In Silico High-Throughput Screening To Identify Novel Indazole-Derived ULK1 Inhibitors

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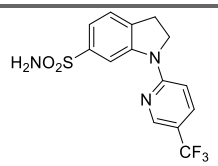
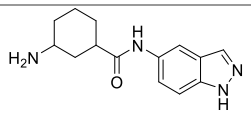
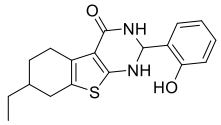
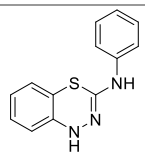
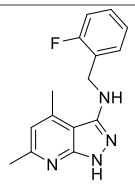
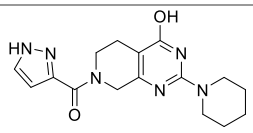
Supplemental Figure S1. ULK1 Biochemical Inhibition Data for SAR by Purchase Compounds.

Entry #	Structure	ULK1 IC_{50} (μM)
S1a		> 33
S1b		22.4
S1c		> 33
S1d		> 33
S1e		> 33
S1f		> 33

Supplemental Figure S2. *in vitro* Microsome stability and CYP P450 inhibition data for selected compounds.

Compound #	*in vitro* Microsome ($t_{1/2}$ min)			CYP P450 Inhibition (% at 10 μM)			
	Human	Mouse	Rat	1A2	2C9	2D6	3A4
1a	81.1	56.2	34.1	23	-4	15	-16
2f	75.1	77.5	19.9	--	--	--	--
3a	45.7	>120	>120	--	--	--	--
3c	134.7	141.7	134.7	24	-2	17	20
3g	224.6	178.4	110.5	31	-6	20	15

In silico HTS Procedures:

The programs LigPrep, Protein Preparation Wizard, and Glide version 2016-3 from the Schrödinger Small Molecule Drug Discovery Suite (1) was utilized for ligand docking and *in silico* HTS studies.

Preparation of Ligand Database. The virtual chemical library collection was obtained from the Scripps Screening core, which comprises around 650,000 commercially available and proprietary in house compounds. The structures were received in an SDF file format which were imported into Schrödinger Maestro. The chemical structures were cleaned up to add/remove hydrogen atoms, remove salt and solvent molecules, and produce relevant protonation states at pH 7.0 ± 2.0 and generation of tautomers using the LigPrep (OPLS2005 force field) workflow to generate ~1.2 million energy minimized compounds total.

Virtual Screening. The virtual screening comprised four steps: Analysis of X-ray structures and preparation of a target structure, Grid generation, Glide docking, and Data analysis. **Preparation of a target structure:** Analysis of X-ray structures and preparation of the target structure coordinates were downloaded for three reported ULK1 crystal structures (4WNO, 4WNP, 5CI7) found in the Protein Data Bank (PDB). Evaluation of the structures, specifically those co-crystalized with an inhibitor was a preliminary step in our evaluation. We aimed to identify ATP competitive inhibitors, so those reported to bind at this site in the kinase were critically evaluated to discern influential interactions in this binding pocket. The X-ray co-crystal structure of ULK1 (PDB ID: 4WNP) was used as the target for the *in silico* HTS campaign within this study.(2) First, the protein structure was prepared by refining the target protein structure using the ProteinPrep workflow. This step includes: assigning bond orders, adding hydrogen atoms, creating disulfide bonds, filling in missing side chains and loops, and deleting water molecules beyond 5 Å from hetero groups. Finally, the structure was subjected for restrained minimization using the OPLS2005 force field. **Receptor grid generation**: a receptor grid was generated for the ligand-binding site of the target protein. The grid was set to a 25 cubic Å box centered on the ATP competitive reference ligand of the ULK1 co-crystal structure (4WNP) and included the hinge binding region of ULK1 and solvent exposed area at the edge of the binding pocket. No constraints were applied in the grid generation to make the docking processes unbiased in any way. **Glide docking:** The

standard precision Glide docking module was used for the *in silico* HTS. The prepared compound collection was directly used without further ligand filtering or preparation. The docking workflow produces numerous poses for each ligand in the active site, recalculating the score for the top 5 possess and outputting a single pose per compound. There is a cutoff point (0.0 k/cal), and any compounds that don't have at least that energy of binding are not included in the data output. The output from the docking was saved for data analysis and hit triage. **Data analysis and hit triage:** Since the ligand interactions with the hinge-binding region of ULK1 were desired, screening hits were initially prioritized by their H-bonding interactions with the hinge-binding region of the ULK1 ATP pocket. Evaluation of the top ~1,000 docked molecules as indicated by glide score (-10.7 through -8.6) was performed. The top hits were grouped into common cores based on repeat scaffolds observed in the top tier. While performing this evaluation, hits containing promiscuous binding groups or PAINS were eliminated via visual identification of molecules or functional groups reported to have promiscuous activity.(3) In this way, we identified a variety of cores and purchased a small set of representative compounds from ChemNavigator.

References:

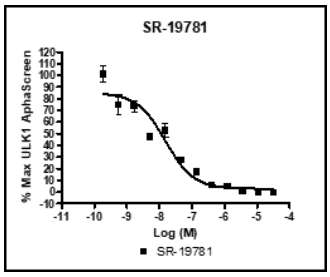
(1) *Schrödinger Release 2016-3: Glide, Schrödinger, LLC, New York, NY, 2016*

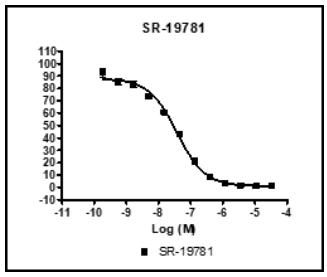
(2) Lazarus, M. B.; Novotny, C. J.; Shokat, K. M. Structure of the Human Autophagy Initiating Kinase ULK1 in Complex with Potent Inhibitors. *ACS Chem. Biol.* **2015**, *10* (1), 257–261.

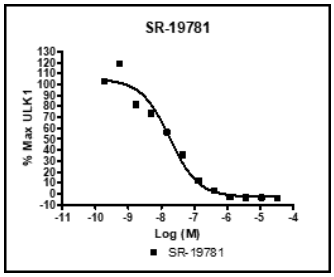
(3) Baell, J. B.; Holloway, G. A. New Substructure Filters for Removal of Pan Assay Interference Compounds (PAINS) from Screening Libraries and for Their Exclusion in Bioassays. *J. Med. Chem.* **2010**, *53* (7), 2719–2740.

Example of deviation in ULK1 IC_{50} assay result for SR-19781:

SR-19781			
Std. Error	2016-07-13	2016-08-02	2016-08-26
EC50	1.53E-08	1.37E-08	1.80E-08
BOTTOM	3.068	1.265	3.729
TOP	4.652	1.974	5.407
LOGEC50	**0.1321**	**0.04504**	0.1204
AntiLogEC50	1.35550149	1.109276979	1.319471457







General Methods: Tetrahydrofuran, dichloromethane, dimethylformamide, diethyl ether, and toluene were purified by passing solvent through a solvent column of activated alumina (A-1). Diisopropyl amine and triethyl amine were purified by distillation from calcium hydride. Anhydrous 1,4-dioxane and methanol were purchased from Aldrich Chemical Company and used as received. All other commercially available reagents were used as received. Unless otherwise indicated, all reactions were conducted under an atmosphere of argon using flame-dried or oven-dried (140 °C) glassware. The phrase "concentrated under reduced pressure" refers to the removal of solvents and volatile reagents using a rotary evaporator with the water bath temperatures below 50 ºC, followed by removal of residual solvent under high vacuum (<1trorr). Standard handling techniques for air-sensitive compounds were also employed for all the operations.

Physical Properties and Spectroscopic Measurements: Proton nuclear magnetic resonance **(**^{1}H NMR) spectra were recorded on a Bruker Avance ULTRAShield instrument at 400 MHz. Carbon-13 nuclear magnetic resonance (^{13}C NMR) spectra were recorded on a Bruker Avance ULTRAShield instrument at 100 MHz. The proton signal for non-deuterated solvents (7.26 ppm for $CHCl_3$, 2.50 ppm for $(CH_3)_2SO$, and 3.31 ppm for CH_3OD) were used as an internal reference for ^{1}HNMR spectra. For ^{13}CNMR spectra, chemical shifts are reported relative to the 77.0 ppm, 39.52 ppm or 49.00 ppm resonance of $CDCl_3$, $(CD_3)_2SO$, or CD_3OD respectively. Optical rotations were measured on a Rudolph Autopol IV polarimeter using a quartz cell with 1 mL capacity and a 1 dm path length.

Analytical thin layer chromatography (TLC) was performed on Kiesel 60 F254 glass plates precoated with a 0.25 mm thickness of silica gel. TLC plates were visualized with UV light and/or by staining with $KMnO_4$[7] or an iodine chamber. Column chromatography was performed using a Biotage Isolera automated flash system. Compound was loaded onto pre-filled cartridges filled with KP-Sil 50μM irregular silica. LCMS was performed with an agilent LCMS using a Kinetex® 5 m EVO C18 100 A˚ LC Column 100 x 4.6 mm (Phenomenex) column.

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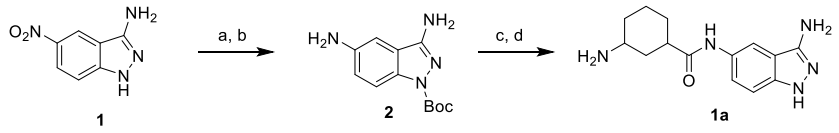
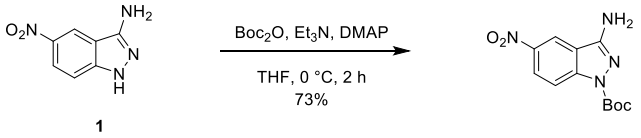
Synthesis of primary 3-amino indazole derivatives 1{*n*}

Scheme S1. Representative synthetic sequence.



[a]Reagents and conditions: (a) Boc_2O, Et_3N, DMAP, THF, 0 °C, 2h, (73% yield); (b) Pd/C, H_2, MeOH, 22 °C, 16h (91% yield); (c) 3-(Boc-amino)cyclohexanecarboxylic acid, HATU, Et_3N, CH_2Cl_2, 22 °C, 2h; (38%) (d) 10% TFA in CH_2Cl_2, 22 °C, 2h (98% yield)

Scaffold Synthesis 1a.

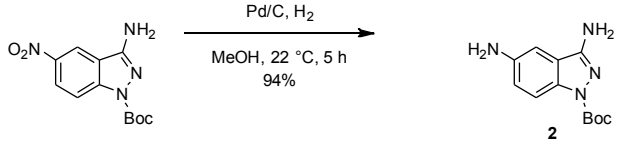


tert-Butyl 3-amino-5-nitro-1H-indazole-1-carboxylate: (See Krishnamurty, R.; Brock, A. M.; Maly, D. J. Bioorganic and Medicinal Chemistry Letters, 2011, 21, 550-554). A 50 mL round bottom flask was charged with 5-nitro-1H-indazole-3-amine (**1**) (1 g, 5.61 mmol) followed by the addition of dry THF (6 mL). This mixture was cooled to 0 °C in an ice/water bath, then di-tertbutyl dicarbonate (1.23g, 5.61 mmol), triethylamine (0.782 mL, 5.61 mmol) and 4-dimethylaminopyridine (6.9 mg, 0.056 mmol) were added sequentially. The reaction was stirred under an atmosphere of argon for 2 hours at 0 °C. The reaction mixture was quenched by the addition of a saturated NH_4Cl aqueous solution then extracted with ethyl acetate three times. The combined organic layers were washed with water followed by brine. The organic layer was collected then dried over Na_2SO_4, filtered through cotton, and concentrated under reduced pressure. The resulting bright yellow/orange solid was suspended in CH_2Cl_2 and the solid was collected via filtration. The filtrate was filtered a second time after resting for 2 hours and the solids were combined to yield 1.14g (4.10 mmol, 73%) of the desired product as a yellow-orange solid.

^{1}H NMR (400 MHz, DMSO-d6) δ 8.96 (d, J = 2.3 Hz, 1H), 8.35 (dd, J = 9.2, 2.3 Hz, 1H), 8.09 (d, J = 9.2 Hz, 1H), 6.74 (s, 2H), 1.60 (s, 9H).

^{13}C NMR (101 MHz, DMSO-d6) δ 152.90 , 148.64 , 142.57 , 142.45 , 124.16 , 119.11 , 118.23 , 114.58 , 83.74 , 27.78.

LCMS(ESI) for $C_{12}H_{14}N_4O_4$: calc. M 278.1, obs. (M+H-Boc)+: m/z = 179.3

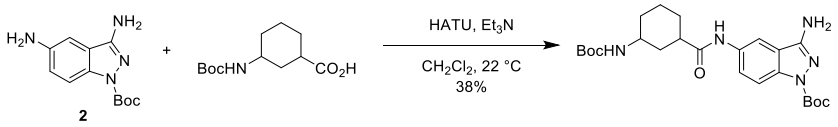


2

tert-butyl 3,5-diamino-1H-indazole-1-carboxylate (2): (See Patent: WO2006/71940 A2, 2006; pg/pg column 409). A 100 mL round bottom flask was charged with tert-butyl 3-amino-5-nitro-1H-indazole-1-carboxylate (400 mg, 1.41 mmol) followed by MeOH (40 mL). 10% Pd/C (400 mg) was added, then hydrogen gas was bubbled into the solution using a balloon. The reaction was stirred under these conditions at 22 °C until complete conversion of the nitro group was observed via LCMS. The reaction mixture was purged of H_2 via bubbling with argon gas. Next the reaction mixture was filtered over celite and the filtrate was concentrated under reduced pressure to yield 327 mg (1.31 mmol, 91%) the crude product as a beige solid.

^{1}H NMR (400 MHz, Methanol-d_4) δ 7.64 (s, 1H), 6.93 (d, J = 7.1 Hz, 2H), 1.56 (s, 9H), 1.54 – 1.50 (m, 2H).

LCMS(ESI) for $C_{12}H_{16}N_4O_2$: calc. M 248.1, obs. (M+H-tBu)+: m/z = 193.2

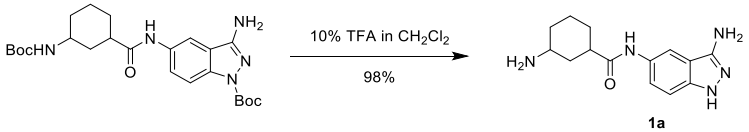


tert-butyl 3-amino-5-(3-((tert-butoxycarbonyl)amino)cyclohexane-1-carboxamido)-1H-indazole-1-carboxylate: A 15 mL round bottom flask was charged with 3-((tert-butoxycarbonyl)amino)cyclohexane-1-carboxylic acid (**2**, 69 mg, 0.283 mmol) and HATU (92 mg, 0.24 mmol) followed by 3 mL CH_2Cl_2. Next, DIPEA (53 □ L, 0.304 mmol) was added dropwise to generate a pale-yellow solution which was stirred at 22 °C for 15 minutes. **2** (50 mg, 0.202 mmol) was then added to the reaction mixture, which was then stirred for 2 hours at 22 °C. At this point the reaction mixture was concentrated under reduced pressure and the resulting brown residue was purified via biotage to yield the desired product as a white solid (36 mg, 0.076 mmol, 38%).

^{1}H NMR (400 MHz, Methanol-d_4) δ 8.11 (d, J = 2.0 Hz, 1H), 7.88 (d, J = 8.6 Hz, 1H), 7.52 (dd, J = 8.9, 2.0 Hz, 1H), 3.41 (s, 1H), 2.48 (t, J = 3.4 Hz, 1H), 2.07 (dt, J = 11.9, 1.9 Hz, 1H), 1.96 – 1.80 (m, 3H), 1.65 (s, 9H), 1.43 (s, 13H), 1.28 – 1.11 (m, 1H).

^{13}C NMR (101 MHz, Methanol-d4) □ 176.32 , 157.73 , 154.17 , 150.70 , 135.32 , 124.44 , 120.28 , 115.68 , 112.70 , 84.88 , 79.92 , 50.33 , 46.00 , 36.96 , 33.42 , 29.78 , 28.78 , 28.50 , 25.52 .

LCMS(ESI) for $C_{24}H_{35}N_5O_5$: calc. M 473.3, obs. (M+H-Boc)+: m/z = 374.3



1a

3-amino-N-(3-amino-1H-indazol-5-yl)cyclohexane-1-carboxamide (1a). To a vial containing 36 mg (0.076 mmol) containing tert-butyl 3-amino-5-(3-((tert-butoxycarbonyl)amino)cyclohexane-1-carboxamido)-

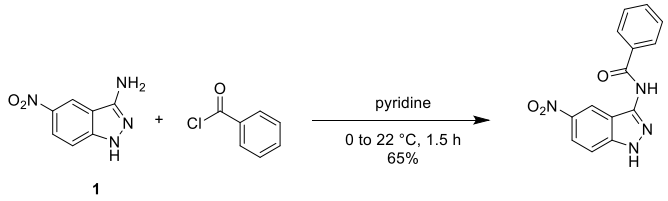
1H-indazole-1-carboxylate was added 10% TFA in CH_2Cl_2 (0.4 mL) and this mixture was stirred for an hour at 22 °C then concentrated under reduced pressure. The crude product was pure as a crude beige solid TFA salt (29 mg, 0.075 mmol, 98%).

^{1}H NMR (400 MHz, Methanol-d4) δ 8.34 (dd, J = 1.9, 0.8 Hz, 1H), 7.64 (dd, J = 9.1, 2.0 Hz, 1H), 7.42 (dd, J = 9.1, 0.8 Hz, 1H), 3.22 (tt, J = 11.8, 3.9 Hz, 1H), 2.59 (tt, J = 11.7, 3.3 Hz, 1H), 2.19 (ddq, J = 9.6, 3.8, 1.9 Hz, 1H), 2.07 (d, J = 12.5 Hz, 1H), 2.02 - 1.92 (m, 2H), 1.68 (q, J = 12.1 Hz, 1H), 1.56 (s, 2H), 1.55 - 1.33 (m, 3H).

^{13}C NMR (101 MHz, DMSO-d6) δ 172.58 , 158.95 , 158.59 , 158.24 , 139.01 , 132.44 , 124.87 , 117.32 , 114.41 , 112.26 , 111.34 , 110.39 , 48.62 , 42.70 , 32.54 , 29.66 , 28.30 , 23.04 .

LCMS(ESI) for $C_{14}H_{19}N_5O$: calc. M 273.2, obs. (M+H)+: m/z = 274.4

Synthesis of compound 2a:

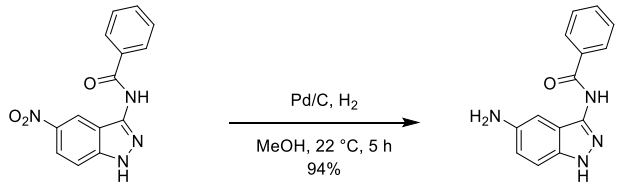


N-(5-nitro-1H-indazol-3-yl)benzamide: (See Patent: US2004/ 106667 A1, **2004**; example 23) A 25 mL round bottom flask was charged with 5-nitro-1H-indazole-3-amine (**1**, 120 mg, 0.674 mmol) followed by pyridine (1 mL). The reaction mixture was cooled to 0 °C in an ice/water bath, then benzoyl chloride (78 □ L, 0.674 mmol) was added dropwise and the mixture is stirred for 10 minutes under an atmosphere of argon. The reaction mixture was then warmed to 22 °C and stirred for an additional 1.5 hours. The reaction was quenched by the addition of water, then extracted three times with EtOAc. The combined organic layers were dried over $MgSO_4$, filtered through cotton and concentrated under reduced pressure. The resulting orange solid was suspended in CH_2Cl_2 and the solid is collected via filtration to yield the desired product (123 mg, 0.438 mmol, 65% yield)

^{1}HNMR (400 MHz, DMSO-d6) δ 13.49 (s, 1H), 11.23 (s, 1H), 8.95 (d, J = 2.2 Hz, 1H), 8.20 (dd, J = 9.2, 2.2 Hz, 1H), 8.16 - 8.08 (m, 2H), 7.68 (d, J = 9.3 Hz, 1H), 7.65 - 7.61 (m, 1H), 7.57 (ddt, J = 8.3, 6.5, 1.6 Hz, 2H);

^{13}C NMR (101 MHz, DMSO-d6) δ 165.62 , 143.34 , 142.73 , 140.63 , 133.34 , 132.11 , 128.46 , 128.11 , 121.20 , 120.98 , 115.37 , 111.22 .

LCMS(ESI) for $C_{14}H_{10}N_4O_3$ (M+H)+: m/z = 283.3

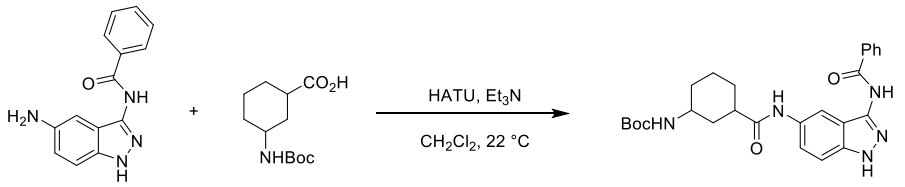


N-(5-amino-1H-indazol-3-yl)benzamide: (See Patent: WO2006/71940 A2, **2006**; pg/pg column 409) A 50 mL round bottom flask was charged with 16 N-(5-nitro-1H-indazol-3-yl)benzamide (70 mg, 0.248 mmol) followed by MeOH (70 mL). 10% Pd/C (40 mg) was added followed by the bubbling of hydrogen gas through the reaction using a balloon. The reaction was stirred under these conditions at 22 °C until determined complete via LCMS. The reaction mixture was purged of H_2 via bubbling with argon gas. Next the mixture was filtered over celite then the filtrate was concentrated under reduced pressure to yield 59 mg the crude product as a light red solid. (0.233 mmol, 94% yield)

^{1}H NMR (400 MHz, DMSO-d6) δ 13.06 (s, 1H), 10.97 (s, 1H), 9.66 (s, 2H), 8.20 - 8.00 (m, 2H), 7.72 (d, J = 2.0 Hz, 1H), 7.67 - 7.51 (m, 4H), 7.29 (dd, J = 8.9, 2.1 Hz, 1H).;

^{13}C NMR (101 MHz, DMSO-d6) δ 165.51 , 140.35 , 139.67 , 133.45 , 132.00 , 128.50 , 127.90 , 125.35 , 121.50 , 116.54 , 115.11 , 111.74 .

LCMS(ESI) for $C_{14}H_{12}N_4O$: calc. M 252.1, obs. (M+H)+: m/z = 253.3

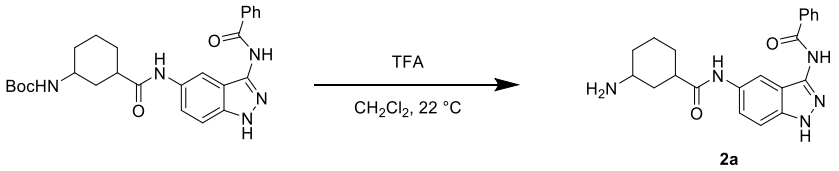


tert-butyl (3-((3-benzamido-1H-indazol-5-yl)carbamoyl)cyclohexyl)carbamate: A 25 mL round bottom flask was charged with 3-((tert-butoxycarbonyl)amino)cyclohexane-1-carboxylic acid (116 mg, 0.248 mmol) and HATU (196 mg, 0.515 mmol) followed by CH_2Cl_2 (6 mL). Triethylamine (0.166 mL, 1.189 mmol) was added to this mixture and then stirred for 10 mins at 22 °C generating a pale yellow solution. Next N-(5-amino-1H-indazol-3-yl)benzamide (100 mg, 0.396 mmol) was added and the reaction was stirred at 22 °C, giving a solution with a bright yellow precipitate. Reaction was maintained at these conditions until determined complete via LCMS. Precipitate was then collected via filtration and washed with CH_2Cl_2. The resulting white solid was dried on the hi-vac to yield 100 mg of desired product (0.209 mmol, 53% yield).

^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 12.72 (s, 1H), 10.70 (s, 1H), 9.86 (s, 1H), 8.13 – 8.02 (m, 2H), 7.97 (d, *J* = 1.9 Hz, 1H), 7.68 – 7.58 (m, 1H), 7.58 – 7.47 (m, 3H), 7.42 (d, *J* = 8.9 Hz, 1H), 6.82 (d, *J* = 8.2 Hz, 1H), 3.33 – 3.23 (m, 1H), 2.37 (dt, *J* = 11.6, 5.9 Hz, 1H), 1.88 (d, *J* = 12.3 Hz, 1H), 1.73 (d, *J* = 11.6 Hz, 3H), 1.37 (s, 10H), 1.33 – 1.20 (m, 3H), 1.10 (s, 1H).

^{13}C NMR (101 MHz, DMSO-d6) δ 165.51 , 140.35 , 139.67 , 133.45 , 132.00 , 128.50 , 127.90 , 125.35 , 121.50 , 116.54 , 115.11 , 111.74 .

LCMS(ESI) for $C_{26}H_{31}N_5O_4$ (M-Boc+H)+: m/z = 378.6



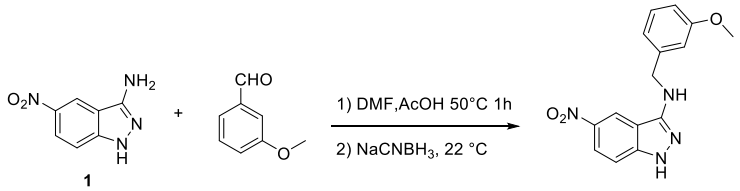
N-(5-(3-aminocyclohexane-1-carboxamido)-1H-indazol-3-yl)benzamide: A vial was charged with tert-butyl (3-((3-benzamido-1H-indazol-5-yl)carbamoyl)cyclohexyl)carbamate (50mg, 0.105 mmol) and 10% TFA in CH_2Cl_2 (5 mL). The reaction mixture was stirred at 22 °C for 2 hours then concentrated under reduced pressure. The crude material was purified via HPLC to yield the title compound as a white solid (38mg, 0.077 mmol, 74%).

1H NMR (400 MHz, DMSO-d6) δ 12.77 (s, 1H), 10.74 (s, 1H), 9.98 (s, 1H), 8.08 (dt, J = 7.2, 1.4 Hz, 2H), 7.98 (dd, J = 1.9, 0.8 Hz, 1H), 7.65 – 7.61 (m, 1H), 7.60 – 7.51 (m, 3H), 7.44 (dd, J = 9.0, 0.8 Hz, 1H), 3.08 (s, 1H), 2.44 (d, J = 11.8 Hz, 1H), 2.01 (d, J = 12.3 Hz, 1H), 1.93 (d, J = 11.8 Hz, 1H), 1.90 – 1.78 (m, 2H), 1.50 (q, J = 12.2 Hz, 1H), 1.28 (dp, J = 23.2, 12.1, 11.5 Hz, 3H).

13C NMR (101 MHz, DMSO-d6) δ 172.31 , 165.50 , 139.86 , 138.05 , 133.62 , 131.82 , 128.43 , 127.81 , 120.73 , 117.07 , 110.73 , 110.29 , 48.67 , 42.76 , 32.61 , 29.69 , 28.32 , 23.07 .

LCMS(ESI) for $C_{21}H_{23}N_5O_2$ (M+H)+: m/z = 378.5

Synthesis of Compound 2b:

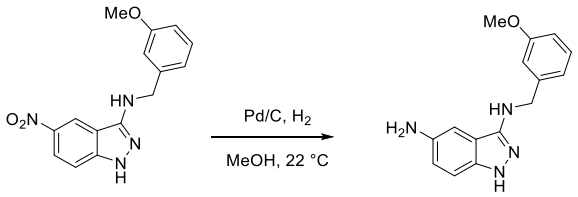


N-(3-methoxybenzyl)-5-nitro-1H-indazol-3-amine: A flame dry 50-mL round bottom flask was charged with 5-nitro-1H-indazol-3-amine (**1**, 250 mg, 1.403 mmol) and DMF (40 ml). Next AcOH (2 mL) was added followed by 3-methoxybenzaldehyde (1.706 ml, 14.03 mmol). Reaction was heated in a 50 °C oil bath for 1 hour. Mixture was cooled to 22 °C after 30 mins then NaCNBH3 in THF (12.63 ml, 12.63 mmol) was added dropwise and the mixture was allowed to stir for 16 hours at 22 °C. The reaction was then diluted in EtOAc and the organic solution was washed with brine followed by water two times. The organic layer was then dried over $MgSO_4$, filtered and concentrated under reduce pressure to yield a thick orange oil. The crude oil was purified using biotage flash chromatography to yield 314 mg of orange solid (1.05 mmol, 75%).

^{1}H NMR (400 MHz, DMSO-d6) δ 12.24 (s, 1H), 8.99 (d, J = 2.2 Hz, 1H), 8.08 (dd, J = 9.2, 2.2 Hz, 1H), 7.36 (d, J = 9.2 Hz, 1H), 7.22 (dt, J = 9.7, 7.0 Hz, 2H), 7.02 - 6.94 (m, 2H), 6.86 - 6.76 (m, 1H), 4.47 (d, J = 5.9 Hz, 2H), 3.73 (s, 3H).

^{13}C NMR (101 MHz, DMSO-d6) δ 159.26 , 152.05 , 143.01 , 141.76 , 138.81 , 129.23 , 121.54 , 119.73 , 119.46 , 113.25 , 112.92 , 111.97 , 109.66 , 54.96 , 46.41.

LCMS(ESI) for $C_{15}H_{14}N_4O_3$: calc. M 298.1, obs. (M+H)+: m/z = 299.4

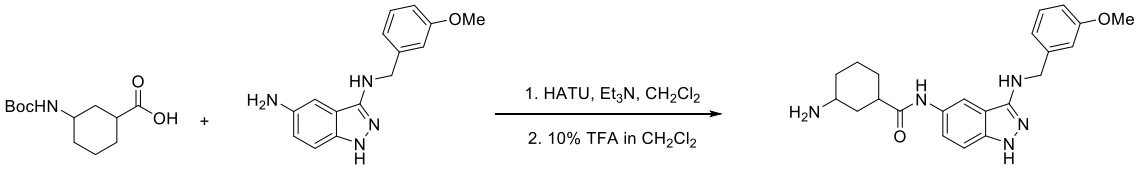


N3-(3-methoxybenzyl)-1H-indazole-3,5-diamine: The procedure used to generate the 5-aminoindazole intermediate in the synthesis of **2** was repeated on a 287 mg scale to yield 207 mg product (0.771 mmol, 80% yield).

^{1}H NMR (400 MHz, Methanol-d4) δ 7.21 (ddd, J = 8.1, 7.2, 0.7 Hz, 1H), 7.16 - 7.09 (m, 1H), 7.04 - 6.95 (m, 3H), 6.92 (ddd, J = 8.8, 2.1, 1.0 Hz, 1H), 6.78 (ddd, J = 8.2, 2.5, 1.1 Hz, 1H), 4.49 (s, 2H), 3.76 (s, 3H).

^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ 159.17 , 148.78 , 143.08 , 140.19 , 136.82 , 128.97 , 119.66 , 118.01 , 114.57 , 113.12 , 111.57 , 109.77 , 101.31 , 54.89 , 46.82 .

LCMS(ESI) for $C_{15}H_{16}N_4O$: calc. M 268.1, obs. (M+H)+: m/z = 269.4



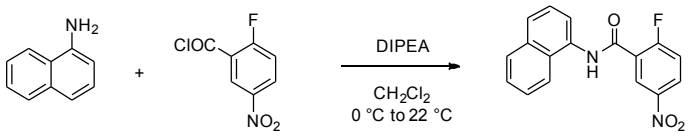
3-amino-N-(3-((3-methoxybenzyl)amino)-1H-indazol-5-yl)cyclohexane-1-carboxamide (2b): The procedure used to generate **3a** was repeated on a 50 mg scale with deprotection carried out on the crude concentrate of the peptide coupling reaction followed by HPLC purification of final product (0.041 mmol, 22% yield).

^{1}H NMR (400 MHz, Methanol-d4) δ 8.41 (dd, J = 2.0, 0.8 Hz, 1H), 7.65 (dd, J = 9.0, 2.0 Hz, 1H), 7.42 (dd, J = 9.0, 0.8 Hz, 1H), 7.34 – 7.26 (m, 1H), 7.01 – 6.96 (m, 2H), 6.92 – 6.85 (m, 1H), 4.59 (s, 2H), 3.79 (s, 3H), 2.58 (ddd, J = 11.8, 8.4, 3.4 Hz, 1H), 2.17 (d, J = 12.7 Hz, 1H), 2.12 – 1.94 (m, 4H), 1.68 (q, J = 12.1 Hz, 1H), 1.58 – 1.32 (m, 04H).

^{13}C NMR (176 MHz, Methanol-d4) δ 175.31 , 161.58 , 150.31 , 142.13 , 139.47 , 134.01 , 130.93 , 128.37 , 120.56 , 114.23 , 114.18 , 113.38 , 112.95 , 112.65 , 55.69 , 50.69 , 48.36 , 44.85 , 33.93 , 31.18 , 29.78 , 24.51 .

LCMS(ESI) for $C_{22}H_{27}N_5O_2$: calc. M 393.2, obs. (M+H)+: m/z = 394.6

Synthesis of Compound 3a:



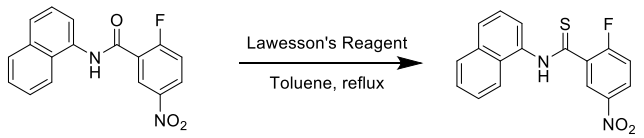
3

2-fluoro-N-(naphthalen-1-yl)-5-nitrobenzamide: (See Abbott Labratories Patent: US2002/156081 A1, 2002) A 100 mL round bottom flask was charged with 2-fluoro-5-nitrobenzoyl chloride (2g, 9.8 mmol) followed by CH_2Cl_2 (30 mL) generating a pale yellow solution. naphthalen-1-amine (1.41g, 9.8 mmol) was added to the reaction mixture generating a precipitate and the solution was cooled to 0 °C. DIPEA (1.88 mL, 10.8 mmol) was added dropwise and the resulting mixture was stirred at 22 °C for 2 hours. A pale yellow precipitate was collected via filtration and washed with CH_2Cl_2, and dried on the hi-vac (2.48g, 7.99 mmol, 81% yield).

^{1}H NMR (400 MHz, DMSO-d6) δ 10.73 (s, 1H), 8.68 (dd, J = 5.8, 3.0 Hz, 1H), 8.50 (ddd, J = 9.1, 4.3, 3.0 Hz, 1H), 8.19 - 8.06 (m, 1H), 8.06 - 7.92 (m, 1H), 7.88 (d, J = 8.2 Hz, 1H), 7.80 (d, J = 7.3 Hz, 1H), 7.73 (t, J = 9.2 Hz, 1H), 7.68 - 7.49 (m, 3H).

^{13}C NMR (101 MHz, DMSO-d6) δ 163.85 ,161.46 , 161.27 , 143.84 , 143.81 , 133.71 , 132.69 , 128.16 , 127.99 , 126.40 , 126.20 , 126.06 , 126.01 , 125.73 , 125.55 , 122.82 , 122.73 , 118.17 , 117.92 .).

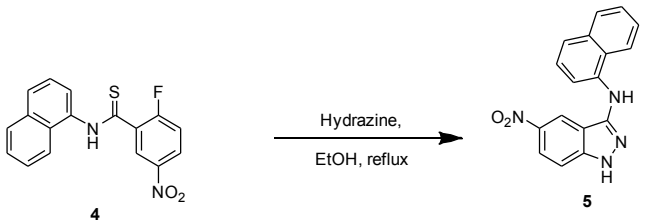
LCMS(ESI) for $C_{17}H_{11}FN_2O$: calc. M 310.1, obs. (M+H)+: m/z = 311.2



4

2-fluoro-N-(naphthalen-1-yl)-5-nitrobenzothioamide (**4**): 2-fluoro-N-(naphthalen-1-yl)-5-nitrobenzamide (1.75g, 5.64) was added to a 250 mL round bottom flask followed by toluene (50mL). Next Lawesson's Reagent(1.825g, 4.51 mmol) was added in a single portion and the suspension was heated in a 115 °C oil bath. After heating for 30 minutes a clear, bright orange solution was generated and stirred for 6 hours at this temperature. After cooling the reaction mixture to 22 °C it was concentrated under reduced pressure. The crude residue was then purified via biotage and product was obtained as a mixture composed mainly of the desired product but also starting material. This material was carried on to the next step without further purification.

LCMS(ESI) for $C_{17}H_{11}FN_2O_2S$: calc. M 326.1, obs. (M+H)+: m/z = 327.4



4 5

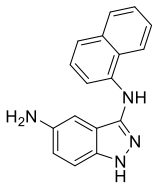
N3-(naphthalen-1-yl)-1H-indazole-3,5-diamine (**5**): A 2-neck 100 mL round bottom flask fitted with a reflux condenser was charged with 2-fluoro-N-(naphthalen-1-yl)-5-nitrobenzothioamide (1.8g 5.52 mmol) followed by ethanol (15mL). Hydrazine (0.530 mL, 16.55 mmol) was added and the solution changes from yellow to orange. The reaction mixture was heated at 79 °C in an oil bath generating a dark red solid after heating for <5 minutes. The reaction mixture was heated at 79 °C for 16 hours then cooled to 22 °C. The red

precipitate that formed was collected via filtration and washed with CH_2Cl_2, then dried on the hi-vac to yield 1.1g (3.61 mmol, 66% over two steps)

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.35 (d, J = 2.1 Hz, 1H), 9.12 (s, 1H), 8.60 – 8.41 (m, 1H), 8.28 – 8.08 (m, 2H), 8.03 – 7.79 (m, 1H), 7.56 (ddd, J = 9.9, 5.0, 2.3 Hz, 4H), 7.47 (t, J = 7.9 Hz, 1H).

^{13}C NMR (101 MHz, DMSO-d6) δ 148.16 , 142.42 , 139.72 , 137.46 , 134.02 , 128.16 , 126.09 , 125.90 , 125.32 , 125.00 , 122.59 , 121.70 , 121.13 , 119.79 , 114.09 , 113.80 , 110.29 .

LCMS(ESI) for $C_{17}H_{12}N_4O_2$: calc. M 304.1, obs. (M+H)+: m/z = 305.4

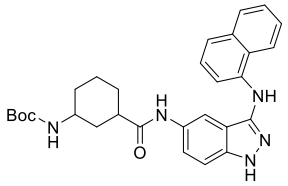


N3-(naphthalen-1-yl)-1H-indazole-3,5-diamine: The procedure for **2** was repeated using 730 mg (2.4 mmol) of **5** as starting material. The yield was 500 mg product as a brown solid (1.82mmol, 76%).

^{1}H NMR (400 MHz, DMSO-d6) δ 11.96 (s, 1H), 8.55 – 8.40 (m, 1H), 8.35 (s, 1H), 7.89 – 7.78 (m, 1H), 7.56 – 7.44 (m, 2H), 7.36 – 7.23 (m, 2H), 7.20 (dd, J = 8.8, 0.8 Hz, 1H), 7.07 (dd, J = 7.2, 1.5 Hz, 1H), 6.79 (dd, J = 8.8, 2.1 Hz, 1H), 6.63 (dd, J = 2.0, 0.8 Hz, 1H), 3.17 (s, 1H).

^{13}C NMR (101 MHz, DMSO-d6) δ 142.44 , 141.44 , 140.92 , 135.98 , 134.12 , 127.98 , 126.33 , 125.69 , 124.47 , 124.02 , 122.39 , 118.41 , 118.23 , 117.24 , 110.58 , 109.01 , 100.61 , 48.61 .

LCMS(ESI) for $C_{17}H_{14}N_4$: calc. M 274.1, obs. (M+H)+: m/z = 275.1

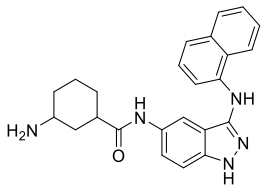


tert-butyl (3-((3-(naphthalen-1-ylamino)-1H-indazol-5 yl)carbamoyl)cyclohexyl) carbamate: HATU conditions used in the synthesis of **1a** were repeated using 50 mg (0.18 mmol) aniline synthesized from **5** above to yield 47 mg product (0.094 mmol, 52%).

^{1}H NMR (400 MHz, Methanol-d4) δ 8.22 (dt, J = 5.8, 3.5 Hz, 1H), 7.98 (d, J = 1.9 Hz, 1H), 7.87 - 7.77 (m, 1H), 7.53 - 7.43 (m, 4H), 7.42 - 7.26 (m, 3H), 3.38 (tt, J = 11.9, 3.9 Hz, 1H), 2.43 (ddq, J = 11.8, 7.1, 3.4 Hz, 1H), 2.02 (dtd, J = 13.0, 3.7, 1.8 Hz, 1H), 1.95 - 1.76 (m, 3H), 1.53 - 1.31 (m, 13H), 1.14 (qd, J = 13.1, 12.5, 4.0 Hz, 1H).

^{13}C NMR (101 MHz, Methanol-d4) δ 157.80 , 147.41 , 140.93 , 139.87 , 136.13 , 132.52 , 129.41 , 127.62 , 127.13 , 127.06 , 126.51 , 124.69 , 123.22 , 122.95 , 116.10 , 115.09 , 112.92 , 111.70 , 79.97, 45.98 , 36.97 , 33.46 , 29.81 , 28.81 , 25.53 .

LCMS(ESI) for $C_{29}H_{33}N_5O_3$: calc. M 499.3, obs. (M+H)+: m/z = 500.5



3a

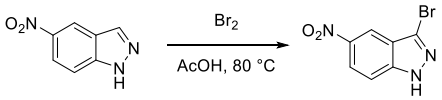
3-amino-N-(3-(naphthalen-1-ylamino)-1H-indazol-5-yl)cyclohexane-1-carboxamide (**3a**). Conditions for Boc deprotection of **1a** were repeated using 26 mg (0.052 mmol) of the amide synthesized above to yield 30 mg of product isolated as a TFA salt (0.048 mmol, 92%).

^{1}H NMR (400 MHz, DMSO-d6) δ 12.31 (s, 1H), 9.90 (s, 1H), 8.59 (s, 1H), 8.48 – 8.41 (m, 1H), 8.05 – 8.00 (m, 1H), 7.93 – 7.80 (m, 3H), 7.59 – 7.49 (m, 2H), 7.49 – 7.34 (m, 3H), 7.34 – 7.23 (m, 2H), 3.06 (s, 1H), 2.42 (td, J = 10.2, 8.8, 5.8 Hz, 1H), 1.95 (dd, J = 26.5, 11.9 Hz, 2H), 1.87 – 1.78 (m, 2H), 1.48 (q, J = 12.2 Hz, 1H), 1.39 – 1.16 (m, 3H).

^{13}C NMR (176 MHz, DMSO-d6) δ 172.25 , 158.30 , 158.10 , 144.32 , 140.30 , 138.28 , 134.11 , 131.02 , 128.02 , 126.26 , 125.78 , 124.61 , 124.41 , 122.48 , 121.02 , 119.06 , 116.67 , 115.73 , 110.24 , 110.16 , 110.07 , 48.71 , 42.73 , 32.63 , 29.71 , 28.35 , 23.09 .

LCMS(ESI) for $C_{24}H_{25}N_5O$: calc. M 399.2, obs. (M+H)+: m/z = 400.4

Synthesis of Compound 2k:



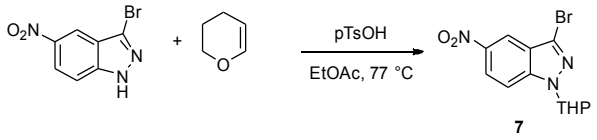
6

3-bromo-5-nitro-1H-indazole: 5-nitro-1H-indazole (**6**, 3 g, 18.39 mmol) was diluted in AcOH (50 mL) in a 250 mL round bottom flask. Br_2 (4.71 mL, 92 mmol) was then added, the mixture was then placed in an 80 °C oil bath and stirred at this temperature for 3 hours. Reaction was cooled to 22 °C. Reaction mixture was concentrated under educed pressure to give a pale yellow solid then residue was suspended in sat. aq. $NaHCO_3$ soln. and extracted one time with CH_2Cl_2 and 2 times with EtOAc. Combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Crude residue was suspended in CH_2Cl_2 and the solid was collected via filtration to yield pure product 4.45g (18.39 mmol, quant.).

^{1}H NMR (400 MHz, DMSO-d6) δ 14.03 (s, 1H), 8.36 (d, J = 2.2 Hz, 1H), 8.18 (dd, J = 9.2, 2.2 Hz, 1H), 7.70 (d, J = 9.2 Hz, 1H).

^{13}C NMR (101 MHz, DMSO-d6) δ 142.80 , 142.11 , 123.52 , 122.03 , 121.41 , 116.86 , 111.97 .

LCMS(ESI) for $C_7H_4BrN_3O_2$: calc. M 241.0, obs. (M+H)+: m/z = 242.1



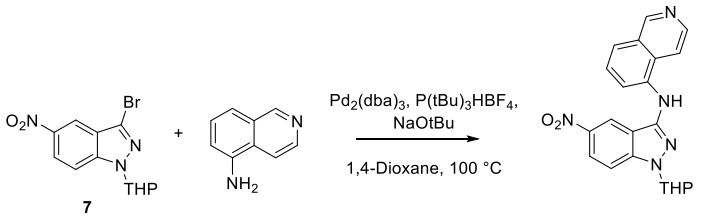
7

3-bromo-5-nitro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole (7): (See Synthesis, 2011 , # 16 p. 2651 – 2663) 3-bromo-5-nitro-1H-indazole 2g was added to a 2-neck 250 mL round bottom flask and diluted in 10 mL EtOAc. Next 3,4-dihydro-2H-pyran (1.508 ml, 16.53 mmol) was added followed by p-TsOH (0.157 g, 0.826 mmol) and the mixture was heated at reflux for 16 hours. Mixture was cooled to 22 °C then quenched with saturated aqueous NH_4OH solution. Layers were partitioned then the organic layer was washed with brine, dried over MgSO4, filtered and concentrated under reduced pressure. The residue was purified via Biotage (0-5% EtOAc in hexanes; 50g column). Product was isolated as a white solid (2.5g, 8.26 mmol, 93%).

^{1}H NMR (400 MHz, DMSO-d6) δ 8.48 (dd, J = 2.2, 0.6 Hz, 1H), 8.35 (dd, J = 9.3, 2.2 Hz, 1H), 8.04 (dd, J = 9.3, 0.6 Hz, 1H), 5.99 (dd, J = 9.5, 2.3 Hz, 1H), 3.97 - 3.83 (m, 1H), 3.83 - 3.70 (m, 1H), 2.42 - 2.23 (m, 1H), 2.11 - 1.94 (m, 2H), 1.84 - 1.66 (m, 1H), 1.59 (tq, J = 7.9, 3.7 Hz, 2H).

^{13}C NMR (101 MHz, DMSO-d6) δ 142.89 , 142.32 , 123.64 , 122.78 , 122.64 , 117.22 , 112.28 , 84.47 , 66.67 , 28.68 , 24.52 , 21.79 .

LCMS(ESI) for $C_{12}H_{12}BrN_3O_3$: calc. M 325.0, obs. (M+H)+: m/z = 326.1



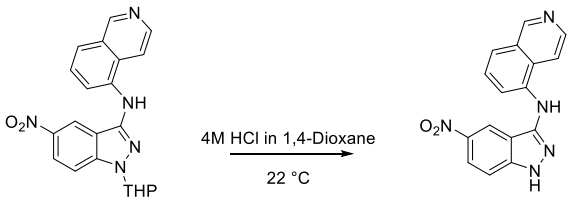
7

N-(5-nitro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)isoquinolin-5-amine: 50 mg of **7**, isoquinolin-5-amine (66.3 mg, 0.460 mmol) and 1,4-dioxane (1 ml) were added to a flame dry argon purged 2-5 mL □ -wave vial. Next, Pd2(dba)3 (14.04 mg, 0.015 mmol), tri-tert-buytlphosphonium tetrafluoroborate (4.65 mg, 0.023 mmol) and NaOtBu (17.68 mg, 0.184 mmol) were added and the mixture was stirred in a 100° C oil bath for 14 hours. Reaction mixture was filtered over celite, and celite was washed with EtOAc. The filtrate was concentrated under reduced pressure to yield a brown oil. The residue was purified via Biotage (0-75% EtOAc in hexanes; 25g column). A yellow solid (25 mg, 0.161 mmol, 35%) was isolated and characterized.

^{1}H NMR (400 MHz, DMSO-d6) δ 9.42 (dd, J = 2.2, 0.5 Hz, 1H), 9.35 (s, 1H), 9.31 (d, J = 0.9 Hz, 1H), 8.58 (d, J = 6.0 Hz, 1H), 8.50 (dd, J = 7.6, 1.3 Hz, 1H), 8.42 (dt, J = 6.2, 1.0 Hz, 1H), 8.28 (dd, J = 9.3, 2.2 Hz, 1H), 7.88 - 7.79 (m, 1H), 7.78 - 7.64 (m, 2H), 5.87 (dd, J = 9.6, 2.4 Hz, 1H), 3.92 (d, J = 11.2 Hz, 1H), 3.84 - 3.69 (m, 1H), 3.17 (d, J = 5.3 Hz, 1H), 2.45 - 2.29 (m, 1H), 2.06 (d, J = 21.3 Hz, 3H), 1.84 - 1.67 (m, 1H), 1.58 (d, J = 8.2 Hz, 2H).

^{13}C NMR (176 MHz, DMSO-d6) δ 152.51 , 146.70 , 142.18 , 141.80 , 140.67 , 136.19 , 128.97 , 127.78 , 127.41 , 122.22 , 120.35 , 119.66 , 116.89 , 115.53 , 110.54 , 83.94 , 66.61 , 31.59 , 28.93 , 24.69 , 22.07 .

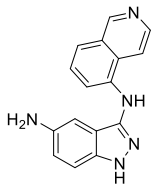
LCMS(ESI) for $C_{21}H_{19}N_5O_3$: calc. M 389.2, obs. (M+H)+: m/z = 390.4



N-(5-nitro-1H-indazol-3-yl)isoquinolin-5-amine (8): A 25 mL round bottom flask was charged with 12 mg (0.031 mmol) N-(5-nitro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)isoquinolin-5-amine and 2 mL 4M HCl in dioxane. The reaction mixture was stirred for 12 hours then concentrated under reduced pressure and the product was isolated as a light orange solid 10 mg (0.031 mmol, quant.).

^{1}H NMR (400 MHz, DMSO-d6) δ 13.02 (s, 1H), 9.62 (s, 1H), 9.49 (s, 1H), 9.37 (d, J = 2.2 Hz, 1H), 8.77 (d, J = 6.5 Hz, 1H), 8.72 - 8.62 (m, 2H), 8.22 (dd, J = 9.2, 2.2 Hz, 1H), 7.92 (d, J = 8.0 Hz, 1H), 7.84 (t, J = 8.0 Hz, 1H), 7.61 (d, J = 9.2 Hz, 1H).

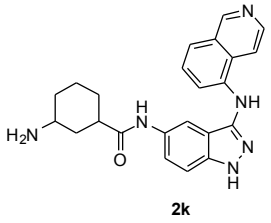
LCMS(ESI) for $C_{16}H_{11}N_5O_2$ (M+H)+: m/z = 305.09



N3-(isoquinolin-5-yl)-1H-indazole-3,5-diamine: : The procedure for **2** was repeated using 36 mg (2.4 mmol) of **8** as starting material. The yield was 26 mg product as a brown solid (0.118 mmol, 80%).

1H NMR (400 MHz, Methanol-d4) δ 9.13 (d, J = 0.9 Hz, 1H), 8.39 (d, J = 6.1 Hz, 1H), 8.22 - 8.17 (m, 1H), 7.53 - 7.49 (m, 1H), 7.44 (t, J = 7.9 Hz, 1H), 7.31 (ddd, J = 18.0, 8.2, 0.9 Hz, 2H), 6.98 (dd, J = 8.8, 2.1 Hz, 1H), 6.85 (dd, J = 2.1, 0.8 Hz, 1H).

LCMS(ESI) for $C_{16}H_{13}N_5$: calc. M 275.1, obs. (M+H)+: m/z = 276.42



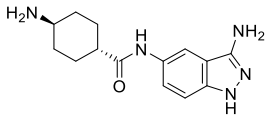
3-amino-N-(3-(isoquinolin-5-ylamino)-1H-indazol-5-yl)cyclohexane-1-carboxamide (2k): Conditions for HATU coupling and Boc deprotection of **1a** were repeated using 18 mg (0.065 mmol) of the product above to yield 18 mg product isolated as a TFA salt (0.033 mmol, 51%).

^{1}H NMR (700 MHz, Methanol-d_4) δ 9.67 (s, 1H), 8.81 (d, J = 6.7 Hz, 1H), 8.54 (d, J = 6.6 Hz, 1H), 8.06 (s, 1H), 7.94 (d, J = 8.0 Hz, 2H), 7.85 (t, J = 8.0 Hz, 1H), 7.48 (d, J = 8.8 Hz, 1H), 7.42 (dd, J = 8.9, 2.0 Hz, 1H), 3.20 (td, J = 12.2, 11.6, 5.9 Hz, 1H), 2.55 (s, 1H), 2.14 (d, J = 12.6 Hz, 1H), 2.05 (d, J = 12.8 Hz, 1H), 1.97 (t,

J = 14.7 Hz, 2H), 1.63 (q, *J* = 12.2 Hz, 1H), 1.49 (dq, *J* = 24.3, 12.9, 12.4 Hz, 2H), 1.37 (td, *J* = 12.4, 3.2 Hz, 1H).

^{13}C NMR (176 MHz, Methanol-*d*$_4$) δ 175.21 , 148.56 , 144.89 , 142.26 , 140.60 , 132.96 , 132.45 , 131.42 , 131.04 , 130.05 , 123.52 , 122.23 , 121.59 , 120.97 , 116.97 , 111.96 , 111.84 , 50.69 , 44.86 , 34.00 , 31.18 , 29.77 , 24.49 .

LCMS(ESI) for $C_{23}H_{24}N_6O$: calc. M 400.2, obs. (M+H)+: m/z = 401.6



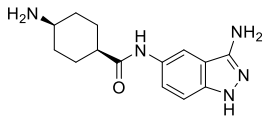
1c

(1r,4r)-4-amino-N-(3-amino-1H-indazol-5-yl)cyclohexane-1-carboxamide (1c): Compound **1c** was prepared using the sequence described for **1a** incorporating (1r,4r)-4-((tert-butoxycarbonyl)amino)cyclohexane-1-carboxylic acid in the peptide coupling step.

^{1}H NMR (400 MHz, Methanol-d4) δ 8.35 (d, J = 1.7 Hz, 1H), 7.64 (dd, J = 9.1, 2.0 Hz, 1H), 7.46 - 7.37 (m, 1H), 3.13 (tt, J = 11.7, 3.9 Hz, 1H), 2.45 (tt, J = 12.0, 3.5 Hz, 1H), 2.18 - 2.02 (m, 6H), 1.70 (qd, J = 13.4, 3.2 Hz, 2H), 1.50 (qd, J = 12.7, 3.5 Hz, 2H).

^{13}C NMR (101 MHz, Methanol-d4) δ 176.15 , 148.88 , 141.88 , 134.33 , 128.46 , 113.08 , 112.78 , 101.4 , 50.77 , 45.19 , 30.94 , 28.63 , 0.78.

LCMS(ESI) for $C_{14}H_{19}N_5O$: calc. M 273.2, obs. (M+H)+: m/z = 274.2



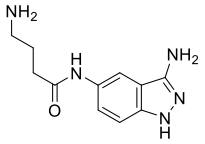
1d

(1s,4s)-4-amino-N-(3-amino-1H-indazol-5-yl)cyclohexane-1-carboxamide (1d): Compound **1d** was prepared using the sequence described for **1a** incorporating (1s,4s)-4-((tert-butoxycarbonyl)amino)cyclohexane-1-carboxylic acid in the peptide coupling step.

^{1}H NMR (400 MHz, Methanol-d4) δ 8.31 (d, J = 1.8 Hz, 1H), 7.66 (dd, J = 9.1, 2.0 Hz, 1H), 7.47 - 7.39 (m, 1H), 3.34 (dt, J = 8.2, 4.2 Hz, 1H), 2.67 (tt, J = 6.5, 4.4 Hz, 1H), 2.11 - 2.00 (m, 3H), 2.00 - 1.88 (m, 4H), 1.82 (ddt, J = 12.7, 8.4, 4.4 Hz, 2H).

^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ 173.06 , 158.07 , 138.88 , 131.12 , 123.07 , 113.00 , 110.72 , 110.24 , 48.61 , 47.46 , 27.00 , 24.36 .

LCMS(ESI) for $C_{14}H_{19}N_5O$: calc. M 273.2, obs. (M+H)+: m/z = 274.4



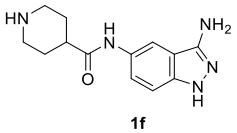
1e

4-amino-N-(3-amino-1H-indazol-5-yl)butanamide (1e): Compound **1e** was prepared using the sequence described for **1a** incorporating 4-((tert-butoxycarbonyl)amino)butanoic acid in the peptide coupling step.

^{1}H NMR (400 MHz, Methanol-d4) δ 8.36 (dd, J = 2.0, 0.7 Hz, 1H), 7.63 (dd, J = 9.0, 2.0 Hz, 1H), 7.42 (dd, J = 9.0, 0.8 Hz, 1H), 3.05 (t, J = 7.6 Hz, 2H), 2.59 (t, J = 7.1 Hz, 2H), 2.13 - 1.97 (m, 2H), 1.67 (s, 1H).

^{13}C NMR (101 MHz, Methanol-d4) δ 172.9 , 148.9 , 141.8 , 134.1 , 128.1 , 113.1 , 112.9 , 112.7 , 40.3 , 34.2 , 24.2.

LCMS(ESI) for $C_{11}H_{15}N_5O$: calc. M 233.1, obs. (M+H)+: m/z = 234.2



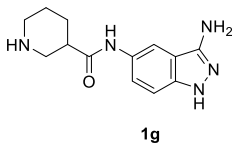
1f

N-(3-amino-1H-indazol-5-yl)piperidine-4-carboxamide (1f): Compound **1f** was prepared using the sequence described for **1a** incorporating 1-(tert-butoxycarbonyl)piperidine-4-carboxylic acid in the peptide coupling step.

^{1}H NMR (400 MHz, Methanol-d4) δ 8.32 (d, J = 2.0 Hz, 1H), 7.65 (dd, J = 9.1, 2.0 Hz, 1H), 7.40 (d, J = 9.1 Hz, 1H), 3.50 (dt, J = 12.9, 3.8 Hz, 2H), 3.10 (td, J = 12.5, 3.5 Hz, 2H), 2.79 (s, 1H), 2.21 - 1.91 (m, 5H).

^{13}C NMR (101 MHz, Methanol-d4) δ 174.3 , 149.0 , 141.8 , 134.0 , 128.5 , 113.2 , 112.9 , 112.7 , 44.2 , 41.54 , 26.6.

LCMS(ESI) for $C_{13}H_{17}N_5O$: calc. M 259.1, obs. (M+H)+: m/z = 260.3



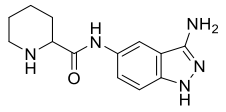
1g

N-(3-amino-1H-indazol-5-yl)piperidine-3-carboxamide (1g): Compound **1g** was prepared using the sequence described for **1a** incorporating 1-(tert-butoxycarbonyl)piperidine-3-carboxylic acid in the peptide coupling step.

^{1}H NMR (400 MHz, Methanol-d4) δ 8.35 (dd, J = 2.0, 0.7 Hz, 1H), 7.65 (dd, J = 9.0, 2.0 Hz, 1H), 7.43 (dd, J = 9.1, 0.8 Hz, 1H), 3.42 (dd, J = 12.8, 4.1 Hz, 1H), 3.37 - 3.25 (m, 2H), 3.13 (td, J = 9.3, 4.7 Hz, 1H), 2.98 (dt, J = 8.6, 4.3 Hz, 1H), 2.22 - 2.10 (m, 1H), 2.07 - 1.95 (m, 1H), 1.95 - 1.81 (m, 2H).

^{13}C NMR (101 MHz, Methanol-d4) δ 173.05 , 148.91 , 141.85 , 133.80 , 127.99 , 113.18 , 113.12 , 112.74 , 46.15 , 45.05 , 40.72 , 27.71 , 27.41 , 22.13 .

LCMS(ESI) for $C_{13}H_{17}N_5O$: calc. M 259.1, obs. (M+H)+: m/z = 260.3



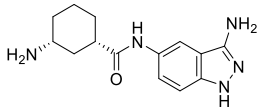
1h

N-(3-amino-1H-indazol-5-yl)piperidine-2-carboxamide (1h): Compound **1h** was prepared using the sequence described for **1a** incorporating 1-(tert-butoxycarbonyl)piperidine-2-carboxylic acid in the peptide coupling step.

^{1}H NMR (400 MHz, Methanol-d4) δ 8.37 (d, J = 1.9 Hz, 1H), 7.67 (dd, J = 9.1, 2.0 Hz, 1H), 7.41 (d, J = 9.1 Hz, 1H), 4.01 (dd, J = 12.0, 3.2 Hz, 1H), 3.46 (dt, J = 12.8, 2.5 Hz, 1H), 3.18 - 3.01 (m, 1H), 2.34 (dd, J = 13.8, 3.5 Hz, 1H), 2.04 - 1.59 (m, 7H).

^{13}C NMR (101 MHz, Methanol-d4) δ 168.5 , 148.9 , 141.8 , 133.4 , 128.1 , 113.2 , 112.9 , 112.8 , 59.7 , 45.0 , 28.6 , 27.6 , 23.1 , 22.7.

LCMS(ESI) for $C_{13}H_{17}N_5O$: calc. M 259.1, obs. (M+H)+: m/z = 260.3



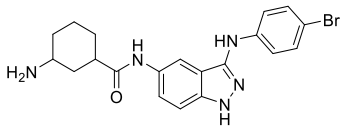
1i

(1S,3R)-3-amino-N-(3-amino-1H-indazol-5-yl)cyclohexane-1-carboxamide (1i): Compound **1i** was prepared using the sequence described for **1a** incorporating (1S,3R)-3-((tert-butoxycarbonyl)amino)cyclohexane-1-carboxylic acid in the peptide coupling step.

^{1}H NMR (400 MHz, Methanol-d4) δ 8.42 - 8.28 (m, 1H), 7.65 (dd, J = 9.0, 2.0 Hz, 1H), 7.42 (dd, J = 9.0, 0.7 Hz, 1H), 3.22 (tt, J = 11.7, 3.9 Hz, 1H), 2.59 (tt, J = 11.8, 3.3 Hz, 1H), 2.19 (ddt, J = 11.3, 4.0, 2.1 Hz, 1H), 2.14 - 2.02 (m, 1H), 1.99 (ddd, J = 9.7, 6.2, 4.0 Hz, 2H), 1.68 (q, J = 12.1 Hz, 1H), 1.60 - 1.31 (m, 5H).

^{13}C NMR (101 MHz, Methanol-d4) δ 175.39, 161.48 , 148.93 , 141.90 , 134.31 , 128.57, 113.17 , 113.01 , 112.84 , 50.69 , 44.85 , 33.98 , 31.16 , 29.70 , 27.71 , 24.48 .

LCMS(ESI) for $C_{14}H_{19}N_5O$: calc. M 273.2, obs. (M+H)+: m/z = 274.4



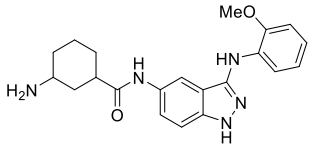
2d

3-amino-N-(3-((4-bromophenyl)amino)-1H-indazol-5-yl)cyclohexane-1-carboxamide(2d): Compound **2d** was prepared using the sequence described for **3a** incorporating 4-bromo-aniline in the aryl amide formation.

^{1}H NMR (400 MHz, Methanol-d_4) δ 8.13 (dd, J = 1.8, 0.8 Hz, 1H), 7.46 (dd, J = 8.9, 2.0 Hz, 1H), 7.35 (q, J = 8.9 Hz, 5H), 3.20 (tq, J = 10.3, 3.2, 2.6 Hz, 1H), 2.57 (tt, J = 11.7, 3.2 Hz, 1H), 2.24 – 2.13 (m, 1H), 2.11 – 1.89 (m, 4H), 1.57 – 1.34 (m, 6H).

^{13}C NMR (101 MHz, Methanol-d_4) δ 175.33 , 132.96 , 132.27 , 125.13 , 119.99 , 115.43 , 112.77 , 111.60 , 50.70 , 44.81 , 42.56 , 34.01 , 31.17 , 29.73 , 27.70 , 24.46 .

LCMS(ESI) for $C_{20}H_{22}BrN_5O$: calc. M 427.1, obs. (M+H)+: m/z = 428.4



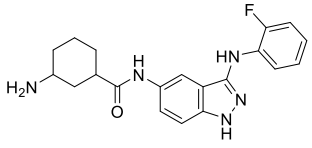
2e

3-amino-N-(3-((2-methoxyphenyl)amino)-1H-indazol-5-yl)cyclohexane-1-carboxamide (**2e**): Compound **2e** was prepared using the sequence described for **3a** incorporating 2-methoxyaniline in the aryl amide formation.

^{1}H NMR (400 MHz, Methanol-d4) δ 8.15 (d, J = 1.9 Hz, 1H), 7.62 - 7.49 (m, 2H), 7.40 (d, J = 9.0 Hz, 1H), 7.03 (d, J = 4.0 Hz, 2H), 6.93 (dt, J = 7.9, 4.4 Hz, 1H), 3.91 (s, 3H), 3.20 (tt, J = 11.7, 3.9 Hz, 1H), 2.64 - 2.51 (m, 1H), 2.24 - 2.12 (m, 1H), 2.11 - 1.91 (m, 4H), 1.67 (q, J = 12.2 Hz, 1H), 1.55 - 1.33 (m, 4H).

^{13}C NMR (101 MHz, Methanol-d4) δ 175.28 , 149.52 , 146.35 , 140.46 , 132.96 , 132.05 , 124.17 , 121.95 , 121.81 , 117.25 , 115.98 , 112.08 , 111.52 , 111.44 , 56.25 , 50.69 , 44.83 , 34.02 , 31.15 , 29.71 , 24.46 .

LCMS(ESI) for $C_{21}H_{25}N_5O_2$: calc. M 379.2, obs. (M+H)+: m/z = 380.9



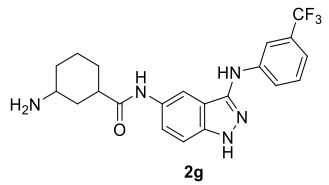
2f

3-amino-N-(3-((2-fluorophenyl)amino)-1H-indazol-5-yl)cyclohexane-1-carboxamide (**2f**): Compound **2f** was prepared using the sequence described for **3a** incorporating 2-fluoroaniline in the aryl amide formation.

^{1}H NMR (400 MHz, Methanol-d4) δ 8.05 (d, J = 1.8 Hz, 1H), 7.60 (td, J = 8.4, 1.7 Hz, 1H), 7.47 (dd, J = 9.0, 1.9 Hz, 1H), 7.40 (d, J = 8.9 Hz, 1H), 7.16 - 7.00 (m, 2H), 6.89 (tdd, J = 7.8, 4.8, 1.7 Hz, 1H), 3.20 (tt, J = 11.8, 3.9 Hz, 1H), 2.56 (tq, J = 11.6, 3.1 Hz, 1H), 2.23 - 2.13 (m, 1H), 2.12 - 1.91 (m, 4H), 1.66 (q, J = 12.1 Hz, 1H), 1.58 - 1.31 (m, 4H).

^{13}C NMR (101 MHz, Methanol-d4) δ 175.28 , 154.78 , 152.39 , 145.66 , 140.44 , 133.13 (d, J = 11.0 Hz), 131.88 , 125.43 (d, J = 3.6 Hz), 123.75 , 121.05 (d, J = 7.1 Hz), 118.56 (d, J = 2.4 Hz), 116.59 , 115.82 (d, J = 19.0 Hz), 111.90 (d, J = 101.2 Hz), 50.68 , 44.81 , 34.00 , 31.16 , 29.72 , 24.46 .

LCMS(ESI) for $C_{20}H_{22}FN_5O$: calc. M 367.2, obs. (M+H)+: m/z = 368.6



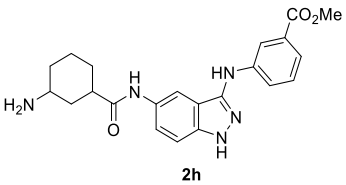
2g

3-amino-N-(3-((3-(trifluoromethyl)phenyl)amino)-1H-indazol-5-yl)cyclohexane-1-carboxamide (**2g**): Compound **2g** was prepared using the sequence described for **3a** incorporating methyl 3-aminobenzoate in the aryl amide formation.

^{1}H NMR (400 MHz, DMSO-d_6) δ 12.11 (s, 1H), 9.94 (s, 1H), 9.31 (s, 1H), 8.40 (d, J = 1.8 Hz, 1H), 8.15 (t, J = 2.0 Hz, 1H), 7.98 – 7.80 (m, 4H), 7.46 (t, J = 7.9 Hz, 1H), 7.39 – 7.25 (m, 2H), 7.13 – 7.06 (m, 1H), 3.10 (s, 1H), 2.04 (d, J = 12.4 Hz, 1H), 1.95 (d, J = 11.6 Hz, 1H), 1.87 (ddd, J = 9.9, 7.2, 3.7 Hz, 2H), 1.55 (d, J = 14.6 Hz, 1H), 1.43 – 1.18 (m, 3H).

^{13}C NMR (101 MHz, DMSO-d_6) δ 172.22 , 144.13 , 143.78 , 137.55 , 130.59 , 129.61 , 121.54 , 114.01 , 110.16 , 109.81 , 48.69 , 42.68 , 32.66 , 29.70 , 28.36 , 23.08 .

LCMS(ESI) for $C_{21}H_{22}F_3N_5O$: calc. M 417.2, obs. (M+H)+: m/z = 418.4



2h

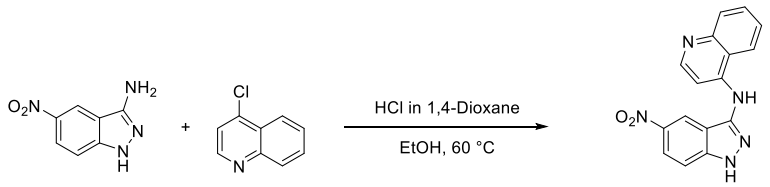
methyl 3-((5-(3-aminocyclohexane-1-carboxamido)-1H-indazol-3-yl)amino)benzoate (**2h**): Compound **2h** was prepared using the sequence described for **3a** incorporating methyl 3-aminobenzoate in the aryl amide formation.

^{1}H NMR (400 MHz, DMSO-d6) δ 12.06 (s, 1H), 9.92 (s, 1H), 9.16 (s, 1H), 8.41 - 8.28 (m, 2H), 7.97 - 7.77 (m, 4H), 7.42 - 7.25 (m, 4H), 3.85 (s, 3H), 2.04 (d, J = 12.3 Hz, 1H), 1.99 - 1.79 (m, 4H), 1.61 - 1.49 (m, 1H), 1.45 - 1.17 (m, 4H).

^{13}C NMR (101 MHz, DMSO-d_6) δ 172.21 , 166.64 , 144.35 , 143.58 , 137.63 , 130.46 , 130.04 , 128.96 , 121.49 , 119.92 , 119.15 , 116.01 , 114.13 , 110.37 , 109.72 , 51.97 , 48.69 , 42.68 , 32.68 , 29.71 , 28.35 , 23.08 .

LCMS(ESI) for $C_{22}H_{25}N_5O_3$: calc. M 407.2, obs. (M+H)+: m/z = 408.4

Synthesis of Compound 2i:



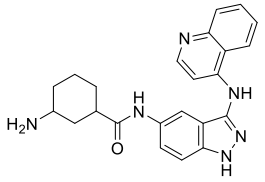
N-(5-nitro-1H-indazol-3-yl)quinolin-4-amine: 4-chloroquinoline (300 mg, 1.834 mmol) and 5-nitro-1H-indazol-3-amine (359 mg, 2.017 mmol) were added to a 2 neck 100 mL round bottom flask equipped with a

reflux condenser and were diluted in Ethanol (30 ml). 4M HCl in 1,4-dioxane (0.138 ml, 0.550 mmol) was added and the mixture was heated in a 60 °C oil bath. After 2 hours an LCMS was taken and product was obsereved. Reaction mixture was cooled to 22 °C then the precipitate was collected and dried on hi-vac. 460 mg solid collected (1.50 mmol, 82% yield).

^{1}H NMR (400 MHz, DMSO-d6) δ 15.19 (s, 1H), 14.00 (s, 1H), 11.30 (s, 1H), 9.23 (d, J = 2.2 Hz, 1H), 9.14 - 9.04 (m, 1H), 8.78 (d, J = 6.9 Hz, 1H), 8.28 (dd, J = 9.3, 2.2 Hz, 1H), 8.20 (dd, J = 8.6, 1.2 Hz, 1H), 8.10 (ddd, J = 8.4, 6.9, 1.2 Hz, 1H), 7.96 (d, J = 6.9 Hz, 1H), 7.91 (ddd, J = 8.4, 6.9, 1.3 Hz, 1H), 7.79 (d, J = 9.3 Hz, 1H).

^{13}C NMR (101 MHz, DMSO-d6) δ 153.16 , 143.52 , 142.81 , 142.47 , 141.40 , 138.13 , 133.93 , 127.35 , 124.02 , 122.01 , 120.37 , 119.17 , 117.66 , 115.15 , 111.62 , 102.55 .

LCMS(ESI) for $C_{16}H_{11}N_5O_3$: calc. M 305.1, obs. (M+H)+: m/z = 306.0



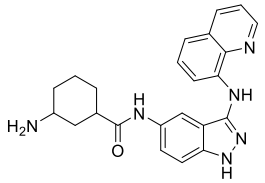
2i

3-amino-N-(3-(quinolin-4-ylamino)-1H-indazol-5-yl)cyclohexane-1-carboxamide (**2i**): From the above 5-nitroindazole the previously described procedure for nitro reduction and the synthesis of the amide formation was followed to access compound **2i**.

^{1}H NMR (400 MHz, DMSO-d6) δ 12.11 (s, 1H), 9.94 (s, 1H), 9.31 (s, 1H), 8.40 (d, J = 1.8 Hz, 1H), 8.15 (t, J = 2.0 Hz, 1H), 7.98 - 7.80 (m, 4H), 7.46 (t, J = 7.9 Hz, 1H), 7.39 - 7.25 (m, 2H), 7.13 - 7.06 (m, 1H), 3.10 (s, 1H), 2.04 (d, J = 12.4 Hz, 1H), 1.95 (d, J = 11.6 Hz, 1H), 1.87 (ddd, J = 9.9, 7.2, 3.7 Hz, 2H), 1.55 (d, J = 14.6 Hz, 2H), 1.43 - 1.18 (m, 3H).

^{13}C NMR (101 MHz, DMSO-d_6) δ 172.58 , 157.84 , 154.49 , 143.53 , 138.62 , 138.09 , 133.92 , 132.81 , 127.34 , 123.32 , 121.48 , 120.76 , 117.11 , 116.30 , 111.31 , 108.14 , 101.31 , 48.60 , 42.78 , 32.52 , 29.65 , 28.32 , 23.04 .

LCMS(ESI) for $C_{23}H_{24}N_6O$: calc. M 400.2, obs. (M+H)+: m/z = 401.3



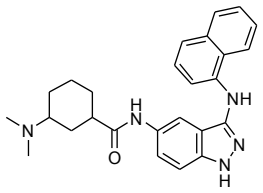
2j

3-amino-N-(3-(quinolin-8-ylamino)-1H-indazol-5-yl)cyclohexane-1-carboxamide (**2j**):Procedure for **2k** is followed substituting quinolin-8-amine in the Buchwald coupling step.

^{1}H NMR (400 MHz, Methanol-d_4) □ 8.88 (d, *J* = 4.1 Hz, 1H), 8.35 (dd, *J* = 8.3, 1.7 Hz, 1H), 8.22 (dd, *J* = 7.7, 1.2 Hz, 1H), 8.20 – 8.14 (m, 1H), 7.59 (dd, *J* = 8.3, 4.3 Hz, 1H), 7.54 (t, *J* = 7.9 Hz, 1H), 7.47 – 7.37 (m, 3H),

3.29 – 3.16 (m, 1H), 2.58 (q, *J* = 7.2, 4.0 Hz, 1H), 2.18 (d, *J* = 12.5 Hz, 1H), 2.14 – 1.92 (m, 4H), 1.69 (q, *J* = 12.1 Hz, 1H), 1.53 (s, 2H), 1.40 (q, *J* = 10.6, 9.2 Hz, 1H).

LCMS(ESI) for $C_{23}H_{24}N_6O$: calc. M 400.2, obs. (M+H)+: m/z = 401.4

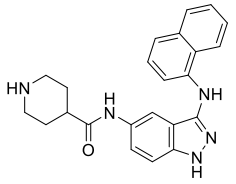


3b

3-(dimethylamino)-N-(3-(naphthalen-1-ylamino)-1H-indazol-5-yl)cyclohexane-1-carboxamide (**3b**): Compound **3b** was prepared using the sequence described for **3a** incorporating 3-(dimethylamino)cyclohexane-1-carboxylic acid in the last peptide coupling step.
^{1}H NMR (400 MHz, DMSO-d_6) δ 12.32 (s, 1H), 10.61 (s, 1H), 8.51 – 8.39 (m, 1H), 8.01 (dd, *J* = 4.0, 1.8 Hz, 1H), 7.90 – 7.81 (m, 1H), 7.50 (ddt, *J* = 9.0, 7.6, 3.3 Hz, 3H), 7.44 – 7.34 (m, 2H), 7.34 – 7.20 (m, 2H), 3.13 (d, *J* = 24.6 Hz, 1H), 2.67 (s, 6H), 2.46 – 2.36 (m, 1H), 2.14 (d, *J* = 12.0 Hz, 1H), 2.01 (s, 1H), 1.88 (s, 1H), 1.81 (d, *J* = 9.9 Hz, 1H), 1.56 (q, *J* = 12.2 Hz, 1H), 1.44 – 1.22 (m, 3H), 1.19 (t, *J* = 7.3 Hz, 1H).

^{13}C NMR (101 MHz, DMSO-d6) δ 172.13 , 144.29 , 140.37 , 138.27 , 134.11 , 131.01 , 128.01 , 126.29 , 125.78 , 124.60 , 124.37 , 122.49 , 120.99 , 118.98 , 115.77 , 110.21 , 109.94 , 63.02 , 43.18 , 28.36 , 25.32 , 23.41 .

LCMS(ESI) for $C_{26}H_{29}N_5O$: calc. M 427.2, obs. (M+H)+: m/z = 428.6



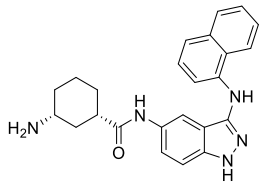
3c

N-(3-(naphthalen-1-ylamino)-1H-indazol-5-yl)piperidine-4-carboxamide (**3c**): Compound **3c** was prepared using the sequence described for **3a** incorporating 1-(tert-butoxycarbonyl)piperidine-4-carboxylic acid in the last peptide coupling step.

^{1}H NMR (400 MHz, DMSO-d6) δ 12.32 (s, 1H), 9.97 (s, 1H), 8.70 - 8.54 (m, 2H), 8.49 - 8.42 (m, 1H), 8.35 (d, J = 10.9 Hz, 1H), 8.02 (d, J = 1.8 Hz, 1H), 7.91 - 7.82 (m, 1H), 7.55 - 7.49 (m, 2H), 7.46 (dd, J = 8.9, 1.9 Hz, 1H), 7.43 - 7.39 (m, 1H), 7.37 (dd, J = 7.8, 1.5 Hz, 1H), 7.33 - 7.25 (m, 2H), 3.33 (dt, J = 12.7, 3.1 Hz, 2H), 2.99 - 2.85 (m, 2H), 2.60 (tt, J = 11.0, 3.8 Hz, 1H), 1.93 (dd, J = 14.5, 3.7 Hz, 2H), 1.78 (dtd, J = 14.4, 11.7, 4.0 Hz, 2H).

^{13}C NMR (101 MHz, DMSO-d6) δ 171.60 , 144.33 , 140.31 , 138.32 , 136.61 , 134.10 , 130.85 , 128.02 , 126.26 , 125.78 , 124.61 , 124.39 , 122.48 , 121.02 , 119.04 , 115.73 , 110.27 , 110.03 , 99.52 , 42.52 , 25.19 .

LCMS(ESI) for $C_{23}H_{23}N_5O$: calc. M 385.2, obs. (M+H)+: m/z = 386.5



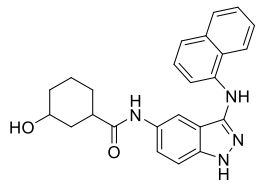
3d

(1S,3R)-3-amino-N-(3-(naphthalen-1-ylamino)-1H-indazol-5-yl)cyclohexane-1-carboxamide (**3d**): Compound **3d** was prepared using the sequence described for **3a** incorporating (1S,3R)-3-((tert-butoxycarbonyl)amino)cyclohexane-1-carboxylic acid in the last peptide coupling step.

^{1}H NMR (400 MHz, Methanol-d4) δ 8.26 (d, J = 1.9 Hz, 1H), 8.17 - 8.08 (m, 1H), 7.99 - 7.90 (m, 1H), 7.74 (dd, J = 7.4, 2.0 Hz, 1H), 7.62 (dd, J = 9.0, 2.0 Hz, 1H), 7.59 - 7.51 (m, 2H), 7.49 - 7.43 (m, 3H), 3.20 (tt, J = 11.6, 3.9 Hz, 1H), 2.57 (tt, J = 11.6, 3.3 Hz, 1H), 2.20 - 2.02 (m, 2H), 2.02 - 1.90 (m, 2H), 1.66 (q, J = 12.1 Hz, 1H), 1.57 - 1.45 (m, 3H), 1.41 - 1.26 (m, 1H).

^{13}C NMR (101 MHz, Methanol-d4) δ 175.32 , 148.00 , 141.26 , 137.91 , 136.26 , 133.18 , 129.57 , 128.72 , 127.42 , 127.16 , 127.13 , 126.37 , 125.57 , 122.97 , 118.57 , 114.70 , 113.12 , 112.22 , 50.68 , 44.82 , 33.95 , 31.16 , 29.73 , 24.47 .

LCMS(ESI) for $C_{24}H_{25}N_5O$: calc. M 399.2, obs. (M+H)+: m/z = 400.4



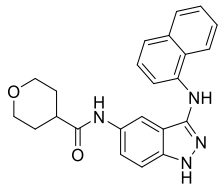
3e

3-hydroxy-N-(3-(naphthalen-1-ylamino)-1H-indazol-5-yl)cyclohexane-1-carboxamide (**3e**): Compound **3e** was prepared using the sequence described for **3a** incorporating 3-hydroxycyclohexane-1-carboxylic acid in the last peptide coupling step.

^{1}H NMR (400 MHz, Methanol-d4) δ 8.25 (d, J = 1.9 Hz, 1H), 8.17 - 8.10 (m, 1H), 7.97 - 7.89 (m, 1H), 7.72 (dd, J = 6.7, 2.7 Hz, 1H), 7.62 - 7.56 (m, 1H), 7.56 - 7.50 (m, 2H), 7.49 - 7.40 (m, 3H), 4.14 (t, J = 3.3 Hz, 1H), 2.84 (tt, J = 11.0, 3.8 Hz, 1H), 1.95 - 1.68 (m, 6H), 1.68 - 1.44 (m, 3H).

^{13}C NMR (101 MHz, Methanol-d4) δ 177.61 , 148.05, 141.22 , 137.79 , 136.26 , 133.48 , 129.57 , 128.75 , 127.41 , 127.18 , 127.14 , 126.64 , 125.65 , 122.97 , 118.71 , 114.68 , 113.13 , 112.11 , 66.62 , 41.02 , 36.42 , 33.08 , 30.47 , 20.68 .

LCMS(ESI) for $C_{24}H_{24}N_4O_2$: calc. M 400.2, obs. (M+H)+: m/z = 401.6



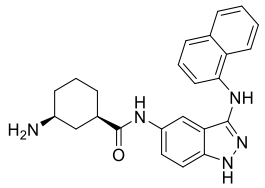
3f

N-(3-(naphthalen-1-ylamino)-1H-indazol-5-yl)tetrahydro-2H-pyran-4-carboxamide (**3f**): Compound **3f** was prepared using the sequence described for **3a** incorporating tetrahydro-2H-pyran-4-carboxylic acidin the last peptide coupling step.

^{1}H NMR (400 MHz, Methanol-d4) δ 8.21 (d, J = 2.0 Hz, 1H), 8.19 - 8.12 (m, 1H), 7.95 - 7.87 (m, 1H), 7.68 (dd, J = 7.0, 2.3 Hz, 1H), 7.57 (dd, J = 9.0, 2.0 Hz, 1H), 7.56 - 7.49 (m, 2H), 7.43 (qd, J = 6.2, 5.0, 2.9 Hz, 3H), 4.00 (ddd, J = 11.5, 4.4, 2.0 Hz, 2H), 3.48 (td, J = 11.7, 2.5 Hz, 2H), 2.64 (tt, J = 11.4, 4.1 Hz, 1H), 2.00 - 1.68 (m, 4H).

^{13}C NMR (101 MHz, Methanol-d4) δ 175.90 , 147.94 , 141.19 , 138.06 , 136.22 , 133.20 , 129.54 , 128.58 , 127.36 , 127.12 , 127.08 , 126.28 , 125.31 , 122.96 , 118.20 , 114.86 , 113.12 , 112.09 , 68.22 , 43.67 , 30.31 .

LCMS(ESI) for $C_{23}H_{22}N_4O_2$: calc. M 386.2, obs. (M+H)+: m/z = 387.5



3g

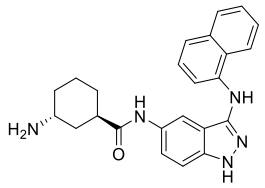
(1R,3S)-3-amino-N-(3-(naphthalen-1-ylamino)-1H-indazol-5-yl)cyclohexane-1-carboxamide (**3g**): Compound **3g** was prepared using the sequence described for **3a** incorporating (1R,3S)-3-((tert-butoxycarbonyl)amino)cyclohexane-1-carboxylic acid in the last peptide coupling step.

^{1}H NMR (400 MHz, DMSO-d6) δ 12.32 (s, 1H), 9.91 (s, 1H), 8.59 (s, 1H), 8.51 - 8.41 (m, 1H), 8.03 (d, J = 1.8 Hz, 1H), 7.98 - 7.81 (m, 4H), 7.59 - 7.48 (m, 2H), 7.49 - 7.34 (m, 3H), 7.35 - 7.21 (m, 2H), 3.06 (s, 1H), 2.43 (td, J = 10.1, 8.6, 5.7 Hz, 1H), 2.05 - 1.87 (m, 2H), 1.87 - 1.74 (m, 2H), 1.49 (q, J = 12.2 Hz, 1H), 1.36 - 1.17 (m, 3H).

^{13}C NMR (101 MHz, DMSO-d6) δ 172.28 , 144.34 , 140.31 , 138.29 , 134.13 , 131.03 , 128.03 , 126.28 , 125.79 , 124.62 , 124.42 , 122.49 , 121.03 , 119.07 , 115.75 , 110.18 , 110.08 , 48.72 , 42.76 , 32.67 , 29.73 , 28.35 , 23.10 .

LCMS(ESI) for $C_{24}H_{25}N_5O$: calc. M 399.2, obs. (M+H)+: m/z = 400.4

HRMS (ESI-TOF) m/z: [M+H] + Calcd for $C_{24}H_{26}N_5O$ 400.2137; Found 400.2133.



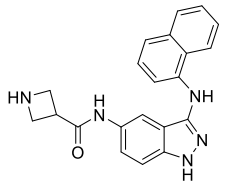
3h

Trans-3-amino-N-(3-(naphthalen-1-ylamino)-1H-indazol-5-yl)cyclohexane-1-carboxamide (**3h**): Compound **3h** was prepared using the sequence described for **3a** incorporating trans-3-((tert-butoxycarbonyl)amino)cyclohexane-1-carboxylic acid in the last peptide coupling step.

^{1}H NMR (400 MHz, DMSO-d6) δ 12.34 (s, 1H), 9.84 (s, 1H), 8.60 (s, 1H), 8.55 - 8.38 (m, 1H), 8.02 (d, J = 1.7 Hz, 1H), 7.94 - 7.84 (m, 1H), 7.80 (d, J = 5.4 Hz, 2H), 7.62 - 7.48 (m, 2H), 7.49 - 7.34 (m, 3H), 7.35 - 7.20 (m, 2H), 3.69 - 3.47 (m, 1H), 2.83 (p, J = 4.6 Hz, 1H), 2.07 (dq, J = 13.5, 4.5, 3.8 Hz, 1H), 1.91 - 1.75 (m, 2H), 1.74 - 1.45 (m, 4H), 1.46 - 1.29 (m, 1H).

^{13}C NMR (101 MHz, DMSO-d6) δ 172.84 , 158.11 , 144.30 , 140.37 , 138.31 , 134.12 , 131.05 , 128.02 , 126.29 , 125.81 , 124.63 , 124.41 , 122.50 , 121.27 , 119.04 , 115.77 , 114.64 , 110.35 , 110.21 , 110.04 , 46.23 , 38.57 , 31.30 , 29.27 , 27.61 , 19.95 .

LCMS(ESI) for $C_{24}H_{25}N_5O$: calc. M 399.2, obs. (M+H)+: m/z = 400.5



3i

N-(3-(naphthalen-1-ylamino)-1H-indazol-5-yl)azetidine-3-carboxamide (**3i**): Compound **3i** was prepared using the sequence described for **3a** incorporating azetidine-3-carboxylic acid in the last peptide coupling step.

^{1}H NMR (400 MHz, DMSO-d6) δ 12.37 (s, 1H), 10.10 (s, 1H), 8.76 (d, J = 40.2 Hz, 2H), 8.63 (s, 1H), 8.52 - 8.37 (m, 1H), 8.00 (d, J = 1.7 Hz, 1H), 7.96 - 7.82 (m, 1H), 7.55 - 7.50 (m, 2H), 7.50 - 7.41 (m, 2H), 7.38 (d, J = 8.0 Hz, 1H), 7.30 (t, J = 7.8 Hz, 1H), 7.22 (dd, J = 7.6, 1.2 Hz, 1H), 4.06 (dt, J = 8.2, 6.3 Hz, 7H), 3.72 (p, J = 8.2 Hz, 2H).

^{13}C NMR (176 MHz, DMSO-d6) δ 168.19 , 144.40 , 140.32 , 138.48 , 134.12 , 130.43 , 128.02 , 126.27 , 125.83 , 124.67 , 124.46 , 122.50 , 120.78 , 119.13 , 115.70 , 110.49 , 110.38 , 110.10 , 47.75 , 35.92 .

LCMS(ESI) for $C_{21}H_{19}N_5O$ (M+H)+: m/z = 358.4