"Synthesis of nuevamine and a cyano-chilenine analog *via* divergent C(sp^3)-H bond functionalization of isoindolinone derivatives"

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SUPPORTING INFORMATION

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General Information

All solvents were dried and distilled prior to use by standard procedures. Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. Reactions were monitored by thin-layer chromatography (TLC), carried out on 0.25 mm silica gel plates using UV light as visualizing agent and vanillin for staining. Column chromatography was performed using silica gel 60 (particle size 0.04−0.063 mm / 230-400 mesh ASTM). Unless stated otherwise, all of the yields refer to isolated products after flash column chromatography. The solvent mixtures employed in TLC analysis and in flash column chromatography purifications are reported as volume by volume. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded using 300 or 400 MHz equipment. For ^{1}H NMR spectra, chemical shifts (δ) are referenced from TMS (0.00 ppm). Coupling constants (*J*) are reported in Hz. For multiplicities the following abbreviations were used: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; dd, double doublet; ddd, double double doublet; br s, broad singlet; br t, broad triplet. Carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded using an NMR spectrometer at 75 or 100 MHz. For ^{13}C NMR spectra, chemical shifts (δ) are given from $CDCl_3$ (77.0 ppm). Infrared spectra were obtained on a Nicolet Magna 750 FT-IR spectrometer and the absorptions are given in wavenumbers (cm^{-1}). The low- and high-resolution mass spectra were obtained on a JEOL JMS-AX505HA.

2-(benzo[*d*][1,3]dioxol-5-yl)-*N*-(2,3-dimethoxybenzyl)ethanamine (9). A stirred solution of 3,4-methylenedioxyphenetylamine hydrochloride (1.22 g, 6.05 mmol) in MeOH (10 mL) over molecular sieve (4 Å), under an inert Argon atmosphere at room temperature was slowly added Et_3N (0.9 mL, 6.46 mmol) and stirred for 30 minutes. Then, to the reaction mixture was added 2,3-dimethoxybenzaldehyde **7** (1.0 g, 6.02 mmol). After 5 h the mixture was cooled down to 0 °C and $NaBH_4$ (227 mg, 6.00 mmol) was carefully added in 3 portions, after that the mixture was stirred for 30 min at 0 °C and 1 h at room temperature. Saturated aqueous solution of NaCl (3 mL) was added and filtered through a pad of celite and washed with EtOAc. The filtrate was recovered and washed with brine (30 mL x 2), dried (Na_2SO_4) and then concentrated under reduced pressure. The residue was purified by column chromatographic on silica gel (hexanes-EtOAc-Et_3N, 75:20:5) to give compound **9** (1.77g, 95%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.02-6.97 (m, 1H), 6.86-6.81 (m, 2H), 6.73-6.65 (m, 3H), 5.90 (s, 2H), 3.85 (s, 3H), 3.80 (s, 2H), 3.79 (s, 3H), 2.85-2.70 (m, 4H), 1.82 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 152.6, 147.5, 147.2, 145.8, 133.9, 133.8, 123.8, 121.6, 121.5, 111.4, 109.0, 108.1, 100.7, 60.6, 55.7, 50.6, 48.6, 36.1; IR (film): 3340, 2934, 1480, 1439, 1005, 747 cm^{-1}; HRMS (FAB^+) calc. for $C_{18}H_{22}NO_4$ [M+1]: 316.1549, found: 316.1558.

2-(benzo[*d*][1,3]dioxol-5-yl)-*N*-(2-bromo-3,4-dimethoxybenzyl)-

ethanamine (10). This compound was prepared by following the preceding procedure as compound **9**: 2-bromo-3,4-dime-thoxybenzaldehyde **8** (1.0 g, 4.08 mmol), 3,4-methylene-dioxyphenetylamine hydrochloride (823 mg, 4.08 mmol), Et_3N (0.6 mL, 4.31 mmol) and $NaBH_4$ (152 mg, 4.03 mmol) to give compound **10** (1.51 g, 93%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.05 (d, *J* = 8.4 Hz, 1H), 6.82 (d, *J* = 8.4 Hz, 1H), 6.74-6.66 (m, 3H),

5.92 (s, 2H), 3.86 (s, 3H), 3.84 (s, 3H), 3.82 (s, 2H), 2.84-2.74 (m, 4H), 1.69 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 152.6, 147.6, 146.5, 145.9, 133.7, 132.1, 125.1, 121.5, 119.6, 111.0, 109.0, 108.2, 100.8, 60.4, 56.1, 53.5, 50.4, 36.0; IR (film): 2936, 2835, 1484, 1243, 1029, 805 cm^{-1}; HRMS (FAB$^+$) calc. for $C_{18}H_{21}BrNO_4$ [M+1]: 394.0654, found: 394.0653.

2-(2-(benzo[*d*][1,3]dioxol-5-yl)ethyl)-4,5-dimethoxyisoindolin-1-one (11). In a round flask bottom equipped with condenser was charged freshly prepared secondary amine **9** (760 mg, 2.410 mmol), $Pd(OAc)_2$ (30 mg, 0.134 mmol) and $Cu(OAc)_2$ (219 mg, 1.205 mmol) in toluene (40 mL); then O_2 and CO atmosphere was delivered from balloons. The mixture reaction was heated at reflux for 8 h, then cooled at room temperature and filtered through a pad of powdered $MgSO_4$ and Celite. Solvent was concentrated under reduced pressure. The residue was purified by column chromatographic on silica gel (hexanes-EtOAc, 1:1) to give compound **11** (679 mg, 81%) as a pale solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.54 (d, *J* = 8.1 Hz, 1H), 7.00 (d, *J* = 8.4 Hz, 1H), 6.74-6.68 (m, 3H), 5.92 (s, 2H), 4.25 (s, 2H), 3.93 (s, 3H), 3.90 (s, 3H), 3.78 (t, *J* = 7.2 Hz, 2H), 2.90 (t, *J* = 7.2 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 168.1, 154.6, 147.8, 146.2, 143.4, 133.1, 132.5, 126.5, 121.6, 119.4, 112.7, 109.1, 108.4, 100.9, 60.3, 56.2, 48.3, 44.3, 34.6; IR (film): 2936, 1683, 1496, 1274 cm^{-1}; HRMS (FAB$^+$) calc. for $C_{19}H_{20}NO_5$ [M+1]: 342.1341, found: 342.1344; m.p. = 126-127 °C.

2-(2-(benzo[*d*][1,3]dioxol-5-yl)ethyl)-6,7-dimethoxyisoindolin-1-one (12). In a round flask bottom equipped with condenser was charged freshly prepared secondary amine **10** (666 mg, 1.693 mmol), $Pd(OAc)_2$ (38 mg, 0.169 mmol), PPh_3 (178 mg, 0.679 mmol) and K_2CO_3 (1.64 g, 11.866 mmol) in toluene (50 mL); then CO atmosphere was delivered from a balloon. The mixture reaction was heated at reflux for 12 h, then cooled at room temperature and filtered through a pad of powdered $MgSO_4$ and Celite. Toluene was concentrated under reduced pressure. The residue was purified by column chromatographic on silica gel (hexanes-EtOAc, 6:4) to give compound **12** (490 mg, 84%) as a pale solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.06 (d, *J* = 8.1 Hz, 1H), 7.01 (d, *J* = 8.4 Hz, 1H), 6.73-6.65 (m, 3H), 5.90 (s, 2H), 4.13 (s, 2H), 4.08 (s, 3H), 3.87 (s, 3H), 3.75 (t, *J* = 7.5 Hz, 2H), 2.88 (t, *J* = 7.5 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 166.5, 152.1, 147.6, 147.0, 146.0, 134.4, 132.4, 124.9, 121.4, 117.5, 116.2, 108.9, 108.2, 100.7, 62.3, 56.6, 49.5, 44.2, 34.3; IR (film): 2924, 1681, 1493, 1268, 1040 cm^{-1}; HRMS (FAB$^+$) calc. for $C_{19}H_{20}NO_5$ [M+1]: 342.1341, found: 342.1342; m.p. = 81-82 °C.

2-(3,4-dimethoxyphenethyl)-4,5-dimethoxyisoindolin-1-one (14).

A solution of 3,4-dimethoxyphenethylamine **13** (500 mg, 2.76 mmol) and 2,3-dimethoxybenzaldehyde **7** (458 mg, 2.76 mmol) in MeOH (10 mL) over molecular sieve (4 Å), under an inert Argon atmosphere at room temperature was stirred for 3 h. After that, the mixture reaction was cooled down to 0 °C and $NaBH_4$ (114 mg, 3.01 mmol) was carefully added in 3 portions; the reaction mixture was stirred for 30 min at 0 °C and 1 h at room temperature. Saturated aqueous solution of NaCl (3 mL) was added and filtered through a pad celite and washed with EtOAc. The filtrate was recovered and washed with brine (30 mL x 2), dried (Na_2SO_4) and concentrated under reduced pressure to give the corresponding secondary amine as a pale oil (895 mg) and used without further purification in the next step. In a round flask bottom equipped with condenser was charged crude amine previously prepared (895 mg, 2.702 mmol), $Pd(OAc)_2$ (42 mg, 0.187 mmol) and $Cu(OAc)_2$ (245 mg,

1.351 mmol) in toluene (40 mL); then an O_2 and CO atmosphere was delivered from balloons. The mixture was heated at reflux for 8 h, cooled at room temperature and filtered through a pad of powdered $MgSO_4$ and Celite. The solvent was concentrated under reduced pressure. The residue was purified by column chromatographic on silica gel (hexanes-EtOAc, 1:1) to give compound **14** (912 mg, 94%) as a pale solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.54 (d, *J* = 8.4 Hz, 1H), 7.00 (d, *J* = 8.4 Hz, 1H), 6.78-6.75 (m, 3H), 4.22 (s, 2H), 3.93 (s, 3H), 3.88 (s, 3H), 3.85 (s, 3H), 3.81 (s, 3H), 3.81 (t, *J* = 7.2 Hz, 2H), 2.94 (t, *J* = 7.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 168.1, 154.6, 149.0, 147.6, 143.4, 133.2, 131.3, 126.5, 120.6, 119.4, 112.6, 111.8, 111.3, 60.3, 56.2, 55.9, 55.8, 48.3, 44.2, 34.3; IR (KBr): 2933, 1671, 1417, 1226, 1145, 761 cm^{-1}; HRMS (FAB$^+$) calc. for $C_{20}H_{24}NO_5$ [M+1]: 358.1654, found: 358.1651; m.p. = 88-90 °C.

General procedure for C-H activation with copper (I):

In a round flask bottom with stirring bar was charged compound **14**, copper salt (20 mol%) and TBHP 5.5 M (3.0-6.0 equiv. solution in decane) in degassed CH_2Cl_2 (2.0 mL) under dry Argon atmosphere at room temperature. The mixture reaction was stirred for 6-7 h and then filtered over a short pad of Celite. The organic phase was recovered, washed with brine and concentrated under reduced pressure. The crude product was purified by column chromatographic on silica gel (hexanes-EtOAc, 8:2) to give compounds **15**, **16** or **17**.

2-(3,4-dimethoxyphenethyl)-4,5-dimethoxyisoindoline-1,3-dione (15). Pale solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.52 (d, *J* = 8.0 Hz, 1H), 7.09 (d, *J* = 8.0 Hz, 1H), 6.79-6.76 (m, 3H), 4.13 (s, 3H), 3.95 (s, 3H), 3.86 (t, *J* = 7.6 Hz, 2H), 3.84 (s, 3H), 3.83 (s, 3H), 2.92 (t, *J* = 7.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 167.4, 166.1, 157.6, 148.8, 147.6, 147.1, 130.6, 124.6, 121.8, 120.8, 119.2, 115.6, 111.9, 111.2, 62.5, 56.6, 55.8, 55.8, 39.3, 34.0; IR (film): 2936, 1706, 1388, 1023 cm^{-1}; HRMS (FAB$^+$) calc. for $C_{20}H_{22}NO_6$ [M+1]: 372.1447, found: 372.1457; m.p. = 117-118 °C.

3-(*tert*-butylperoxy)-2-(3,4-dimethoxyphenethyl)-4,5-dimethoxy-isoindolin-1-one (16). Pale viscous oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.49 (d, *J* = 8.1 Hz, 1H), 7.02 (d, *J* = 8.1 Hz, 1H), 6.81-6.75 (m, 3H), 5.96 (s, 1H), 4.14-4.07 (m, 1H), 3.95 (s, 3H), 3.92 (s, 3H), 3.84 (s, 3H), 3.8 (s, 3H), 3.83-3.75 (m, 1H), 3.07-2.90 (m, 2H), 1.29 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 167.4, 155.7, 148.8, 147.5, 145.1, 131.8, 130.0, 126.1, 120.7, 119, 113.9, 112.0, 111.3, 89.1, 81.1, 60.6, 56.2, 55.8, 55.7, 43.1, 34.1, 26.3; IR (film): 2978, 1705, 1495, 1271, 1039 cm^{-1}; HRMS (FAB$^+$) calc. for $C_{24}H_{32}NO_7$ [M+1]: 446.2179, found: 446.2172.

12b-(*tert*-butylperoxy)-2,3,11,12-tetramethoxy-5,6-dihydroiso-indolo[1,2-*a*]isoquinolin-8(12b*H*)-one (17). Red viscous oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.29 (s, 1H), 7.55 (d, *J* = 8.0 Hz, 1H), 7.03 (d, *J* = 8.4 Hz, 1H), 6.59 (s, 1H), 4.41 (ddd, *J* = 2.0, 6.2, 12.8 Hz, 1H), 4.11 (s, 3H), 3.95 (s, 3H), 3.93 (s, 3H), 3.85 (s, 3H), 3.54 (ddd, *J* = 4.4, 11.6, 12.8 Hz, 1H), 3.01-2.93 (m, 1H), 2.73 (ddd, *J* = 2.4, 4.4, 16.0 Hz 1H), 1.16 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 167.3, 156.8, 149.4, 147.4, 144.4, 136.8, 129.1, 125.4, 124.6, 119.4, 113.5, 113.3, 110.9, 94.8, 80.3, 60.5, 56.2, 56.0, 55.7, 35.9, 28.6, 26.7; IR (film): 2937, 1702, 1263, 1014, 729 cm^{-1}; HRMS (FAB$^+$) calc. for $C_{24}H_{30}NO_7$ [M+1]: 444.2024, found: 444.2022.

12b-(*tert*-butylperoxy)-11,12-dimethoxy-5,6-dihydro-[1,3]dioxolo-[4,5-*g*]isoindolo[1,2-*a*]isoquinolin-8(12b*H*)-one (18). In a round flask bottom with stirring bar was charged

compound **11** (43 mg, 0.126 mmol), CuOTf•Toluene complex (13 mg, 0.025 mmol) and TBHP 5.5 M (0.14 mL, 0.756 mmol) in degassed CH_2Cl_2 (2.0 mL), under dry Argon atmosphere at room temperature. The mixture reaction was heated at reflux for 6 h, and then filtered through a pad of Celite. Organic phase was recovered, washed with brine and concentrated under reduced pressure. The crude was purified by preparative thin layer chromatography (hexanes-EtOAc, 8:2) to give compound **18** (31 mg, 57%) as light red viscous oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.10 (s, 1H), 7.54 (d, *J* = 8.1 Hz, 1H), 7.03 (d, *J* = 8.1 Hz, 1H), 6.58 (s, 1H), 5.93 (d, *J* = 1.5 Hz, 1H), 5.88 (d, *J* = 1.2 Hz, 1H), 4.31 (ddd, *J* = 3.4, 6.0, 13.0 Hz, 1H), 4.07 (s, 3H), 3.95 (s, 3H), 3.51 (ddd, *J* = 4.9, 10.6, 13.2 Hz, 1H), 2.93 (ddd, *J* = 6.0, 10.5, 16.2 Hz, 1H), 2.77 (td, *J* = 4.0, 15.8 Hz, 1H), 1.16 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 167.4, 156.7, 148.2, 146.4, 144.4, 136.5, 130.8, 125.9, 125.4, 119.3, 113.4, 110.6, 108.4, 101.1, 95.0, 80.4, 60.6, 56.2, 36.0, 29.0, 26.7; IR (film): 2979, 1704, 1490, 1394, 1269, 751 cm^{-1}; HRMS (FAB$^+$) calc. for $C_{23}H_{26}NO_7$ [M+1]: 428.1709, found: 428.1702.

C-H activation with copper (I) drive to synthesis of nuevamine:

In a round flask bottom with stirring bar was charged compound **11** (76 mg, 0.223 mmol), CuCl (4.4 mg, 0.044 mmol) and TBHP 5.5 M (0.12 mL, 0.668 mmol) in degassed CH_2Cl_2 (2.0 mL), under dry Argon atmosphere at room temperature. The reaction mixture was stirred for 7 h and then filtered through a pad of Celite. The organic phase was recovered, washed with brine and concentrated under reduced pressure. Crude product was purified by column chromatographic on silica gel (hexanes-EtOAc, 8:2) to give compounds **19** (22 mg, 27%) and **20** (49 mg, 51%).

2-(2-(benzo[*d*][1,3]dioxol-5-yl)ethyl)-4,5-dimethoxyisoindoline-1,3-dione (19). Pale solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.52 (d, *J* = 7.8 Hz, 1H), 7.09 (d, *J* = 8.1 Hz, 1H), 6.75-6.69 (m, 3H), 5.91 (s, 2H), 4.13 (s, 3H), 3.95 (s, 3H), 3.85-3.8 (m, 2H), 2.90-2.85 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 167.5, 166.1, 157.7, 147.6, 147.2, 146.2, 131.9, 124.6, 121.8, 119.3, 115.7, 109.3, 108.3, 100.8, 62.6, 56.6, 39.5, 34.3; IR (film): 2941, 1706, 1494, 1271, 1043 cm^{-1}; HRMS (FAB$^+$) calc. for $C_{19}H_{18}NO_6$ [M+1]: 356.1056, found: 356.1054; m.p. = 149-150 °C.

2-(2-(benzo[*d*][1,3]dioxol-5-yl)ethyl)-3-(*tert*-butylperoxy)-4,5-dimethoxyisoindolin-1-one (20). Pale viscous oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.49 (d, *J* = 8.1 Hz, 1H), 7.03 (d, *J* = 8.1 Hz, 1H), 6.75-6.68 (m, 3H), 6.01 (s, 1H), 5.92 (s, 2H), 4.05-3.95 (m, 1H), 3.96 (s, 3H), 3.93 (s, 3H), 3.80-3.73 (m, 1H), 3.01-2.88 (m, 2H), 1.30 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 167.3, 155.7, 147.6, 146.0, 145.1, 133.0, 130.0, 126.1, 121.7, 119.1, 113.9, 109.2, 108.3, 100.8, 89.2, 81.3, 60.7, 56.2, 43.3, 34.5, 26.4; IR (film): 2977, 1705, 1495, 1271, 1039 cm^{-1}; HRMS (FAB$^+$) calc. for $C_{23}H_{28}NO_7$ [M+1]: 430.1709, found: 430.1704.

Synthesis of (+/-)-nuevamine:

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

From compound 18: To a solution of compound **18** (30 mg, 0.070 mmol) in MeOH (2 mL) and under dry Argon atmosphere at 0 °C, was added TFA (0.01 mL, 0.140 mmol). Then $NaBH_4$ (30 mg, 0.793 mmol) was carefully added in 3 portions. The mixture reaction was stirred for 30 min at 0 °C and then for 1 h at room temperature. Saturated solution of

NaCl (1 mL) was added and then filtered through a pad of celite and washed with EtOAc. The filtrate was recovered and washed with brine (5 mL x 2). The organic phase was recovered, dried (Na_2SO_4) and concentrated under reduced pressure. The crude was purified by column chromatographic on silica gel (hexanes-EtOAc, 6:4) to give compound **1** (21 mg, 88%) as white solid.

From compound 20: To a solution of compound **20** (55 mg, 0.128 mmol) in dry CH_2Cl_2 (2 mL) under dry Argon atmosphere at 0 °C, was added triflic acid (0.1 mL, 1.13 mmol). The mixture was stirred for 30 minutes, and then a solution of 7% aqueous of Na_2CO_3 was added dropwise until gas evolution ceased. The mixture was diluted with CH_2Cl_2 and washed with brine. The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. The crude was purified by column chromatographic on silica gel (hexanes-EtOAc, 6:4) to give compound **1** (41 mg, 94%) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.59 (d, *J* = 8.1 Hz, 1H), 7.33 (s, 1H), 7.07 (d, *J* = 8.4 Hz, 1H), 6.67 (s, 1H), 5.92 (d, *J* = 1.5 Hz, 1H), 5.86 (d, *J* = 1.5 Hz, 1H), 5.63 (s, 1H), 4.08-4.02 (m, 1H), 4.0 (s, 3H), 3.98 (s, 3H), 3.56 (ddd, *J* = 5.7, 6.7, 12.5 Hz, 1H), 3.07-2.97 (m, 1H), 2.91-2.81 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 167.6, 155.5, 146.8, 146.4, 144.4, 136.2, 128.8, 128.4, 126.7, 119.8, 113.2, 108.4, 107.5, 101, 60.5, 58.4, 56.3, 38.8, 28.9; IR (film): 2933, 1685, 1487, 1274, 1038 cm^{-1}; HRMS (FAB$^+$) calc. for $C_{19}H_{18}NO_5$ [M+1]: 340.1028, found: 340.1022. m.p. = 210-211°C. Lit: 212°C.[1c]

2-(3,4-dimethoxyphenethyl)-6,7-dimethoxy-3-oxoisoindoline-1,1-dicarbonitrile (23). To a solution of compound **14** (64 mg, 0.179 mmol) in dry THF (2 mL) and under dry Argon atmosphere at -78 °C, was added a solution of KHMDS 0.5 M in toluene (0.8 mL, 0.394 mmol). The mixture reaction was stirred for 30 minutes whereupon was quickly added TsCN (97 mg, 0.537 mmol), heated at 0 °C and stirred for 1 h. The mixture was quenched with saturated aqueous NH_4Cl (0.5 mL), diluted with EtOAc and washed with brine. The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The crude was purified by column chromatographic on silica gel (hexanes-EtOAc, 7:3) to give compound **23** (65 mg, 89%) as a pale viscous oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.59 (d, *J* = 8.1 Hz, 1H), 7.22 (d, *J* = 8.4 Hz, 1H), 6.91-6.82 (m, 3H), 4.18 (s, 3H), 4.00 (s, 3H), 3.98-3.93 (m, 2H), 3.90 (s, 3H), 3.87 (s, 3H), 3.19-3.14 (dd, *J* = 6.8, 9.4 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 165.8, 156.6, 149.0, 147.9, 144.1, 129.8, 127.6, 121.8, 120.9, 120.4, 116.5, 112.0, 111.4, 111.2, 61.00, 56.6, 55.9, 49.9, 44.0, 33.4; IR (film): 2997, 1729, 1507, 1280, 1081; HRMS (FAB$^+$) calc. for $C_{22}H_{22}N_3O_5$ [M+1]: 408.1481, found: 408.1481.

General Procedure of Cyclization catalyzed with TfOH:

To a solution of compound **23** (100 mg, 0.246 mmol) in CH_2Cl_2 (2 mL) under dry Ar atmosphere at 0 °C, was added triflic acid (0.5 mL, 1.964 mmol). The mixture reaction was stirred for 20 min at 0 °C and 2 h at room temperature; then ice was added (2 g, 0.111 mol) and finally stirred for 12 h. The mixture was diluted with CH_2Cl_2 (10 mL) and washed with brine. Organic phase was additionally washed with a solution 7% of $NaHCO_3$. The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by column chromatographic on silica gel (hexanes-EtOAc, 1:1 $\rightarrow$ 3:7) to give compounds **26** (62 mg, 62%) and **27** (18 mg, 16%).

1,2,10,11-tetramethoxy-5,13-dioxo-7,8,13,13a-tetrahydro-5*H*-benzo[4,5]azepino[2,1-*a*]isoindole-13a-carbonitrile (26). White solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.50 (d, *J* =

8.1 Hz, 1H), 7.13 (d, *J* = 8.1 Hz, 1H), 7.00 (s, 1H), 6.74 (s, 1H), 4.28 (ddd, *J* = 5.1, 11.8, 13.7 Hz, 1H), 4.13 (S, 3H), 3.98 (s, 3H), 3.94 (s, 3H), 3.90-3.83 (m, 1H), 3.81 (s, 3H), 3.60 (ddd, *J* = 5.1, 11.8, 16.6 Hz, 1H), 3.19 (dt, *J* = 4.5, 16.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 190.2, 167.0, 157.1, 153.2, 148.2, 145.4, 132.2, 130.3, 126.9, 123.2, 119.7, 115.1, 114.4, 112.5, 112.3, 66.1, 60.8, 56.3, 56.1, 56.0, 39.7, 31.9; IR (film): 2942, 1711, 1501, 1272 cm^{-1}; HRMS (FAB^+) calc. for $C_{22}H_{21}N_2O_6$ [M+1]: 409.1321, found: 409.1323. m.p. = 216-218 °C.

2-(2-(3-cyano-4,5-dimethoxy-1-oxoisoindolin-2-yl)ethyl)-4,5-dimethoxybenzamide (27). White solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.51 (d, *J* = 8.1 Hz, 1H), 7.09 (d, *J* = 8.1 Hz, 1H), 6.99 (s, 1H), 6.79 (s, 1H), 5.98 (br s, exchange with D_2O, 2H), 5.39 (s, 1H), 4.27-4.20 (m, 1H), 4.03 (s, 3H), 3.95 (s, 3H), 3.87 (s, 3H), 3.84 (s, 3H), 3.69 (dt, *J* = 6.9, 14.1 Hz, 1H), 3.20 (t, *J* = 6.9 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 171.4, 167.2, 155.8, 150.7, 147.3, 143.9, 130.6, 129.9, 126.7, 124.2, 119.9, 115.2, 114.6, 113.6, 110.8, 60.7, 56.3, 56.1, 56.0, 47.7, 42.8, 31.5; IR (film): 3348, 2942, 1699, 1666, 1276, 1077 cm^{-1}; HRMS (FAB^+) calc. for $C_{22}H_{24}N_3O_6$ [M+1]: 426.1665, found: 426.1673. m.p. = 150-152 °C.

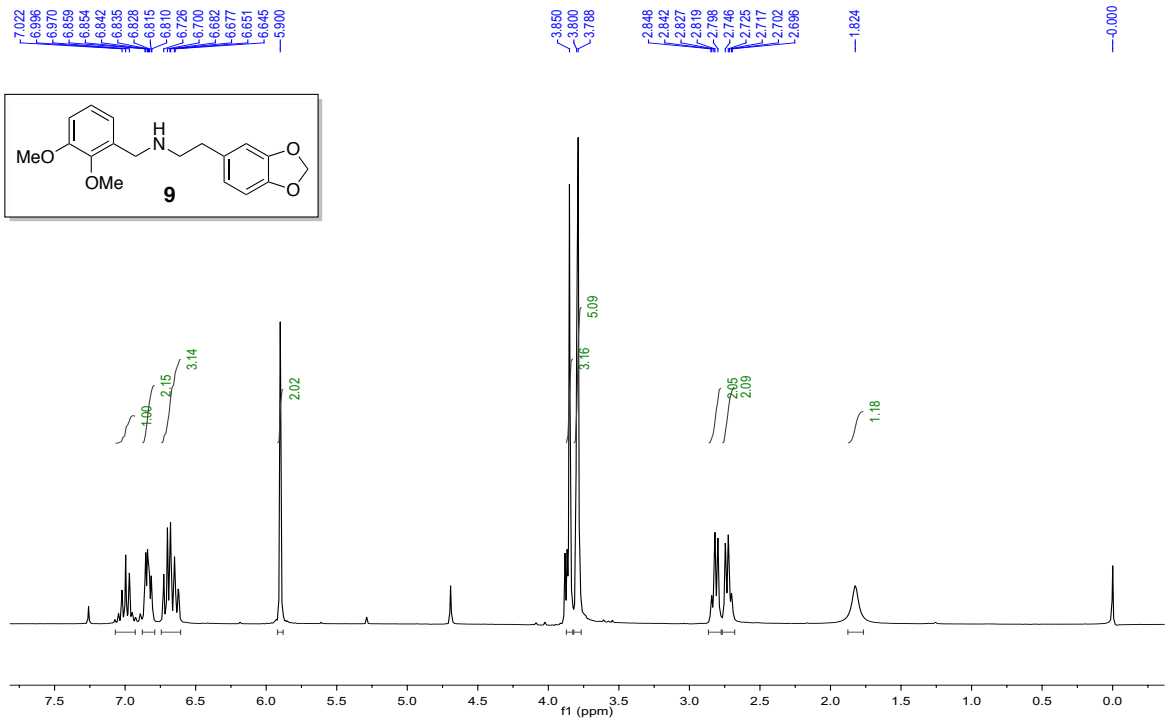
2-(2-(benzo[*d*][1,3]dioxol-5-yl)ethyl)-4,5-dimethoxy-3-oxoisoindoline-1,1-dicarbonitrile (28). This compound was prepared by following the preceding procedure as compound **23**: compound **12** (120 mg, 0.352 mmol), KHMDS 0.5 M in toluene (1.5 mL, 0.774 mmol) and TsCN (191 mg, 1.054 mmol) were charged to give corresponding dinitrile compound **28** (117 mg, 91%) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.48 (d, *J* = 8.4 Hz, 1H), 7.27 (d, *J* = 8.4 Hz, 1H), 6.81-6.76 (m, 3H), 5.94 (s, 2H), 4.11 (s, 3H), 3.96 (s, 3H), 3.90-3.85 (m, 2H), 3.14-3.09 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 164.1, 155.7, 148.0, 147.9, 146.5, 130.9, 127.2, 121.8, 120.9, 118.4, 117.6, 111.7, 109.2, 108.5, 100.9, 62.7, 56.7, 51.8, 44.4, 33.5; IR (KBr): 2940, 1713, 1493, 1253, 1032, 807 cm^{-1}; HRMS (FAB^+) calc. for $C_{21}H_{18}N_3O_5$ [M+1]: 392.1246, found: 392.1239. m.p. = 152-154 °C.

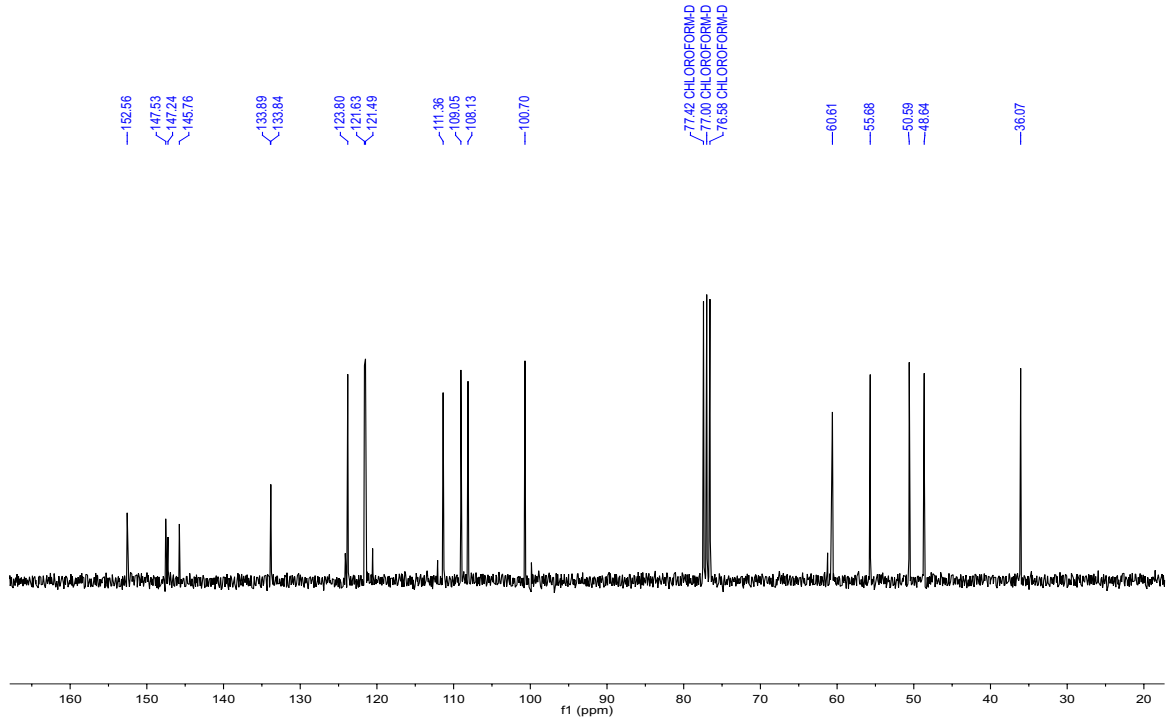
Synthesis of (+/-)-cyano-chilenine:

9,10-dimethoxy-8,13-dioxo-6,8,12b,13-tetrahydro-5*H*-[1,3]-dioxolo[4'',5'':4',5']benzo[1',2':4,5]azepino[2,1-*a*]isoindole-12b-carbonitrile (29). This compound was prepared by following the preceding procedure as compounds 26 and 27: Di-nitrile compound 28 (74 mg, 0.189 mmol), TfOH (0.5 mL, 1.964 mmol) and H_2O ice (2 g, 0.111 mol) were charged to give compound 29 (48 mg, 65%). Pale semisolid. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.67 (d, *J* = 8.4 Hz, 1H), 7.20 (d, *J* = 8.4 Hz, 1H), 6.71 (s, 2H), 6.00 (d, *J* = 1.2 Hz, 1H), 5.98 (d, *J* = 1.2 Hz, 1H), 4.44 (dt, *J* = 5.7, 13.5 Hz, 1H), 4.01 (s, 3H), 3.92 (s, 3H), 3.63 (ddd, *J* = 1.5, 6.2, 13.4 Hz, 1H), 3.33 (ddd, *J* = 6.2, 13.8, 15.1 Hz, 1H), 3.05 (ddd, *J* = 1.5, 5.7, 15.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 196.0, 165.7, 154.7, 152.4, 147.4, 146.9, 133.1, 129.4, 128.5, 122.2, 119.7, 117.4, 114.2, 109.5, 108.9, 102.2, 65.3, 62.5, 56.6, 38.9, 31.1; IR (film): 2925, 1711, 1498, 1272, 1038 cm^{-1}; HRMS (FAB^+) calc. for $C_{21}H_{17}N_2O_6$ [M+1]: 393.1087, found: 393.1089.

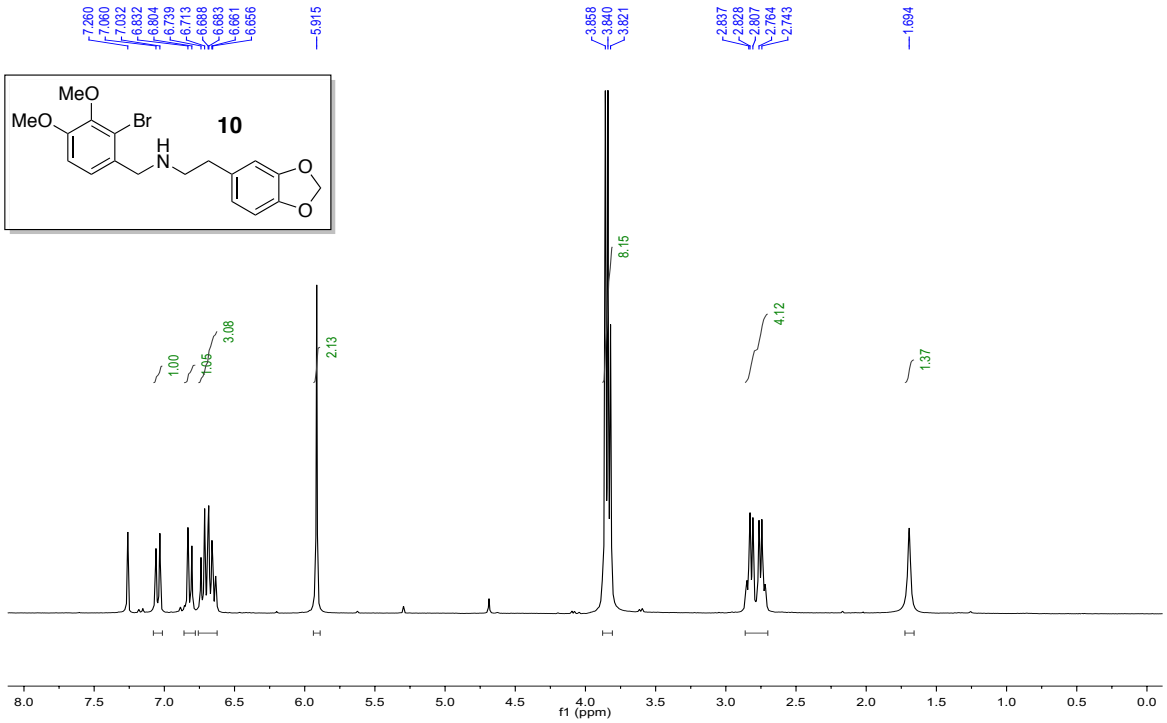
1. ^{1}H NMR and ^{13}C NMR Copies of New Products

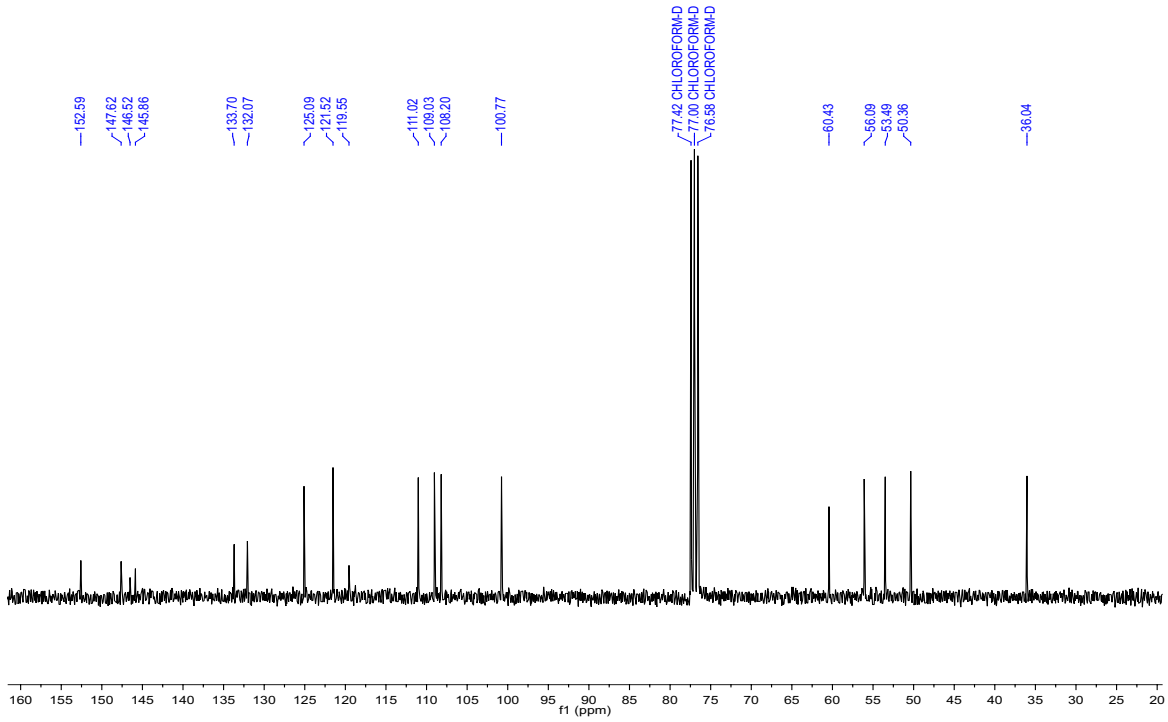
2-(benzo[*d*][1,3]dioxol-5-yl)-*N*-(2,3-dimethoxybenzyl)ethanamine (9).



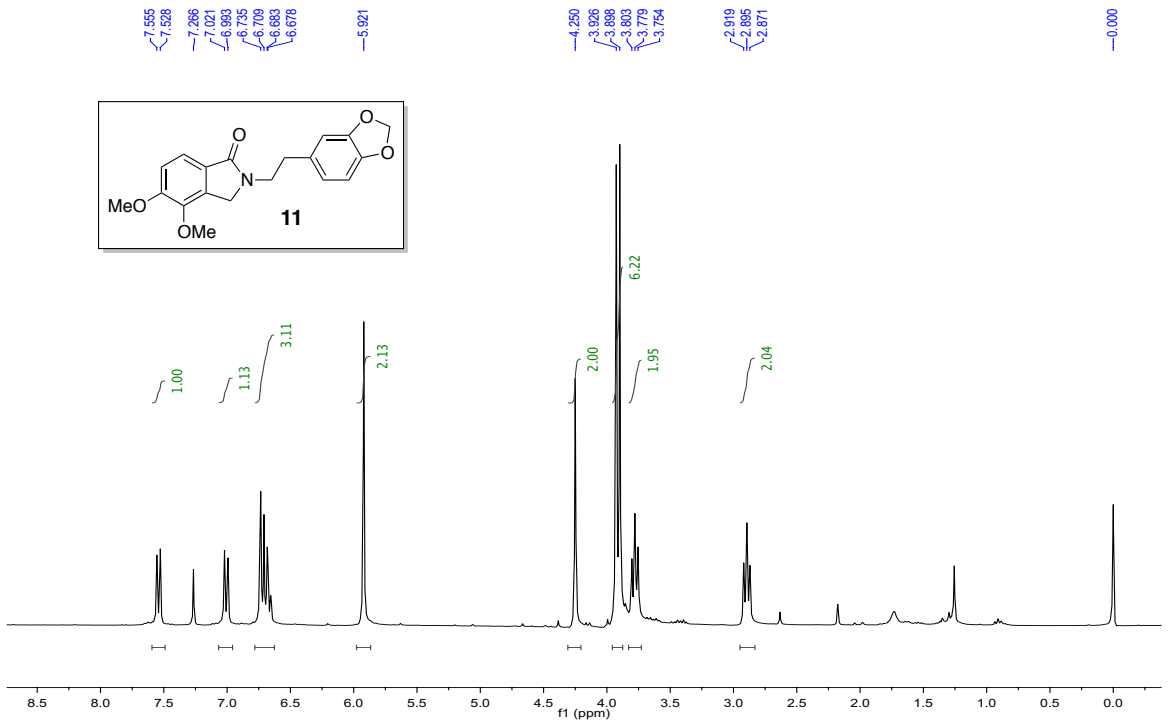


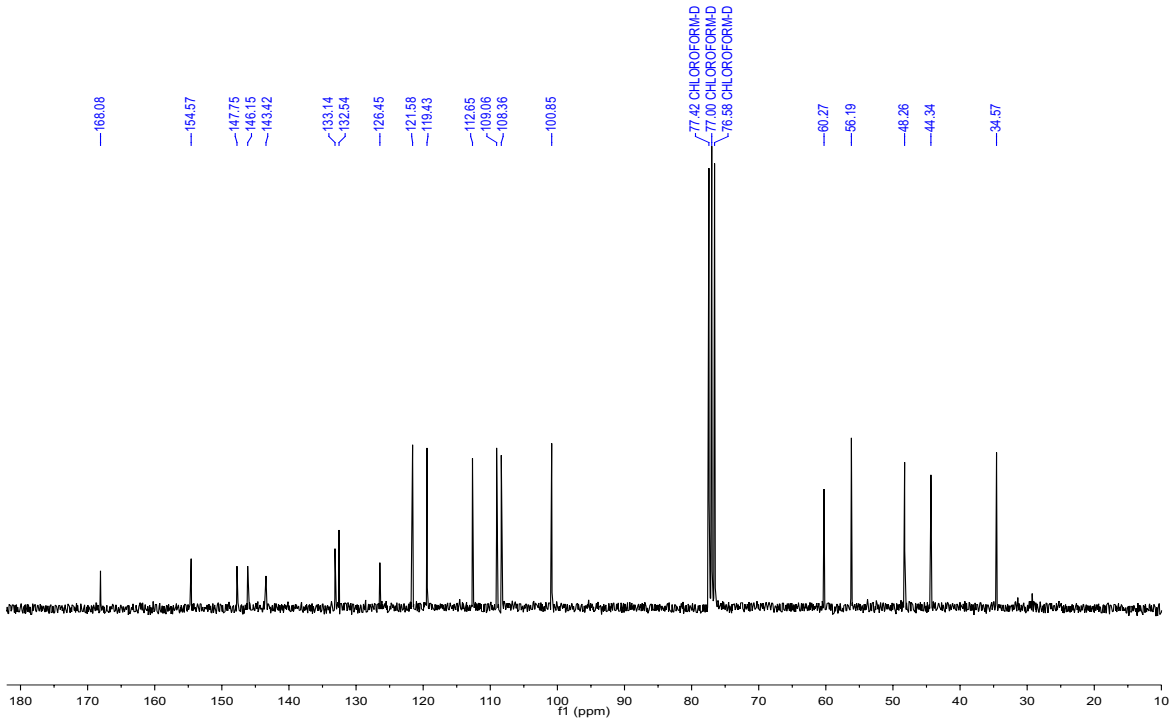
2-(benzo[*d*][1,3]dioxol-5-yl)-*N*-(2-bromo-3,4-dimethoxybenzyl)-ethanamine (10).



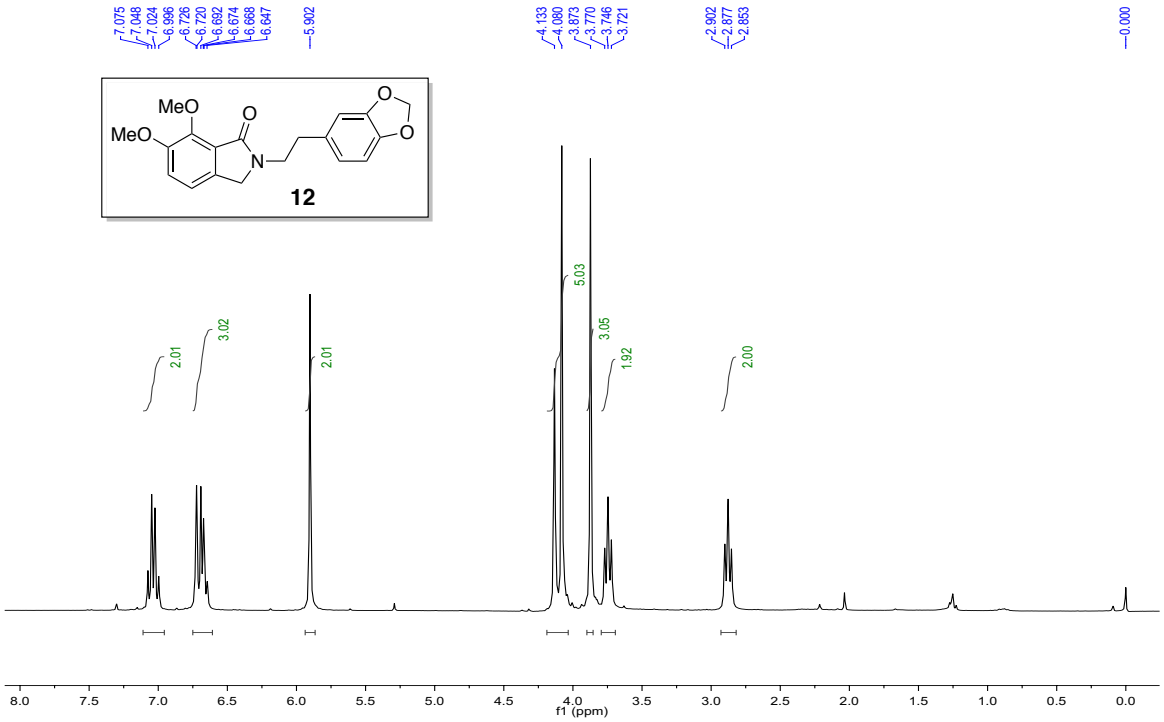


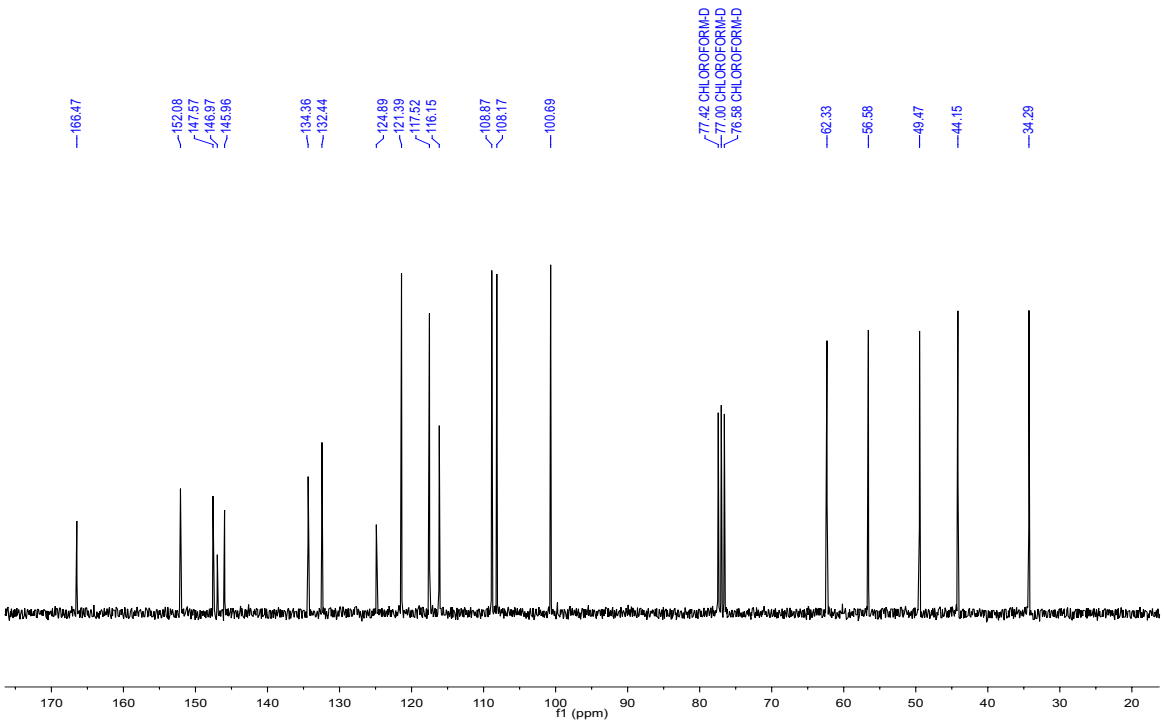
2-(2-(benzo[*d*][1,3]dioxol-5-yl)ethyl)-4,5-dimethoxyisoindolin-1-one (11).



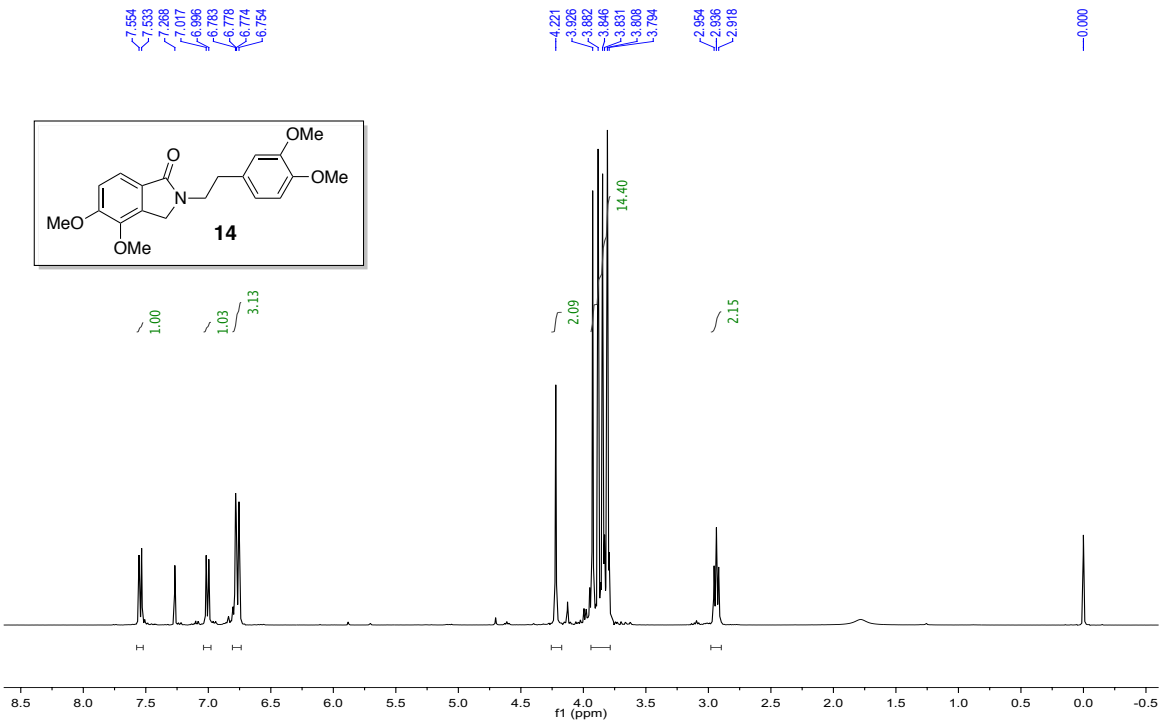


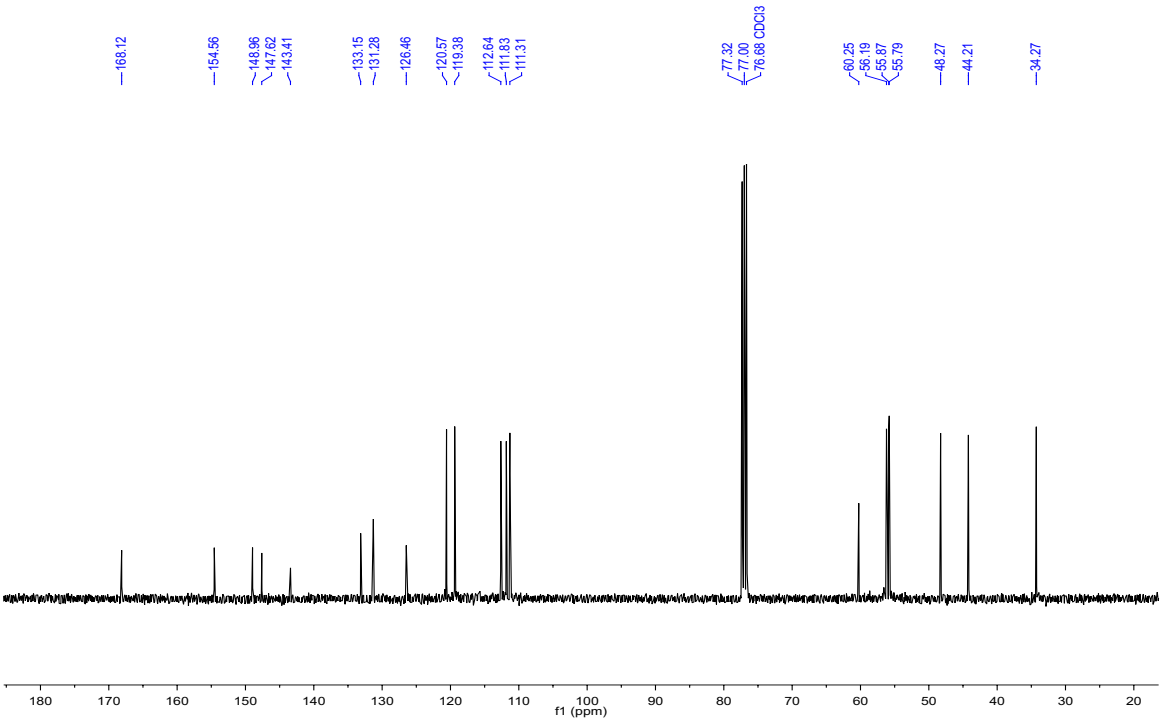
2-(2-(benzo[*d*][1,3]dioxol-5-yl)ethyl)-6,7-dimethoxyisoindolin-1-one (12).



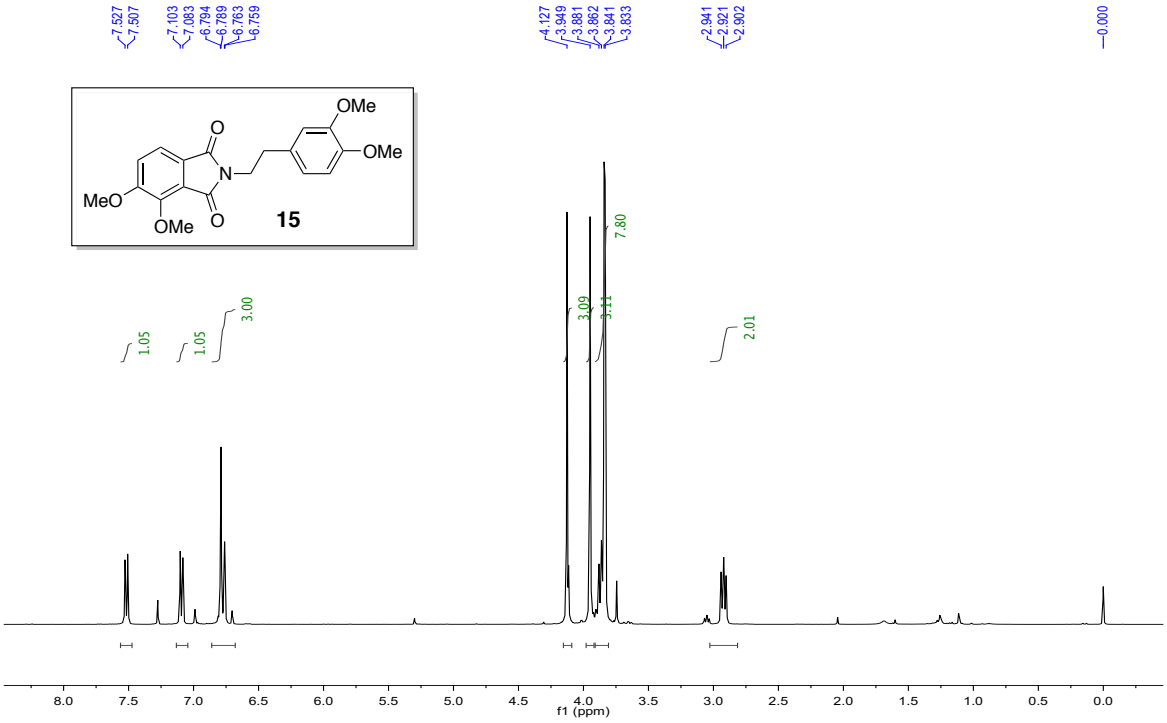


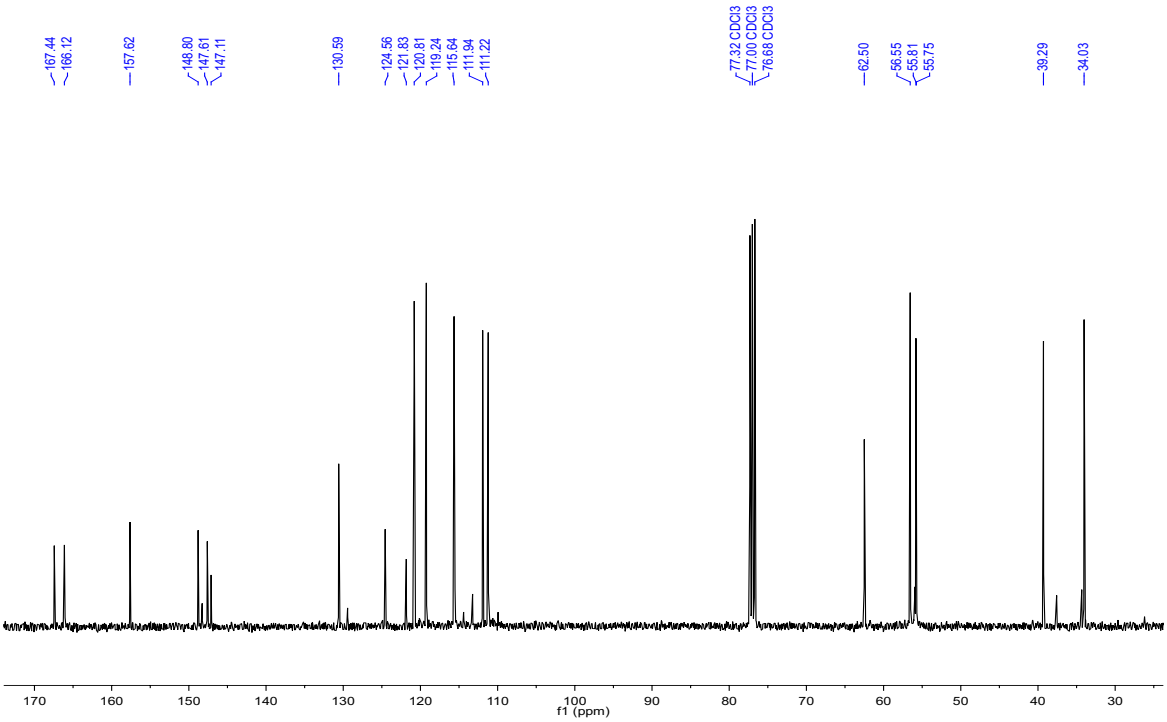
2-(3,4-dimethoxyphenethyl)-4,5-dimethoxyisoindolin-1-one (14).



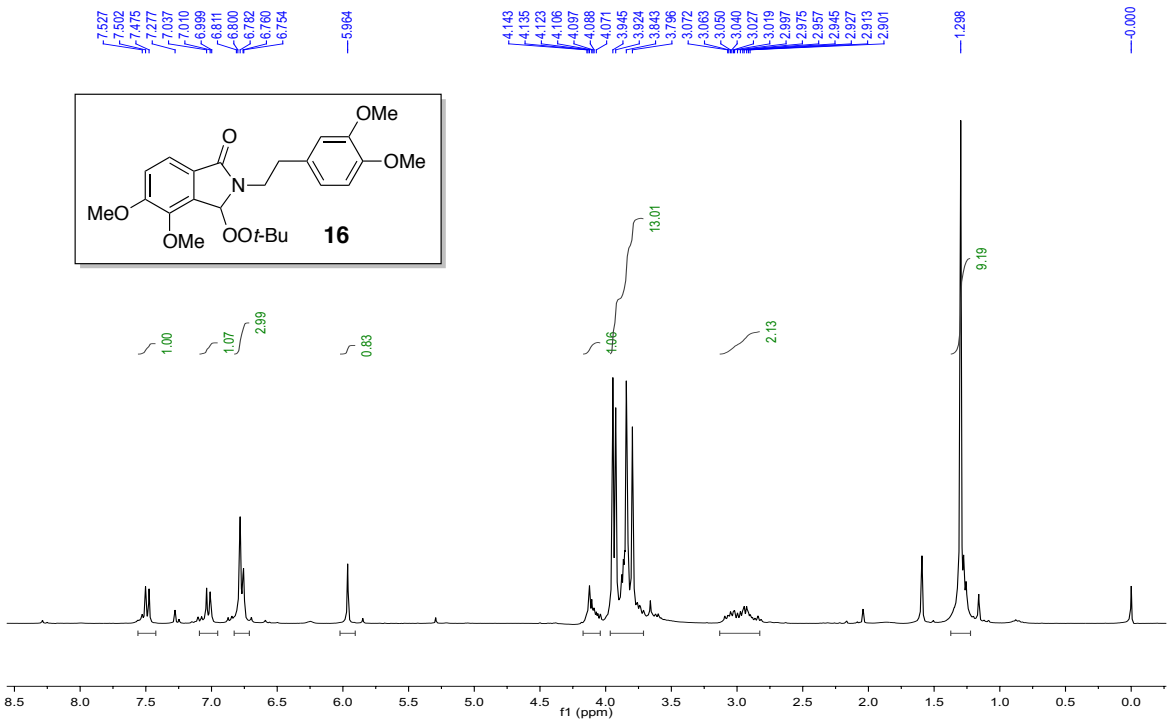


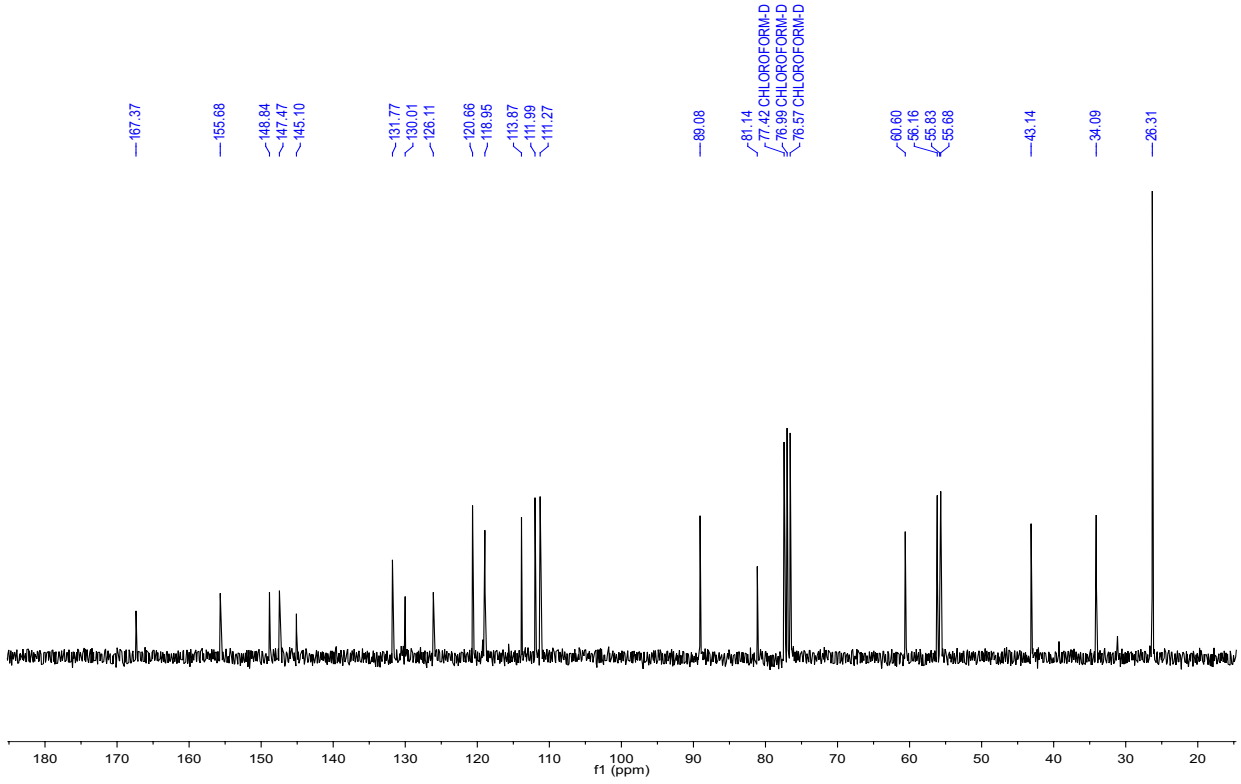
2-(3,4-dimethoxyphenethyl)-4,5-dimethoxyisoindoline-1,3-dione (15).



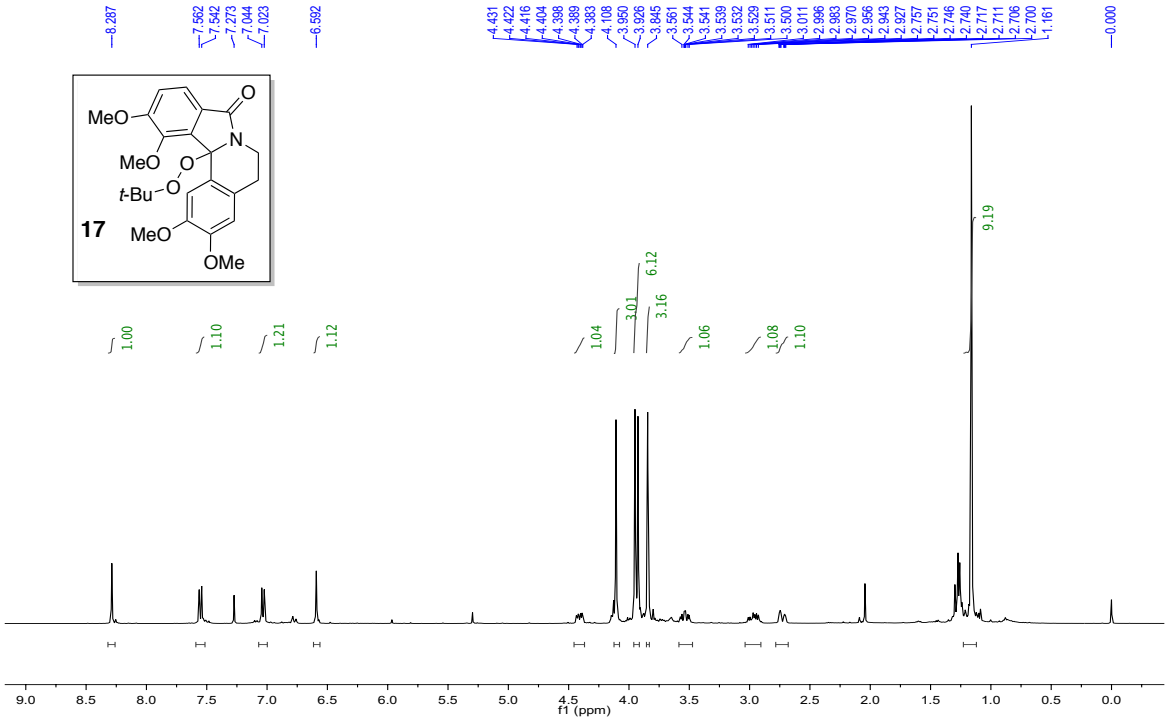


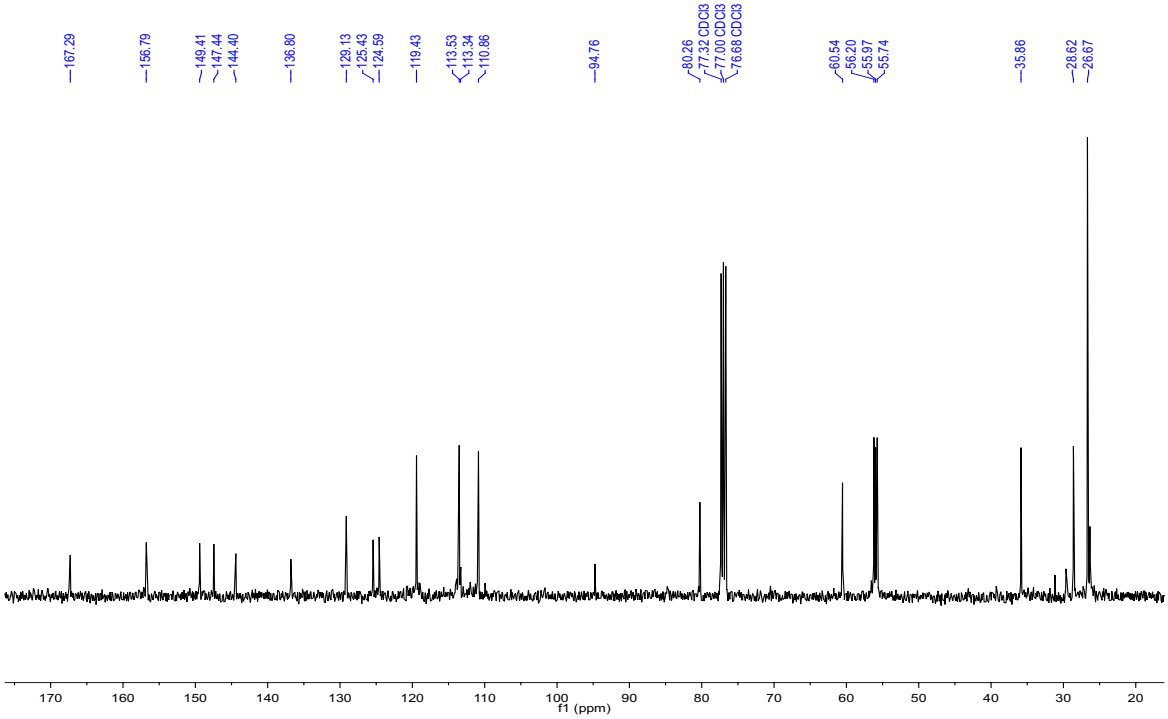
3-(*tert*-butylperoxy)-2-(3,4-dimethoxyphenethyl)-4,5-dimethoxyisoindolin-1-one (16).



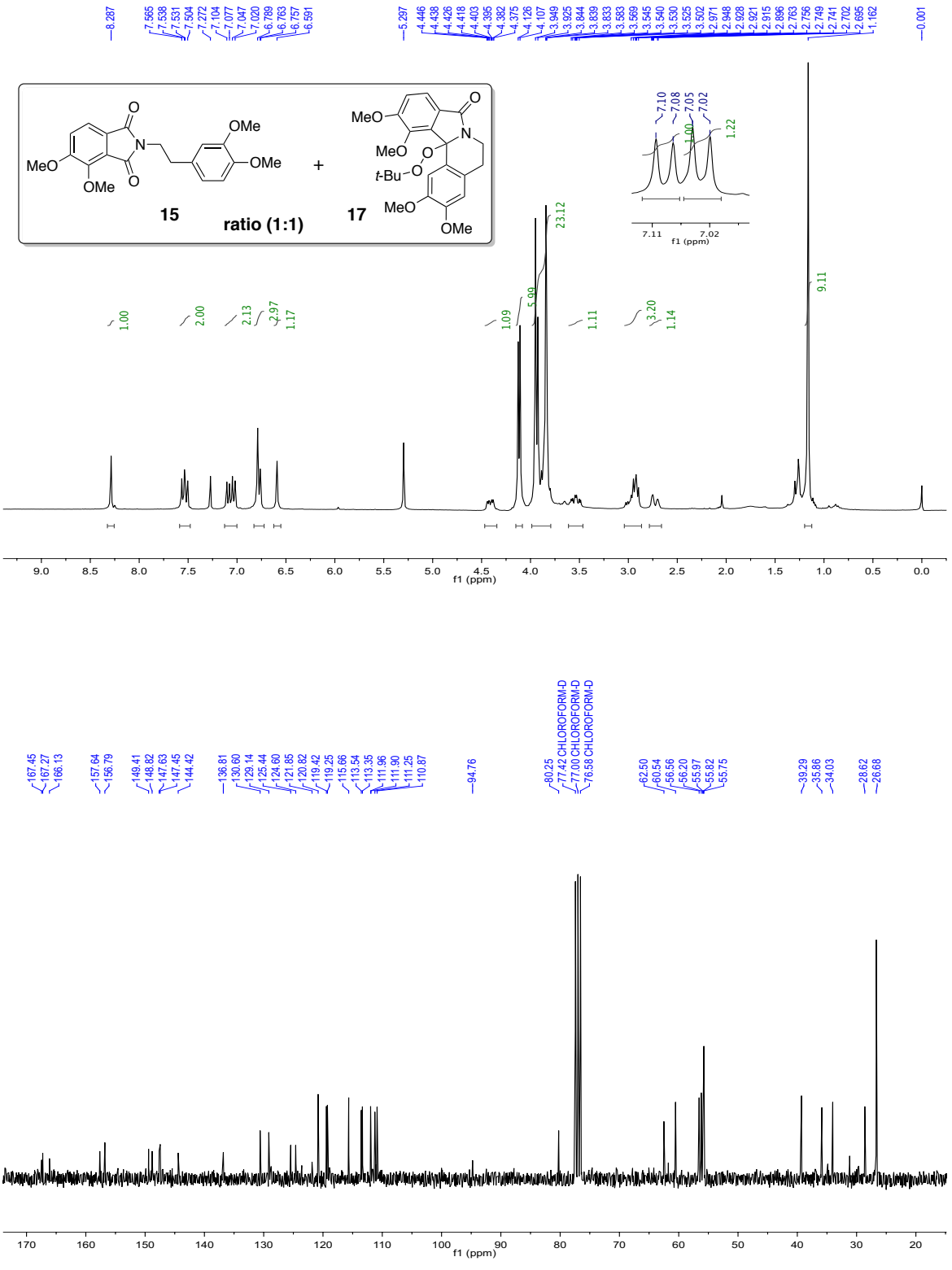


12b-(*tert*-butylperoxy)-2,3,11,12-tetramethoxy-5,6-dihydroisoindolo[1,2-*a*]isoquinolin-8(12b*H*)-one (17).

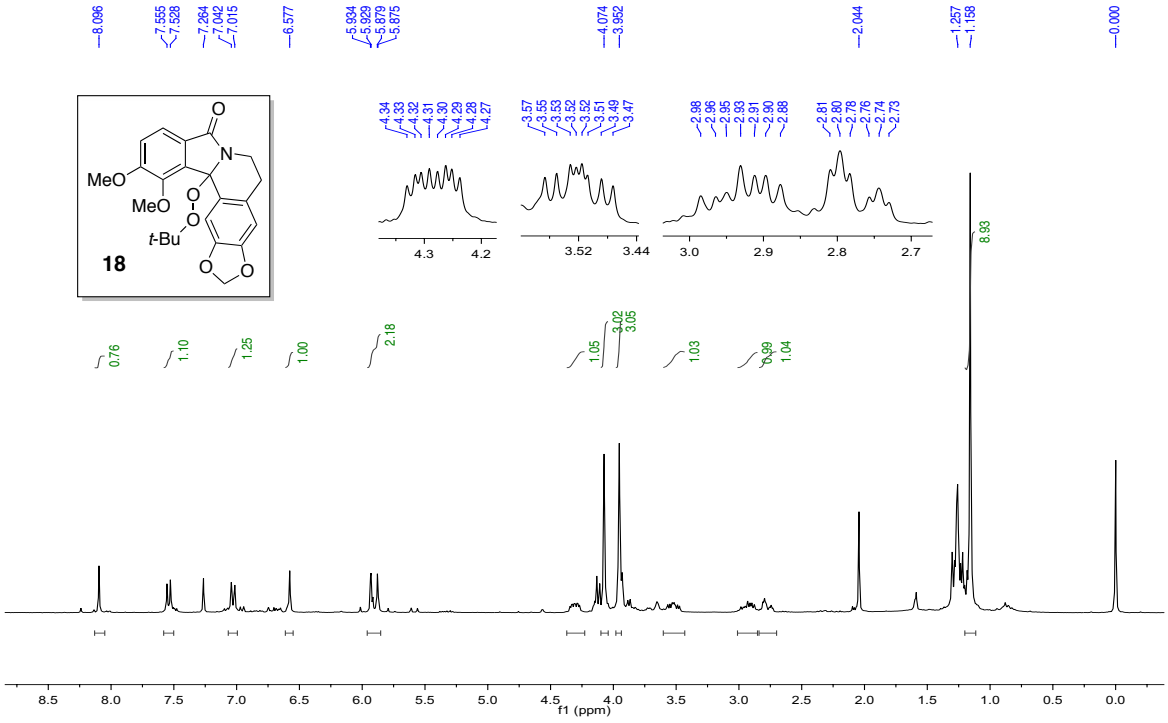


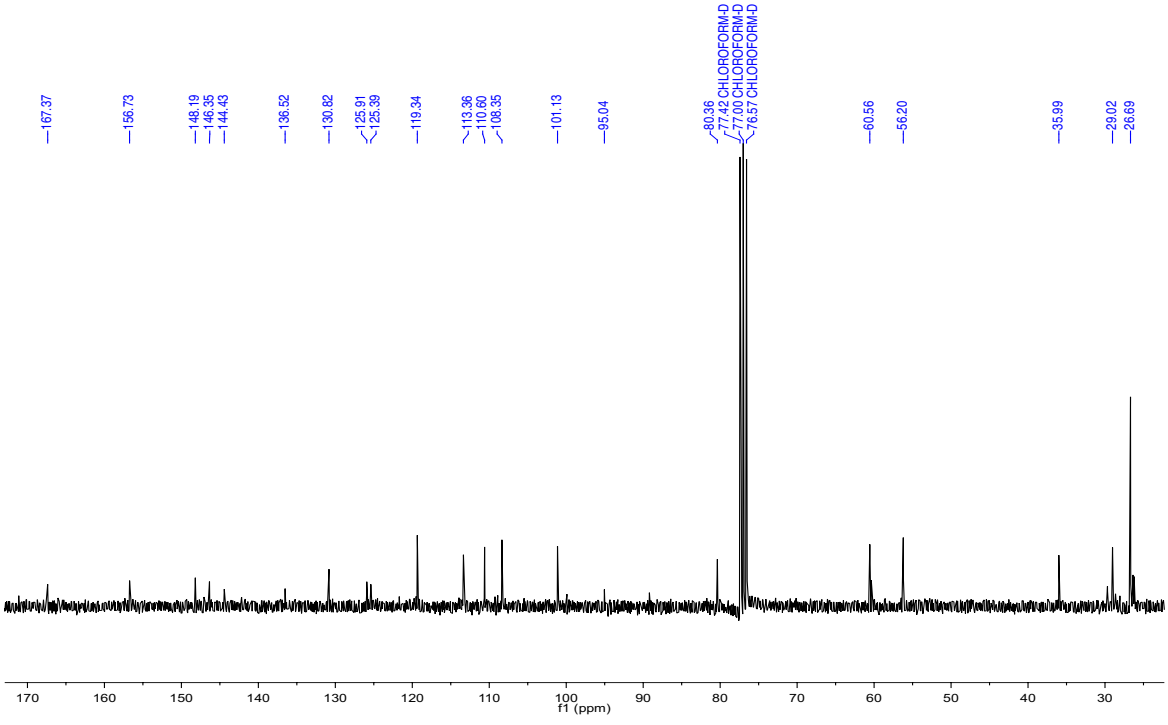


Inseparable mixture of compounds 15+17 (reaction with CuI)

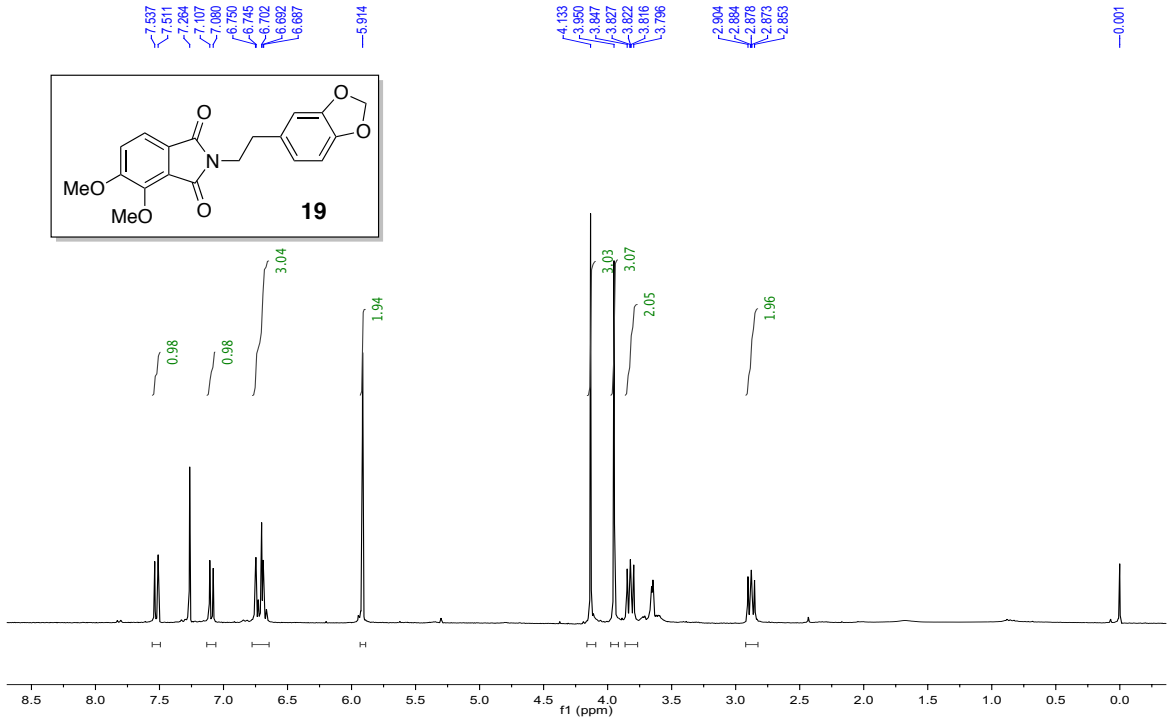


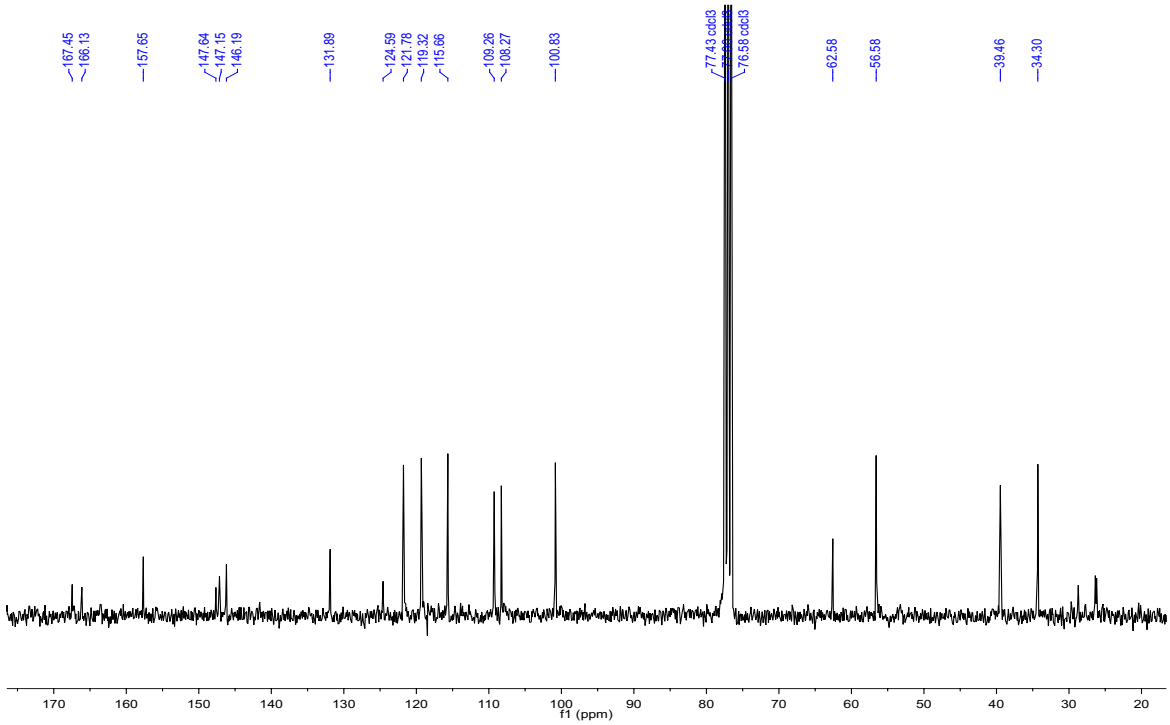
12b-(*tert*-butylperoxy)-11,12-dimethoxy-5,6-dihydro-[1,3]dioxolo[4,5-*g*]isoindolo[1,2-*a*]isoquinolin-8(12b*H*)-one (18).



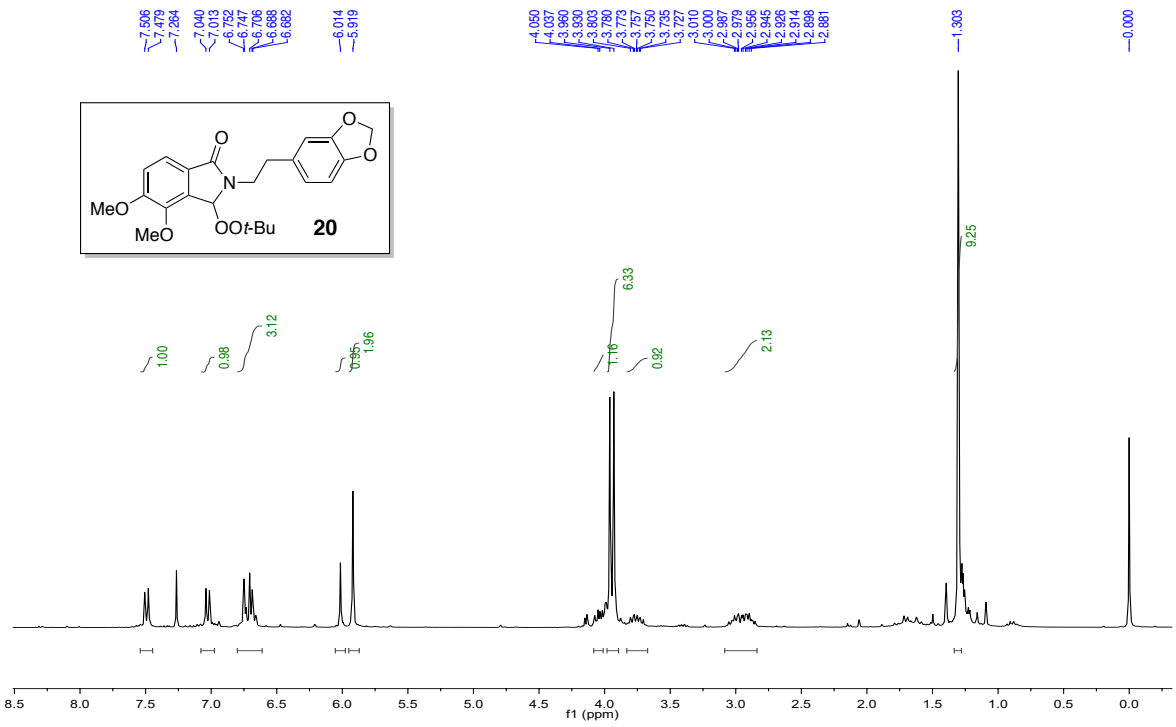


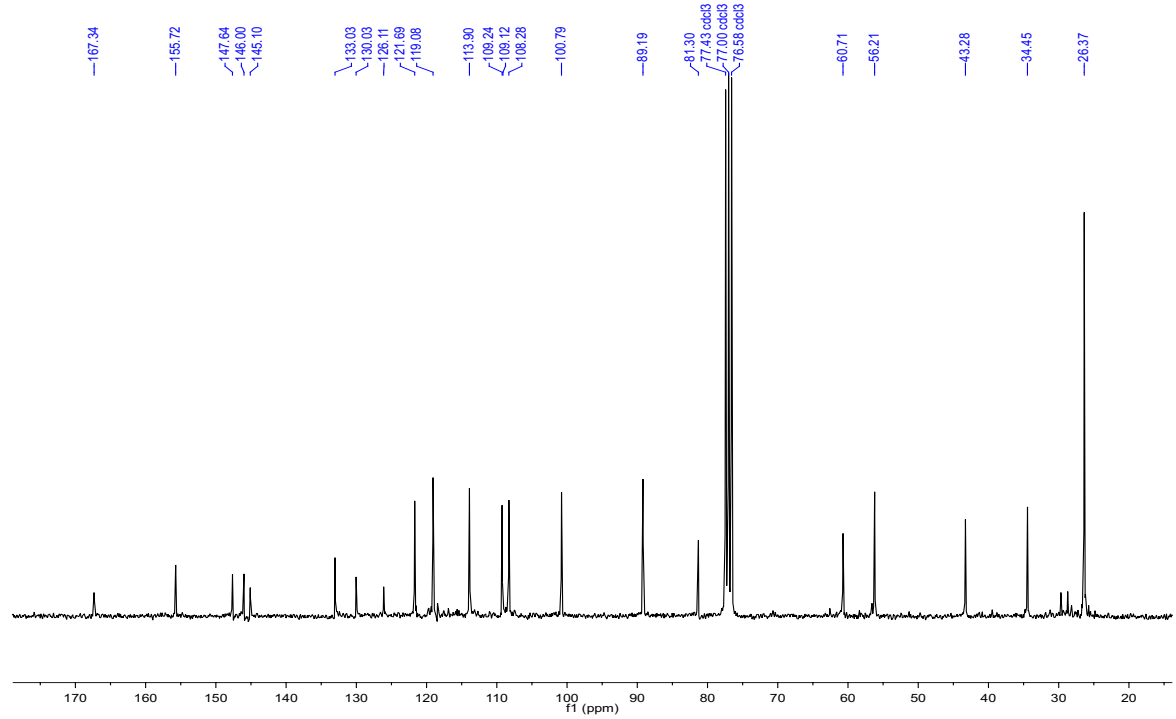
2-(2-(benzo[*d*][1,3]dioxol-5-yl)ethyl)-4,5-dimethoxyisoindoline-1,3-dione (19).



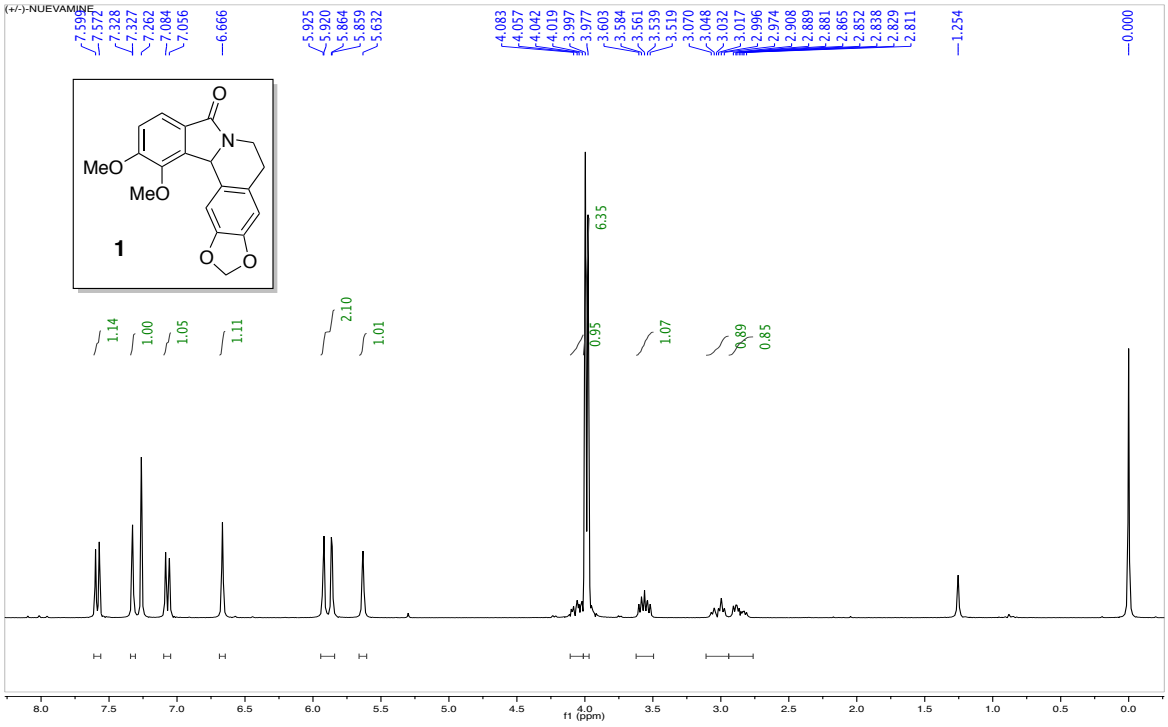


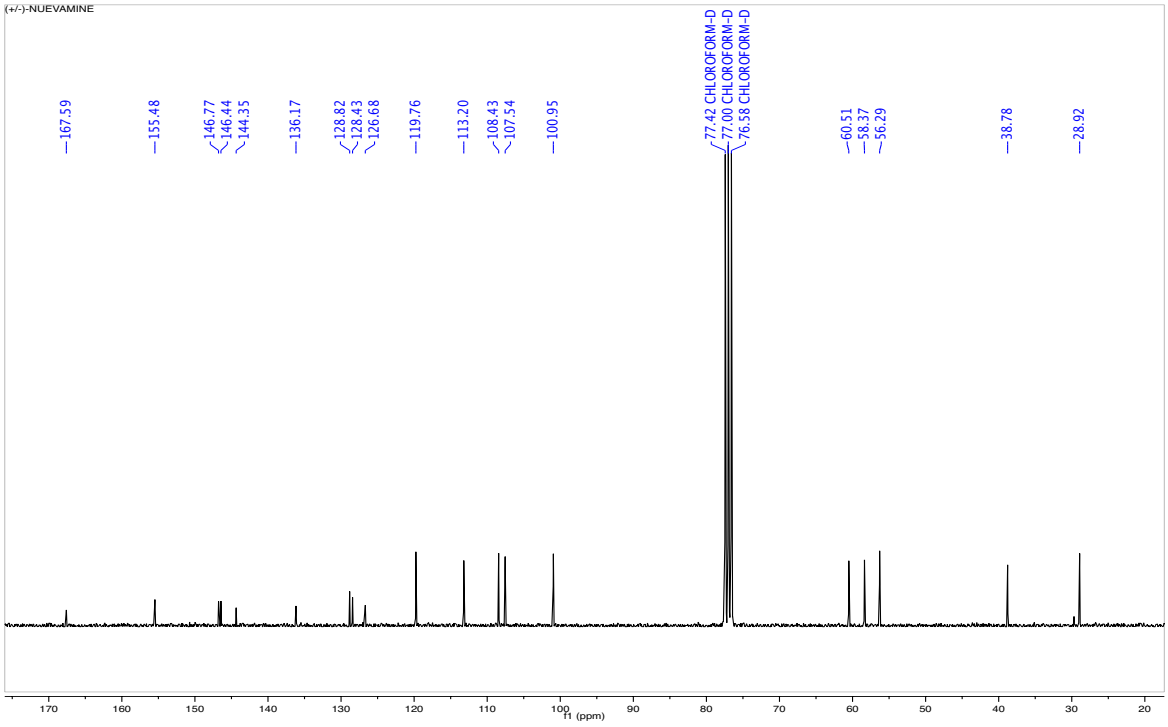
2-(2-(benzo[*d*][1,3]dioxol-5-yl)ethyl)-3-(*tert*-butylperoxy)-4,5-dimethoxyisoindolin-1-one (20).



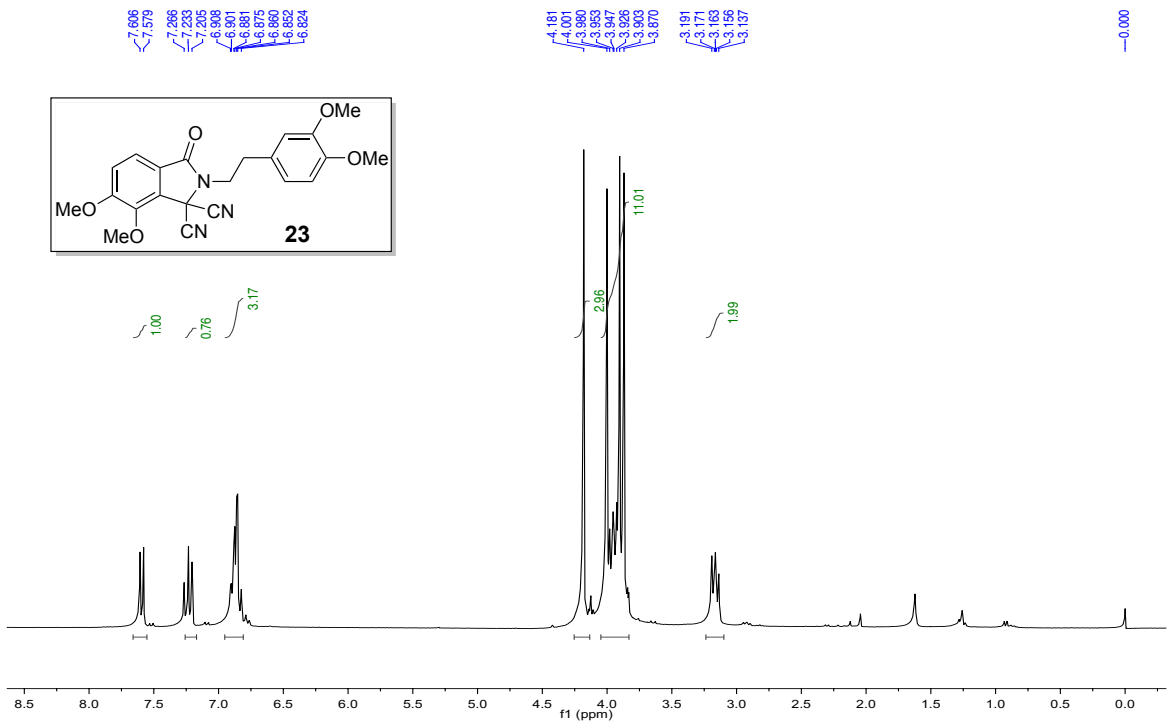


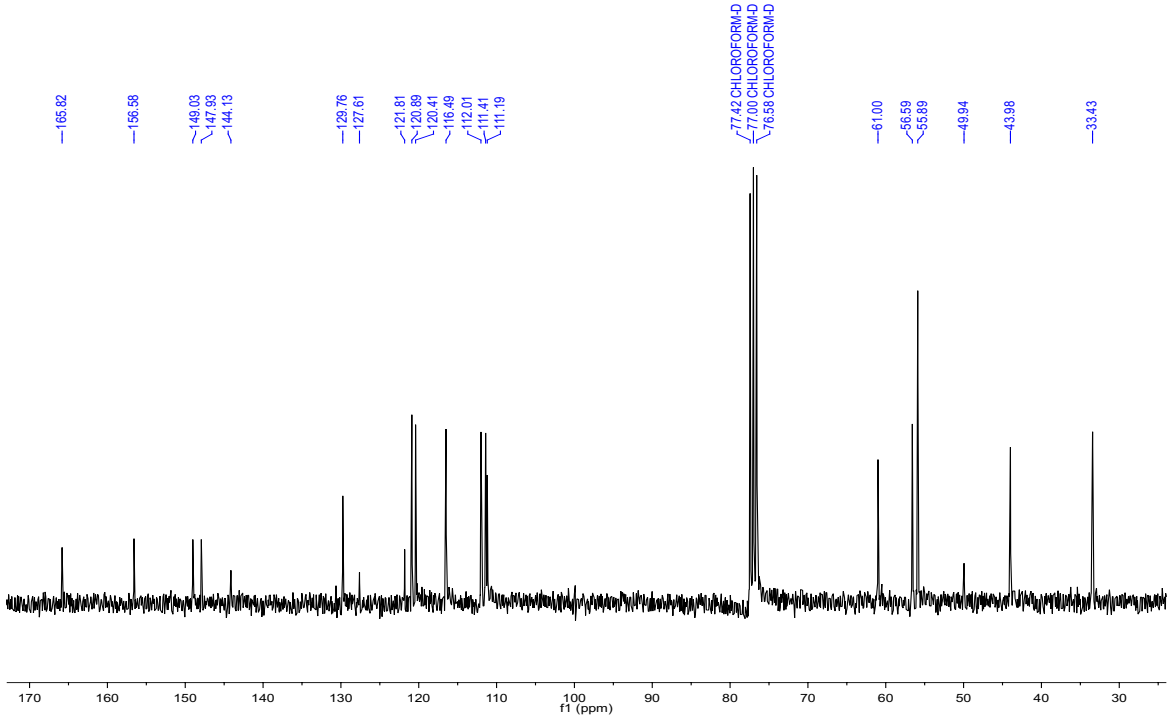
11,12-dimethoxy-5,6-dihydro-[1,3]dioxolo[4,5-*g*]isoindolo[1,2-*a*]isoquinolin-8(12b*H*)-one (1, (+/-)-nuevamine).



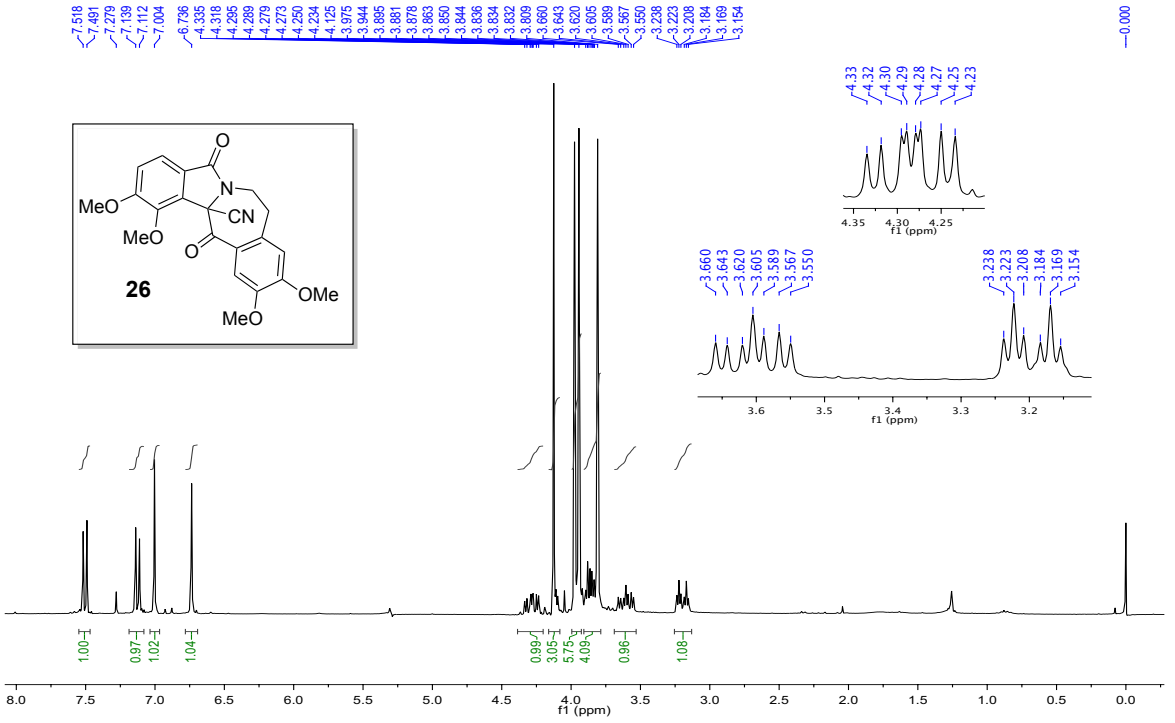


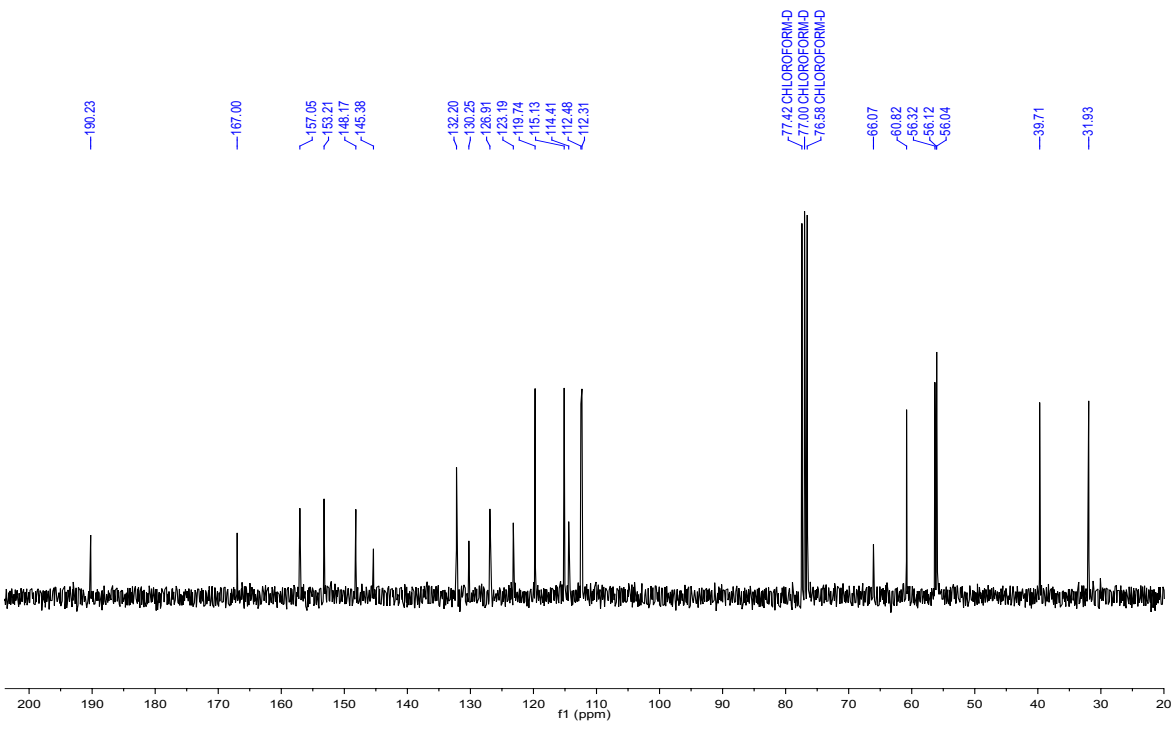
2-(3,4-dimethoxyphenethyl)-6,7-dimethoxy-3-oxoisoindoline-1,1-dicarbonitrile (23).



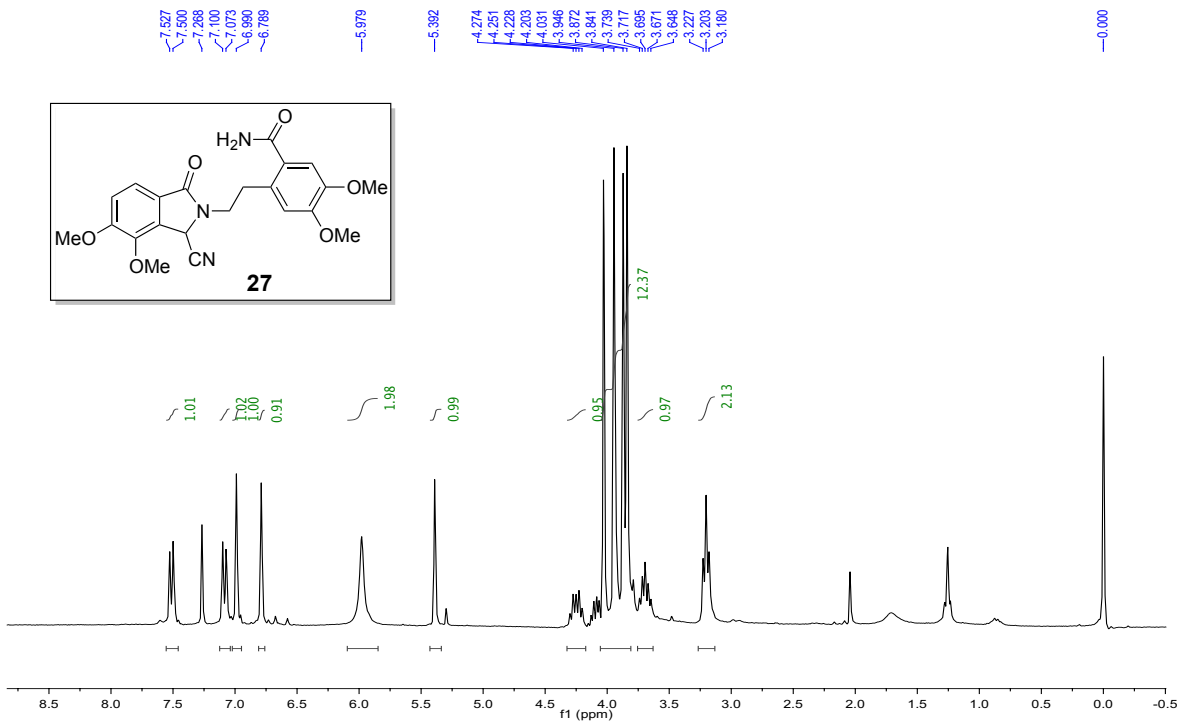


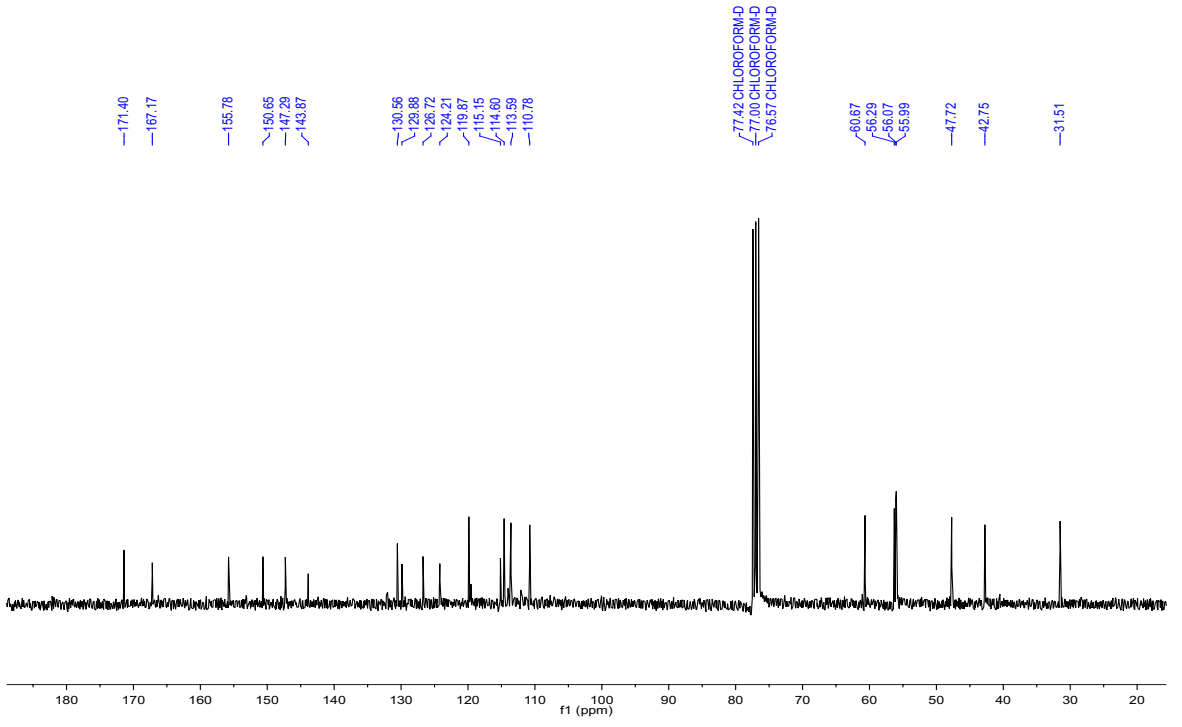
1,2,10,11-tetramethoxy-5,13-dioxo-7,8,13,13a-tetrahydro-5*H*-benzo[4,5]azepino[2,1-*a*]isoindole-13a-carbonitrile (26).



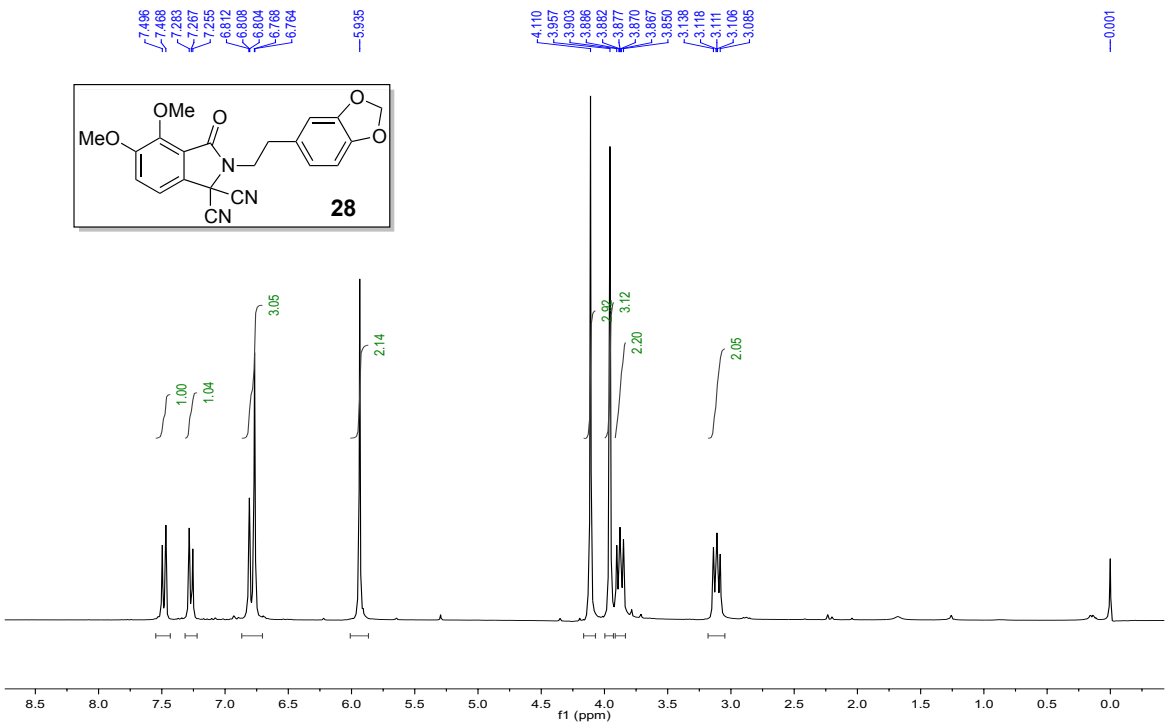


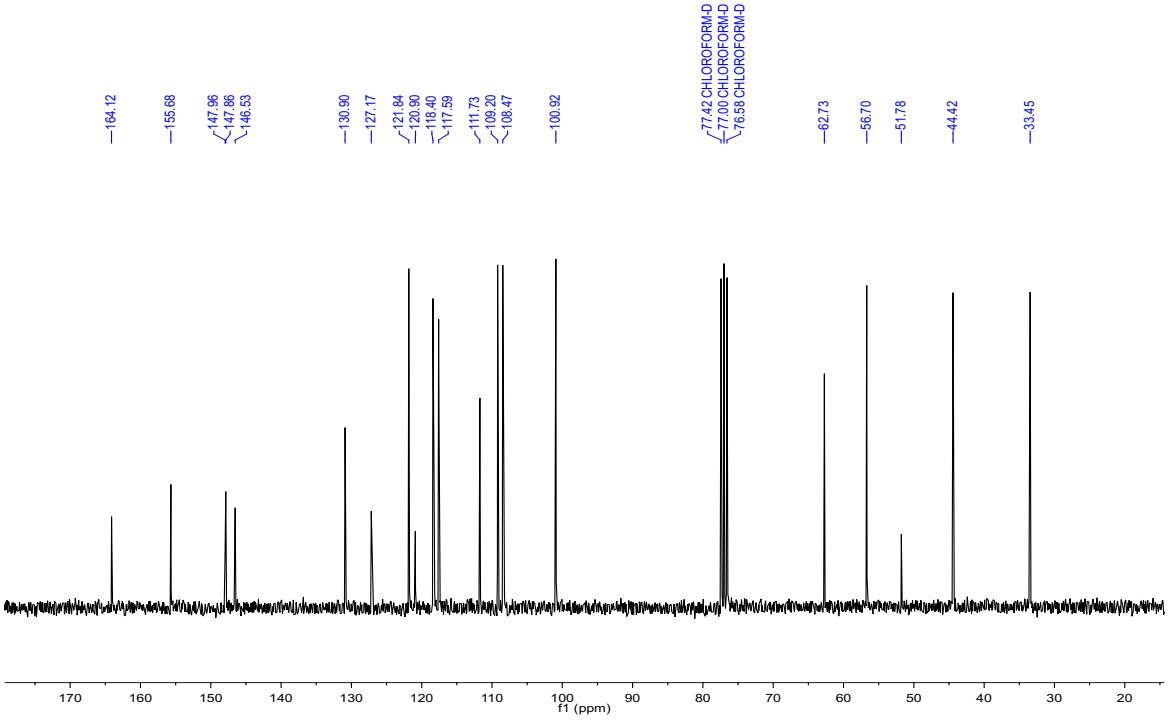
2-(2-(3-cyano-4,5-dimethoxy-1-oxoisoindolin-2-yl)ethyl)-4,5-dimethoxybenzamide (27).



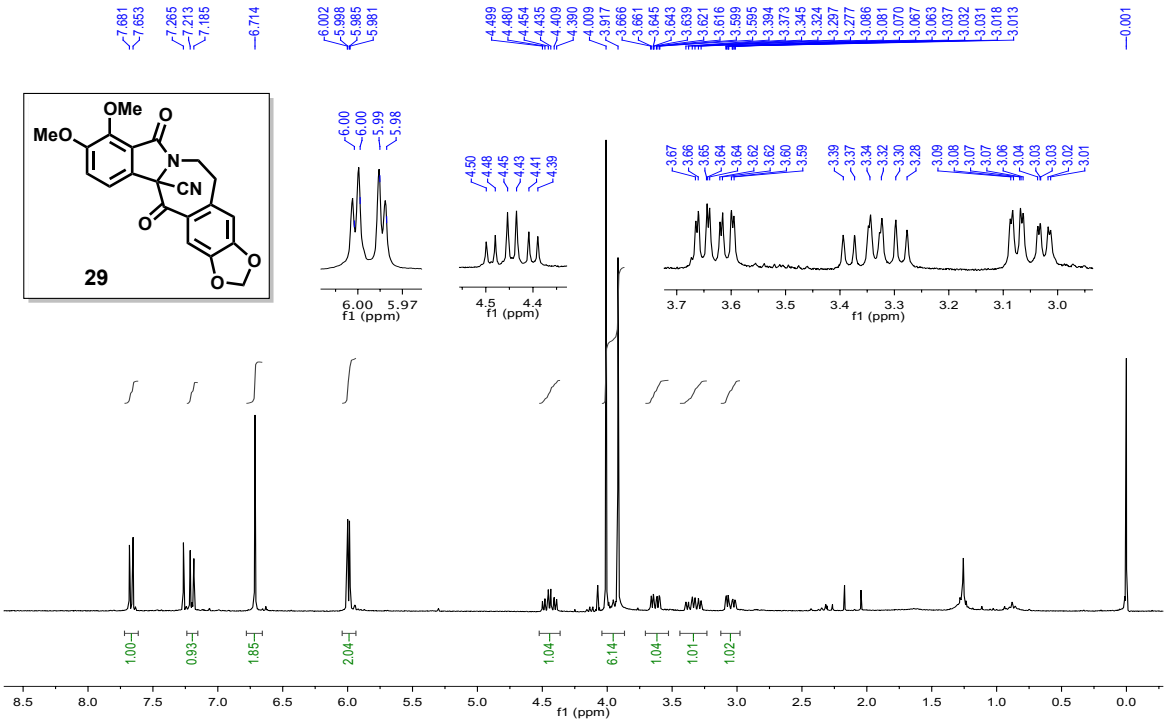


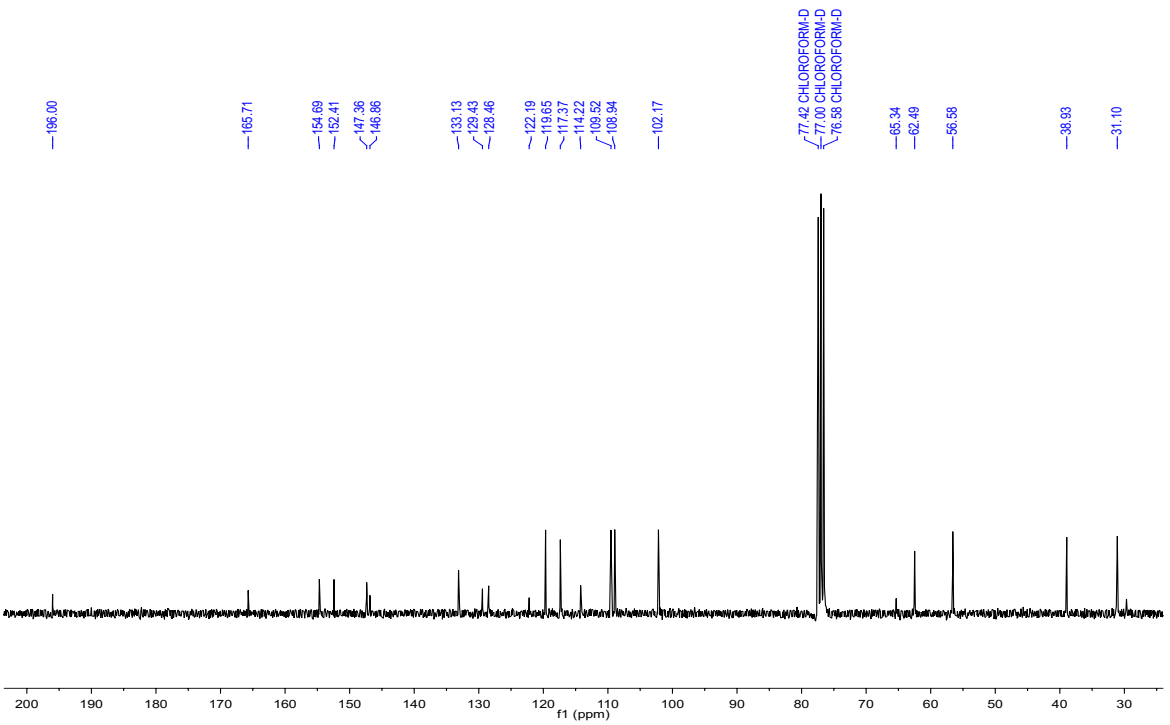
2-(2-(benzo[*d*][1,3]dioxol-5-yl)ethyl)-4,5-dimethoxy-3-oxoisoindoline-1,1-dicarbonitrile (28):





9,10-dimethoxy-8,13-dioxo-6,8,12b,13-tetrahydro-5*H*-[1,3]dioxolo[4'',5'':4',5']benzo[1',2':4,5]azepino[2,1-*a*]isoindole-12b-carbonitrile (29, (+/-)-cyano-chilenine):





2. Crystal report for product 26

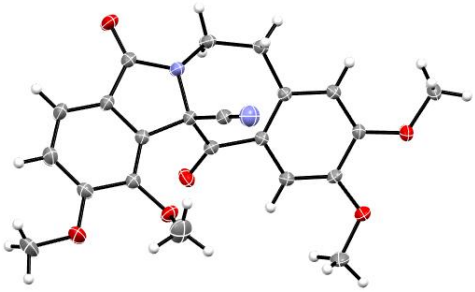


Table 1. Crystal data and structure refinement for **RAGOPA-5089**.

Identification code	002MGL14 (Solved by: R. A. Toscano)	
Project Title	**RAGOPA-5089**	
Empirical formula	$C_{22}H_{20}N_2O_6$	
Formula weight	408.40	
Temperature	298(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	*P* -1	
Unit cell dimensions	*a* = 8.3790(13) Å	α= 94.605(3)°
	b = 10.2477(16) Å	β= 108.730(4)°
	c = 12.547(2) Å	γ = 98.534(4)°
Volume	999.6(3) Å^3	
Z	2	
Density (calculated)	1.357 Mg/m^3	
Absorption coefficient	0.100 mm^{-1}	
F(000)	428	
Crystal size / colour / shape	0.347 **x** 0.213 **x** 0.070 mm / colourless / platy prism	
Theta range for data collection	1.730 to 27.567°	
Index ranges	$-10 \le h \le 10, -13 \le k \le 13, -16 \le l \le 16$	
Reflections collected	12191	
Independent reflections	4597 [*R*(int) = 0.0474]	
Completeness to theta = 25.242°	99.8 %	
Measurement device	Bruker Smart Apex CCD diffractometer 01-670-01	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9930 and 0.9661	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4597 / 0 / 275	
Goodness-of-fit on F^2	1.066	
Final *R* indices [$I>2\sigma(I)$]	*R*1 = 0.0558, *wR*2 = 0.1340	
R indices (all data)	*R*1 = 0.0943, *wR*2 = 0.1607	
Largest diff. peak and hole	0.234 and -0.260 e.Å^{-3}	