Supporting Information

C(3)-Arylisoindolinones: A PTSA-mediated access and improved synthesis of (±)-Nuevamine

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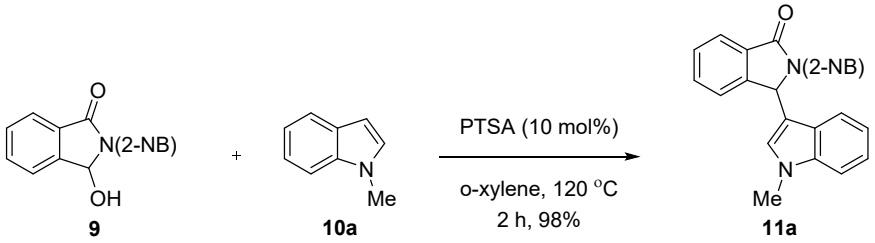
1. Experimental section

General Experimental Methods: All reactions were carried out in oven-dried glassware with magnetic stirring. All solvents were purified and dried according to standard methods prior to use.[1] The reactions were monitored by TLC using hexane (60-80 °C boiling mixture)/ ethyl acetate mixture as eluent. Column chromatography was performed on silica gel (100-200 mesh) using increasing percentages of ethyl acetate in hexanes. ^{1}H NMR (400 MHz), ^{13}C NMR (100 MHz), and DEPT-135 spectra were recorded for $CDCl_3$, $CDCl_3/CCl_4$ (1/1), or DMSO-d_6 solutions on a Bruker Avance 400 MHz spectrometer with TMS as internal standard. Coupling constants *J* are given in Hz. Data for ^{1}H NMR and ^{13}C NMR are reported as follows: chemical shift (δ, ppm) and multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, and m = multiplet). High-resolution mass spectra were recorded on the (QTOF) mass spectrometer instruments. The X-ray diffraction measurements were carried out at 298 K on a diffractometer equipped with a graphite monochromator and a Mo Kα fine-focus sealed tube (λ = 0.71073 Å). IR spectra were recorded as KBr pellets on a FT-IR spectrometer. Light-mediated deprotection of the NB group to generate isoindolinones was carried out using a home-built reactor having four UV-LED (3 μW) lamps with an emission maximum at 370 nm. Melting points were recorded using a melting point apparatus and are uncorrected.

Synthesis of C(3)-arylisoindolinones: **General procedure for the synthesis of 3-(1-methyl-1*H*-indol-3-yl)-2-(2-nitrobenzyl)-2,3-dihydro-1*H*-inden-1-one 11a**:



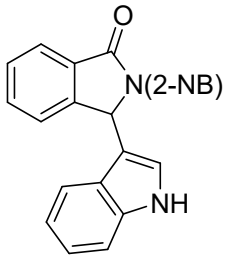
An oven-dried round bottom flask connected to a reflux condenser was charged with 3-hydroxy-2-(2-nitrobenzyl)isoindolin-1-one **9** (100 mg, 0.35 mmol), *N*-methylindole **10a** (46 mg, 0.35 mmol) and *p*-toluenesulfonic acid (6 mg, 0.03 mmol). To this 5 mL of *o*-xylene was added. The round bottom flask was lowered into a preheated (120 °C) oil bath. The resulting reaction mixture was agitated by using a magnetic stirrer. Upon completion of the reaction (TLC, 2 h), the reaction mixture was cooled to rt and PTSA was quenched with solid $NaHCO_3$ (10 mg). The solvent was evaporated by using a rotary evaporator. The crude product was directly subjected to

column chromatography to give as 3-(1-methyl-1*H*-indol-3-yl)-2-(2-nitrobenzyl)-2,3-dihydro-1*H*-inden-1-one **11a** as yellow solid (137 mg, 98% yield); mp 178 °C; IR (KBr, cm^{-1}) 3070, 2938, 1692, 1612, 1578, 1524, 1472, 1338, 1301, 1257, 1183, 1154, 1132, 1067, 985, 860,739, 716, 512; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 – 7.98 (m, 1H), 7.83 (d, *J* = 8.0 Hz, 1H), 7.54 – 7.46 (m, 2H), 7.42 – 7.33 (m, 2H), 7.27 – 7.20 (m, 3H), 7.14 – 7.10 (m, 1H), 7.02 (s, 1H), 6.81 (t, *J* = 7.4 Hz, 1H), 6.58 (s, 1H), 5.69 (s, 1H), 5.24 (d, *J* = 16.8 Hz, 1H), 4.68 (d, *J* = 16.8 Hz, 1H), 3.73 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.9 (C), 148.4 (C), 146.1 (C), 137.7 (C), 133.3 (CH), 133.1 (C), 132.2 (CH), 131.5 (C), 130.1 (CH), 129.5 (C), 128.5 (CH), 127.8 (CH), 125.5 (C), 124.4 (CH), 123.8 (CH), 123.5 (CH), 122.3 (CH), 119.7 (CH), 119.0 (CH), 109.6 (CH), 108.4 (CH), 58.8 (CH), 40.8 (CH_2), 32.9 (CH_3); HRMS (ESI) calcd for $C_{24}H_{20}N_3O_3$ (M + H) 398.1505, found 398.1498.

Synthesis of 3-(1-methyl-1*H*-indol-3-yl)-2-(2-nitrobenzyl)-2,3-dihydro-1*H*-inden-1-one 11a on the gram scale:

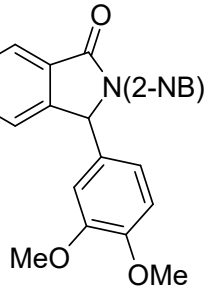
An oven-dried round bottom flask connected to a reflux condenser was charged with 3-hydroxy-2-(2-nitrobenzyl)isoindolin-1-one **9** (5.0 g, 17.60 mmol), *N*-methylindole **10a** (2.30 g, 17.60 mmol) and *p*-toluenesulfonic acid (0.30 g, 1.76 mmol). To this 100 mL of *o*-xylene was added. The round bottom flask was lowered into a preheated (120 °C) oil bath. The resulting reaction mixture was agitated by using a magnetic stirrer. Upon completion of the reaction (TLC, 3 h), the reaction mixture was cooled to rt and PTSA was quenched with solid $NaHCO_3$ (0.50 g). The solvent was evaporated by using a rotary evaporator. The crude product was directly subjected to column chromatography to give as 3-(1-methyl-1*H*-indol-3-yl)-2-(2-nitrobenzyl)-2,3-dihydro-1*H*-inden-1-one **11a** as yellow solid (6.50 g, 93% yield);. The analytical data is identical to that reported above for **11a**.

3-(1*H*-Indol-3-yl)-2-(2-nitrobenzyl)isoindolin-1-one 11b:



Yellow solid (129 mg, 95% yield); mp 215 ˚C; IR (KBr, cm^{-1}) 3315, 3034, 2922, 1688, 1595, 1521, 1423, 1340, 1306, 1250, 1205, 1125, 1079, 956, 904, 911, 857, 820, 789, 749, 724, 702, 645, 548, 506, 434; ^{1}H NMR (400 MHz, DMSO-d_6 + CCl_4; 1:1) δ 11.10 (s, 1H), 8.00 – 7.83 (m, 2H), 7.61 – 7.46 (m, 3H), 7.44-7.25 (m, 5H), 6.99 (dd, *J* = 11.6, 4.3 Hz, 1H), 6.74 (t, *J* = 7.5 Hz, 1H), 6.52 (s, 1H), 5.86 (s, 1H), 5.16 (d, *J* = 16.0 Hz, 1H), 4.45 (d, *J* = 16.0 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6 + CCl_4; 1:1) δ 167.5 (C), 147.8 (C), 146.3 (C), 136.8 (C), 133.2 (CH), 132.5 (C), 131.7 (CH), 131.0 (CH), 129.0 (CH), 128.0 (CH), 127.8 (CH), 125.9 (CH), 124.6 (C), 124.3 (CH), 123.4 (CH), 122.8 (CH), 121.2 (CH), 118.9 (CH), 117.7 (CH), 111.8 (CH), 108.3 (CH), 58.2 (CH), 40.1 (CH_2); HRMS (ESI) calcd for $C_{23}H_{18}N_3O_3$ (M + H) 384.1348, found 384.1371.

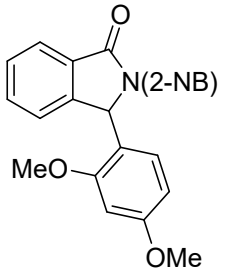
3-(3,4-Dimethoxyphenyl)-2-(2-nitrobenzyl)isoindolin-1-one 11c:



White solid (136 mg, 95% yield); mp 132 ˚C; IR (KBr, cm^{-1}) 2936, 2837, 1694, 1605, 1521, 1465, 1419, 1399, 1346, 1301, 1261, 1235, 1139, 1025, 857, 787, 729, 608; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 – 7.90 (m, 2H), 7.50 – 7.46 (m, 3H), 7.37 (dd, *J* = 15.3, 7.2 Hz, 2H), 7.21 – 7.16 (m, 1H), 6.76 (d, *J* = 8.2 Hz, 1H), 6.65 (dd, *J* = 8.2, 2.0 Hz, 1H), 6.32 (d, *J* = 2.0 Hz, 1H), 5.37 (s, 1H), 5.32 (s, 1H), 4.53 (d, *J* = 16.7 Hz, 1H), 3.82 (s, 3H), 3.67 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.1 (C), 149.6 (C), 149.5 (C), 148.4 (C), 146.4 (C), 133.5 (CH), 132.7 (C), 132.3 (CH), 130.8 (C), 130.0 (CH), 128.5 (CH), 128.29 (C), 128.26 (CH), 124.8 (CH), 123.8

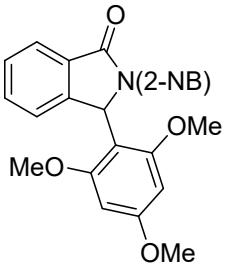
(CH), 123.3 (CH), 120.7 (CH), 111.3 (CH), 109.6 (CH), 64.9 (CH), 55.9 (CH_3), 55.9 (CH_3), 41.0 (CH_2); HRMS (ESI) calcd for $C_{23}H_{21}N_2O_5$ (M + H) 405.1450, found 405.1444.

3-(2,4-Dimethoxyphenyl)-2-(2-nitrobenzyl)isoindolin-1-one 11d:



White solid (139 mg, 97% yield); mp 126 ˚C; IR (KBr, cm^{-1}) 2939, 2840, 1690, 1610, 1525, 1461, 1417, 1398, 1344, 1304, 1262, 1233, 1138, 1027, 860; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (dd, *J* = 11.2, 5.1 Hz, 2H), 7.56 – 7.43 (m, 4H), 7.38 – 7.35 (m, 1H), 7.34 – 7.30 (m, 1H), 6.54 (s, 1H), 6.50-6.37 (m, 2H), 5.97 (s, 1H), 5.37 (d, *J* = 17.0 Hz, 1H), 4.53 (d, *J* = 17.1 Hz, 1H), 3.76 (s, 3H), 3.67 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.3 (CH), 161.0 (CH), 158.9 (CH), 148.3 (CH), 146.7 (CH), 133.4 (CH), 133.4 (CH), 132.0 (CH), 131.5 (CH), 129.3 (CH), 128.2 (CH), 127.7 (CH), 124.7 (CH), 123.76 (CH), 123.71 (CH), 123.4 (CH), 116.4 (CH), 105.3 (CH), 98.3 (CH), 77.2 (CH), 55.3 (CH_3), 55.3 (CH_3), 41.1 (CH_2); HRMS (ESI) calcd for $C_{23}H_{21}N_2O_5$ (M + H) 405.1450, found 405.1455.

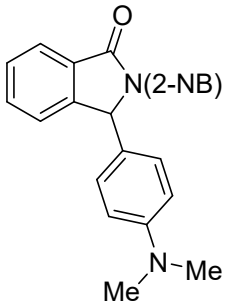
2-(2-Nitrobenzyl)-3-(2,4,6-trimethoxyphenyl)isoindolin-1-one 11e:



Brown solid (152 mg, 99% yield); mp 170 ˚C; IR (KBr, cm^{-1}) 3074, 2939, 2842, 1683, 1605, 1517, 1464, 1428, 1341, 1232, 1202, 1152, 1118, 1036, 948, 822, 785, 730, 548; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 – 7.83 (m, 2H), 7.48 – 7.38 (m, 4H), 7.30 (ddd, *J* = 8.6, 6.7, 2.1 Hz, 1H), 7.15 (ddd, *J* = 4.1, 2.1, 0.8 Hz, 1H), 6.06 – 5.99 (m, 2H), 5.82 (d, *J* = 2.2 Hz, 1H), 5.24 (d, *J* = 17.0 Hz, 1H), 4.54 (d, *J* = 17.0 Hz, 1H), 3.75 (s, 3H), 3.64 (s, 3H), 3.21 (s, 3H); ^{13}C NMR (100

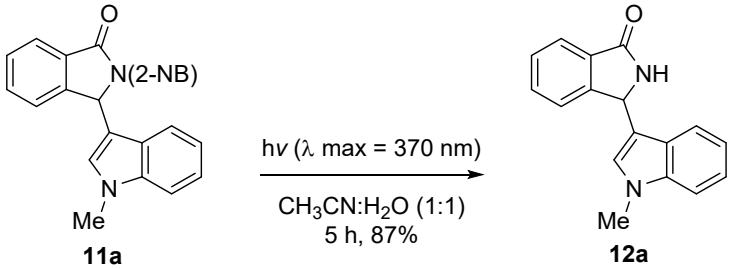
MHz, $CDCl_3$) δ 169.7 (C), 161.9 (C), 160.1 (C), 160.0 (C), 148.3 (C), 147.2 (C), 133.9 (C), 133.1 (CH), 132.3 (C), 131.3 (CH), 129.9 (CH), 127.5 (CH), 127.3 (CH), 124.4 (CH), 123.2 (CH), 121.9 (CH), 103.0 (C), 91.3 (CH), 90.2 (CH), 55.7 (CH), 55.5 (CH_3), 55.3 (CH_3), 55.2 (CH_3), 40.9 (CH_2); HRMS (ESI) calcd for $C_{24}H_{23}N_2O_6$ (M + H) 435.1556, found 435.1561.

3-(4-(Dimethylamino)phenyl)-2-(2-nitrobenzyl)isoindolin-1-one 11f:



White solid (120 mg, 88% yield); mp 153 °C; IR (KBr, cm^{-1}) 3077, 3031, 2896, 2808, 1677, 1612, 1571, 1522, 1475, 1450, 1404, 1336, 1219, 1172, 1120, 945, 862, 802, 755, 718, 616, 557; ^1H NMR (400 MHz, $CDCl_3$ + CCl_4; 1:1) δ 7.95 – 7.89 (m, 2H), 7.52 – 7.48 (m, 1H), 7.48 – 7.41 (m, 2H), 7.37 (ddd, *J* = 15.4, 8.2, 4.2 Hz, 2H), 7.19 – 7.14 (m, 1H), 6.81 (d, *J* = 8.7 Hz, 2H), 6.56 (d, *J* = 8.8 Hz, 2H), 5.32 (d, *J* = 16.9 Hz, 1H), 5.28 (s, 1H), 4.45 (d, *J*= 16.9 Hz, 1H), 2.92 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$ + CCl_4; 1:1) δ 168.9 (C), 150.8 (C), 148.6 (C), 147.1 (C), 133.4 (C), 133.4 (CH), 132.1 (C), 131.3 (CH), 130.2 (CH), 128.7 (CH), 128.3 (CH), 128.0 (CH), 124.9 (CH), 123.9 (C), 123.5 (CH), 123.0 (C), 112.8 (CH), 64.7 (CH), 40.9 (CH_2), 40.5 (CH_3); HRMS (ESI) calcd for $C_{23}H_{22}N_3O_3$ (M + H) 388.1661, found 388.1681.

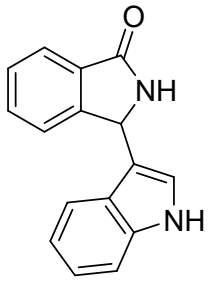
3-(1-Methyl-1*H*-indol-3-yl)isoindolin-1-one 12a:



A stirred solution of 3-(1-methyl-1*H*-indol-3-yl)-2-(2-nitrobenzyl)-2,3-dihydro-1*H*-inden-1-one **11a** (50 mg, 0.12 mmol) in CH_3CN:H_2O (1:1, 2 mL) in a Pyrex test tube. It was exposed to light irradiation with an emission maximum of 370 nm emitted by UV-LED (4 × 3

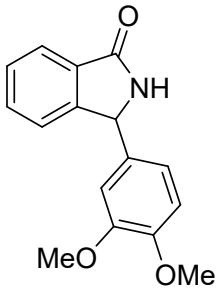
μW) lamps. After completion of deprotection, the solvent was removed under reduced pressure, and the resulting mixture was purified by column chromatography to give 3-(1-methyl-1*H*-indol-3-yl)isoindolin-1-one **12a** as yellow solid (29 mg, 87% yield); mp 203 °C; IR (KBr, cm^{-1}) 3197, 3072, 2920, 2852, 1710, 1612, 1549, 1469, 1419, 1335, 1130, 1049, 740, 698, 473; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.94 (s, 1H), 7.76 (dd, *J* = 5.6, 2.6 Hz, 1H), 7.56 – 7.44 (m, 2H), 7.39 (d, *J* = 7.4 Hz, 2H), 7.33 – 7.25 (m, 1H), 7.10 (t, *J* = 7.6 Hz, 1H), 6.94 (d, *J* = 7.8 Hz, 1H), 6.87 (t, *J* = 7.4 Hz, 1H), 5.95 (s, 1H), 3.75 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 169.4 (C), 148.3 (C), 137.2 (C), 132.1 (CH), 131.8 (C), 128.5 (CH), 128.1 (CH), 125.52 (C), 123.57 (CH), 122.8 (CH), 121.5 (CH), 118.9 (CH), 118.7 (CH), 111.0 (C), 110.1 (CH), 53.5 (CH), 32.4 (CH_3); HRMS (ESI) calcd for $C_{17}H_{15}N_2O$ (M + H) 263.1184, found 263.1181.

3-(1*H*-Indol-3-yl)isoindolin-1-one 12b:



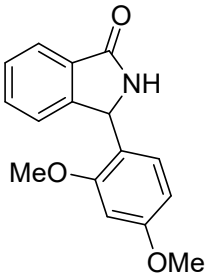
Yellow solid (27 mg, 84% yield); IR (KBr, cm^{-1}) 3347, 2854, 1695, 1525, 1435, 1344, 1197, 1132, 1059, 984, 922, 857, 792, 740, 691, 608; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.08 (s, 1H), 8.94 (s, 1H), 7.81 – 7.72 (m, 1H), 7.53 – 7.47 (m, 2H), 7.45 (d, *J* = 2.5 Hz, 1H), 7.36 (d, *J* = 8.2 Hz, 1H), 7.31 – 7.26 (m, 1H), 7.03 (ddd, *J* = 8.1, 6.9, 1.2 Hz, 1H), 6.89 (d, *J* = 8.0 Hz, 1H), 6.85-6.79 (m, 1H), 5.96 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 169.3 (C), 148.3 (C), 136.8 (C), 132.1 (C), 131.6 (CH), 127.9 (CH), 125.0 (C), 124.4 (CH), 123.4 (CH), 122.7 (CH), 121.3 (CH), 118.7 (CH), 118.5 (CH), 111.8 (CH), 111.7 (C), 53.8 (CH); HRMS (ESI) calcd for $C_{16}H_{13}N_2O$ (M + H) 249.1028, found 249.1036.

3-(3,4-Dimethoxyphenyl)isoindolin-1-one 12c:



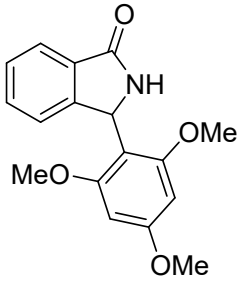
White solid (27 mg, 81% yield); mp 168 °C; IR (KBr, cm^{-1}) 3381, 3067, 2925, 2850, 1695, 1600, 1515, 1458, 1350, 1268, 1246, 1136, 1024, 805, 729, 600; ^1H NMR (400 MHz, $CDCl_3 + CCl_4$; 1:1) δ 7.81 (dd, *J* = 6.7, 1.0 Hz, 1H), 7.75 (s, 1H), 7.49 – 7.40 (m, 2H), 7.20 (d, *J* = 7.5 Hz, 1H), 6.85 (dd, *J* = 8.2, 2.0 Hz, 1H), 6.78 (d, *J* = 8.2 Hz, 1H), 6.62 (d, *J* = 2.0 Hz, 1H), 5.53 (s, 1H), 3.82 (s, 3H), 3.75 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3 + CCl_4$; 1:1) δ 171.3 (C), 149.7 (C), 149.3 (C), 148.2 (C), 132.2 (CH), 131.2 (C), 130.8 (C), 128.3 (CH), 123.9 (CH), 123.3 (CH), 119.5 (CH), 111.4 (CH), 109.4 (CH), 60.9 (CH), 55.9 (CH_3), 54.5 (CH_3); HRMS (ESI) calcd for $C_{16}H_{16}NO_3$ (M + H) 270.1130, found 270.1104.

3-(2,4-Dimethoxyphenyl)isoindolin-1-one 12d:



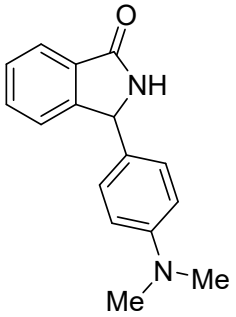
White solid (30 mg, 90% yield); mp 179 °C; IR (KBr, cm^{-1}) 3379, 3070, 2923, 2847, 1693, 1599, 1512, 1461, 1349, 1270, 1250, 1137, 1025, 806; ^1H NMR (400 MHz, $CDCl_3$) δ 7.89 – 7.83 (m, 1H), 7.54 – 7.43 (m, 2H), 7.38 (dd, *J* = 7.5, 0.8 Hz, 1H), 6.91 (d, *J* = 8.5 Hz, 1H), 6.67 (s, 1H), 6.53 (d, *J* = 2.4 Hz, 1H), 6.37 (dd, *J* = 8.5, 2.4 Hz, 1H), 6.03 (s, 1H), 3.91 (s, 3H), 3.78 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.8 (C), 160.8 (C), 158.3 (C), 147.6 (C), 131.9 (CH), 131.5 (C), 128.0 (CH), 127.3 (CH), 123.7 (CH), 123.6 (CH), 118.7 (C), 104.4 (CH), 98.8 (CH), 77.2 (CH), 55.5 (CH_3), 55.4 (CH_3); HRMS (ESI) calcd for $C_{16}H_{16}NO_3$ (M + H) 270.1130, found 270.1130.

3-(2,4,6-Trimethoxyphenyl)isoindolin-1-one 12e:



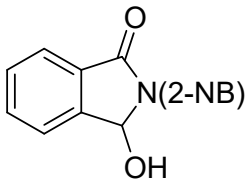
White solid (29 mg, 84% yield); mp 215 °C; IR (KBr, cm^{-1}) 3183, 3072, 2935, 2840, 1690, 1606, 1462, 1415, 1361, 1319, 1227, 1201, 1150, 1120, 1054, 1035, 949, 886, 810, 780, 738, 708, 589, 560; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 – 7.79 (m, 1H), 7.46 – 7.35 (m, 2H), 7.20 – 7.14 (m, 1H), 6.31 (s, 1H), 6.21 (s, 1H), 6.07 (s, 2H), 3.78 (s, 3H), 3.59 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.6 (C), 161.4 (C), 159.9 (C), 148.9 (C), 132.3 (C), 131.3 (CH), 127.1 (CH), 123.0 (CH), 122.1 (CH), 105.5 (C), 91.0 (CH), 55.7 (CH), 55.3 (CH_3), 51.3 (CH_3); HRMS (ESI) calcd for $C_{17}H_{18}NO_4$ (M + H) 300.1236, found 300.1244.

3-(4-(Dimethylamino)phenyl)isoindolin-1-one 12f:



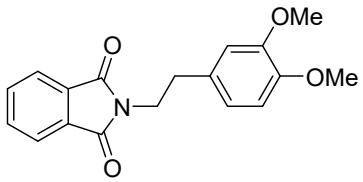
White solid (29 mg, 87% yield); mp 188 °C; IR (KBr, cm^{-1}) 3455, 3064, 2853, 1686, 1616, 1524, 1467, 1360, 1227, 1161, 1133, 1057, 948, 885, 805, 753, 721, 614, 582, 543, 422; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 – 7.84 (m, 1H), 7.48 (dt, *J* = 7.4, 3.8 Hz, 1H), 7.44 (dt, *J* = 7.4, 3.9 Hz, 1H), 7.22 (dd, *J* = 7.5, 0.8 Hz, 1H), 7.11 – 7.06 (m, 2H), 6.67 (d, *J* = 8.8 Hz, 2H), 6.59 (s, 1H), 5.53 (s, 1H), 2.93 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.9 (C), 150.7 (C), 148.7 (C), 132.2 (CH), 131.0 (C), 128.2 (CH), 127.9 (CH), 125.3 (C), 123.7 (CH), 123.4 (CH), 112.7 (CH), 60.6 (CH), 40.5 (CH_3); HRMS (ESI) calcd for $C_{16}H_{17}N_2O$ (M + H) 253.1341, found 253.1349.

Synthesis of 3-hydroxy-2-(2-nitrobenzyl)isoindolin-1-one 9:



To a stirred solution of 2-(2-nitrobenzyl)isoindoline-1,3-dione (500 mg, 1.77 mmol) in a mixture of tetrahydrofuran and methanol (9:1 mL) was added sodium borohydride (65 mg, 1.77 mmol) over 10 min at -10 °C. The resulting mixture was stirred at -10 °C for 3 h. Subsequently, excess sodium borohydride was quenched with aqueous 3 N HCl (2 mL). The solvent was evaporated under reduced pressure resulted in a white solid which was washed with water to provide 3-hydroxy-2-(2-nitrobenzyl)isoindolin-1-one **9** as white solid (480 mg, 95% yield); mp 150 °C; IR (KBr, cm^{-1}) 3347, 2854, 1695, 1525, 1435, 1344, 1197, 1132, 1059, 984, 922, 857, 792, 740, 691, 608; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.10 (dd, J = 8.1, 1.2 Hz, 1H), 7.74 (d, J = 7.4 Hz, 1H), 7.66 (ddd, J = 13.1, 7.4, 3.4 Hz, 3H), 7.60 – 7.53 (m, 2H), 7.43 (dd, J = 7.8, 0.9 Hz, 1H), 6.80 (d, J = 8.4 Hz, 1H), 5.85 (d, J = 8.4 Hz, 1H), 5.06 (d, J = 16 Hz, 1H), 4.89 (d, J = 16 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 166.8 (C), 147.9 (C), 145.0 (C), 133.96 (CH), 132.95 (C), 132.4 (CH), 131.0 (CH), 129.5 (CH), 129.0 (CH), 128.3 (CH), 124.8 (CH), 123.8 (CH), 122.6 (CH), 81.4 (CH), 40.0 (CH_2); HRMS (ESI) calcd for $C_{15}H_{13}N_2O_4$ (M + H) 285.0875, found 285.0896.

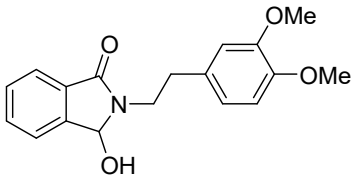
2-(3,4-Dimethoxyphenethyl)isoindoline-1,3-dione 14a:



A suspension of phthalic anhydride (250 mg, 1.68 mmol) in 5 mL of toluene in an oven-dried round bottom flask fitted with Dean-Stark apparatus was heated to reflux until complete dissolution of the anhydride and no additional water was removed. To this 3,4-dimethoxy phenylethylamine (305 mg, 1.68 mmol) was added and refluxing was continued until the water evolution was completed. After completion of the reaction, the reaction mixture was

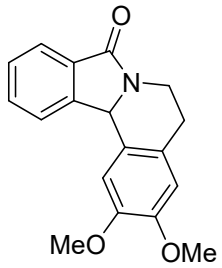
concentrated under reduced pressure to give a residue which was purified by column chromatography to furnished 2-(3,4-dimethoxyphenethyl)isoindoline-1,3-dione **14a** as yellow solid (450 mg, 85% yield); mp 170 ˚C; IR (KBr, cm^{-1}) 3003, 2942, 2841, 1763, 1713, 1594, 1517, 1464, 1395, 1359, 1333, 1265, 1230, 1190, 1147, 1095, 1024, 1000, 938, 867, 806, 766, 719, 641, 524; ^{1}H NMR (400 MHz, $CDCl_3$ + CCl_4; 1:1) δ 7.84 – 7.76 (m, 2H), 7.71 – 7.63 (m, 2H), 6.77 – 6.69 (m, 3H), 3.90 – 3.86 (m, 2H), 3.82 (s, 3H), 3.80 (s, 3H), 2.91 (dd, *J* = 8.5, 6.9 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$ + CCl_4; 1:1) δ 168.1 (C), 149.0 (C), 147.9 (C), 133.9 (CH), 132.3 (C), 130.5 (C), 123.3 (CH), 121.0 (CH), 112.1 (CH), 111.4 (CH), 55.9 (CH_3), 55.8 (CH_3), 39.4 (CH_2), 34.2 (CH_2); HRMS (ESI) calcd for $C_{18}H_{18}NO_4$ (M + H) 312.1236, found 312.1231.

2-(3,4-Dimethoxyphenethyl)-3-hydroxyisoindolin-1-one 15a:



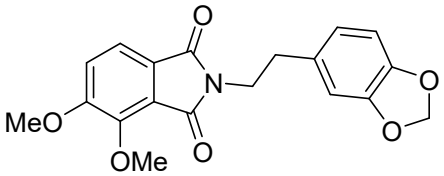
To a stirred solution of 2-(3,4-dimethoxyphenethyl)isoindoline-1,3-dione (430 mg, 1.38 mmol) in a mixture of tetrahydrofuran and methanol (9:1 mL) was added sodium borohydride (51 mg, 1.38 mmol) for 10 min at -10 °C. The resulting mixture was stirred at -10 °C for 3 h. Subsequently, excess sodium borohydride was quenched with aqueous 3 N HCl (10 mL). Evaporation of solvents on rotary evaporator resulted in a white solid which was washed with water to give 2-(3,4-dimethoxyphenethyl)-3-hydroxyisoindolin-1-one **15a** (428 mg, 99% yield); mp 135 ˚C; IR (KBr, cm^{-1}) 3290, 3005, 2937, 1670, 1600, 1519, 1446, 1330, 1253, 1146, 1108, 1057, 1027, 934, 845, 797, 746, 690, 547; ^{1}H NMR (400 MHz, $CDCl_3$ + CCl_4; 1:1) δ 7.45 (dd, *J* = 10.6, 4.2 Hz, 3H), 7.32 (ddd, *J* = 8.1, 6.1, 2.1 Hz, 1H), 6.71 – 6.59 (m, 3H), 5.39 (s, 1H), 3.76 (s, 3H), 3.68 (s, 3H), 3.58 (ddd, *J* = 14.2, 8.2, 6.2 Hz, 1H), 3.45 – 3.35 (m, 1H), 2.86 – 2.70 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$ + CCl_4; 1:1) δ 167.5 (C), 149.0 (C), 147.7 (C), 144.2 (C), 132.1 (CH), 131.4 (C), 131.2 (C), 129.5 (CH), 123.3 (CH), 123.0 (CH), 120.7 (CH), 112.1 (CH), 111.5 (CH), 82.1 (CH), 55.86 (CH_3), 55.80 (CH_3), 40.7 (CH_2), 34.0 (CH_2); HRMS (ESI) calcd for $C_{18}H_{20}NO_4$ (M + H) 314.1392, found 314.1364.

2,3-Dimethoxy-5,12*b*-dihydroisoindolo[1,2-*a*]isoquinolin-8(6*H*)-one 16:



A 10 mL RB flask was charged with 2-(3,4-dimethoxyphenethyl)-3-hydroxyisoindolin-1-one (400 mg, 1.27 mmol), and *p*-toluenesulfonic acid (21 mg, 0.12 mmol). To this 8 mL of *o*-xylene was added. The reaction mixture was stirred at 120 ˚C for 3 h. The reaction was periodically monitored by TLC to check for the completion of the reaction. After completion of the reaction, the reaction mixture was cooled to rt, and PTSA was quenched with solid $NaHCO_3$ (20 mg). The solvent was removed by using a rotary evaporator. The crude product was directly subjected to column chromatography to give 2,3-dimethoxy-5,12*b*-dihydroisoindolo[1,2-*a*]isoquinolin-8(6*H*)-one **16** as yellow solid (348 mg, 92% yield); mp 127 ˚C; IR (KBr, cm^{-1}) 3404, 3065, 2926, 2853, 1718, 1620, 1563, 1506, 1476, 1417, 1280, 1124, 1077, 1036, 861, 763, 717, 538, 464; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 – 7.79 (m, 2H), 7.60 (td, *J* = 7.5, 1.2 Hz, 1H), 7.49 (t, *J* = 7.5 Hz, 1H), 7.11 (s, 1H), 6.66 (s, 1H), 5.61 (s, 1H), 4.48 (ddd, *J* = 12.9, 5.9, 3.5 Hz, 1H), 3.92 (s, 3H), 3.84 (d, *J* = 2.1 Hz, 3H), 3.41 (ddd, *J* = 13.0, 10.2, 4.6 Hz, 1H), 2.99 (dt, *J* = 16.1, 5.2 Hz, 1H), 2.76 (dt, *J* = 15.8, 4.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.1 (C), 148.5 (C), 148.0 (C), 144.7 (C), 132.8 (C), 131.7 (CH), 128.6 (CH), 127.0 (C), 126.1 (C), 124.1 (CH), 123.1 (CH), 112.1 (CH), 108.8 (CH), 59.1 (CH), 56.3 (CH_3), 56.0 (CH_3), 38.3 (CH_2), 29.1 (CH_2); HRMS (ESI) calcd for $C_{18}H_{18}NO_3$ (M + H) 296.1287, found 296.1293.

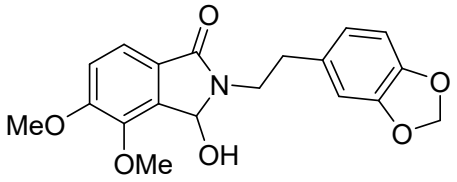
2-(2-(Benzo[*d*][1,3]dioxol-5-yl)ethyl)-4,5-dimethoxyisoindoline-1,3-dione 14b:



A suspension of 4,5-dimethoxyisobenzofuran-1,3-dione (250 mg, 1.20 mmol) in 5 mL of toluene in an oven-dried round bottom flask fitted with Dean-Stark apparatus was heated to

reflux until complete dissolution of the anhydride and no additional water was removed. To this, 2-(benzo[*d*][1,3]dioxol-5-yl)ethan-1-amine (198 mg, 1.20 mmol) was added and refluxing was continued until the water evolution was completed. After completion of the reaction, the mixture was concentrated under reduced pressure to afford 2-(2-(benzo[*d*][1,3]dioxol-5-yl)ethyl)-4,5-dimethoxyisoindoline-1,3-dione **14b** as white solid (375 mg, 87% yield); mp 159 °C; IR (KBr, cm^{-1}) 3448, 2936, 2857, 1767, 1712, 1608, 1498, 1443, 1390, 1349, 1275, 1216, 1192, 1042, 976, 924, 809, 747, 608, 463; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (d, *J* = 8.0 Hz, 1H), 7.08 (d, *J* = 8.1 Hz, 1H), 6.75 – 6.64 (m, 3H), 5.90 (s, 2H), 4.12 (s, 3H), 3.94 (s, 3H), 3.84 – 3.77 (m, 2H), 2.86 (dd, *J* = 8.6, 6.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.6 (C), 166.2 (C), 157.7 (C), 147.7 (C), 147.2 (C), 146.3 (C), 132.0 (C), 124.6 (C), 121.97 (C), 121.91 (CH), 119.4 (CH), 115.8 (CH), 109.3 (CH), 108.4 (CH), 100.9 (CH_2), 62.6 (CH_3), 56.7 (CH_3), 39.5 (CH_2), 34.4 (CH_2).

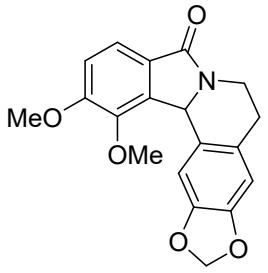
2-(2-(Benzo[*d*][1,3]dioxol-5-yl)ethyl)-3-hydroxy-4,5-dimethoxyisoindolin-1-one 15b:



To a stirred solution of 2-(2-(benzo[*d*][1,3]dioxol-5-yl)ethyl)-4,5-dimethoxy isoindoline-1,3-dione (360 mg, 1.01 mmol) in a mixture of tetrahydrofuran and methanol (9:1 mL) was added sodium borohydride (37 mg, 1.01 mmol) for 10 min at -10 °C. The resulting mixture was stirred at -10 °C for 3 h. Subsequently, excess sodium borohydride was quenched with aqueous 3 N HCl (10 mL). Evaporation of solvents on rotary evaporator resulted residue washed with water to give 2-(2-(benzo[*d*][1,3]dioxol-5-yl)ethyl)-3-hydroxy-4,5-dimethoxyisoindolin-1-one **15b** as white solid (358 mg, 98% yield); mp 245 °C; IR (KBr, cm^{-1}) 3227, 2922, 1664, 1492, 1441, 1262, 1111, 930, 810, 726, 616; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.32 (d, *J* = 8.1 Hz, 1H), 7.15 (d, *J* = 8.2 Hz, 1H), 6.81 (dd, *J* = 12.2, 4.7 Hz, 2H), 6.69 – 6.66 (m, 1H), 5.95 (s, 2H), 5.82 (s, 1H), 3.86 (s, 3H), 3.84 (s, 3H), 3.74 (ddd, *J* = 15.0, 8.6, 6.7 Hz, 1H), 3.41 – 3.33 (m, 1H), 2.87 – 2.70 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 165.7 (C), 155.3 (C), 147.3 (C), 145.6 (C), 144.6 (C), 135.3 (C), 133.1 (C), 125.1 (C), 121.6 (CH), 118.2 (CH), 113.7 (CH), 109.1 (CH),

108.3 (CH), 100.8 (CH_2), 79.1 (CH), 60.1 (CH_3), 56.3 (CH_3), 38.9 (CH_2), 33.7 (CH_2); HRMS (ESI) calcd for $C_{19}H_{20}NO_6$ (M + H) 358.1291, found 358.1284.

11,12-Dimethoxy-5,12*b*-dihydro-[1,3]dioxolo[4,5-*g*]isoindolo[1,2-*a*]isoquinolin-8(6*H*)-one (Nuevamine) 1:



A 10 mL RB flask was charged with 2-(2-(benzo[*d*][1,3]dioxol-5-yl)ethyl)-3-hydroxy-4,5-dimethoxyisoindolin-1-one (350 mg, 0.98 mmol), and *p*-toluenesulfonic acid (16 mg, 0.09 mmol). To this 7 mL of *o*-xylene was added. The reaction mixture was stirred at 120 ˚C for 3 h. The reaction was periodically monitored by TLC to check for the completion of the reaction. After completion of the reaction, the reaction mixture was cooled to rt. Following this 20 mg of $NaHCO_3$ was added to the reaction mixture to quench PTSA. The solvent was evaporated by using a rotary evaporator. The crude product was directly subjected to column chromatography to give 11,12-dimethoxy-5,12*b*-dihydro-[1,3]dioxolo[4,5-*g*]isoindolo[1,2-*a*]isoquinolin-8(6*H*)-one **1** as white solid (297 mg, 89% yield); mp 193 ˚C; IR (KBr, cm^{-1}) 2972, 2927, 2870, 2841, 1683, 1619, 1593, 1495, 1446, 1407, 1356, 1275, 1219, 1077, 1032, 983, 922, 865, 833, 773, 743, 675, 643, 608, 585, 539; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, *J* = 8.4 Hz, 1H), 7.31 (s, 1H), 7.07 (d, *J* = 8.0 Hz, 1H), 6.66 (s, 1H), 5.92 (d, *J* = 1.6 Hz, 1H), 5.86 (d, *J* = 1.2 Hz, 1H), 5.63 (s, 1H), 4.04 (m, 1H), 3.99 (s, 3H), 3.97 (s, 3H), 3.57 (m, 1H), 3.02 (m, 1H), 2.86 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.8 (C), 155.6 (C), 146.9 (C), 146.5 (C), 144.4 (C), 136.2 (C), 128.9 (C), 128.4 (C), 126.6 (C), 119.9 (CH), 113.3 (CH), 108.5 (CH), 107.6 (CH), 101.0 (CH_2), 60.6 (CH), 58.5 (CH_3), 56.4 (CH_3), 38.9 (CH_2), 29.0 (CH_2); HRMS (ESI) calcd for $C_{19}H_{18}NO_5$ (M + H) 340.1185, found 340.1171.

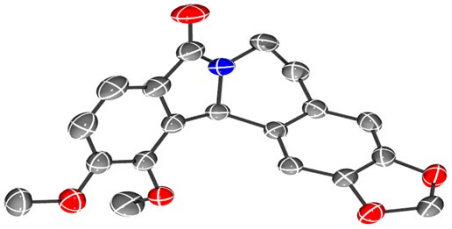


Figure 2. ORTEP diagram of nuevamine **1**.

Empirical formula, $C_{19}H_{17}NO_5$; Formula weight, 339; Crystal colour, colourless; Crystal dimensions a = 10.6688 (5) Å, b = 11.5902(5) Å, c = 12.7186(13) Å; α = 90.00, β = 90.00, γ = 90.00; Crystal system, orthorhombic; V = 1572.71; Space group $P2_12_12_1$; Z = 4; ρ_{calc} = 1.433 g/mm^3; F (000) = 712.0; R [I>=2σ (I)] = 0.0462, wR2 = 0.1198. Detailed X-ray crystallographic data was available from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK (for compound **1**, CCDC 1963219).

Synthesis of 11,12-Dimethoxy-5,12*b*-dihydro-[1,3]dioxolo[4,5-*g*]isoindolo[1,2-*a*]isoquinolin-8(6*H*)-one (Nuevamine) 1 on the gram scale

A 250 mL RB flask was charged with 2-(2-(benzo[*d*][1,3]dioxol-5-yl)ethyl)-3-hydroxy-4,5-dimethoxyisoindolin-1-one (5.0 g, 14.0 mmol), and *p*-toluenesulfonic acid (0.24 g, 1.40 mmol). To this 100 mL of *o*-xylene was added. The reaction mixture was stirred at 120 °C for 5 h. The reaction was periodically monitored by TLC to check for the completion of the reaction. After completion of the reaction, the reaction mixture was cooled to rt. Following this 0.50 g of $NaHCO_3$ was added to the reaction mixture to quench PTSA. The solvent was evaporated by using a rotary evaporator. The crude product was directly subjected to column chromatography to give 11,12-dimethoxy-5,12*b*-dihydro-[1,3]dioxolo[4,5-*g*]isoindolo[1,2-*a*]isoquinolin-8(6*H*)-one **1** as white solid (4.10 g, 86% yield). The analytical data is identical to that reported above for **1**.

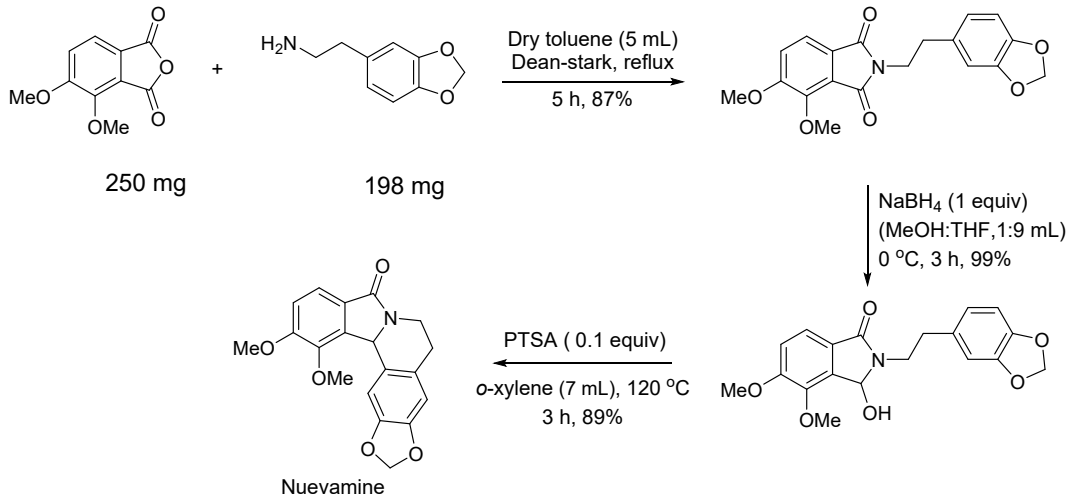
2. (1) **Nuevamine E-Factor calculation**

We have calculated E factor in the total synthesis of (±)-nuevamine[2] according to the formula.

E factor = Mass of total waste (g) / Mass of desired product (g)

(1) Present method

Our method



The lower E Factor, the better-performing product.

Reagents	Amount
4,5-Dimethoxyisobenzofuran-1,3-dione	0.250 g
2-(Benzo[d][1,3]dioxol-5-yl)ethan-1-amine	0.198 g
Toluene	5 mL × 0.867 g/mL = 4.30 g
Sodium borohydride	0.037 g
Tetrahydrofuran	9 mL × 0.887 g/mL = 7.98 g
Methanol	1 mL x = 0.792 g/mL = 0.792 g
3*N* HCl	10 mL × 1.20 g/mL = 12.0 g
p-Toluene sulfonic acid (PTSA)	0.016 g
o-xylene	7 mL × 0.879 g/mL = 6.0 g
Sodium bicarbonate	0.020 g
Hexane (assuming as 90% recovery)	190 mL × 0.661 g/mL × 10% = 12.5 g
EtOAc (assuming as 90% recovery)	50 mL × 0.902 g/mL × 10% = 4.51 g
Total	**48.60 g**

Amount of final product = 0.297 g

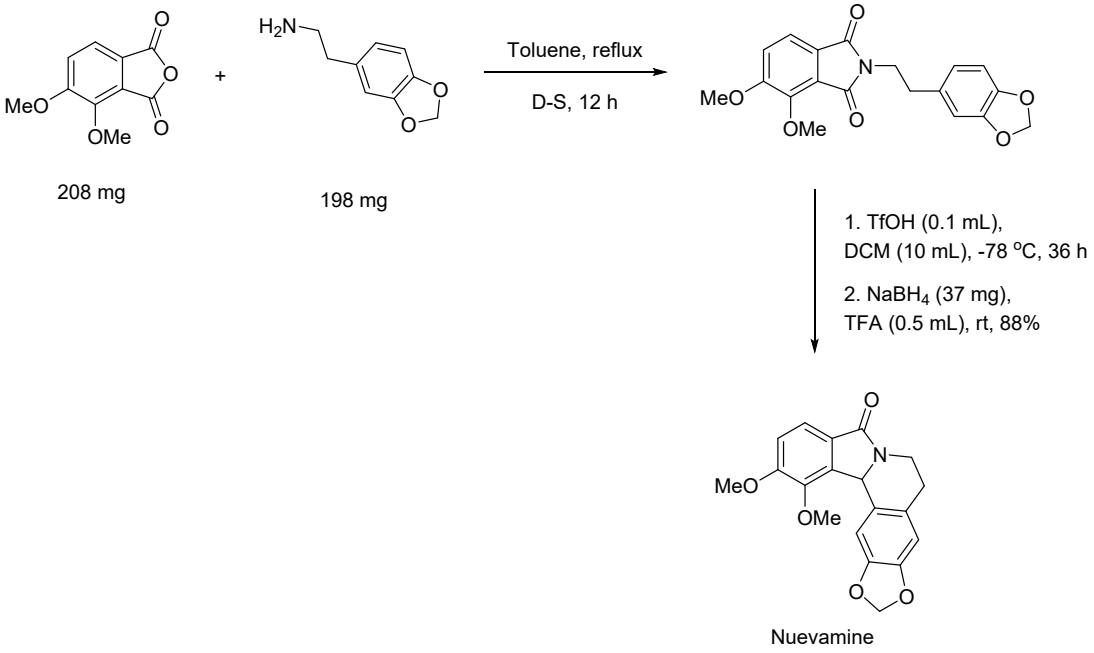
Amount of waste = 48.30 g

E-Factor = Amount of waste/Amount of product = **162.6**

(2) **The method reported by Selvakumar, J. and Ramanathan**

(Selvakumar, J.; Ramanathan, C. R. Bronsted Acid Assisted Activation of Imide Carbonyl Group: Regioselective Synthesis of Isoindoloisoquinolinone Alkaloid (±)-Nuevamine. *Org. Biomol. Chem*. **2011**, *9*, 7643-7646.)

C. R. Ramanathan. *Org. Biomol. Chem*. 2011



Reagents	Amount
4,5-Dimethoxyisobenzofuran-1,3-dione	0.208 g
2-(Benzo[d][1,3]dioxol-5-yl)ethan-1-amine	0.198 g
Toluene	5 mL × 0.867 g/mL = 4.30 g
Dichloromethane	10 mL × 1.33 g/mL = 13.3 g
Trifluoromethanesulfonic acid	0.1 mL × 1.70 g/mL = 0.17 g
Sodium borohydride	0.037 g
Trifluro acetic acid	0.5 mL × 1.49 g/mL = 0.745 g
Dichloromethane	20 mL × 1.33 g/mL = 26.6 g
Sodium sulfate	0.020 g
Hexane (assuming as 90% recovery)	160 mL × 0.661 g/mL / 10% = 10.57 g
EtOAc (assuming as 90% recovery)	90 mL × 0.902 g/mL / 10% = 8.10 g
Total	**64.24 g**

Amount of final product = 0.059 g

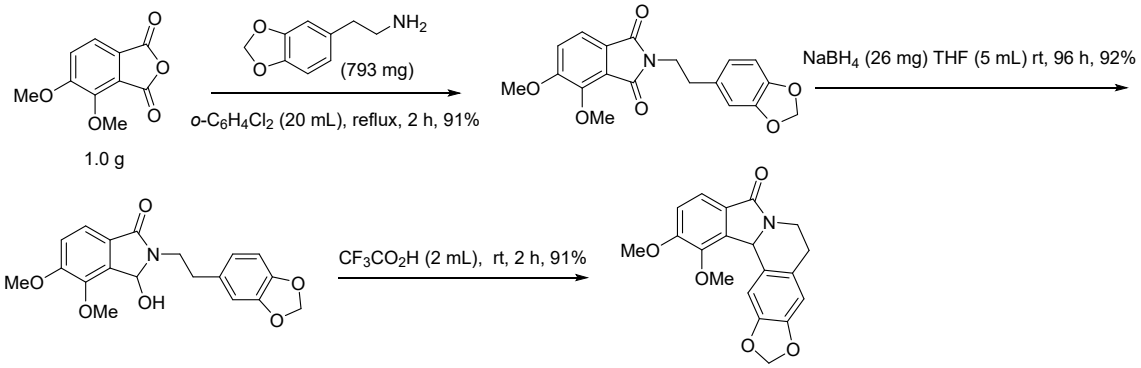
Amount of waste = 64.18 g

E-Factor = Amount of waste/Amount of product = **1087**

(3) **The method reported by Argade, N. P et al.**

(Wakchaure, P. B.; Kunte, S. S.; Regioselective $NaBH_4$ and DIBAL-H Reductions of 3,4-Dimethoxyhomopiperonyl Phthalimide: Concise and Efficient Synthesis of Nuevamine and Isonuevamine. *Indian J. Chem. Sect. B: Org. Chem. Incl. Med. Chem*. **2011**, *50*B, 868-871.)

Narshinha P. Argade. *IJCB*, 2011



E factor = Mass of total waste/ Mass of desired product

Reagents	**Amount**
4,5-Dimethoxyisobenzofuran-1,3-dione	1.0 g
2-(Benzo[d][1,3]dioxol-5-yl)ethan-1-amine	0.793 g
o-Dichlorobenzene	20 mL × 1.30 g/mL = 26.0 g
Sodium borohydride	0.026 g
Tetrahydrofuran	5.0 mL × 0.887 g/mL = 4.43 g
Sodium borohydride	0.037 g
Trifluoroacetic acid	2.0 mL × 1.49 g/mL = 2.98 g
$NaHCO_3$	0.020 g
Petether (assuming as 90% recovery)	300 mL × 0.653 g/mL × 10% = 19.59 g
EtOAc (assuming as 90% recovery)	100 mL × 0.902 g/mL × 10% = 9.0 g
Total	**63.87 g**

Amount of final product = 0.044 g

Amount of waste = 63.82 g

E-Factor = Amount of waste/Amount of product = **1450**

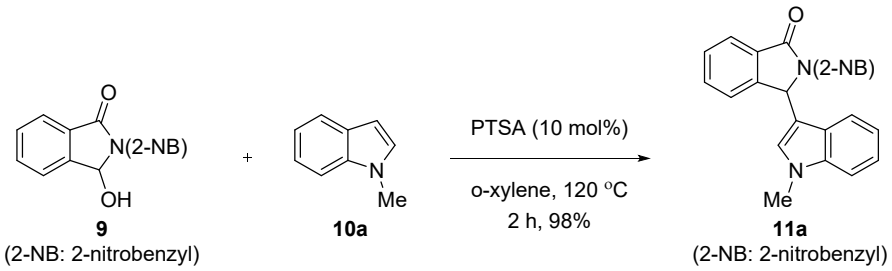
3. Table 1. ^{1}H NMR spectra comparison of natural and synthetic nuevamine 1.

Natural (^{1}H NMR, $CDCl_3$, 200 MHz) δ (*J* in Hz)	Synthetic (^{1}H NMR, $CDCl_3$, 400 MHz) δ (*J* in Hz)	Δδ, ppm
7.59 (d, *J* = 8.2 Hz, 1H)	7.58 (d, *J* = 8.4 Hz, 1H)	0.01
7.07 (d, *J* = 8.2 Hz, 1H)	7.07 (d, *J* = 8.0 Hz, 1H)	0.00
7.32 (s, 1H)	7.31 (s, 1H)	0.01
6.67 (s, 1H)	6.66 (s, 1H)	0.01
5.92 (d, *J* = 1.3 Hz, 1H)	5.92 (d, *J* = 1.6 Hz, 1H)	0.00
5.86 (d, *J* = 1.3 Hz, 1H)	5.86 (d, *J* = 1.2 Hz, 1H)	0.00
5.64 (s, 1H)	5.63 (s, 1H)	0.01
4.05 (m, 1H)	4.04 (m, 1H)	0.01
3.98 (s, 3H)	3.97 (s, 3H)	0.01
3.99 (s, 3H)	3.99 (s, 3H)	0.00
3.53 (m, 1H)	3.57 (m, 1H)	0.04
2.97 (m, 1H)	3.02 (m, 1H)	0.05
2.86 (m, 1H)	2.86 (m, 1H)	0.00

Table 2. ^{13}C NMR spectra comparison of natural and synthetic nuevamine 1.

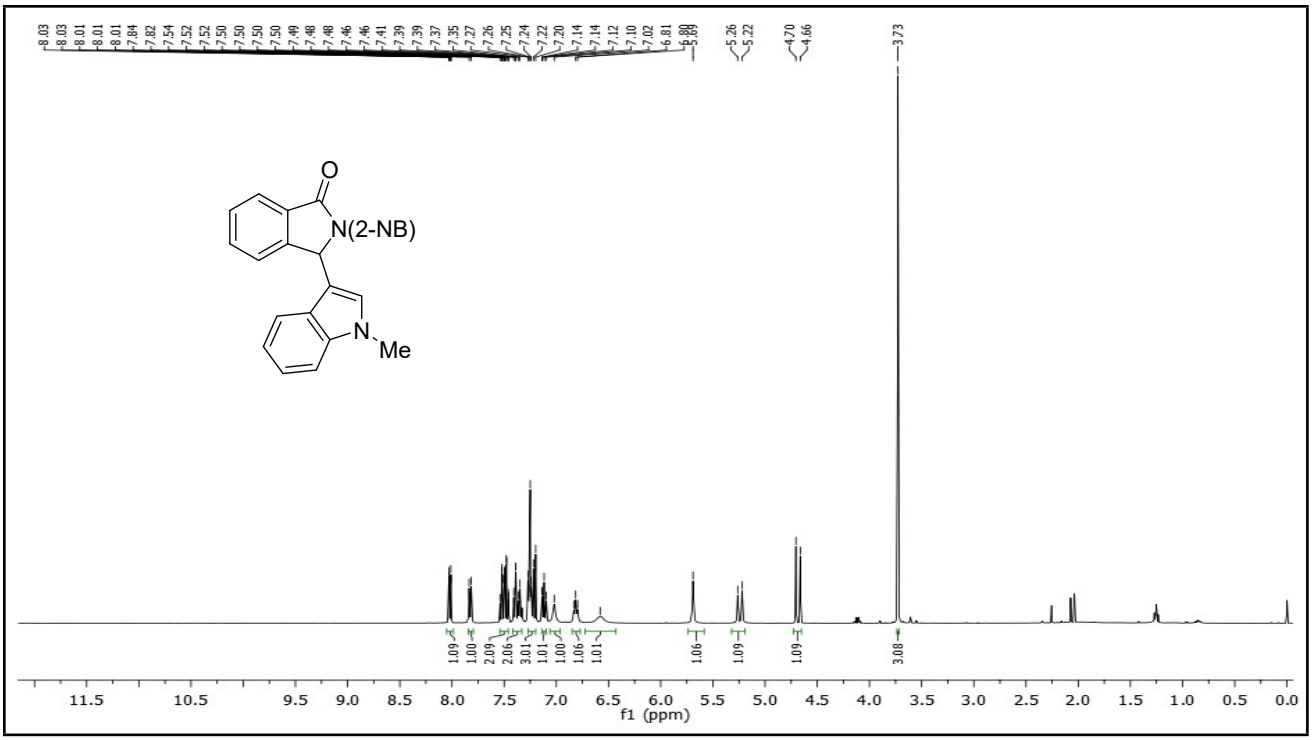
Natural (^{13}C NMR, $CDCl_3$, 75 MHz) δ (*J* in Hz)	Synthetic (^{13}C NMR, $CDCl_3$, 100 MHz) δ (*J* in Hz)	Δδ, ppm
167.9	167.8	0.1
155.6	155.6	0.0
146.8	146.9	0.1
146.5	146.5	0.0
144.4	144.4	0.0
136.0	136.2	0.2
128.8	128.9	0.1
128.2	128.4	0.2
126.4	126.6	0.2
119.8	119.9	0.1
113.3	113.3	0.0
108.4	108.5	0.1
107.5	107.6	0.1
101.0	101.0	0.0
60.5	60.6	0.1
58.5	58.5	0.0
56.3	56.4	0.1
38.9	38.9	0.0
28.9	29.0	0.1

4. **Table 3. Screening of Reaction Condition**

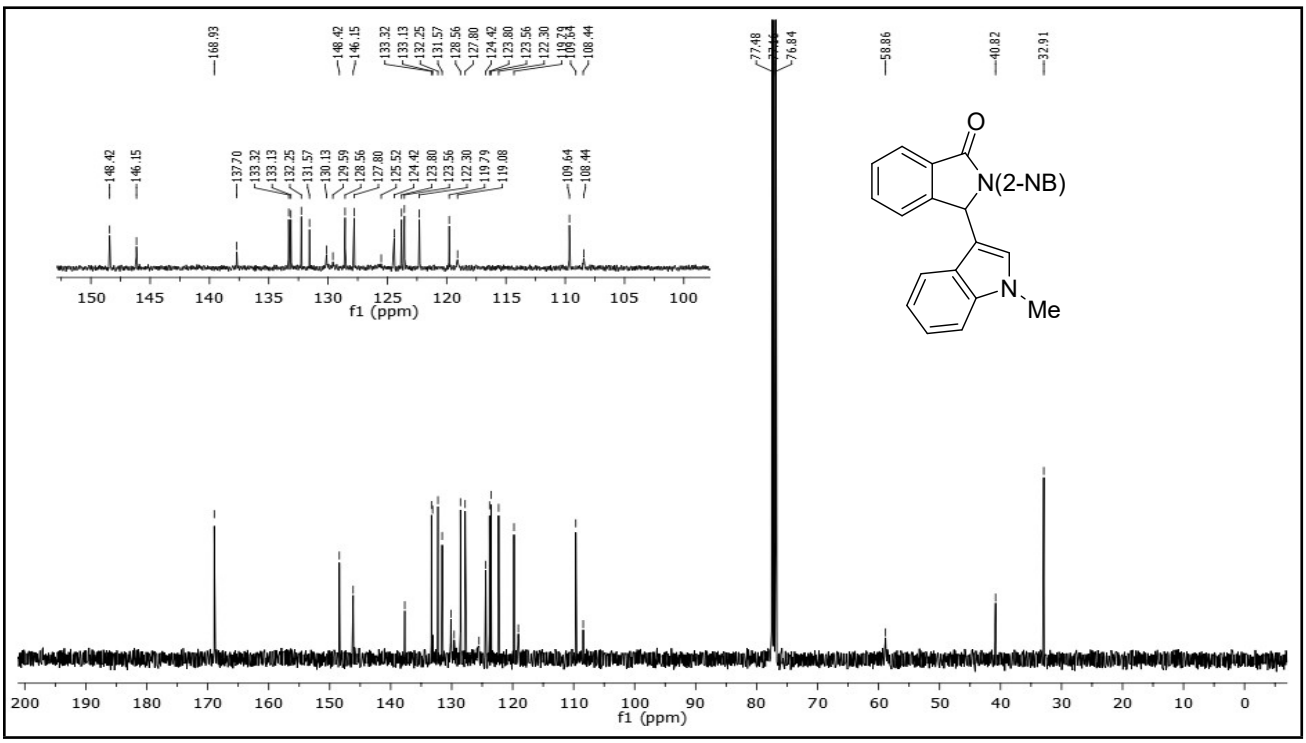


entry	variation from standard conditions	yield of **11a** (%)
1	-	**98**
2	CH_3COOH instead of PTSA	21
3	TFA instead of PTSA	30
4	CH_3SO_3H instead of PTSA	26
5	CF_3SO_3H instead of PTSA	29
6	MeOH instead of o-xylene	Trace
7	EtOH instead of o-xylene	Trace
8	*n*-BuOH instead of o-xylene	Trace
9	DMF instead of o-xylene	15
10	ACN instead of o-xylene	24
11	Toluene instead of o-xylene	45
12	rt instead of 120 °C	nr
13	100 °C instead of 120 °C	54
14	1 mol% instead of 10 mol%	17
15	no acid catalyst	nr

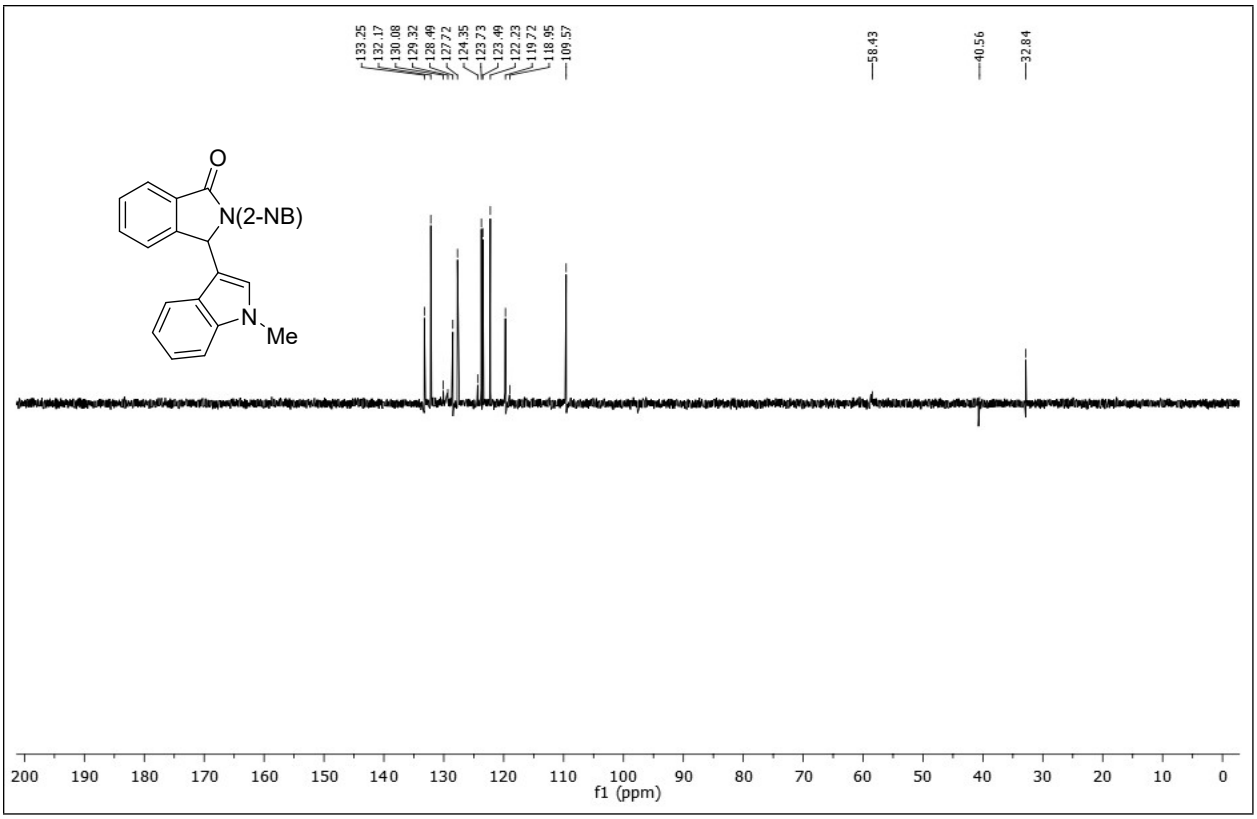
Reaction condition: **9** (0.35 mmol, 1.0 equiv), **10a** (0.35 mmol, 1.0 equiv), PTSA (0.035 mmol, 0.1 equiv), o-xylene, 120 °C, 2 h, 98%.



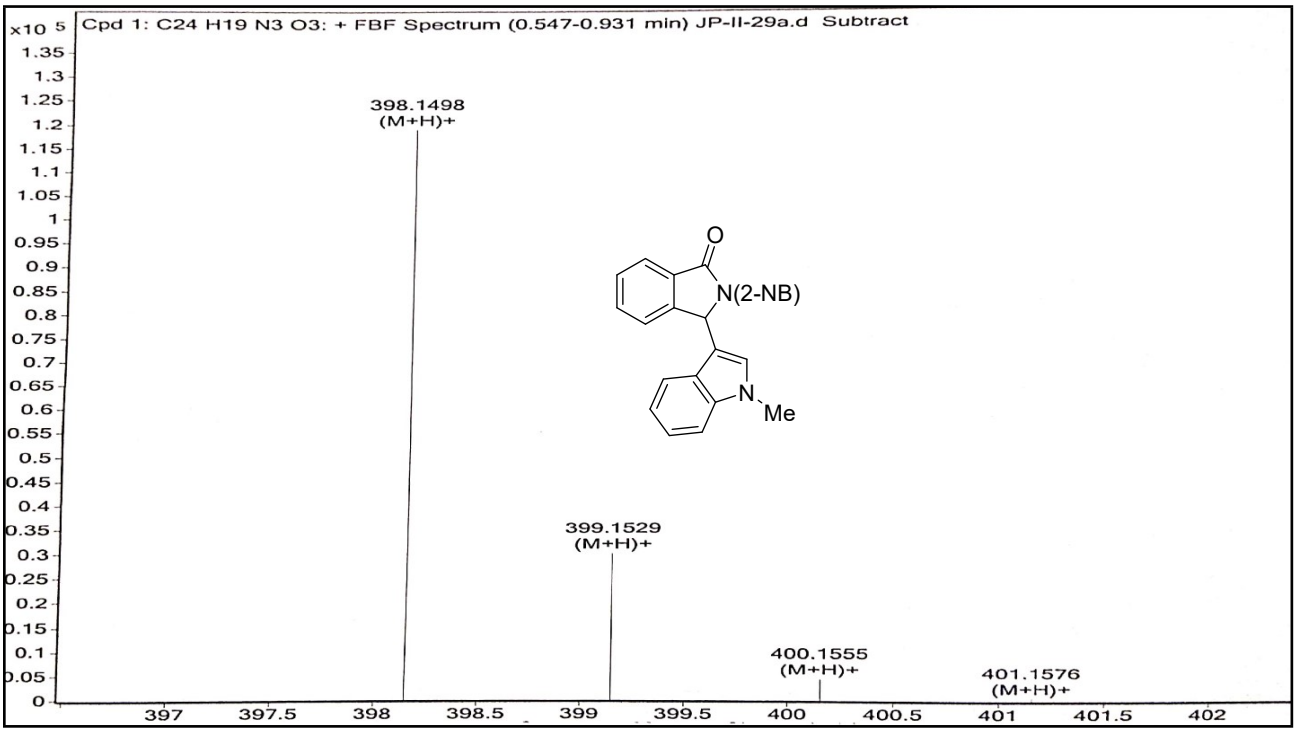
^{1}H NMR (400 MH_Z, $CDCl_3$) spectrum of 3-(1-methyl-1*H*-indol-3-yl)-2-(2-nitrobenzyl)-2,3-dihydro-1*H*-inden-1-one **11a**.



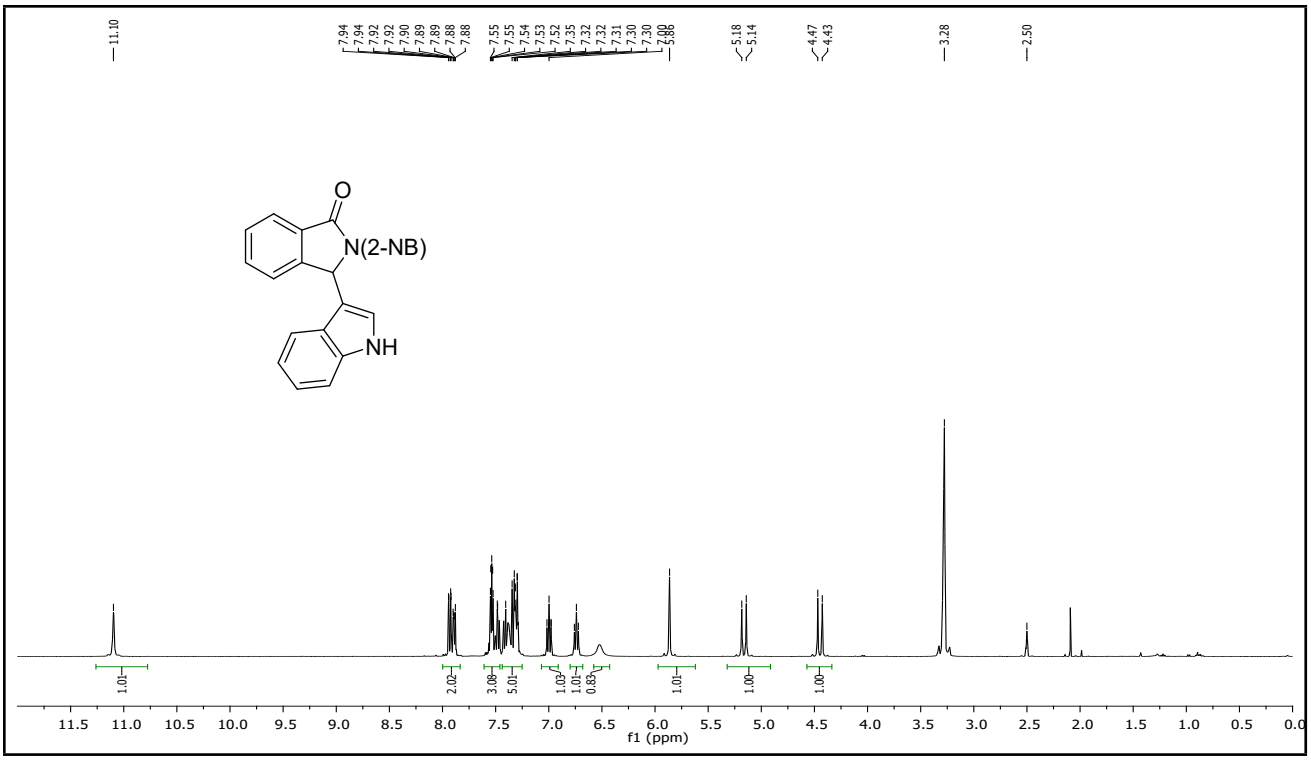
^{13}C NMR (100 MH_Z, $CDCl_3$) spectrum of 3-(1-methyl-1*H*-indol-3-yl)-2-(2-nitrobenzyl)-2,3-dihydro-1*H*-inden-1-one **11a**.



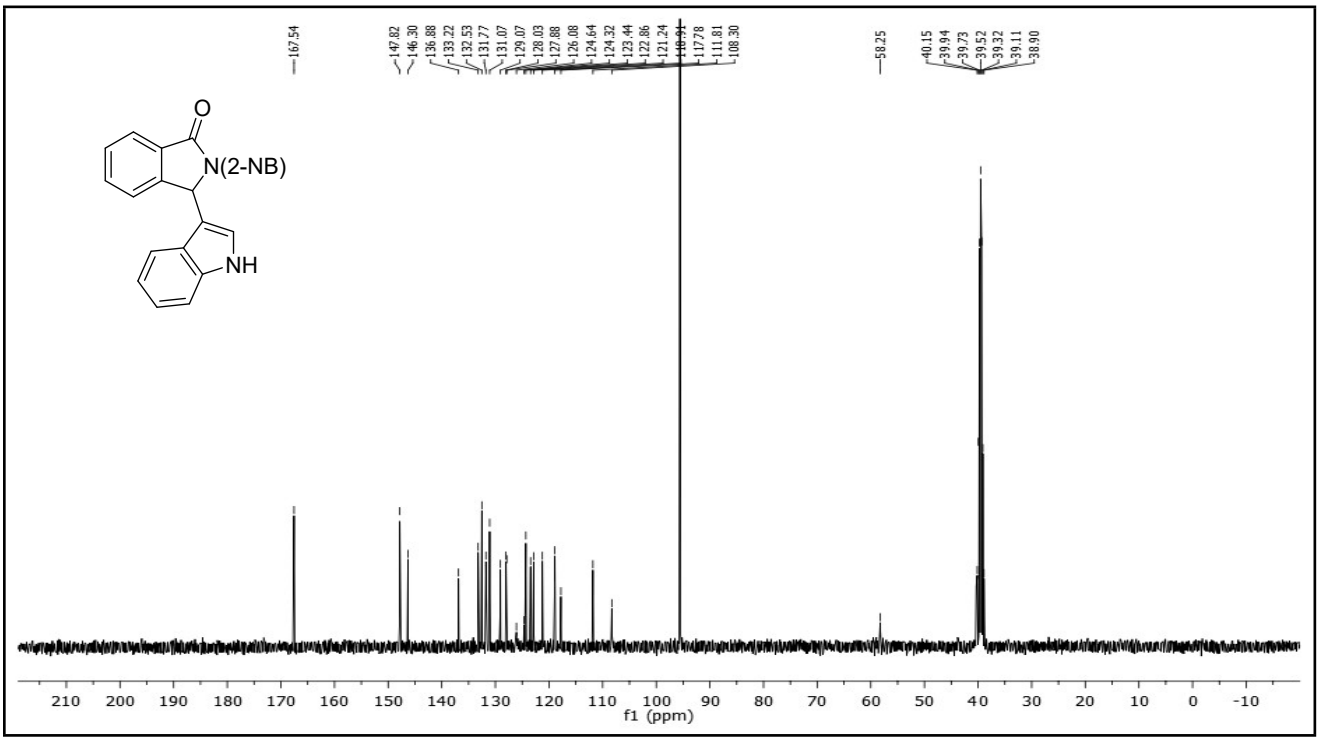
DEPT-135 spectrum of 3-(1-methyl-1*H*-indol-3-yl)-2-(2-nitrobenzyl)-2,3-dihydro-1*H*-inden-1-one **11a**.



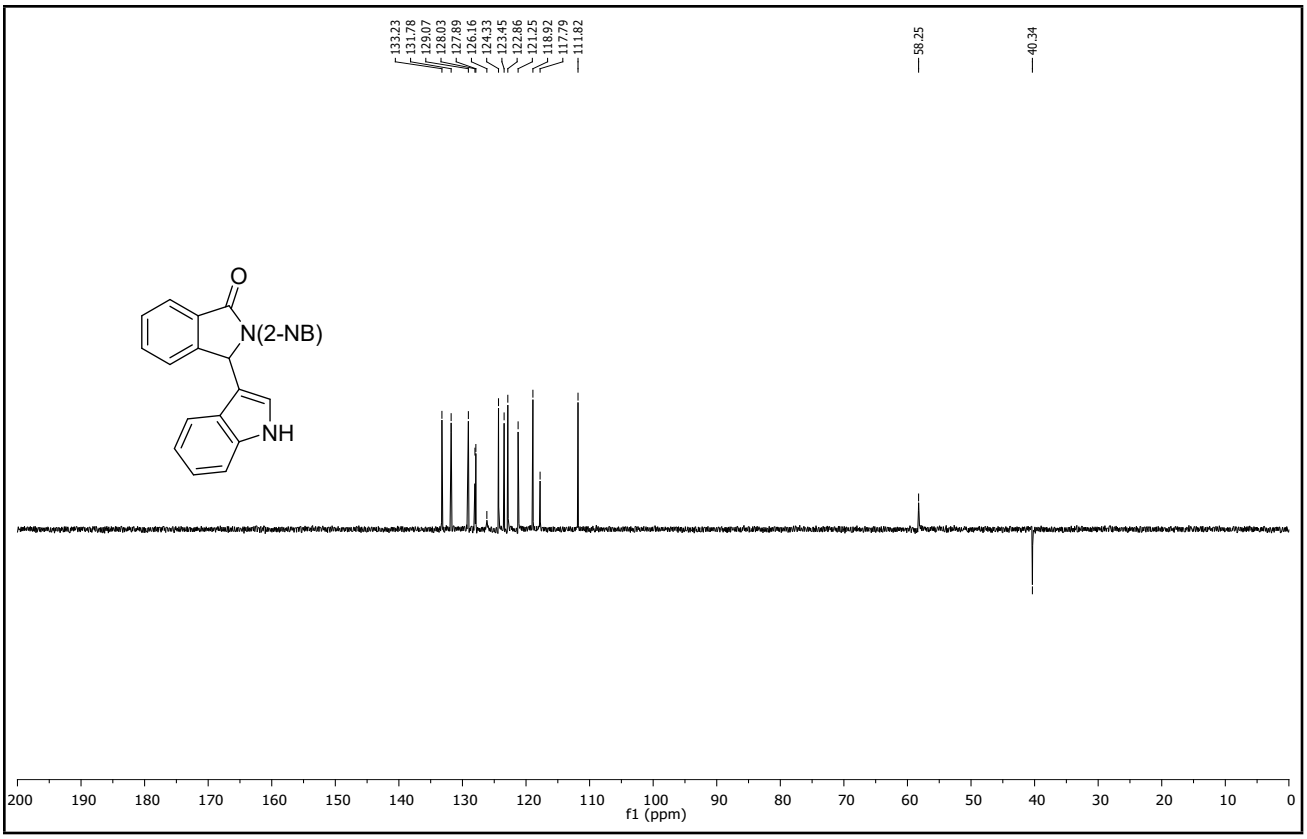
HRMS spectrum of 3-(1-methyl-1*H*-indol-3-yl)-2-(2-nitrobenzyl)-2,3-dihydro-1*H*-inden-1-one **11a**.



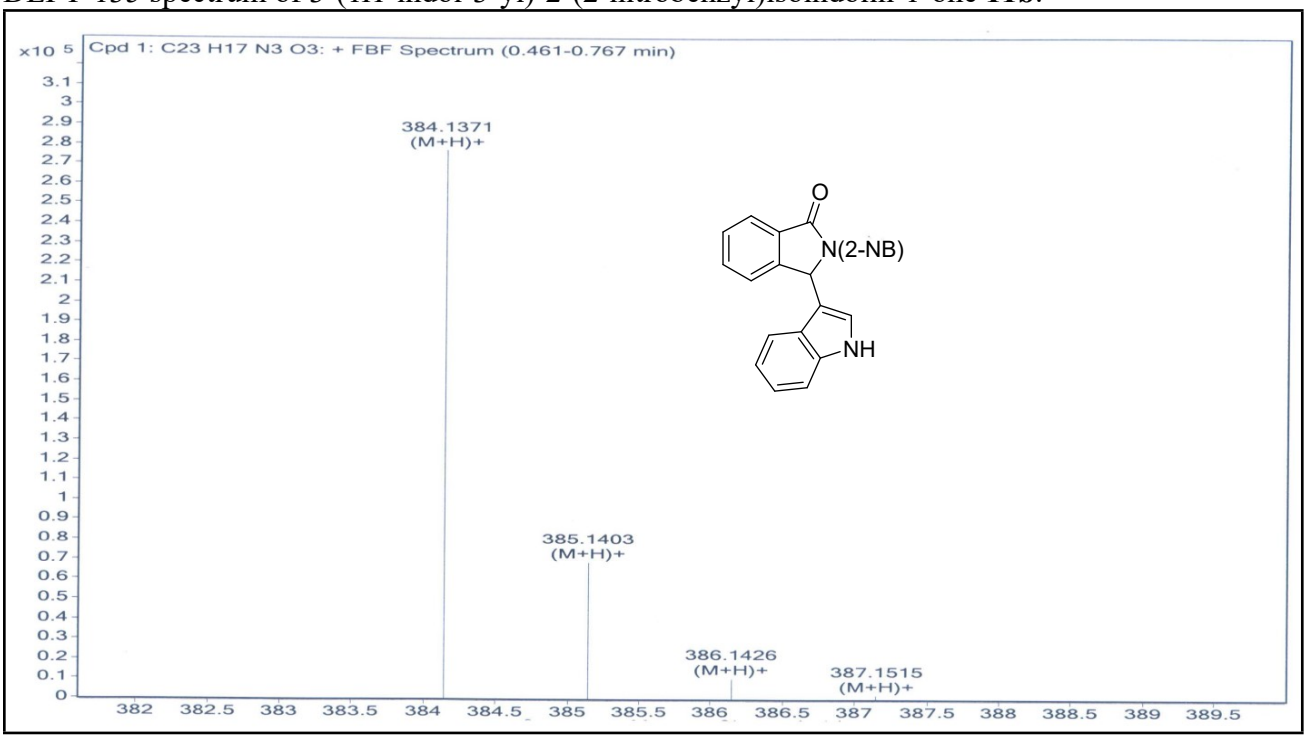
^{1}H NMR (400 MH_Z, DMSO-d_6 + CCl_4; 1:1) spectrum of 3-(1*H*-indol-3-yl)-2-(2-nitrobenzyl) isoindolin-1-one **11b**.



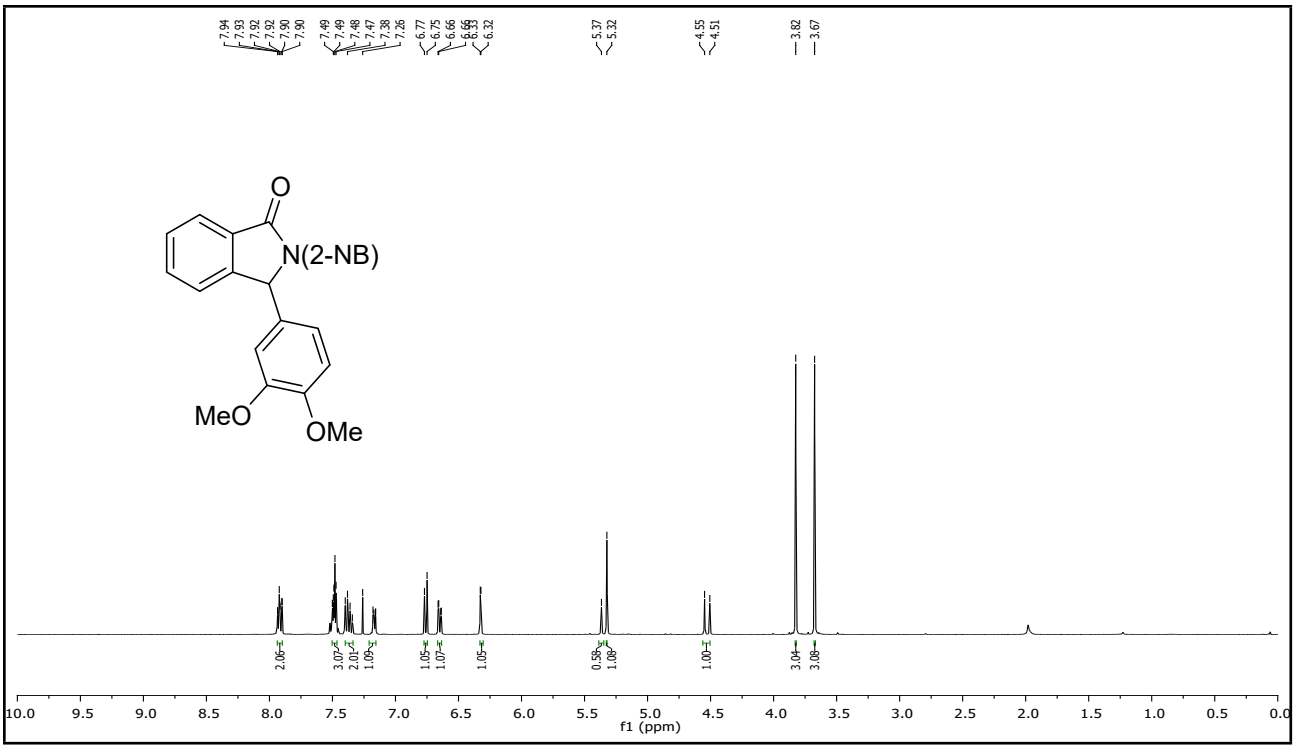
^{13}C NMR (100 MH_Z, DMSO-d_6 + CCl_4; 1:1) spectrum of 3-(1*H*-indol-3-yl)-2-(2-nitrobenzyl) isoindolin-1-one **11b**.



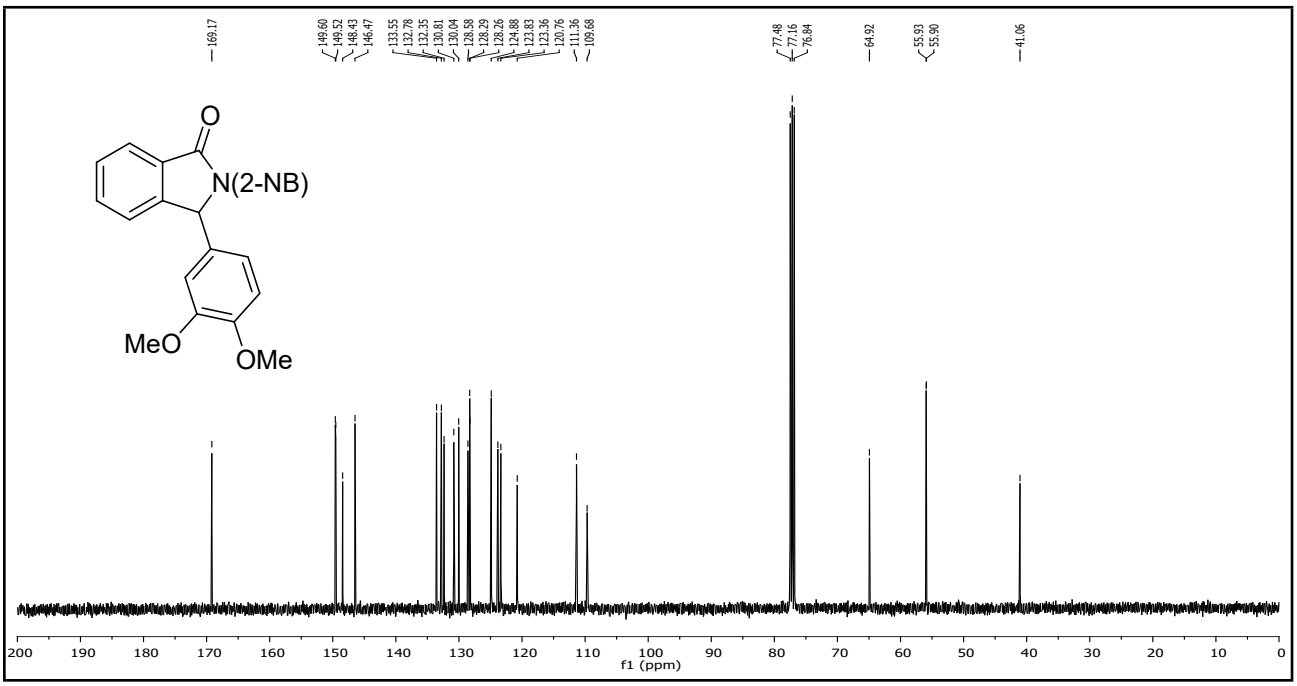
DEPT-135 spectrum of 3-(1*H*-indol-3-yl)-2-(2-nitrobenzyl)isoindolin-1-one **11b**.



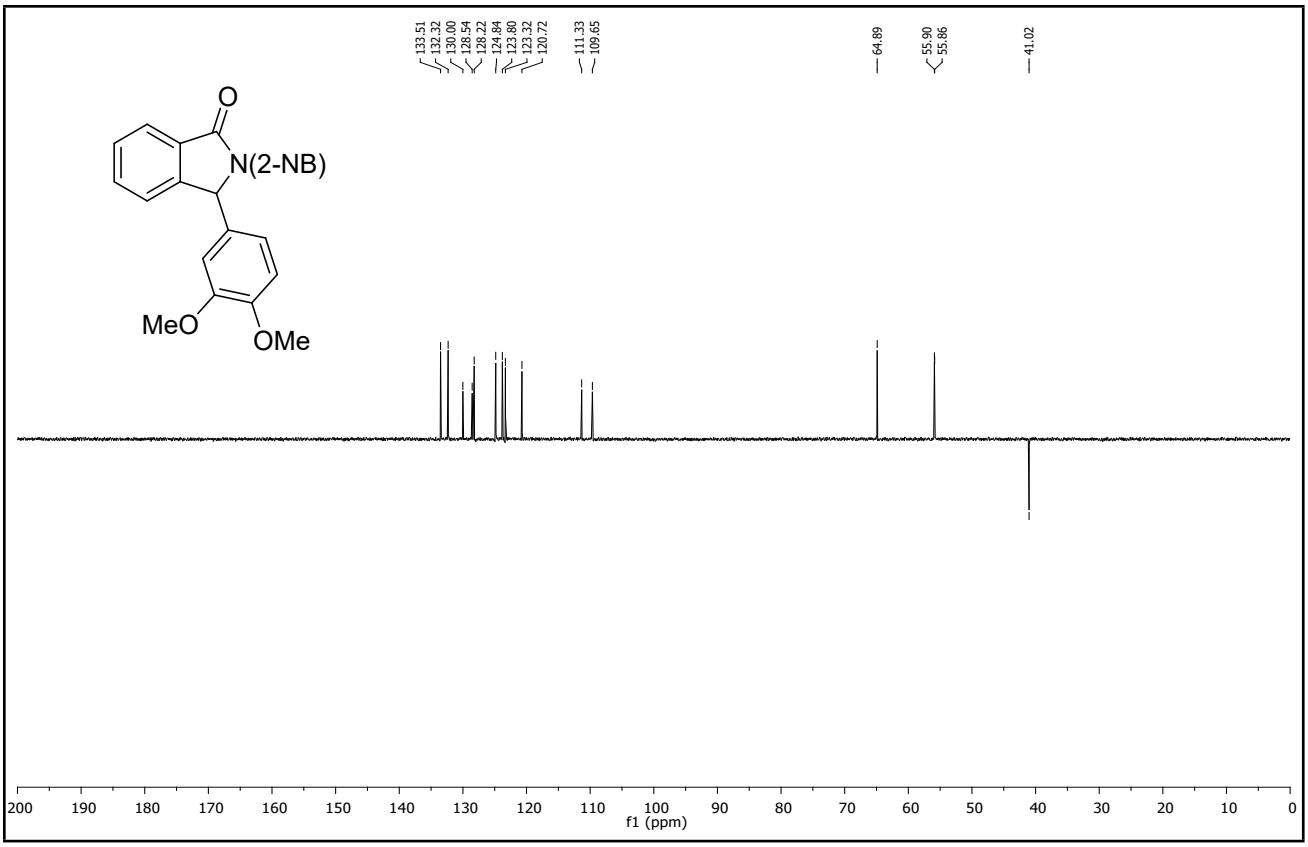
HRMS spectrum of 3-(1*H*-indol-3-yl)-2-(2-nitrobenzyl)isoindolin-1-one **11b**.



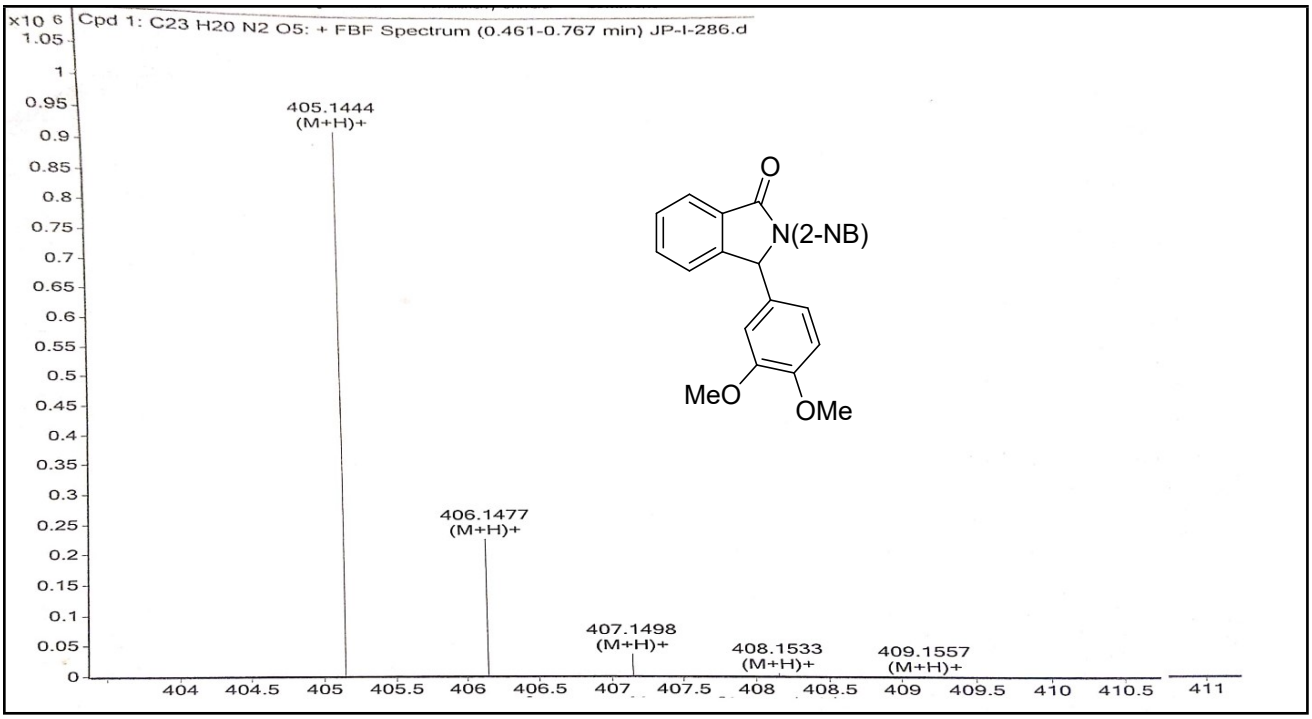
^{1}H NMR (400 MH_Z, $CDCl_3$) spectrum of 3-(3,4-dimethoxyphenyl)-2-(2-nitrobenzyl)isoindolin-1-one **11c**.



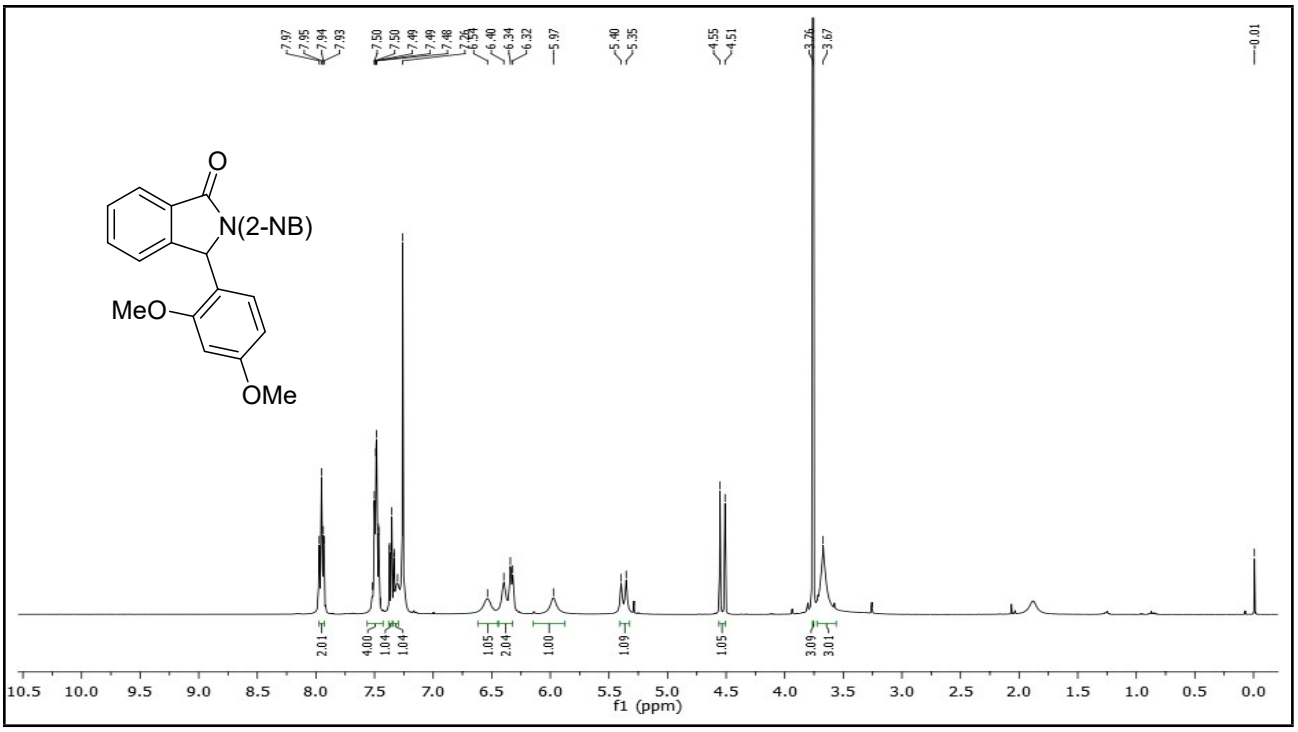
^{13}C NMR (100 MH_Z, $CDCl_3$) spectrum of 3-(3,4-dimethoxyphenyl)-2-(2-nitrobenzyl)isoindolin-1-one **11c**.



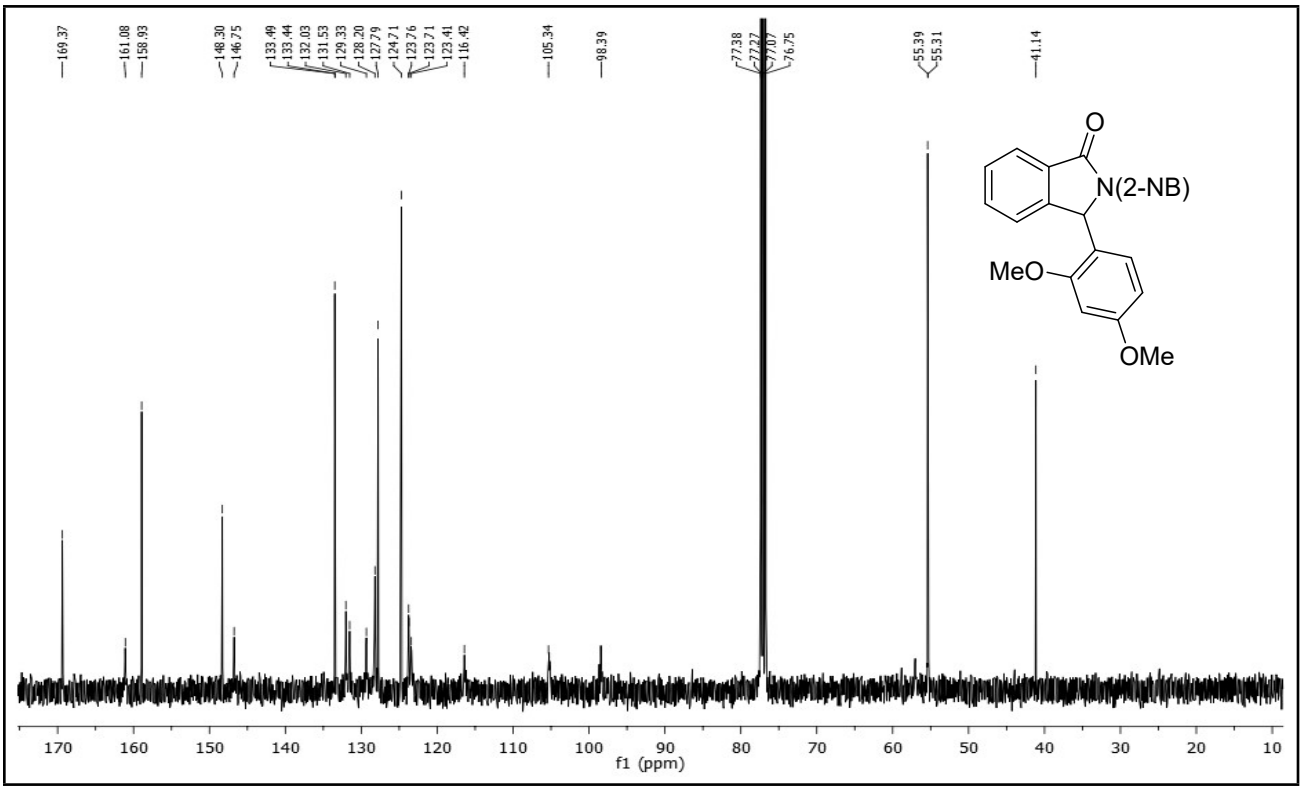
DEPT-135 spectrum of 3-(3,4-dimethoxyphenyl)-2-(2-nitrobenzyl)isoindolin-1-one **11c**.



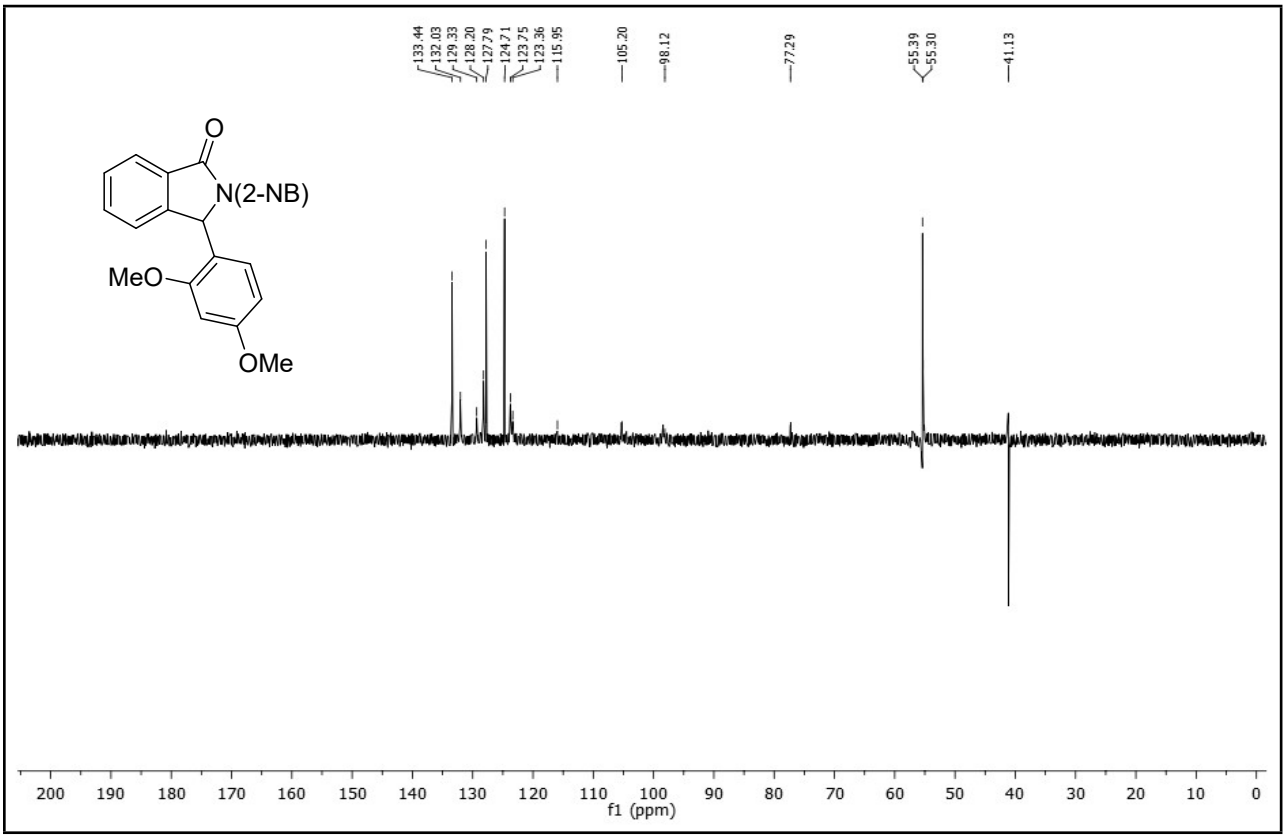
HRMS spectrum of 3-(3,4-dimethoxyphenyl)-2-(2-nitrobenzyl)isoindolin-1-one **11c**.



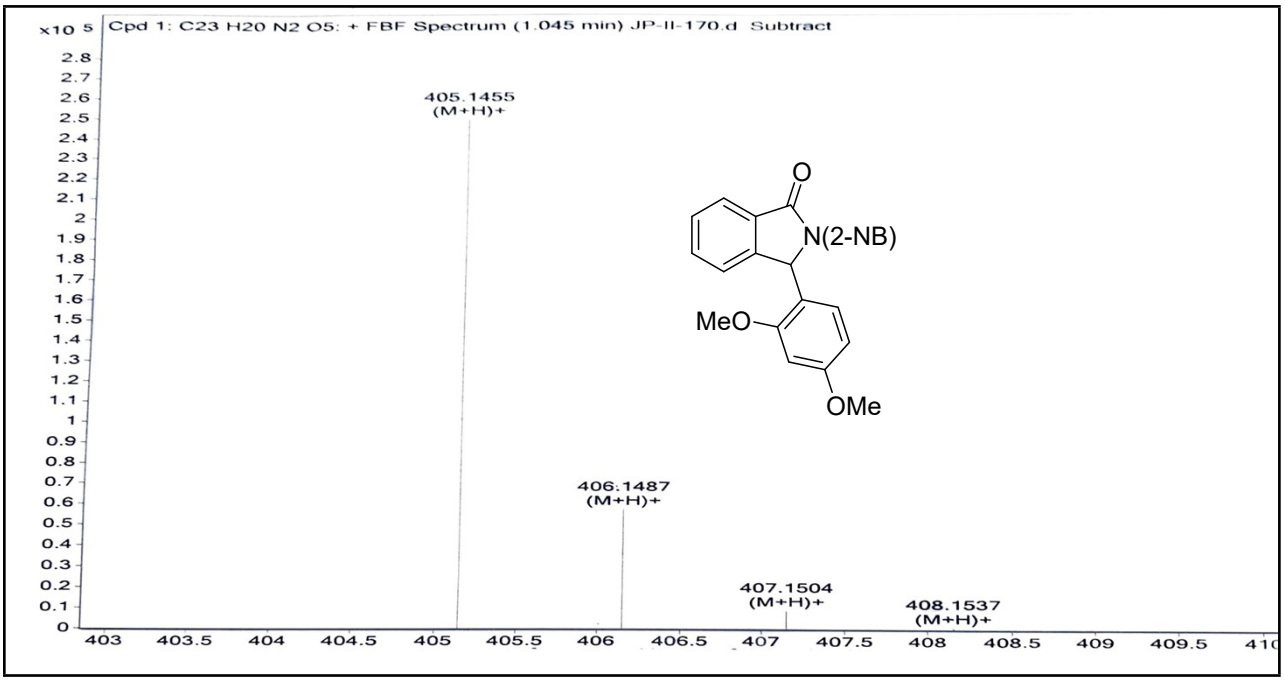
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of 3-(2,6-dimethoxyphenyl)-2-(2-nitrobenzyl)isoindolin-1-one **11d**.



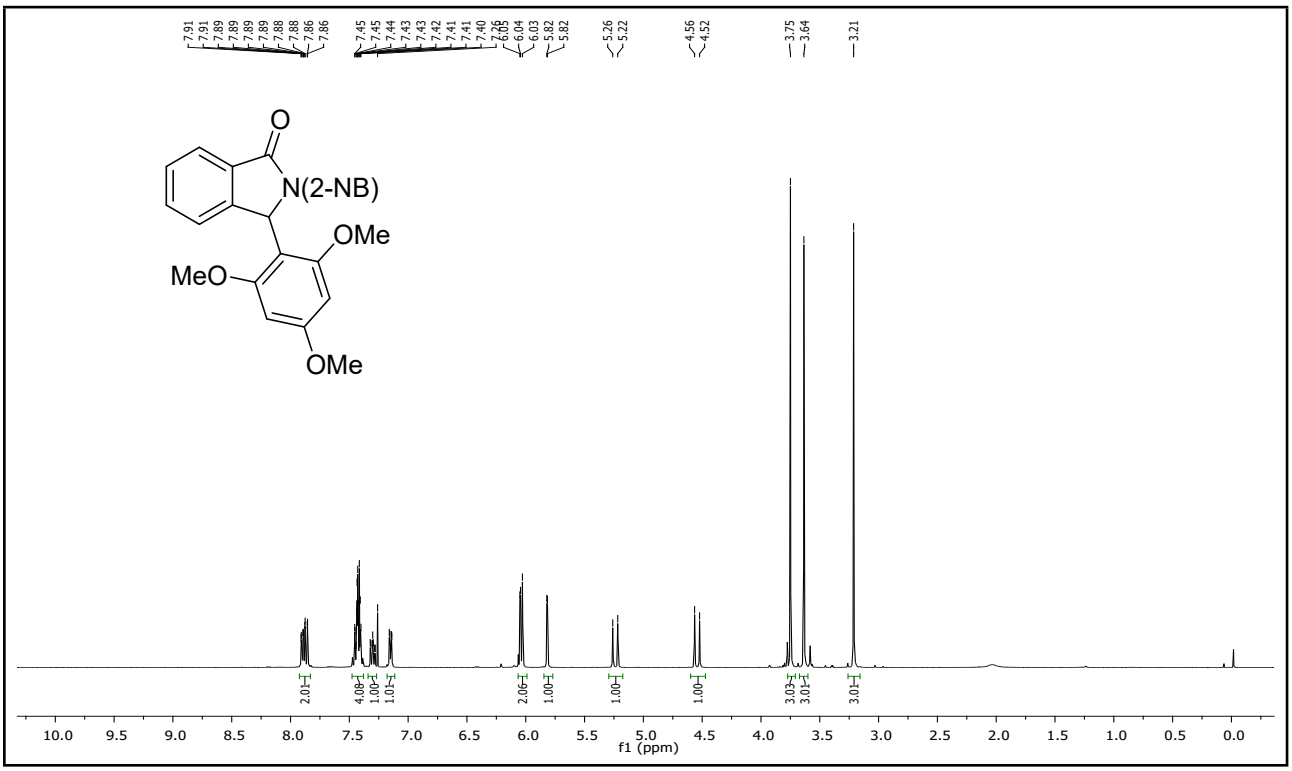
^{13}C NMR (100 MHz, $CDCl_3$) spectrum of 3-(2,6-dimethoxyphenyl)-2-(2-nitrobenzyl)isoindolin-1-one **11d**.



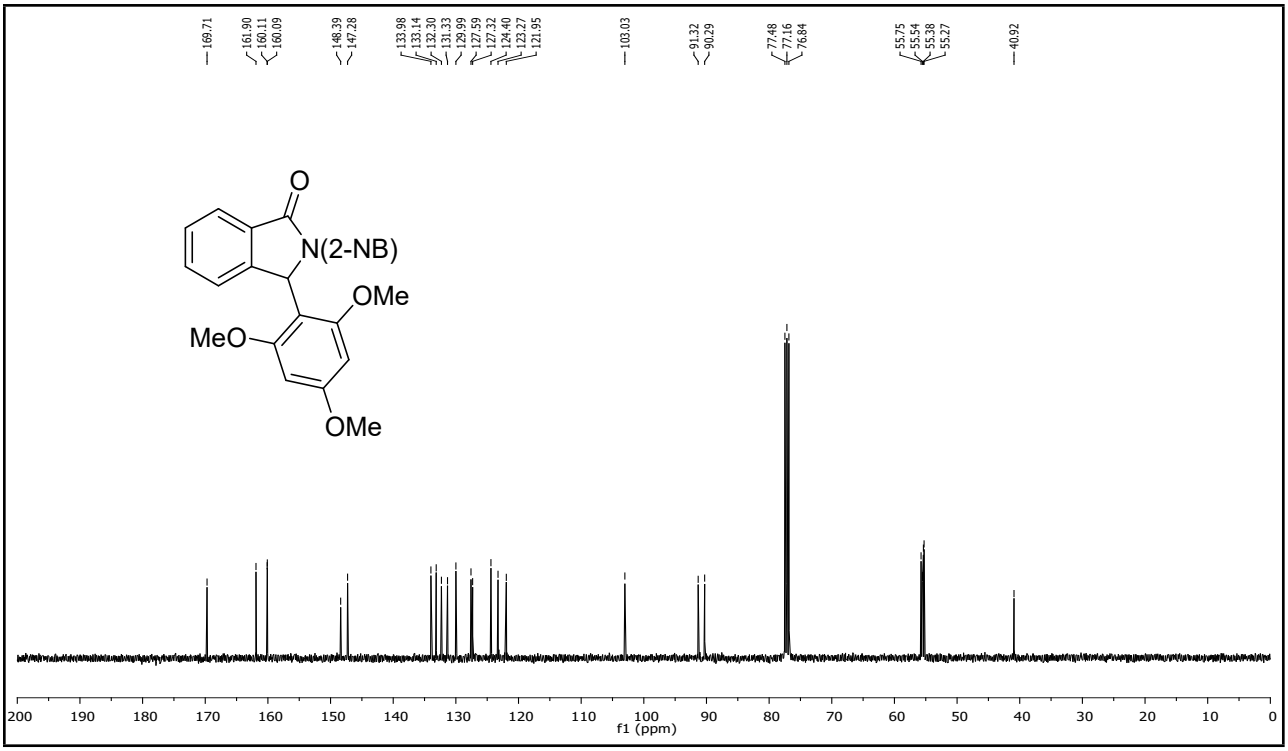
DEPT-135 spectrum of 3-(2,6-dimethoxyphenyl)-2-(2-nitrobenzyl)isoindolin-1-one **11d**.



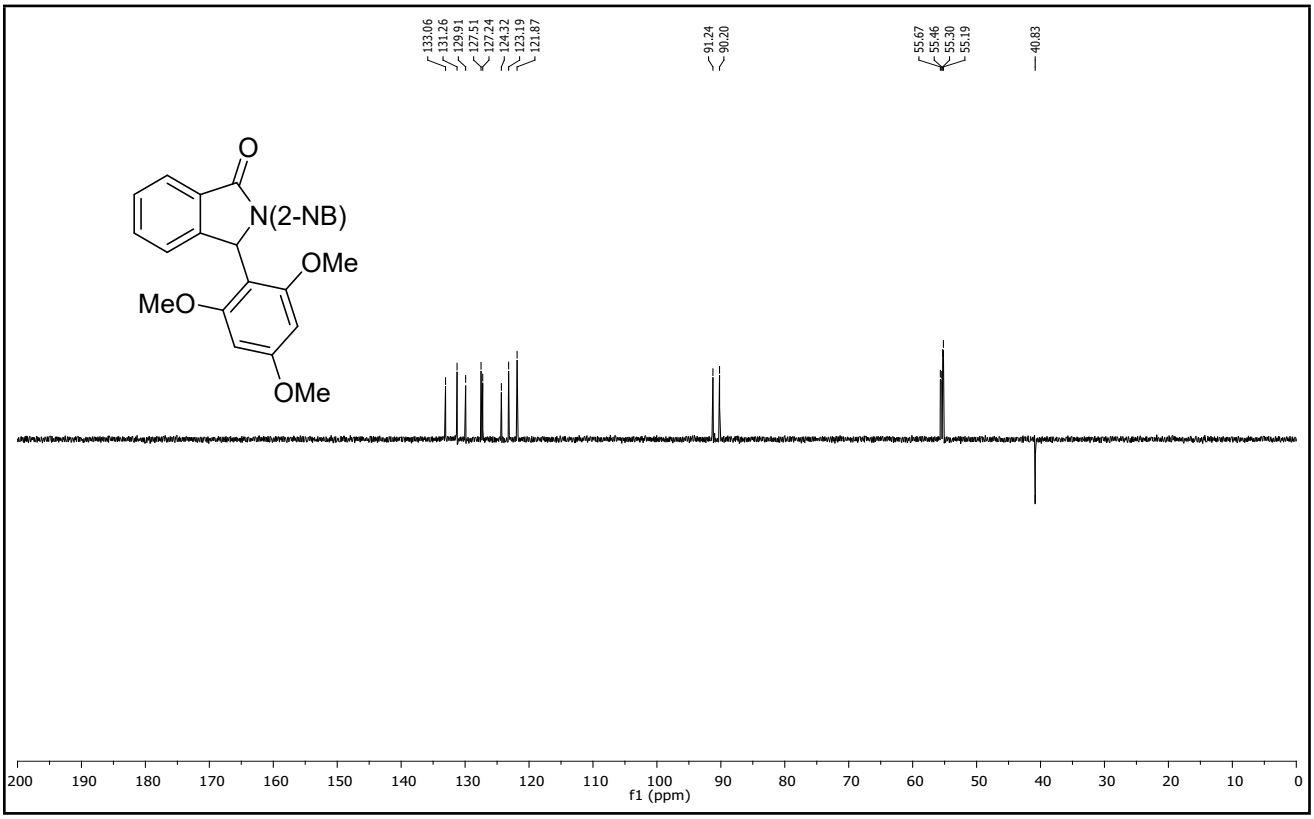
HRMS spectrum of 3-(2,6-dimethoxyphenyl)-2-(2-nitrobenzyl)isoindolin-1-one **11d**.



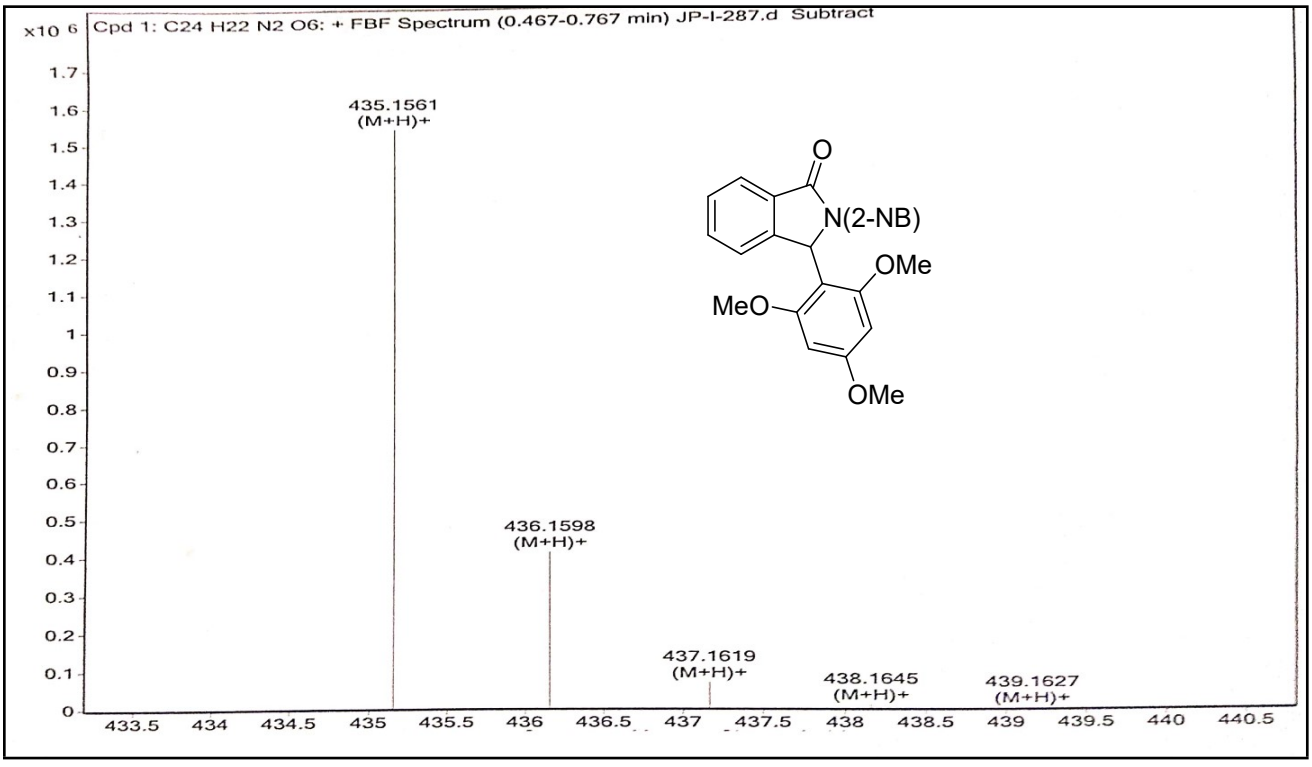
^{1}H NMR (400 MH_Z, $CDCl_3$) spectrum of 2-(2-nitrobenzyl)-3-(2,4,6-trimethoxyphenyl) isoindolin-1-one **11e**.



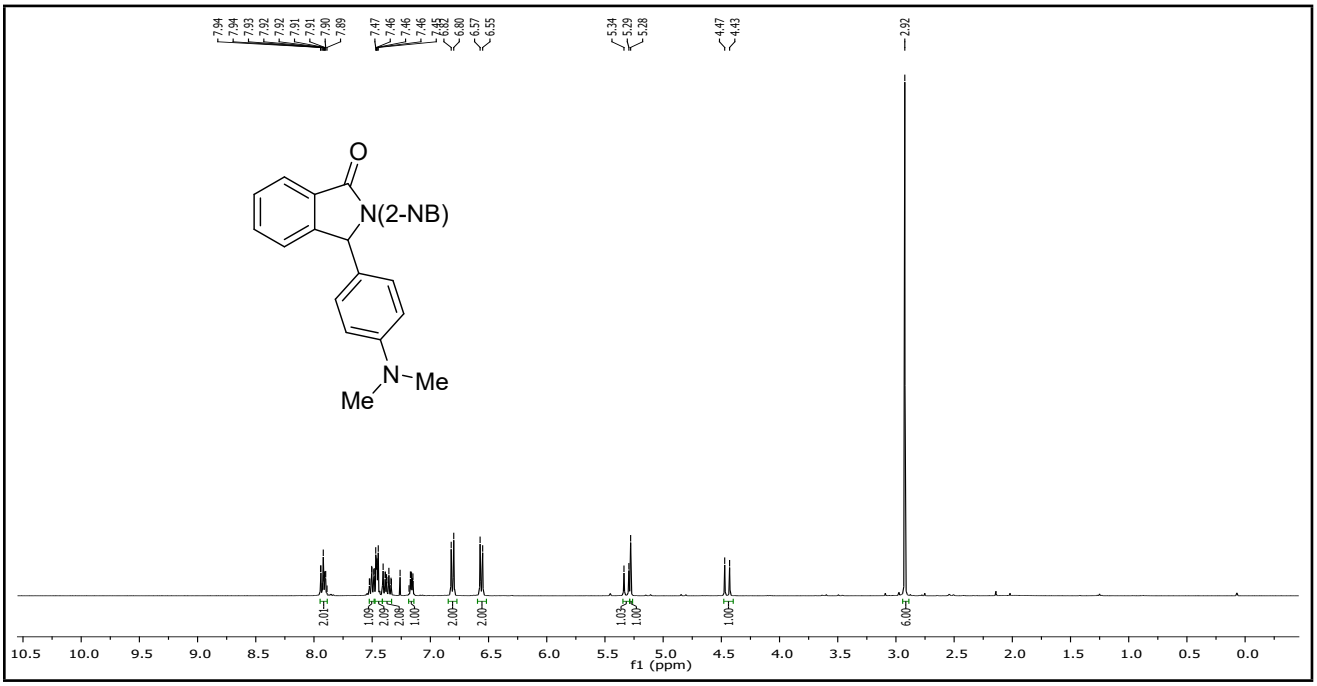
^{13}C NMR (100 MH_Z, $CDCl_3$) spectrum of 2-(2-nitrobenzyl)-3-(2,4,6-trimethoxyphenyl) isoindolin-1-one **11e**.



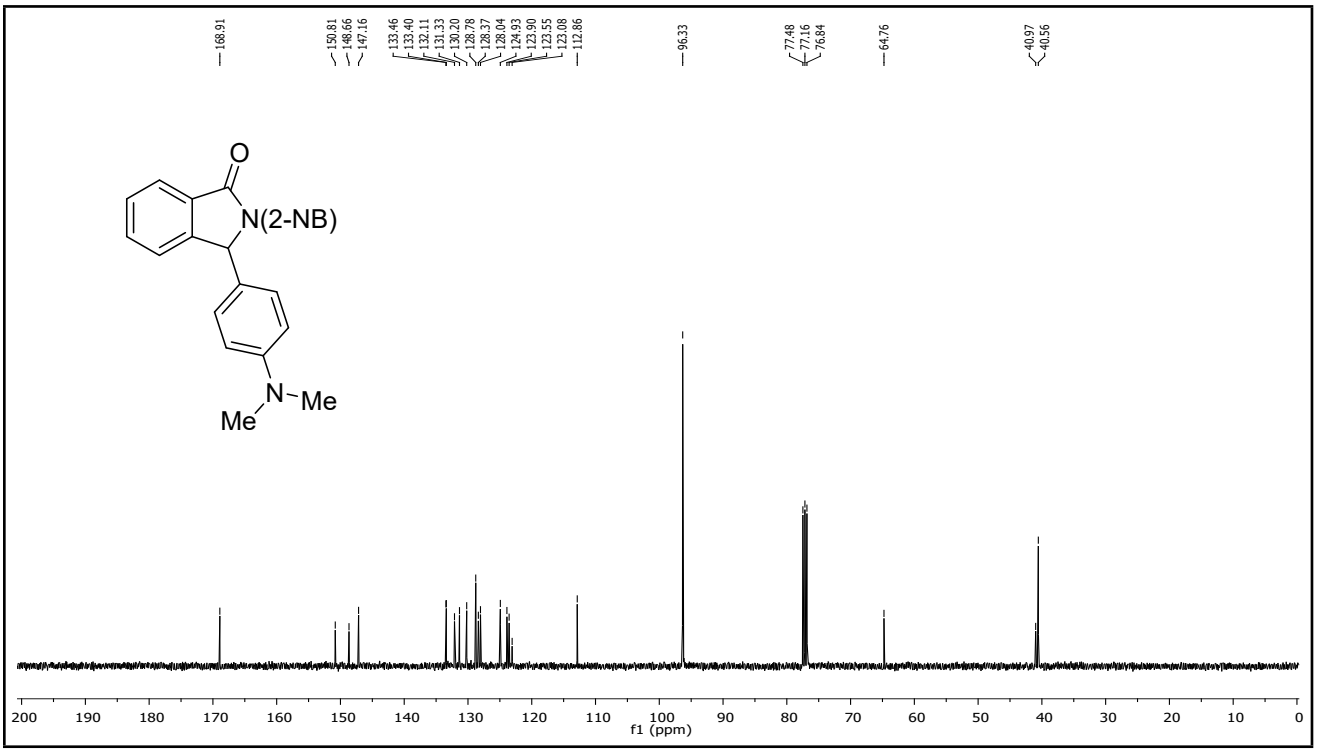
DEPT-135 spectrum of 2-(2-nitrobenzyl)-3-(2,4,6-trimethoxyphenyl)isoindolin-1-one **11e**.



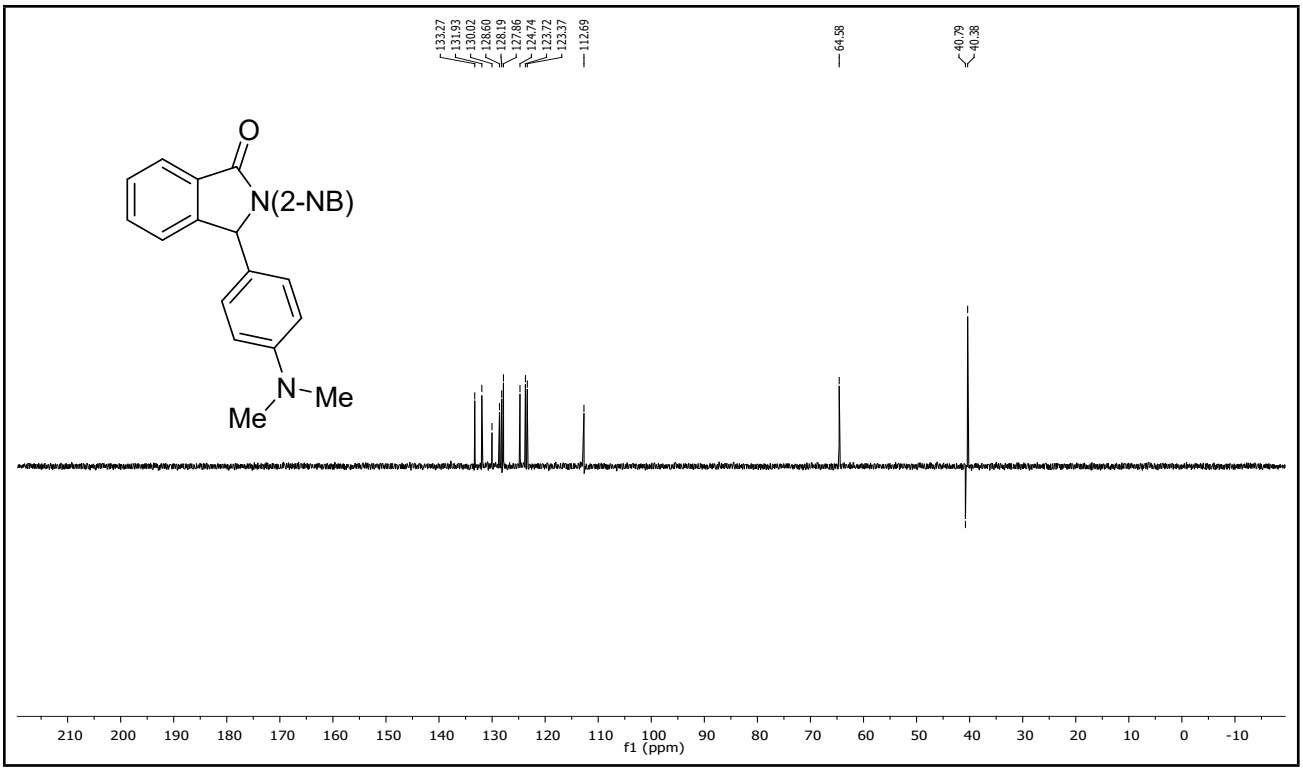
HRMS spectrum of 2-(2-nitrobenzyl)-3-(2,4,6-trimethoxyphenyl)isoindolin-1-one **11e**.



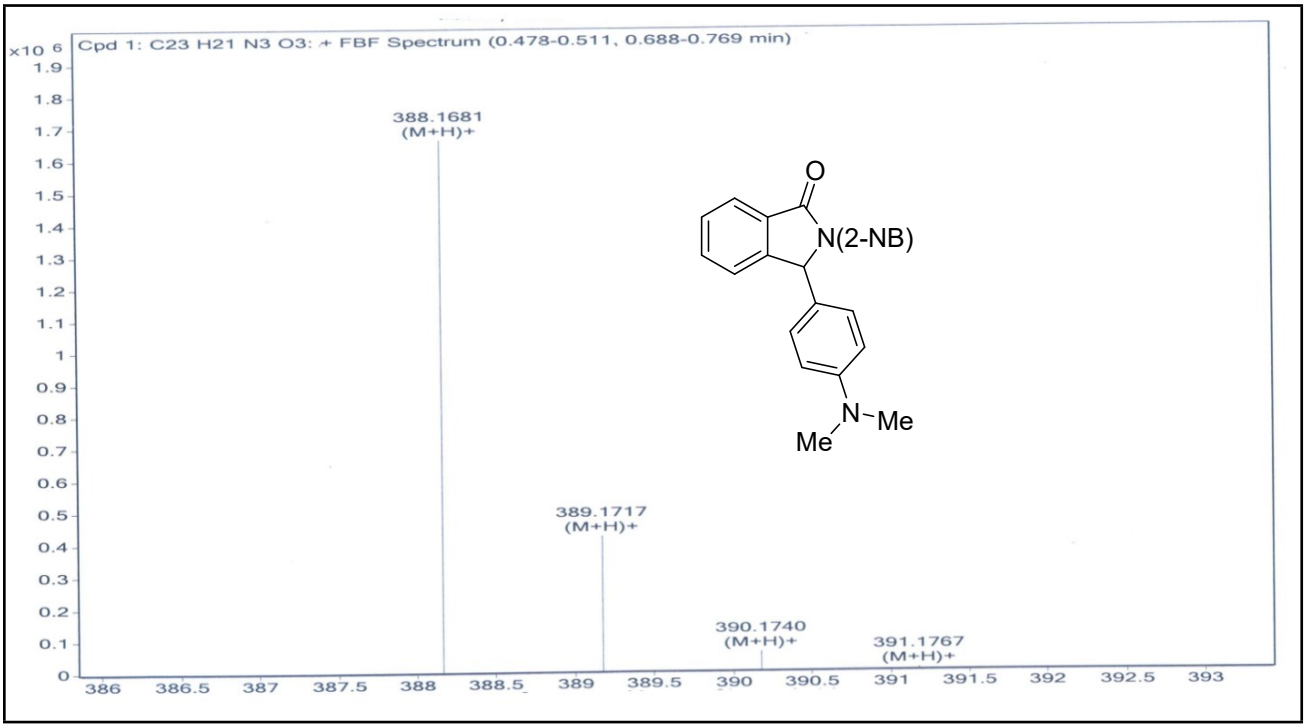
^{1}H NMR (400 MH_Z, $CDCl_3$ + CCl_4; 1:1) spectrum of 3-(4-(dimethylamino)phenyl)-2-(2-nitrobenzyl)isoindolin-1-one **11f**.



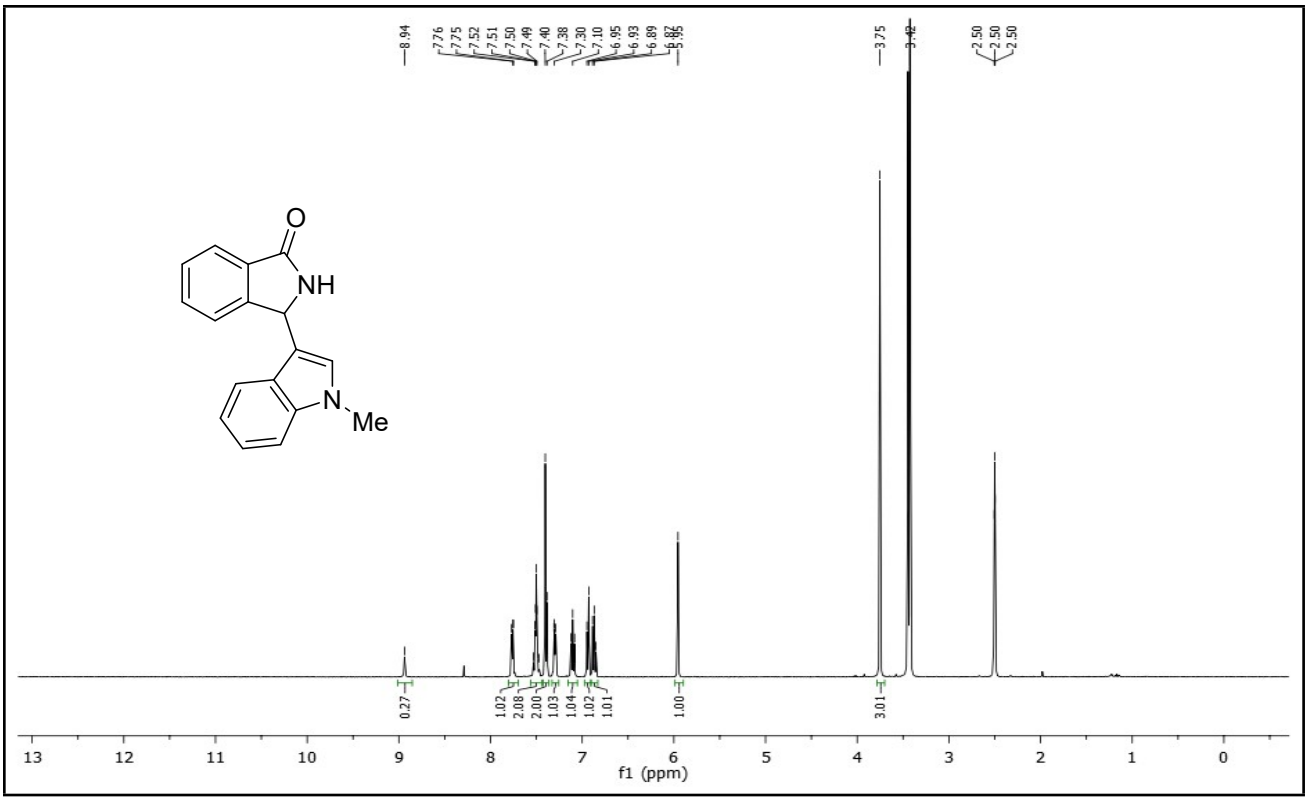
^{13}C NMR (100 MH_Z, $CDCl_3$ + CCl_4; 1:1) spectrum of 3-(4-(dimethylamino)phenyl)-2-(2-nitrobenzyl)isoindolin-1-one **11f**.



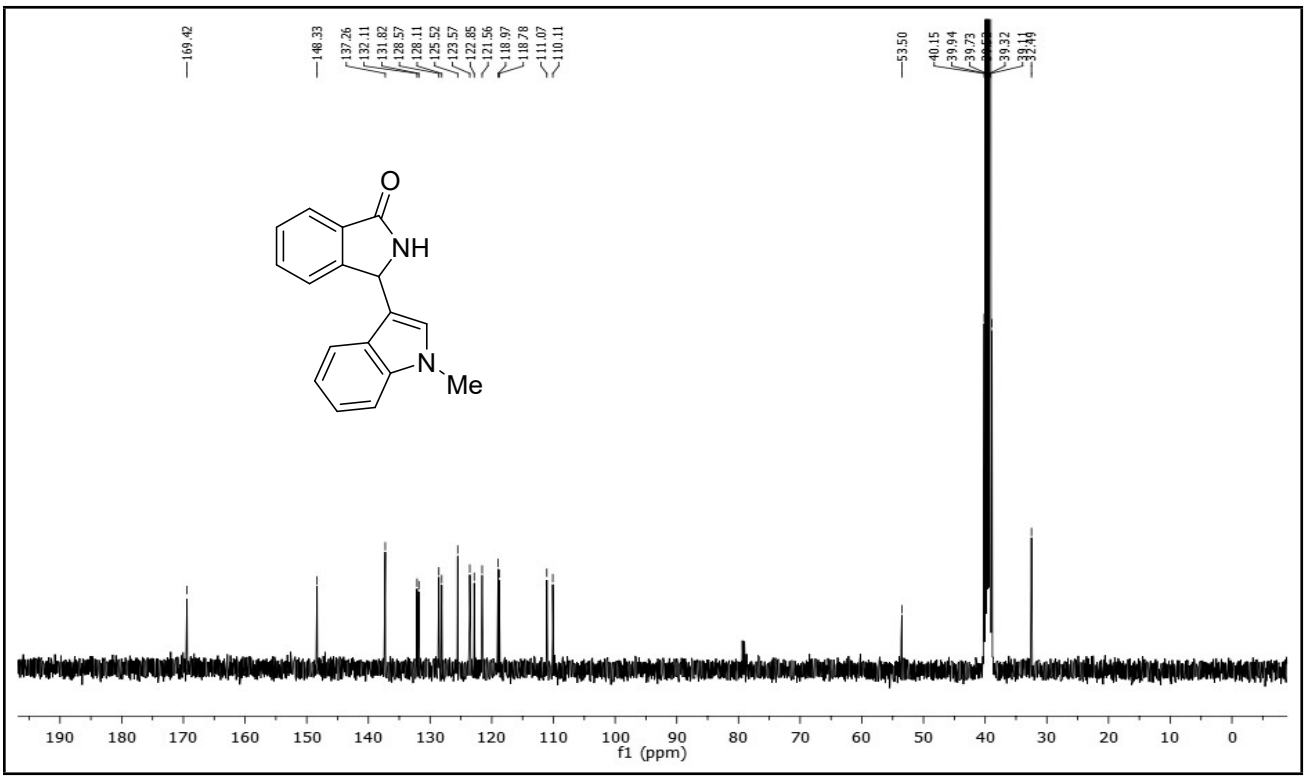
DEPT-135 spectrum of 3-(4-(dimethylamino)phenyl)-2-(2-nitrobenzyl)isoindolin-1-one **11f**.



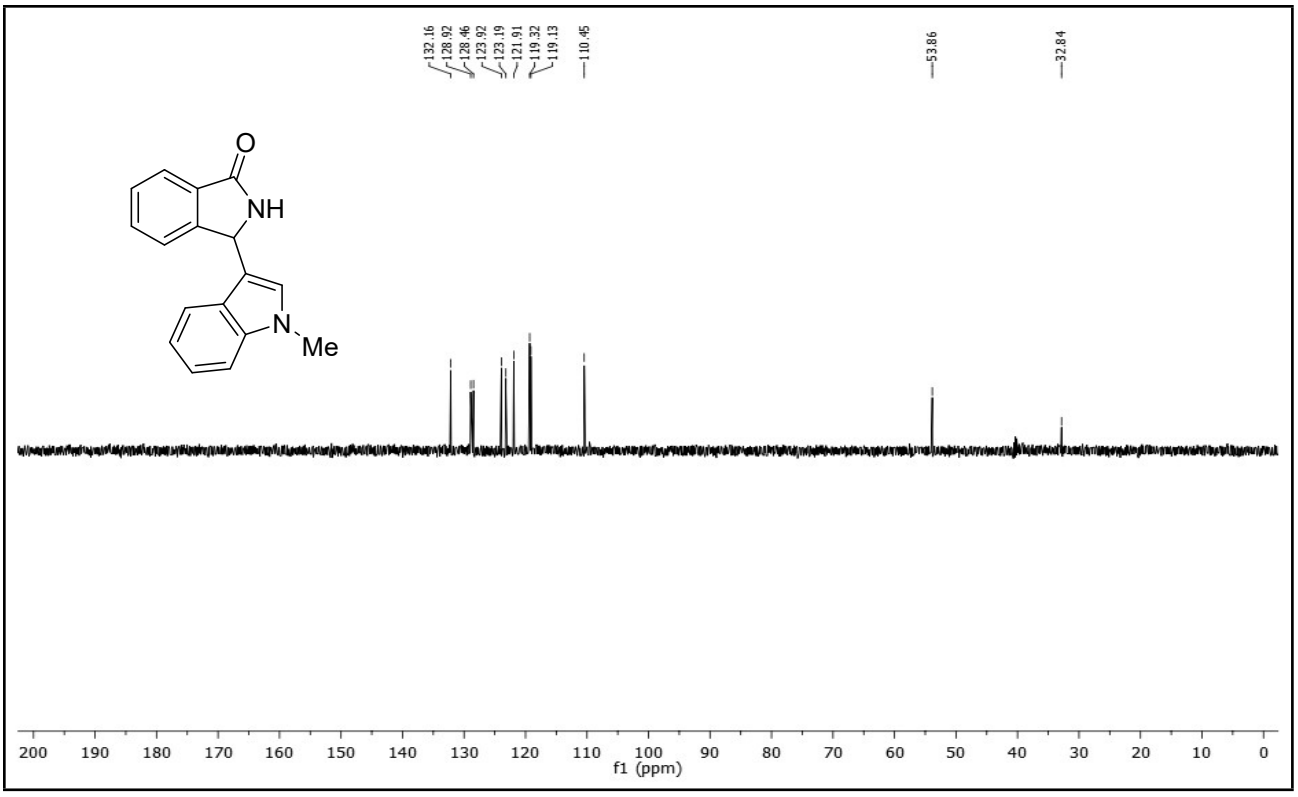
HRMS spectrum of 3-(4-(dimethylamino)phenyl)-2-(2-nitrobenzyl)isoindolin-1-one **11f**.



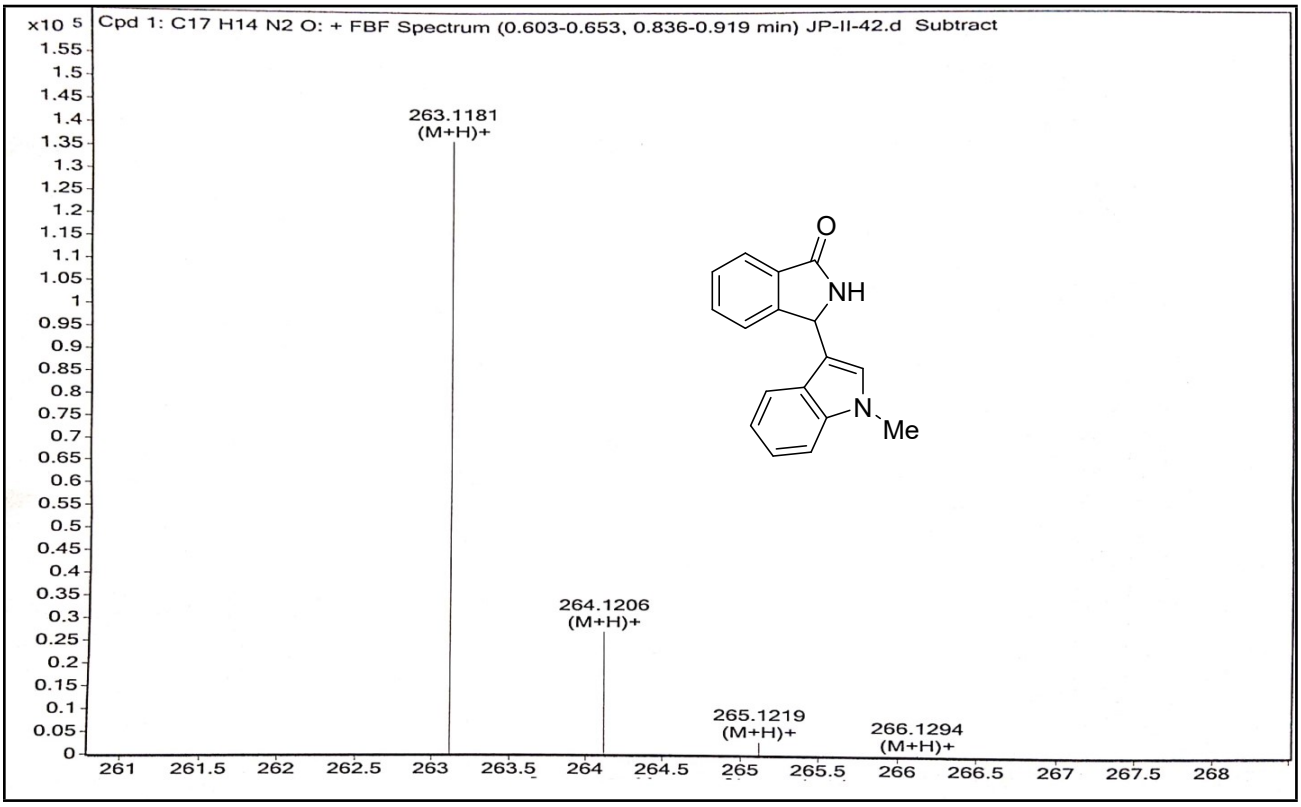
^{1}H NMR (400 MH_Z, DMSO-d_6) spectrum of 3-(1-methyl-1*H*-indol-3-yl)isoindolin-1-one **12a**.



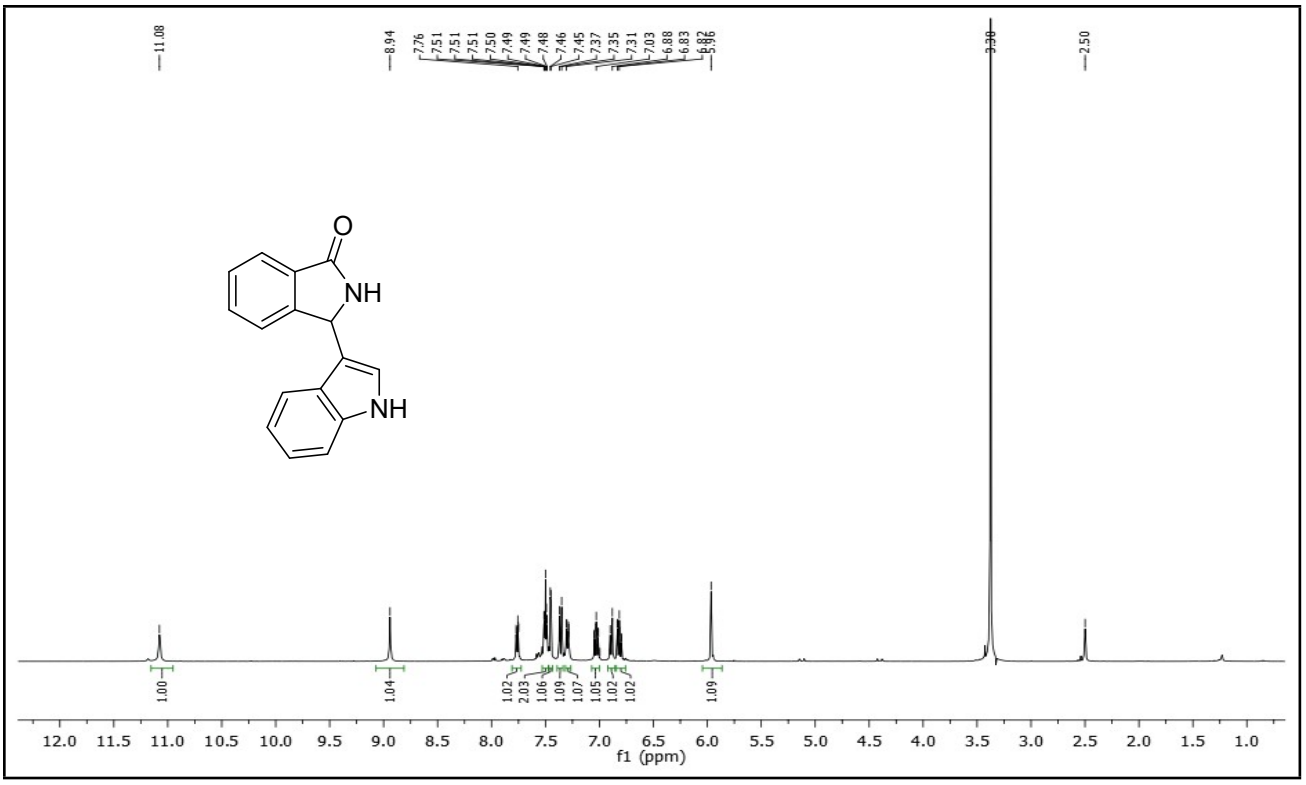
^{13}C NMR (100 MH_Z, DMSO-d_6) spectrum of 3-(1-methyl-1*H*-indol-3-yl)isoindolin-1-one **12a**.



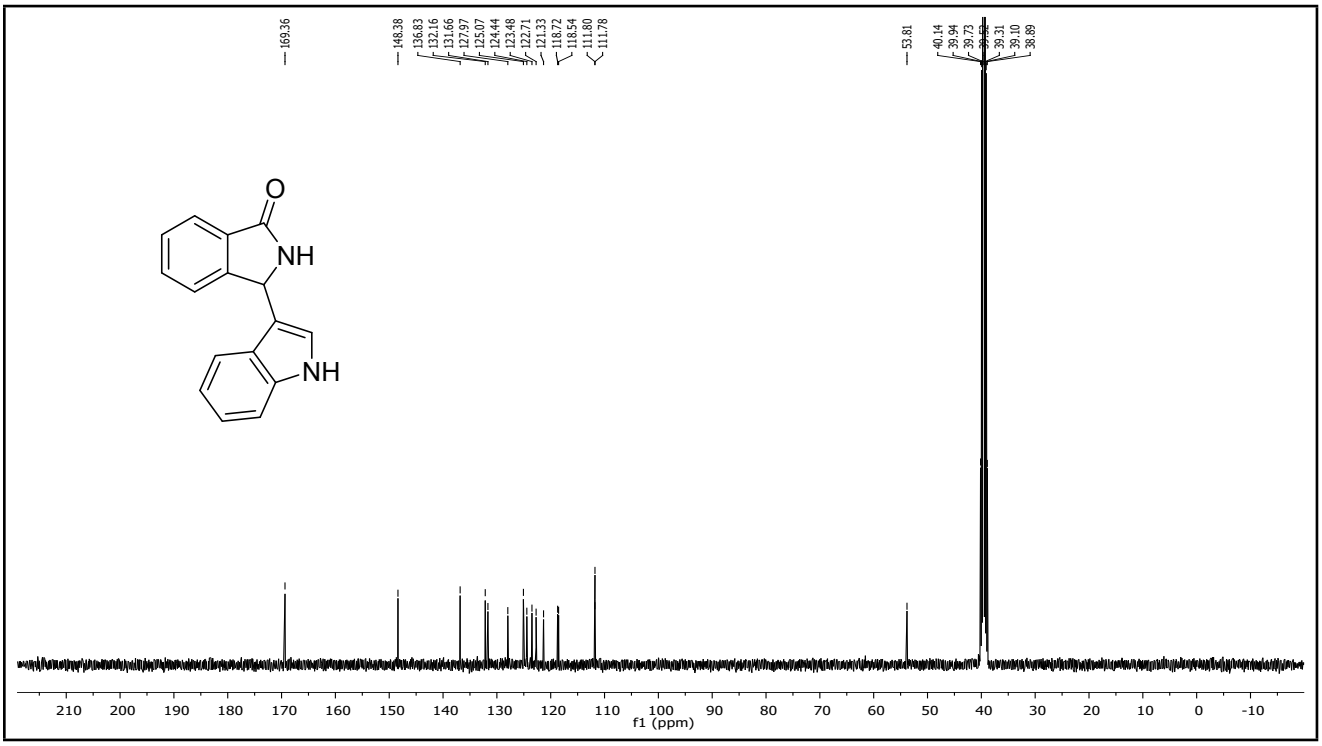
DEPT-135 spectrum of 3-(1-methyl-1*H*-indol-3-yl)isoindolin-1-one **12a**.



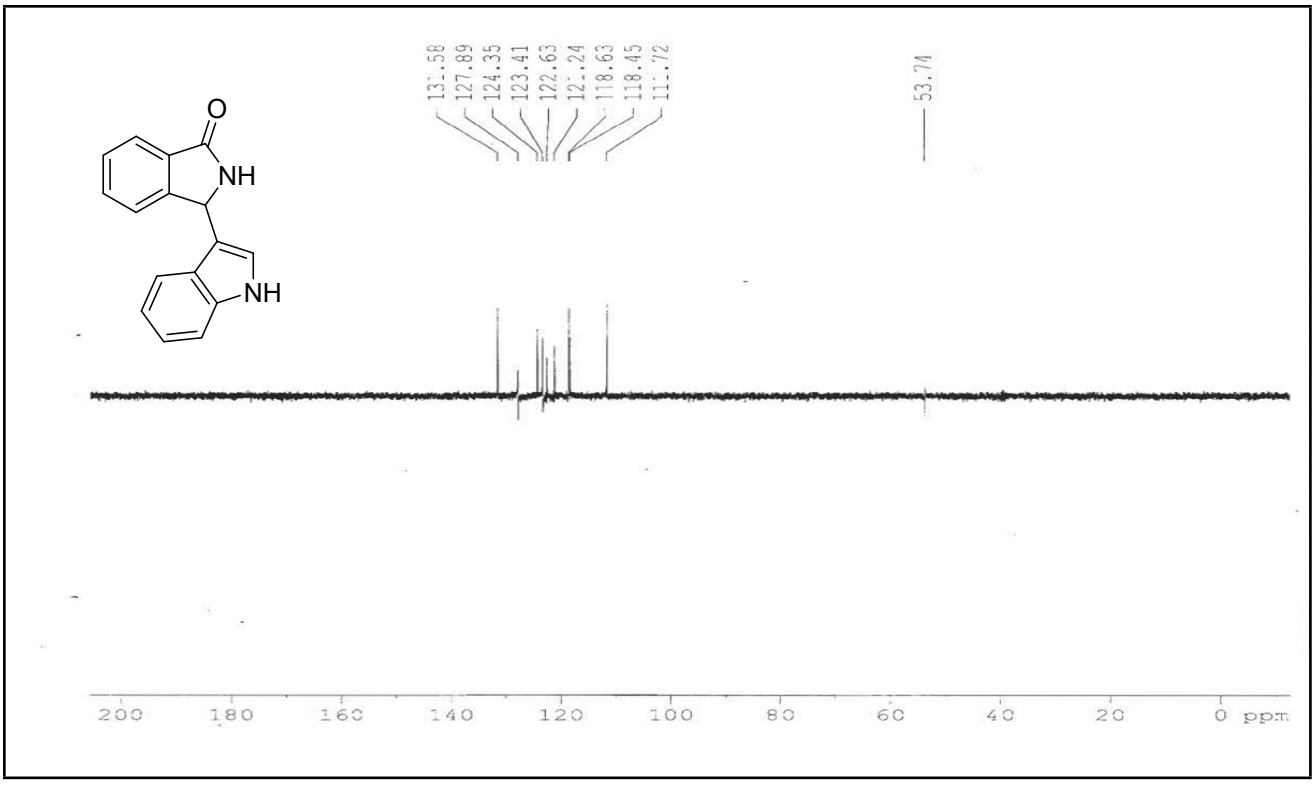
HRMS spectrum of 3-(1-methyl-1*H*-indol-3-yl)isoindolin-1-one **12a**.



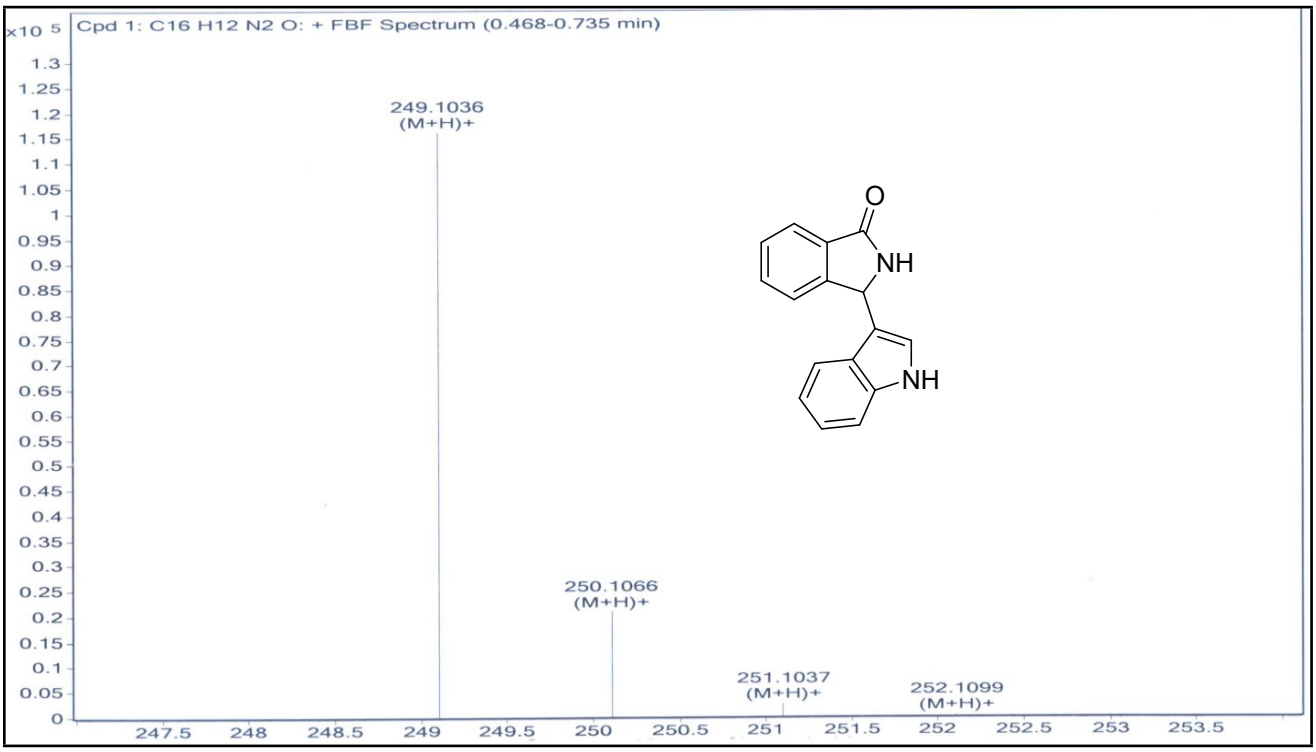
^{1}H NMR (400 MH$_Z$, DMSO-d_6) spectrum of 3-(1*H*-indol-3-yl)isoindolin-1-one **12b**.



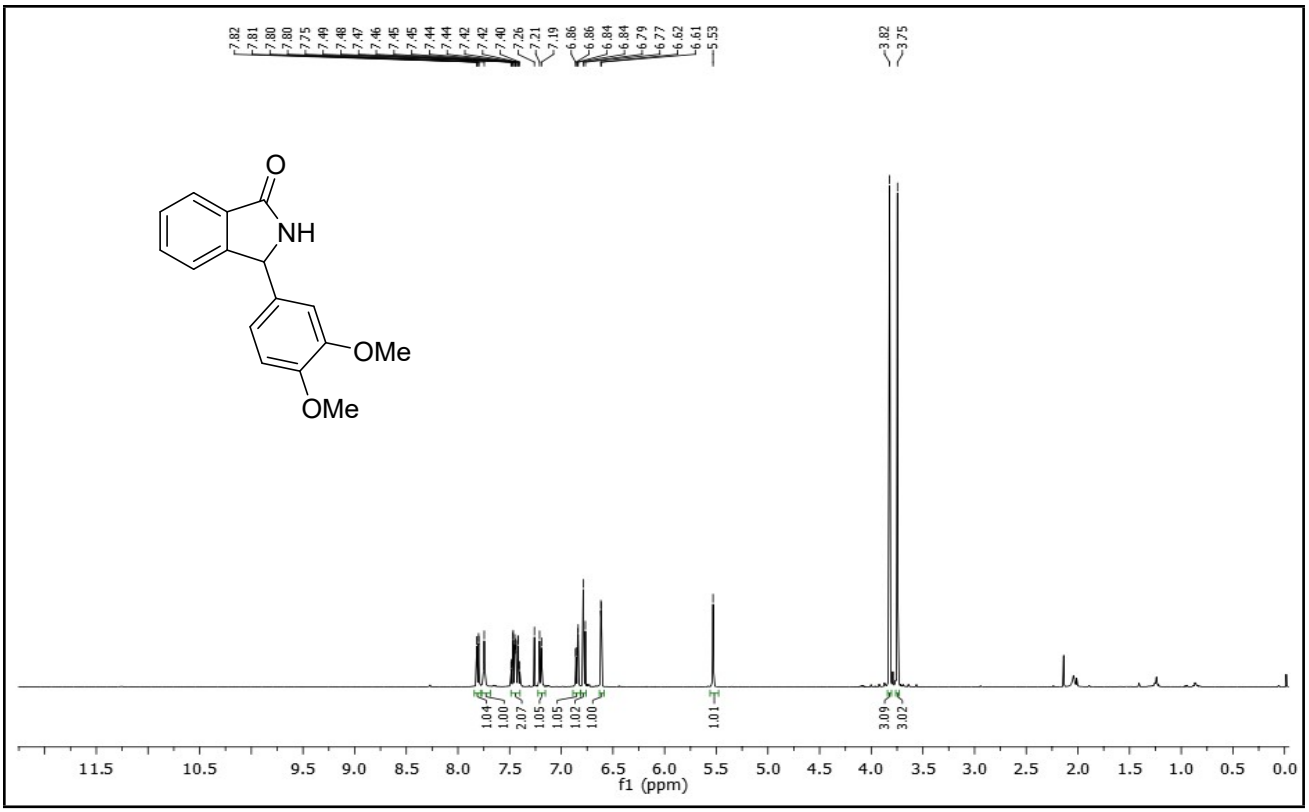
^{13}C NMR (100 MH$_Z$, DMSO-d_6) spectrum of 3-(1*H*-indol-3-yl)isoindolin-1-one **12b**.



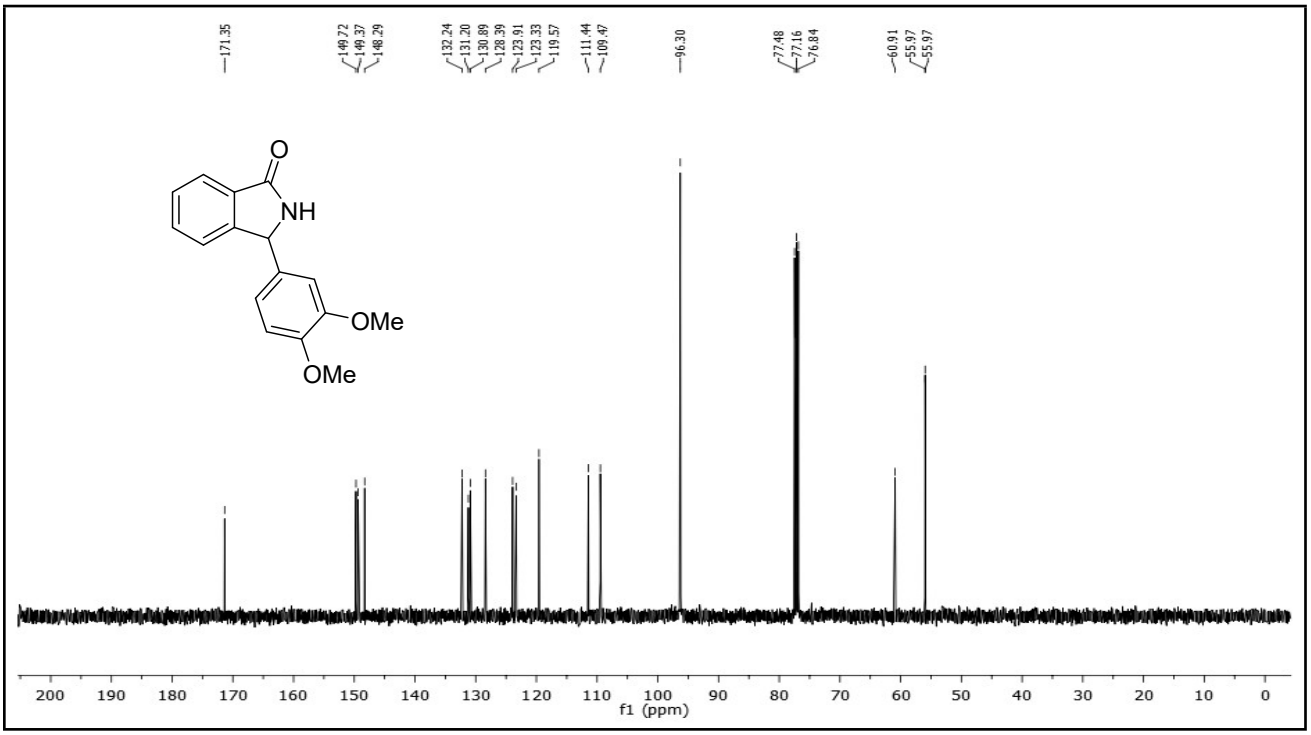
DEPT-135 spectrum of 3-(1*H*-indol-3-yl)isoindolin-1-one **12b**.



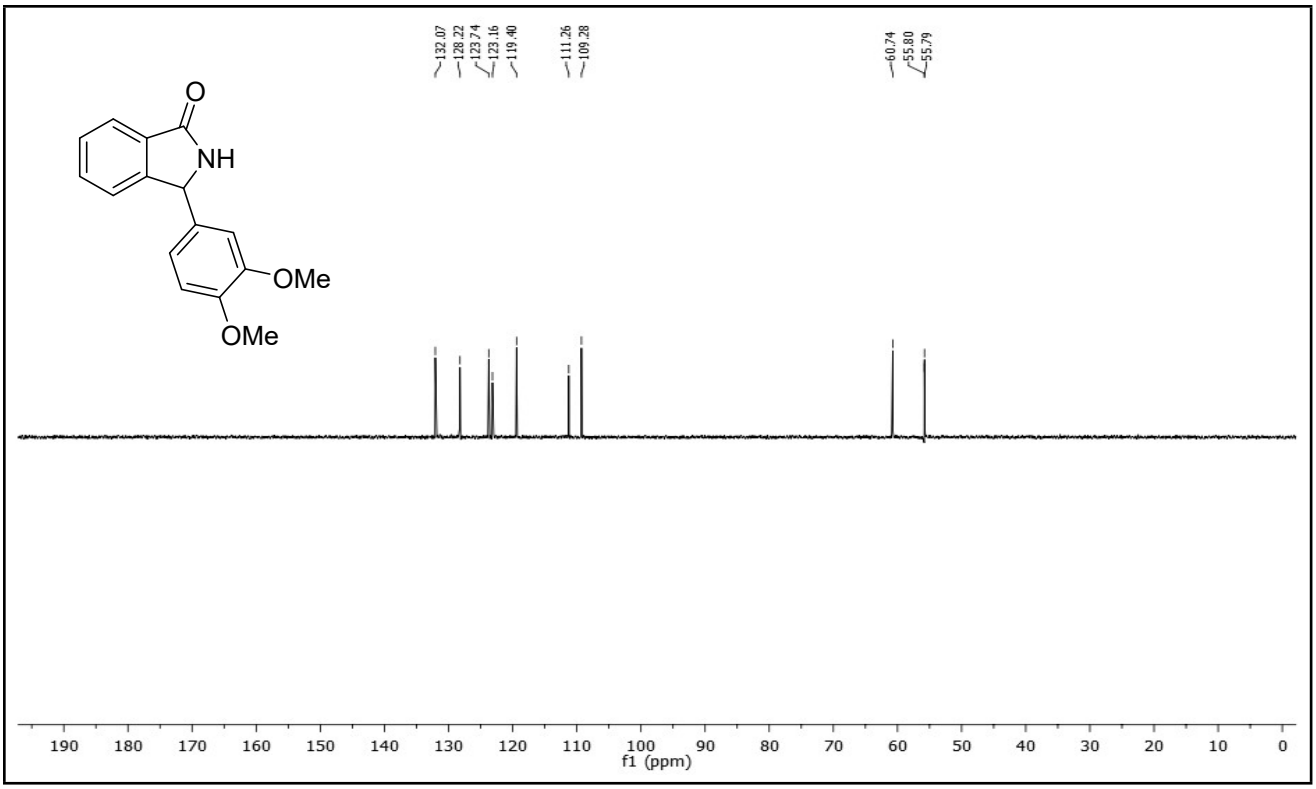
HRMS spectrum of 3-(1*H*-indol-3-yl)isoindolin-1-one **12b**.



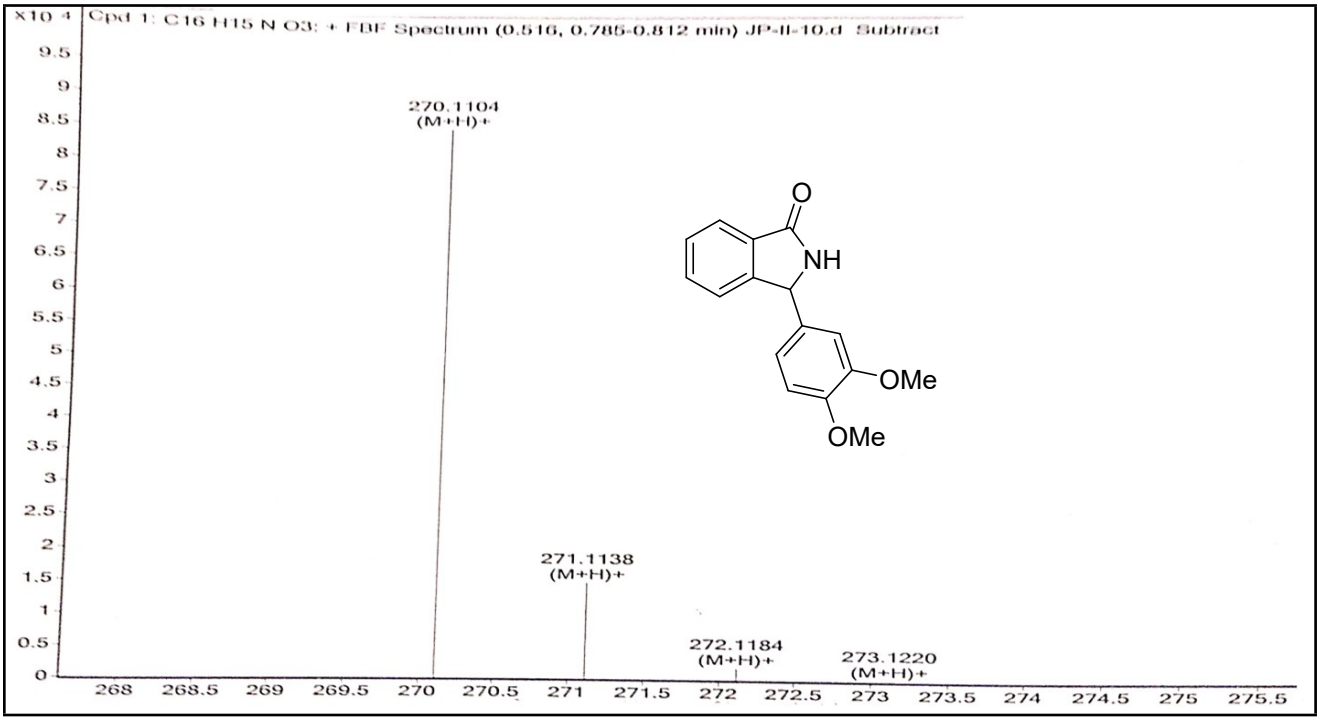
^{1}H NMR (400 MH_Z, $CDCl_3$ + CCl_4; 1:1) spectrum of 3-(3,4-dimethoxyphenyl)isoindolin-1-one **12c**.



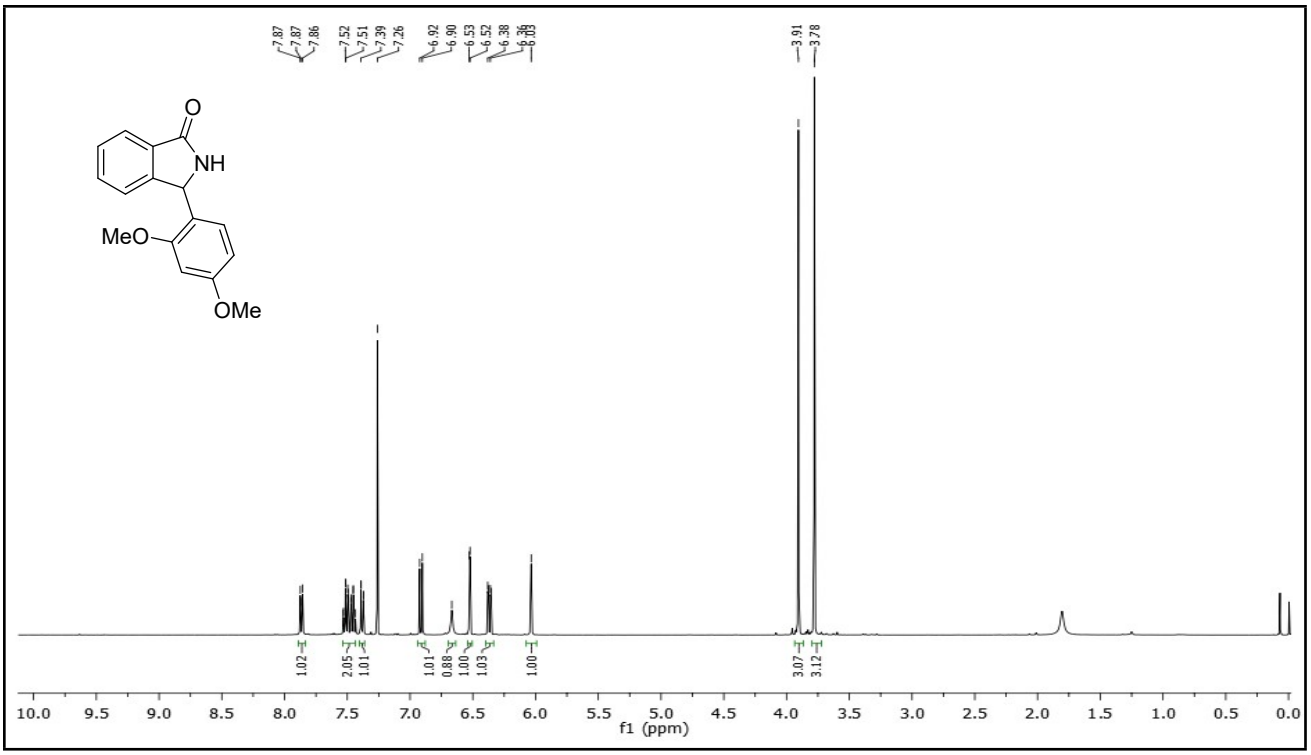
^{13}C NMR (100 MH_Z, $CDCl_3$ + CCl_4; 1:1) spectrum of 3-(3,4-dimethoxyphenyl)isoindolin-1-one **12c**.



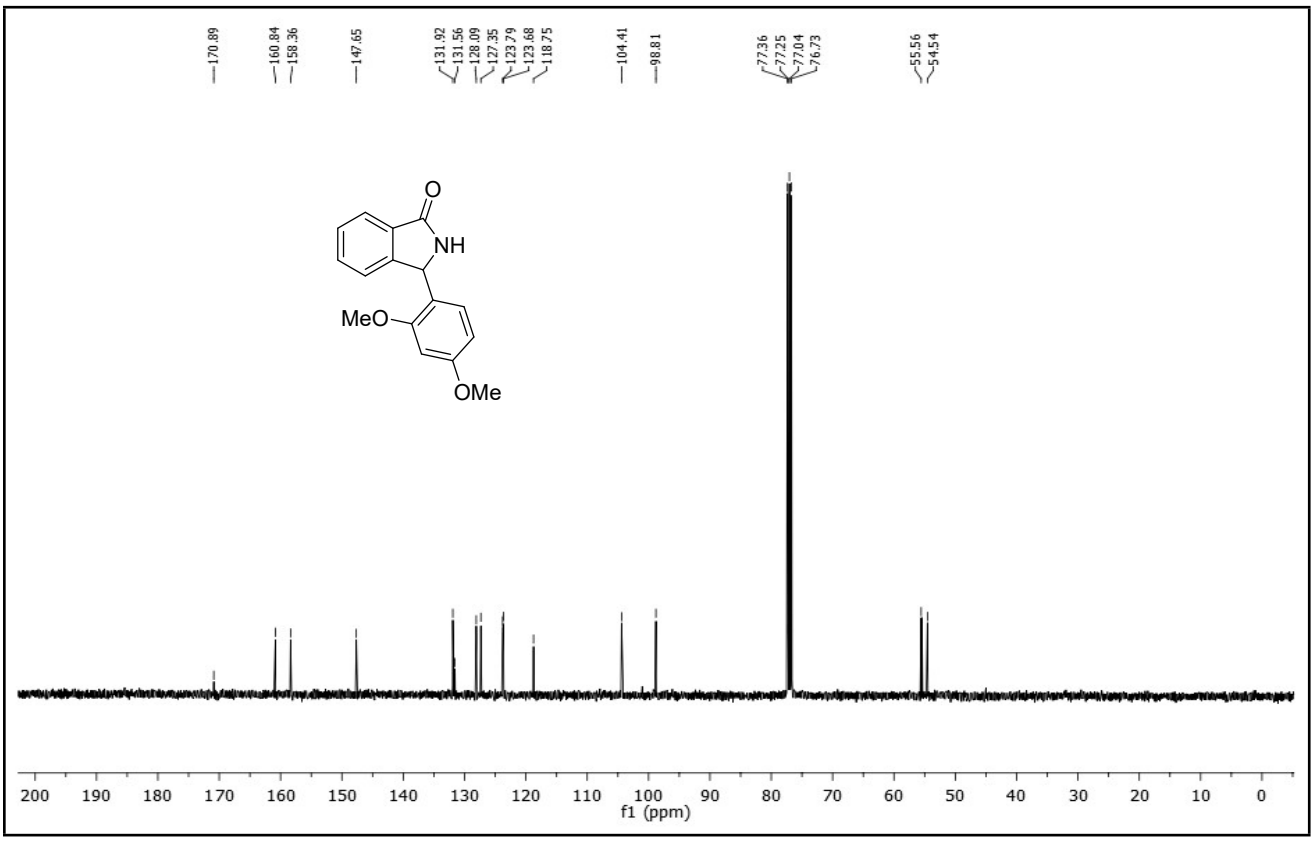
DEPT-135 spectrum of 3-(3,4-dimethoxyphenyl)isoindolin-1-one **12c**.



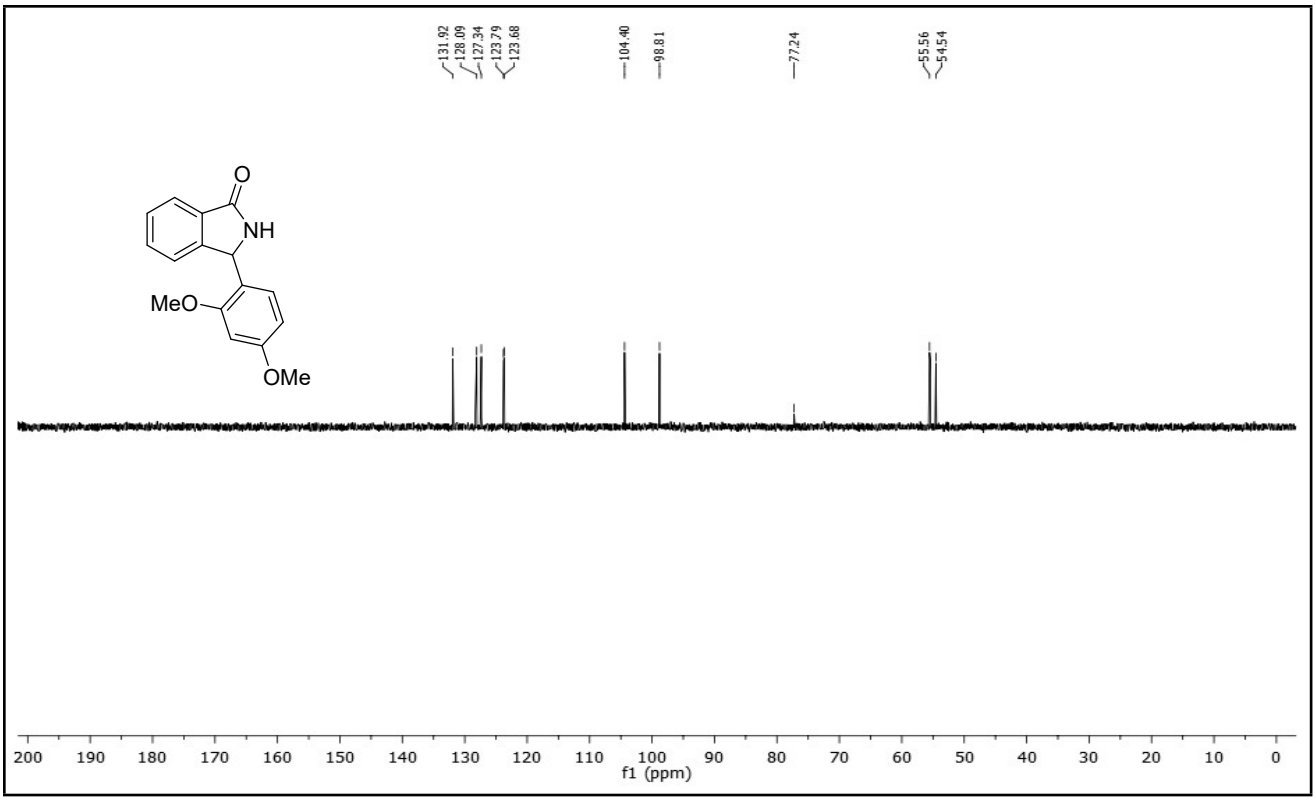
HRMS spectrum of 3-(3,4-dimethoxyphenyl)isoindolin-1-one **12c**.



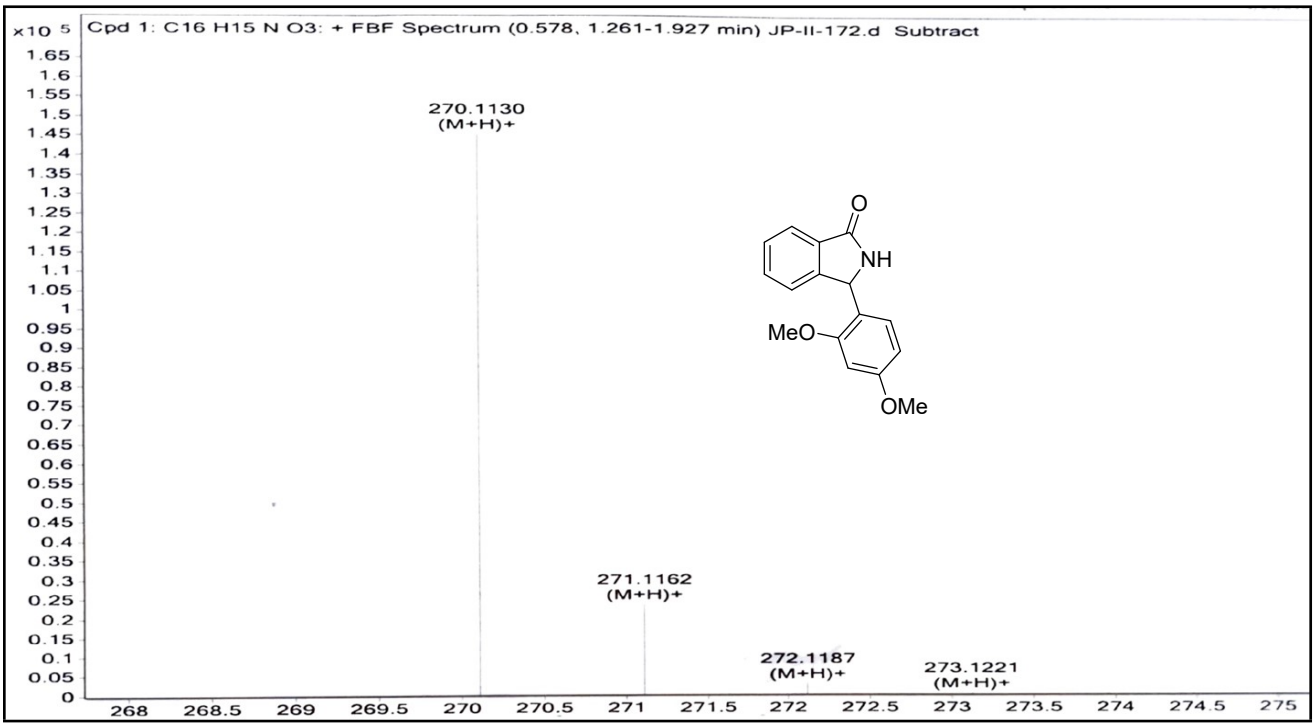
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of 3-(2,4-dimethoxyphenyl)isoindolin-1-one **12d**.



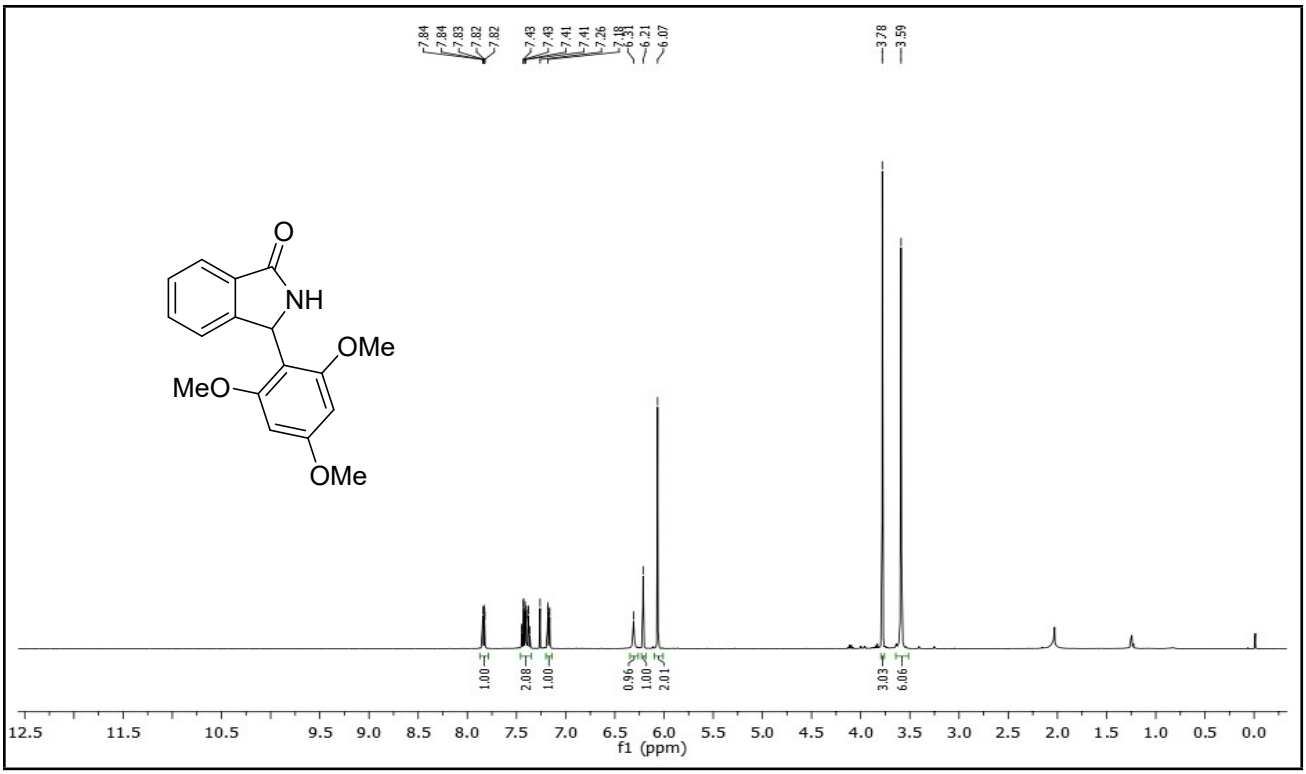
^{13}C NMR (100 MHz, $CDCl_3$) spectrum of 3-(2,4-dimethoxyphenyl)isoindolin-1-one **12d**.



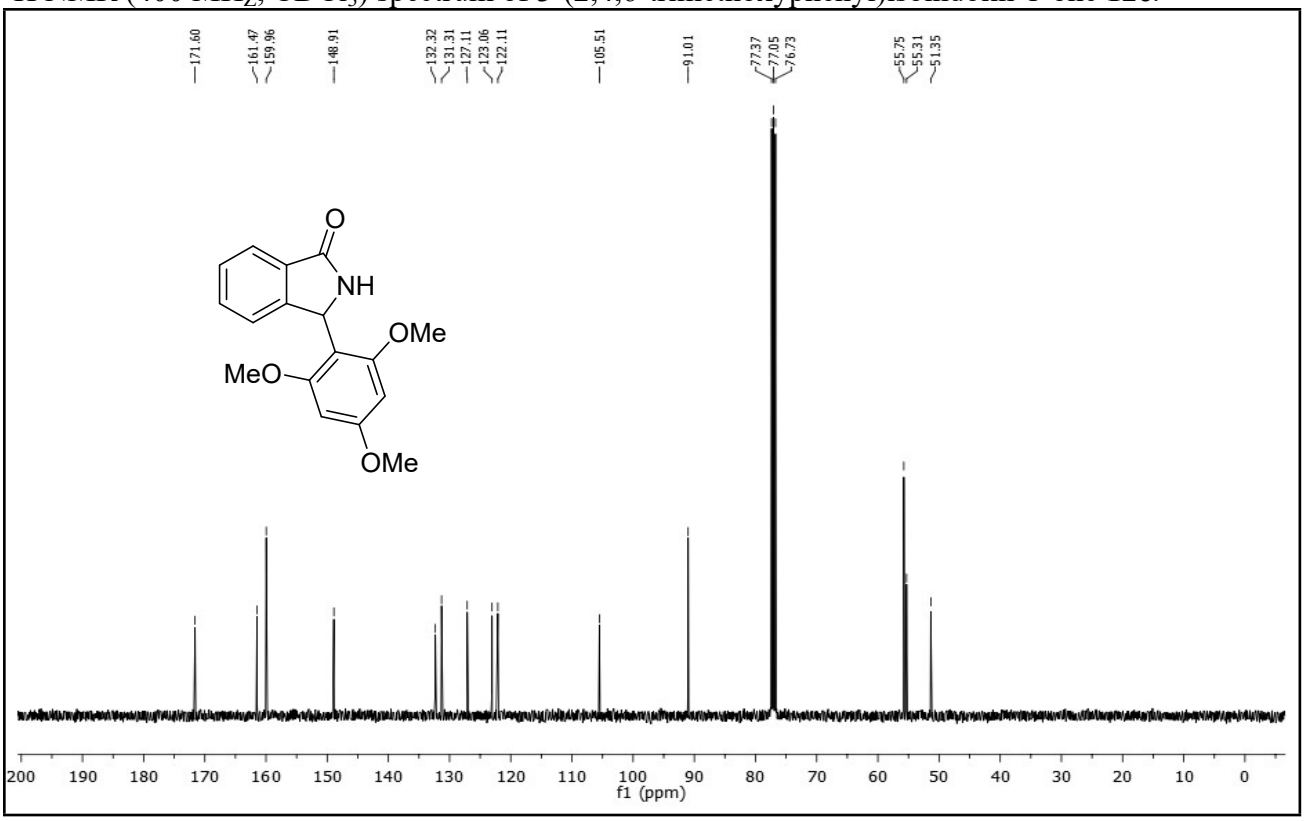
DEPT-135 spectrum of 3-(2,4-dimethoxyphenyl)isoindolin-1-one **12d**.



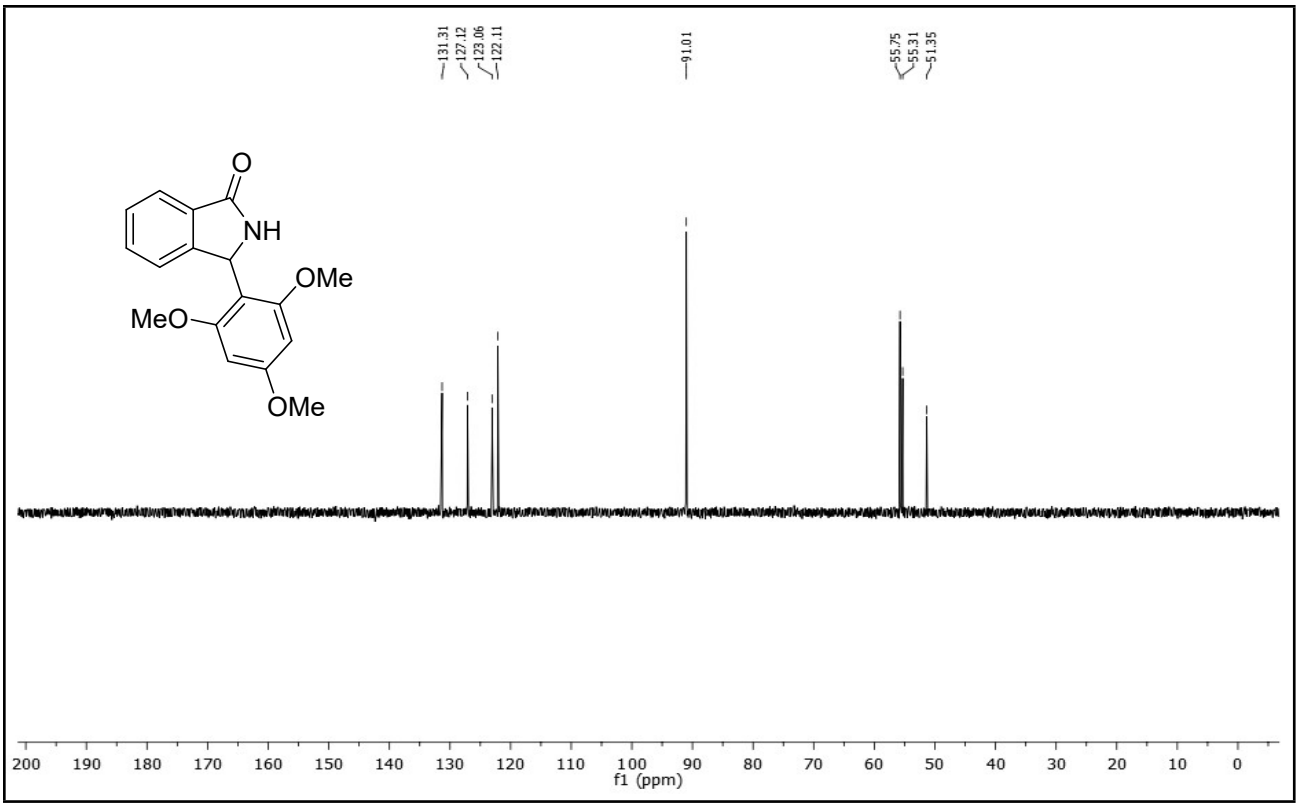
HRMS spectrum of 3-(2,4-dimethoxyphenyl)isoindolin-1-one **12d**.



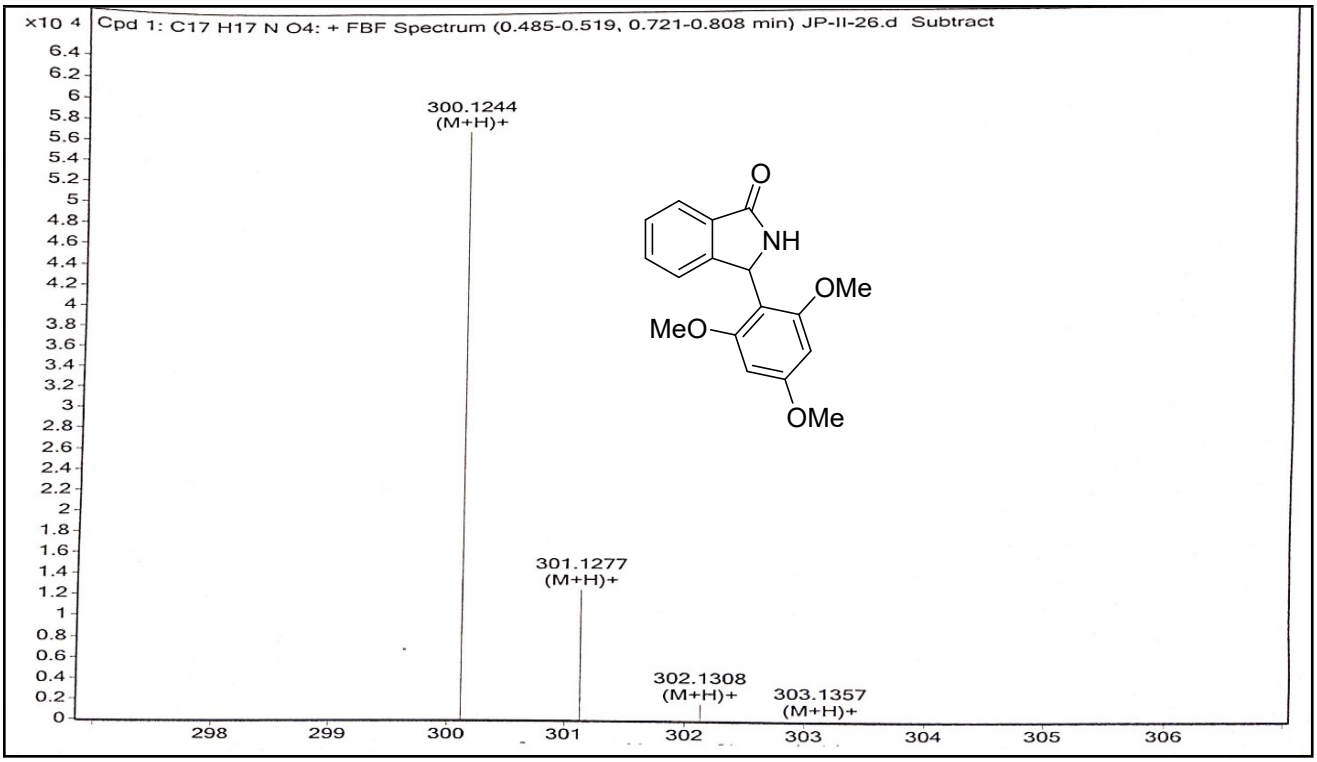
^{1}H NMR (400 MH_Z, $CDCl_3$) spectrum of 3-(2,4,6-trimethoxyphenyl)isoindolin-1-one **12e**.



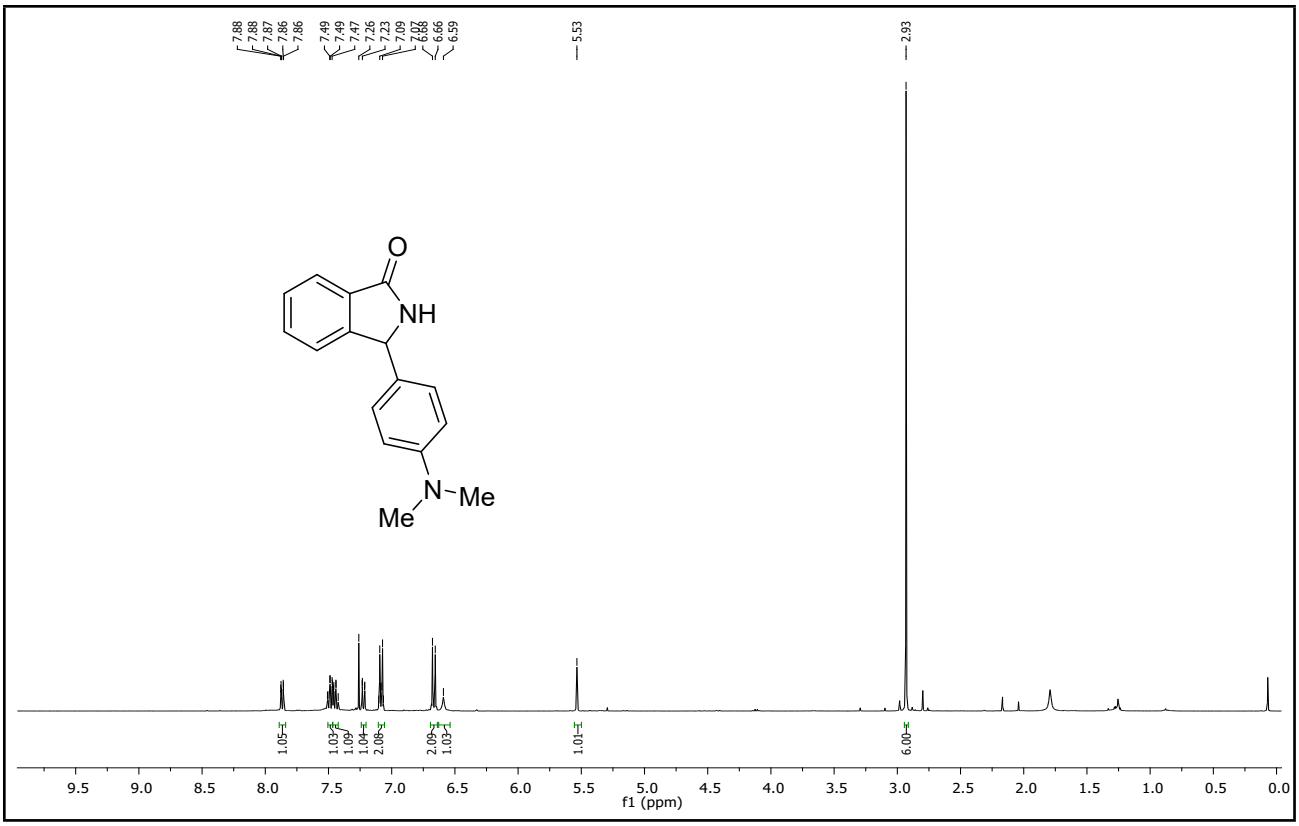
^{13}C NMR (100 MH_Z, $CDCl_3$) spectrum of 3-(2,4,6-trimethoxyphenyl)isoindolin-1-one **12e**.



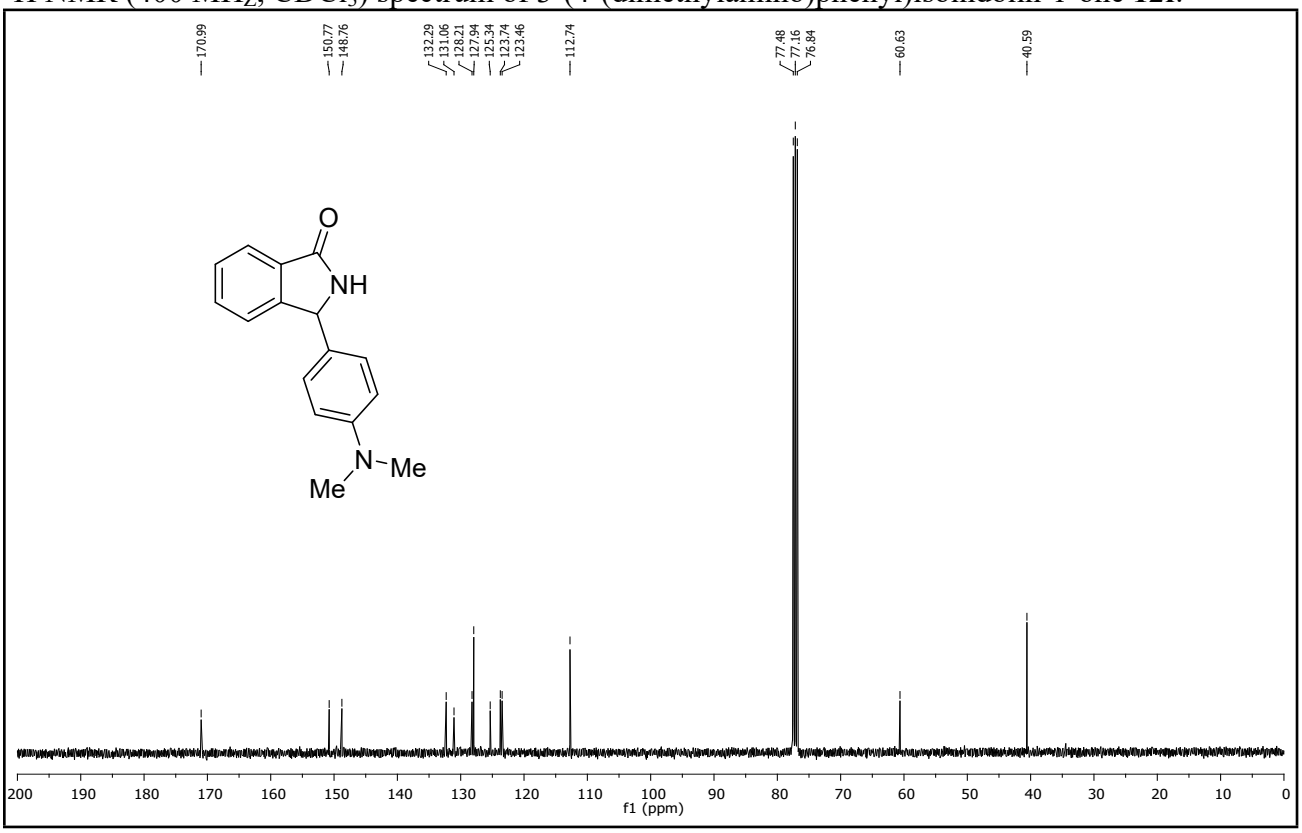
DEPT-135 spectrum of 3-(2,4,6-trimethoxyphenyl)isoindolin-1-one **12e**.



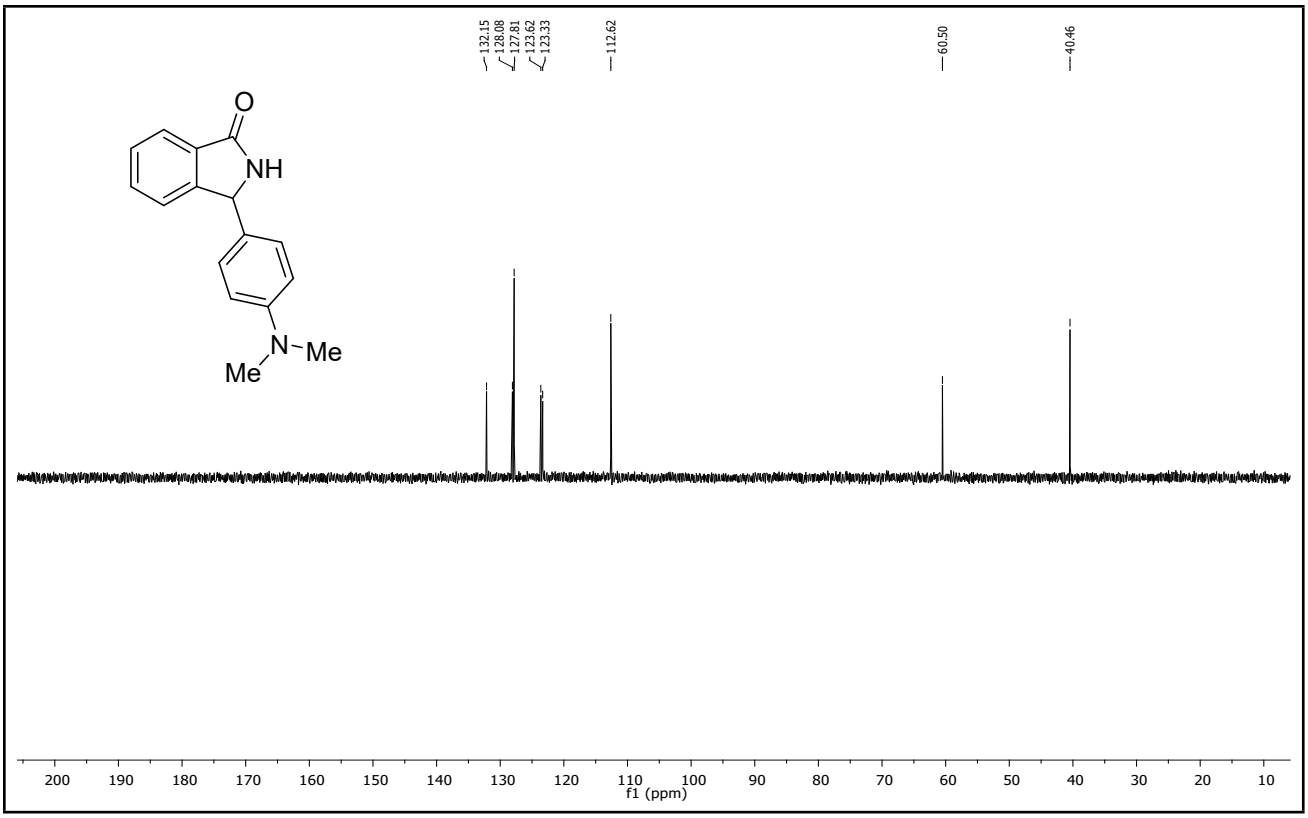
HRMS spectrum of 3-(2,4,6-trimethoxyphenyl)isoindolin-1-one **12e**.



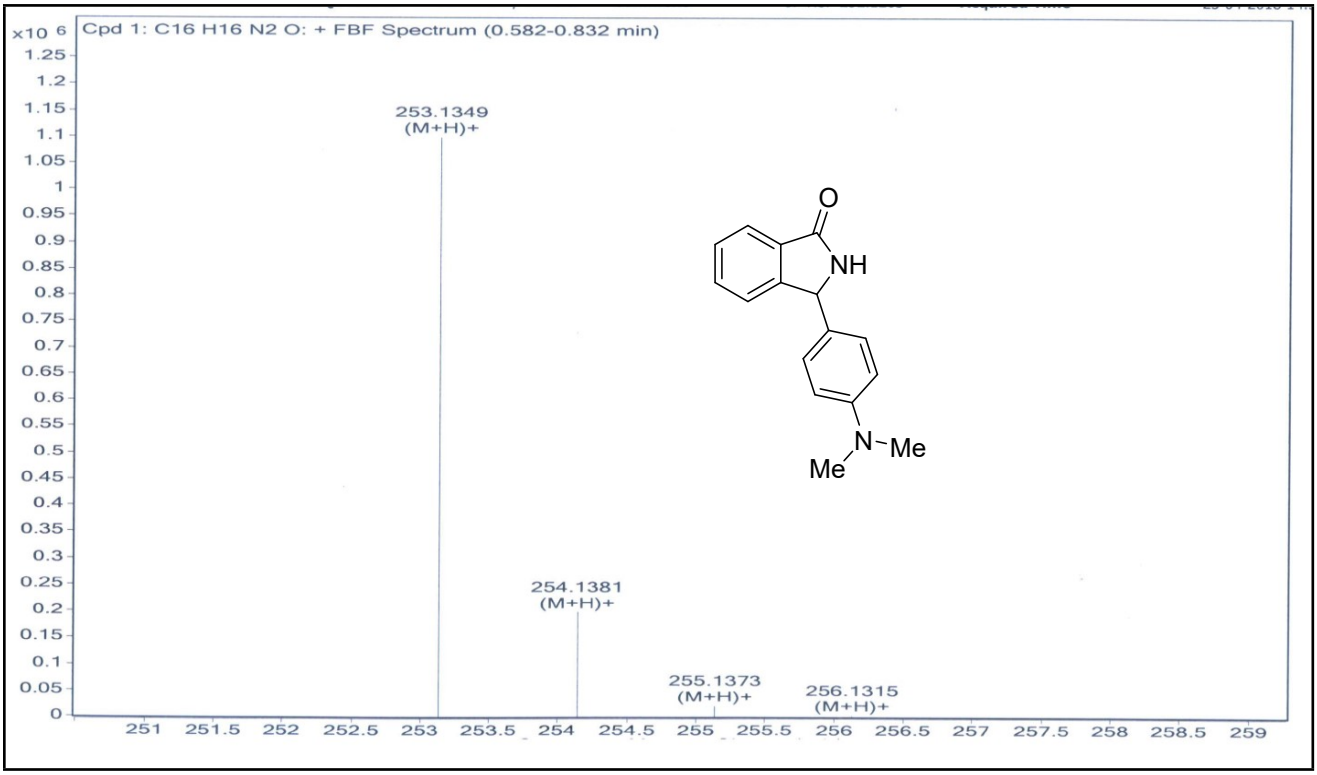
^{1}H NMR (400 MH_Z, $CDCl_3$) spectrum of 3-(4-(dimethylamino)phenyl)isoindolin-1-one **12f**.



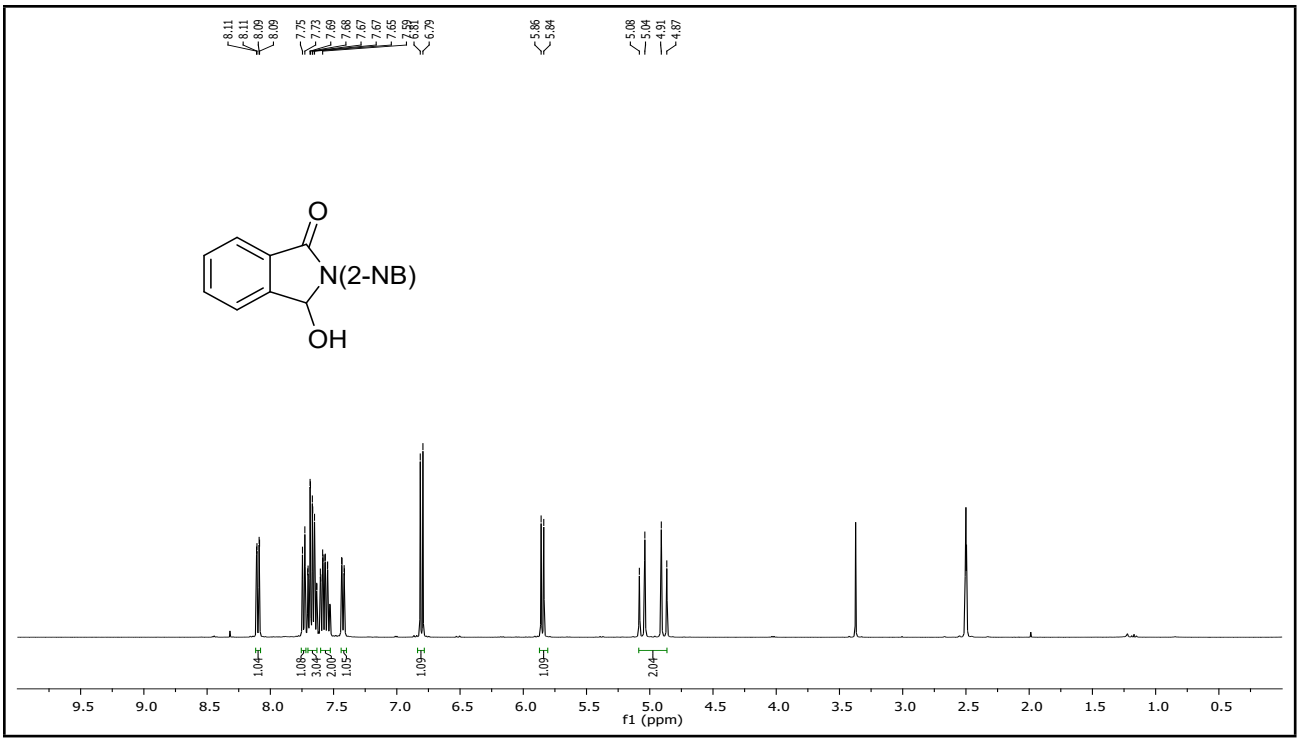
^{13}C NMR (100 MH_Z, $CDCl_3$) spectrum of 3-(4-(dimethylamino)phenyl)isoindolin-1-one **12f**.



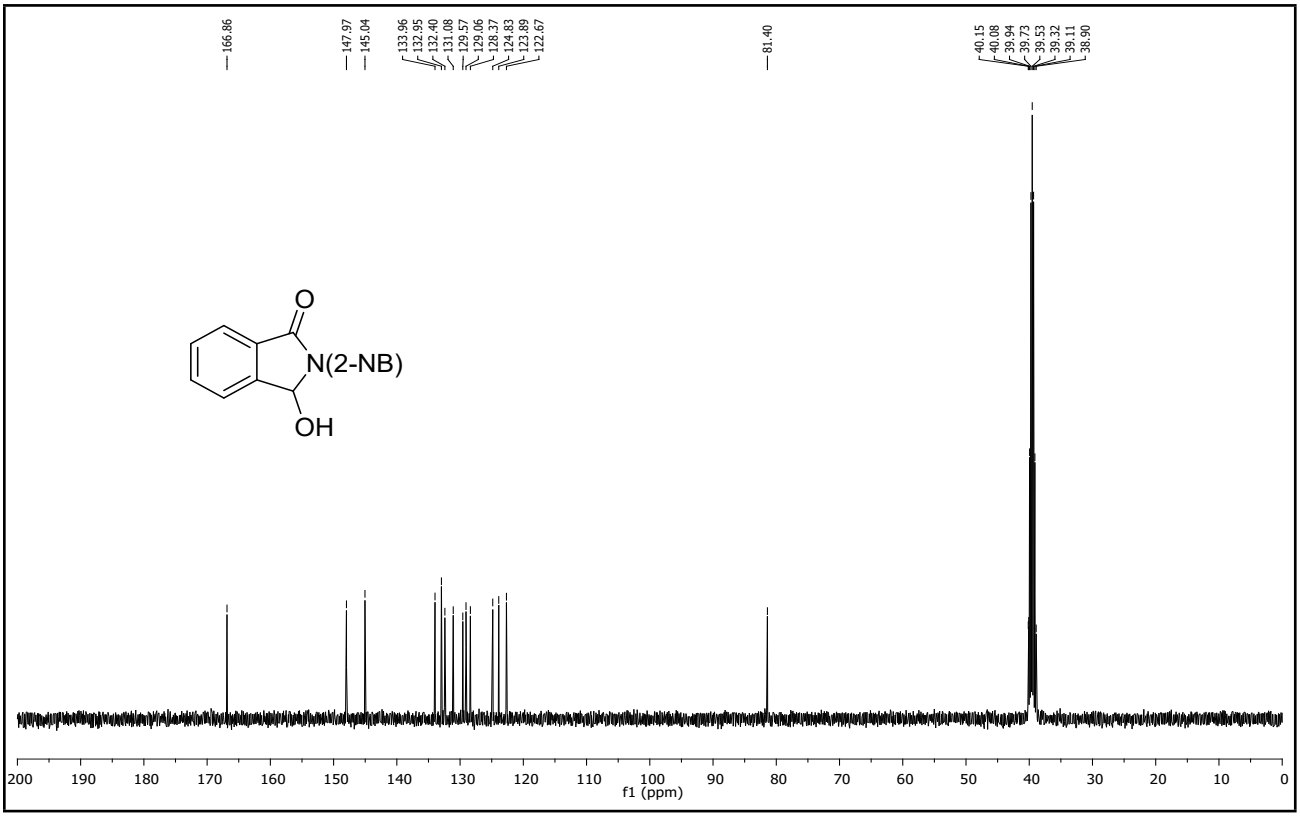
DEPT-135 spectrum of 3-(4-(dimethylamino)phenyl)isoindolin-1-one **12f**.



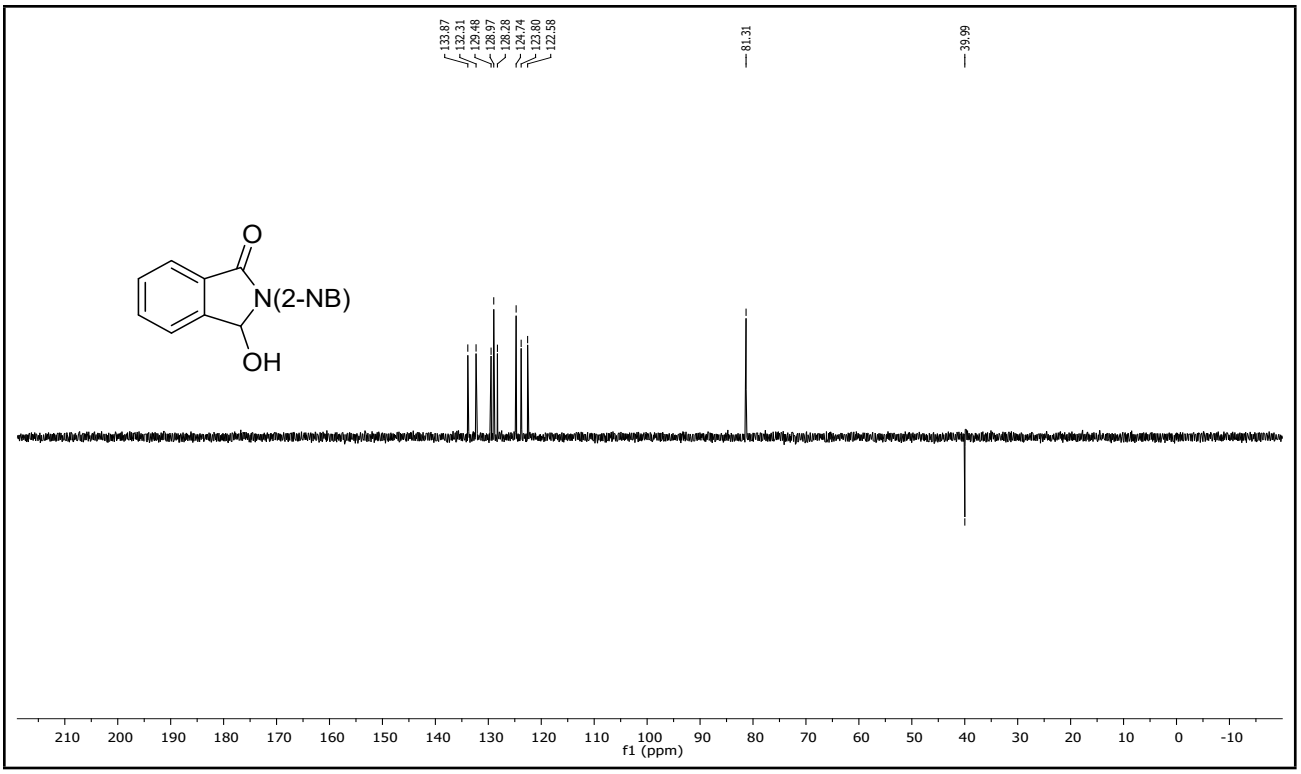
HRMS spectrum of 3-(4-(dimethylamino)phenyl)isoindolin-1-one **12f**.



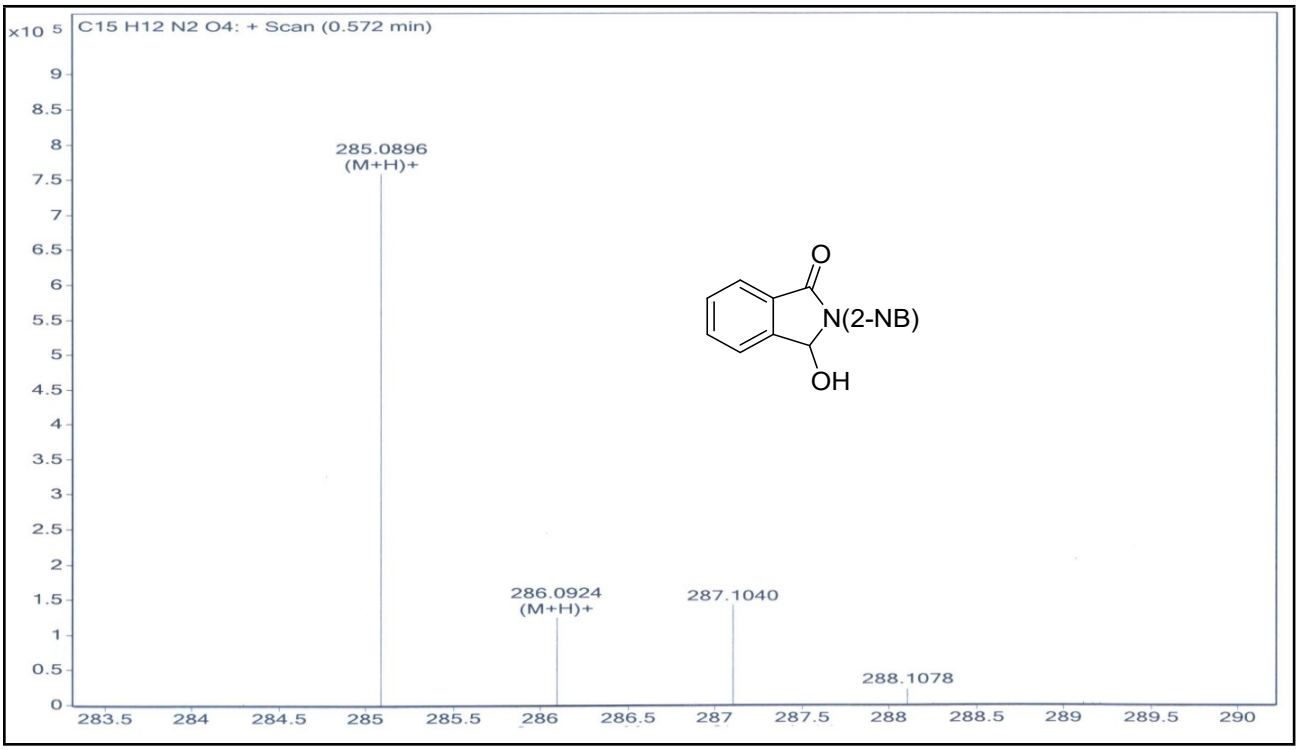
^{1}H NMR (400 MH_Z, DMSO-d_6) spectrum of 3-hydroxy-2-(2-nitrobenzyl)isoindolin-1-one **9**.



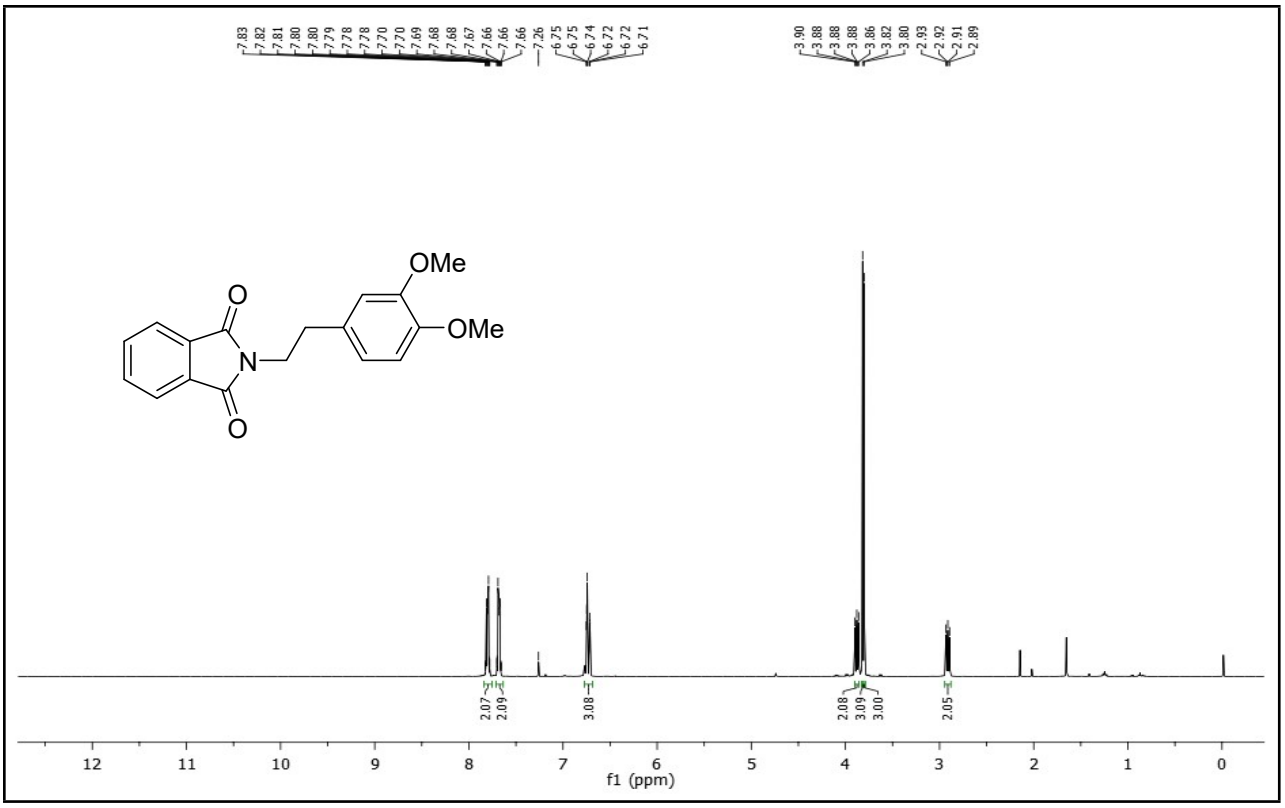
^{13}C NMR (100 MH_Z, DMSO-d_6) spectrum of 3-hydroxy-2-(2-nitrobenzyl)isoindolin-1-one **9**.



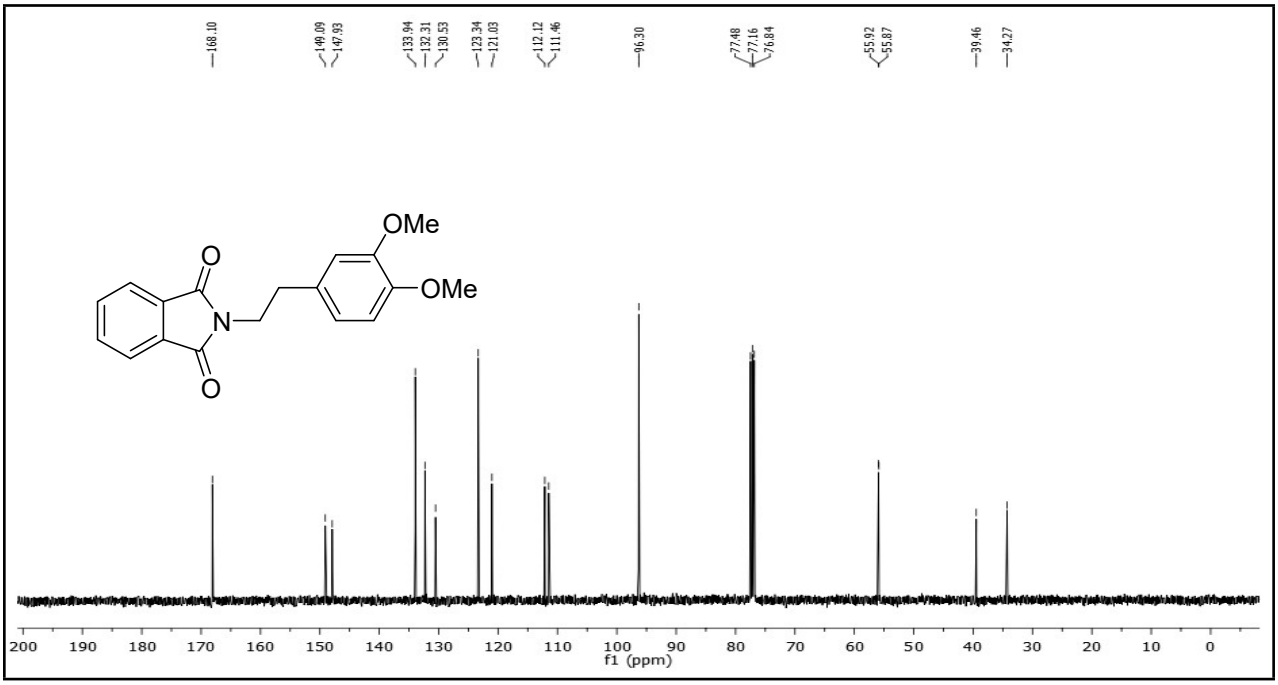
DEPT-135 spectrum of 3-hydroxy-2-(2-nitrobenzyl)isoindolin-1-one **9**.



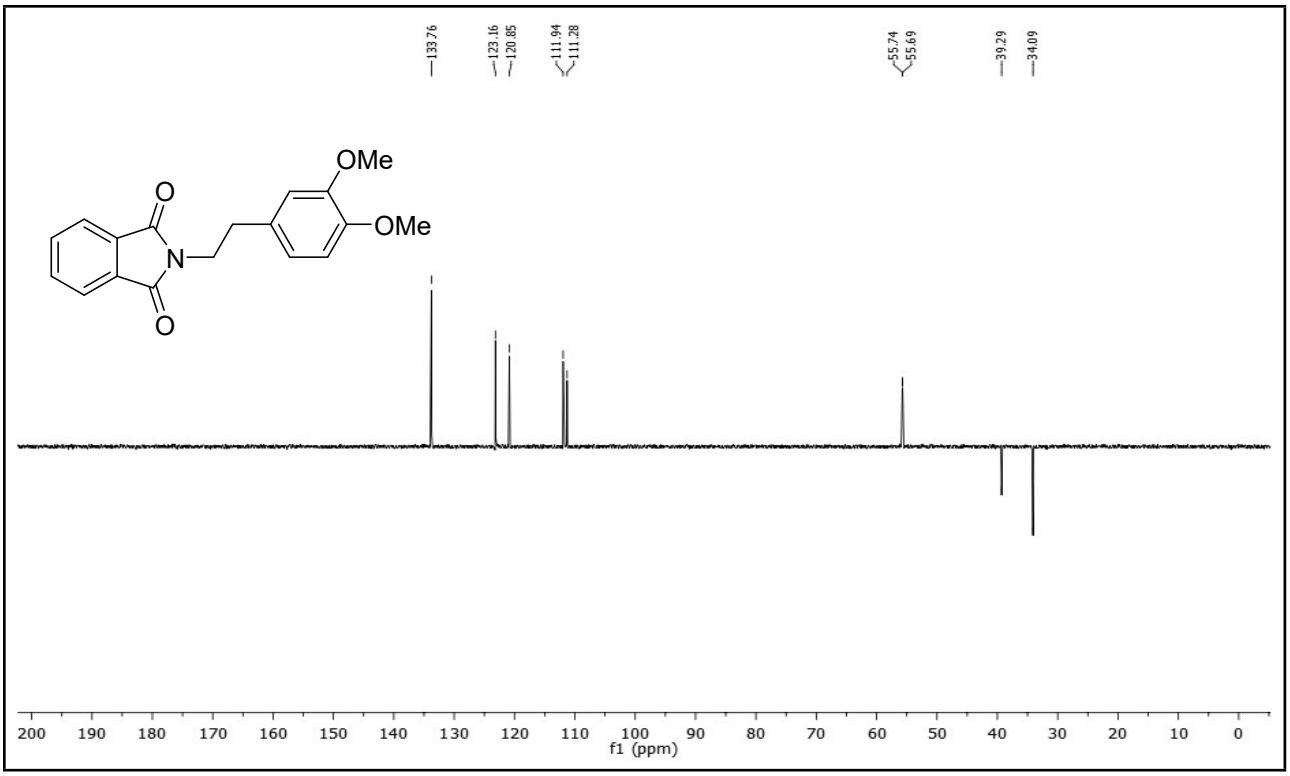
HRMS spectrum of 3-hydroxy-2-(2-nitrobenzyl)isoindolin-1-one **9**.



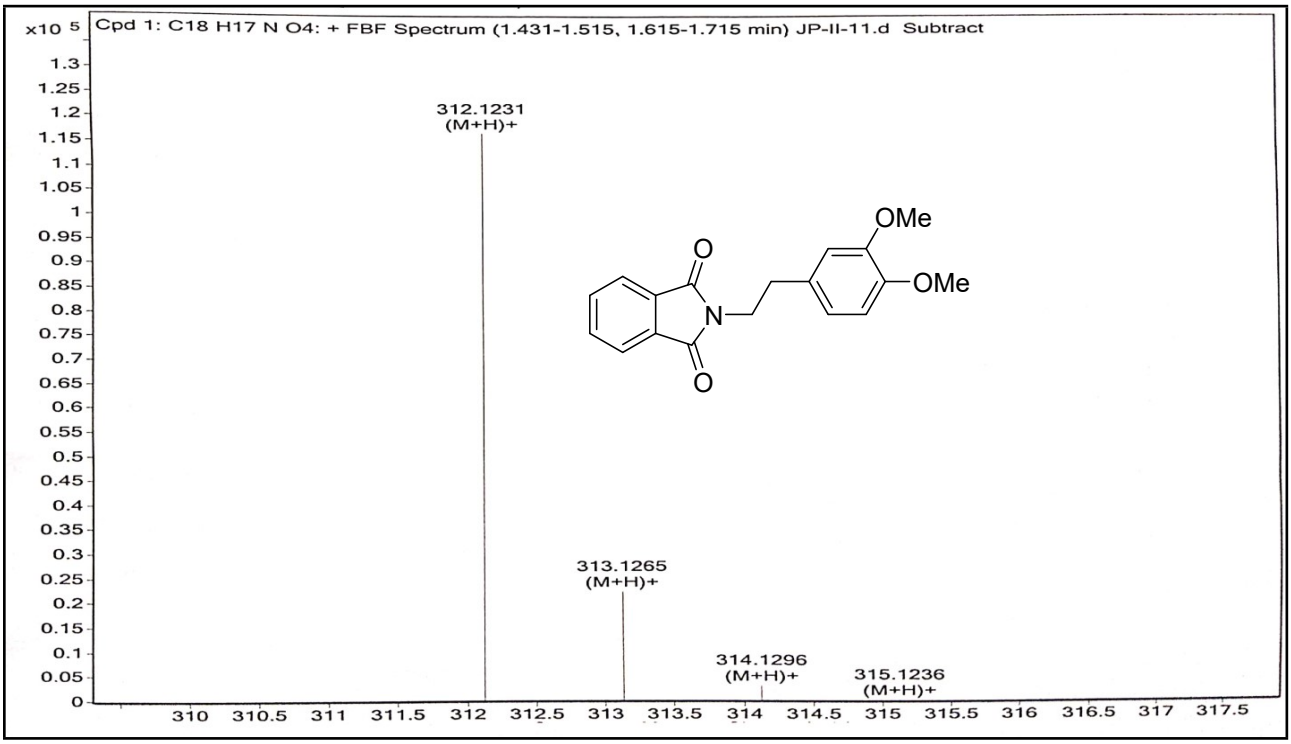
^{1}H NMR (400 MHz, $CDCl_3$ + CCl_4; 1:1) spectrum of 2-(3,4-dimethoxyphenethyl)isoindoline-1,3-dione **14a**.



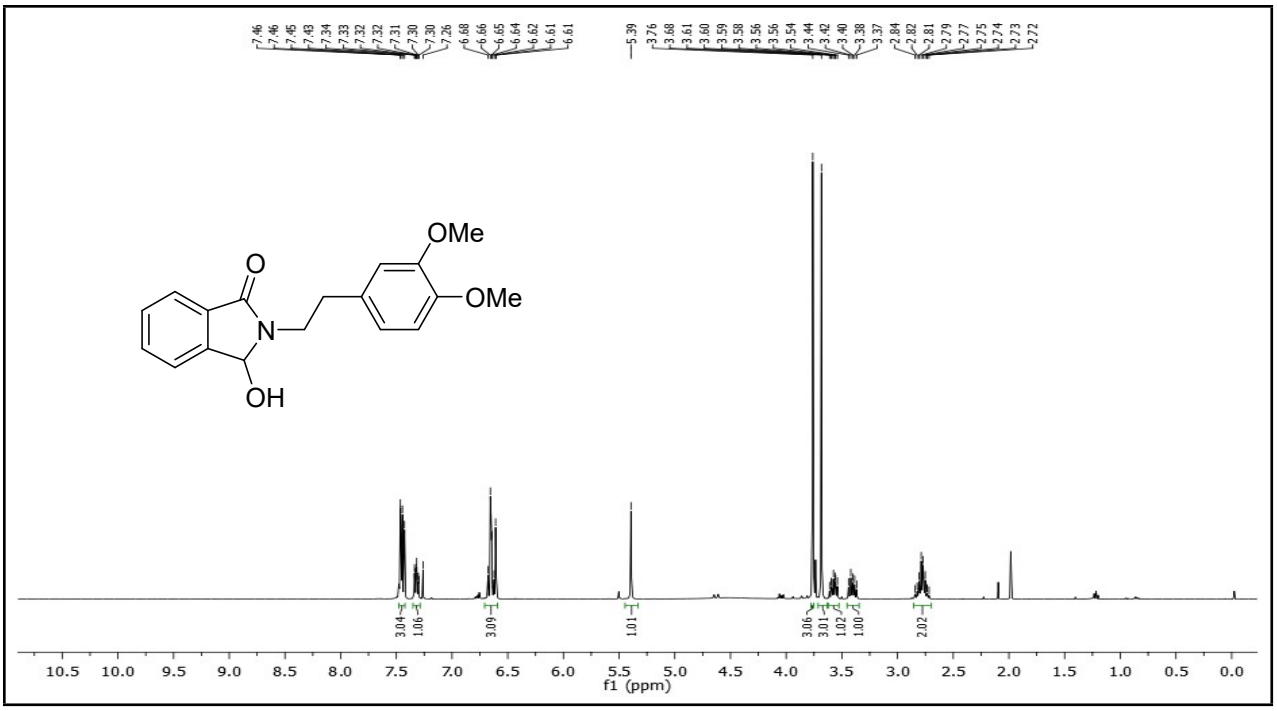
^{13}C NMR (100 MHz, $CDCl_3$ + CCl_4; 1:1) spectrum of 2-(3,4-dimethoxyphenethyl)isoindoline-1,3-dione **14a**.



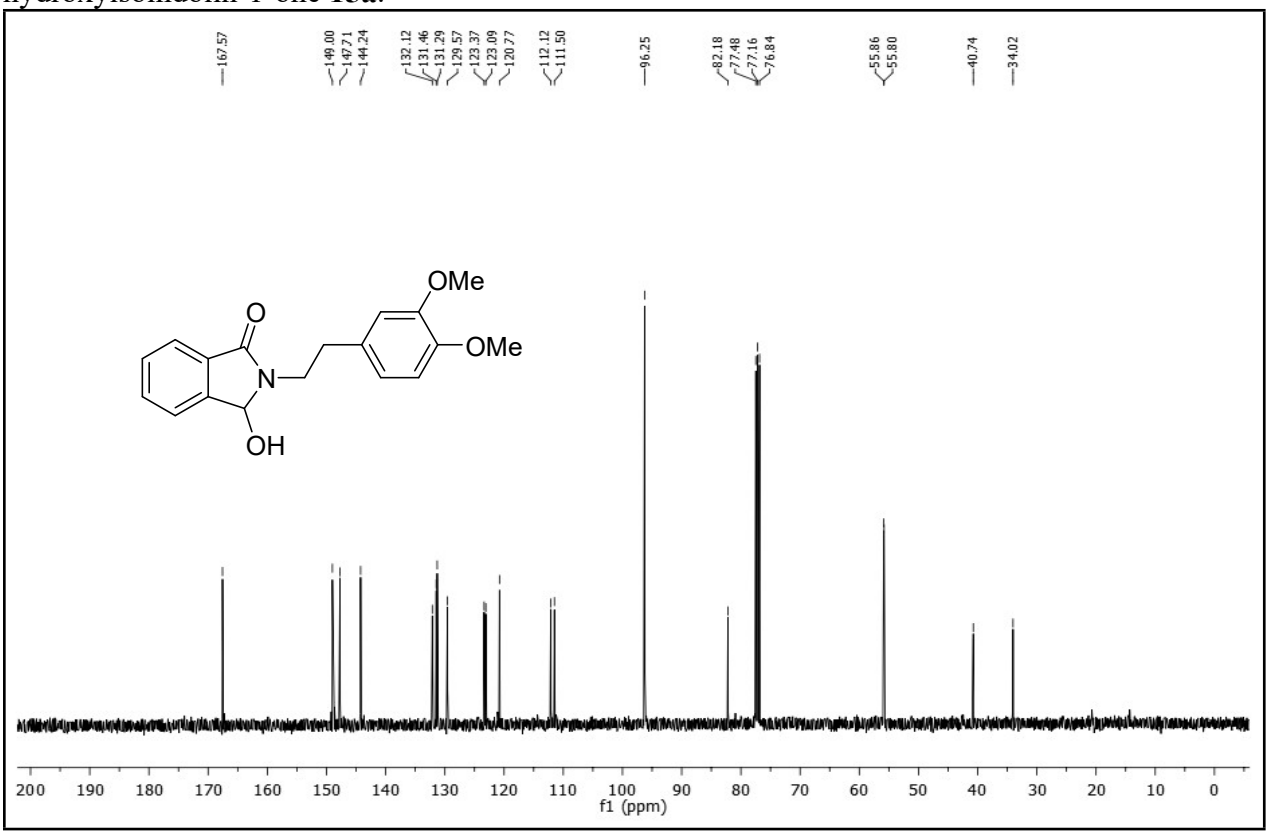
DEPT-135 spectrum of 2-(3,4-dimethoxyphenethyl)isoindoline-1,3-dione **14a**.



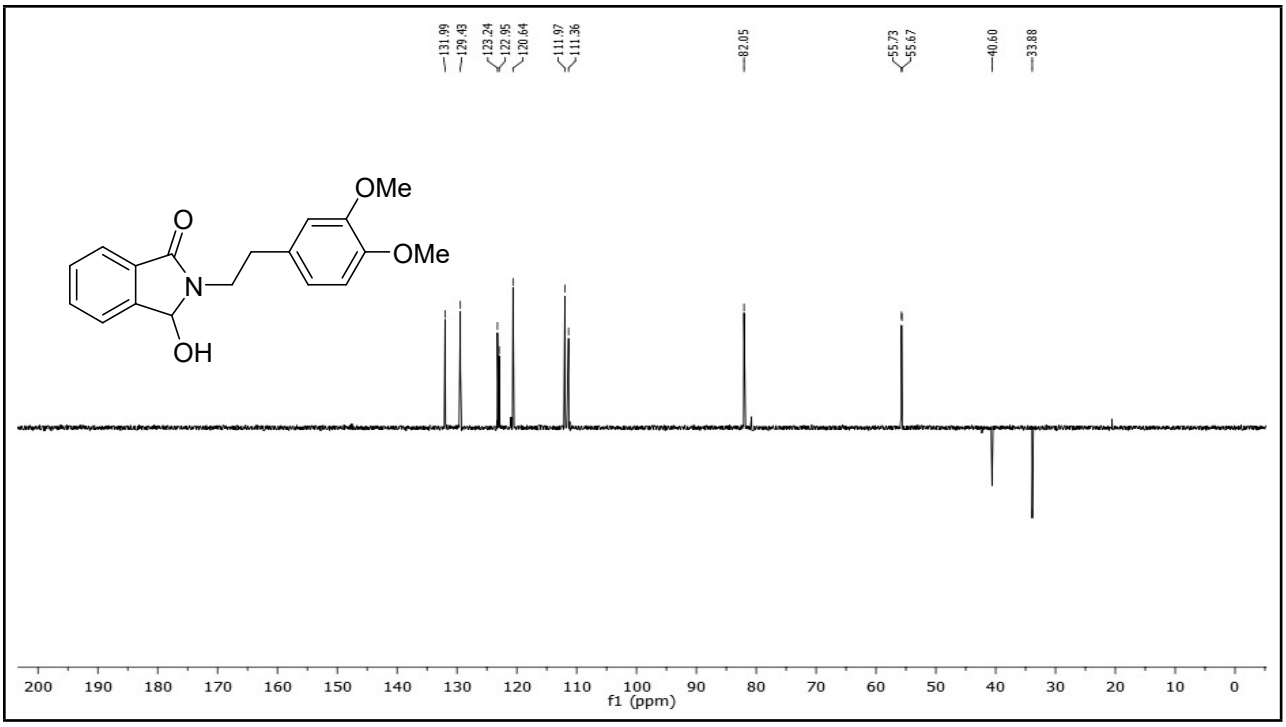
HRMS spectrum of 2-(3,4-dimethoxyphenethyl)isoindoline-1,3-dione **14a**.



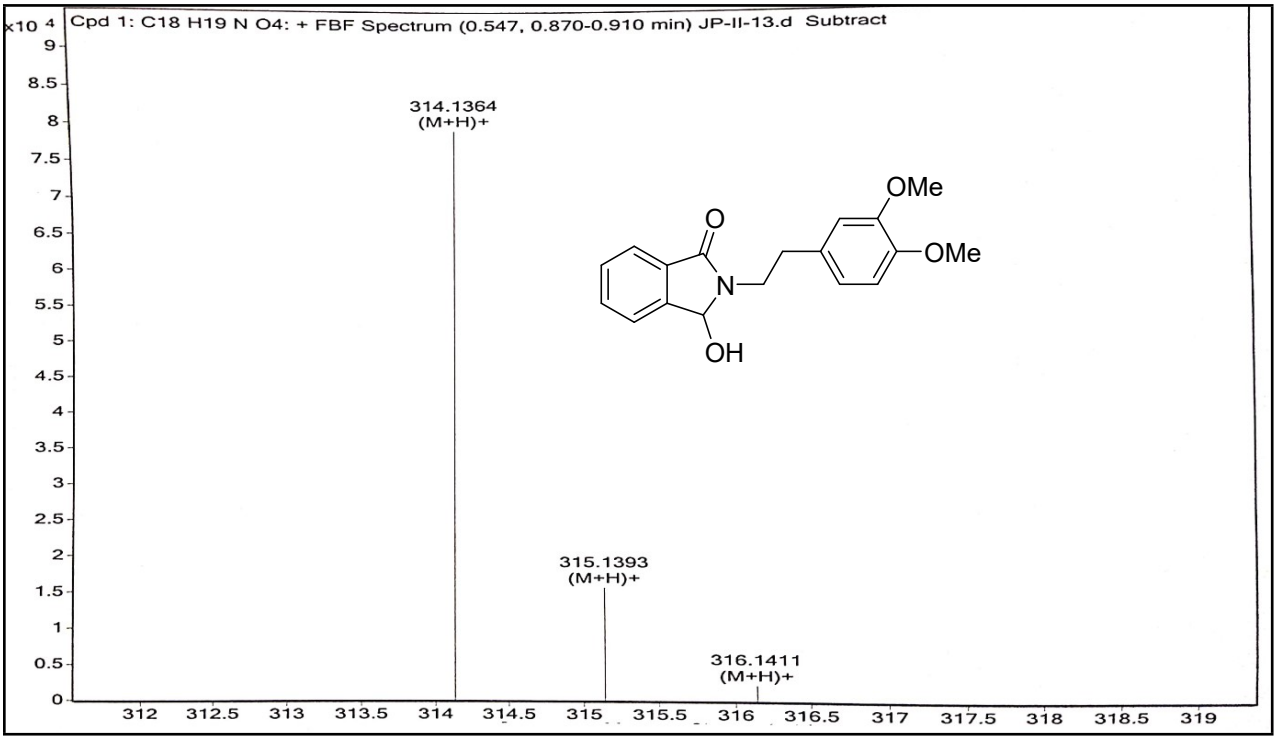
^{1}H NMR (400 MHz, $CDCl_3$ + CCl_4; 1:1) spectrum of 2-(3,4-dimethoxyphenethyl)-3-hydroxyisoindolin-1-one **15a**.



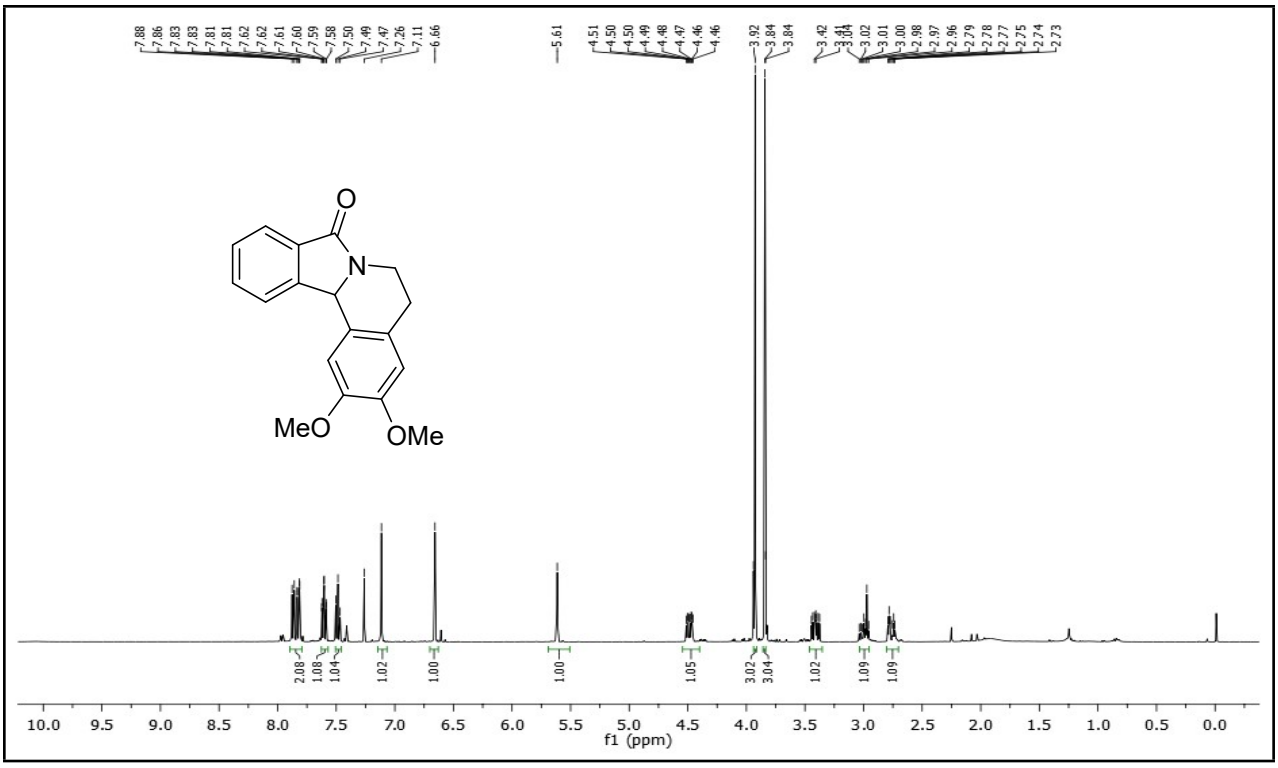
^{13}C NMR (100 MHz, $CDCl_3$ + CCl_4; 1:1) spectrum of 2-(3,4-dimethoxyphenethyl)-3-hydroxyisoindolin-1-one **15a**.



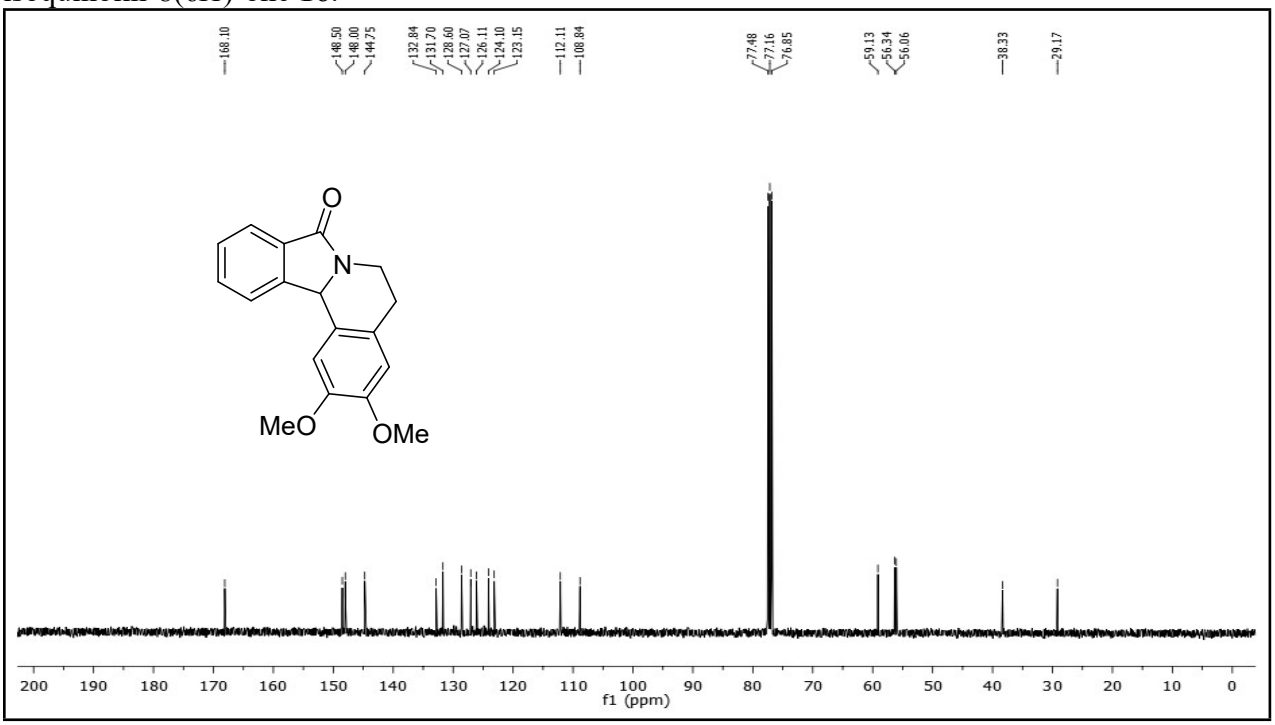
DEPT-135 spectrum of 2-(3,4-dimethoxyphenethyl)-3-hydroxyisoindolin-1-one **15a**.



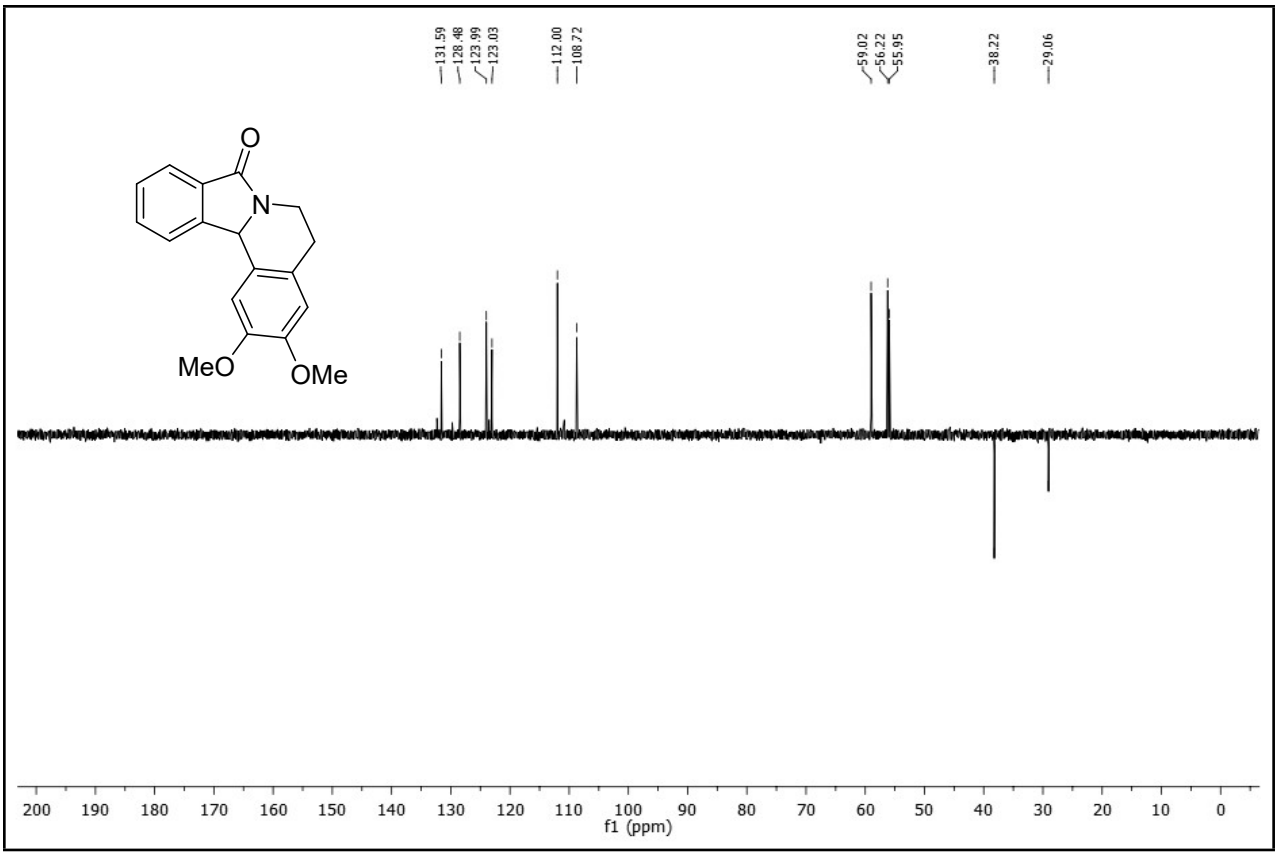
HRMS spectrum of 2-(3,4-dimethoxyphenethyl)-3-hydroxyisoindolin-1-one **15a**.



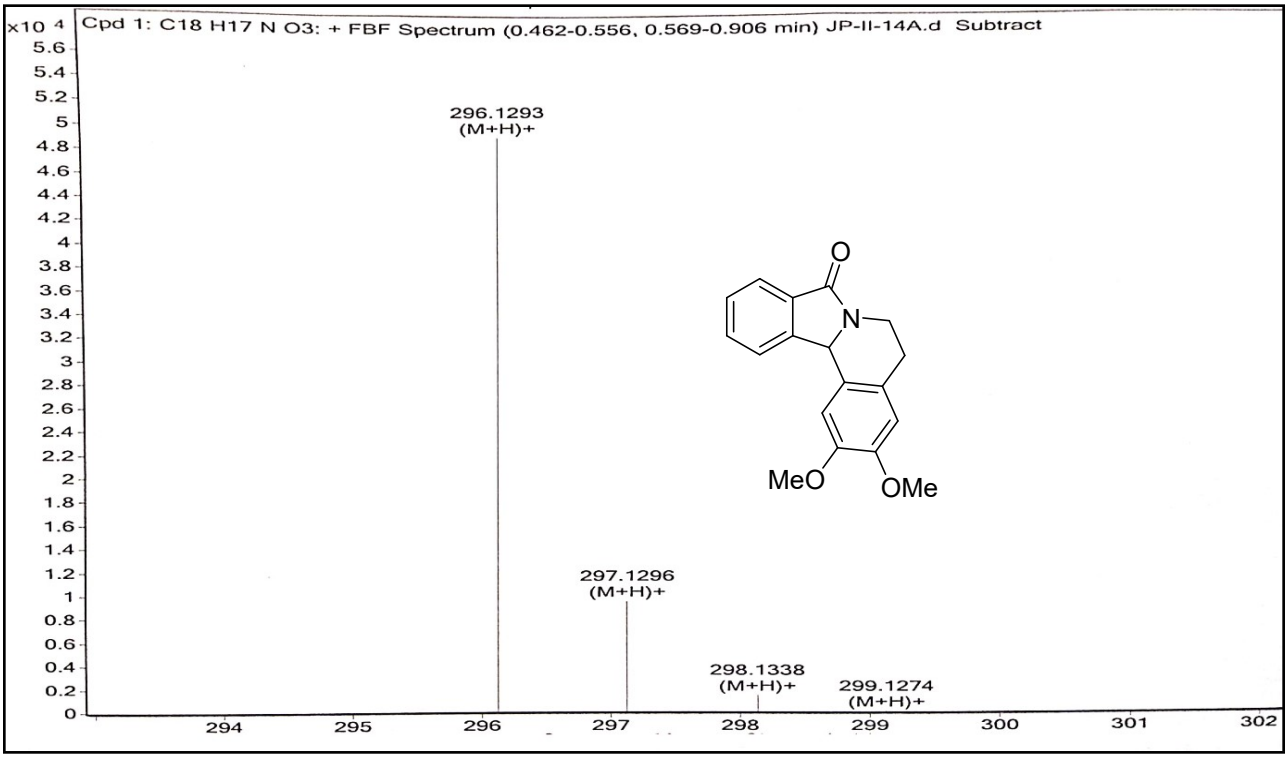
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of 2,3-dimethoxy-5,12b-dihydroisoindolo[1,2-a] isoquinolin-8(6*H*)-one **16**.



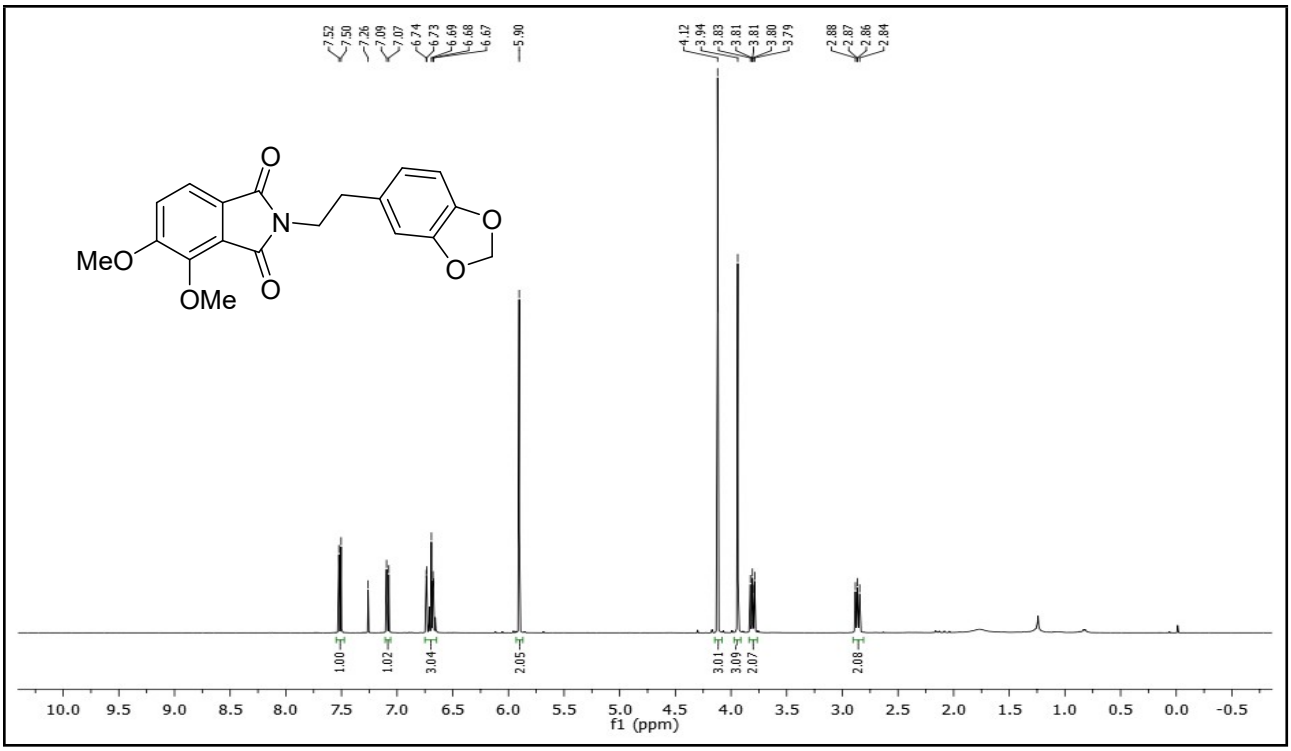
^{13}C NMR (100 MHz, $CDCl_3$) spectrum of 2,3-dimethoxy-5,12b-dihydroisoindolo[1,2-a] isoquinolin-8(6*H*)-one **16**.



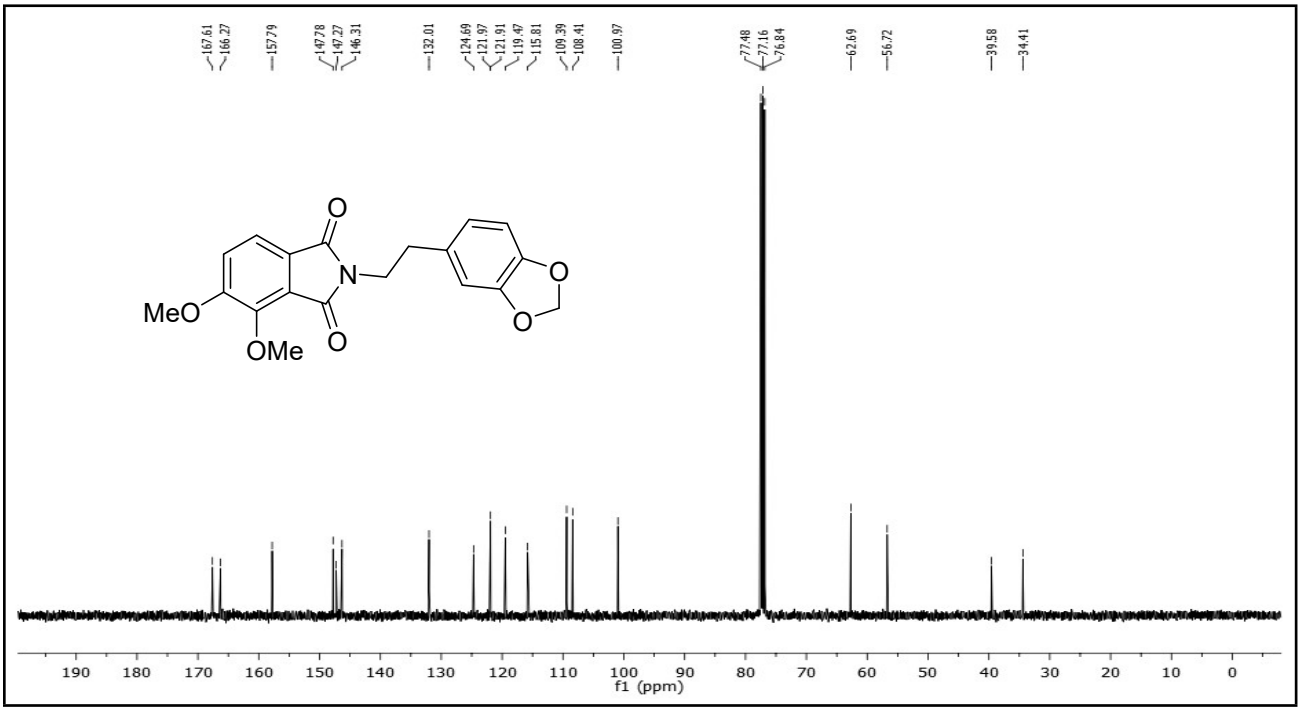
DEPT-135 spectrum of 2,3-dimethoxy-5,12b-dihydroisoindolo[1,2-a]isoquinolin-8(6*H*)-one **16**.



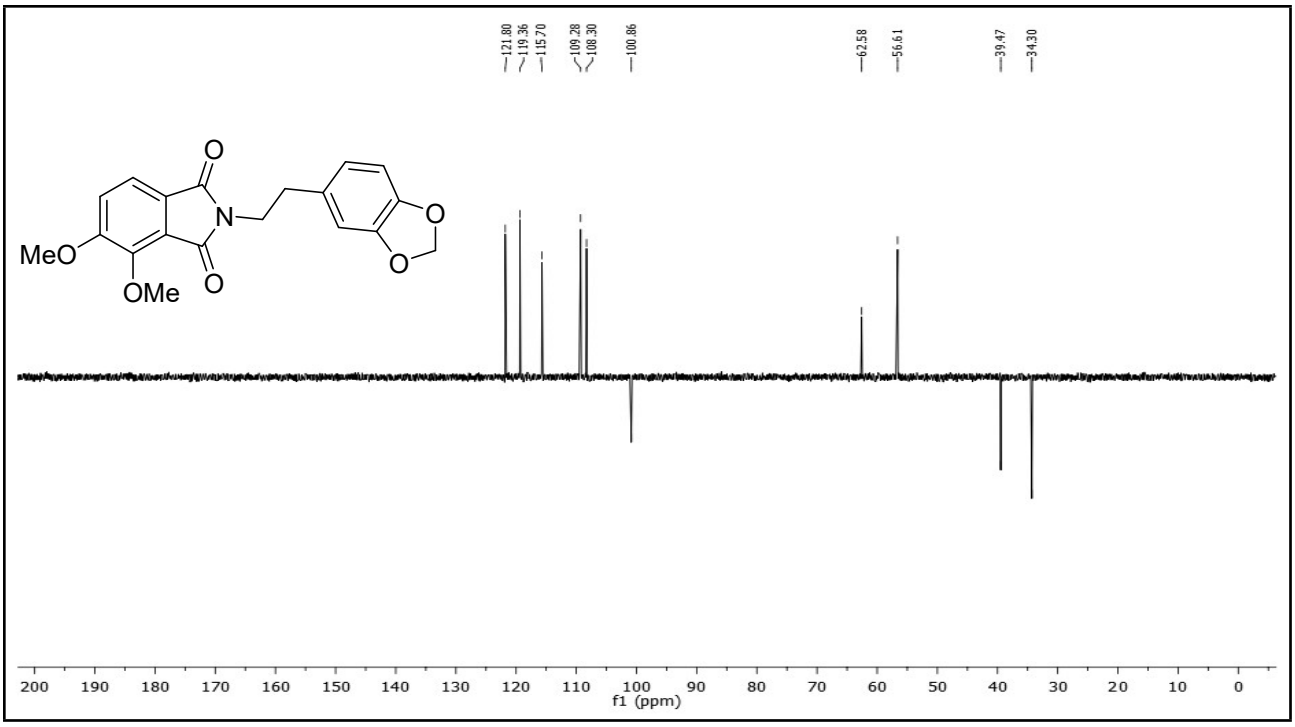
HRMS spectrum of 2,3-dimethoxy-5,12b-dihydroisoindolo[1,2-a]isoquinolin-8(6*H*)-one **16**.



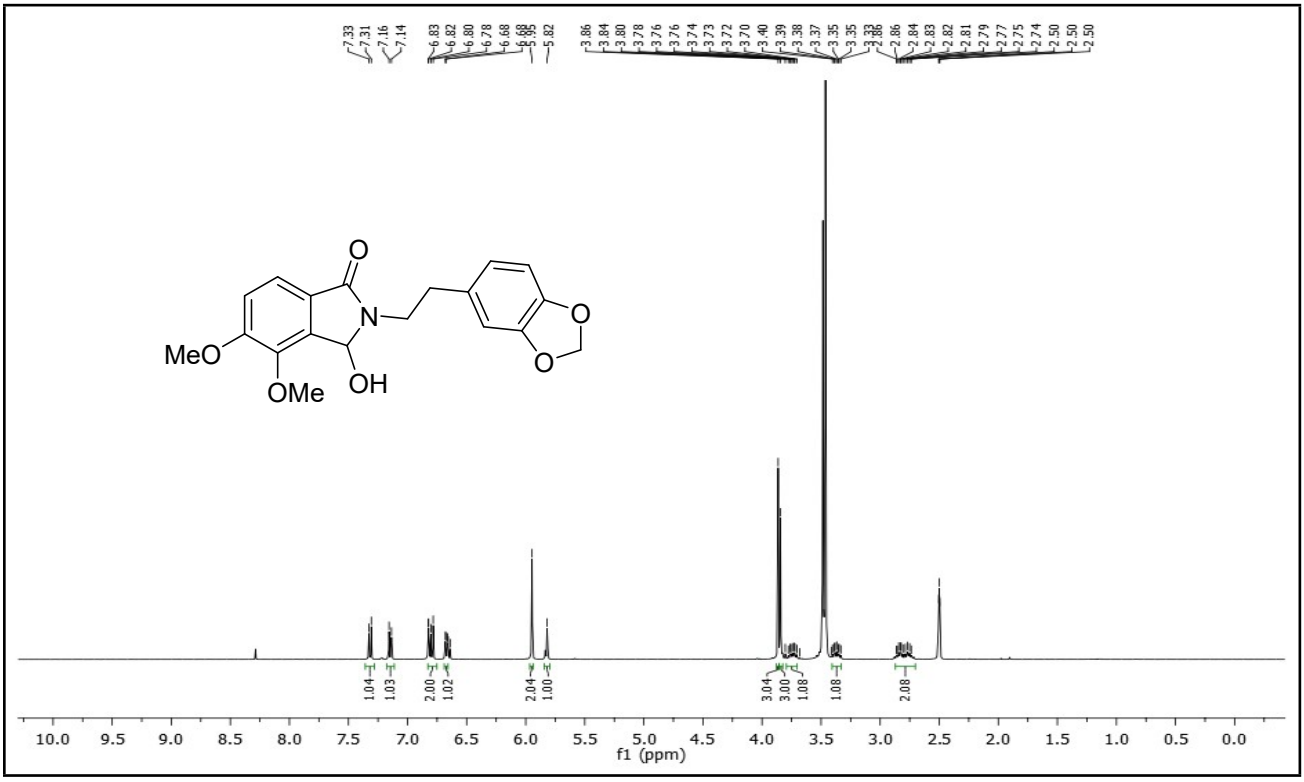
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of 2-(2-(benzo[d][1,3]dioxol-5-yl)ethyl)-4,5-dimethoxy isoindoline-1,3-dione **14b**.



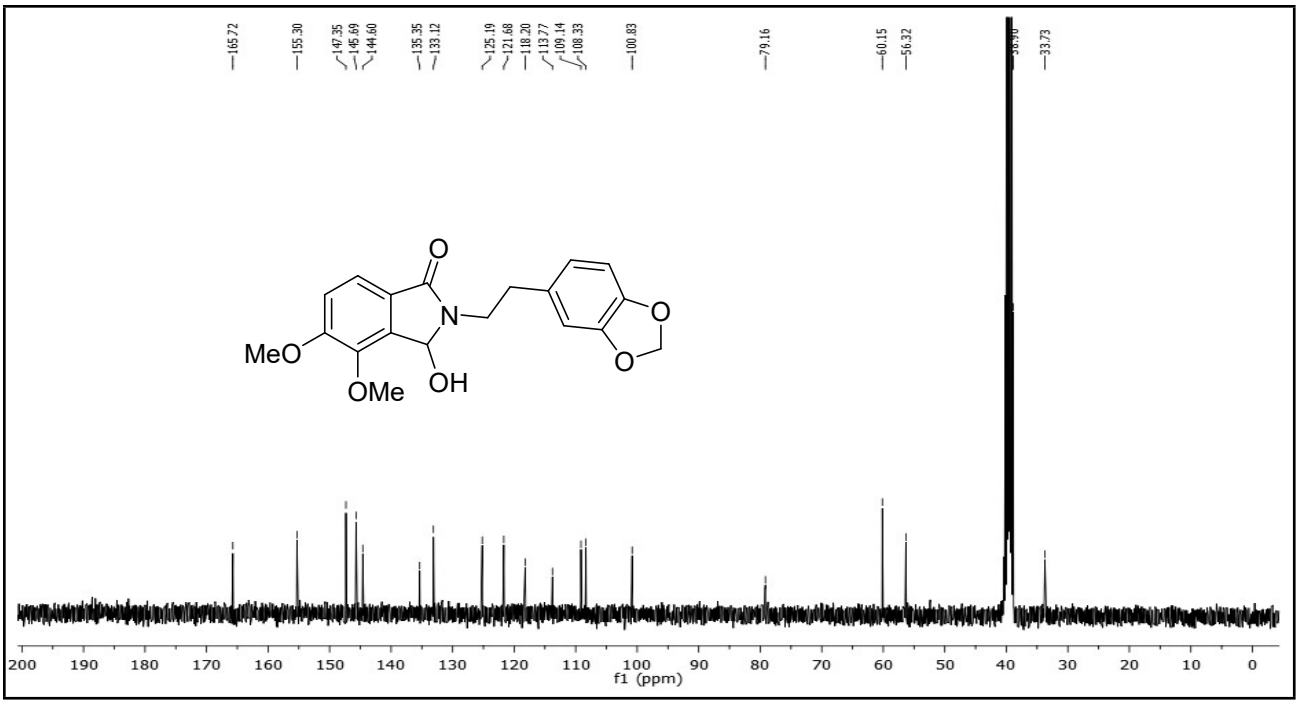
^{13}C NMR (100 MHz, $CDCl_3$) spectrum of 2-(2-(benzo[d][1,3]dioxol-5-yl)ethyl)-4,5-dimethoxy isoindoline-1,3-dione **14b**.



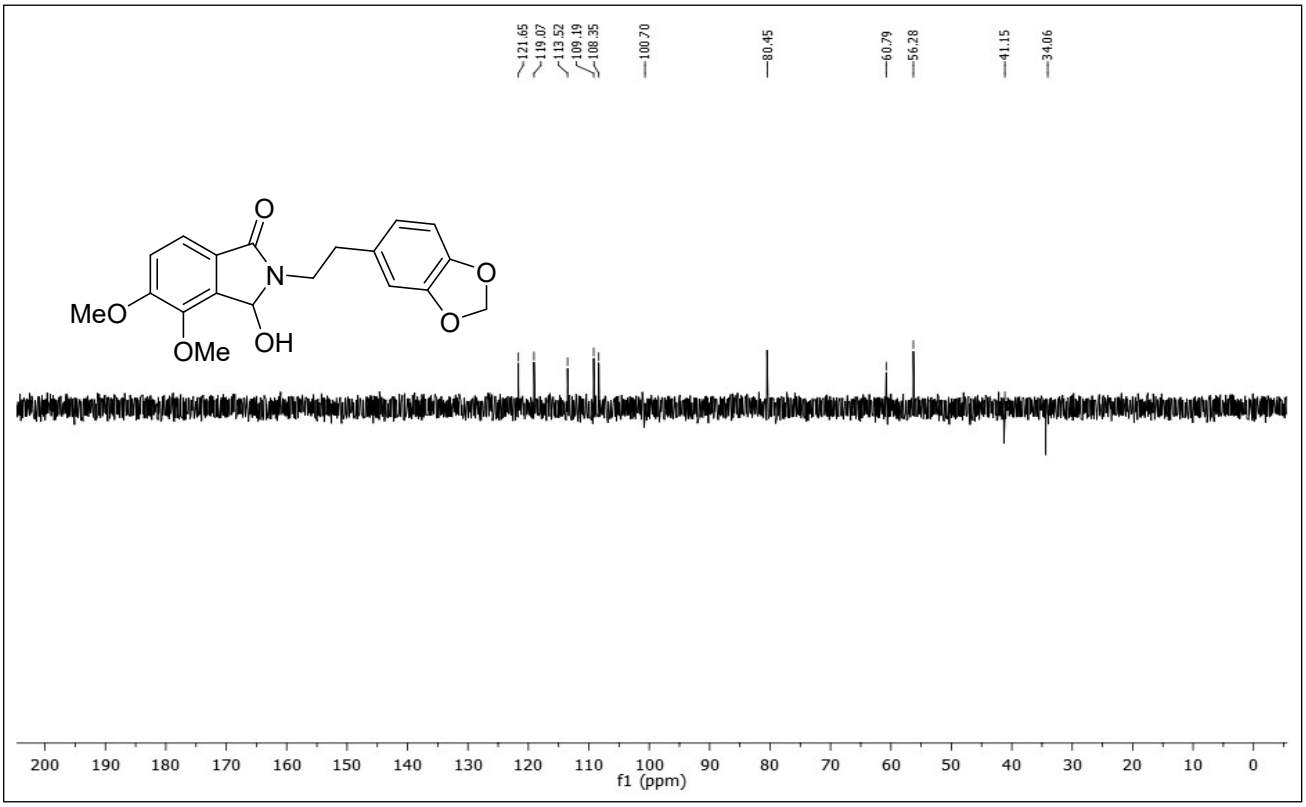
DEPT-135 spectrum of 2-(2-(benzo[d][1,3]dioxol-5-yl)ethyl)-4,5-dimethoxyisoindoline-1,3-dione **14b**.



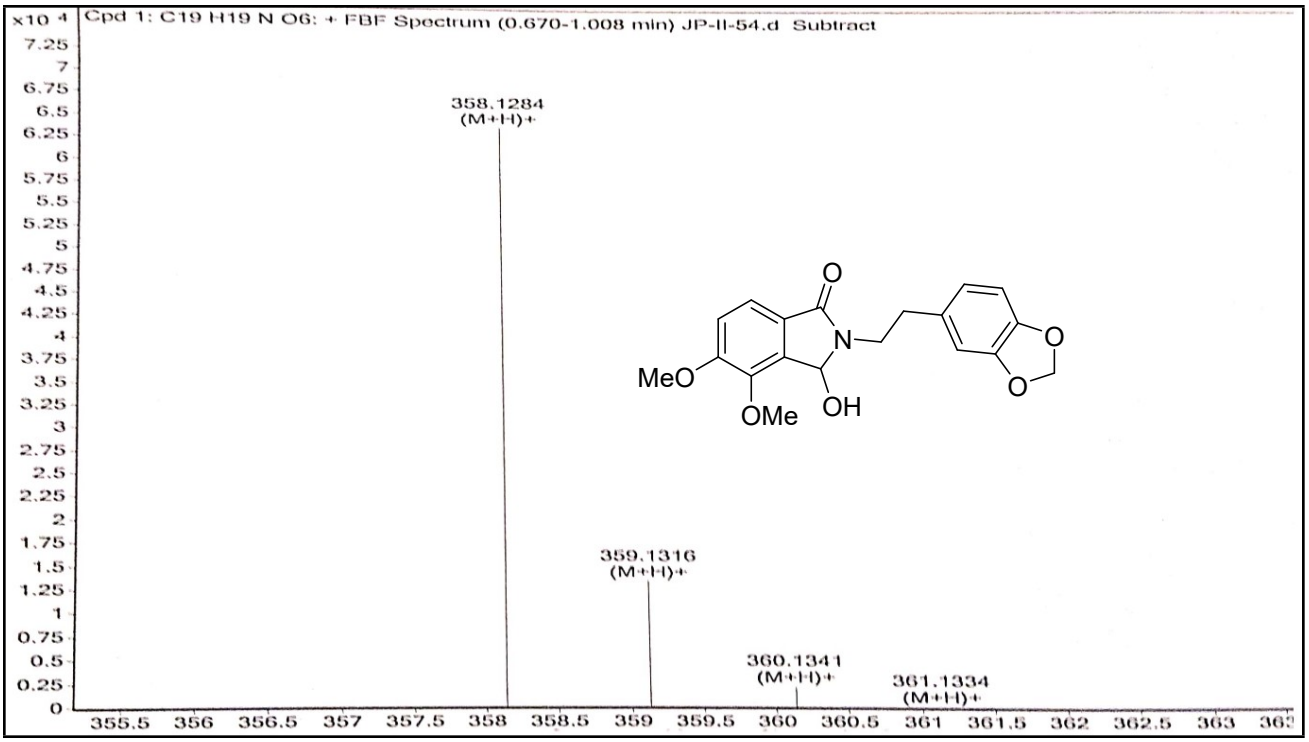
^{1}H NMR (400 MHz, DMSO-d_6) spectrum of 2-(2-(benzo[d][1,3]dioxol-5-yl)ethyl)-3-hydroxy-4,5-dimethoxyisoindolin-1-one **15b**.



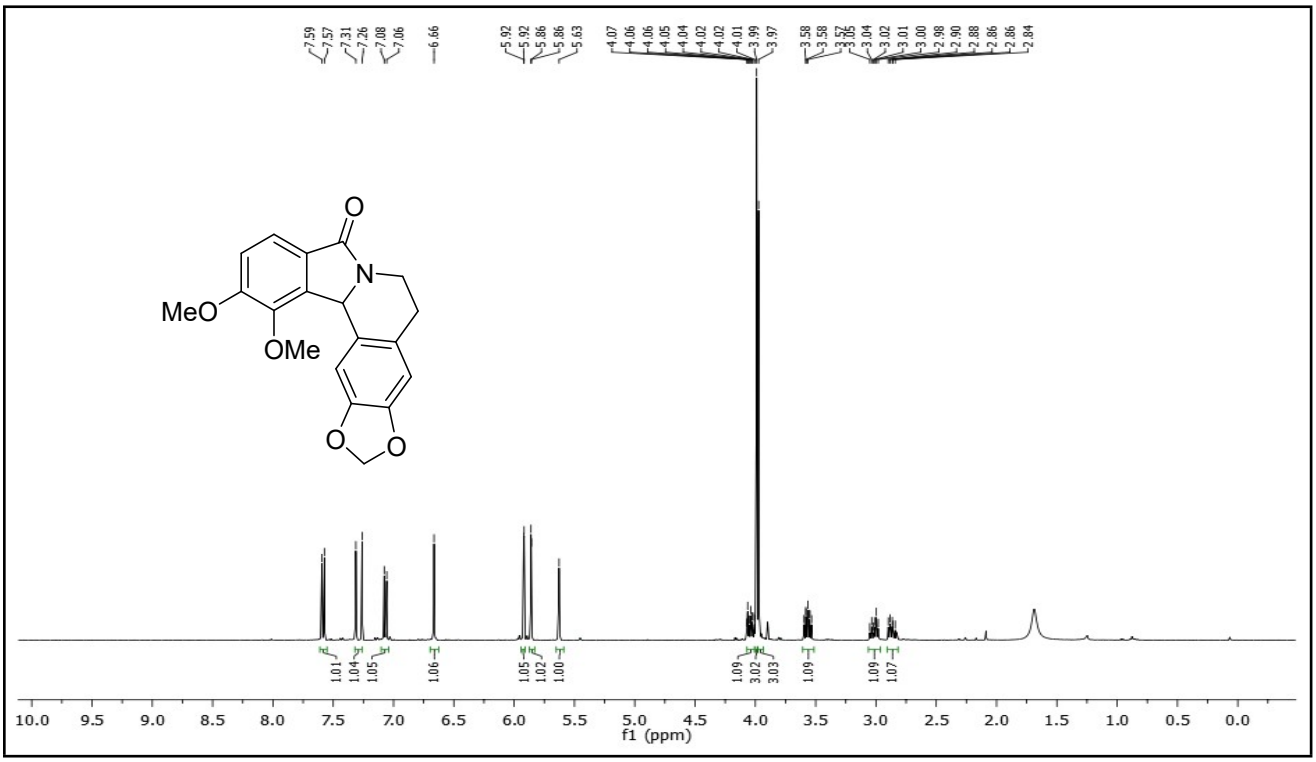
^{13}C NMR (100 MHz, DMSO-d_6) spectrum of 2-(2-(benzo[d][1,3]dioxol-5-yl)ethyl)-3-hydroxy-4,5-dimethoxyisoindolin-1-one **15b**.



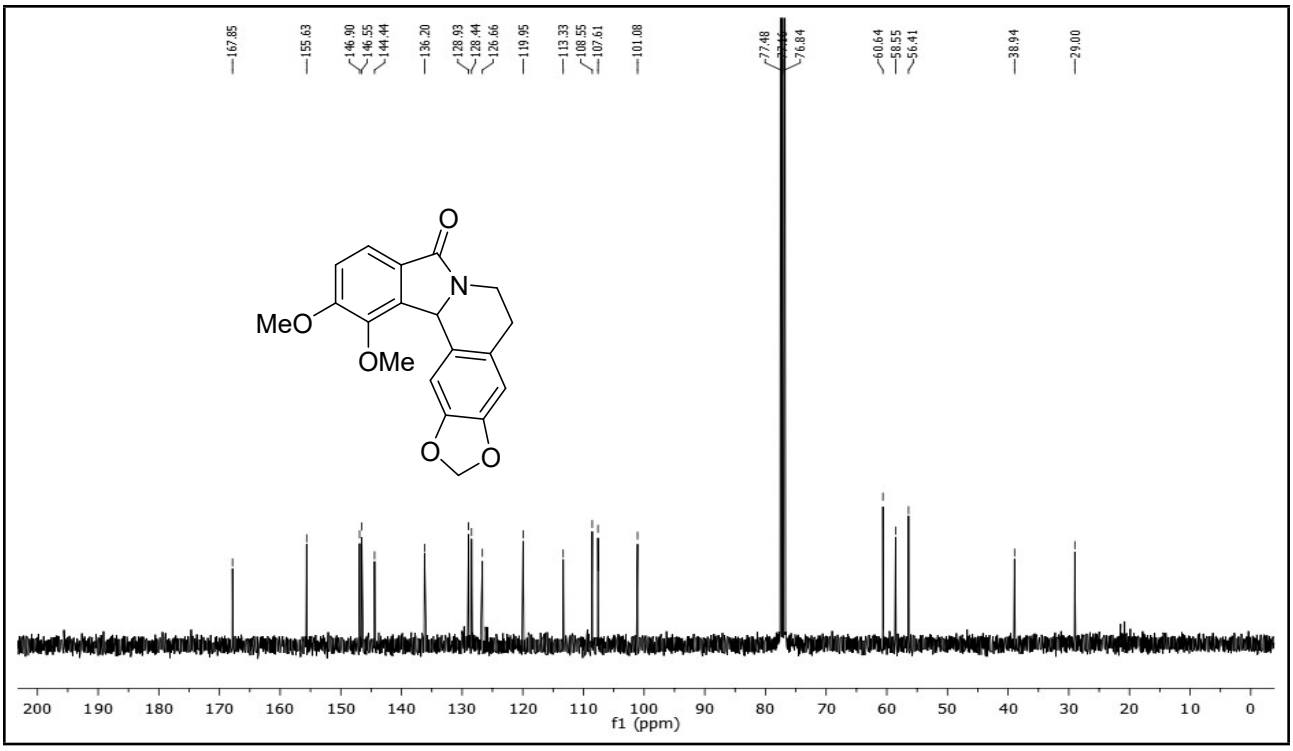
DEPT-135 spectrum of 2-(2-(benzo[d][1,3]dioxol-5-yl)ethyl)-3-hydroxy-4,5-dimethoxy isoindolin-1-one **15b**.



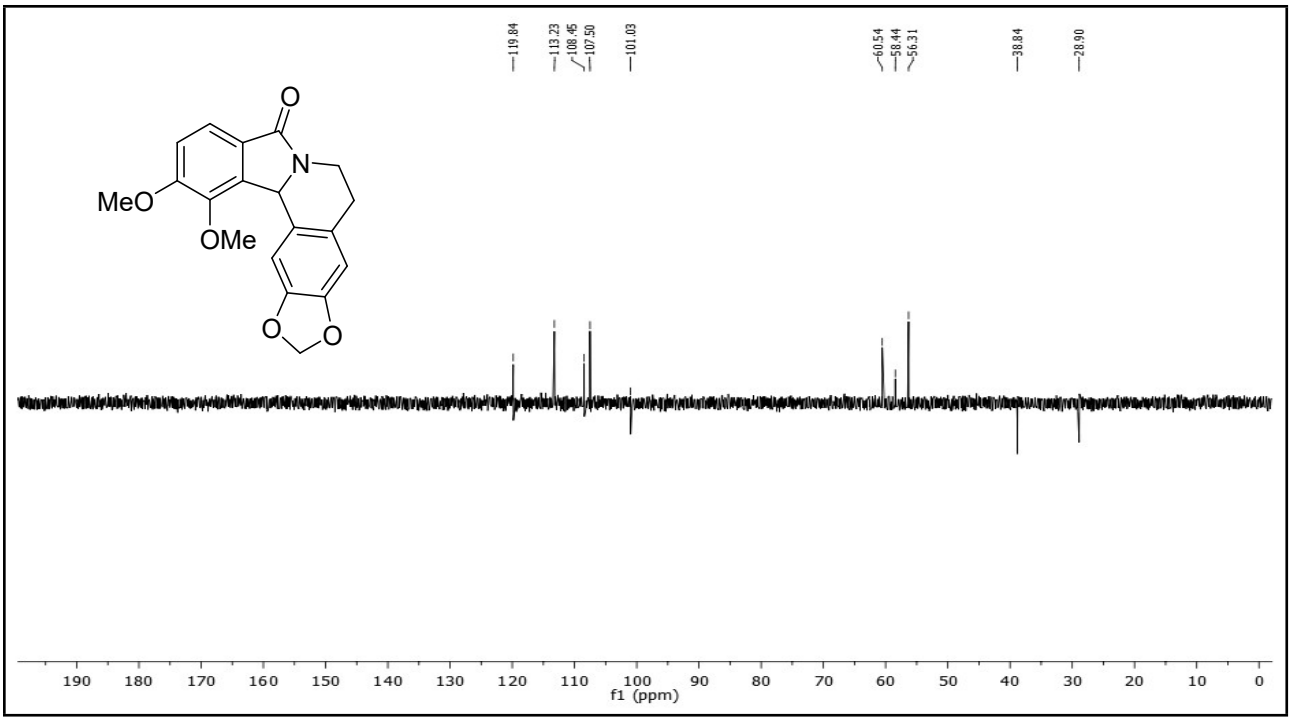
HRMS spectrum of 2-(2-(benzo[d][1,3]dioxol-5-yl)ethyl)-3-hydroxy-4,5-dimethoxy isoindolin-1-one **15b**.



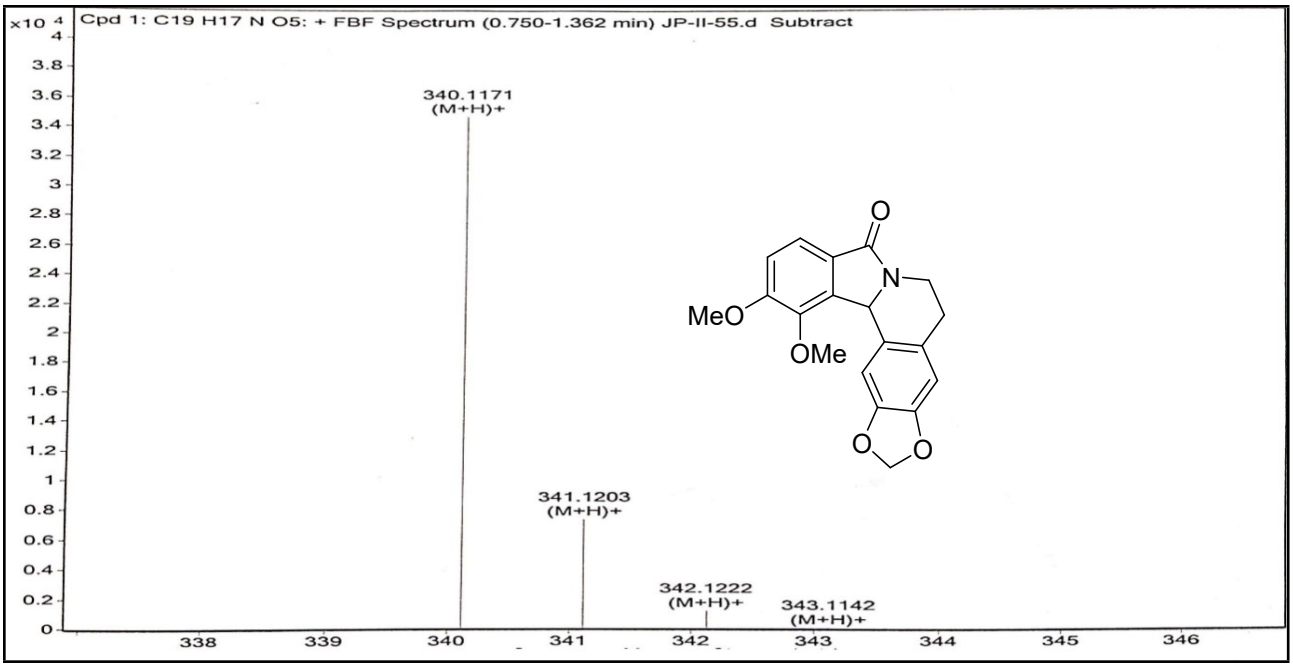
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of 11,12-dimethoxy-5,12*b*-dihydro-[1,3]dioxolo[4,5-g]isoindolo[1,2-a]isoquinolin-8(6*H*)-one **1**.



^{13}C NMR (100 MHz, $CDCl_3$) spectrum of 11,12-dimethoxy-5,12*b*-dihydro-[1,3]dioxolo[4,5-g]isoindolo[1,2-a]isoquinolin-8(6*H*)-one **1**.



DEPT-135 spectrum of 11,12-dimethoxy-5,12*b*-dihydro-[1,3]dioxolo[4,5-g]isoindolo[1,2-a]isoquinolin-8(6*H*)-one **1**.



HRMS spectrum of 11,12-dimethoxy-5,12*b*-dihydro-[1,3]dioxolo[4,5-g]isoindolo[1,2-a] isoquinolin-8(6*H*)-one **1**.

References

[1] Armarego, W. L. F.; Chai, C. L. L. *Purification of Laboratory Chemicals.* 5th Ed (Oxford, UK: Elsevier) **2003**.

[2] (a) We have taken into consideration of the previous work only where experimental details are available. (b) Starting compounds for all three schemes are 2-(3,4-dimethoxyphenyl)ethan-1-amine and 3,4-dimethoxyphthalic anhydride (4,5-dimethoxyisobenzofuran-1,3-dione).