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Noncatalytic on water aldol reaction of isatins with cyclic 1,3-diketones at room temperature without the need for subsequent chromatography

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General information

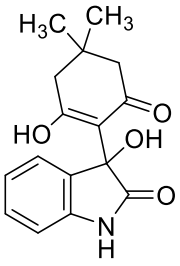
The solvents and reagents were purchased from commercial sources and used as received. Isatin **1e** was obtained from isatin **1a** and bromine in acetic acid according to literature data [1]. Isatin **1f** was synthesized from isatin **1a** and ethyl iodide according to a known method [2].

All melting points were measured with a Gallenkamp melting-point apparatus and were uncorrected. ^{1}H and ^{13}C NMR spectra were recorded in DMSO-d_6 with Bruker AM300 and Bruker AV500 spectrometers at ambient temperature. Chemical shift values are relative to Me_4Si. Some OH and NH signals in ^{1}H NMR spectra have an underestimated integral or are absent due to exchange processes (deuterated water was contained as an impurity in DMSO-d_6). Some carbon signals in the ^{13}C NMR spectra are strongly broadened due to dynamic processes (tautomerism) and are absent from the spectra. The IR spectra were recorded with a Bruker ALPHA-T FT-IR spectrometer in a KBr pellet. MS spectra (EI = 70 eV) were obtained directly with a Kratos MS-30 spectrometer. For elemental analysis, a 2400 Elemental Analyzer was used.

Typical procedure

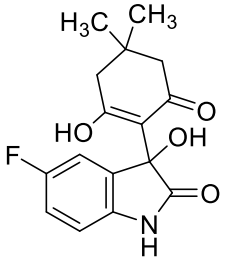
Isatin **1** (3 mmol) and 1,3-cyclohexanedione **2** (3 mmol) were stirred in 10 mL of H_2O for 3 h at room temperature (23° C). After the reaction was completed, the formed solid was filtered, washed with well-chilled ethanol (3 mL × 2), and dried to isolate pure 3-hydroxy-3-(2-hydroxy-6-oxocyclohex-1-en-1-yl)indolin-2-one **3**.

Characterization of synthesized compounds



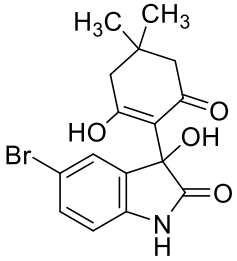
3-Hydroxy-3-(2-hydroxy-4,4-dimethyl-6-oxocyclohex-1-en-1-yl)indolin-2-one (3a).

Yield 0.85 g (98%), mp: 167-168 °C (lit. [3] mp: 166-167 °C). ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.98 (s, 6H, 2 CH_3), 1.74-2.65 (m, 2H, CH_2), 6.76 (d, ^{3}J = 7.2 Hz, 1H, CH Ar), 6.87 (t, ^{3}J = 7.2 Hz, 1H, CH Ar), 7.07 (d, ^{3}J = 7.2 Hz, 1H, CH Ar), 7.16 (t, ^{3}J = 7.2 Hz, 1H, CH Ar), 8.17 (br s, 1H, OH), 10.16 (s, 1H, NH), 11.78 (br s, 1H, OH) ppm.



5-Fluoro-3-hydroxy-3-(2-hydroxy-4,4-dimethyl-6-oxocyclohex-1-en-1-yl)indolin-2-one (3b).

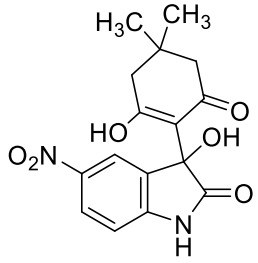
Yield 0.84 g (92%), mp: 185-186 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ 0.99 (s, 6H, 2 CH_3), 1.78-2.59 (m, 2H, CH_2), 6.72-6.79 (m, 1H, CH Ar), 6.90 (dd, $^{4}J_{H\text{-}H}$ = 1.8 Hz, $^{3}J_{H\text{-}F}$ = 7.2 Hz, 1H, CH Ar), 6.97-7.04 (m, 1H, CH Ar), 8.35 (br s, 1H, OH), 10.22 (s, 1H, NH), 11.73 (br s, 1H, OH) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ 27.5, 27.9, 31.7, 46.0 (br s, 2C), 78.0, 102.4, 110.0, 110.1 (d, $^{3}J_{C\text{-}F}$ = 7.2 Hz), 110.7 (d, $^{2}J_{C\text{-}F}$ = 23.1 Hz), 115.2 (d, $^{2}J_{C\text{-}F}$ = 23.1 Hz), 134.0 (d, $^{3}J_{C\text{-}F}$ = 7.2 Hz), 138.9, 157.8 (d, $^{1}J_{C\text{-}F}$ = 236.7 Hz), 176.4 ppm. MS (*m/z* relative intensity %): 305 [M^{+}] (8), 260 (40), 244 (9), 206 (9), 165 (48), 137 (96), 109 (60), 83 (100), 56 (90), 41 (83). IR (KBr) ν = 3148, 2963, 2718, 1737, 1629, 1590, 1488, 1370, 1248, 594 cm^{-1}. Anal. calcd for $C_{16}H_{16}FNO_4$: C, 62.95; H, 5.28; N, 4.59%. Found: C, 62.84; H, 5.35; N, 4.53%.



5-Bromo-3-hydroxy-3-(2-hydroxy-4,4-dimethyl-6-oxocyclohex-1-en-1-yl)indolin-2-one (3c).

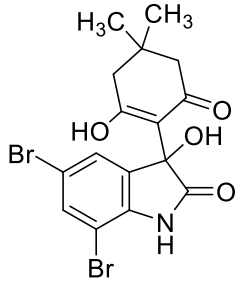
Yield 1.065 g (97%), mp: 170-171 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.98 (s, 6H, 2 CH_3), 1.95-2.50 (m, 2H, CH_2), 6.75 (d, ^{3}J = 7.8 Hz, 1H, CH Ar), 7.15 (s, 1H, CH Ar), 7.35 (d, ^{3}J = 7.8 Hz, 1H, CH Ar), 10.32 (s, 1H, NH, exch.) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ 27.5 (2C), 31.7, 46.1 (br s, 2C), 77.7, 110.0, 111.4, 112.6, 125.8, 131.7, 134.7, 142.0, 175.9 ppm. MS (*m/z* relative intensity %): 322 [^{81}Br, M – CHNO – 2H]$^{+}$ (9), 320 [^{79}Br, M – CHNO – 2H]$^{+}$ (9), 242 (1), 227 (^{81}Br, 20), 225 (^{79}Br, 21), 199 (^{81}Br, 56), 197 (^{79}Br, 60), 140 (37), 112 (17), 83 (99), 56 (79), 39 (100), 15 (53). IR (KBr) ν = 3179, 2960, 2723, 1737, 1711, 1594, 1476, 1367, 1248, 817

cm^{-1}. Anal. calcd for $C_{16}H_{16}BrNO_4$: C, 52.48; H, 4.40; N, 3.82%. Found: C, 52.42; H, 4.49; N, 3.75%.



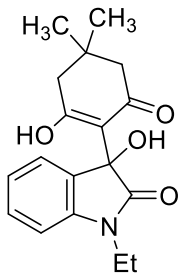
3-Hydroxy-3-(2-hydroxy-4,4-dimethyl-6-oxocyclohex-1-en-1-yl)-5-nitroindolin-2-one (3d).

Yield 0.927 g (93%), mp: 192-193 °C. ^{1}H NMR (300 MHz, DMSO-*d*$_6$): δ 0.98 (s, 6H, 2 CH$_3$), 1.96-2.51 (m, 2H, CH$_2$), 6.99 (d, ^3J = 8.7 Hz, 1H, CH Ar), 7.87 (d, ^4J = 2.1 Hz, 1H, CH Ar), 8.17 (dd, ^3J = 7.8 Hz, ^4J = 2.1 Hz, 1H, CH Ar), 10.96 (s, 1H, NH, exch.) ppm. ^{13}C NMR (75 MHz, DMSO-*d*$_6$): δ 27.5, 28.0, 31.9, 45.8 (br s, 2C), 77.1, 109.7, 118.6, 126.7, 133.3, 142.0, 149.2, 149.4, 176.8, 176.9 ppm. MS (*m/z* relative intensity %): 287 [M – NO$_2$]$^+$ (3), 271 (3), 233 (1), 192 (31), 164 (78), 140 (26), 106 (18), 83 (100), 56 (61), 30 (80). IR (KBr) ν = 3323, 3106, 1715, 1691, 1626, 1341, 1300, 1239, 1082, 752 cm^{-1}. Anal. calcd for $C_{16}H_{16}N_2O_6$: C, 57.83; H, 4.85; N, 8.43%. Found: C, 57.75; H, 4.88; N, 8.35%.



5,7-Dibromo-3-hydroxy-3-(2-hydroxy-4,4-dimethyl-6-oxocyclohex-1-en-1-yl)indolin-2-one (3e).

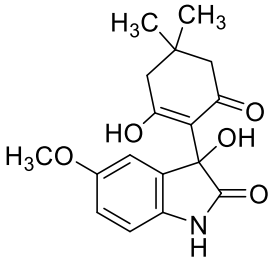
Yield 1.134 g (85%), mp: 153-154 °C. ^{1}H NMR (300 MHz, DMSO-*d*$_6$): δ 1.00 (s, 6H, 2 CH$_3$), 1.95-2.50 (m, 2H, CH$_2$), 7.20 (d, ^4J = 1.4 Hz, 1H, CH Ar), 7.64 (d, ^4J = 1.4 Hz, 1H, CH Ar), 8.21-9.11 (br s, 1H, OH), 10.69 (s, 1H, NH), 10.91-12.00 (br s, 1H, OH) ppm. ^{13}C NMR (75 MHz, DMSO-*d*$_6$): δ 27.5, 28.0, 31.8, 45.2 (br s, 2C), 78.5, 102.7, 109.8, 113.2, 125.0, 126.0, 133.6, 136.0, 141.7, 175.9 ppm. MS (*m/z* relative intensity %): 400 [^{81}Br, ^{79}Br, M – CHNO – 2H]$^+$ (1), 307 (^{81}Br, ^{81}Br, 10), 305 (^{81}Br, ^{79}Br, 21), 303 (^{79}Br, ^{79}Br, 11), 279 (^{81}Br, ^{81}Br, 38), 277 (^{81}Br, ^{79}Br, 80), 275 (^{79}Br, ^{79}Br, 41), 222 (1), 170 (20), 140 (33), 112 (17), 83 (100), 56 (69), 42 (75). IR (KBr) ν = 3350, 2962, 2728, 1735, 1605, 1426, 1367, 1157, 1013, 864 cm^{-1}. Anal. calcd for $C_{16}H_{15}Br_2NO_4$: C, 43.18; H, 3.40; N, 3.15%. Found: C, 43.12; H, 3.46; N, 3.08%.



1-Ethyl-3-hydroxy-3-(2-hydroxy-4,4-dimethyl-6-oxocyclohex-1-en-1-yl)indolin-2-one (3f).

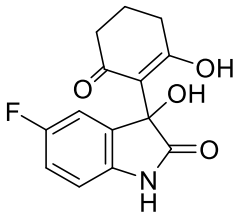
Yield 0.804 g (85%), mp: 131-132 °C. ^{1}H NMR (300 MHz, DMSO-*d*$_6$): δ 0.99 (s, 6H, 2 CH$_3$), 1.20 (t, ^3J = 7.0 Hz, 3H, CH$_3$), 1.89-2.50 (m, 2H, CH$_2$), 3.51-3.85 (m, 2H, CH$_2$), 6.90-7.05 (m,

2H, 2 CH Ar), 7.15 (d, ^{3}J = 7.1 Hz, 1H, CH Ar), 7.28 (t, ^{3}J = 7.1 Hz, 1H, CH Ar), 7.90-8.81 (br s, 1H, OH, exch.), 10.97-12.28 (br s, 1H, OH, exch.) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ 11.8, 27.5 (br s), 27.9, 31.7, 33.8, 45.8 (2C, br s), 77.4, 108.3, 121.7, 122.9, 124.5, 129.2, 131.7, 138.2, 143.1, 174.3 ppm. MS (*m/z* relative intensity %): 315 [M^+] (27), 270 (15), 254 (32), 226 (4), 175 (10), 140 (38), 118 (68), 83 (80), 56 (49), 27 (65). IR (KBr) ν = 3379, 3215, 2958, 1703, 1612, 1562, 1472, 1365, 1268, 756 cm^{-1}. Anal. calcd for $C_{18}H_{21}NO_4$: C, 68.55; H, 6.71; N, 4.44%. Found: C, 68.49; H, 6.74; N, 4.41%.



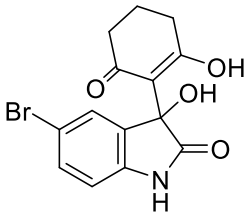
3-Hydroxy-3-(2-hydroxy-4,4-dimethyl-6-oxocyclohex-1-en-1-yl)-5-methoxyindolin-2-one (3g).

Yield 0.867 g (91%), mp: 161-162 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.96 (s, 6H, 2 CH_3), 1.79-2.52 (m, 2H, CH_2), 3.63 (s, 3H, OCH_3), 6.55-6.79 (m, 3H, 3 CH Ar), 9.97 (s, 1H, NH, exch.) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ 27.0 (br s), 27.4, 31.2, 43.5 (br s), 49.0 (br s), 54.9, 77.6, 109.3, 109.7, 109.9, 113.0, 124.4, 132.9, 135.3, 154.1, 175.7 ppm. MS (*m/z* relative intensity %): 317 [M^+] (2), 272 (10), 256 (3), 218 (1), 177 (24), 149 (50), 106 (78), 83 (60), 56 (46), 15 (100). IR (KBr) ν = 3258, 3053, 2959, 1702, 1626, 1588, 1487, 1333, 1293, 1024 cm^{-1}. Anal. calcd for $C_{17}H_{19}NO_5$: C, 64.34; H, 6.04; N, 4.41%. Found: C, 64.27; H, 6.12; N, 4.36%.



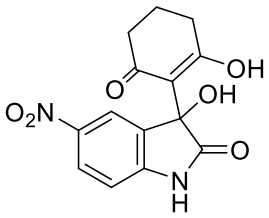
5-Fluoro-3-hydroxy-3-(2-hydroxy-6-oxocyclohex-1-en-1-yl)indolin-2-one (3h).

Yield 0.732 g (88%), mp: 210-211 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.74-1.92 (m, 2H, CH_2), 1.98-2.59 (m, 4H, 2 CH_2), 6.68-6.80 (m, 1H, CH Ar), 6.87-7.09 (m, 2H, 2 CH Ar), 7.82-8.98 (br s, 1H, OH, exch.), 10.20 (s, 1H, NH), 10.95-12.30 (br s, 1H, OH, exch.) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ 20.2, 32.8 (br s, 2C), 78.0, 110.0 (d, $^{3}J_{C\text{-}F}$ = 7.3 Hz), 110.9 (d, $^{2}J_{C\text{-}F}$ = 23.0 Hz), 111.4, 113.4, 115.1 (d, $^{2}J_{C\text{-}F}$ = 23.0 Hz), 134.1 (d, $^{3}J_{C\text{-}F}$ = 7.3 Hz), 138.8, 157.8 (d, $^{1}J_{C\text{-}F}$ = 236.7 Hz), 176.5 ppm. MS (*m/z* relative intensity %): 277 [M^+] (3), 232 (18), 206 (4), 177 (3), 165 (41), 137 (74), 109 (44), 84 (39), 42 (100), 27 (35). IR (KBr) ν = 3135, 3089, 2947, 1701, 1590, 1483, 1366, 1267, 1197, 883 cm^{-1}. Anal. calcd for $C_{14}H_{12}FNO_4$: C, 60.65; H, 4.36; N, 5.05%. Found: C, 60.57; H, 4.40; N, 4.98%.



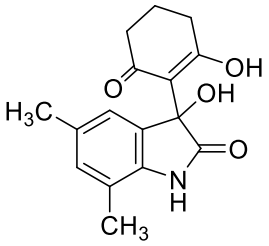
5-Bromo-3-hydroxy-3-(2-hydroxy-6-oxocyclohex-1-en-1-yl)indolin-2-one (3i).

Yield 0.975 g (96%), mp: 140-141 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.71-1.94 (m, 2H, CH_2), 2.12-2.67 (m, 4H, 2 CH_2), 6.74 (d, ^{3}J = 7.8 Hz, 1H, CH Ar), 7.20 (s, 1H, CH Ar), 7.35 (d, ^{3}J = 7.8 Hz, 1H, CH Ar), 10.34 (s, 1H, NH, exch.) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ 19.7, 32.1 (br s, 2C), 77.1, 110.9, 112.3, 113.8, 125.5, 126.4, 131.2, 134.2, 141.3, 175.5 ppm. MS (*m/z* relative intensity %): 294 [^{81}Br, M – CHNO – 2H]$^{+}$ (1), 292 [^{79}Br, M – CHNO – 2H]$^{+}$ (1), 277 (^{81}Br, 1), 275 (^{79}Br, 1), 237 (^{81}Br, 1), 235 (^{79}Br, 1), 199 (^{81}Br, 64), 197 (^{79}Br, 54), 142 (5), 112 (33), 84 (58), 63 (41), 42 (100), 27 (26). IR (KBr) ν = 3491, 3204, 2959, 1748, 1701, 1602, 1476, 1398, 1184, 1816 cm^{-1}. Anal. calcd for $C_{14}H_{12}BrNO_4$: C, 49.73; H, 3.58; N, 4.14%. Found: C, 49.68; H, 3.65; N, 4.08%.



3-Hydroxy-3-(2-hydroxy-6-oxocyclohex-1-en-1-yl)-5-nitroindolin-2-one (3j).

Yield 0.885 g (97%), mp: 143-144 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.74-1.92 (m, 2H, CH_2), 2.16-2.51 (m, 4H, 2 CH_2), 6.96 (d, ^{3}J = 8.6 Hz, 1H, CH Ar), 7.89 (d, ^{4}J = 2.2 Hz, 1H, CH Ar), 8.15 (dd, ^{3}J = 8.6 Hz, ^{4}J = 2.2 Hz, 1H, CH Ar), 10.94 (s, 1H, NH, exch.) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ 19.6, 32.1 (br s, 2C), 76.5, 109.0, 110.5, 118.3, 126.1, 131.8, 141.4, 148.5, 148.7, 176.3 ppm. MS (*m/z* relative intensity %): 258 [M – NO_2 – H]$^{+}$ (1), 230 (1), 192 (17), 164 (50), 148 (2), 134 (7), 90 (38), 84 (48), 42 (100), 30 (52). IR (KBr) ν = 3463, 3014, 2865, 1731, 1624, 1603, 1566, 1519, 1341, 757 cm^{-1}. Anal. calcd for $C_{14}H_{12}N_2O_6$: C, 55.27; H, 3.98; N, 9.21%. Found: C, 55.21; H, 4.04; N, 9.15%.

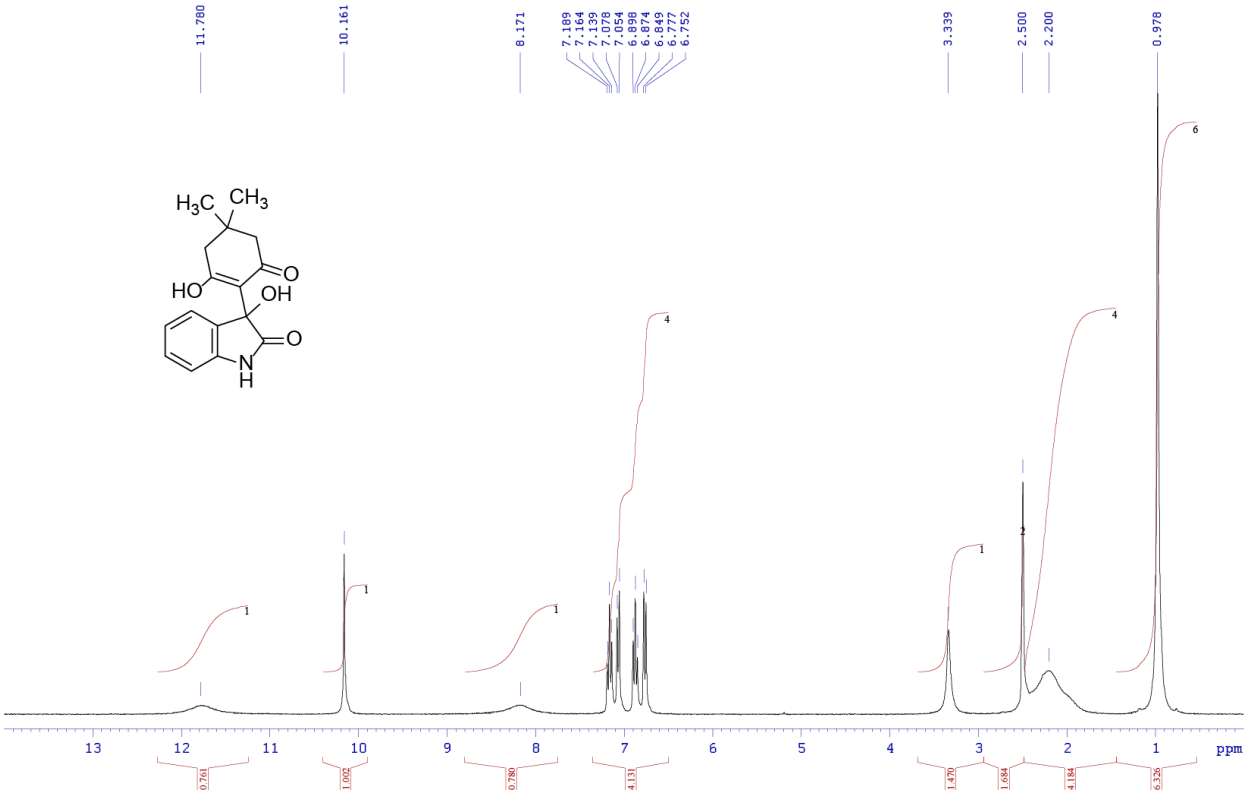


3-Hydroxy-3-(2-hydroxy-6-oxocyclohex-1-en-1-yl)-5,7-dimethylindolin-2-one (3k).

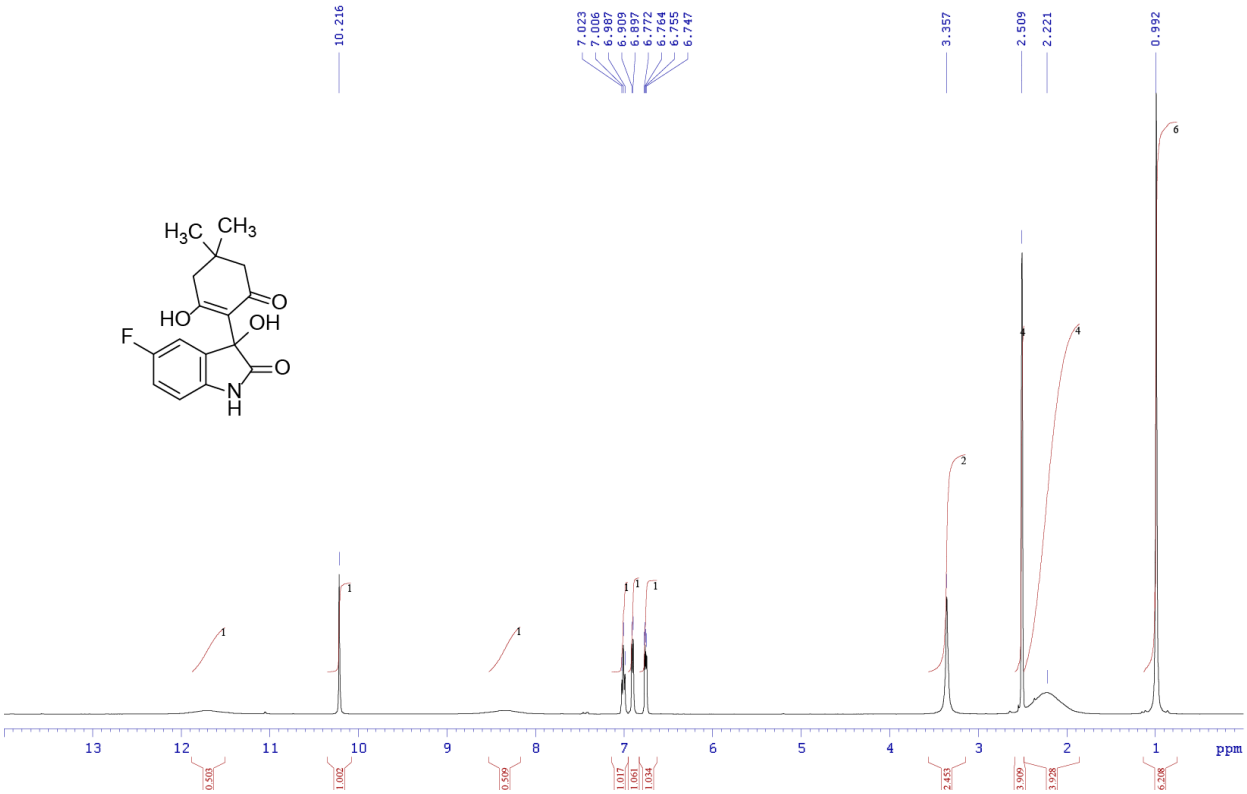
Yield 0.732 g (85%), mp: 259-260 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.77-1.93 (m, 2H, CH_2), 2.17 (s, 3H, CH_3), 2.19 (s, 3H, CH_3), 2.05-2.58 (m, 4H, 2 CH_2), 6.75 (s, 1H, CH Ar), 6.82 (s, 1H, CH Ar), 7.46-9.11 (br s, 1H, OH, exch.), 10.10 (s, 1H, NH), 10.82-12.40 (br s, 1H, OH, exch.) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ 16.2, 20.3, 20.5, 31.7 (br s), 36.7 (br s), 78.2, 103.8, 112.1, 121.2, 122.1, 129.9, 130.8, 138.7, 140.1, 176.8 ppm. MS (*m/z* relative intensity %): 287 [M^{+}] (8), 242 (35), 216 (5), 187 (3), 175 (44), 119 (76), 84 (46), 58 (100), 55 (30), 42 (100). IR (KBr) ν = 3250, 3102, 2921, 1695, 1629, 1594, 1486, 1308, 1200, 866 cm^{-1}. Anal. calcd for $C_{16}H_{17}NO_4$: C, 66.89; H, 5.96; N, 4.88%. Found: C, 66.81; H, 5.99; N, 4.79%.

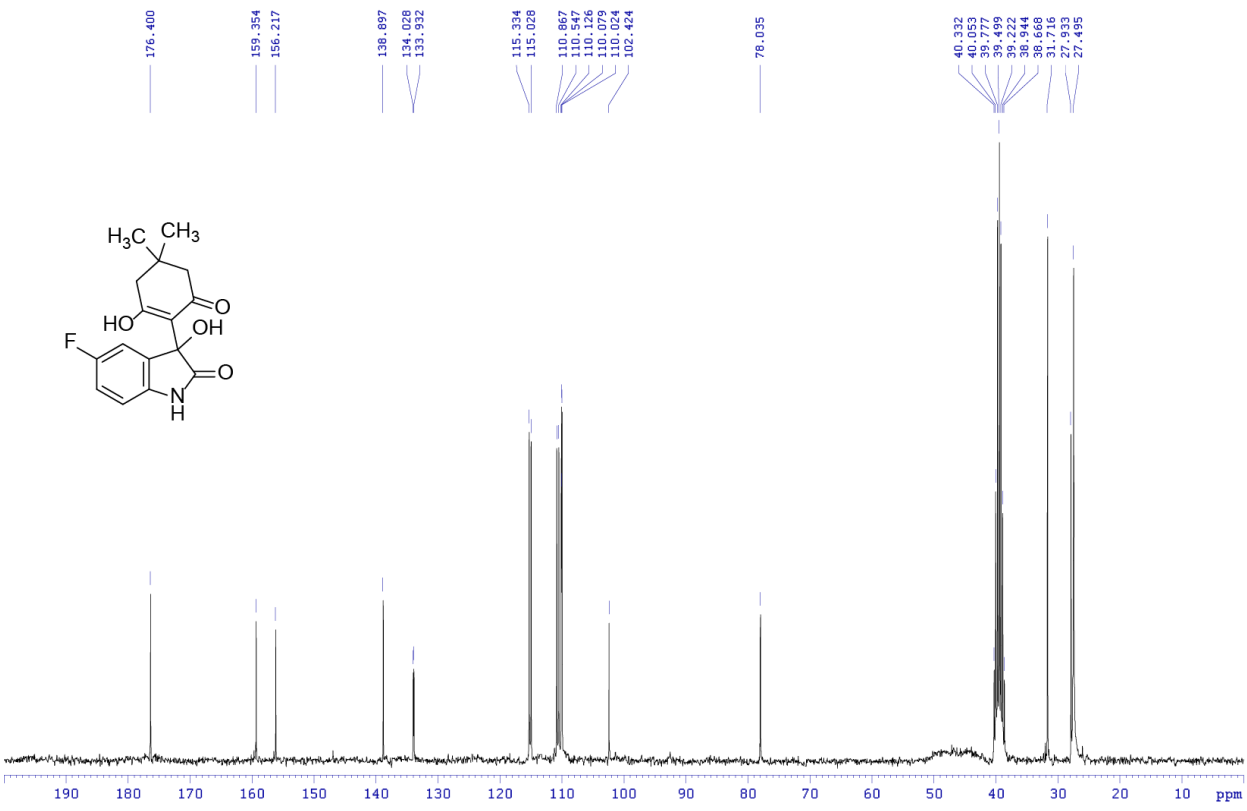
^{1}H and ^{13}C NMR spectra

3-Hydroxy-3-(2-hydroxy-4,4-dimethyl-6-oxocyclohex-1-en-1-yl)indolin-2-one (3a).

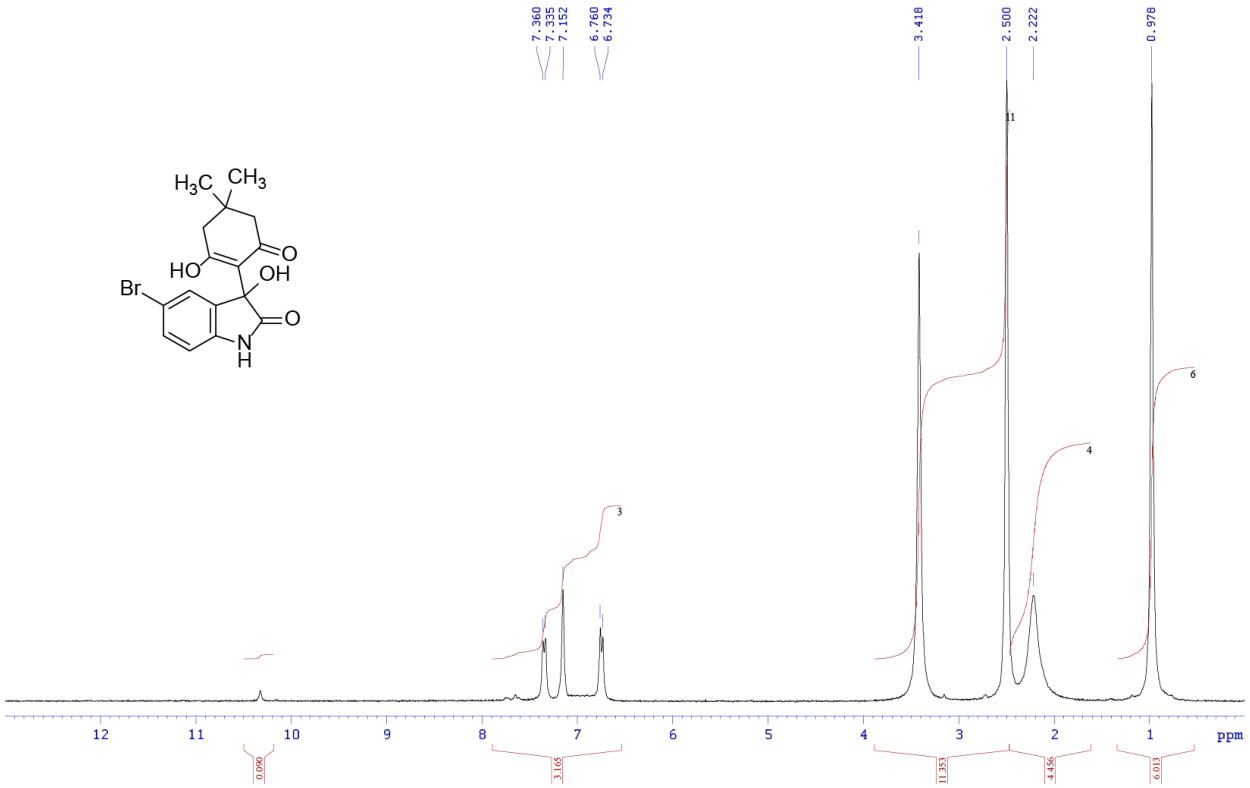


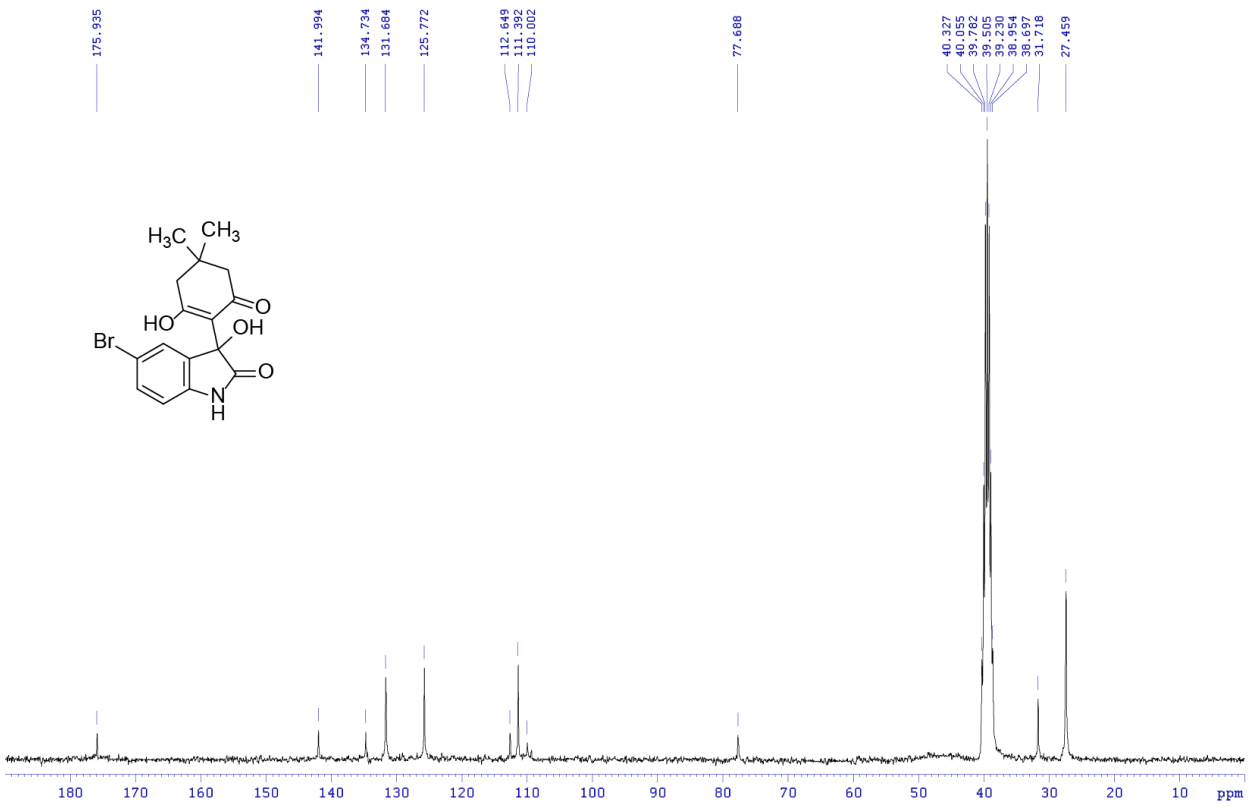
5-Fluoro-3-hydroxy-3-(2-hydroxy-4,4-dimethyl-6-oxocyclohex-1-en-1-yl)indolin-2-one (3b).



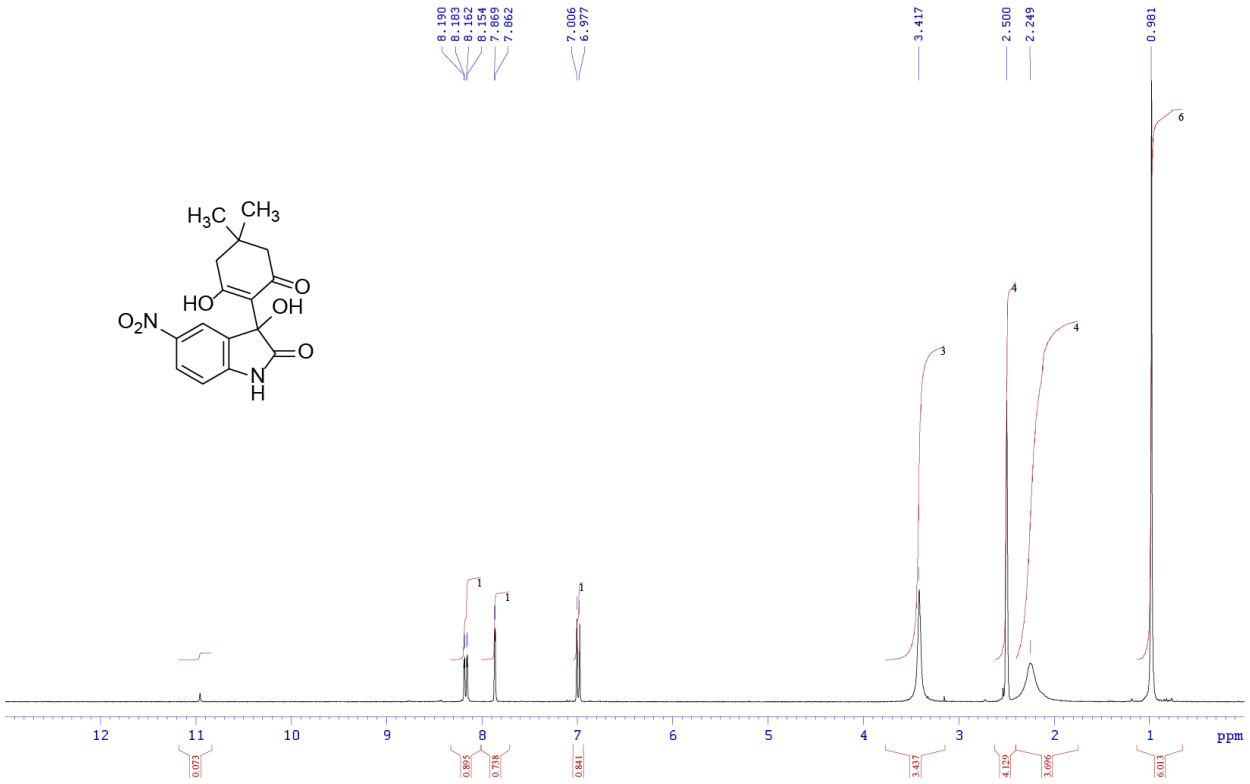


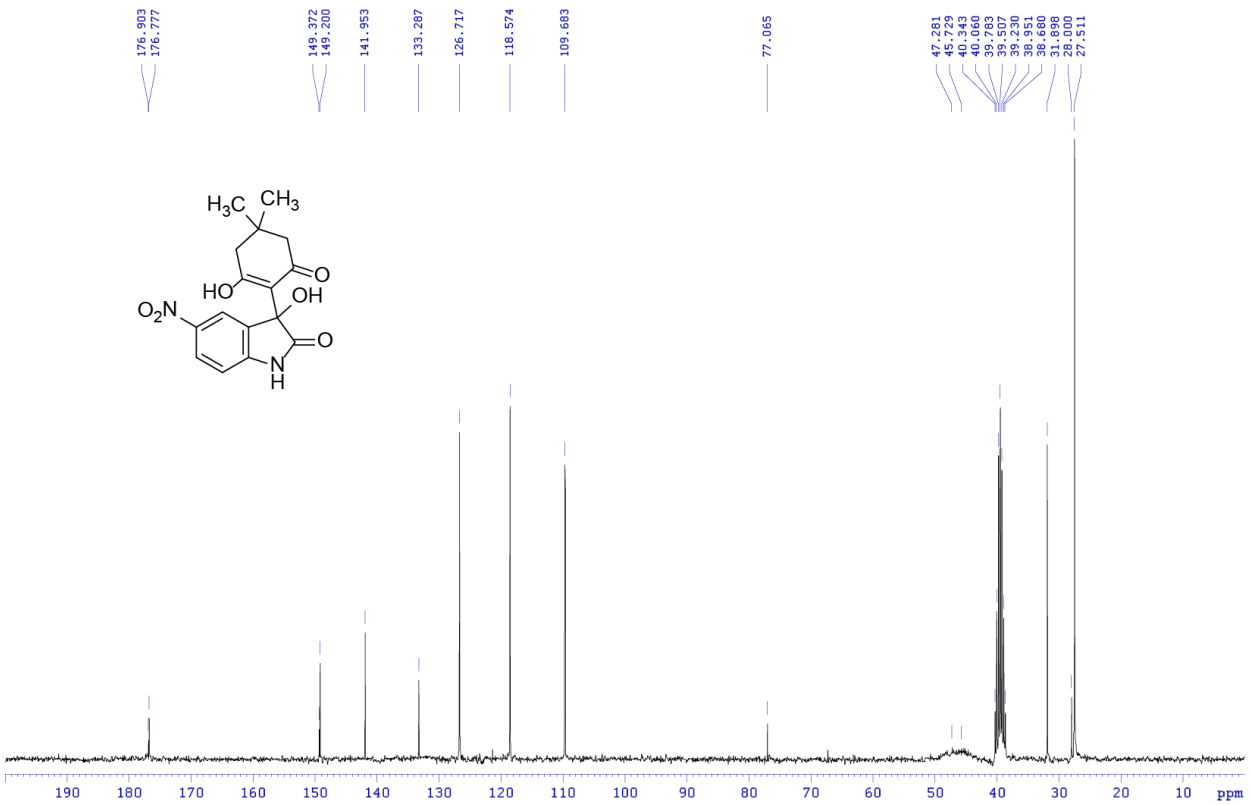
5-Bromo-3-hydroxy-3-(2-hydroxy-4,4-dimethyl-6-oxocyclohex-1-en-1-yl)indolin-2-one (3c).



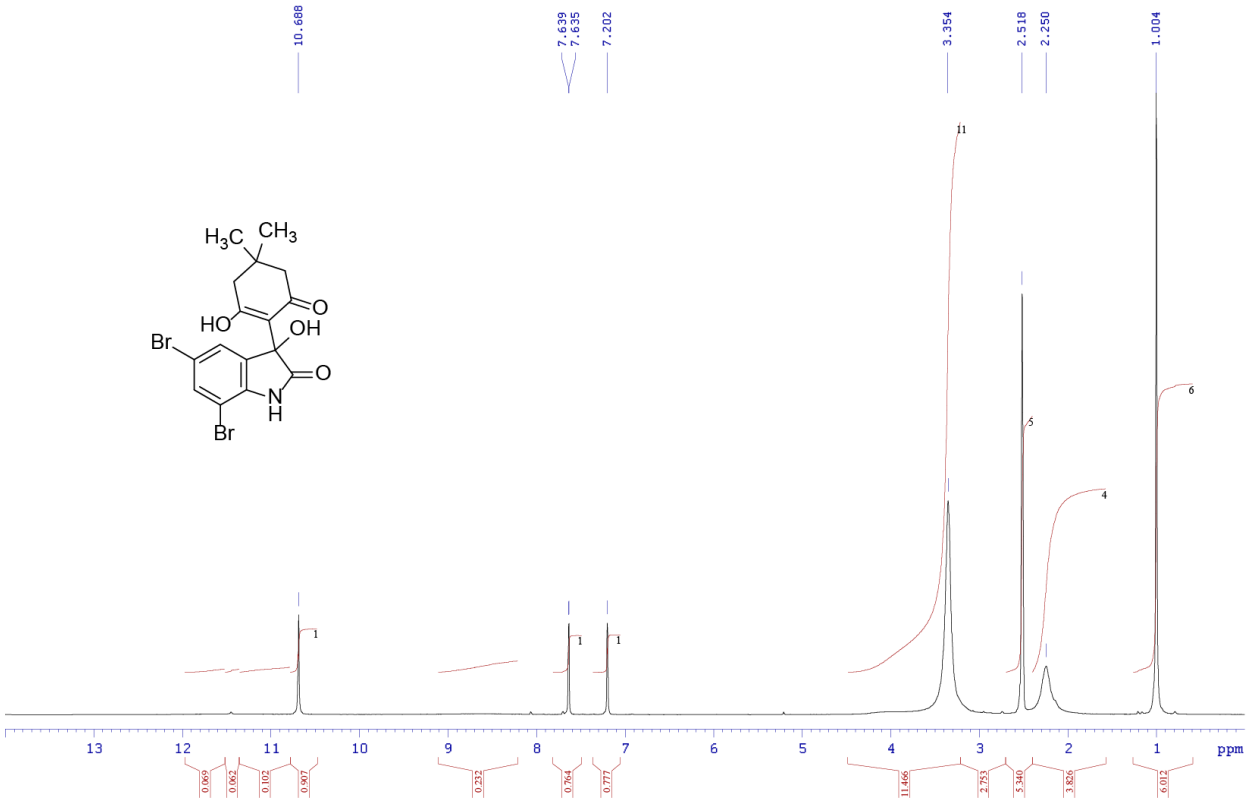


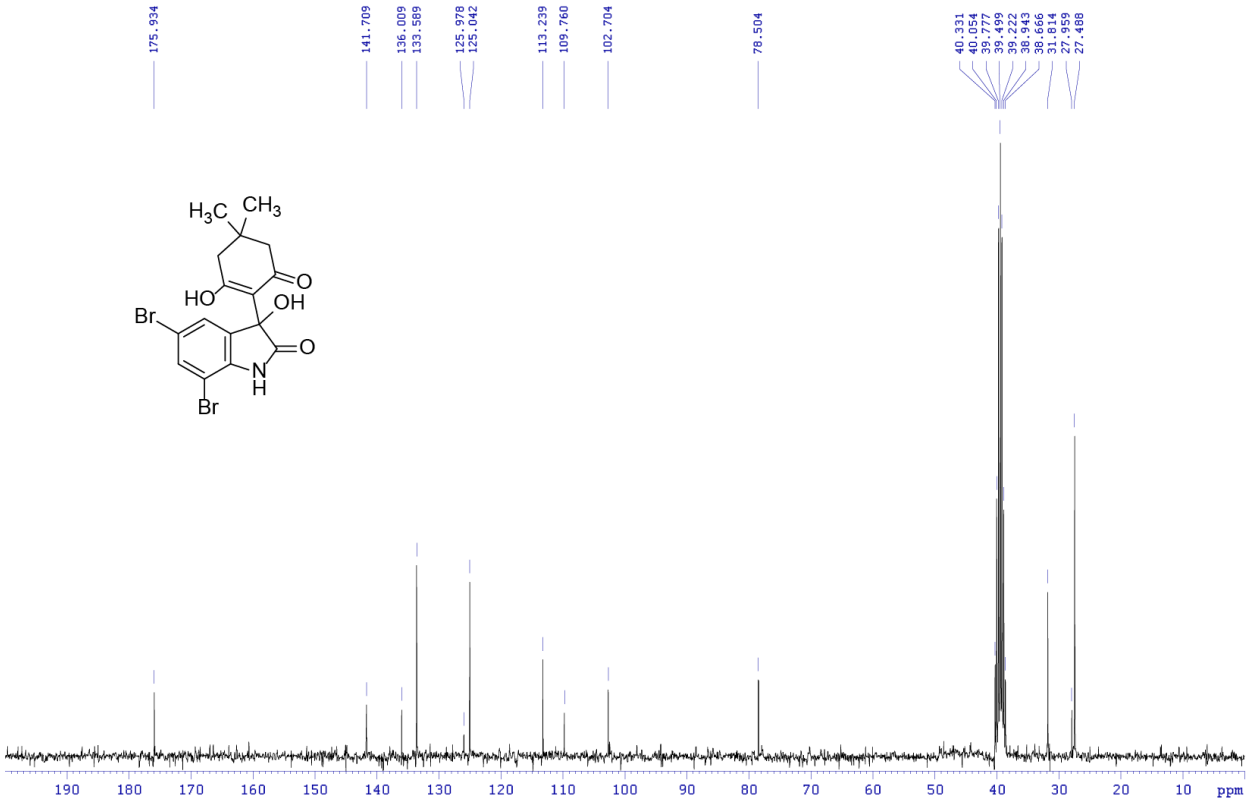
3-Hydroxy-3-(2-hydroxy-4,4-dimethyl-6-oxocyclohex-1-en-1-yl)-5-nitroindolin-2-one (3d).



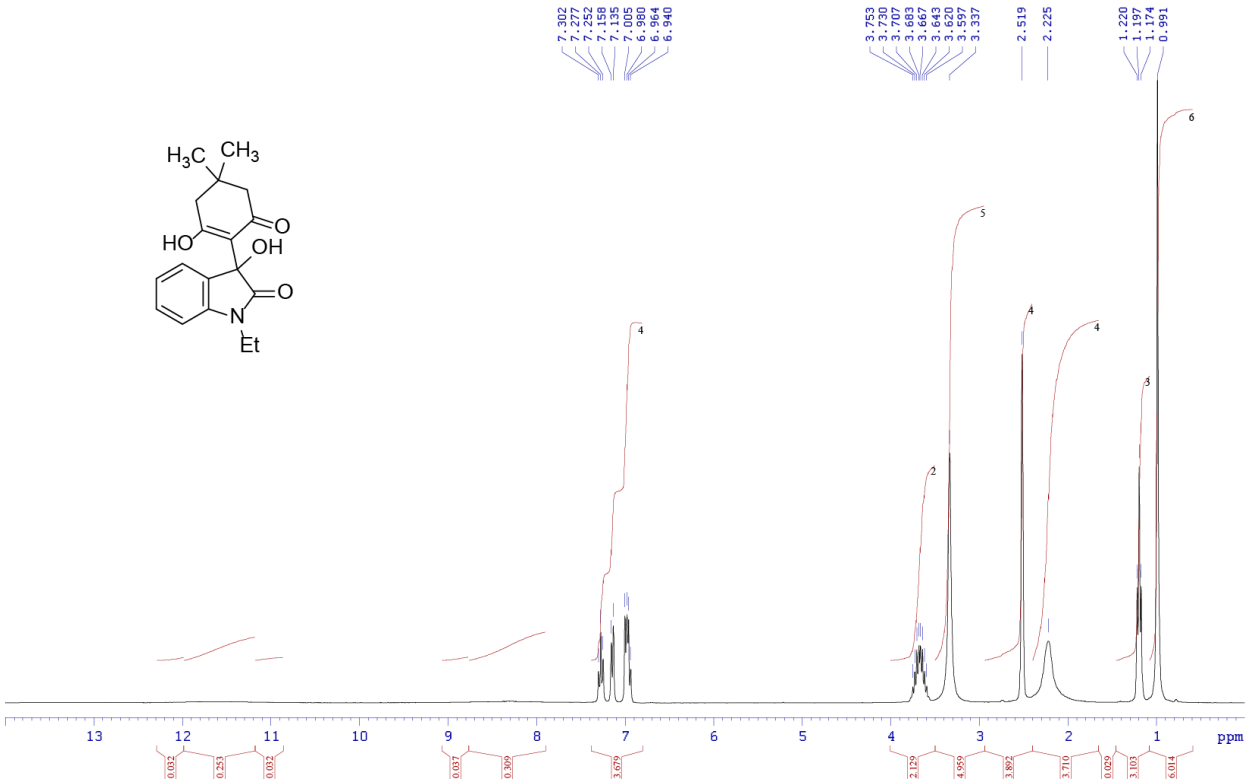


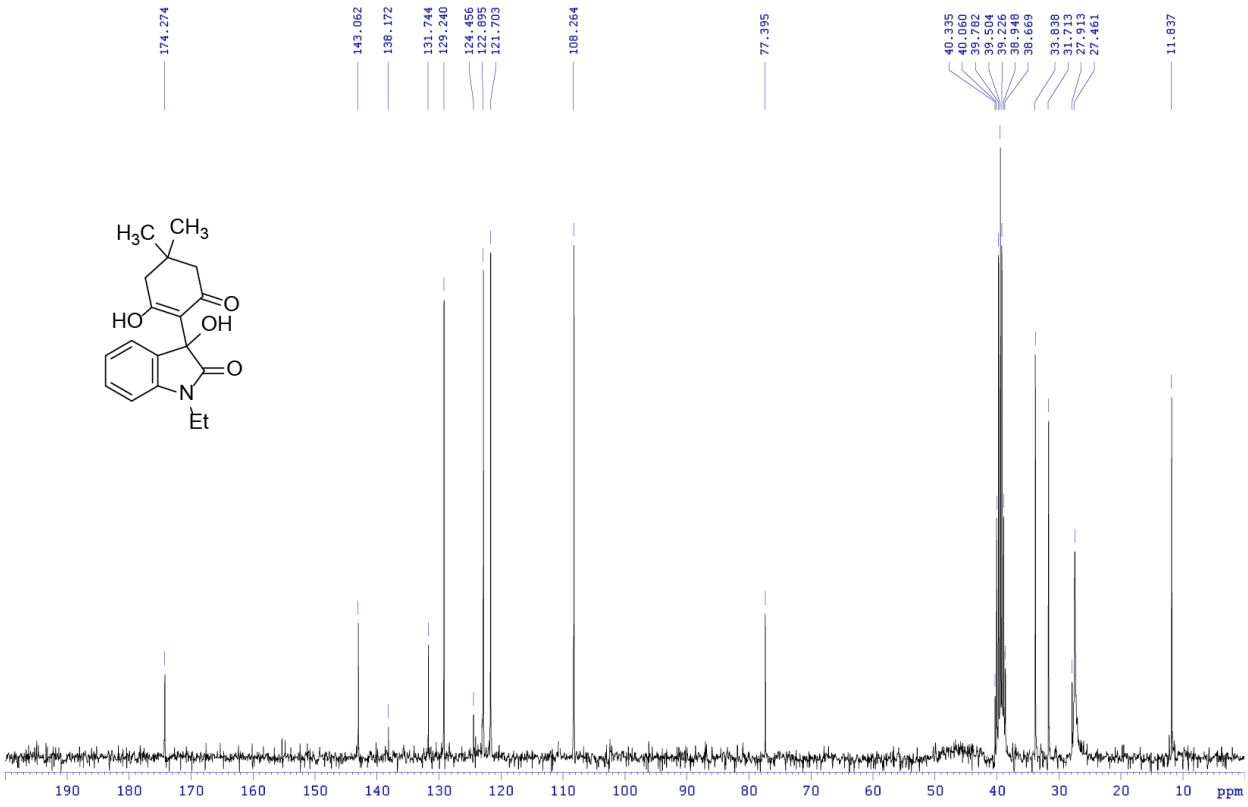
5,7-Dibromo-3-hydroxy-3-(2-hydroxy-4,4-dimethyl-6-oxocyclohex-1-en-1-yl)indolin-2-one (3e).



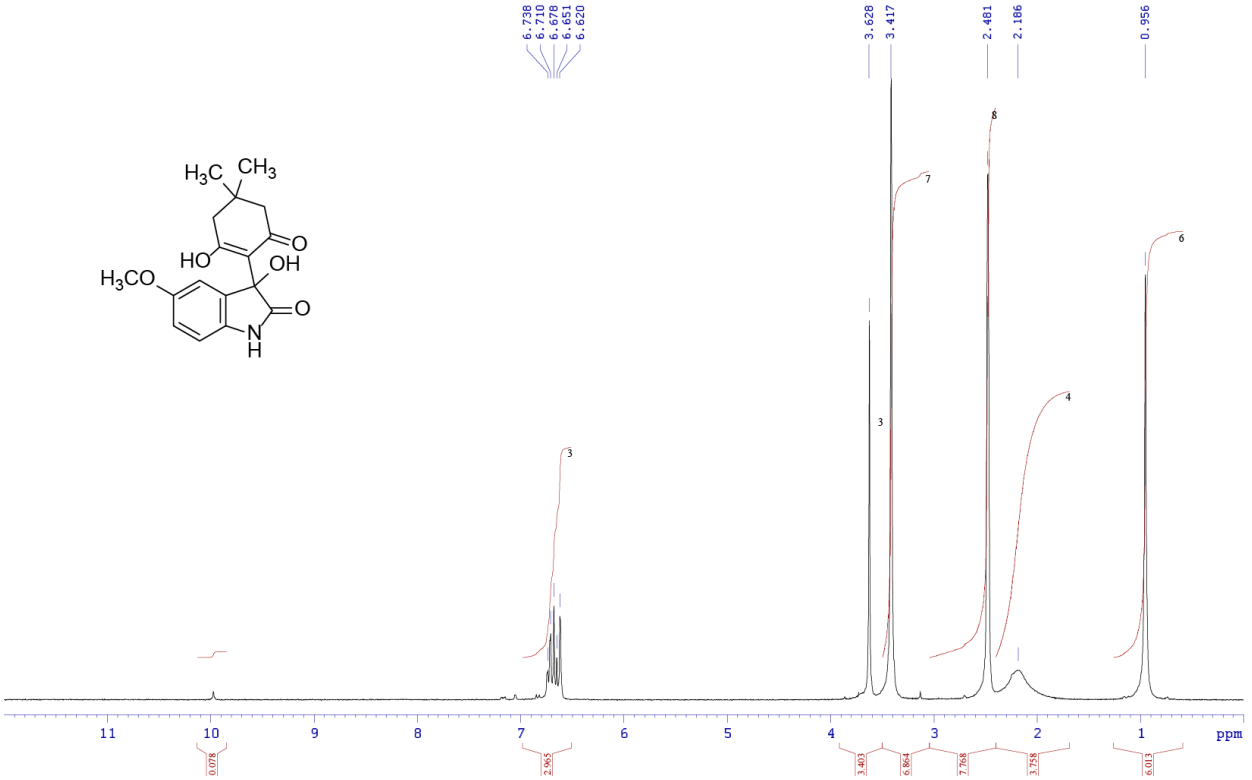


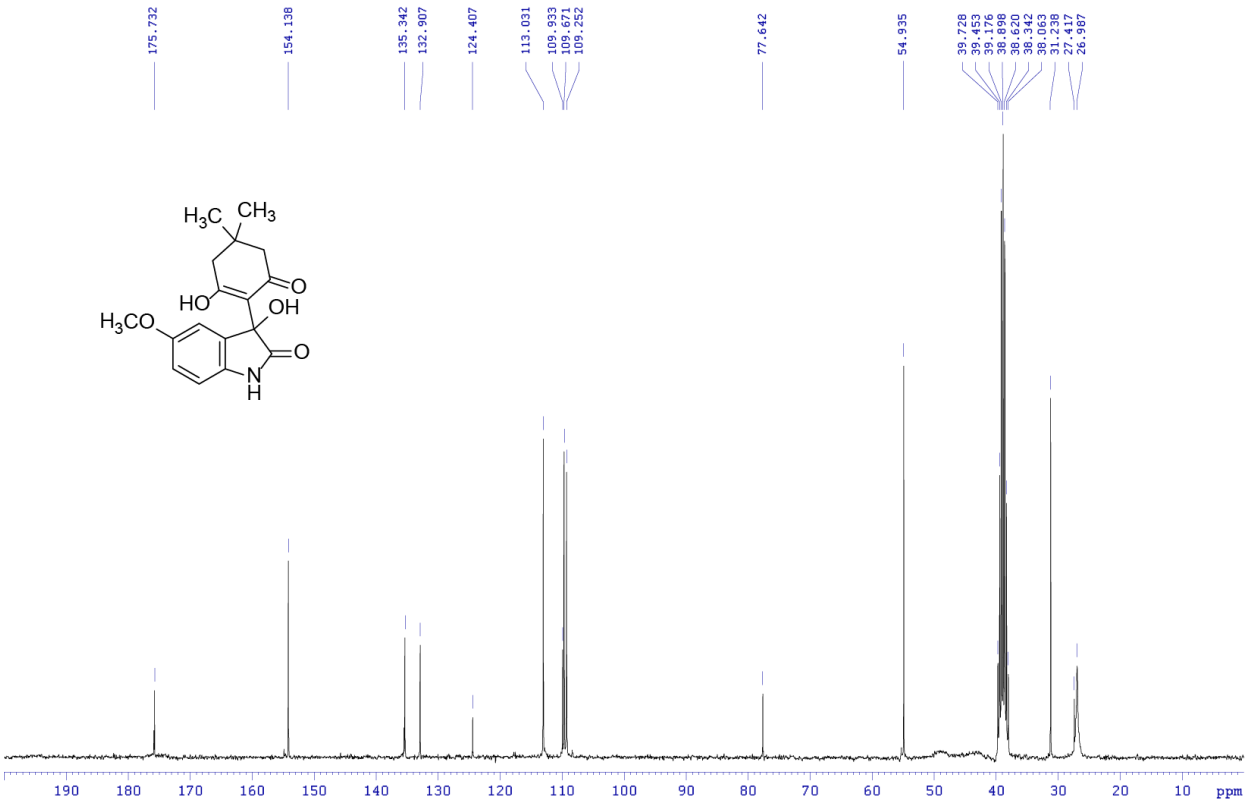
1-Ethyl-3-hydroxy-3-(2-hydroxy-4,4-dimethyl-6-oxocyclohex-1-en-1-yl)indolin-2-one (3f).



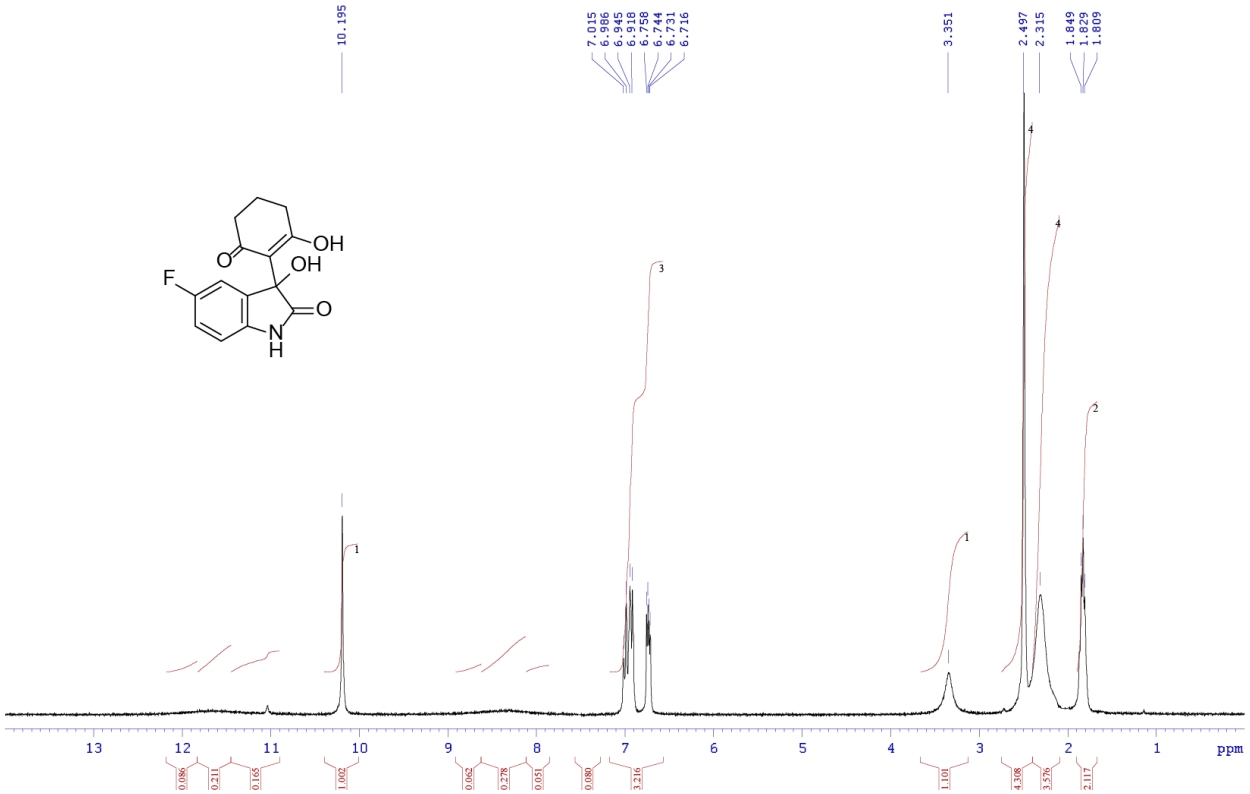


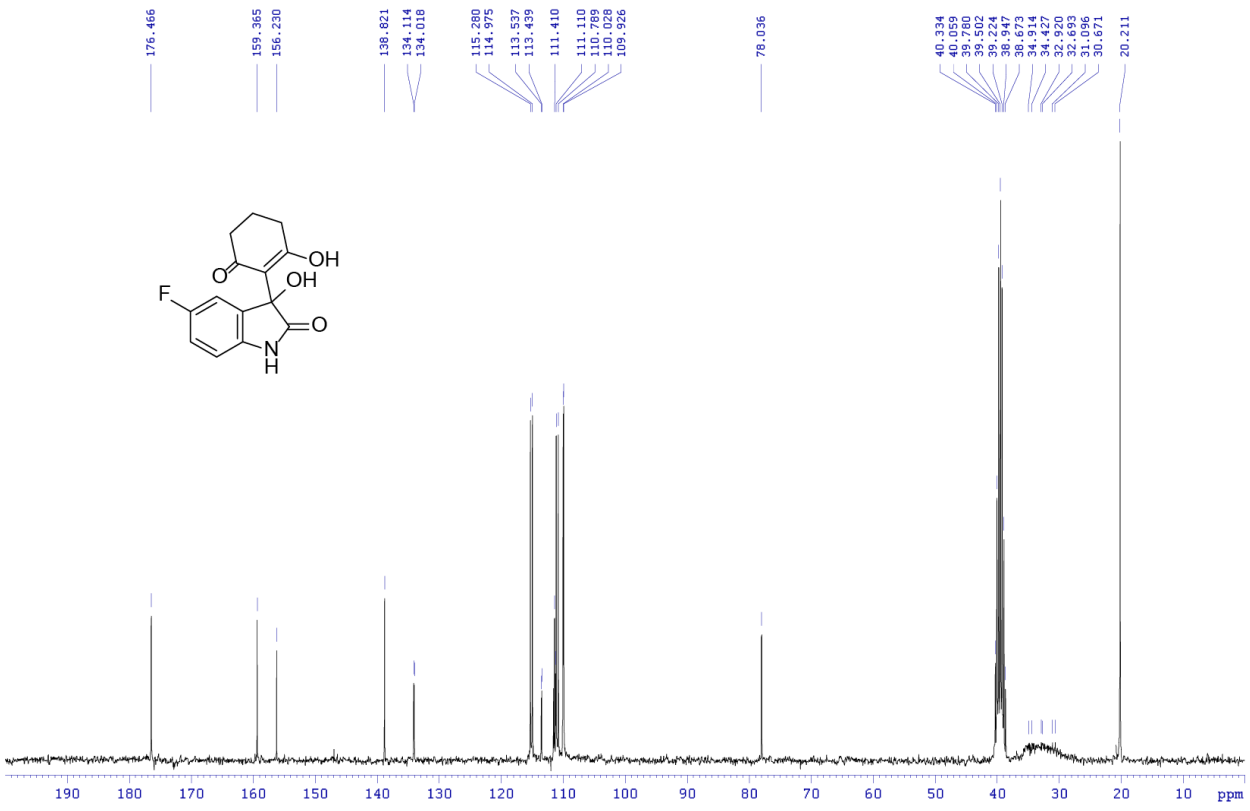
3-Hydroxy-3-(2-hydroxy-4,4-dimethyl-6-oxocyclohex-1-en-1-yl)-5-methoxyindolin-2-one (3g).



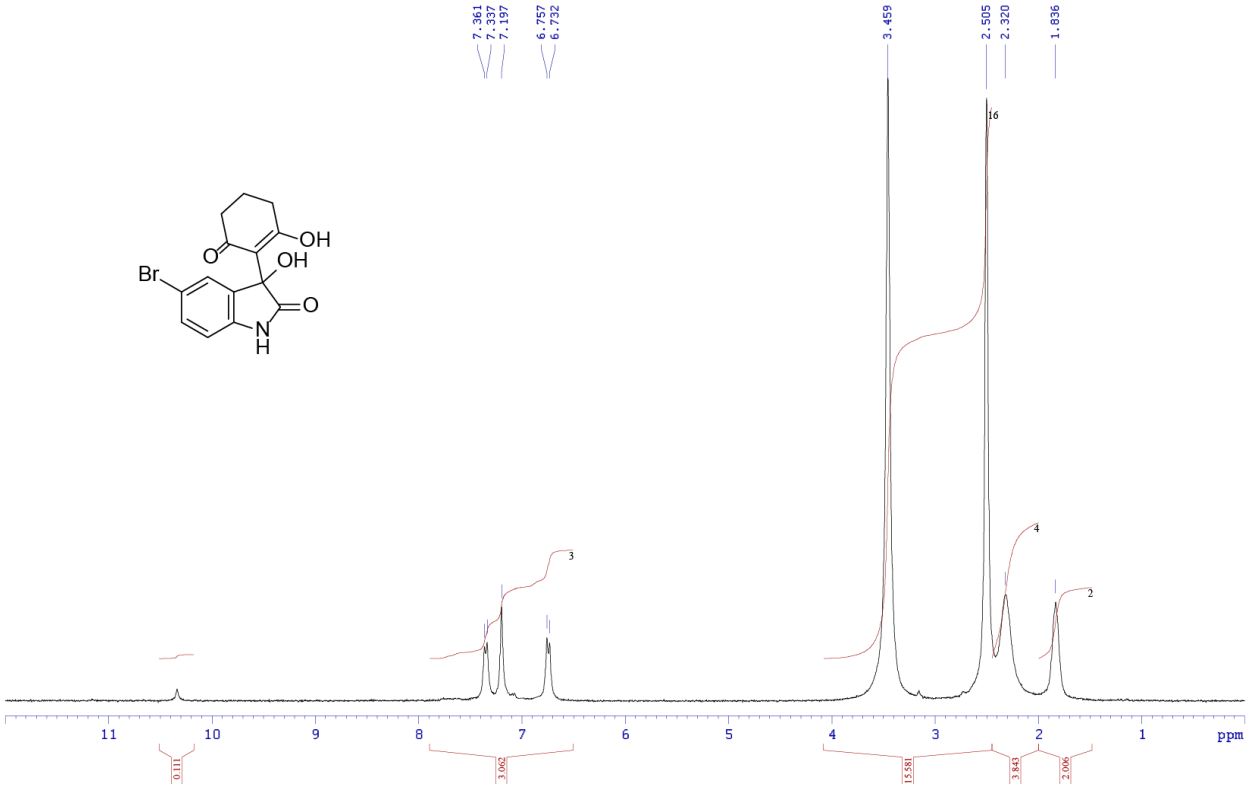


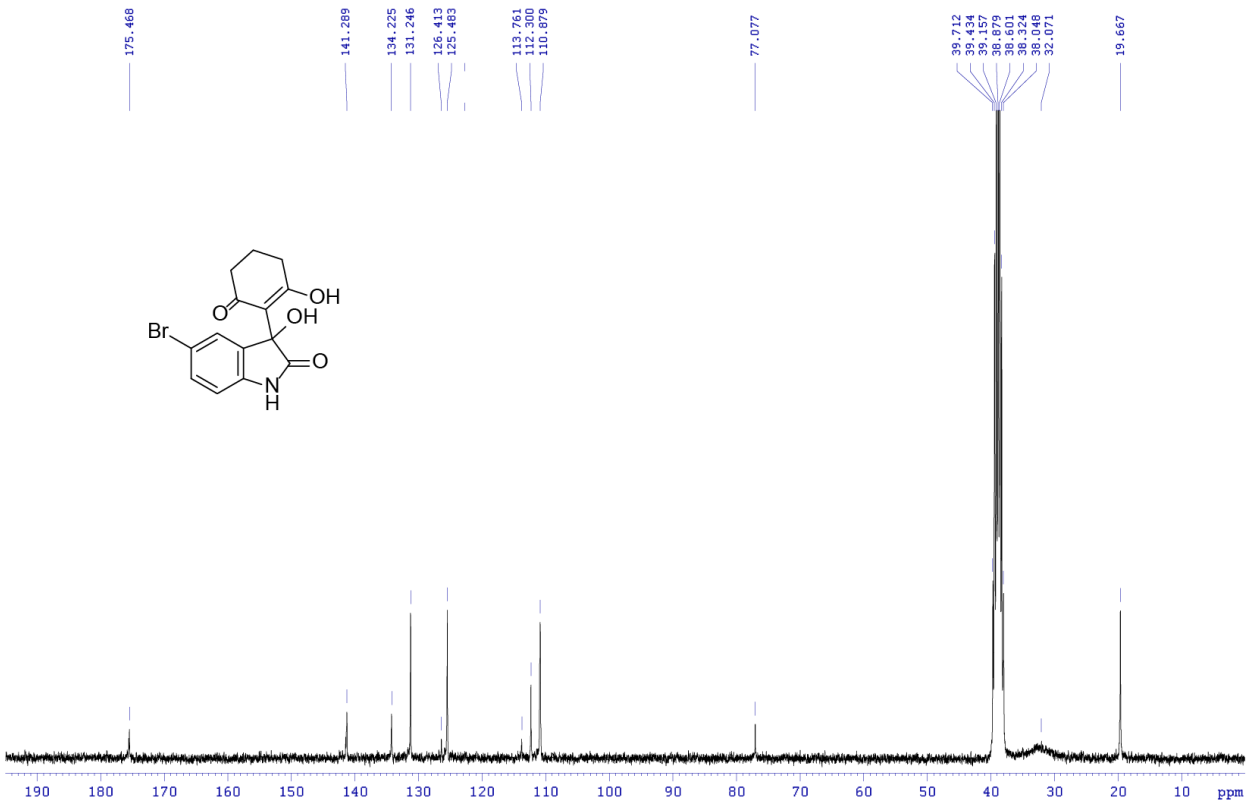
5-Fluoro-3-hydroxy-3-(2-hydroxy-6-oxocyclohex-1-en-1-yl)indolin-2-one (3h).



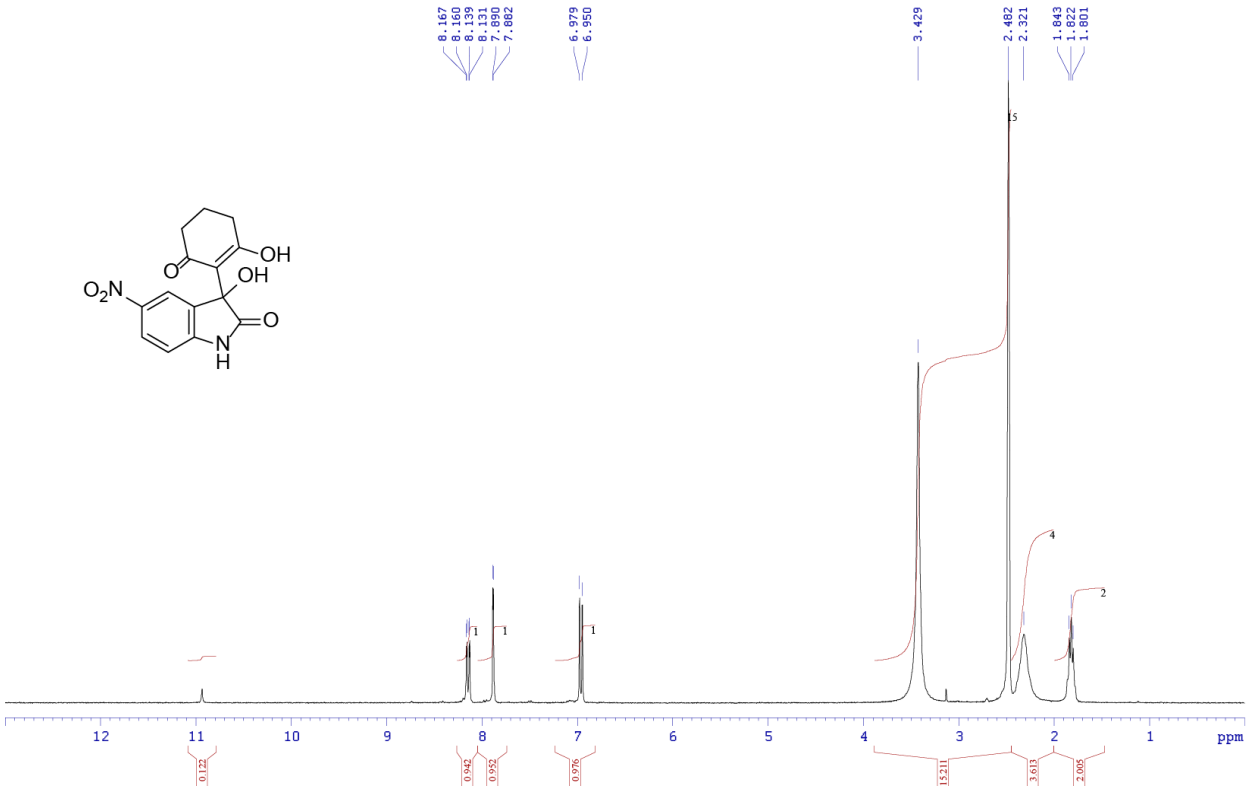


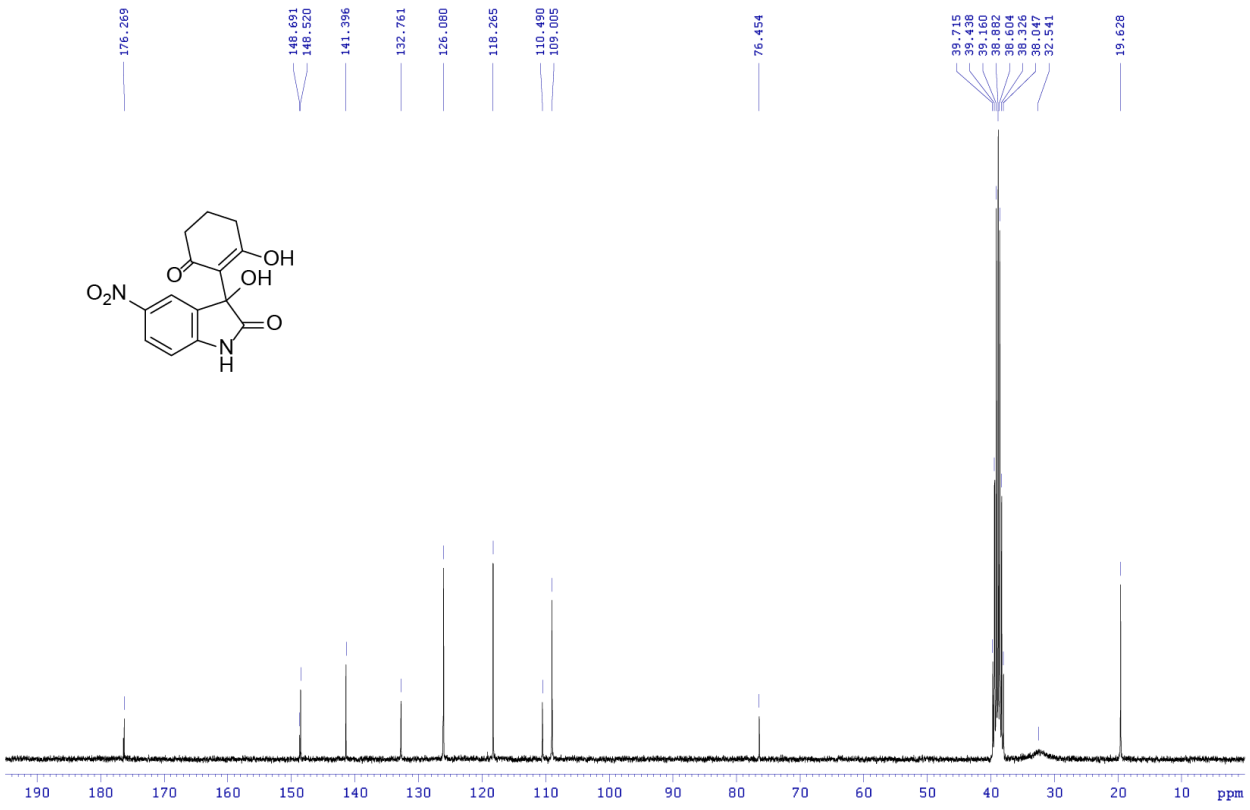
5-Bromo-3-hydroxy-3-(2-hydroxy-6-oxocyclohex-1-en-1-yl)indolin-2-one (3i).



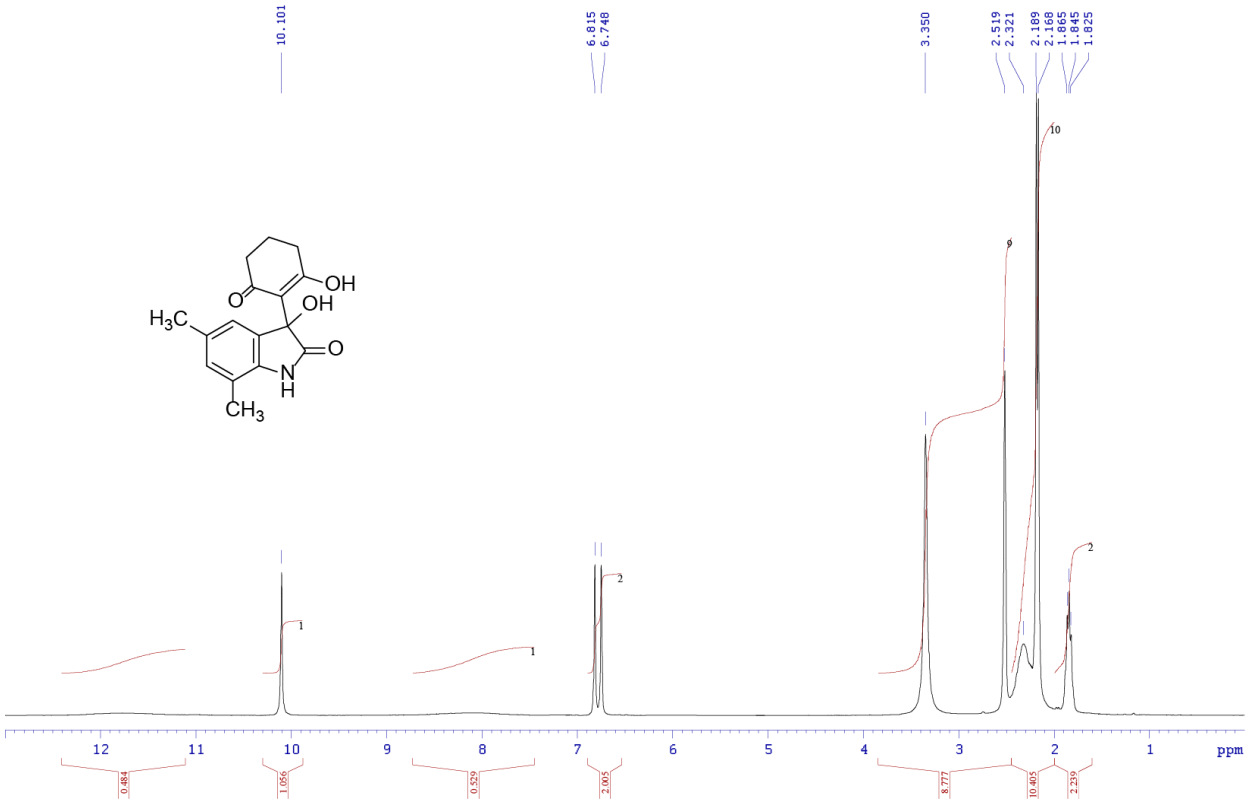


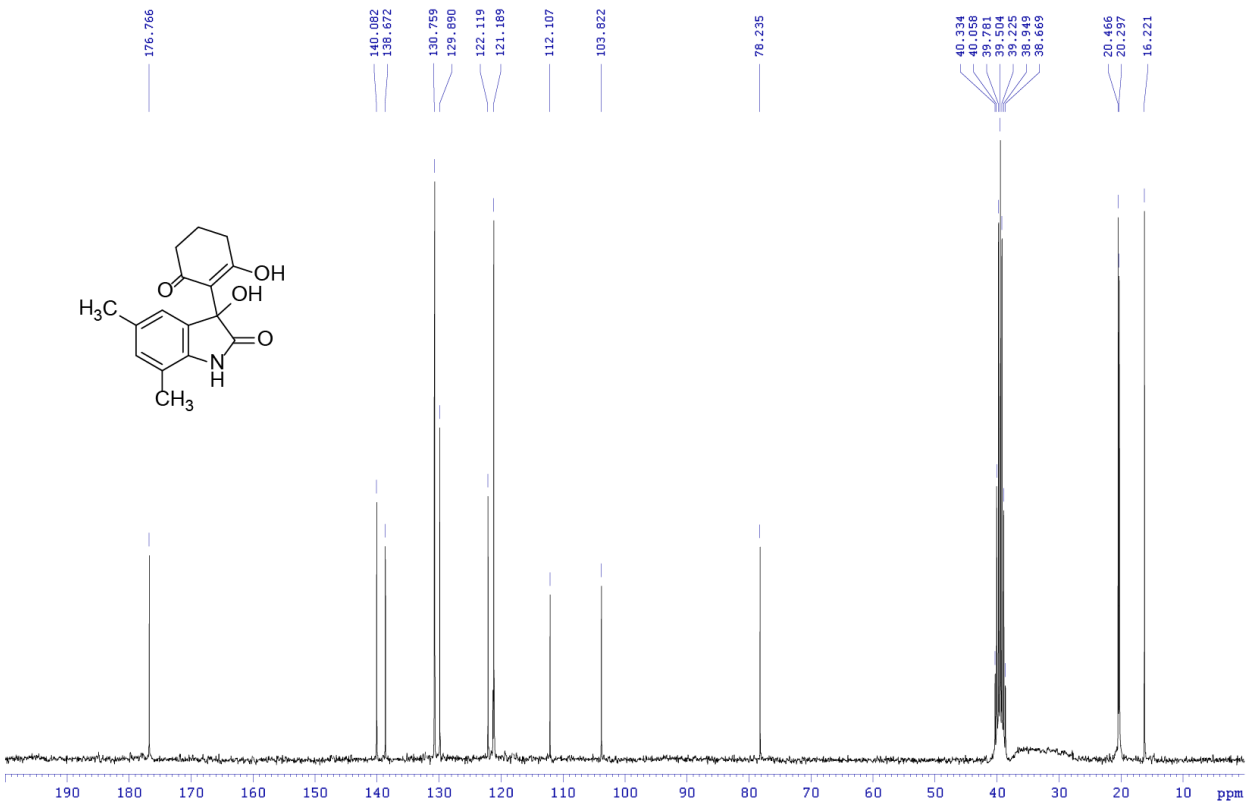
3-Hydroxy-3-(2-hydroxy-6-oxocyclohex-1-en-1-yl)-5-nitroindolin-2-one (3j).





3-Hydroxy-3-(2-hydroxy-6-oxocyclohex-1-en-1-yl)-5,7-dimethylindolin-2-one (3k).





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