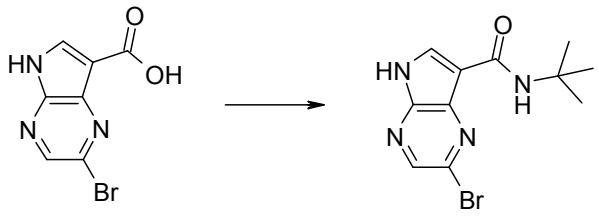
To a solution of **110** (120 mg, 0.22 mmol) and **112** (200 mg, 0.26 mmol) in DMF (10 mL) were added CuI (30 mg, 0.16 mmol) and $Pd(PPh_3)_4$ (47 mg, 0.041 mmol), Then the reaction mixture was degassed by bubbling nitrogen for 3 minutes. The mixture was heated to 80 ^oC for 5 hours under nitrogen. After cooling to room temperature, water (50 mL) was added and the product extracted with EtOAc (3 × 40 mL), the combined organic layers were dried over Na_2SO_4, filtered and concentrated. Crude *N*-(1-(*tert*-butyldimethylsilyloxy)-2-methylpropan-2-yl)-2-(5-(difluoromethoxy)-1-(3-(dimethylamino)propyl)-1H-indazol-3-yl)-5-trityl-5H-pyrrolo[3,2-b]pyrazine-7-carboxamide (88 mg, 0.12 mmol) was dissolved in dichloromethane (3 mL) and treated with trifluoroacetic acid (3 mL) and the reaction mixture was stirred overnight at room temperature. After solvent evaporation, the residue was purified by preparative-HPLC (Gemini 5u C18 150×21.2 mm; inject volume: 3 mL/inj, flow rate: 20 mL/min; wavelength: 214 nm and 254 nm; gradient: 40% acetonitrile/60% water (0.1% trifluoroacetic acid) to 50% acetonitrile/50% water (0.1% trifluoroacetic acid) in a linear fashion over 9 min) to afford **30** (22 mg, 10.3% for two steps) as a yellow solid. LCMS $(M+H)^+$ = 502; ^1H NMR (300 MHz, CD_3OD) δ: 9.04 (s, 1H), 8.17 (s, 1H), 8.11 (s, 1H), 7.66 (d, 1H, *J* = 8.7 Hz), 7.35 (d, 1H, *J* = 8.1 Hz), 6.85 (*t*, 1H, *J* = 74.1 Hz), 4.59 (s, 2H), 3.84 (s, 2H), 3.34 - 3.32 (m, 2H), 2.89 (s, 6H), 2.44 (s, 2H), 1.64 (s, 6H).

N-*tert*-Butyl-2-(5-(difluoromethoxy)-1-(3-(methylsulfonyl)propyl)-1H-indazol-3-yl)-5H-pyrrolo[3,2-b]pyrazine-7-carboxamide **31**



Step 1

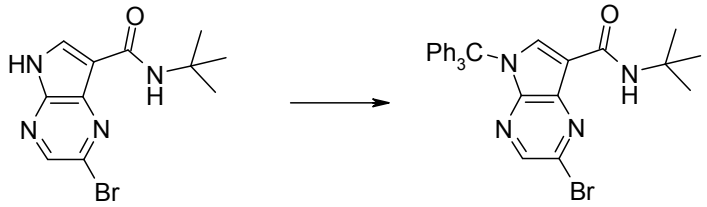
2-Bromo-*N*-*tert*-butyl-5H-pyrrolo[3,2-b]pyrazine-7-carboxamide **113**



A mixture of **90** (0.2 g, 0.83 mmol), 2-methylpropan-2-amine (66 mg, 0.91 mmol), EDCI (476 mg, 2.49 mmol) and HOBt (112 mg, 0.83 mmol) in dry dichloromethane (20 mL) was stirred at room temperature for16 h. Reaction mixture was concentrated to about half the volume and the formed precipitate was separated by filtration, the filter cake was washed with dichloromethane and dried to afford **113** (103 mg, 42%) as a yellow solid. LCMS $(M+H)^+$ = 297. ^{1}H NMR (CHLOROFORM-d) δ: 9.07 (br. s., 1H), 8.45 (s, 1H), 8.35 (d, J = 2.5 Hz, 1H), 7.93 (br. s., 1H), 1.59 (s, 9H).

Step 2

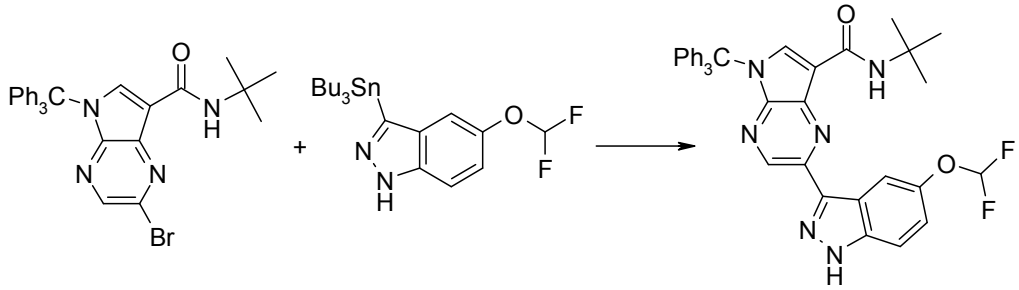
2-Bromo-*N*-*tert*-butyl-5-trityl-5H-pyrrolo[3,2-b]pyrazine-7-carboxamide **114**



A mixture of **113** (378 mg, 1.272 mmol), (chloromethanetriyl)tribenzene (426 mg, 1.53 mmol) and triethylamine (193 mg, 1.91 mmol) in dry DMF (20 mL) was heated to 90 ^{o}C for 16 h. After cooling to room temperature the reaction was quenched with water and the reaction mixture was extracted with ethyl acetate (100 mL), organic phase was washed with water (3 × 10 mL) and brine (2 × 10 mL), then dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography eluting with EtOAc:petroleum ether (1:15) to afford **114** (515 mg, 75%) as a white solid. LCMS $(M+H)^+$ = 539; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.29 (s, 1H), 8.01 (s, 1H), 7.29 - 7.26 (m, 10H), 7.13 - 7.11 (m, 5H), 1.51 (s, 9H).

Step 3

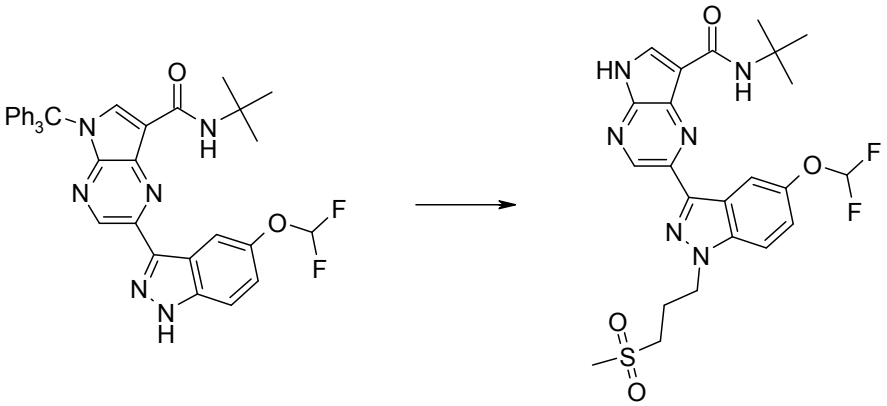
N-*tert*-Butyl-2-(5-(difluoromethoxy)-1H-indazol-3-yl)-5-trityl-5H-pyrrolo[3,2-b]pyrazine-7-carboxamide **115**



In a round-bottomed flask, **114** (530 mg, 1 mmol) and **81** (470 mg, 1 mmol) were dissolved in DMF (10 mL) under nitrogen. $Pd(PPh_3)_4$ (58 mg, 0.05 mmol) and CuI (38 mg, 0.2 mmol) were added and the mixture sonicated for 5 min while bubbling nitrogen through the solution. The reaction mixture was heated to 80 °C with stirring for 4 hours. After cooling down to room temperature the mixture was concentrated and the residue purified by flash chromatography eluting with petroleum ether:EtOAc (3:1 to 1:1) to give **115** (410 mg, 64%) as a solid. LCMS $(M+H)^+$ = 643.2; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.85 (d, 1H, *J*=2.4 Hz), 8.35 (s, 1H), 8.26 (s, 1H), 8.13 (s, 1H,), 7.52 - 7.48 (m, 1H), 6.51 (t, 1H, *J*=74.0 Hz), 1.60 (s, 9H).

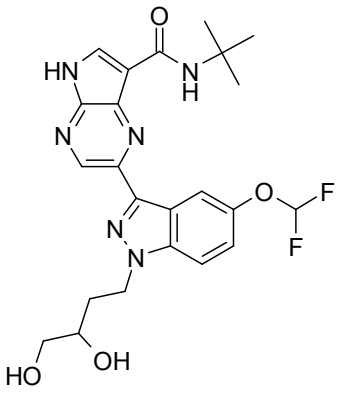
Step 4

N-tert-Butyl-2-(5-(difluoromethoxy)-1-(3-(methylsulfonyl)propyl)-1H-indazol-3-yl)-5H-pyrrolo[3,2-b]pyrazine-7-carboxamide **31**



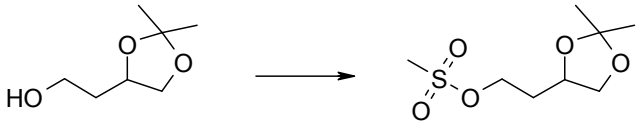
To a solution of **115** (100 mg, 0.156 mmol) in DMF (5 mL) was added 1-chloro-3-(methylsulfonyl)propane (30 mg, 0.187 mmol) followed by K_2CO_3 (65 mg, 0.468 mmol). The mixture was heated at 65 °C for 3 hours. After cooling to room temperature, the mixture was poured into water, the solid formed was separated by filtration and dried. Crude *N-tert*-butyl-2-(5-(difluoromethoxy)-1-(3-(methylsulfonyl)propyl)-1H-indazol-3-yl)-5-trityl-5H-pyrrolo[3,2-b]pyrazine-7-carboxamide (105 mg, 0.138 mmol) was dissolved in dichloromethane (4 mL), to this solution was added drop-wise trifluoroacetic acid (2 mL) and the reaction mixture stirred for 2 hours at room temperature. The solvent was removed under reduced pressure and the residue purified by preparative-TLC (silica gel, EtOAc as eluent) to give **31** (50 mg, 40% for two steps) as a white solid. LCMS $(M+H)^+$ = 521.1; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 12.85 (brs, 1H), 9.13 (s, 1H), 8.42 (s, 1H), 8.25 (s, 1H), 7.93 (t, 1H, *J*=7.8 Hz), 7.47 (d, 1H, *J*=9.0 Hz), 7.24 (s, 1H), 4.72 (d, 2H, *J*=6.6 Hz), 3.28 - 3.18 (m, 2H), 3.02 (s, 3H), 2.40 - 2.38 (m, 2H), 1.53 (s, 9H).

N-tert-Butyl-2-(5-(difluoromethoxy)-1-(3,4-dihydroxybutyl)-1H-indazol-3-yl)-5H-pyrrolo[3,2-b]pyrazine-7-carboxamide **32**



Step 1

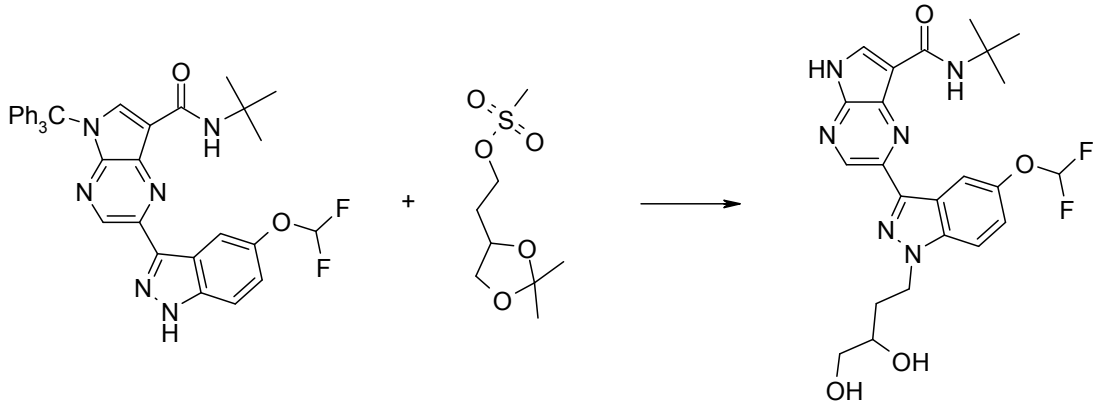
2-(2,2-Dimethyl-1,3-dioxolan-4-yl)ethyl methanesulfonate **116**



To a stirred solution of 2-(2,2-dimethyl-1,3-dioxolan-4-yl)ethanol (292 mg, 2.0 mmol, commercially available from ACC Corporation) in dichloromethane (10 mL) at 0 ^{o}C was added DIPEA (284 mg, 2.20 mmol), followed by slow addition of methanesulfonyl chloride (252 mg, 2.20 mmol). Then the reaction mixture was stirred at 0 ^{o}C for 30 minutes. The reaction was quenched with saturated sodium bicarbonate solution (3 mL), the organic phase was separated, dried over anhydrous sodium sulfate and evaporated to give **116** (360 mg, 80.2%) as a colorless oil. It was used directly in the next step without further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 4.40 - 4.36 (m, 2H), 4.34 - 4.23 (m, 1H), 4.20 - 4.19 (m, 1H), 4.12 - 4.08 (m, 1H), 3.032 (s, 3H), 2.00 - 1.99 (m, 2H), 1.41 (s, 3H), 1.35 (s, 3H).

Step 2

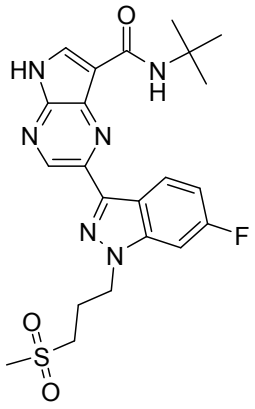
N-tert-Butyl-2-(5-(difluoromethoxy)-1-(3,4-dihydroxybutyl)-1H-indazol-3-yl)-5H-pyrrolo[3,2-b]pyrazine-7-carboxamide **32**



To a solution of **115** (100 mg, 0.156 mmol) in DMF (5 mL) was added **116** (42 mg, 0.187 mmol) followed by K_2CO_3 (65 mg, 0.468 mmol). The mixture was heated at 65 ^{o}C for 2

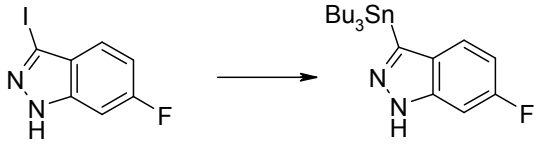
hours. After cooling to room temperature, the mixture was poured into water, the solid formed was separated by filtered, the filter cake washed with water and dried. Crude *N*-*tert*-butyl-2-(5-(difluoromethoxy)-1-(2-(2,2-dimethyl-1,3-dioxolan-4-yl)ethyl)-1H-indazol-3-yl)-5-trityl-5H-pyrrolo[3,2-b]pyrazine-7-carboxamide was dissolved in dichloromethane (1 mL), to this solution was added drop-wise trifluoroacetic acid (1 mL) at room temperature and the reaction mixture was stirred for 2 hours. The solvents were removed under reduced pressure and the residue was purified by preparative-HPLC (Gemini 5u C18 150×21.2 mm; inject volume: 3 mL/inj, flow rate: 20 mL/min; wavelength: 214 nm and 254 nm; gradient: 38% acetonitrile/62% water (0.1% trifluoroacetic acid) to 46% acetonitrile/54% water (0.1% trifluoroacetic acid) in a linear fashion over 9 min) to give **32** (30 mg, 39% over two steps) as a white solid. LCMS $(M+H)^+$ = 489.1; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 12.85 (s, 1H), 9.11 (s, 1H), 8.42 (d, 1H, *J*=3.0 Hz), 8.24 (d, 1H, *J*=1.2 Hz), 7.92 - 7.88 (m, 2H), 7.45 (t, 1H, *J*=9.2 Hz), 7.23 (t, 1H, *J*=74.4 Hz), 4.67 - 4.64 (m, 2H), 3.48 - 3.26 (m, 4H), 2.16 - 2.10 (m, 4H), 1.86 - 1.83 (m, 4H), 1.54 (s, 9H).

N-*tert*-Butyl-2-(6-fluoro-1-(3-(methylsulfonyl)propyl)-1H-indazol-3-yl)-5H-pyrrolo[3,2-b]pyrazine-7-carboxamide **33**



Step 1

6-Fluoro-3-tributylstannanyl-1H-indazole **117**

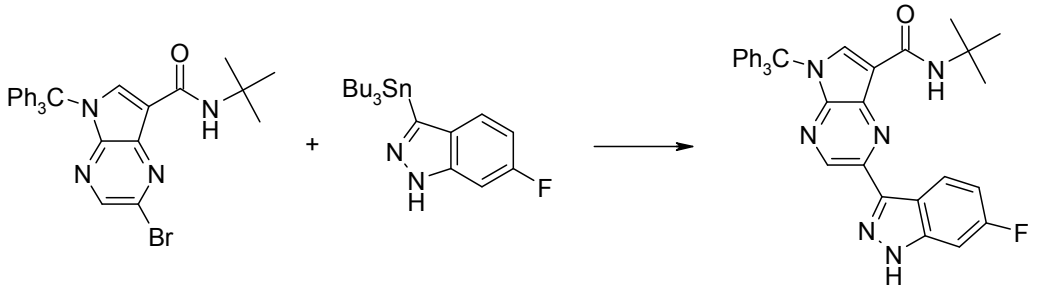


To a solution of 6-fluoro-3-iodo-1H-indazole (8.6 g, 32.8 mmol, available commercially from Beta Pharma Scientific, Inc.) in THF (200 mL) at 0 °C was slowly added portion-wise sodium hydride (60% in mineral oil, 1.58 g, 39.4 mmol). The reaction mixture was stirred at room temperature for 10 min then cooled to -10°C and isopropylmagnesium chloride (2.0 M in THF, 19.7 mL, 39.4 mmol) was added. The reaction mixture was stirred at -10°C for 30 min then additional isopropylmagnesium chloride (2.0 M in THF, 8.2 mL, 16.4 mmol) was added. The reaction mixture was stirred at -10°C for 30 min then tributylchlorostannane (11.6 mL, 42.7 mmol) was slowly added. Stirring was continued at -10°C for 20 min then at room temperature for 3 h. The reaction mixture was quenched with saturated aqueous NH_4Cl then

diluted with water and extracted with EtOAc (2x). The combined organics were washed with brine then dried over $MgSO_4$ and concentrated. The residue was purified by flash chromatography with 10% to 20% EtOAc/heptane (containing 0.5% Et_3N) to afford **117** (6.53 g, 47%) as a light brown viscous oil. ^1H NMR ($CDCl_3$, 300 MHz) δ: 7.65 (dd, *J*=8.7, 5.3 Hz, 1H), 7.20 (dd, *J*=9.3, 2.1 Hz, 1H), 6.92 (td, *J*=9.0, 2.1 Hz, 1H), 1.53 - 1.67 (m, 6H), 1.28 - 1.43 (m, 6H), 1.20 - 1.28 (m, 6H), 0.89 (t, *J*=7.4 Hz, 9H).

Step 2

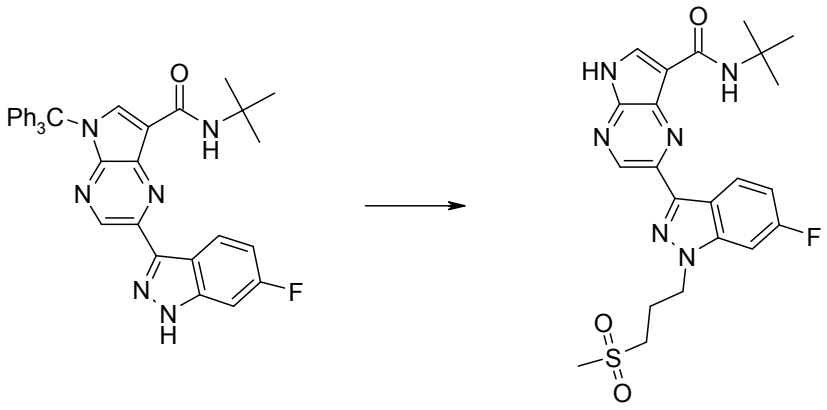
N-tert-Butyl-2-(6-fluoro-1H-indazol-3-yl)-5-trityl-5H-pyrrolo[3,2-b]pyrazine-7-carboxamide **118**



In a round-bottomed flask, **114** (600 mg, 1.12 mmol) and **117** (475 mg, 1.12 mmol) were dissolved in DMF (10 mL) under nitrogen. $Pd(PPh_3)_4$ (65 mg, 0.056 mmol) and CuI (43 mg, 0.224 mmol) were added and the mixture sonicated for 5 min while bubbling nitrogen through the solution. The reaction mixture was heated to 85 ^oC with stirring for 16 hours. After cooling to room temperature solvent was evaporated and the residue was purified by flash chromatography eluting with petroleum ether:EtOAc (3:1) to give **118** (180 mg, 27%) as a white solid. LCMS $(M+H)^+$ = 595; ^1H NMR (300 MHz, DMSO-d_6) δ: 13.60 (s, 1H), 8.78 (s, 1H), 8.45 - 8.40 (m, 1H), 8.01 (s, 1H), 7.95 (s, 1H), 7.45 - 7.33 (m, 10H), 7.21 - 7.09 (m, 7H), 1.50 (s, 9H).

Step 3

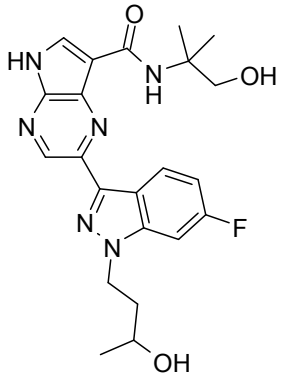
N-tert-Butyl-2-(6-fluoro-1-(3-(methylsulfonyl)propyl)-1H-indazol-3-yl)-5H-pyrrolo[3,2-b]pyrazine-7-carboxamide **33**



To a solution of **118** (60 mg, 0.1 mmol) in DMF (5 mL) was added 1-chloro-3-(methylsulfonyl)propane (19 mg, 0.12 mmol) followed by K_2CO_3 (42 mg, 0.3 mmol). The

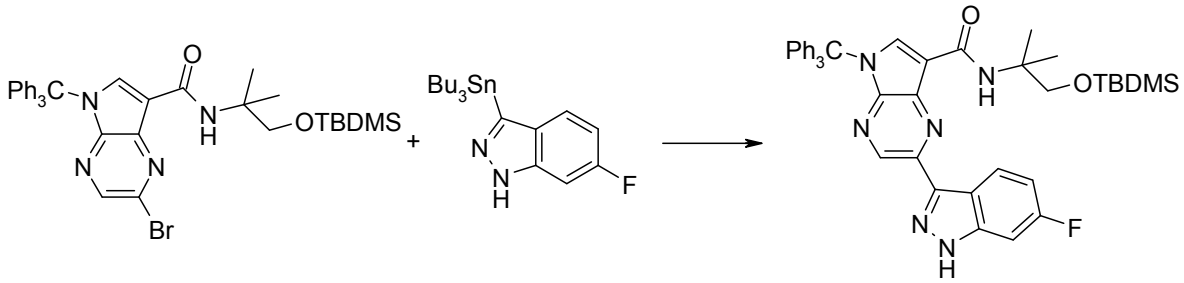
mixture was heated at 65 ^{o}C for 4 hours. After cooling to room temperature, the mixture was poured into water; the solid formed was separated by filtration and dried. Crude *N*-*tert*-butyl-2-(6-fluoro-1-(3-(methylsulfonyl)propyl)-1H-indazol-3-yl)-5-trityl-5H-pyrrolo[3,2-b]pyrazine-7-carboxamide (55 mg, 0.077 mmol) was dissolved in dichloromethane (2 mL), to this solution was added drop-wise trifluoroacetic acid (2 mL) at room temperature and the reaction mixture was stirred for 2 hours. The solvents were removed under reduced pressure and the residue was triturated with MeOH then decanted and dried to give **33** (26 mg, 33.7% for two steps) as a white solid. LCMS $(M+H)^+ = 473$; $(M+Na)^+ = 495$; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 12.84 (s, 1H), 9.09 (s, 1H), 8.51 - 8.46 (m, 1H), 8.38 (s, 1H), 7.93 (s, 1H), 7.74 (d, 1H, J = 9.9 Hz), 7.18 (t, 1H, J = 9.0 Hz), 4.63 (t, 2H, J = 6.6 Hz), 3.22 (t, 2H, J = 7.8 Hz), 2.99 (s, 3H), 2.33 (t, 2H, J = 7.4 Hz), 1.52 (s, 9H).

2-(6-Fluoro-1-(3-hydroxybutyl)-1H-indazol-3-yl)-*N*-(1-hydroxy-2-methylpropan-2-yl)-5H-pyrrolo[3,2-b]pyrazine-7-carboxamide **34**



Step 1

N-(1-(*tert*-Butyldimethylsilyloxy)-2-methylpropan-2-yl)-2-(6-fluoro-1H-indazol-3-yl)-5-trityl-5H-pyrrolo[3,2-b]pyrazine-7-carboxamide **119**

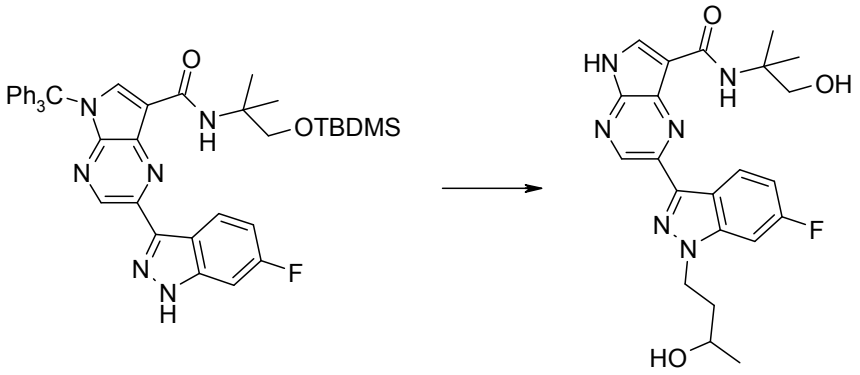


Compound **112** (287 mg, 0.674 mmol) and **117** (450 mg, 0.674 mmol) were dissolved in DMF (8 mL) under nitrogen. $Pd(PPh_3)_4$ (39 mg, 0.034 mmol) and CuI (26 mg, 0.136 mmol) were added and the mixture was sonicated for 5 min while bubbling nitrogen through the solution. The reaction mixture was then stirred at 85 ^{o}C for 4 h. The mixture was cooled down to room temperature, concentrated *in vacuo* and the residue purified by flash chromatography eluting with petroleum ether:EtOAC (5:1) to give **119** (100 mg, 20 %) as a white solid. LCMS $[M + H]^+$ 725.3; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.55 (*s*, 1H), 8.35 (*s*, 1H),

8.13 (*s*, 1H), 8.32 (*s*, 1H), 7.49 - 7.47 (*m*, 3H), 7.29 – 7.01 (*m*, 15H), 3.87 (*s*, 2H), 1.55 (*s*, 6H), 0.78 (*s*, 9H), 0.02 (*s*, 6H).

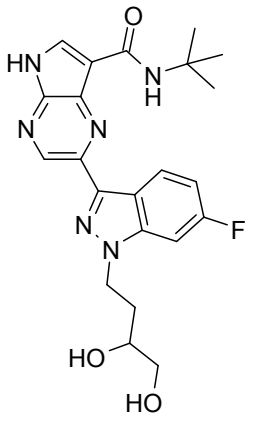
Step 2

2-(6-Fluoro-1-(3-hydroxybutyl)-1H-indazol-3-yl)-*N*-(1-hydroxy-2-methylpropan-2-yl)-5H-pyrrolo[3,2-b]pyrazine-7-carboxamide **34**

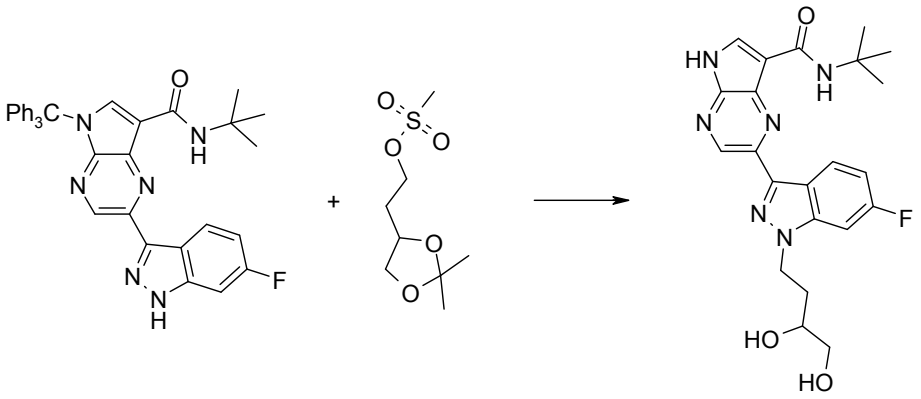


To a solution of **119** (60 mg, 0.083 mmol) in DMF (4 mL) was added 4-chlorobutan-2-one (11 mg, 0.1 mmol) followed by K_2CO_3 (34 mg, 0.25 mmol). The mixture was heated at 65 ^oC for 1.5 h. After cooling to room temperature, the mixture was poured into water and the formed solid was separated by filtration and dried. To crude *N*-(1-(*tert*-butyldimethylsilyloxy)-2-methylpropan-2-yl)-2-(6-fluoro-1-(3-oxobutyl)-1H-indazol-3-yl)-5-trityl-5H-pyrrolo[3,2-b]pyrazine-7-carboxamide (40 mg, 0.05 mmol) in MeOH (5 mL) was added $NaBH_4$ (10 mg, 0.25 mmol) at 0 ^oC. The mixture was stirred at room temperature for 1 hour. Aqueous NH_4Cl was added to the mixture to quench the reaction. The mixture was extracted with EtOAc (3×5 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated. Crude *N*-(1-(*tert*-butyldimethylsilyloxy)-2-methylpropan-2-yl)-2-(6-fluoro-1-(3-hydroxybutyl)-1H-indazol-3-yl)-5-trityl-5H-pyrrolo[3,2-b]pyrazine-7-carboxamide was dissolved in dichloromethane (2 mL), to this solution was added drop-wise trifluoroacetic acid (1 mL) at room temperature and the reaction mixture was stirred for 1 hour. The solvent was removed under reduced pressure, the residue was dissolved in dichloromethane and washed with an aqueous solution of $NaHCO_3$. The organic layer was dried (Na_2SO_4), concentrated and the residue was purified by preparative-HPLC (Gemini 5u C18 150×21.2 mm; inject volume: 3 mL/inj, flow rate: 20 mL/min; wavelength: 214 nm and 254 nm; gradient: 36% acetonitrile/64% water (0.1% trifluoroacetic acid) to 42% acetonitrile/58% water (0.1% trifluoroacetic acid) in a linear fashion over 9 min) to give **34** (10 mg, 33.3% over three steps) as a white solid. LCMS $(M+H)^+ = 441$; ^1H NMR (300 MHz, CD_3OD): δ 9.15 (s, 1H), 8.58 (dd, 1H, J_1 = 9. Hz, J_2 = 5.4 Hz), 8.29 (s, 1H), 7.42 (d, 1H, J = 7.8 Hz), 7.10 (d, 1H, J = 7.2 Hz), 4.62 - 4.56 (m, 2H), 3.82 (s, 2H), 3.76 (*br*s, 1H), 2.19 - 2.13 (m, 2H), 2.04 - 1.99 (m, 2H), 1.55 (s, 6H), 1.22 (d, 3H, J = 6.3 Hz).

N-*tert*-Butyl-2-(1-(3,4-dihydroxybutyl)-6-fluoro-1H-indazol-3-yl)-5H-pyrrolo[3,2-b]pyrazine-7-carboxamide **35**

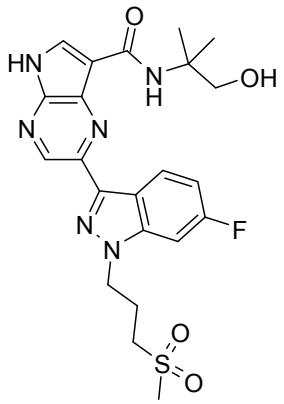


N-tert-Butyl-2-(1-(3,4-dihydroxybutyl)-6-fluoro-1H-indazol-3-yl)-5H-pyrrolo[3,2-b]pyrazine-7-carboxamide **35**

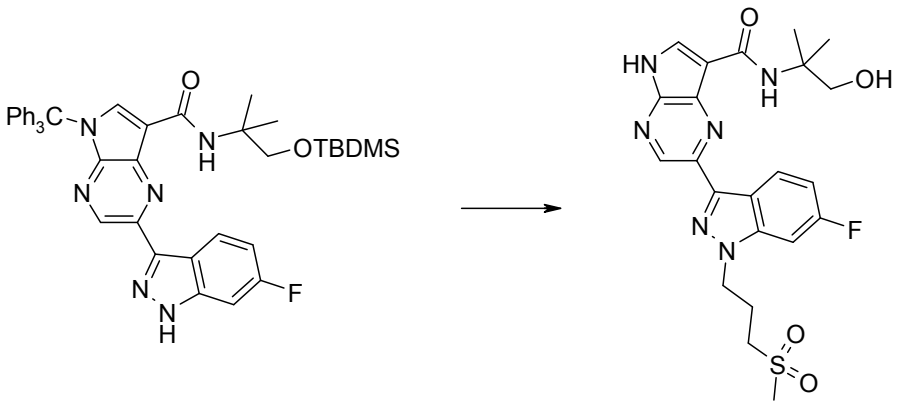


To a solution of **118** (80 mg, 0.135 mmol) in DMF (5 mL) was added **116** (36 mg, 0.162 mmol) followed by K_2CO_3 (56 mg, 0.405 mmol). The mixture was heated at 65 ^oC for 4 hours. After cooling to room temperature, the mixture was poured into water, the formed solid was separated by filtration and dried. Crude *N-tert*-butyl-2-(1-(2-(2,2-dimethyl-1,3-dioxolan-4-yl)ethyl)-6-fluoro-1H-indazol-3-yl)-5-trityl-5H-pyrrolo[3,2-b]pyrazine-7-carboxamide (90 mg, 0.125 mmol) was dissolved in dichloromethane (2 mL), to this solution was added drop-wise trifluoroacetic acid (2 mL) at room temperature and the reaction mixture was stirred for 2 hours. The solvent was removed under reduced pressure and the residue was purified by preparative-HPLC (Gemini 5u C18 150×21.2 mm; inject volume: 3 mL/inj, flow rate: 20 mL/min; wavelength: 214 nm and 254 nm; gradient: 30% acetonitrile/70% water (0.1% trifluoroacetic acid) to 70% acetonitrile/30% water (0.1% trifluoroacetic acid) in a linear fashion over 9 min) to give **35** (30 mg, 31.2% for two steps) as a white solid. LCMS $(M+H)^+ = 441$, $(M+Na)^+ = 463$; ^1H NMR (300 MHz, DMSO-d_6) δ: 12.81 (s, 1H), 9.06 (s, 1H), 8.47 - 8.42 (m, 1H), 8.37 (s, 1H), 7.91 (s, 1H), 7.64 (d, 1H, J = 9.9 Hz), 7.14 (dd, 1H, J1 = 9.0 Hz, J2 = 1.8 Hz), 4.57 (t, 2H, J = 6.5 Hz), 3.46 - 3.24 (m, 5H), 2.10 - 2.08 (m, 1H), 2.06 - 1.77 (m, 1H), 1.51 (s, 9H).

2-(6-Fluoro-1-(3-(methylsulfonyl)propyl)-1H-indazol-3-yl)-*N*-(1-hydroxy-2-methylpropan-2-yl)-5H-pyrrolo[3,2-b]pyrazine-7-carboxamide **36**

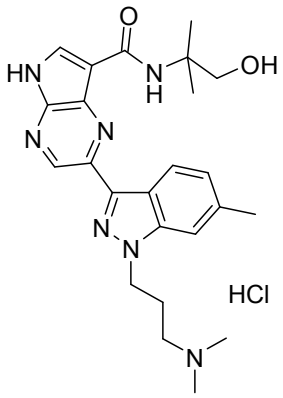


N-*tert*-2-(6-Fluoro-1-(3-(methylsulfonyl)propyl)-1H-indazol-3-yl)-*N*-(1-hydroxy-2-methylpropan-2-yl)-5H-pyrrolo[3,2-b]pyrazine-7-carboxamide **36**



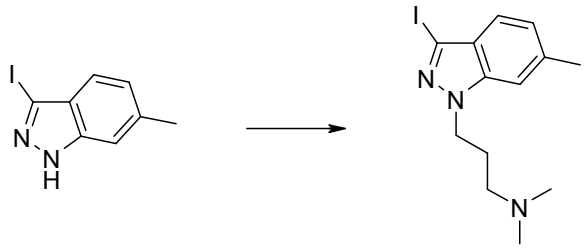
To a mixture of **119** (40 mg, 0.055 mmol) in DMF (3 mL) was added 1-chloro-3-(methylsulfonyl)propane (13 mg, 0.083 mmol) followed by K_2CO_3(23 mg, 0.165 mmol). The mixture was heated at 40 ^oC for 16 h, then cooled to room temperature and poured into water. The solid formed was separated by filtration and dried. Crude *N*-(1-(*tert*-butyldimethylsilyloxy)-2-methylpropan-2-yl)-2-(6-fluoro-1-(3-(methylsulfonyl)propyl)-1H-indazol-3-yl)-5-trityl-5H-pyrrolo[3,2-b]pyrazine-7-carboxamide (35 mg, 0.042 mmol) was dissolved in dichloromethane (2 mL), to this solution was added trifluoroacetic acid (1 mL) drop-wise at room temperature. The reaction mixture was stirred at room temperature for 1 h, and then concentrated *in vacuo*. The residue was dissolved in dichloromethane, washed with $NaHCO_3$ (aq.), dried (Na_2SO_4), concentrated and the residue was purified by preparative-HPLC (Gemini 5u C18 150×21.2 mm; inject volume: 3mL/inj, flow rate: 20 mL/min; wavelength: 214 nm and 254 nm; gradient: 25% acetonitrile/75% water (doped with 0.1% TFA) to 42% acetonitrile/58% water (doped with 0.1% TFA) in a linear fashion over 9 min) to give **36** (10 mg, 25 % for two steps) as a white solid. LCMS $(M + H)^+$ 489.2, $(M - H)^-$ 487.0; ^1H NMR (300 MHz, DMSO-d_6): δ 12.81 (*s*, 1H), 9.10 (*s*, 1H), 8.63 - 8.58 (*m*, 1H), 8.37 (*s*, 1H), 7.90 (*s*, 1H), 7.71 (*d*, 1H, *J* = 8.1 Hz), 7.16 (*t*, 1H, *J* = 9.2 Hz), 5.08 (*t*, 1H, *J* = 5.5 Hz), 4.62 (*t*, 2H, *J* = 6.6 Hz), 3.60 (*d*, 2H, *J* = 5.4 Hz), 3.18 (*t*, 2H, *J* = 6.4 Hz), 2.96 (*s*, 3H), 2.32 (*t*, 2H, *J* = 7.6 Hz), 1.43 (*s*, 6H).

2-(1-(3-(Dimethylamino)propyl)-6-methyl-1H-indazol-3-yl)-*N*-(1-hydroxy-2-methylpropan-2-yl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide hydrochloride **37**



Step 1

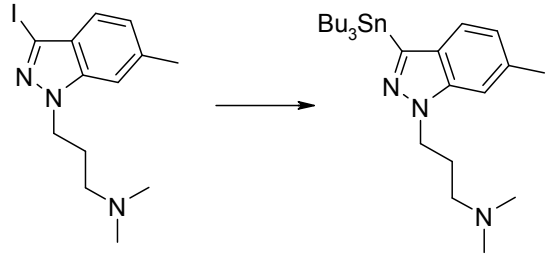
3-(3-Iodo-6-methyl-1H-indazol-1-yl)-N,N-dimethylpropan-1-amine **120**



A mixture of 3-iodo-6-methyl-1H-indazole (2.58 g, 10 mmol, available commercially from Anichem Inc.), 3-chloro-*N,N*-dimethylpropan-1-amine hydrochloride (2.37 g, 15 mmol) and potassium carbonate (4.14 g, 30 mmol) in DMF (50 mL) was heated to 85 ^{o}C for 3 hours. After cooling to room temperature, water (100 mL) was added and the mixture was extracted with ethyl acetate (4 ×100 mL). The combined organic layers were dried with sodium sulphate and concentrated to give **120** (1.74 g, 50.6%). LCMS $(M+H)^+$ = 344; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.33 (d, 1H, J = 8.4 Hz), 7.21 (s, 1H), 7.03 (d, 1H, J = 8.4 Hz), 4.43 (t, 2H, J = 6.6 Hz), 2.51 (s, 3H), 2.27 - 2.23 (m, 8H), 2.09 - 2.07 (m, 2H).

Step 2

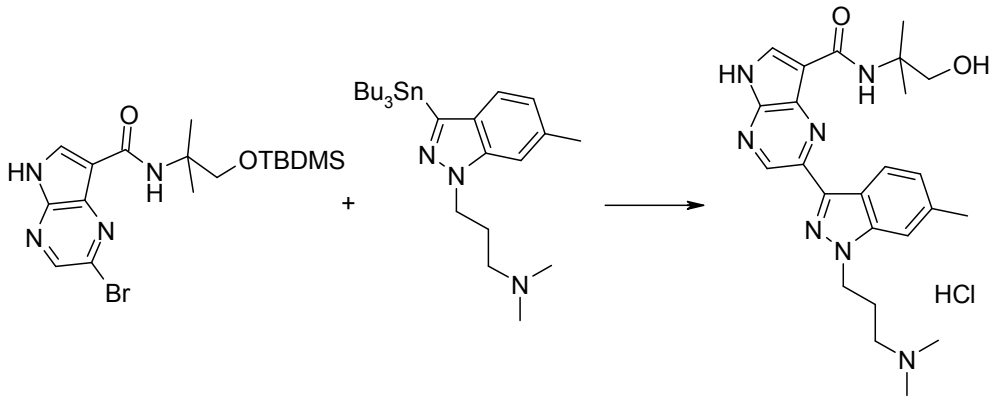
N,N-Dimethyl-3-(6-methyl-3-(tributylstannyl)-1H-indazol-1-yl)propan-1-amine **121**



A solution of **120** (480 mg, 1.4 mmol) in dry THF (20 mL) was cooled to -20 ^{o}C under nitrogen atmosphere, isopropylmagnesium chloride 2M in THF (1.4 mL, 2.8 mmol,) was added and stirred for 15 min at -20 ^{o}C. Then tributylchlorostannane (0.8 mL, 2.8 mmol) was added and allowed to warm to room temperature. The reaction was cooled in an ice bath and quenched with saturated ammonium chloride solution, product extracted with ethyl acetate (3 ×50 mL), combined organics dried with sodium sulfate and concentrated to give crude **121** (0.71 g, 100%) as an oil which was used immediately in the next step without further purification.

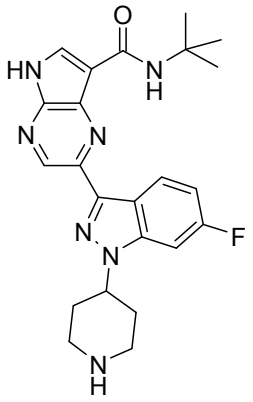
Step 3

2-(1-(3-(Dimethylamino)propyl)-6-methyl-1H-indazol-3-yl)-*N*-(1-hydroxy-2-methylpropan-2-yl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide hydrochloride **37**



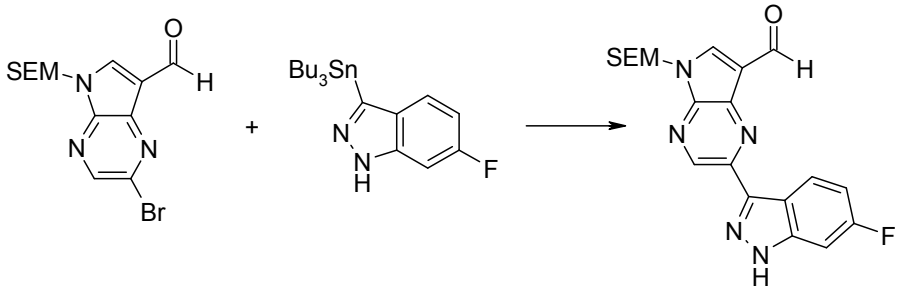
A mixture of **111** (300 mg, 0.7 mmol) and **120** (0.71 g, 1.4 mmol), tetrakis(triphenylphosphine)palladium (0) (10 mg, 0.087 mmol) and copper iodide (10 mg, 0.52 mmol) in dry DMF (15 mL) was heated to 85 ^{o}C overnight under N_2. The reaction mixture was cooled to room temperature, diluted with 50 mL of water and the formed solid was separated by filtration. The solid was washed with 2-methoxy-2-methylpropane (5 mL) and dried. Crude *N*-(1-(*tert*-butyldimethylsilyloxy)-2-methylpropan-2-yl)-2-(1-(3-(dimethylamino)propyl)-6-methyl-1H-indazol-3-yl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide (0.395 g, 0.7 mmol) was dissolved in methanol (10 mL), to this solution was added concentrated HCl (1 mL) and the mixture stirred for 3 hours at room temperature. The precipitate formed was separated by filtration, filter cake washed with 2-methoxy-2-methylpropane and dried to give **37** (25 mg, 7.3% for two steps). LCMS $(M+H)^{+}$ = 450; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 12.84 (s, 1H), 9.55 (s, 1H), 9.14 (s, 1H), 8.49 (d, 1H, *J* = 8.1 Hz), 8.40 (s, 1H), 7.96 (s, 1H), 7.62 (s, 1H), 7.17 (d, 1H, *J* = 8.4 Hz), 4.61 - 4.58 (m, 2H), 3.67 (s, 2H), 3.21 (s, 2H), 2.82 (s, 6H), 2.55 (s, 3H), 2.33 (*br*s, 2H), 1.49 (s, 6H).

2-(6-Fluoro-1-piperidin-4-yl-1H-indazol-3-yl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxylic acid *tert*-butylamide **38**



Step 1

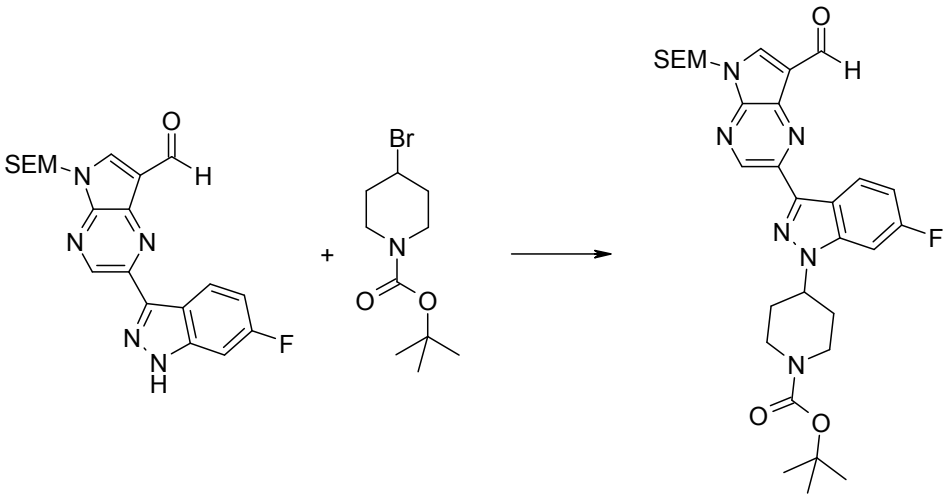
2-(6-Fluoro-1H-indazol-3-yl)-5-(2-trimethylsilanyl-ethoxymethyl)-5H-pyrrolo[2,3-b]pyrazine-7-carbaldehyde **122**



In a round-bottomed flask, **52** (5.47 g, 15.4 mmol) and **117** (6.53 g, 15.4 mmol) were dissolved in DMF (140 mL), then tetrakis(triphenylphosphine)palladium (0) (888 mg, 0.76 mmol) and copper (I) iodide (585 mg, 3.07 mmol) were added. The reaction mixture was purged with argon then heated at 80 °C for 1 h. The reaction was cooled to room temperature, quenched with saturated solution of NH_4Cl and extracted with EtOAc (2x). The combined organics were washed with saturated solution of LiCl and brine then dried over $MgSO_4$ and concentrated. The crude solid residue was recrystallized from EtOAc to afford 3.74 g of a white solid. The mother liquor was concentrated and purified by flash chromatography eluting with 50% to 100% EtOAc/heptane to provide an additional 1.75 g of material to yield **122** (5.49 g , 87%) as a white solid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 10.49 (s, 1H), 9.34 (s, 1H), 8.83 (dd, *J*=9.1, 5.3 Hz, 1H), 8.32 (s, 1H), 7.08 - 7.25 (m, 2H), 5.77 (s, 2H), 3.55 - 3.71 (m, 2H), 0.87 - 1.03 (m, 2H), -0.03 (s, 9H).

Step 2

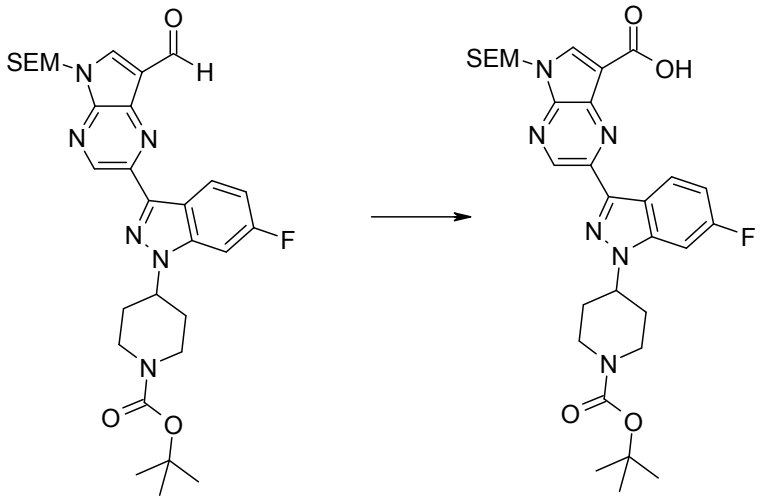
4-{6-Fluoro-3-[7-formyl-5-(2-trimethylsilanyl-ethoxymethyl)-5H-pyrrolo[2,3-b]pyrazin-2-yl]-indazol-1-yl}-piperidine-1-carboxylic acid *tert*-butyl ester **123**



A microwave vial was charged with **122** (182 mg, 0.44 mmol), *tert*-butyl 4-bromopiperidine-1-carboxylate (234 mg, 0.89 mmol, available commercially from Sigma-Aldrich), cesium carbonate (432 mg, 1.33 mmol) and DMF (2 mL). The vial was flushed with argon, sealed, and heated in a microwave reactor at 100 °C for 2 h. The reaction was quenched with water and extracted with diethyl ether (2x). The combined organic layers were washed twice with water and once with brine then dried over sodium sulfate, filtered and concentrated. The residue was purified by flash chromatography eluting with 0-30% EtOAc/hexanes to give **123** (108 mg, 41%) as a light brown solid. ^{1}H NMR (CHLOROFORM-d) δ: 10.52 (s, 1H), 9.33 (s, 1H), 8.84 (dd, J = 9.1, 5.1 Hz, 1H), 8.32 (s, 1H), 7.09 - 7.22 (m, 2H), 5.79 (s, 2H), 4.51 - 4.67 (m, 1H), 4.39 (d, J = 11.9 Hz, 2H), 3.56 - 3.71 (m, 2H), 3.07 (t, J = 12.3 Hz, 2H), 2.27 - 2.46 (m, 2H), 2.13 (d, J = 10.1 Hz, 2H), 1.56 (s, 9H), 0.94 - 1.09 (m, 2H), 0.00 (s, 9H).

Step 3

2-[1-(1-*tert*-Butoxycarbonyl-piperidin-4-yl)-6-fluoro-1H-indazol-3-yl]-5-(2-trimethylsilanyl-ethoxymethyl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxylic acid **124**

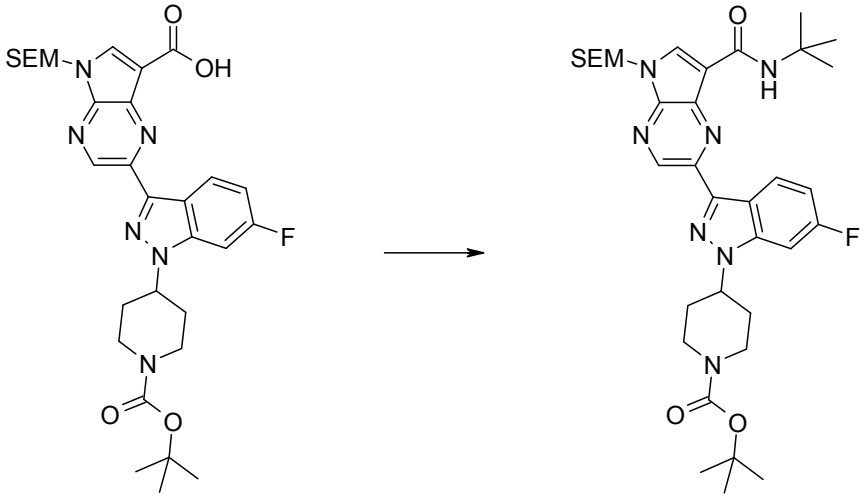


In a 50 mL round-bottomed flask, **123** (190 mg, 0.32 mmol) was dissolved in THF (7 mL) and water (1.4 mL). The light yellow solution was cooled to 0 °C and sulfamic acid (186 mg,

1.92 mmol) was added. Then, a solution of sodium chlorite (80%, 50 mg, 0.44 mmol) and potassium dihydrogen phosphate (522 mg, 3.83 mmol) in water (4.2 mL) was added drop-wise via pipette. After the addition was complete, the ice bath was removed and the reaction mixture was stirred at room temperature for 1.5 h. The reaction was diluted with water and extracted with EtOAc (2x). The combined organic layers were washed with water and brine then dried over sodium sulfate, filtered and concentrated. The residue was triturated with hexanes and dried to afford **124** (176 mg, 90%) as a light yellow powder. ^{1}H NMR (CHLOROFORM-d) δ: 9.36 (s, 1H), 8.48 (dd, J = 9.1, 5.3 Hz, 1H), 8.41 (s, 1H), 6.97 - 7.24 (m, 2H), 5.79 (s, 2H), 4.48 - 4.67 (m, 1H), 4.38 (d, J = 13.6 Hz, 2H), 3.52 - 3.81 (m, 2H), 3.06 (t, J = 11.5 Hz, 2H), 2.24 - 2.48 (m, 2H), 2.08 - 2.23 (m, 2H), 1.55 (s, 9H), 0.86 - 1.07 (m, 2H), 0.00 (s, 9H).

Step 4

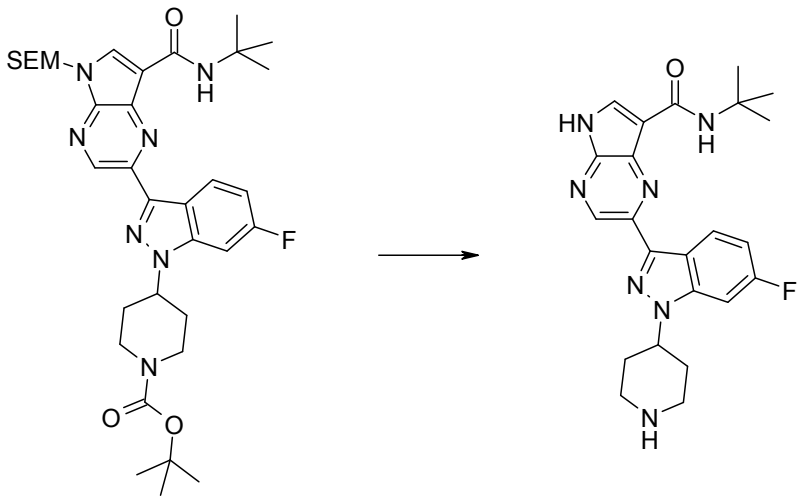
2-[1-(1-*tert*-Butoxycarbonyl-piperidin-4-yl)-6-fluoro-1H-indazol-3-yl]-5-(2-trimethylsilanyl-ethoxymethyl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxylic acid *tert*-butylamide **125**



In a 10 mL round-bottomed flask, **124** (85 mg, 0.14 mmol) was dissolved in DMF (1.5 mL), then *tert*-butylamine (0.06 mL, 0.57 mmol) and HATU (59 mg, 0.155 mmol) were added. The light yellow suspension was stirred at room temperature overnight then water and petroleum ether were added. The resulting suspension was filtered. The filter cake was washed with water and petroleum ether, dried under high vacuum and then purified by flash chromatography eluting with 0-30% EtOAc/hexanes to afford **125** (47 mg, 51%) as an off-white solid. ^{1}H NMR (CHLOROFORM-d) δ: 9.25 (s, 1H), 8.56 (dd, J = 8.6, 5.1 Hz, 1H), 8.40 (s, 1H), 8.15 (s, 1H), 7.21 (dd, J = 9.5, 1.9 Hz, 1H), 6.98 - 7.10 (m, 1H), 5.75 (s, 2H), 4.59 (s, 1H), 4.41 (br. s., 2H), 3.54 - 3.69 (m, 2H), 3.07 (t, J = 12.9 Hz, 2H), 2.28 - 2.47 (m, 2H), 2.14 (d, J = 9.1 Hz, 2H), 1.65 (s, 9H), 1.56 (s, 9H), 0.92 - 1.07 (m, 2H), 0.00 (s, 9H).

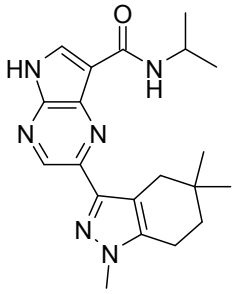
Step 5

2-(6-Fluoro-1-piperidin-4-yl-1H-indazol-3-yl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxylic acid *tert*-butylamide **38**



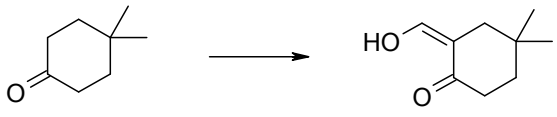
In a 10 mL round-bottomed flask, **125** (46 mg, 0.069 mmol) was dissolved in dichloromethane (0.4 mL) and trifluoroacetic acid (0.22 mL, 2.86 mmol) was added. The reaction mixture was stirred at room temperature for 2 h then concentrated. The residue was suspended in dichloromethane (0.4 mL) and ethylenediamine (0.28 mL, 4.15 mmol) was added. The light yellow suspension was stirred at room temperature for 1 h then quenched with water and diluted with ethyl acetate. The suspension was filtered, the filter cake washed with hot water and ethyl acetate then dried under high vacuum to give **38** (27 mg, 85%) as a light yellow powder. LCMS $(M+H)^+ = 436$; ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 9.08 (s, 1H), 8.47 (dd, *J*=8.9, 5.5 Hz, 1H), 8.39 (s, 1H), 7.96 (s, 1H), 7.77 - 7.85 (m, 1H), 7.10 - 7.22 (m, 1H), 4.70 - 4.88 (m, 1H), 3.13 (d, *J*=12.1 Hz, 2H), 2.67 - 2.81 (m, 2H), 2.01 - 2.20 (m, 2H), 1.88 - 2.01 (m, 2H), 1.52 (s, 9H).

N-Isopropyl-2-(1,5,5-trimethyl-4,5,6,7-tetrahydro-1H-indazol-3-yl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide **39**



Step 1

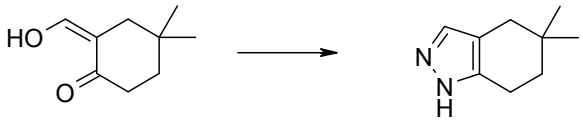
2-[1-Hydroxy-meth-(Z)-ylidene]-4,4-dimethyl-cyclohexanone **126**



A dry round-bottomed flask was charged with sodium hydride (60% dispersion in mineral oil, 475 mg, 11.9 mmol) and diethyl ether (24 mL). The reaction was cooled to 0 °C and ethanol (0.06 mL, 1.03 mmol) was added drop-wise. The suspension was stirred for at 0 °C for 20 min then a solution of 4,4-dimethylcyclohexanone (1.50 g, 11.9 mmol) and ethyl formate (1.45 mL, 17.8 mmol) in diethyl ether (3 mL) was added drop-wise over 15 min. The yellow solution was stirred at 0 °C for 3 h then slowly allowed to warm to room temperature overnight. Ethanol (0.24 mL) was added and the mixture was stirred at room temperature for 1 h then quenched with water and extracted with diethyl ether. The aqueous layer was acidified with 6M HCl until pH=2 then extracted with diethyl ether (2x). The combined organic layers were washed with brine then dried over sodium sulfate, filtered and concentrated to give **126** (1.30 g, 71%) of as a pale brown oil which was used without further purification. ^{1}H NMR (CDCl3, 300 MHz): δ (ppm) 14.40 (br. s., 1H), 8.58 (s, 1H), 2.39 (t, J=6.8 Hz, 2H), 2.13 (s, 2H), 1.48 (t, J=6.8 Hz, 2H), 1.00 (s, 6H).

Step 2

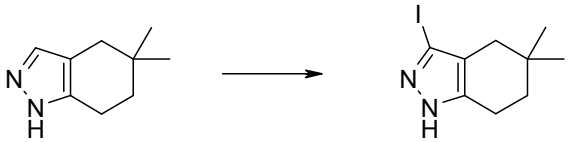
5,5-Dimethyl-4,5,6,7-tetrahydro-1H-indazole **127**



In a 100 mL round-bottomed flask, **126** (1.30 g, 8.43 mmol) was dissolved in methanol (8.5 mL). Hydrazine (0.27 mL, 8.43 mmol) was added very slowly which resulted in an exothermic reaction. The reaction mixture was stirred at room temperature for 50 min then concentrated. The residue was triturated with petroleum ether to afford **127** (1.05 g, 83%) as a light brown solid. ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) 7.28 (s, 1H), 2.67 (t, J=6.6 Hz, 2H), 2.32 (s, 2H), 1.60 (t, J=6.6 Hz, 2H), 0.99 (s, 6H).

Step 3

3-Iodo-5,5-dimethyl-4,5,6,7-tetrahydro-1H-indazole **128**

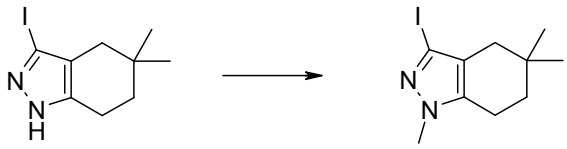


In a round-bottomed flask, **127** (0.50 g, 3.33 mmol) was dissolved in DMF (7 mL). Iodine (1.69 g, 6.66 mmol) was added followed by potassium hydroxide (723 mg, 12.9 mmol). The dark reaction mixture was stirred at room temperature for 1.25 h. Additional iodine (1.69 g, 6.66 mmol) and potassium hydroxide (723 mg, 12.9 mmol) were added and the dark brown reaction mixture was stirred at room temperature for 1.5 h. The reaction was quenched with 10% aqueous $NaHSO_3$ solution and extracted with diethyl ether (2x). The combined organic layers were washed twice with water and once with brine then dried over sodium sulfate, filtered and concentrated. The residue was adsorbed on silica gel and purified by flash

chromatography eluting with 0-20% EtOAc/Hexanes to give **128** (645 mg, 70%) as a white solid. ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) 2.66 (t, J=6.6 Hz, 2H), 2.14 (s, 2H), 1.59 (t, J=6.4 Hz, 2H), 1.01 (s, 6H).

Step 4

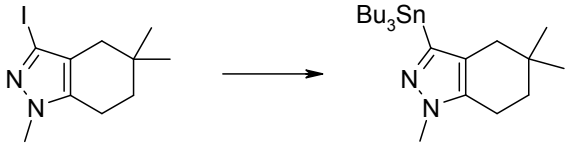
3-Iodo-1,5,5-trimethyl-4,5,6,7-tetrahydro-1H-indazole **129**



In a round-bottomed flask, **128** (642 mg, 2.33 mmol) was dissolved in THF (8.5 mL). The solution was cooled to 0 °C and potassium *tert*-butoxide (365 mg, 3.26 mmol) was added. The reaction mixture was stirred at 0 °C for 40 min then methyl iodide (0.18 mL, 2.88 mmol) was added drop-wise. The reaction mixture was warmed to room temperature and stirred for 1.5 h then quenched with water and extracted with EtOAc (2x). The combined organic layers were washed with water and brine then dried over sodium sulfate, filtered and concentrated. The residue was purified by flash chromatography eluting with 0-15% EtOAc/Hexanes to yield **129** (497 mg, 74%) as a white solid. ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) 3.76 (s, 3H), 2.53 (t, J=6.4 Hz, 2H), 2.11 (s, 2H), 1.58 (t, J=6.6 Hz, 2H), 0.99 (s, 6H).

Step 5

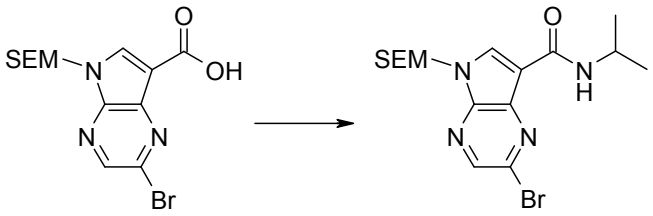
1,5,5-Trimethyl-3-tributylstannanyl-4,5,6,7-tetrahydro-1H-indazole **130**



In a round-bottomed flask, **129** (140 mg, 0.48 mmol) was dissolved in THF (3 mL). The colorless solution was cooled to -16 °C (NaCl/ice bath) and isopropylmagnesium chloride (2M in THF, 0.27 mL, 0.54 mmol) was added drop-wise. The reaction mixture was stirred at -16 °C for 20 min then tributylchlorostannane (0.15 mL, 0.55 mmol) was slowly added. The reaction mixture was allowed to warm to room temperature over 1.5 h then quenched with saturated NH_4Cl, diluted with water and extracted with EtOAc (2x). The combined organic layers were washed with water and brine then dried over sodium sulfate, filtered and concentrated to afford **130** as a colorless oil which was used immediately into the next step without further purification.

Step 6

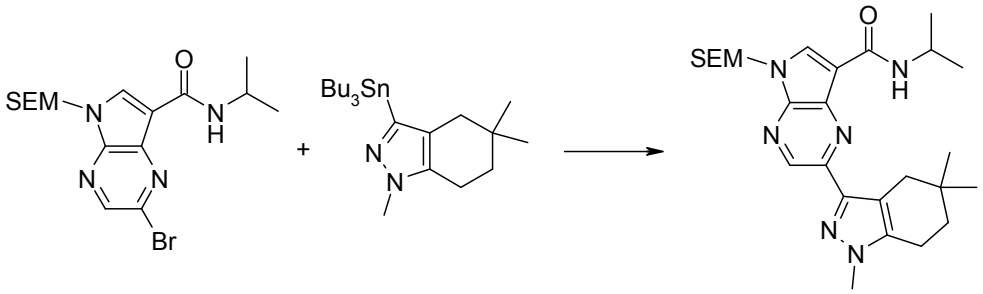
2-Bromo-*N*-isopropyl-5-((2-(trimethylsilyl)ethoxy)methyl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide **131**



Compound **59** (1.12 g, 3.01 mmol) and HATU (1.37 g, 3.61 mmol) were combined with DMF (5.2 mL) then propan-2-amine (711 mg, 1.03 mL) was added via syringe. The reaction mixture was stirred at 25 °C. After 14 h, water (50 mL) was added and the mixture extracted with EtOAc (4 x 50 mL). The combined organics were washed with water (30 mL), saturated sodium chloride solution (3 x 20 mL) and dried with $MgSO_4$. Solvents were evaporated and the residue purified by flash chromatography eluting with 0 to 30% EtOAc in hexanes to yield **131** (1.17 g, 94%) as a white solid. LCMS $(M+Na)^+$ = 435; ^1H NMR ($CDCl_3$) δ: 8.41 (s, 1H), 8.35 (s, 1H), 7.72 (d, *J*=4.9 Hz, 1H), 5.65 (s, 2H), 4.19 - 4.45 (m, 1H), 3.41 - 3.69 (m, 2H), 1.34 (d, *J*=6.8 Hz, 6H), 0.82 - 0.97 (m, 2H), -0.13 - 0.09 (m, 9H) .

Step 7

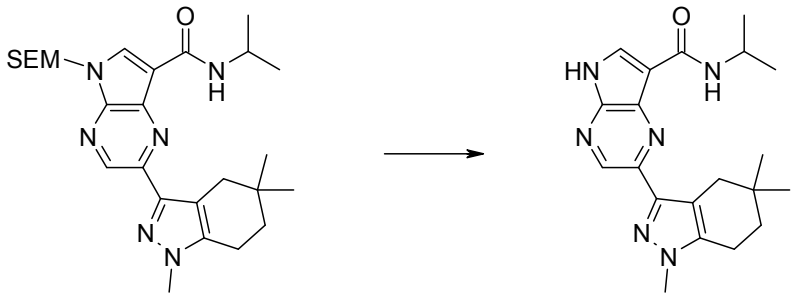
N-Isopropyl-2-(1,5,5-trimethyl-4,5,6,7-tetrahydro-1H-indazol-3-yl)-5-((2-(trimethylsilyl)ethoxy)methyl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide **132**



Compound **131** (124 mg, 301 µmol) and **130** (219 mg, 483 µmol.61) were dissolved in DMF (2.5 mL) under argon, tetrakis(triphenylphosphine)palladium (0) (17.4 mg, 15.0 µmol) and CuI (5.39 mg, 60.2 µmol) were added and the mixture sonicated for 5 min with bubbling argon through the solution. The reaction mixture was stirred at 90 °C (oil bath temperature) for 2.5 h. The reaction mixture was concentrated under high vacuum and the residue was purified by flash chromatography eluting with 0-70% EtOAc/hexanes to give **132** (113 mg, 76%) as a light yellow solid. LCMS $(M+Na)^+$ = 497; ^1H NMR ($CDCl_3$) δ: 9.08 (s, 1H), 8.28 (s, 1H), 5.68 (s, 2H), 4.38 - 4.56 (m, 1H), 3.86 (s, 3H), 3.50 - 3.59 (m, 2H), 2.80 (s, 2H), 2.65 (t, *J*=6.4 Hz, 2H), 1.69 (t, *J*=6.6 Hz, 2H), 1.36 (d, *J*=6.8 Hz, 6H), 1.07 (s, 6H), 0.88 - 0.96 (m, 2H), -0.06 (s, 9H).

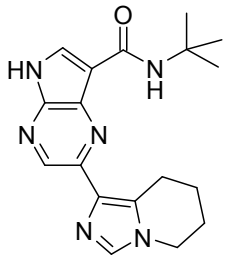
Step 8

N-isopropyl-2-(1,5,5-trimethyl-4,5,6,7-tetrahydro-1H-indazol-3-yl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide **39**



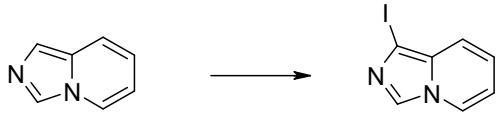
To a solution of **132** (113 mg, 227 µmol) in dichloromethane (3 mL) was added TFA (1.48 g, 1 mL). The reaction mixture was stirred at 25 °C for 15 h then concentrated. The residue was re-dissolved in 5 mL of a solution of dichloromethane/MeOH/ammonium hydroxide; 60:10:1 and stirred at 25 °C for 3 h, then evaporated to a yellow solid. The solid was purified by flash chromatography eluting with 0 to 5% (MeOH containing 10% ammonium hydroxide) in dichloromethane to give **39** (60 mg, 72%) as a white solid. LCMS $(M+H)^+$ = 367; ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 12.47 - 12.74 (m, 1 H), 8.91 (s, 1 H), 8.31 (s, 1 H), 7.92 (d, *J*=8.31 Hz, 1 H), 4.07 - 4.48 (m, 1 H), 3.78 (s, 3 H), 2.72 (s, 2 H), 2.64 (t, *J*=6.42 Hz, 2 H), 1.60 (t, *J*=6.42 Hz, 2 H), 1.26 (d, *J*=6.42 Hz, 6 H), 1.01 (s, 6 H).

2-(5,6,7,8-Tetrahydro-imidazo[1,5-a]pyridin-1-yl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxylic acid *tert*-butylamide **40**



Step 1

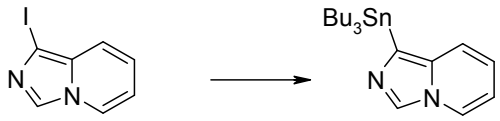
1-Iodo-imidazo[1,5-a]pyridine **133**



To a solution of imidazo[1,5-a]pyridine (0.50 g, 4.23 mmol) in EtOH (8 mL) and water (4 mL) was added sodium bicarbonate (1.07 g, 12.7 mmol) followed by iodine (1.61 g, 6.35 mmol). The dark maroon-brown heterogeneous reaction mixture was stirred at room temperature overnight then quenched with aqueous 10% $Na_2S_2O_3$, diluted with water and extracted with EtOAc (3x). The combined organics were washed with water, dried over $MgSO_4$ and concentrated. The residue was purified by flash chromatography eluting with 20 to 50% EtOAc/hexanes to afford **133** (649 mg, 63%) as a light brown solid (light sensitive). ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) 8.13 (s, 1H), 7.92 (d, *J*=6.8 Hz, 1H), 7.33 (d, *J*=9.4 Hz, 1H), 6.80 (dd, *J*=9.4, 6.8 Hz, 1H), 6.56 - 6.69 (m, 1H).

Step 2

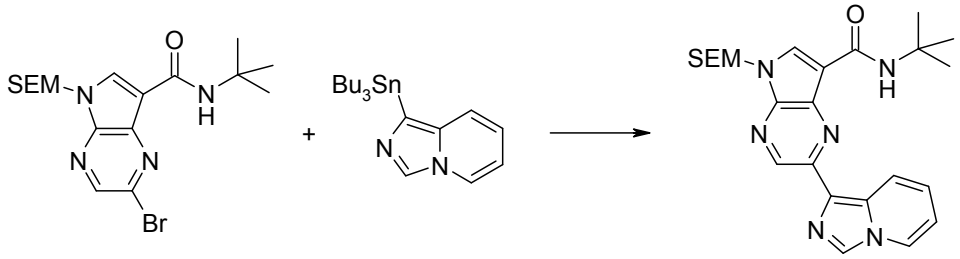
1-Tributylstannanyl-imidazo[1,5-a]pyridine **134**



To a solution of **133** (150 mg, 0.62 mmol) in THF (3 mL) at -10°C (ice/acetone bath) was added isopropylmagnesium chloride (2M in THF, 37 mL, 0.74 mmol). The reaction mixture was stirred at -10 °C for 20 min then tributylchlorostannane (0.20 mL, 0.74 mmol) was added. The reaction was stirred at -10 °C for 30 min then warmed to room temperature and stirred for 1 h. The reaction was quenched with water and extracted with EtOAc (2x). The combined organics were dried over $MgSO_4$ and concentrated to afford **134** as a yellow oil which was used immediately into the next step without further purification.

Step 3

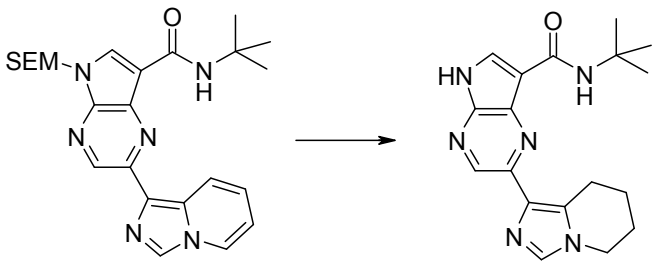
2-Imidazo[1,5-a]pyridin-1-yl-5-(2-trimethylsilanyl-ethoxymethyl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxylic acid *tert*-butylamide **135**



To a solution of **134** (250 mg, 0.61 mmol) and **60** (150 mg, 0.35 mmol) in DMF (2 mL) were added $Pd(PPh_3)_4$ (20 mg, 0.018 mmol) and copper (I) iodide (13 mg, 0.07 mmol). The reaction mixture was heated at 90 °C for 2 h then cooled to room temperature overnight. The reaction was quenched with water and extracted with EtOAc (3x). The combined organics were washed with water (3x) then dried over $MgSO_4$ and concentrated. The residue was purified by flash chromatography once with 0% to 3% MeOH/CH_2Cl_2 (containing 0.5%NH_4OH) and then with 30% to 60% EtOAc/hexanes to afford **135** (74 mg, 45%) as a bright yellow solid. ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) 9.35 (s, 1H), 8.53 (d, *J*=9.4 Hz, 1H), 8.38 (s, 1H), 8.32 (s, 1H), 8.12 (d, *J*=7.2 Hz, 1H), 8.05 (s, 1H), 6.99 (dd, *J*=9.4, 6.6 Hz, 1H), 6.77 - 6.87 (m, 1H), 5.74 (s, 2H), 3.54 - 3.68 (m, 2H), 1.67 (s, 9H), 0.90 - 1.06 (m, 2H), 0.00 (s, 9H).

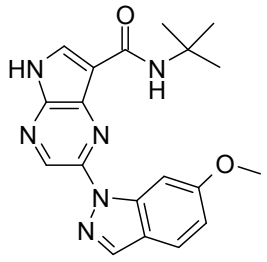
Step 4

2-(5,6,7,8-Tetrahydro-imidazo[1,5-a]pyridin-1-yl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxylic acid *tert*-butylamide **40**



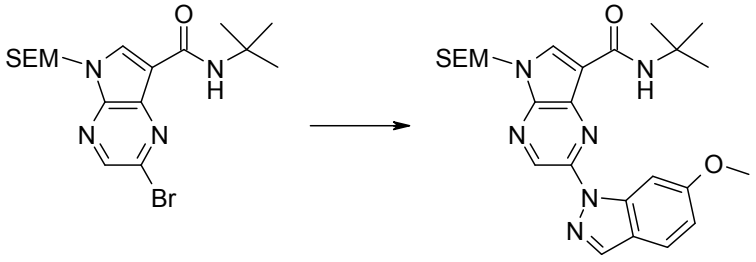
To a solution of **135** (70 mg, 0.15 mmol) in TFA (2 mL) was added platinum (IV) oxide (7 mg, 0.03 mmol). The reaction mixture was stirred under hydrogen filled balloon for 6 h then filtered over celite, rinsing with CH_2Cl_2. The filtrate was concentrated and the residue was dissolved in CH_2Cl_2 (3 mL) and treated with ethylenediamine (0.4 mL). The reaction mixture was stirred for 1 h then quenched with water and extracted with CH_2Cl_2 (2x). The combined organics were dried over $MgSO_4$ and concentrated. The residue was purified by flash chromatography eluting with 0 to 3% MeOH/CH_2Cl_2 (containing 0.5% NH_4OH) to afford a yellow solid which was triturated with Et_2O to obtain **40** (13 mg, 26%) as a pale yellow solid. LCMS $(M+H)^+ = 339$; ^1H NMR (DMSO-d_6, 300 MHz): δ (ppm) 12.50 (br. s., 1H), 8.96 (s, 1H), 8.21 (s, 1H), 7.75 (s, 1H), 7.66 (s, 1H), 4.06 (t, *J*=5.9 Hz, 2H), 3.21 (t, *J*=6.2 Hz, 2H), 1.76 - 1.98 (m, 4H), 1.46 (s, 9H).

2-(6-Methoxy-indazol-1-yl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxylic acid *tert*-butylamide **41**



Step 1

N-*tert*-Butyl-2-(6-methoxy-1H-indazol-1-yl)-5-((2-(trimethylsilyl)ethoxy)methyl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide **136**

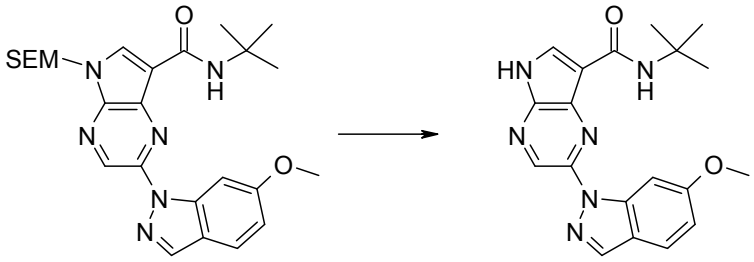


To a stirred solution of **60** (200 mg, 468 µmol), 6-methoxy-1H-indazole (69.3 mg, 468 µmol) in dioxane (3.5 mL) was added sodium *tert*-butoxide (98.9 mg, 1.03 mmol) and bis(tri-*tert*-butylphosphine)palladium (0) (23.9 mg, 46.8 µmol). The mixture was degassed then heated in sealed tube at 125 °C for two days. The mixture was cooled, filtered through celite, the

filter cake washed with ethyl acetate, and the combined filtrates were concentrated *in vacuo*. The residue was purified by flash chromatography eluting with 0-30% ethyl acetate in hexanes to give **136** (131 mg, 57%). ^{1}H NMR ($CDCl_3$) δ: 9.06 (s, 1H), 8.33 (s, 1H), 8.18 (d, *J*=0.8 Hz, 1H), 7.95 (d, *J*=2.0 Hz, 1H), 7.80 (s, 1H), 7.73 (d, *J*=8.8 Hz, 1H), 7.01 (dd, *J*=8.8, 2.3 Hz, 1H), 5.71 (s, 2H), 3.94 (s, 3H), 3.53 - 3.63 (m, 2H), 1.57 (s, 9H), 0.91 - 0.98 (m, 2H), -0.03 (s, 9H).

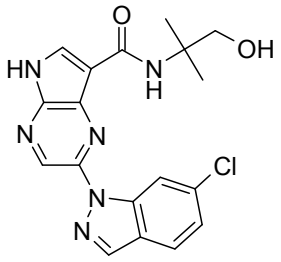
Step 2

2-(6-Methoxy-indazol-1-yl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxylic acid *tert*-butylamide **41**



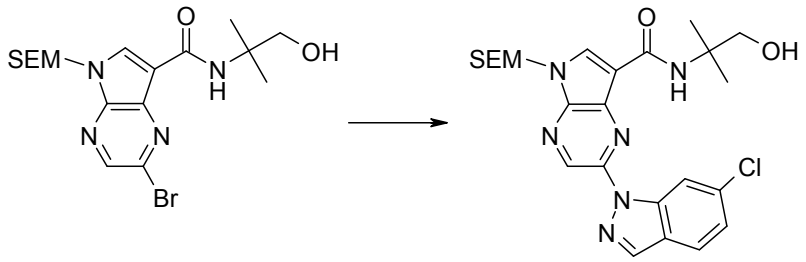
To a stirred solution of **136** (130 mg, 263 μmol) in dichloromethane (3 mL) was added trifluoroacetic acid (1 mL). After 15 h, the mixture was concentrated *in vacuo*, the residue dissolved in 25 mL of a mixture of ammonium hydroxide/methanol/dichloromethane (1/10/60) and mixture stirred for 1 h then concentrated *in vacuo*. The residue was purified by flash chromatography eluting with 0-4% (methanol containing 10% ammonium hydroxide) in dichloromethane) to give **41** (63 mg, 66%). LCMS $(M+H)^+$ = 365; ^{1}H NMR (DMSO-d_6) δ: 8.92 (s, 1H), 8.40 (d, *J*=5.1 Hz, 2H), 8.01 (s, 1H), 7.85 (d, *J*=8.9 Hz, 1H), 7.67 (s, 1H), 7.07 (dd, *J*=8.9, 2.0 Hz, 1H), 3.91 (s, 3H), 1.46 (s, 9H).

2-(6-Chloro-indazol-1-yl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxylic acid (2-hydroxy-1,1-dimethyl-ethyl)-amide **42**



Step 1

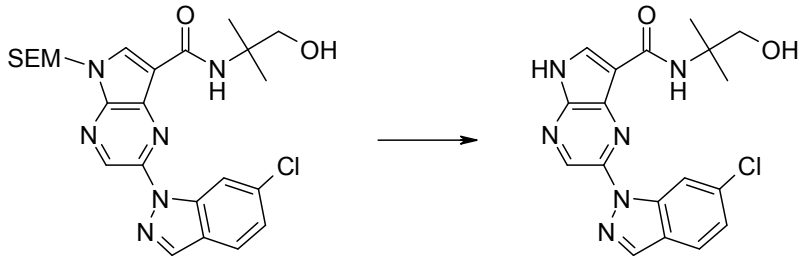
2-(6-Chloro-1H-indazol-1-yl)-*N*-(1-hydroxy-2-methylpropan-2-yl)-5-((2-(trimethylsilyl)ethoxy)methyl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide **137**



A resealable vessel was charged with **65** (140 mg, 316 µmol), copper (I) iodide (3.17 mg, 35.4 µmol), sodium iodide (94.7 mg, 631 µmol) and trans-*N,N*'-dimethylcyclohexane-1,2-diamine (11.5 mg, 80.5 µmol) in toluene (2 mL). The reaction mixture was sealed under nitrogen and then heated at 110 °C for 15 h. 6-Chloro-1H-indazole (48.2 mg, 316 µmol) and potassium phosphate tribasic (141 mg, 663 µmol) were added and the mixture degassed and backfilled with nitrogen, then heated at 110 °C for 15 h. After cooling to room temperature the mixture was filtered, the filter cake washed with ethyl acetate and the filtrate concentrated *in vacuo*. Purification by flash chromatography eluting with 0-40% ethyl acetate in hexanes gave **137** (124 mg, 76%). ^{1}H NMR ($CDCl_3$) δ: 9.14 (s, 1H), 8.51 - 8.55 (m, 1H), 8.38 (s, 1H), 8.26 (d, *J*=1.0 Hz, 1H), 7.91 (s, 1H), 7.78 (dd, *J*=8.5, 0.5 Hz, 1H), 7.33 (dd, *J*=8.5, 1.8 Hz, 1H), 5.73 (s, 2H), 3.80 (s, 2H), 3.57 - 3.64 (m, 2H), 1.56 (s, 6H), 0.96 (dd, *J*=8.8, 7.8 Hz, 2H), -0.02 (s, 9H).

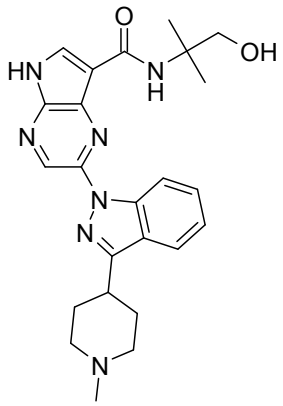
Step 2

2-(6-Chloro-indazol-1-yl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxylic acid (2-hydroxy-1,1-dimethyl-ethyl)-amide **42**



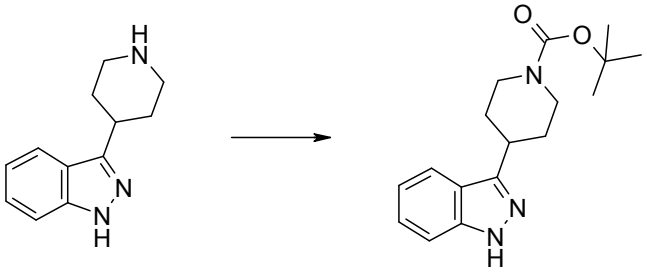
To a stirred solution of **137** (124 mg, 241 µmol) in dichloromethane (2 mL) was added trifluoroacetic acid (1 mL). After 15 h the mixture was concentrated and the residue dissolved in 25 mL of a 1/10/60 mixture of ammonium hydroxide/methanol/dichloromethane with stirring. After 1h the mixture was concentrated *in vacuo*. Purification by flash chromatography eluting with 0-4% (methanol containing 10% ammonium hydroxide) in dichloromethane gave **42** (75 mg, 81%). LCMS $(M+H)^+$ = 385; ^{1}H NMR (DMSO-d_6) δ: 8.97 (s, 1H), 8.56 (s, 2H), 8.44 (s, 1H), 7.99 (d, *J*=8.7 Hz, 1H), 7.64 (s, 1H), 7.36 - 7.48 (m, 1H), 3.62 (d, *J*=5.7 Hz, 2H), 1.43 (s, 6H).

2-[3-(1-Methyl-piperidin-4-yl)-indazol-1-yl]-5H-pyrrolo[2,3-b]pyrazine-7-carboxylic acid (2-hydroxy-1,1-dimethyl-ethyl)-amide **43**



Step 1

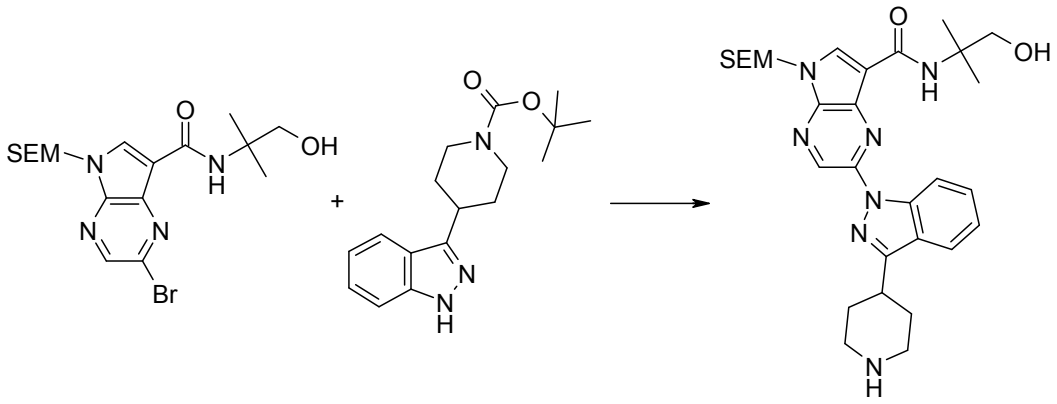
tert-Butyl 4-(1H-indazol-3-yl)piperidine-1-carboxylate **138**



A round bottom flask was charged with 3-(piperidin-4-yl)-1H-indazole (200 mg, 994 µmol), di-*tert*-butyl dicarbonate (217 mg, 994 µmol, available commercially from J & W PharmLab, LLC) and triethylamine (121 mg, 166 µL, 1.19 mmol) in dichloromethane (4 mL). The mixture was stirred at room temperature for 18 h, then added some methanol and the mixture partitioned between water and ethyl acetate. The organic layer was washed with water (3x), dried over $MgSO_4$ and concentrated to yield **138** (263 mg, 87.8%). ^{1}H NMR (300 MHz, CHLOROFORM-d) δ 7.69 (d, *J* = 8.10 Hz, 1H), 7.37 - 7.48 (m, 1H), 7.27 - 7.36 (m, 1H), 7.08 (ddd, *J* = 0.94, 6.88, 8.01 Hz, 1H), 4.08 - 4.30 (m, 2H), 3.08 - 3.27 (m, 1H), 2.88 (t, *J* = 11.02 Hz, 2H), 1.78 - 2.05 (m, 4H), 1.42 (s, 9H).

Step 2

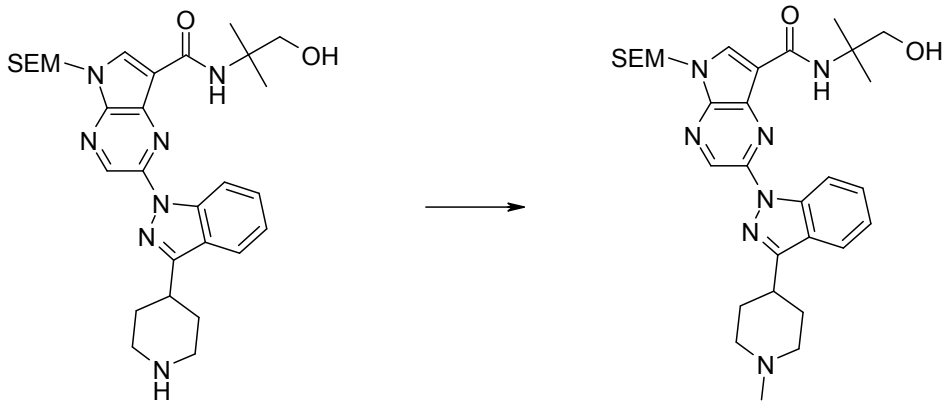
N-(1-Hydroxy-2-methylpropan-2-yl)-2-(3-(piperidin-4-yl)-1H-indazol-1-yl)-5-((2-(trimethylsilyl)ethoxy)methyl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide **139**



A resealable vessel was charged with **65** (150 mg, 338 µmol), **138** (102 mg, 338 µmol), sodium *tert*-butoxide (71.5 mg, 744 µmol) and bis(tri-*tert*-butylphosphine)palladium (0) (17.3 mg, 33.8 µmol) in dioxane (2.5 mL). The mixture was degassed with nitrogen then sealed and heated to 125 °C for 15 h. The mixture was cooled to room temperature, filtered through celite, and the filter cake washed with ethyl acetate. The combined filtrates were concentrated *in vacuo*. Filtered through a plug of silica gel eluting with 40% ethyl acetate in hexanes to give **139** (198 mg, 88%). A portion of this material (120 mg, 181 µmol) was dissolved in 2,2,2-trifluoroethanol (2 mL) was heated under microwaves at 150 °C for 4 h. The mixture was concentrated *in vacuo* and used immediately in the next step without purification.

Step 3

N-(1-Hydroxy-2-methylpropan-2-yl)-2-(3-(1-methylpiperidin-4-yl)-1H-indazol-1-yl)-5-((2-(trimethylsilyl)ethoxy)methyl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide **140**

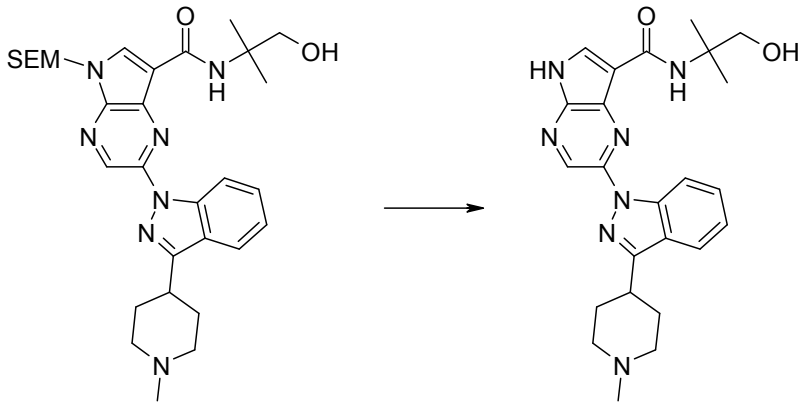


A stirred solution of **139** (100 mg, 177 µmol) in methanol (4 mL) was cooled to 0 °C and added 37% aqueous formaldehyde (1 mL, 13.4 mmol), followed by the addition of sodium triacetoxyborohydride (84.6 mg, 399 µmol). The reaction mixture was stirred at room temperature for 15 h then concentrated *in vacuo*. The residue was purified by flash chromatography eluting with 0-6% (methanol containing 10% ammonium hydroxide) in dichloromethane to give **140** (57 mg, 56%). LCMS $(M+H)^+$ = 578. ^{1}H NMR (CHLOROFORM-d) δ: 9.19 (s, 1H), 8.58 (d, J = 8.5 Hz, 1H), 8.35 (s, 1H), 8.05 (s, 1H), 7.93 (d, J = 8.1 Hz, 1H), 7.52 (t, J = 7.6 Hz, 1H), 7.35 (t, J = 7.3 Hz, 1H), 5.74 (s, 2H), 3.83 (s,

2H), 3.62 (t, J = 8.3 Hz, 2H), 3.02 - 3.31 (m, 3H), 2.46 (s, 3H), 2.11 - 2.38 (m, 6H), 1.56 (s, 6H), 0.91 - 1.02 (m, 2H), 0.00 (s, 9H).

Step 4

2-[3-(1-Methyl-piperidin-4-yl)-indazol-1-yl]-5H-pyrrolo[2,3-b]pyrazine-7-carboxylic acid (2-hydroxy-1,1-dimethyl-ethyl)-amide **43**



To a stirred solution of **140** (57 mg, 98.7 μmol) in dichloromethane (3 mL) was added trifluoroacetic acid (1 mL). After 15 h the mixture was concentrated *in vacuo* and the residue dissolved with stirring in 25 mL of a 1/10/60 mixture of ammonium hydroxide/methanol/dichloromethane. After 1 h the mixture was concentrated *in vacuo* and the residue purified by flash chromatography eluting with 0-6% (methanol containing 10% ammonium hydroxide) in dichloromethane to give **43** (10 mg, 23%). LCMS $(M+H)^+$ = 447; ^{1}H NMR (DMSO-d_6) δ: 9.00 (s, 1H), 8.64 (d, *J*=8.5 Hz, 1H), 8.37 (s, 1H), 7.99 (d, *J*=7.9 Hz, 1H), 7.65 (s, 1H), 7.57 (t, *J*=7.3 Hz, 1H), 7.35 (t, *J*=7.5 Hz, 1H), 5.06 (t, *J*=5.7 Hz, 2H), 3.62 (d, *J*=5.7 Hz, 2H), 2.98 (d, *J*=11.5 Hz, 2H), 2.30 (s, 3H), 1.94 - 2.24 (m, 5H), 1.44 (s, 6H).

SYK Assay Information

Determination of IC_{50} of Spleen Tyrosine Kinase (SYK) inhibition:
SYK kinase assay is a standard kinase assay adapted to a 96 well plate format. This assay is performed in 96-well format for IC_{50} determination with 8 samples which represented 10 half log dilutions and a 40 μL reaction volume. The assay measures the incorporation of radiolabeled ^{33}P -ATP into an *N*-terminally biotinylated peptide substrate, derived from naturally occurring phosphoacceptor consensus sequence (Biotin-11aa DY*E). Phosphorylated products were detected upon termination of reactions with EDTA and the addition of Streptavidin coated beads.
Assay plates: 96-well MultiScreen 0.65 μm filter plates (Millipore Cat. No.: MADVNOB10)
Streptavidin coated beads: Streptavidin Sepharose TM, suspension 5.0 mL, in 50 mM EDTA/PBS (Phosphate buffered saline) diluted (1:100), (Amersham, Cat. No.: 17-5113-01).
Compounds: 10 mM in 100% dimethylsulfoxide (DMSO), final conc.: compound 0.003-100 μM in 10% DMSO.
Enzyme: SYK RPA purified, truncated construct of Spleen Tyrosine Kinase aa 360-635, stock solution 1 mg/mL, MW: 31.2 KDa, final conc.: 0.0005 μM.

Peptide 1: biotinylated peptide is derived from a naturally occurring phosphor-acceptor consensus sequence (Biotin-EPEGDYEEVLE), special order from QCB, stock solution 20 mM, final conc.: 5.0 μM.
ATP: Adenosine-5□-triphosphate 20 mM, (ROCHE Cat. No.: 93202720), final concentration: 20 μM.
Buffer: HEPES: 2-Hydroxyethyl piperazine-2-ethanesulfonic acid (Sigma, Cat. No.: H-3375) final concentration: 50 mM HEPES, pH 7.5.
BSA: Bovine Serum Albumin Fraction V, fatty acid free (Roche Diagnostics GmbH, Cat. No. 9100221) diluted to a final concentration of 0.1%.
EDTA: EDTA stock solution 500 mM, (GIBCO, Cat. No.: 15575-038) final concentration: 0.1 mM.
DTT: 1,4-Dithiothreitol (Roche Diagnostics GmbH, Cat. No.: 197777), final conc.: 1 mM.
$MgCl_2x6H_2O$: MERCK, Cat. No.: 105833.1000, final concentration: 10 mM
Assay Dilution Buffer (ADB): 50 mM HEPES, 0.1 mM EGTA, 0.1 mM Na Vanadate, 0.1 mM β-glycerophosphate, 10 mM $MgCl_2$, 1 mM DTT, 0.1% BSA, pH 7.5.
Bead wash buffer: 10 g/L PBS (Phosphate buffered saline) with 2M NaCl + 1% phosphoric acid.

Experimental Method:

In 40 μL volume, 26 μL of ADB diluted, purified recombinant human SYK360-635 [0.5 nM] was mixed with 4 μL of 10X concentrations of the test compounds, [usually 100 μM- 0.003 μM] in [10%] DMSO and the mixture was incubated for 10 min at RT.
The kinase reaction was initiated by the addition of 10 μL 4x substrate cocktail containing the DYE peptide substrate [0 or 5 μM], ATP [20 μM] and $^{33}P\gamma ATP$ [2μCi/rxn]. After incubation at 30° C for 15 min, the reaction was terminated by the transfer of 25 μL of the reaction sample to a 96 well 0.65 μm Millipore MADVNOB membrane/plate containing 200 μL 5 mM EDTA and 20% Streptavidine coated beads in PBS.
The unbound radionucleotides were washed under vacuum with 3 x 250 μL 2M NaCl; 2 x 250 μL 2M NaCl + 1% phosphoric acid; 1 x 250 μL H_2O. After the last wash membrane/ plates were transferred to an adaptor plate, heat dried for 15 min at 60° C, and 50 μL scintillation cocktail was added to each well and 4 h later the amount of radioactivity was counted in a top counter.
The percent inhibition was calculated based on the uninhibited enzyme rate:
% Inhibition= $100 / (1 + (IC_{50}/\text{Inhibitor conc})^n)$
The IC_{50} was calculated using a non-linear curve fit with XLfit software (ID Business Solution Ltd., Guilford, Surrey, UK).