A Ruthenium-Catalyzed Alkenylation-Annulation Approach for the Synthesis of Indazole Derivatives via C-H Bond Activation

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Supporting Information

Contents

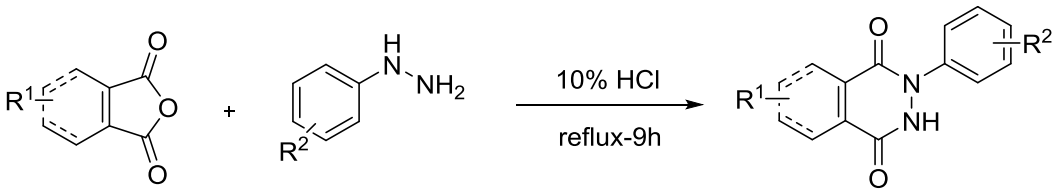
1. General information:

Solvents, Ruthenium catalyst, alkenes, phenylhydrazine, maleic anhydride and phthalic anhydride derivatives were purchased from Merck and Sigma. Other reagents were purchased from commercial distributors and used without further purification. *N*-aryl pyridazinedione and *N*-aryl phthalazinedione derivatives were synthesized according to the literature. Analytical thin layer chromatography (TLC) was performed on pre-coated silica gel 60 F254 plates. The products were purified by preparative column chromatography on silica gel (0.063-0.200 mm; Merck). ^{1}H and ^{13}C-NMR Spectra: were recorded on Bruker, 500 and 400 Advance instrument in $CDCl_3$ and DMSO; δ in ppm, *J* in Hz. Mass spectrometry was obtained on Agilent 5975C VL MSD (Ion source: EI+, 70eV, 230°C).

2. General procedure for synthesis of indazolo[1,2-b]phthalazines and pyridazino[1,2-a]indazoles:

A 15 mL microvawe vial was charged with *N*-aryl pyridazinedione or *N*-aryl phthalazinedione derivatives (1 equiv, 0.5 mmol), alkene (3 equiv, 1.5 mmol), copper acetate monohydrate (1 equiv, 0.5 mmol), Ru catalyst (5 mol %), potassium hexafluorophosphate (10 mol %) and H_2O or DCE (2 mL). The vial was then sealed and immersed in an oil bath at 120 °C, for 24 h. After this time the reaction mixture was cooled to room temperature and then diluted with water and extracted by chloroform. The residue was purified by using column chromatography (n-hexane/EtOAc, 1/1) to yield the desired products.

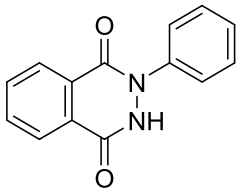
3. General Synthetic procedure for the preparation of *N*- aryl phthalazine/pyridazine dione[1]



The appropriate phenylhydrazine (1.1 equiv) was added to a stirred mixture of phthalic or malonic anhydride (1.0 equiv) in 10% HCl and the mixture was heated at 120 °C for 9 h. After this time, the reaction mixture was cooled and the resulting solid was collected by filtration and washed with water and then recrystallized by using ethanol.

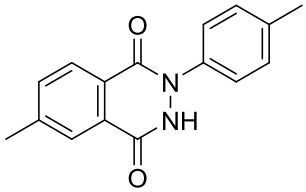
4. Characterization of starting materials[1]

2-phenyl-2,3-dihydrophthalazine-1,4-dione:



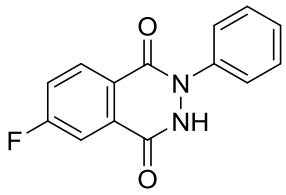
^{1}H NMR (500 MHz, DMSO) δ 11.85 (s, 1H), 8.30 (d, *J* = 7.6 Hz, 1H), 8.01 (d, *J* = 7.6 Hz, 1H), 7.96- 7.88 (m, 2H), 7.66 (d, *J* = 8.1 Hz, 2H), 7.49 (t, *J* = 7.6 Hz, 2H), 7.36 (t, *J* = 7.2 Hz, 1H). ^{13}C NMR (126 MHz, DMSO) δ 157.8, 150.9, 142.3, 133.9, 132.8, 129.7, 128.8, 127.5, 127.3, 126.4, 125.1, 124.6.

6-methyl-2-(p-tolyl)-2,3-dihydrophthalazine-1,4-dione:



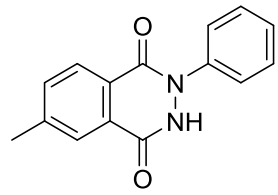
^{1}H NMR (500 MHz, DMSO) δ 11.72 (s, 1H), 8.17 (d, *J* = 8.2 Hz, 1H), 8.09 (s, 1H), 7.89 (d, *J* = 7.9 Hz, 1H), 7.51 (d, *J* = 8.2 Hz, 2H), 7.27 (d, *J* = 7.9 Hz, 2H), 2.53 (s, 3H), 2.36 (s, 3H).^{13}C NMR (126 MHz, DMSO) δ 157.7, 150.9, 144.4, 143.3, 136.7, 135.0, 134.0, 129.7, 129.3, 127.5, 126.1, 124.6, 21.8, 21.1.

6-fluoro-2-phenyl-2,3-dihydrophthalazine-1,4-dione:



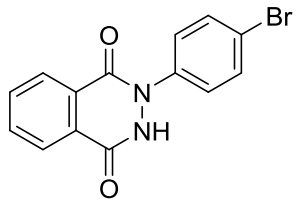
^{1}H NMR (500 MHz, DMSO) δ 11.99 (s, 1H), 8.35 (dd, *J* = 8.7, 5.2 Hz, 1H), 8.09 (dd, *J* = 8.7, 5.2 Hz, 1H), 7.96 (dd, *J* = 8.9, 2.2 Hz, 1H), 7.63 (t, *J* = 6.1 Hz, 2H), 7.54 – 7.42 (m, 2H), 7.38 (t, *J* = 7.3 Hz, 1H). ^{13}C NMR (126 MHz, DMSO) δ 165.3 (d, $^{1}J_{C\text{-}F}$= 252.6 Hz), 157.1, 157.0, 142.0, 132.2 (d, $^{3}J_{C\text{-}F}$= 9.2 Hz), 128.9, 127.7, 127.6, 126.6, 126.3, 122.3 (d, $^{2}J_{C\text{-}F}$= 23.8 Hz), 112.8 (d, $^{2}J_{C\text{-}F}$= 24.8 Hz). Anal. Calcd for $C_{14}H_9FN_2O_2$: C, 65.62; H, 3.54; N, 10.93; found: C, 65.81; H, 3.57; N, 10.88.

6-methyl-2-phenyl-2,3-dihydrophthalazine-1,4-dione:



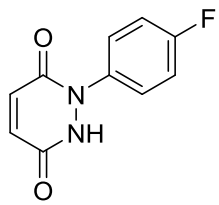
^{1}H NMR (500 MHz, DMSO) δ 11.75 (s, 1H), 8.18 (d, *J* = 7.9 Hz, 1H), 8.10 (s, 1H), 7.90 (d, *J* = 7.9 Hz, 1H), 7.64 (d, *J* = 7.6 Hz, 2H), 7.48 (t, *J* = 7.4 Hz, 2H), 7.40 – 7.32 (m, 1H), 2.53 (s, 3H). ^{13}C NMR (126 MHz, DMSO) δ 144.5, 143.3, 142.3, 135.0, 134.1, 129.7, 128.8, 127.4, 127.0, 126.3, 124.6, 124.2, 21.8.

2-(4-bromophenyl)-2,3-dihydrophthalazine-1,4-dione:



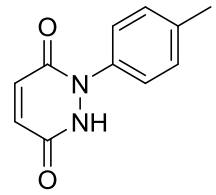
^{1}H NMR (500 MHz, DMSO) δ 11.94 (s, 1H), 8.28 (d, *J* = 7.7 Hz, 1H), 8.00 (d, *J* = 7.9 Hz, 1H), 7.96- 7.88 (m, 2H), 7.80 – 7.40 (m, 4H). ^{13}C NMR (126 MHz, DMSO) 157.80, 151.1, 141.4, 134.1, 133.0, 131.7, 129.6, 128.2, 127.3, 126.4, 124.7, 120.0.

1-(4-fluorophenyl)-1,2-dihydropyridazine-3,6-dione:



^{1}H NMR (500 MHz, DMSO) δ 11.37 (s, 1H), 7.61 (dd, *J* = 8.3, 5.2 Hz, 2H), 7.30 (t, *J* = 8.7 Hz, 2H), 7.17 (d, *J* = 9.9 Hz, 1H), 7.02 (d, *J* = 9.9 Hz, 1H). ^{13}C NMR (126 MHz, DMSO) δ 161.1 (d, $^{1}J_{C\text{-}F}$= 244.5 Hz), 158.2, 153.3, 138.2 (d, $^{4}J_{C\text{-}F}$ = 3.3 Hz), 134.4 (d, $^{3}J_{C\text{-}F}$= 9.3 Hz), 128.1, 128.0, 115.7 (d, $^{2}J_{C\text{-}F}$ = 26.4 Hz).

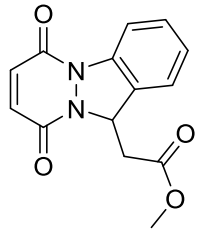
1-(p-tolyl)-1,2-dihydropyridazine-3,6-dione:



^{1}H NMR (500 MHz, DMSO) δ 11.28 (s, 1H), 7.44 (d, *J* = 8.0 Hz, 2H), 7.26 (d, *J* = 8.0 Hz, 2H), 7.15 (d, *J* = 9.7 Hz, 1H), 7.00 (d, *J* = 9.7 Hz, 1H), 2.34 (s, 3H). ^{13}C NMR (126 MHz, DMSO) δ 158.2, 153.1, 139.5, 137.2, 134.4, 129.3, 127.9, 125.7, 21.1. Anal. Calcd for $C_{11}H_{10}N_2O_2$: C, 65.34; H, 4.98; N, 13.85; found: C, 65.59; H, 4.96; N, 13.92.

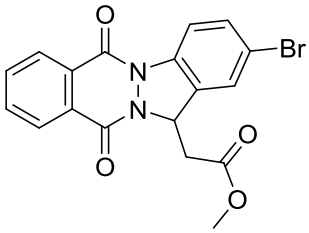
5. Characterization of the products

Methyl 2-(6,9-dioxo-6,9-dihydro-11H-pyridazino[1,2-a]indazol-11-yl)acetate (3a):



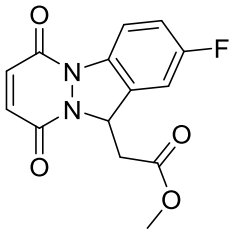
3a (95% yield) as a yellow solid; M.p.: 157-159 ºC; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.29 (d, *J* = 7.9 Hz, 1H), 7.44- 7.40 (m, 2H), 7.28 (t, *J* = 7.4 Hz, 1H), 7.00 (d, *J* = 10.2 Hz, 1H), 6.91 (d, *J* = 10.2 Hz, 1H), 5.98 (dd, *J* = 7.1, 3.4 Hz, 1H), 3.63 (s, 3H), 3.40 (dd, *J* = 16.5, 3.5 Hz, 1H), 3.08 (dd, *J* = 16.5, 7.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.8, 154.3, 153.7, 136.2, 136.0, 134.1, 129.9, 126.8, 126.5, 122.9, 115.5, 59.4, 52.1, 36.3; MS (EI): *m*/*z* (%) = 272 (59) $[M]^+$, 199 (100), 171 (100), 131 (70), 102 (15), 82 (40), 54 (39). Anal. Calcd for $C_{14}H_{12}N_2O_4$: C, 61.76; H, 4.44; N, 10.29; found: C, 61.48; H, 4.46; N, 10.33.

Methyl 2-(2-bromo-6,11-dioxo-6,11-dihydro-13H-indazolo[1,2-b]phthalazin-13-yl)acetate (3b):



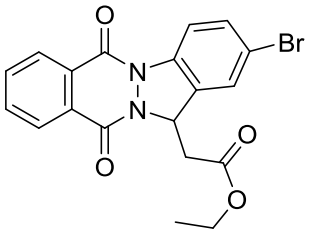
3b (99% yield) as an off white solid; M.p.: 205-207 ºC; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.43 (dd, *J* = 6.0, 3.1 Hz, 1H), 8.36 (dd, *J* = 6.0, 3.1 Hz, 1H), 8.31 (d, *J* = 8.5 Hz, 1H), 7.90 – 7.81 (m, 2H), 7.71 – 7.45 (m, 2H), 6.14 (dd, *J* = 7.5, 3.2 Hz, 1H), 3.69 (s, 3H), 3.48 (dd, *J* = 16.8, 3.3 Hz, 1H), 3.15 (dd, *J* = 16.8, 7.6 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.2, 155.3, 152.7, 136.0, 133.7, 133.6, 132.9, 128.9, 127.7, 127.4, 126.3, 125.9, 124.9, 119.1, 117.0, 58.5, 52.0, 37.0; ; MS (EI): *m*/*z* (%) = 402 (21) $[M+1]^+$,401 (21) $[M]^+$, 340 (7), 329 (100), 328 (98), 248 (8), 220 (15), 192 (8), 164 (10), 104 (28), 104 (33), 76 (30), 50 (8). Anal. Calcd for $C_{18}H_{13}BrN_2O_4$: C, 53.89; H, 3.27; N, 6.98; found: C, 53.89; H, 3.29; N, 6.94.

Methyl 2-(2-fluoro-6,9-dioxo-6,9-dihydro-11H-pyridazino[1,2-a]indazol-11-yl)acetate (3c):



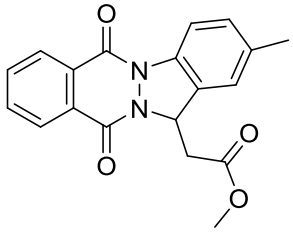
3c (71% yield) as an off white solid; M.p.: 205-208 ºC; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.32 (dd, *J* = 8.9, 4.6 Hz, 1H), 7.22 – 7.12 (m, 2H), 7.04 (d, *J* = 10.2 Hz, 1H), 6.94 (d, *J* = 10.2 Hz, 1H), 6.00 (dd, *J* = 7.9, 2.9 Hz, 1H), 3.69 (s, 3H), 3.48 (dd, *J* = 16.8, 3.4 Hz, 1H), 3.08 (dd, *J* = 16.8, 7.8 Hz, 1H^{13}C NMR (100 MHz, $CDCl_3$) δ 169.7, 161.0 (d, $^{1}J_{C\text{-}F}$= 247.4 Hz), 154.4, 153.5, 136.0, 134.0, 132.5, 128.6 (d, $^{3}J_{C\text{-}F}$= 9.4 Hz), 117.0, 116.8 (d, $^{2}J_{C\text{-}F}$= 24.1 Hz), 111.0 (d, $^{2}J_{C\text{-}F}$= 26.3 Hz), 59.2, 52.2, 36.0; MS (EI): *m*/*z* (%) = 290 (48) $[M]^+$, 230 (50), 217 (100), 208 (33), 189 (90), 149 (85), 137 (22), 101 (21), 82 (66), 69 (9), 54 (48), 43 (20). Anal. Calcd for $C_{14}H_{11}FN_2O_4$: C, 57.93; H, 3.82; N, 9.65; found: C, 57.55; H, 3.85; N, 9.69.

Ethyl 2-(2-bromo-6,11-dioxo-6,11-dihydro-13H-indazolo[1,2-b]phthalazin-13-yl)acetate (3d):



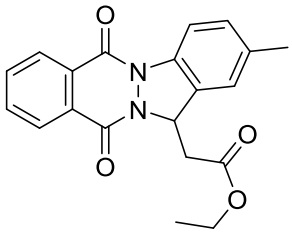
3d (96% yield) as a white solid; M.p.: 173-176 ºC; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.42 (dd, *J* = 6.0, 3.2 Hz, 1H), 8.36 (dd, *J* = 5.8, 3.4 Hz, 1H), 8.30 (d, *J* = 8.6 Hz, 1H), 7.89 – 7.86 (m, 2H), 7.61 (s, 1H), 7.60 – 7.57 (m, 1H), 6.13 (dd, *J* = 7.5, 3.3 Hz, 1H), 4.11 (q, *J* = 7.2 Hz, 2H), 3.44 (dd, *J* = 16.7, 3.4 Hz, 1H), 3.19 (dd, *J* = 16.7, 7.5 Hz, 1H), 1.16 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.2, 155.1, 154.7, 135.8, 133.7, 133.6, 132.8, 129.6, 128.9, 128.6, 127.7, 127.4, 126.3, 119.0, 117.0, 61.1, 58.6, 37.2, 14.0; MS (EI): *m*/*z* (%) = 416 (29) $[M+1]^+$, 415 (28) $[M]^+$, 342 (14), 341 (13), 329 (100), 328 (90), 283 (7), 248 (8), 220 (10), 192 (7), 164 (7), 104 (10), 76 (13). Anal. Calcd for $C_{19}H_{15}BrN_2O_4$: C, 54.96; H, 3.64; N, 6.75; found: C, 54.85; H, 3.67; N, 6.70.

Methyl 2-(2-methyl-6,11-dioxo-6,11-dihydro-13H-indazolo[1,2-b]phthalazin-13-yl)acetate (3e):



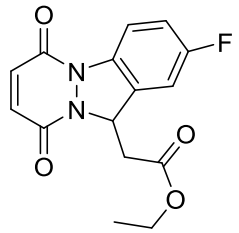
3e (89% yield) as a white solid; M.p.: 182-184 ºC; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.43 (dd, *J* = 6.3, 2.9 Hz, 1H), 8.36 (dd, *J* = 6.4, 2.8 Hz, 1H), 8.29 (d, *J* = 8.2 Hz, 1H), 7.93 – 7.81 (m, 2H), 7.29 – 7.20 (m, 2H), 6.13 (dd, *J* = 7.3, 3.6 Hz, 1H), 3.67 (s, 3H), 3.47 (dd, *J* = 16.5, 3.6 Hz, 1H), 3.13 (dd, *J* = 16.5, 7.4 Hz, 1H), 2.40 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.0, 155.21,. 154.3, 136.4, 134.5, 133.4, 133.3, 130.3, 130.0, 128.6, 127.6, 127.2, 127.0, 123.3, 115.5, 59.0, 51.9, 37.4, 21.3; MS (EI): *m*/*z* (%) = 336 (18) $[M]^+$, 276 (7), 263 (100), 178 (8), 104 (10), 76 (10), 50 (7). Anal. Calcd for $C_{19}H_{16}N_2O_4$: C, 67.85; H, 4.79; N, 8.33; found: C, 67.57; H, 4.82; N, 8.29.

Ethyl 2-(2-methyl-6,11-dioxo-6,11-dihydro-13H-indazolo[1,2-b]phthalazin-13-yl)acetate (3f):



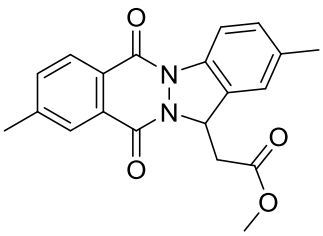
3f (98% yield) as an off white solid; M.p.: 168-169 ºC; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.42 (dd, *J* = 6.1, 2.9 Hz, 1H), 8.35 (dd, *J* = 5.9, 3.0 Hz, 1H), 8.27 (d, *J* = 8.7 Hz, 1H), 7.92 – 7.65 (m, 2H), 7.30 – 7.07 (m, 2H), 6.10 (dd, *J* = 7.0, 3.4 Hz, 1H), 4.07 (q, *J* = 7.1 Hz, 2H), 3.39 (dd, *J* = 16.3, 3.5 Hz, 1H), 3.20 (dd, *J* = 16.3, 7.1 Hz, 1H), 2.39 (s, 3H), 1.11 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.5, 155.1, 154.3, 136.3, 134.5, 133.34, 133.30, 131.4, 130.3, 130.0, 127.5, 127.2, 126.9, 123.4, 115.5, 60.9, 49.9, 37.4, 21.3, 14.0; MS (EI): *m*/*z* (%) = 350 (18) $[M]^+$, 276 (8), 263 (100), 178 (6), 104 (7), 76 (7), 50 (5). Anal. Calcd for $C_{20}H_{18}N_2O_4$: C, 68.56; H, 5.18; N, 8.00; found: C, 68.24; H, 5.20; N, 8.04.

Ethyl 2-(2-fluoro-6,9-dioxo-6,9-dihydro-11H-pyridazino[1,2-a]indazol-11-yl)acetate (3g):



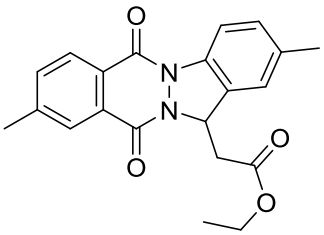
3g (74% yield) as a yellow solid; M.p.: 147-149 ºC; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.28 (dd, *J* = 8.9, 4.5 Hz, 1H), 7.20 – 7.11 (m, 2H), 7.01 (d, *J* = 10.2 Hz, 1H), 6.92 (d, *J* = 10.2 Hz, 1H), 5.96 (dd, *J* = 7.4, 3.0 Hz, 1H), 4.09 (q, *J* = 7.1 Hz, 2H), 3.39 (dd, *J* = 16.7, 3.3 Hz, 1H), 3.12 (dd, *J* = 16.7, 7.5 Hz, 1H), 1.16 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.0, 160.8 (d, $^{1}J_{C\text{-}F}$= 248.2 Hz), 154.3, 153.4, 135.9, 133.0, 132.5, 128.6 (d, $^{3}J_{C\text{-}F}$= 12.2 Hz), 116.9 (d, $^{3}J_{C\text{-}F}$= 10.2 Hz), 116.7 (d, $^{2}J_{C\text{-}F}$= 23.2 Hz), 110.9 (d, $^{2}J_{C\text{-}F}$= 28.0 Hz), 61.1, 59.2, 36.1, 14.0; MS (EI): *m*/*z* (%) = 305 (30) $[M+1]^+$, 304(81) $[M]^+$, 275 (11), 258 (11), 230 (66), 217 (100), 189 (89), 188(69), 149(67), 137 (11), 101 (11), 82 (37), 54 (37). Anal. Calcd for $C_{15}H_{13}FN_2O_4$: C, 59.21; H, 4.31; N, 9.21; found: C, 59.50; H, 4.33; N, 9.18.

Methyl 2-(2,9-dimethyl-6,11-dioxo-6,11-dihydro-13H-indazolo[1,2-b] phthalazin-13-yl) acetate (3h):



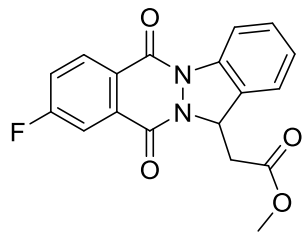
3h (86% yield) as a white solid; M.p.: 155-158 ºC; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.34 – 8.20 (m, 3H), 8.15 (s, 1H), 7.65 (t, *J* = 8.0 Hz, 1H), 7.23 (s, 1H), 6.11 (dt, *J* = 7.4, 3.7 Hz, 1H), 3.67 (s, 3H), 3.46 (dt, *J* = 16.4, 3.7 Hz, 1H), 3.12 (dd, *J* = 16.5, 7.4 Hz, 1H), 2.56 (d, *J* = 4.7 Hz, 3H), 2.40 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.0, 155.3, 154.5, 144.5, 136.3, 134.5, 134.4, 130.3, 127.6, 127.5, 127.3, 127.2, 123.3, 115.5, 115.4, 58.9, 51.9, 37.4, 21.8, 21.3; MS (EI): *m*/*z* (%) = 350 (21) $[M]^+$, 277 (100), 178 (7), 145 (7), 118 (9), 89 (10). Anal. Calcd for $C_{20}H_{18}N_2O_4$: C, 68.56; H, 5.18; N, 8.00; found: C, 68.92; H, 5.21; N, 8.05.

Ethyl 2-(2,9-dimethyl-6,11-dioxo-6,11-dihydro-13H-indazolo[1,2-b]phthalazin-13-yl)acetate (3i):



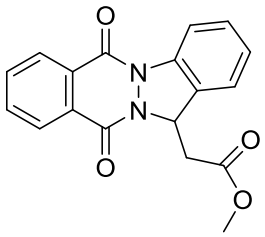
3i (89% yield) as a white solid; M.p.: 148-150 ºC; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.32 – 8.21 (m, 3H), 8.15 (s, 1H), 7.65 (td, *J* = 8.0, 1.6 Hz, 1H), 7.24 (s, 1H), 6.10 (dt, *J* = 7.3, 3.7 Hz, 1H), 4.07 (q, *J* = 7.1 Hz, 2H), 3.40 (dt, *J* = 16.3, 3.4 Hz, 1H), 3.19 (dd, *J* = 16.3, 7.2 Hz, 1H), 2.56 (d, *J* = 4.1 Hz, 3H), 2.39 (s, 3H), 1.16 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.5, 155.3, 154.5, 144.5, 130.3, 127.6, 127.5, 127.3, 127.2, 123.3, 115.5, 115.4, 60.8, 58.9, 37.4, 21.8, 21.3, 14.0; MS (EI): *m*/*z* (%) = 364 (18) $[M]^+$, 290 (7), 277 (100), 178 (6), 145 (3), 118 (7), 89 (7). Anal. Calcd for $C_{21}H_{20}N_2O_4$: C, 69.22; H, 5.53; N, 7.69; found: C, 69.54; H, 5.56; N, 7.74.

Methyl 2-(9-fluoro-6,11-dioxo-6,11-dihydro-13H-indazolo[1,2-b]phthalazin-13-yl)acetate (3j):



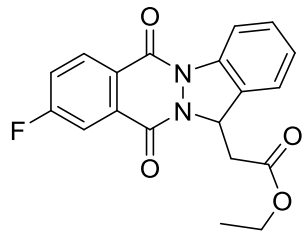
3j (63% yield) as a yellow solid; M.p.: 154-155 ºC; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.41 – 8.35 (m, 2H), 8.06 (dd, *J* = 8.6, 2.6 Hz, 1H), 7.54 – 7.48 (m, 1H), 7.48 – 7.43 (m, 2H), 7.30 (t, *J* = 7.6 Hz, 1H), 6.15 (dd, *J* = 7.3, 3.6 Hz, 1H), 3.65 (s, 3H), 3.45 (dd, *J* = 16.5, 3.6 Hz, 1H), 3.16 (dd, *J* = 16.5, 7.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.0, 165.9 (d, $^{1}J_{C\text{-}F}$= 256.4 Hz), 154.5, 153.6, 136.4, 132.6, 130.6 (d, $^{3}J_{C\text{-}F}$= 9.0 Hz), 129.9, 126.9, 126.6, 125.7, 123.0, 121.6 ($^{2}J_{C\text{-}F}$= 23.0 Hz), 115.9, 113.9 (d, $^{2}J_{C\text{-}F}$= 24.0 Hz), 59.1, 52.1, 37.2; MS (EI): *m*/*z* (%) = 340 (28) $[M]^+$, 280 (25), 267 (100), 256 (51), 238 (7), 211 (9), 183 (49), 122 (45), 94 (40), 77 (21), 51 (9). Anal. Calcd for $C_{18}H_{13}FN_2O_4$: C, 63.53; H, 3.85; N, 8.23; found: C, 63.18; H, 3.82; N, 8.18.

Methyl 2-(6,11-dioxo-6,11-dihydro-13H-indazolo[1,2-b]phthalazin-13-yl)acetate (3k):



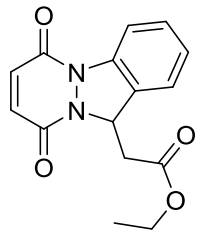
3k (81% yield) as a yellow solid; M.p.: 146-147 ºC; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.46- 8.43 (m, 2H), 8.39– 8.37 (m, 1H), 7.87 (dd, *J* = 6.2, 2.7 Hz, 2H), 7.48 – 7.44 (m, 2H), 7.30 (t, *J* = 7.2 Hz, 1H), 6.19 (dd, *J* = 6.8, 3.2 Hz, 1H), 3.66 (s, 3H), 3.49 (dd, *J* = 16.4, 3.6 Hz, 1H), 3.15 (dd, *J* = 16.4, 7.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.0, 155.2, 154.7, 136.7, 133.6, 133.5, 129.9, 129.8, 128.6, 127.7, 127.3, 126.8, 126.3, 123.0, 115.8, 59.0, 52.0, 37.4; MS (EI): *m*/*z* (%) = 322 (33) $[M]^+$, 279 (7), 249 (100), 221 (7), 190 (21), 165 (55), 131 (41), 104 (48), 76 (49), 43 (25). Anal. Calcd for $C_{18}H_{14}N_2O_4$: C, 67.08; H, 4.38; N, 8.69; found: C, 67.29; H, 4.40; N, 8.72.

Ethyl 2-(9-fluoro-6,11-dioxo-6,11-dihydro-13H-indazolo[1,2-b]phthalazin-13-yl)acetate (3l):



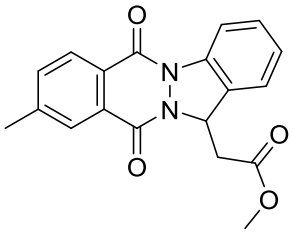
3l (66% yield) as a white solid; M.p.: 146-148 ºC; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.45 – 8.35 (m, 2H), 8.05 (dd, *J* = 8.5, 2.4 Hz, 1H), 7.53 (td, *J* = 8.3, 2.5 Hz, 1H), 7.48 – 7.42 (m, 2H), 7.30 (t, *J* = 7.5 Hz, 1H), 6.13 (dd, *J* = 6.9, 3.4 Hz, 1H), 4.06 (q, *J* = 7.1 Hz, 2H), 3.39 (dd, *J* = 16.4, 3.5 Hz, 1H), 3.22 (dd, *J* = 16.4, 7.1 Hz, 1H), 1.11 (t, *J* = 7.1 Hz, 3H);); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.3,166.9 (d, $^{1}J_{C\text{-}F}$= 255.9 Hz) 154.4, 153.5, 136.5, 130.5 (d, $^{3}J_{C\text{-}F}$= 12.5 Hz), 129.8, 126.9, 126.5, 125.1, 122.9, 121.5 (d, $^{2}J_{C\text{-}F}$= 25.4 Hz), 115.8, 113.9 (d, $^{2}J_{C\text{-}F}$= 24.3 Hz), 60.9, 59.1, 37.3, 14.0; MS (EI): *m*/*z* (%) = 354 (18) $[M]^+$, 280 (17), 268 (20), 267 (100), 183 (11), 122 (13), 102 (3), 94 (14). Anal. Calcd for $C_{19}H_{15}FN_2O_4$: C, 64.40; H, 4.27; N, 7.91; found: C, 64.69; H, 4.29; N, 7.94.

Ethyl 2-(6,9-dioxo-6,9-dihydro-11H-pyridazino[1,2-a]indazol-11-yl)acetate (3m):



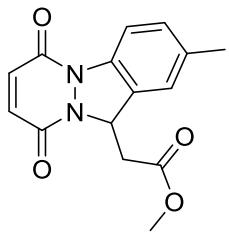
3m (98% yield) as a yellow solid; M.p.: 132-133 ºC;^{1}H NMR (500 MHz, $CDCl_3$) δ 8.35 (d, *J* = 8.1 Hz, 1H), 7.51 – 7.46 (m, 2H), 7.33 (t, *J* = 7.5 Hz, 1H), 7.06 (d, *J* = 10.2 Hz, 1H), 6.97 (d, *J* = 10.2 Hz, 1H), 6.03 (dd, *J* = 7.0, 3.5 Hz, 1H), 4.10 (q, *J* = 7.2 Hz, 2H), 3.39 (dd, *J* = 16.4, 3.6 Hz, 1H), 3.21 (dd, *J* = 16.4, 7.1 Hz, 1H), 1.17 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.7, 154.9, 153.7, 140.7, 130.8, 128.3, 125.6, 124.8, 124.3, 119.0, 116.6, 59.3, 51.1, 37.1, 14.2; MS (EI): *m*/*z* (%) = 286 (43) $[M]^+$, 212 (42), 204 (9), 199 (100), 171 (66), 131 (37), 119 (11), 102 (11), 82 (18), 54 (23). Anal. Calcd for $C_{15}H_{14}N_2O_4$: C, 62.93; H, 4.93; N, 9.79; found: C, 62.64; H, 4.95; N, 9.85.

Methyl 2-(9-methyl-6,11-dioxo-6,11-dihydro-13H-indazolo[1,2-b]phthalazin-13-yl)acetate (3n):



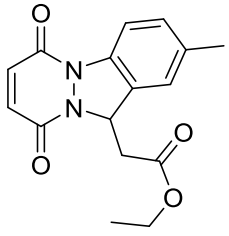
3n (94% yield) as an orange solid; M.p.: 61-63 ºC;^{1}H NMR (500 MHz, $CDCl_3$) δ 8.47 – 8.41 (m, 1H), 8.33 (d, *J* = 8.2 Hz, 1H), 8.29 – 8.23 (m, 1H), 8.18 (s, 1H), 7.67 (t, *J* = 6.8 Hz, 1H), 7.53 – 7.41 (m, 2H), 6.16 (dd, *J* = 6.5, 3.2 Hz, 1H), 3.84 (s, 3H), 3.43 (dt, *J* = 16.2, 3.1 Hz, 1H), 3.22 (dd, *J* = 16.2, 7.1 Hz, 1H), 2.58 (d, *J* = 4.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.1, 155.4, 154.9, 136.7, 134.7, 134.6, 129.8, 127.7, 127.6, 127.3, 126.9, 126.3, 126.2, 123.0, 115.8, 58.9, 52.0, 37.4, 21.9; MS (EI): *m*/*z* (%) = 336 (14) $[M]^+$, 263 (100), 237(15), 190 (60), 163 (14), 131 (100), 104 (14), 84 (29), 57 (20). Anal. Calcd for $C_{19}H_{16}N_2O_4$: C, 67.85; H, 4.79; N, 8.33; found: C, 67.71; H, 4.76; N, 8.37.

Methyl 2-(2-methyl-6,9-dioxo-6,9-dihydro-11H-pyridazino[1,2-a]indazol-11-yl)acetate (3o):



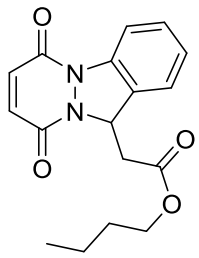
3o (98% yield) as a yellow solid; M.p.: 150-152 ºC; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.22 (d, *J* = 8.2 Hz, 1H), 7.27- 7.25 (m, 2H), 7.05 (d, *J* = 10.2 Hz, 1H), 6.95 (d, *J* = 10.2 Hz, 1H), 5.99 (dd, *J* = 7.3, 3.6 Hz, 1H), 3.69 (s, 3H), 3.43 (dd, *J* = 16.6, 3.6 Hz, 1H), 3.13 (dd, *J* = 16.6, 7.3 Hz, 1H), 2.43 (s, 3H); ^{13}C NMR (125 MHz, DMSO) δ 170.1, 154.4, 153.7, 136.4, 136.1, 134.6, 134.5, 130.1, 127.8, 123.8, 114.5, 59.5, 52.0, 35.7, 21.3; MS (EI): *m*/*z* (%) = 286 (48) $[M]^+$, 226 (21), 213 (100), 204 (14), 185 (55), 145 (29), 131 (7), 145 (29), 115 (14), 82 (14), 54 (20). Anal. Calcd for $C_{15}H_{14}N_2O_4$: C, 62.93; H, 4.93; N, 9.79; found: C, 62.70; H, 4.95; N, 9.75.

Ethyl 2-(2-methyl-6,9-dioxo-6,9-dihydro-11H-pyridazino[1,2-a]indazol-11-yl)acetate (3p):



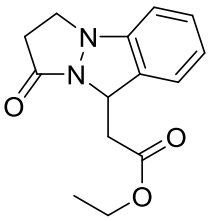
3p (97% yield) as a yellow solid; M.p.: 156-158 ºC;^{1}H NMR (500 MHz, $CDCl_3$) δ 8.16 (d, *J* = 8.6 Hz, 1H), 7.25 (d, *J* = 8.9 Hz, 1H), 7.22 (s, 1H), 7.01 (d, *J* = 10.2 Hz, 1H), 6.91 (d, *J* = 10.2 Hz, 1H), 5.92 (dd, *J* = 7.0, 3.5 Hz, 1H), 4.06 (q, *J* = 7.1 Hz, 2H), 3.32 (dd, *J* = 16.4, 3.6 Hz, 1H), 3.16 (dd, *J* = 16.4, 7.0 Hz, 1H), 2.38 (s, 3H), 1.13 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.2, 154.3, 153.4, 136.9, 135.9, 134.1, 133.8, 130.3, 126.6, 123.3, 115.2, 60.9, 59.4, 36.4, 21.3, 14.0; MS (EI): *m*/*z* (%) = 300 (42) $[M]^+$, 226 (36), 219 (14), 213 (100), 185 (42), 145 (36), 131 (7), 115 (14), 82 (14), 54 (16). Anal. Calcd for $C_{16}H_{16}N_2O_4$: C, 63.99; H, 5.37; N, 9.33; found: C, 63.78; H, 5.34; N, 9.37.

Butyl 2-(6,9-dioxo-6,9-dihydro-11H-pyridazino[1,2-a]indazol-11-yl)acetate (3q):



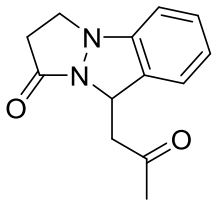
3q (82% yield) as a black oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.33 (d, *J* = 8.2 Hz, 1H), 7.46- 7.43 (m, 2H), 7.31 (t, *J* = 8.0 Hz, 1H), 7.04 (d, *J* = 10.2 Hz, 1H), 6.95 (d, *J* = 10.2 Hz, 1H), 6.00 (dd, *J* = 6.9, 3.4 Hz, 1H), 4.02 (t, *J* = 6.7 Hz, 2H), 3.38 (dd, *J* = 16.4, 3.5 Hz, 1H), 3.19 (dd, *J* = 16.4, 7.1 Hz, 1H), 1.51- 1.46 (m, 2H), 1.30 – 1.22 (m, 2H), 0.87 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.3, 154.3, 153.8, 136.3, 136.0, 134.1, 130.0, 126.8, 126.5, 123.0, 115.5, 65.0, 59.5, 36.3, 30.4, 19.0, 13.6; MS (EI): *m*/*z* (%) = 314 (18) $[M]^+$, 231 (13), 212 (41), 199 (100), 171 (41), 149 (12), 131 (41), 82 (15), 57 (13). Anal. Calcd for $C_{17}H_{18}N_2O_4$: C, 64.96; H, 5.77; N, 8.91; found: C, 64.73; H, 5.79; N, 8.94.

Ethyl 2-(1-oxo-2,3-dihydro-1H,9H-pyrazolo[1,2-a]indazol-9-yl)acetate (3r):



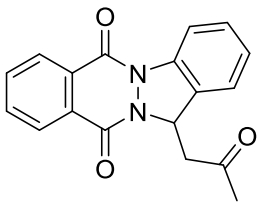
3r (31% yield) as a yellow oil; ^{1}H NMR (500 MHz, DMSO) δ 7.62 (d, *J* = 7.9 Hz, 1H), 7.07 (t, *J* = 7.6 Hz, 1H), 6.99 (t, *J* = 7.7 Hz, 1H), 6.79 (d, *J* = 7.9 Hz, 1H), 5.71 (t, *J* = 6.8 Hz, 1H), 4.17 (q, *J* = 7.2 Hz, 2H), 2.99 – 2.80 (m, 3H), 2.68 (dd, *J* = 15.9, 7.8 Hz, 1H), 2.64 – 2.53 (m, 2H), 1.20 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.6, 170.1, 149.1, 1230.0, 129.0, 126.6, 123.7, 122.9, 66.5, 61.2, 55.9, 39.4, 32.7, 14.1; MS (EI): *m*/*z* (%) = 260 (15) $[M]^+$, 232 (13), 217 (50), 204 (20), 173 (15), 159 (13), 131 (80), 104 (13), 93 (28), 84 (100), 59 (30), 43 (27). Anal. Calcd for $C_{14}H_{16}N_2O_3$: C, 64.60; H, 6.20; N, 10.76; found: C, 64.84; H, 6.23; N, 10.81.

9-(2-oxopropyl)-2,3-dihydro-1H,9H-pyrazolo[1,2-a]indazol-1-one (3s):



3s (42% yield) as a yellow oil; ^{1}H NMR (500 MHz, DMSO) δ 7.51 (d, *J* = 8.0 Hz, 1H), 7.34 (t, *J* = 7.6 Hz, 1H), 7.11 (t, *J* = 7.2 Hz, 1H), 6.95 (d, *J* = 8.0 Hz, 1H), 5.73 (t, *J* = 6.0 Hz 1H), 3.74 (dd, *J* = 15.3, 2.8 Hz, 1H), , 3.55 (dd, *J* = 14.9, 5.3 Hz, 1H), 2.73 (t, *J* = 6.8 Hz, 2H), 2.51 (t, *J* = 7.3 Hz, 2H), 2.14 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 194.8, 173.0, 149.6, 129.4, 128.8, 126.67, 124.1, 123.0, 66.6, 55.9, 40.8, 38.4, 29.5; MS (EI): *m*/*z* (%) = 230 (21) $[M]^+$, 203 (40), 161 (50), 145 (15), 131 (70), 119 (11), 105 (16), 91 (10), 77 (90), 43 (100). Anal. Calcd for $C_{13}H_{14}N_2O_2$: C, 67.81; H, 6.13; N, 12.17; found: C, 67.57; H, 6.15; N, 12.21.

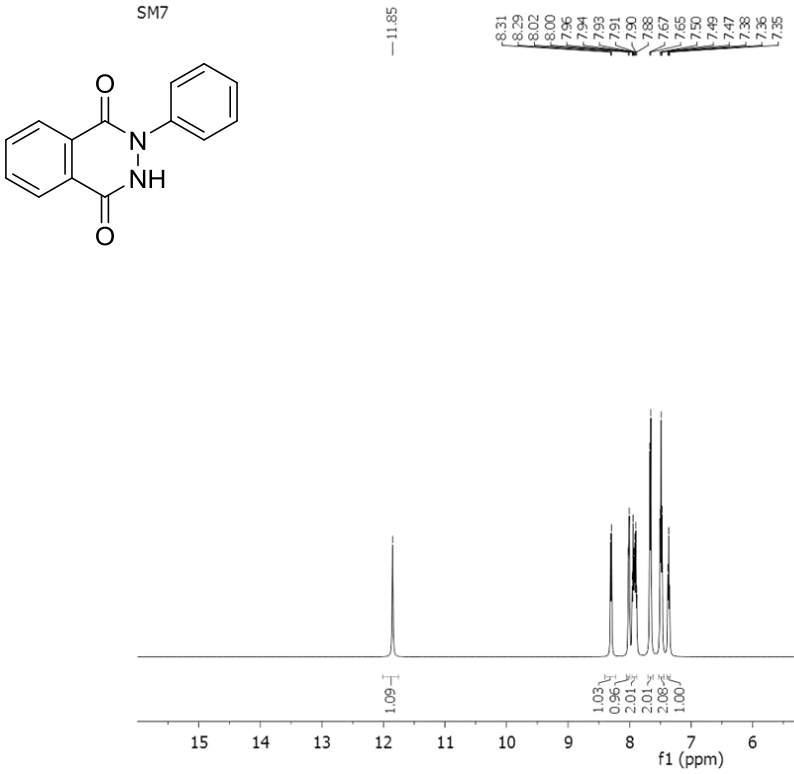
13-(2-oxopropyl)-13H-indazolo[1,2-b]phthalazine-6,11-dione (3t):

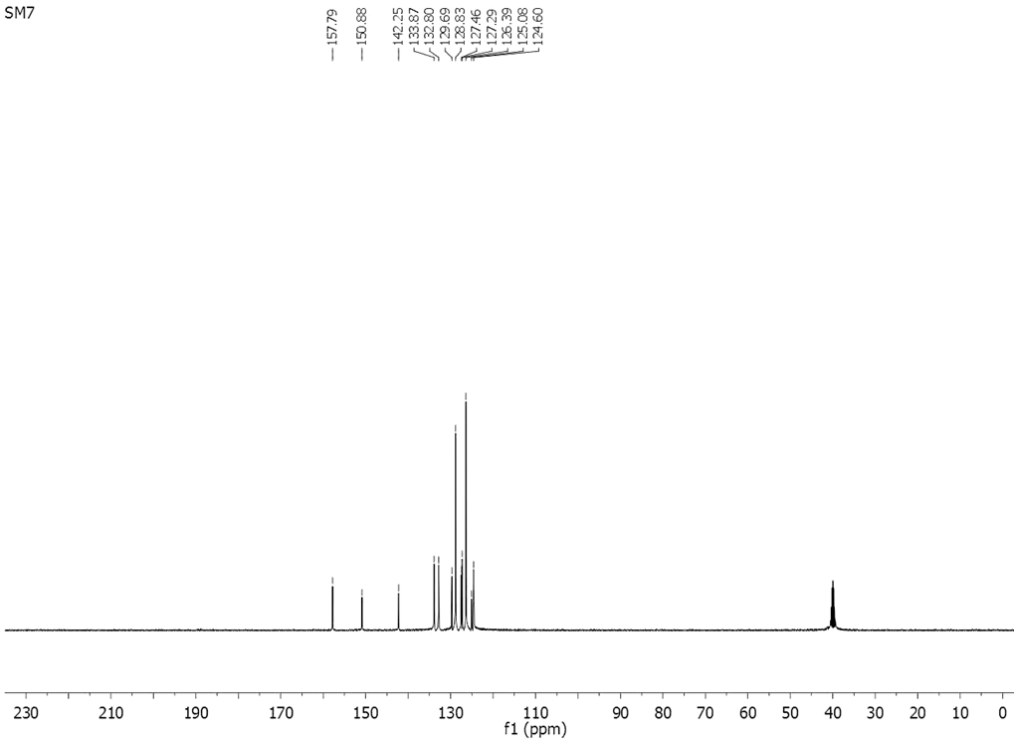


3t (33% yield) as a yellow oil; ^{1}H NMR (500 MHz, DMSO) δ 8.36-8.32 (m, 2H), 8.26 – 8.24 (m, 2H), 7.88 (d, *J* = 6.6 Hz, 1H), 7.68 (d, *J* = 6.4 Hz, 1H), 7.18- 7.16 (m, 2H), 6.28 (dd, *J* = 5.0, 2.5 Hz, 1H), 3.37 (dd, *J* = 15.0, 2.6 Hz, 1H), 3.24 (dd, *J* = 14.8, 5.0 Hz, 1H), 2.25 (s, 3H). ^{13}C NMR (126 MHz, DMSO) δ 189.5, 188.9, 152.6, 141.4, 134.8, 132.0, 130.1, 125.3, 123.7, 123.6, 122.9, 118.9, 58.7, 36.8, 21.4; MS (EI): *m*/*z* (%) = 306 (14) $[M]^+$, 291 (22), 264 (22), 191 (30), 165 (26), 135 (26), 107 (48), 71 (40), 43 (100). Anal. Calcd for $C_{18}H_{14}N_2O_3$: C, 70.58; H, 4.61; N, 9.15; found: C, 70.73; H, 4.59; N, 9.20.

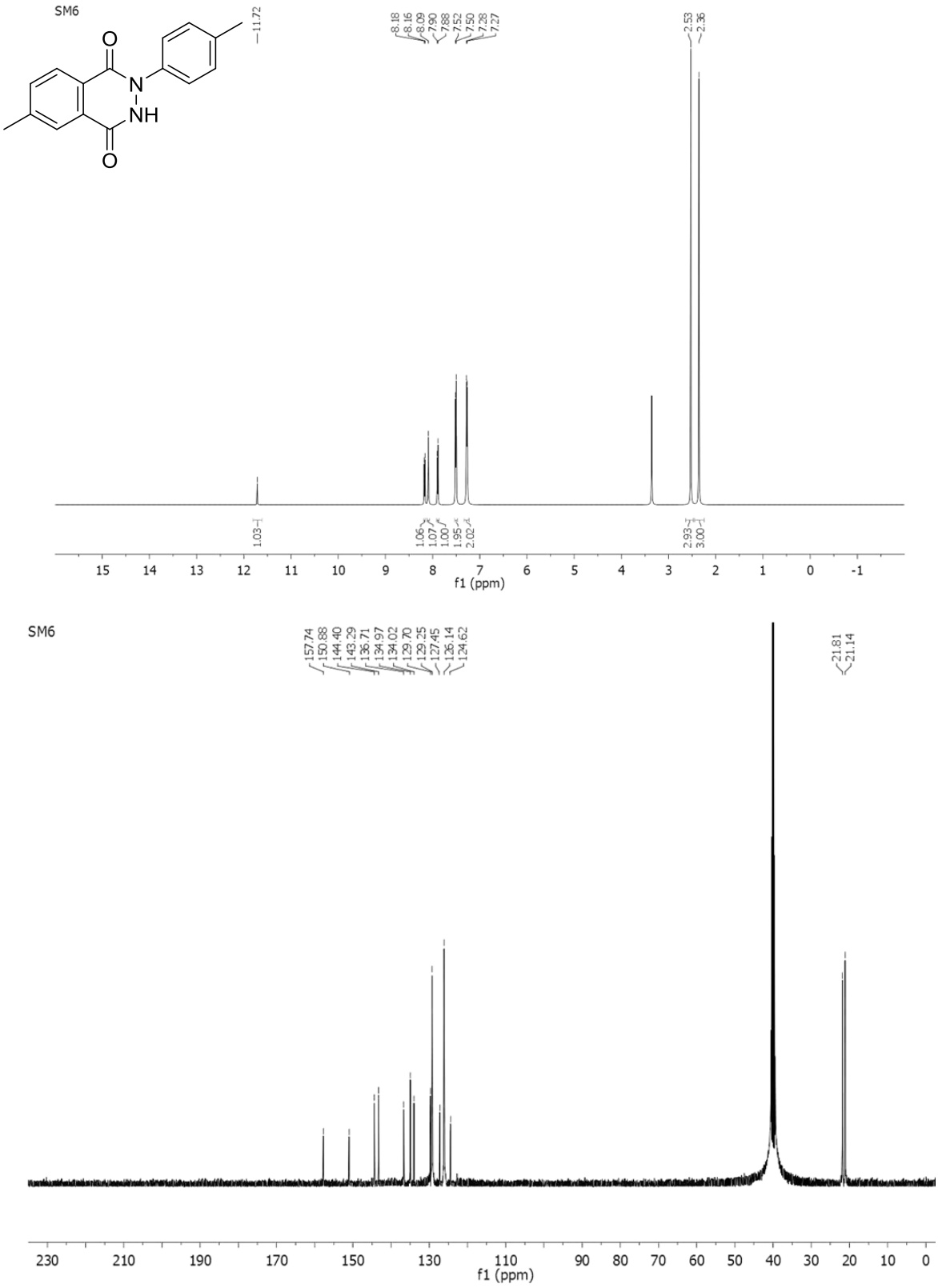
6. Spectral Data

2-phenyl-2,3-dihydrophthalazine-1,4-dione

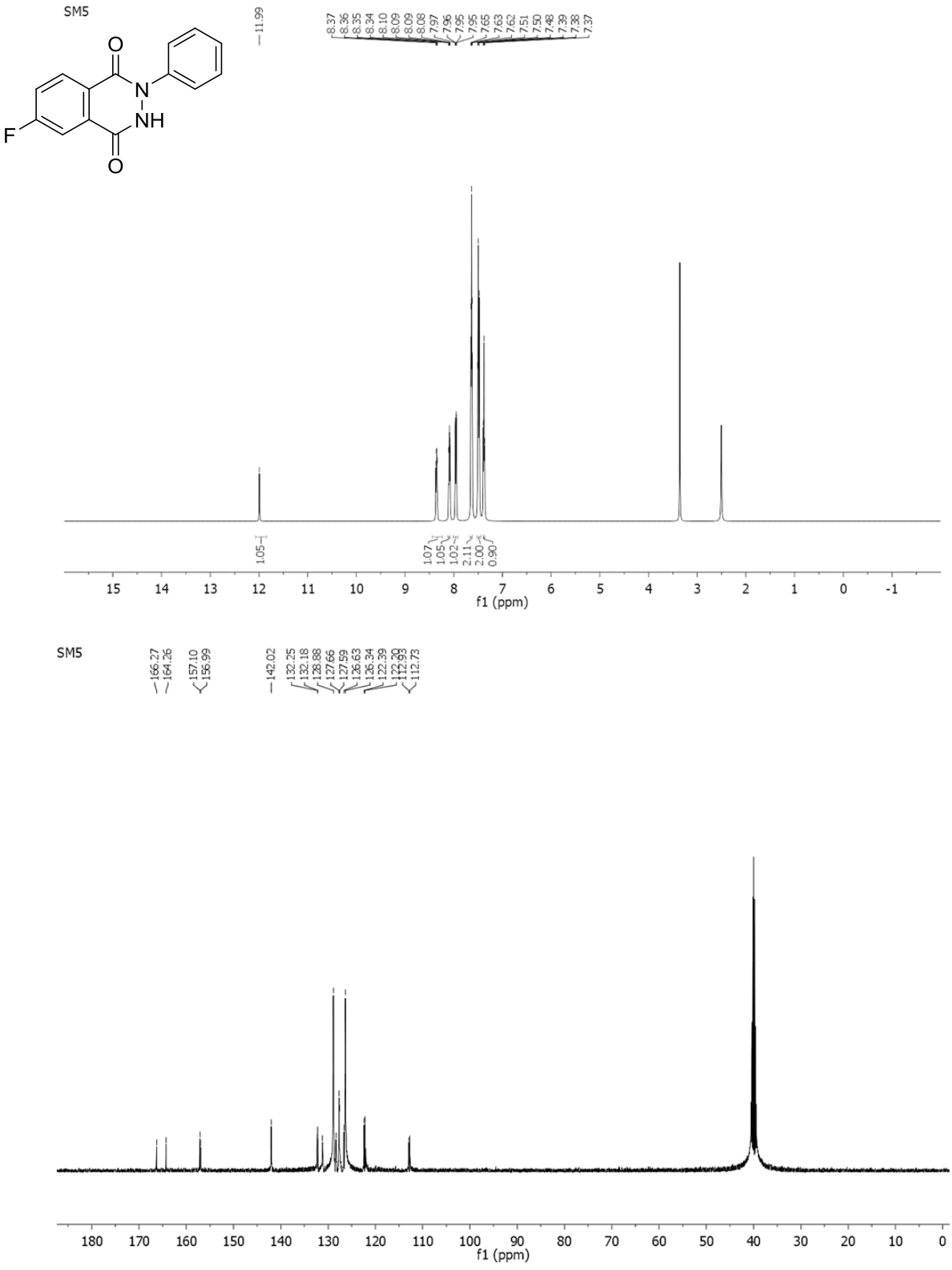




6-methyl-2-(p-tolyl)-2,3-dihydrophthalazine-1,4-dione



6-fluoro-2-phenyl-2,3-dihydrophthalazine-1,4-dione



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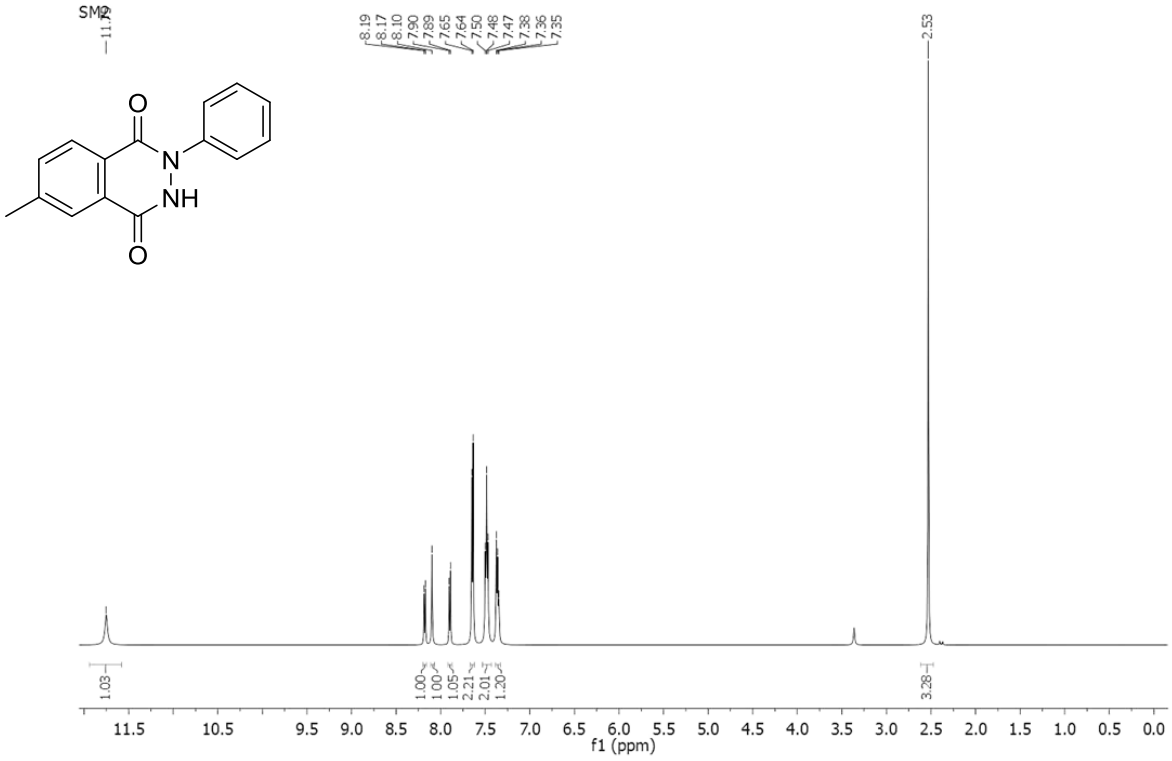
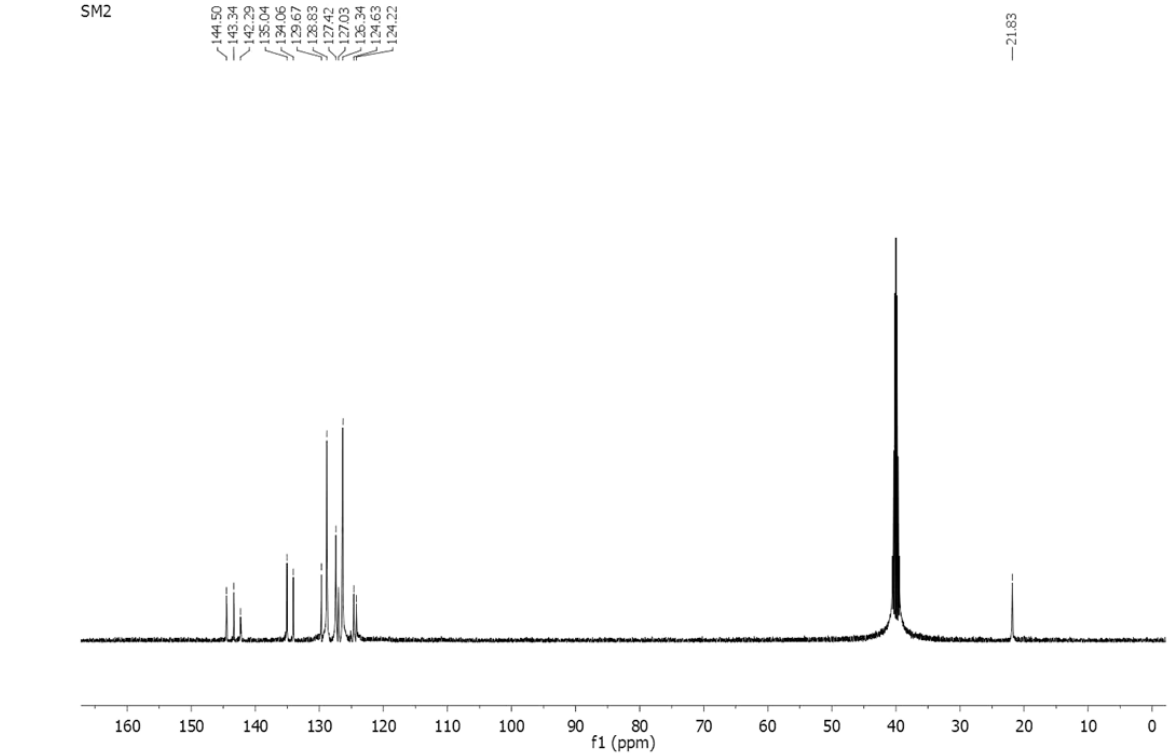
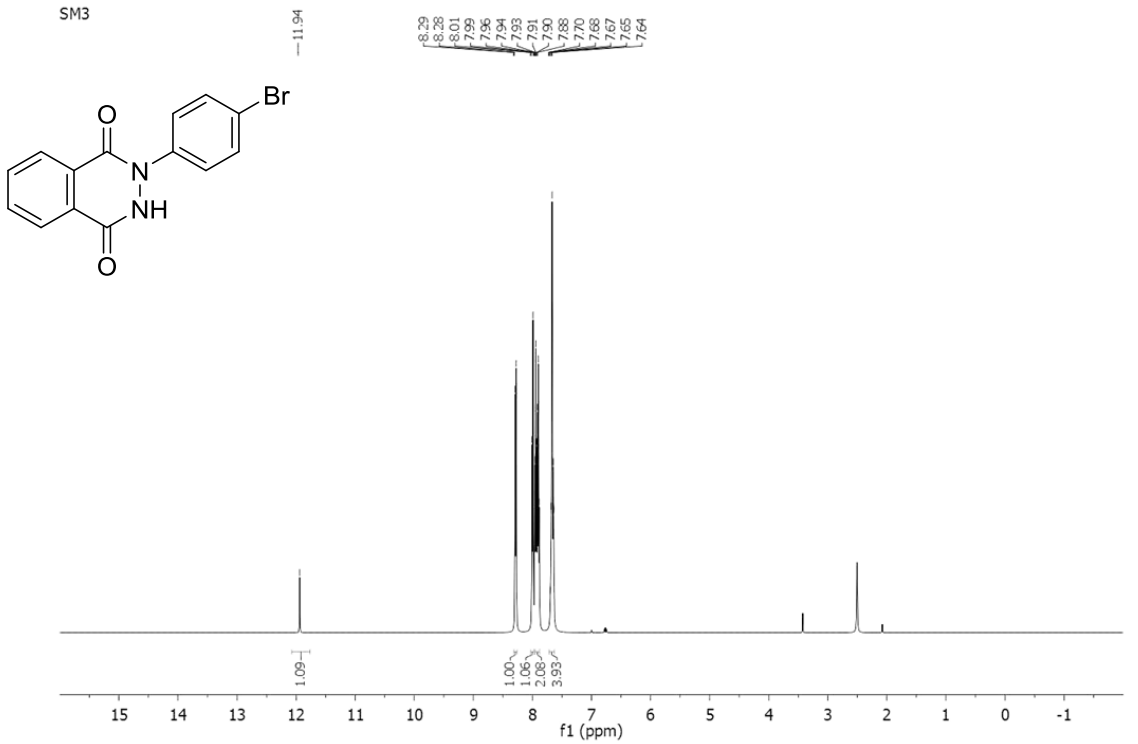
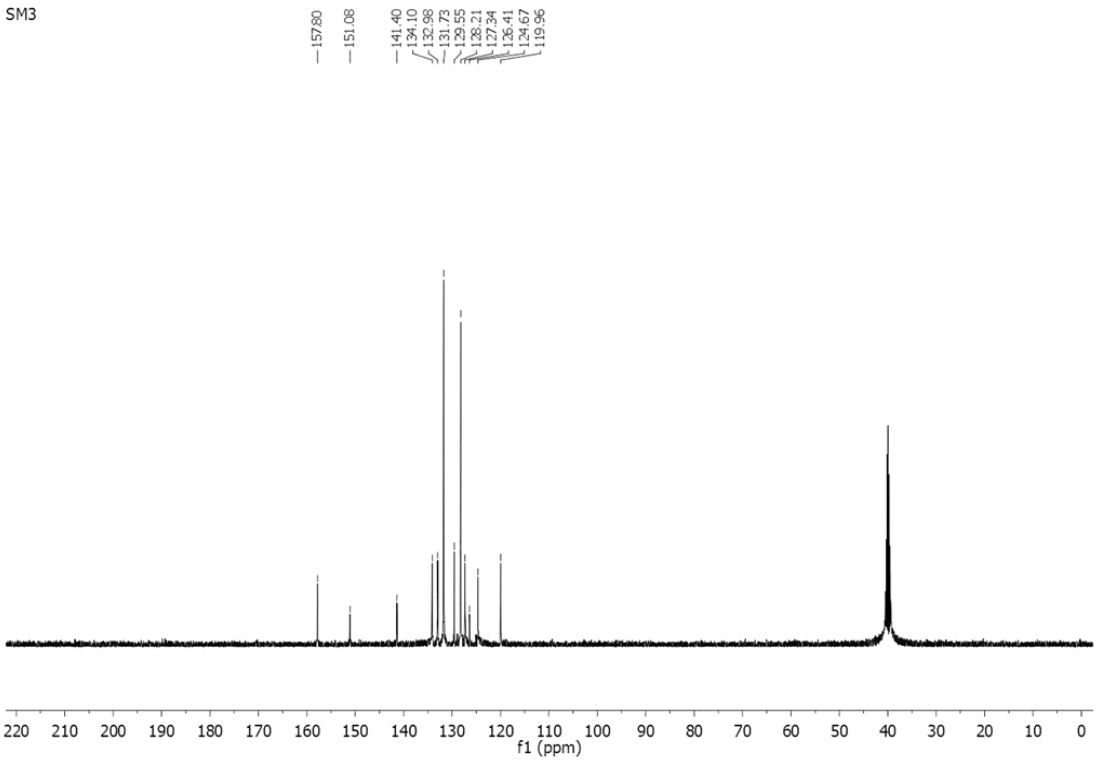


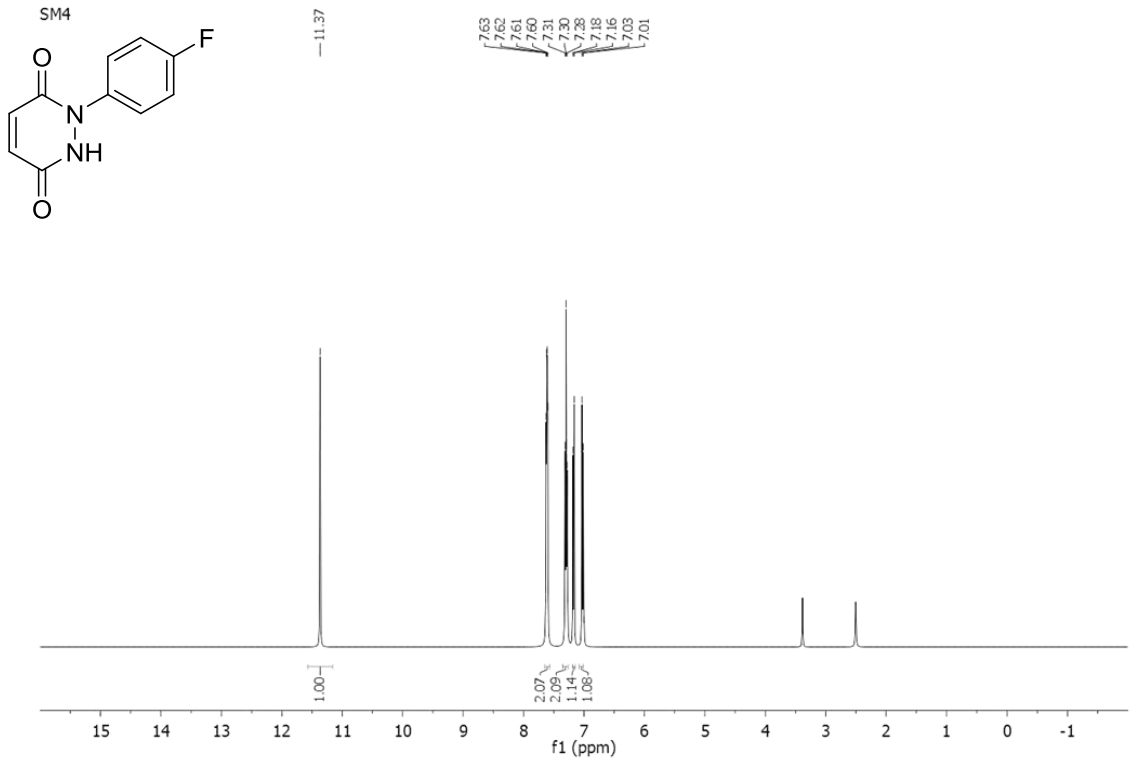


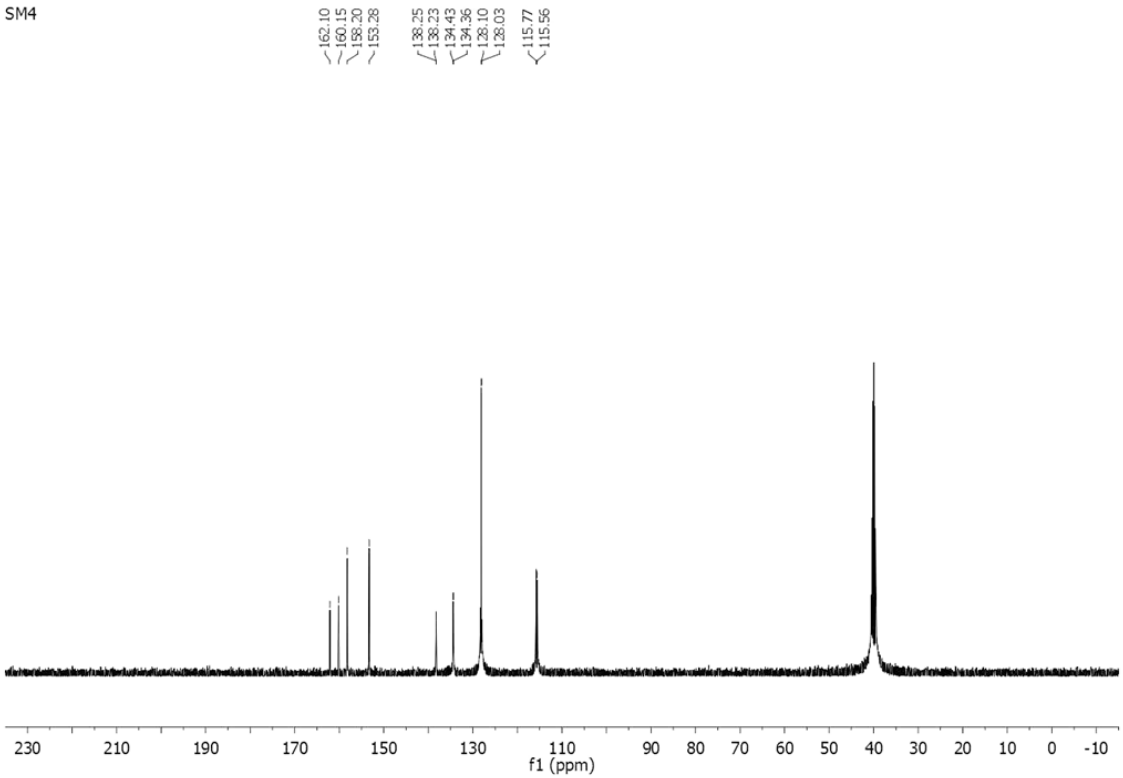
2-(4-bromophenyl)-2,3-dihydrophthalazine-1,4-dione



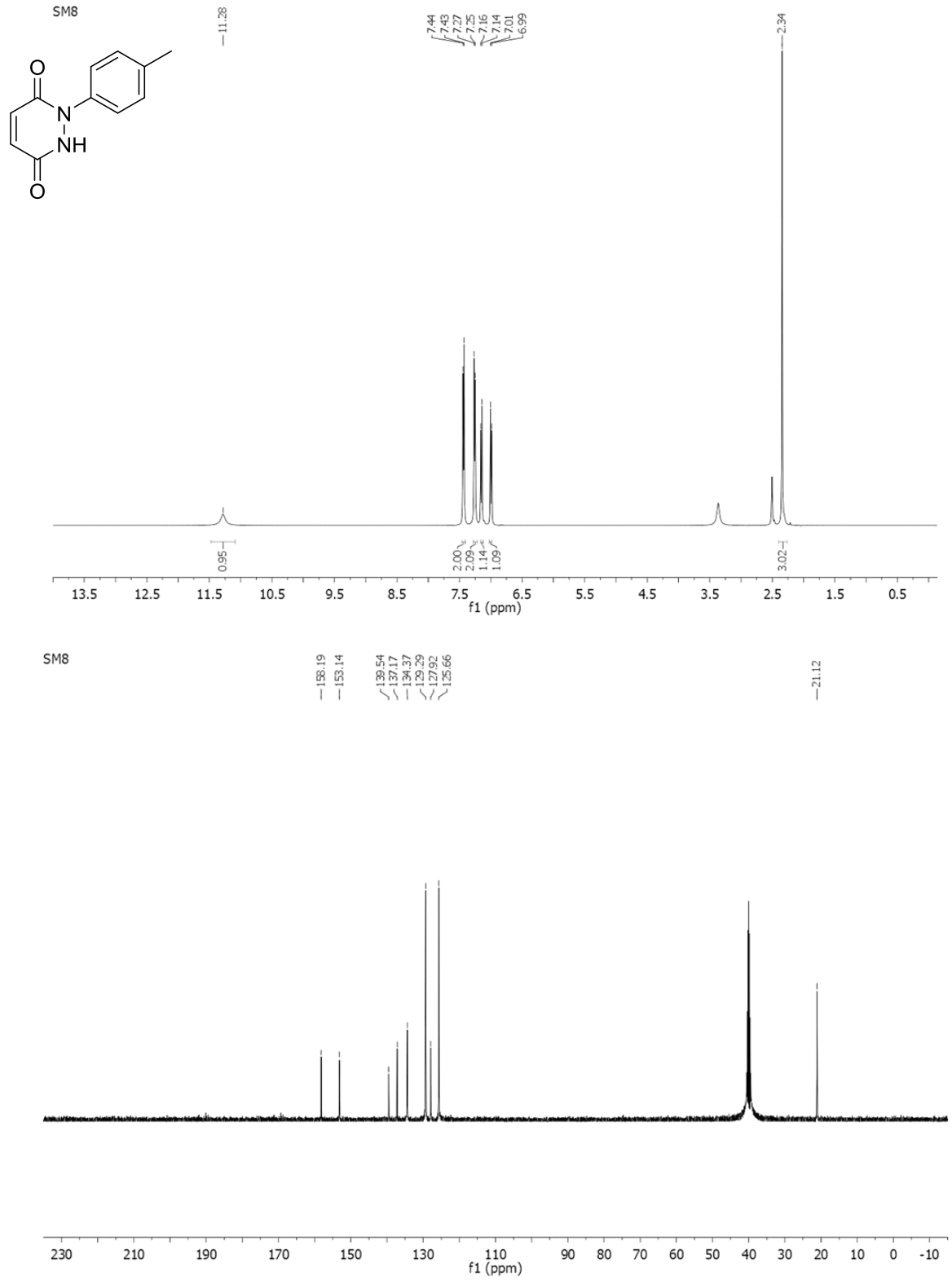


1-(4-fluorophenyl)-1,2-dihydropyridazine-3,6-dione

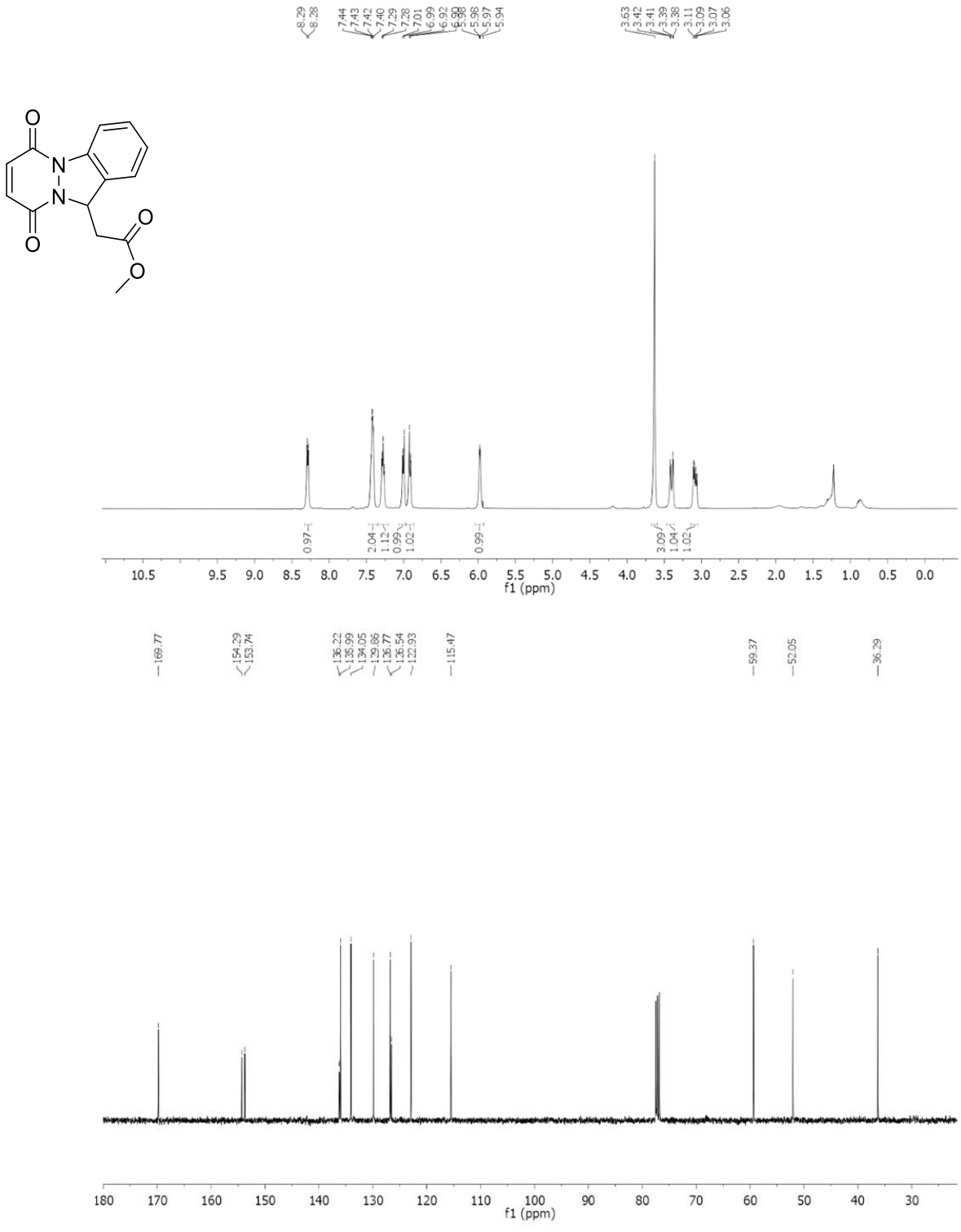




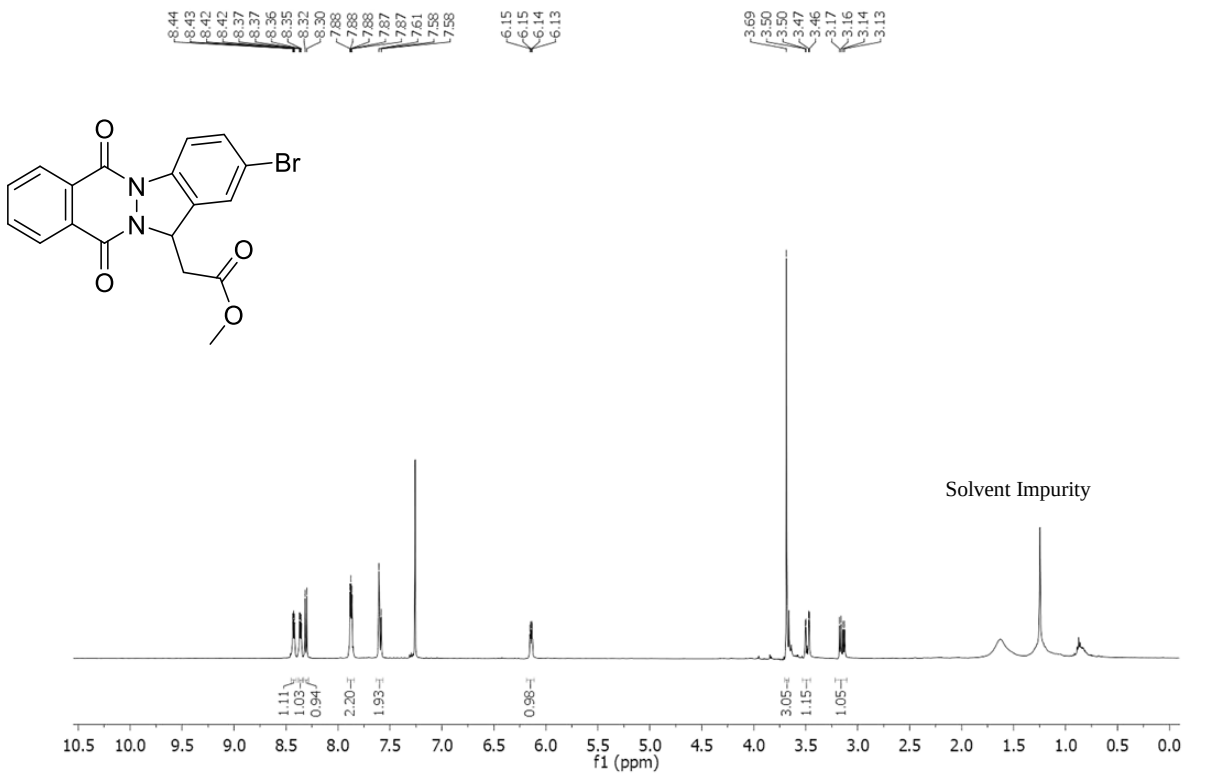
1-(p-tolyl)-1,2-dihydropyridazine-3,6-dione

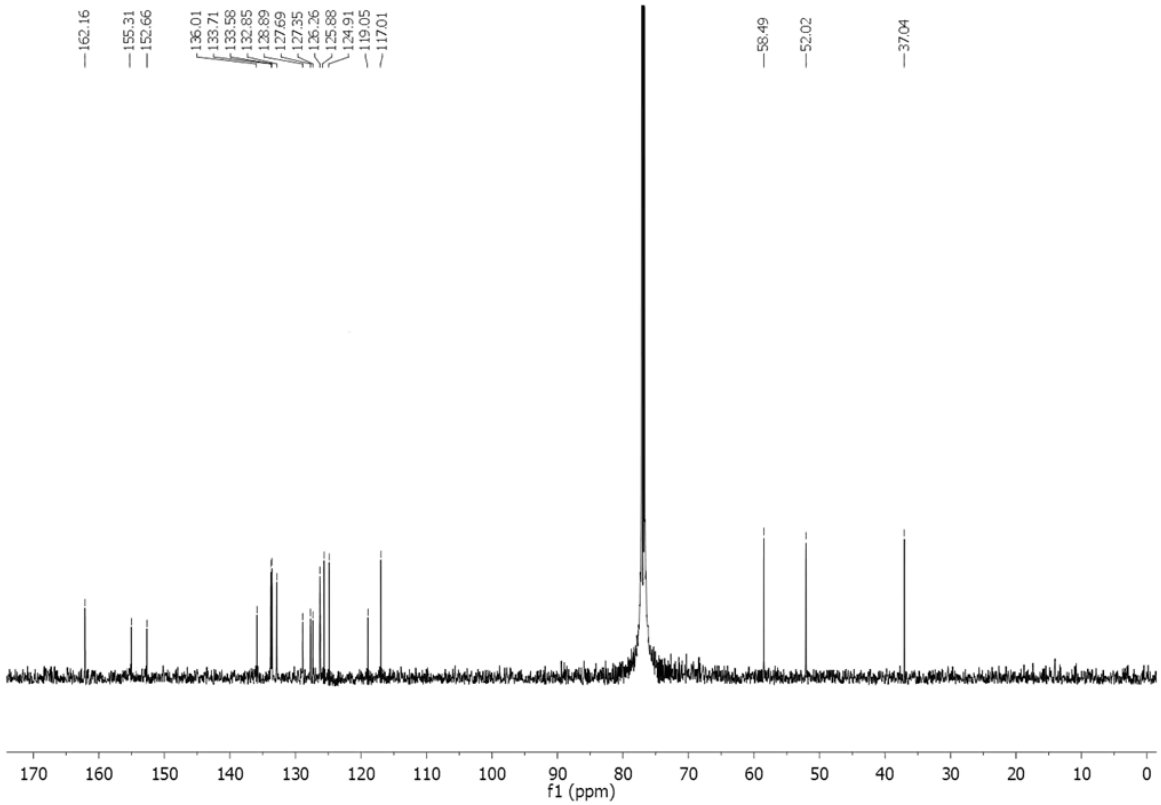


Methyl 2-(6,9-dioxo-6,9-dihydro-11H-pyridazino[1,2-a]indazol-11-yl)acetate (3a)

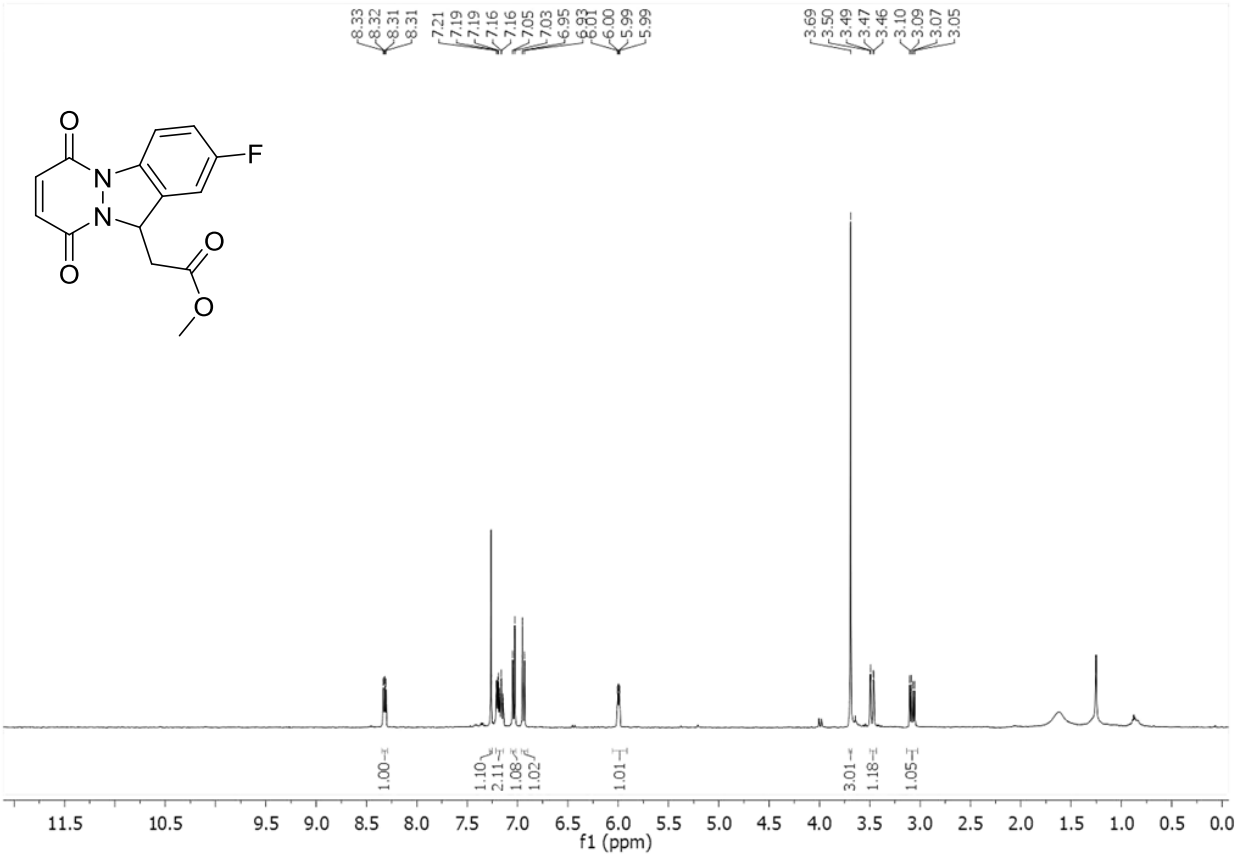


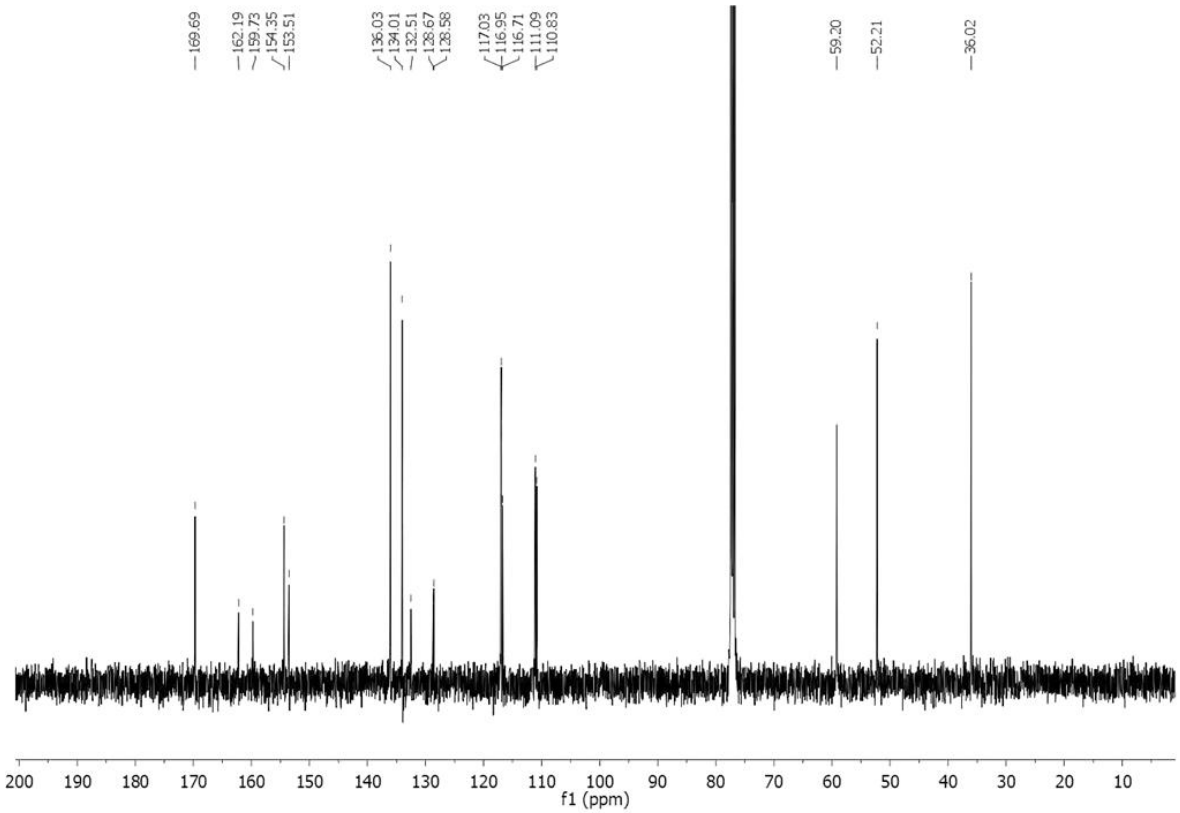
Methyl 2-(2-bromo-6,11-dioxo-6,11-dihydro-13H-indazolo[1,2-b]phthalazin-13-yl)acetate (3b)



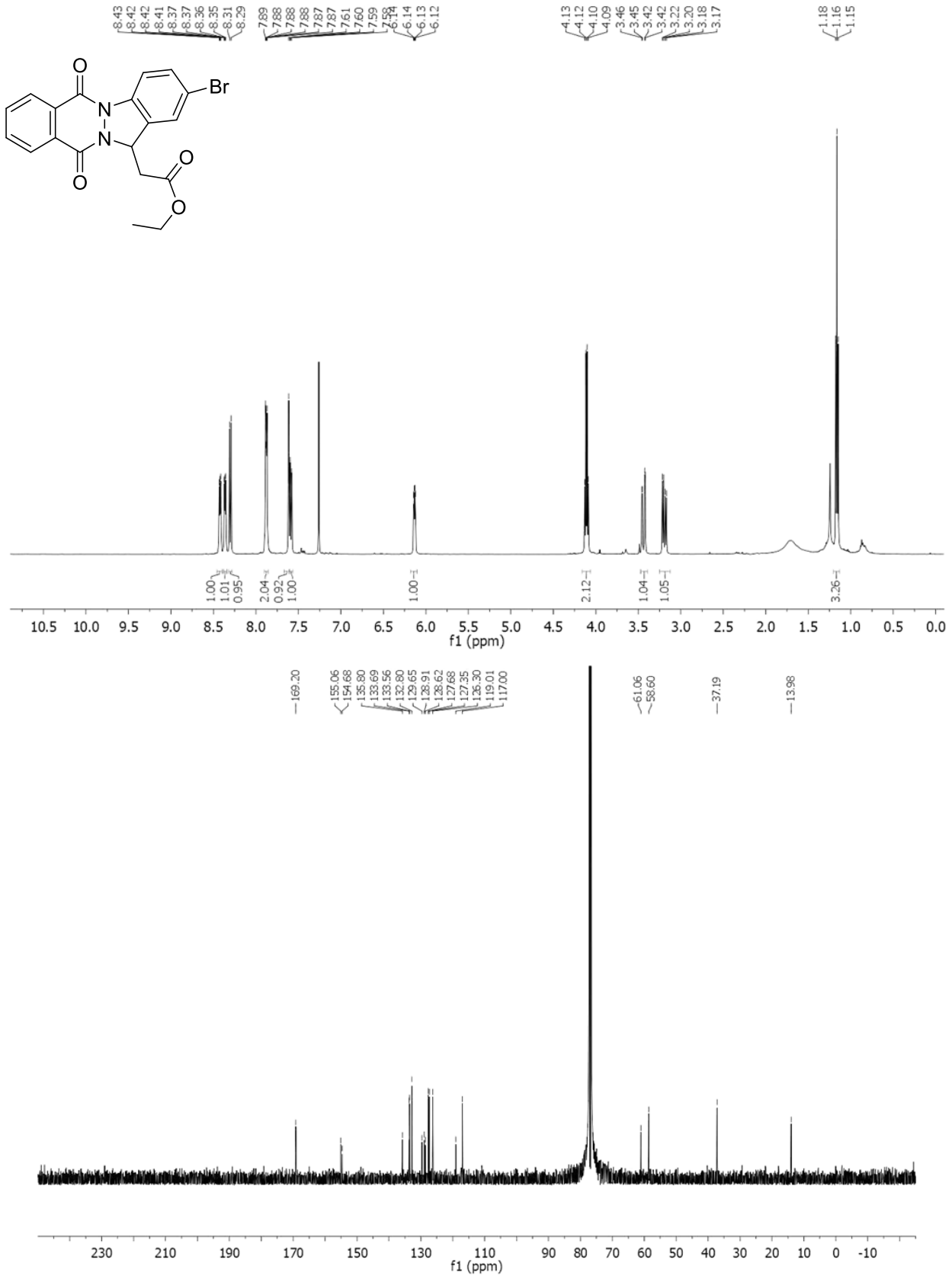


Methyl 2-(2-fluoro-6,9-dioxo-6,9-dihydro-11H-pyridazino[1,2-a]indazol-11-yl)acetate (3c)

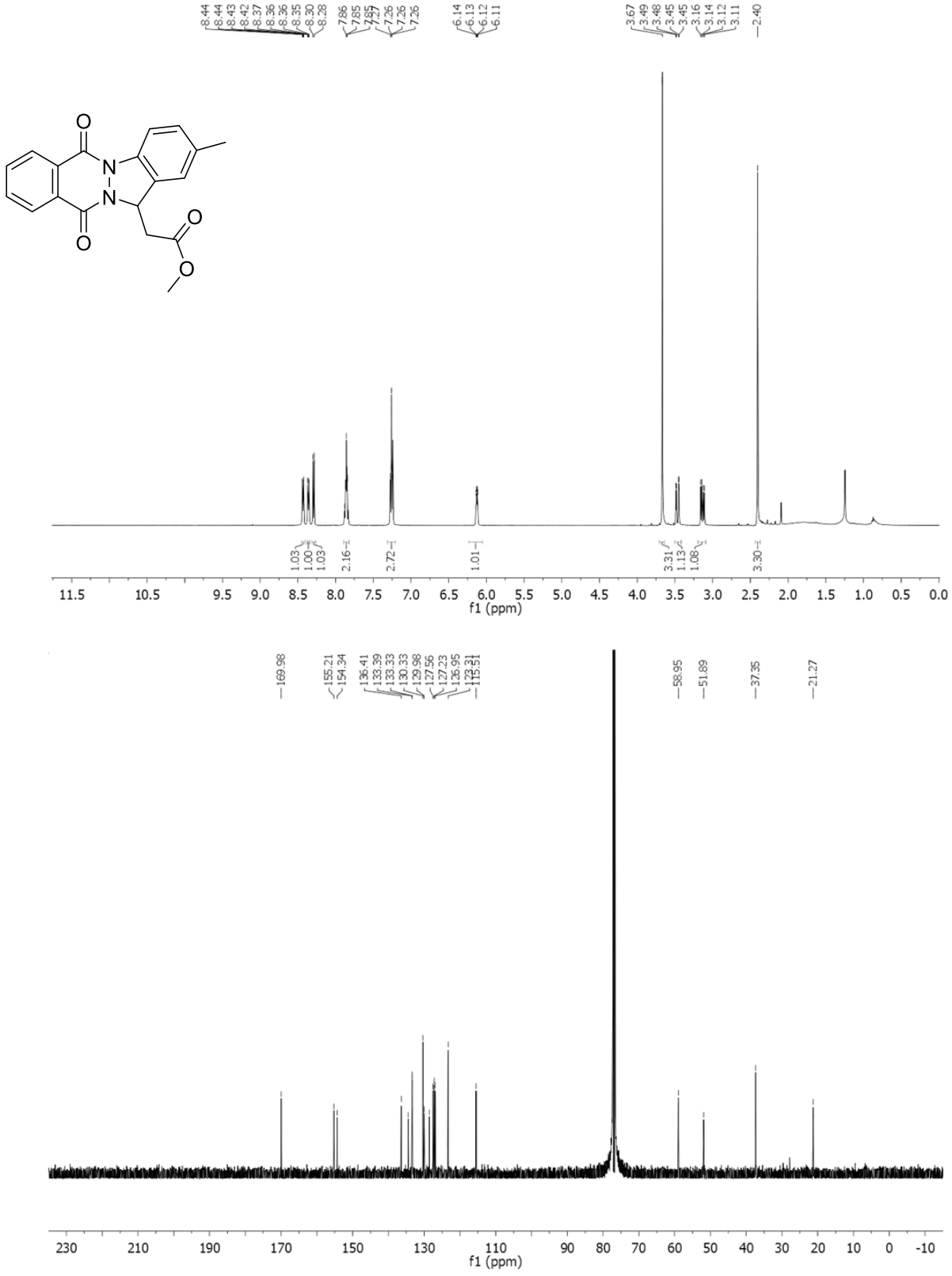




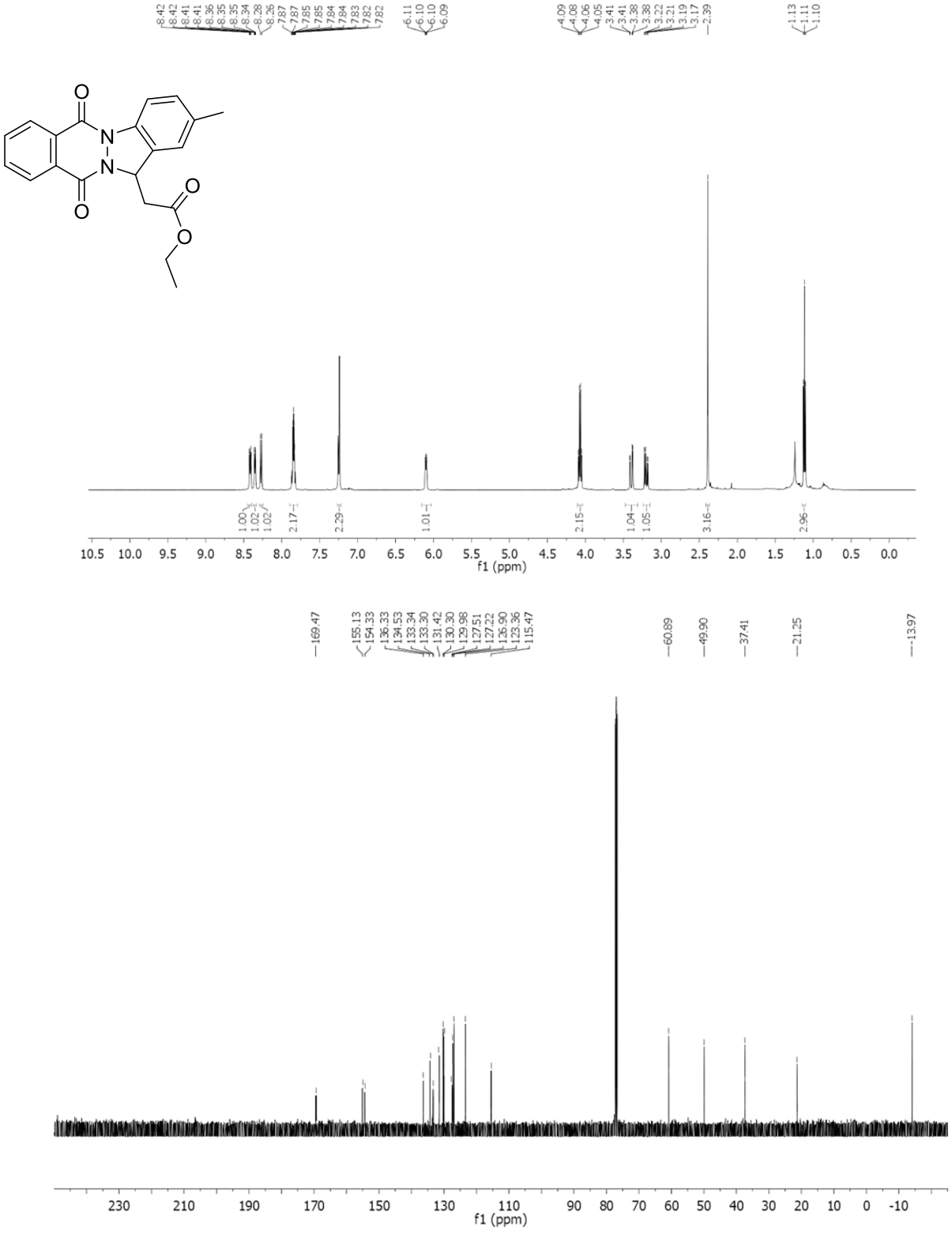
Ethyl 2-(2-bromo-6,11-dioxo-6,11-dihydro-13H-indazolo[1,2-b]phthalazin-13-yl)acetate (3d)



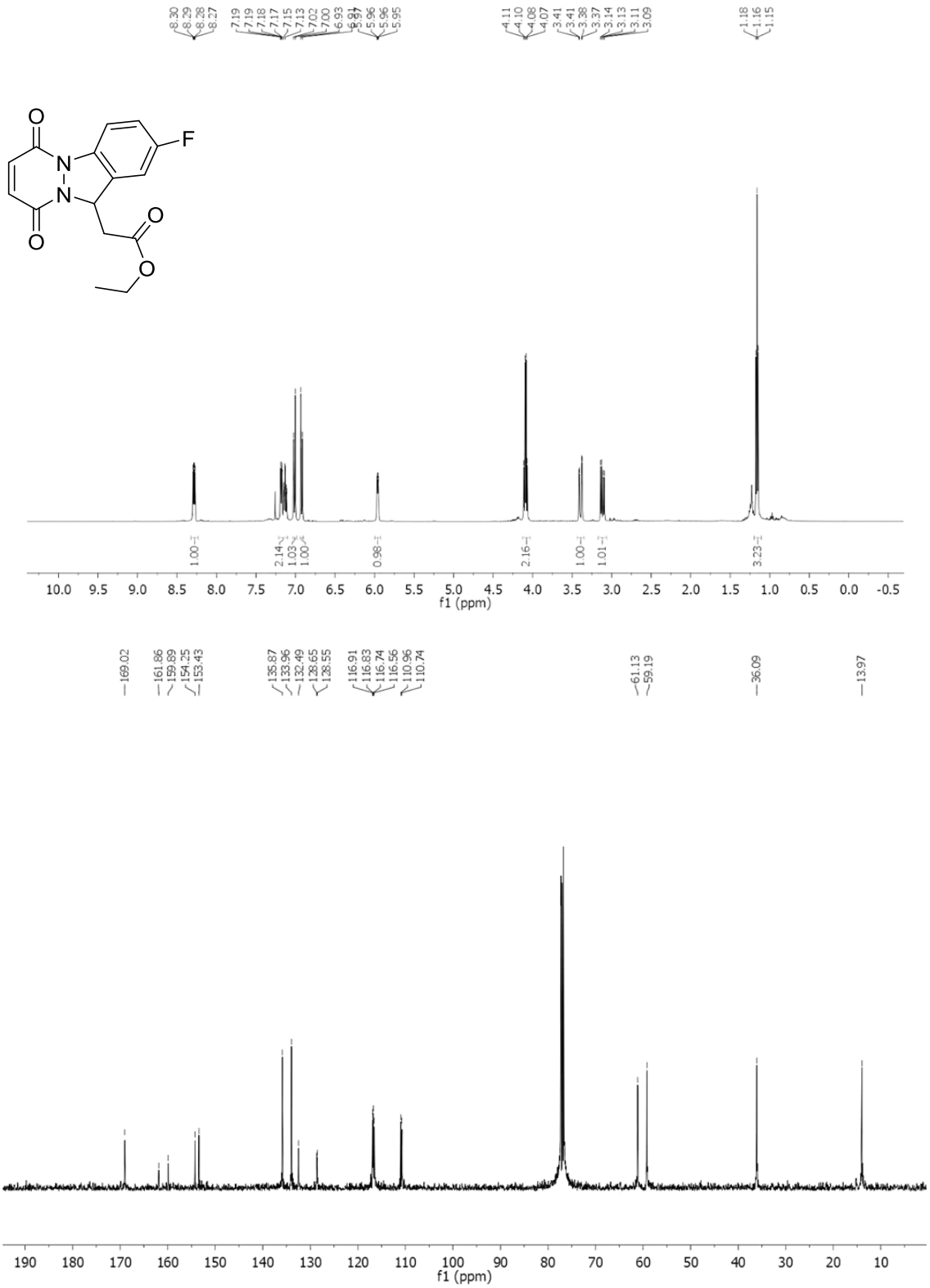
Methyl 2-(2-methyl-6,11-dioxo-6,11-dihydro-13H-indazolo[1,2-b]phthalazin-13-yl)acetate (3e)



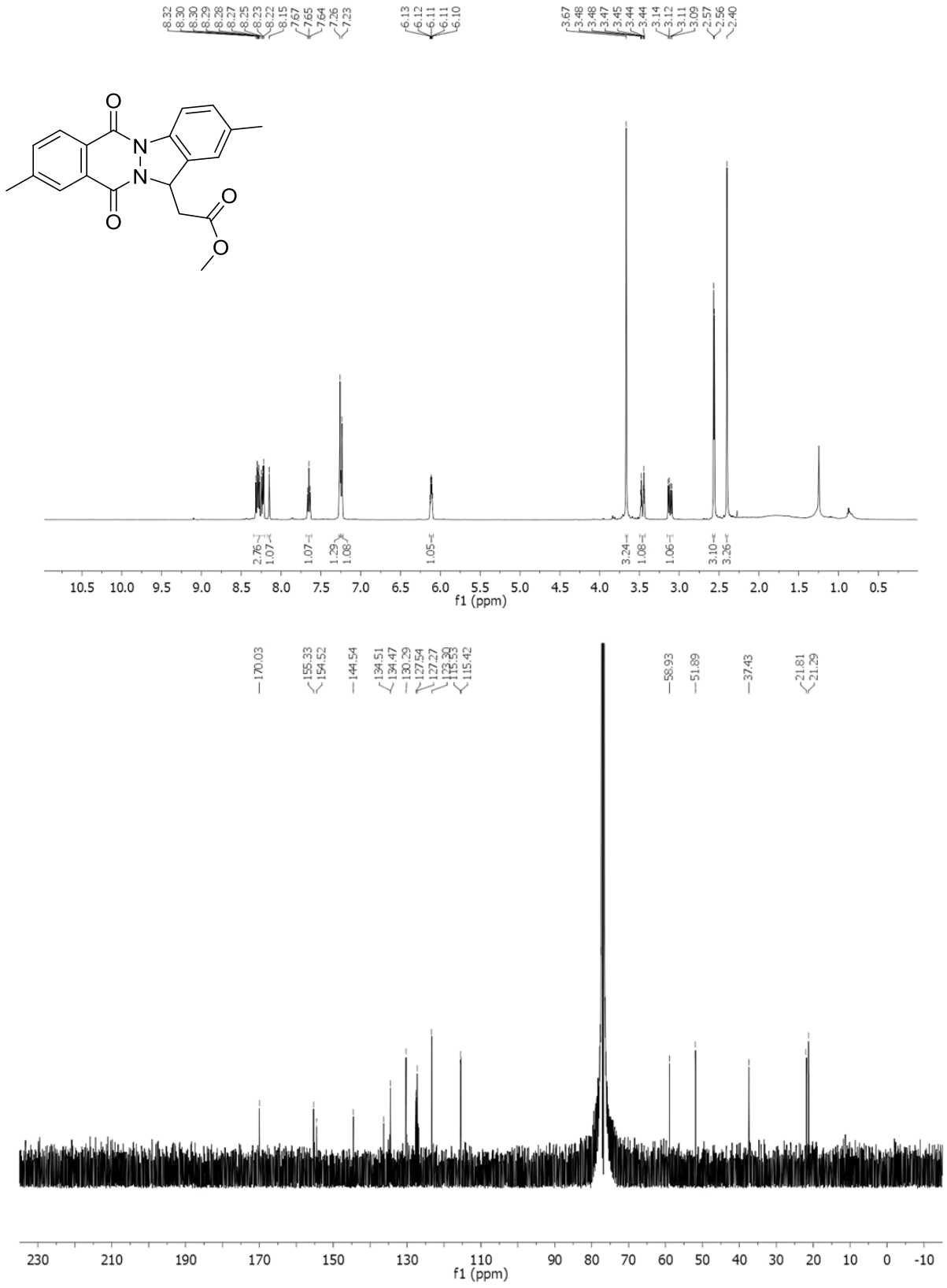
Ethyl 2-(2-methyl-6,11-dioxo-6,11-dihydro-13H-indazolo[1,2-b]phthalazin-13-yl)acetate (3f)



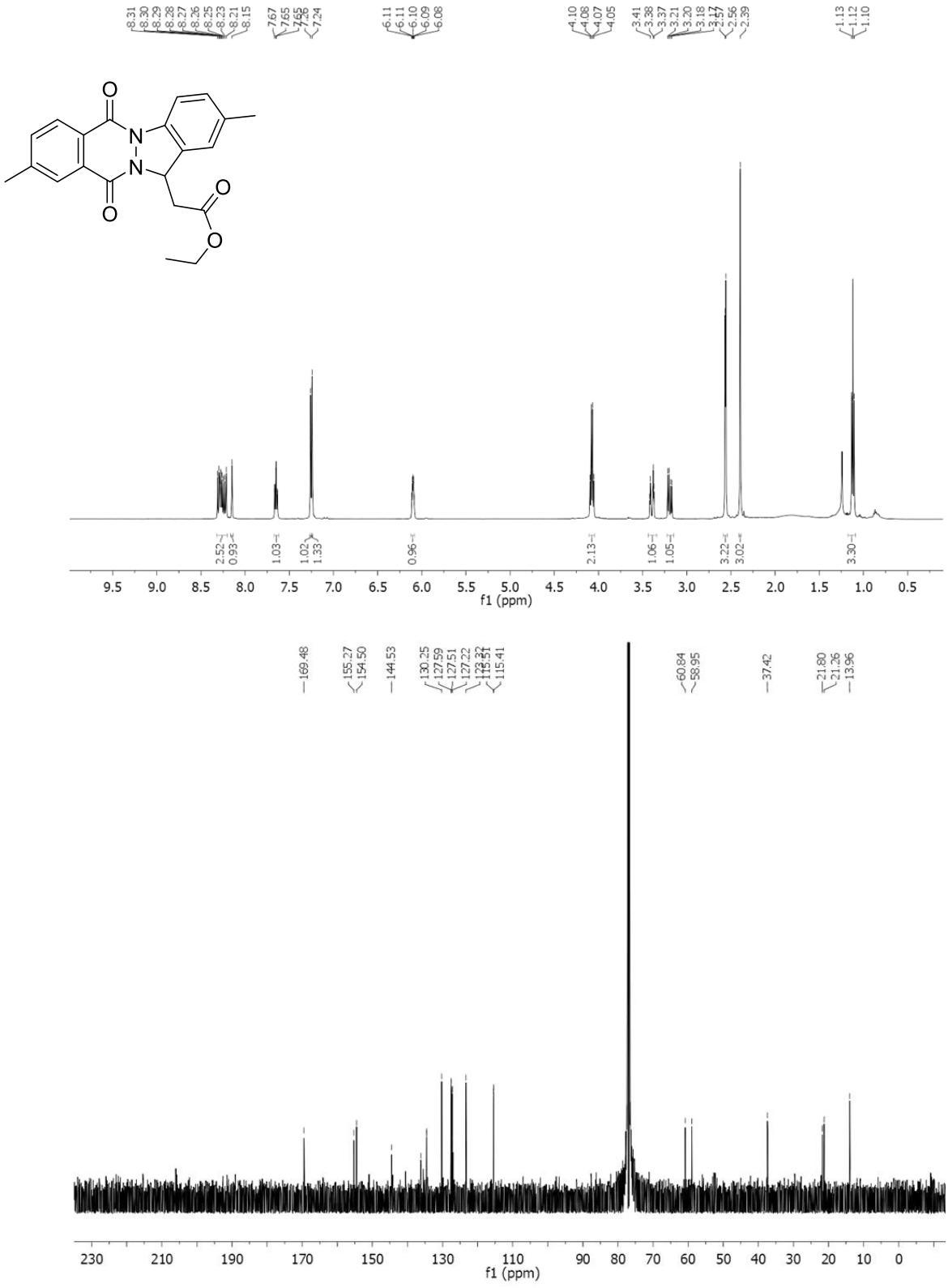
Ethyl 2-(2-fluoro-6,9-dioxo-6,9-dihydro-11H-pyridazino[1,2-a]indazol-11-yl)acetate (3g)



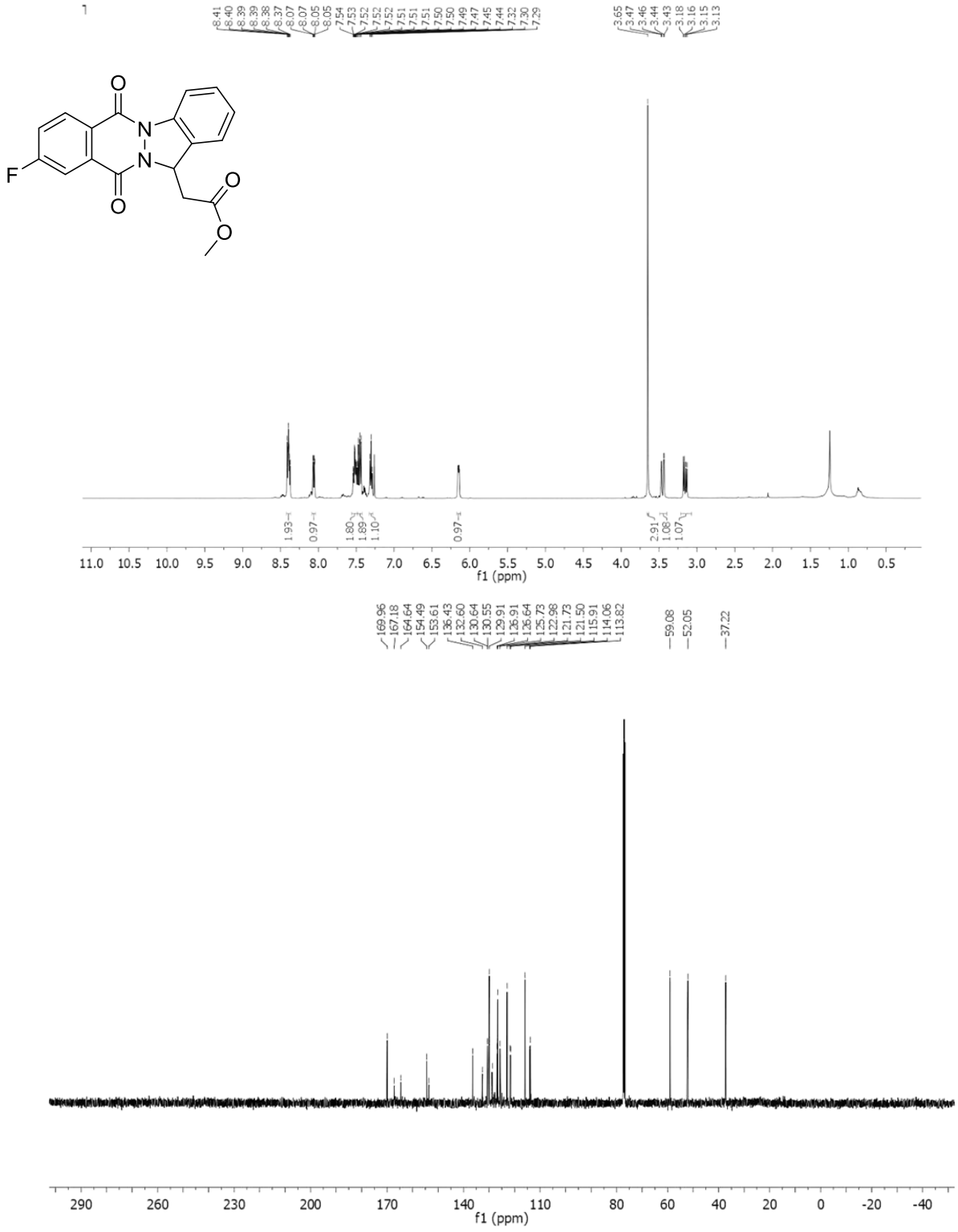
Methyl 2-(2,9-dimethyl-6,11-dioxo-6,11-dihydro-13H-indazolo[1,2-b]phthalazin-13-yl)acetate (3h)



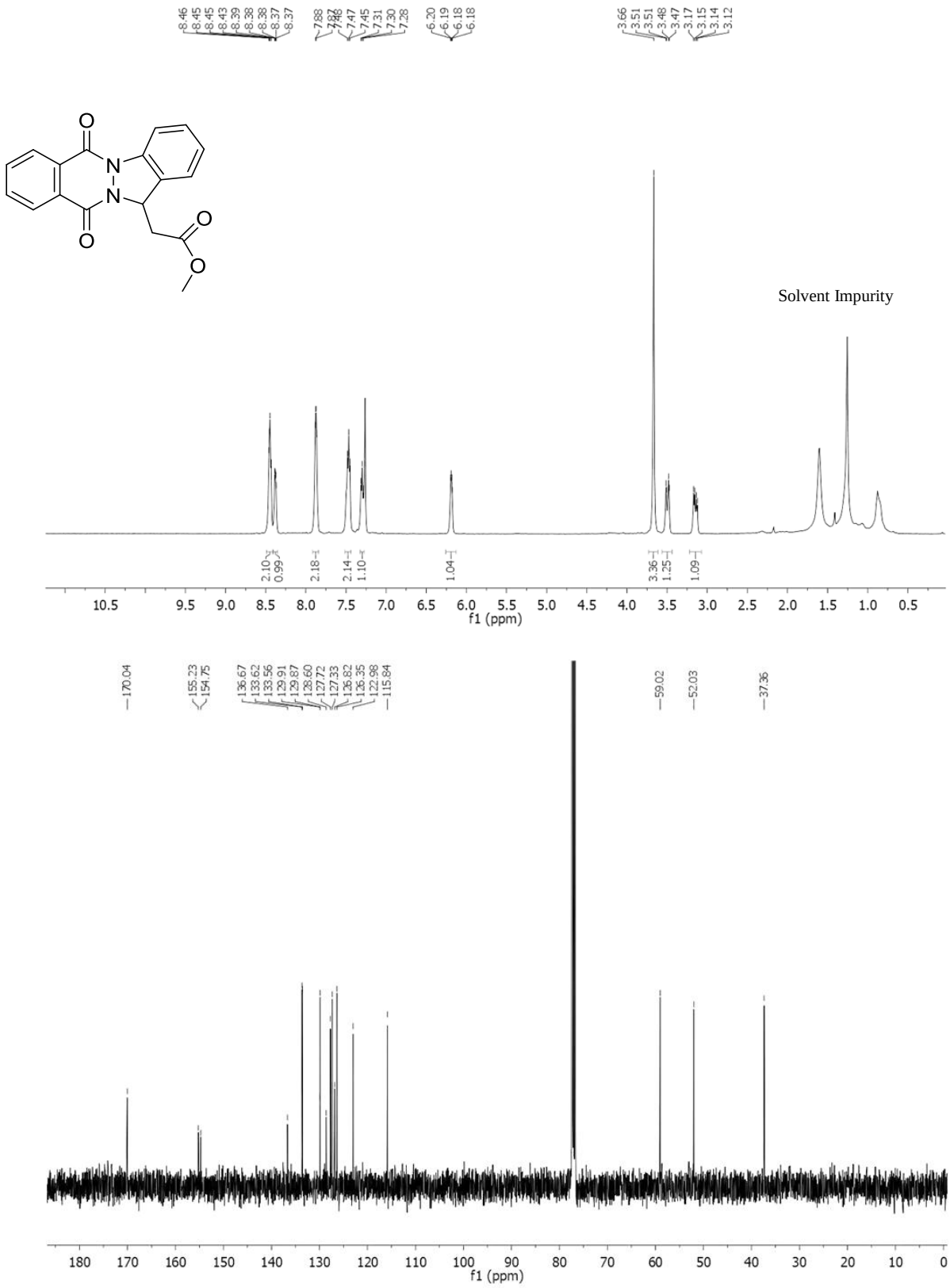
Ethyl 2-(2,9-dimethyl-6,11-dioxo-6,11-dihydro-13H-indazolo[1,2-b]phthalazin-13-yl)acetate (3i)



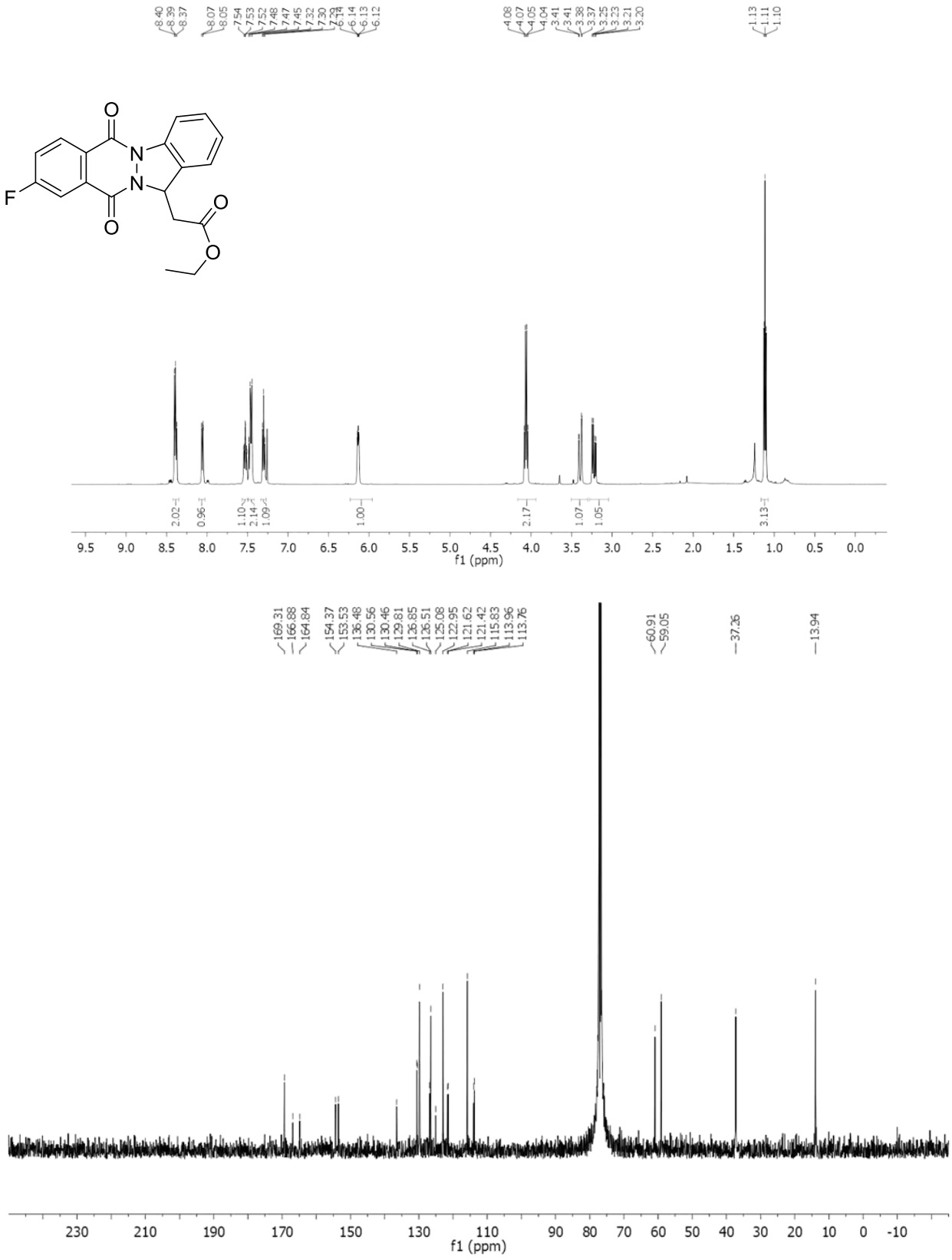
Methyl 2-(9-fluoro-6,11-dioxo-6,11-dihydro-13H-indazolo[1,2-b]phthalazin-13-yl)acetate (3j)



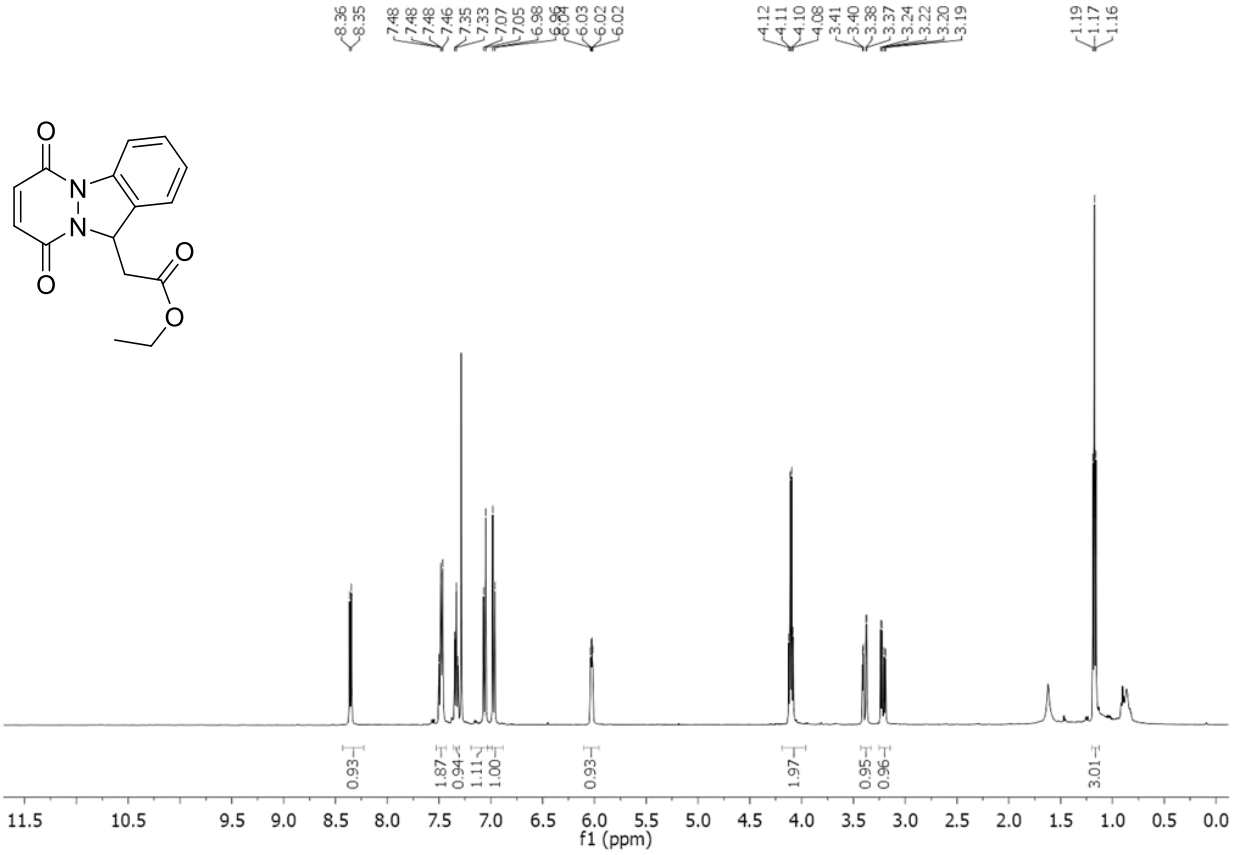
Methyl 2-(6,11-dioxo-6,11-dihydro-13H-indazolo[1,2-b]phthalazin-13-yl)acetate (3k)

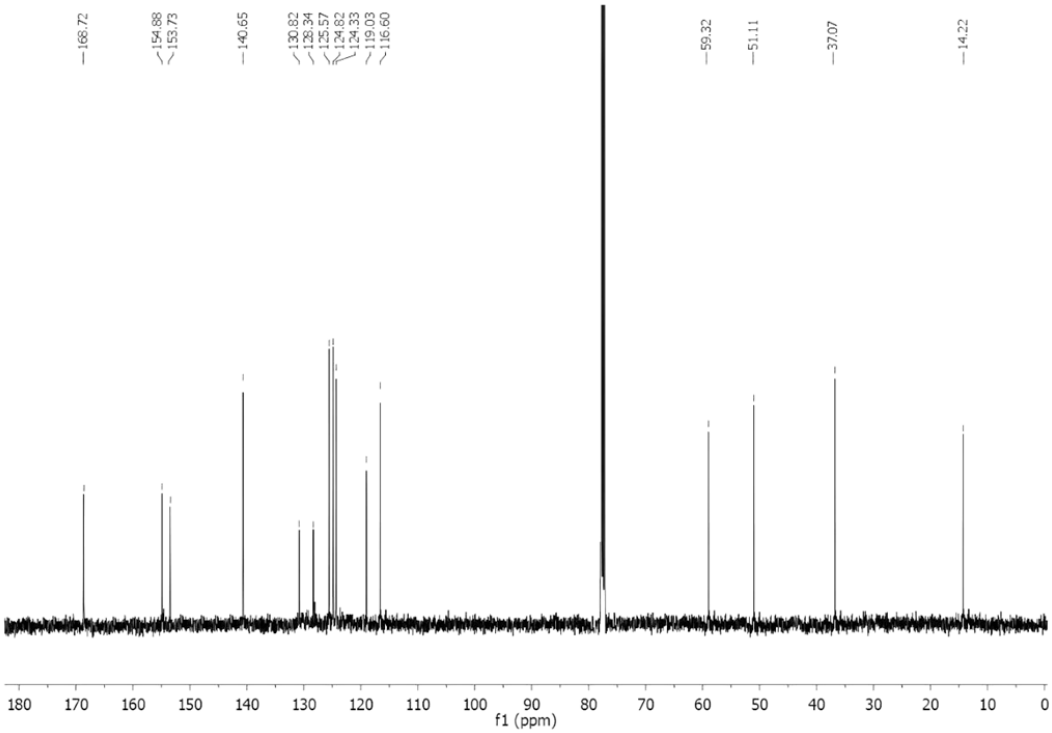


Ethyl 2-(9-fluoro-6,11-dioxo-6,11-dihydro-13H-indazolo[1,2-b]phthalazin-13-yl)acetate (3l)

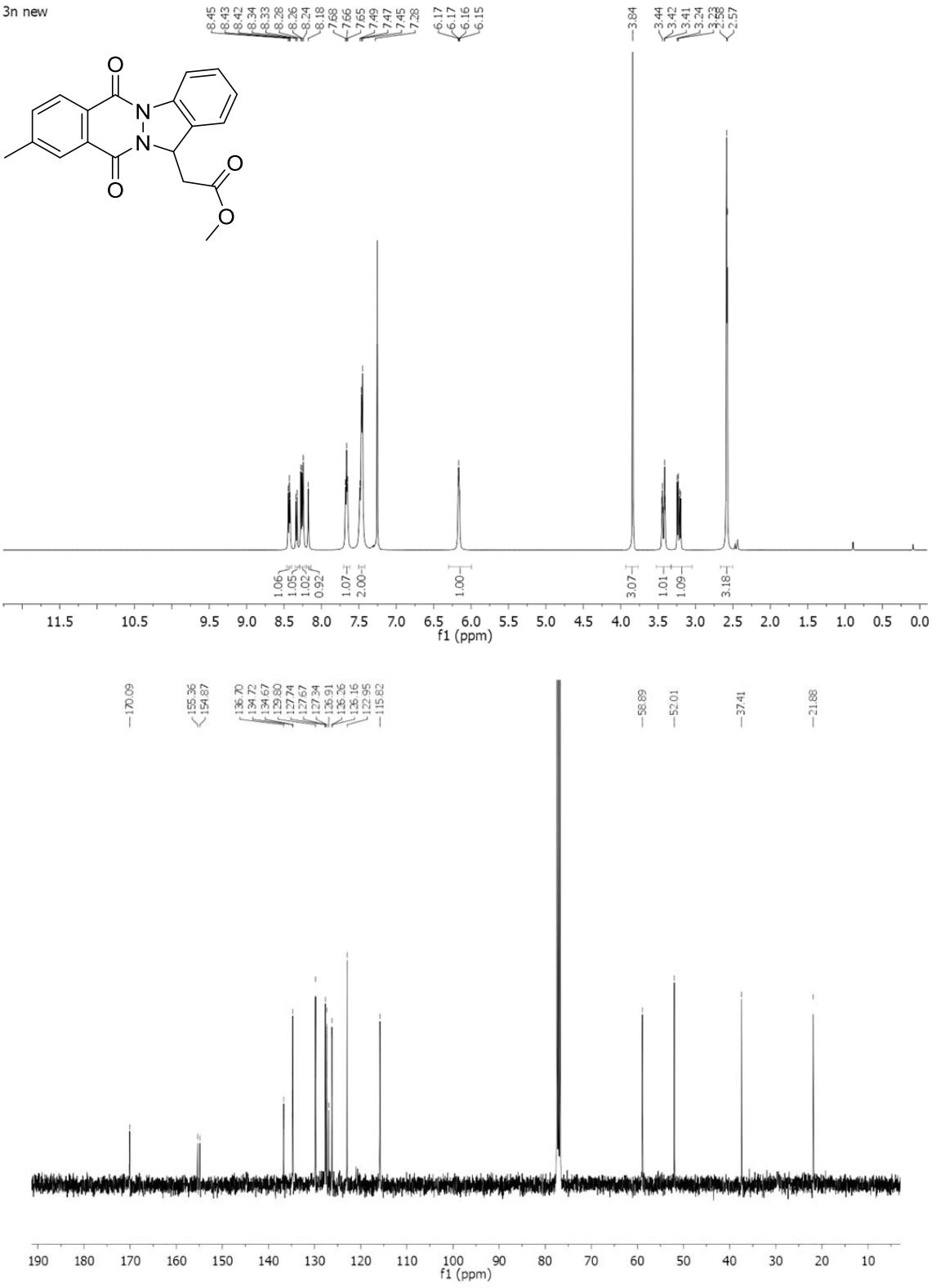


Ethyl 2-(6,9-dioxo-6,9-dihydro-11H-pyridazino[1,2-a]indazol-11-yl)acetate (3m)

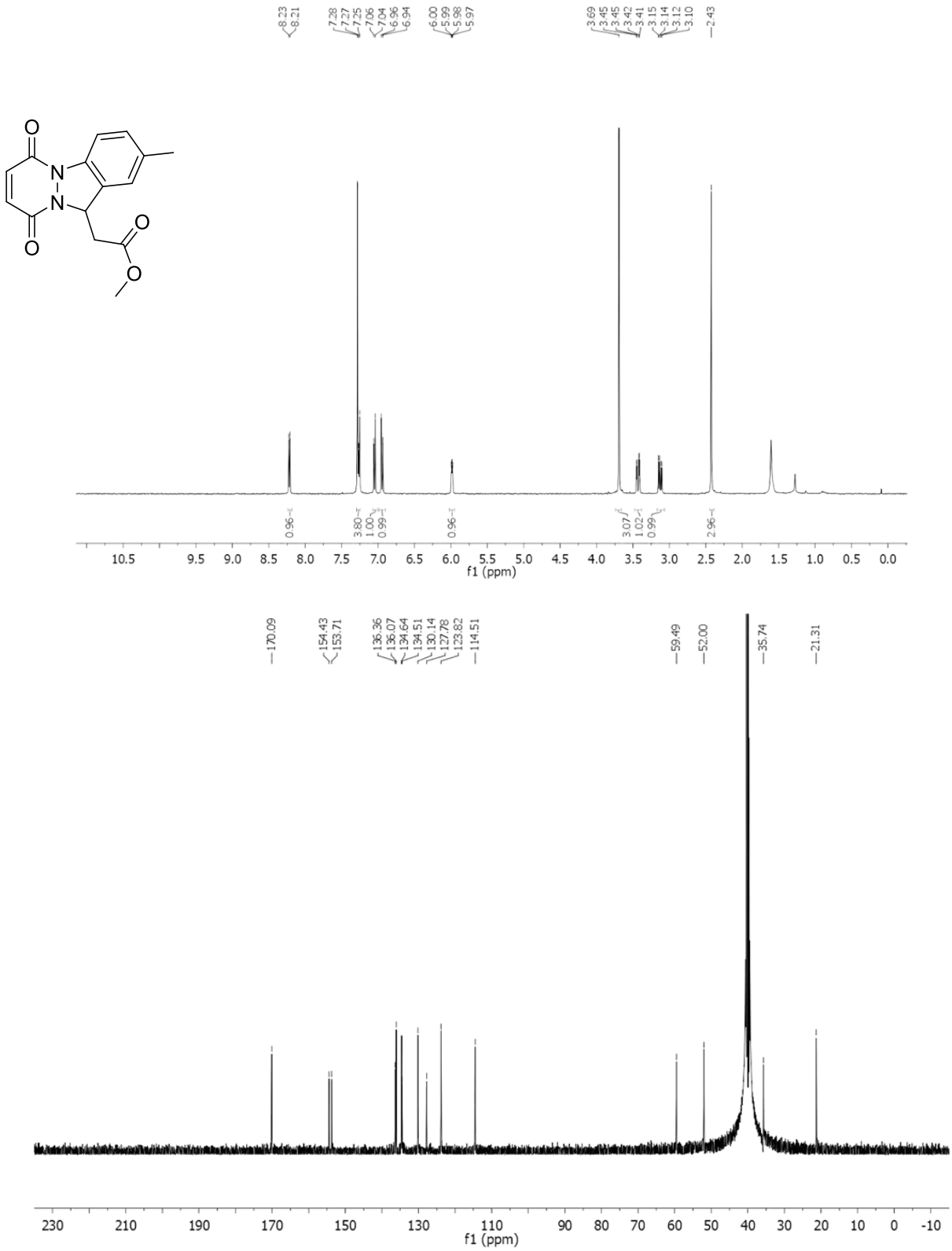




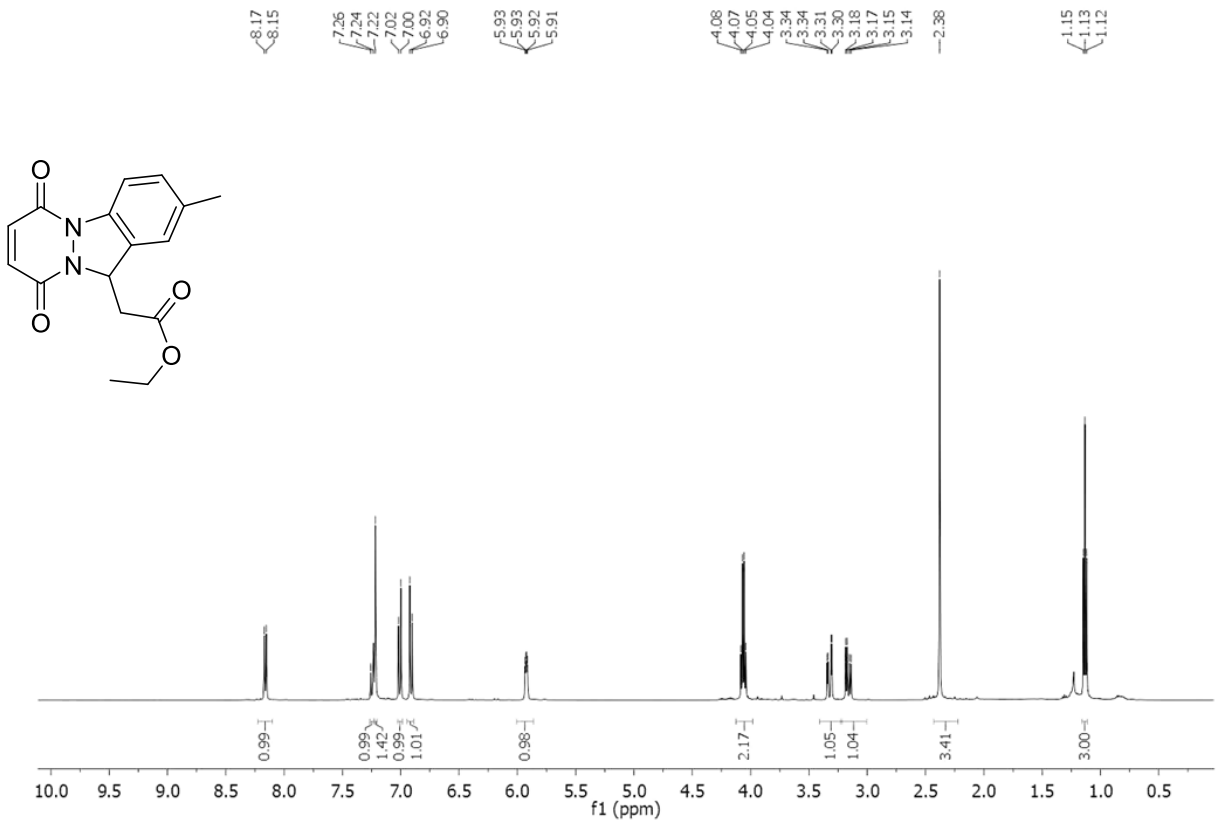
Methyl 2-(9-methyl-6,11-dioxo-6,11-dihydro-13H-indazolo[1,2-b]phthalazin-13-yl)acetate (3n)

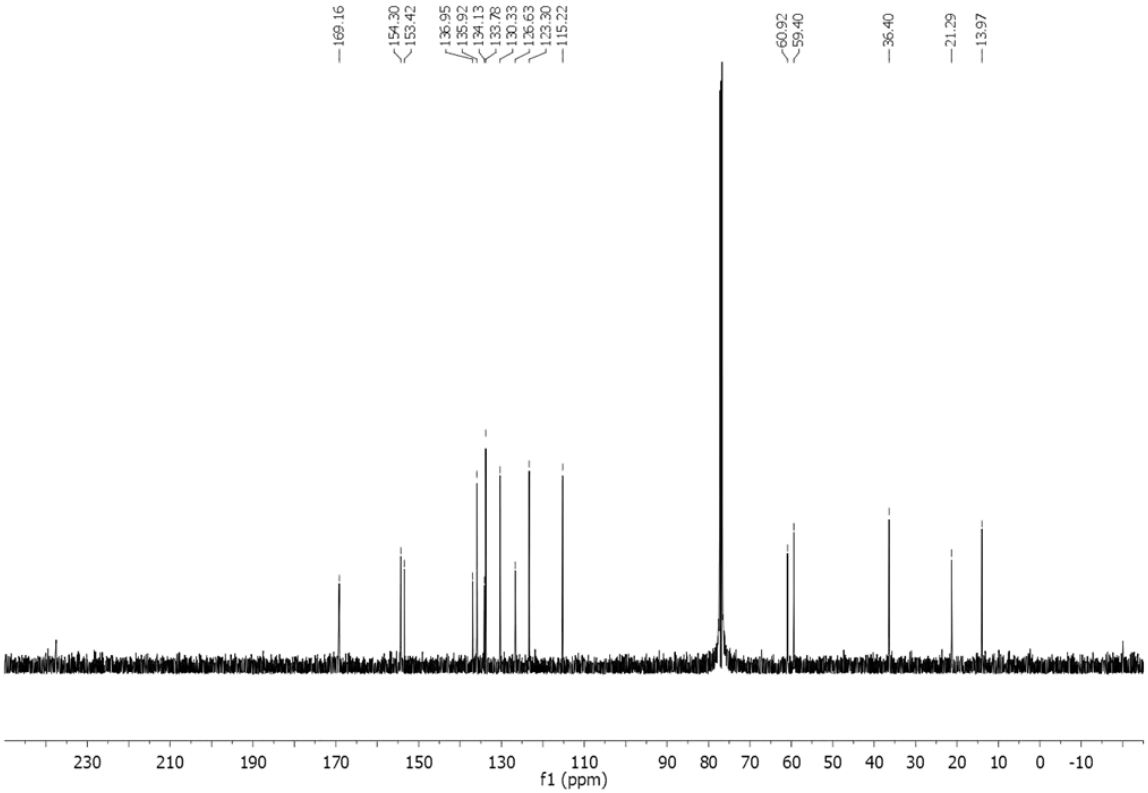


Methyl 2-(2-methyl-6,9-dioxo-6,9-dihydro-11H-pyridazino[1,2-a]indazol-11-yl)acetate (3o)

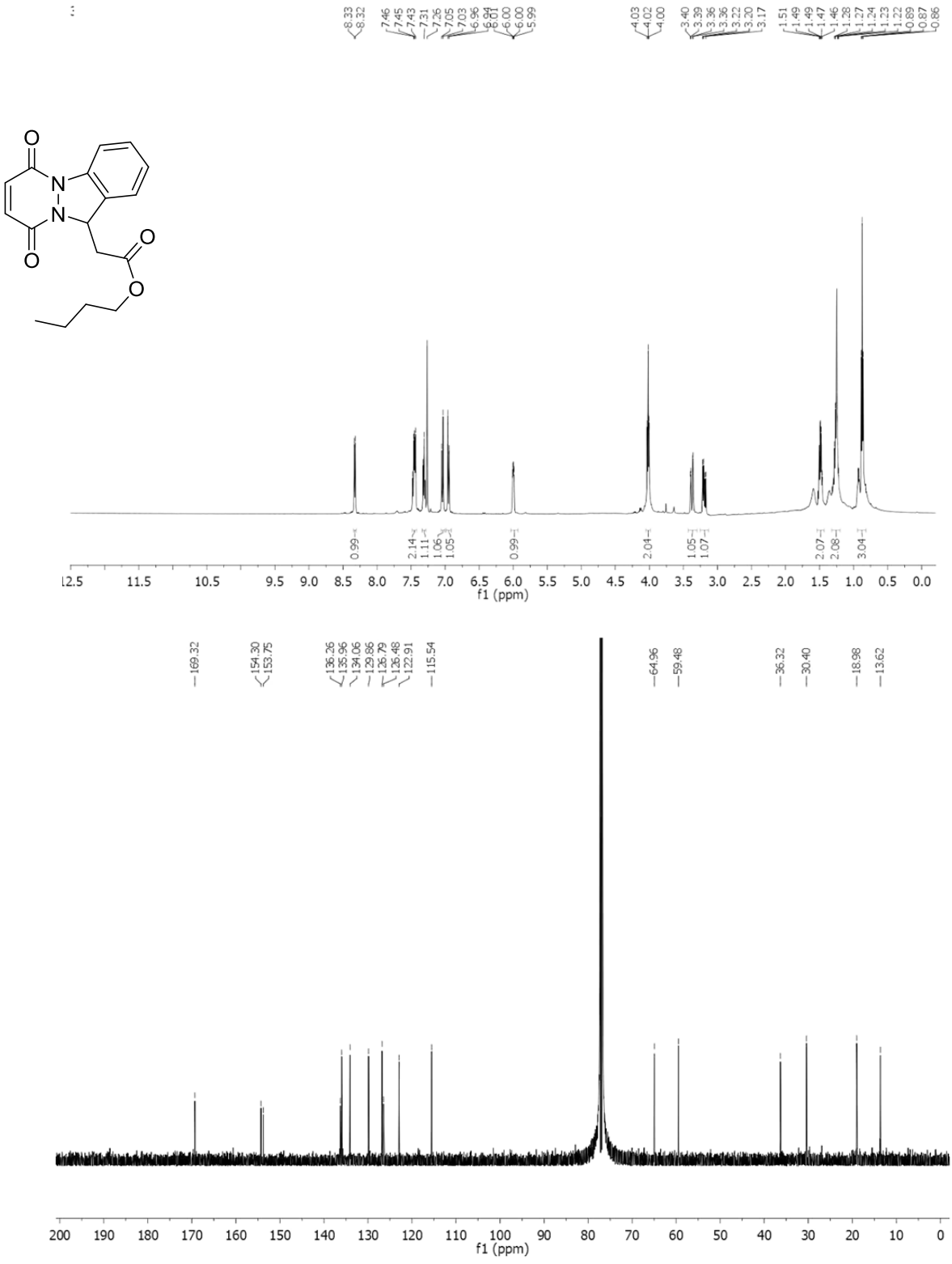


Ethyl 2-(2-methyl-6,9-dioxo-6,9-dihydro-11H-pyridazino[1,2-a]indazol-11-yl)acetate (3p)

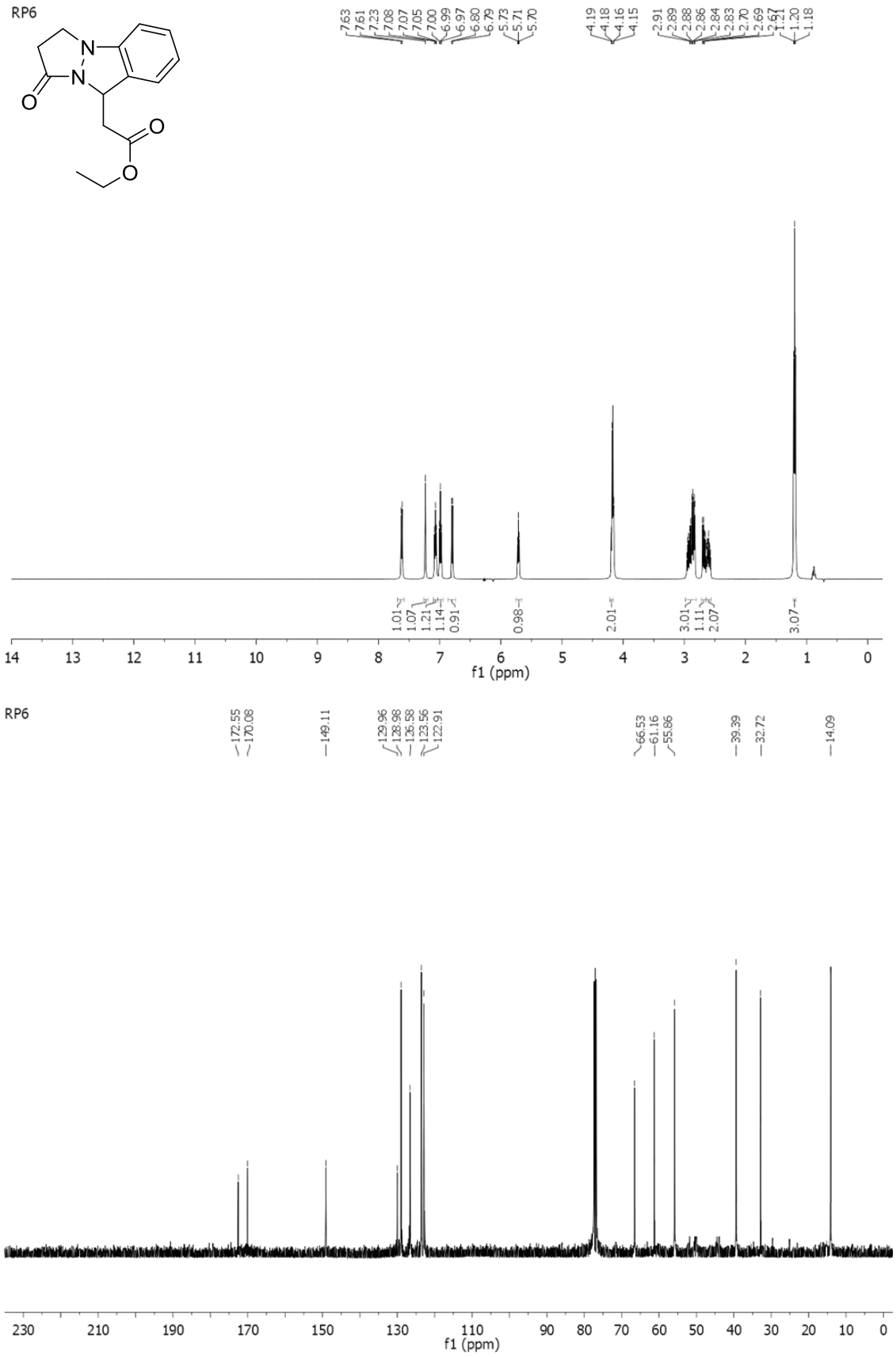




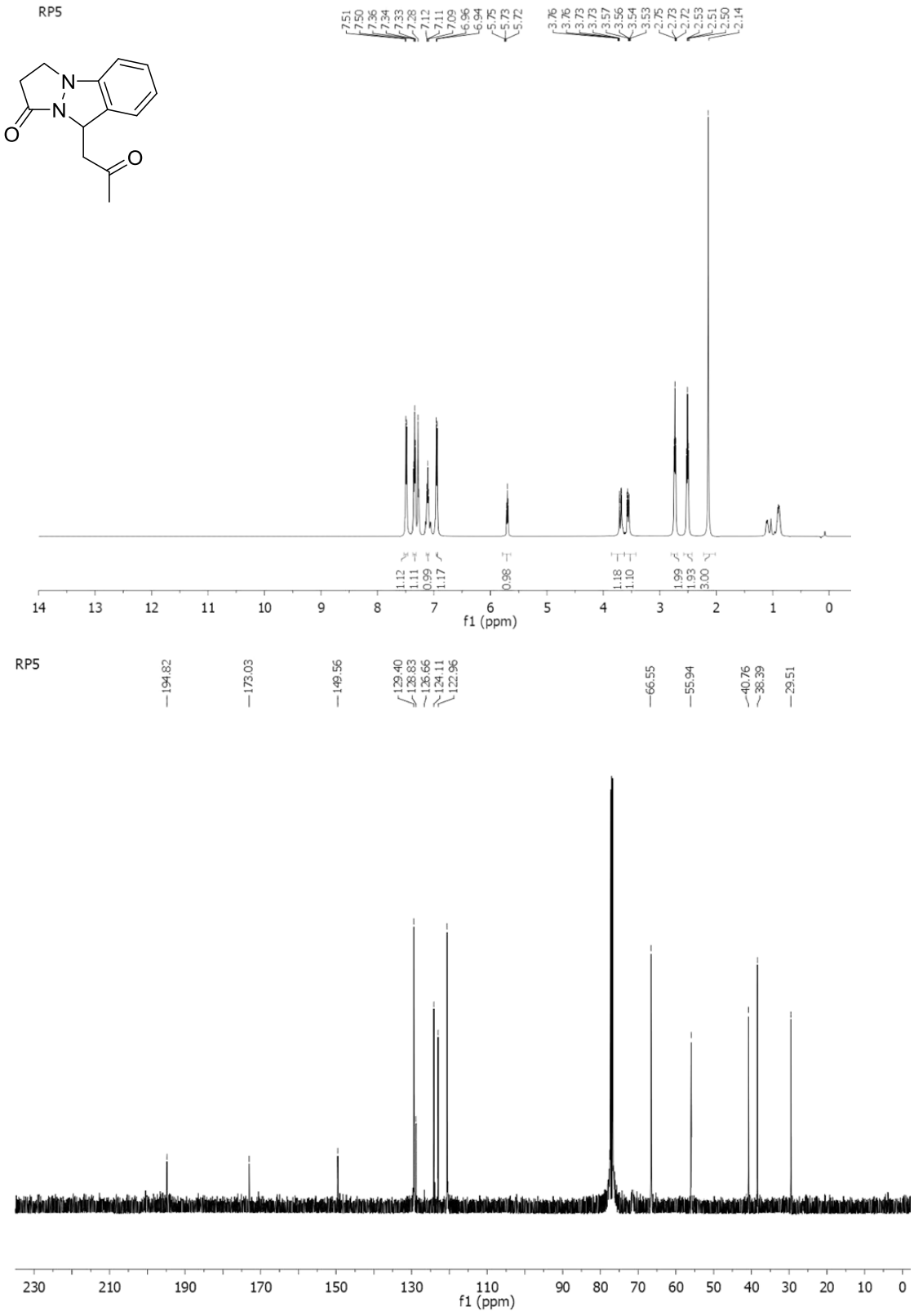
Butyl 2-(6,9-dioxo-6,9-dihydro-11H-pyridazino[1,2-a]indazol-11-yl)acetate (3q)



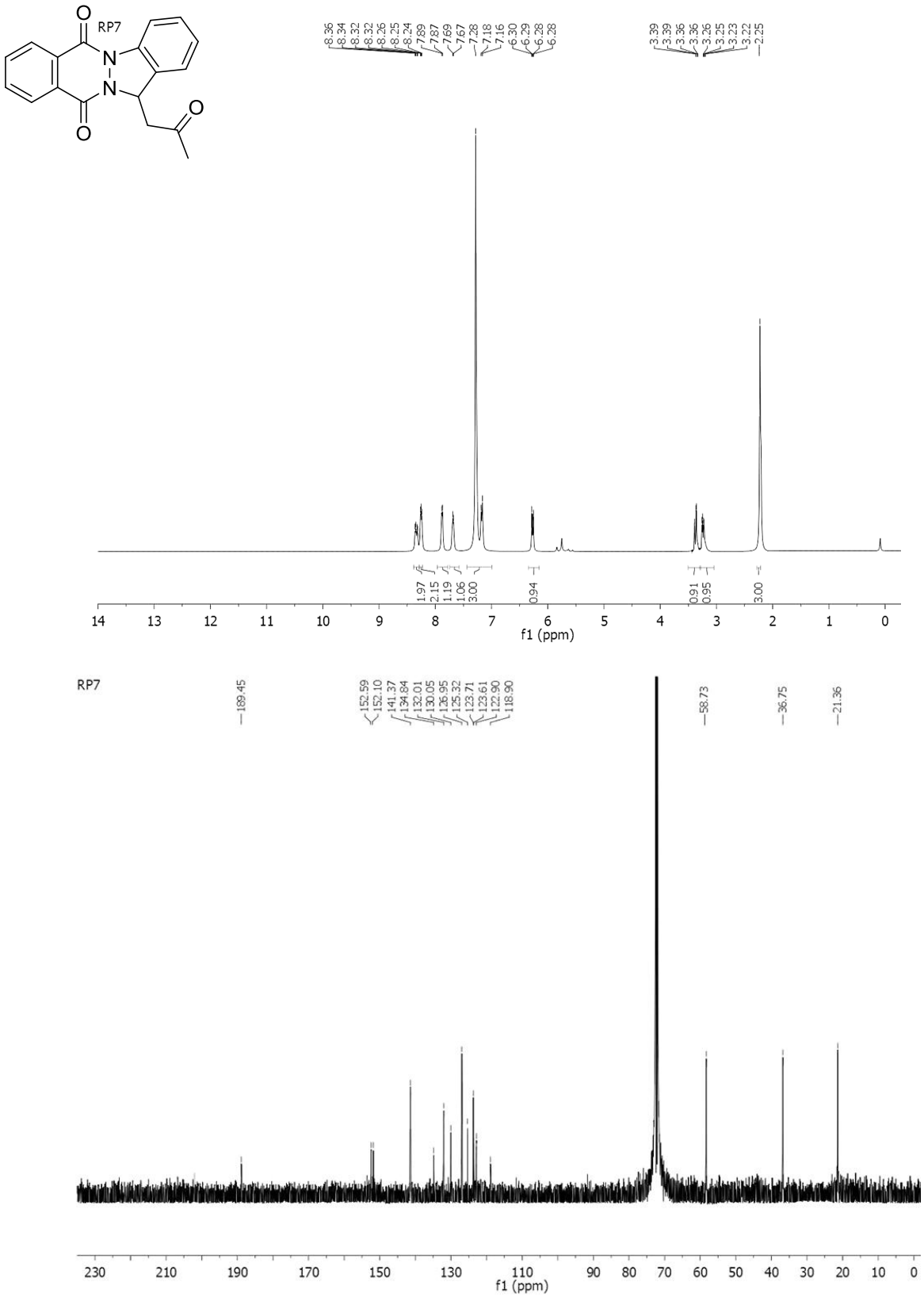
Ethyl 2-(1-oxo-2,3-dihydro-1H,9H-pyrazolo[1,2-a]indazol-9-yl)acetate (3r):



9-(2-oxopropyl)-2,3-dihydro-1H,9H-pyrazolo[1,2-a]indazol-1-one (3s):



13-(2-oxopropyl)-13H-indazolo[1,2-b]phthalazine-6,11-dione (3t):



7. Reference

1. (a) D. Poli, D. Catarzi, V. Colotta, F. Varano, G. Filacchioni, S. Daniele, L. Trincavelli, C. Martini, S. Paoletta and S. Moro, *J. Med. Chem.*, 2011, **54**, 2102- 2013; (b) S. Mayakrishnan, Y. Arun, Ch. Balachandran, N, Emi, D, Muralidharan and P. Thirumalai Perumal, *Org. Biomol. Chem.*, 2016, **14**, 1958-1968.