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Supporting Information

Synthesis and Biological Activity of Furanylindazoles as Inhibitors of Hypoxia Inducible Factor (HIF)-1 Transcriptional Activity

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General Information. ^{1}H and ^{13}C NMR spectra were recorded on VARIAN UNITY-INOVA 400 (400 MHz) spectrometer. The chemical shifts are reported in δ units relative to internal tetramethylsilane. IR spectra were recorded on a Shimadzu FTIR-8200A spectrometer. High-resolution mass spectra (ESI) were recorded on a Bruker Daltonics micro TOF-15 focus. Analytical thin layer chromatography (TLC) was performed on a glass plates of silica gel 60 GF_{254} (Merck). Column chromatography was conducted on silica gel (Merck Kieselgel 70-230 mesh). Most commercially supplied chemicals were used without further purification. Compounds **9**,[1] **10a**,[1] **10c**,[2] **11a**,[1] **11h**,[3] **11j**,[3] **11q-s**,[3] **12a**,[1] **12c-j**,[2,3] **12o-s**,[3] **12w**[3] were known.

Typical procedure for preparation of 1-benzyl-3-Iodo-1H-Inazole (10a)[1]

To a solution of **9** (1.4 g, 5.6 mmol) in THF (17 mL) cooled at 0 °C was added potassium tert-butoxide (0.88 g, 7.8 mmol). After 1 h at 0 °C , benzyl bromide (0.67 mL, 5.6 mmol) was added dropwise. The resulting mixture was sttired 4 h at rt then evaporated. The residue was dissolved with EtOAc, washed with water and brine, dried over $MgSO_4$, and concentrated in vacuo. Purification by column chromatography on silica gel with EtOAc/hexane (1:100) gave **10a** in 85% yield (1.6 g, 4.8 mmol) as pale yellow solid. The product was identified by comparison with the reported ^{1}H NMR spectra in the literature.[1] ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.49 (d, *J*=8.4 Hz, 1H), 7.38 (t, *J*=8.4 Hz, 1H), 7.32-7.17 (m, 7H), 5.61 (s, 2H).

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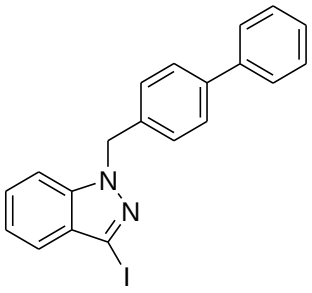
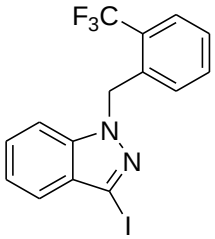
1-(4-Biphenylmethyl)-3-iodo-1H-indazole (10b)



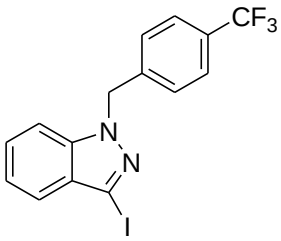
Yield 90%; a white solid; ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.54-7.50 (m, 5H), 7.41 (q, *J*=7.6 Hz, 3H), 7.34 (d, *J*=8.0 Hz, 2H), 7.28 (t, *J*=8.0 Hz, 3H), 7.21 (t, *J*=8.0 Hz, 1H), 5.65 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.9, 140.5, 140.2, 135.3, 128.8, 128.7, 127.7, 127.6, 127.5, 127.4, 127.0, 122.7, 121.5, 109.5, 91.7, 53.3.; IR (KBr) 3436, 1611, 1488, 1459, 1314, 1246, 1168, 751 cm^{-1}; Anal. Calcd for $C_{20}H_{15}IN_2$: C, 58.55; H, 3.69; N, 6.83; found: C, 58.58; H, 3.71 N, 6.79.

1-(2-(trifluoromethyl)benzyl)-3-iodo-1H-indazole (10d)



Yield 99%; a white solid; ^{1}H NMR (400 MHz; $CDCl_3$) 7.71 (t, *J*=4.4 Hz, 1H), 7.54 (d, *J*=8.0 Hz, 1H), 7.42-7.34 (m, 3H), 7.24 (t, *J*=8.0 Hz, 2H), 6.71 (d, *J*=4.4 Hz, 1H), 5.85 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.5, 135.3 (d, *J*=1.5 Hz), 132.4, 128.7, 128.0, 127.7 (d, *J*=4.4 Hz), 127.3, 126.9, 126.0 (q, *J*=5.9 Hz), 125.7, 123.0, 121.8 (d, *J*=2.2 Hz), 109.2, 92.3, 49.4 (d, *J*=3.8 Hz); IR (KBr) 1614, 1491, 1460, 1315, 1252, 1167, 1126, 1069, 1038, 966, 775, 764, 746, 656 cm^{-1}; Anal. Calcd for $C_{15}H_{10}F_3IN_2$: C, 44.80; H, 2.51; N, 6.97; found: C, 44.83; H, 2.54; N, 7.07.

1-(4-(Trifluoromethyl)benzyl)-3-iodo-1H-indazole (10e)



Yield 88%; a white solid; ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.45 (t, *J*=8.0 Hz, 3H), 7.32 (t, *J*=8.0 Hz, 1H), 7.22-7.20 (m, 3H), 7.14 (t, *J*=7.6 Hz, 1H), 5.55 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.2, 140.0, 129.8 (q, *J*=32.8 Hz), 128.5, 127.7, 127.2, 125.5 (q, *J*=3.7 Hz), 125.1, 122.4, 121.6, 109.0,

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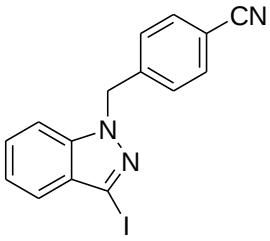
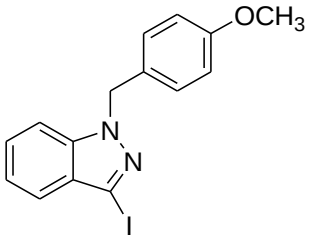
92.2, 52.5; IR (KBr) 1616, 1491, 1458, 1323, 1246, 1165, 1123, 1065, 1018, 822, 775, 745, 648 cm^{-1}; Anal. Calcd for $C_{15}H_{10}F_3IN_2$: C, 44.80; H, 2.51; N, 6.97; found: C, 44.78; H, 2.26; N, 6.99.

4-((3-Iodo-1H-indazol-1-yl)methyl)benzonitrile (10f)



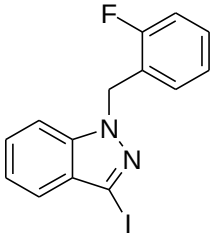
Yield 89%; a white solid; ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.59-7.57 (m, 2H), 7.52 (d, *J*=8.0 Hz, 1H), 7.42 (t, *J*=8.0 Hz, 1H), 7.27-7.25 (m, 4H), 5.65 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.6, 140.2, 132.6, 128.8, 128.1, 127.7, 122.0, 121.9, 118.4, 111.9, 109.0, 92.7, 52.7; IR (KBr) 2226, 1614, 1607, 1493, 1458, 1317, 1246, 1169, 1118, 1009, 964, 850, 763, 745, 607 cm^{-1}; HRMS *m/z* (ESI) Calc. for $C_{15}H_{10}IN_3$ $[M+H]^+$: 359.9998, found: 359.9995.

1-(4-Methoxybenzyl)-3-iodo-1H-indazole (10g)



Yield 97% yield; a white solid; ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.69 (d, *J*=8.8 Hz, 1H), 7.38 (d, *J*=8.4 Hz, 1H), 7.29 (t, *J*=8.8 Hz, 1H), 7.24 (d, *J*=8.8 Hz, 2H), 7.09 (t, *J*=8.0 Hz, 1H), 6.82 (d, *J*=8.8 Hz, 2H), 5.63 (s, 2H), 3.73 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.3, 149.4, 129.0, 127.6, 127.5, 126.8, 122.5, 120.5, 118.0, 113.9, 75.3, 56.4, 55.1; IR (KBr) 1611, 1516, 1435, 1354, 1299, 1277, 1246, 1188, 1039, 1028, 851, 814, 737, 565 cm^{-1}; Anal. Calcd for $C_{15}H_{13}IN_2O$: C, 49.47; H,3.60; N, 7.69; found: C, 49.45; H, 3.30 N, 7.97.

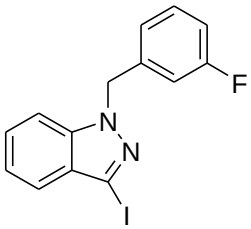
1-(2-Fluorobenzyl)-3-iodo-1H-indazole (10h)



Yield 93%; a white solid; ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.49 (d, *J*=4.0 Hz, 1H), 7.44-7.38 (m, 2H),

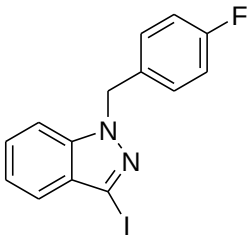
7.28-7.19 (m, 2H), 7.12-7.01 (m, 3H), 5.66 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.6 (d, *J*=7.5 Hz), 160.1 (d, *J*=7.5 Hz), 139.9, 130.3 (t, *J*=9.6 Hz), 128.2, 127.4, 121.3 (d, *J*=7.4 Hz), 111.9 (t *J*=18.6 Hz), 111.5 (d, *J*=6.0 Hz), 111.3 (d, *J*=6.7 Hz), 109.2 (t, *J*=2.2 Hz), 92.0, 40.7 (t, *J*=3.7 Hz); IR (KBr) 1603, 1508, 1488, 1458, 1346, 1319, 1223, 1163, 1119, 964, 841, 766, 748, 609 cm^{-1}; Anal. Calcd for $C_{14}H_{10}FIN_2$: C, 47.75; H, 2.86; N, 7.96; found: C, 47.95; H, 2.83 N, 7.85.

1-(3-Fluorobenzyl)-3-iodo-1H-indazole (10i)



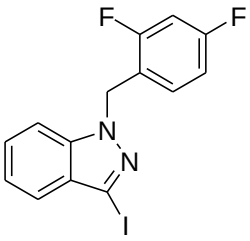
Yield 84%; a white solid; ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.42 (d, *J*=8.0 Hz, 1H), 7.29 (t, *J*=8.0 Hz, 1H), 7.20 (d, *J*=8.4 Hz, 1H), 7.15-7.09 (m, 2H), 6.91-6.82 (m, 3H), 5.48 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.8, 161.4, 138.6 (d, *J*=6.7 Hz), 130.1 (d, *J*=8.2 Hz), 128.4, 127.5, 122.5 (d, *J*=3.0 Hz), 121.4 (d, *J*=3.0 Hz), 114.6 (d, *J*=20.0 Hz), 113.9 (d, *J*=21.6 Hz), 109.4, 91.9, 52.5 (d, *J*=1.4 Hz); IR (KBr) 1614, 1591, 1489, 1450, 1321, 1252, 1165, 1138, 953, 762, 741, 692 cm^{-1}; Anal. Calcd for $C_{14}H_{10}FIN_2$: C, 47.75; H, 2.86; N, 7.96; found: C, 47.70; H, 2.89 N, 7.78.

1-(4-Fluorobenzyl)-3-iodo-1H-indazole (10j)



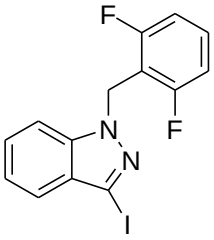
Yield 93%; a white solid; ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.42 (d, *J*=8.0 Hz, 1H), 7.30 (t, *J*=8.0 Hz, 1H), 7.21 (d, *J*=8.8 Hz, 1H), 7.14-7.10 (m, 3H), 6.89 (t, *J*=8.8 Hz, 2H), 5.46 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.3, 160.8, 139.8, 131.8 (d, *J*=2.9 Hz), 128.8 (d, *J*=8.2 Hz), 128.4, 127.4, 121.4 (d, *J*=8.9 Hz), 115.4 (d, *J*=21.6 Hz), 109.1, 91.7, 52.5; IR (KBr) 1603, 1508, 1488, 1458, 1346, 1319, 1223, 1163, 1189, 1099, 1007, 964, 853, 841, 766, 748, 610, 480 cm^{-1}; Anal. Calcd for $C_{14}H_{10}FIN_2$: C, 47.75; H, 2.86; N, 7.96; found: C, 48.00; H, 2.81 N, 7.91.

1-(2,4-Difluorobenzyl)-3-iodo-1H-indazole (10k)



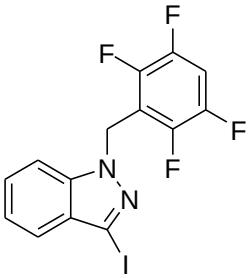
Yield 91%; a white solid; ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.43 (d, *J*=8.0 Hz, 1H), 7.40-7.33 (m, 2H), 7.16 (t, *J*=8.0 Hz, 1H), 7.09 (q, *J*=8.4 Hz, 1H), 6.80-6.70 (m, 2H), 5.54 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.7 (m), 161.3 (m), 158.8 (m), 139.9, 131.0 (m), 130.2 (m), 127.8 (m), 121.4 (m), 119.3 (m), 111.6 (m), 109.1 (m), 103.8 (m), 92.1, 45.5 (m); IR (KBr) 1616, 1506, 1493, 1456, 1429, 1321, 1271, 1242, 1165, 1140, 1105, 972, 959, 775, 763, 741, 619 cm^{-1}; Anal. Calcd for $C_{14}H_9F_2IN_2$: C, 45.43; H, 2.45; N, 7.57; found: C, 45.31; H, 2.34 N, 7.58.

1-(2,6-Difluorobenzyl)-3-iodo-1H-indazole (10l)



Yield 90%; a white solid; ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.47 (d, *J*=8.8 Hz, 1H), 7.38 (t, *J*=8.8 Hz, 2H), 7.21-7.12 (m, 2H), 6.82 (t, *J*=8.0 Hz, 2H), 5.58 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.6 (d, *J*=7.5 Hz), 160.1 (d, *J*=7.4 Hz), 139.9, 130.3 (t, *J*=9.6 Hz), 127.4, 121.3 (d, *J*=7.4 Hz), 111.7 (m), 109.2 (t, *J*=2.2 Hz), 92.0, 40.7 (t, *J*=3.8 Hz); IR (KBr) 1674, 1537, 1506, 1435, 1359, 1271, 1199, 970, 746, 692 cm^{-1}; HRMS *m/z* (ESI) Calc. for $C_{14}H_9F_2IN_2$ $[M+Na]^+$: 392.9676, found: 392.9674.

1-(2,3,5,6-Tetrafluorobenzyl)-3-iodo-1H-indazole (10m)



Yield 97%; a white solid; ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.49-7.46 (m, 3H), 7.26-7.22 (m, 1H), 7.09-7.01 (m, 1H), 5.66 (s, 2H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 146.7 (m), 144.3 (m), 140.1, 128.5, 128.0, 121.8 (d, *J*=4.5 Hz), 115.3 (t, *J*=17.1 Hz), 109.0, 106.6 (t, *J*=22.4 Hz), 93.0, 40.7; IR (KBr) 1614, 1510, 1491, 1458, 1383, 1319, 1259, 1184, 1067, 1001, 953, 881, 762, 746, 712, 623 cm^{-1}; Anal. Calcd for $C_{14}H_7F_4IN_2$: C, 41.40; H, 1.74; N, 6.90; found: C, 41.39; H, 1.93 N, 6.83.

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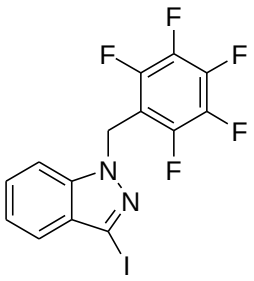
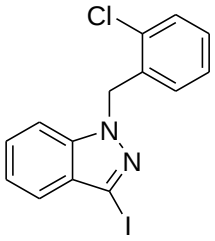
3-Iodo-1-(perfluorobenzyl)-1H-indazole (10n)



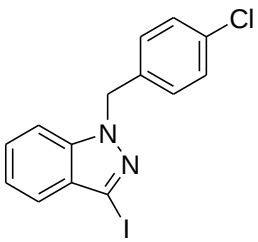
Yield 79%; a white solid; ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.50-7.46 (m, 3H), 7.26-7.22 (m, 1H), 5.62 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.7 (m), 144.2 (m), 142.7 (m), 140.0, 138.8 (m), 136.3 (m), 128.4, 128.0, 121.8 (d, *J*=17.6 Hz), 108.8, 93.2, 40.1; IR (KBr) 1655, 1614, 1508, 1458, 1317, 1250, 1173, 1123, 1080, 1005, 953, 912, 764, 750, 609 cm^{-1}; Anal. Calcd for $C_{14}H_4F_5IN_2$: C, 39.65; H, 1.43; N, 6.61; found: C, 39.67; H, 1.43 N, 6.61.

1-(2-Chlorobenzyl)-3-iodo-1H-indazole (10o)



Yield 92%; a white solid; ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.46 (d, *J*=8.0 Hz, 1H), 7.36-7.32 (m, 2H), 7.26 (d, *J*=8.4 Hz, 1H), 7.18-7.11 (m, 2H), 7.04 (t, *J*=8.0 Hz, 1H), 6.76 (d, *J*=7.6 Hz, 1H), 5.66 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.4, 134.1, 132.4, 129.5, 129.1, 128.6, 127.8, 127.2, 121.7, 121.7, 109.5, 92.1, 50.5; IR (KBr) 1614, 1572, 1477, 1460, 1445, 1321, 1249, 1170, 1118, 1070, 1040, 966, 762, 746, 712, 680 cm^{-1}; Anal. Calcd for $C_{14}H_{10}ClIN_2$: C, 45.62; H, 2.73; N, 7.60; found: C, 45.48; H, 2.45 N, 7.50.

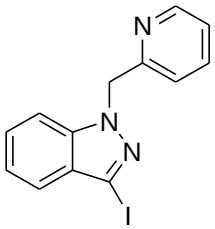
1-(4-Chlorobenzyl)-3-iodo-1H-indazole (10p)



Yield 88%; a white solid; ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.40 (d, *J*=8.0 Hz, 1H), 7.28 (t, *J*=7.2 Hz, 1H), 7.18-7.08 (m, 4H), 7.03 (d, *J*=8.4 Hz, 2H), 5.43 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.1, 134.4, 133.9, 129.0, 128.8, 128.6, 127.7, 121.8, 121.6, 109.3, 92.0, 52.8; IR (KBr) 1612, 1595, 1489,

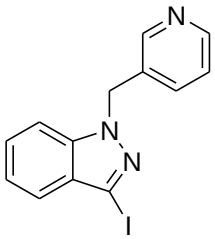
1458, 1409, 1317, 1242, 1165, 1105, 1092, 1004, 966, 843, 804, 767, 750, 654 cm^{-1}; HRMS *m/z* (ESI) Calc. for $C_{14}H_{10}ClIN_2$ $[M+Na]^+$: 390.9475, found: 390.9472.

3-Iodo-1-(pyridin-2-ylmethyl)-1H-indazole (10q)



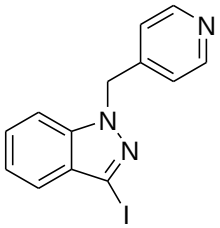
Yield 53%; a white solid; ^1H NMR (400 MHz; $CDCl_3$) δ 8.54 (d, *J*=4.8 Hz, 1H), 7.53-7.46 (m, 2H), 7.36 (d, *J*=3.6 Hz, 2H), 7.20-7.11 (m, 2H), 6.90 (d, *J*=7.6 Hz, 1H), 5.72 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.3, 149.4, 140.4, 137.0, 128.6, 127.7, 122.7, 121.6, 121.6, 121.4, 109.6, 92.1, 55.2; IR (KBr) 1614, 1593, 1572, 1491, 1460, 1437, 1319, 1248, 1169, 1121, 1097, 1005, 995, 962, 935, 766, 745, 613 cm^{-1}; Anal. Calcd for $C_{13}H_{10}IN_3$: C, 46.59; H, 3.01; N, 12.54; found: C, 46.75; H, 3.02 N,12.64.

3-Iodo-1-(pyridin-3-ylmethyl)-1H-indazole (10r)



Yield 65%; a white solid; ^1H NMR (400 MHz; $CDCl_3$) δ 8.58 (s, 1H), 8.51 (d, *J*=3.6 Hz, 1H), 7.48 (d, *J*=8.4 Hz, 2H), 7.40 (t, *J*=8.4 Hz, 1H), 7.30 (d, *J*=8.8 Hz, 1H), 7.22-7.14 (m, 2H), 5.59 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.4, 148.5, 139.9, 134.9, 131.9, 128.6, 127.8, 123.6, 121.8, 121.6, 109.0, 92.3, 50.7; IR (KBr) 3048, 2939, 2359, 1578, 1459, 1317, 1168, 960, 754 cm^{-1}; HRMS *m/z* (ESI) Calc. for $C_{13}H_{11}IN_3$ $[M+H]^+$: 335.9998, found: 335.9997.

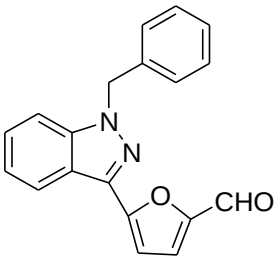
3-Iodo-1-(pyridin-4-ylmethyl)-1H-indazole (10s)



Yield 38%; a white solid; ^1H NMR (400 MHz; $CDCl_3$) δ 8.54 (d, *J*=2.8 Hz, 2H), 7.53 (d, *J*=8.0 Hz, 1H), 7.43 (t, *J*=8.0 Hz, 1H), 7.24 (t, *J*=7.6 Hz, 2H), 7.04 (d, *J*=4.4 Hz, 2H), 5.61 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.0, 145.1, 140.1, 128.5, 127.9, 121.7, 121.7, 121.5, 108.9, 92.5, 51.9; IR

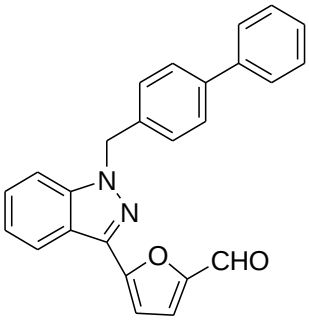
(KBr) 3066, 2932, 2363, 1600, 1459, 1415, 1315, 1170, 1067, 743 cm^{-1}; HRMS *m/z* (ESI) Calc. for $C_{13}H_{10}IN_3$ $[M+Na]^+$: 335.9998, found: 335.9999.

Typical procedure for synthesis of 5-(1-benzyl-1H-indazol-3-yl)furan-2-carbaldehyde (11a)[1]



To a mixture of **10a** (0.15 g, 0.44 mmol) and $Pd(PPh_3)_4$ (25 mg, 0.018 mmol) in DME (3.5 mL), 5-Formyl-2-furanboronic Acid (93 mg, 0.66 mmol) was added followed by the addition of sodium hydrogen carbonate (0.11 g, 1.3 mmol) in H_2O (2 mL). After the reaction mixture was refluxed under nitrogen atmosphere for overnight, quenched with H_2O and added EtOAc. The organic layer was dried over anhydrous Mg_2SO_4, and concentrated in vacuo. Purification by column chromatography on silica gel with EtOAc/hexane (1:5) gave **11a** in 42% yield (57 mg, 0.19 mmol) as a white solid. The product was identified by comparison with the reported ^1H NMR spectra in the literature. ^1H NMR (400 MHz; $CDCl_3$) δ 9.74 (s, 1H), 8.26 (d, *J*=8.4 Hz, 1H), 7.42-7.21 (m, 9H), 7.11 (d, *J*=4.0 Hz, 1H), 5.66 (s, 2H).

5-(1-(Biphenyl-methyl)-1H-indazol-3-yl)furan-2-carbaldehyde (11b)



Yield 29%; a white solid; ^1H NMR (400 MHz; $CDCl_3$) δ 9.73 (s, 1H), 8.27 (d, *J*=8.0 Hz, 1H), 7.51 (d, *J*=8.4 Hz, 4H), 7.41-7.37 (m, 5H), 7.33-7.28 (m, 4H), 7.11 (d, *J*=3.6 Hz, 1H), 5.68 (s, 2H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 171.1, 154.9, 152.0, 140.9, 140.5, 140.4, 135.2, 134.9, 128.7, 127.6, 127.5, 127.4, 127.3, 127.0, 122.5, 121.9, 121.8, 109.7, 108.8, 53.2; IR (KBr) 1677, 1536, 1365, 1255, 1020, 756 cm^{-1}; Anal. Calcd for $C_{25}H_{18}N_2O_2$: C, 79.35; H, 4.79; N, 7.40; found: C, 79.15; H, 4.83 N, 7.32.

5-(1-(4-Azidobenzyl)-1H-indazol-3-yl)furan-2-carbaldehyde (11c)

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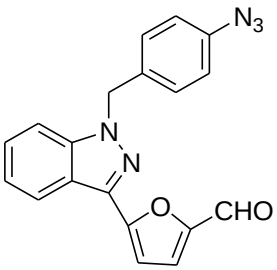
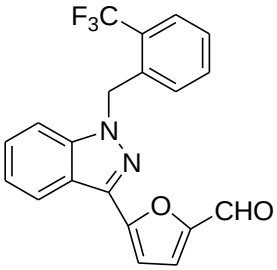


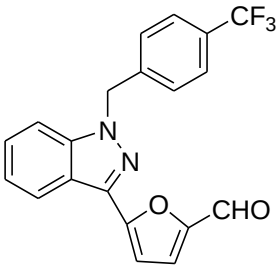
Yield 39%; a yellow solid; ^{1}H NMR (400 MHz; $CDCl_3$) δ 9.71 (s, 1H), 8.22 (d, *J*=8.4 Hz, 1H), 7.40-7.32 (m, 3H), 7.26 (t, *J*=8.0 Hz, 1H), 7.20 (d, *J*=8.4 Hz, 2H), 7.07 (d, *J*=3.6 Hz, 1H), 6.91 (d, *J*=8.4 Hz, 2H), 5.57 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.0, 154.6, 151.9, 140.3, 139.7, 134.8, 132.6, 128.6, 127.2, 122.8, 122.4, 121.8, 121.6, 119.2, 109.5, 108.8, 52.7; IR (KBr) 3124, 2834, 2103, 1681, 1504, 1299, 1025, 806, 744 cm^{-1}; HRMS *m/z* (ESI) Calc. for $C_{19}H_{13}N_5O_2$ $[M+Na]^+$: 366.0967, found: 366.0966.

5-(1-(2-(Trifluoromethyl)benzyl)-1H-indazol-3-yl)furan-2-carbaldehyde (11d)



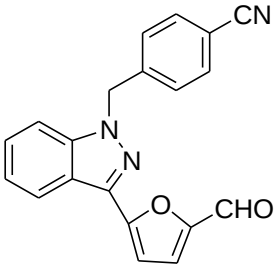
Compound **11d** was synthesized from **10d** (0.73 g, 1.8 mmol) applying the procedure described for **11a**. The reaction mixture stirring for 7 h gave the crude **11d**, which was used for the next step without further purification.

5-(1-(4-(Trifluoromethyl)benzyl)-1H-indazol-3-yl)furan-2-carbaldehyde (11e)



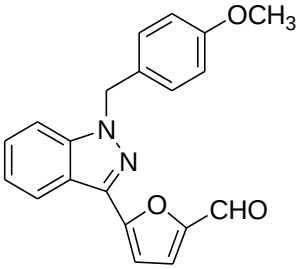
Yield 27%; a yellow solid; ^{1}H NMR (400 MHz; $CDCl_3$) δ 9.75 (s, 1H), 8.29 (d, *J*=8.0 Hz, 1H), 7.57 (d, *J*=8.0 Hz, 2H), 7.45-7.40 (m, 2H), 7.36-7.31 (m, 4H), 7.12 (d, *J*=3.6 Hz, 1H), 5.72 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.2, 154.6, 151.2, 140.6, 140.1, 135.4, 130.5, 130.1, 127.6, 127.3, 125.8 (m), 122.7, 122.1, 121.8, 109.4, 109.1, 52.8, 29.7; IR (KBr) 1674, 1539, 1464, 1421, 1327, 1263, 1163, 1109, 1067, 1020, cm^{-1}; Anal. Calcd for $C_{20}H_{13}F_3N_2O_2$: C, 64.87; H, 3.54; N, 7.56; found: C, 64.70; H, 3.55 N, 7.35.

4-((3-(5-Formylfuran-2-yl)-1H-indazol-1-yl)methyl)benzonitrile (11f)



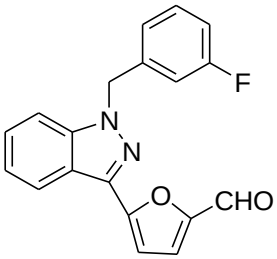
Yield 27%; a yellow solid; ^{1}H NMR (400 MHz; $CDCl_3$) δ 9.75 (s, 1H), 8.29 (d, *J*=4.0 Hz, 1H), 7.61 (d, *J*=8.0 Hz, 2H), 7.47-7.40 (m, 2H), 7.36-7.26 (m, 4H), 7.12 (d, *J*=3.6 Hz, 1H), 5.72 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.2, 154.4, 152.1, 140.6, 135.5, 132.6, 127.8, 127.7, 127.7, 127.6, 122.8, 122.0, 121.7, 118.5, 111.9, 109.4, 109.2, 52.7; IR (KBr); 2361, 1672, 1537, 1464, 1416, 1359, 1259, 1204, 1161, 1096 cm^{-1}; Anal. Calcd for $C_{20}H_{13}N_3O_2$: C, 73.38; H, 4.00; N, 12.84; found: C, 73.17; H, 4.29; N, 12.63.

5-(1-(4-Methoxybenzyl)-1H-indazol-3-yl)furan-2-carbaldehyde (11g)



Yield 39%; a yellow solid; ^{1}H NMR (400 MHz; $CDCl_3$) δ 9.74 (s, 1H), 8.25 (d, *J*=8.0 Hz, 1H), 7.40-7.38 (m, 3H), 7.28 (t, *J*=8.0 Hz, 1H), 7.20 (d, *J*=8.8 Hz, 2H), 7.10 (d, *J*=3.6 Hz, 1H), 6.83 (d, *J*=8.8 Hz, 2H), 5.59 (s, 2H), 3.76 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.0, 159.2, 154.8, 151.8, 140.3, 134.5, 128.5, 128.0, 127.0, 122.9, 122.3, 121.7, 114.0, 109.7, 108.7, 55.1, 52.9; IR (KBr) 1665, 1611, 1541, 1512, 1466, 1360, 1248, 1205, 1177, 1028 cm^{-1}; Anal. Calcd for $C_{20}H_{16}N_2O_3$: C, 72.28; H, 4.85; N, 8.43; found: C, 72.10; H, 4.94 N, 8.75.

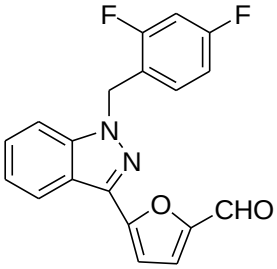
5-(1-(3-fluorobenzyl)-1H-indazol-3-yl)furan-2-carbaldehyde (11i)



Yield 33% yield; a yellow solid; ^{1}H NMR (400 MHz; $CDCl_3$) δ 9.73 (s, 2H), 8.26 (d, *J*=8.0 Hz, 1H), 7.42-7.23 (m, 5H), 7.10 (d, *J*=3.6 Hz, 1H), 7.00-6.88 (m, 3H), 5.63 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.1, 164.1, 161.7, 154.6, 152.0, 140.5, 138.5 (d, *J*=6.7 Hz), 135.1, 130.4 (d, *J*=8.2 Hz),

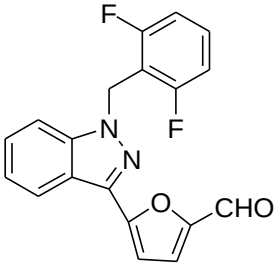
127.4, 122.8, 122.6 (m), 121.9, 121.7, 114.9 (d, *J*=20.8 Hz), 114.1 (d, *J*=22.2 Hz), 109.5, 108.9, 52.7 (d, *J*=1.5 Hz); IR (KBr) 1678, 1591, 1335, 1487, 1366, 1259, 1198, 1161, 1024, 901, 762, 748, 694 cm^{-1}; Anal. Calcd for $C_{19}H_{13}FN_2O_2$: C, 71.24; H, 4.09; N, 8.75; found: C, 71.21; H, 3.84 N, 8.75

5-(1-(2,4-Difluorobenzyl)-1H-indazol-3-yl)furan-2-carbaldehyde (11k)



Yield 42%; a yellow solid; ^{1}H NMR (400 MHz; $CDCl_3$) δ 9.73 (s, 1H), 8.25 (d. *J*=8.4 Hz, 1H), 7.44 (d, *J*=3.6 Hz, 2H), 7.39 (d, *J*=4.0 Hz, 1H), 7.32-7.28 (m, 1H), 7.14-7.08 (m, 2H), 6.87-6.75 (m, 2H), 5.64 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.1, 163.9 (d, *J*=11.1 Hz), 161.4 (d, *J*=11.9 Hz), 154.6, 152.1, 140.5, 135.3, 130.6 (dd, *J*=9.6 Hz, *J*=5.2 Hz), 127.4, 122.8, 122.6, 121.9, 121.6, 119.2 (dd, *J*=14.9 Hz, *J*=3.8 Hz), 111.8 (dd, *J*=20.8 Hz, *J*=3.7 Hz), 109.4, 109.0, 104.0 (t, *J*=25.3 Hz), 46.0 (d, *J*=4.5 Hz); IR (KBr) 1674, 1537, 1506, 1435, 1360, 1271, 1099, 970, 746, 692, 520 cm^{-1}; Anal. Calcd for $C_{19}H_{12}F_2N_2O_2$: C, 67.45; H, 3.58; N, 8.28; found: C, 67.30; H, 3.62 N, 8.49

5-(1-(2,6-Difluorobenzyl)-1H-indazol-3-yl)furan-2-carbaldehyde (11l)



Yield 53%; a yellow solid; ^{1}H NMR (400 MHz; $CDCl_3$) δ 9.67 (s, 1H), 8.20 (d, *J*=8.0 Hz, 1H), 7.55 (d, *J*=8.4 Hz, 1H), 7.45-7.40 (m, 1H), 7.33-7.22 (m, 3H), 7.04 (d, *J*=3.6 Hz, 1H), 6.91-6.86 (m, 2H), 5.65 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.0, 162.7 (d, *J*=7.4 Hz), 160.2 (d, *J*=7.5 Hz), 154.8, 151.9, 140.4, 135.0, 130.5 (t, *J*=9.6 Hz), 127.1, 122.8, 122.3, 121.7, 121.4, 111.8 (m), 109.4, 108.8, 40.9; IR (KBr) 3121, 2855, 2362, 1665, 1470, 1361, 1258, 1164, 1035, 794 cm^{-1}; Anal. Calcd for $C_{19}H_{12}F_2N_2O_2$: C, 67.45; H, 3.58; N, 8.28; found: C, 67.70; H, 3.52 N, 8.23

5-(1-(2,3,5,6-Tetrafluorobenzyl)-1H-indazol-3-yl)furan-2-carbaldehyde (11m)

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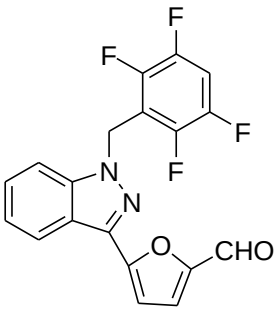
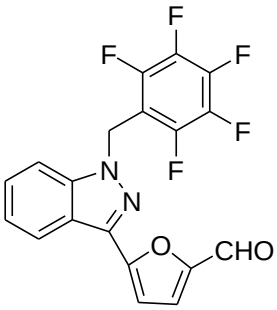


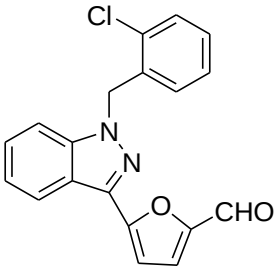
Yield 18%; a yellow solid; ^{1}H NMR (400 MHz; $CDCl_3$) δ 9.73 (s, 1H), 8.27 (d, *J*=8.0 Hz, 1H), 7.58 (d, *J*=8.4 Hz, 1H), 7.50 (t, *J*=7.6 Hz, 1H), 7.37 (d, *J*=3.6 Hz, 1H), 7.33 (t, *J*=8.0 Hz, 1H), 7.11-7.03 (m, 2H), 5.72 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.2, 154.6, 152.2, 146.7 (m), 144.3 (m), 140.5, 135.7, 127.6, 122.7, 122.0, 121.5, 115.1 (t, *J*=17.1 Hz), 109.2, 109.2, 106.7 (t, *J*=22.4 Hz), 40.8; IR (KBr) 1661, 1537, 1508, 1385, 1367, 1259, 1198, 1182, 1024, 810, 764, 745, 712 cm^{-1}; HRMS *m/z* (ESI) Calc. for $C_{19}H_{10}F_4N_2NaO_2$ $[M+Na]^+$: 397.0576, found: 397.0578.

5-(1-(Perfluorobenzyl)-1H-indazol-3-yl)furan-2-carbaldehyde (11n).



Compound **11n** was synthesized from **10n** (0.60 g, 1.4 mmol) applying the procedure described for **11a**. Purification by column chromatography on silica gel with hexane/ethyl acetate (10/1) gave the crude **11n**, which was used for the next step without further purification.

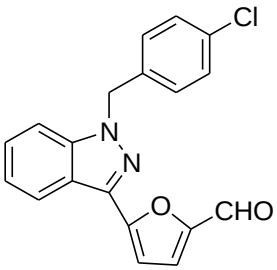
5-(1-(2-Chlorobenzyl)-1H-indazol-3-yl)furan-2-carbaldehyde (11o)



Yield 36%; a yellow solid; ^{1}H NMR (400 MHz; $CDCl_3$) δ 9.74 (s, 1H), 8.28 (d, *J*=8.4 Hz, 1H), 7.44-7.37 (m, 4H), 7.31 (t, *J*=8.0 Hz, 1H), 7.21 (t, *J*=8.0 Hz, 1H), 7.11-7.08 (m, 2H), 6.75 (d, *J*=7.6 Hz, 1H), 5.77 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.1, 154.7, 152.1, 140.8, 135.3, 133.8, 132.3, 129.5, 129.1, 128.3, 127.4, 127.2, 122.8, 122.6, 121.9, 121.6, 109.6, 109.0, 50.5; IR (KBr) 1672, 1591, 1537, 1464, 1435, 1360, 1261, 1161, 1096, 1020, 901, 746, 692 cm^{-1}; Anal. Calcd for

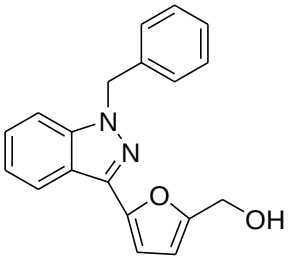
$C_{19}H_{13}ClN_2O_2$: C, 67.76; H, 3.89; N, 8.32; found: C, 67.61; H, 3.86 N, 8.41.

5-(1-(4-Chlorobenzyl)-1H-indazol-3-yl)furan-2-carbaldehyde (11p)



Yield 14%; a yellow solid; ^{1}H NMR (400 MHz; $CDCl_3$) δ 9.74 (s, 1H), 8.26 (d, *J*=8.4 Hz, 1H), 7.43-7.39 (m, 2H), 7.34-7.26 (m, 4H), 7.15 (d, *J*=8.4 Hz, 2H), 7.10 (d, *J*=3.6 Hz, 1H), 5.61 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.2, 154.7, 152.1, 140.5, 135.1, 134.5, 133.9, 129.0, 128.5, 127.4, 122.9, 122.6, 122.0, 121.8, 109.5, 108.9, 52.7; IR (KBr) 1672, 1591, 1533, 1491, 1464, 1439, 1408, 1362, 1327, 1254, 1188, 1153, 1096, 1015, 968, 898, 804, 758, 744, 694 cm^{-1}; HRMS *m/z* (ESI) Calc. for $C_{19}H_{13}ClN_2O_2$ $[M+Na]^+$: 359.0563, found: 359.0566.

Typical procedure for synthesis of (5-(1-benzyl-1H-indazol-3-yl)furan-2-yl)methanol (12a)[1]



To a mixture of **11a** (1.24 g, 4.1 mmol) in MeOH (1003 mL) was added sodium borohydride (311 mg, 16.1 mmol) and the mixture was stirred at room temperature for 1 h. The solvent was removed under reduced pressure and the mixture was dissolved in ethyl acetate, washed with aqueous HCl solution (2M) followed by water, dried over $MgSO_4$ anhydride, and the concentrated. Purification by column chromatography on silica gel with hexane/ethyl acetate (2/1) gave 12a (0.98 g, 3.2 mmol, 79%) as a white solid. The product was identified by comparison with the reported ^{1}H NMR spectra. ^{1}H NMR (400 MHz; $CDCl_3$) δ 8.05 (d, *J*=8.0 Hz, 1H), 7.37-7.18 (m, 8H), 6.87 (d, *J*=3.6 Hz, 1H), 6.46 (d, *J*=3.2 Hz, 1H), 5.64 (s, 2H), 4.74 (d, *J*=4.8 Hz, 2H), 2.35 (brs, 1H).

(5-(1-(Biphenyl-methyl)-1H-indazol-3-yl)furan-2-yl)methanol (12b)

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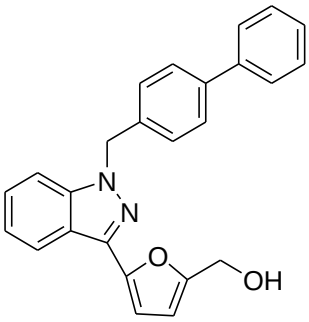
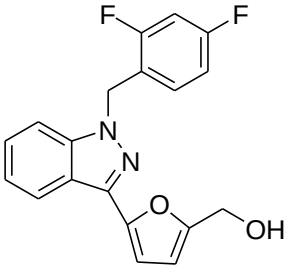


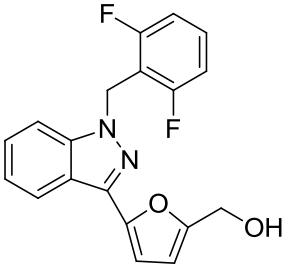
Yeild 62%; a white solid; ^{1}H NMR (400 MHz; $CDCl_3$) δ 8.05 (d, *J*=8.0 Hz, 1H), 7.50 (t, *J*=8.0 Hz, 4H), 7.41-7.18 (m, 8H), 6.87 (d, *J*=3.6 Hz, 1H), 6.45 (d, *J*=3.2 Hz, 1H), 5.67 (s, 2H), 4.74 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.0, 148.4, 140.6, 140.4, 136.2, 135.5, 128.6, 127.5, 127.4, 127.3, 126.9, 126.9, 121,5, 121.4, 121.2, 109.5, 109.5, 107.9, 57.4, 52.8; IR (KBr) 3388, 3029, 2361, 1618, 1494, 1318, 1160, 1009, 754, 699 cm^{-1}; HRMS *m/z* (ESI) Calc. for $C_{25}H_{20}N_2O_2$ $[M+Na]^+$: 403.1422, found: 403.1419.

(5-(1-(2,4-Difluorobenzyl)-1H-indazol-3-yl)furan-2-yl)methanol (12k)



Yield 52% yield; a white solid; ^{1}H NMR (400 MHz; $CDCl_3$) δ 8.03 (d, *J*=8.4 Hz, 1H), 7.39-7.26 (m, 2H), 7.20 (t, *J*=8.0 Hz, 1H), 7.04 (q, *J*=8.8 Hz, 1H), 6.86-6.79 (m, 2H), 6.73 (t, *J*=8.0 Hz, 1H), 6.45 (d, *J*=3.2 Hz, 1H), 5.61 (s, 2H), 4.74 (s, 2H), 2.63 (brs, 1H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 163.8 (d, *J*=11.9 Hz), 161.3 (d, *J*=14.1 Hz), 154.0, 148.4, 140.4, 136.6, 130.4 (dd, *J*=9.6 Hz, *J*=5.2 Hz), 127.1, 121.6, 121.6, 121.2, 119.6 (dd, *J*=14.9 Hz, *J*=3.7 Hz), 111.7 (dd, *J*=20.8 Hz, *J*=3.7 Hz), 109.6, 109.2, 108.1, 103.8 (t, *J*=25.3 Hz), 57.6, 45.7 (d, *J*=4.4 Hz); IR (KBr) 3396, 1618, 1605, 1506, 1472, 1429, 1271, 1140, 1099, 1016, 972, 851, 779, 743, 683 cm^{-1}; Anal. Calcd for $C_{19}H_{14}F_2N_2O_2$: C, 67.05; H, 4.15; N, 8.23; found: C, 66.94; H, 4.11 N, 8.10.

(5-(1-(2,6-Difluorobenzyl)-1H-indazol-3-yl)furan-2-yl)methanol (12l)



Yield 85% yield; a white solid; mp 113 °C; ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.97 (d, *J*=8.4 Hz, 1H),

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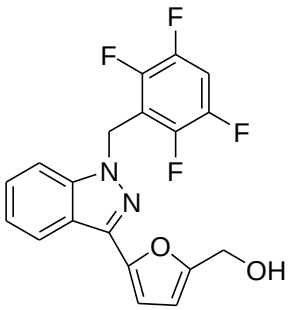
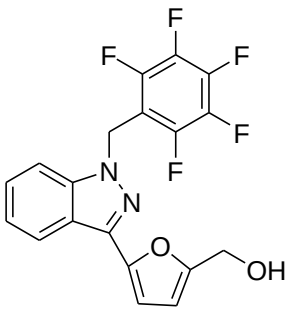
7.48 (d, *J*=8.4 Hz, 1H), 7.36 (t, *J*=8.0 Hz, 1H), 7.25-7.12 (m, 2H), 6.88-6.79 (m, 3H), 6.38 (d, *J*=2.3 Hz, 1H), 5.64 (s, 2H), 4.70 (s, 2H), 2.79 (brs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ162.8 (d, *J*=8.2 Hz, 1H), 160.3 (d, *J*=8.2 Hz), 154.0, 148.4, 140.3, 136.4, 130.2 (t, *J*=10.5 Hz) , 126.8, 121.5, 120.3, 121.0. 111.7 (d, *J*=6.0 Hz), 111.5 (d, *J*=6.0 Hz), 109.4 (d, *J*=13.4 Hz), 107.9, 57.5, 40.8, 40.7; IR (KBr) 3288, 1626, 1593, 1472, 1423, 1338, 1161, 1088, 1626, 1005 cm^{-1}. HRMS *m/z* (ESI) Calc. for $C_{19}H_{14}F_2N_2O_2$ $[M+Na]^+$: 363.0921, found: 363.0923.

(5-(1-(2,3,5,6-Tetrafluorobenzyl)-1H-indazol-3-yl)furan-2-yl)methanol (12m)



Yield 88% yield; a white solid; mp 126-127 °C; ^{1}H NMR (400 MHz; $CDCl_3$) δ 8.05 (d, *J*=8.4 Hz, 1H), 7.51 (d, *J*=8.4 Hz, 1H), 7.45 (t, *J*=8.4 Hz, 1H), 7.26-7.21 (m, 1H), 7.03 (pent, *J*=9.6 Hz, 1H), 6.85 (d, *J*=3.2 Hz, 1H), 6.44 (d, *J*=3.2 Hz, 1H), 5.70 (s, 2H), 4.73 (s, 2H), 2.13 (brs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.1, 148.2, 146.7 (m), 144.2 (m), 140.4, 137.0, 127.2, 121.7, 121.6, 121.1, 115.4 (t, *J*=17.2 Hz), 109.5, 109.0, 108.2, 106.4 (t, *J*=22.3 Hz), 57.5, 40.6; IR (KBr) 3364, 1614, 1510, 1470, 1306, 1259, 1173, 1084, 1009 cm^{-1}; HRMS *m/z* (ESI) Calc. for $C_{19}H_{12}F_4N_2O_2$ $[M+Na]^+$: 399.0733, found: 399.0731.

(5-(1-(Perfluorobenzyl)-1H-indazol-3-yl)furan-2-yl)methanol (12n)



Yield 45% yield; a white solid; ^{1}H NMR (400 MHz; $CDCl_3$) δ 8.04 (d, *J*=8.4 Hz, 1H), 7.50-7.43 (m, 2H), 7.26-7.21 (m, 1H), 6.85 (d, *J*=3.2 Hz, 1H), 6.44 (d, *J*=3.2 Hz, 1H), 5.65 (s, 2H), 4.73 (s, 2H), 2.28 (brs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.2, 148.2, 146.7, 144.3, 140.3, 138.8, 137.2, 136.3, 127.3, 121.7, 121.7, 121.1, 109.6, 108.9, 108.3, 57.5, 40.0; IR (KBr) 3340, 1659, 1611, 1524, 1506, 1306, 1163, 1124, 1084, 1022, 995, 961, 922, 788, 750, 615 cm^{-1}; Anal. Calcd for $C_{19}H_{11}F_5N_2O_2$: C, 57.88; H, 2.81; N, 7.10; found: C, 57.81; H, 2.67 N, 7.33.

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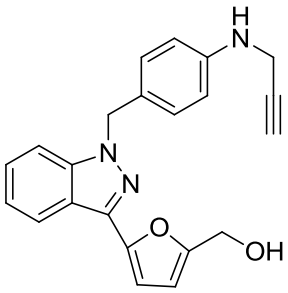
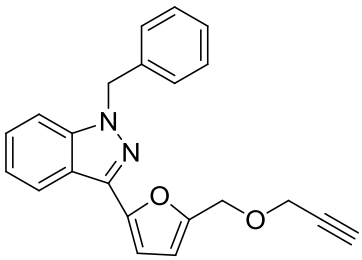
Synthesis of (5-(1-(4-(prop-2-yn-1-ylamino)benzyl)-1H-indazol-3-yl)furan-2-yl)methanol (12u)



Compound **12u** was prepared from **12c** in two steps. To a mixture of lithium aluminum hydride (170 mg, 4.48 mmol) in THF (18 mL) was added a THF solution (2 mL) of **12c** (778 mg, 2.24 mmol) at -15 °C. The mixture was stirred at room temperature for 12 h. The reaction was quenched by addition of iced water and the generating aluminum hydroxide was removed by suction filtration. The filtrate was extracted ether, dried over $MgSO_4$ anhydride, and concentrated. The residue was recrystalized from methanol and the resulting amine (204 mg, 0.638 mmol) was dissolved in THF (3 mL). K_2CO_3 (87 mg, 0.63 mmol) and propargylbromide (47 μL, 0.63 mmol) were added to the solution. The reaction mixture was stirred at 50 °C for 3 d and the solvent was removed under reduced pressure. The residue was purified by preparative TLC with hexane/ethyl acetate (1/1) to give **12u** (59 mg, 0.164 mmol, 25%) as a white solid; mp 106-107 °C; ^{1}H NMR (400 MHz; $CDCl_3$) δ 8.03 (d, *J*=8.4 Hz, 1H), 7.33 (s, 2H), 7.21-7.17 (m, 1H), 7.12 (d, *J*=8.4 Hz, 2H), 6.85 (d, *J*=3.2 Hz, 1H), 6.60 (d, *J*=8.4 Hz, 2H), 6.46 (d, *J*=3.2 Hz, 1H), 5.54 (s, 2H), 4.74 (s, 2H), 3.88 (d, *J*=2.0 Hz, 2H), 2.18 (s, 1H).; ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.8, 148.7, 146.4, 140.3, 135.8, 128.4, 126.6, 126.4, 121.4, 121.3, 121.2, 113.5, 109.8, 109.6, 107.7, 80.7, 71.3, 56.7, 53.0, 33.5.; IR (KBr) 3396, 1616, 1521, 1079, 745, 464 cm^{-1}; HRMS *m/z* (ESI) Calc. for $C_{22}H_{19}N_3O_2$ $[M+Na]^+$: 380.1375, found: 380.1379.

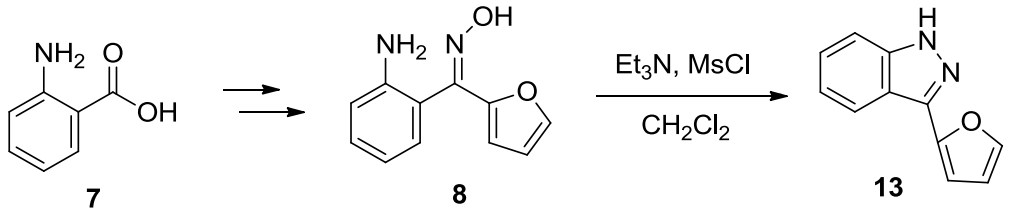
Synthesis of 1-benzyl-3-(5-((prop-2-yn-1-yloxy)methyl)furan-2-yl)-1H-indazole (12v)



$NaBH_4$ (111 mg, 4.58 mmol) was dissoleved in DMF (5 mL) and **12a** (302 mg, 0.993 mmol) was then added at 0 °C with stirring. After 10 min with stirring, propargylbromide (83 μL, 1.10 mmil) was then added to the mixture and the reaction mixture was stirred at room temperature for 4 h. The reaction was quenched by addition of water and the mixture was extracted with ether, dried over $MgSO_4$ anhydride, and then concentrated. The residue was purified by silica gel column chromatography with hexane/ethyl acetate (50/1) to give **12v** (301 mg, 0.878 mmol, 88%) as a white solid; ^{1}H NMR (400 MHz; $CDCl_3$) δ 8.11 (d. *J*=8.0 Hz, 1H), 7.36-7.19 (m, 8H), 6.89 (d, *J*=3.6 Hz,

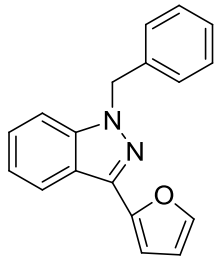
1H), 6.55 (d, *J*=3.2 Hz, 1H), 5.64 (s, 2H), 4.71 (s, 2H), 4.23 (d, *J*=2.4 Hz, 2H), 2.49 (t, *J*=2.4 Hz, 1H).; ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.5, 149.4, 140.5, 136.6, 136.1, 128.7, 127.7, 127.0, 126.8, 121.7, 121.4, 121.4, 112.0, 109.5, 107.6, 79.4, 74.9, 63.2, 56.7, 53.2.; IR (KBr) 3275, 3060, 2857, 1607, 1496, 1338, 1160, 1082, 1010, 794, 747, 642 cm^{-1}; HRMS *m/z* (ESI) Calcd. for $C_{22}H_{18}N_2O_2$ $[M+Na]^+$: 365.1266, found: 365.1263.

Preparation of 3-(Furan-2-yl)-1H-indazole (13)[4]



(Z)-(2-Aminophenyl)(furan-2-yl)methanone oxime **8** was synthesized from anthranilic acid **7** in two steps according to the literature procedure.[4] To a mixture of **8** (52.8 mg, 0.261 mmol), triethylamine (73 μL, 0.522 mmol) in CH_2Cl_2 (4 mL) was added methanesulfonyl chloride (24.3 mL, 0.313 mmol) dissolved in CH_2Cl_2 (1.3 mL) at 0 °C with stirring. The mixture was allowed to room temperature and stirred for 5 h. The solvent was evaporated and the residue was purified by column chromatography on silica gel with hexane/ethyl acetate (5/1) to give **13** in 88% yield (42.3 mg, 0.23 mmol) as a white solid. The product was identified by comparison with the reported ^{1}H NMR spectra in the literature. ^{1}H NMR (400 MHz; $CDCl_3$) δ 11.0 (brs, 1H), 8.12 (d, *J*=8.4 Hz, 1H), 7.61-7.60 (m, 1H), 7.48 (d, *J*=8.4 Hz, 1H), 7.42 (t, *J*=8.0 Hz, 1H), 7.25 (t, *J*=9.2 Hz, 1H), 6.97 (d, *J*=3.2 Hz, 1H), 6.59-6.58 (m, 1H).

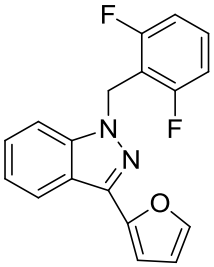
Synthesis of 1-benzyl-3-(furan-2-yl)-1H-indazole (14a)[1]



To a mixture of 13 (32.7 mg, 0.178 mmol) in THF (3 mL) was added potassium *tert*-butoxyde (30 mg, 0.266 mol) and the micture was stirred at 0 °C for 1 h. Benzylbromide (23 μL, 0.19 mmol) was added at 0 °C and the reaction mixture was stirred at room temperature for 12h. The reaction was quenched by addition of aqueous HCl solution (1M) and ectracted with ethyl acetate. The organic layer was washed with saturated $NaHCO_3$ followed by brine, dried over $MgSO_4$ anhydride, and concentrated. Purification by column chromatography on silica gel with hexane/ethyl acetate (15/1) gave **14a** (42 mg, 0.154 mmol, 87%) as a white solid. The product was identified by comparison with the reported ^{1}H NMR spectra. ^{1}H NMR (400 MHz; $CDCl_3$) δ 8.08 (d, *J*=8.4 Hz, 1H), 7.57 (s, 1H), 7.35-7.18 (m,

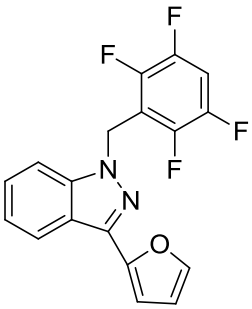
8H), 6.92 (d, *J*=3.2 Hz, 1H), 6.56-6.55 (m, 1H), 5.62 (s, 2H).

1-(2,6-Difluorobenzyl)-3-(furan-2-yl)-1H-indazole (14b).



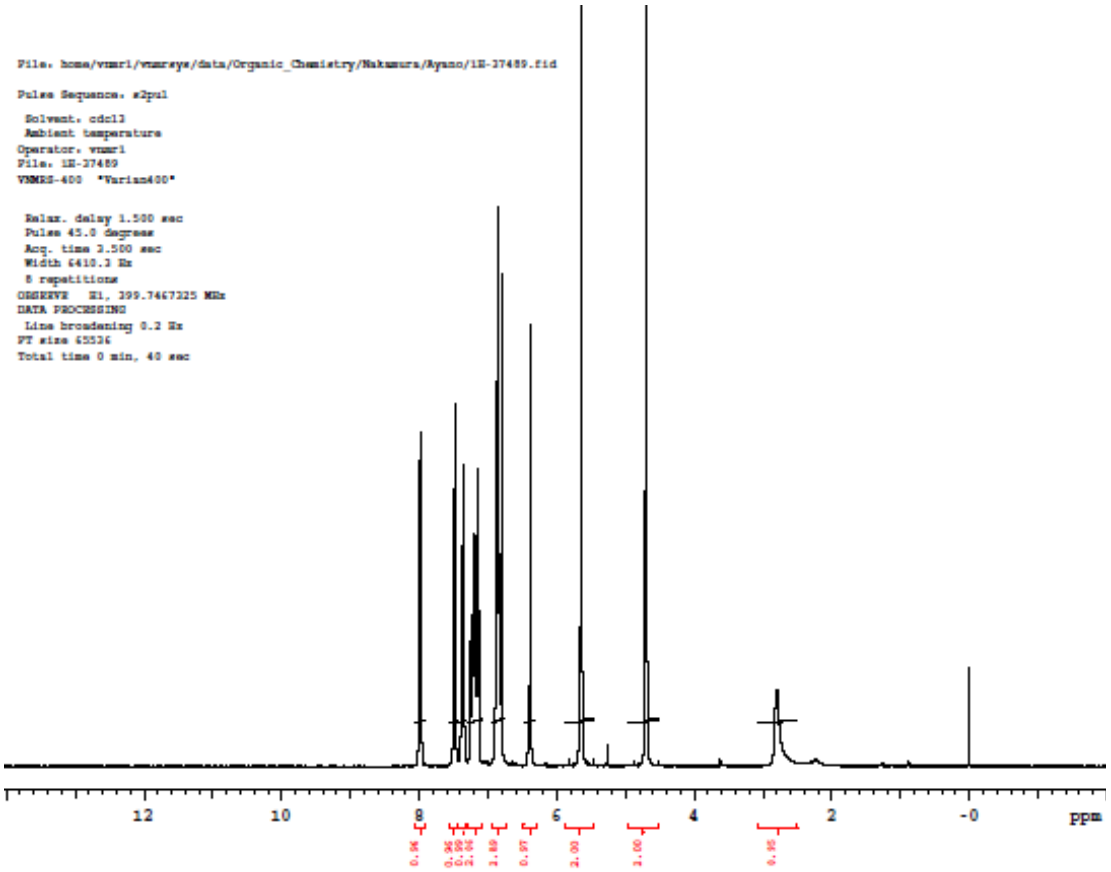
White solid; mp 119-120 °C; ^{1}H NMR (400 MHz; $CDCl_3$) δ 8.06 (d, *J*=8.0 Hz, 1H), 7.54 (t, *J*=7.6 Hz, 2H), 7.40 (t, *J*=8.0 Hz, 1H), 7.28-7.19 (m, 2H), 6.91-6.86 (m, 3H), 6.54-6.53 (m, 1H), 5.68 (s, 2H).; ^{13}C NMR (100 MHz, $CDCl_3$) 162.8 (d, *J*=7.4 Hz), 160.3 (d, *J*=7.4 Hz), 158.8, 142.1, 140.3, 136.6, 130.2 (t, *J*=10.4 Hz), 126.7, 121.4 (d, *J*=25.3 Hz), 121.1, 112.3 (t, *J*=18.6 Hz), 111.6 (m), 111.4 (m), 109.3 (m), 107.0, 40.8 (m).; IR (KBr) 3437, 2923, 2853, 1627, 1469, 1171, 1011, 747 cm^{-1}; HRMS *m/z* (ESI) Calc. for $C_{18}H_{12}F_2N_2O$ $[M+Na]^+$: 333.0815, found: 333.0812.

1-(2,3,5,6-Tetrafluorobenzyl)-3-(furan-2-yl)-1H-indazole (14c).

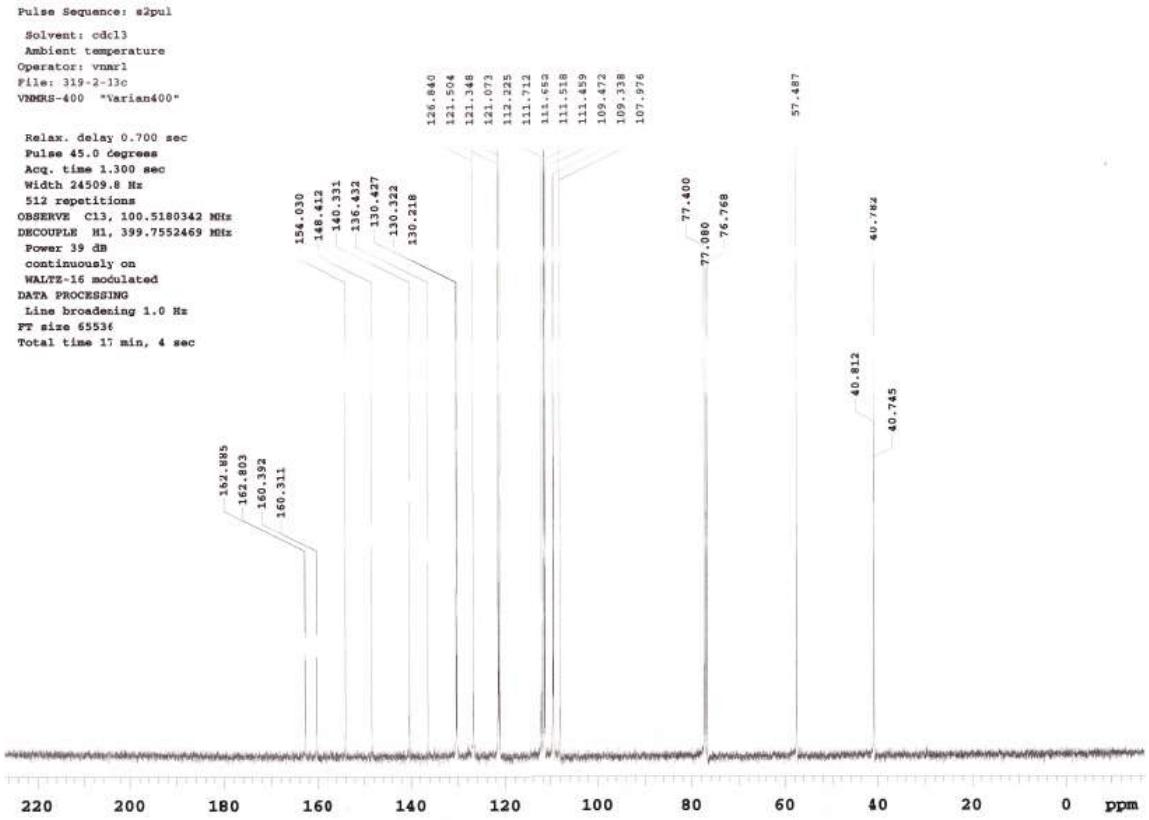


White solid; mp 108 °C; ^{1}H NMR (400 MHz; $CDCl_3$) δ 8.06 (d, *J*=8.0 Hz, 1H), 7.57-7.54 (m, 1H), 7.49 (d, *J*=8.4 Hz, 1H), 7.42 (t, *J*=8.0 Hz, 1H), 7.21 (t, *J*=8.0 Hz, 1H), 7.02-6.94 (m, 1H), 6.90 (d, *J*=3.2 Hz, 1H), 6.52-6.51 (m, 1H), 5.65 (s, 2H).; ^{13}C NMR (100 MHz, $CDCl_3$); 148.5, 147.0 (m), 146.3 (m), 144.5 (m), 143.8 (m), 142.3, 140.4, 137.2, 127.1, 121.6 (d, *J*=14.1 Hz), 121.1, 115.5 (t, *J*=17.1 Hz), 111.3, 108.9, 107.3, 106.3 (t, *J*=22.3 Hz), 40.5.; IR (KBr) 3085, 1605, 1513, 1263, 1171, 1007, 892, 743 cm^{-1}; HRMS *m/z* (ESI) Calc. for $C_{18}H_{10}F_4N_2O$ $[M+Na]^+$: 369.0627, found: 369.0625.

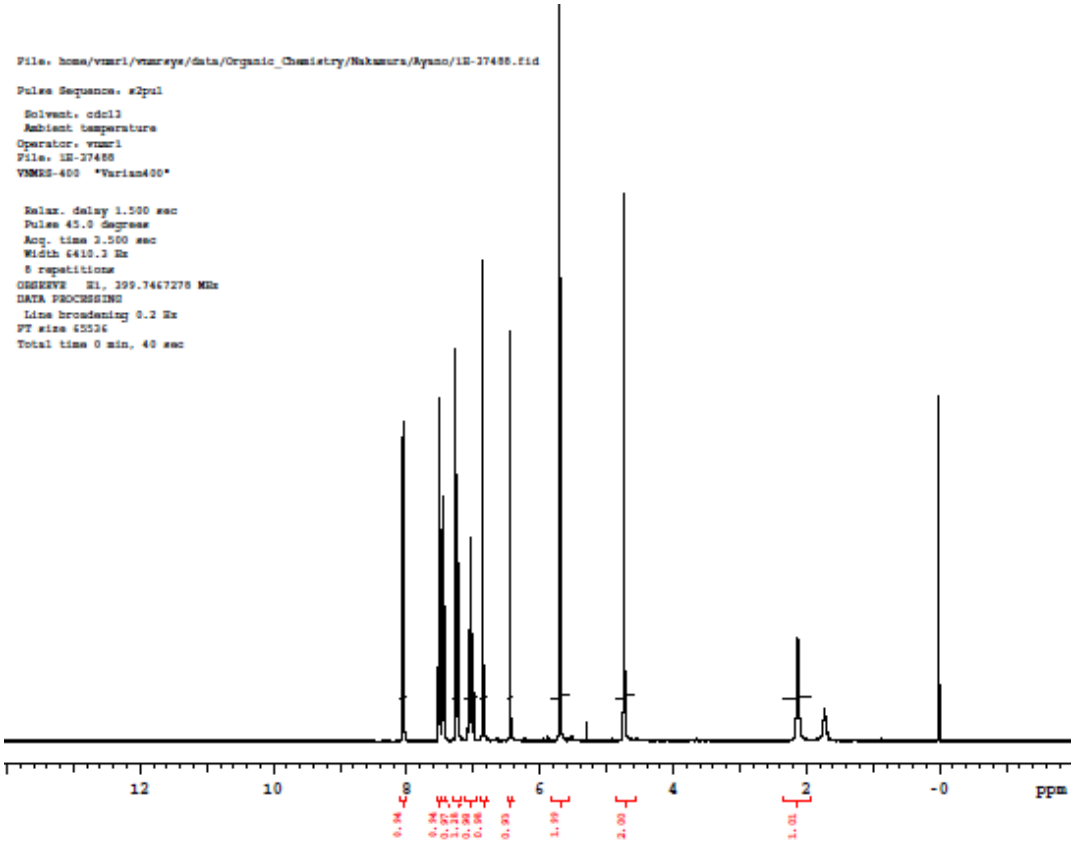
^{1}H NMR of 12l (400 Hz, $CDCl_3$)



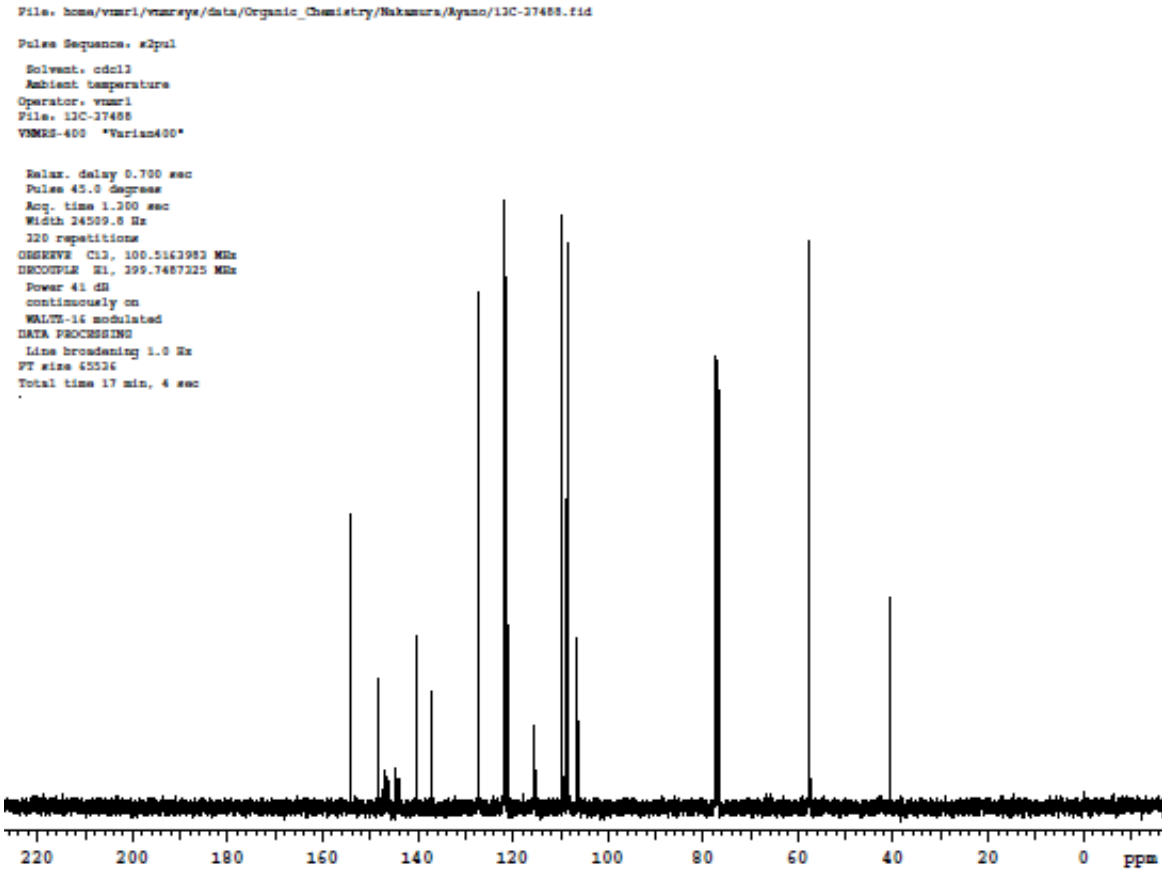
^{13}C NMR of 12l (100 Hz, $CDCl_3$)



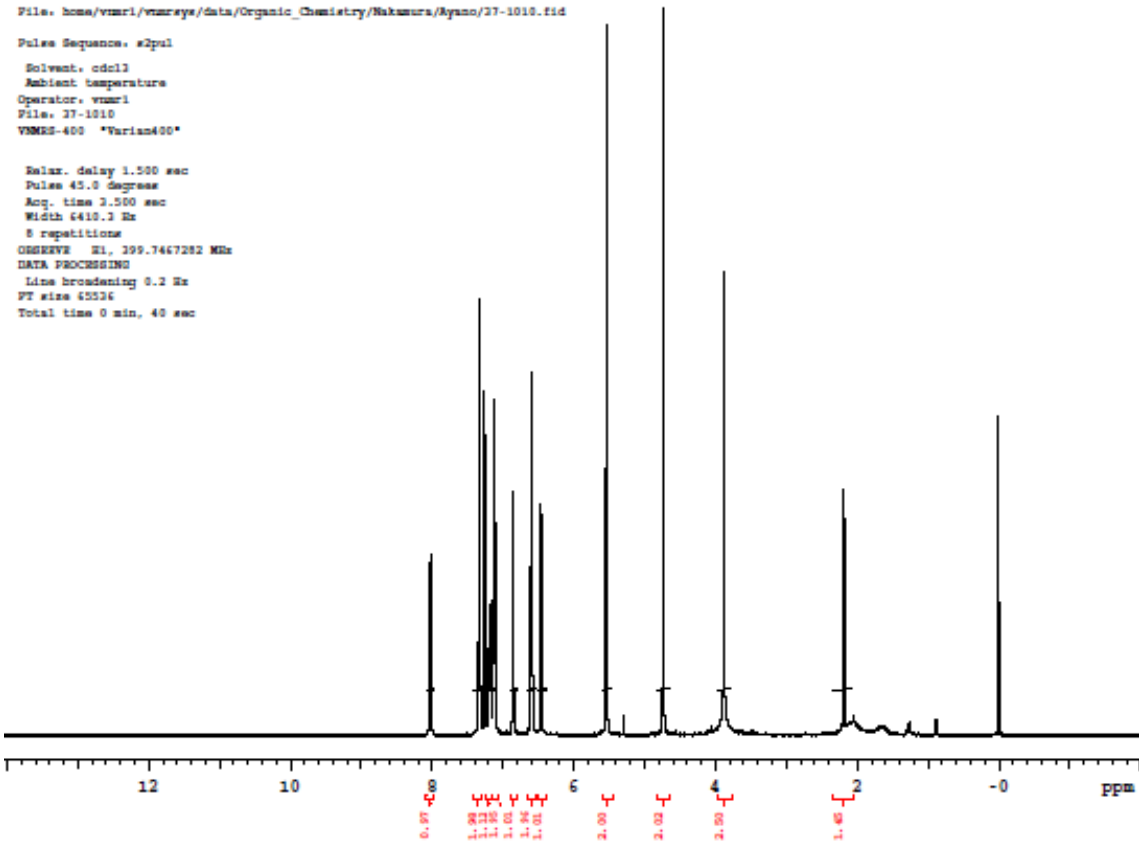
^{1}H NMR of 12m (400 Hz, $CDCl_3$)



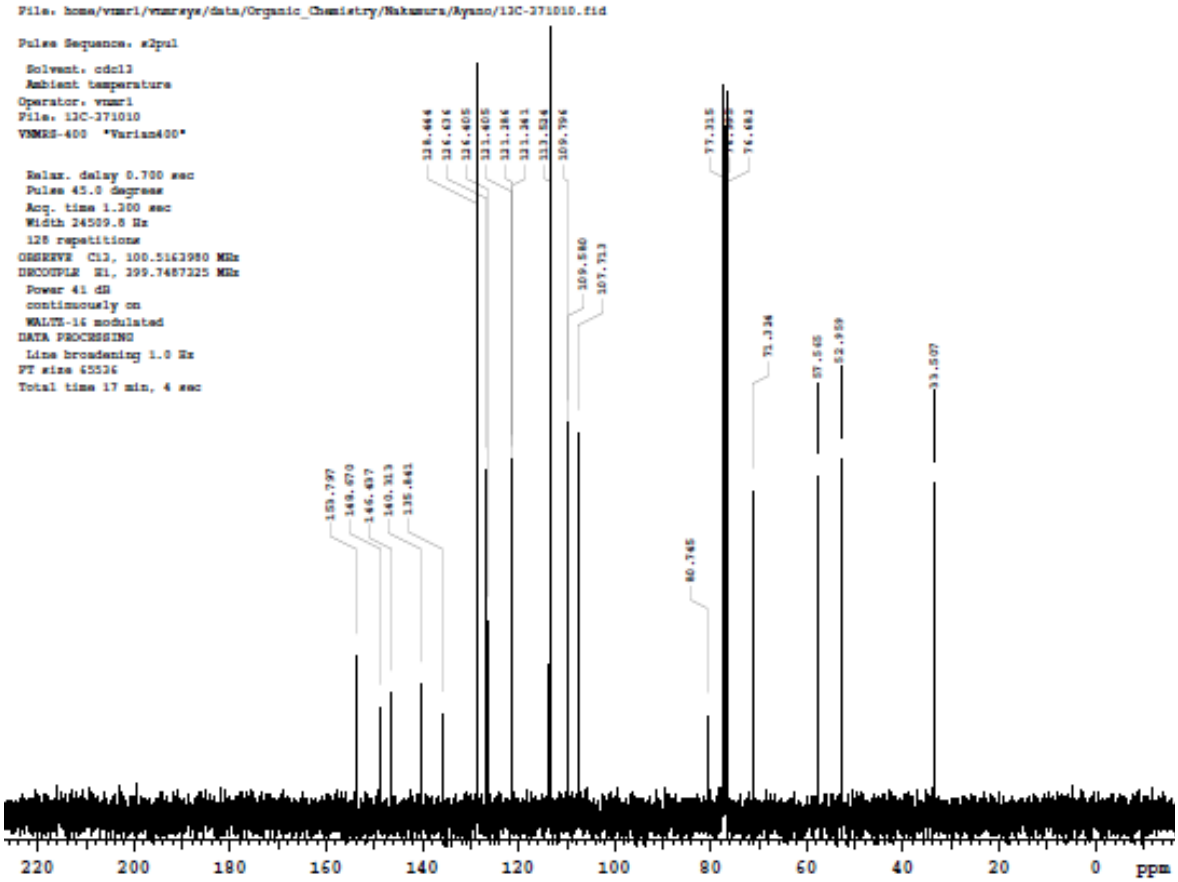
^{13}C NMR of 12m (100 Hz, $CDCl_3$)



^{1}H NMR of 12u (400 Hz, $CDCl_3$)



^{13}C NMR of 12u (100 Hz, $CDCl_3$)



Human cancer cell line panel experiment

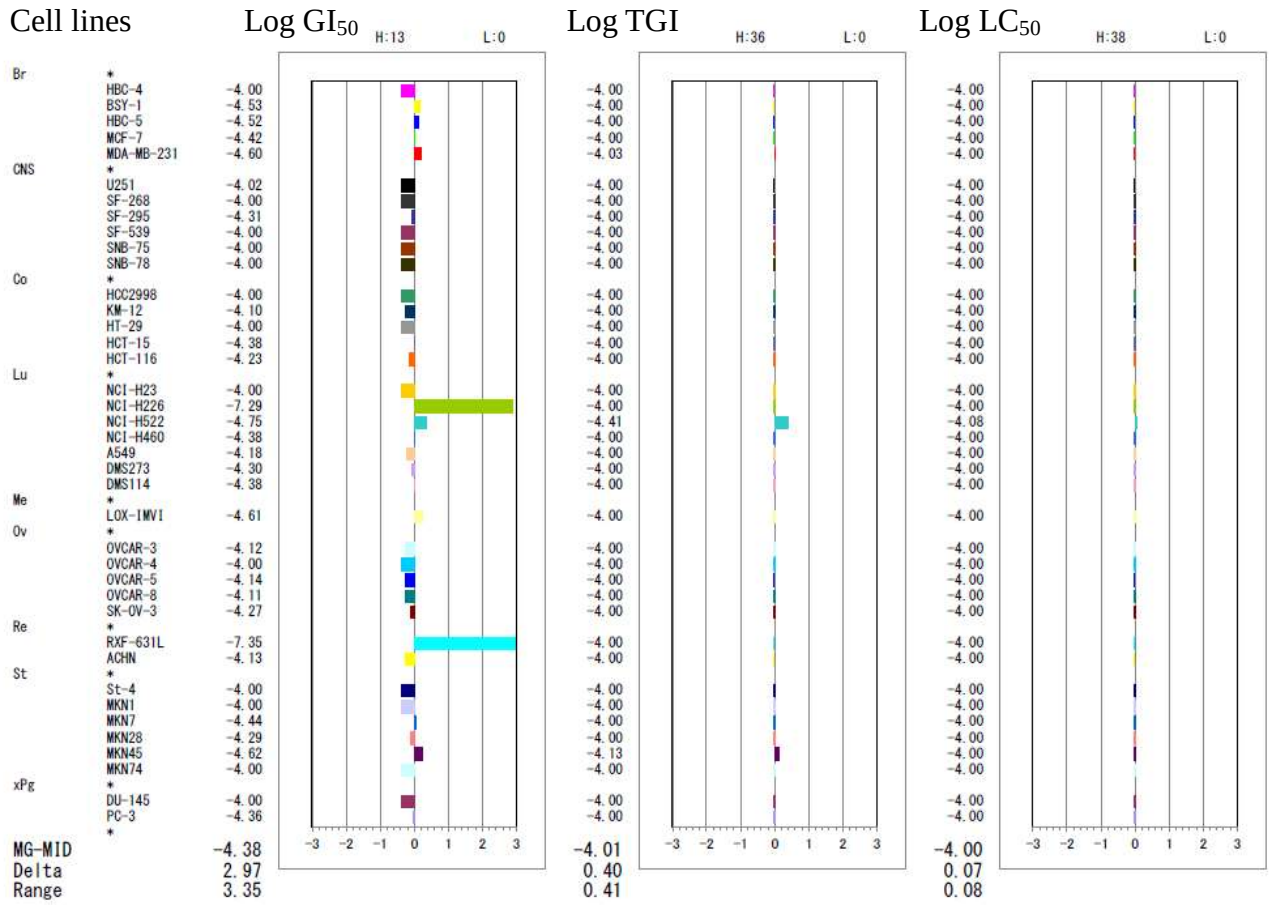


Figure S1. Differential activity patterns for compound **12l** against 39 human cancer cell lines. MG-MID: mean of log X values (X = GI_{50}, TGI, and LC_{50}). Delta: logarithm of the difference between the MG-MID and the log X of the most sensitive cell line. Range: logarithm of the difference between the log X of the most resistant cell line and the log X of the most sensitive cell line.

Localization of 12u in cancer cells

Cells (1.0×10^4 cells) were plated on 18 x 18 mm slide grass in 35 mm dish, 2 mL RPMI 1640 medium supplemented with 1% penicilline-streptomycin and 5% heat-inactivated fetal bovine serum and incubated for 12 h in a humidified incubator at 37 °C under 5% CO2/95% air. Cells were preincubated with MitoTracker Red (100 nM), LysoTracker Red (100 nM) or Nile Red (1 μM) for 30 min, then **12u** (3 μM) was treated for 4 h in CO_2 incubator. After incubation, cells were washed with PBS buffer, fixed with 4% paraformaldehyde PBS solution for 15 min at r.t. and treated with 0.4% Triton-X for 5 min at r.t. After washing cells twice, alkyne-tagged compound **12u** was visualized with Alexa Fluor™ 488 azide and Click-it™ Cell Reaction Buffer Kit (Molecular Probes). Then nuclei was stained with DAPI (100 nM) for for 5 min at r.t. Immunostained slides were cover-mounted with Prolong Gold antifade reagent (invitrogen), and monitored under a fluorescence

microscope (Olympus).

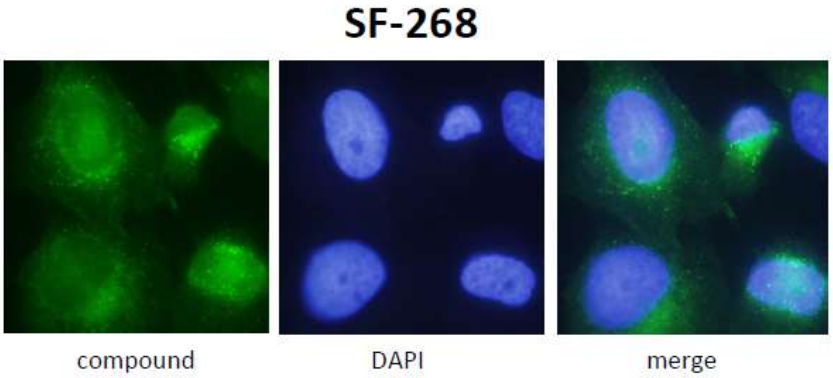


Figure S2. Localization of **12u** in SF-268. DAPI was merged with localization of **12u** in SF-268 cells.

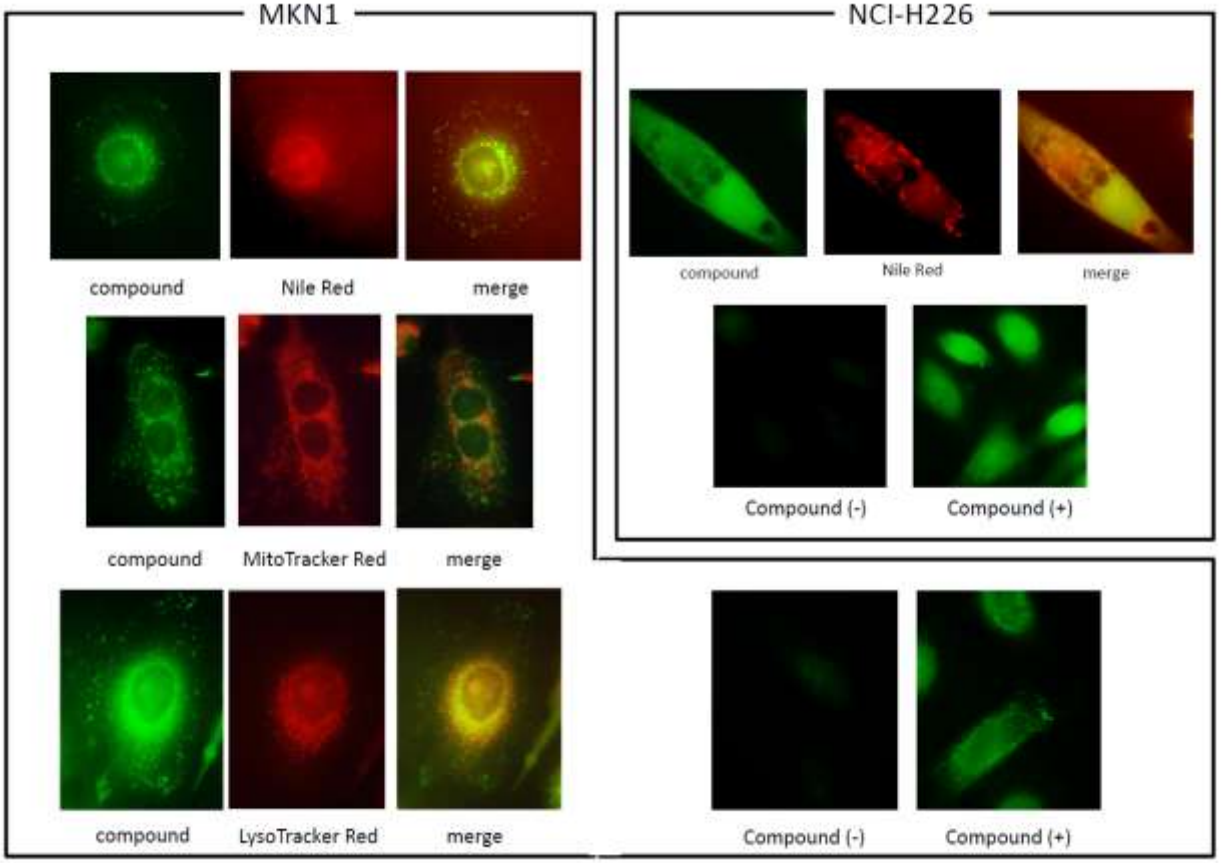


Figure S3. Localization of **12u** in MKN1 and NCI-H226 cells. Nile Red, MitoTracker Red, and LysoTracker Red were merged with localization of **12u** in MKN1 cells and Nile Red was merged in NCI-H226 cells.

Ethics statement

All animal experiments were performed with the approval of the Animal Ethics Committees of Tokyo Institute of Technology (No. 2010008) and in accordance with the Ethical Guidelines for Animal

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Experimentation of Tokyo Institute of Technology.

Mice

Male Balb/c nu/nu were purchased from Oriental Yeast Co., Ltd. All mice underwent experiments at 6–10 weeks of age.

Cells and culture conditions

In SUIT-2/HRE-Luc cells, HIF-1α stability is strictly regulated by oxygen concentration (HIF-1α expression is undetectable under normoxic conditions but significantly increased under hypoxic conditions [ref]. All the cells were maintained at 37°C in 5% FCS-Dulbecco's-modified Eagle's medium (Nacalai Tesque, Kyoto, Japan) supplemented with penicillin (100 units/ml) and streptomycin (100 µg/ml). Hypoxic cell cultures were performed in 5% CO_2/1% O_2 in a multi-gas incubator (ASTEC, Fukuoka, Japan).

***In vivo* bioluminescence imaging**

For *in vivo* photon counting to assess bioluminescence, tumor-bearing mice were intraperitoneally injected with 200 µl of D-luciferin solution (10 mg/ml in PBS, Promega) and placed in an IVIS®-Spectrum *in vivo* photon-counting device (Caliper Life Sciences, Alameda, CA, USA). Bioluminescence images were acquired at 20 min after the intraperitoneal injection of D-luciferin. The following conditions were used for image acquisition: exposure time = 2 min, lamp level = high, binning = medium:8, field of view = 19 × 19 cm, and f/stop = 1. The bioluminescence was analyzed by Living Image 3.10 software (Caliper Life Sciences).[5]

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