Discovery of Pyridazinone and Pyrazolo[1,5-*a*]pyridine Inhibitors of C-terminal Src Kinase

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Production of LCK protein for crystallography:
Large scale protein production was carried out in a 50 L cell bag using WAVE-Bioreactor System 20/50 (GE Healthcare Bioscience). A 24L of 2 × 10^6 cells/ml Sf9 cells in ESF921 insect medium (Expression System) was infected with His-TVMV-hLck(225-509)-pFB P2 virus stock (5ml/L) at 27 °C for 66 hours. The infected cells were harvested by centrifugation at 2000 rpm for 20 min at 4 ºC in a SORVALL® RC12BP centrifuge. The cell pellets were washed once with cold PBS buffer and was stored at -70 ºC before protein was purified.

Purification of LCK protein for crystallography:
All steps performed at 4°C unless otherwise noted. SF9 Baculovirus transfected cell paste was re-suspended in 50mM Tris-HCl pH 8.0, 300mM NaCl, 20mM Imidazole, 5% (v/v) Glycerol, 1mM DTT with 25U/ml Benzonase (Sigma-Aldrich) and complete protease inhibitors (Roche). Cells lysed by nitrogen cavitation and clarified by centrifugation at 17,080 x g for 75 minutes. Protein prepared on AKTA FPLC: initial capture by nickel affinity, followed by TVMV protease digest and dialysis, nickel affinity in flow-through mode to remove residual reaction components and final size exclusion chromatography on Superdex 200 26/60 (GE). Purified hLCK kinase pool activated by incubation with ATP and $MgCl_2$ at room temperature for 6 minutes, enzymatic reaction quenched with excess EDTA. As a final polishing step to separate mono-phosphorylated and bis-phosphorylated hLCK, the activated kinase pool was loaded on a Mono-Q 10/100 GL (GE), a shallow NaCl elution gradient allowed separation of two species: obtained 5 mg of mono-phosphorylated hLCK and 1 mg of bis-phosphorylated hLCK, protein stored at -80°C. Purified and activated mono-phosphorylated hLCK was used for crystallography studies.

Crystallization
Apo LCK was crystallized as follows: 1 µL LCK at 4 mg/mL was combined with an equal volume of precipitant (1.5 M ammonium sulfate, 120 mM lithium chloride, 10 mM nickel(II) chloride, 100 mM CAPS pH 10.5) on a cover slide over a reservoir containing 500 µL precipitant in a hanging drop vapor diffusion crystallization tray incubated at 18°C. Initial crystals developed within one day and grew to full size within one week. Full-size crystals were transferred to a 1 µL drop of precipitant solution supplemented with 1 mM of **11** and soaked for ~18 hours at 18°C. Soaked crystals were cryoprotected by brief washing through a 1 µL drop of precipitant supplemented with 1 mM of **11** and 10% (v/v) each of glycerol and PEG 400, after which they were flash frozen in liquid nitrogen prior to X-ray data collection.
Data Processing and Structure Determination
Crystallographic diffraction data for the LCK+**11** complex was collected at a wavelength of 1.0 Å and temperature of 100 K at Advanced Photon Source IMCA-CAT beamline 17ID, with data reduction carried out using autoPROC (Vonrhein *et al.* (2011) *Acta Cryst. D* **v67**: pp293–302). The crystal structure of the LCK+**11** complex was determined by molecular replacement using the Phaser crystallographic software (McCoy *et al.* (2007) *J. Appl. Cryst.* **v40**: pp658–674) and the protein coordinates from the LCK+staurosporine complex (RCSB PDBID 1QPJ) as an input model; model building was completed using Coot (Emsley *et al.* (2010) *Acta Cryst. D* **v66**: pp486–501) and refinement carried out using autoBUSTER (Global Phasing Ltd.).
Accession Numbers
Coordinates and structure factors for the LCK+**11** complex have been deposited in the Rutgers Center for Structural Biology (RCSB) Protein Data Bank (PDB) under accession number 6DPJ.
Procedure for HTRF assays:
A time resolved FRET-based competition binding assay was used to assess test article binding to the kinase of interest. His-tagged or GST-tagged kinase at a concentration of 1 nM was incubated with 0.2

nM Tb-labeled detection antibody (anti-His or anti-GST), test compound, and fluorescein-labeled ATP competitive probe at a concentration corresponding to the probe's equilibrium dissociation constant for one hour. Fluorescence at 495 nm and 520 nm was measured using an EnVision microplate reader to quantify FRET between Tb-labeled detection antibody and fluorescein-labeled probe. Background subtracted FRET ratios were normalized to the maximum signal obtained in the absence of test compound. These values were converted to a percent inhibition. Percent inhibition was determined for test compounds at 11 concentrations. The IC_{50}, defined as the concentration of competing test compound needed to reduce specific binding of the probe by 50%, was calculated using the 4 parameter logistic equation to fit the data.

Procedure for Caliper assays:

10 mM $MgCl_2$, 0.015 % Brij-15 and 2 mM DTT containing 1.5 uM fluorescently-labeled peptide substrate, ATP at Km, and various concentrations of compound. Reaction incubation times and enzyme concentrations were optimized to obtain a maximum peptide substrate conversion of 10-30% and reactions were quenched with 1 mM EDTA solution. Reaction mixtures were analyzed by capilary electrophoresis on a Caliper LabChip EZ Reader to resolve phosphorylated and unphosphorylated peptide species and determine peptide substrate conversion. Percent inhibition was calculated from the substrate conversion generated by no enzyme control reactions for 100% inhibition and vehicle-only reactions for 0% inhibition. Compounds were dissolved in DMSO and evaluated at 11 concentrations to determine IC_{50}.

Procedure for protein binding assay:

Compounds were tested in a panel of multi-species serum protein binding assays to determine the extent to which this compound binds to serum proteins in various species. Compounds were assayed in triplicate by combining with serum from an individual species of interest (human or mouse serum) to achieve final concentration of 10 µM. Dialysis was performed for 5 hours at 37 °C, in a 10% CO_2 atmosphere against sodium phosphate buffer using the two-chamber Rapid Equilibrium Dialysis (RED) Assay Plates from Thermo Fisher (Waltham, Massachusetts). Assay samples from buffer and serum chambers were collected at time zero (T0[Serum] and T0[Buffer]) and at 5 hours post-incubation (post-equilibration, T5h[Serum] and T5h[Buffer]). Samples were analyzed by liquid chromatography followed by tandem mass spectrometry (LC-MS/MS) to assess the fraction of compound (percentage) free to diffuse and equilibrate between the buffer and serum chambers in the dialysis device. Prior to LC-MS/MS analysis, assay samples were diluted with either buffer or serum to result in the same final serum concentration in each sample. Subsequently, these samples were extracted by protein precipitation in acetonitrile containing analytical internal standards. Samples were analyzed by LC-MS/MS and relative amounts of test compound were determined by calculating the peak area ratio of test compound to internal standard in each sample. Results were expressed as the percent of test compound free (unbound), percent bound, and percent recovered after incubation.

Procedure for metabolic stability assays:

Compounds were tested in a panel of Metabolic Stability Assays to determine its in vitro half-life (T-HALF) and the rate of CYP-mediated metabolism in incubations with NADPH-fortified human and mouse liver microsomes. Test compound (0.5 µM) was incubated with NADPH-fortified liver microsomes (1 mg/mL) at 37 °C. Metabolic reactions were terminated after 0, 5, 10, 15, 30, and 45 minutes by transferring an aliquot of the reaction mixtures into a quench solution to denature microsomal enzymes. The relative amount of the test compound remaining in the reaction mixtures at each time point was quantified using LC-MS/MS analysis. The results for each time point were normalized to the relative amount of test compound in the 0-minute sample and expressed as percent remaining. The half-life (T-HALF), rate of metabolism, hepatic intrinsic clearance (CLh,int), and hepatic blood clearance (CLh,b) for

test compound were calculated based on elimination rate constant (kel), which was determined using linear regression model (natural logarithm of % Remaining versus time).

Procedure for ZAP 70 assay:

Jurkat cells were pre-treated with CSK compounds for 30 minutes then stimulated with anti-CD3/CD28 at 1 ug/ml for 10 minutes. Cells were then harvested and lysed with RIPA buffer. Levels of phosphorylated Zap70 was detected with pZAP70 antibody (Tyr493) from Cell Signaling (#2704) and normalized to total ZAP70 antibody from Cell Signaling (#2705).

Procedure for PK/PD assay:

C57bl/6 mice were dosed PO with the indicated CSK compound. At the indicated time points spleens were harvested and homogenized in RIPA buffer using Tissuelyser (Qiagen). Levels of phosphorylated LCK tyrosine 505 protein was detected with Cell Signaling antibody (#2751) and normalized to total LCK (#2752)

Procedure for CHO-OKT3 assay:

CHO cells were stably engineered to overexpress the anti-human CD3 IgG monoclonal antibody clone OKT3. Primary human T cells were pre-treated with DMSO control or CSK compound in a 96 U-bottom plate for 15 minutes followed by a complete media exchange. CHO-OKT3 cells were then added at a 1:8 ratio of CHO-OKT3 to primary human T cells. Supernatant was collected at 48 hours post-treatment to measure IL2 levels by AlphaLISA (PerkinElmer) and 72 hours to measure proliferation by MTS (Promega).

Replicate numbers for Table 1 and Table 2:

Table 1. Characterization of Csk inhibitors 1-6.[b]

Cpd	Csk IC_{50} (nM)	n	Lck IC_{50} (nM)	n	ZAP-70 EC_{50} (nM) (Y_{max})	n	HLM/MsLM %Rem.
1	5600	1	>50000	1	7900(73%)	1	2/33
2	79	1	24000	1	5700(180%)	2	65/15
3	80	1	31000	1	4050(350%)	2	68/9
4	70	3	43000	3	2000(350%)	6	53/78
5	430	1	34000	1	2700(280%)	1	72/1
6	8	3	26000	3	420(270)%	2	61/59

[b]HLM: Human liver microsomes. MsLM: Mouse liver microsomes.

Table 2. Characterization of Csk inhibitors 7-14.[b]

Cpd	Csk IC_{50} (nM)				Lck IC_{50} (nM)	n	ZAP-70 EC_{50} (nM) (Y_{max})	n	HLM/ MsLM %Rem
	HTRF	n	Caliper	n					
7	5	1	4	1	300	1	49(250%)	1	84/24
8	<3	2	4	2	120	2	42(190%)	4	72/10
9	26	2	21	2	3100	2	1400(240%)	1	71/21
10	<3	2	2	2	26	2	28(220%)	2	80/2
11	42	1	13	1	42	1	>20000	1	NT/59
12	<3	1	4	1	230	1	88(370%)	1	85/9
13	<3	3	4	4	260	3	41(360%)	4	91/100
14	4	2	6	2	110	2	56(210%)	4	85/99

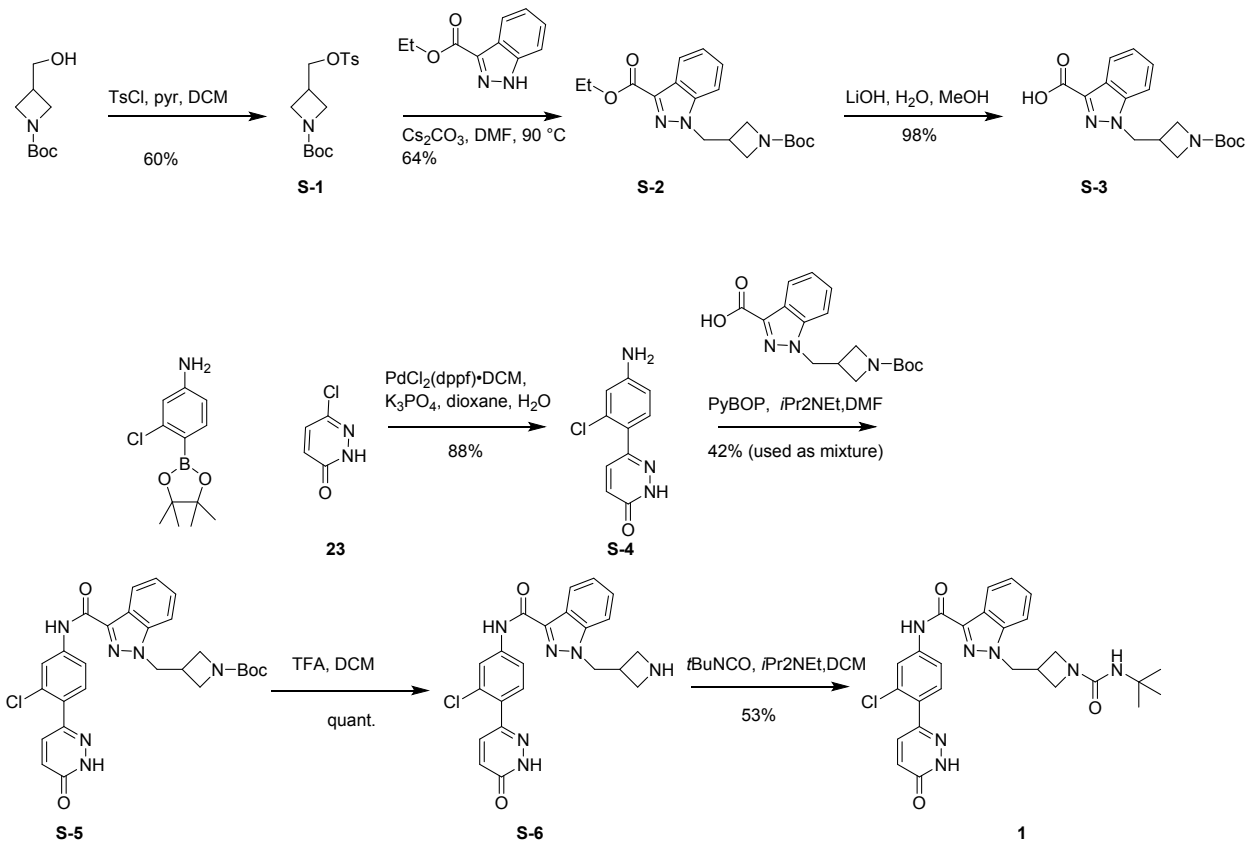
[b]NT: not tested.

Procedure for metabolic soft spot analysis:

These experiments were performed as described in Paiva, A. A.; Klakouski, C.; Li, S.; Johnson, B. M.; Shu, Y.-Z.; Josephs, J.; Zvyaga, T; Zamora, I.; Shou, W. Z. Development, optimization, and implementation of a centralized metabolic soft spot assay. *Bioanal.* **2017**, *9*, 541-552.

Experimentals:
General Synthetic Methods:
Reactions were carried out under an inert atmosphere and at room temperature unless otherwise noted. Anhydrous solvents were purchased and used without further purification or drying.
LCMS methods:
Method A: Column: Acquity BEH C18, 2.1 mm x 50 mm, 1.7 µm particles; Mobile Phase A: water with with 0.05% TFA; Mobile Phase B: acetonitrile 0.05% TFA; Gradient: 2 %B to 98 %B over 1 min ,then a 0.5 min hold at 98 %B; Flow: 0.8 mL/min;
Method B: Column: Waters Acquity UPLC BEH C18, 2.1 x 50 mm, 1.7-µm particles; Mobile Phase A: 5:95 acetonitrile:water with 10 mM ammonium acetate; Mobile Phase B: 95:5 acetonitrile:water with 10 mM ammonium acetate; Temperature: 50 °C; Gradient: 0-100% B over 3 minutes, then a 0.75-minute hold at 100% B; Flow: 1.11 mL/min; Detection: UV at 220 nm.
Method C: Column: Waters Acquity UPLC BEH C18, 2.1 x 50 mm, 1.7-µm particles; Mobile Phase A: 5:95 acetonitrile:water with 0.1% trifluoroacetic acid; Mobile Phase B: 95:5 acetonitrile:water with 0.1% trifluoroacetic acid; Temperature: 50 °C; Gradient: 0-100% B over 3 minutes, then a 0.75-minute hold at 100% B; Flow: 1.0 mL/min; Detection: UV at 220 nm.
HPLC methods:
Method A: Column: Xbridge phenyl, 4.6 x 150 mm, 3.5-µm particles; Mobile Phase A: 5:95 methanol:water with 10 mM NH_4HCO_3; Mobile Phase B: 95:5 methanol:water with 10 mM NH_4HCO_3;; Gradient: 10-100% B over 25 minutes, then a 5-minute hold at 100% B; Flow: 2.0 mL/min; Detection: UV at 254 nm.
Method B: Column: Sunfire C18 3.6 x 150 mm, 3.5-µm particles; Mobile Phase A: 5:95 methanol:water with 0.05% TFA; Mobile Phase B: 95:5 methanol:water with 0.05% TF;; Gradient: 10-100% B over 12 minutes, then a 3-minute hold at 100% B; Flow: 1.0 mL/min; Detection: UV at 220 nm.

Preparation of compound **1**:



Synthesis of tert-butyl 3-((tosyloxy)methyl)azetidine-1-carboxylate (**S-1**):
Tert-butyl 3-(hydroxymethyl)azetidine-1-carboxylate (1 g, 5.34 mmol) and pyridine (0.5 mL) was dissolved in DCM 10 mL and cooled to 0°C. Tosyl Chloride (1.069 g, 5.61 mmol) was added and the reaction was stirred in the ice bath for 30 minutes and stirred at rt for an additional 12 h. Then the mixture was diluted with 20 mL of $NaHCO_3$ (aq) and 40 mL of DCM. The organic layer was washed with brine and dried over Na_2SO_4, then concentrated. The residue was was loaded onto 24g ISCO silica column, eluted with 0 → 60% EtOAc in Hexane to afford tert-butyl 3-((tosyloxy)methyl)azetidine-1-carboxylate (**S-1**) (1.1 g, 3.22 mmol, 60.3 % yield). ^{1}H NMR (400 MHz, CHLOROFORM-d) δ 7.78 - 7.74 (m, 2H), 7.34 (dd, J=8.6, 0.6 Hz, 2H), 4.11 (d, J=6.8 Hz, 2H), 3.95 - 3.89 (m, 3H), 3.66 (dd, J=8.7, 5.2 Hz, 1H), 3.56 (br dd, J=8.8, 5.3 Hz, 2H), 2.80 (tddd, J=10.1, 5.1, 3.4, 1.6 Hz, 1H), 2.43 (s, 3H), 1.39 (s, 9H)

Preparation of (ethyl 1-((1-(tert-butoxycarbonyl)azetidin-3-yl)methyl)-1H-indazole-3-carboxylate (**S-2**):
A mixture of ethyl 1H-indazole-3-carboxylate (300 mg, 1.577 mmol), tert-butyl 3-((tosyloxy)methyl)azetidine-1-carboxylate (**S-1**) (754 mg, 2.208 mmol) and cesium carbonate (1028 mg, 3.15 mmol) in DMF (7.89 mL) was stirred at 90 °C for 12 h. The reaction was iluted with water, extracted with EtOAc, washed organic layer with, brine, concentrated and the residue was loaded onto a 40g ISCO silica column, eluted with EtOAc/Hex (0-60%). The undesired regioisomer eluted first and the desired regioisomer eluted second. Fractions containing the desired product were concentrated to give ethyl 1-((1-(tert-butoxycarbonyl)azetidin-3-yl)methyl)-1H-indazole-3-carboxylate (**S-2**) (362 mg, 1.007 mmol, 63.9 % yield). ^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.25 - 8.19 (m, 1H), 7.53 - 7.42 (m, 2H), 7.36 - 7.27 (m, 1H), 4.67 (d, J=7.6 Hz, 2H), 4.57 - 4.48 (m, 2H), 4.02 (t, J=8.6 Hz, 2H), 3.80 (dd, J=8.8, 5.1 Hz, 2H), 3.30 - 3.19 (m, 1H), 1.51 - 1.46 (m, 3H), 1.45 - 1.41 (m, 9H)

Preparation of 1-((1-(tert-butoxycarbonyl)azetidin-3-yl)methyl)-1H-indazole-3-carboxylic acid (S-3):

A mixture of ethyl 1-((1-(tert-butoxycarbonyl)azetidin-3-yl)methyl)-1H-indazole-3-carboxylate (2.77 g, 7.71 mmol) and lithium hydroxide (0.554 g, 23.12 mmol) in MeOH (17.13 ml) was stirred at rt for 16 hours. The reaction was quenched with acetic acid, diluted with water and transferred to a seperatory funnel. The aqueous layer was washed with EtOAc (3x). The organic layers were concentrated to afford 1-((1-(tert-butoxycarbonyl)azetidin-3-yl)methyl)-1H-indazole-3-carboxylic acid (**S-3**) (2.5 g, 7.54 mmol, 98 % yield). ^{1}H NMR (400MHz, CHLOROFORM-d) δ 8.30 (d, *J*=8.2 Hz, 1H), 7.58 - 7.49 (m, 2H), 7.40 (ddd, *J*=8.1, 6.5, 1.3 Hz, 1H), 4.71 (d, *J*=7.6 Hz, 2H), 4.11 - 4.05 (m, 2H), 3.85 (dd, *J*=8.9, 5.1 Hz, 2H), 3.38 - 3.25 (m, 1H), 1.48 - 1.45 (m, 9H).

Preparation of 6-(4-amino-2-chlorophenyl)pyridazin-3(2H)-one (**S-4**):

3-chloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (0.364 g, 1.436 mmol), 6-chloropyridazin-3(2H)-one (**S-3**) (0.150 g, 1.149 mmol), and $PdCl_2$(dppf)-DCM adduct (0.094 g, 0.115 mmol) were placed in a pressure vial and placed under vacuum. The vial was backfilled with nitrogen, then this process was repeated twice more. Dioxane (5.75 ml) and tripotassium phosphate (2M aqueous) (1.724 ml, 3.45 mmol) were added, then the reaction was heated to 100 °C overnight. The reaction was cooled, diluted with EtOAc and water, and filtered. The reaction was extracted twice with EtOAc, then the organic layers were washed with brine, dried with sodium sulfate, and concentrated. The solid was triturated with DCM to give 6-(4-amino-2-chlorophenyl)pyridazin-3(2H)-one (**S-4**) (0.088 g, 0.397 mmol, 34.6 % yield). ^{1}H NMR (400MHz, DMSO-d_6) δ 13.07 (br s, 1H), 7.58 (d, *J*=9.8 Hz, 1H), 7.17 (d, *J*=8.3 Hz, 1H), 6.87 (d, *J*=9.8 Hz, 1H), 6.69 (d, *J*=2.2 Hz, 1H), 6.58 (dd, *J*=8.4, 2.2 Hz, 1H), 5.71 (s, 2H).

Preparation of (tert-butyl 3-((3-((3-chloro-4-(6-oxo-1,6-dihydropyridazin-3-yl)phenyl)carbamoyl)-1H-indazol-1-yl)methyl)azetidine-1-carboxylate (**S-5**).

To a suspension of 1-((1-(tert-butoxycarbonyl)azetidin-3-yl)methyl)-1H-indazole-3-carboxylic acid (0.063 g, 0.189 mmol) (**S-3**) and 6-(4-amino-2-chlorophenyl)pyridazin-3(2H)-one (**S-4**) (0.035 g, 0.158 mmol) in DMF (1.053 ml) was added PyBOP (0.164 g, 0.316 mmol) and Hunig'sBase (0.083 ml, 0.474 mmol). The reaction was stirred overnight. The reaction was diluted with water and extracted with EtOAc. The organic layer was washed with 10% LiCl solution, dried with sodium sulfate, and concentrated. The residue was purified via ISCO (12g column; DCM/EtOAc; 0 to 100% gradient) to give tert-butyl 3-((3-((3-chloro-4-(6-oxo-1,6-dihydropyridazin-3-yl)phenyl)carbamoyl)-1H-indazol-1-yl)methyl)azetidine-1-carboxylate (**S-5**) (36 mg of product containing 0.15 equivalents of aniline starting material) which was taken forward directly to the next reaction.

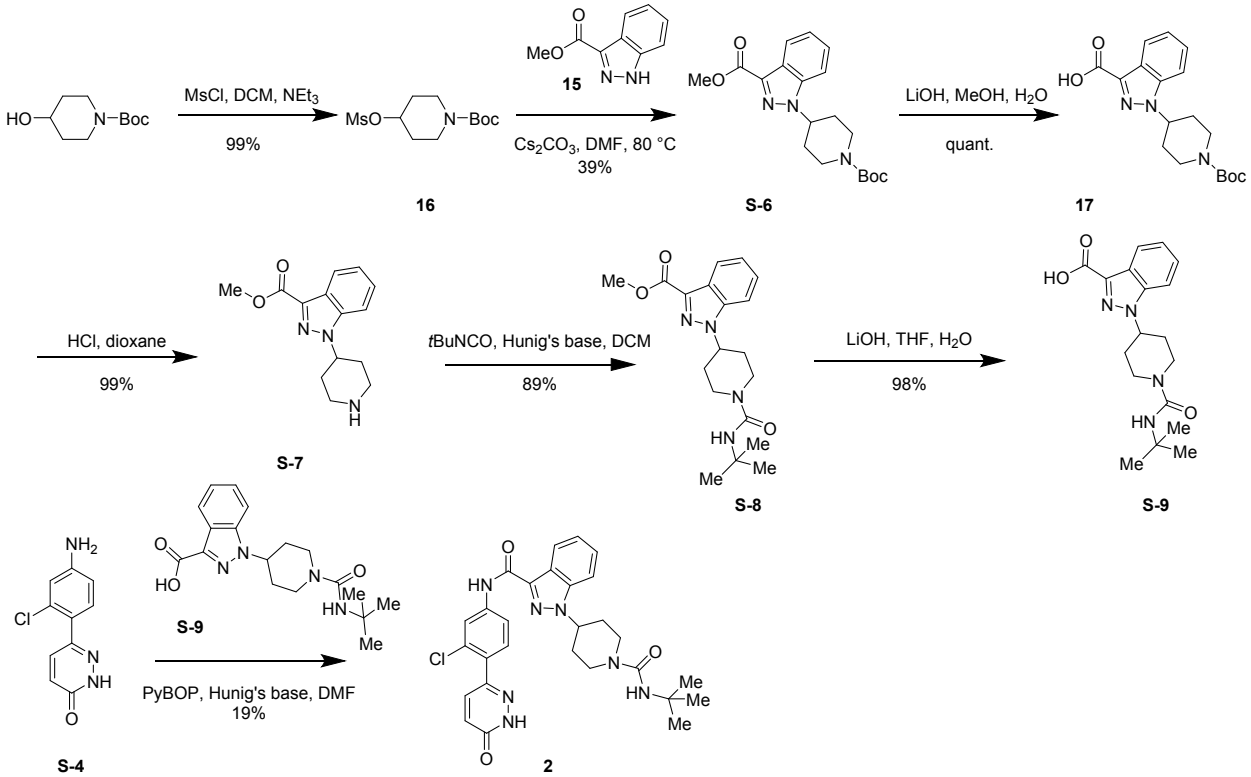
Preparation of 1-(azetidin-3-ylmethyl)-N-(3-chloro-4-(6-oxo-1,6-dihydropyridazin-3-yl)phenyl)-1H-indazole-3-carboxamide (TFA salt) (**S-6**):

To a suspension of tert-butyl 3-((3-((3-chloro-4-(6-oxo-1,6-dihydropyridazin-3-yl)phenyl)carbamoyl)-1H-indazol-1-yl)methyl)azetidine-1-carboxylate (**S-6**) (0.024 g, 0.045 mmol) in DCM (0.6 mL) was added TFA (0.15 mL). Suspended material dissolved upon addition of TFA. After ca. 1 hour, the reaction was concentrated, then azeotroped with DCM and toluene to give 1-(azetidin-3-ylmethyl)-N-(3-chloro-4-(6-oxo-1,6-dihydropyridazin-3-yl)phenyl)-1H-indazole-3-carboxamide, TFA(**S-6**): (0.027 g, 0.049 mmol, 110 % yield). LCMS RT: 0.66 min (Method A). M/Z=435.2.

Preparation of 1-((1-(tert-butylcarbamoyl)azetidin-3-yl)methyl)-N-(3-chloro-4-(6-oxo-1,6-dihydropyridazin-3-yl)phenyl)-1H-indazole-3-carboxamide (**1**):

To a suspension of 1-(azetidin-3-ylmethyl)-N-(3-chloro-4-(6-oxo-1,6-dihydropyridazin-3-yl)phenyl)-1H-indazole-3-carboxamide, TFA (12.08 mg, 0.022 mmol) in DCM (0.3 mL) was added Hunig'sBase (9.61 µl, 0.055 mmol) and 2-isocyanato-2-methylpropane (3.77 µl, 0.033 mmol). After ca. 3 hours, the reaction was concentrated. The residue was dissolved in DMF. The crude material was purified via preparative LC/MS with the following conditions: Column: Waters XBridge C18, 19 x 200 mm, 5-µm particles; Mobile Phase A: 5:95 acetonitrile: water with 10-mM ammonium acetate; Mobile Phase B: 95:5 acetonitrile: water with 10-mM ammonium acetate; Gradient: 15-70% B over 20 minutes, then a 5-minute hold at 100% B; Flow: 20 mL/min. Fractions containing the desired product were combined and dried via

centrifugal evaporation to give 1-((1-(tert-butylcarbamoyl)azetidin-3-yl)methyl)-N-(3-chloro-4-(6-oxo-1,6-dihydropyridazin-3-yl)phenyl)-1H-indazole-3-carboxamide (**1**) (6.2 mg, 53%).
LCMS RT: 1.58 min (Method B). M/Z= 533.2. Purity: 100%. ^{1}H NMR (500MHz, DMSO-d_6) δ 13.35 (s, 1H), 10.61 (s, 1H), 8.26 - 8.16 (m, 2H), 7.94 (br d, *J*=8.5 Hz, 1H), 7.89 (d, *J*=8.6 Hz, 1H), 7.71 (d, *J*=9.8 Hz, 1H), 7.60 - 7.49 (m, 2H), 7.36 (t, *J*=7.5 Hz, 1H), 6.98 (d, *J*=9.8 Hz, 1H), 5.62 (s, 1H), 4.76 (br d, *J*=7.2 Hz, 2H), 3.84 (t, *J*=8.2 Hz, 1H), 3.75 - 3.66 (m, 1H), 3.62 (br s, 2H), 3.19 - 3.07 (m, 1H), 1.19 (s, 9H)
Preparation of Compound **2**:

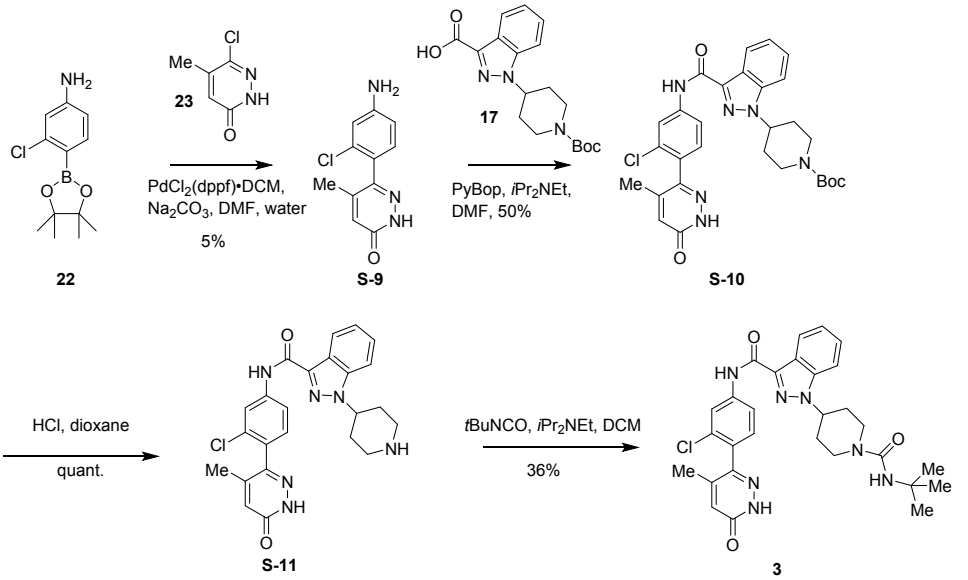


Preparation of tert-butyl 4-((methylsulfonyl)oxy)piperidine-1-carboxylate (**16**):
Tert-butyl 4-hydroxypiperidine-1-carboxylate (5 g, 24.84 mmol) and Et_3N (5.19 ml, 37.3 mmol) were dissolved in DCM (10 mL) and cooled to 0°C under N_2. Methanesulfonyl chloride (2.307 ml, 29.8 mmol) was added and the reaction was stirred in an ice bath for 30 minutes, then stirred at rt for additional 2 hours. The mixture was diluted with 20 mL of water and 40 mL of DCM. The organic layer was washed with brine and dried over Na_2SO_4, then concentrated to afford tert-butyl 4-((methylsulfonyl)oxy)piperidine-1-carboxylate (**16**) (6.9 g, 24.70 mmol, 99 % yield). ^{1}H NMR (400 MHz, CHLOROFORM-d) δ 4.89 (tt, *J*=7.8, 3.8 Hz, 1H), 3.71 (ddd, *J*=13.3, 7.1, 3.9 Hz, 2H), 3.30 (ddd, *J*=13.7, 8.2, 3.8 Hz, 2H), 3.04 (s, 3H), 2.02 - 1.92 (m, 2H), 1.87 - 1.76 (m, 2H), 1.46 (s, 9H).
Preparation of methyl 1-(1-(tert-butoxycarbonyl)piperidin-4-yl)-1H-indazole-3-carboxylate (**S-6**):
A solution of methyl 1H-indazole-3-carboxylate (3 g, 17.03 mmol), Cs_2CO_3 (11.65 g, 35.8 mmol) and tert-butyl 4-((methylsulfonyl)oxy)piperidine-1-carboxylate (**16**) (6.66 g, 23.84 mmol) in DMF (56.8 ml) was stirred at 80 °C for 3 h. The reaction was diluted with 40 mL water. The aqueous layer was extracted with EtOAc. The organic layer was separated and concentrated. The residue was purified by ISCO (120 g column, 0 → 50% EtOAc in hexanes) to afford methyl 1-(1-(tert-butoxycarbonyl)piperidin-4-yl)-1H-indazole-3-carboxylate (**S-6**): (2.4 g, 6.68 mmol, 39.2 % yield). The desired regioisomer eluted after the undesired one. ^{1}H NMR (400MHz, DMSO-d_6) d 8.15 - 8.07 (m, 1H), 7.92 (d, J=8.6 Hz, 1H), 7.56 - 7.47 (m, 1H), 7.37 (td, J=7.6, 0.7 Hz, 1H), 5.14 - 4.97 (m, 1H), 4.23 - 4.07 (m, 2H), 3.93 (s, 3H), 3.15 - 2.86 (m, 2H), 2.00 (s, 4H), 1.55 - 1.35 (m, 9H)

Preparation of 1-(1-(tert-butoxycarbonyl)piperidin-4-yl)-1H-indazole-3-carboxylic acid (**17**):
To a solution of ethyl 1-(1-(tert-butoxycarbonyl)piperidin-4-yl)-1H-indazole-3-carboxylate (**S-6**) (2.7 g, 7.23 mmol) in methanol (21.69 ml) and water (7.23 ml) was added lithium hydroxide, H_2O (0.910 g, 21.69 mmol). The reaction was heated to 65 °C. After ca. 2 hours, the reaction was cooled. The reaction was acidified with 1M HCl and extracted twice with EtOAc. The organic layers were washed with brine and concentrated to give 1-(1-(tert-butoxycarbonyl)piperidin-4-yl)-1H-indazole-3-carboxylic acid (**17**) (2.52 g, 7.30 mmol, 101 % yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.17 (d, *J*=7.9 Hz, 1H), 7.78 - 7.66 (m, 1H), 7.42 - 7.32 (m, 1H), 7.26 - 7.15 (m, 1H), 4.93 - 4.79 (m, 1H), 4.20 - 4.07 (m, 2H), 3.07 - 2.90 (m, 2H), 2.02 - 1.88 (m, 4H), 1.52 - 1.41 (m, 9H).
Preparation of methyl 1-(piperidin-4-yl)-1H-indazole-3-carboxylate, HCl (**S-7**)
Methyl 1-(1-(tert-butoxycarbonyl)piperidin-4-yl)-1H-indazole-3-carboxylate (**17**) (281 mg, 0.782 mmol) was dissolved in 4M HCl in dioxane (0.5 mL) and stirred at rt for 3 hours. The reaction was concentrated followed by addition of ether. The resulting white precipitate was collected to afford methyl 1-(piperidin-4-yl)-1H-indazole-3-carboxylate, HCl (**S-7**) (229 mg, 0.774 mmol, 99 % yield) as a desired product. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.13 - 8.08 (m, 1H), 7.91 (d, *J*=8.6 Hz, 1H), 7.54 (ddd, *J*=8.4, 7.0, 1.0 Hz, 1H), 7.42 - 7.35 (m, 1H), 5.21 - 5.11 (m, 1H), 3.93 (s, 3H), 3.51 - 3.42 (m, 2H), 3.22 - 3.08 (m, 2H), 2.42 - 2.29 (m, 2H), 2.18 (br d, *J*=11.2 Hz, 2H).
Preparation of methyl 1-(1-(tert-butylcarbamoyl)piperidin-4-yl)-1H-indazole-3-carboxylate (**S-8**):
To a suspension of methyl 1-(piperidin-4-yl)-1H-indazole-3-carboxylate, HCl (**S-7**) (229 mg, 0.774 mmol) in DCM (1.9 mL) was added Hunig'sBase (811 µl, 4.65 mmol) and 2-isocyanato-2-methylpropane (133 µl, 1.161 mmol). The reaction was stirred at rt for 3 h. The solvent was evaporated and the residue purified by ISCO (12 g column, 0 → 80% EtOAc in Hexane) to afford methyl 1-(1-(tert-butylcarbamoyl)piperidin-4-yl)-1H-indazole-3-carboxylate (247 mg, 0.689 mmol, 89 % yield) (**S-8**) as a white solid. LCMS RT: 0.88 min (Method A). M/Z= 359.3.
Preparation of 1-(1-(tert-butylcarbamoyl)piperidin-4-yl)-1H-indazole-3-carboxylic acid (**S-9**):
A mixture of methyl 1-(1-(tert-butylcarbamoyl)piperidin-4-yl)-1H-indazole-3-carboxylate (247 mg, 0.689 mmol) and lithium hydroxide (49.5 mg, 2.067 mmol) in MeOH (3132 µl) and Water (313 µl) was stirred at rt for 3 days. The reaction was concentrated, quenched with citric acid, diluted with water and transferred to a seperatory funnel. The aqueous layer was washed with EtOAc (3x). The organic layer was separated and concentrated to afford 1-(1-(tert-butylcarbamoyl)piperidin-4-yl)-1H-indazole-3-carboxylic acid (233 mg, 0.677 mmol, 98 % yield) as the desired product. LC/MS RT: 0.77 min (Method A). M/Z= 345.3.
Preparation of 1-(1-(tert-butylcarbamoyl)piperidin-4-yl)-N-(3-chloro-4-(6-oxo-1,6-dihydropyridazin-3-yl)phenyl)-1H-indazole-3-carboxamide (**2**):
To a suspension of 1-(1-(tert-butylcarbamoyl)piperidin-4-yl)-1H-indazole-3-carboxylic acid (**S-9**) (0.016 g, 0.045 mmol) and 6-(4-amino-2-chlorophenyl)pyridazin-3(2H)-one (**S-4**) (0.010 g, 0.045 mmol) in DMF (0.3 mL) was added Hunig'sBase (0.024 mL, 0.135 mmol) and PyBOP (0.029 g, 0.056 mmol). The reaction was stirred overnight, then 15 mg PyBOP was added. After a further three hours, the reaction was diluted with DMF, filtered through a syringe filter, and purified via preparative LC/MS with the following conditions: Column: XBridge C18, 19 x 200 mm, 5-µm particles; Mobile Phase A: 5:95 acetonitrile: water with 10-mM ammonium acetate; Mobile Phase B: 95:5 acetonitrile: water with 10-mM ammonium acetate; Gradient: 30-68% B over 20 minutes, then a 5-minute hold at 100% B; Flow: 20 mL/min. Fractions containing the desired product were combined and dried via centrifugal evaporation to give 1-(1-(tert-butylcarbamoyl)piperidin-4-yl)-N-(3-chloro-4-(6-oxo-1,6-dihydropyridazin-3-yl)phenyl)-1H-indazole-3-carboxamide (**2**) (4.9 mg, 19%).
LC/MS RT: 1.76 min (Method C) M/Z= 548.1 Purity 96.2%. ^{1}H NMR (500MHz, DMSO-d_6) δ 13.31 (br s, 1H), 10.44 (s, 1H), 8.28 - 8.15 (m, 2H), 7.97 (br d, *J*=8.2 Hz, 1H), 7.91 (br d, *J*=8.5 Hz, 1H), 7.71 (d, *J*=9.8 Hz, 1H), 7.60 - 7.45 (m, 2H), 7.35 (t, *J*=7.5 Hz, 1H), 6.97 (br d, *J*=9.8 Hz, 1H), 5.89 (s, 1H), 4.97 (br t, *J*=11.4

Hz, 1H), 4.20 (br d, *J*=12.7 Hz, 2H), 2.90 (br t, *J*=12.3 Hz, 2H), 2.23 - 2.08 (m, 2H), 1.98 (br d, *J*=10.5 Hz, 2H), 1.28 (s, 9H).

Preparation of Compound **3**:



Preparation of 6-(4-amino-2-chlorophenyl)-5-methylpyridazin-3(2H)-one (**S-9**):

6-chloro-5-methylpyridazin-3(2H)-one (150 mg, 1.038 mmol), 3-chloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (289 mg, 1.141 mmol), and $PdCl_2$(dppf)-DCM adduct (85 mg, 0.104 mmol) were placed in a pressure vial. The vial was degassed with nitrogen three times. DMF (6918 µl) and sodium carbonate (2M aqueous) (1556 µl, 3.11 mmol) were added and the reaction was heated to 100 °C for 16h. The reaction mixture was transferred to a separatory funnel containing saturated aqueous $NaHCO_3$ solution (15 mL). The aqueous layer was extracted with ethyl acetate (3 x 15 mL). The combined organic layers were washed with brine (15 mL), dried over $MgSO_4$, filtered, and concentrated. The residue was purified by ISCO (0% → 100% ethyl acetate in hexanes; 24g column) to afford 6-(4-amino-2-chlorophenyl)-5-methylpyridazin-3(2H)-one (**S-9**) (11 mg, 0.047 mmol, 4.50 % yield). LC/MS RT: 0.58 min (Method A). M/Z= 236.0.

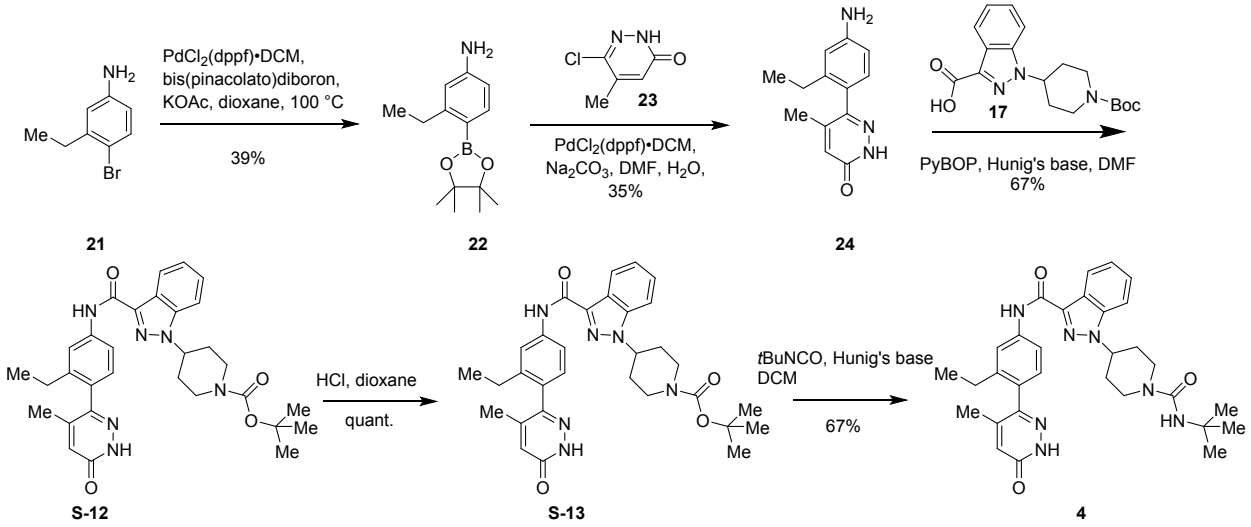
Preparation of tert-butyl 4-(3-((3-chloro-4-(4-methyl-6-oxo-1,6-dihydropyridazin-3-yl)phenyl)carbamoyl)-1H-indazol-1-yl)piperidine-1-carboxylate (**S-10**):

To a suspension of 1-(1-(tert-butoxycarbonyl)piperidin-4-yl)-1H-indazole-3-carboxylic acid (19.05 mg, 0.055 mmol) and 6-(4-amino-2-chlorophenyl)-5-methylpyridazin-3(2H)-one (**S-9**) (10 mg, 0.042 mmol) in DMF (283 µl) was added PyBOP (44.2 mg, 0.085 mmol) and Hunig's Base (22.23 µl, 0.127 mmol). The reaction was stirred at rt for 16 h. The reaction was diluted with water and extracted twice with EtOAc. The organic layer was washed with 10% LiCl solution, dried with sodium sulfate, and concentrated. The residue was purified via reverse phase HPLC (water:MeOH) to give tert-butyl 4-(3-((3-chloro-4-(4-methyl-6-oxo-1,6-dihydropyridazin-3-yl)phenyl)carbamoyl)-1H-indazol-1-yl)piperidine-1-carboxylate (**S-10**) (12 mg, 0.021 mmol, 50.2 % yield). LC/MS RT: 1.09 min (Method A). M/Z= 563.3.

Preparation of N-(3-chloro-4-(4-methyl-6-oxo-1,6-dihydropyridazin-3-yl)phenyl)-1-(piperidin-4-yl)-1H-indazole-3-carboxamide, HCl (**S-11**):

HCl (4M in Dioxane) (160 µl, 0.639 mmol) was added to tert-butyl 4-(3-((3-chloro-4-(4-methyl-6-oxo-1,6-dihydropyridazin-3-yl)phenyl)carbamoyl)-1H-indazol-1-yl)piperidine-1-carboxylate (**S-10**) (12 mg, 0.021 mmol) in a vial. The reaction was stirred at rt for 3 h. The reaction was concentrated, triturated with ether and filtered to give N-(3-chloro-4-(4-methyl-6-oxo-1,6-dihydropyridazin-3-yl)phenyl)-1-(piperidin-4-yl)-1H-indazole-3-carboxamide, HCl (**S-11**) (10.5 mg, 0.021 mmol, 99 % yield), which was taken on directly to the next step. LC/MS RT: 0.74 min (Method A). M/Z= 463.3.

Preparation of 1-(1-(tert-butylcarbamoyl)piperidin-4-yl)-N-(3-chloro-4-(4-methyl-6-oxo-1,6-dihydropyridazin-3-yl)phenyl)-1H-indazole-3-carboxamide (**3**):
To a suspension of N-(3-chloro-4-(4-methyl-6-oxo-1,6-dihydropyridazin-3-yl)phenyl)-1-(piperidin-4-yl)-1H-indazole-3-carboxamide, HCl (**S-11**)(10 mg, 0.020 mmol) in DCM (0.300 mL) was added Hunig'sBase (0.021 mL, 0.120 mmol) and 2-isocyanato-2-methylpropane (3.43 µl, 0.030 mmol). The reaction was stirred at rt for 3 h. The solvent was evaporated and the residue was dissolved in MeOH and purified by reverse phase HPLC (Water:MeOH) to afford 1-(1-(tert-butylcarbamoyl)piperidin-4-yl)-N-(3-chloro-4-(4-methyl-6-oxo-1,6-dihydropyridazin-3-yl)phenyl)-1H-indazole-3-carboxamide (**3**) (4.1 mg, 7.22 µmol, 36.1 % yield).
HPLC RT: 23.87 min (Method A) M/Z= 562.3 Purity 95.4%. ^{1}H NMR (400MHz, METHANOL-d$_4$) 8.32 (d, *J*=8.2 Hz, 1H), 8.20 (d, *J*=2.1 Hz, 1H), 7.83 (dd, *J*=8.5, 2.1 Hz, 1H), 7.79 (d, *J*=8.7 Hz, 1H), 7.65 (d, *J*=1.2 Hz, 1H), 7.55 (d, *J*=8.3 Hz, 1H), 7.52 (d, *J*=1.1 Hz, 1H), 7.39 - 7.33 (m, 1H), 5.02 - 4.93 (m, 1H), 4.25 (d, *J*=13.8 Hz, 2H), 3.09 (t, *J*=11.9 Hz, 2H), 2.26 (d, *J*=1.2 Hz, 3H), 2.12 (d, *J*=12.2 Hz, 2H), 1.59 (br. s., 2H), 1.40 (s, 9H
Preparation of Compound **4**:



Preparation of 3-ethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (**22**):
A vial containing 4-bromo-3-ethylaniline (2.0 g, 10.00 mmol), $PdCl_2$(dppf)-DCM adduct (0.245 g, 0.300 mmol), bis(pinacolato)diboron (6.35 g, 24.99 mmol), and potassium acetate (2.94 g, 30.0 mmol) was placed under vacuum and backfilled with nitrogen three times. Dioxane (50.0 ml) was added and the reaction was heated to 100 °C. After three hours, the reaction was cooled and filtered. The filtrate was concentrated. The residue was purified via ISCO (40g column; Hex/EtOAc; 0 to 30% gradient). Product eluted along with debrominated starting material; debrominated starting material was removed by washing with hexanes. 3-ethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (**22**) (0.970 g, 3.92 mmol, 39.3 % yield) was obtained. ^{1}H NMR (400 MHz, CHLOROFORM-d) δ 7.62 (d, *J*=7.8 Hz, 1H), 6.53 - 6.47 (m, 2H), 3.76 (br s, 2H), 2.84 (q, *J*=7.5 Hz, 2H), 1.35 - 1.30 (m, 12H), 1.18 (t, *J*=7.5 Hz, 3H)
Preparation of 6-(4-amino-2-ethylphenyl)-5-methylpyridazin-3(2H)-one (**24**):
6-chloro-5-methylpyridazin-3(2H)-one (0.400 g, 2.77 mmol), 3-ethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (**22**) (0.752 g, 3.04 mmol), and $PdCl_2$(dppf)-DCM adduct (0.226 g, 0.277 mmol) were placed in a pressure vial. The vial was placed under vacuum and backfilled with nitrogen three times. DMF (18.45 ml) and sodium carbonate (2M aqueous) (6.92 ml, 13.84 mmol) were added and the reaction was heated to 100 °C. Reaction became very thick; 5 mL additional DMF was added. The reaction was transferred to a larger flask with a larger stirring bar to enable stirring, then heated overnight. The reaction was partially concentrated, diluted with water, and extracted three times with EtOAc. The organic layer was washed with 10% LiCl solution, dried with sodium sulfate, and

concentrated. The residue was purified via ISCO (120g column; DCM/MeOH; 0 to 8% gradient) to give 6-(4-amino-2-ethylphenyl)-5-methylpyridazin-3(2H)-one (**24**) (0.224 g, 0.977 mmol, 35.3 % yield). LC/MS RT: 0.49 min (Method A). M/Z= 230.0.

Preparation of tert-butyl 4-(3-((3-ethyl-4-(4-methyl-6-oxo-1,6-dihydropyridazin-3-yl)phenyl)carbamoyl)-1H-indazol-1-yl)piperidine-1-carboxylate (**S-12**):

To a solution of 1-(1-(tert-butoxycarbonyl)piperidin-4-yl)-1H-indazole-3-carboxylic acid (**17**) (0.030 g, 0.087 mmol) and 6-(4-amino-2-ethylphenyl)-5-methylpyridazin-3(2H)-one (**24**) (0.016 g, 0.070 mmol) in DMF (0.4 mL) was added PyBOP (0.058 g, 0.112 mmol) and Hunig'sBase (0.037 mL, 0.209 mmol). After 4 hours, 15 mg (**17**) and 30 mg PyBOP were added. After ca. 2.5 hours, water was added and the precipitated solid was filtered off. The residue was purified via ISCO (12g column; Hex/EtOAc; 0 to 75% gradient, then DCM/MeOH 0 to 10% gradient) to give tert-butyl 4-(3-((3-ethyl-4-(4-methyl-6-oxo-1,6-dihydropyridazin-3-yl)phenyl)carbamoyl)-1H-indazol-1-yl)piperidine-1-carboxylate (**S-12**) (0.026 g, 0.047 mmol, 66.9 % yield). ^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 11.25 (1 H, br s), 8.91 (1 H, s), 8.47 (1 H, d, *J*=8.19 Hz), 7.76 (1 H, d, *J*=2.08 Hz), 7.72 (1 H, dd, *J*=8.25, 2.14 Hz), 7.44 - 7.55 (2 H, m), 7.35 (1 H, ddd, *J*=8.01, 6.79, 0.98 Hz), 7.17 (1 H, d, *J*=8.19 Hz), 6.86 (1 H, d, *J*=1.10 Hz), 4.67 (1 H, tt, *J*=11.39, 4.02 Hz), 4.30 - 4.46 (2 H, m), 3.02 (2 H, br t, *J*=12.29 Hz), 2.51 (2 H, q, *J*=7.42 Hz), 2.25 - 2.40 (2 H, m), 2.11 (2 H, br d, *J*=11.37 Hz), 2.00 (3 H, d, *J*=1.10 Hz), 1.53 (9 H, s), 1.18 (3 H, t, *J*=7.58 Hz)

Preparation of (N-(3-ethyl-4-(4-methyl-6-oxo-1,6-dihydropyridazin-3-yl)phenyl)-1-(piperidin-4-yl)-1H-indazole-3-carboxamide, HCl (**S-13**)

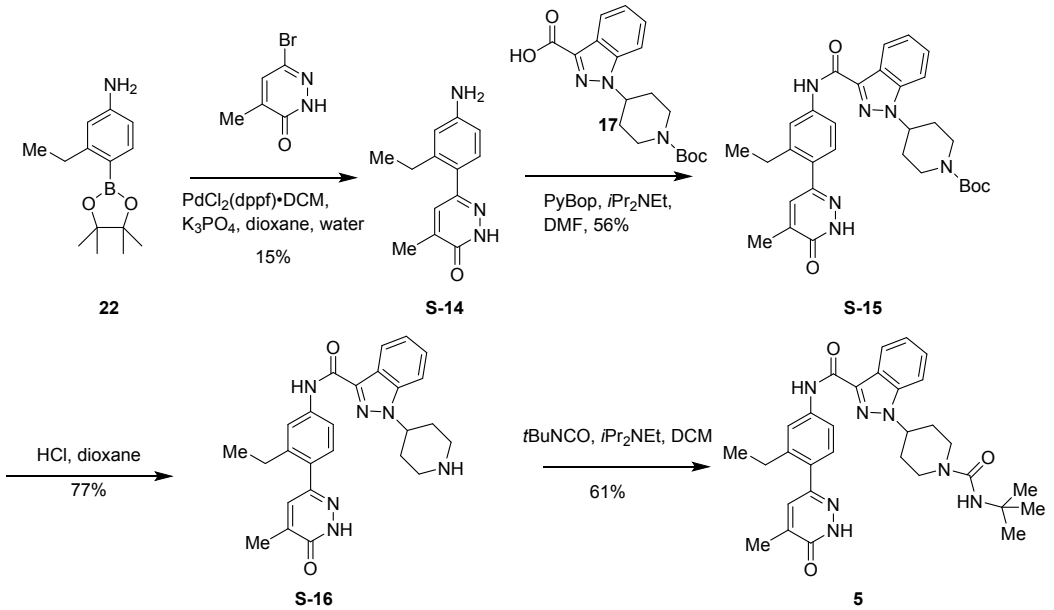
Tert-butyl 4-(3-((3-ethyl-4-(4-methyl-6-oxo-1,6-dihydropyridazin-3-yl)phenyl)carbamoyl)-1H-indazol-1-yl)piperidine-1-carboxylate (**S-12**) (0.328 g, 0.589 mmol) was suspended in 4M HCl in dioxane (5.89 ml). After 1.5 hours, the reaction was concentrated and dried under vacuum, then slurried with hexanes and dried under vacuum again. Weight still exceeds theoretical; compuound was used as 85% purity in next reaction. N-(3-ethyl-4-(4-methyl-6-oxo-1,6-dihydropyridazin-3-yl)phenyl)-1-(piperidin-4-yl)-1H-indazole-3-carboxamide, HCl (**S-13**) (0.360 g, 0.621 mmol, 105 % yield) was obtained. LC/MS RT: 0.66 min (Method A). M/Z= 457.3.

Preparation of (1-(1-(tert-butylcarbamoyl)piperidin-4-yl)-N-(3-ethyl-4-(4-methyl-6-oxo-1,6-dihydropyridazin-3-yl)phenyl)-1H-indazole-3-carboxamide (**4**):

To a suspension of N-(3-ethyl-4-(4-methyl-6-oxo-1,6-dihydropyridazin-3-yl)phenyl)-1-(piperidin-4-yl)-1H-indazole-3-carboxamide, HCl (**S-13**) (purity estimated as 85%) (0.175 g, 0.302 mmol) in DCM (3 mL) was added Hunig'sBase (0.211 mL, 1.207 mmol) and *t*butyl isocyanate (0.052 mL, 0.453 mmol). Suspended material dissolved after the addition of the amine. After ca. 1 hour, the reaction was concentrated. A second reaction was run using the same conditions on an additional portion of **S-13** (0.090 g, 0.155 mmol). The reactions were combined and the residue was purified via ISCO (40g column; DCM/MeOH; 1 to 10% gradient). Mixed fractions were repurified using the same conditions to obtain 1-(1-(tert-butylcarbamoyl)piperidin-4-yl)-N-(3-ethyl-4-(4-methyl-6-oxo-1,6-dihydropyridazin-3-yl)phenyl)-1H-indazole-3-carboxamide (**4**) (169 mg, 0.301 mmol, 51 % yield from **S-12**)

HPLC RT: 8.88 min (Method B). Purity 99.1%. ^{1}H NMR (400 MHz, METHANOL-d4) δ 8.31 (d, J=8.2 Hz, 1H), 7.83 (d, J=2.0 Hz, 1H), 7.77 (dd, J=8.3, 2.4 Hz, 2H), 7.49 (ddd, J=8.4, 7.1, 1.0 Hz, 1H), 7.33 (t, J=7.6 Hz, 1H), 7.20 (d, J=8.3 Hz, 1H), 6.91 (d, J=1.2 Hz, 1H), 5.80 (s, 1H), 4.93 (tt, J=11.4, 4.2 Hz, 1H), 4.23 (br d, J=13.6 Hz, 2H), 3.14 - 3.00 (m, 2H), 2.50 (q, J=7.5 Hz, 2H), 2.30 (qd, J=12.3, 4.1 Hz, 2H), 2.15 - 2.05 (m, 2H), 2.02 (d, J=1.1 Hz, 3H), 1.38 (s, 9H), 1.17 (t, J=7.5 Hz, 3H). ^{13}C NMR (101 MHz, METHANOL-d_4) δ 163.9, 163.2, 159.5, 151.0, 147.6, 144.9, 142.1, 140.6, 138.5, 131.6, 131.0, 128.9, 128.2, 124.4, 124.3, 123.4, 122.0, 119.3, 111.2, 57.8, 51.9, 44.5, 32.8, 29.9, 27.6, 20.0, 15.7. HRMS calculated for $C_{31}H_{38}O_3N_7$ (M+H) 556.3031, found 556.3022.

Preparation of compound **5**:



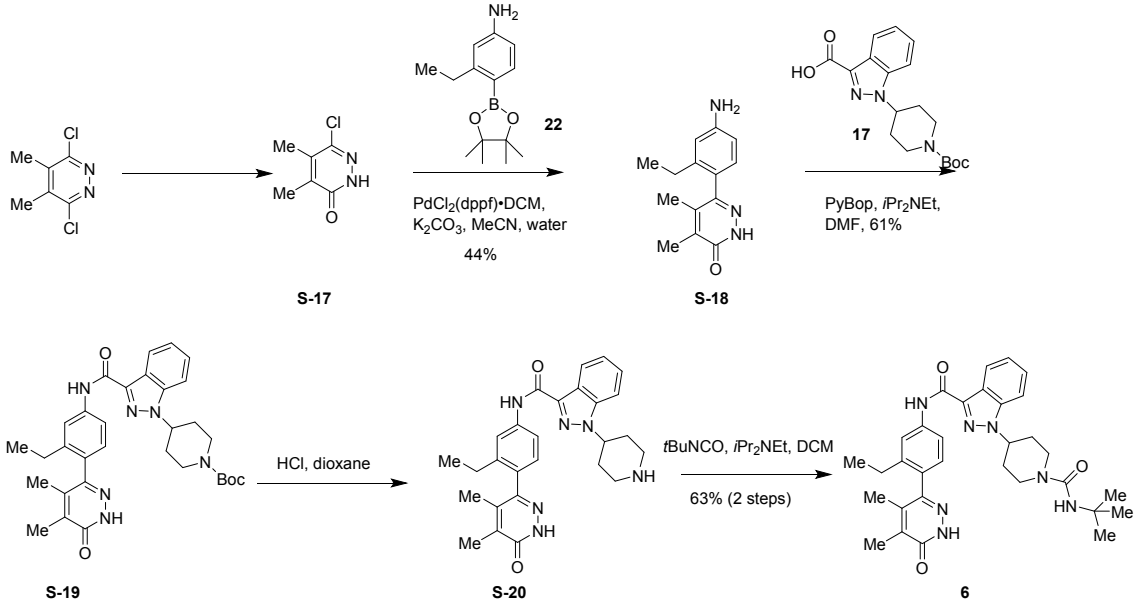
Preparation of (6-(4-amino-2-ethylphenyl)-4-methylpyridazin-3(2H)-one (**S-14**):
A vial containing 6-bromo-4-methylpyridazin-3(2H)-one (0.075 g, 0.397 mmol), 3-ethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (**22**) (0.118 g, 0.476 mmol), and $PdCl_2$(dppf)-DCM adduct (0.032 g, 0.040 mmol) was placed under vacuum and backfilled with nitrogen three times. Dioxane (3.97 ml) and tripotassium phosphate (2M aqueous) (0.595 ml, 1.190 mmol) were added. Reaction was stirred overnight. tripotassium phosphate (2M aqueous) (0.595 ml, 1.190 mmol) and $PdCl_2$(dppf)-DCM Adduct (0.032 g, 0.040 mmol) were added and the reaction was heated to 100 °C. After 8 hours, the reaction was cooled. The reaction was diluted with water and extracted twice with EtOAc. The organic layers were washed with brine, dried with sodium sulfate and concentrated. The residue was purified via ISCO (24g column; DCM/EtOAc; 0 to 100% gradient) to give 6-(4-amino-2-ethylphenyl)-4-methylpyridazin-3(2H)-one (**S-14**) (0.014 g, 0.061 mmol, 15.39 % yield). ^{1}H NMR (400MHz, METHANOL-d_4) δ 7.41 (d, *J*=1.2 Hz, 1H), 7.07 (d, *J*=8.2 Hz, 1H), 6.69 (d, *J*=2.2 Hz, 1H), 6.64 (dd, *J*=8.2, 2.3 Hz, 1H), 2.63 (q, *J*=7.5 Hz, 2H), 2.20 (d, *J*=1.2 Hz, 3H), 1.11 (t, *J*=7.6 Hz, 3H).
Preparation of (tert-butyl 4-(3-((3-ethyl-4-(5-methyl-6-oxo-1,6-dihydropyridazin-3-yl)phenyl)carbamoyl)-1H-indazol-1-yl)piperidine-1-carboxylate (**S-15**):
To a solution of 1-(1-(tert-butoxycarbonyl)piperidin-4-yl)-1H-indazole-3-carboxylic acid (**17**) (0.027 g, 0.079 mmol) and 6-(4-amino-2-ethylphenyl)-4-methylpyridazin-3(2H)-one (**S-14**) (0.014 g, 0.061 mmol) in DMF (0.3 mL) was added PyBOP (0.048 g, 0.092 mmol) and Hunig'sBase (0.032 mL, 0.183 mmol). The reaction was stirred overnight, then 13 mg (**17**), 24 mg PyBOP, and 30 µL Hunig's base were added. After 6 hours, the reaction was diluted with water and extracted twice with EtOAc. The organic layer was concentrated. The residue was purified via ISCO (12g column; Hex/EtOAc; 0 to 100% gradient) to give tert-butyl 4-(3-((3-ethyl-4-(5-methyl-6-oxo-1,6-dihydropyridazin-3-yl)phenyl)carbamoyl)-1H-indazol-1-yl)piperidine-1-carboxylate (**S-15**) (0.019 g, 0.034 mmol, 55.9 % yield). ^{1}H NMR (400MHz, CHLOROFORM-d) δ 11.00 (s, 1H), 8.90 (s, 1H), 8.47 (d, *J*=8.2 Hz, 1H), 7.81 - 7.67 (m, 2H), 7.62 - 7.44 (m, 2H), 7.41 - 7.31 (m, 2H), 7.28 (br d, *J*=1.1 Hz, 1H), 4.72 - 4.60 (m, 1H), 4.39 (br s, 2H), 3.01 (br t, *J*=12.2 Hz, 2H), 2.76 (q, *J*=7.3 Hz, 2H), 2.29 (s, 5H), 2.11 (br d, *J*=11.1 Hz, 2H), 1.53 (s, 9H), 1.24 - 1.18 (m, 3H).
Preparation of N-(3-ethyl-4-(5-methyl-6-oxo-1,6-dihydropyridazin-3-yl)phenyl)-1-(piperidin-4-yl)-1H-indazole-3-carboxamide, HCl (**S-16**):
Tert-butyl 4-(3-((3-ethyl-4-(5-methyl-6-oxo-1,6-dihydropyridazin-3-yl)phenyl)carbamoyl)-1H-indazol-1-yl)piperidine-1-carboxylate (0.019 g, 0.034 mmol) (**S-15**) was suspended in 4M HCl in dioxane (0.341 ml). After ca. 1 hour, Et2O was added, and the precipitated solid was filtered off, washed with Et2O, and

dried to give N-(3-ethyl-4-(5-methyl-6-oxo-1,6-dihydropyridazin-3-yl)phenyl)-1-(piperidin-4-yl)-1H-indazole-3-carboxamide, HCl (0.013 g, 0.026 mmol, 77 % yield). LC/MS RT: 0.69 min (Method A). M/Z= 457.5.

Preparation of 1-(1-(tert-butylcarbamoyl)piperidin-4-yl)-N-(3-ethyl-4-(5-methyl-6-oxo-1,6-dihydropyridazin-3-yl)phenyl)-1H-indazole-3-carboxamide (**5**):

To a suspension of N-(3-ethyl-4-(5-methyl-6-oxo-1,6-dihydropyridazin-3-yl)phenyl)-1-(piperidin-4-yl)-1H-indazole-3-carboxamide, HCl (**S-15**) (0.013 g, 0.026 mmol) in dichloromethane (0.300 mL) was added Hunig'sBase (0.014 mL, 0.079 mmol) and tbutyl isocyanate (4.52 µl, 0.040 mmol). After 45 minutes, the reaction was concentrated. The residue was dissolved in DMF, filtered through a syringe filter, The crude material was purified via preparative LC/MS with the following conditions: Column: XBridge C18, 19 x 200 mm, 5-µm particles; Mobile Phase A: 5:95 acetonitrile: water with 10-mM ammonium acetate; Mobile Phase B: 95:5 acetonitrile: water with 10-mM ammonium acetate; Gradient: 10-100% B over 15 minutes, then a 5-minute hold at 100% B; Flow: 20 mL/min. Fractions containing the desired product were combined and dried via centrifugal evaporation to give 1-(1-(tert-butylcarbamoyl)piperidin-4-yl)-N-(3-ethyl-4-(5-methyl-6-oxo-1,6-dihydropyridazin-3-yl)phenyl)-1H-indazole-3-carboxamide (8.9 mg, 61%). LC/MS RT: 1.79 min (Method B) M/Z= 556.2 Purity 100%. ^{1}H NMR (500MHz, DMSO-d_6) δ 13.03 (s, 1H), 10.16 (s, 1H), 8.23 (br d, *J*=8.1 Hz, 1H), 7.98 - 7.79 (m, 3H), 7.54 - 7.44 (m, 2H), 7.38 - 7.20 (m, 2H), 5.89 (s, 1H), 4.95 (br t, *J*=11.1 Hz, 1H), 4.18 (br d, *J*=12.5 Hz, 2H), 2.97 - 2.88 (m, 2H), 2.67 (q, *J*=7.5 Hz, 2H), 2.21 - 2.06 (m, 5H), 1.98 (br d, *J*=10.8 Hz, 2H), 1.28 (s, 9H), 1.12 (t, *J*=7.4 Hz, 3H)

Preparation of Compound **6**:



Preparation of 6-chloro-4,5-dimethylpyridazin-3(2H)-one (**S-17**):

3,6-dichloro-4,5-dimethylpyridazine (1.0 g, 5.65 mmol) was dissolved in acetic acid (22.59 ml) and heated to 110 °C overnight. The reaction was concentrated, then carefully neutralized with sat. NaHCO3 solution and dried under vacuum to give 6-chloro-4,5-dimethylpyridazin-3(2H)-one (**S-17**) (0.448 g, 2.82 mmol, 50.0 % yield), which was used without purification. LC/MS RT: 0.57 min (Method A). M/Z= 159.1.

Preparation of 6-(4-amino-2-ethylphenyl)-4,5-dimethylpyridazin-3(2H)-one (**S-18**):

3-ethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (0.203 g, 0.820 mmol), 6-chloro-4,5-dimethylpyridazin-3(2H)-one (**S-17**) (0.100 g, 0.631 mmol), $PdCl_2$(dppf)-DCM adduct (0.051 g, 0.063 mmol), and potassium carbonate (0.200 g, 1.450 mmol) were placed in a pressure vial. The vial was placed under vacuum and backfilled with nitrogen. Acetonitrile (2.52 ml) and water (1.682 ml) were added, then the reaction was heated at 100 °C for 7 hours. The reaction was cooled and extracted

three times with EtOAc. The organic layers were dried with sodium sulfate and concentrated. The residue was purified via ISCO (24g column; DCM/EtOAc; 0 to 100% gradient ;) to give 6-(4-amino-2-ethylphenyl)-4,5-dimethylpyridazin-3(2H)-one (**S-18**) (0.067 g, 0.275 mmol, 43.7 % yield). LC/MS RT: 0.49 min (Method A). M/Z= 244.2.

Preparation of tert-butyl 4-(3-((4-(4,5-dimethyl-6-oxo-1,6-dihydropyridazin-3-yl)-3-ethylphenyl)carbamoyl)-1H-indazol-1-yl)piperidine-1-carboxylate (**S-19**):

To a solution of 1-(1-(tert-butoxycarbonyl)piperidin-4-yl)-1H-indazole-3-carboxylic acid (**17**) (0.124 g, 0.358 mmol) and 6-(4-amino-2-ethylphenyl)-4,5-dimethylpyridazin-3(2H)-one (**S-18**) (0.067 g, 0.275 mmol) in DMF (1.836 ml) was added Hunig's Base (0.192 ml, 1.102 mmol) and PyBOP (0.186 g, 0.358 mmol). The reaction was stirred overnight, then diluted with water and extracted three times with EtOAc. The organic layers were washed with 10% LiCl solution, dried with sodium sulfate, and concentrated. The residue was purified via ISCO (24g column; Hex/EtOAc; 0 to 100% gradient) to give tert-butyl 4-(3-((4-(4,5-dimethyl-6-oxo-1,6-dihydropyridazin-3-yl)-3-ethylphenyl)carbamoyl)-1H-indazol-1-yl)piperidine-1-carboxylate (**S-19**) (0.096 g, 0.168 mmol, 61.1 % yield). ^{1}H NMR (400MHz, CHLOROFORM-d) δ 12.12 (s, 1H), 8.92 (s, 1H), 8.47 (d, *J*=8.2 Hz, 1H), 7.79 - 7.66 (m, 2H), 7.55 - 7.50 (m, 1H), 7.46 (td, *J*=7.6, 0.9 Hz, 1H), 7.34 (t, *J*=7.5 Hz, 1H), 7.16 (d, *J*=8.2 Hz, 1H), 4.67 (tt, *J*=11.3, 4.0 Hz, 1H), 4.37 (br s, 2H), 3.02 (br t, *J*=12.2 Hz, 2H), 2.62 - 2.27 (m, 4H), 2.24 (s, 3H), 2.10 (br d, *J*=11.0 Hz, 2H), 1.96 (s, 3H), 1.53 (s, 9H), 1.17 (t, *J*=7.6 Hz, 3H)

Preparation of N-(4-(4,5-dimethyl-6-oxo-1,6-dihydropyridazin-3-yl)-3-ethylphenyl)-1-(piperidin-4-yl)-1H-indazole-3-carboxamide, 2 HCl (**S-20**):

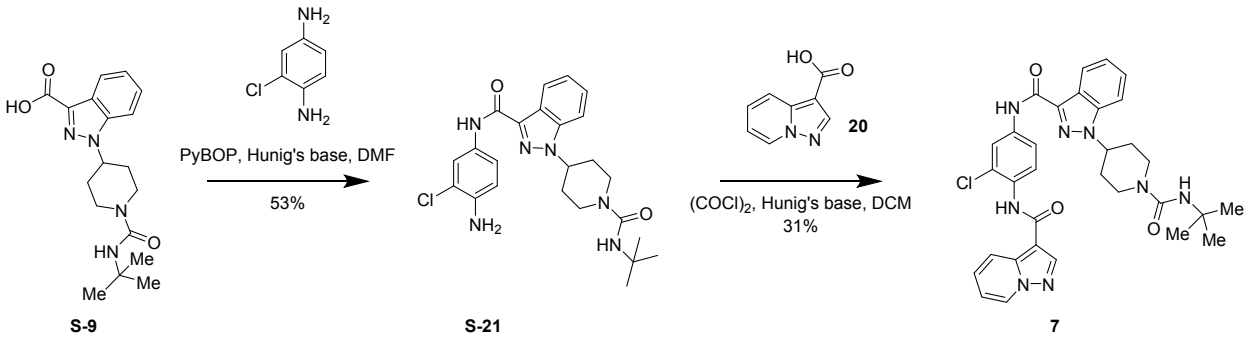
tert-butyl 4-(3-((4-(4,5-dimethyl-6-oxo-1,6-dihydropyridazin-3-yl)-3-ethylphenyl)carbamoyl)-1H-indazol-1-yl)piperidine-1-carboxylate (**S-19**) (0.096 g, 0.168 mmol) was suspended in 4M HCl in dioxane (3 mL). After 45 minutes, the reaction was concentrated and azeotroped with hexanes to give N-(4-(4,5-dimethyl-6-oxo-1,6-dihydropyridazin-3-yl)-3-ethylphenyl)-1-(piperidin-4-yl)-1H-indazole-3-carboxamide, 2 HCl, (**S-20**) (142 mg, >100% yield) which was used directly in subsequent reactions. LC/MS RT: 0.69 min (Method A). M/Z= 471.2.

Preparation of 1-(1-(tert-butylcarbamoyl)piperidin-4-yl)-N-(4-(4,5-dimethyl-6-oxo-1,6-dihydropyridazin-3-yl)-3-ethylphenyl)-1H-indazole-3-carboxamide (**6)**:

To a suspension of N-(4-(4,5-dimethyl-6-oxo-1,6-dihydropyridazin-3-yl)-3-ethylphenyl)-1-(piperidin-4-yl)-1H-indazole-3-carboxamide, 2 HCl (**S-20**) (0.071 g, 0.131 mmol) in DCM (1.5 mL) was added Hunig's Base (0.091 mL, 0.523 mmol) and *t*-butyl isocyanate (0.019 mL, 0.170 mmol). After 1.75 hours, the reaction was quenched with MeOH and concentrated, then azeotroped twice with MeOH. The solid was triturated with MeOH, filtered, and dried to give 1-(1-(tert-butylcarbamoyl)piperidin-4-yl)-N-(4-(4,5-dimethyl-6-oxo-1,6-dihydropyridazin-3-yl)-3-ethylphenyl)-1H-indazole-3-carboxamide (**6**) (0.047 g, 0.082 mmol, 63.2 % yield from **S-19**).

HPLC RT: 9.58 min (Method B). Purity 100%. M/Z= 570.4. ^{1}H NMR (400MHz, DMSO-d_6) δ 12.88 (s, 1H), 10.13 (s, 1H), 8.24 (d, *J*=8.1 Hz, 1H), 7.90 (d, *J*=8.8 Hz, 1H), 7.85 - 7.78 (m, 2H), 7.50 (t, *J*=7.3 Hz, 1H), 7.33 (t, *J*=7.4 Hz, 1H), 7.15 (d, *J*=8.6 Hz, 1H), 5.87 (s, 1H), 4.96 (br t, *J*=11.0 Hz, 1H), 4.20 (br d, *J*=13.4 Hz, 2H), 2.98 - 2.84 (m, 2H), 2.46 - 2.42 (m, 2H) (ovelaps DMSO), 2.21 - 2.11 (m, 2H), 2.08 (s, 3H), 1.99 (br d, *J*=9.2 Hz, 2H), 1.87 (s, 3H), 1.29 (s, 9H), 1.07 (t, *J*=7.6 Hz, 3H)

Preparation of compound **7**:



Preparation of N-(4-amino-3-chlorophenyl)-1-(1-(tert-butylcarbamoyl)piperidin-4-yl)-1H-indazole-3-carboxamide (**S-21**):

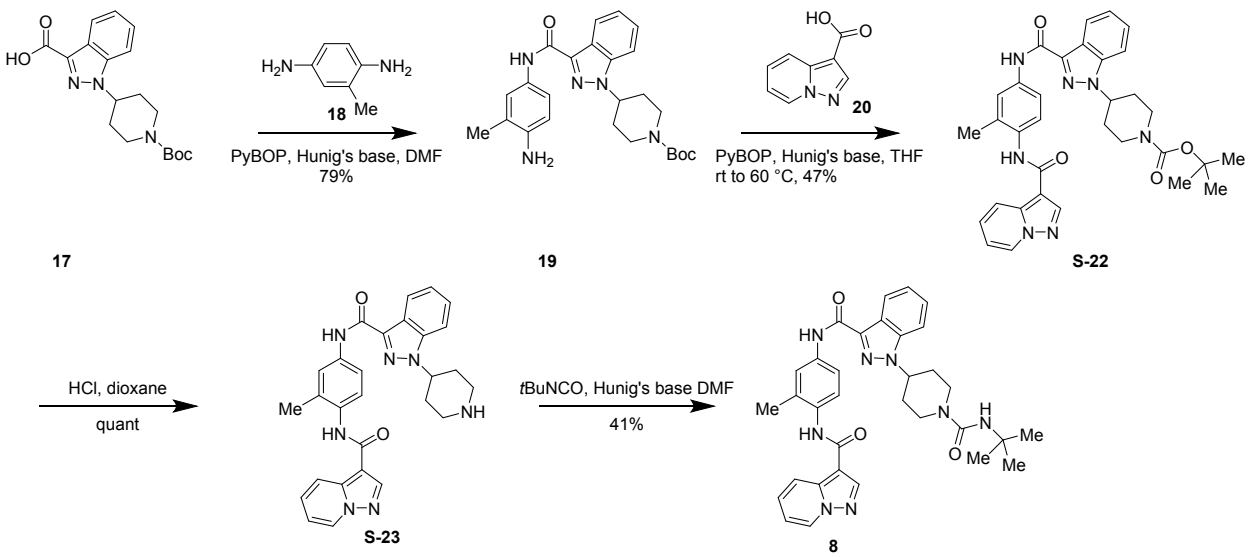
To a suspension of 2-chlorobenzene-1,4-diamine, sulfuric acid salt (30 mg, 0.125 mmol) and 1-(1-(tert-butylcarbamoyl)piperidin-4-yl)-1H-indazole-3-carboxylic acid (**S-9**) (51.5 mg, 0.150 mmol) in DMF (831 µl) was added PyBOP (97 mg, 0.187 mmol) and Hunig'sBase (87 µl, 0.499 mmol). The mixture was stirred at rt for 16 hours. The solvent was evaporated and the residue was purified by ISCO (12 g column, 0 → 100% EtOAc in Hexanes) to afford N-(4-amino-3-chlorophenyl)-1-(1-(tert-butylcarbamoyl)piperidin-4-yl)-1H-indazole-3-carboxamide (**S-21**) (31 mg, 0.066 mmol, 53.0 % yield). LC/MS RT: 0.93 min (Method A). M/Z= 469.3.

Preparation of 1-(1-(tert-butylcarbamoyl)piperidin-4-yl)-N-(3-chloro-4-(pyrazolo[1,5-a]pyridine-3-carboxamido)phenyl)-1H-indazole-3-carboxamide (**7**):

To a suspension of pyrazolo[1,5-a]pyridine-3-carboxylic acid (**S-21**) (5.19 mg, 0.032 mmol) in DCM (350 µl), oxalyl chloride (5.60 µl, 0.064 mmol) was added. The reaction was stirred at rt for 1 hour. The solvent was evaporated and the residue was dried in vacuo. The residue was then dissolved in DCM (350 µl) followed by addition of N-(4-amino-3-chlorophenyl)-1-(1-(tert-butylcarbamoyl)piperidin-4-yl)-1H-indazole-3-carboxamide (15 mg, 0.032 mmol) and Hunig'sBase (27.9 µl, 0.160 mmol). The reaction was for 16 hours, then quenched with MeOH. The solvent was evaporated and the residue was purified by reverse phase HPLC (Water:MeOH) to afford 1-(1-(tert-butylcarbamoyl)piperidin-4-yl)-N-(3-chloro-4-(pyrazolo[1,5-a]pyridine-3-carboxamido)phenyl)-1H-indazole-3-carboxamide (**7**) (6 mg, 9.79 µmol, 31 % yield).

HPLC RT: 23.53 min (Method A). Purity 96.8%. M/Z= 613.3. ^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.87 (s, 1H), 8.66 - 8.60 (m, 1H), 8.51 (d, *J*=8.9 Hz, 1H), 8.47 - 8.43 (m, 1H), 8.40 (dt, *J*=8.9, 1.1 Hz, 1H), 8.36 (s, 1H), 8.23 (d, *J*=2.3 Hz, 1H), 8.15 (s, 1H), 7.55 - 7.45 (m, 4H), 7.39 - 7.33 (m, 1H), 7.05 (td, *J*=6.9, 1.3 Hz, 1H), 4.75 - 4.65 (m, 1H), 4.20 - 4.07 (m, 2H), 3.19 - 3.04 (m, 2H), 2.45 - 2.30 (m, 2H), 2.16 (br dd, *J*=12.7, 2.3 Hz, 2H), 1.42 (s, 9H)

Preparation of compound **8**:



Preparation of tert-butyl 4-(3-((4-amino-3-methylphenyl)carbamoyl)-1H-indazol-1-yl)piperidine-1-carboxylate (**19**):

1-(1-(tert-butoxycarbonyl)piperidin-4-yl)-1H-indazole-3-carboxylic acid (**17**) (0.130 g, 0.376 mmol) and 2-methylbenzene-1,4-diamine, sulfuric acid salt (0.166 g, 0.753 mmol) were suspended in DMF (1.882 ml). Hunig'sBase (0.197 ml, 1.129 mmol) and PyBOP (0.274 g, 0.527 mmol) were added, and the reaction was stirred overnight. The reaction was diluted with water and extracted three times with EtOAc. The organic layers were washed with 10% LiCl solution, dried with sodium sulfate, and concentrated. The residue was purified via ISCO (24g column; DCM/MeOH; 0 to 7% gradient0 to give tert-butyl 4-(3-((4-amino-3-methylphenyl)carbamoyl)-1H-indazol-1-yl)piperidine-1-carboxylate (**19**) (0.133 g, 0.296 mmol, 79 % yield). ^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.66 (s, 1H), 8.47 (d, *J*=8.2 Hz, 1H), 7.52 - 7.48 (m, 2H), 7.46 - 7.37 (m, 2H), 7.34 - 7.28 (m, 1H), 6.70 (d, *J*=8.3 Hz, 1H), 4.68 - 4.58 (m, 1H), 4.36 (br s, 2H), 3.58 (br s, 2H), 3.10 - 2.91 (m, 2H), 2.36 - 2.24 (m, 2H), 2.23 - 2.16 (m, 3H), 2.12 - 2.04 (m, 2H), 1.53 (s, 9H). The regiochemistry of the acylation was confirmed by observation of NOEs from the amide NH to the adjacent aryl protons.

Preparation of tert-butyl 4-(3-((3-methyl-4-(pyrazolo[1,5-a]pyridine-3-carboxamido)phenyl)carbamoyl)-1H-indazol-1-yl)piperidine-1-carboxylate (**S-22**):

To a suspension of pyrazolo[1,5-a]pyridine-3-carboxylic acid (0.053 g, 0.327 mmol) and tert-butyl 4-(3-((4-amino-3-methylphenyl)carbamoyl)-1H-indazol-1-yl)piperidine-1-carboxylate (**19**) (0.105 g, 0.234 mmol) in THF (1.557 ml) was added Hunig'sBase (0.122 ml, 0.701 mmol) and PyBOP (0.194 g, 0.374 mmol). The reaction was stirred overnight, then heated to 60 °C for 8 hours. The reaction was cooled, diluted with water, and extracted twice with EtOAc. The organic layers were dried with sodium sulfate and concentrated. The residue was purified via ISCO (24g column; Hex/EtOAc; 0 to 100% gradient;) to give tert-butyl 4-(3-((3-methyl-4-(pyrazolo[1,5-a]pyridine-3-carboxamido)phenyl)carbamoyl)-1H-indazol-1-yl)piperidine-1-carboxylate (**S-22**) (0.065 g, 0.109 mmol, 46.9 % yield). LC/MS RT: 1.03 min (Method A). M/Z= 594.5.

Preparation of N-(3-methyl-4-(pyrazolo[1,5-a]pyridine-3-carboxamido)phenyl)-1-(piperidin-4-yl)-1H-indazole-3-carboxamide, 2 HCl (**S-23**):

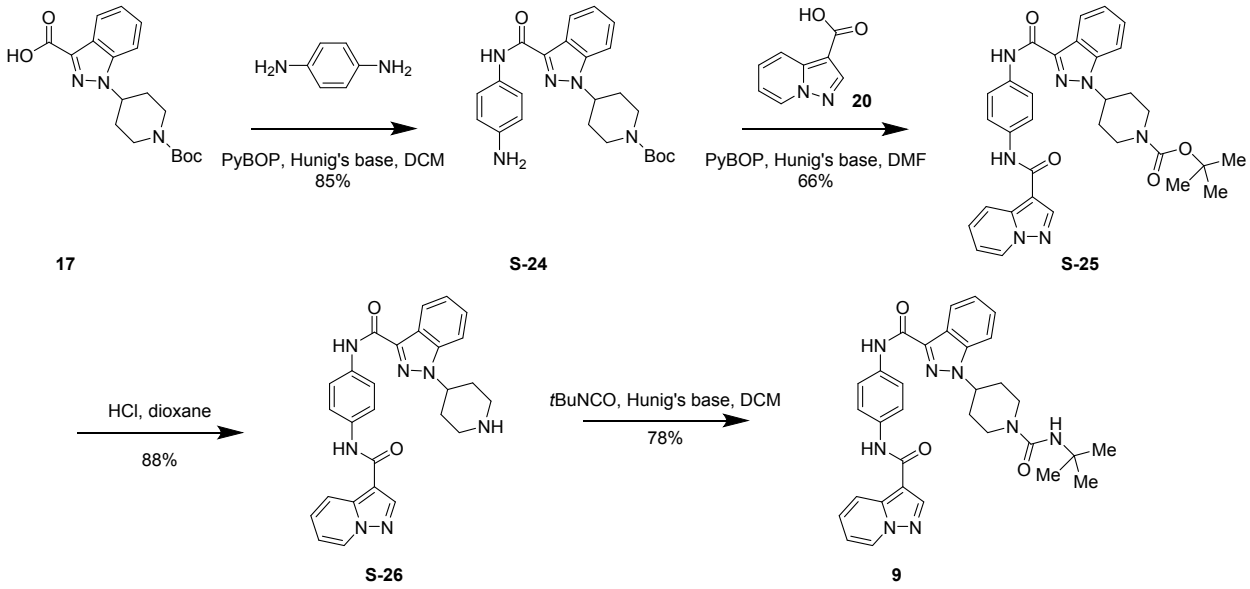
tert-butyl 4-(3-((3-methyl-4-(pyrazolo[1,5-a]pyridine-3-carboxamido)phenyl)carbamoyl)-1H-indazol-1-yl)piperidine-1-carboxylate (**S-22**) (0.065 g, 0.109 mmol) was suspended in 4M HCl in dioxane (2 mL). After ca 2 hours, the reaction was concentrated to give N-(3-methyl-4-(pyrazolo[1,5-a]pyridine-3-carboxamido)phenyl)-1-(piperidin-4-yl)-1H-indazole-3-carboxamide, 2 HCl (**S-23**) (0.066 g, 0.117 mmol, 106 % yield). LC/MS RT: 0.70 min (Method A). M/Z= 494.1.

Preparation of 1-(1-(tert-butylcarbamoyl)piperidin-4-yl)-N-(3-methyl-4-(pyrazolo[1,5-a]pyridine-3-carboxamido)phenyl)-1H-indazole-3-carboxamide (**8**):

To a solution of N-(3-methyl-4-(pyrazolo[1,5-a]pyridine-3-carboxamido)phenyl)-1-(piperidin-4-yl)-1H-indazole-3-carboxamide, 2 HCl (**S-23**) (0.024 g, 0.042 mmol) in DMF (0.4 mL) was added Hunig'sBase (0.030 mL, 0.169 mmol) and tbutyl isocyanate (6.29 µl, 0.055 mmol). The reaction was stirred overnight.The crude material was purified via preparative HPLC with the following conditions: Column: Luna C18, 30 x 100 mm, 5-µm particles; Mobile Phase A: 10:90 MeOH: water with 0.1%TFA; Mobile Phase B: 90:10 MeOH: water with 100.1%TFA; Gradient:0-100% B over 12 minutes, then a 4-minute hold at 100% B; Flow: 25 mL/min. The material was purified a second time via preparative LC/MS with the following conditions: Column: XBridge Shield RP18, 19 x 200 mm, 5-µm particles; Mobile Phase A: 5:95 acetonitrile: water with 10-mM ammonium acetate; Mobile Phase B: 95:5 acetonitrile: water with 10-mM ammonium acetate; Gradient: 20-60% B over 25 minutes, then a 5-minute hold at 100% B; Flow: 20 mL/min to give 1-(1-(tert-butylcarbamoyl)piperidin-4-yl)-N-(3-methyl-4-(pyrazolo[1,5-a]pyridine-3-carboxamido)phenyl)-1H-indazole-3-carboxamide (**8**) (10.4 mg, 41%).

LCMS RT: 1.82 min (Method B). Purity 98.8%. M/Z= 593.1. ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.06 (s, 1H), 9.61 (s, 1H), 8.82 (d, *J*=6.9 Hz, 1H), 8.74 (br s, 1H), 8.23 (br d, *J*=8.2 Hz, 2H), 7.89 (d, *J*=8.7 Hz, 1H), 7.78 (s, 1H), 7.75 - 7.69 (m, 1H), 7.54 - 7.46 (m, 2H), 7.38 - 7.29 (m, 2H), 7.10 (t, *J*=6.6 Hz, 1H), 5.89 (s, 1H), 5.03 - 4.88 (m, 1H), 4.19 (br d, *J*=12.9 Hz, 2H), 2.94 - 2.87 (m, 2H), 2.27 (s, 3H), 2.20 - 2.08 (m, 2H), 1.98 (br d, *J*=10.5 Hz, 2H), 1.29 (s, 9H)

Preparation of compound **9**:



Preparation of tert-butyl 4-(3-((4-aminophenyl)carbamoyl)-1H-indazol-1-yl)piperidine-1-carboxylate (**S-24**):

To a suspension of benzene-1,4-diamine (50 mg, 0.462 mmol) and 1-(1-(tert-butoxycarbonyl)piperidin-4-yl)-1H-indazole-3-carboxylic acid (**17**) (160 mg, 0.462 mmol) in DCM (1541 µl) was added PyBOP (241 mg, 0.462 mmol) and Hunig'sBase (250 µl, 1.433 mmol). The mixture was stirred at rt for 72 hours. The reaction was quenched with MeOH, concentrated and purified by ISCO (24 g column, 0 → 100% EtOAc in Hexanes) to afford tert-butyl 4-(3-((4-aminophenyl)carbamoyl)-1H-indazol-1-yl)piperidine-1-carboxylate (**S-24**) (172 mg, 0.395 mmol, 85 % yield). LC/MS RT: 0.86 min (Method A). M/Z= 436.4.

Preparation of (tert-butyl 4-(3-((4-(pyrazolo[1,5-a]pyridine-3-carboxamido)phenyl)carbamoyl)-1H-indazol-1-yl)piperidine-1-carboxylate (**S-25**):

To a suspension of tert-butyl 4-(3-((4-aminophenyl)carbamoyl)-1H-indazol-1-yl)piperidine-1-carboxylate (100 mg, 0.230 mmol) (**S-24**) and pyrazolo[1,5-a]pyridine-3-carboxylic acid (**17**) (41.0 mg, 0.253 mmol) in DMF (1531 µl) was added PyBOP (143 mg, 0.276 mmol) and Hunig'sBase (160 µl, 0.918 mmol). The mixture was stirred at rt for 12 hours. The reaction was diluted with water and extracted twice with EtOAc. The organic layer was washed with 10% LiCl solution, dried with sodium sulfate, and concentrated. The residue was purified via ISCO (24g column; Hex/EtOAc; 0 to 100% gradient) to give tert-butyl 4-(3-((4-(pyrazolo[1,5-a]pyridine-3-carboxamido)phenyl)carbamoyl)-1H-indazol-1-yl)piperidine-1-carboxylate (**S-25**) (88 mg, 0.152 mmol, 66.1 % yield). LC/MS RT: 1.11 min (Method A). M/Z= 580.3.

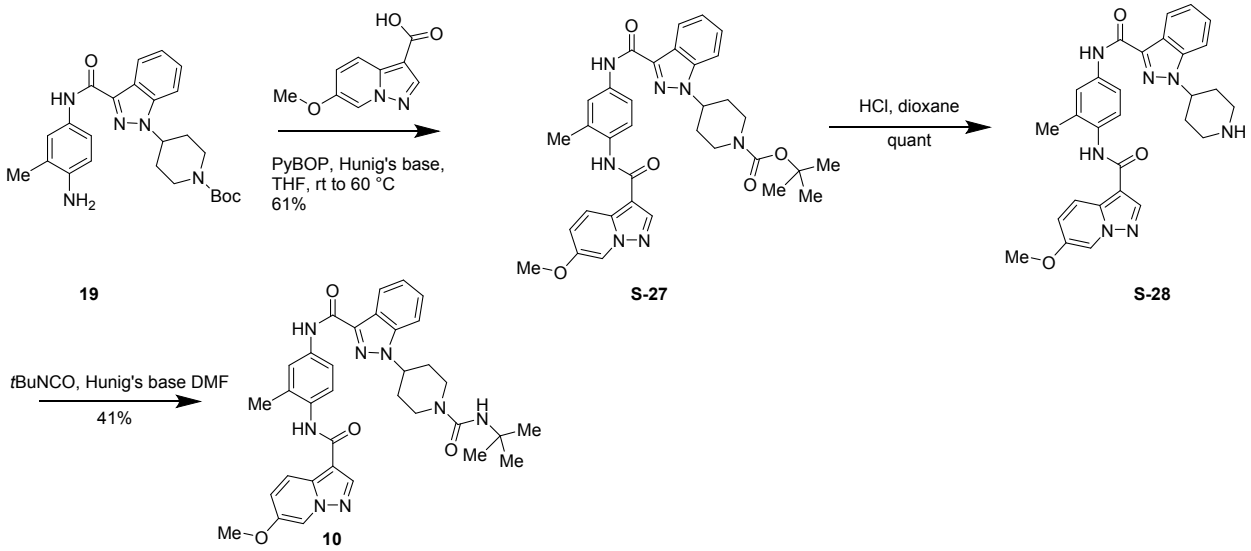
Preparation of (1-(piperidin-4-yl)-N-(4-(pyrazolo[1,5-a]pyridine-3-carboxamido)phenyl)-1H-indazole-3-carboxamide, 2 HCl (**S-26**):

HCl (4M in Dioxane) (1139 µl, 4.55 mmol) was added to tert-butyl 4-(3-((4-(pyrazolo[1,5-a]pyridine-3-carboxamido)phenyl)carbamoyl)-1H-indazol-1-yl)piperidine-1-carboxylate (**S-25**) (88 mg, 0.152 mmol) in a vial. The reaction was stirred at rt for 3 hours. The reaction was concentrated, triturated with ether and filtered to give 1-(piperidin-4-yl)-N-(4-(pyrazolo[1,5-a]pyridine-3-carboxamido)phenyl)-1H-indazole-3-carboxamide, 2 HCl (**S-26**) (74 mg, 0.134 mmol, 88 % yield). Used as is for the next step. LC/MS RT: 0.80 min (Method A). M/Z= 480.3.

Preparation of 1-(1-(tert-butylcarbamoyl)piperidin-4-yl)-N-(4-(pyrazolo[1,5-a]pyridine-3-carboxamido)phenyl)-1H-indazole-3-carboxamide (**9**):

To a suspension of 1-(piperidin-4-yl)-N-(4-(pyrazolo[1,5-a]pyridine-3-carboxamido)phenyl)-1H-indazole-3-carboxamide, 2 HCl (**S-26**) (15 mg, 0.027 mmol) in DCM (0.300 mL) was added Hunig'sBase (0.028 mL, 0.163 mmol) and 2-isocyanato-2-methylpropane (4.65 µl, 0.041 mmol). The reaction was stirred at rt for 3 hours. The solvent was evaporated and the residue was dissolved in MeOH and the crude material was purified via preparative LC/MS with the following conditions: Column: XBridge C18, 19 x 200 mm, 5-µm particles; Mobile Phase A: 5:95 acetonitrile: water with 10-mM ammonium acetate; Mobile Phase B: 95:5 acetonitrile: water with 10-mM ammonium acetate; Gradient: 20-80% B over 20 minutes, then a 5-minute hold at 100% B; Flow: 20 mL/min. Fractions containing the desired product were combined and dried via centrifugal evaporation to give 1-(1-(tert-butylcarbamoyl)piperidin-4-yl)-N-(4-(pyrazolo[1,5-a]pyridine-3-carboxamido)phenyl)-1H-indazole-3-carboxamide (**9**) (12.2 mg, 78%). LCMS RT: 1.82 min (Method B). Purity 100%. M/Z= 579.2. ^{1}H NMR (500MHz, DMSO-d_6) 10.09 (s, 1H), 10.00 (s, 1H), 8.83 (d, *J*=6.9 Hz, 1H), 8.80 (s, 1H), 8.29 (d, *J*=8.8 Hz, 1H), 8.24 (d, *J*=8.2 Hz, 1H), 7.89 (d, *J*=8.6 Hz, 1H), 7.85 - 7.82 (m, 2H), 7.75 (d, *J*=8.9 Hz, 2H), 7.58 - 7.47 (m, 2H), 7.34 (t, *J*=7.5 Hz, 1H), 7.13 (t, *J*=6.9 Hz, 1H), 5.90 (s, 1H), 4.96 (t, *J*=11.2 Hz, 1H), 4.20 (d, *J*=13.0 Hz, 2H), 2.97 - 2.88 (m, 2H), 2.21 - 2.09 (m, 2H), 1.99 (d, *J*=10.8 Hz, 2H), 1.30 (s, 9H).

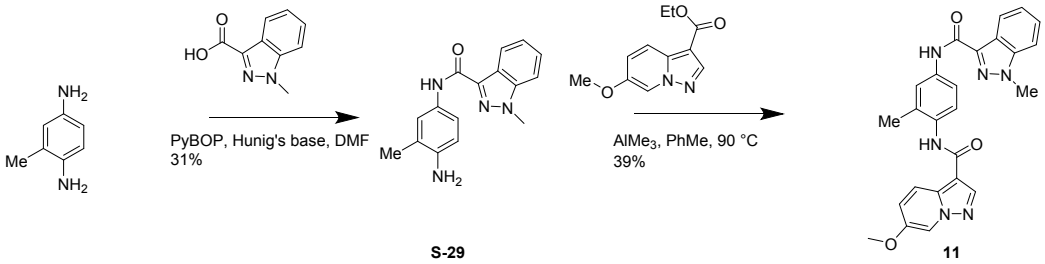
Preparation of compound **10**:



Preparation of tert-butyl 4-(3-((4-(6-methoxypyrazolo[1,5-a]pyridine-3-carboxamido)-3-methylphenyl)carbamoyl)-1H-indazol-1-yl)piperidine-1-carboxylate (**S-27**):
To a suspension of 6-methoxypyrazolo[1,5-a]pyridine-3-carboxylic acid (0.015 g, 0.078 mmol) and tert-butyl 4-(3-((4-amino-3-methylphenyl)carbamoyl)-1H-indazol-1-yl)piperidine-1-carboxylate (**19**) (0.025 g, 0.056 mmol) in THF (0.371 ml) was added Hunig'sBase (0.029 ml, 0.167 mmol) and PyBOP (0.046 g, 0.089 mmol) and stirred overnight. The reaction was then heated to 60 °C for 1 hour. The reaction was loaded directly onto an ISCO column. The residue was purified via ISCO (24g column; Hex/EtOAc; 0 to 100% gradient) to give tert-butyl 4-(3-((4-(6-methoxypyrazolo[1,5-a]pyridine-3-carboxamido)-3-methylphenyl)carbamoyl)-1H-indazol-1-yl)piperidine-1-carboxylate (**S-27**) (0.021 g, 0.034 mmol, 60.5 % yield). LC/MS RT: 1.05min (Method A). M/Z= 624.2.
Preparation of N-(4-(6-methoxypyrazolo[1,5-a]pyridine-3-carboxamido)-3-methylphenyl)-1-(piperidin-4-yl)-1H-indazole-3-carboxamide, 2 HCl (**S-28**):
tert-butyl 4-(3-((4-(6-methoxypyrazolo[1,5-a]pyridine-3-carboxamido)-3-methylphenyl)carbamoyl)-1H-indazol-1-yl)piperidine-1-carboxylate (**S-27**) (0.020 g, 0.032 mmol) was suspended in 4M HCl in dioxane (1 mL). After ca. 1 hour, the reaction was concentrated to give N-(4-(6-methoxypyrazolo[1,5-a]pyridine-3-carboxamido)-3-methylphenyl)-1-(piperidin-4-yl)-1H-indazole-3-carboxamide, 2 HCl (**S-28**) (0.023 g, 0.039 mmol, 120 % yield). LC/MS RT: 0.73 min (Method A). M/Z= 524.5.
Preparation of 1-(1-(tert-butylcarbamoyl)piperidin-4-yl)-N-(4-(6-methoxypyrazolo[1,5-a]pyridine-3-carboxamido)-3-methylphenyl)-1H-indazole-3-carboxamide (**10**):
To a solution of N-(4-(6-methoxypyrazolo[1,5-a]pyridine-3-carboxamido)-3-methylphenyl)-1-(piperidin-4-yl)-1H-indazole-3-carboxamide, 2 HCl (**S-28**) (0.023 g, 0.039 mmol) in DMF (0.4 mL) was added Hunig'sBase (0.020 mL, 0.116 mmol) and tbutyl isocyanate (6.61 µl, 0.058 mmol). After 1.5 hours, the reaction was diluted with DMF, filtered through a syringe filter, and The crude material was purified via preparative LC/MS with the following conditions: Column: XBridge C18, 19 x 200 mm, 5-µm particles; Mobile Phase A: 5:95 acetonitrile: water with 10-mM ammonium acetate; Mobile Phase B: 95:5 acetonitrile: water with 10-mM ammonium acetate; Gradient: 20-75% B over 20 minutes, then a 5-minute hold at 100% B; Flow: 20 mL/min. Fractions containing the desired product were combined and dried via centrifugal evaporation to give 1-(1-(tert-butylcarbamoyl)piperidin-4-yl)-N-(4-(6-methoxypyrazolo[1,5-a]pyridine-3-carboxamido)-3-methylphenyl)-1H-indazole-3-carboxamide (**10**) (10.4 mg, 41%). LCMS RT: 1.82 min (Method C). Purity 95%. M/Z= 623.2. ^{1}H NMR (500MHz, DMSO-d_6) δ 10.06 (s, 1H), 9.57 (s, 1H), 8.64 (br s, 1H), 8.52 (s, 1H), 8.23 (d, *J*=8.1 Hz, 1H), 8.11 (d, *J*=9.6 Hz, 1H), 7.88

(d, *J*=8.7 Hz, 1H), 7.77 (s, 1H), 7.72 (br d, *J*=8.5 Hz, 1H), 7.49 (t, *J*=7.7 Hz, 1H), 7.36 - 7.27 (m, 3H), 5.89 (s, 1H), 4.95 (br t, *J*=11.3 Hz, 1H), 4.19 (br d, *J*=12.9 Hz, 2H), 3.86 (s, 3H), 2.95 - 2.86 (m, 2H), 2.27 (s, 3H), 2.20 - 2.07 (m, 2H), 1.98 (br d, *J*=11.3 Hz, 2H), 1.28 (s, 9H)

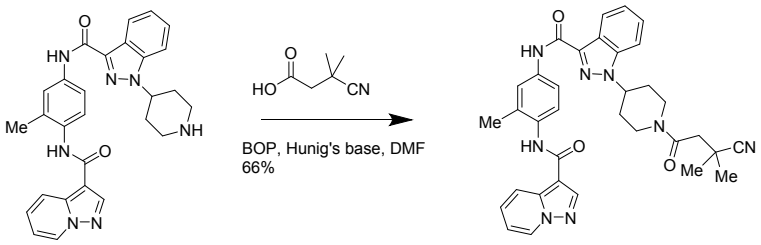
Preparation of compound **11**:



Preparation of (N-(4-amino-3-methylphenyl)-1-methyl-1H-indazole-3-carboxamide (**S-29**):
1-methyl-1H-indazole-3-carboxylic acid (0.100 g, 0.568 mmol) and 2-methylbenzene-1,4-diamine, sulfuric acid salt (0.250 g, 1.135 mmol) were suspended in DMF (1.892 ml). Hunig'sBase (0.297 ml, 1.703 mmol) and PyBOP (0.414 g, 0.795 mmol) were added and stirred for three days. The reaction was diluted with water and extracted twice with EtOAc. The organic layers were washed with 10% LiCl solution, dried with sodium sulfate, and concentrated. The residue was purified via ISCO (24g column; DCM/EtOAc; 0 to 25% gradient) to give N-(4-amino-3-methylphenyl)-1-methyl-1H-indazole-3-carboxamide (**S-29**) (0.050 g, 0.178 mmol, 31.4 % yield). LC/MS RT: 0.63 min (Method A). M/Z= 281.1.

Preparation of (N-(4-(6-methoxypyrazolo[1,5-a]pyridine-3-carboxamido)-3-methylphenyl)-1-methyl-1H-indazole-3-carboxamide (**11**):
To a suspension of ethyl 6-methoxypyrazolo[1,5-a]pyridine-3-carboxylate (0.029 g, 0.134 mmol) andN-(4-amino-3-methylphenyl)-1-methyl-1H-indazole-3-carboxamide (**S-29**) (0.025 g, 0.089 mmol) in Toluene (0.892 ml) was added trimethylaluminum (2M in toluene) (0.067 ml, 0.134 mmol). After ca. 5 minutes, the suspended solid had dissolved and the reaction was heated to 90 °C overnight. The reaction was cooled, then quenched with MeOH. 1M HCl was added, then the reaction was extracted once with EtOAc and once with DCM. The organic layers were concentrated. The material was dissolved in DMF, filtered through a syringe filter, and purified via preparative LC/MS with the following conditions: Column: XBridge C18, 19 x 200 mm, 5-µm particles; Mobile Phase A: 5:95 acetonitrile: water with 10-mM ammonium acetate; Mobile Phase B: 95:5 acetonitrile: water with 10-mM ammonium acetate; Gradient: 10-80% B over 17 minutes, then a 5-minute hold at 100% B; Flow: 20 mL/min. Fractions containing the desired product were combined and dried via centrifugal evaporation to giv(N-(4-(6-methoxypyrazolo[1,5-a]pyridine-3-carboxamido)-3-methylphenyl)-1-methyl-1H-indazole-3-carboxamide (**11**) (16.3 mg, 37%). LCMS RT: 1.67 min (Method B). Purity 97%. M/Z= 455.3 and 909.1 (2M+H)
^{1}H NMR (500MHz, DMSO-d_6) δ 10.28 (s, 1H), 9.56 (s, 1H), 8.64 (br s, 1H), 8.53 (d, *J*=1.6 Hz, 1H), 8.24 (d, *J*=8.2 Hz, 1H), 8.11 (d, *J*=9.7 Hz, 1H), 7.83 (s, 1H), 7.79 (d, *J*=8.5 Hz, 1H), 7.71 (dd, *J*=8.5, 1.9 Hz, 1H), 7.51 (t, *J*=7.7 Hz, 1H), 7.40 - 7.25 (m, 3H), 4.21 (s, 3H), 3.86 (s, 3H), 2.26 (s, 3H)

Preparation of compound **12**:

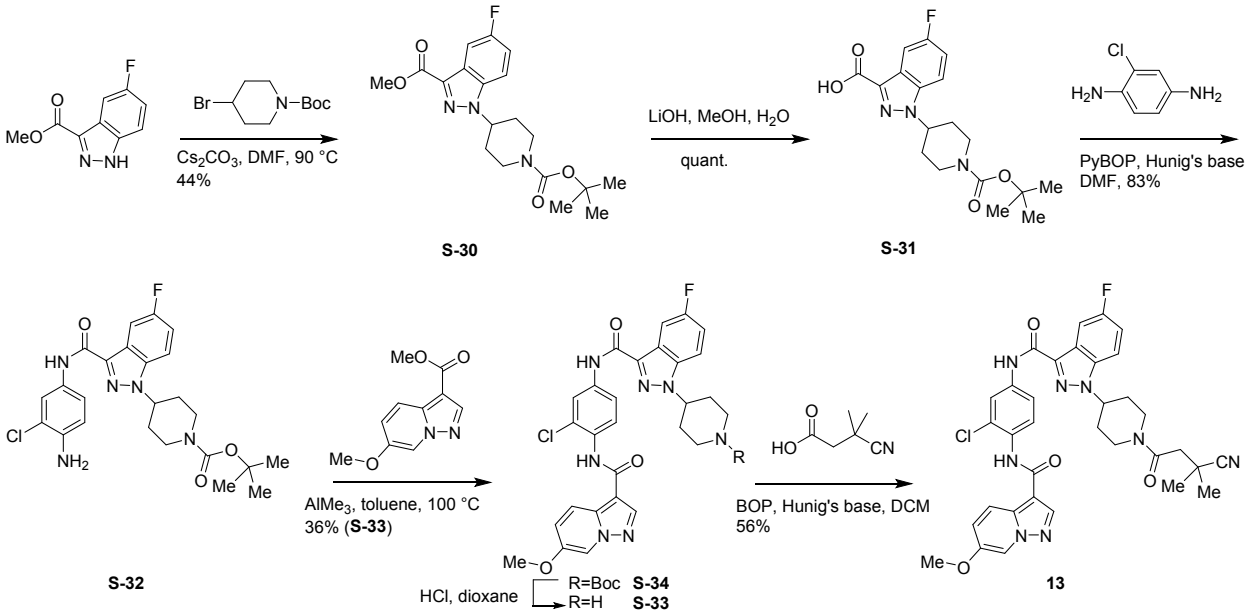


S-23 **12**

Preparation of 1-(1-(3-cyano-3-methylbutanoyl)piperidin-4-yl)-N-(3-methyl-4-(pyrazolo[1,5-a]pyridine-3-carboxamido)phenyl)-1H-indazole-3-carboxamide (**12**)

To a solution of 3-cyano-3-methylbutanoic acid (5.05 mg, 0.040 mmol) and N-(3-methyl-4-(pyrazolo[1,5-a]pyridine-3-carboxamido)phenyl)-1-(piperidin-4-yl)-1H-indazole-3-carboxamide, 2 HCl (**S-23**) (0.015 g, 0.026 mmol) in DMF (0.3 mL) was added Hunig'sBase (0.018 mL, 0.106 mmol) and BOP (0.018 g, 0.040 mmol). After ca. 30 minutes, the reaction was quenched with MeOH, diluted with DMF, and the crude material was purified via preparative LC/MS with the following conditions: Column: XBridge C18, 19 x 200 mm, 5-µm particles; Mobile Phase A: 5:95 acetonitrile: water with 10-mM ammonium acetate; Mobile Phase B: 95:5 acetonitrile: water with 10-mM ammonium acetate; Gradient: 20-80% B over 18 minutes, then a 5-minute hold at 100% B; Flow: 20 mL/min. Fractions containing the desired product were combined and dried via centrifugal evaporation to give 1-(1-(3-cyano-3-methylbutanoyl)piperidin-4-yl)-N-(3-methyl-4-(pyrazolo[1,5-a]pyridine-3-carboxamido)phenyl)-1H-indazole-3-carboxamide (**12**) (10.6 mg, 66%). LCMS RT: 1.71 min (Method B). Purity 100%. M/Z= 603.0. ^{1}H NMR (500 MHz, *DMSO-d*$_6$) δ ppm 10.06 (1 H, s), 9.60 (1 H, s), 8.83 (1 H, d, *J*=6.98 Hz), 8.75 (1 H, br s), 8.20 - 8.30 (2 H, m), 7.91 (1 H, d, *J*=8.67 Hz), 7.79 (1 H, s), 7.73 (1 H, br d, *J*=8.58 Hz), 7.51 (2 H, br t, *J*=9.51 Hz), 7.27 - 7.39 (2 H, m), 7.10 (1 H, t, *J*=6.77 Hz), 5.10 (1 H, br t, *J*=10.98 Hz), 4.66 (1 H, br d, *J*=12.79 Hz), 4.07 (1 H, br d, *J*=13.21 Hz), 3.30 (1 H, br d, *J*=12.03 Hz), 2.89 (1 H, s), 2.74 - 2.85 (2 H, m), 2.28 (3 H, s), 2.01 - 2.22 (4 H, m), 1.41 (6 H, br d, *J*=8.16 Hz).

Preparation of compound **13**:



S-30 **S-31** **S-32** **13**

Preparation of methyl 1-(1-(tert-butoxycarbonyl)piperidin-4-yl)-5-fluoro-1H-indazole-3-carboxylate (**S-30**):

A solution of methyl 5-fluoro-1H-indazole-3-carboxylate (1 g, 5.15 mmol) and tert-butyl 4-bromopiperidine-1-carboxylate (2.041 g, 7.73 mmol) in DMF (17.17 ml) was stirred at 90 °C for 16 hours. Then the mixture was diluted with 20 mL of aqueous $NaHCO_3$ and 40 mL of DCM. The organic layer was washed with brine and dried over Na_2SO_4, then concentrated. The residue was purified by ISCO (24 g column, 0 → 60% EtOAc in Hexane) to afford the undesired regioisomer methyl 2-(1-(tert-butoxycarbonyl)piperidin-4-yl)-5-fluoro-2H-indazole-3-carboxylate and the desired regioisomer methyl 1-(1-(tert-butoxycarbonyl)piperidin-4-yl)-5-fluoro-1H-indazole-3-carboxylate (**S-30**) (855 mg, 2.265 mmol, 44.0 % yield). The desired isomer eluted after the undesired one. ^{1}H NMR (400 MHz, CHLOROFORM-d) δ 7.83 (dd, *J*=8.6, 2.2 Hz, 1H), 7.46 (dd, *J*=9.2, 3.8 Hz, 1H), 7.19 (td, *J*=8.9, 2.4 Hz, 1H), 4.63 (tt, *J*=11.6, 4.1 Hz, 1H), 4.33 (br s, 2H), 4.00 (s, 3H), 2.93 (br s, 2H), 2.29 (br d, *J*=10.4 Hz, 2H), 2.07 - 1.97 (m, 2H), 1.47 (s, 9H).

Preparation 1-(1-(tert-butoxycarbonyl)piperidin-4-yl)-5-fluoro-1H-indazole-3-carboxylic acid (**S-31**):
To a solution of methyl 1-(1-(tert-butoxycarbonyl)piperidin-4-yl)-5-fluoro-1H-indazole-3-carboxylate (0.130 g, 0.344 mmol) (**S-30**) in methanol (2.76 ml) and H_2O (0.689 ml) was added lithium hydroxide, H2O (0.043 g, 1.033 mmol). After 4 hours, the reaction was partially concentrated, acidified to pH 1 with 1M HCl, and extracted twice with EtOAc. The organic layers were concentrated to give 1-(1-(tert-butoxycarbonyl)piperidin-4-yl)-5-fluoro-1H-indazole-3-carboxylic acid (**S-31**) (0.125 g, 0.344 mmol, 100 % yield). LC/MS RT: 0.89 min (Method A). M/Z= 308.1.

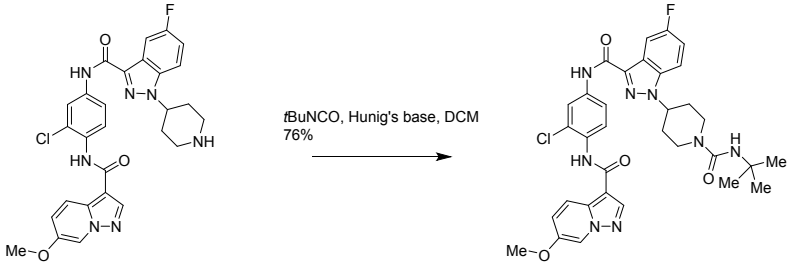
Preparation of tert-butyl 4-(3-((4-amino-3-chlorophenyl)carbamoyl)-5-fluoro-1H-indazol-1-yl)piperidine-1-carboxylate (**S-32**):
To a solution of 2-chlorobenzene-1,4-diamine, sulfuric acid salt (0.993 g, 4.13 mmol) and 1-(1-(tert-butoxycarbonyl)piperidin-4-yl)-5-fluoro-1H-indazole-3-carboxylic acid (**S-31**) (1.0 g, 2.75 mmol) in DMF (13.76 ml) was added Hunig's Base (2.403 ml, 13.76 mmol) and PyBOP (1.862 g, 3.58 mmol). After 6 hours, 250 mg PyBOP and 0.5 mL Hunig's base were added. The reaction was stirred overnight, then diluted with water and extracted twice with EtOAc. The organic layers were washed with 10% LiCl solution, dried with sodium sulfate, and concentrated. The residue was purified via ISCO (120g column; CH2Cl2/EtOAc; 0 to 30% gradient) to give tert-butyl 4-(3-((4-amino-3-chlorophenyl)carbamoyl)-5-fluoro-1H-indazol-1-yl)piperidine-1-carboxylate (**S-32**) (1.11 g, 2.275 mmol, 83 % yield). LC/MS RT: 1.06 min (Method A). M/Z= 488.1.

Preparation of (N-(3-chloro-4-(6-methoxypyrazolo[1,5-a]pyridine-3-carboxamido)phenyl)-5-fluoro-1-(piperidin-4-yl)-1H-indazole-3-carboxamide (**S-33**):
To a suspension of methyl 6-methoxypyrazolo[1,5-a]pyridine-3-carboxylate (0.169 g, 0.820 mmol) and tert-butyl 4-(3-((4-amino-3-chlorophenyl)carbamoyl)-5-fluoro-1H-indazol-1-yl)piperidine-1-carboxylate (**S-32**) (0.250 g, 0.512 mmol) in toluene (5.12 ml) was added trimethylaluminum (2M in toluene) (0.640 ml, 1.281 mmol). Suspended material dissolved slowly and the reaction was heated to 100 °C overnight. LCMS showed that the Boc group was partially cleaved during the reaction. The reaction was cooled, then quenched with MeOH and 1M NaOH. The reaction was absorbed onto sillica gel. The residue was purified via ISCO (40g column; DCM; 0 to 10% gradient, then flush to 35% MeOH). N-(3-chloro-4-(6-methoxypyrazolo[1,5-a]pyridine-3-carboxamido)phenyl)-5-fluoro-1-(piperidin-4-yl)-1H-indazole-3-carboxamide (**S-33**) (0.104 g, 0.185 mmol, 36.1 % yield) was obtained. LC/MS RT: 0.78 min (Method A). M/Z= 562.1.

260 mg of a ca. 1:1-1.3 mixture of **S-34** and ester starting material was also obtained. **S-34** could be converted to **S-33** as described for the preparation of **S-28**.

Preparation of N-(3-chloro-4-(6-methoxypyrazolo[1,5-a]pyridine-3-carboxamido)phenyl)-1-(1-(3-cyano-3-methylbutanoyl)piperidin-4-yl)-5-fluoro-1H-indazole-3-carboxamide (**13**):
To a suspension of N-(3-chloro-4-(6-methoxypyrazolo[1,5-a]pyridine-3-carboxamido)phenyl)-5-fluoro-1-(piperidin-4-yl)-1H-indazole-3-carboxamide, 2 HCl (**S-33**) (0.250 g, 0.393 mmol) and 3-cyano-3-methylbutanoic acid (0.050 g, 0.393 mmol) in DCM (3.93 ml) was added Hunig's Base (0.480 ml, 2.75 mmol) and BOP (0.174 g, 0.393 mmol). After 1.75 hours, 35 mg 3-cyano-3-methylbutanoic acid, 90 mg BOP, and 300 µL Hunig's base were added. After 1 hour, the reaction was quenched with MeOH and concentrated. The residue was absorbed onto silica gel. The residue was purified via ISCO (24g column; DCM/MeOH; 0 to 7% gradient, then flush to 20%). The solid was washed with water/MeOH and dried to give N-(3-chloro-4-(6-methoxypyrazolo[1,5-a]pyridine-3-carboxamido)phenyl)-1-(1-(3-cyano-3-methylbutanoyl)piperidin-4-yl)-5-fluoro-1H-indazole-3-carboxamide (**13**) (0.152 g, 0.219 mmol, 55.7 % yield). HPLC RT: 10.68 min (Method B). Purity 97%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.32 (s, 1H), 9.69 (s, 1H), 8.68 (s, 1H), 8.55 (d, *J*=1.8 Hz, 1H), 8.17 (d, *J*=2.3 Hz, 1H), 8.11 (d, *J*=9.6 Hz, 1H), 8.02 (dd, *J*=9.3, 4.3 Hz, 1H), 7.87 (td, *J*=8.5, 2.4 Hz, 2H), 7.59 (d, *J*=8.7 Hz, 1H), 7.46 (td, *J*=9.1, 2.5 Hz, 1H), 7.33 (dd, *J*=9.6, 2.2 Hz, 1H), 5.19 - 5.07 (m, 1H), 4.70 - 4.62 (m, 1H), 4.14 - 4.03 (m, 1H), 3.87 (s, 3H), 3.30 - 3.25 (m, 1H), 2.93 - 2.73 (m, 3H), 2.25 - 2.05 (m, 4H), 1.42 (d, *J*=5.9 Hz, 6H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 166.9, 161.2, 160.4, 158.5 (br d, *J*=238.9 Hz, 1C), 149.8, 141.0, 137.2, 137.1, 136.5 (br d, *J*=5.4 Hz, 1C), 136.3, 130.3, 129.0, 128.5, 125.2, 122.5 (br d, *J*=11.8 Hz, 1C), 121.7, 120.8, 119.2, 118.4, 116.4 (br d, *J*=27.2 Hz, 1C), 112.6 (br d, *J*=10.0 Hz, 1C), 112.3, 105.9, 105.4 (br d, *J*=24.5 Hz, 1C), 56.4, 55.5, 43.8 (br s, 1C), 41.4, 39.45 - 39.42 (m, 1C), 31.9 (br s, 1C), 30.9 (br s, 1C), 29.7, 26.7, 26.4. ^{19}F NMR (376 MHz, DMSO-d_6) δ -119.63 (s, 1F) HRMS: calculated for $C_{34}H_{33}O_4N_8ClF$ 671.2292 found 671.2283.

Preparation of compound **14**:

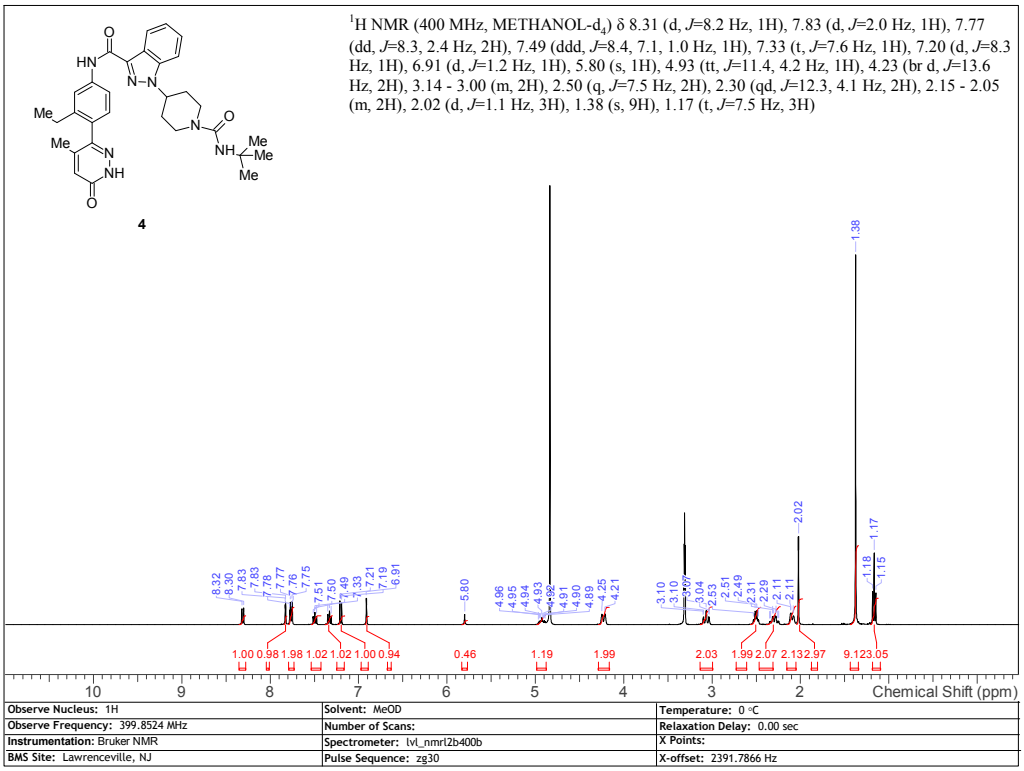


S-33 **14**

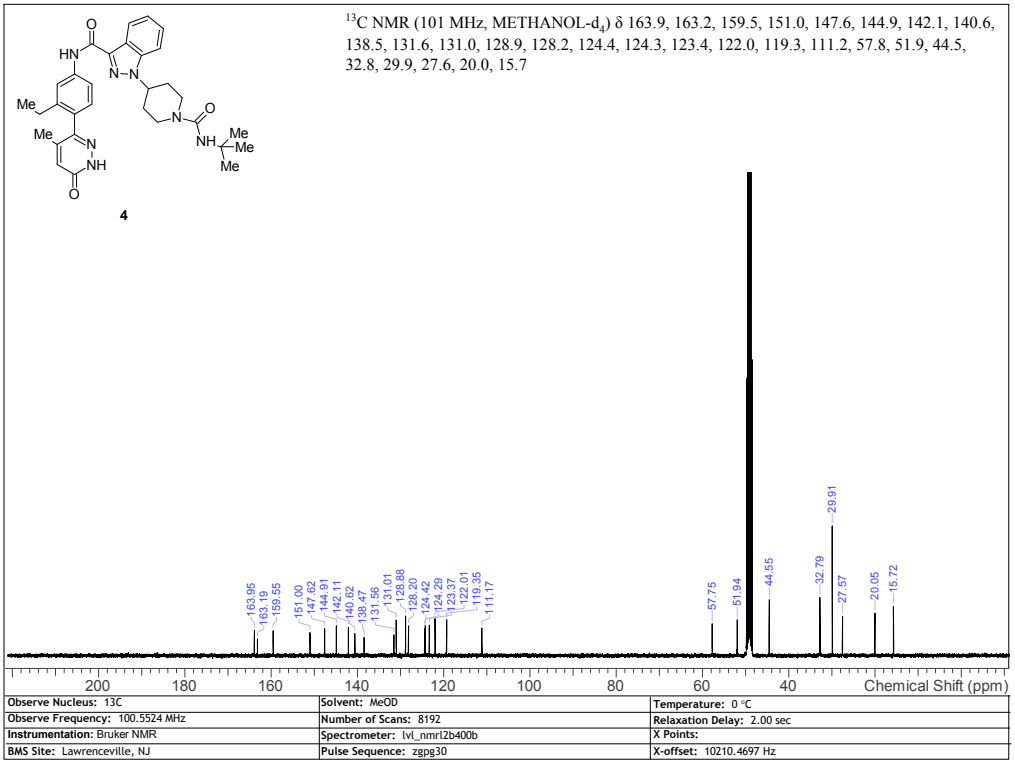
Preparation of 1-(1-(tert-butylcarbamoyl)piperidin-4-yl)-N-(3-chloro-4-(6-methoxypyrazolo[1,5-a]pyridine-3-carboxamido)phenyl)-5-fluoro-1H-indazole-3-carboxamide (**14**):
To a suspension of N-(3-chloro-4-(6-methoxypyrazolo[1,5-a]pyridine-3-carboxamido)phenyl)-5-fluoro-1-(piperidin-4-yl)-1H-indazole-3-carboxamide (**S-33**) (20 mg, 0.036 mmol) in DCM (0.300 mL) was added Hunig'sBase (0.037 mL, 0.214 mmol) and 2-isocyanato-2-methylpropane (4.88 µl, 0.043 mmol). The reaction was stirred at rt for 3 hours. The solvent was evaporated and the residue was purified by ISCO (12 g column, 0 → 10% MeOH in DCM) to afford 1-(1-(tert-butylcarbamoyl)piperidin-4-yl)-N-(3-chloro-4-(6-methoxypyrazolo[1,5-a]pyridine-3-carboxamido)phenyl)-5-fluoro-1H-indazole-3-carboxamide (**14**) (18 mg, 0.027 mmol, 76 % yield) as an offwhite solid. HPLC RT: 22.73min (Method A). Purity 97%. M/Z = 661.5. ^{1}H NMR (400MHz, METHANOL-d_4) δ 8.55 (s, 1H), 8.35 (d, *J*=1.6 Hz, 1H), 8.19 - 8.15 (m, 2H), 7.94 (dd, *J*=8.8, 2.3 Hz, 1H), 7.82 (dd, *J*=9.3, 3.9 Hz, 1H), 7.77 - 7.74 (m, 2H), 7.38 - 7.27 (m, 2H), 4.97 - 4.92 (m, 1H), 4.25 (d, *J*=13.3 Hz, 2H), 3.93 (s, 3H), 3.08 (t, *J*=12.0 Hz, 2H), 2.36 - 2.23 (m, 2H), 2.11 (d, *J*=10.3 Hz, 2H), 1.40 (s, 9H).

NMR Spectra of compound **4**:

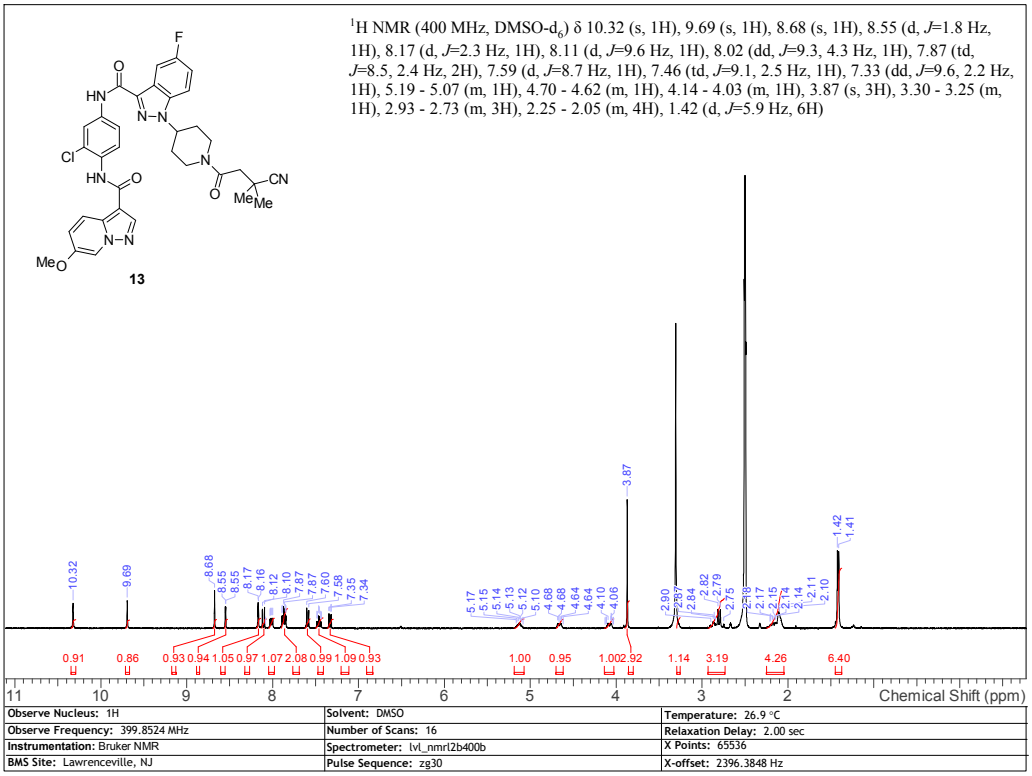
Compound **4** ^{1}H Spectrum (CD_3OD):



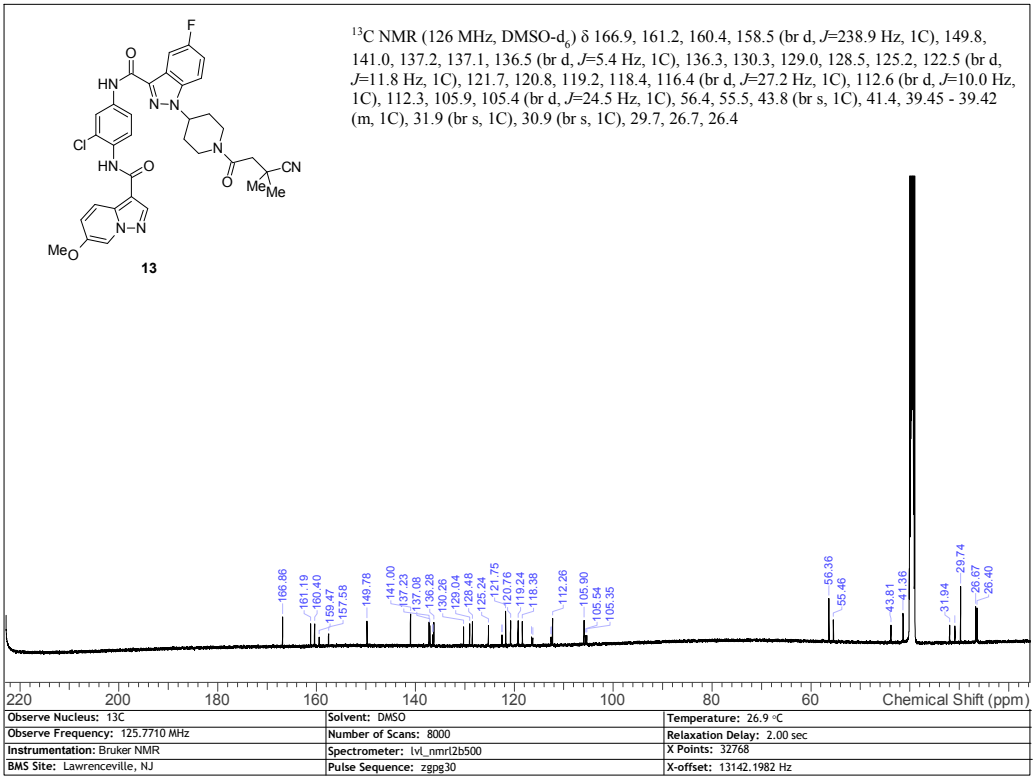
Compound **4** ^{13}C Spectrum (CD_3OD):



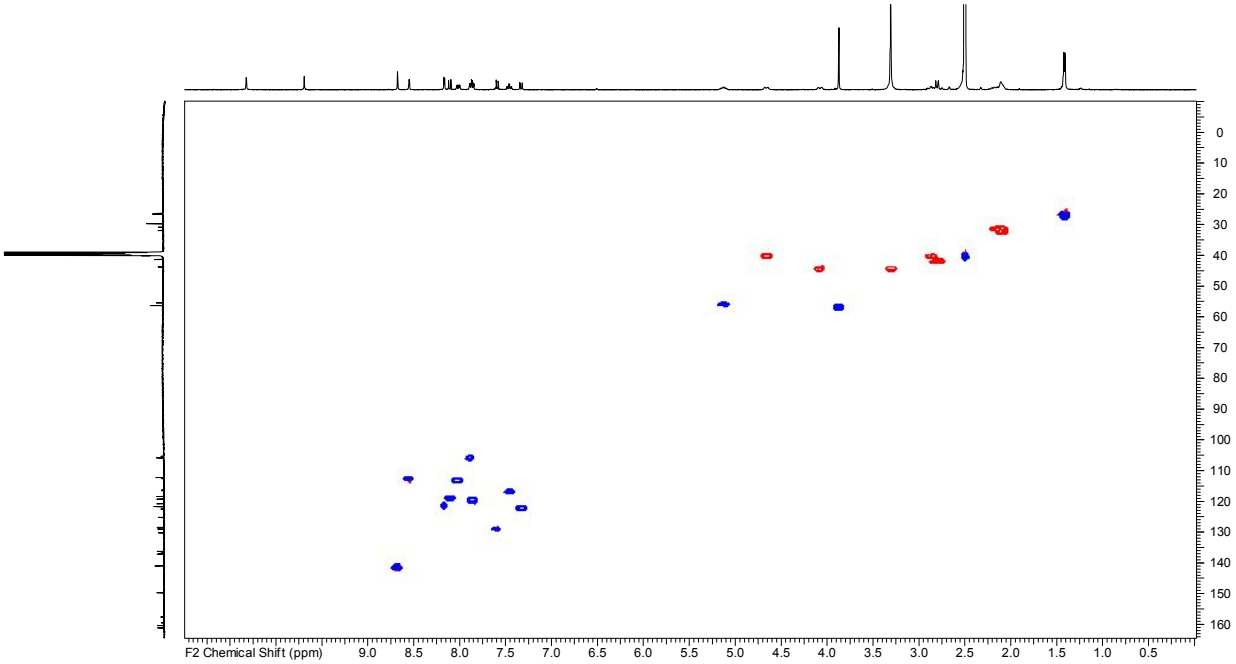
^{1}H Spectrum of Compound **13** (DMSO-d_6):



^{13}C Spectrum of Compound **13** (DMSO-d_6):



HMQC Spectrum of Compound **13** (DMSO-d_6)::



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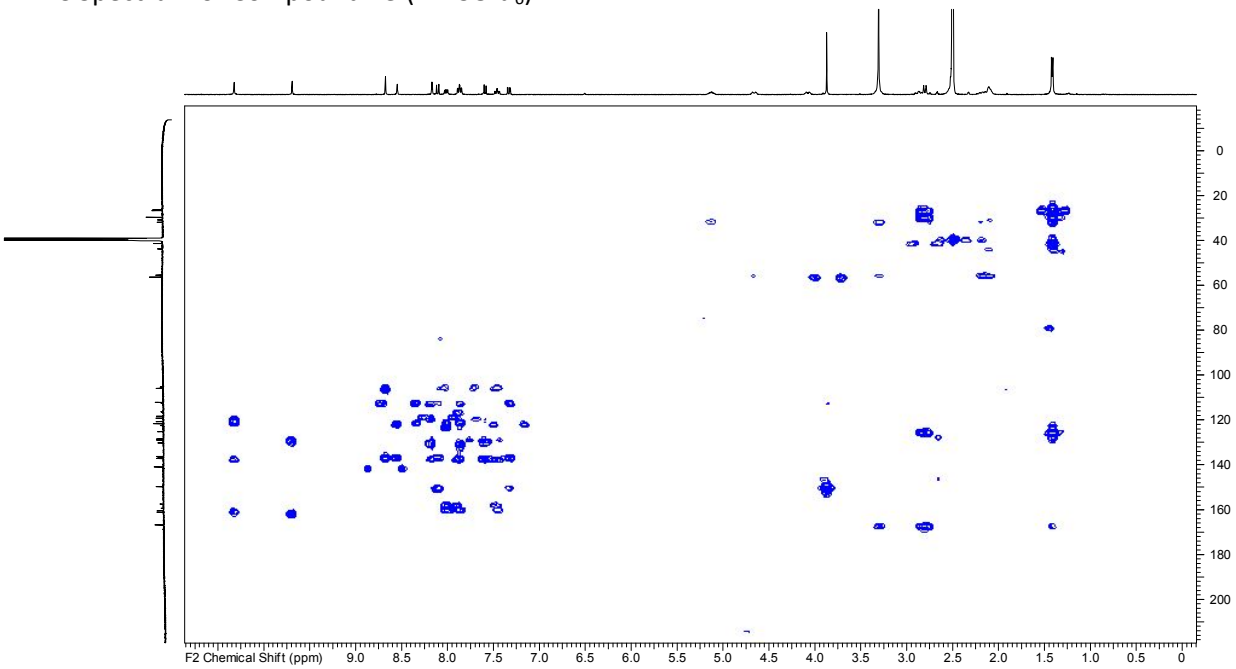
Observe Frequency: (500.1300, 125.7578) MHz	**Number of Scans:**	**Spectrum Type** HSQC-DEPT
Instrumentation: Bruker NMR	**Spectrometer:** lvl_nmrl2b500	**Original Points Count** (1024, 256)
BMS Site: Lawrenceville, NJ	**Pulse Sequence:** hsqcedetgp	**User:** omalleyd

HMBC Spectrum of Compound **13** (DMSO-d_6):



Nucleus (1H, 13C)	**Solvent:** DMSO	**Temperature:** 0 °C
Observe Frequency: (500.1300, 125.7578) MHz	**Number of Scans:** 32	**Spectrum Type** HMBC
Instrumentation: Bruker NMR	**Spectrometer:** lvl_nmrl2b500	**Original Points Count** (1024, 256)
BMS Site: Lawrenceville, NJ	**Pulse Sequence:** hmbcgplpndqf	**User:** omalleyd

Kinome Selectivity Data for Compounds **4,6,13,** and **14**. Kinases with an IC_{50} value within 100 fold of the Csk value are listed; only kinases with IC_{50} values <1 μM are listed for compound **4**.

Kinome Selectivity for Compound **4**

Kinase	Kinase
BMX	MAP4K3
FES	Sek1

Kinome Selectivity for Compound **6**

Kinase	Kinase	Kinase
BMX	FES	ROCK1
MAP4K3	ROCK2	

Kinome Selectivity for Compound **13**

Kinase	Kinase	Kinase
BMX	EPHA4	EPHB4
EPH2B	BTK	FGR
HER4	EPHA8	LCK
ARG	Abl	BRAF
RAF1	LYN	EPHA2
EPHA5	EPHB1	

Kinome Selectivity for Compound **14**

Kinase	Kinase	Kinase
Abl	EPHB2	RAF1
BMX	EPHB1	BTK
FGR	EPHA4	EPHA2
EPHA5	HER4	YES
EPHA8	LCK	SRC
ARG	EPHB4	
TYK2b	LYN	