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Regioselective Zincation of Indazoles using $TMP_2Zn \cdot 2LiCl$ and Negishi Cross-Coupling with Aryl and Heteroaryl Iodides

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General All reactions were carried out under an argon atmosphere in flame-dried glassware. Syringes which were used to transfer anhydrous solvents or reagents were purged with argon prior to use. THF was continuously refluxed and freshly distilled from sodium benzophenone ketyl under nitrogen. Yields refer to isolated yields of compounds estimated to be > 95 % pure as determined by 1H-NMR (25 °C) and capillary GC. NMR spectra were recorded on solutions in deuterated chloroform ($CDCl_3$) with residual chloroform (δ 7.25 ppm for ^1H NMR and δ 77.0 ppm for ^{13}C NMR) or *d6*-DMSO (δ 2.49 ppm for ^1H NMR and δ 39.5 ppm for ^{13}C NMR). Column chromatographical purifications were performed using SiO_2 (0.040–0.063 mm, 230–400 mesh ASTM) from Merck if not indicated otherwise. TMPH and liquid acid chlorides were distilled prior to use.

Preparation of the reagent $(TMP)_2Zn \cdot 2MgCl_2 \cdot 2LiCl$ (1):

In an argon-flushed Schlenk-flask, $ZnCl_2$ (53.0 mmol, 7.22 g) was dried *in vacuo* at 140 °C for 4 h. After cooling to 25 °C, dry THF (25 mL) and freshly titrated TMPMgCl·LiCl (100 mmol, 1.00 M, 100 mL) was added slowly. The resulting mixture was stirred for 15 h at 25 °C. The freshly prepared $(TMP)_2Zn \cdot 2MgCl_2 \cdot 2LiCl$ (**1**) solution was titrated prior to use at 0 °C with benzoic acid using 4-(phenylazo)diphenylamine as indicator. A concentration of 0.4 M in THF was obtained.

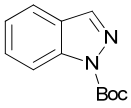
Typical procedure for the zincation of Indazoles with $(TMP)_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (TP 1):

A dry and argon flushed 10 mL Schlenk-flask, equipped with a magnetic stirring bar and a septum was charged with a solution of the corresponding indazole (2.0 mmol) in dry THF (2 mL) as well as 50 µL of tetradecane (internal standard for GC analysis). After setting the desired temperature (Table 1), the zinc base (1.1 mmol) was added dropwise and stirred at the same temperature. The completion of the metalation was checked by GC-analysis of reaction aliquots quenched with a solution of I_2 in dry THF.

Typical procedure for the SEM-protection of Indazoles (TP 2):

To an ice-bath cooled mixture of the indazole **2** (20 mmol)**,** tetra-butylammonium bromide (0.01 equiv), aqueous potassium hydroxide (50 percent, 15 mL) and dichloromethane (20 mL) 2-(Trimethylsilyl)ethoxymethyl chloride (22 mmol, 1.1 equiv) was added dropwise. The mixture was stirred for 3h, poured into water (50 mL) and extracted with dichloromethane (3x30ml). The combined extracts were washed with water (50 mL), dried ($MgSO_4$) and concentrated under vacuum. In order to separate the (N-1 and N-2)-SEM-indazoles the residual oil was purified by column chromatography on silica eluting with ether/pentane to give the title compound.

Synthesis of 4 *tert*-butyl 1*H*-indazole-1-carboxylate (2a):



To a stirred solution of 1*H*-indazole (1.181 g, 10 mmol), MeCN (20 mL) and DMAP (27 mg, cat.) was added Boc_2O (2.6 g, 12 mmol). Bubbling was then observed. After 3 h, the solvent was evaporated *in vacuo* and the remaining residue was partitioned between diethyl ether (100 mL) and H_2O (50 mL). The aqueous phase was extracted with diethyl ether (3 × 75 mL). The organic layer was washed with aq sat $NaHCO_3$ (75 mL), brine (75 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (pentane:diethyl ether = 2:1) to give **2a** (2.07 g, 95%) as a yellow oil.

^{1}H-NMR (*d6*-DMSO, 400 MHz) δ: 8.40 (s, 1H), 8.08 (d, J = 8.0 Hz, 1H), 7.87 (d, J = 8.0 Hz, 1H), 7.62–7.55 (m, 1H), 7.39–7.33 (m, 1H), 1.63 (s, 9H).

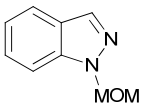
^{13}C-NMR (*d6*-DMSO, 100 MHz) δ: 148.6, 139.9, 138.9, 129.0, 125.6, 123.7, 121.6, 114.0, 84.4, 27.7.

MS (70 eV, EI) *m/z* (%): 218 (3) [M^+], 119 (10), 118 (100), 97 (12), 91 (20), 85 (20), 83 (13), 71 (27), 69 (12), 57 (49), 56 (18), 55 (17), 44 (26), 43 (16), 41 (25).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2981, 2934, 1755, 1732, 1613, 1504, 1478, 1469, 1458, 1429, 1381, 1370, 1343, 1317, 1289, 1281, 1246, 1200, 1157, 1142, 1112, 1040, 1028, 1010, 966, 946, 908, 874, 842, 765, 746, 642, 621.

HRMS (EI) for **$C_{12}H_{14}N_2O_2$** (218.1055): 218.1035.

Synthesis of 1-(methoxymethyl)-1*H*-indazole (2b):



1*H*-indazole (2.362 g, 20 mmol) was dissolved in 50 ml of N,N-dimethylformamide, and sodium hydride (60 percent in oil, 1.0 g, 25 mmol) was added under ice-cooling, followed by stirring for 30 minutes. To the reaction mixture was added chloromethyl methyl ether (1.76 g, 22 mmol) followed by stirring at room temperature for 30 min. To the reaction mixture was added water and the mixture was extracted with ethyl acetate for two times. The organic layer was washed with brine, dried over anhydrous magnesium sulfate and the solvent was evaporated. The residue was purified and separated by silica gel column chromatography (pentane:diethyl ether = 10:1), to give **2b** (2.60 g, 80%) as colorless oil.

^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 8.03 (s, 1H), 7.74 (d, J = 8.0 Hz, 1H), 7.57 (d, J = 8.6 Hz, 1H), 7.42 (t, J = 7.6 Hz, 1H), 7.20 (t, J = 7.5 Hz, 1H), 5.71 (s, 2H), 3.30 (s, 2H).

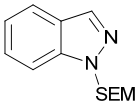
^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 139.8, 134.2, 126.9, 124.8, 121.4, 121.1, 109.5, 79.4, 56.5.

MS (70 eV, EI) *m/z* (%):162 (47) [M^+], 132 (31), 131 (100), 104 (10), 103 (10), 77 (20), 45 (52), 43 (35).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2932, 1617, 1500, 1466, 1423, 1369, 1316, 1216, 1173, 1132, 1103, 1071, 1006, 973, 906, 835, 740.

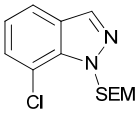
HRMS (EI) for **$C_9H_{10}N_2O$** (162.0793): 162.0791.

Synthesis of 1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-indazole (2c):



This compound was prepared from commercially available 1*H*-indazole and 2-(Trimethylsilyl)ethoxymethyl chloride according to the procedure reported by Luo *et al*.[1]

Synthesis of 7-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-indazole (2d)



Prepared according to **TP 2** from 7-chloro-1*H*-indazole[2]. Purification by silica gel column chromatography (pentane:diethyl ether = 10:1) gave **2b** (3.51 g, 62%) as orange oil.

^{1}H-NMR (CDCl$_3$, 300 MHz) δ: 8.08 (s, 1H), 7.47 (d, J = 8.3 Hz, 1H), 7.31 (d, J = 7.9 Hz, 1H), 7.16 (d, J = 7.5 Hz, 1H), 5.72 (s, 2H), 3.59 – 3.49 (m, 2H), 0.91 – 0.82 (m, 2H), -0.08 (s, 9H).

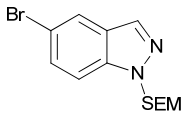
^{13}C-NMR (CDCl$_3$, 75 MHz) δ: 140.7, 132.6, 127.4, 126.6, 124.1, 121.0, 108.3, 78.0, 66.6, 17.7, -1.5.

MS (70 eV, EI) *m/z* (%): 282 (1) [M$^+$], 209 (13), 166 (15), 73 (22), 70 (11), 61 (18), 15 (16), 43 (100).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2953, 1614, 1496, 1446, 1365, 1303, 1248, 1169, 1118, 1078, 927, 832, 775, 757, 732, 693.

HRMS (EI) for **$C_{13}H_{19}ClN_2OSi$** (282.0955): 282.0950.

Synthesis of 5-bromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-indazole (2e)



Prepared according to **TP 2** from 5-bromo-1*H*-indazole[3]. Purification by silica gel column chromatography (pentane:diethyl ether = 10:1) gave **2e** (5.30 g, 81%) as orange oil.

^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 7.94 (s, 1H), 7.87 (s, 1H), 7.51 – 7.43 (m, 2H), 5.71 (s, 2H), 3.56 – 3.47 (m, 2H), 0.91 – 0.82 (m, 2H), -0.08 (s, 9H).

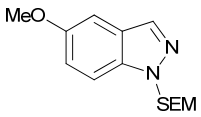
^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 138.4, 133.1, 129.8, 126.3, 123.5, 114.5, 111.2, 77.9, 66.5, 17.7, -1.5.

MS (70 eV, EI) *m/z* (%): 328 (1) [M^+], 211 (7), 87 (5), 73 (13), 70 (11), 61 (18), 45 (15), 43 (100).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2953, 2895, 1485, 1440, 1419, 1370, 1300, 1248, 1189, 1076, 1050, 989, 938, 912, 857, 832, 786, 760, 693, 664.

HRMS (EI) for **$C_{13}H_{19}BrN_2OSi$** (326.0450): 326.0441.

Synthesis of 5-methoxy-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-indazole (2f)



Prepared according to **TP 2** from 5-methoxy-1*H*-indazole[4]. Purification by silica gel column chromatography (pentane:diethyl ether = 10:1) gave **2f** (4.40 g, 79%) as orange solid.

m.p.: 56.8 – 58.5 °C.

^{1}H-NMR (*d6*-DMSO, 400 MHz) δ: 7.99 (s, 1H), 7.62 (d, J = 9.2 Hz, 1H), 7.19 (d, J = 2.1 Hz, 1H), 7.07 (dd, J = 9.0 Hz, 2.3 Hz, 1H), 5.67 (s, 2H), 3.78 (s, 3H), 3.50 – 3.44 (m, 2H), 0.80 – 0.74 (m, 2H), -0.14 (s, 9H).

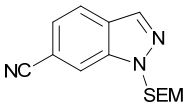
^{13}C-NMR (*d6*-DMSO, 100 MHz) δ: 154.4, 135.4, 133.2, 124.6, 118.2, 110.9, 100.2, 76.8, 65.4, 55.3, 17.1, -1.4.

MS (70 eV, EI) *m/z* (%): 278 (23) [M^+], 233 (14), 220 (32), 178 (18), 162 (32), 148 (12), 121 (34), 73 (100), 61 (13), 45 (11), 43 (78).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2952, 1738, 1600, 1507, 1451, 1374, 1305, 1225, 1153, 1100, 1075, 1030, 916, 832, 768, 719.

HRMS (EI) for **$C_{14}H_{22}N_2O_2Si$** (278.1451): 278.1452.

Synthesis of 1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-indazole-6-carbonitrile (2g)



Prepared according to **TP 2** from 1*H*-indazole-6-carbonitrile[5]. Purification by silica gel column chromatography (pentane:diethyl ether = 4:1) gave **2g** (3.72 g, 68%) as orange oil.

^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 8.13 (s, 1H), 8.10 (s, 1H), 7.68 – 7.58 (m, 2H), 5.75 (s, 2H), 3.57 – 3.50 (m, 2H), 0.91 – 0.83 (m, 2H), -0.09 (s, 9H).

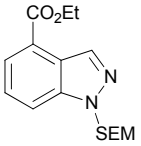
^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 140.5, 134.6, 128.9, 127.4, 124.4, 119.4, 111.0, 105.0, 78.0, 66.8, 17.7, -1.5.

MS (70 eV, EI) *m/z* (%): 273 (1) [M^+], 200 (11), 157 (13), 156 (16), 73 (17), 70 (13), 61 (20), 45 (16), 43 (100).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2956, 2926, 2902, 2218, 1620, 1503, 1449, 1425, 1386, 1371, 1356, 1296, 1249, 1175, 1140, 1092, 1076, 990, 914, 817, 752, 696.

HRMS (EI) for **$C_{14}H_{19}N_3OSi$** (273.1297): 273.1294.

Synthesis of ethyl 1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-indazole-4-carboxylate (2h)



1H-indazole-4-carboxylate[6] (2.362 g, 20 mmol) was dissolved in 50 mL of N,N-dimethylformamide, and sodium hydride (60 percent in oil, 1.0 g, 25 mmol) was added under ice-cooling, followed by stirring for 30 minutes. To the reaction mixture was added chloromethyl methyl ether (1.76 g, 22 mmol) followed by stirring at room temperature for 30 min. To the reaction mixture was added water and the mixture was extracted with ethyl acetate for two times. The organic layer was washed with brine, dried over anhydrous magnesium sulfate and the solvent was evaporated. The residue was purified and separated by silica gel column chromatography (pentane:diethyl ether = 4:1), to give **2h** (3.59 g, 56%) as yellow oil.

^{1}H-NMR (*d6*-DMSO, 400 MHz) δ: 8.44 (s, 1H), 8.07 (d, J = 8.4 Hz, 1H), 7.87 (d, J = 6.8 Hz, 1H), 7.57 (dd, J = 8.3 Hz, 7.3 Hz, 1H), 5.82 (s, 2H), 4.40 (q, J = 7.0 Hz, 2H), 3.54 – 3.45 (m, 2H), 1.39 (t, J = 7.1 Hz, 3 H), 0.85 – 0.72 (m, 2H), -0.14 (s, 9H).

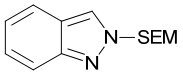
^{13}C-NMR (*d6*-DMSO, 100 MHz) δ: 165.4, 140.1, 134.0, 126.1, 124.3, 122.3, 122.2, 115.4, 76.9, 65.7, 60.9, 17.1, 14.2, -1.4.

MS (70 eV, EI) *m/z* (%): 320 (1) [M^+], 204 (14), 203 (17), 190 (5), 145 (5), 88 (5), 75 (10), 73 (16), 70 (11), 61 (16), 45 (16), 43 (100).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2953, 2897, 1714, 1609, 1449, 1417, 1372, 1305, 1270, 1249, 1169, 1150, 1120, 1079, 1029, 964, 936, 856, 834, 752, 693.

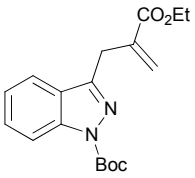
HRMS (EI) for **$C_{16}H_{24}N_2O_3Si$** (320.1556): 320.1557.

Synthesis 2-((2-(trimethylsilyl)ethoxy)methyl)-2*H*-indazole (2i):



This compound was prepared from commercially available 1*H*-indazole and 2-(Trimethylsilyl)ethoxymethyl chloride according to the procedure reported by Luo *et al*.[1]

Synthesis of *tert*-butyl 3-(2-(ethoxycarbonyl)prop-2-en-1-yl)-1*H*-indazole-1-carboxylate (4a):



According to **TP 1**, the metalation of 4 *tert*-butyl 1*H*-indazole-1-carboxylate (**2a**; 436 mg, 2 mmol) was completed within 1 h at 25 °C. The reaction mixture was cooled to -40 °C, then CuCN·2LiCl (1 M in THF, 0.1 mL, 0.1 mmol) and ethyl 2-(bromomethyl)acrylate[7] (463 mg, 2.4 mmol) were added. The mixture was allowed to warm to 25 °C and was further stirred for 2 h. The reaction mixture was quenched with a sat. aq. NH_4Cl solution (10 mL), extracted with diethyl ether (3 × 20 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (pentane:diethyl ether = 2:1) to give **4a** (548 mg, 89%) as a yellow oil.

^{1}H-NMR ($CDCl_3$, 600 MHz) δ: 7.61 (d, J = 7.5 Hz, 1 H), 7.54 (td, J = 7.8 Hz, 1.6 Hz, 1 H), 7.33–7.25 (m, 2 H), 6.32 (d, J = 1.6 Hz, 1 H), 5.87 (s, 1 H), 4.54 (s, 2 H), 4.14 (q, J = 7.2 Hz, 2 H), 1.39 (s, 9 H), 1.21 (t, J=7.2 Hz, 3 H).

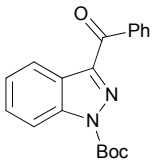
^{13}C-NMR ($CDCl_3$, 150 MHz) δ: 165.8, 153.2, 145.1, 135.8, 133.4, 133.1, 127.8, 127.0, 116.9, 113.2, 81.7, 60.9, 50.4, 28.1, 14.0.

MS (70 eV, EI) *m/z* (%): 257 (7), 231 (15), 230 (100), 229 (17), 202 (17), 185 (13), 184 (31), 183 (40), 157 (22), 156 (60), 155 (50), 144 (11), 131 (31), 129 (29), 118 (11), 103 (11), 102 (11), 57 (64), 56 (11), 55 (22), 44(17), 41 (21).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2980, 2935, 1705, 1638, 1598, 1576, 1491, 1452, 1424, 1367, 1307, 1258, 1237, 1150, 1107, 1047, 1023, 956, 940, 856, 818, 762, 657, 646, 608.

HRMS (EI) for **$C_{18}H_{22}N_2O_4$** (330.1580): 330.1562.

Synthesis of *tert*-butyl 3-benzoyl-1*H*-indazole-1-carboxylate (4b):



According to **TP 1**, the metalation of 4 *tert*-butyl 1*H*-indazole-1-carboxylate (**2a**, 436 mg, 2 mmol) was completed within 1 h at 25 °C. The reaction mixture was cooled to -40 °C, then CuCN·2LiCl (1 M in THF, 2.2 mL, 2.2 mmol) and benzoyl chloride (336 mg, 2.4 mmol) were added. The mixture was allowed to warm to 25 °C and was further stirred for 2 h. The reaction mixture was quenched with a sat. aq. NH_4Cl solution (10 mL), extracted with diethyl ether (3 × 20 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (pentane:diethyl ether = 3:2) to give **4b** (465 mg, 72%) as a colourless solid.

m.p.: 111.0 – 113.5 °C.

^{1}H-NMR ($CDCl_3$, 600 MHz) δ: 7.81 (d, J = 7.1 Hz, 2 H), 7.75 (d, J = 9.1 Hz, 1 H), 7.68 (t, J = 7.9 Hz, 1 H), 7.39 (t, J = 7.4 Hz, 2 H), 7.51–7.42 (m, 4 H), 1.23 (s, 9 H).

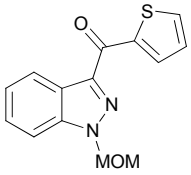
^{13}C-NMR ($CDCl_3$, 150 MHz) δ: 171.9, 151.9, 141.5, 136.2, 133.6, 133.3, 131.9, 130.2, 128.6, 128.3, 128.2, 116.2, 113.3, 84.7, 27.4.

MS (70 eV, EI) *m/z* (%): 223 (3), 222 (22), 144 (5), 119 (2), 106 (6), 105 (100), 78 (2), 77 (29), 57 (6), 56 (4), 55 (2), 51 (6), 50 (2), 44 (5), 41 (7).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3110, 2982, 2927, 1736, 1663, 1578, 1544, 1471, 1447, 1370, 1358, 1324, 1308, 1236, 1207, 1178, 1155, 1150, 1136, 1114, 1086, 1026, 999, 978, 949, 898, 874, 849, 832, 815, 796, 770, 757, 741, 716, 689, 624, 616, 603.

HRMS (EI) for **$C_{19}H_{18}N_2O_3$** (322.1317): 322.1305.

Synthesis of (1-(methoxymethyl)-1*H*-indazol-3-yl)(thiophen-2-yl)methanone (4c):



According to **TP 1**, the metalation of 1-(methoxymethyl)-1*H*-indazole (**2b,** 324 mg, 2 mmol) was completed within 2 h at 25 °C. The reaction mixture was cooled to -40 °C, then CuCN·2LiCl (1 M in THF, 2.2 mL, 2.2 mmol) and thiophene-2-carbonyl chloride (322 mg, 2.2 mmol) were added. The mixture was allowed to warm to 25 °C and was further stirred for 2 h. The reaction mixture was quenched with a sat. aq. NH_4Cl solution (10 mL), extracted with diethyl ether (3 × 20 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (pentane:diethyl ether = 3:1) to give **4e** (532 mg, 76 %) as a colourless solid.

m.p.: 87.9 – 89.3 °C.

^{1}H-NMR (*d6*-DMSO, 400 MHz) δ: 8.54 (d, J = 3.1 Hz, 1 H), 8.30 (d, J = 8.0 Hz, 1 H), 8.11 (d, J = 4.5 Hz, 1 H), 7.93 (d, J = 8.4 Hz, 1 H), 7.58 (t, J = 7.5 Hz, 1 H), 7.43 (t, J = 7.5 Hz, 1 H), 7.36 – 7.30 (m, 1H), 5.93 (s, 2H), 3.31 (s, 3H).

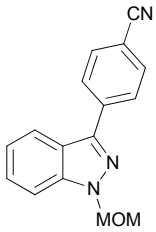
^{13}C-NMR (*d6*-DMSO, 100 MHz) δ: 178.9, 141.9, 141.3, 140.6, 135.8, 135.4, 128.6, 127.7, 124.2, 123.5, 122.0, 111.0, 79.6, 56.5.

MS (70 eV, EI) *m/z* (%):273 (15), 272 (100) [M^+], 244 (10), 243 (43), 145 (41), 129 (26), 111 (92), 103 (12), 45 (70), 44 (30), 43 (16).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2932, 1738, 1609, 1513, 1472, 1419, 1348, 1312, 1217, 1154, 1126, 1079, 1051, 1003, 916, 868, 812, 781, 753, 723, 718, 686.

HRMS (EI) for **$C_{14}H_{12}N_2O_2S$** (272.0619): 272.0613.

Synthesis of 4-(1-(methoxymethyl)-1*H*-indazol-3-yl)benzonitrile (4d):



According to **TP 1**, the metalation of 1-(methoxymethyl)-1*H*-indazole (**2b,** 324 mg, 2 mmol) was completed within 2 h at 25 °C. A solution of $Pd(dba)_2$ (56 mg) and $P(2\text{-furyl})_3$ (46 mg) in THF (2 mL) was added, followed by 4-iodobenzonitrile (504 mg, 2.2 mmol). The reaction mixture was stirred at 50 °C for 8 h. The reaction mixture was quenched with a sat. aq. NH_4Cl solution (10 mL), extracted with diethyl ether (3 × 20 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (pentane:diethyl ether = 3:1) to give **4e** (398 mg, 76 %) as a colourless solid.

m.p.: 102.6 – 104.5 °C.

^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 8.11 (d, J = 8.3 Hz, 2H), 8.00 (d, J = 8.3 Hz, 1H), 7.77 (d, J = 8.3 Hz, 2H), 7.63 (d, J = 8.6 Hz, 1H), 7.49 (t, J = 7.6 Hz, 1H), 7.31 (t, J = 7.6 Hz, 1H), 5.76 (s, 2H), 3.36 (s, 3H).

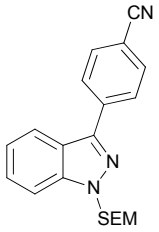
^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 142.9, 141.4, 137.9, 132.6, 127.8, 127.2, 122.6, 122.3, 120.8, 118.9, 111.4, 110.2, 79.7, 56.7.

MS (70 eV, EI) *m/z* (%): 264 (7), 263 (42) [M^+], 233 (28), 232 (100), 205 (3), 190 (5), 129 (4), 102 (5), 77 (4), 45 (57).

IR (ATR) $\tilde{\nu}$ (cm^{-1}):. 2940, 2226, 1738, 1608, 1520, 1489, 1372, 1317, 1234, 1142, 1090, 1016, 956, 911, 848, 768, 745, 666.

HRMS (EI) for **$C_{16}H_{13}N_3O$** (263.1059): 263.1051.

Synthesis of 4-(1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-indazol-3-yl)benzonitrile (4e):



According to **TP 1**, the metalation of 1-((2-(trimethylsilyl)ethoxy)methyl}-1*H*-indazole (**2c,** 497 mg, 2 mmol) was completed within 2 h at 25 °C. A solution of $Pd(dba)_2$ (56 mg) and P(2-furyl)$_3$ (46 mg) in THF (2 mL) was added, followed by 4-iodobenzonitrile (504 mg, 2.2 mmol). The reaction mixture was stirred at 50 °C for 8 h. The reaction mixture was quenched with a sat. aq. NH_4Cl solution (10 mL), extracted with diethyl ether (3 × 20 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (pentane:diethyl ether = 3:1) to give **4e** (532 mg, 76 %) as a colourless solid.

m.p.: 105.4 – 106.8 °C.

^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 7.95 – 7.90 (m, 2H), 7.86 – 7.81 (m, 2H), 7.80 – 7.74 (m, 2H), 7.67 – 7.62 (m, 2H), 7.40 – 7.32 (m, 1H), 7.20 – 7.14 (m, 1H), 5.69 (s, 2H), 3.90 – 3.83 (m, 2H), 0.99 – 0.93 (m, 2H), 0.00 (s, 9H).

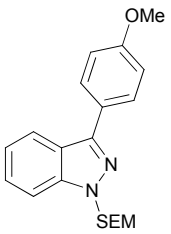
^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 148.2, 134.5, 134.1, 132.7, 130.2, 127.8, 127.1, 123.5, 121.5, 119.9, 118.5, 118.2, 112.2, 79.5, 76.6, 67.9, 18.0, -1.4.

MS (70 eV, EI) *m/z* (%): 349 (5) [M^+], 306 (13), 304 (15), 291 (38), 290 (36), 277 (16), 276 (71), 234 (14), 233 (100), 232 (62), 219 (14), 148 (22), 138 (11), 73 (79).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3397, 3126, 3075, 2218, 1691, 1602, 1578, 1518, 1458, 1396, 1304, 1273, 1158, 1122, 1010, 933, 884, 853, 833, 754.

HRMS (EI) for **$C_{20}H_{23}N_3OSi$** (349.1610): 349.1601.

Synthesis of 3-(4-methoxyphenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-indazole (4f):



According to **TP 1**, the metalation of 1-((2-(trimethylsilyl)ethoxy)methyl}-1*H*-indazole (**2c,** 497 mg, 2 mmol) was completed within 2 h at 25 °C. A solution of $Pd(dba)_2$ (56 mg) and P(2-furyl)$_3$ (46 mg) in THF (2 mL) was added, followed by 4-iodoanisole (515 mg, 2.2 mmol). The reaction mixture was stirred at 50 °C for 12 h. The reaction mixture was quenched with a sat. aq. NH_4Cl solution (10 mL), extracted with diethyl ether (3 × 20 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (pentane:diethyl ether = 3:1) to give **4f** (575 mg, 81 %) as a colourless solid.

m.p.: 85.6 – 87.3 °C.

^{1}H-NMR (*d6*-DMSO, 400 MHz) δ:.7.67 – 7.63 (m, 3H), 7.60 (d, J = 8.4 Hz, 1H), 7.32 – 7.27 (m, 1H), 7.16 (d, J = 8.8 Hz, 2H), 7.10 – 7.04 (m, 1H), 5.65 (s, 2H), 3.84 (s, 3H), 3.73 – 3.65 (m, 2H), 0.88 – 0.80 (m, 2H), -0.09 (s, 9H).

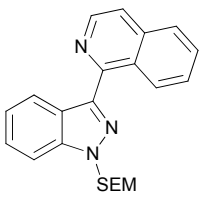
^{13}C-NMR (*d6*-DMSO, 100 MHz) δ: 159.7, 147.4, 135.8, 130.8, 126.5, 121.9, 121.1, 120.6, 120.3, 117.5, 114.6, 78.7, 66.6, 55.3, 17.3, -1.4.

MS (70 eV, EI) *m/z* (%):355 (10), 354 (47) [M^+], 311 (10), 309 (26), 297 (14), 296 (54), 295 (48), 282 (11), 281 (71), 239 (12), 238 (83), 237 (100), 224 (33), 223 (12), 209 (13), 152 (15), 148 (15), 140 (17), 75 (15), 61 (16), 43 (80).

IR (ATR) $\tilde{\nu}$ (cm^{-1}):. 3052, 3006, 2935, 1739, 1609, 1504, 1472, 1361, 1270, 1248, 1177, 1085, 1015, 940, 860, 834, 795, 755, 732, 652.

HRMS (EI) for **$C_{20}H_{26}N_2O_2Si$** (354.1764): 354.1751.

Synthesis of 1-(1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazol-3-yl)isoquinoline (4g):



According to **TP 1**, the metalation of 1-((2-(trimethylsilyl)ethoxy)methyl}-1*H*-indazole (**2c,** 497 mg, 2 mmol) was completed within 2 h at 25 °C. A solution of $Pd(dba)_2$ (56 mg) and P(2-furyl)$_3$ (46 mg) in THF (2 mL) was added, followed by 2-iodoisoquinoline[8] (561 mg, 2.2 mmol). The reaction mixture was stirred at 50 °C for 6 h. The reaction mixture was quenched with a sat. aq. NH_4Cl solution (10 mL), extracted with diethyl ether (3 × 20 mL) and dried

over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (pentane:diethyl ether = 3:1) to give **4g** (464 mg, 76 %) as a yellowish oil.

^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 9.10 (d, J = 8.6 Hz, 1H), 8.73 (d, J = 5.8 Hz, 1H), 8.36 (d, J = 8.3 Hz, 1H), 7.89 (d, J = 8.0 Hz, 1H) 7.76 – 7.56 (m, 3H), 7.50 (t, J = 7.3 Hz, 1H), 7.36 – 7.27 (m, 1H), 5.92 (s, 2H), 3.76 – 3.68 (m, 2H), 1.01 – 0.92 (m, 2H), -0.04 (s, 9H).

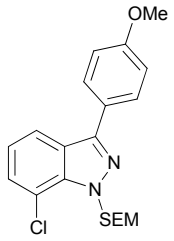
^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 152.2, 143.9, 141.9, 140.8, 137.1, 130.1, 128.0, 127.7, 127.1, 127.1, 127.0, 124.8, 123.2, 122.4, 120.5, 109.6, 78.1, 66.6, 17.8, -1.4.

MS (70 eV, EI) *m/z* (%): 376 (10), 375 (30) [M^+], 316 (21), 303 (18), 302 (69), 259 (55), 258 (100), 244 (10), 151 (17), 128 (23), 73 (33).

IR (ATR) $\tilde{\nu}$ (cm^{-1}):. 2951, 1554, 1493, 1303, 1248, 1237, 1152, 1129, 1121, 1075, 1050, 943, 915, 857, 826, 798, 778, 743, 693.

HRMS (EI) for **$C_{22}H_{25}N_3OSi$** (375.1767): 375.1765.

Synthesis of 7-chloro-3-(4-methoxyphenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-indazole (4h):



According to **TP 1**, the metalation of 7-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-indazole (**2d**, 564 mg, 2 mmol) was completed within 2 h at 25 °C. A solution of $Pd(dba)_2$ (56 mg) and $P(2\text{-furyl})_3$ (46 mg) in THF (2 mL) was added, followed by 4-iodoanisole (515 mg, 2.2 mmol). The reaction mixture was stirred at 50 °C for 12 h. The reaction mixture was quenched with a sat. aq. NH_4Cl solution (10 mL), extracted with diethyl ether (3 × 20 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (pentane:diethyl ether = 3:1) to give **4h** (552 mg, 71 %) as a colourless oil.

^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 7.62 (d, J = 8.9 Hz, 2H), 7.51 (d, J = 8.2 Hz, 1H), 7.36 – 7.29 (m, 1H), 7.18 (d, J = 7.9 Hz, 1H), 6.99 (d, J = 8.6 Hz, 2H), 5.76 (s, 2H), 3.87 (s, 3H), 3.64 – 3.59 (m, 2H), 0.94 – 0.86 (m, 2H), -0.06 (s, 9H).

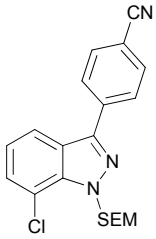
^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 159.8, 145.4, 142.2, 131.8, 127.3, 127.3, 125.1, 122.2, 120.6, 113.2, 108.6, 78.0, 66.6, 55.3, 17.8, -1.5.

MS (70 eV, EI) *m/z* (%):390 (17), 389 (11), 388 (50) [M^+], 343 (16), 332 (15), 331 (14), 330 (43), 329 (14), 317 (12), 315 (34), 273 (29), 272 (32), 271 (100), 258 (12), 73 (67).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2952, 2896, 1613, 1563, 1529, 1486, 1338, 1290, 1245, 1211, 1174, 1111, 1076, 1032, 962, 915, 831, 783, 765, 750, 726, 692.

HRMS (EI) for **$C_{20}H_{25}ClN_2O_2Si$** (388.1374): 388.1370.

Synthesis of 4-(7-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-indazol-3-yl)benzonitrile (4i):



According to **TP 1**, the metalation of 7-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-indazole (**2d**, 564 mg, 2 mmol) was completed within 2 h at 25 °C. A solution of $Pd(dba)_2$ (56 mg) and P(2-furyl)$_3$ (46 mg) in THF (2 mL) was added, followed by 4-iodobenzonitrile (504 mg, 2.2 mmol). The reaction mixture was stirred at 50 °C for 8 h. The reaction mixture was quenched with a sat. aq. NH_4Cl solution (10 mL), extracted with diethyl ether (3 × 20 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (pentane:diethyl ether = 3:1) to give **4h** (658 mg, 86 %) as a colourless solid.

m.p.: 46.6 – 48.4 °C.

^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 7.84 (d, J = 8.3 Hz, 2H), 7.74 (d, J = 8.3 Hz, 2H), 7.56 (d, J = 8.3 Hz, 1H), 7.38 (t, J = 8.0 Hz, 1H), 7.24 (d, J = 8.3 Hz, 1H), 5.76 (s, 2H), 3.64 – 3.58 (m, 2H), 0.93 – 0.87 (m, 2H), -0.06 (s, 9H).

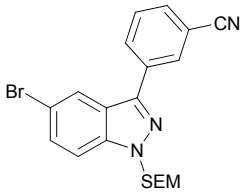
^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 143.7, 142.3, 137.5, 131.5, 131.2, 127.8, 126.8, 123.0, 120.3, 118.9, 111.9, 108.9, 78.2, 66.9, 17.7, -1.5.

MS (70 eV, EI) *m/z* (%): 383 (10) [M^+], 340 (10), 338 (10), 327 (14), 326 (12), 325 (38), 324 (10), 312 (13), 310 (36), 269 (19), 268 (27), 267 (58), 266 (60), 155 (10), 73 (100).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2954, 2224, 1606, 1485, 1339, 1297, 1244, 1153, 1108, 1068, 962, 923, 830, 777, 758, 744, 692.

HRMS (EI) for **$C_{20}H_{22}ClN_3OSi$** (383.1221): 383.1217.

Synthesis of 3-(5-bromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-indazol-3-yl)benzonitrile (4j):



According to **TP 1**, the metalation of 5-bromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-indazole (**2e**, 654 mg, 2 mmol) was completed within 2 h at 25 °C. A solution of $Pd(dba)_2$ (56 mg) and P(2-furyl)$_3$ (46 mg) in THF (2 mL) was added, followed by 3-iodobenzonitrile (504 mg, 2.2 mmol). The reaction mixture was stirred at 50 °C for 6 h. The reaction mixture was quenched with a sat. aq. NH_4Cl solution (10 mL), extracted with diethyl ether (3 × 20 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (pentane:diethyl ether = 3:1) to give **4j** (533 mg, 62 %) as a colourless oil.

^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 8.23 – 8.09 (m, 3H), 7.72 – 7.66 (m, 1H), 7.65 – 7.50 (m, 3H), 5.76 (s, 2H), 3.64 – 3.55 (m, 2H), 0.94 – 0.85 (m, 2H), -0.07 (s, 9H).

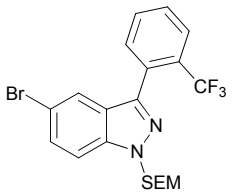
^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 141.7, 140.0, 134.2, 131.6, 131.4, 130.8, 130.3, 129.7, 123.7, 123.2, 118.6, 115.7, 113.3, 111.8, 78.2, 66.8, 17.7, -1.5.

MS (70 eV, EI) *m/z* (%): 429 (9), 427 (9) [M^+], 371 (31), 370 (20), 369 (28), 368 (12), 356 (19), 354 (18), 313 (32), 312 (40), 311 (33), 310 (37), 73 (100).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2926, 1584, 1468, 1446, 1394, 1340, 1296, 1236, 1162, 1150, 1078, 1052, 1038, 874, 858, 824, 774, 766, 756, 728, 698, 676.

HRMS (EI) for **$C_{20}H_{22}BrN_3OSi$** (427.0716): 427.0711.

Synthesis of 5-bromo-3-(2-(trifluoromethyl)phenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-indazole (4k):



According to **TP 1**, the metalation of 5-bromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-indazole (**2e**, 654 mg, 2 mmol) was completed within 2 h at 25 °C. A solution of $Pd(dba)_2$ (56 mg) and $P(2\text{-furyl})_3$ (46 mg) in THF (2 mL) was added, followed by 1-iodo-2-(trifluoromethyl)benzene (598 mg, 2.2 mmol). The reaction mixture was stirred at 50 °C for 10 h. The reaction mixture was quenched with a sat. aq. NH_4Cl solution (10 mL), extracted with diethyl ether (3 × 20 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (pentane:diethyl ether = 4:1) to give **4j** (587 mg, 62 %) as a colourless oil.

^{1}H-NMR (*d6*-DMSO, 400 MHz) δ: 7.94 (d, J = 7.8 Hz, 1H), 7.86 – 7.78 (m, 2H), 7.73 (t, J = 7.5 Hz, 1H), 7.71 – 7.61 (m, 3H), 5.82 (s, 1H), 3.55 – 3.48 (m, 2H), 0.84 – 0.78 (m, 2H), -0.12 (s, 9H)

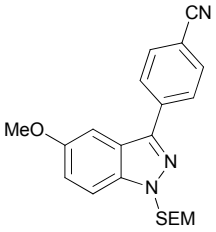
^{13}C-NMR (*d6*-DMSO, 100 MHz) δ: 141.5, 138.8, 132.5, 130.1 (q, J = 1.9 Hz), 129.7, 129.4, 128.2 (q, J = 30.1 Hz), 126.7 (q, J = 5.2 Hz), 124.9, 124.3 (q, J = 273.8 Hz), 124.2, 122.3, 114.2, 112.5, 77.2, 65.6, 17.2, -1.6.

MS (70 eV, EI) *m/z* (%): 472 (5), 470 (6) [M^+], 427 (10), 425 (9), 354 (36), 345 (17), 343 (15), 222 (7), 127 (7), 75 (7), 74 (9), 73 (100), 61 (7), 43 (38).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2954, 1470, 1368, 1316, 1244, 1172, 1130, 1108, 1081, 922, 834, 812, 806, 784, 765, 699.

HRMS (EI) for **$C_{20}H_{22}BrF_3N_2OSi$** (470.0637): 470.0634.

Synthesis of 4-(5-methoxy-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-indazol-3-yl)benzonitrile (4l):



According to **TP 1**, the metalation of 5-methoxy-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-indazole (**2f**, 556 mg, 2 mmol) was completed within 2 h at 25 °C. A solution of $Pd(dba)_2$ (56 mg) and P(2-furyl)$_3$ (46 mg) in THF (2 mL) was added, followed by 4-iodobenzonitrile (504 mg, 2.2 mmol). The reaction mixture was stirred at 50 °C for 6 h. The reaction mixture was quenched with a sat. aq. NH_4Cl solution (10 mL), extracted with diethyl ether (3 × 20 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (pentane:diethyl ether = 2:1) to give **4h** (552 mg, 71 %) as a colourless solid.

m.p.: 69.1 – 70.7 °C.

^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 8.05 (d, J = 8.3 Hz, 2H), 7.77 (d, J = 8.3 Hz, 2H), 7.53 (d, J = 9.1 Hz, 1H), 7.28 (d, J = 1.9 Hz, 1H), 7.15 (dd, J = 9.1 Hz, 2.2 Hz, 1H), 5.74 (s, 2H), 3.89 (s, 3H), 3.62 – 3.56 (m, 2H), 0.92 – 0.87 (m, 2H), -0.08 (s, 9H).

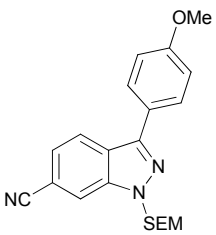
^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 156.0, 141.8, 138.3, 137.2, 132.6, 127.5, 122.7, 119.0, 111.3, 111.0, 111.0, 100.3, 78.1, 66.6, 55.8, 17.7, -1.5.

MS (70 eV, EI) *m/z* (%): 380 (11), 379 (34) [M^+], 334 (16), 322 (18), 321 (55), 320 (15), 306 (24), 263 (42), 262 (66), 249 (10), 219 (10), 178 (22), 73 (100).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2960, 1670, 1592, 1580, 1550, 1448, 1420, 1314, 1290, 1256, 1158, 1132, 1096, 1054, 1022, 972, 924, 808, 752, 700, 682, 668.

HRMS (EI) for **$C_{21}H_{25}N_3O_2Si$** (379.1716): 379.1711.

Synthesis of 3-(4-methoxyphenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-indazole-6-carbonitrile (4m):



According to **TP 1**, the metalation of 1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-indazole-6-carbonitrile (**2g**, 546 mg, 2 mmol) was completed within 2 h at 25 °C. A solution of $Pd(dba)_2$ (56 mg) and P(2-furyl)$_3$ (46 mg) in THF (2 mL) was added, followed by 4-iodoanisole (515 mg, 2.2 mmol). The reaction mixture was stirred at 50 °C for 10 h. The reaction mixture was quenched with a sat. aq. NH_4Cl solution (10 mL), extracted with diethyl ether (3 × 20 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (pentane:diethyl ether = 2:1) to give **4m** (537 mg, 71 %) as a colourless solid.

m.p.: 77.9 – 79.7 °C.

^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 8.05 (d, J = 8.3 Hz, 1H), 7.95 (s, 1H), 7.84 (d, J = 8.9 Hz, 2H), 7.43 (d, J = 8.3 Hz, 1H), 7.05 (d, J = 8.6 Hz, 2H), 5.78 (s, 2H), 3.87 (s, 3H), 3.63 – 3.58 (m, 2H), 0.98 – 0.87 (m, 2H), -0.06 (s, 9H).

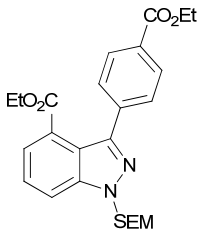
^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 160.1, 145.1, 139.9, 128.8, 124.7, 124.6, 123.6, 122.7, 119.1, 115.2, 114.5, 109.9, 78.1, 66.8, 55.4, 17.7, -1.5.

MS (70 eV, EI) *m/z* (%): 380 (13), 379 (37) [M^+], 334 (13), 322 (18), 321 (68), 320 (20), 306 (39), 263 (36), 262 (69), 249 (13), 153 (12), 75 (10), 73 (100), 61 (10), 44 (19), 43 (70).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2936, 2227, 1610, 1529, 1481, 1416, 1378, 1350, 1300, 1246, 1178, 1135, 1087, 1034, 968, 914, 832, 810, 770, 762, 715, 661.

HRMS (EI) for **$C_{21}H_{25}N_3O_2Si$** (379.1716): 379.1714.

Synthesis of ethyl 3-(4-(ethoxycarbonyl)phenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-indazole-4-carboxylate (4n):



According to **TP 1**, the metalation of ethyl 1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-indazole-4-carboxylate (**2h**, 640 mg, 2 mmol) was completed within 12 h at 50 °C. A solution of $Pd(dba)_2$ (56 mg) and P(2-furyl)$_3$ (46 mg) in THF (2 mL) was added, followed by ethyl 4-iodobenzoate (607 mg, 2.2 mmol). The reaction mixture was stirred at 50 °C for 24 h. The

reaction mixture was quenched with a sat. aq. NH_4Cl solution (10 mL), extracted with diethyl ether (3 × 20 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (pentane:diethyl ether = 2:1) to give **4m** (424 mg, 45 %) as a colourless oil.

^{1}H-NMR (*d6*-DMSO, 400 MHz) δ: 8.11 – 8.02 (m, 3H), 7.67 – 7.55 (m, 4H), 5.89 (s, 2H), 4.35 (q, J = 6.9 Hz, 2H), 3.81 (q, J = 7.2 Hz, 2H), 3.62 – 3.55 (m, 2H), 1.34 (t, J = 7.1 Hz, 3H), 0.84 – 0.78 (m, 2H), 0.74 (t, J = 7.1 Hz, 3H), -0.13 (s, 9H)

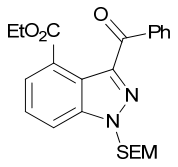
^{13}C-NMR (*d6*-DMSO, 100 MHz) δ: 167.0, 166.0, 144.4, 142.0, 139.5, 129.5, 129.3, 129.0, 127.0, 125.9, 124.4, 118.4, 114.9, 77.5, 66.4, 61.3 (2x), 17.6, 14.6, 13.6, -1.0.

MS (70 eV, EI) *m/z* (%):468 (10) [M^+], 423 (25), 410 (19), 409 (13), 348 (19), 347 (100), 346 (91), 334 (10), 73 (72), 71 (11), 59 (11), 57 (19), 43 (28), 42 (14), 41 (17).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2954, 1714, 1606, 1464, 1368, 1270, 1248, 1208, 1175, 1111, 1099, 1023, 984, 922, 858, 834, 780, 752, 706.

HRMS (EI) for **$C_{25}H_{32}N_2O_5Si$** (468.2080): 468.2068.

Synthesis of ethyl 3-benzoyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-indazole-4-carboxylate (4o):



According to **TP 1**, the metalation of ethyl 1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-indazole-4-carboxylate (**2h**, 640 mg, 2 mmol) was completed within 12 h at 50 °C. The reaction mixture was cooled to -40 °C, then CuCN·2LiCl (1 M in THF, 2.2 mL, 2.2 mmol) and benzoyl chloride (336 mg, 2.4 mmol) were added. The mixture was allowed to warm to 25 °C and was further stirred for 2 h. The reaction mixture was quenched with a sat. aq. NH_4Cl solution (10 mL), extracted with diethyl ether (3 × 20 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (pentane:diethyl ether = 3:1) to give **4o** (653 mg, 77 %) as a colourless oil.

^{1}H-NMR (*d6*-DMSO, 400 MHz) δ: 8.16 (d, J = 8.0 Hz, 1H), 7.97 – 7.92 (m, 2H), 7.75 – 7.65 (m, 3H), 7.55 (t, J = 7.80 Hz, 2H), 5.92 (s, 2H), 4.04 (q, J = 7.2 Hz, 2H), 3.60 – 3.54 (m, 2H), 0.96 (t, J = 7.1 Hz, 3H), 0.84 – 0.79 (m, 2H), -0.12 (s, 9H)

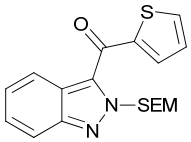
^{13}C-NMR (*d6*-DMSO, 100 MHz) δ: 188.9, 165.9, 142.8, 140.8, 136.8, 133.6, 129.7, 128.6, 127.2, 124.9, 124.6, 119.4, 114.9, 77.5, 66.1, 60.8, 17.1, 13.6, -1.5.

MS (70 eV, EI) *m/z* (%):424 (3) [M^+], 379 (24), 352 (26), 323 (15), 309 (20), 308 (91), 262 (27), 249 (12), 247 (11), 153 (17), 77 (37), 73 (100), 71 (27), 59 (40), 57 (36), 45 (30), 43 (64).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2953, 1720, 1663, 1599, 1463, 1371, 1276, 1189, 1173, 1139, 1070, 1050, 1027, 938, 880, 835, 752, 713, 694.

HRMS (EI) for **$C_{23}H_{28}N_2O_4Si$** (424.1818): 424.1806.

Synthesis of thienyl(2-{[2-(trimethylsilyl)ethoxy]methyl}-2*H*-indazol-3-yl)methanone (4p):



According to **TP 1**, the metalation of 2-{[2-(trimethylsilyl)ethoxy]methyl}-2*H*-indazole (**2i**; 497 mg, 2 mmol) was completed within 2 h at 25 °C. The reaction mixture was cooled to -40 °C, then CuCN·2LiCl (1 M in THF, 2.2 mL, 2.2 mmol) and benzoyl chloride (336 mg, 2.4 mmol) were added. The mixture was allowed to warm to 25 °C and was further stirred for 2 h. The reaction mixture was quenched with a sat. aq. NH_4Cl solution (10 mL), extracted with diethyl ether (3 × 20 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (pentane:diethyl ether = 3:2) to give **4p** (577 mg, 81%) as a yellowish oil.

^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 7.85 – 7.80 (m, 2H), 7.70 (dd, J = 3.7 Hz, 1.2 Hz, 1H), 7.55 (dt, J = 8.6 Hz, 1.1 Hz, 1H), 7.34 (ddd, J = 8.9 Hz, 6.6 Hz, 1.1 Hz, 1H), 7.20 – 7.15 (m, 2H), 6.07 (s, 2H), 3.60 (m, 2H), 0.83 (m, 2H), -0.13 (s, 9H).

^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 177.8, 147.7, 144.3, 135.4, 135.4, 131.4, 128.1, 126.6, 124.8, 122.9, 120.7, 118.8, 80.7, 67.4, 17.7, -1.6.

MS (70 eV, EI) *m/z* (%):358 (2) [M^+], 286 (19), 285 (100), 256 (59), 243 (8), 145 (15), 111 (19), 97 (11), 73 (48).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2952, 2895, 1619, 1514, 1459, 1411, 1354, 1330, 1306, 1268, 1247, 1220, 1090, 1044, 995, 944, 914, 825, 754, 719, 690.

HRMS (EI) for **$C_{18}H_{22}N_2O_2SSi$** (358.1171): 358.1167.

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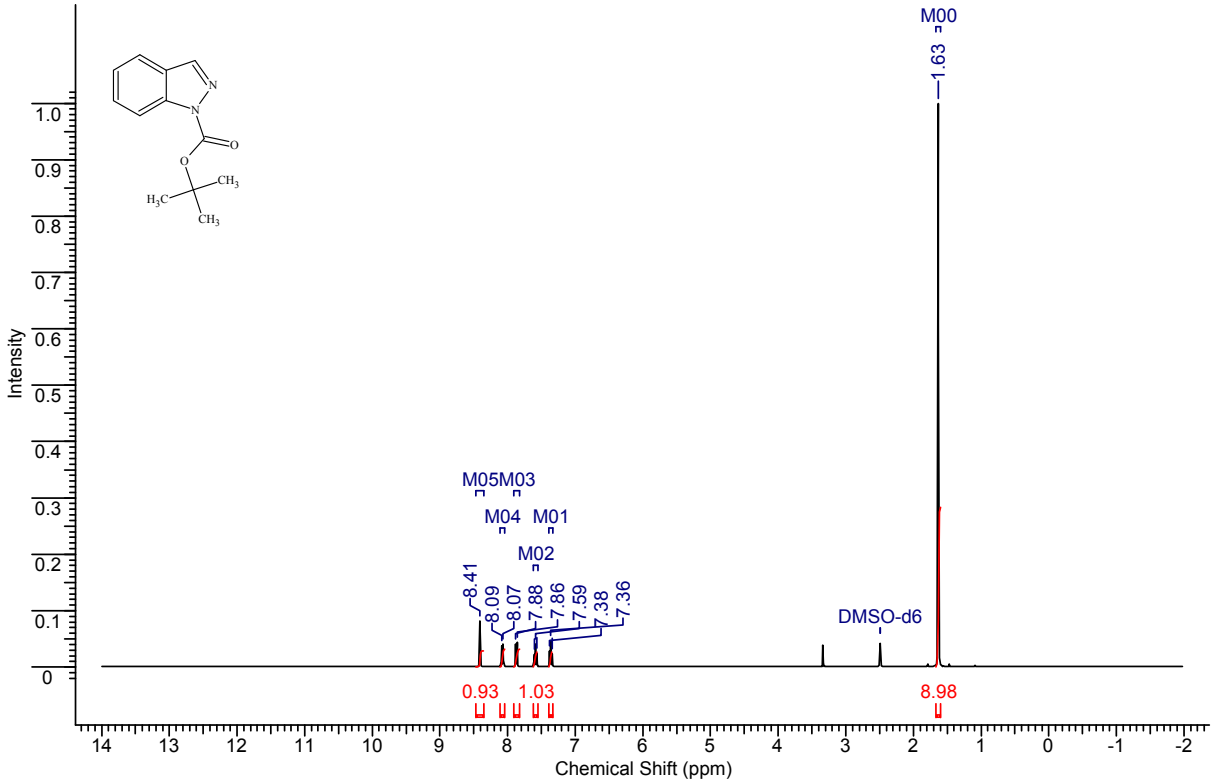
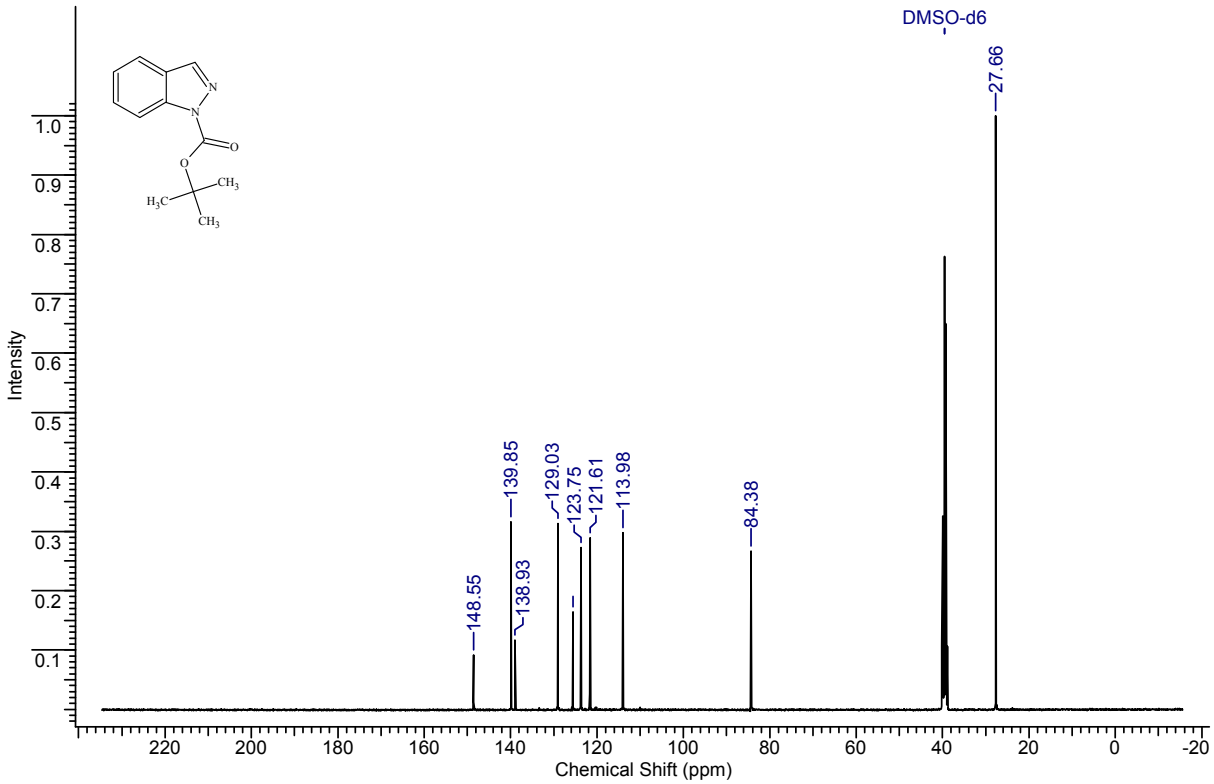
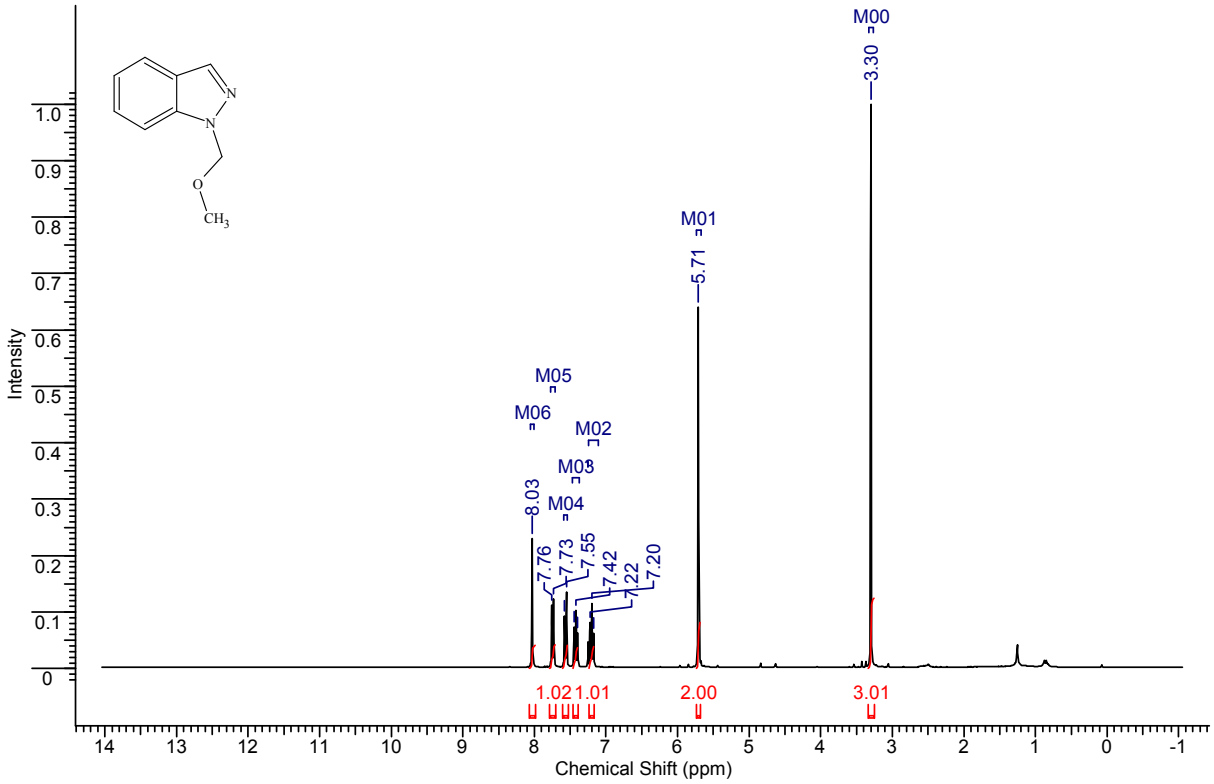
NMR Spectras:

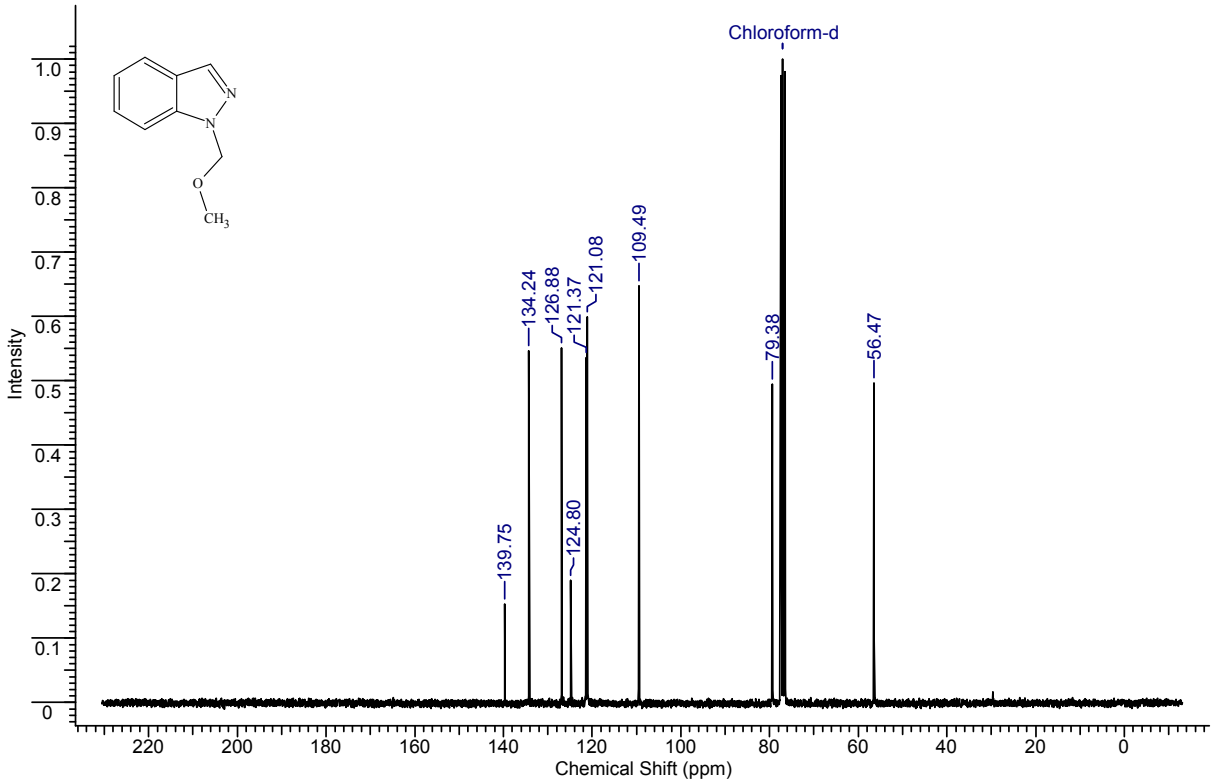
4 *tert*-butyl 1*H*-indazole-1-carboxylate (2a)



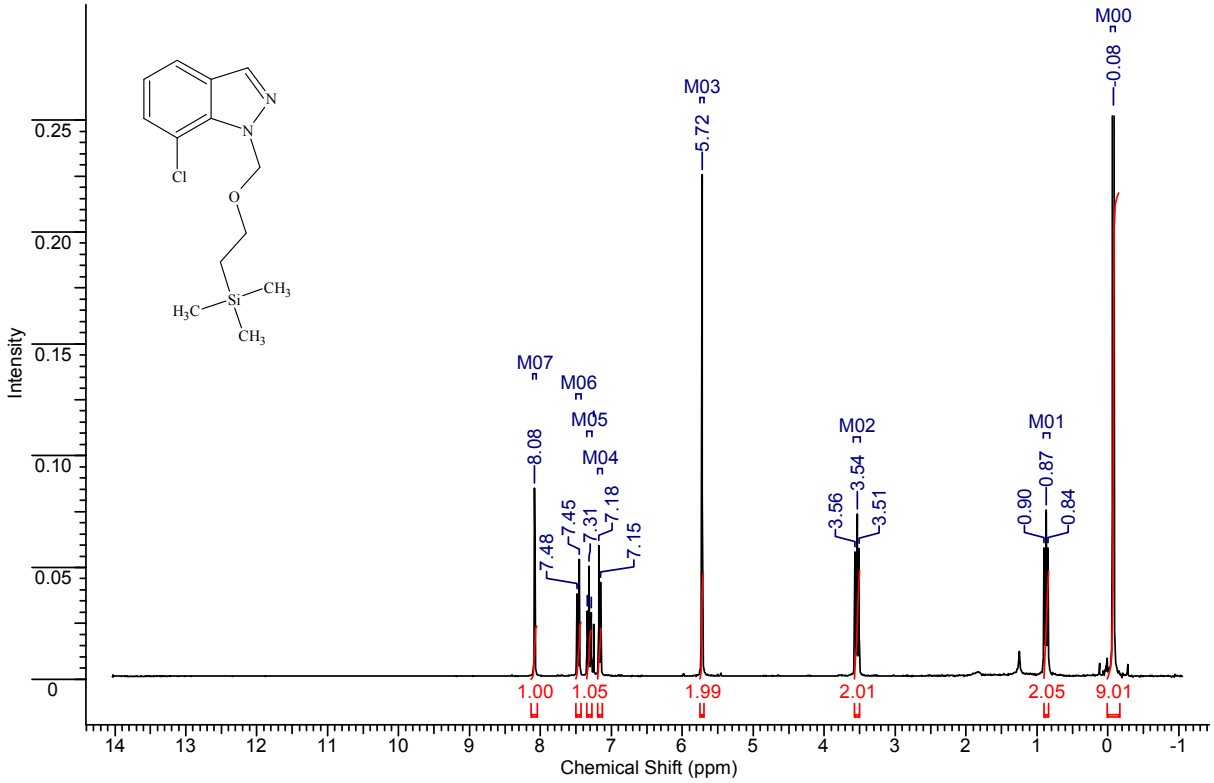


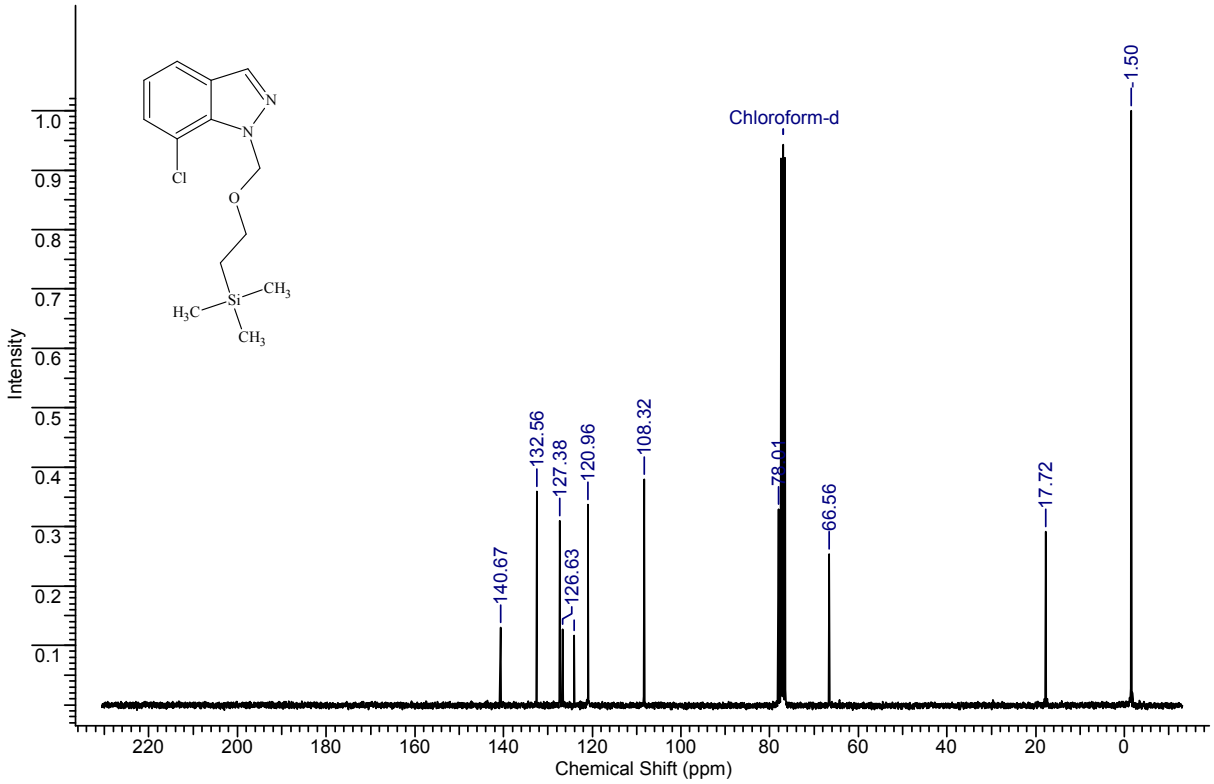
1-(methoxymethyl)-1*H*-indazole (2b)



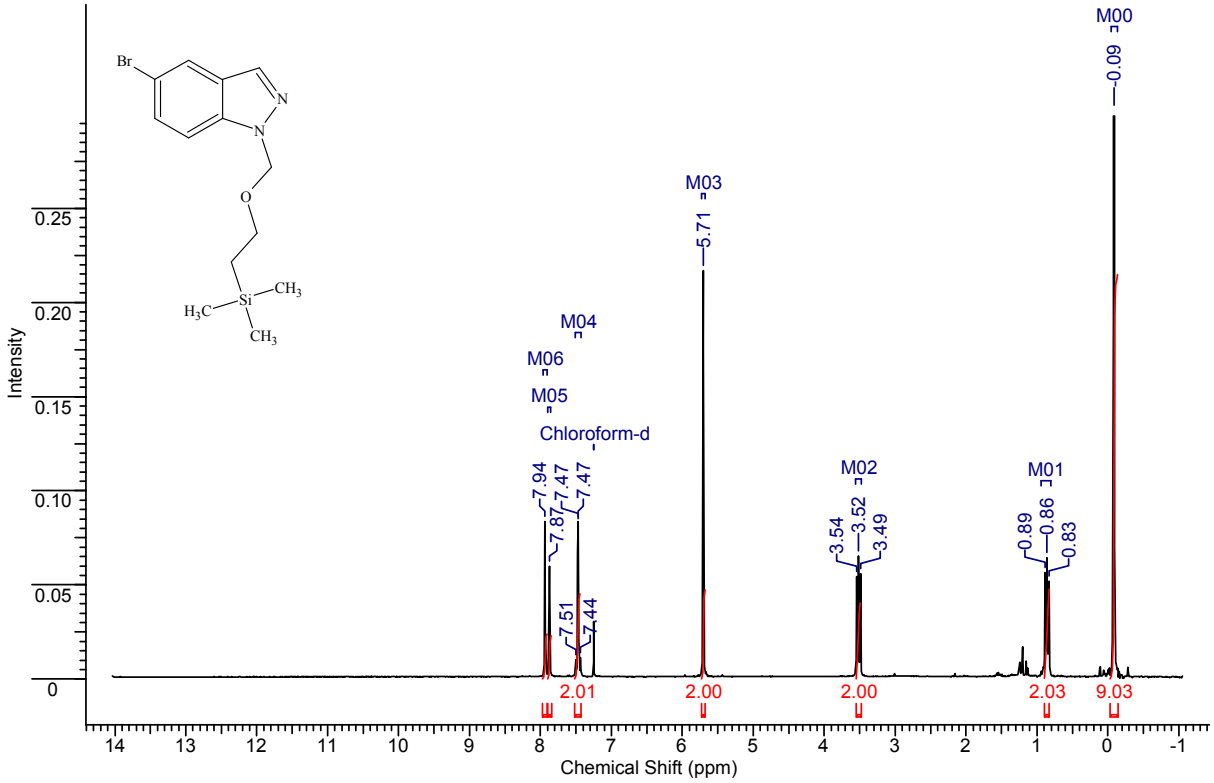


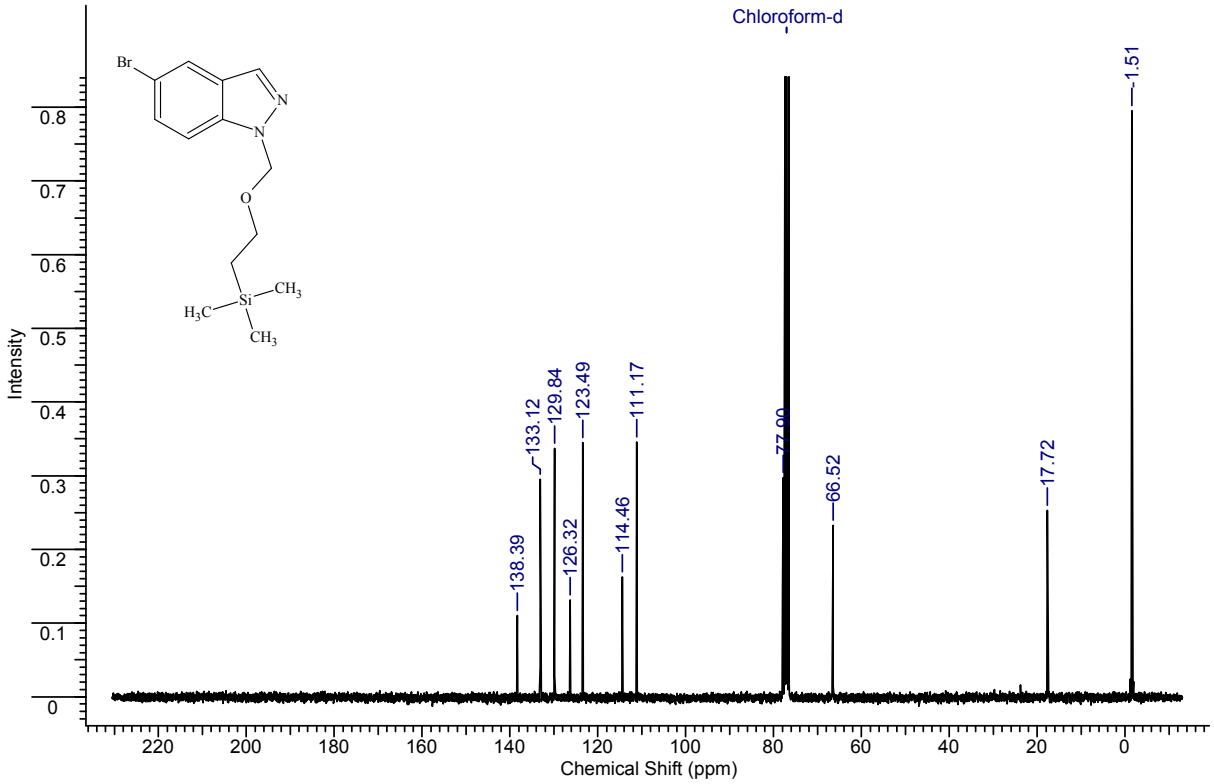
7-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-indazole (2d)



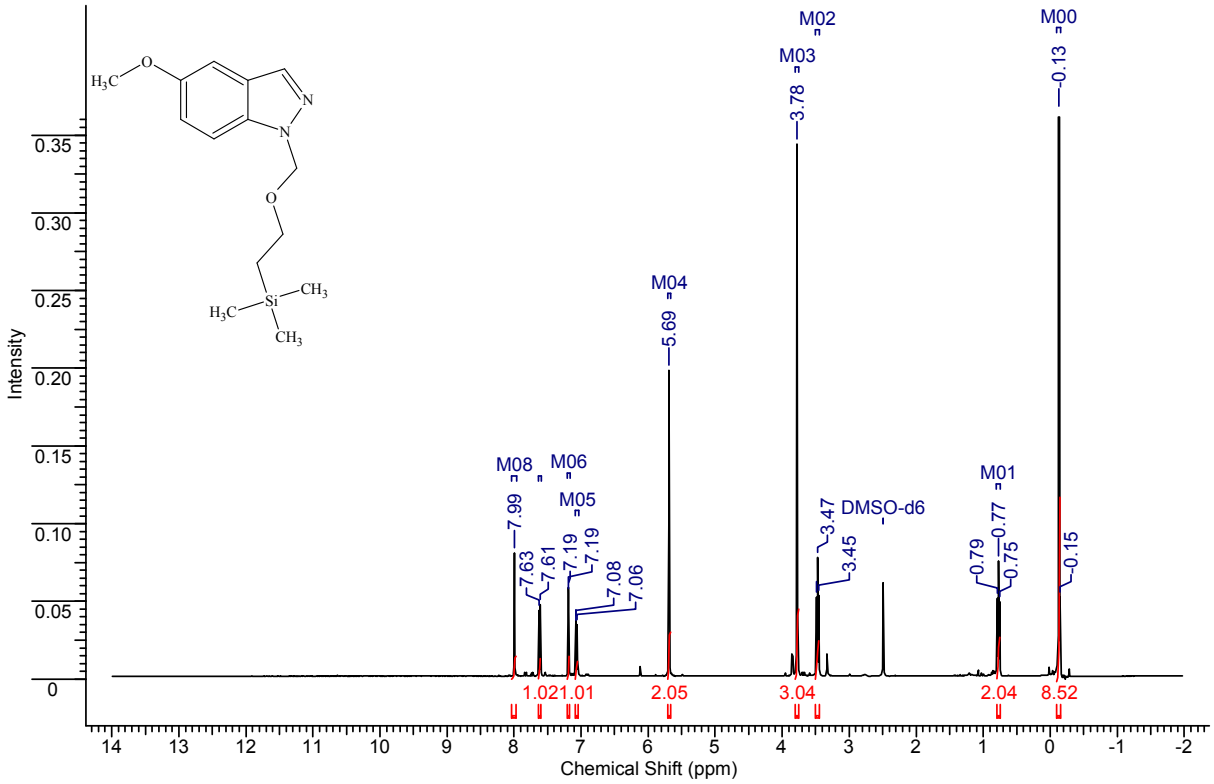


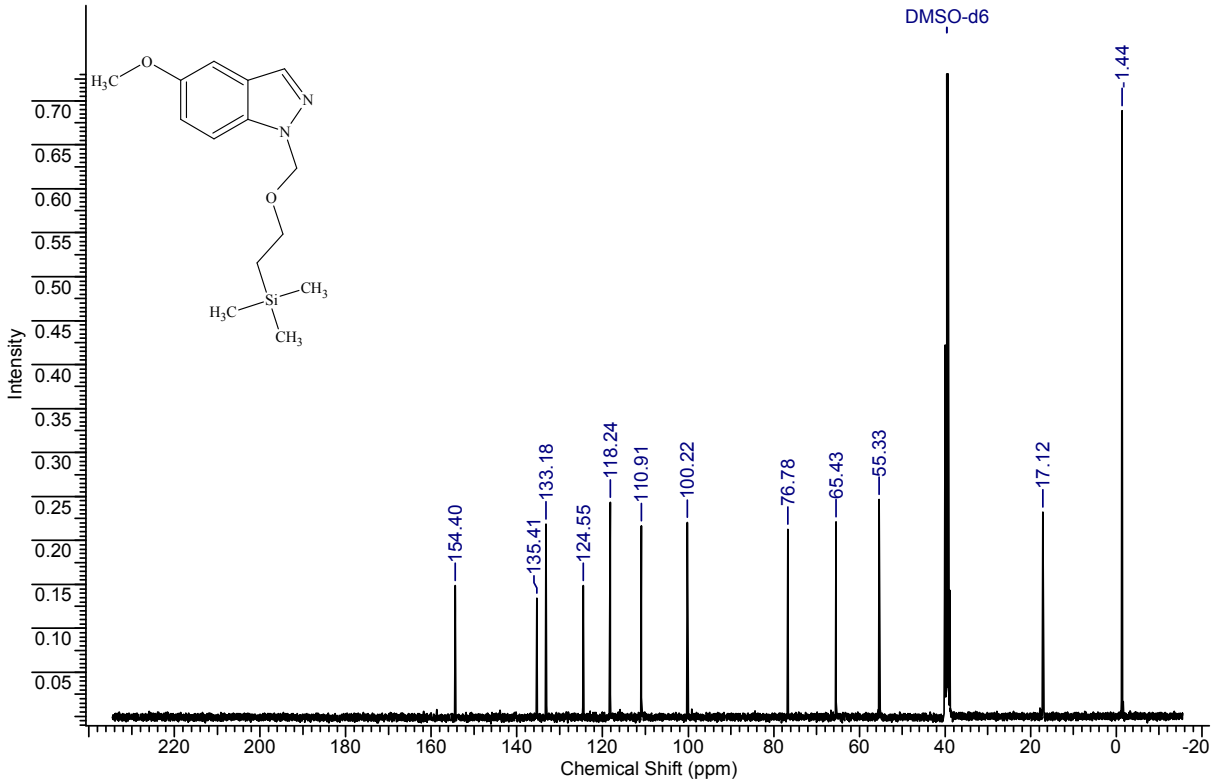
5-bromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-indazole (2e)



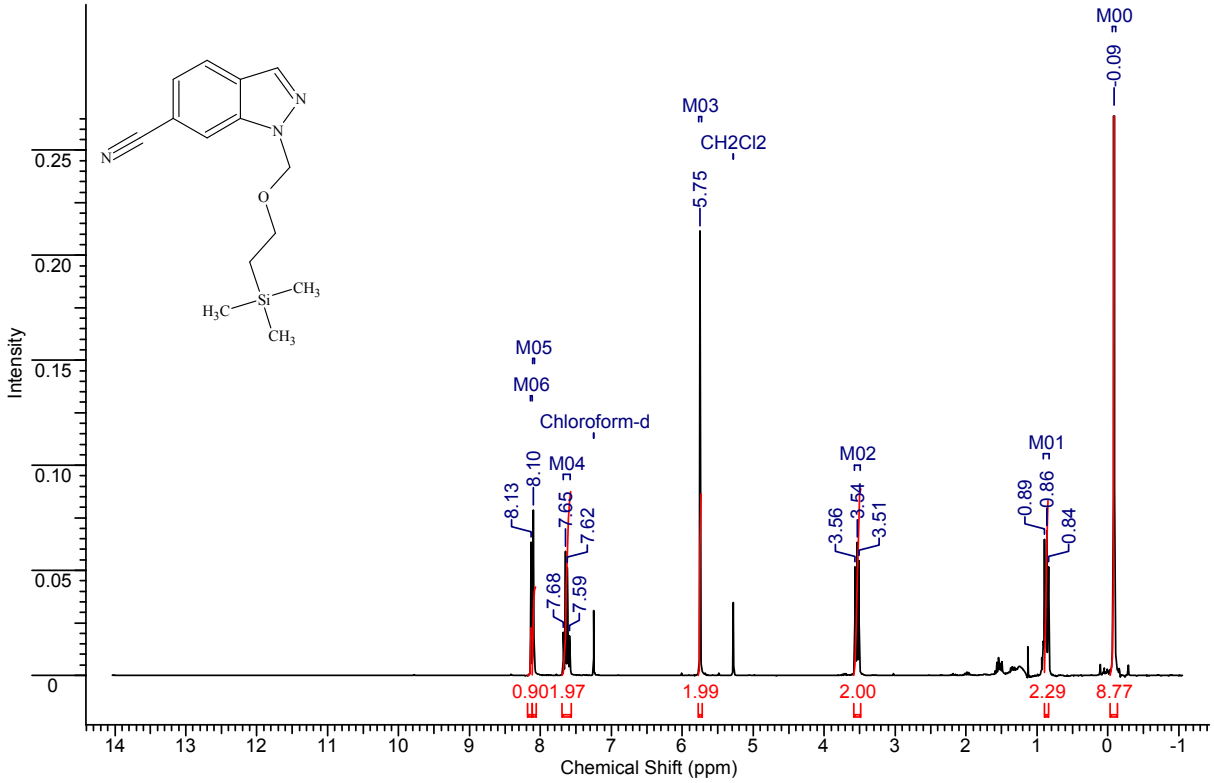


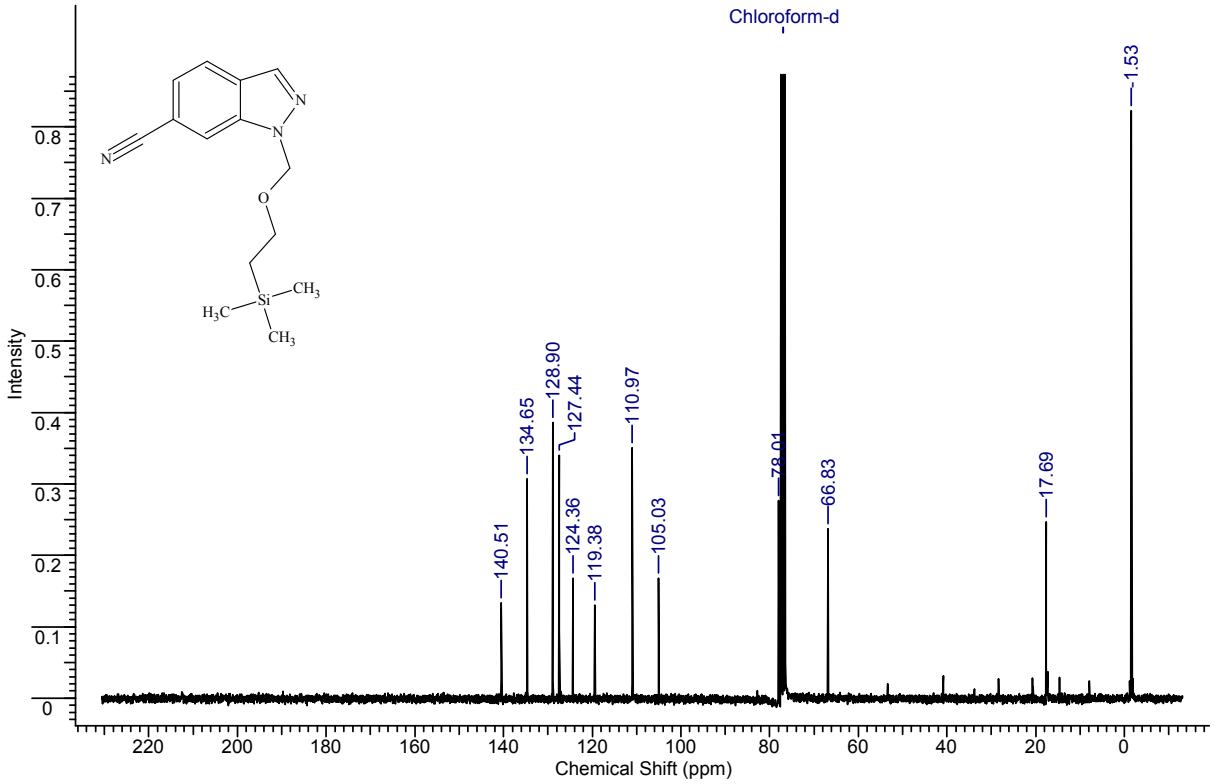
5-methoxy-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-indazole (2f)



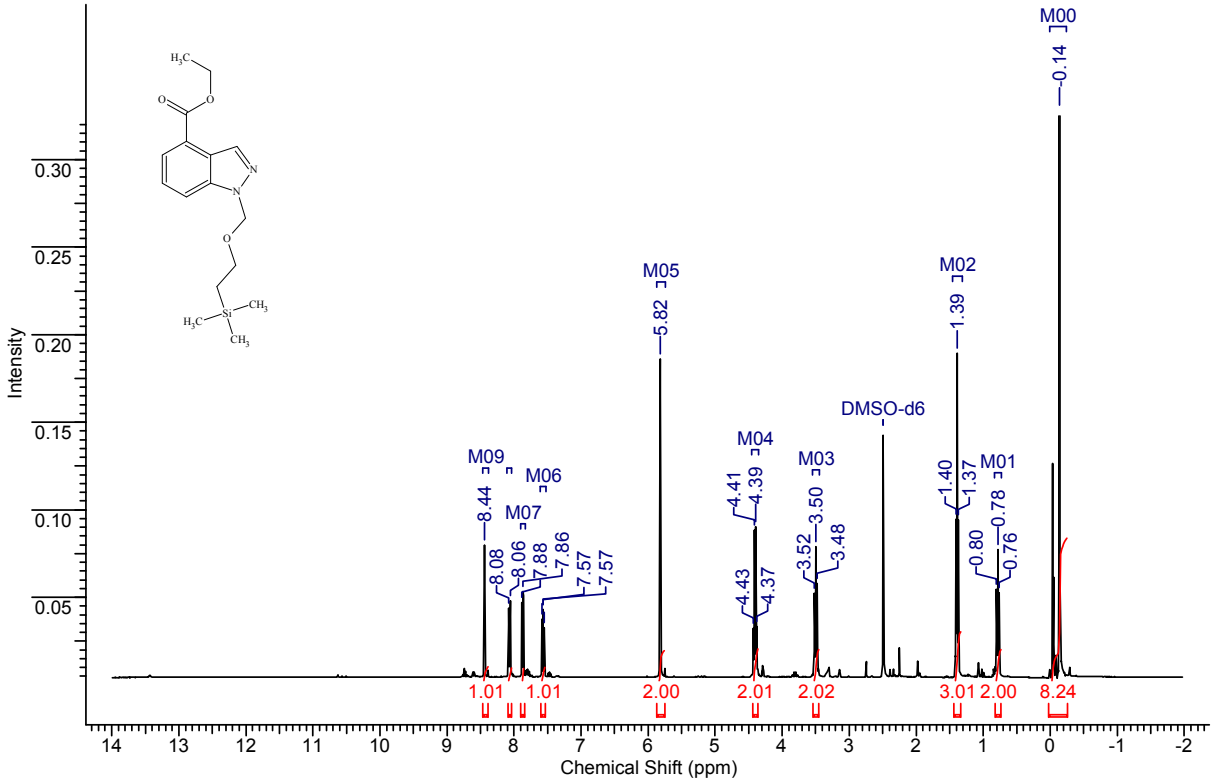


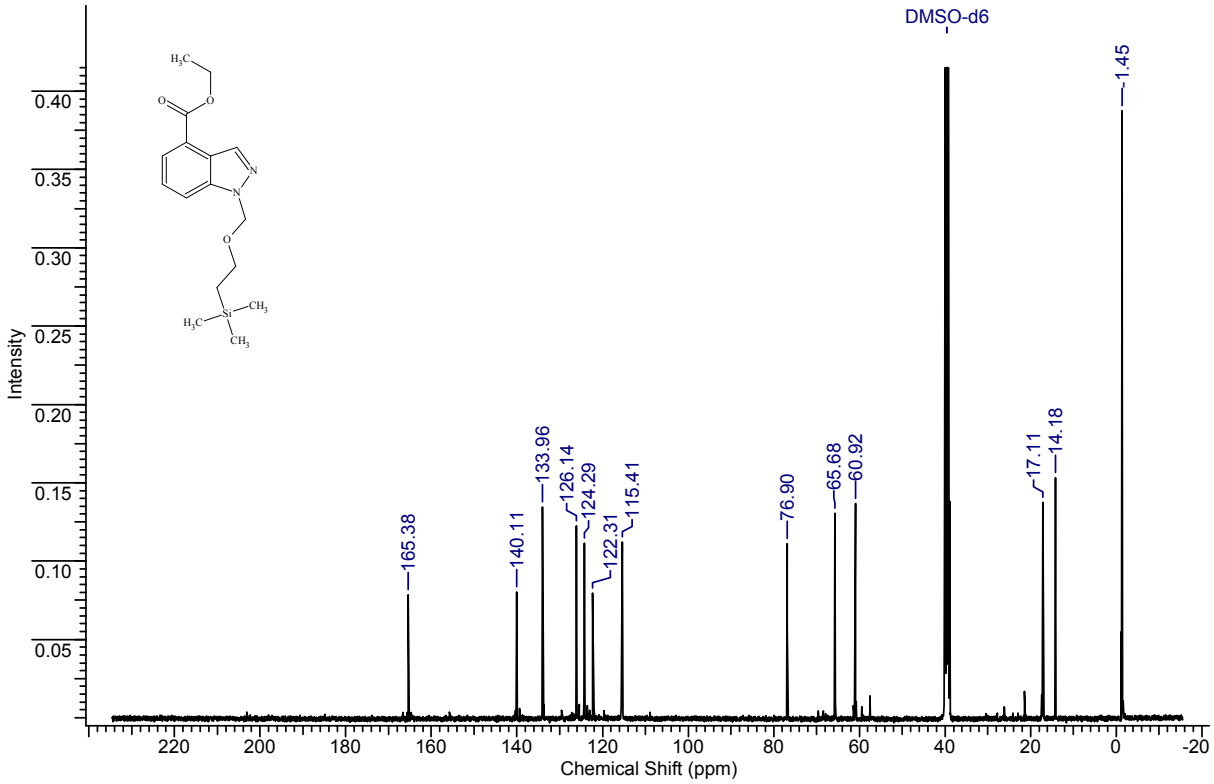
1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-indazole-6-carbonitrile (2g)



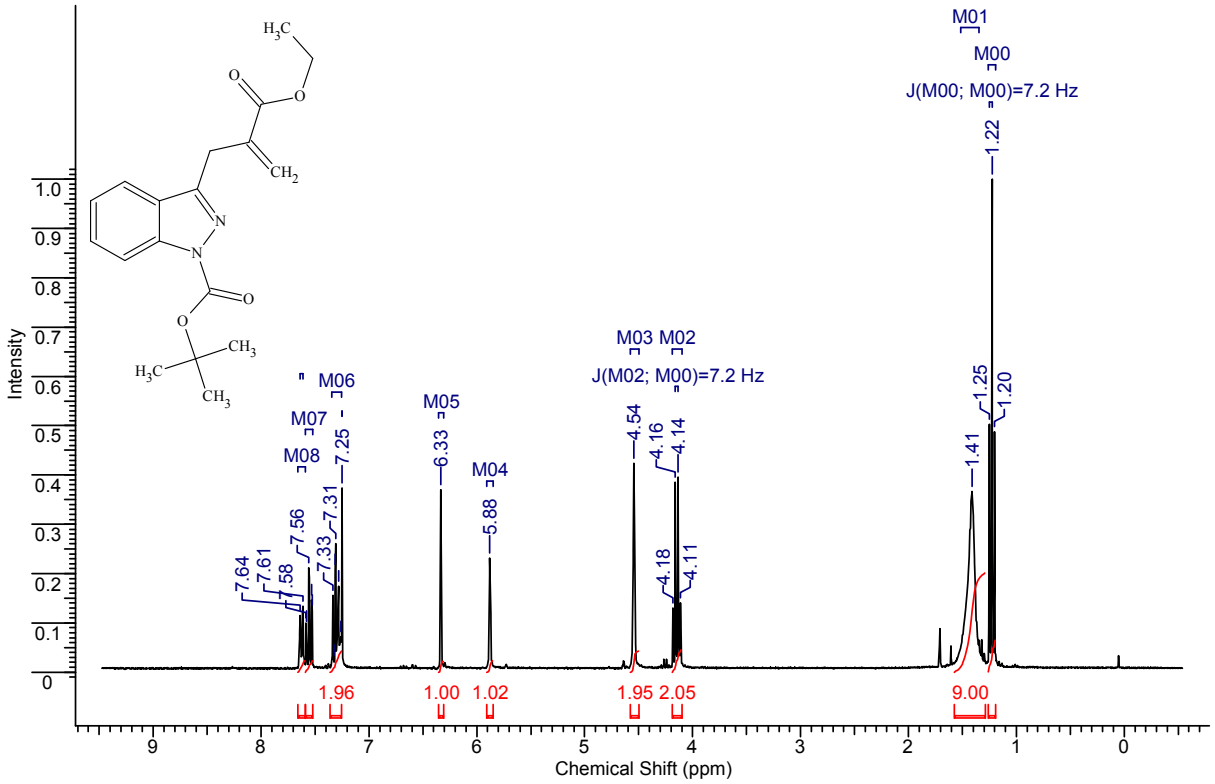


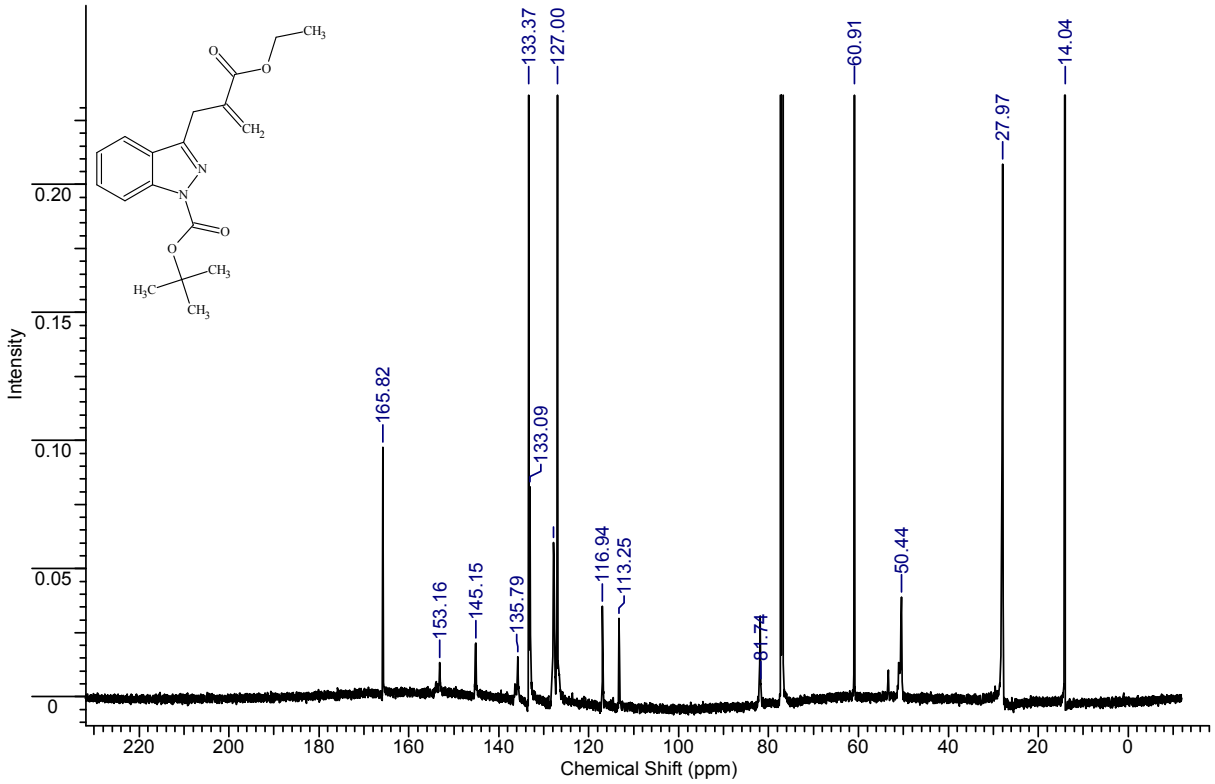
ethyl 1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-indazole-4-carboxylate (2h)



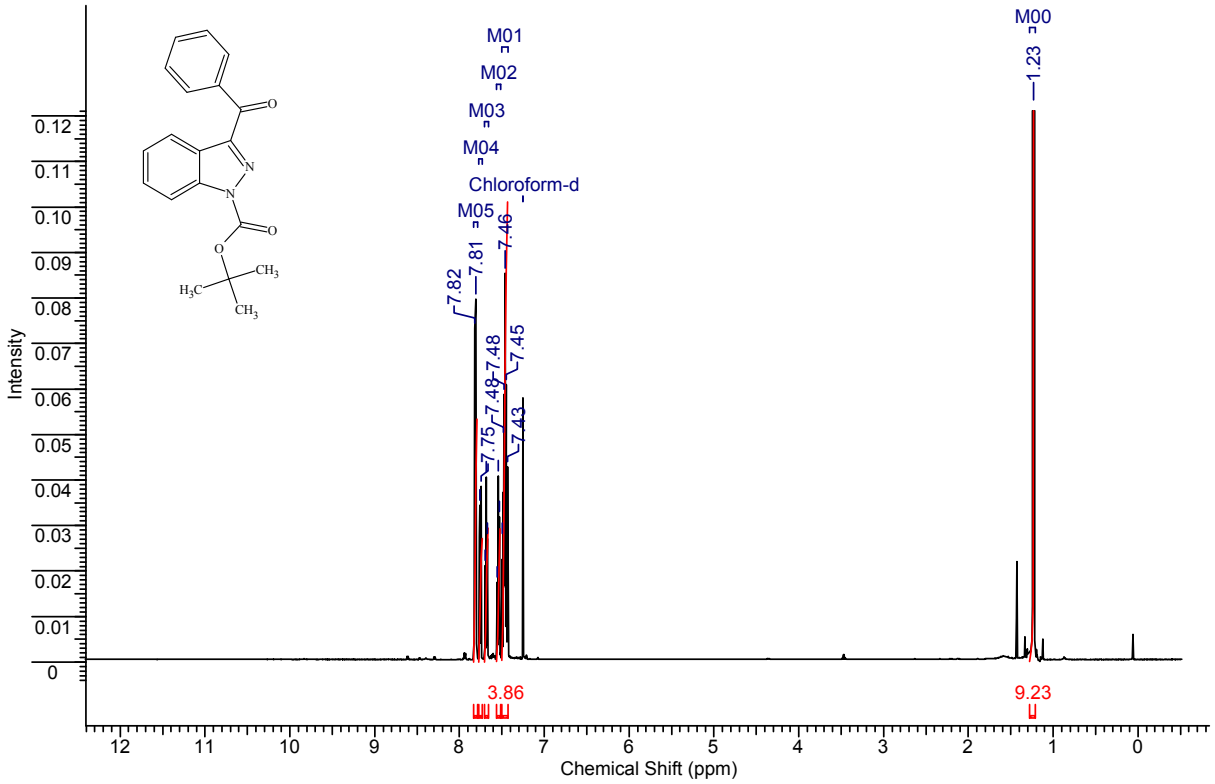


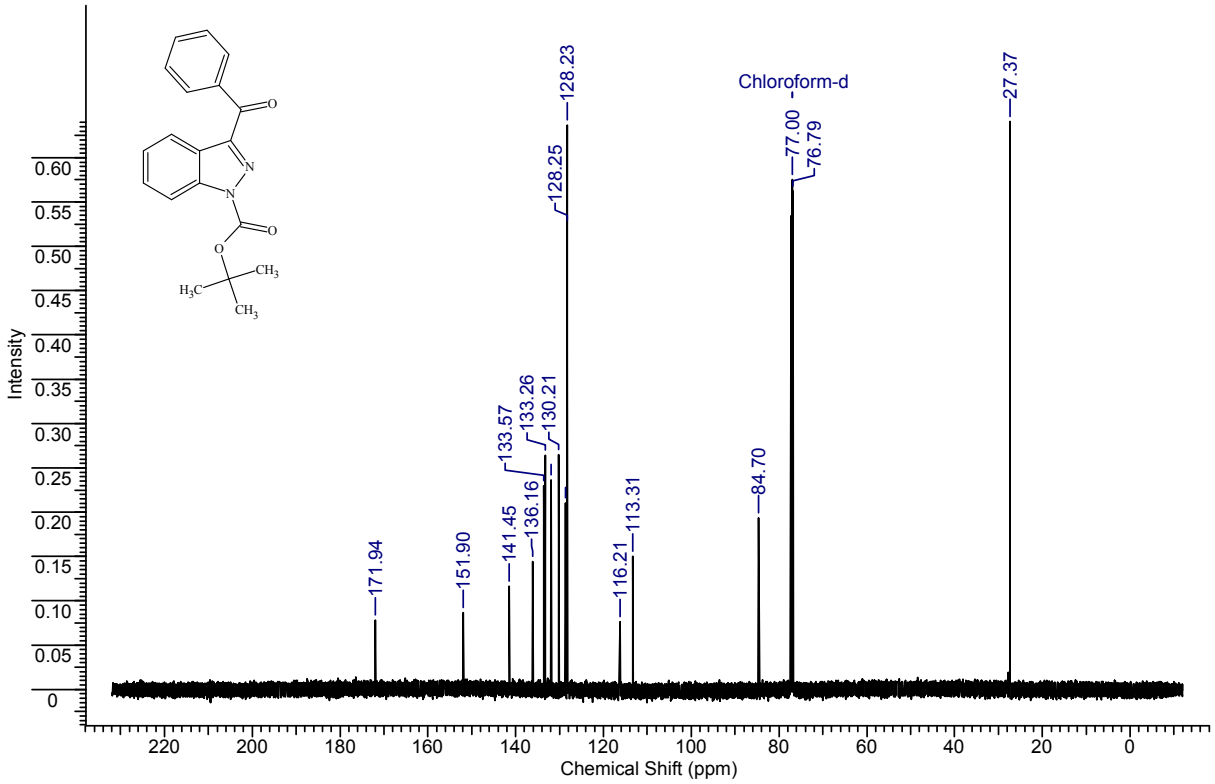
tert-butyl 3-(2-(ethoxycarbonyl)prop-2-en-1-yl)-1_H_-indazole-1-carboxylate (4a)



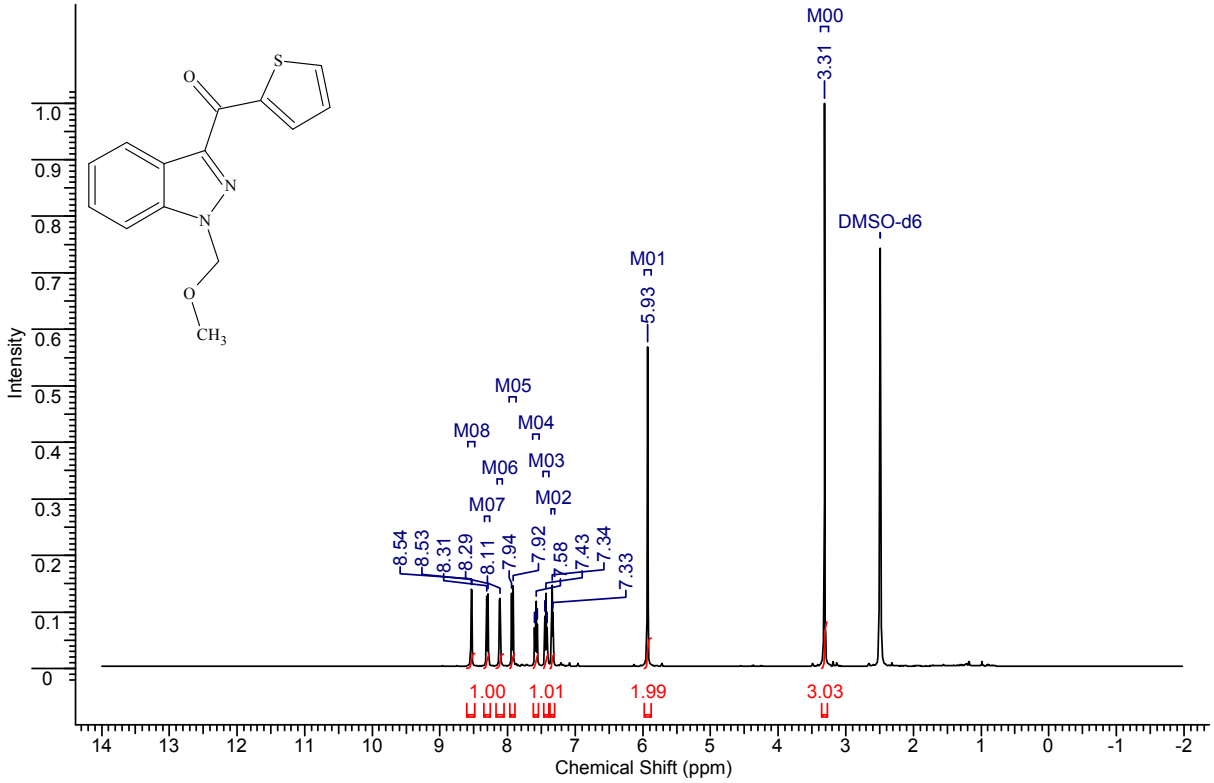


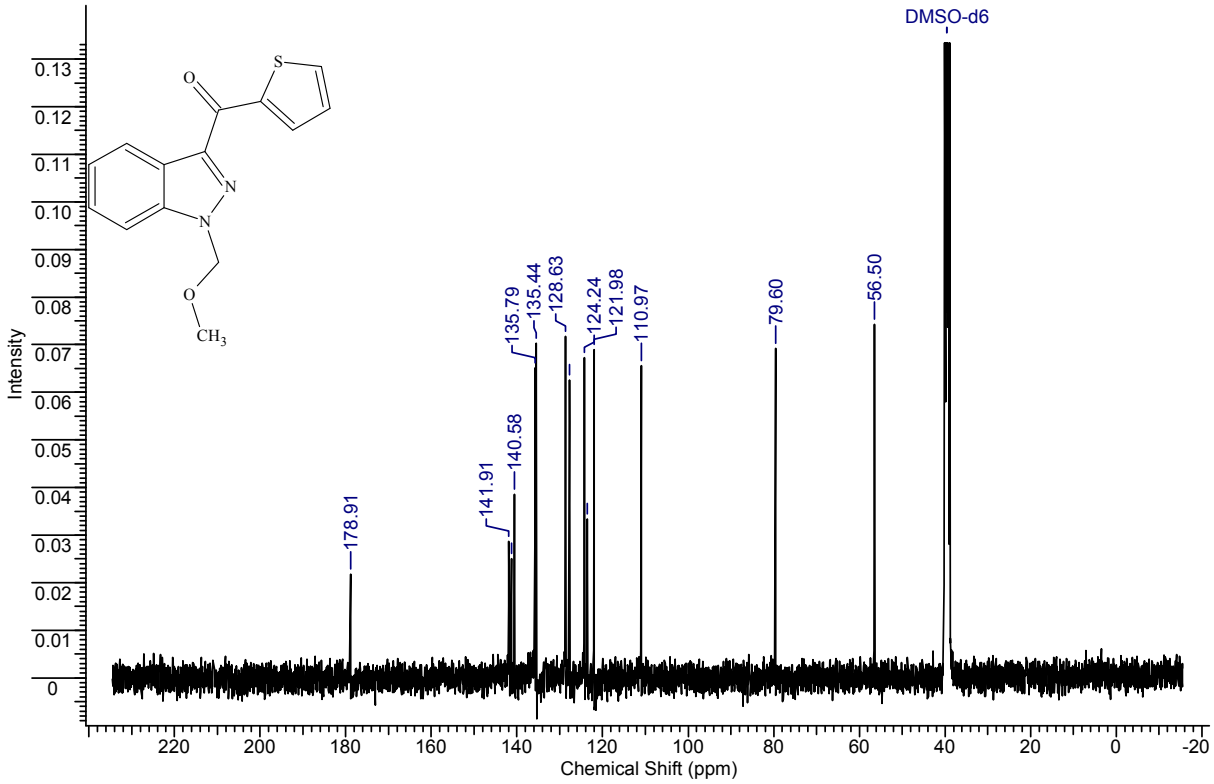
tert-butyl 3-benzoyl-1*H*-indazole-1-carboxylate (4b)



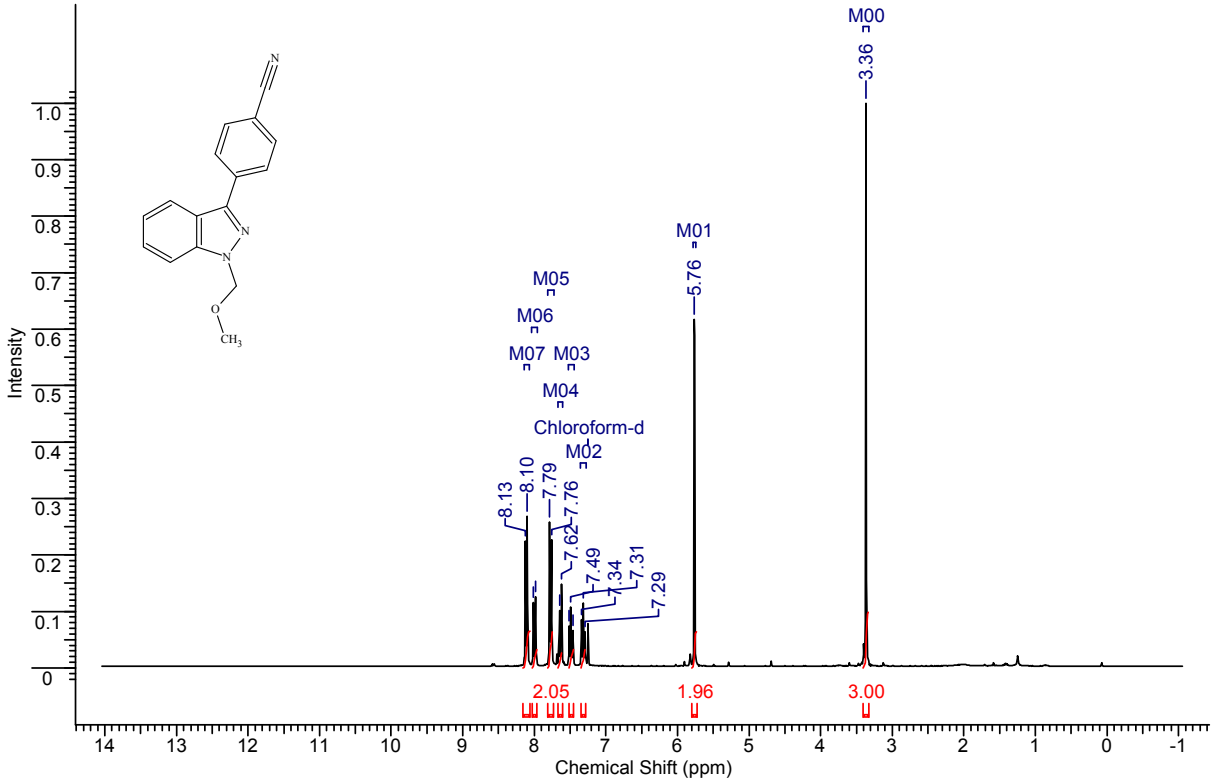


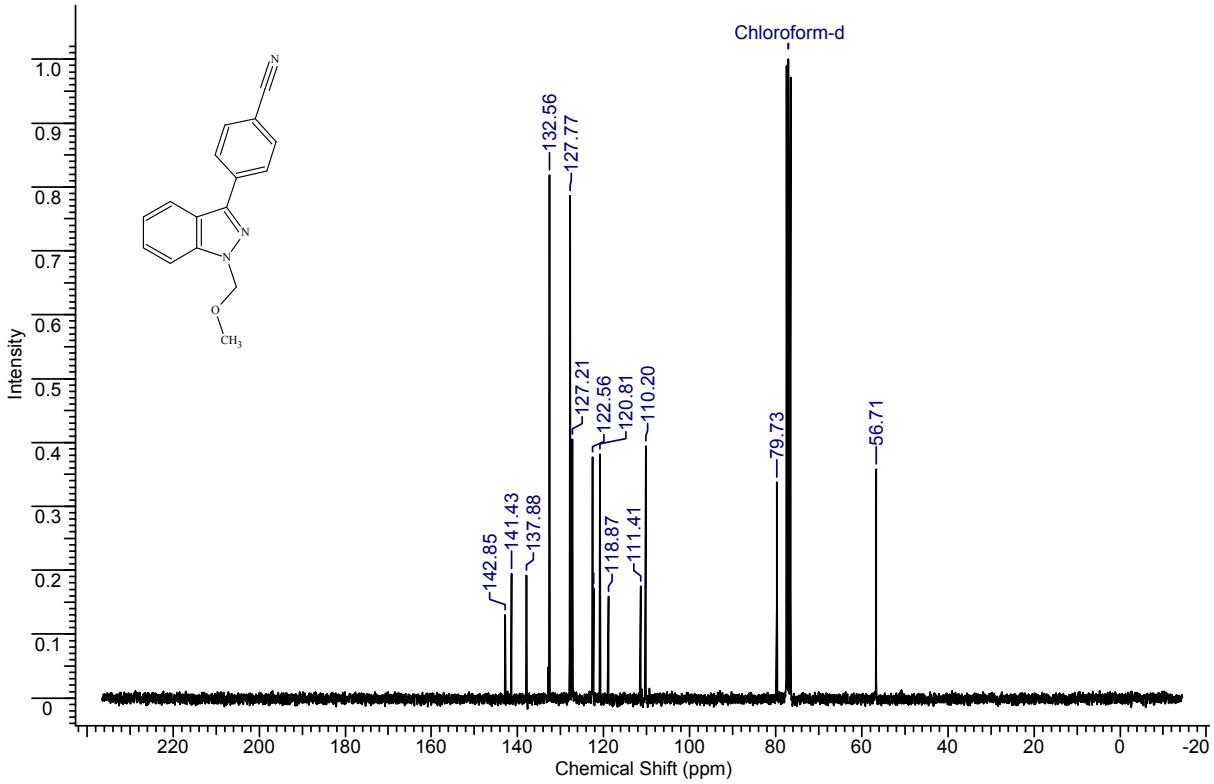
(1-(methoxymethyl)-1*H*-indazol-3-yl)(thiophen-2-yl)methanone (4c)



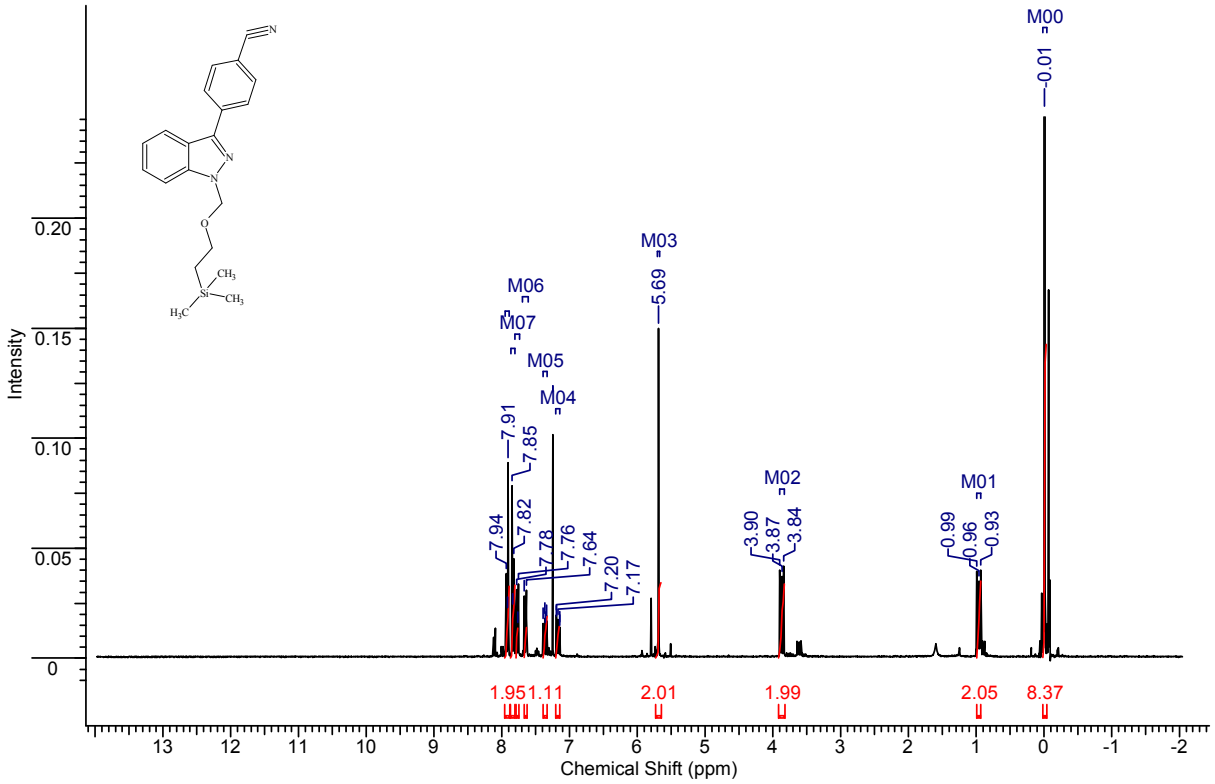


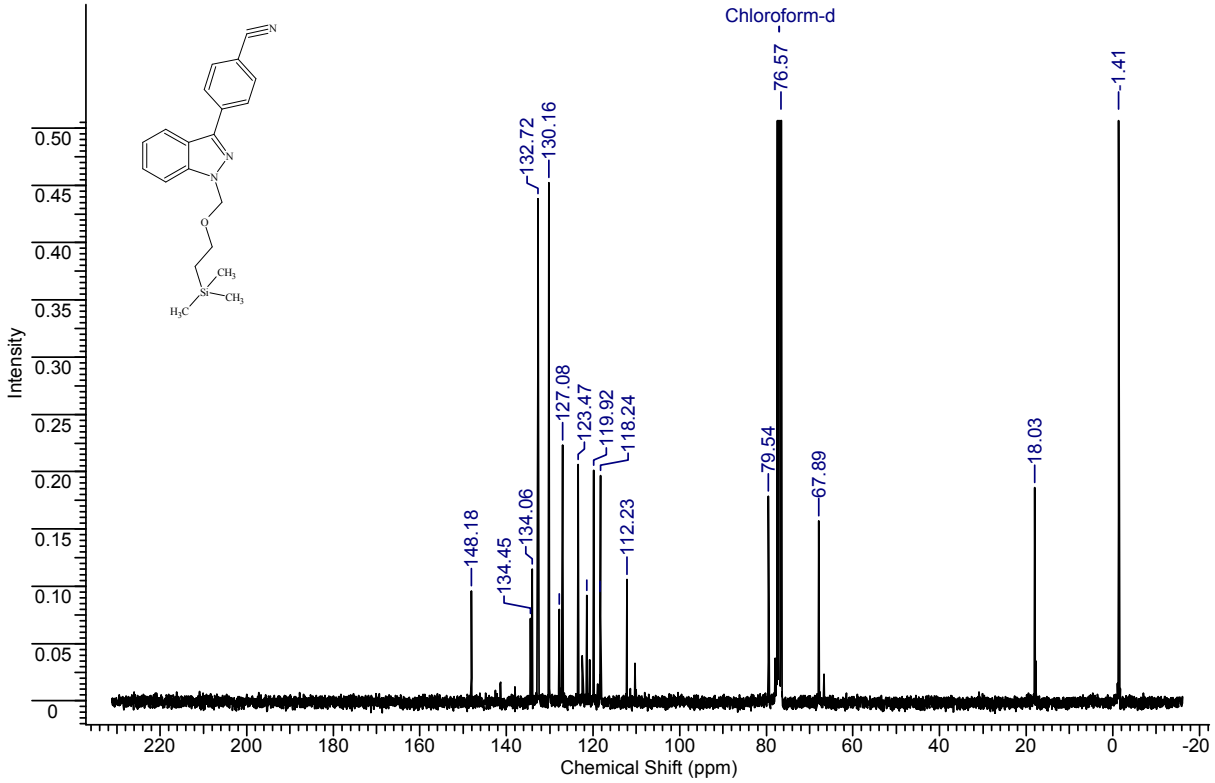
4-(1-(methoxymethyl)-1*H*-indazol-3-yl)benzonitrile (4d)



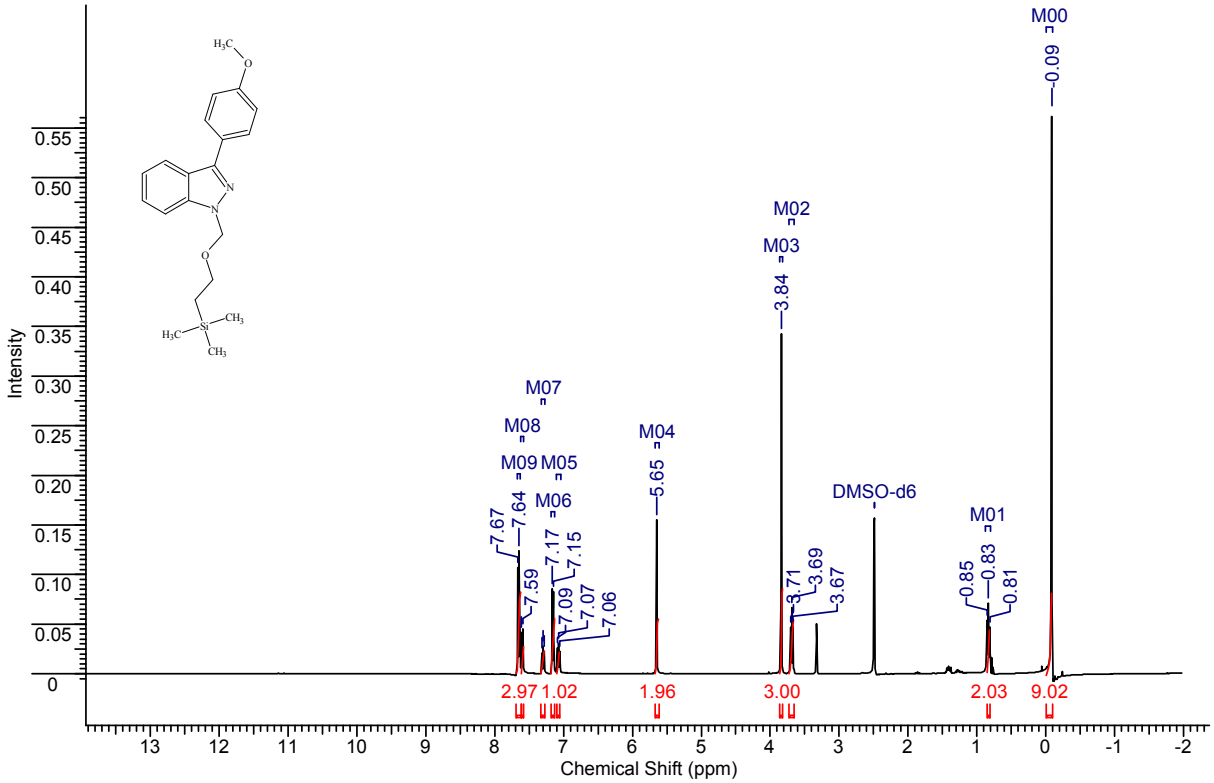


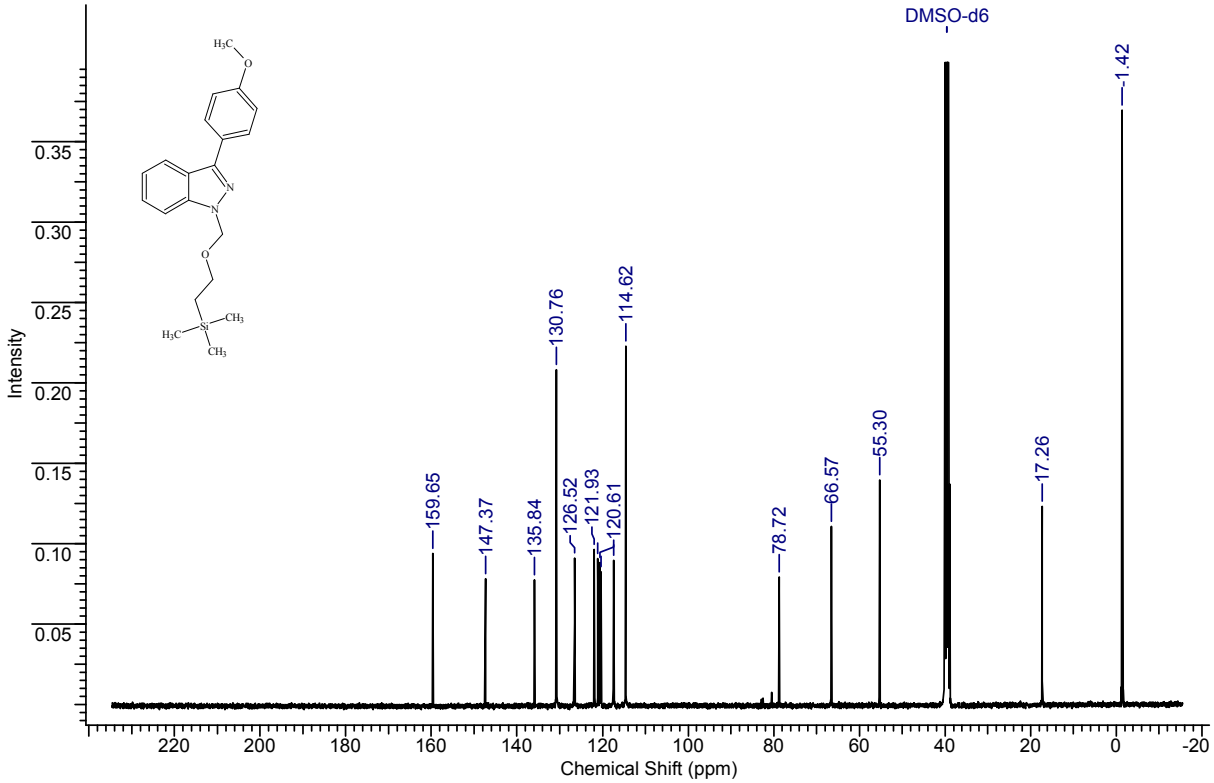
(4-(1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-indazol-3-yl)benzonitrile (4e)



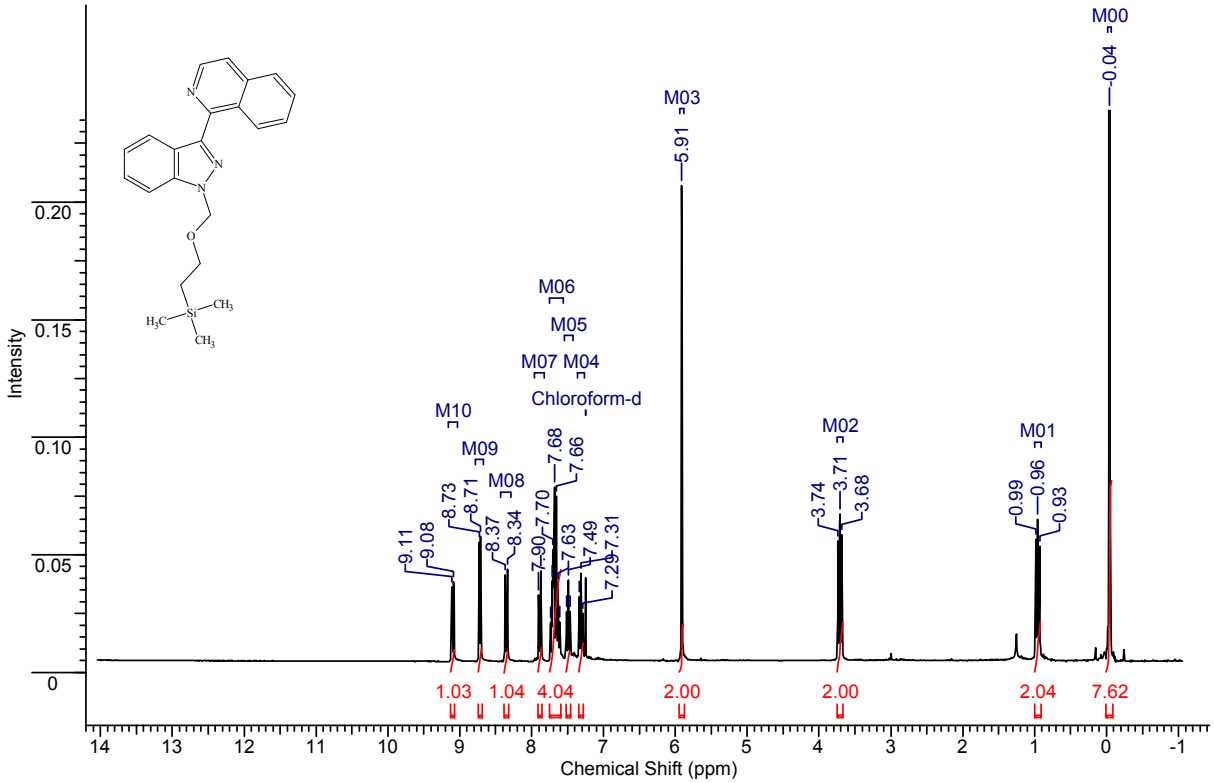


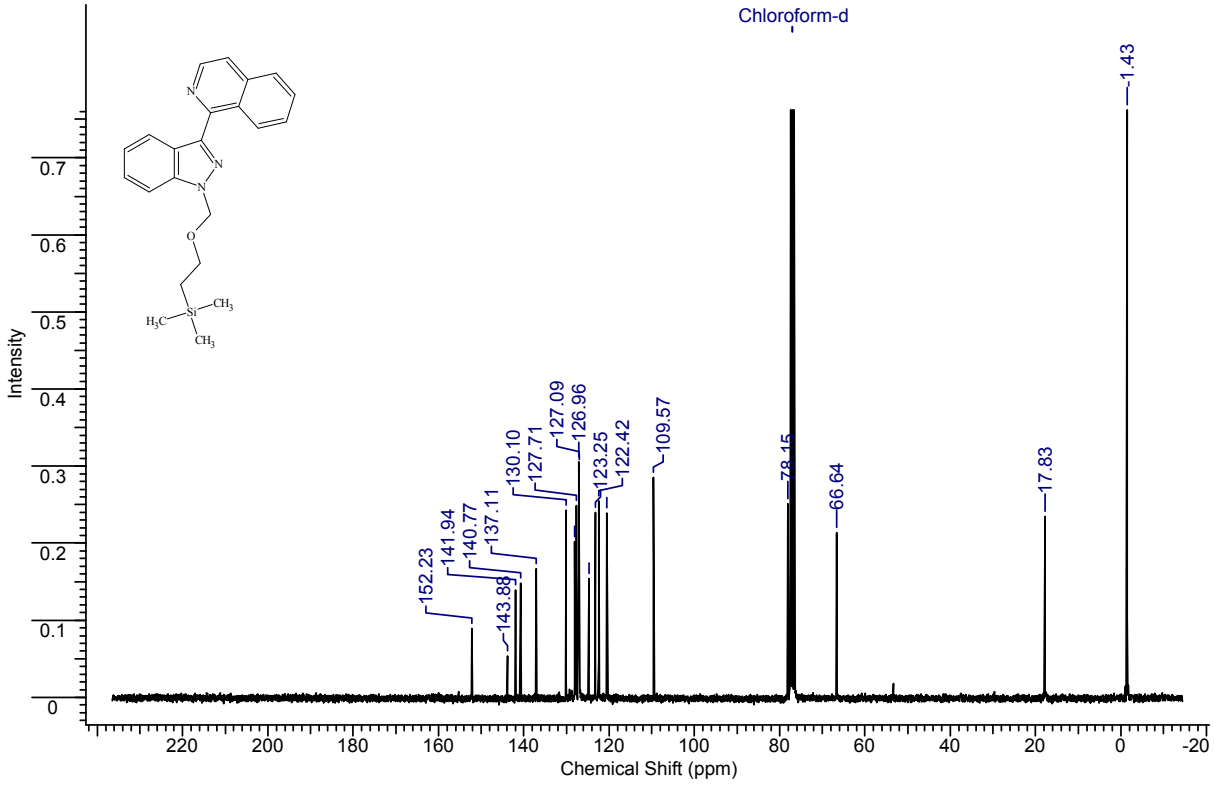
3-(4-methoxyphenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-indazole (4f)



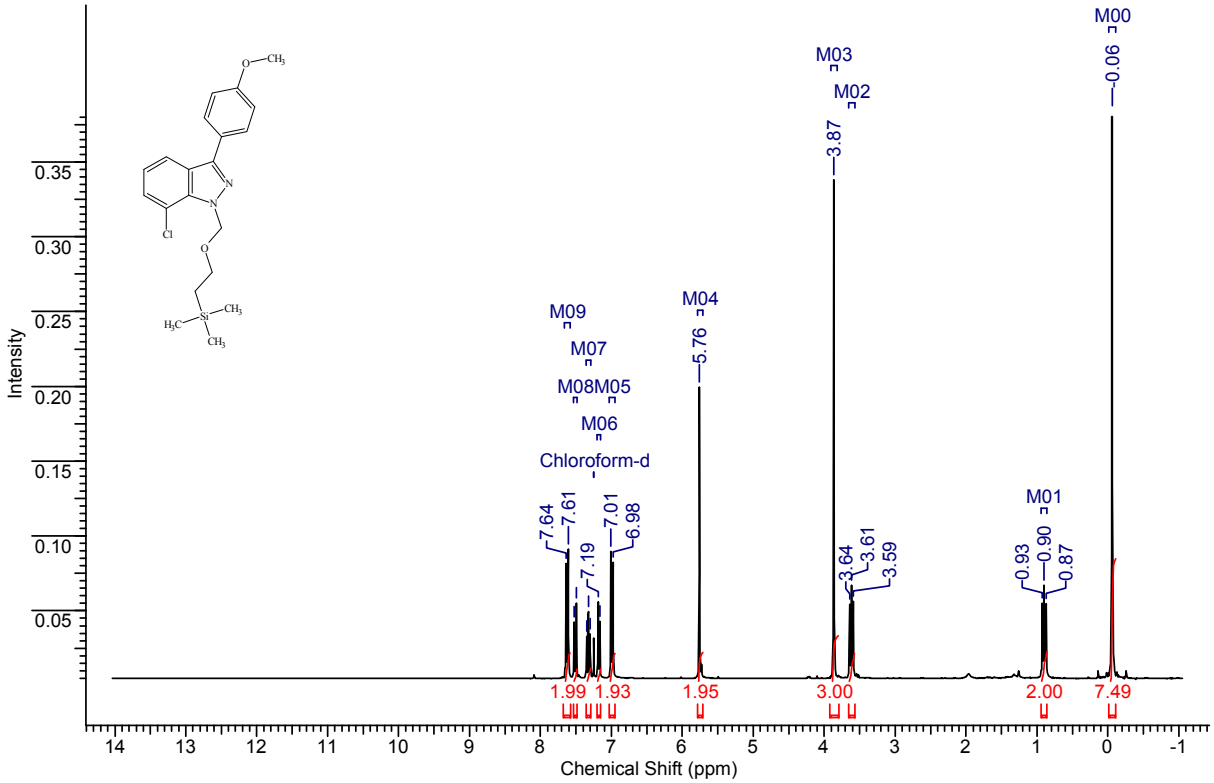


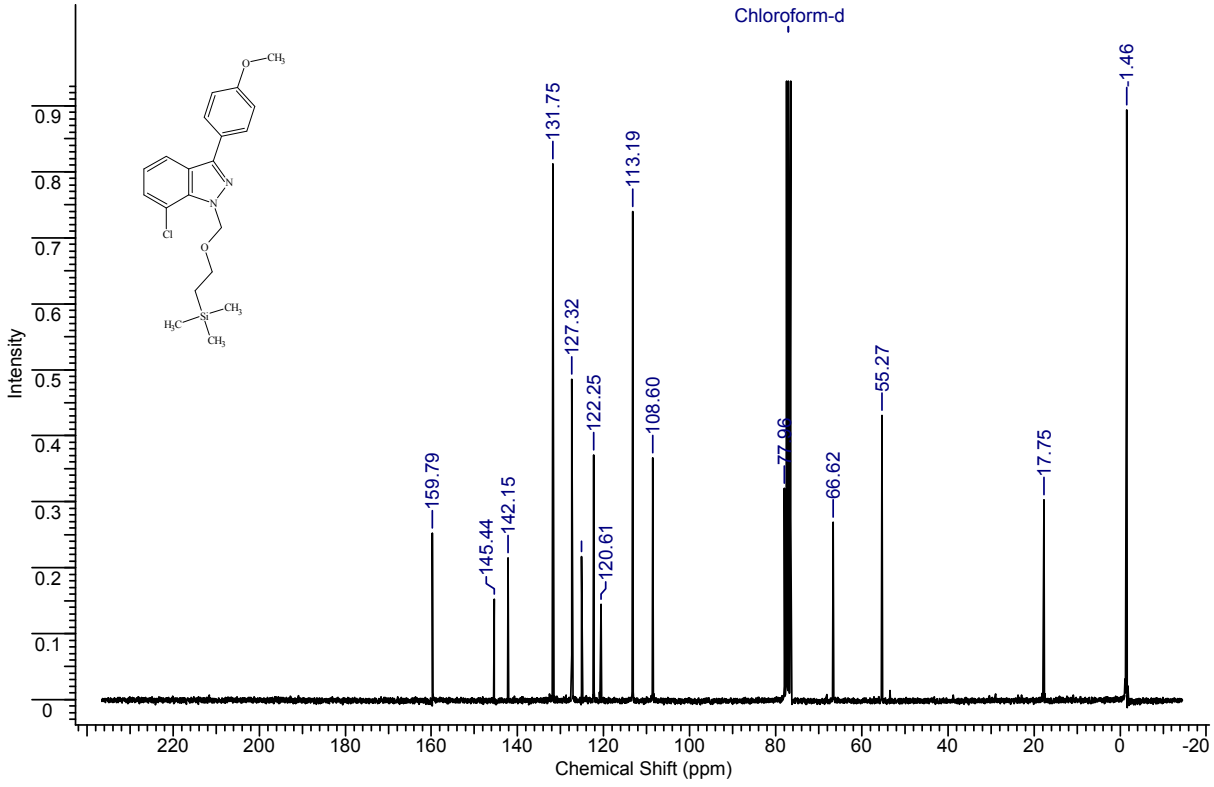
1-(1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazol-3-yl)isoquinoline (4g)



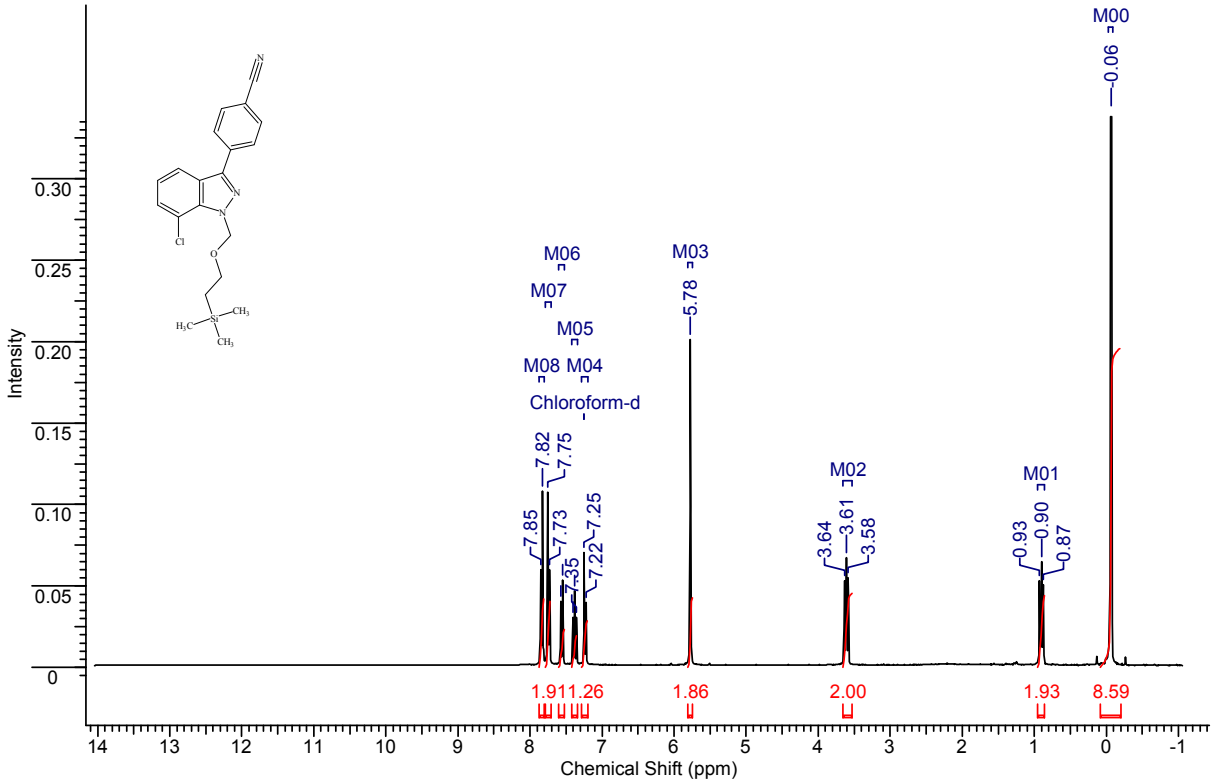


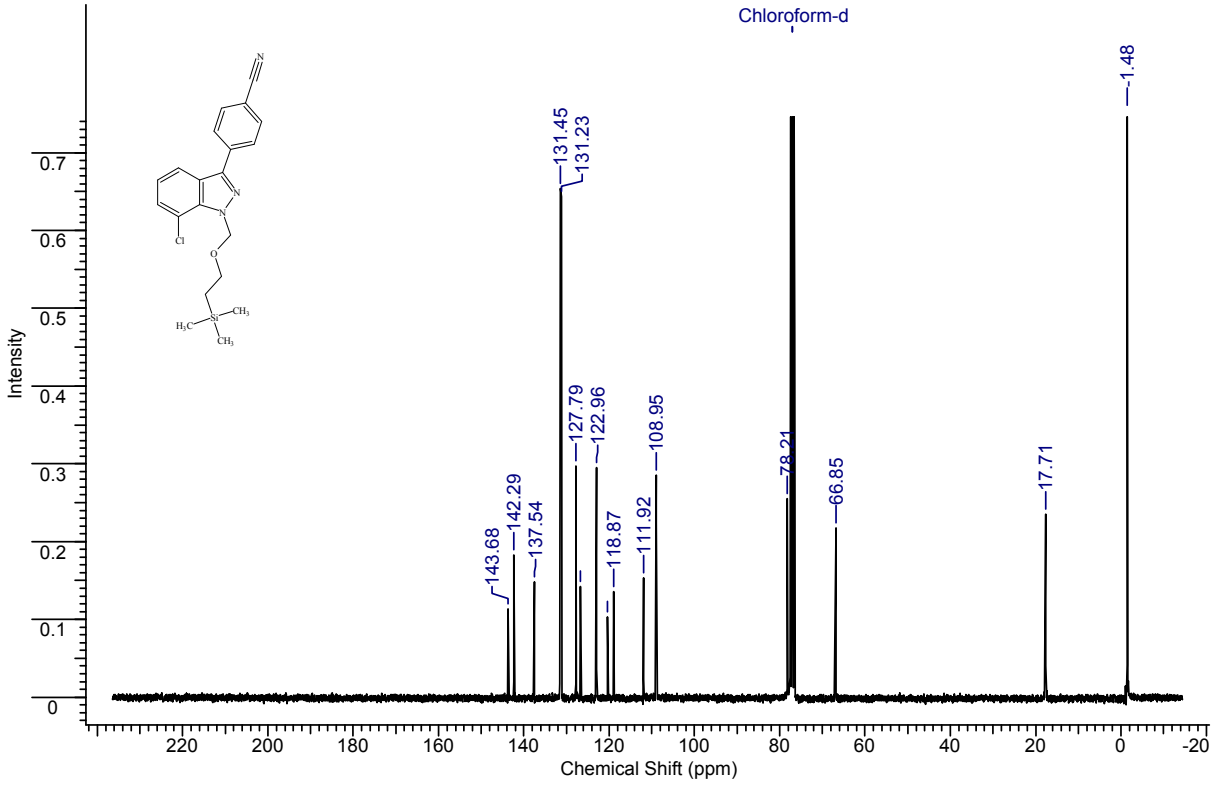
7-chloro-3-(4-methoxyphenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-indazole (4h)



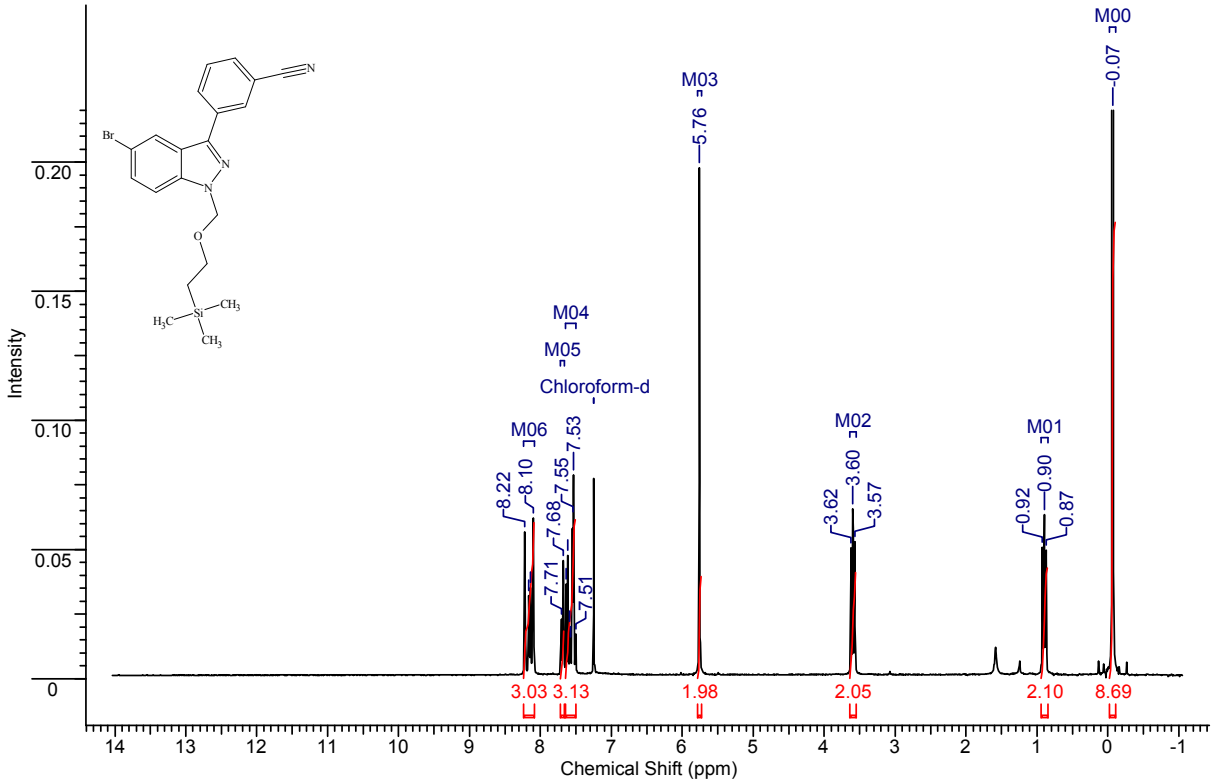


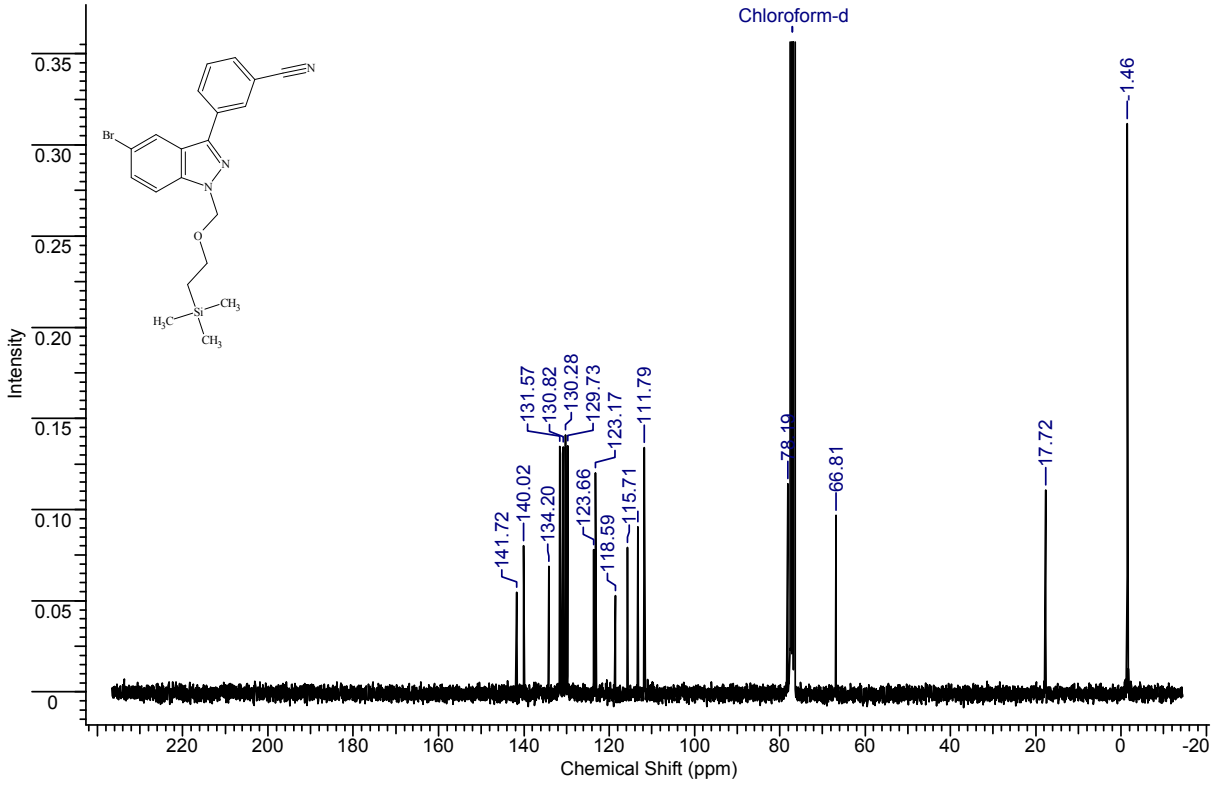
4-(7-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazol-3-yl)benzonitrile (4i)



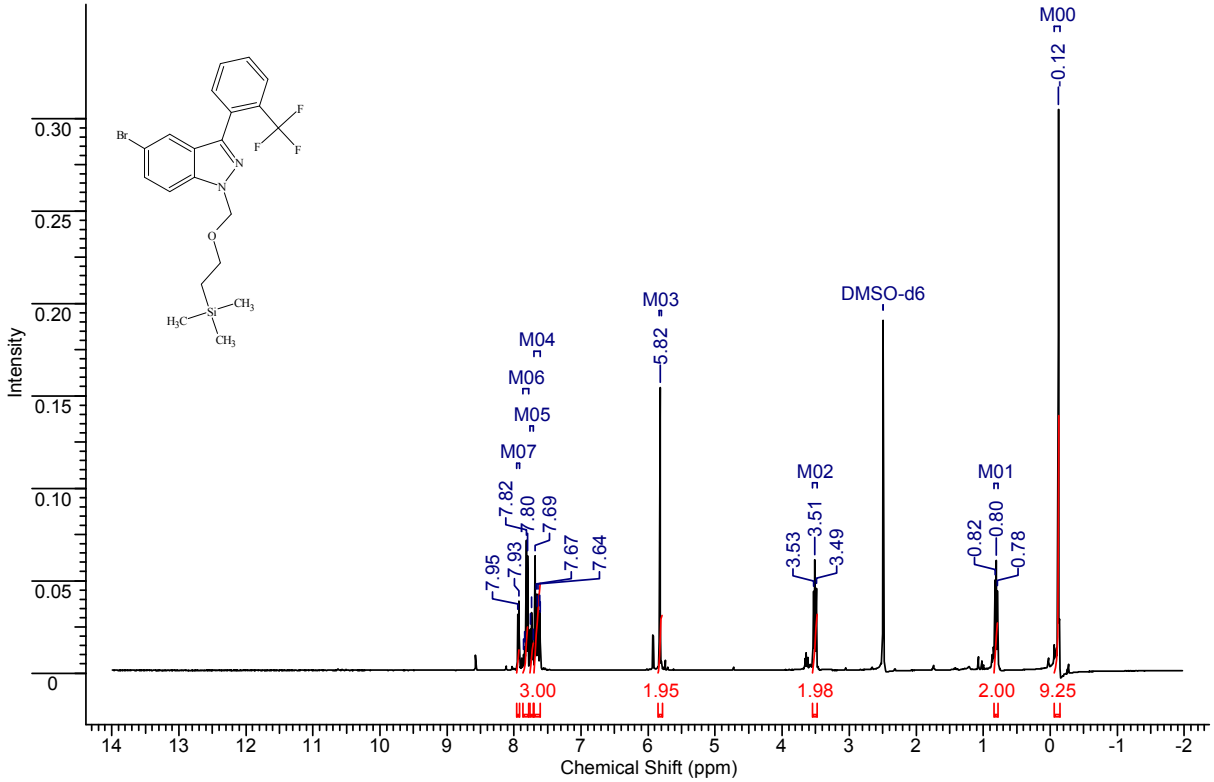


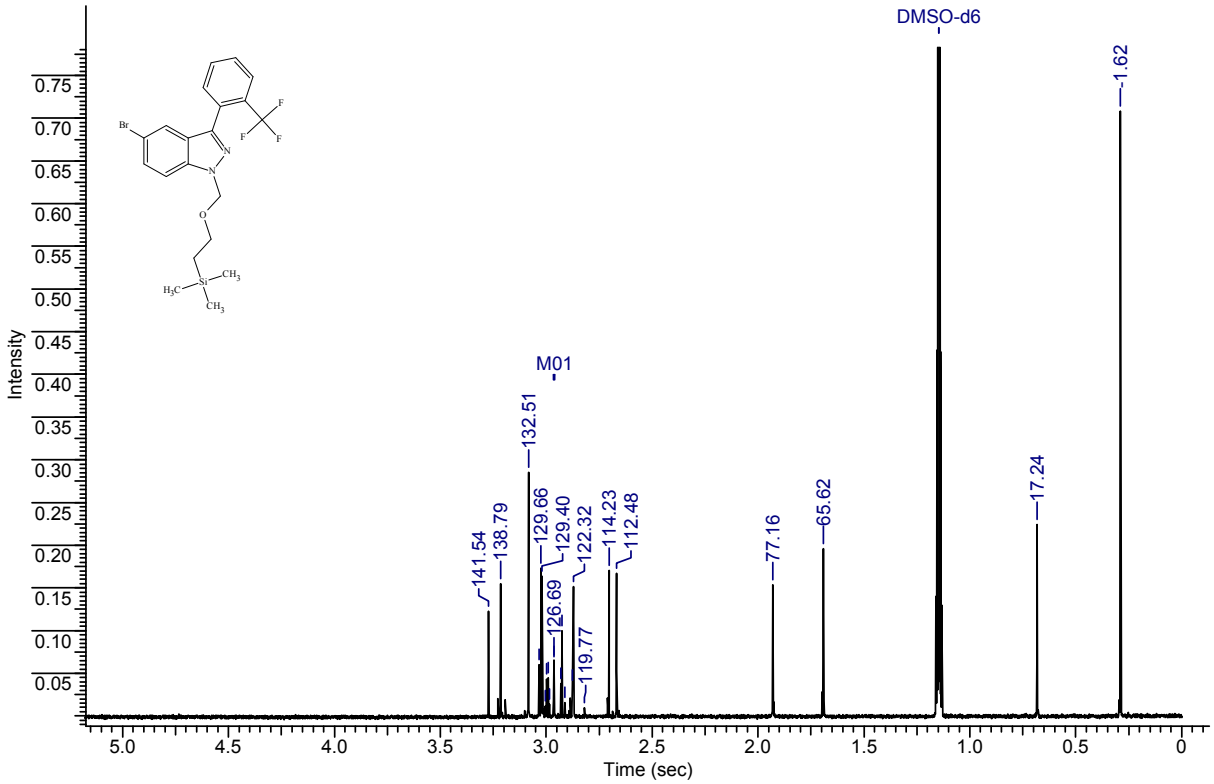
3-(5-bromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-indazol-3-yl)benzonitrile (4j)



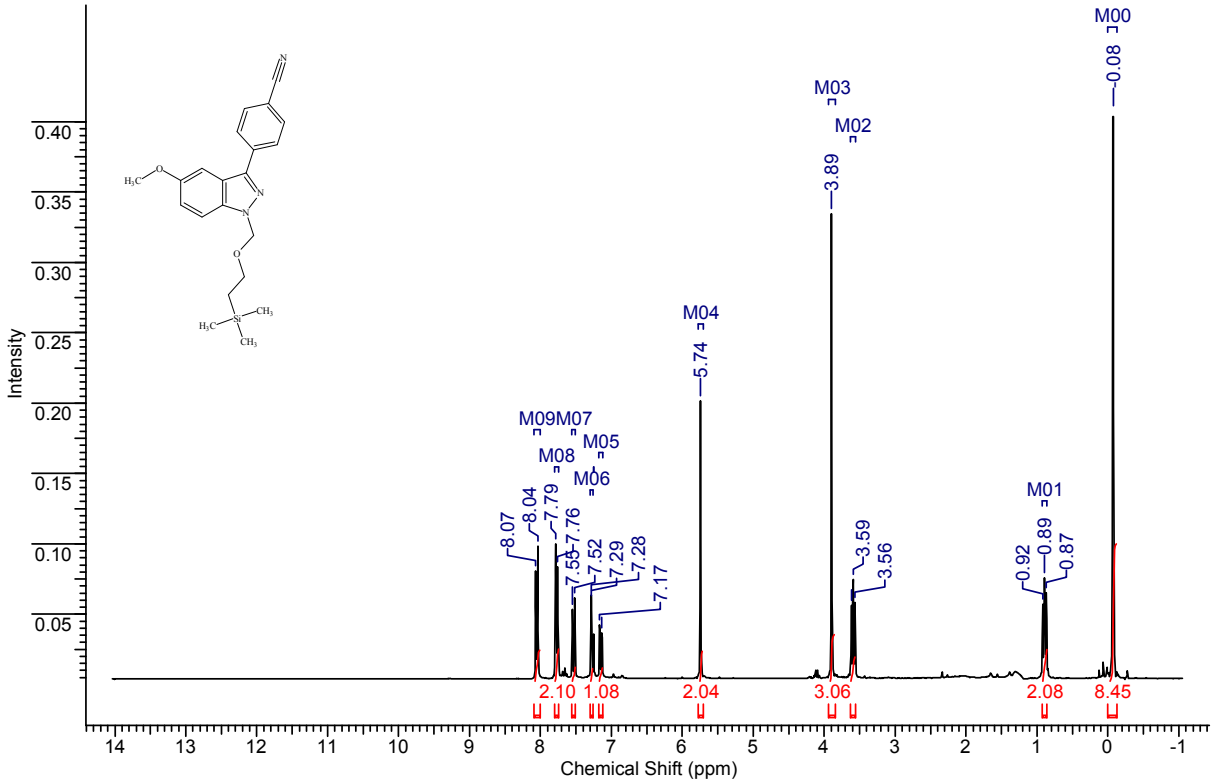


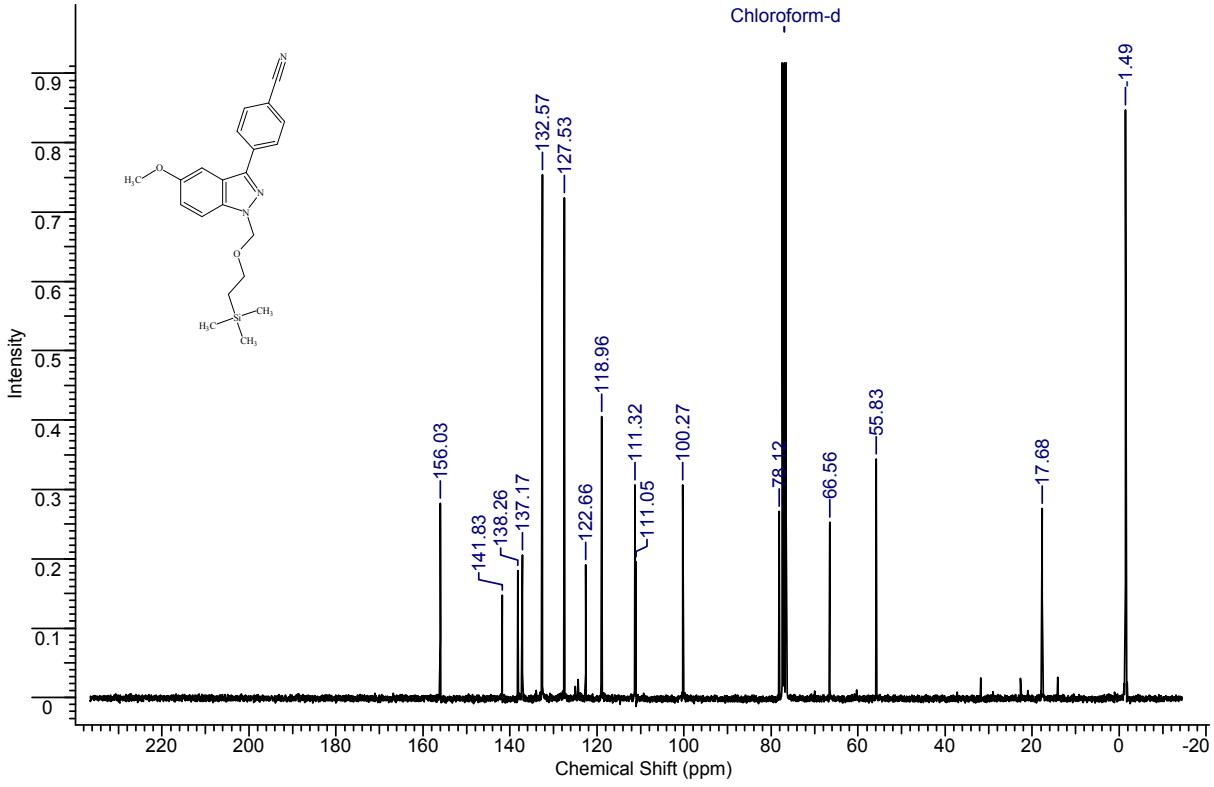
5-bromo-3-(2-(trifluoromethyl)phenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-indazole (4k)



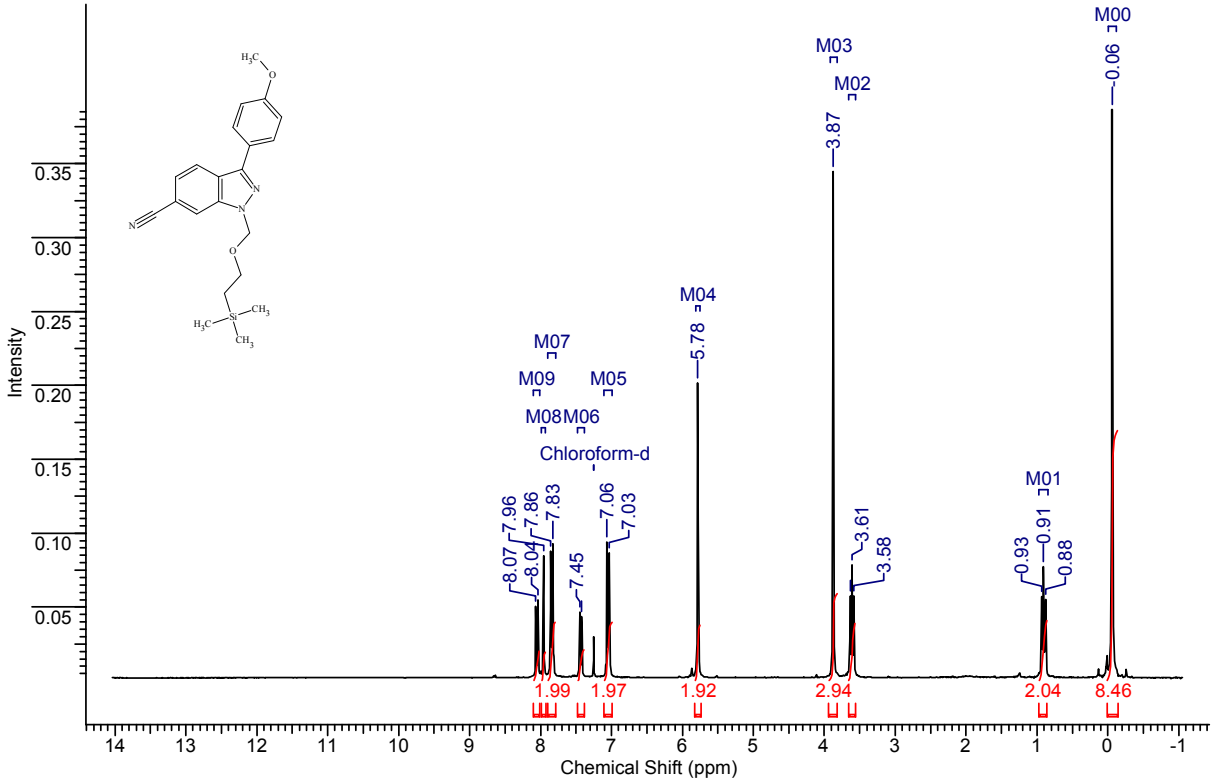


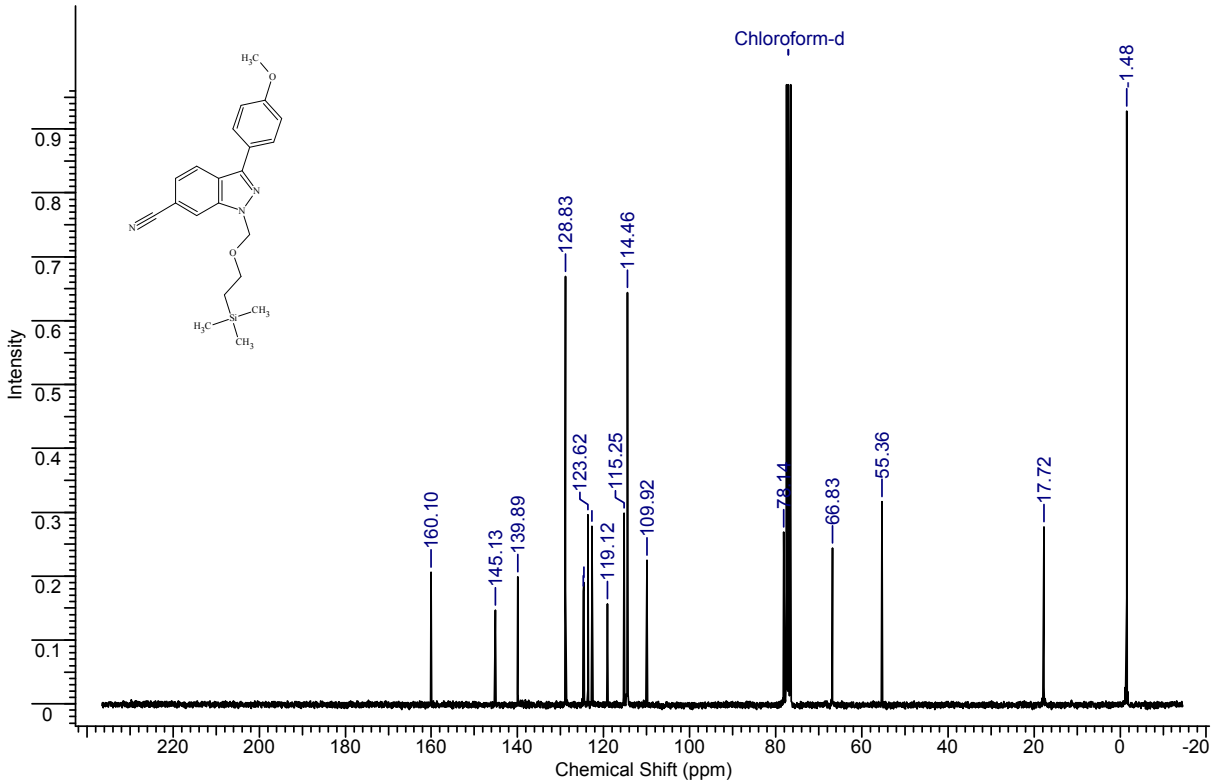
4-(5-methoxy-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazol-3-yl)benzonitrile (4l)



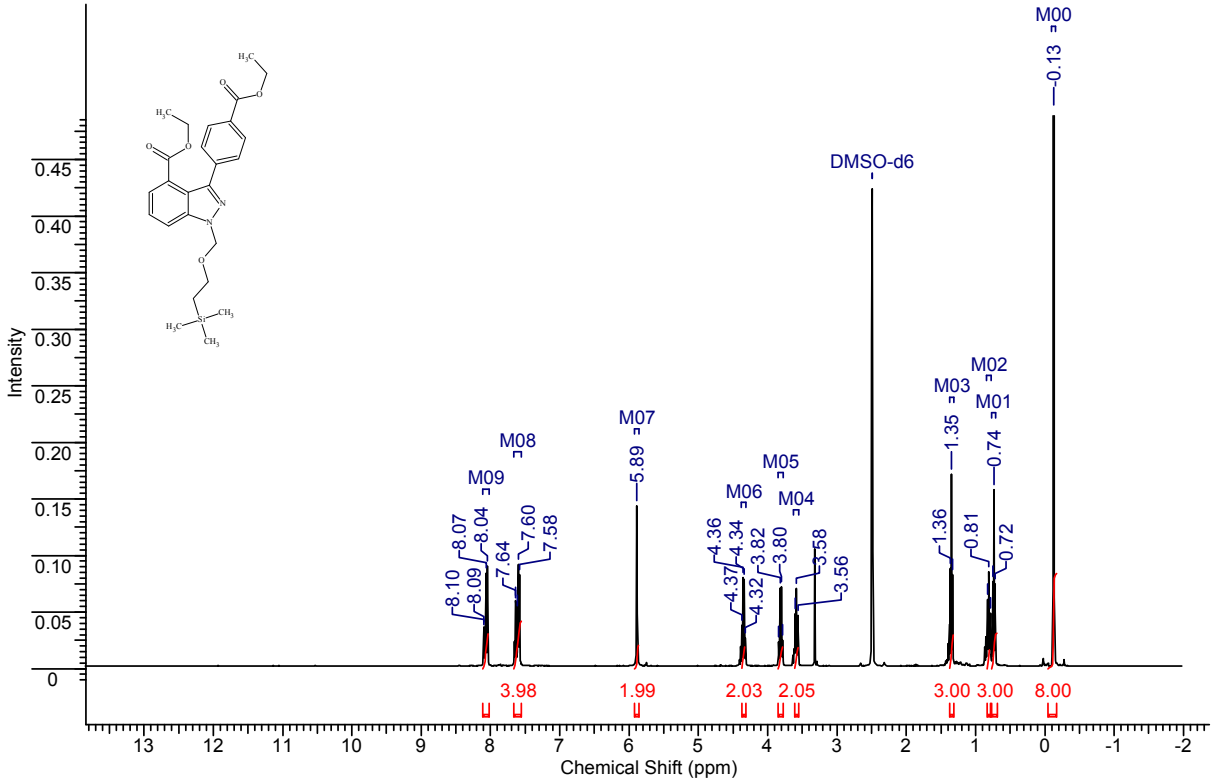


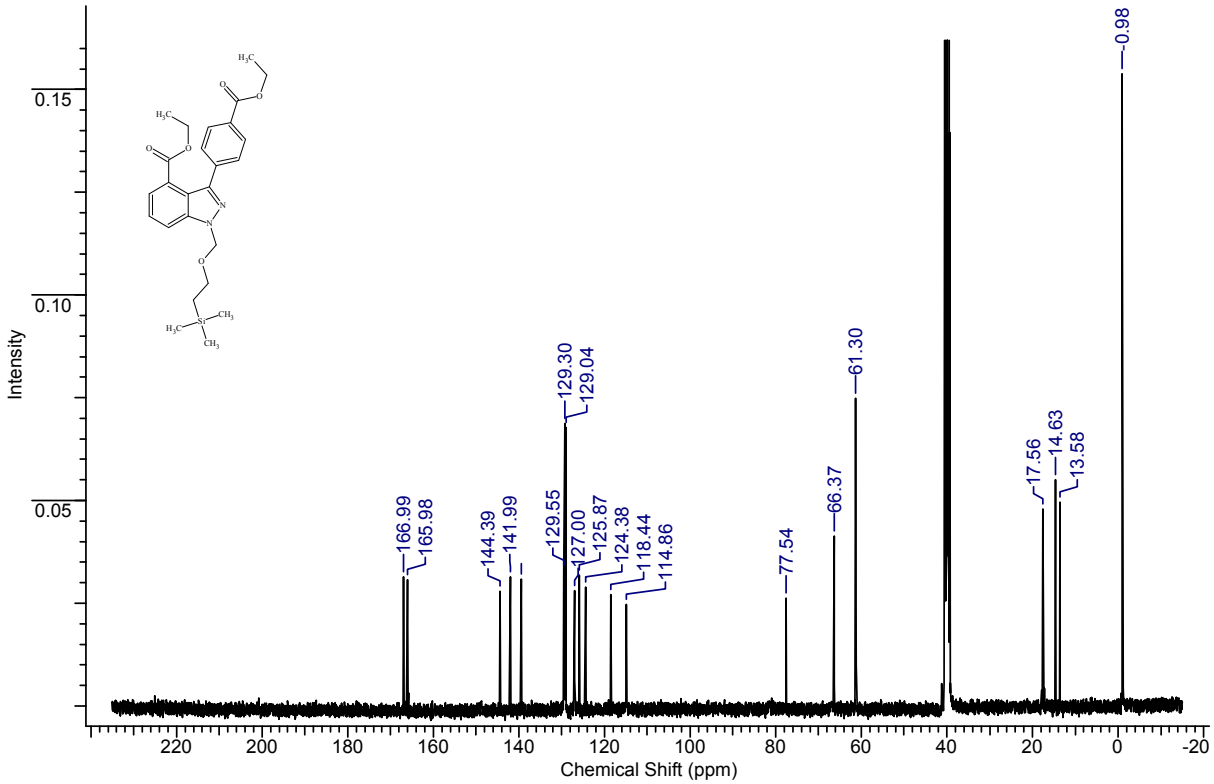
3-(4-methoxyphenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-indazole-6-carbonitrile (4m)



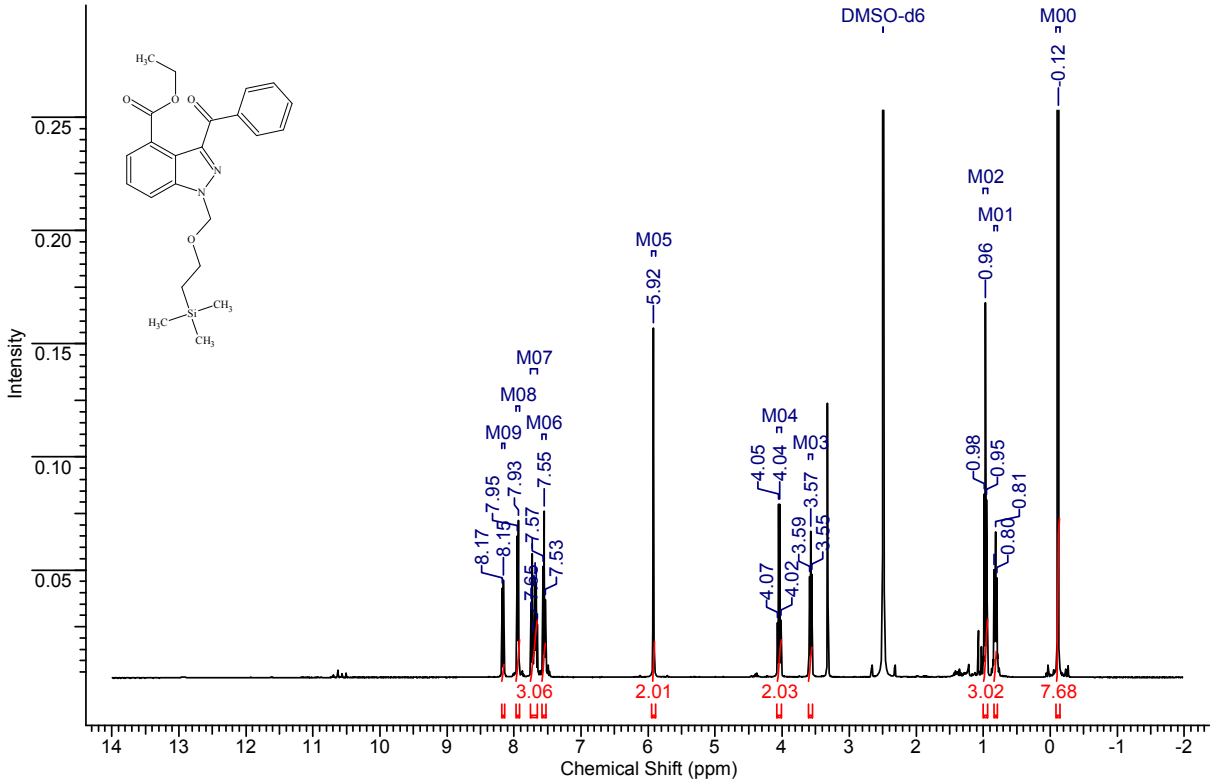


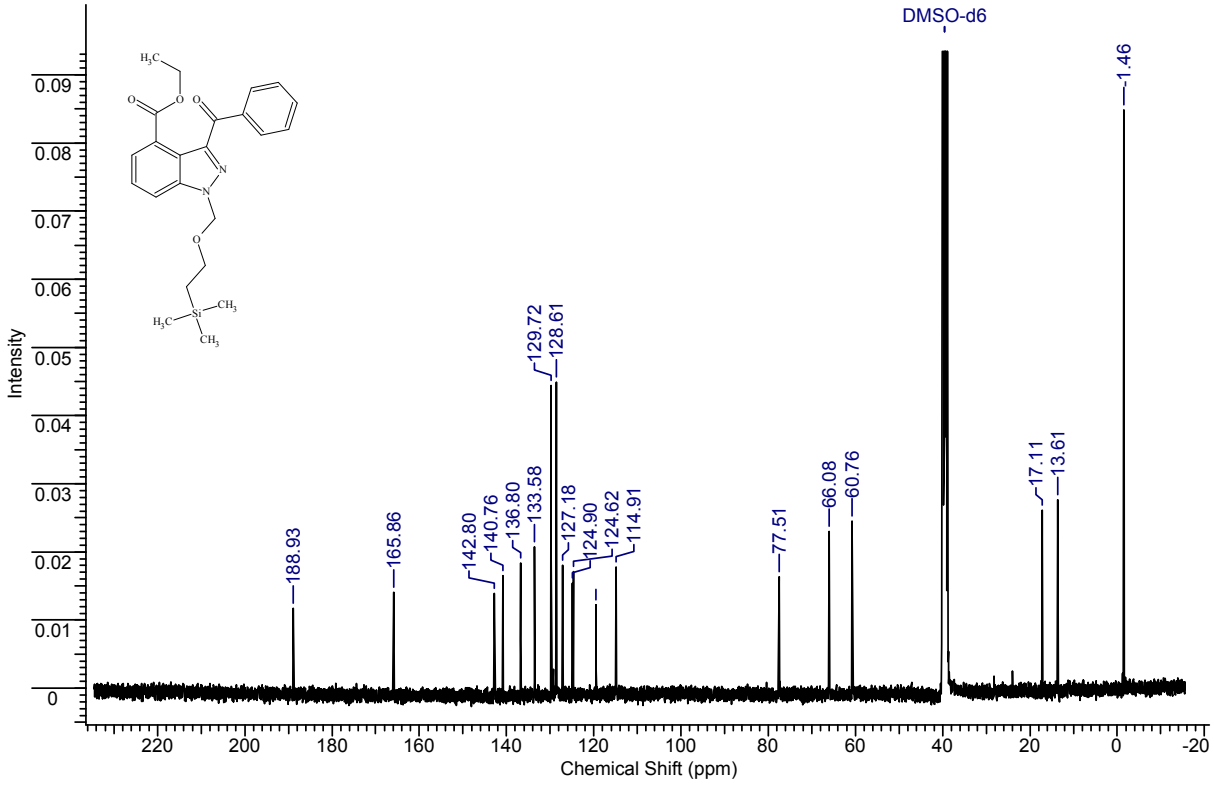
ethyl 3-(4-(ethoxycarbonyl)phenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-indazole-4-carboxylate (4n)





ethyl 3-benzoyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-indazole-4-carboxylate (4o)





thienyl(2-((2-(trimethylsilyl)ethoxy)methyl)-2*H*-indazol-3-yl)methanone (4p)