Supporting Information

Indazole-Based Covalent Inhibitors to Target Drug Resistant Epidermal Growth Factor Receptor

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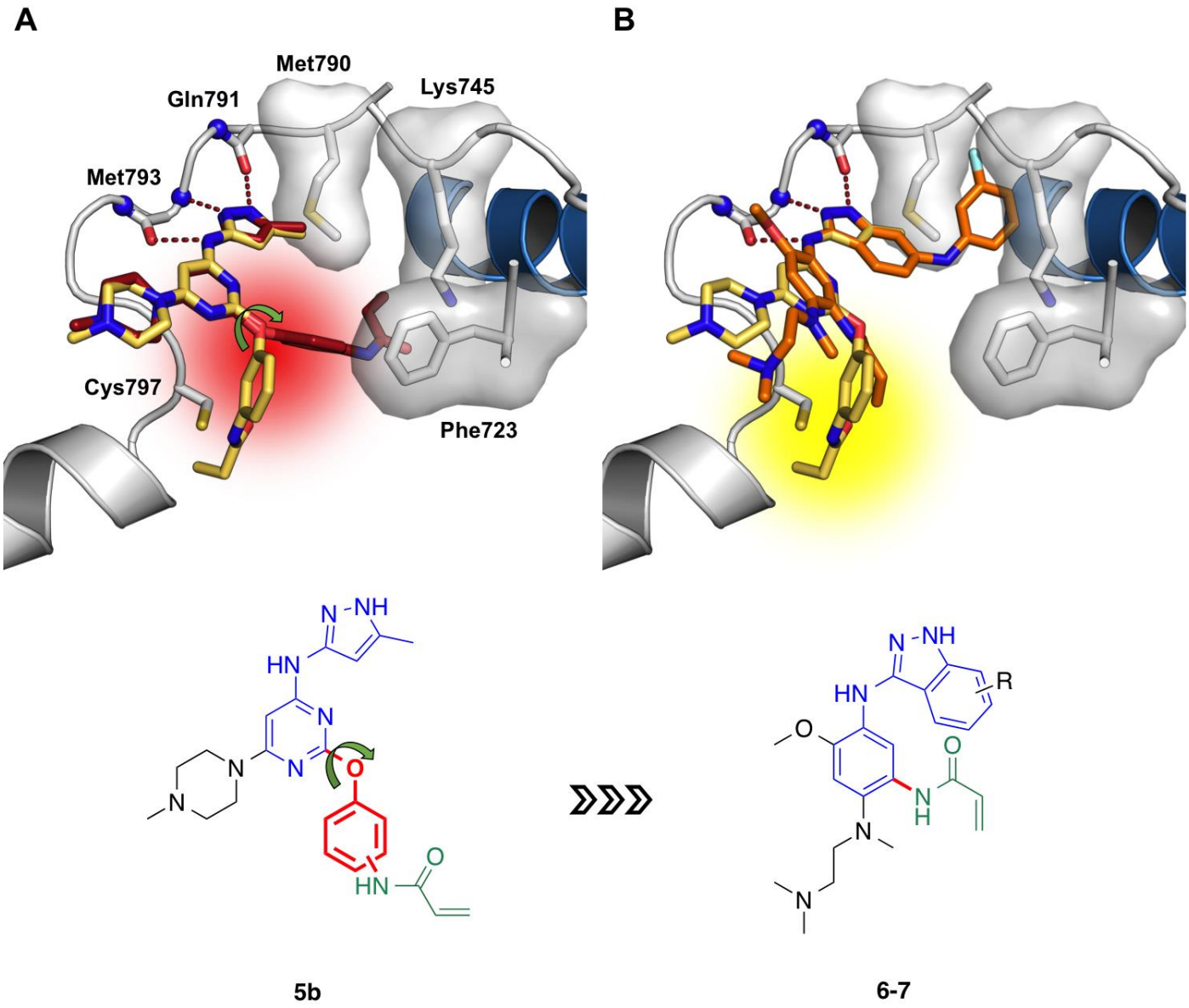


Figure S1.

Structural analysis of the conformational flexibility of methyl pyrazole and indazole based EGFR inhibitors. (A) Alignment of the binding pose of two methyl pyrazole inhibitors bearing a phenoxy-linker possessing the Michael-acceptor, highlighting the flexibility of this linker moiety (PDB ID: 5D10, 5D11, 5J9Y). (B) Alignment of the binding pose that allows for covalent modification of Cys797 (PDB ID: 5D11) with the proposed binding pose of less flexible inhibitors **7-8** (based on PDB ID: 5J9Y).

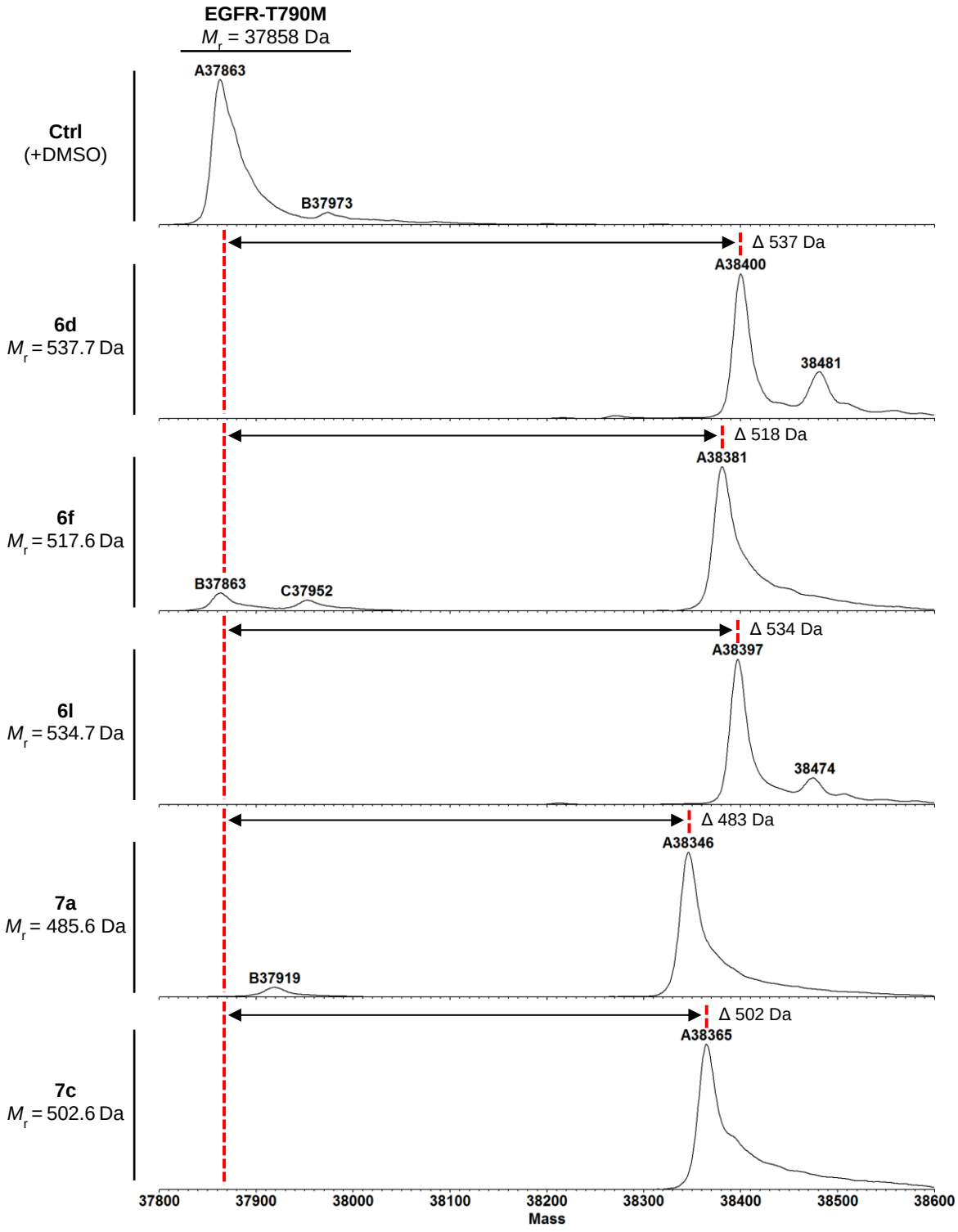


Figure S2.

Mass spectrometry-based analysis of covalent bond formation of EGFR-T790M with selected indazole-based inhibitors.

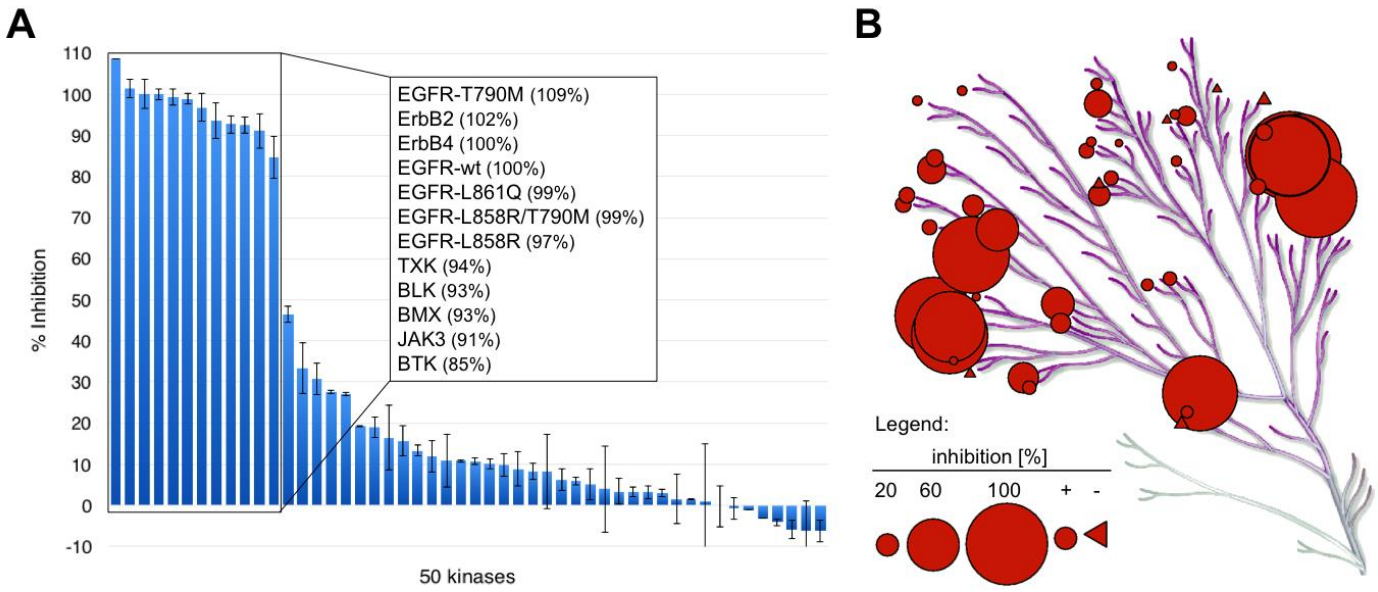
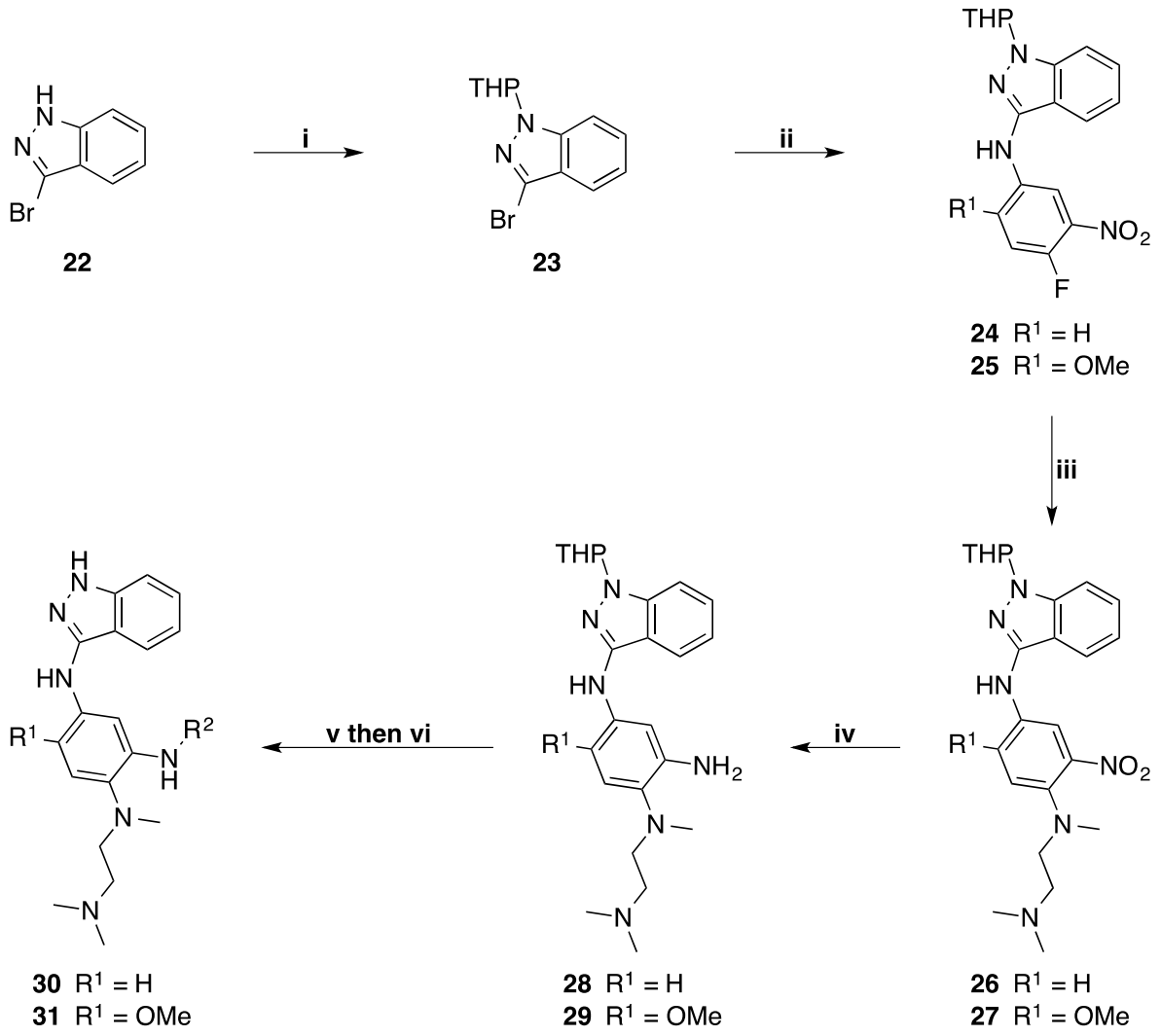


Figure S3.

Kinase profiling of compound **6l** at a concentration of 1 µM generated with the SelectScreen® Profiling Service from Life Technologies. (A) Illustration as waterfall plot and as (B) Kinase dendrogram adapted from Kinome Render and the illustration is reproduced courtesy of Cell Signaling Technology, Inc. (www.cellsignal.com) (M. Chartier, T. Chenard, J. Barker, R. Najmanovich, *PeerJ* **2013**, *1*, e126.).

Scheme S1.

Synthesis of indazole based EGFR inhibitors **30-31**.[a]



[a]Reagents and conditions: i) DHP, *p*TSA cat., DCM, rt; ii) 4-fluoro-2-methoxy-5-nitroaniline or 4-fluoro-3-nitroaniline, Xantphos, $Pd(OAc)_2$, Cs_2CO_3, dry toluene, 80 °C, Ar atm; iii) N^1,N^1,N^2-trimethylethane-1,2-diamine, DIPEA, DMF, 90 °C, MW; iv) Ammonium formate, Pd/C, EtOH reflux, Ar atm; v) acryloyl chloride or propionyl chloride, DIPEA, dry THF, 0 °C then rt; vi) TFA 30% in DCM, 0 °C then rt.

Table S1.

Cellular evaluation of indazole EGFR inhibitors on kRas-mutant cell lines.

Compound	EGFR CTG EC_{50} [nM]	
	A549	H358
30a	7976 ± 1128	11448 ± 5747
30b	>30000	>30000
31a	23637 ± 5576	20032 ± 2222
31b	>30000	>30000
6a	2875 ± 1083	3038 ± 671
6b	2261 ± 497	4315 ± 739
6c	659 ± 193	4740 ± 1902
6d	2163 ± 412	2575 ± 545
6e	6877 ± 2663	8712 ± 1037
6f	5560 ± 1516	5842 ± 1368
6g	3564 ± 1769	5292 ± 748
6h	1387 ± 176	1637 ± 325
6i	3017 ± 1143	3481 ± 796
6j	2863 ± 568	3743 ± 336
6k	3702 ± 862	4696 ± 1312
6l	1637 ± 957	2650 ± 1066
7a	2869 ± 934	3146 ± 720
7b	3435 ± 427	4992 ± 555
7c	3033 ± 927	3387 ± 910
1 (Gefitinib)	8499 ± 1788	13512 ± 4380
4 (AZD9291)	1827 ± 183	2835 ± 256

Table S2.

Selected Indazole-Based Inhibitors and corresponding IC_{50} Determinations on the EGFR-L858R/T790M/C797S Mutant Variant.

Compound	EGFR HTRF IC_{50} [nM]
	L858R/T790M/ C797S
6d	>10000
6f	>10000
6l	>10000
7a	>10000
7c	>10000
3 (CO-1686)	69 ± 13
4 (AZD9291)	77 ± 22

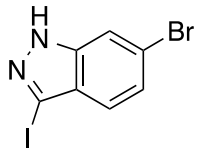
Table S3.

Selected Indazole-Based Inhibitors and corresponding Pharmakokinetic Parameters.

Compound	Microsomal Stability Phase I CL_{int} [µL min^{-1} mg^{-1}]		Plasma Stability [% remaining]	
	human	mouse	human	mouse
6d	1.2	28.2	75.8	95.9
6f	3.6	<1	85.7	91.7
6l	3.4	21.6	77.8	97.9
7a	<1	<1	91.7	95.9
7c	<1	3.9	82.3	90.0
1 (Gefitinib)	39.5	157.5	90.3	91.5
3 (CO-1686)	5.1	51.2	>99	>99
4 (AZD9291)	4.1	81.1	77.8	75.2

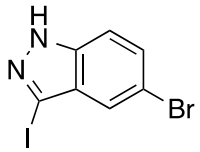
Experimental Section – Chemistry.

Unless otherwise reported, all reagents and solvents were purchased from Acros, Fluka, Sigma-Aldrich or Merck and used without further purification. Dry solvents were purchased as anhydrous reagents from commercial suppliers. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance DRX 400 or Bruker Avance DRX 500 spectrometer at 400 or 500 and 101 or 126 MHz, respectively. ^{1}H chemical shifts are reported in δ (ppm) as s (singlet), d (doublet), dd (doublet of doublet), t (triplet), q (quartet), m (multiplet), and bs (broad singlet) and are referenced to the residual solvent signal DMSO-d_6 (2.50) or $CDCl_3$ (7.26). Coupling constants (*J*) are expressed in hertz (Hz). ^{13}C spectra are referenced to the residual solvent signal DMSO-d_6 (39.52) or $CDCl_3$ (77.16). High-resolution electrospray ionization mass spectra (ESI-FTMS) were recorded on a Thermo LTQ Orbitrap (high-resolution mass spectrometer from Thermo Electron) coupled to an "Accela" HPLC system supplied with a "Hypersil GOLD" column (Thermo Eletron). Analytical TLC was carried out on Merck 60 F245 aluminum-backed silica gel plates. Compounds were purified by column chromatography using Baker silica gel (40-70 μm particle size). All final compounds were purified to ≥95% purity confirmed by NMR analysis as well as LCMS analysis on LCQ Advantage MAX (1200 series, Agilent) with Eclipse XDB-C18-column (5 μM 150 x 1.6 mm, Phenomenex).

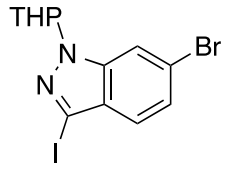


6-bromo-3-iodo-1*H*-indazole (10). General method (GM) A: A solution of 6-bromo-1*H*-indazole (**8**, 735 mg, 3.730 mmol) in THF (10.4 mL) was cooled down on an ice bath and KO*t*Bu (837 mg, 7.461 mmol) was added portionwise. The resulting slurry was stirred at 0 °C for 5 minutes and a solution of iodine (2840 mg, 11.190 mmol) in THF (7.9 mL) was added dropwise. The mixture was allowed to stir at room temperature for 30 minutes when conversion was complete. The mixture was extracted with DCM (200 mL)

and washed with a saturated solution of $Na_2S_2O_3$ (2 x 80 mL). The aqueous phases were collected and backextracted with DCM (2 x 40 mL). The organic layers were combined, dried over anhydrous Na_2SO_4 and volatiles removed under reduced pressure to afford 1202 mg the desired compound (3.730 mmol, 100%) as a pale yellow solid. ^{1}H NMR (500 MHz, DMSO) δ 13.61 (bs, 1H), 7.94 – 7.74 (m, 1H), 7.39 (dd, J = 8.6, 0.4 Hz, 1H), 7.31 (dd, J = 8.6, 1.5 Hz, 1H). ^{13}C NMR (126 MHz, DMSO) δ 141.08, 125.90, 124.38, 122.30, 120.85, 113.07, 93.85. LC-MS (ESI-MS): Calculated: 322.87 for $C_7H_5BrIN_2$ [M+H$^+$]. Found: 323.03. Calculated: 324.87 for $C_7H_5{}^{81}BrIN_2$ [M+H$^+$]. Found: 324.95.

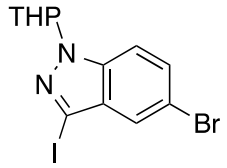


5-Bromo-3-iodo-1*H*-indazole (11). According to GM A. Yield: 99%. ^{1}H NMR (500 MHz, DMSO) δ 13.69 (bs, 1H), 7.61 (d, *J* = 0.5 Hz, 1H), 7.58 – 7.50 (m, 2H). ^{13}C NMR (126 MHz, DMSO) δ 139.22, 129.97, 128.45, 122.57, 113.43, 112.73, 92.45. LC-MS (ESI-MS): Calculated: 322.87 for $C_7H_5BrIN_2$ [M+H$^+$]. Found: 323.18. Calculated: 324.87 for $C_7H_5{}^{81}BrIN_2$ [M+H$^+$]. Found: 325.04.

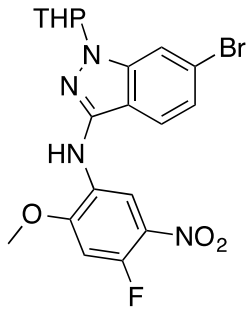


6-Bromo-3-iodo-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazole (12). General method (GM) B: To a vigorously stirring solution of compound **10** (1150 mg, 3.561 mmol) and 3,4-dihydro-2*H*-pyran (0.970 mL, 10.683 mmol) in $CHCl_3$ (25 mL), methanesulfonic acid (12 □L, 0.178 mmol) was added dropwise and the resulting solution was stirred at refluxing condition for 2 h. After complete conversion, the reaction was

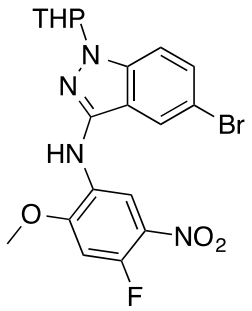
allowed to cool down and extracted in DCM (200 mL). The organic phase was washed with a saturated solution of $NaHCO_3$ and combined aqueous layers backextracted with another aliquot of DCM (100 mL). The organic layers were combined, dried over anhydrous Na_2SO_4 and volatiles removed under reduced pressure. The following silica gel column chromatography (Petroleum ether/EtOAc 85:15) led to 1305 mg (3.205 mmol, 90%) of the desired product as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77 (s, 1H), 7.36 – 7.29 (m, 2H), 5.64 (dd, J = 9.2, 2.7 Hz, 1H), 4.05 – 3.98 (m, 1H), 3.79 – 3.68 (m, 1H), 2.55 – 2.44 (m, 1H), 2.20 – 2.10 (m, 1H), 2.06 (dd, J = 13.2, 3.2 Hz, 1H), 1.79 – 1.71 (m, 2H), 1.71 – 1.61 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 140.98, 128.35, 125.96, 123.24, 122.82, 113.84, 93.51, 86.40, 67.84, 29.78, 25.36, 22.67. LC-MS (ESI-MS): Calculated: 406.93 for $C_{12}H_{13}BrIN_2O$ [M+H$^+$]. Found: 406.82. Calculated: 408.92 for $C_{12}H_{13}{}^{81}BrIN_2O$ [M+H$^+$]. Found: 408.59.



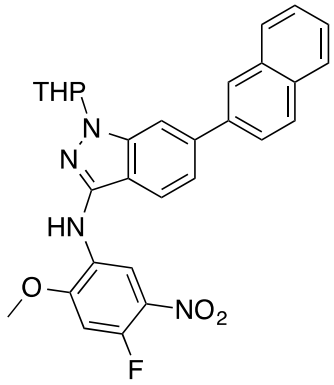
5-Bromo-3-iodo-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazole (13). According to GM B. Yield: 80%. ^{1}H NMR (500 MHz, DMSO) δ 7.79 – 7.73 (m, 1H), 7.66 – 7.59 (m, 2H), 5.86 (dd, J = 9.7, 2.1 Hz, 1H), 3.91 – 3.84 (m, 1H), 3.77 – 3.67 (m, 1H), 2.39 – 2.28 (m, 1H), 2.05 – 1.94 (m, 2H), 1.78 – 1.67 (m, 1H), 1.61 – 1.52 (m, 2H). ^{13}C NMR (126 MHz, DMSO) δ 138.67, 130.39, 129.73, 123.05, 114.31, 112.90, 93.31, 84.25, 66.60, 28.79, 24.60, 21.99. LC-MS (ESI-MS): Calculated: 406.93 for $C_{12}H_{13}BrIN_2O$ [M+H$^+$]. Found: 406.90. Calculated: 408.92 for $C_{12}H_{13}{}^{81}BrIN_2O$ [M+H$^+$]. Found: 408.87.



6-Bromo-*N*-(4-fluoro-2-methoxy-5-nitrophenyl)-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-3-amine (14). General method (GM) C: Compound **12** (300 mg, 0.737 mmol), caesium carbonate (437 mg, 1.340 mmol) and 4-fluoro-2-methoxy-5-nitroaniline (125 mg, 0.670 mmol) were suspended in freshly distilled dry toluene (4 mL) and stirred in a sealed vial under Argon flush for 5 min. Then a solution of palladium diacetate (12 mg, 0.054 mmol, 8% mol) and Xantphos (62 mg, 0.107 mmol, 16% mol) in dry toluene (1.7 mL), was added under vigorous stirring and the resulting suspension was stirred at 60 °C under Argon atmosphere for 6 h. The mixture was diluted in EtOAc (150 mL) and washed with water (2 x 75 mL), the combined aqueous phases were then backextracted with EtOAc (50 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and volatiles removed under reduced pressure to afford a crude which was purified by silica gel column chromatography (Petroleum ether/DCM/EtOAc 60:36:4) to afford 293 mg (0.630 mmol, 94%) of the desired product as an orange solid. ^{1}H NMR (500 MHz, DMSO) δ 9.23 (d, J = 8.3 Hz, 1H), 8.54 (s, 1H), 8.09 (d, J = 8.6 Hz, 1H), 7.91 (d, J = 1.2 Hz, 1H), 7.30 – 7.21 (m, 2H), 5.79 (dd, J = 9.1, 2.4 Hz, 1H), 4.06 (s, 3H), 3.90 – 3.83 (m, 1H), 3.79 – 3.71 (m, 1H), 2.47 – 2.39 (m, 1H), 2.14 – 2.09 (m, 1H), 2.06 – 1.99 (m, 1H), 1.81 – 1.70 (m, 1H), 1.63 – 1.51 (m, 2H). ^{13}C NMR (126 MHz, DMSO) δ 206.36, 153.57, 153.50, 151.47, 149.42, 143.68, 143.68, 140.83, 128.56, 128.50, 127.85, 122.72, 122.66, 121.23, 114.83, 112.44, 111.10, 100.70, 100.49, 83.10, 66.05, 57.23, 30.62, 28.68, 24.86, 22.10. HRMS (ESI-MS): Calculated: 465.05682 for $C_{19}H_{19}BrFN_4O_4$ [M+H$^+$], Found: 465.05744. Calculated: 467.05478 for $C_{19}H_{19}{}^{81}BrFN_4O_4$ [M+H$^+$], Found: 467.05518.

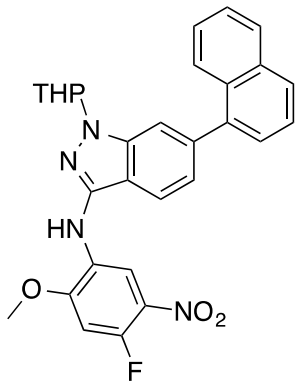


5-Bromo-*N*-(4-fluoro-2-methoxy-5-nitrophenyl)-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-3-amine (15). According to GM C. Yield: 99%. ^{1}H NMR (500 MHz, DMSO) δ 9.27 (d, *J* = 8.3 Hz, 1H), 8.61 – 8.52 (m, 1H), 8.49 (d, *J* = 1.6 Hz, 1H), 7.63 – 7.55 (m, 1H), 7.55 – 7.49 (m, 1H), 7.31 – 7.21 (m, 1H), 5.79 – 5.75 (m, 1H), 4.07 (s, 3H), 3.90 – 3.81 (m, 1H), 3.76 – 3.66 (m, 1H), 2.48 – 2.39 (m, 1H), 2.15 – 2.09 (m, 1H), 2.07 – 2.01 (m, 1H), 1.81 – 1.72 (m, 1H), 1.62 – 1.51 (m, 2H). ^{13}C NMR (126 MHz, DMSO) δ 153.57, 153.50, 151.44, 149.40, 147.93, 142.86, 138.80, 129.94, 128.46, 127.81, 123.32, 117.20, 111.77, 111.62, 111.02, 111.01, 100.70, 100.68, 100.47, 83.28, 66.03, 57.22, 28.67, 24.84, 22.03. HRMS (ESI-MS): Calculated: 465.05682 for $C_{19}H_{19}BrFN_4O_4$ [M+H$^+$]. Found: 465.05722. Calculated: 467.05478 for $C_{19}H_{19}{}^{81}BrFN_4O_4$ [M+H$^+$]. Found: 467.05508.

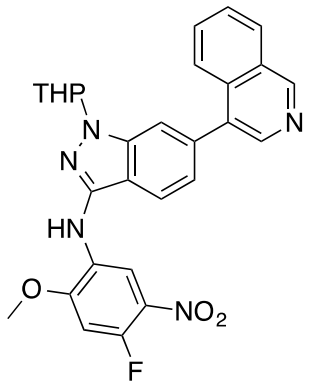


***N*-(4-fluoro-2-methoxy-5-nitrophenyl)-6-(naphthalen-2-yl)-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-3-amine (16a).** General method (GM) D: Compound **14** (80 mg, 0.172 mmol), K_3PO_4 monohydrate (79 mg, 0.344 mmol) and 2-naphthaleneboronic acid (39 mg, 0.224 mmol) were suspended in a mixture of *n*-

butanol/water (2.45 mL/0.150 mL) and the resulting suspension was stirred at room temperature for 5 minutes under argon flush. Then a solution of Xphos (4.9 mg, 0.010 mmol, 6% mol) and Pd_2dba_3 (4.7 mg, 0.005 mmol, 3% mol) in *n*-butanol (0.4 mL) was added through a silicone septum. The reaction was then stirred in a microwave reactor at 95 °C for 30 minutes. The mixture was diluted in EtOAc (75 mL) and washed abundantly with water for three times, then the combined aqueous layers where backextracted with EtOAc (50 mL). The combined organic layers were then washed with a saturated solution of $NaHCO_3$ and brine. The organic phase was dried over anhydrous Na_2SO_4 and volatiles removed under reduced pressure to afford a crude which was purified by silica gel column chromatography (Petroleum ether/DCM/EtOAc 60:36:4) to afford 78 mg (0.152 mmol, 89%) of the desired product as a yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.27 (d, J = 8.1 Hz, 1H), 8.12 (s, 1H), 7.97 – 7.92 (m, 2H), 7.90 – 7.87 (m, 1H), 7.81 (dd, J = 8.5, 1.7 Hz, 1H), 7.77 (s, 1H), 7.70 (d, J = 8.3 Hz, 1H), 7.56 – 7.49 (m, 3H), 6.96 (s, 1H), 6.74 (d, J = 12.1 Hz, 1H), 5.78 (dd, J = 8.7, 2.8 Hz, 1H), 4.13 – 4.02 (m, 4H), 3.84 – 3.74 (m, 1H), 2.85 – 2.64 (m, 1H), 2.37 – 2.26 (m, 1H), 2.23 – 2.15 (m, 1H), 1.92 – 1.74 (m, 2H), 1.72 – 1.66 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 143.45, 141.59, 141.48, 139.33, 138.99, 134.03, 133.18, 128.90, 128.90, 128.62, 128.32, 128.08, 128.08, 126.87, 126.84, 126.57, 126.30, 121.12, 119.21, 115.79, 112.08, 109.00, 99.90, 84.93, 67.48, 57.23, 29.61, 25.64, 22.92. HRMS (ESI-MS): Calculated: 513.19326 for $C_{29}H_{26}FN_4O_4$ [$M+H^+$]. Found: 513.19331.

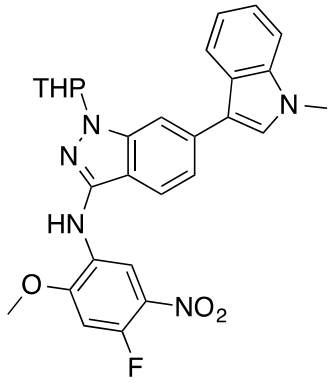


***N*-(4-fluoro-2-methoxy-5-nitrophenyl)-6-(naphthalen-1-yl)-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-3-amine (16b).** According to GM D. Yield: 87%. ^{1}H NMR (500 MHz, DMSO) δ 9.32 (d, *J* = 8.4 Hz, 2H), 8.55 (s, 2H), 8.25 (d, *J* = 8.3 Hz, 2H), 8.04 (d, *J* = 8.0 Hz, 1H), 8.01 (d, *J* = 8.2 Hz, 1H), 7.82 (d, *J* = 8.4 Hz, 2H), 7.73 (s, 2H), 7.69 – 7.60 (m, 1H), 7.59 – 7.47 (m, 3H), 7.32 (d, *J* = 13.2 Hz, 2H), 7.24 (dd, *J* = 8.3, 1.1 Hz, 1H), 5.87 (dd, *J* = 9.2, 2.0 Hz, 1H), 4.11 (s, 3H), 3.89 – 3.83 (m, 1H), 3.77 – 3.66 (m, 1H), 2.58 – 2.47 (m, 1H), 2.16 – 2.04 (m, 2H), 1.82 – 1.69 (m, 1H), 1.64 – 1.53 (m, 2H). ^{13}C NMR (126 MHz, DMSO) δ 153.53, 153.46, 143.58, 140.39, 139.59, 139.47, 133.35, 131.01, 128.62, 128.57, 128.31, 128.21, 128.19, 127.78, 127.14, 126.40, 125.92, 125.44, 125.34, 122.14, 120.51, 115.07, 110.89, 110.86, 110.54, 100.73, 100.53, 83.11, 66.07, 57.29, 39.52, 28.86, 24.92, 22.22. LC-MS (ESI-MS): Calculated: 512.19 for $C_{29}H_{25}FN_4O_4$ [M+H$^+$]. Found: 512.84.

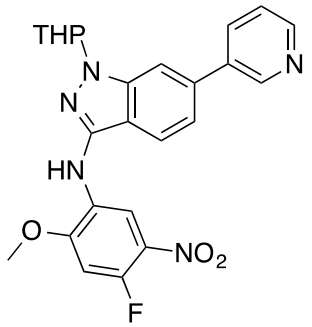


***N*-(4-fluoro-2-methoxy-5-nitrophenyl)-6-(isoquinolin-4-yl)-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-3-amine (16c).** According to GM D. Yield: 74%. ^{1}H NMR (500 MHz, DMSO) δ 9.40 (s, 1H), 9.38 – 9.26 (m, 1H), 8.58 (s, 1H), 8.54 (s, 1H), 8.38 – 8.20 (m, 2H), 7.91 – 7.71 (m, 4H), 7.39 – 7.23 (m, 2H), 5.97 – 5.82 (m, 1H), 4.09 (s, 3H), 3.91 – 3.81 (m, 1H), 3.79 – 3.65 (m, 1H), 2.17 – 2.02 (m, 2H), 1.83 – 1.68 (m, 1H), 1.63 – 1.51 (m, 2H). ^{13}C NMR (126 MHz, DMSO) δ 153.58, 153.50, 152.04, 149.37, 143.63, 142.43, 141.97, 140.41, 135.74, 135.16, 133.45, 132.77, 131.27, 130.99, 128.61, 128.15, 127.95, 127.77, 127.59,

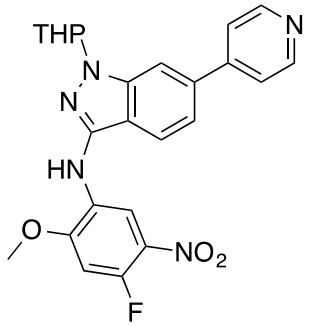
124.19, 122.04, 120.93, 115.42, 110.94, 110.89, 110.38, 100.75, 100.54, 83.11, 66.09, 57.30, 28.85, 24.91, 22.23. LC-MS (ESI-MS): Calculated: 514.19 for $C_{28}H_{25}FN_5O_4$ [M+H$^+$]. Found: 514.39.



***N*-(4-fluoro-2-methoxy-5-nitrophenyl)-6-(1-methyl-1*H*-indol-3-yl)-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-3-amine (16d).** According to GM D. Yield: 98%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.24 (d, *J* = 8.1 Hz, 1H), 7.99 (d, *J* = 8.0 Hz, 1H), 7.74 (s, 1H), 7.63 (d, *J* = 8.3 Hz, 1H), 7.45 (dd, *J* = 8.3, 1.1 Hz, 1H), 7.40 (d, *J* = 8.2 Hz, 1H), 7.34 (s, 1H), 7.31 (dd, *J* = 7.7, 0.4 Hz, 1H), 7.26 – 7.21 (m, 1H), 6.98 (s, 1H), 6.73 (d, *J* = 12.1 Hz, 1H), 5.73 (dd, *J* = 8.6, 2.8 Hz, 1H), 4.09 – 4.01 (m, 4H), 3.87 (s, 3H), 3.81 – 3.74 (m, 1H), 2.79 – 2.67 (m, 1H), 2.34 – 2.24 (m, 1H), 2.24 – 2.16 (m, 1H), 1.89 – 1.74 (m, 2H), 1.73 – 1.63 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.96, 143.38, 141.61, 137.82, 135.86, 130.32, 128.23, 127.49, 126.44, 122.44, 121.26, 120.43, 120.02, 118.92, 116.90, 114.55, 111.99, 111.97, 109.93, 107.97, 99.72, 99.51, 84.80, 67.24, 57.04, 33.19, 29.42, 25.50, 22.76. LC-MS (ESI-MS): Calculated: 516.21 for $C_{28}H_{27}FN_5O_4$ [M+H$^+$]. Found: 516.07.

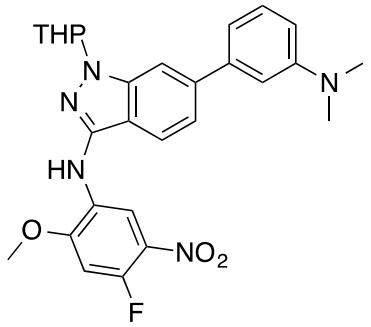


***N*-(4-fluoro-2-methoxy-5-nitrophenyl)-6-(pyridin-3-yl)-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-3-amine (16e).** According to GM D. Yield: 94%. ^{1}H NMR (500 MHz, DMSO) δ 9.28 (d, *J* = 8.4 Hz, 1H), 9.03 (d, *J* = 1.8 Hz, 1H), 8.62 (dd, *J* = 4.7, 1.3 Hz, 1H), 8.52 (s, 1H), 8.23 (d, *J* = 8.4 Hz, 1H), 8.20 (dt, *J* = 8.0, 1.7 Hz, 1H), 8.01 (s, 1H), 7.53 (dd, *J* = 7.8, 4.8 Hz, 1H), 7.50 (dd, *J* = 8.5, 1.3 Hz, 1H), 7.29 (d, *J* = 13.2 Hz, 1H), 5.94 (dd, *J* = 9.2, 2.4 Hz, 1H), 4.08 (s, 3H), 3.92 – 3.85 (m, 1H), 3.82 – 3.74 (m, 1H), 2.57 – 2.51 (m, 1H), 2.19 – 2.10 (m, 1H), 2.10 – 2.03 (m, 1H), 1.85 – 1.71 (m, 1H), 1.65 – 1.53 (m, 2H). ^{13}C NMR (126 MHz, DMSO) δ 153.52, 153.45, 151.38, 148.58, 148.05, 143.53, 140.79, 136.41, 135.70, 134.65, 131.66, 128.58, 128.53, 128.09, 123.81, 121.53, 119.05, 115.41, 114.43, 110.92, 107.84, 103.51, 100.71, 100.50, 82.91, 66.16, 57.26, 28.86, 24.94, 22.35. LC-MS (ESI-MS): Calculated: 464.17 for $C_{24}H_{23}FN_5O_4$ [M+H$^+$]. Found: 464.28.

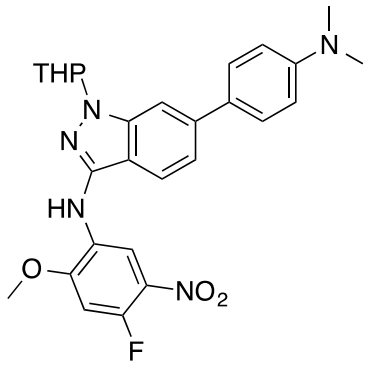


***N*-(4-fluoro-2-methoxy-5-nitrophenyl)-6-(pyridin-4-yl)-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-3-amine (16f).** According to GM D. Yield: 70%. ^{1}H NMR (500 MHz, DMSO) δ 9.27 (d, *J* = 8.4 Hz, 1H), 8.72 (d, *J* = 5.7 Hz, 2H), 8.57 (s, 1H), 8.27 (d, *J* = 8.5 Hz, 1H), 8.12 (s, 1H), 7.92 (d, *J* = 5.7 Hz, 2H), 7.59

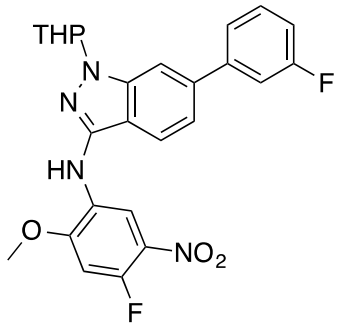
(dd, J = 8.5, 1.3 Hz, 1H), 7.30 (d, J = 13.2 Hz, 1H), 5.97 (dd, J = 9.2, 2.4 Hz, 1H), 4.08 (s, 3H), 3.93 – 3.86 (m, 1H), 3.82 – 3.74 (m, 1H), 2.19 – 2.11 (m, 1H), 2.11 – 2.03 (m, 1H), 1.86 – 1.73 (m, 1H), 1.66 – 1.55 (m, 2H). ^{13}C NMR (126 MHz, DMSO) δ 179.33, 162.48, 158.67, 153.59, 149.40, 149.31, 146.95, 143.58, 140.68, 136.16, 128.59, 128.06, 128.04, 122.02, 121.73, 118.77, 116.21, 110.99, 110.97, 108.24, 93.69, 82.90, 66.17, 57.29, 28.86, 24.93, 22.32. LC-MS (ESI-MS): Calculated: 464.17 for $C_{24}H_{23}FN_5O_4$ [M+H$^+$]. Found: 464.37.



6-(3-(dimethylamino)phenyl)-*N*-(4-fluoro-2-methoxy-5-nitrophenyl)-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-3-amine (16g). According to GM D. Yield: 95%. ^{1}H NMR (500 MHz, DMSO) δ 9.28 (d, J = 8.4 Hz, 1H), 8.47 (s, 1H), 8.15 (d, J = 8.4 Hz, 1H), 7.82 (s, 1H), 7.42 (dd, J = 8.5, 1.1 Hz, 1H), 7.34 – 7.25 (m, 2H), 7.06 – 6.97 (m, 2H), 6.77 (dd, J = 8.3, 1.5 Hz, 1H), 5.92 (dd, J = 9.0, 2.4 Hz, 1H), 4.08 (s, 3H), 3.92 – 3.83 (m, 1H), 3.81 – 3.70 (m, 1H), 2.99 (s, 6H), 2.54 – 2.51 (m, 1H), 2.19 – 2.10 (m, 1H), 2.10 – 2.03 (m, 1H), 1.85 – 1.74 (m, 1H), 1.64 – 1.54 (m, 2H). ^{13}C NMR (126 MHz, DMSO) δ 154.38, 154.31, 151.74, 150.18, 144.33, 142.08, 141.77, 130.23, 129.49, 129.45, 129.44, 129.10, 129.09, 121.80, 120.49, 118.25, 116.34, 115.90, 112.71, 112.11, 111.73, 111.71, 108.35, 101.59, 101.39, 83.72, 66.89, 58.16, 41.16, 29.73, 25.86, 23.11. LC-MS (ESI-MS): Calculated: 506.22 for $C_{27}H_{29}FN_5O_4$ [M+H$^+$]. Found: 506.38.

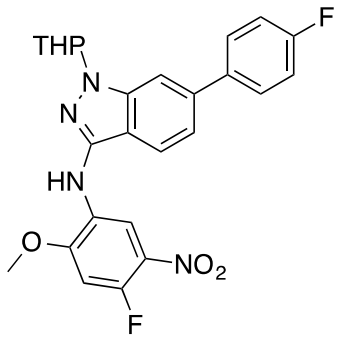


6-(4-(dimethylamino)phenyl)-*N*-(4-fluoro-2-methoxy-5-nitrophenyl)-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-3-amine (16h). According to GM D. Yield: 90%. ^{1}H NMR (500 MHz, DMSO) δ 9.27 (d, *J* = 8.4 Hz, 1H), 8.41 (s, 1H), 8.08 (d, *J* = 8.5 Hz, 1H), 7.76 (s, 1H), 7.65 (d, *J* = 8.8 Hz, 2H), 7.39 (dd, *J* = 8.5, 1.2 Hz, 1H), 7.28 (d, *J* = 13.2 Hz, 1H), 6.84 (d, *J* = 8.6 Hz, 2H), 5.89 (dd, *J* = 9.1, 2.3 Hz, 1H), 4.08 (s, 3H), 3.93 – 3.83 (m, 1H), 3.82 – 3.73 (m, 1H), 2.96 (s, 6H), 2.57 – 2.51 (m, 1H), 2.18 – 2.10 (m, 1H), 2.10 – 2.02 (m, 1H), 1.84 – 1.72 (m, 1H), 1.64 – 1.53 (m, 2H). ^{13}C NMR (126 MHz, DMSO) δ 174.44, 153.42, 153.35, 149.23, 143.39, 141.17, 139.85, 128.54, 128.23, 127.66, 120.83, 118.63, 114.23, 112.58, 110.74, 105.63, 100.65, 100.44, 82.86, 66.04, 57.24, 28.86, 24.98, 22.29. LC-MS (ESI-MS): Calculated: 506.22 for $C_{27}H_{29}FN_5O_4$ [M+H$^+$]. Found: 506.46.

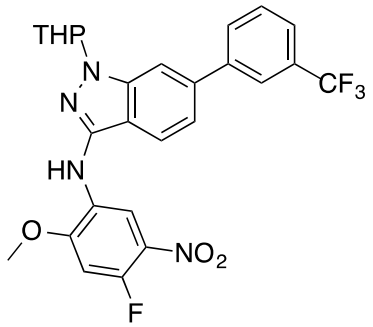


***N*-(4-fluoro-2-methoxy-5-nitrophenyl)-6-(3-fluorophenyl)-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-3-amine (16i).** According to GM D. Yield: 90%. ^{1}H NMR (500 MHz, DMSO) δ 9.28 (d, *J* = 8.3 Hz, 1H), 8.51 (s, 1H), 8.20 (d, *J* = 8.5 Hz, 1H), 7.98 (s, 1H), 7.72 – 7.62 (m, 2H), 7.55 (dd, *J* = 14.4, 7.5 Hz, 1H), 7.49 (d,

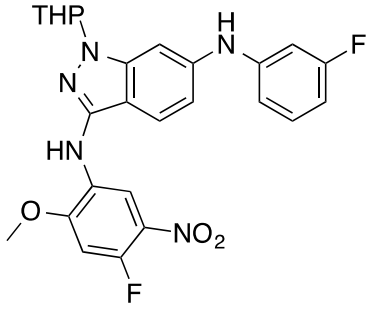
J = 8.7 Hz, 1H), 7.29 (d, *J* = 13.1 Hz, 1H), 7.27 – 7.19 (m, 1H), 5.95 (dd, *J* = 9.0, 1.7 Hz, 1H), 4.09 (s, 3H), 3.97 – 3.84 (m, 1H), 3.84 – 3.74 (m, 1H), 2.59 – 2.52 (m, 1H), 2.20 – 2.11 (m, 1H), 2.11 – 2.02 (m, 1H), 1.90 – 1.74 (m, 1H), 1.67 – 1.54 (m, 2H). ^{13}C NMR (126 MHz, DMSO) δ 163.62, 161.68, 153.51, 153.44, 151.36, 149.32, 143.49, 142.73, 142.67, 140.80, 138.14, 138.12, 130.81, 130.74, 128.58, 128.53, 128.12, 128.10, 123.28, 123.26, 121.31, 119.13, 115.38, 114.40, 114.24, 113.98, 113.80, 110.87, 107.72, 100.70, 100.49, 82.84, 66.14, 57.25, 39.52, 28.88, 24.95, 22.35. LC-MS (ESI-MS): Calculated: 481.17 for $C_{25}H_{23}F_2N_4O_4$ [M+H$^+$]. Found: 481.13.



N-(4-fluoro-2-methoxy-5-nitrophenyl)-6-(4-fluorophenyl)-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-amine (16j). According to GM D. Yield: 90%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.24 (d, *J* = 8.1 Hz, 1H), 7.68 – 7.58 (m, 4H), 7.32 (dd, *J* = 8.3, 1.2 Hz, 1H), 7.20 – 7.12 (m, 2H), 6.95 (s, 1H), 6.74 (d, *J* = 12.1 Hz, 1H), 5.72 (dd, *J* = 8.7, 2.6 Hz, 1H), 4.08 – 4.00 (m, 4H), 3.81 – 3.72 (m, 1H), 2.76 – 2.66 (m, 1H), 2.33 – 2.23 (m, 1H), 2.21 – 2.13 (m, 1H), 1.89 – 1.74 (m, 2H), 1.72 – 1.65 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 163.81, 161.85, 152.10, 152.02, 143.16, 141.11, 140.45, 137.55, 137.52, 131.13, 129.44, 129.37, 129.11, 128.53, 128.02, 128.00, 120.50, 119.01, 115.94, 115.77, 115.46, 111.86, 111.83, 108.39, 99.67, 99.46, 84.71, 67.22, 56.97, 29.32, 25.36, 22.64. LC-MS (ESI-MS): Calculated: 481.17 for $C_{25}H_{23}F_2N_4O_4$ [M+H$^+$]. Found: 481.09.

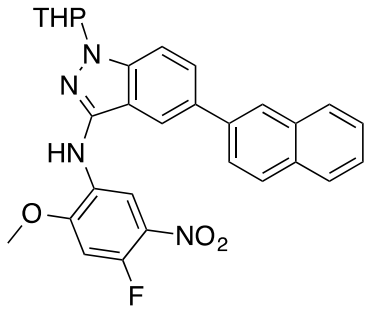


***N*-(4-fluoro-2-methoxy-5-nitrophenyl)-1-(tetrahydro-2*H*-pyran-2-yl)-6-(3-(trifluoromethyl)phenyl)-1*H*-indazol-3-amine (16k).** According to GM D. Yield: 98%. ^{1}H NMR (500 MHz, DMSO) δ 9.28 (d, *J* = 8.4 Hz, 1H), 8.53 (s, 1H), 8.22 (d, *J* = 8.5 Hz, 1H), 8.13 – 8.06 (m, 2H), 8.00 (s, 1H), 7.79 – 7.73 (m, 2H), 7.51 (dd, *J* = 8.5, 1.4 Hz, 1H), 7.28 (d, *J* = 13.2 Hz, 1H), 5.97 (dd, *J* = 9.1, 2.4 Hz, 1H), 4.08 (s, 3H), 3.91 – 3.85 (m, 1H), 3.81 – 3.74 (m, 1H), 2.57 – 2.51 (m, 1H), 2.18 – 2.11 (m, 1H), 2.11 – 2.03 (m, 1H), 1.85 – 1.73 (m, 1H), 1.65 – 1.54 (m, 2H). ^{13}C NMR (126 MHz, DMSO) δ 153.53, 153.45, 151.38, 149.33, 143.52, 141.35, 140.80, 137.96, 131.40, 129.97, 129.86, 129.61, 128.93, 128.58, 128.53, 128.50, 128.10, 128.09, 125.32, 124.23, 124.20, 123.61, 123.58, 123.15, 121.49, 119.26, 115.46, 110.91, 110.90, 107.92, 100.70, 100.49, 82.73, 66.07, 57.26, 28.86, 24.95, 22.27. LC-MS (ESI-MS): Calculated: 531.17 for $C_{26}H_{23}F_4N_4O_4$ [M+H$^+$]. Found: 531.09.



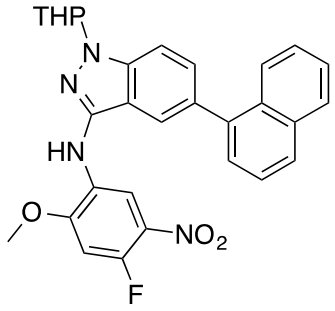
***N*^{3}-(4-fluoro-2-methoxy-5-nitrophenyl)-*N*^{6}-(3-fluorophenyl)-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazole-3,6-diamine (16l).** Compound **14** (85 mg, 0.183 mmol), caesium carbonate (119 mg, 0.362 mmol)

and 3-fluoroaniline (23 □L, 0.239 mmol) were suspended in freshly distilled dry toluene (3.4 mL) and stirred in a sealed vial under Argon flush for 5 min. Then a solution of palladium diacetate (3.3 mg, 0.015 mmol, 8% mol) and Xantphos (17.4 mg, 0.030 mmol, 16% mol) in dry toluene (0.8 mL), was added under vigorous stirring and the resulting suspension was stirred at 90 °C under Argon atmosphere for 1 h. The mixture was diluted in EtOAc (80 mL) and washed with water (40 mL), saturated solution of $NaHCO_3$ (40 mL) and a saturated solution of NH_4Cl (40 mL). The organic layer was dried over anhydrous Na_2SO_4 and volatiles removed under reduced pressure to afford a crude which was purified by silica gel column chromatography (Petroleum ether/DCM/EtOAc 60:36:4) to afford 78 mg (0.157 mmol, 86%) of the desired product as a dark red solid. ^{1}H NMR (500 MHz, DMSO) δ 9.24 (d, *J* = 8.4 Hz, 1H), 8.66 (s, 1H), 8.32 (s, 1H), 7.96 (d, *J* = 8.7 Hz, 1H), 7.35 – 7.24 (m, 2H), 7.20 (d, *J* = 1.2 Hz, 1H), 6.97 (dd, *J* = 8.2, 1.3 Hz, 1H), 6.93 – 6.87 (m, 2H), 6.64 (td, *J* = 8.4, 1.9 Hz, 1H), 5.68 (dd, *J* = 8.7, 2.5 Hz, 1H), 4.07 (s, 3H), 3.84 (d, *J* = 11.3 Hz, 1H), 3.68 (td, *J* = 11.4, 3.2 Hz, 1H), 2.48 – 2.40 (m, 1H), 2.16 – 2.07 (m, 1H), 2.07 – 2.00 (m, 1H), 1.84 – 1.72 (m, 1H), 1.64 – 1.51 (m, 2H). ^{13}C NMR (126 MHz, DMSO) δ 164.00, 162.08, 153.37, 151.22, 149.17, 145.45, 143.38, 142.36, 141.51, 130.78, 130.70, 128.60, 128.28, 121.48, 113.17, 112.57, 110.74, 106.11, 105.94, 102.96, 102.77, 100.63, 100.42, 95.57, 83.16, 65.77, 57.23, 39.52, 28.66, 24.95, 21.98. LC-MS (ESI-MS): 496.18 Calculated: for [M+H$^+$]. Found: 496.16.

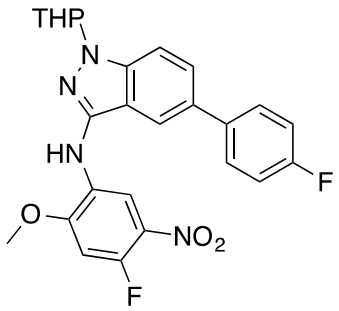


***N*-(4-fluoro-2-methoxy-5-nitrophenyl)-5-(naphthalen-2-yl)-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-3-amine (17a).** According to GM D. Yield: 82%. ^{1}H NMR (500 MHz, DMSO) δ 9.37 (d, *J* = 8.4 Hz, 1H),

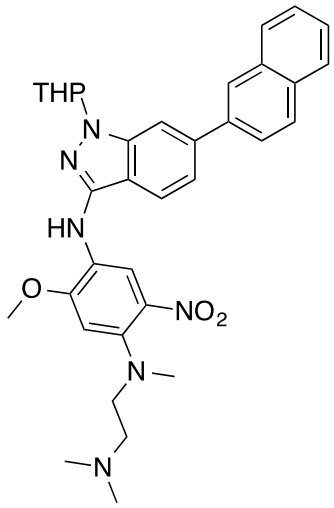
8.66 (s, 1H), 8.62 (s, 1H), 8.27 (s, 1H), 8.06 – 7.91 (m, 5H), 7.74 (d, *J* = 8.8 Hz, 1H), 7.59 – 7.48 (m, 2H), 7.31 (d, *J* = 13.2 Hz, 1H), 5.84 (dd, *J* = 9.0, 2.3 Hz, 1H), 4.11 (s, 3H), 3.95 – 3.88 (m, 1H), 3.79 – 3.72 (m, 1H), 2.57 – 2.51 (m, 1H), 2.19 – 2.11 (m, 1H), 2.11 – 2.04 (m, 1H), 1.87 – 1.74 (m, 1H), 1.67 – 1.55 (m, 2H). ^{13}C NMR (126 MHz, DMSO) δ 153.55, 153.47, 151.36, 149.32, 143.99, 139.65, 137.82, 133.96, 133.40, 131.96, 131.92, 128.59, 128.54, 128.39, 128.35, 128.04, 127.95, 127.50, 126.94, 126.39, 125.80, 125.43, 124.76, 119.06, 116.57, 111.04, 110.33, 100.74, 100.53, 83.34, 66.07, 57.34, 28.80, 24.92, 22.15. LC-MS (ESI-MS): Calculated: 513.19 for $C_{29}H_{26}FN_4O_4$ [M+H$^+$]. Found: 513.13.



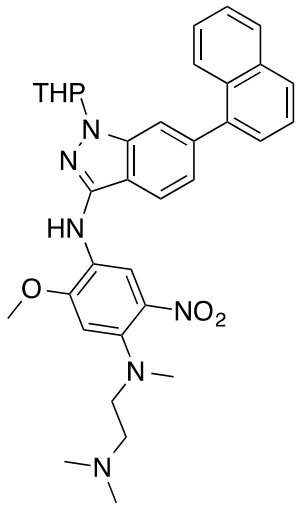
***N*-(4-fluoro-2-methoxy-5-nitrophenyl)-5-(naphthalen-1-yl)-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-3-amine (17b).** According to GM D. Yield: 77%. ^{1}H NMR (500 MHz, DMSO) δ 9.33 (d, *J* = 8.4 Hz, 1H), 8.52 (s, 1H), 8.29 (d, *J* = 0.6 Hz, 1H), 8.02 (d, *J* = 8.0 Hz, 1H), 7.97 (d, *J* = 8.2 Hz, 1H), 7.84 (d, *J* = 8.4 Hz, 1H), 7.76 (d, *J* = 8.6 Hz, 1H), 7.64 – 7.58 (m, 1H), 7.58 – 7.52 (m, 2H), 7.52 – 7.46 (m, 2H), 7.26 (d, *J* = 13.2 Hz, 1H), 5.87 (dd, *J* = 9.1, 2.3 Hz, 1H), 4.01 (s, 3H), 3.96 – 3.89 (m, 1H), 3.81 – 3.72 (m, 1H), 2.59 – 2.52 (m, 1H), 2.20 – 2.06 (m, 2H), 1.88 – 1.76 (m, 1H), 1.68 – 1.57 (m, 2H). ^{13}C NMR (126 MHz, DMSO) δ 153.54, 153.46, 151.37, 149.50, 149.33, 143.74, 139.70, 139.49, 133.42, 131.76, 131.29, 129.57, 128.57, 128.52, 128.28, 128.11, 128.10, 127.36, 127.26, 126.30, 125.84, 125.53, 125.48, 121.65, 116.08, 110.86, 109.70, 100.69, 100.48, 83.43, 66.12, 57.18, 28.82, 24.94, 22.19. LC-MS (ESI-MS): Calculated: 513.19 for $C_{29}H_{26}FN_4O_4$ [M+H$^+$]. Found: 513.11.



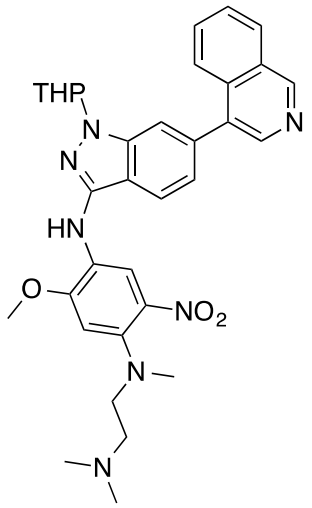
***N*-(4-fluoro-2-methoxy-5-nitrophenyl)-5-(4-fluorophenyl)-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-3-amine (17c).** According to GM D. Yield: 70%. ^{1}H NMR (500 MHz, DMSO) δ 9.35 (d, *J* = 8.4 Hz, 1H), 8.53 (s, 1H), 8.48 (s, 1H), 7.80 – 7.72 (m, 3H), 7.68 (d, *J* = 8.7 Hz, 1H), 7.35 – 7.27 (m, 3H), 5.80 (dd, *J* = 9.0, 2.4 Hz, 1H), 4.09 (s, 3H), 3.91 – 3.84 (m, 1H), 3.77 – 3.70 (m, 1H), 2.18 – 2.10 (m, 1H), 2.10 – 2.03 (m, 1H), 1.84 – 1.73 (m, 1H), 1.65 – 1.55 (m, 2H). ^{13}C NMR (126 MHz, DMSO) δ 162.46, 160.53, 153.48, 153.41, 151.35, 149.30, 143.88, 139.50, 136.93, 136.91, 131.17, 128.56, 128.53, 128.50, 127.98, 127.97, 126.61, 118.63, 116.43, 115.67, 115.51, 110.96, 110.24, 100.72, 100.51, 83.34, 66.04, 57.33, 28.76, 24.91, 22.13. LC-MS (ESI-MS): Calculated: 481.17 for [M+H^{+}]. Found: 481.15.



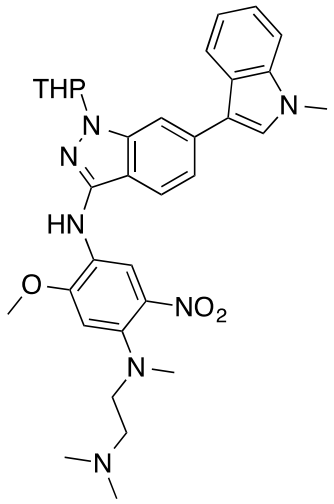
N^1-(2-(dimethylamino)ethyl)-5-methoxy-N^1-methyl-N^4-(6-(naphthalen-2-yl)-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-3-yl)-2-nitrobenzene-1,4-diamine (18a). General method (GM) E: To a solution of compound **16a** (78 mg, 0.152 mmol) in DMF (1.2 mL), DIPEA (0.106 mL, 0.609 mmol) and N^1,N^1,N^2-trimethylethane-1,2-diamine (0.077 mL, 0.609 mmol) were added. The reaction was then stirred in a microwave reactor at 90 C for 40 min. The mixture was diluted in EtOAc (50 mL) and washed abundantly with water three times, the combined aqueous phases were then backextracted with EtOAc (30 mL). The organic phases were combined, dried over anhydrous Na_2SO_4 and volatiles removed under reduced pressure to afford 90 mg (0.152 mmol, 100%) of the desired product as red solid. ^{1}H NMR (500 MHz, DMSO) δ 9.09 (s, 1H), 8.15 (s, 1H), 8.00 – 7.93 (m, 2H), 7.91 (d, *J* = 7.4 Hz, 1H), 7.84 (dd, *J* = 8.5, 1.7 Hz, 1H), 7.79 (s, 1H), 7.73 (d, *J* = 8.3 Hz, 1H), 7.59 – 7.48 (m, 3H), 6.93 (s, 1H), 6.72 (s, 1H), 5.79 (dd, *J* = 8.6, 2.7 Hz, 1H), 4.14 – 4.00 (m, 4H), 3.84 – 3.78 (m, 1H), 3.27 (t, *J* = 7.1 Hz, 2H), 2.90 (s, 3H), 2.81 – 2.70 (m, 1H), 2.60 (t, *J* = 7.1 Hz, 2H), 2.38 – 2.28 (m, 7H), 2.25 – 2.16 (m, 1H), 1.92 – 1.75 (m, 2H), 1.75 – 1.65 (m, 1H). ^{13}C NMR (126 MHz, DMSO) δ 150.85, 143.37, 141.19, 140.88, 140.66, 138.49, 135.29, 133.43, 132.53, 128.23, 128.01, 127.45, 126.17, 125.87, 125.72, 125.42, 120.15, 118.79, 115.40, 112.85, 110.78, 108.23, 102.08, 84.30, 66.75, 56.86, 55.94, 54.07, 45.52, 41.40, 29.50, 25.06, 22.29. HRMS (ESI-MS): Calculated: 595.30273 for $C_{34}H_{39}N_6O_4$ [M+H^+]. Found: 595.30514.



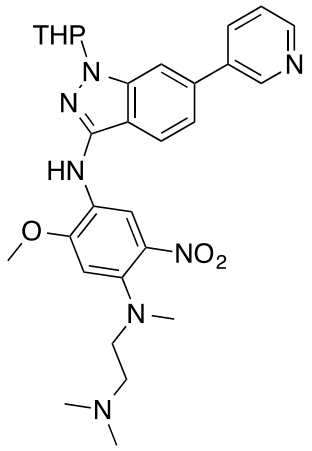
***N*^{1}-(2-(dimethylamino)ethyl)-5-methoxy-*N*^{1}-methyl-*N*^{4}-(6-(naphthalen-1-yl)-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-3-yl)-2-nitrobenzene-1,4-diamine (18b).** According to GM E. Yield: 99%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.01 (s, 1H), 7.93 (d, *J* = 7.9 Hz, 1H), 7.91 – 7.88 (m, 2H), 7.72 (d, *J* = 8.2 Hz, 1H), 7.59 (s, 1H), 7.57 – 7.53 (m, 1H), 7.53 – 7.48 (m, 2H), 7.44 (ddd, *J* = 8.2, 6.8, 1.2 Hz, 1H), 7.28 (dd, *J* = 8.2, 1.1 Hz, 1H), 7.00 (s, 1H), 6.89 (s, 1H), 5.65 (dd, *J* = 9.1, 2.6 Hz, 1H), 4.10 (s, 3H), 4.04 – 3.98 (m, 1H), 3.74 – 3.65 (m, 1H), 3.47 (t, *J* = 7.0 Hz, 2H), 2.94 (t, *J* = 6.8 Hz, 2H), 2.89 (s, 3H), 2.73 – 2.63 (m, 1H), 2.60 (s, 6H), 2.27 – 2.18 (m, 1H), 2.18 – 2.11 (m, 1H), 1.81 – 1.68 (m, 2H), 1.67 – 1.58 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ LC-MS (ESI-MS): Calculated: 595.30 for $C_{34}H_{39}N_6O_4$ [M+H$^+$]. Found: 595.10.



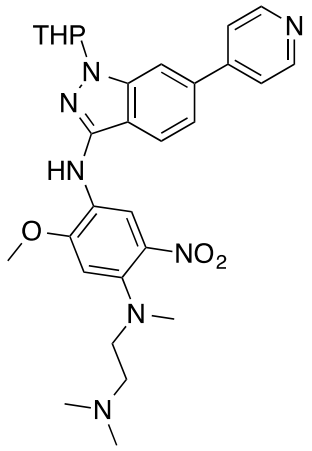
N^1-(2-(dimethylamino)ethyl)-N^4-(6-(isoquinolin-4-yl)-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-3-yl)-5-methoxy-N^1-methyl-2-nitrobenzene-1,4-diamine (18c). According to GM E. Yield: 99%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.27 (s, 1H), 9.01 (s, 1H), 8.56 (s, 1H), 8.04 (d, *J* = 7.9 Hz, 1H), 7.91 (d, *J* = 8.3 Hz, 1H), 7.74 (d, *J* = 8.2 Hz, 1H), 7.69 – 7.58 (m, 3H), 7.25 (d, *J* = 8.5 Hz, 1H), 6.93 (s, 1H), 6.71 (s, 1H), 5.67 (dd, *J* = 8.9, 2.5 Hz, 1H), 4.05 – 3.97 (m, 4H), 3.73 – 3.65 (m, 1H), 3.24 (t, *J* = 6.9 Hz, 2H), 2.86 (s, 3H), 2.73 – 2.63 (m, 1H), 2.56 (t, *J* = 6.9 Hz, 2H), 2.27 (s, 6H), 2.25 – 2.20 (m, 1H), 2.20 – 2.12 (m, 1H), 1.80 – 1.68 (m, 2H), 1.65 – 1.58 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 152.27, 151.13, 143.73, 143.09, 141.47, 140.67, 136.56, 134.43, 133.46, 130.77, 128.46, 127.96, 127.34, 125.74, 124.94, 122.61, 118.80, 116.06, 113.15, 111.43, 102.51, 84.90, 67.22, 57.15, 56.27, 54.31, 45.80, 41.76, 29.31, 25.25, 22.63. LC-MS (ESI-MS): Calculated: 596.30 for $C_{33}H_{38}N_7O_4$ [M+H^+]. Found: 596.31.



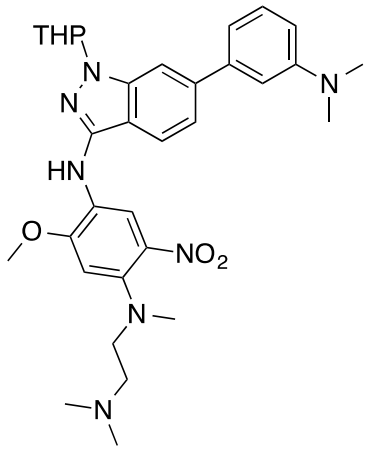
N^1-(2-(dimethylamino)ethyl)-5-methoxy-N^1-methyl-N^4-(6-(1-methyl-1*H*-indol-3-yl)-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-3-yl)-2-nitrobenzene-1,4-diamine (18d). According to GM E. Yield: 99%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.01 (s, 1H), 7.96 (d, *J* = 8.0 Hz, 1H), 7.68 (s, 1H), 7.59 (d, *J* = 8.3 Hz, 1H), 7.38 (dd, *J* = 8.3, 1.0 Hz, 1H), 7.33 (d, *J* = 8.2 Hz, 1H), 7.29 – 7.23 (m, 2H), 7.19 (td, *J* = 7.8, 0.8 Hz, 1H), 6.83 (s, 1H), 6.64 (s, 1H), 5.67 (dd, *J* = 8.6, 2.7 Hz, 1H), 4.02 – 3.97 (m, 1H), 3.95 (s, 3H), 3.77 (s, 3H), 3.75 – 3.67 (m, 1H), 3.18 (t, *J* = 7.3 Hz, 2H), 2.84 – 2.78 (m, 4H), 2.73 – 2.63 (m, 1H), 2.51 (t, *J* = 7.3 Hz, 2H), 2.25 – 2.21 (m, 7H), 2.18 – 2.09 (m, 1H), 1.84 – 1.68 (m, 2H), 1.68 – 1.57 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 151.05, 143.66, 141.36, 141.28, 137.59, 135.63, 135.28, 127.24, 126.25, 125.86, 122.13, 120.67, 120.12, 119.83, 118.81, 116.75, 114.63, 112.97, 109.70, 107.63, 102.34, 84.57, 66.91, 57.11, 56.16, 54.33, 45.77, 41.65, 32.90, 29.22, 25.33, 22.56. LC-MS (ESI-MS): Calculated: 598.31 for $C_{33}H_{40}N_7O_4$ [M+H^+]. Found: 598.21.



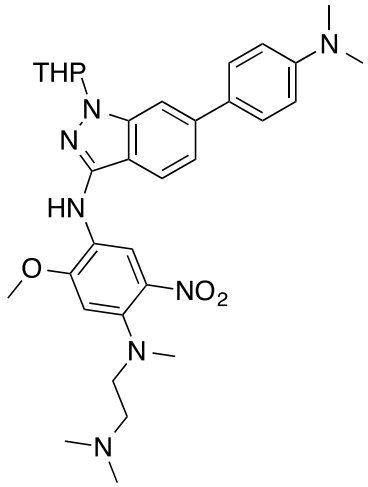
***N*^{1}-(2-(dimethylamino)ethyl)-5-methoxy-*N*^{1}-methyl-2-nitro-*N*^{4}-(6-(pyridin-3-yl)-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-3-yl)benzene-1,4-diamine (18e).** According to GM E. Yield: 99%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.98 (s, 1H), 8.89 (s, 1H), 8.59 (d, *J* = 4.6 Hz, 1H), 7.92 (d, *J* = 7.8 Hz, 1H), 7.68 (d, *J* = 8.3 Hz, 1H), 7.61 (s, 1H), 7.36 (dd, *J* = 7.8, 4.9 Hz, 1H), 7.28 (d, *J* = 8.3 Hz, 1H), 6.87 (s, 1H), 6.67 (s, 1H), 5.68 (dd, *J* = 8.6, 2.4 Hz, 1H), 4.04 – 3.94 (m, 4H), 3.77 – 3.69 (m, 1H), 3.21 (t, *J* = 7.0 Hz, 2H), 2.82 (s, 3H), 2.71 – 2.61 (m, 1H), 2.54 (t, *J* = 7.0 Hz, 2H), 2.30 – 2.19 (m, 7H), 2.18 – 2.09 (m, 1H), 1.83 – 1.69 (m, 2H), 1.68 – 1.60 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.54, 151.11, 148.70, 143.58, 141.47, 140.89, 137.45, 136.93, 135.50, 134.91, 125.55, 123.58, 119.74, 119.49, 116.07, 113.11, 108.51, 102.39, 84.73, 67.05, 57.06, 56.22, 54.21, 45.72, 41.64, 29.20, 25.26, 22.50. LC-MS (ESI-MS): Calculated: 546.28 for $C_{29}H_{36}N_7O_4$ [M+H$^+$]. Found: 546.20.



***N*^{1}-(2-(dimethylamino)ethyl)-5-methoxy-*N*^{1}-methyl-2-nitro-*N*^{4}-(6-(pyridin-4-yl)-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-3-yl)benzene-1,4-diamine (18f).** According to GM E. Yield: 98%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.98 (s, 1H), 8.67 (d, *J* = 5.3 Hz, 2H), 7.73 – 7.66 (m, 2H), 7.56 (d, *J* = 5.9 Hz, 2H), 7.35 (d, *J* = 8.3 Hz, 1H), 6.87 (s, 1H), 6.69 (s, 1H), 5.71 (dd, *J* = 8.8, 2.8 Hz, 1H), 4.06 – 3.95 (m, 4H), 3.81 – 3.71 (m, 1H), 3.23 (t, *J* = 7.1 Hz, 2H), 2.85 (s, 3H), 2.71 – 2.61 (m, 1H), 2.55 (t, *J* = 7.1 Hz, 2H), 2.31 – 2.21 (m, 7H), 2.19 – 2.11 (m, 1H), 1.86 – 1.72 (m, 2H), 1.69 – 1.62 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 151.14, 150.34, 148.73, 143.62, 141.59, 140.85, 137.85, 135.51, 125.50, 122.26, 119.59, 119.43, 116.68, 113.21, 108.65, 102.43, 84.75, 67.04, 57.17, 56.27, 54.33, 45.84, 41.67, 29.24, 25.30, 22.48. LC-MS (ESI-MS): Calculated: 546.28 for $C_{29}H_{36}N_7O_4$ [M+H$^+$]. Found: 546.29.

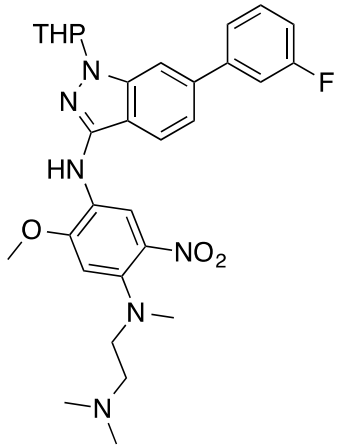


N^1-(2-(dimethylamino)ethyl)-N^4-(6-(3-(dimethylamino)phenyl)-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-3-yl)-5-methoxy-N^1-methyl-2-nitrobenzene-1,4-diamine (18g). According to GM E. Yield: 100%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.02 (s, 1H), 7.69 – 7.61 (m, 2H), 7.36 (d, *J* = 9.5 Hz, 1H), 7.35 – 7.30 (m, 1H), 7.01 (d, *J* = 7.6 Hz, 1H), 6.99 (d, *J* = 2.2 Hz, 1H), 6.88 (s, 1H), 6.78 (dd, *J* = 8.3, 2.2 Hz, 1H), 6.69 (s, 1H), 5.71 (dd, *J* = 8.7, 2.8 Hz, 1H), 4.07 – 3.97 (m, 4H), 3.78 – 3.69 (m, 1H), 3.23 (t, *J* = 7.0 Hz, 2H), 3.02 (s, 6H), 2.86 (s, 3H), 2.70 (ddd, *J* = 13.1, 10.0, 5.4 Hz, 1H), 2.55 (t, *J* = 6.9 Hz, 2H), 2.33 – 2.21 (m, 7H), 2.19 – 2.11 (m, 1H), 1.86 – 1.73 (m, 2H), 1.72 – 1.61 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 151.08, 151.04, 143.60, 142.57, 142.23, 141.35, 141.06, 135.71, 129.48, 125.83, 120.58, 118.73, 116.43, 115.57, 113.05, 112.11, 111.96, 108.39, 102.42, 84.56, 67.04, 57.15, 56.21, 54.36, 45.81, 41.71, 40.81, 29.26, 25.32, 22.61. LC-MS (ESI-MS): Calculated: 588.33 for $C_{32}H_{42}N_7O_4$ [M+H$^+$]. Found: 588.29.

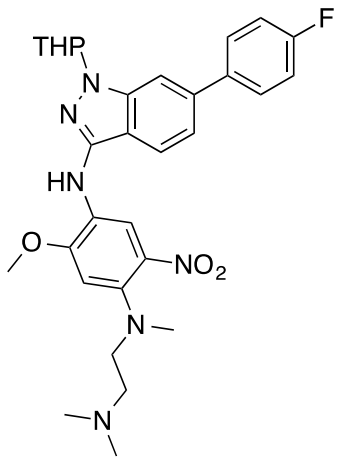


N^1-(2-(dimethylamino)ethyl)-N^4-(6-(4-(dimethylamino)phenyl)-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-3-yl)-5-methoxy-N^1-methyl-2-nitrobenzene-1,4-diamine (18h). According to GM E. Yield: 100%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.01 (s, 1H), 7.64 – 7.55 (m, 4H), 7.34 (dd, *J* = 8.4, 1.2 Hz, 1H), 6.86 (s, 1H), 6.82 (d, *J* = 8.8 Hz, 2H), 6.69 (s, 1H), 5.69 (dd, *J* = 8.7, 2.7 Hz, 1H), 4.06 – 3.97 (m, 4H), 3.78 – 3.70 (m, 1H), 3.23 (t, *J* = 6.8 Hz, 2H), 3.00 (s, 6H), 2.86 (s, 3H), 2.75 – 2.64 (m, 1H), 2.56 (t, *J* = 6.8 Hz, 2H), 2.33 – 2.22 (m, 7H), 2.19 – 2.11 (m, 1H), 1.86 – 1.72 (m, 2H), 1.71 – 1.61 (m, 1H). ^{13}C NMR

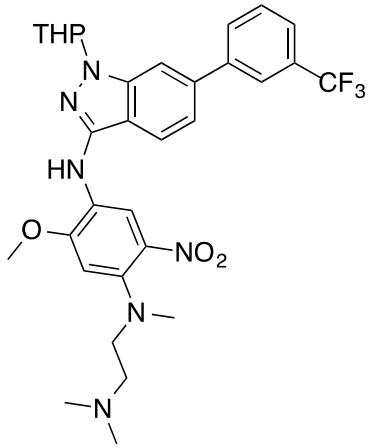
(126 MHz, $CDCl_3$) δ 151.05, 150.26, 143.60, 141.39, 141.20, 135.91, 129.30, 128.30, 126.03, 119.85, 118.73, 114.91, 113.00, 112.79, 106.93, 102.51, 84.54, 67.03, 57.11, 56.23, 54.30, 45.74, 41.81, 40.60, 29.27, 25.36, 22.65. LC-MS (ESI-MS): Calculated: 588.33 for $C_{32}H_{42}N_7O_4$ [M+H^+]. Found: 588.19.



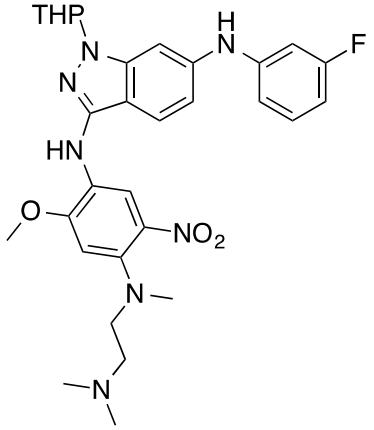
***N*^{1}-(2-(dimethylamino)ethyl)-*N*^{4}-(6-(3-fluorophenyl)-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-3-yl)-5-methoxy-*N*^{1}-methyl-2-nitrobenzene-1,4-diamine (18i).** According to GM E. Yield: 100%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.00 (s, 1H), 7.66 (d, *J* = 8.4 Hz, 1H), 7.61 (s, 1H), 7.46 – 7.38 (m, 2H), 7.35 (d, *J* = 10.0 Hz, 1H), 7.31 (d, *J* = 8.4 Hz, 1H), 7.06 (dt, *J* = 13.6, 4.2 Hz, 1H), 6.87 (s, 1H), 6.69 (s, 1H), 5.70 (dd, *J* = 8.7, 2.7 Hz, 1H), 4.06 – 3.96 (m, 4H), 3.79 – 3.71 (m, 1H), 3.23 (t, *J* = 7.0 Hz, 2H), 2.85 (s, 3H), 2.73 – 2.63 (m, 1H), 2.56 (t, *J* = 7.0 Hz, 2H), 2.33 – 2.20 (m, 7H), 2.19 – 2.10 (m, 1H), 1.86 – 1.71 (m, 2H), 1.71 – 1.62 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.12, 162.16, 151.04, 143.73, 143.67, 143.52, 141.37, 140.88, 139.65, 135.59, 130.28, 130.22, 128.95, 128.38, 125.63, 123.34, 123.31, 119.89, 119.11, 115.90, 114.62, 114.45, 114.37, 114.21, 113.05, 108.34, 102.37, 84.60, 67.00, 57.05, 56.17, 54.22, 45.70, 41.65, 29.18, 25.24, 22.49. LC-MS (ESI-MS): Calculated: 563.28 for $C_{30}H_{36}FN_6O_4$ [M+H^+]. Found: 563.37.



***N*^{1}-(2-(dimethylamino)ethyl)-*N*^{4}-(6-(4-fluorophenyl)-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-3-yl)-5-methoxy-*N*^{1}-methyl-2-nitrobenzene-1,4-diamine (18j).** According to GM E. Yield: 100%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.00 (s, 1H), 7.67 – 7.54 (m, 4H), 7.27 (dd, *J* = 8.4, 1.1 Hz, 1H), 7.16 – 7.10 (m, 2H), 6.86 (s, 1H), 6.68 (s, 1H), 5.69 (dd, *J* = 8.6, 2.7 Hz, 1H), 4.07 – 3.95 (m, 4H), 3.78 – 3.70 (m, 1H), 3.22 (t, *J* = 6.9 Hz, 2H), 2.84 (s, 3H), 2.74 – 2.63 (m, 1H), 2.55 (t, *J* = 6.9 Hz, 2H), 2.30 – 2.22 (m, 7H), 2.19 – 2.10 (m, 1H), 1.86 – 1.71 (m, 2H), 1.70 – 1.60 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 163.65, 161.69, 151.10, 143.59, 141.43, 141.02, 140.03, 137.60, 135.59, 129.32, 129.26, 129.01, 128.44, 125.68, 120.05, 119.08, 115.78, 115.62, 113.09, 108.15, 102.40, 84.62, 67.03, 57.13, 56.22, 54.31, 45.79, 41.67, 29.24, 25.31, 22.56. LC-MS (ESI-MS): Calculated: 563.28 for $C_{30}H_{36}FN_6O_4$ [M+H$^+$]. Found: 563.17.

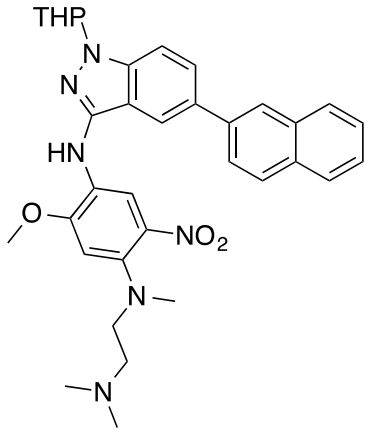


***N*^{1}-(2-(dimethylamino)ethyl)-5-methoxy-*N*^{1}-methyl-2-nitro-*N*^{4}-(1-(tetrahydro-2*H*-pyran-2-yl)-6-(3-(trifluoromethyl)phenyl)-1*H*-indazol-3-yl)benzene-1,4-diamine (18k).** According to GM E. Yield: 99%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.01 (s, 1H), 7.89 (s, 1H), 7.82 (d, *J* = 7.6 Hz, 1H), 7.68 (d, *J* = 8.3 Hz, 1H), 7.65 – 7.60 (m, 2H), 7.57 (t, *J* = 7.7 Hz, 1H), 7.32 (d, *J* = 8.3 Hz, 1H), 6.88 (s, 1H), 6.69 (s, 1H), 5.72 (dd, *J* = 8.6, 2.8 Hz, 1H), 4.04 – 3.98 (m, 4H), 3.80 – 3.72 (m, 1H), 3.23 (t, *J* = 6.9 Hz, 2H), 2.85 (s, 3H), 2.75 – 2.65 (m, 1H), 2.56 (t, *J* = 6.9 Hz, 2H), 2.33 – 2.22 (m, 7H), 2.19 – 2.12 (m, 1H), 1.88 – 1.73 (m, 2H), 1.71 – 1.62 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 151.15, 143.64, 143.37, 142.34, 141.54, 140.98, 139.54, 135.59, 131.38, 131.11, 130.57, 129.36, 129.04, 128.46, 125.62, 125.37, 124.53, 124.50, 124.47, 124.44, 124.29, 124.27, 124.24, 124.21, 123.20, 119.98, 119.38, 116.07, 113.20, 108.55, 102.43, 84.62, 67.05, 57.16, 56.26, 54.34, 45.81, 41.70, 29.27, 25.32, 22.53. LC-MS (ESI-MS): Calculated: 613.28 for $C_{31}H_{36}F_3N_6O_4$ [M+H$^+$]. Found: 613.43.

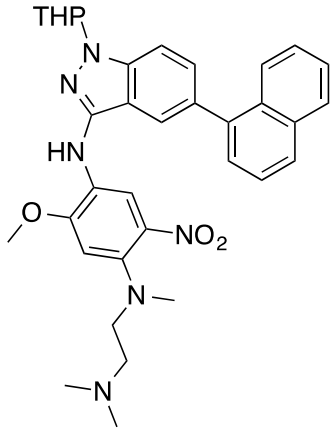


***N*^{3}-(4-((2-(dimethylamino)ethyl)(methyl)amino)-2-methoxy-5-nitrophenyl)-*N*^{6}-(3-fluorophenyl)-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazole-3,6-diamine (18l).** According to GM E. Yield: 100%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.95 (bs, 1H), 7.45 (d, *J* = 8.6 Hz, 1H), 7.19 (dd, *J* = 15.0, 7.7 Hz, 1H), 7.11 (s, 1H), 6.86 – 6.78 (m, 3H), 6.76 (s, 1H), 6.66 (s, 1H), 6.61 (dd, *J* = 8.8, 6.7 Hz, 1H), 6.12 (s, 1H), 5.51 (dd, *J* = 8.8, 2.7 Hz, 1H), 4.02 – 3.98 (m, 1H), 3.98 (s, 3H), 3.73 – 3.64 (m, 1H), 3.21 (t, *J* = 7.1 Hz, 2H), 2.84 (s, 3H),

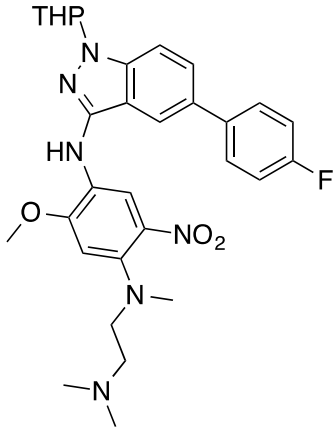
2.67 – 2.57 (m, 1H), 2.54 (t, *J* = 7.1 Hz, 2H), 2.26 (s, 6H), 2.22 (dd, *J* = 9.6, 4.1 Hz, 1H), 2.14 – 2.07 (m, 1H), 1.80 – 1.67 (m, 2H), 1.67 – 1.57 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.80, 162.86, 151.10, 145.12, 145.04, 143.73, 142.33, 141.79, 141.37, 135.70, 130.63, 130.55, 125.87, 119.72, 113.89, 113.32, 113.05, 112.01, 107.71, 107.53, 104.48, 104.29, 102.41, 97.55, 84.62, 77.16, 67.02, 57.17, 56.21, 54.38, 45.83, 41.75, 29.78, 29.19, 25.32, 22.57. LC-MS (ESI-MS): 578.29 Calculated: for [M+H$^+$]. Found: 578.36.



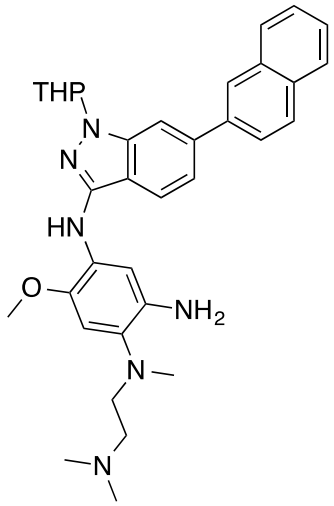
***N*^{1}-(2-(dimethylamino)ethyl)-5-methoxy-*N*^{1}-methyl-*N*^{4}-(5-(naphthalen-2-yl)-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-3-yl)-2-nitrobenzene-1,4-diamine (19a).** According to GM E. Yield: 100%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.05 (s, 1H), 8.06 (s, 1H), 7.96 – 7.89 (m, 2H), 7.89 – 7.84 (m, 2H), 7.82 – 7.75 (m, 2H), 7.58 (d, *J* = 8.7 Hz, 1H), 7.54 – 7.45 (m, 2H), 6.93 (s, 1H), 6.69 (s, 1H), 5.68 (dd, *J* = 8.6, 2.6 Hz, 1H), 4.08 – 3.98 (m, 4H), 3.79 – 3.72 (m, 1H), 3.23 (t, *J* = 7.1 Hz, 2H), 2.85 (s, 3H), 2.75 – 2.63 (m, 1H), 2.55 (t, *J* = 7.1 Hz, 2H), 2.33 – 2.21 (m, 7H), 2.21 – 2.10 (m, 1H), 1.87 – 1.72 (m, 2H), 1.69 (d, *J* = 10.3 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 151.16, 144.02, 141.51, 139.98, 138.82, 135.60, 133.87, 133.67, 132.48, 128.53, 128.15, 127.75, 126.43, 125.96, 125.87, 125.78, 125.64, 117.26, 117.16, 113.24, 110.52, 102.40, 84.86, 67.06, 57.22, 56.25, 54.42, 45.89, 41.68, 29.26, 25.35, 22.56. LC-MS (ESI-MS): Calculated: 595.30 for $C_{34}H_{39}N_6O_4$ [M+H$^+$]. Found: 595.32.



***N*^{1}-(2-(dimethylamino)ethyl)-5-methoxy-*N*^{1}-methyl-*N*^{4}-(5-(naphthalen-1-yl)-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-3-yl)-2-nitrobenzene-1,4-diamine (19b).** According to GM E. Yield: 100%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.05 (s, 1H), 7.94 – 7.84 (m, 3H), 7.71 (s, 1H), 7.60 (d, *J* = 8.5 Hz, 1H), 7.57 – 7.40 (m, 5H), 6.88 (s, 1H), 6.67 (s, 1H), 5.72 (dd, *J* = 8.8, 2.7 Hz, 1H), 4.10 – 4.03 (m, 1H), 3.94 (s, 3H), 3.84 – 3.72 (m, 1H), 3.23 (t, *J* = 7.0 Hz, 2H), 2.85 (s, 3H), 2.78 – 2.67 (m, 1H), 2.54 (t, *J* = 7.0 Hz, 2H), 2.33 – 2.23 (m, 7H), 2.23 – 2.14 (m, 1H), 1.88 – 1.74 (m, 2H), 1.68 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.54, 151.08, 143.82, 141.44, 140.20, 139.79, 135.58, 133.87, 132.82, 132.12, 130.06, 128.32, 127.62, 127.35, 126.15, 125.84, 125.68, 125.42, 119.71, 116.66, 113.06, 109.78, 102.38, 84.90, 67.14, 57.14, 56.13, 54.33, 45.80, 41.67, 29.28, 25.31, 22.60. LC-MS (ESI-MS): Calculated: 595.30 for $C_{34}H_{39}N_6O_4$ [M+H$^+$]. Found: 595.33.

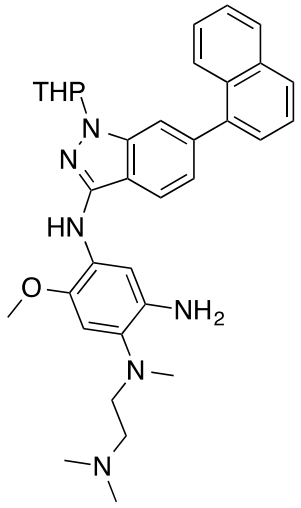


N^1-(2-(dimethylamino)ethyl)-N^4-(5-(4-fluorophenyl)-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-3-yl)-5-methoxy-N^1-methyl-2-nitrobenzene-1,4-diamine (19c). According to GM E. Yield: 100%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.00 (s, 1H), 7.69 (s, 1H), 7.61 – 7.48 (m, 4H), 7.15 – 7.07 (m, 2H), 6.87 (s, 1H), 6.67 (s, 1H), 5.68 – 5.61 (m, 1H), 4.03 – 3.93 (m, 4H), 3.77 – 3.67 (m, 1H), 3.21 (t, *J* = 7.0 Hz, 2H), 2.82 (s, 3H), 2.74 – 2.59 (m, 1H), 2.55 (t, *J* = 7.1 Hz, 2H), 2.32 – 2.19 (m, 7H), 2.18 – 2.08 (m, 1H), 1.84 – 1.69 (m, 2H), 1.69 – 1.59 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 163.25, 161.29, 151.13, 143.89, 141.44, 139.83, 137.60, 137.58, 135.55, 132.79, 128.90, 128.83, 127.34, 125.62, 117.00, 116.83, 115.74, 115.57, 113.12, 110.42, 102.36, 84.83, 67.05, 57.05, 56.22, 54.21, 45.73, 41.68, 29.23, 25.30, 22.54. LC-MS (ESI-MS): Calculated: 563.28 for [M+H$^+$]. Found: 563.36.



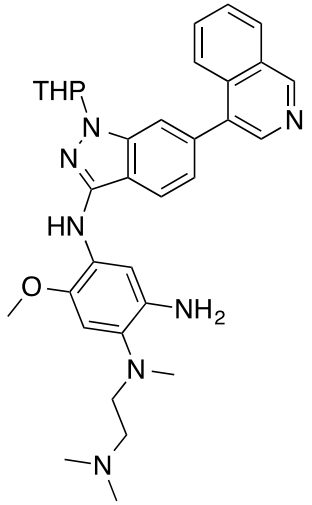
N^1-(2-(dimethylamino)ethyl)-5-methoxy-N^1-methyl-N^4-(6-(naphthalen-2-yl)-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-3-yl)benzene-1,2,4-triamine (20a). General method (GM) F: Compound **18a** (150 mg, 0.269 mmol) and Pd/C 10% w/w (32 mg) were suspended in EtOH (8 mL) and the mixture stirred under Argon atmosphere at 90 °C. When refluxing was established ammonium formate (85 mg, 1.345 mmol) was added and the mixture stirred at reflux for 10 minutes. The mixture was cooled down, diluted with EtOAc and filtered through filter papers. The solution was then transferred into a separatory funnel, washed twice

with a saturated solution of $NaHCO_3$ and the organic layer was then dried over anhydrous Na_2SO_4 and volatiles removed under reduced pressure. Silica gel chromatography (DCM/MeOH 96:4 + 1% NH_3) led to 125 mg (0.237 mmol, 88%) of the desired product as an off-white solid. ^{1}H NMR (500 MHz, DMSO) δ 8.34 (s, 1H), 8.09 – 7.96 (m, 6H), 7.61 – 7.51 (m, 5H), 6.77 (s, 1H), 5.89 (dd, *J* = 9.8, 2.0 Hz, 1H), 3.96 – 3.88 (m, 1H), 3.88 – 3.74 (m, 6H), 2.91 (t, *J* = 6.5 Hz, 2H), 2.63 – 2.54 (m, 4H), 2.47 (t, *J* = 6.5 Hz, 2H), 2.25 (s, 6H), 2.13 – 2.05 (m, 1H), 2.02 – 1.96 (m, 1H), 1.83 – 1.73 (m, 1H), 1.69 – 1.54 (m, 2H). ^{13}C NMR (126 MHz, DMSO) δ 144.54, 141.05, 139.42, 139.09, 137.79, 137.25, 133.30, 132.31, 130.29, 128.55, 128.39, 128.21, 127.50, 126.43, 126.17, 125.77, 125.59, 120.72, 119.13, 115.64, 107.69, 105.63, 104.33, 83.40, 66.51, 56.93, 56.76, 53.69, 45.16, 42.07, 39.52, 29.07, 24.91, 22.68. LC-MS (ESI-MS): Calculated: 565.33 for $C_{34}H_{41}N_6O_2$ [M+H$^+$]. Found: 565.62.



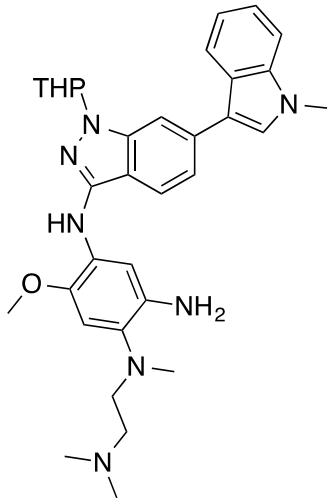
***N*^{1}-(2-(dimethylamino)ethyl)-5-methoxy-*N*^{1}-methyl-*N*^{4}-(6-(naphthalen-1-yl)-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-3-yl)benzene-1,2,4-triamine (20b).** According to GM F. Yield: 81%. ^{1}H NMR (500 MHz, DMSO) δ 8.06 – 7.96 (m, 3H), 7.82 (d, *J* = 8.4 Hz, 1H), 7.65 (s, 1H), 7.64 – 7.59 (m, 1H), 7.58 – 7.46 (m, 5H), 7.16 (dd, *J* = 8.2, 1.1 Hz, 1H), 6.76 (s, 1H), 5.80 – 5.71 (m, 1H), 4.65 (s, 2H), 3.93 – 3.85 (m, 1H), 3.81 (s, 3H), 3.68 (td, *J* = 11.2, 2.6 Hz, 1H), 2.87 (t, *J* = 6.7 Hz, 2H), 2.60 (s, 3H), 2.57 – 2.51 (m,

1H), 2.35 (t, *J* = 6.7 Hz, 2H), 2.18 (s, 6H), 2.09 – 2.01 (m, 1H), 2.01 – 1.93 (m, 1H), 1.78 – 1.66 (m, 1H), 1.64 – 1.48 (m, 2H). ^{13}C NMR (126 MHz, DMSO) δ 144.61, 140.42, 139.76, 139.42, 139.04, 137.22, 133.34, 131.05, 130.44, 128.45, 128.29, 127.69, 127.08, 126.34, 125.90, 125.44, 121.71, 119.96, 119.90, 115.53, 110.46, 105.65, 104.37, 83.66, 66.44, 57.37, 56.77, 54.20, 45.59, 42.04, 29.02, 24.84, 22.56. LC-MS (ESI-MS): Calculated: 565.33 for $C_{34}H_{41}N_6O_2$ [M+H$^+$]. Found: 565.12.

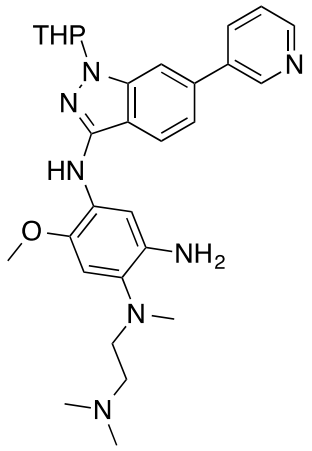


***N*^{1}-(2-(dimethylamino)ethyl)-*N*^{4}-(6-(isoquinolin-4-yl)-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-3-yl)-5-methoxy-*N*^{1}-methylbenzene-1,2,4-triamine (20c).** According to GM F. Yield: 88%. ^{1}H NMR (500 MHz, DMSO) δ 9.38 (s, 1H), 8.53 (s, 1H), 8.25 (d, *J* = 8.0 Hz, 1H), 8.06 (d, *J* = 8.2 Hz, 1H), 7.88 (d, *J* = 8.4 Hz, 1H), 7.80 (dd, *J* = 11.2, 4.0 Hz, 1H), 7.77 – 7.71 (m, 2H), 7.56 (s, 1H), 7.54 (s, 1H), 7.22 (dd, *J* = 8.2, 0.9 Hz, 1H), 6.76 (s, 1H), 5.78 (dd, *J* = 9.8, 1.8 Hz, 1H), 4.63 (bs, 2H), 3.91 – 3.84 (m, 1H), 3.81 (s, 3H), 3.74 – 3.64 (m, 1H), 2.86 (t, *J* = 6.7 Hz, 2H), 2.60 (s, 3H), 2.57 – 2.52 (m, 1H), 2.33 (t, *J* = 6.7 Hz, 2H), 2.16 (s, 6H), 2.08 – 2.01 (m, 1H), 2.01 – 1.94 (m, 1H), 1.77 – 1.66 (m, 1H), 1.64 – 1.56 (m, 1H), 1.56 – 1.50 (m, 1H). ^{13}C NMR (126 MHz, DMSO) δ 152.04, 144.68, 142.63, 140.46, 139.47, 137.22, 135.36, 133.42, 132.81, 131.09, 130.54, 128.36, 128.04, 127.95, 127.50, 124.21, 121.61, 120.32, 115.86, 110.78,

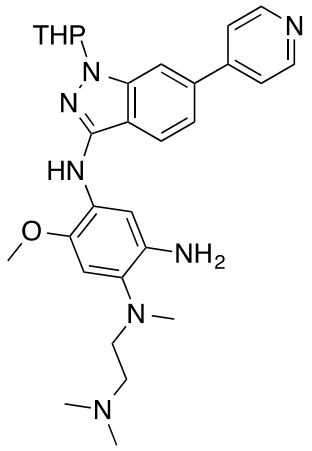
105.65, 104.45, 83.63, 66.46, 57.45, 56.78, 54.28, 45.66, 42.03, 29.00, 24.82, 22.58. LC-MS (ESI-MS): Calculated: 566.32 for $C_{33}H_{40}N_7O_2$ [M+H$^+$]. Found: 566.40.



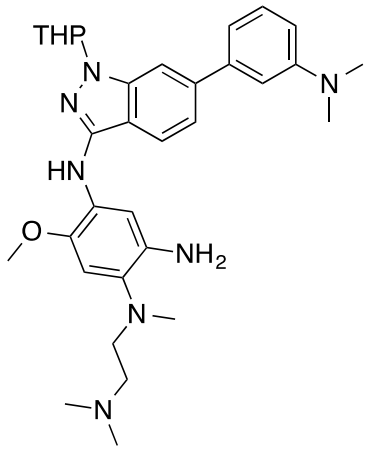
***N*^{1}-(2-(dimethylamino)ethyl)-5-methoxy-*N*^{1}-methyl-*N*^{4}-(6-(1-methyl-1*H*-indol-3-yl)-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-3-yl)benzene-1,2,4-triamine (20d).** According to GM F. Yield: 50%. 1H NMR (500 MHz, $CDCl_3$) δ 7.99 (d, *J* = 7.9 Hz, 1H), 7.71 (d, *J* = 5.0 Hz, 2H), 7.66 (d, *J* = 8.3 Hz, 1H), 7.41 – 7.38 (m, 2H), 7.35 – 7.28 (m, 2H), 7.23 (t, *J* = 7.4 Hz, 1H), 6.87 (s, 1H), 6.71 (s, 1H), 5.67 (dd, *J* = 9.1, 2.3 Hz, 1H), 4.10 – 4.02 (m, 1H), 3.89 (s, 3H), 3.87 (s, 3H), 3.78 – 3.71 (m, 1H), 3.02 (t, *J* = 6.5 Hz, 2H), 2.71 – 2.61 (m, 4H), 2.49 (t, *J* = 6.5 Hz, 2H), 2.35 (s, 6H), 2.26 – 2.18 (m, 1H), 2.15 – 2.09 (m, 1H), 1.85 – 1.71 (m, 2H), 1.70 – 1.60 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 144.62, 141.45, 140.25, 137.67, 137.28, 135.10, 130.22, 129.77, 127.22, 126.43, 122.22, 120.61, 120.18, 120.00, 119.49, 117.09, 115.47, 109.74, 107.73, 105.06, 104.22, 84.98, 67.35, 57.68, 56.90, 45.66, 43.45, 33.04, 29.82, 29.54, 25.41, 22.93. LC-MS (ESI-MS): Calculated: 568.34 for $C_{33}H_{42}N_7O_2$ [M+H$^+$]. Found: 568.24.



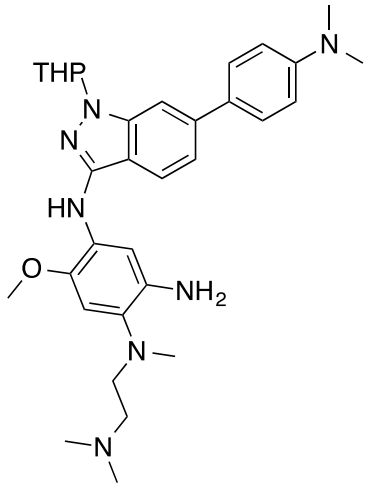
N^1-(2-(dimethylamino)ethyl)-5-methoxy-N^1-methyl-N^4-(6-(pyridin-3-yl)-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-3-yl)benzene-1,2,4-triamine (20e). According to GM F. Yield: 81%. ^{1}H NMR (500 MHz, DMSO) δ 9.01 (d, *J* = 1.7 Hz, 1H), 8.61 (dd, *J* = 4.7, 1.4 Hz, 1H), 8.18 (dt, *J* = 3.9, 2.0 Hz, 1H), 8.01 (d, *J* = 8.4 Hz, 1H), 7.94 (s, 1H), 7.56 – 7.48 (m, 3H), 7.43 (dd, *J* = 8.4, 1.2 Hz, 1H), 6.75 (s, 1H), 5.84 (dd, *J* = 9.8, 1.9 Hz, 1H), 4.57 (bs, 2H), 3.94 – 3.87 (m, 1H), 3.80 – 3.73 (m, 4H), 2.85 (t, *J* = 6.7 Hz, 2H), 2.59 (s, 3H), 2.57 – 2.52 (m, 1H), 2.32 (t, *J* = 6.7 Hz, 2H), 2.16 (s, 6H), 2.10 – 2.03 (m, 1H), 2.00 – 1.93 (m, 1H), 1.81 – 1.69 (m, 1H), 1.69 – 1.55 (m, 2H). ^{13}C NMR (126 MHz, DMSO) δ 148.53, 148.07, 144.59, 140.86, 139.44, 137.17, 136.04, 135.86, 134.56, 130.50, 128.30, 123.78, 121.00, 118.63, 115.90, 107.78, 105.59, 104.41, 83.42, 66.52, 57.45, 56.73, 54.28, 45.67, 42.02, 29.00, 24.84, 22.69. LC-MS (ESI-MS): Calculated: 516.31 for $C_{29}H_{38}N_7O_2$ [M+H$^+$]. Found: 516.33.



N^1-(2-(dimethylamino)ethyl)-5-methoxy-N^1-methyl-N^4-(6-(pyridin-4-yl)-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-3-yl)benzene-1,2,4-triamine (20f). According to GM F. Yield: 85%. ^{1}H NMR (500 MHz, DMSO) δ 8.67 (dd, *J* = 4.6, 1.4 Hz, 2H), 8.06 – 8.01 (m, 2H), 7.82 (dd, *J* = 4.6, 1.5 Hz, 2H), 7.55 (s, 1H), 7.52 (s, 1H), 7.51 – 7.47 (m, 1H), 6.75 (s, 1H), 5.86 (dd, *J* = 9.9, 2.1 Hz, 1H), 4.56 (bs, 2H), 3.96 – 3.88 (m, 1H), 3.80 (s, 3H), 3.78 – 3.74 (m, 1H), 2.85 (t, *J* = 6.7 Hz, 2H), 2.59 (s, 3H), 2.58 – 2.53 (m, 1H), 2.32 (t, *J* = 6.7 Hz, 2H), 2.16 (s, 6H), 2.12 – 2.04 (m, 1H), 2.01 – 1.94 (m, 1H), 1.82 – 1.71 (m, 1H), 1.68 – 1.54 (m, 2H). ^{13}C NMR (126 MHz, DMSO) δ 150.15, 147.33, 144.62, 140.75, 139.47, 137.18, 136.11, 130.55, 128.27, 121.68, 121.10, 118.28, 116.57, 107.93, 105.58, 104.44, 83.43, 66.52, 57.43, 56.72, 54.26, 45.64, 42.01, 29.01, 24.85, 22.66. LC-MS (ESI-MS): Calculated: 516.31 for $C_{29}H_{38}N_7O_2$ [M+H$^+$]. Found: 516.35.

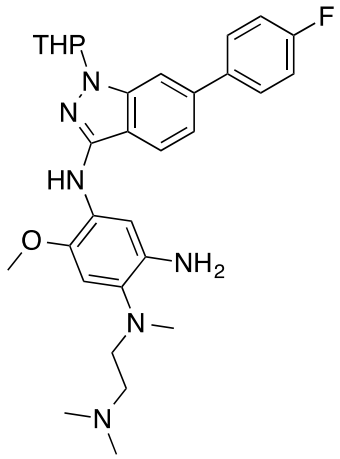


***N*^{1}-(2-(dimethylamino)ethyl)-*N*^{4}-(6-(3-(dimethylamino)phenyl)-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-3-yl)-5-methoxy-*N*^{1}-methylbenzene-1,2,4-triamine (20g).** According to GM F. Yield: 86%. ^{1}H NMR (500 MHz, DMSO) δ 7.91 (d, *J* = 8.4 Hz, 1H), 7.76 (s, 1H), 7.49 (s, 1H), 7.44 (s, 1H), 7.35 (d, *J* = 8.4 Hz, 1H), 7.29 (t, *J* = 8.0 Hz, 1H), 7.04 – 6.98 (m, 2H), 6.80 – 6.72 (m, 2H), 5.81 (dd, *J* = 9.8, 2.0 Hz, 1H), 4.56 (bs, 2H), 3.93 – 3.87 (m, 1H), 3.83 – 3.71 (m, 4H), 2.98 (s, 6H), 2.85 (t, *J* = 6.7 Hz, 2H), 2.59 (s, 3H), 2.57 – 2.52 (m, 1H), 2.32 (t, *J* = 6.7 Hz, 2H), 2.16 (s, 6H), 2.11 – 2.03 (m, 1H), 2.00 – 1.93 (m, 1H), 1.82 – 1.72 (m, 1H), 1.67 – 1.53 (m, 2H). ^{13}C NMR (126 MHz, DMSO) δ 150.83, 144.46, 141.39, 140.92, 140.50, 139.35, 137.19, 130.38, 129.32, 128.44, 120.32, 119.18, 115.51, 115.43, 111.72, 111.21, 107.43, 105.56, 104.28, 83.38, 66.39, 57.45, 56.72, 54.30, 45.67, 42.05, 40.26, 28.98, 24.88, 22.58. LC-MS (ESI-MS): Calculated: 558.36 for $C_{32}H_{44}N_7O_2$ [M+H$^+$]. Found: 558.37.

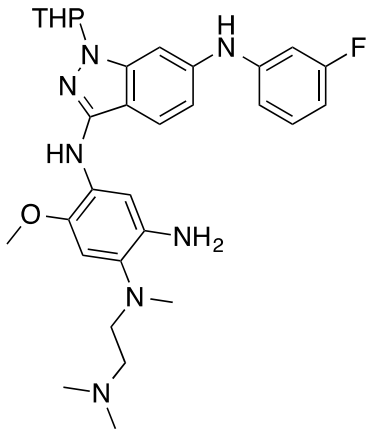


***N*^{1}-(2-(dimethylamino)ethyl)-*N*^{4}-(6-(4-(dimethylamino)phenyl)-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-3-yl)-5-methoxy-*N*^{1}-methylbenzene-1,2,4-triamine (20h).** According to GM F. Yield: 86%. ^{1}H NMR (600 MHz, MeOD) δ 7.70 (s, 1H), 7.59 – 7.51 (m, 2H), 7.50 – 7.43 (m, 2H), 7.21 (d, *J* = 8.4 Hz, 1H), 6.76 – 6.67 (m, 4H), 5.66 – 5.57 (m, 1H), 3.94 – 3.87 (m, 1H), 3.81 (s, 3H), 3.73 – 3.64 (m, 1H), 2.92 (t, *J* = 6.8 Hz, 2H), 2.85 (s, 6H), 2.60 – 2.51 (m, 4H), 2.35 (t, *J* = 6.7 Hz, 2H), 2.22 – 2.14 (m, 6H), 2.08 –

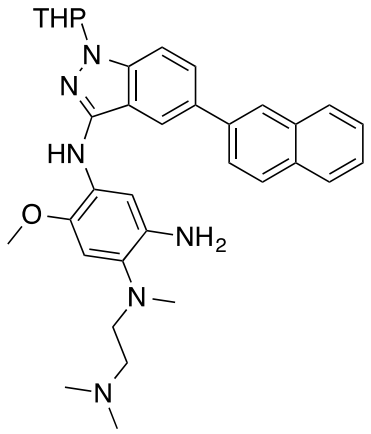
2.00 (m, 1H), 1.97 – 1.90 (m, 1H), 1.76 – 1.65 (m, 1H), 1.65 – 1.57 (m, 1H), 1.57 – 1.47 (m, 1H). ^{13}C NMR (151 MHz, MeOD) δ 151.65, 145.95, 142.84, 142.39, 142.25, 137.60, 132.40, 130.79, 130.33, 128.97, 120.54, 120.48, 116.53, 114.03, 107.16, 106.25, 105.84, 85.80, 68.38, 58.40, 57.04, 55.38, 45.71, 43.93, 40.80, 30.58, 26.38, 23.94. LC-MS (ESI-MS): Calculated: 558.36 for $C_{32}H_{44}N_7O_2$ [M+H$^+$]. Found: 558.32.



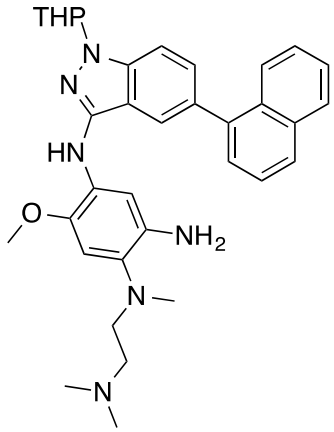
***N*^{1}-(2-(dimethylamino)ethyl)-*N*^{4}-(6-(4-fluorophenyl)-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-3-yl)-5-methoxy-*N*^{1}-methylbenzene-1,2,4-triamine (20j).** According to GM F. Yield: 75%. ^{1}H NMR (600 MHz, DMSO) δ 7.96 (d, *J* = 8.4 Hz, 1H), 7.84 – 7.78 (m, 3H), 7.52 – 7.48 (m, 2H), 7.39 – 7.30 (m, 3H), 6.74 (s, 1H), 5.82 (dd, *J* = 9.9, 1.5 Hz, 1H), 4.65 (bs, 2H), 3.92 – 3.87 (m, 1H), 3.81 – 3.72 (m, 4H), 2.85 (t, *J* = 6.6 Hz, 2H), 2.59 (s, 3H), 2.57 – 2.52 (m, 1H), 2.33 (t, *J* = 6.5 Hz, 2H), 2.17 (s, 6H), 2.09 – 2.03 (m, 1H), 1.99 – 1.93 (m, 1H), 1.78 – 1.73 (m, 1H), 1.64 – 1.54 (m, 2H). ^{13}C NMR (151 MHz, DMSO) δ 162.81, 161.17, 144.58, 140.95, 139.40, 138.27, 137.22, 136.97, 130.42, 129.27, 129.22, 128.37, 128.29, 120.79, 118.81, 115.78, 115.64, 115.54, 107.40, 105.53, 104.38, 83.43, 66.57, 57.41, 56.73, 54.25, 45.66, 42.08, 29.05, 25.15, 22.76. LC-MS (ESI-MS): Calculated: 533.30 for $C_{30}H_{38}FN_6O_2$ [M+H$^+$]. Found: 533.39.



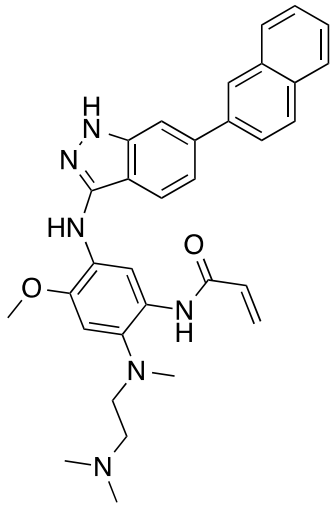
***N*^{1}-(2-(dimethylamino)ethyl)-*N*^{4}-(6-((3-fluorophenyl)amino)-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-3-yl)-5-methoxy-*N*^{1}-methylbenzene-1,2,4-triamine (20l).** According to GM F. Yield: 100%. ^{1}H NMR (500 MHz, DMSO) δ 8.62 (s, 1H), 7.75 (d, *J* = 8.6 Hz, 1H), 7.49 (s, 1H), 7.28 (dd, *J* = 15.3, 8.1 Hz, 2H), 7.17 (d, *J* = 1.3 Hz, 1H), 6.95 (dd, *J* = 8.2, 1.4 Hz, 1H), 6.93 – 6.83 (m, 2H), 6.74 (s, 1H), 6.63 (td, *J* = 8.4, 2.0 Hz, 1H), 5.58 (dd, *J* = 9.6, 2.3 Hz, 1H), 4.56 (s, 2H), 3.89 (d, *J* = 11.1 Hz, 1H), 3.79 (s, 3H), 3.72 – 3.62 (m, 1H), 2.85 (t, *J* = 6.7 Hz, 2H), 2.59 (s, 3H), 2.50 – 2.41 (m, 1H), 2.32 (t, *J* = 6.7 Hz, 2H), 2.17 (s, 6H), 2.11 – 2.01 (m, 1H), 2.01 – 1.92 (m, 1H), 1.75 (d, *J* = 8.7 Hz, 1H), 1.59 (d, *J* = 10.0 Hz, 2H). ^{13}C NMR (126 MHz, DMSO) δ 145.80, 145.73, 145.64, 144.39, 142.30, 141.95, 141.48, 141.45, 137.18, 134.78, 132.21, 130.76, 130.20, 128.50, 122.33, 120.86, 112.87, 112.32, 111.39, 105.86, 105.69, 105.50, 104.15, 102.66, 102.46, 96.15, 83.84, 66.28, 57.44, 56.71, 45.64, 42.08, 39.52, 28.85, 24.90, 22.40. LC-MS (ESI-MS): Calculated: 548.31 for [M+H$^+$]. Found: 548.38.



***N*^{1}-(2-(dimethylamino)ethyl)-5-methoxy-*N*^{1}-methyl-*N*^{4}-(5-(naphthalen-2-yl)-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-3-yl)benzene-1,2,4-triamine (21a).** According to GM F. Yield: 87%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.06 (s, 1H), 7.97 – 7.89 (m, 3H), 7.87 (d, *J* = 7.9 Hz, 1H), 7.82 – 7.73 (m, 3H), 7.57 (d, *J* = 8.7 Hz, 1H), 7.55 – 7.44 (m, 2H), 6.95 (s, 1H), 6.72 (s, 1H), 5.66 (dd, *J* = 9.1, 2.3 Hz, 1H), 4.13 – 4.02 (m, 1H), 3.90 (s, 3H), 3.80 – 3.72 (m, 1H), 3.00 (t, *J* = 6.7 Hz, 2H), 2.68 (s, 3H), 2.66 – 2.59 (m, 1H), 2.45 (t, *J* = 6.7 Hz, 2H), 2.31 (s, *J* = 16.2 Hz, 6H), 2.26 – 2.19 (m, 1H), 2.16 – 2.09 (m, 1H), 1.83 – 1.72 (m, 2H), 1.71 – 1.63 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 144.84, 140.14, 139.88, 138.84, 137.10, 133.78, 133.33, 132.36, 130.47, 129.25, 128.40, 128.06, 127.65, 127.44, 126.30, 125.93, 125.72, 125.65, 117.76, 117.64, 110.26, 104.89, 104.27, 85.10, 67.28, 57.71, 56.76, 54.96, 45.72, 43.24, 29.41, 25.25, 22.75. LC-MS (ESI-MS): Calculated: 565.33 for $C_{34}H_{41}N_6O_2$ [M+H$^+$]. Found: 565.37.

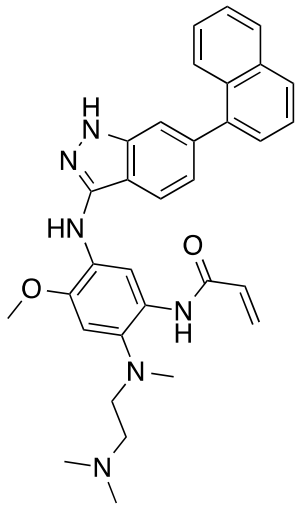


***N*^{1}-(2-(dimethylamino)ethyl)-5-methoxy-*N*^{1}-methyl-*N*^{4}-(5-(naphthalen-1-yl)-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-3-yl)benzene-1,2,4-triamine (21b).** According to GM F. Yield: 90%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.95 – 7.85 (m, 3H), 7.82 (s, 1H), 7.72 (s, 1H), 7.61 – 7.41 (m, 6H), 6.90 (s, 1H), 6.68 (s, 1H), 5.70 (dd, *J* = 9.1, 2.1 Hz, 1H), 4.17 – 4.06 (m, 1H), 4.06 – 3.69 (m, 6H), 2.98 (t, *J* = 6.7 Hz, 2H), 2.75 – 2.59 (m, 4H), 2.44 (t, *J* = 6.6 Hz, 2H), 2.35 – 2.20 (m, 7H), 2.20 – 2.11 (m, 1H), 1.89 – 1.73 (m, 2H), 1.73 – 1.64 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 144.80, 140.41, 140.17, 139.80, 137.16, 133.93, 132.56, 132.22, 130.51, 129.92, 129.27, 128.36, 127.60, 127.40, 126.29, 126.17, 125.87, 125.48, 120.17, 117.33, 109.61, 104.87, 104.32, 85.28, 67.49, 57.83, 56.71, 55.10, 45.84, 43.34, 29.57, 25.38, 22.95. LC-MS (ESI-MS): Calculated: 565.33 for $C_{34}H_{41}N_6O_2$ [M+H$^+$]. Found: 565.41.

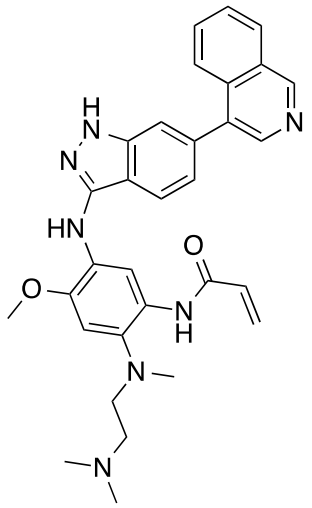


***N*-(2-((2-(dimethylamino)ethyl)(methyl)amino)-4-methoxy-5-((6-(naphthalen-2-yl)-1*H*-indazol-3-yl)amino)phenyl)acrylamide (6a).** General method (GM) G: Compound **20a** (100 mg, 0.177 mmol) and *N*-ethyl-*N*-isopropylpropan-2-amine (0.158 mL, 0.885 mmol) were dissolved in dry THF (4 mL) and stirred at 0 °C under inert atmosphere for 5 minutes. A solution of acryloyl chloride (0.014 mL, 0.177 mmol) in dry THF (1 mL) was then added dropwise under vigorous stirring and the reaction allowed to stir at room temperature for 1 h. The reaction was diluted with a mixture of DCM/MeOH 9:1 (50 mL) and the organic

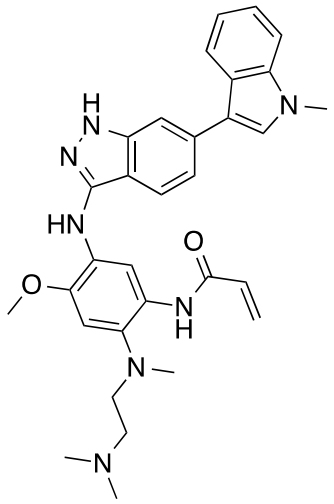
phase washed with H_2O (30 mL), a saturated solution of $NaHCO_3$ (30 mL) and brine (10 mL). The organic phase was collected, dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to give a pale yellow solid. The crude was re-dissolved in DCM (4 mL), placed at 0 °C on ice and a solution of TFA 50% in DCM (4 mL) was slowly added dropwise under stirring. The mixture was allowed to stir at room temperature for 1 h when the starting material was completely deprotected. The reaction was diluted with a mixture of DCM/MeOH 9:1 (60 mL) and washed with a saturated solution of $NaHCO_3$ (50 mL) in a separatory funnel. The organic layer was dried over anhydrous Na_2SO_4 and concentrated *in vacuo*, the following purification by silica gel chromatography (DCM/MeOH 95:5 + 0.8% NH_3) led to 48 mg (0.090 mmol, 50%) of the desired compound as an off-white solid. ^{1}H NMR (500 MHz, DMSO) δ 12.24 (s, 1H), 10.12 (s, 1H), 8.91 (s, 1H), 8.30 (s, 1H), 8.07 – 7.99 (m, 3H), 7.96 (d, *J* = 7.7 Hz, 1H), 7.92 (dd, *J* = 8.6, 1.3 Hz, 1H), 7.74 (s, 1H), 7.60 (s, 1H), 7.58 – 7.51 (m, 2H), 7.49 (d, *J* = 8.4 Hz, 1H), 6.98 (s, 1H), 6.35 (dd, *J* = 16.9, 10.1 Hz, 1H), 6.21 (dd, *J* = 16.9, 1.7 Hz, 1H), 5.71 (dd, *J* = 10.1, 1.7 Hz, 1H), 3.91 (s, 3H), 2.86 (t, *J* = 5.6 Hz, 2H), 2.68 (s, 3H), 2.25 (t, *J* = 5.5 Hz, 2H), 2.20 (s, 6H). ^{13}C NMR (126 MHz, DMSO) δ 162.99, 145.28, 144.95, 142.34, 139.53, 138.88, 135.30, 134.24, 133.29, 133.12, 129.91, 129.30, 129.10, 129.05, 128.34, 127.26, 126.97, 126.71, 126.54, 126.38, 121.47, 119.23, 115.21, 109.91, 108.49, 105.97, 57.76, 56.90, 56.55, 45.89, 44.00. HRMS (ESI-MS): Calculated: 535.28160 for $C_{32}H_{35}N_6O_2$ [M+H$^+$]. Found: 535.28125.



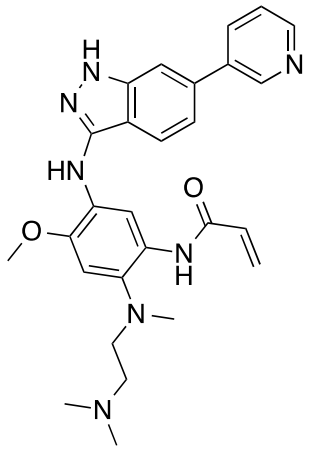
***N*-(2-((2-(dimethylamino)ethyl)(methyl)amino)-4-methoxy-5-((6-(naphthalen-1-yl)-1*H*-indazol-3-yl)amino)phenyl)acrylamide (6b).** According to GM G. Yield: 53%. ^{1}H NMR (500 MHz, DMSO) δ 12.22 (s, 1H), 10.14 (s, 1H), 8.92 (s, 1H), 8.02 (d, *J* = 3.9 Hz, 1H), 8.00 (d, *J* = 3.6 Hz, 1H), 7.96 (d, *J* = 8.2 Hz, 1H), 7.87 (d, *J* = 8.4 Hz, 1H), 7.66 – 7.46 (m, 5H), 7.43 (s, 1H), 7.12 (dd, *J* = 8.3, 1.1 Hz, 1H), 6.99 (s, 1H), 6.36 (dd, *J* = 16.9, 10.1 Hz, 1H), 6.22 (dd, *J* = 16.9, 1.9 Hz, 1H), 5.72 (dd, *J* = 10.1, 1.7 Hz, 1H), 3.92 (s, 3H), 2.86 (t, *J* = 5.6 Hz, 2H), 2.68 (s, 3H), 2.25 (t, *J* = 5.3 Hz, 2H), 2.19 (s, 6H). ^{13}C NMR (126 MHz, DMSO) δ 162.99, 145.39, 145.00, 141.81, 140.78, 139.37, 135.33, 134.31, 133.30, 131.93, 129.98, 129.20, 129.10, 128.49, 127.91, 127.18, 126.77, 126.69, 126.40, 126.31, 125.73, 121.88, 120.72, 115.10, 111.27, 109.98, 106.01, 57.77, 56.92, 56.59, 45.89, 44.01. HRMS (ESI-MS): Calculated: 535.28160 for $C_{32}H_{35}N_6O_2$ [M+H$^+$], Found: 535.28178.



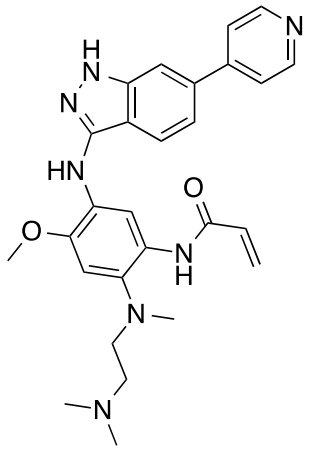
***N*-(2-((2-(dimethylamino)ethyl)(methyl)amino)-5-((6-(isoquinolin-4-yl)-1*H*-indazol-3-yl)amino)-4-methoxyphenyl)acrylamide (6c).** According to GM G. Yield: 39%. ^{1}H NMR (600 MHz, DMSO) δ 12.29 (s, 1H), 10.14 (s, 1H), 9.36 (s, 1H), 8.89 (s, 1H), 8.52 (s, 1H), 8.24 (d, *J* = 8.1 Hz, 1H), 8.06 (d, *J* = 8.2 Hz, 1H), 7.91 (d, *J* = 8.4 Hz, 1H), 7.80 (t, *J* = 7.5 Hz, 1H), 7.74 (t, *J* = 7.4 Hz, 1H), 7.66 (s, 1H), 7.50 (s, 1H), 7.16 (d, *J* = 8.2 Hz, 1H), 6.99 (s, 1H), 6.37 (dd, *J* = 16.8, 10.1 Hz, 1H), 6.18 (dd, *J* = 33.0, 17.0 Hz, 1H), 5.76 – 5.69 (m, 1H), 3.91 (s, 3H), 2.87 (t, *J* = 5.1 Hz, 2H), 2.68 (s, 3H), 2.27 (s, 2H), 2.20 (s, 6H). ^{13}C NMR (151 MHz, DMSO) δ 162.22, 152.01, 144.62, 144.24, 142.62, 140.95, 134.86, 134.64, 133.47, 132.98, 132.43, 131.12, 129.03, 128.13, 128.07, 127.56, 125.96, 124.29, 120.88, 120.33, 114.57, 110.76, 109.31, 105.13, 80.90, 56.84, 56.06, 44.99, 43.18, 39.52, 24.12. HRMS (ESI-MS): Calculated: 536.27685 for $C_{31}H_{34}N_7O_2$ [M+H$^+$], Found: 536.27942.



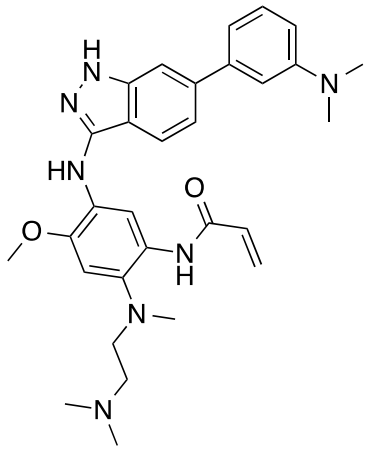
***N*-(2-((2-(dimethylamino)ethyl)(methyl)amino)-4-methoxy-5-((6-(1-methyl-1*H*-indol-3-yl)-1*H*-indazol-3-yl)amino)phenyl)acrylamide (6d).** According to GM G. Yield: 50%. ^{1}H NMR (500 MHz, DMSO) δ 12.00 (bs, 1H), 10.11 (bs, 1H), 8.87 (bs, 1H), 7.94 (d, *J* = 7.9 Hz, 1H), 7.90 (d, *J* = 8.4 Hz, 1H), 7.78 (s, 1H), 7.60 (s, 1H), 7.52 (d, *J* = 8.2 Hz, 1H), 7.49 (s, 1H), 7.34 (dd, *J* = 8.4, 1.0 Hz, 1H), 7.25 (t, *J* = 7.2 Hz, 1H), 7.18 (t, *J* = 7.4 Hz, 1H), 6.98 (s, 1H), 6.35 (dd, *J* = 16.9, 10.1 Hz, 1H), 6.20 (dd, *J* = 16.9, 1.8 Hz, 1H), 5.71 (dd, *J* = 10.2, 1.5 Hz, 1H), 3.91 (s, 3H), 3.86 (s, 3H), 2.91 – 2.83 (m, 2H), 2.68 (s, 3H), 2.31 – 2.24 (m, 2H), 2.20 (s, 6H). ^{13}C NMR (126 MHz, DMSO) δ 144.31, 143.97, 141.66, 137.31, 134.28, 133.94, 132.39, 129.14, 128.16, 125.81, 125.39, 121.57, 120.19, 119.82, 119.16, 118.54, 116.45, 115.12, 113.02, 111.50, 110.28, 108.93, 106.09, 105.02, 56.82, 56.01, 44.96, 43.15, 32.57. HRMS (ESI-MS): Calculated: 538.29250 for $C_{31}H_{36}N_7O_2$ [M+H$^+$], Found: 538.29221.



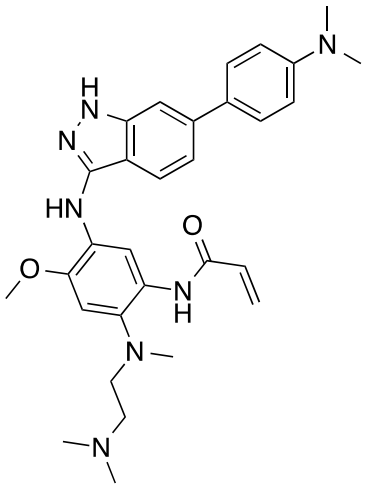
***N*-(2-((2-(dimethylamino)ethyl)(methyl)amino)-4-methoxy-5-((6-(pyridin-3-yl)-1*H*-indazol-3-yl)amino)phenyl)acrylamide (6e).** According to GM G. Yield: 58%. ^{1}H NMR (500 MHz, DMSO) δ 12.26 (s, 1H), 10.10 (s, 1H), 8.96 (d, *J* = 1.7 Hz, 1H), 8.86 (s, 1H), 8.59 (dd, *J* = 4.7, 1.4 Hz, 1H), 8.18 – 8.12 (m, 1H), 8.01 (d, *J* = 8.4 Hz, 1H), 7.65 (s, 1H), 7.61 (s, 1H), 7.50 (dd, *J* = 7.4, 4.7 Hz, 1H), 7.36 (dd, *J* = 8.4, 1.3 Hz, 1H), 6.98 (s, 1H), 6.35 (dd, *J* = 16.9, 10.1 Hz, 1H), 6.20 (dd, *J* = 16.9, 1.9 Hz, 1H), 5.71 (dd, *J* = 10.1, 1.7 Hz, 1H), 3.90 (s, 3H), 2.93 – 2.81 (m, 2H), 2.68 (s, 3H), 2.31 – 2.24 (m, 2H), 2.20 (s, 6H). ^{13}C NMR (126 MHz, DMSO) δ 163.02, 149.29, 148.85, 145.32, 145.04, 142.17, 142.13, 137.01, 136.52, 135.42, 133.26, 129.83, 128.94, 126.73, 124.72, 121.74, 118.84, 115.48, 110.10, 108.60, 105.96, 57.68, 56.90, 45.84, 43.99. ^{13}C NMR (126 MHz, DMSO) δ 163.02, 149.29, 148.85, 145.32, 145.04, 142.17, 142.13, 137.01, 136.52, 135.42, 133.26, 129.83, 128.94, 126.73, 124.72, 121.74, 118.84, 115.48, 110.10, 108.60, 105.96, 57.68, 56.90, 55.76, 45.84, 43.99. HRMS (ESI-MS): Calculated: 486.26120 for $C_{27}H_{32}N_7O_2$ [M+H$^+$], Found: 486.26137.



***N*-(2-((2-(dimethylamino)ethyl)(methyl)amino)-4-methoxy-5-((6-(pyridin-4-yl)-1*H*-indazol-3-yl)amino)phenyl)acrylamide (6f).** According to GM G. Yield: 43%. ^{1}H NMR (500 MHz, DMSO) δ 12.32 (s, 1H), 10.10 (s, 1H), 8.86 (s, 1H), 8.70 – 8.62 (m, 2H), 8.03 (d, *J* = 8.4 Hz, 1H), 7.81 – 7.76 (m, 2H), 7.75 (s, 1H), 7.64 (s, 1H), 7.42 (dd, *J* = 8.5, 1.1 Hz, 1H), 6.98 (s, 1H), 6.36 (dd, *J* = 16.9, 10.1 Hz, 1H), 6.20 (dd, *J* = 16.9, 1.8 Hz, 1H), 5.71 (dd, *J* = 10.2, 1.6 Hz, 1H), 3.90 (s, 3H), 2.87 (t, *J* = 5.3 Hz, 2H), 2.67 (s, 3H), 2.28 (t, *J* = 5.2 Hz, 2H), 2.21 (s, 6H). ^{13}C NMR (126 MHz, DMSO) δ 162.15, 150.16, 147.59, 144.48, 144.18, 141.13, 135.70, 134.60, 132.36, 129.45, 128.89, 125.85, 121.65, 120.97, 117.53, 115.21, 109.23, 107.89, 105.09, 56.78, 56.01, 55.47, 44.94, 43.10. HRMS (ESI-MS): Calculated: 486.26120 for $C_{27}H_{32}N_7O_2$ [M+H$^+$], Found: 486.26180.

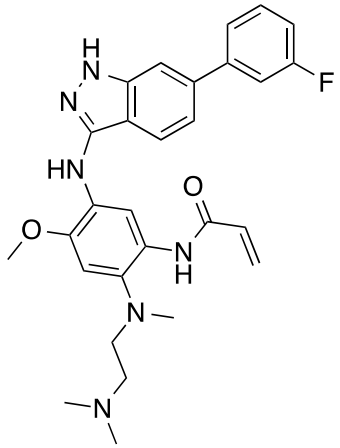


***N*-(2-((2-(dimethylamino)ethyl)(methyl)amino)-5-((6-(3-(dimethylamino)phenyl)-1*H*-indazol-3-yl)amino)-4-methoxyphenyl)acrylamide (6g).** According to GM G. Yield: 50%. ^{1}H NMR (500 MHz, DMSO) δ 12.11 (s, 1H), 10.11 (s, 1H), 8.85 (s, 1H), 7.92 (d, *J* = 8.4 Hz, 1H), 7.59 – 7.50 (m, 2H), 7.33 – 7.23 (m, 2H), 7.02 – 6.94 (m, 3H), 6.75 (dd, *J* = 8.4, 1.4 Hz, 1H), 6.35 (dd, *J* = 16.9, 10.1 Hz, 1H), 6.20 (dd, *J* = 16.9, 1.9 Hz, 1H), 5.71 (dd, *J* = 10.1, 1.7 Hz, 1H), 3.90 (s, 3H), 2.97 (s, 6H), 2.86 (t, *J* = 5.4 Hz, 2H), 2.67 (s, 3H), 2.31 – 2.23 (m, 2H), 2.20 (s, 6H). ^{13}C NMR (126 MHz, DMSO) δ 163.00, 151.73, 145.17, 144.93, 142.44, 142.26, 140.90, 135.28, 133.26, 130.26, 129.95, 128.99, 126.72, 121.06, 119.39, 119.32, 116.14, 115.07, 112.50, 111.92, 109.93, 108.16, 105.93, 57.71, 56.89, 45.85, 44.02, 41.12. HRMS (ESI-MS): Calculated: 528.30815 for $C_{30}H_{38}N_7O_2$ [M+H$^+$], Found: 528.30875.

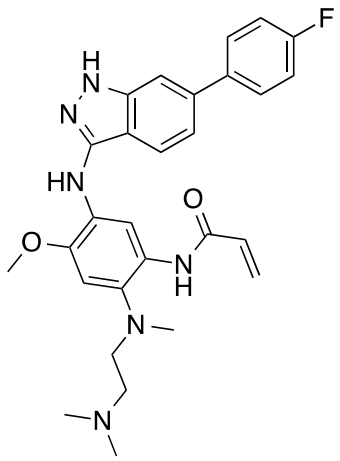


***N*-(2-((2-(dimethylamino)ethyl)(methyl)amino)-5-((6-(4-(dimethylamino)phenyl)-1*H*-indazol-3-yl)amino)-4-methoxyphenyl)acrylamide (6h).** According to GM G. Yield: 45%. ^{1}H NMR (500 MHz, DMSO) δ 12.03 (s, 1H), 10.10 (s, 1H), 8.85 (s, 1H), 7.86 (d, *J* = 8.4 Hz, 1H), 7.58 (d, *J* = 8.4 Hz, 2H), 7.48 (s, 1H), 7.46 (s, 1H), 7.27 (d, *J* = 8.4 Hz, 1H), 6.97 (s, 1H), 6.82 (d, *J* = 8.4 Hz, 2H), 6.35 (dd, *J* = 16.8, 10.0 Hz, 1H), 6.20 (d, *J* = 16.8 Hz, 1H), 5.71 (d, *J* = 10.3 Hz, 1H), 3.90 (s, 3H), 2.95 (s, 6H), 2.91 – 2.83 (m, 2H), 2.67 (s, 3H), 2.32 – 2.23 (m, 2H), 2.20 (s, 6H). ^{13}C NMR (126 MHz, DMSO) δ 162.08, 149.85,

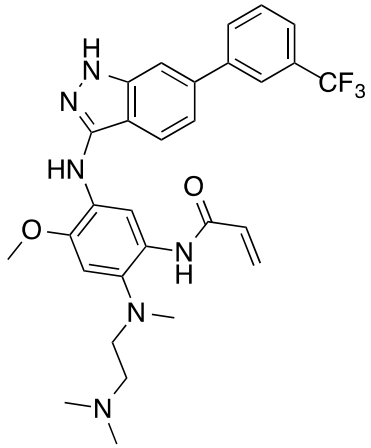
144.22, 143.97, 141.67, 139.69, 139.07, 134.28, 132.38, 129.10, 128.07, 127.48, 125.80, 120.11, 117.60, 113.46, 112.65, 108.97, 105.51, 105.01, 56.83, 56.00, 44.95, 43.14. HRMS (ESI-MS): Calculated: 528.30815 for $C_{30}H_{38}N_7O_2$ [M+H$^+$], Found: 528.30854.



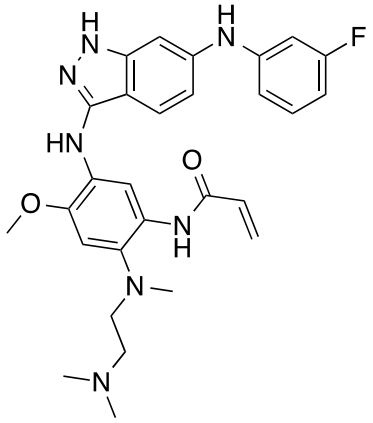
***N*-(2-((2-(dimethylamino)ethyl)(methyl)amino)-5-((6-(3-fluorophenyl)-1*H*-indazol-3-yl)amino)-4-methoxyphenyl)acrylamide (6i).** According to GM G. Yield: 15% (two steps). ^{1}H NMR (500 MHz, DMSO) δ 12.22 (s, 1H), 10.09 (s, 1H), 8.84 (s, 1H), 7.97 (d, *J* = 8.4 Hz, 1H), 7.66 – 7.55 (m, 4H), 7.52 (dt, *J* = 14.2, 7.3 Hz, 1H), 7.34 (dd, *J* = 8.5, 1.3 Hz, 1H), 7.21 (td, *J* = 8.4, 1.8 Hz, 1H), 6.97 (s, 1H), 6.36 (dd, *J* = 16.9, 10.1 Hz, 1H), 6.20 (dd, *J* = 16.9, 1.8 Hz, 1H), 5.71 (dd, *J* = 10.2, 1.6 Hz, 1H), 3.90 (s, 3H), 2.94 – 2.83 (m, 2H), 2.67 (s, 3H), 2.35 – 2.26 (m, 2H), 2.22 (s, 6H). ^{13}C NMR (126 MHz, DMSO) δ 163.61, 162.17, 161.68, 144.38, 144.15, 143.23, 143.17, 142.76, 141.23, 139.60, 137.42, 137.41, 132.35, 130.82, 130.75, 128.97, 125.86, 123.17, 120.62, 118.04, 114.56, 113.98, 113.87, 113.70, 107.62, 105.05, 105.02, 56.01, 44.86, 43.13, 30.65. HRMS (ESI-MS): Calculated: 503.25653 for $C_{28}H_{32}FN_6O_2$ [M+H$^+$], Found: 503.25701.



***N*-(2-((2-(dimethylamino)ethyl)(methyl)amino)-5-((6-(4-fluorophenyl)-1*H*-indazol-3-yl)amino)-4-methoxyphenyl)acrylamide (6j).** According to GM G. Yield: 52%. ^{1}H NMR (500 MHz, DMSO) δ 12.19 (s, 1H), 10.11 (s, 1H), 8.87 (s, 1H), 7.96 (d, *J* = 8.4 Hz, 1H), 7.81 – 7.72 (m, 2H), 7.62 – 7.52 (m, 2H), 7.35 – 7.26 (m, 3H), 6.97 (s, 1H), 6.35 (dd, *J* = 16.9, 10.1 Hz, 1H), 6.20 (dd, *J* = 16.8, 0.5 Hz, 1H), 5.71 (dd, *J* = 10.8, 0.6 Hz, 1H), 3.90 (s, 3H), 2.93 – 2.81 (m, 2H), 2.67 (s, 3H), 2.30 – 2.22 (m, 2H), 2.19 (s, 6H). ^{13}C NMR (126 MHz, DMSO) δ 162.82, 162.11, 160.88, 144.36, 144.08, 141.33, 137.83, 137.17, 137.14, 134.43, 132.39, 129.09, 129.03, 128.13, 125.82, 120.53, 118.08, 115.75, 115.58, 114.22, 109.06, 107.27, 105.07, 56.85, 56.00, 55.64, 44.98, 43.11. HRMS (ESI-MS): Calculated: 503.25653 for $C_{28}H_{32}FN_6O_2$ [M+H$^+$], Found: 503.25652.

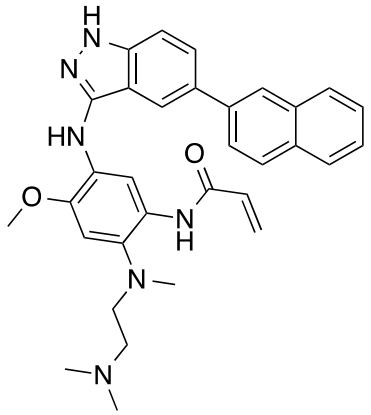


***N*-(2-((2-(dimethylamino)ethyl)(methyl)amino)-4-methoxy-5-((6-(3-(trifluoromethyl)phenyl)-1*H*-indazol-3-yl)amino)phenyl)acrylamide (6k).** According to GM G. Yield: 16% (two steps). ^{1}H NMR (500 MHz, DMSO) δ 12.24 (s, 1H), 10.08 (d, *J* = 6.2 Hz, 1H), 8.85 (s, 1H), 8.12 – 7.98 (m, 3H), 7.83 – 7.60 (m, 4H), 7.38 (d, *J* = 8.3 Hz, 1H), 6.98 (s, 1H), 6.44 – 6.31 (m, 1H), 6.20 (d, *J* = 16.8 Hz, 1H), 5.71 (d, *J* = 10.0 Hz, 1H), 3.91 (s, 3H), 2.95 – 2.83 (m, 2H), 2.67 (s, 3H), 2.40 – 2.18 (m, 8H). ^{13}C NMR (126 MHz, DMSO) δ 144.41, 144.19, 141.75, 141.22, 137.16, 132.34, 131.24, 130.01, 129.61, 128.95, 128.93, 125.92, 125.90, 125.89, 125.87, 125.31, 123.98, 123.53, 123.50, 123.49, 123.47, 120.82, 118.03, 114.70, 114.64, 111.70, 111.69, 111.26, 111.24, 109.41, 107.89, 105.02, 87.11, 73.64, 56.01, 44.81, 43.14, 30.65. HRMS (ESI-MS): Calculated: 553.25334 for $C_{29}H_{32}F_3N_6O_2$ [M+H$^+$], Found: 553.25447.

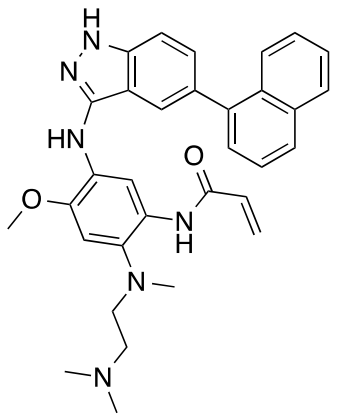


***N*-(2-((2-(dimethylamino)ethyl)(methyl)amino)-5-((6-((3-fluorophenyl)amino)-1*H*-indazol-3-yl)amino)-4-methoxyphenyl)acrylamide (6l).** According to GM G. Yield: 10%. ^{1}H NMR (500 MHz, DMSO) δ 11.72 (s, 1H), 10.12 (s, 1H), 8.79 (s, 1H), 8.57 (s, 1H), 7.75 (d, *J* = 8.7 Hz, 1H), 7.43 (s, 1H), 7.27 (dd, *J* = 15.4, 8.1 Hz, 1H), 7.02 (d, *J* = 1.2 Hz, 1H), 6.94 (d, *J* = 12.1 Hz, 2H), 6.89 (dd, *J* = 11.8, 2.1 Hz, 1H), 6.77 (dd, *J* = 8.7, 1.6 Hz, 1H), 6.62 (td, *J* = 8.4, 2.1 Hz, 1H), 6.36 (dd, *J* = 12.5, 11.3 Hz, 1H), 6.20 (dd, *J* = 16.8, 1.1 Hz, 1H), 5.71 (dd, *J* = 10.0, 1.5 Hz, 1H), 3.89 (s, 3H), 2.88 (d, *J* = 4.3 Hz, 2H), 2.66 (s, 3H), 2.23 (s, 6H), 2.18 (d, *J* = 7.6 Hz, 2H). ^{13}C NMR (151 MHz, DMSO) δ 163.89, 162.29, 145.71, 145.64,

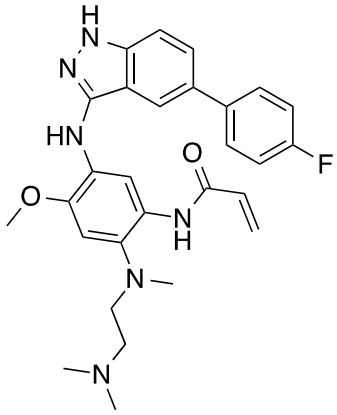
144.32, 142.01, 141.66, 132.36, 130.82, 130.75, 129.09, 126.05, 120.80, 112.60, 112.43, 110.00, 105.89, 105.75, 104.91, 102.86, 102.69, 94.94, 69.80, 56.01, 54.95, 43.28, 39.52, 31.32, 22.12, 13.99. HRMS (ESI-MS): Calculated: 518.26743 for [M+H$^+$], Found: 518.26595.



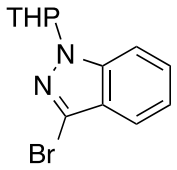
***N*-(2-((2-(dimethylamino)ethyl)(methyl)amino)-4-methoxy-5-((5-(naphthalen-2-yl)-1*H*-indazol-3-yl)amino)phenyl)acrylamide (7a).** According to GM G. Yield: 48%. ^{1}H NMR (500 MHz, DMSO) δ 12.18 (s, 1H), 10.13 (s, 1H), 8.96 (s, 1H), 8.42 (s, 1H), 8.25 (s, 1H), 8.06 – 7.97 (m, 2H), 7.97 – 7.90 (m, 2H), 7.82 (dd, *J* = 8.7, 1.5 Hz, 1H), 7.75 (s, 1H), 7.57 – 7.45 (m, 3H), 6.99 (s, 1H), 6.36 (dd, *J* = 16.9, 10.1 Hz, 1H), 6.21 (dd, *J* = 16.9, 1.8 Hz, 1H), 5.78 – 5.68 (m, 1H), 3.92 (s, 3H), 2.93 – 2.83 (m, 2H), 2.68 (s, 3H), 2.32 – 2.24 (m, 2H), 2.20 (s, 6H). ^{13}C NMR (126 MHz, DMSO) δ 187.16, 163.03, 145.90, 145.13, 141.10, 139.17, 135.44, 134.35, 133.29, 132.69, 131.45, 129.74, 129.13, 128.95, 128.82, 128.35, 127.17, 127.12, 126.72, 126.51, 126.39, 125.51, 119.39, 116.46, 111.04, 110.32, 105.95, 57.71, 56.91, 56.44, 45.84, 44.01. HRMS (ESI-MS): Calculated: 535.28160 for $C_{32}H_{35}N_6O_2$ [M+H$^+$], Found: 535.28295.



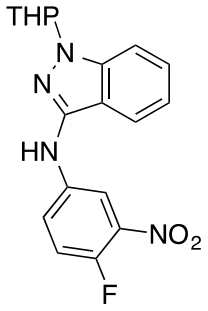
***N*-(2-((2-(dimethylamino)ethyl)(methyl)amino)-4-methoxy-5-((5-(naphthalen-1-yl)-1*H*-indazol-3-yl)amino)phenyl)acrylamide (7b).** According to GM G. Yield: 60%. ^{1}H NMR (500 MHz, DMSO) δ 12.24 (s, 1H), 10.11 (s, 1H), 8.90 (s, 1H), 8.03 – 7.96 (m, 2H), 7.93 (d, *J* = 8.0 Hz, 1H), 7.87 (d, *J* = 8.4 Hz, 1H), 7.63 (s, 1H), 7.57 (t, *J* = 7.5 Hz, 1H), 7.55 – 7.40 (m, 5H), 6.94 (s, 1H), 6.36 (dd, *J* = 16.8, 10.1 Hz, 1H), 6.21 (d, *J* = 16.9 Hz, 1H), 5.72 (d, *J* = 10.1 Hz, 1H), 3.83 (s, 3H), 2.88 – 2.79 (m, 2H), 2.65 (s, 3H), 2.28 – 2.21 (m, 2H), 2.18 (s, 6H). ^{13}C NMR (126 MHz, DMSO) δ 162.09, 144.69, 144.14, 140.14, 140.08, 134.38, 133.44, 132.40, 131.37, 130.31, 129.05, 128.80, 128.22, 128.16, 127.21, 127.12, 126.13, 125.82, 125.75, 125.65, 125.48, 121.01, 115.14, 109.51, 108.97, 105.12, 56.83, 55.92, 55.66, 44.97, 43.10. HRMS (ESI-MS): Calculated: 535.28160 for $C_{32}H_{35}N_6O_2$ [M+H$^+$], Found: 535.28305.



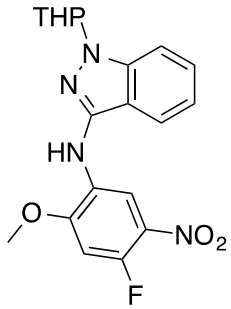
***N*-(2-((2-(dimethylamino)ethyl)(methyl)amino)-5-((5-(4-fluorophenyl)-1*H*-indazol-3-yl)amino)-4-methoxyphenyl)acrylamide (7c).** According to GM G. Yield: 27% (two steps). ^{1}H NMR (500 MHz, DMSO) δ 12.16 (s, 1H), 10.16 (s, 1H), 8.94 (s, 1H), 8.26 (s, 1H), 7.80 – 7.71 (m, 3H), 7.63 (dd, *J* = 8.7, 1.5 Hz, 1H), 7.43 (d, *J* = 8.7 Hz, 1H), 7.29 (t, *J* = 8.8 Hz, 2H), 6.98 (s, 1H), 6.37 (dd, *J* = 16.7, 10.1 Hz, 1H), 6.21 (dd, *J* = 16.9, 1.8 Hz, 1H), 5.72 (dd, *J* = 10.2, 1.7 Hz, 1H), 3.91 (s, 3H), 2.88 (s, 2H), 2.67 (s, 3H), 2.29 (s, 2H), 2.22 (s, 6H). ^{13}C NMR (101 MHz, DMSO) δ 162.56, 162.23, 162.21, 144.91, 144.24, 140.05, 137.42, 134.58, 132.36, 129.80, 128.79, 128.51, 128.43, 125.94, 118.11, 115.63, 115.42, 110.06, 104.99, 56.64, 56.02, 55.82, 54.90, 44.80, 43.17, 39.52, 29.59. HRMS (ESI-MS): Calculated: 503.25653 for [M+H^{+}], Found: 503.25596.



3-bromo-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazole (23). According to GM B. Yield: 97%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.61 (d, *J* = 8.1 Hz, 1H), 7.57 (d, *J* = 8.5 Hz, 1H), 7.46 – 7.42 (m, 1H), 7.23 (ddd, *J* = 7.8, 7.0, 0.6 Hz, 1H), 5.68 (dd, *J* = 9.2, 2.8 Hz, 1H), 4.05 – 3.99 (m, 1H), 3.73 (ddd, *J* = 13.3, 9.1, 2.8 Hz, 1H), 2.61 – 2.51 (m, 1H), 2.20 – 2.11 (m, 1H), 2.11 – 2.04 (m, 1H), 1.79 – 1.70 (m, 2H), 1.70 – 1.61 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 140.74, 127.87, 124.62, 122.24, 122.10, 120.54, 110.51, 85.65, 67.55, 29.47, 25.18, 22.58. LC-MS (ESI-MS): Calculated 281.03 for $C_{12}H_{14}BrN_2O$ [M+H^{+}]. Found: 280.77. Calculated 283.03 for $C_{12}H_{14}{}^{81}BrN_2O$ [M+H^{+}]. Found: 282.75.

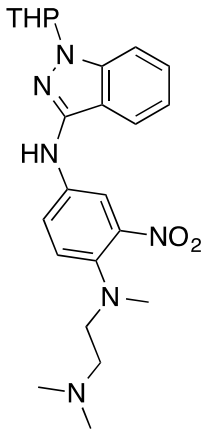


***N*-(4-fluoro-3-nitrophenyl)-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-3-amine (24).** According to GM C. Yield: 54%. ^{1}H NMR (500 MHz, DMSO) δ 9.58 (s, 1H), 8.73 (dd, *J* = 6.6, 2.9 Hz, 1H), 8.06 – 7.91 (m, 2H), 7.62 (d, *J* = 8.5 Hz, 1H), 7.53 (dd, *J* = 11.2, 9.2 Hz, 1H), 7.48 – 7.40 (m, 1H), 7.17 (t, *J* = 7.3 Hz, 1H), 5.75 (dd, *J* = 9.4, 2.5 Hz, 1H), 3.92 – 3.83 (m, 1H), 3.77 – 3.69 (m, 1H), 2.45 (ddd, *J* = 13.2, 9.4, 3.6 Hz, 1H), 2.15 – 2.06 (m, 1H), 2.06 – 1.98 (m, 1H), 1.83 – 1.72 (m, 1H), 1.62 – 1.51 (m, 2H). ^{13}C NMR (126 MHz, DMSO) 153.50, 153.11, 151.01, 149.24, 144.98, 140.41, 136.27, 128.50, 128.46, 128.07, 127.91, 127.66, 120.60, 119.57, 115.30, 111.04, 109.59, 100.70, 83.07, 65.81, 29.10, 24.87, 22.35. LC-MS (ESI-MS): Calculated 357.14 for $C_{18}H_{18}FN_4O_3$ [M+H$^+$]. Found: 356.85.

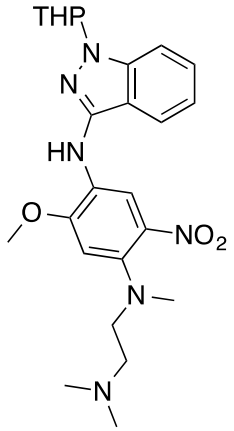


***N*-(4-fluoro-2-methoxy-5-nitrophenyl)-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-3-amine (25).** According to GM C. Yield: 76%. ^{1}H NMR (500 MHz, DMSO) δ 9.25 (d, *J* = 8.4 Hz, 1H), 8.41 (s, 1H), 8.10 (d, *J* = 8.1 Hz, 1H), 7.62 (d, *J* = 8.5 Hz, 1H), 7.44 (t, *J* = 7.4 Hz, 1H), 7.28 (d, *J* = 13.2 Hz, 1H), 7.14 (t, *J* = 7.5 Hz, 1H), 5.79 (dd, *J* = 9.1, 2.5 Hz, 1H), 4.08 (s, 3H), 3.90 – 3.84 (m, 1H), 3.77 – 3.69 (m, 1H), 2.50 – 2.44 (m, 1H), 2.17 – 2.09 (m, 1H), 2.09 – 2.01 (m, 1H), 1.85 – 1.73 (m, 1H), 1.63 – 1.52 (m, 2H).

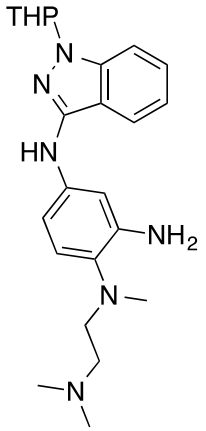
^{13}C NMR (126 MHz, DMSO) δ 153.46, 153.38, 151.31, 149.28, 143.43, 140.12, 136.50, 128.58, 128.53, 128.19, 128.18, 127.33, 120.62, 119.68, 115.84, 110.72, 109.75, 100.68, 100.46, 83.21, 66.06, 57.24, 28.78, 24.91, 22.19. LC-MS (ESI-MS): Calculated: 387.15 for $C_{19}H_{20}FN_4O_4$ [M+H$^+$]. Found: 386.87.



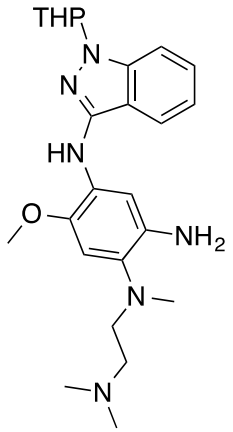
***N*^{1}-(2-(dimethylamino)ethyl)-*N*^{1}-methyl-2-nitro-*N*^{4}-(1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-3-yl)benzene-1,4-diamine (26).** According to GM E. Yield: 94%. ^{1}H NMR (500 MHz, DMSO) δ 9.32 (s, 1H), 8.32 (d, *J* = 2.6 Hz, 1H), 7.99 (d, *J* = 8.1 Hz, 1H), 7.81 (dd, *J* = 9.0, 2.7 Hz, 1H), 7.58 (d, *J* = 8.5 Hz, 1H), 7.43 – 7.39 (m, 1H), 7.38 (d, *J* = 9.0 Hz, 1H), 7.13 (t, *J* = 7.5 Hz, 1H), 5.71 (dd, *J* = 9.4, 2.3 Hz, 1H), 3.89 – 3.83 (m, 1H), 3.74 – 3.65 (m, 1H), 3.05 (t, *J* = 7.2 Hz, 2H), 2.72 (s, 3H), 2.47 – 2.37 (m, 1H), 2.33 (t, *J* = 7.2 Hz, 2H), 2.11 (s, 6H), 2.09 – 2.04 (m, 1H), 2.03 – 1.96 (m, 1H), 1.82 – 1.69 (m, 1H), 1.61 – 1.53 (m, 2H). ^{13}C NMR (126 MHz, DMSO) δ 144.13, 143.74, 140.05, 137.72, 137.09, 127.27, 123.06, 121.14, 119.99, 119.57, 115.73, 110.88, 109.76, 83.40, 66.21, 56.70, 53.75, 45.34, 41.81, 28.89, 24.89, 22.29. LC-MS (ESI-MS): Calculated: 439.25 for $C_{23}H_{31}N_6O_3$ [M+H$^+$]. Found: 439.16.



***N*^{1}-(2-(dimethylamino)ethyl)-5-methoxy-*N*^{1}-methyl-2-nitro-*N*^{4}-(1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-3-yl)benzene-1,4-diamine (27).** According to GM E. Yield: 99%. ^{1}H NMR (500 MHz, DMSO) δ 8.96 (s, 1H), 8.12 – 8.01 (m, 2H), 7.57 (d, *J* = 8.4 Hz, 1H), 7.43 – 7.38 (m, 1H), 7.10 (t, *J* = 7.5 Hz, 1H), 6.85 (s, 1H), 5.73 (dd, *J* = 9.2, 2.3 Hz, 1H), 4.02 (s, 3H), 3.89 – 3.83 (m, 1H), 3.74 – 3.65 (m, 1H), 3.19 (t, *J* = 6.9 Hz, 2H), 2.81 (s, 3H), 2.48 – 2.36 (m, 4H), 2.14 (s, 6H), 2.13 – 2.05 (m, 1H), 2.04 – 1.97 (m, 1H), 1.82 – 1.70 (m, 1H), 1.61 – 1.51 (m, 2H). ^{13}C NMR (126 MHz, DMSO) δ 152.20, 143.99, 141.69, 140.18, 133.07, 127.20, 124.75, 120.50, 119.46, 115.90, 112.82, 109.66, 102.38, 83.27, 66.11, 56.59, 56.29, 53.19, 45.44, 40.88, 28.82, 24.94, 22.26. LC-MS (ESI-MS): Calculated: 469.26 for $C_{24}H_{33}N_6O_4$ [M+H$^+$]. Found: 469.04.

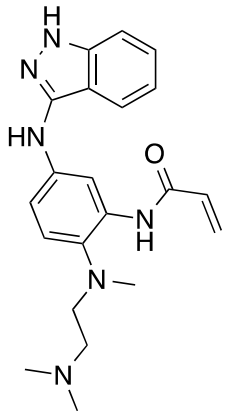


***N*^{1}-(2-(dimethylamino)ethyl)-*N*^{1}-methyl-*N*^{4}-(1-(tetrahydro-2H-pyran-2-yl)-1*H*-indazol-3-yl)benzene-1,2,4-triamine (28).** According to GM F. Yield: 70%. ^{1}H NMR (500 MHz, DMSO) δ 8.52 (s, 1H), 7.97 (d, *J* = 8.1 Hz, 1H), 7.53 (d, *J* = 8.4 Hz, 1H), 7.36 (t, *J* = 7.6 Hz, 1H), 7.07 (t, *J* = 7.1 Hz, 1H), 7.01 (s, 1H), 6.95 (d, *J* = 8.5 Hz, 1H), 6.89 (d, *J* = 8.4 Hz, 1H), 5.65 (d, *J* = 9.7 Hz, 1H), 4.89 (bs, 2H), 3.92 – 3.84 (m, 1H), 3.74 – 3.65 (m, 1H), 2.81 (t, *J* = 6.2 Hz, 2H), 2.56 (s, 3H), 2.50 – 2.41 (m, 1H), 2.31 (t, *J* = 6.2 Hz, 2H), 2.15 (d, *J* = 1.2 Hz, 6H), 2.10 – 2.00 (m, 1H), 1.99 – 1.90 (m, 1H), 1.81 – 1.68 (m, 1H), 1.64 – 1.52 (m, 2H). ^{13}C NMR (126 MHz, DMSO) δ 144.97, 143.58, 140.11, 139.35, 131.42, 126.88, 120.65, 120.33, 119.05, 116.33, 109.54, 105.00, 102.58, 83.67, 66.41, 57.43, 54.51, 45.69, 42.13, 29.00, 24.91, 22.55. LC-MS (ESI-MS): Calculated: 409.27 for $C_{23}H_{33}N_6O$ [M+H$^+$]. Found: 409.21.

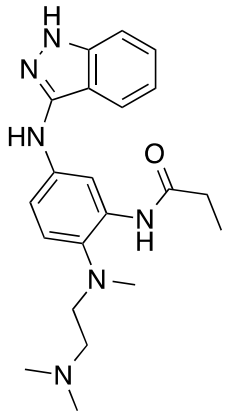


***N*^{1}-(2-(dimethylamino)ethyl)-5-methoxy-*N*^{1}-methyl-*N*^{4}-(1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-3-yl)benzene-1,2,4-triamine (29).** According to GM F. Yield: 83%. ^{1}H NMR (500 MHz, DMSO) δ 7.88 (d, *J* = 8.2 Hz, 1H), 7.60 – 7.50 (m, 2H), 7.42 – 7.35 (m, 2H), 7.08 (t, *J* = 7.4 Hz, 1H), 6.75 (s, 1H), 5.67 (d, *J* = 9.8 Hz, 1H), 3.93 – 3.86 (m, 1H), 3.80 (s, 3H), 3.70 (t, *J* = 9.9 Hz, 1H), 2.85 (t, *J* = 6.6 Hz, 2H), 2.59 (s, 3H), 2.55 – 2.51 (m, 1H), 2.32 (t, *J* = 6.6 Hz, 2H), 2.16 (s, 6H), 2.09 – 2.02 (m, 1H), 1.99 – 1.91 (m, 1H), 1.81 – 1.69 (m, 1H), 1.66 – 1.52 (m, 2H). ^{13}C NMR (126 MHz, DMSO) δ 144.46, 140.15, 139.31, 137.20, 130.34, 128.43, 126.91, 120.00, 119.27, 116.33, 109.68, 105.51, 104.21, 83.83, 66.49, 57.43, 56.71, 54.29,

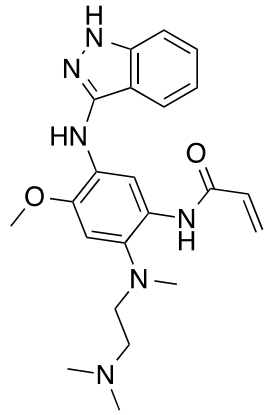
45.63, 42.05, 28.96, 24.85, 22.57. LC-MS (ESI-MS): Calculated: 439.28 for $C_{24}H_{35}N_6O_2$ [M+H$^+$]. Found: 439.32.



***N*-(5-((1H-indazol-3-yl)amino)-2-((2-(dimethylamino)ethyl)(methyl)amino)phenyl)acrylamide (30a).** According to GM G. Yield: 45%. ^{1}H NMR (600 MHz, DMSO) δ 10.21 (s, 1H), 8.83 (s, 1H), 8.51 (d, *J* = 2.0 Hz, 1H), 7.99 (d, *J* = 8.1 Hz, 1H), 7.59 (dd, *J* = 8.6, 2.5 Hz, 1H), 7.35 (d, *J* = 8.3 Hz, 1H), 7.33 – 7.29 (m, 1H), 7.22 (d, *J* = 8.7 Hz, 1H), 7.01 (ddd, *J* = 7.9, 6.6, 1.0 Hz, 1H), 6.38 (dd, *J* = 16.9, 10.1 Hz, 1H), 6.27 (dd, *J* = 16.9, 2.0 Hz, 1H), 5.77 (dd, *J* = 10.0, 2.0 Hz, 1H), 2.80 (t, *J* = 5.6 Hz, 2H), 2.64 (s, 3H), 2.23 (t, *J* = 5.6 Hz, 2H), 2.19 (s, 6H). ^{13}C NMR (126 MHz, DMSO) δ 172.51, 145.17, 141.20, 140.97, 137.03, 133.71, 128.56, 126.96, 123.09, 120.77, 119.33, 117.83, 114.65, 111.49, 110.20, 108.32, 57.11, 56.64, 45.72, 43.95. LC-MS (ESI-MS): Calculated: 379.22 for $C_{21}H_{27}N_6O$ [M+H$^+$]. Found: 379.10.

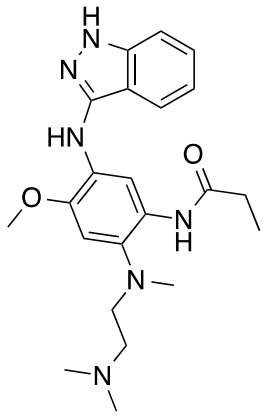


***N*-(5-((1H-indazol-3-yl)amino)-2-((2-(dimethylamino)ethyl)(methyl)amino)phenyl)propionamide (30b).** According to GM G. Yield: 50%. ^{1}H NMR (500 MHz, DMSO) δ 11.92 (s, 1H), 9.87 (s, 1H), 8.78 (s, 1H), 8.41 (s, 1H), 7.99 (d, *J* = 8.1 Hz, 1H), 7.56 (dd, *J* = 8.6, 1.7 Hz, 1H), 7.43 – 7.26 (m, 2H), 7.18 (d, *J* = 8.7 Hz, 1H), 7.00 (t, *J* = 7.3 Hz, 1H), 2.80 (t, *J* = 5.3 Hz, 2H), 2.62 (s, 3H), 2.33 (q, *J* = 7.5 Hz, 2H), 2.22 (t, *J* = 5.6 Hz, 2H), 2.19 (s, 6H), 1.13 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (126 MHz, DMSO) δ 171.15, 145.07, 140.53, 140.28, 135.45, 133.55, 126.52, 122.28, 120.13, 118.09, 114.58, 110.81, 109.44, 107.60, 56.97, 56.04, 45.24, 43.25, 29.73, 9.81. LC-MS (ESI-MS): Calculated: 381.24 for $C_{21}H_{29}N_6O$ [M+H$^+$]. Found: 381.09.



***N*-(5-((1H-indazol-3-yl)amino)-2-((2-(dimethylamino)ethyl)(methyl)amino)-4-methoxyphenyl)acryl-amide (31a).** According to GM G. Yield: 43%. ^{1}H NMR (500 MHz, DMSO) δ 12.10 (s, 1H), 10.11 (s, 1H),

8.85 (s, 1H), 7.86 (d, *J* = 8.1 Hz, 1H), 7.47 (s, 1H), 7.38 (d, *J* = 8.3 Hz, 1H), 7.35 – 7.28 (m, 1H), 7.01 (t, *J* = 7.4 Hz, 1H), 6.97 (s, 1H), 6.34 (dd, *J* = 16.9, 10.1 Hz, 1H), 6.19 (d, *J* = 16.9 Hz, 1H), 5.70 (d, *J* = 10.3 Hz, 1H), 3.89 (s, 3H), 2.85 (t, *J* = 5.5 Hz, 2H), 2.67 (s, 3H), 2.23 (t, *J* = 5.4 Hz, 2H), 2.18 (s, 6H). ^{13}C NMR (126 MHz, DMSO) δ 172.94, 145.20, 144.86, 141.56, 135.18, 133.28, 129.98, 129.07, 127.39, 126.66, 120.70, 119.25, 115.77, 110.51, 109.75, 105.94, 57.77, 56.89, 56.60, 45.89, 44.01. LC-MS (ESI-MS): Calculated: 409.24 for $C_{22}H_{29}N_6O_2$ [M+H$^+$]. Found: 409.13.



***N*-(5-((1H-indazol-3-yl)amino)-2-((2-(dimethylamino)ethyl)(methyl)amino)-4-methoxyphenyl)propion-amide (31b).** According to GM G. Yield: 48%. ^{1}H NMR (500 MHz, DMSO) δ 12.08 (s, 1H), 9.75 (s, 1H), 8.74 (s, 1H), 7.85 (d, *J* = 8.1 Hz, 1H), 7.42 (s, 1H), 7.37 (d, *J* = 8.4 Hz, 1H), 7.35 – 7.29 (m, 1H), 7.04 – 6.97 (m, 1H), 6.93 (s, 1H), 3.87 (s, 3H), 2.84 (t, *J* = 5.7 Hz, 2H), 2.65 (s, 3H), 2.27 (q, *J* = 7.6 Hz, 2H), 2.23 (t, *J* = 5.7 Hz, 2H), 2.19 (s, 6H), 1.08 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (126 MHz, DMSO) δ 170.61, 144.39, 143.59, 140.71, 133.92, 129.04, 128.56, 126.52, 119.82, 118.38, 114.90, 109.64, 108.91, 105.04, 56.94, 56.02, 55.64, 45.12, 43.20, 29.50, 9.79. LC-MS (ESI-MS): Calculated: 411.25 for $C_{22}H_{31}N_6O_2$ [M+H$^+$]. Found: 411.12.