Pd-catalysed synthesis of isoquinolinones and analogues via C-H and N-H bonds double activation

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Supporting Information

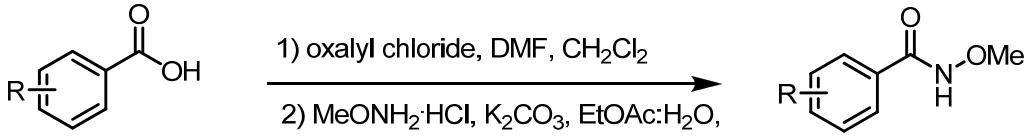
General Information

Flash chromatography was performed on silica gel 100-200 m. The solvent system used was a gradient of petroleum ether/ethyl acetate, increasing in polarity to ethyl acetate. Thin layer chromatography (TLC) was performed on glass backed plates pre-coated with silica (GF254), which were developed using standard visualizing agents. ^{1}H and ^{13}C NMR spectra were recorded on a 400 MHz BRUKER AVANCE spectrometer at 25 ^{o}C. ^{1}H: Chemical shifts are reported in ppm with the solvent resonance as the internal standard ($CHCl_3$: δ 7.27 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet, sept = sepetet), integration, coupling constants (*J*) in Hz. ^{13}C NMR spectra were recorded with complete proton decoupling. Chemical shifts are reported in ppm with the solvent resonance as the internal standard ($CDCl_3$: δ 77.0 ppm). Low resolution mass spectra were recorded on Micromass Autospec, operating in Agilent GC-MS operating in either E.I. or C.I mode. High-resolution mass spectra (HRMS) recorded for accurate mass analysis, were performed on either a Q-TOF micro (Waters) spectrometer. Melting points were performed on recrystallised solids and recorded on a national standard melting point apparatus and are uncorrected.

General Procedures:

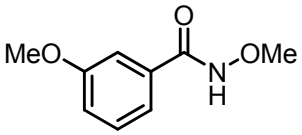
All the known amides **1a**[2], **1b**[1], **1d**[3], **1f**[3], **1h**[4] were prepared following literature procedure[1] and the analytical data are agreed with those data which have been reported previously.

General Procedure A: Synthesis of *N*-methoxybenzamides



Following same procedure by Guimond *et. al*[1]

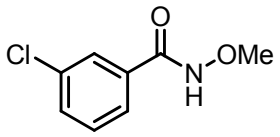
To a solution of the carboxylic acid (10 mmol) in CH_2Cl_2 (0.3 M) at 0 ^oC under N_2 was added dropwise oxalyl chloride (12 mmol) followed by a catalytic amount of DMF (2 drops). The reaction was allowed to stir at room temperature until completion (typically 4h). The solvent was then removed under reduce pressure to afford the corresponding crude acid chloride. Methoxyamine hydrochloride (11 mmol) was added to a biphasic mixture of K_2CO_3 (20 mmol) in a 2:1 mixture of EtOAc:H_2O (0.2 M). The resulting solution was cooled to 0°C followed by addition of a solution unpurified acid chloride in a minimum amount of EtOAc dropwise. The flask containing the acid chloride was then rinsed with additional EtOAc. The reaction was stirring for 4h and slowly warmed up to room temperature. The two layers were separated and extracted with EtOAc (20 mL x 2). The combined organic phase was dried over anhydrous Na_2SO_4, filtered, and evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel.



1c

***N*,3-Dimethoxybenzamide (1c)**

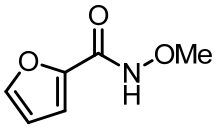
Following the general procedure A, amide **1c** was isolated as a colorless oil: ^1H NMR (400 MHz, $CDCl_3$): δ 7.35-7.27 (m, 3H, ArH), 7.07-7.05 (m, 1H, ArH), 3.89 (s, 3H, OMe), 3.85 (s, 3H, OMe); ^{13}C NMR (101 MHz, $CDCl_3$): δ 166.0, 159.7, 133.1, 129.6, 119.2, 118.3, 112.2, 64.2, 55.4; HRMS (ESI) *m/z* calcd for $C_9H_{11}NO_3$ (M+H) 182.0815; found 182.0817.



1e

3-Chloro-*N*-methoxybenzamide (1e)

Following the general procedure A, amide **1e** was isolated as a white solid: Mp: 116-118 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.47 (br s, 1H, NH), 7.78 (s, 1H, ArH), 7.67 (d, J = 8.0 Hz, 1H, ArH), 7.45 (d, J = 8.0 Hz, 1H, ArH), 7.32 (t, J = 8.0 Hz, 1H, ArH), 3.83 (s, 3H, OMe); ^{13}C NMR (101 MHz, $CDCl_3$): δ 165.1, 134.7, 133.5, 132.0, 130.0, 127.5, 125.4, 64.3; HRMS (ESI) *m/z* calcd for $C_8H_8{}^{35}ClNO_2$ (M+H) 186.0322 found 186.0323.



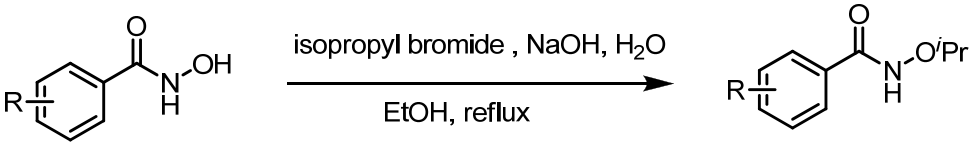
1g

***N*-Methoxyfuran-2-carboxamide (1g)**

Following the general procedure A, amide **1g** was isolated as a purple oil: ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.28 (br s, 1H, NH), 7.45 (br s, 1H, ArH), 7.20 (d, J = 3.5 Hz, ArH), 6.51 (dd, J = 3.5 and 1.5 Hz, 1H, ArH), 3.88 (s, 3H, OMe); ^{13}C NMR (101 MHz, $CDCl_3$): δ 157.2, 145.7, 144.5, 115.6, 112.0, 64.9; HRMS (ESI) *m/z* calcd for $C_6H_7NO_3$ (M+H) 142.0501; found 142.0503.

General Procedure B: Synthesis of *N*-isopropoxybenzamides

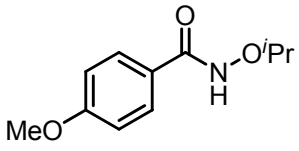
The amide **1l** was prepared by following the procedure reported by A. Nickon *et al*[5], and the analytical data are consistently agreed with those ones are reported in the literature.[6]



Following samilar procedure reported by Nickon *et. al*[5]

Benzohydroxamic acid[7] (3 mmol) was added into a solution of sodium hydroxide (4.5 mmol) in 1.5 mL H_2O, the mixture was warmed to 50 ^{o}C until the solids were dissolved, the resulting solution was added to isopropyl bromide (15 mmol) in absolute ethanol (6 mL), and the mixture was heated to reflux for 5 h. After the reaction was completed, the solvents were removed under reduced pressure. The residue was

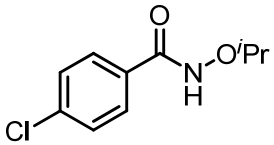
dissolved in EtOAc (20 mL), washed with H_2O (15 mL x 2). The organic layer was dried over anhydrous Na_2SO_4, filtered, and evaporated under reduced pressure. The crude product was purified by flash column chromatography on silica gel.



1m

***N*-isopropoxy-4-methoxybenzamide (1m)**

Following the general procedure B, amide **1m** was isolated as a white solid: Mp: 96-97 ^oC; ^1H NMR (400 MHz, $CDCl_3$): δ 7.74 (d, J = 8.5 Hz, 2H, ArH), 6.90 (d, J = 8.5 Hz, 2H, ArH), 4.25 (sept, J = 6.0 Hz, 1H, CH), 3.84 (s, 3H, OMe), 1.29 (d, J = 6.0 Hz, 6H, Me); ^{13}C NMR (101 MHz, $CDCl_3$): δ 166.4, 162.5, 129.0, 124.3, 113.9, 78.1, 55.4, 20.6; HRMS (ESI) *m/z* calcd for $C_{11}H_{15}NO_3$ (M+H) 210.1132; found 210.1132.



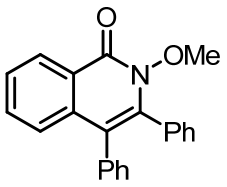
1n

4-Chloro-*N*-isopropoxybenzamide (1n)

Following the general procedure B, amide **1n** was isolated as a white solid: Mp: 84-85 ^oC; ^1H NMR (400 MHz, $CDCl_3$): δ 8.89 (br s, 1H, NH), 7.71 (d, J = 8.0 Hz, 2H, ArH), 7.37 (d, J = 8.0 Hz, 2H, ArH), 4.27 (sept, J = 6.0 Hz, 1H, CH), 1.28 (d, J = 6.0 Hz, 6H, Me); ^{13}C NMR (101 MHz, $CDCl_3$): δ 165.3, 138.0, 130.4, 128.8, 128.5, 78.2, 20.6; HRMS (ESI) *m/z* calcd for $C_{10}H_{12}{}^{35}ClNO_2$ (M+H) 214.0636; found 214.0635.

General Procedure C: Synthesis of *N*-alkoxyl isoquinolinones and analogues

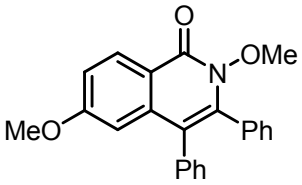
A solution of amide (0.3 mmol), alkyne (0.9 mmol), $Pd(OAc)_2$ (10 mol%) and $NaI{\cdot}2H_2O$ (0.3 mmol) in DMF (1.5 mL) was heated at 120 ^oC under air. The reaction was monitored by TLC. After the reaction was completed, the reaction mixture was allowed to cool down to room temperature and EtOAc (10 mL) was added. The resulting mixture was washed with saturated aqueous $Na_2S_2O_3$ (5 mL x 3). The organic layer was dried over anhydrous Na_2SO_4, filtered and the solvent was removed under reduced pressure to provide the crude product. The purification was performed by flash column chromatography on silica gel.



3a

2-Methoxy-3,4-diphenylisoquinolin-1(*2H*)-one (3a)

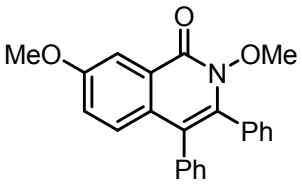
Following general procedure C, a solution of amide **1a** (45 mg, 0.3 mmol), diphenylethyne (160 mg, 0.9 mmol), $Pd(OAc)_2$ (6.7 mg, 10 mol%) and $NaI{\cdot}2H_2O$ (56 mg, 0.3 mmol) in DMF (1.5 mL) was heated at 120 ^oC for 7 h gave the desired isoquinolinone **3a** (91 mg, 93%) as a white solid: Mp 211-212 ^oC; ^1H NMR (400 MHz, $CDCl_3$): δ 8.61 (d, J = 7.5 Hz, 1H, ArH), 7.59 (t, J = 7.5, 1H, ArH), 7.54 (t, J = 7.5, 1H, ArH), 7.26-7.23 (m, 9H, ArH), 7.12 (d, J = 7.0 Hz, 2H, ArH), 3.76 (s, 3H, OMe); ^{13}C NMR (101 MHz, $CDCl_3$): δ 158.2, 140.0, 136.5, 135.5, 132.2, 131.7, 131.6, 130.7, 128.3, 128.1, 127.8, 127.5, 127.2, 126.7, 126.5, 125.7, 118.3, 63.5; HRMS (ESI) *m/z* calcd for $C_{22}H_{17}NO_2$ (M+H) 328.1332; found 328.1334.



3b

2,6-Dimethoxy-3,4-diphenylisoquinolin-1(*2H*)-one (3b)

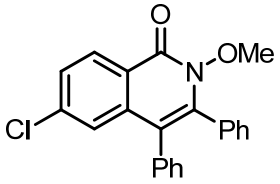
Following general procedure C, a solution of amide **1b** (54 mg, 0.3 mmol), diphenylethyne (160 mg, 0.9 mmol), $Pd(OAc)_2$ (6.7 mg, 10 mol%) and $NaI{\cdot}2H_2O$ (56 mg, 0.3 mmol) in DMF (1.5 mL) was heated at 120 ^oC for 8 h gave the desired isoquinolinone **3b** (98 mg, 92%) as a white solid: Mp 220-221 ^oC. ^1H NMR (400 MHz, $CDCl_3$): δ 8.52 (d, J = 9.0 Hz, 1H, ArH), 7.24-7.20 (m, 8H, ArH), 7.12-7.10 (m, 3H, ArH), 6.63 (d, J = 2.0 Hz, 1H, ArH), 3.73 (s, 3H, OMe), 3.72 (s, 3H, OMe), ^{13}C NMR (101 MHz, $CDCl_3$): δ 162.8, 157.9, 140.6, 138.6, 135.5, 131.8, 131.6, 130.6, 129.9, 128.2, 128.1, 127.5, 127.2, 120.2, 117.8, 115.6, 107.6, 63.5, 55.3; HRMS (ESI) *m/z* calcd for $C_{23}H_{19}NO_3$ (M+H) 358.1446; found 358.1444.



3c

2,7-Dimethoxy-3,4-diphenylisoquinolin-1(*2H*)-one (3c)

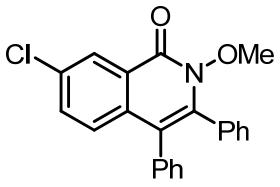
Following general procedure C, a solution of amide **1c** (54 mg, 0.3 mmol), diphenylethyne (160 mg, 0.9 mmol), $Pd(OAc)_2$ (6.7 mg, 10 mol%) and $NaI{\cdot}2H_2O$ (56 mg, 0.3 mmol) in DMF (1.5 mL) was heated at 120 ^oC for 4 h gave the desired isoquinolinone **3c** (81 mg, 76%) as a white solid: Mp 189-190 ^oC; ^1H NMR (400 MHz, $CDCl_3$): δ 7.99 (d, J = 2.0 Hz, 1H, ArH), 7.24-7.16 (m, 10H, ArH), 7.10 (d, J = 6.5 Hz, 2H, ArH), 3.98 (s, 3H, OMe), 3.75 (s, 3H, OMe); ^{13}C NMR (101 MHz, $CDCl_3$): δ 158.7, 157.8, 137.6, 135.7, 131.7, 131.6, 130.9, 130.6, 128.1, 128.0, 127.7, 127.5, 127.4, 127.1, 122.7, 118.3, 107.6, 63.4, 55.8; HRMS (ESI) *m/z* calcd for $C_{23}H_{19}NO_3$ (M+H) 358.1441; found 357.1443.



3d

6-Chloro-2-methoxy-3,4-diphenylisoquinolin-1(*2H*)-one (3d)

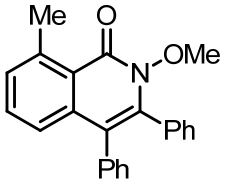
Following general procedure C, a solution of amide **1d** (56 mg, 0.3 mmol), diphenylethyne (160 mg, 0.9 mmol), $Pd(OAc)_2$ (6.7 mg, 10 mol%) and $NaI{\cdot}2H_2O$ (56 mg, 0.3 mmol) in DMF (1.5 mL) was heated at 120 ^oC for 20 h gave the desired isoquinolinone **3d** (60 mg, 55%) as a white solid: Mp 214-217 ^oC; ^1H NMR (400 MHz, $CDCl_3$): δ 8.53 (d, J = 8.5 Hz, 1H, ArH), 7.47 (dd, J = 8.5 and 2.0 Hz, 1H, ArH), 7.27-7.25 (m, 9H, ArH), 7.11-7.09 (m, 2H, ArH), 3.75 (s, 3H, OMe); ^{13}C NMR (101 MHz, $CDCl_3$): δ 157.6, 141.4, 139.1, 137.9, 134.8, 131.5, 131.3, 130.5, 129.6, 128.5, 128.3, 127.6, 127.5, 127.3, 125.1, 124.8, 117.4, 63.6; HRMS (ESI) *m/z* calcd for $C_{22}H_{16}{}^{35}ClNO_2$ (M+H) 362.0945; found 362.0946.



3e

7-Chloro-2-methoxy-3,4-diphenylisoquinolin-1(*2H*)-one (3e)

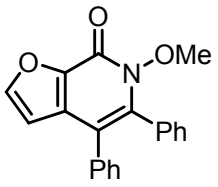
Following general procedure C, a solution of amide **1e** (56 mg, 0.3 mmol), diphenylethyne (160 mg, 0.9 mmol), $Pd(OAc)_2$ (6.7 mg, 10 mol%) and $NaI{\cdot}2H_2O$ (56 mg, 0.3 mmol) in DMF (1.5 mL) was heated at 120 ^oC for 9 h gave the desired isoquinolinone **3e** (78 mg, 72%) as a white solid: Mp 185-186 ^oC; ^1H NMR (400 MHz, $CDCl_3$): δ 8.56 (d, J = 2.0 Hz, 1H, ArH), 7.50 (dd, J = 9.0 and 2.0 Hz, 1H, ArH), 7.25-7.21 (m, 9H, ArH), 7.10-7.08 (m, 2H, ArH), 3.74 (s, 3H, OMe); ^{13}C NMR (101 MHz, $CDCl_3$): δ 157.1, 140.3, 135.0, 134.9, 132.9, 132.7, 131.5, 131.3, 130.6, 128.5, 128.3, 127.6, 127.5, 127.4, 127.1, 117.8, 63.5 (one signal missing due to overlap); HRMS (ESI) *m/z* calcd for $C_{22}H_{16}{}^{35}ClNO_2$ (M+H) 362.0942; found 362.0944.



3f

2-Methoxy-8-methyl-3,4-diphenylisoquinolin-1(*2H*)-one (3f)

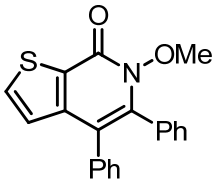
Following general procedure C, a solution of amide **1f** (50 mg, 0.3 mmol), diphenylethyne (160 mg, 0.9 mmol), $Pd(OAc)_2$ (6.7 mg, 10 mol%) and $NaI{\cdot}2H_2O$ (56 mg, 0.3 mmol) in DMF (1.5 mL) was heated at 120 ^oC for 3 h gave the desired isoquinolone **3f** (83 mg, 81%) as a white solid: Mp 207-208 ^oC; ^1H NMR (400 MHz, $CDCl_3$): δ 7.39 (t, J = 8.0 Hz, 1H, ArH), 7.27-7.19 (m, 9H, ArH), 7.11-7.07 (m, 3H, ArH), 3.74 (s, 3H, OMe), 3.07 (s, 3H, Me); ^{13}C NMR (101 MHz, $CDCl_3$): δ 159.0, 142.1, 140.0, 138.3, 136.2, 131.9, 131.7, 131.4, 130.5, 129.9, 128.1, 128.1, 127.4, 127.0, 124.8, 124.1, 118.0, 63.3, 24.0; HRMS (ESI) *m/z* calcd for $C_{23}H_{19}NO_2$ (M+H) 342.1497; found 342.1495.



3g

6-Methoxy-4,5-diphenylfuro[2,3-c]pyridin-7(*6H*)-one (3g)

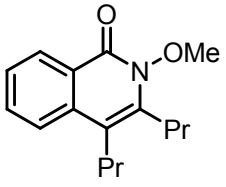
Following general procedure C, a solution of amide **1g** (42 mg, 0.3 mmol), diphenylethyne (160 mg, 0.9 mmol), $Pd(OAc)_2$ (6.7 mg, 10 mol%) and $NaI{\cdot}2H_2O$ (56 mg, 0.3 mmol) in DMF (1.5 mL) was heated at 120 ^oC for 20 h gave the desired isoquinolinone **3g** (65 mg, 69%) as a white solid: Mp 150-151 ^oC; ^1H NMR (400 MHz, $CDCl_3$): δ 7.78 (d, *J* = 2.0 Hz, 1H, ArH), 7.31-7.27 (m, 5H, ArH), 7.23-7.17 (m, 3H, ArH), 7.08-7.06 (m, 2H, ArH), 6.56 (d, *J* = 2.0 Hz, 1H, ArH), 3.70 (s, 3H, OMe); ^{13}C NMR (101 MHz, $CDCl_3$): δ 149.8, 148.6, 142.5, 140.3, 135.1, 133.1, 131.1, 131.0, 130.2, 128.7, 128.2, 127.8, 127.1, 113.3, 107.5, 63.9; HRMS (ESI) *m/z* calcd for $C_{20}H_{15}NO_3$ (M+H) 318.1130; found 318.1132.



3h

6-Methoxy-4,5-diphenylthieno[2,3-c]pyridin-7(*6H*)-one (3h)

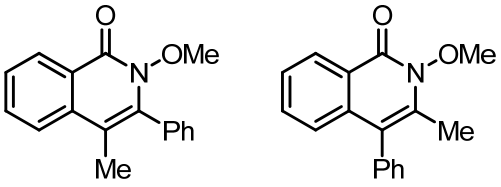
Following general procedure C, a solution of amide **1h** (47 mg, 0.3 mmol), diphenylethyne (160 mg, 0.9 mmol), $Pd(OAc)_2$ (6.7 mg, 10 mol%) and $NaI{\cdot}2H_2O$ (56 mg, 0.3 mmol) in DMF (1.5 mL) was heated at 120 ^oC for 12 h gave the desired isoquinolinone **3h** (61 mg, 61%) as a white solid: Mp 205-207 ^oC; ^1H NMR (400 MHz, $CDCl_3$): δ 7.66 (d, *J* = 5.0 Hz, 1H, ArH), 7.30-7.18 (m, 8H, ArH), 7.12-7.10 (m, 2H, ArH), 6.99 (d, *J* = 5.0 Hz, 1H, ArH), 3.74 (s, 3H, OMe); ^{13}C NMR (101 MHz, $CDCl_3$): δ 154.5, 144.9, 141.0, 136.0, 133.1, 131.2, 130.9, 130.7, 129.7, 128.5, 128.1, 127.6, 127.2, 124.9, 116.6, 63.8; HRMS (ESI) *m/z* calcd for $C_{20}H_{15}NO_2S$ (M+H) 334.0902; found 334.0900.



3i

2-Methoxy-3,4-dipropylisoquinolin-1(*2H*)-one (3i)

Following general procedure C, a solution of amide **1a** (45 mg, 0.3 mmol), oct-4-yne (100 mg, 0.9 mmol), $Pd(OAc)_2$ (6.7 mg, 10 mol%) and $NaI{\cdot}2H_2O$ (56 mg, 0.3 mmol) in DMF (1.5 mL) was heated at 120 ^oC for 15 h gave the desired isoquinolinone **3i** (51 mg, 66%) as a white solid: Mp: 70-71 ^oC; ^1H NMR (400 MHz, $CDCl_3$): δ 8.48 (d, J = 8.0 Hz, 1H, ArH), 7.68-7.64 (m, 2H, ArH), 7.46-7.42 (m, 1H, ArH), 4.09 (s, 3H, OMe), 2.77-2.69 (m, 4H, CH_2), 1.76-1.68 (m, 2H, CH_2), 1.66-1.58 (m, 2H, CH_2), 1.08 (t, J = 7.0 Hz, 3H, Me), 1.06 (t, J = 7.0 Hz, 3H, Me); ^{13}C NMR (101 MHz, $CDCl_3$): δ 158.2, 139.8, 136.0, 132.1, 128.0, 126.3, 125.7, 123.0, 113.2, 63.7, 29.8, 29.5, 23.7, 23.0, 14.4, 14.3; HRMS (ESI) *m/z* calcd for $C_{16}H_{21}NO_2$ (M+H) 260.1651; found 260.1654.

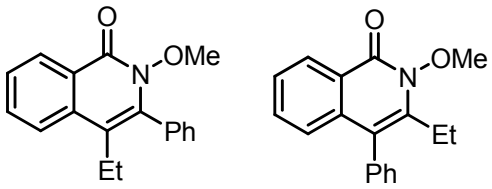


3ja **3jb**

2-Methoxy-4-methyl-3-phenylisoquinolin-1(*2H*)-one (3ja)

2-Methoxy-3-methyl-4-phenylisoquinolin-1(*2H*)-one (3jb)

Following general procedure C, a solution of amide **1a** (50 mg, 0.33 mmol), 1-phenylpropyne (116 mg, 1.0 mmol), $Pd(OAc)_2$ (7.5 mg, 10 mol%) and $NaI{\cdot}2H_2O$ (62 mg, 0.33 mmol) in DMF (1.7 mL) was heated at 120 ^oC for 15 h gave the desired isoquinolinone **3ja** (53 mg, 60%) as a white solid: Mp 177-178 ^oC; ^1H NMR (400 MHz, $CDCl_3$): δ 8.57 (d, J = 8.0 Hz, 1H, ArH), 7.77-7.71 (m, 2H, ArH), 7.57-7.47 (m, 4H, ArH), 7.43-7.41 (m, 2H, ArH), 3.70 (s, 3H, OMe), 2.11 (s, 3H, Me); ^{13}C NMR (101 MHz, $CDCl_3$): δ 158.0, 139.2, 136.5, 132.4, 132.3, 130.1, 128.8, 128.2, 128.0, 126.7, 126.6, 123.6, 110.3, 63.3, 14.4; HRMS (ESI) *m/z* calcd for $C_{17}H_{15}NO_2$ (M+H) 266.1176; found 266.1176 and **3jb** (10 mg, 11%) as an off-white solid: Mp 142-144 ^oC; ^1H NMR (400 MHz, $CDCl_3$): δ 8.51 (dd, J = 8.0 Hz and 1.0 Hz, 1H, ArH), 7.53-7.43 (m, 5H, ArH), 7.28-7.27 (m, 2H, ArH), 7.07 (d, J = 8.0 Hz, 1H, ArH), 4.16 (s, 3H, OMe), 2.27 (s, 3H, Me); ^{13}C NMR (101 MHz, $CDCl_3$): δ 158.4, 136.7, 136.4, 132.1, 131.1, 128.9, 128.2, 127.8, 127.6, 125.9, 125.6, 125.1, 116.6, 63.6, 14.9; HRMS (ESI) *m/z* calcd for $C_{17}H_{15}NO_2$ (M+H) 266.1176; found 266.1178.



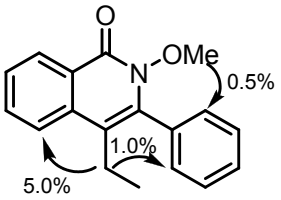
3ka **3kb**

4-Ethyl-2-methoxy-3-phenylisoquinolin-1(*2H*)-one (3ka)

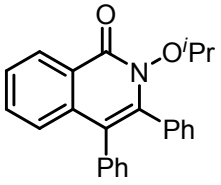
3-Ethyl-2-methoxy-4-phenylisoquinolin-1(*2H*)-one (3kb)

Following general procedure C, a solution of amide **1a** (90 mg, 0.6 mmol), 1-phenylpropyne (232 mg, 1.8 mmol), $Pd(OAc)_2$ (13.4 mg, 10 mol%) and $NaI{\cdot}2H_2O$ (111 mg, 0.6 mmol) in DMF (3.0 mL) was heated at 120 ^oC for 6 h gave the desired isoquinolinone **3ka** (127 mg, 76%) as a white solid: Mp 178-179 ^oC; ^1H NMR (400 MHz, $CDCl_3$): δ 8.58 (d, J = 8.0 Hz, 1H, ArH), 7.77-7.72 (m, 2H, ArH), 7.56-7.50 (m, 4H, ArH), 7.43-7.41 (m, 2H, ArH), 3.73 (s, 3H, OMe), 2.52 (q, J = 7.5 Hz, 2H, CH_2), 1.12 (t, J = 7.5 Hz, 3H, Me); ^{13}C NMR (101 MHz, $CDCl_3$): δ 157.9, 139.2, 135.4, 132.3, 132.2, 129.7, 128.8, 128.3, 128.2, 127.1, 126.5, 123.6, 116.5, 63.4, 21.2, 14.9; HRMS (ESI) *m/z* calcd for $C_{18}H_{17}NO_2$ (M+H) 280.1336; found 280.1338 and **3kb** (15 mg, 9%) as an off-white solid: Mp 129-130 ^oC; ^1H NMR (400 MHz, $CDCl_3$): δ 8.51 (d, J = 8.0 Hz, 1H, ArH), 7.53-7.30 (m, 7H, ArH), 7.00 (d, J = 8.0 Hz, 1H, ArH), 4.18 (s, 3H, OMe), 2.56 (q, J = 7.5 Hz, 2H, CH_2), 1.19 (t, J = 7.5 Hz, 3H, Me); ^{13}C NMR (101 MHz, $CDCl_3$): δ 158.6, 142.0, 137.0, 136.2, 132.0, 131.0, 128.8, 127.8, 127.5, 126.0, 125.6, 125.3, 116.4, 64.0, 22.5, 14.2; HRMS (ESI) *m/z* calcd for $C_{18}H_{17}NO_2$ (M+H) 280.1336; found 280.1335.

NOE of 3ka:



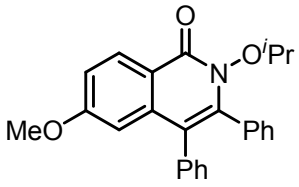
3ka



3l

2-Isopropoxy-3, 4-diphenylisoquinolin-1(*2H*)-one (3l)

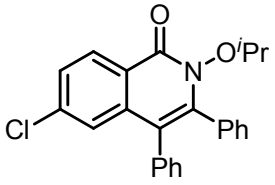
Following general procedure C, a solution of amide **1l** (60 mg, 0.34 mmol), diphenylethyne (179 mg, 1.02 mmol), $Pd(OAc)_2$ (7.5 mg, 10 mol%) and $NaI{\cdot}2H_2O$ (62 mg, 0.34 mmol) in DMF (1.7 mL) was heated at 120 ^oC for 8 h gave the desired isoquinolinone **3l** (107 mg, 90%) as a white solid: Mp 172-173 ^oC; ^1H NMR (400 MHz, $CDCl_3$): δ 8.59 (dd, J = 8.0 Hz and 1.0 Hz, 1H, ArH), 7.59-7.50 (m, 2H, ArH), 7.30-7.19 (m, 9H, ArH), 7.12 (d, J = 6.0 Hz, 2H, ArH), 4.45 (sept, J = 6.0 Hz, 1H, CH), 0.99 (d, J = 6.0 Hz, 6H, Me); ^{13}C NMR (101 MHz, $CDCl_3$): δ 159.2, 141.2, 136.5, 135.8, 132.3, 132.1, 131.7, 131.5, 128.1, 128.0, 127.9, 127.1, 127.0, 126.6, 126.4, 125.7, 118.0, 79.0, 20.4; HRMS (ESI) *m/z* calcd for $C_{24}H_{21}NO_2$ (M+H) 356.1553; found 3556.1552.



3m

2-Isopropoxy-6-methoxy-3,4-diphenylisoquinolin-1(*2H*)-one (3m)

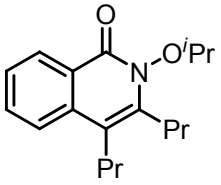
Following general procedure C, a solution of amide **1m** (63 mg, 0.3 mmol), diphenylethyne (161 mg, 0.9 mmol), $Pd(OAc)_2$ (6.7 mg, 10 mol%) and $NaI{\cdot}2H_2O$ (56 mg, 0.3 mmol) in DMF (1.5 mL) was heated at 120 ^oC for 13 h gave the desired isoquinolinone **3m** (78 mg, 67%) as a white solid: Mp 190-191 ^oC; ^1H NMR (400 MHz, $CDCl_3$): δ 8.51 (d, J = 9.0 Hz, 1H, ArH), 7.26-7.20 (m, 8H, ArH), 7.12-7.09 (m, 3H, ArH), 6.65 (d, J = 2.0 Hz, 1H, ArH), 4.42 (sept, J = 6.0 Hz, 1H, CH), 3.73 (s, 3H, OMe), 0.97 (d, J = 6.0 Hz, 6H, Me); ^{13}C NMR (101 MHz, $CDCl_3$): δ 162.7, 159.0, 141.7, 138.5, 135.9, 132.4, 131.7, 131.5, 130.0, 128.1, 128.0, 127.1, 120.1, 117.6, 115.5, 107.5, 78.8, 55.3, 20.4 (one signal missing due to overlap); HRMS (ESI) *m/z* calcd for $C_{25}H_{23}NO_3$ (M+H) 386.1751; found 386.1750.



3n

6-Chloro-2-isopropoxy-3,4-diphenylisoquinolin-1(*2H*)-one (3n)

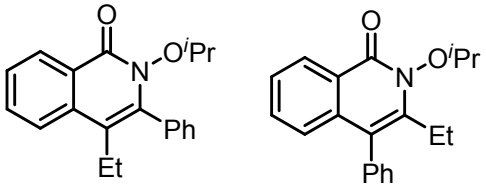
Following general procedure C, a solution of amide **1n** (64 mg, 0.3 mmol), diphenylethyne (160 mg, 0.9 mmol), $Pd(OAc)_2$ (6.7 mg, 10 mol%) and $NaI{\cdot}2H_2O$ (56 mg, 0.3 mmol) in DMF (1.5 mL) was heated at 120 ^oC for 11 h gave the desired isoquinolinone **3n** (62 mg, 53%) as a white solid: Mp 179-180 ^oC; ^1H NMR (400 MHz, $CDCl_3$): δ 8.51 (d, J = 8.5 Hz, 1H, ArH), 7.46 (dd, J = 8.5 Hz and 2.0 Hz, 1H, ArH), 7.27-7.21 (m, 9H, ArH), 7.09 (d, J = 6.0 Hz, 2H, ArH), 4.43 (sept, J = 6.0 Hz, 1H, CH), 0.98 (d, J = 6.0 Hz, 6H, Me); ^{13}C NMR (101 MHz, $CDCl_3$): δ 158.7, 142.6, 138.9, 137.8, 135.1, 131.9, 131.6, 131.4, 129.7, 128.3, 128.2, 127.4, 127.2, 127.1, 125.0, 124.6, 117.1, 79.2, 20.4; HRMS (ESI) *m/z* calcd for $C_{24}H_{20}{}^{35}ClNO_2$ (M+H) 390.1255; found 390.1255.



3o

2-Isopropoxy-3,4-dipropylisoquinolin-1(*2H*)-one (3o)

Following general procedure C, a solution of amide **1l** (54 mg, 0.3 mmol), oct-4-yne (100 mg, 0.9 mmol), $Pd(OAc)_2$ (6.7 mg, 10 mol%) and $NaI{\cdot}2H_2O$ (56 mg, 0.3 mmol) in DMF (1.5 mL) was heated at 120 ^oC for 18 h gave the desired isoquinolinone **3o** (54 mg, 62%) as a yellow oil: ^1H NMR (400 MHz, $CDCl_3$): δ 8.46 (d, J = 8.0 Hz, 1H, ArH), 7.66 (d, J = 4.0 Hz, 2H, ArH), 7.46-7.42 (m, 1H, ArH), 5.03 (sept, J = 6.0 Hz, 1H, CH), 2.79 (app. t, J = 8.0 Hz, 2H, CH_2), 2.72 (app. t, J = 8.0 Hz, 2H, CH_2), 1.70-1.59 (m, 4H, CH_2), 1.31 (d, J = 6.0 Hz, 6H, Me), 1.07 (t, J = 7.5 Hz, 3H, Me), 1.02 (t, J = 7.5 Hz, 3H, Me); ^{13}C NMR (101 MHz, $CDCl_3$): δ 158.9, 141.5, 136.0, 131.9, 128.0, 126.2, 125.6, 123.0, 112.7, 77.3, 30.3, 29.6, 23.7, 22.5, 20.4, 14.2, 8.2; HRMS (ESI) *m/z* calcd for $C_{18}H_{25}NO_2$ (M+H) 288.1967; found 288.1969.



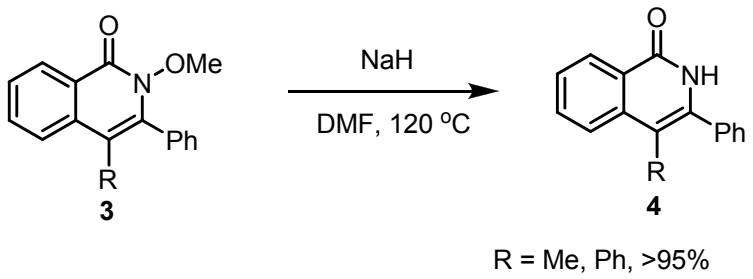
3pa **3pb**

4-Ethyl-2-isopropoxy-3-phenylisoquinolin-1(*2H*)-one (3pa)

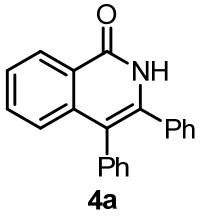
3-Ethyl-2-isopropoxy-4-phenylisoquinolin-1(*2H*)-one (3pb)

Following general procedure C, a solution of **1l** (216 mg, 1.2 mmol), 1-phenylpropyne (472 mg, 3.6 mmol), $Pd(OAc)_2$ (26.8 mg, 10 mol%) and $NaI{\cdot}2H_2O$ (224 mg, 1.2 mmol) in DMF (6.0 mL) was heated at 120 ^oC for 20 h gave the desired isoquinolinone **3pa** (237 mg, 64%) as a white solid.: Mp 109-110 ^oC; ^1H NMR (400 MHz, $CDCl_3$): δ 8.57 (d, *J* = 8.0 Hz, 1H, ArH), 7.78-7.72 (m, 2H, ArH), 7.53-7.40 (m, 6H, ArH), 4.40 (sept, *J* = 6.0 Hz, 1H, CH), 2.57 (q, *J* = 7.5 Hz, 2H, CH_2), 1.13 (t, *J* = 7.5 Hz, 3H, Me), 0.95 (d, *J* = 6.0 Hz, 6H, Me); ^{13}C NMR (101 MHz, $CDCl_3$): δ 159.1, 140.4, 135.5, 132.7, 132.1, 130.6, 128.5, 128.4, 127.8, 127.2, 126.4, 123.6, 116.3, 78.9, 21.3, 20.5, 15.1; HRMS (ESI) *m/z* calcd for $C_{20}H_{21}NO_2$ (M+H) 308.1645; found 308.1643 and **3pb** (23 mg, 6%) as a yellow oil: ^1H NMR (400 MHz, $CDCl_3$): δ 8.49 (d, *J* = 8.0Hz 1H, ArH), 7.52-7.30 (m, 7H, ArH), 7.00 (d, *J* = 8.0 Hz, 1H, ArH), 5.10 (sept, *J* = 6.0 Hz, 1H, CH), 2.58 (q, *J* = 7.5 Hz, 2H, CH_2), 1.38 (d, *J* = 6.0 Hz, 6H, Me), 1.12 (t, *J* = 7.5 Hz, 3H, Me); ^{13}C NMR (101 MHz, $CDCl_3$): δ 159.3, 143.6, 137.0, 136.5, 131.9, 131.0, 128.8, 127.7, 127.5, 125.8, 125.6, 125.2, 115.9, 77.6, 23.1, 20.5, 13.6; HRMS (ESI) *m/z* calcd for $C_{20}H_{21}NO_2$ (M+H) 308.1645; found 308.1645.

General Procedure D: Synthesis of N-H isoquinolinones:

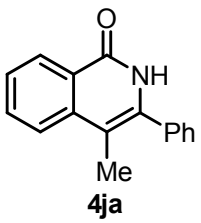


NaH (0.3 mmol, 60% in mineral oil) was added into a stirred solution of *N*-methoxyl isoquinolone **3** (0.1 mmol) in DMF (0.5 mL) and the resulting mixture was heated at 120 °C for 0.5-1.0 h. After the reaction was completed, the reaction mixture was allowed to cool down to room temperature, and H_2O (8 mL) was added, extracted with CH_2Cl_2 (5 mL x 3), The combined organic layer was dried over anhydrous Na_2SO_4, filtered and evaporated under reduced pressure. The crude product was purified by flash column chromatography on silica gel.



3,4-Diphenylisoquinolin-1(*2H*)-one (4a):

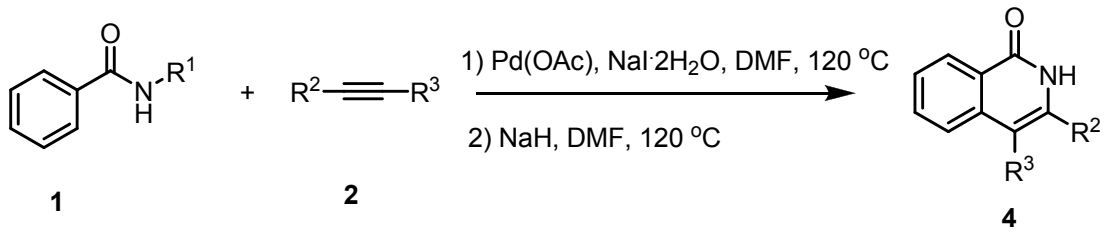
Following general procedure D, N-H isoquinolinone **4a** was isolated in greater than 95% yield: Mp: 256-257 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.54 (br s, 1H, NH), 8.32 (d, *J* = 7.5 Hz, 1H, ArH), 7.65 (t, *J* = 7.5 Hz, 1H, ArH), 7.52 (t, *J* = 7.5 Hz, 1H, ArH), 7.32-7.23 (m, 8H, ArH), 7.16 (d, *J* = 7.5, 3H, ArH). The analytical data are consistently agreed with the ones previously reported in the literature.[1, 8]



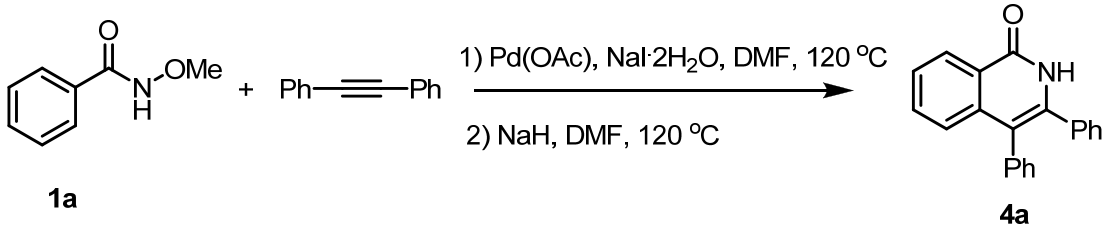
4-Methyl-3-phenylisoquinolin-1(*2H*)-one (4ja):

Following general procedure D, N-H isoquinolinone **4ja** was isolated in greater than 95% yield: Mp: 211-212 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.89 (br s, 1H, NH), 8.43 (d, J = 8.0 Hz, 1H, ArH), 7.76-7.73 (m, 2H, ArH), 7.54-7.47 (m, 6H, ArH), 2.29 (s, 3H, Me). The analytical data are consistently agreed with the ones previously reported in the literature.[1, 8]

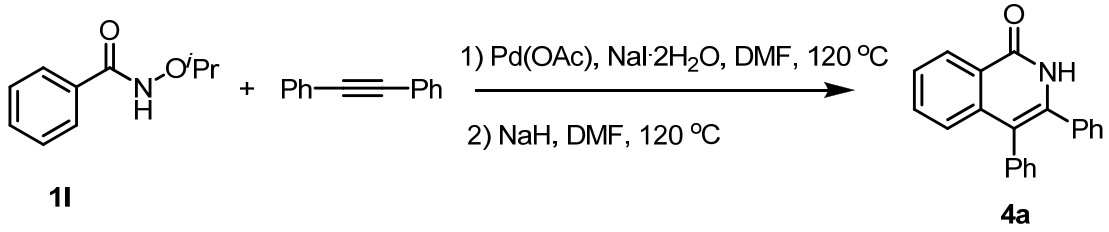
General Procedure E: One-pot synthesis of N-H isoquinolinones:



A solution of amide (0.3 mmol), alkyne (0.9 mmol), $Pd(OAc)_2$ (10 mol%) and $NaI{\cdot}2H_2O$ (0.3 mmol) in DMF (1.5 mL) was heated at 120 °C under air. The reaction was monitored by TLC. After the reaction was completed, the reaction mixture was allowed to cool down to room temperature, NaH (0.9 mmol, 60% in mineral oil) was added, then the mixture was heated at 120 °C for 0.5-1.0 h, after the reaction was completed, the reaction mixture was allowed to cool down to room temperature, and saturated aqueous $Na_2S_2O_3$ (20 mL) was added, extracted with CH_2Cl_2 (15 mL x 3), The combined organic layer was dried over anhydrous Na_2SO_4, filtered, and evaporated under reduced pressure. The crude product was purified by flash column chromatography on silica gel.

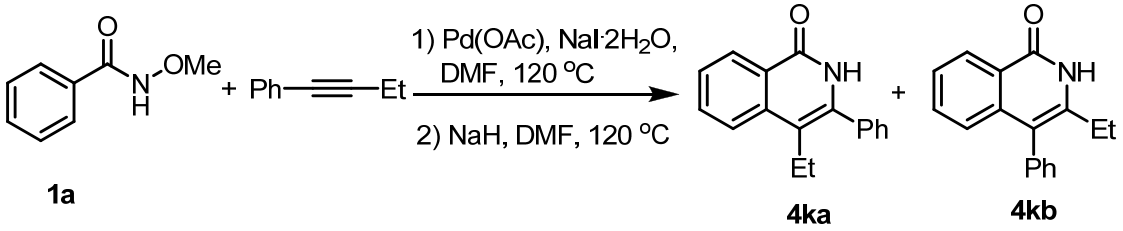


Following general procedure E, a solution of amide **1a** (45 mg, 0.3 mmol), diphenylethyne (160 mg, 0.9 mmol), $Pd(OAc)_2$ (10 mol%) and $Pd(OAc)_2$ (6.7 mg, 10 mol%) and $NaI{\cdot}2H_2O$ (56 mg, 0.3 mmol) in DMF (1.5 mL) was heated at 120 °C for 7 h. After the reaction was completed, the reaction mixture was allowed to cool down to room temperature, NaH (0.9 mmol, 60% in mineral oil) was added, then the mixture was heated at 120 °C for 0.5 h, the desired N-H isoquinolinone **4a** (85 mg, 96%) was isolated as a white solid.



1l **4a**

Following general procedure E, a solution of amide **1l** (54 mg, 0.3 mmol), diphenylethyne (160 mg, 0.9 mmol), $Pd(OAc)_2$ (10 mol%) and $Pd(OAc)_2$ (6.7 mg, 10 mol%) and $NaI{\cdot}2H_2O$ (56 mg, 0.3 mmol) in DMF (1.5 mL) was heated at 120 ^oC for 8 h. After the reaction was completed, the reaction mixture was allowed to cool down to room temperature, NaH (0.9 mmol, 60% in mineral oil) was added, then the mixture was heated at 120 ^oC for 1 h, the desired N-H isoquinolinone **4a** (82 mg, 92%) was isolated as a white solid.



1a **4ka** **4kb**

4-Ethyl-3-phenylisoquinolin-1(*2H*)-one (4ka)

3-Ethyl-4-phenylisoquinolin-1(2H)-one (4kb)

Following general procedure E, a solution of amide **1a** (90 mg, 0.6 mmol), 1-phenylpropyne (232 mg, 1.8 mmol), $Pd(OAc)_2$ (13.4 mg, 10 mol%) and $NaI{\cdot}2H_2O$ (111 mg, 0.6 mmol) in DMF (3.0 mL) was heated at 120 ^oC for 6 h. After the reaction was completed, the reaction mixture was allowed to cool down to room temperature, NaH (1.8 mmol, 60% in mineral oil) was added, then the mixture was heated at 120 ^oC for 0.5 h gave the desired N-H isoquinolinone **4ka** (135 mg, 81%) as a white solid: Mp: 226-228 ^oC; ^1H NMR (400 MHz, $CDCl_3$): δ 9.08 (br s, 1H, NH), 8.47 (d, J = 8.0 Hz, 1H, ArH), 7.82-7.74 (m, 2H, ArH), 7.55-7.47 (m, 6H, ArH), 2.70 (q, J = 7.5 Hz, 2H, CH_2), 1.23 (t, J = 7.5 Hz, 3H, Me). The analytical data are consistently agreed with the ones previously reported in the literature[9] and **4kb** (13 mg, 8%) as a white solid: Mp: 257-258 ^oC; ^1H NMR (400 MHz, $CDCl_3$): δ 11.12 (br s, 1H, NH) 8.49 (d, J = 8.0 Hz, 1H, ArH), 7.56-7.43 (m, 5H, ArH), 7.31 (d, J = 7.0 Hz, 2H, ArH), 7.12 (d, J = 8.0 Hz, 1H, ArH), 2.52 (q, J = 7.5 Hz, 2H, CH_2), 1.27 (t, J = 7.5 Hz, 3H, Me); ^{13}C NMR (101 MHz, $CDCl_3$): δ 164.1, 140.1, 139.2, 136.3, 132.4, 131.1, 128.7, 127.6, 127.2, 125.7, 125.2, 124.3, 116.5, 24.9, 13.8. HRMS (ESI) *m/z* calcd for $C_{17}H_{15}NO$ (M+H) 250.1234; found 250.1236.

References:

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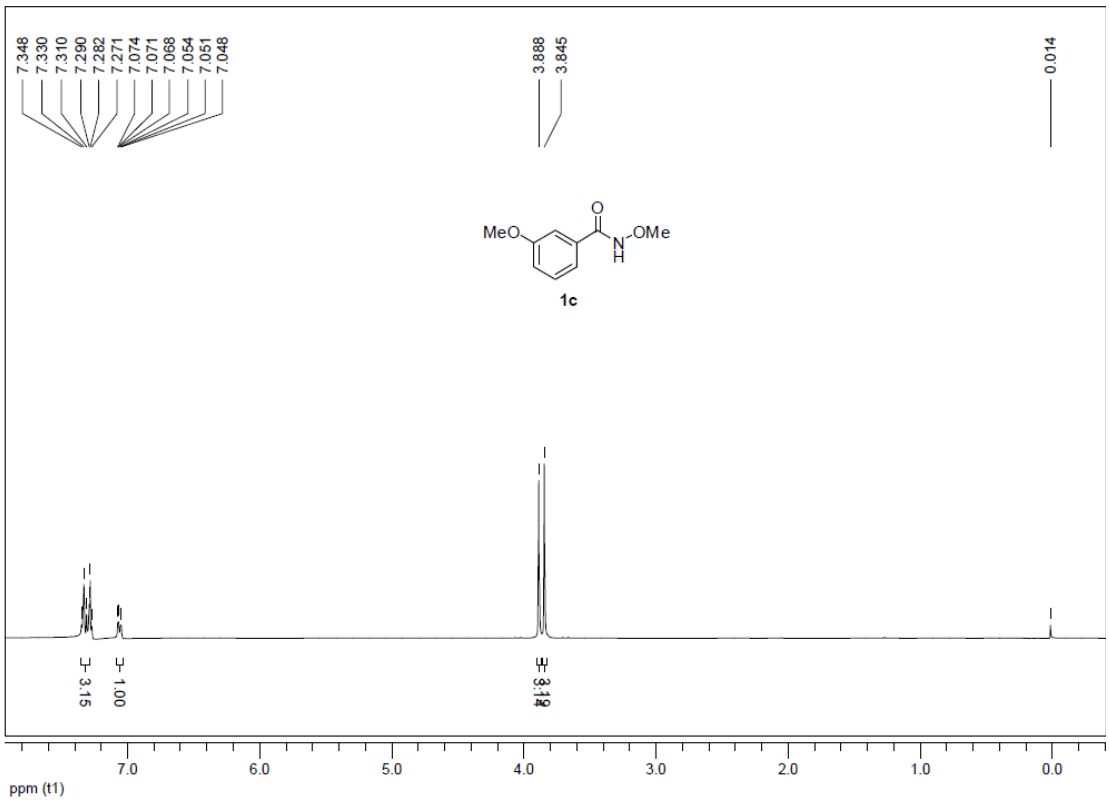
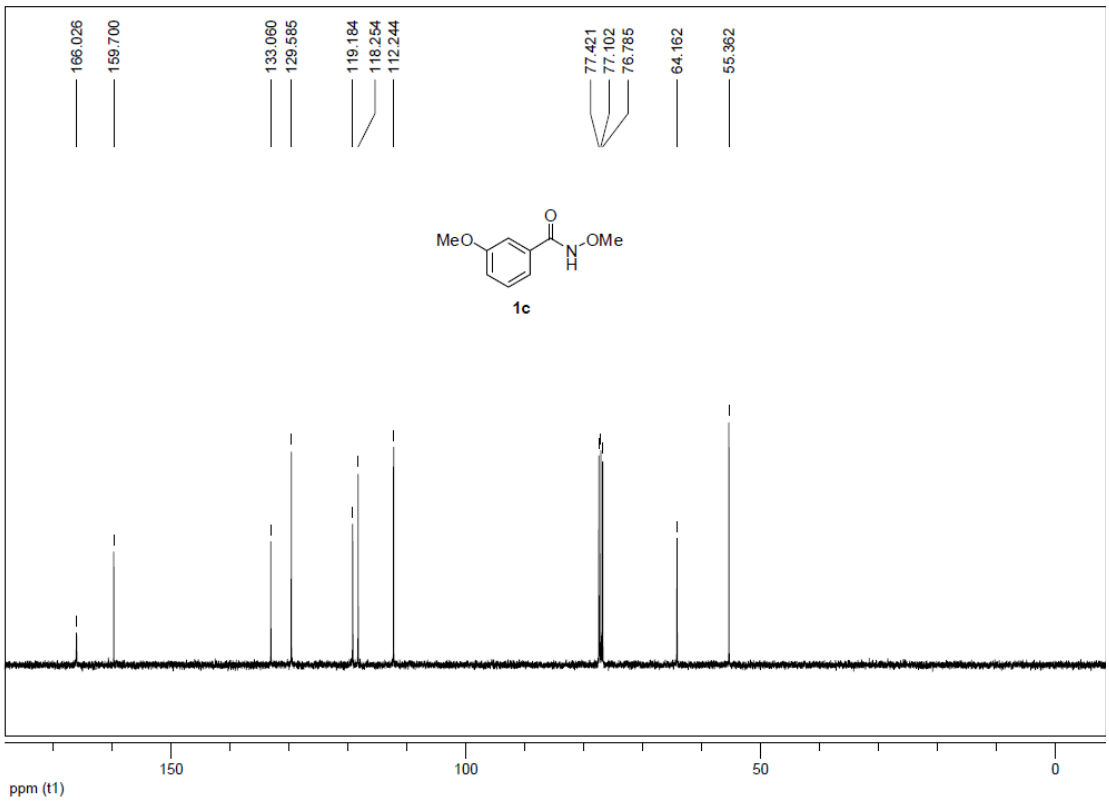
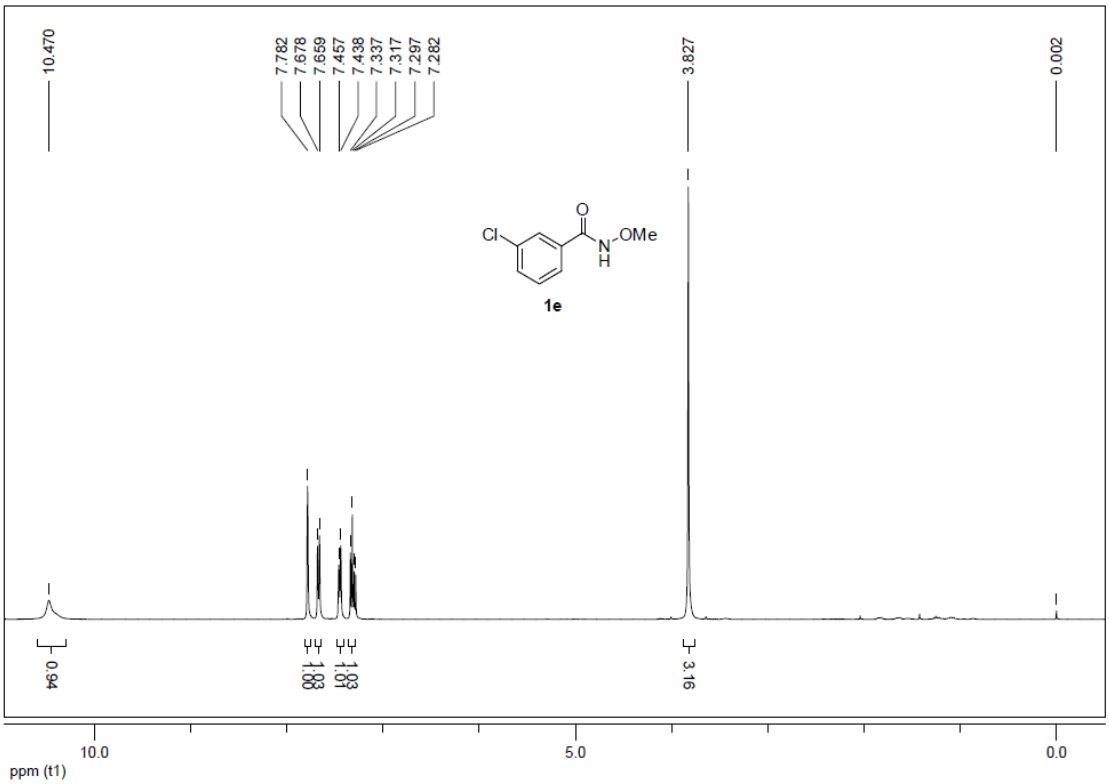
Spectral data



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N
H
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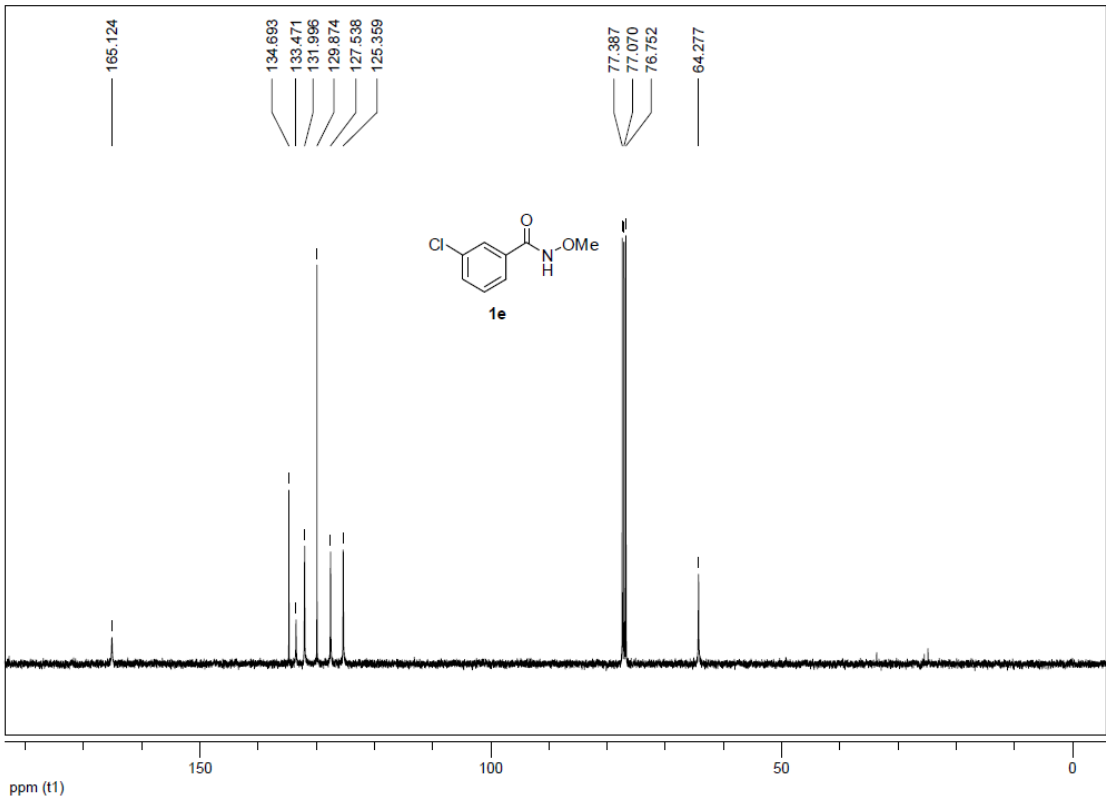
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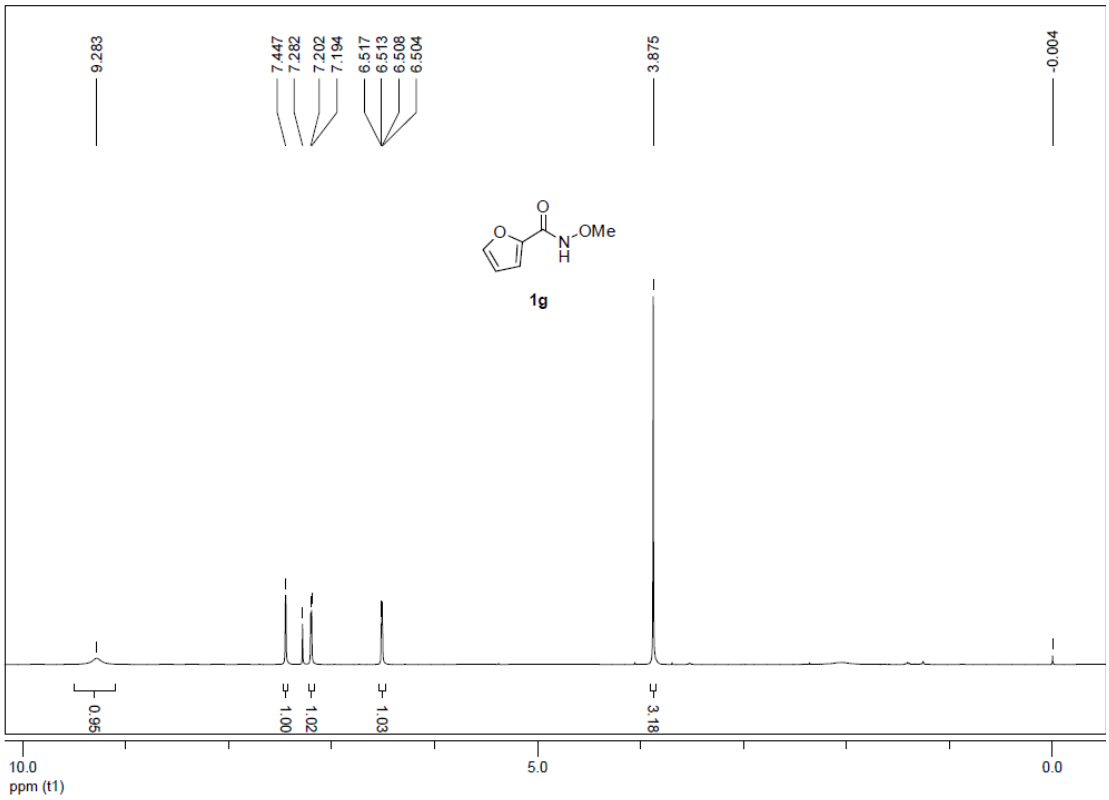
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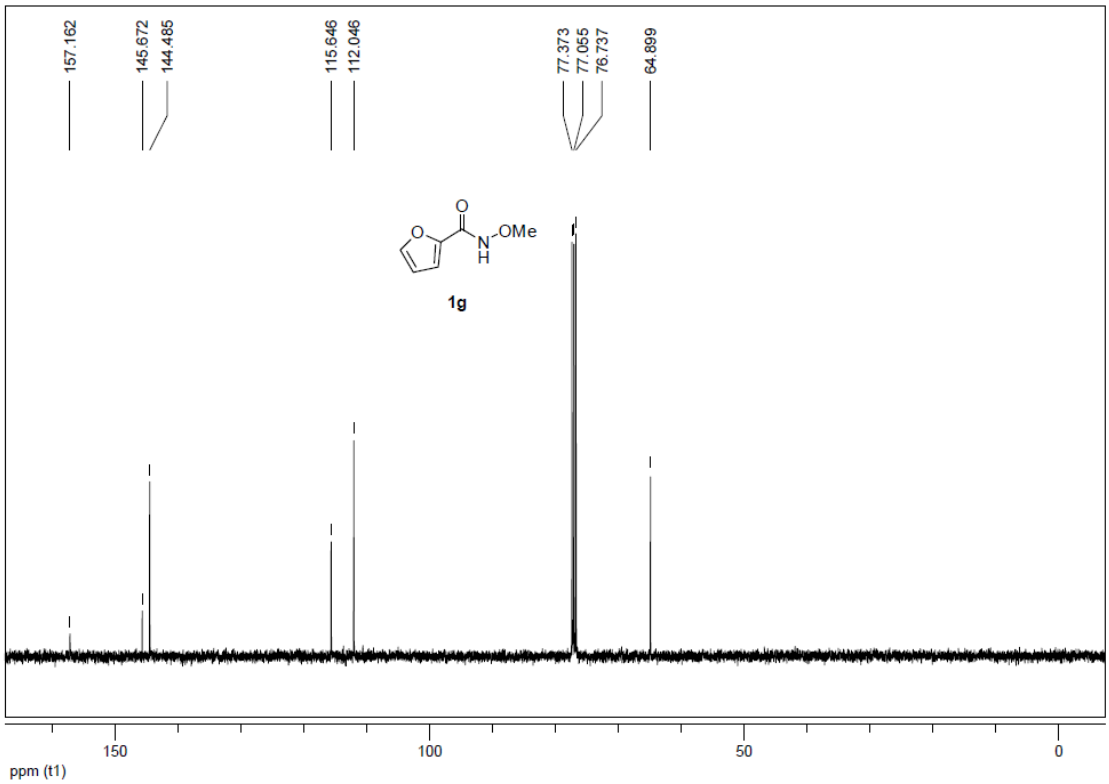
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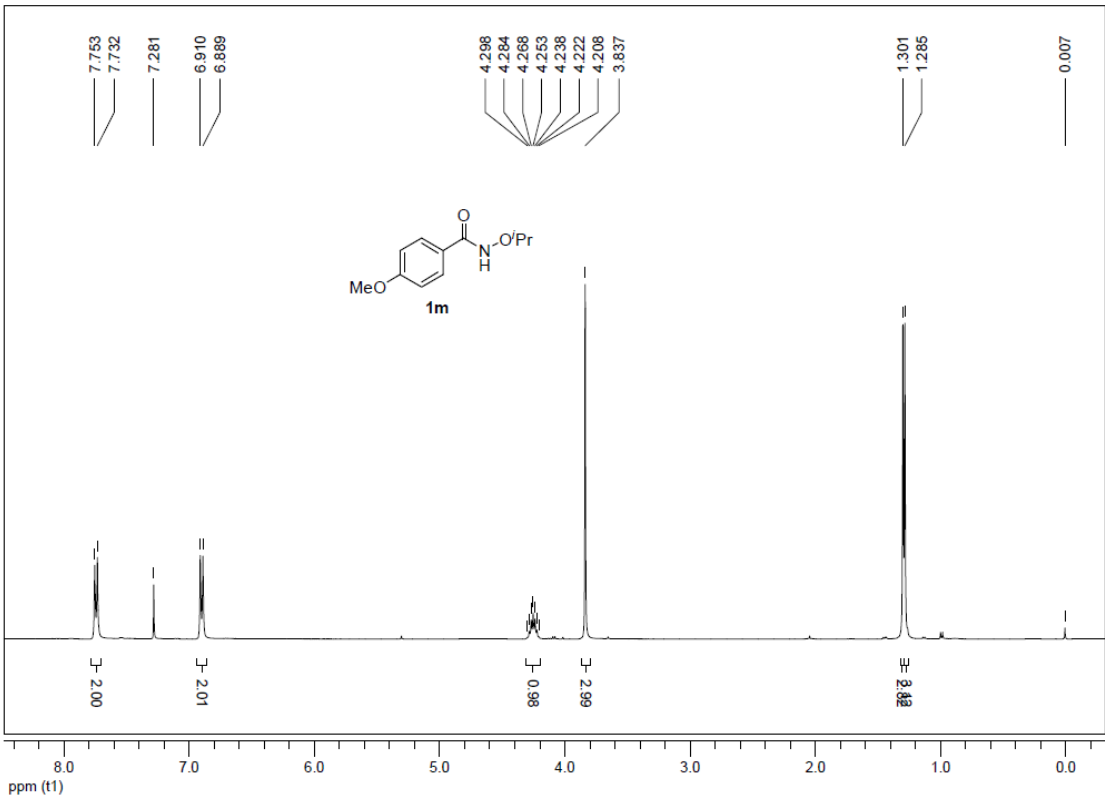
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H
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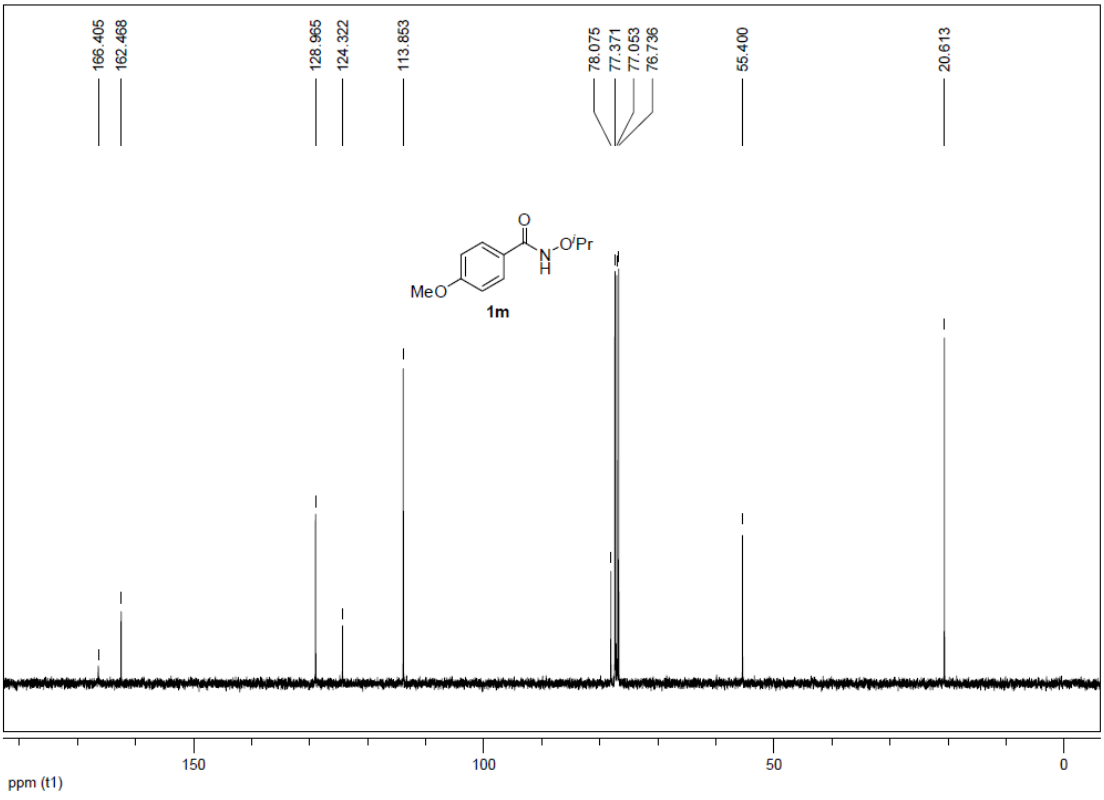
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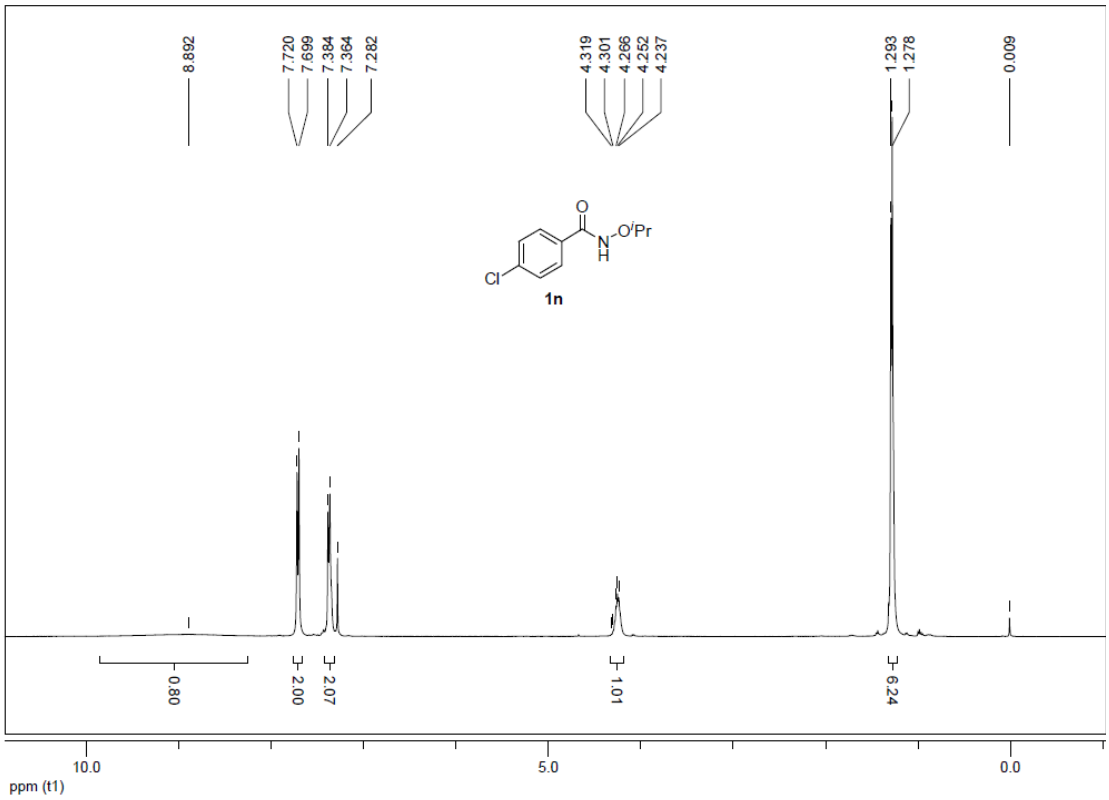
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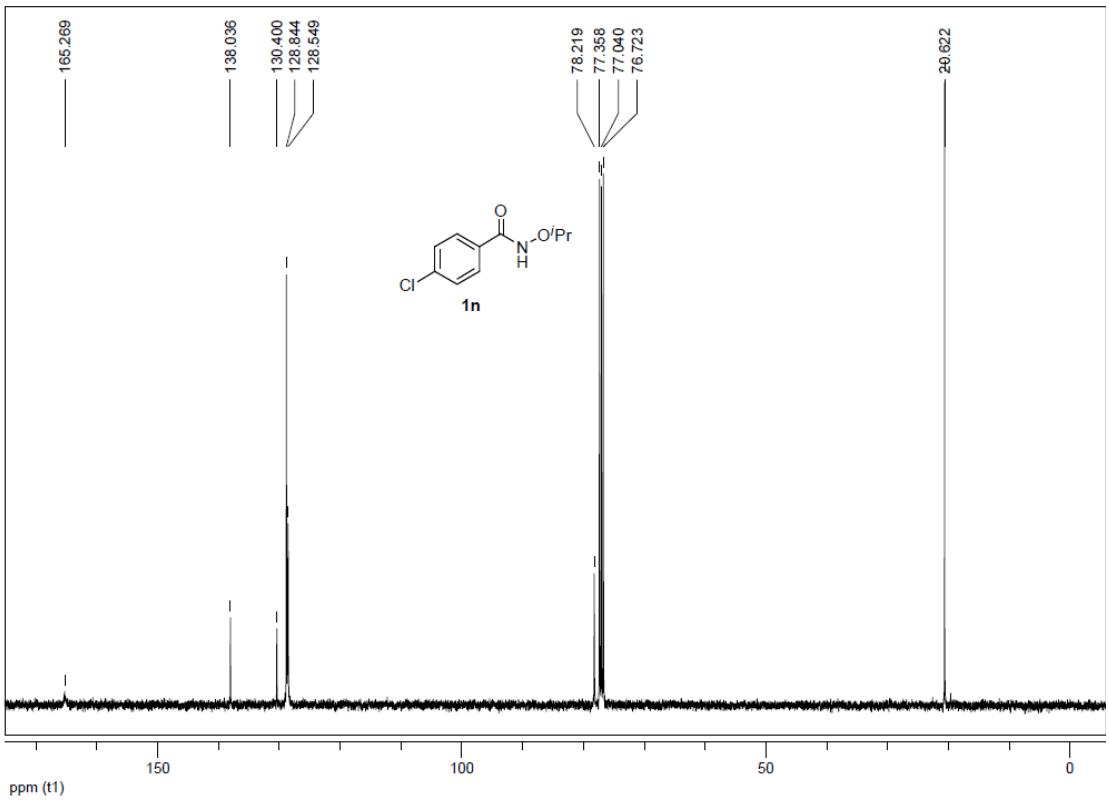
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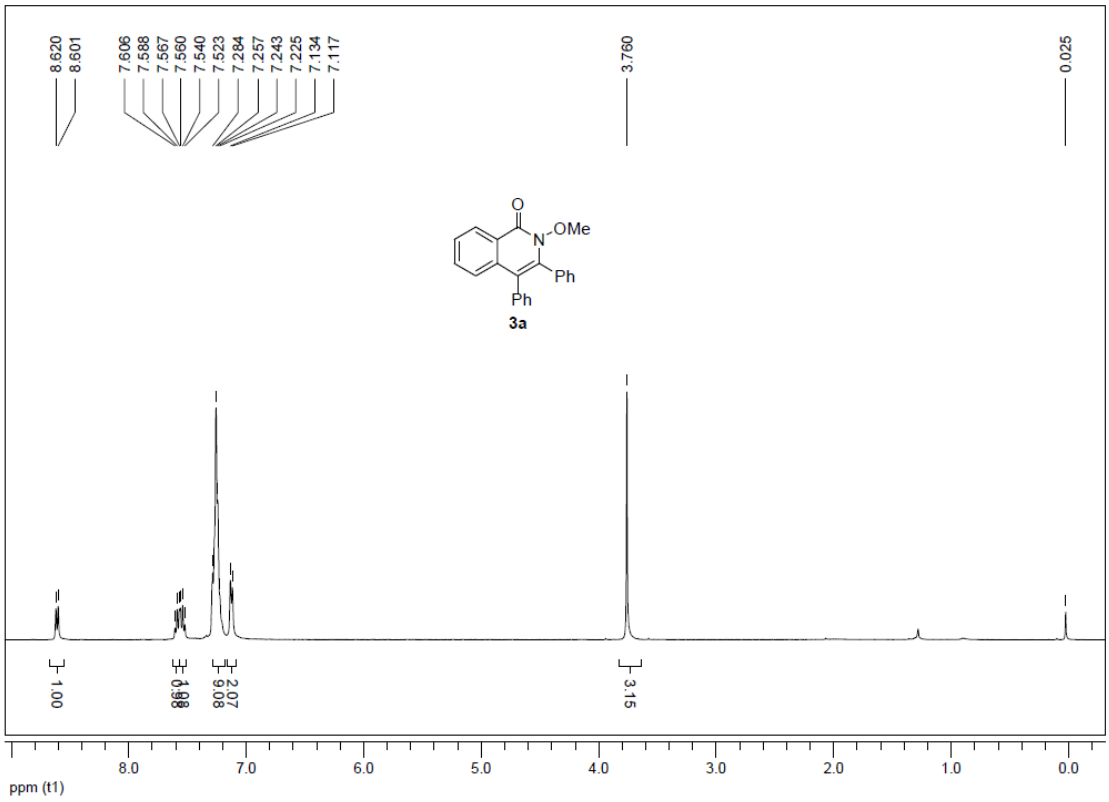
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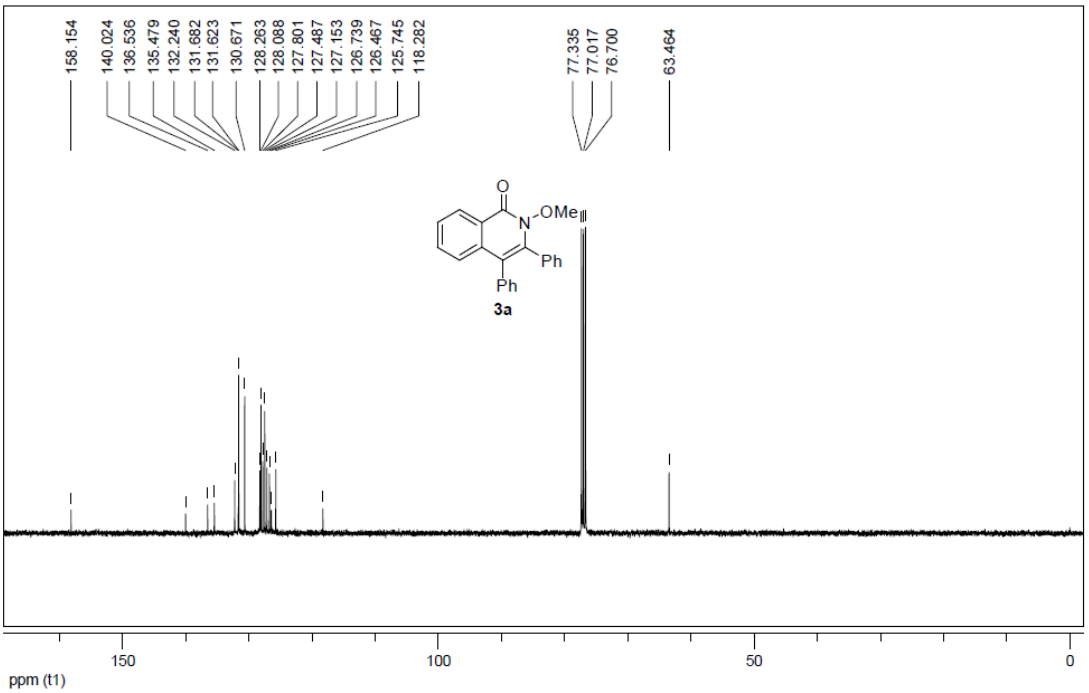
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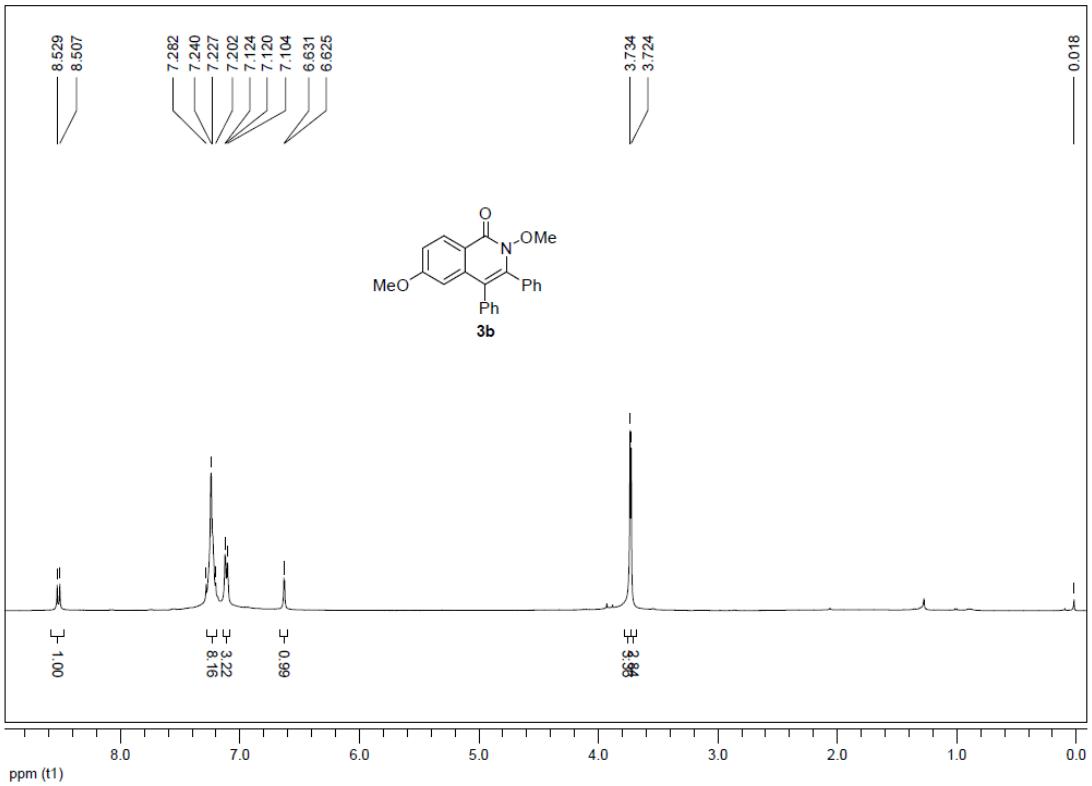
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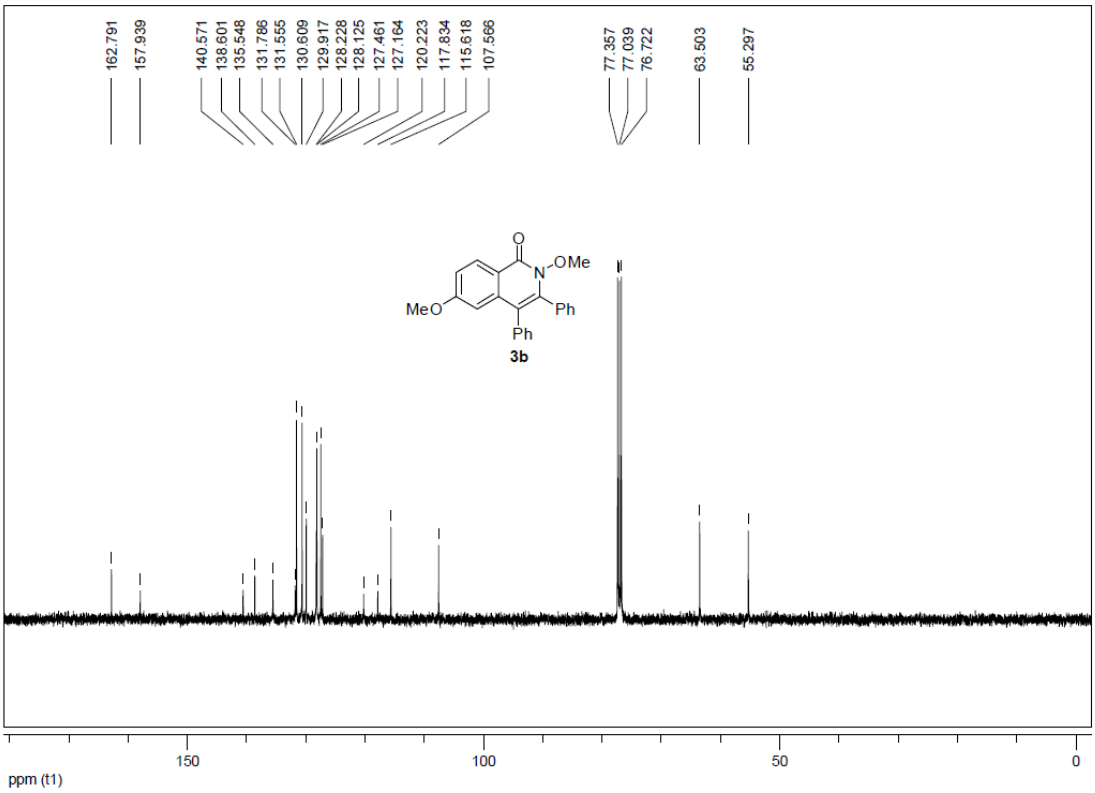
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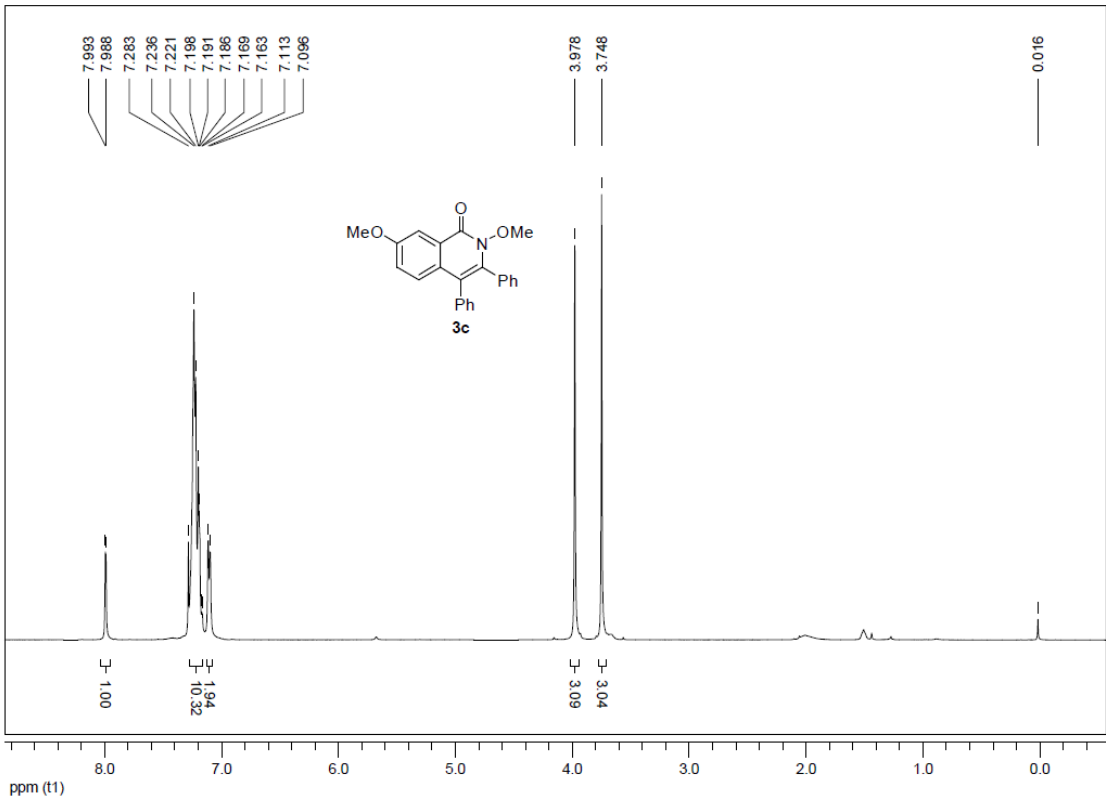
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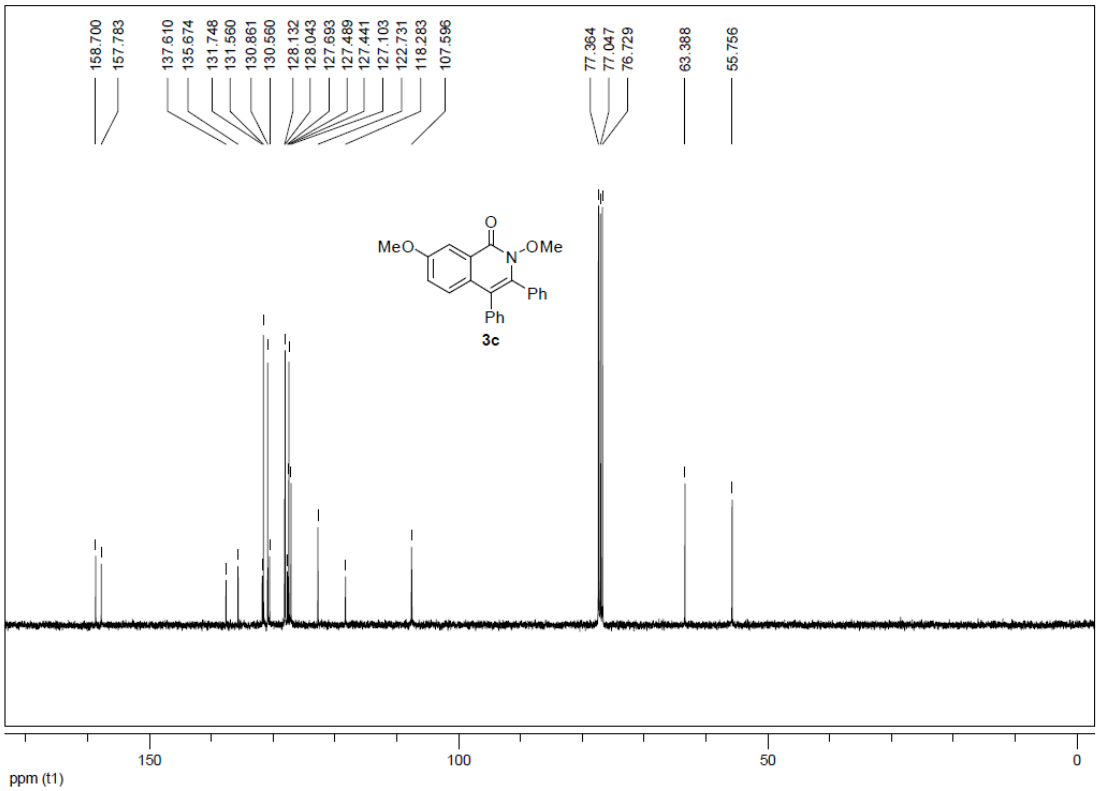
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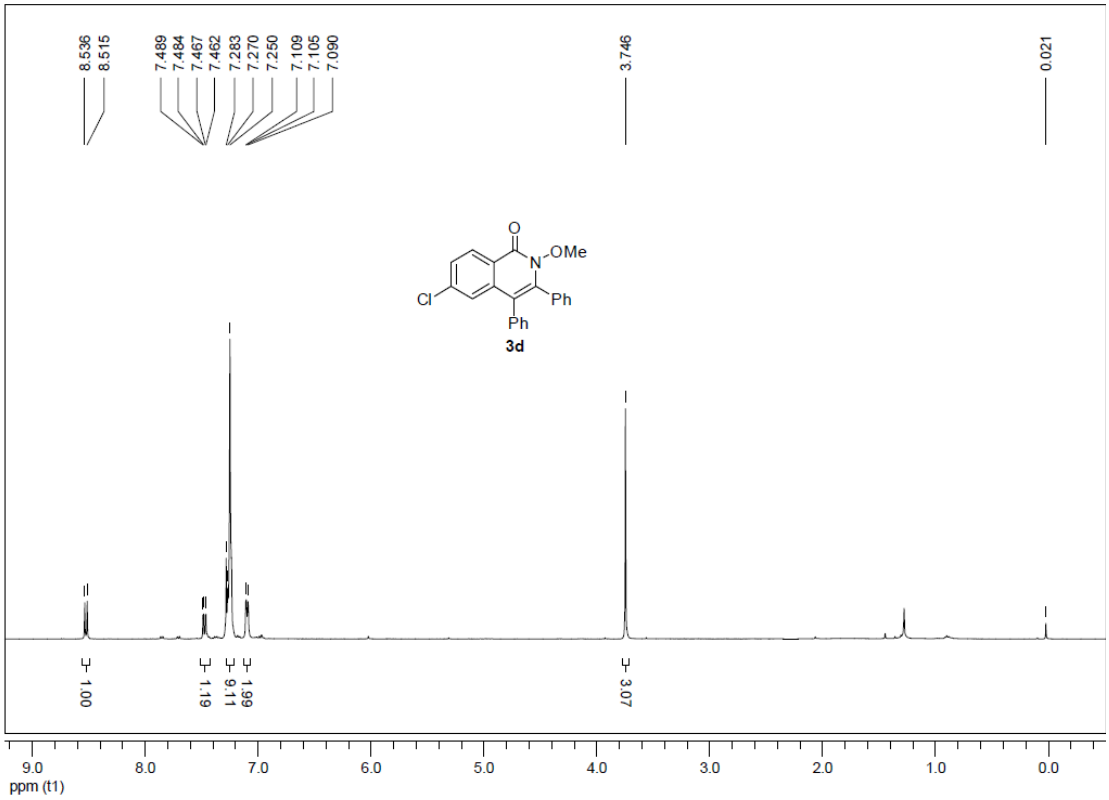
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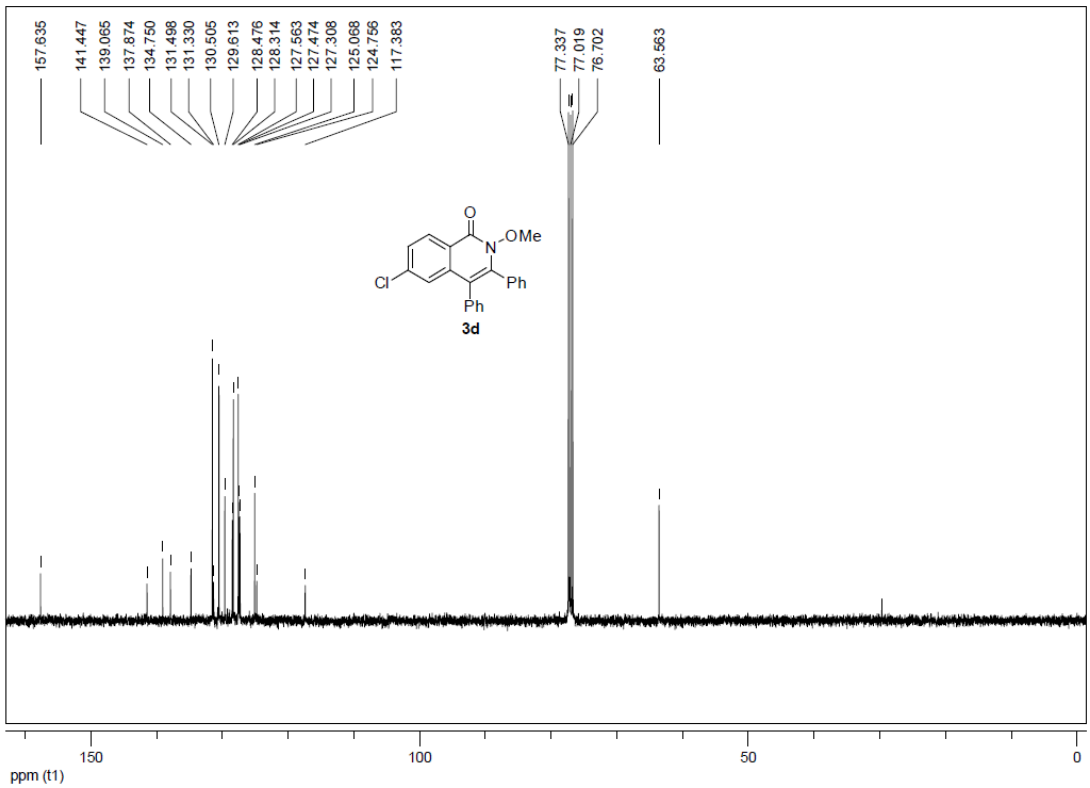
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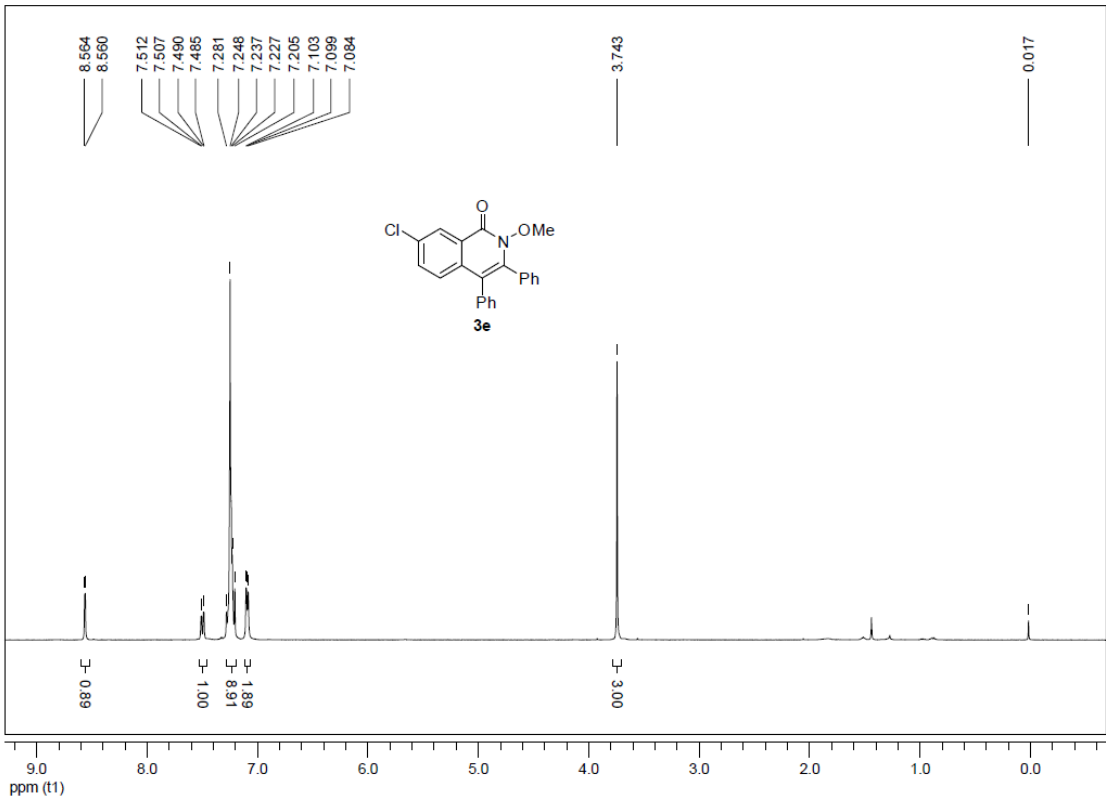
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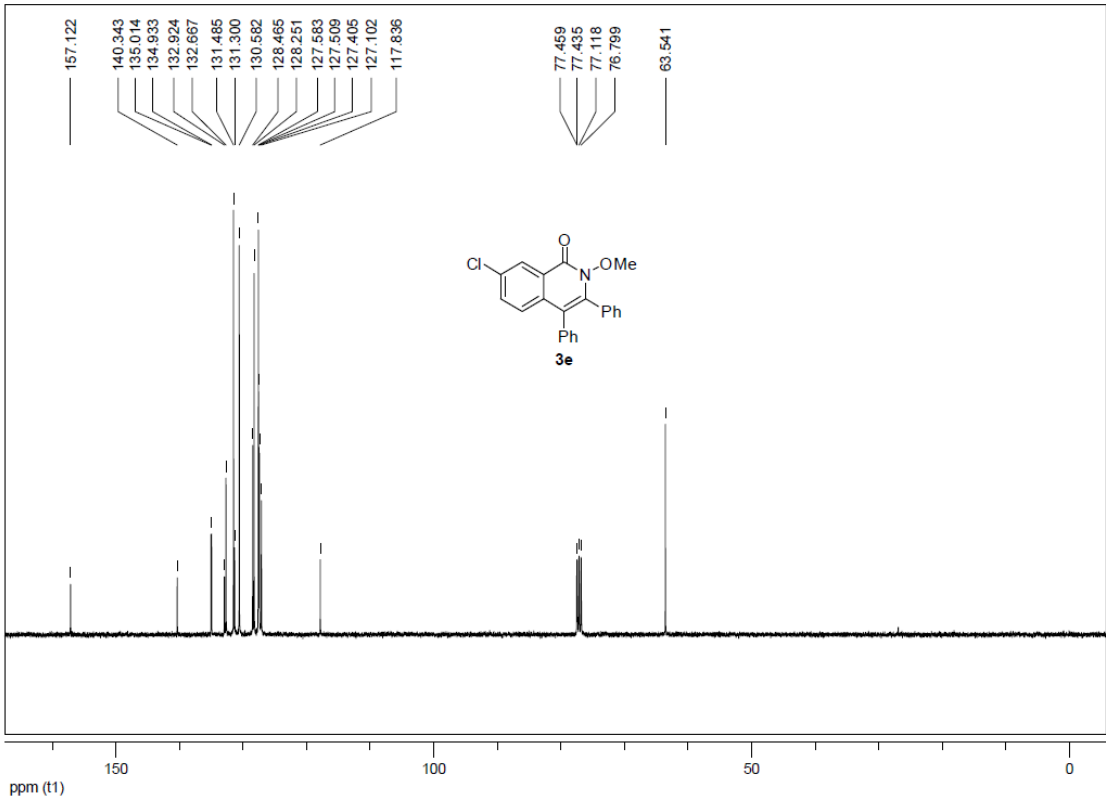
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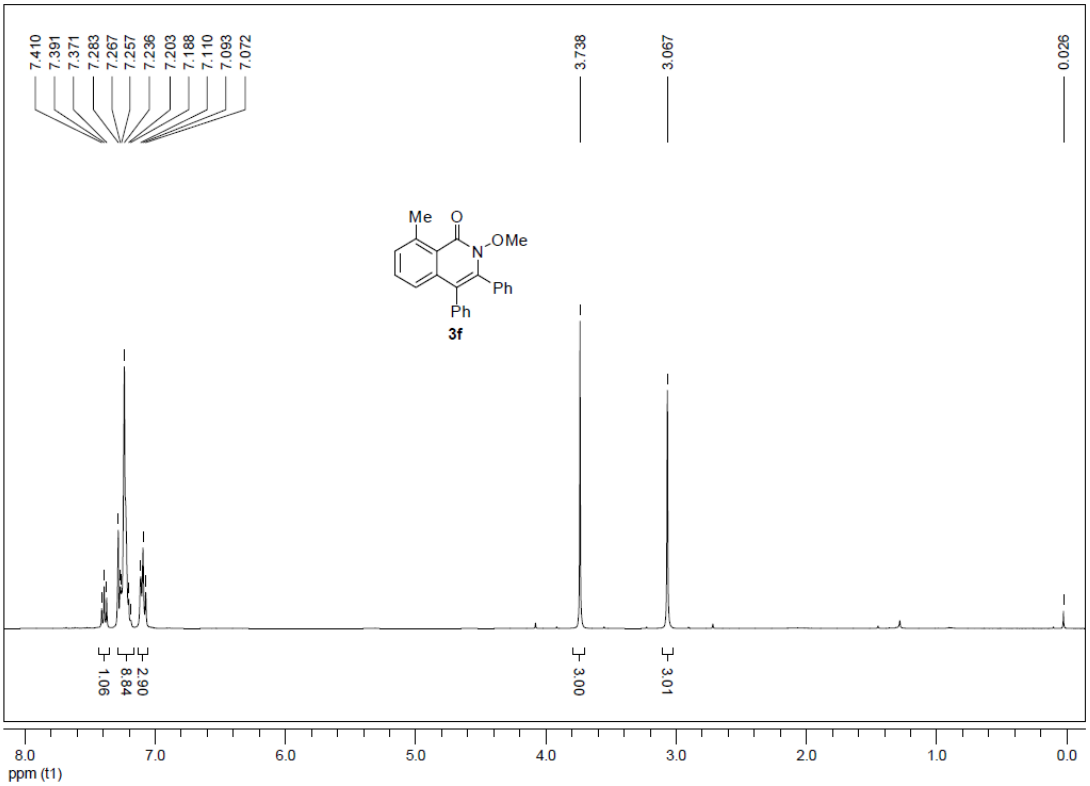
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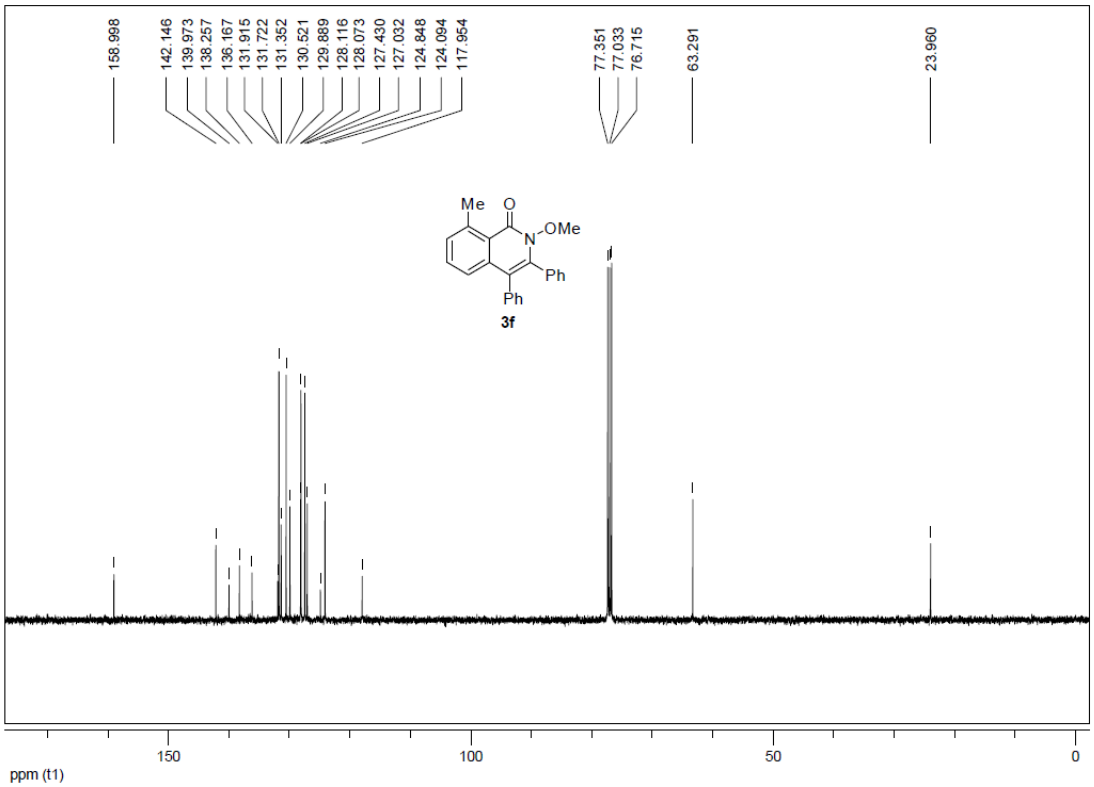
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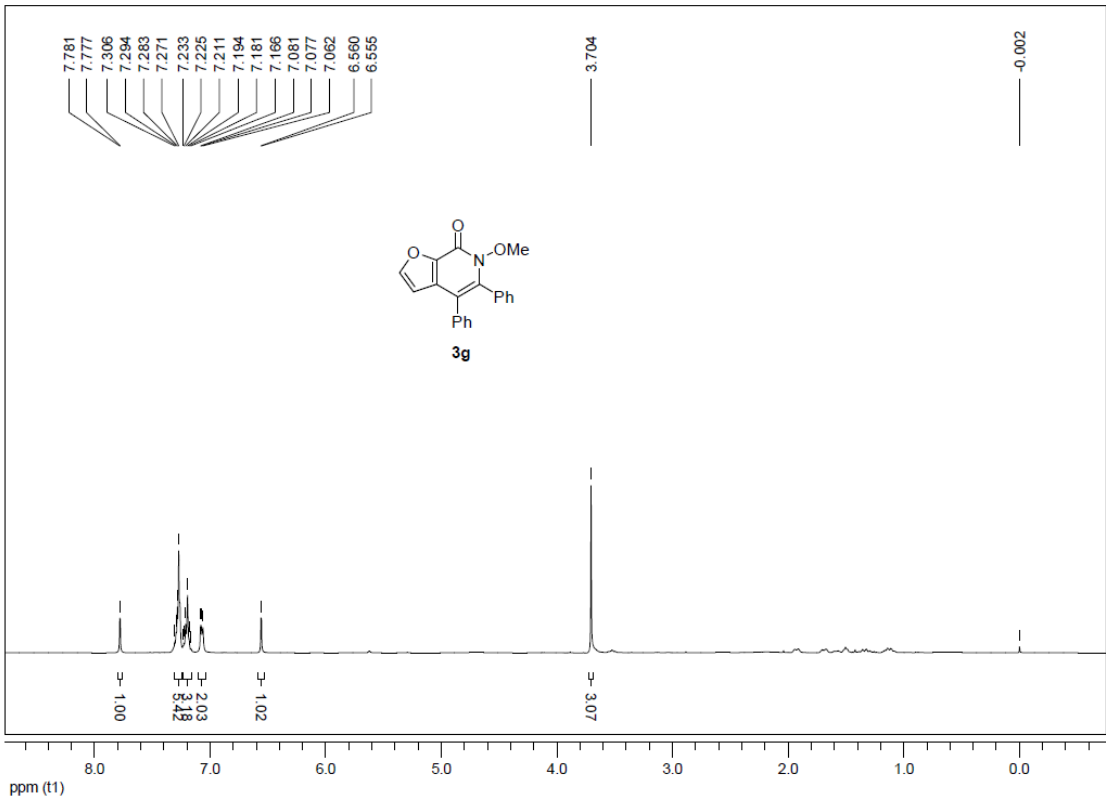
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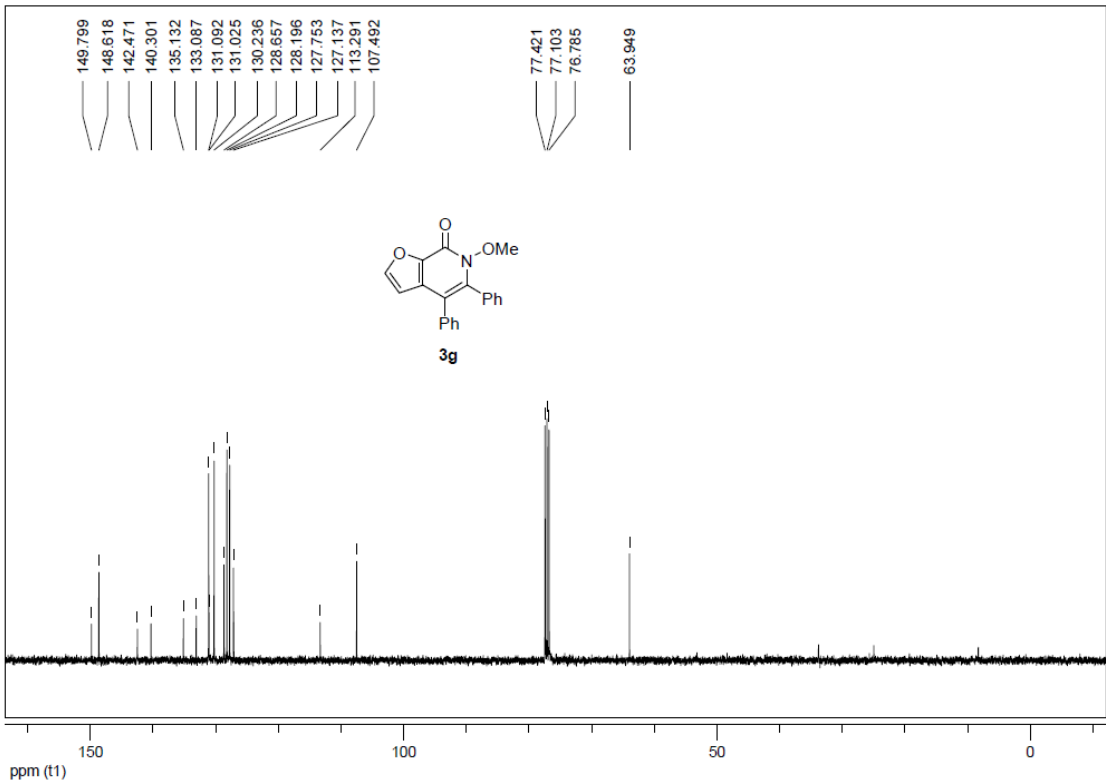
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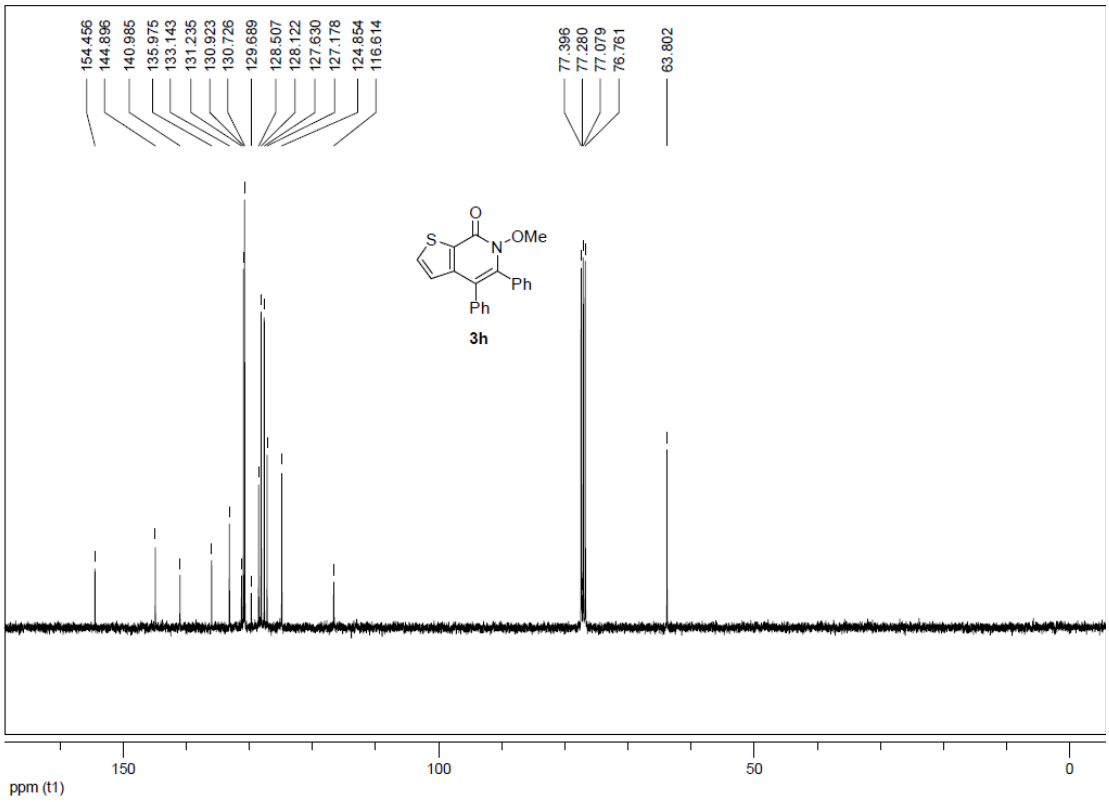
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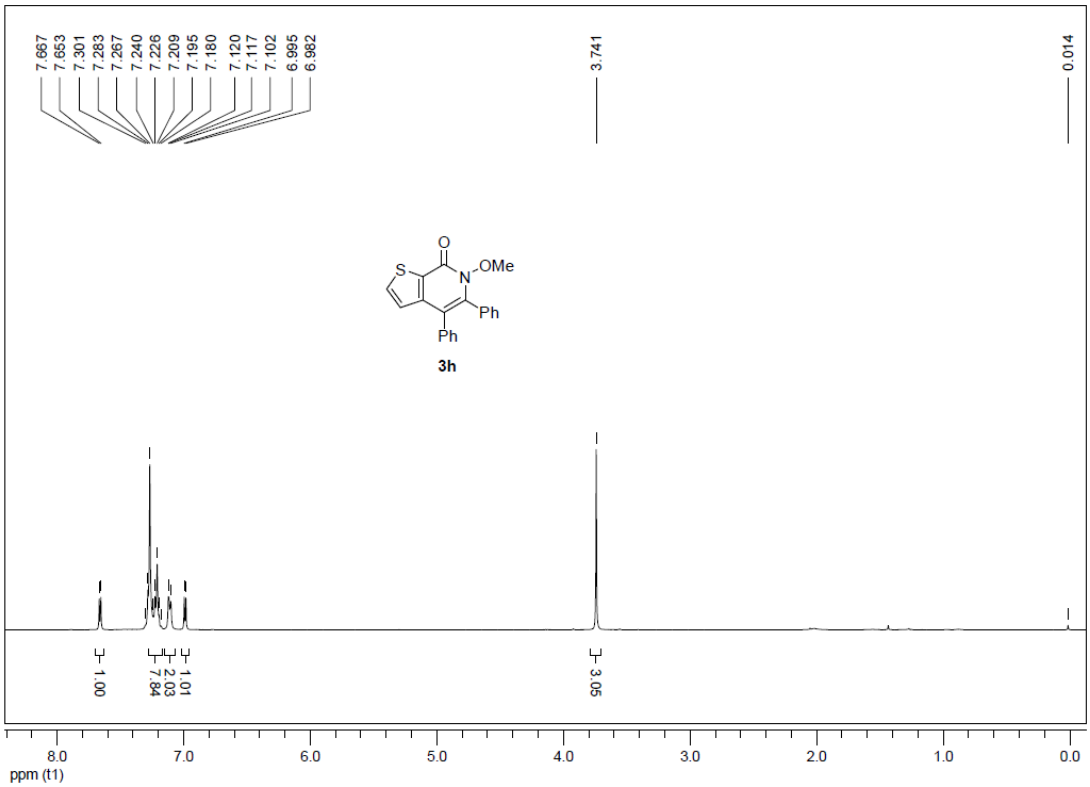
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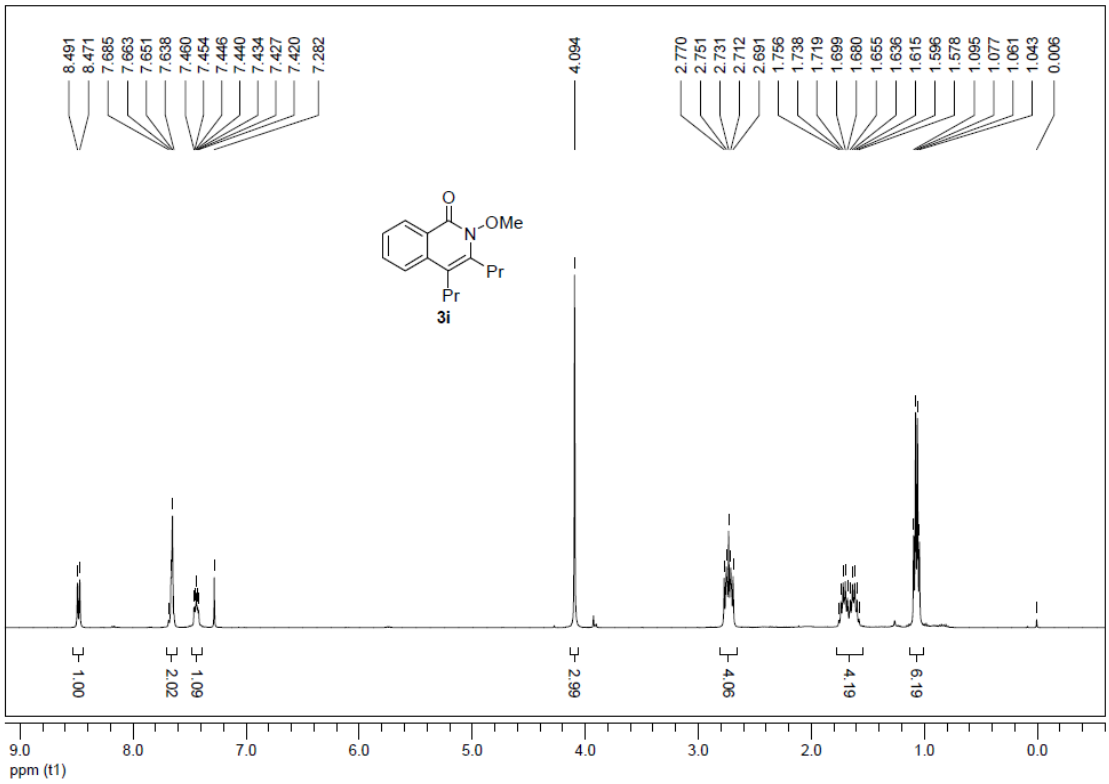
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7.446
7.440
7.434
7.427
7.420
7.282
4.094
2.770
2.751
2.731
2.712
2.691
1.756
1.738
1.719
1.699
1.680
1.655
1.636
1.615
1.596
1.578
1.095
1.077
1.061
1.043
0.006
O
N
OMe
Pr
Pr
3i
1.00
2.02
1.09
2.99
4.06
4.19
6.19
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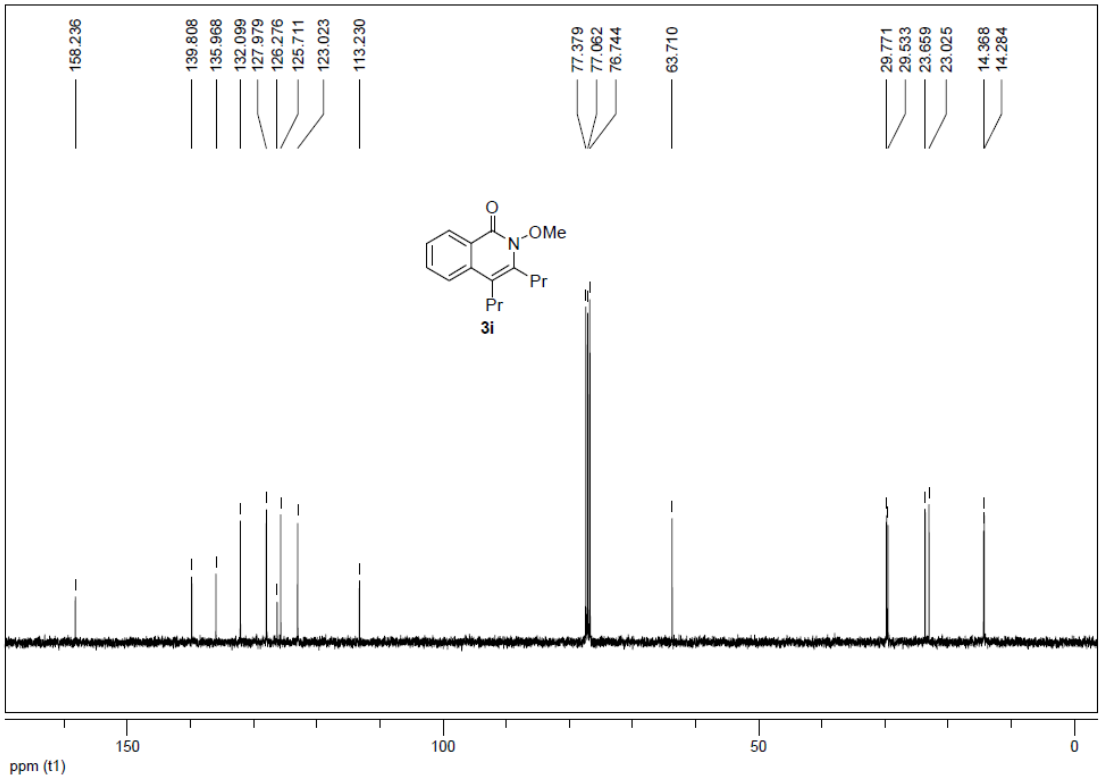
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)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135.968
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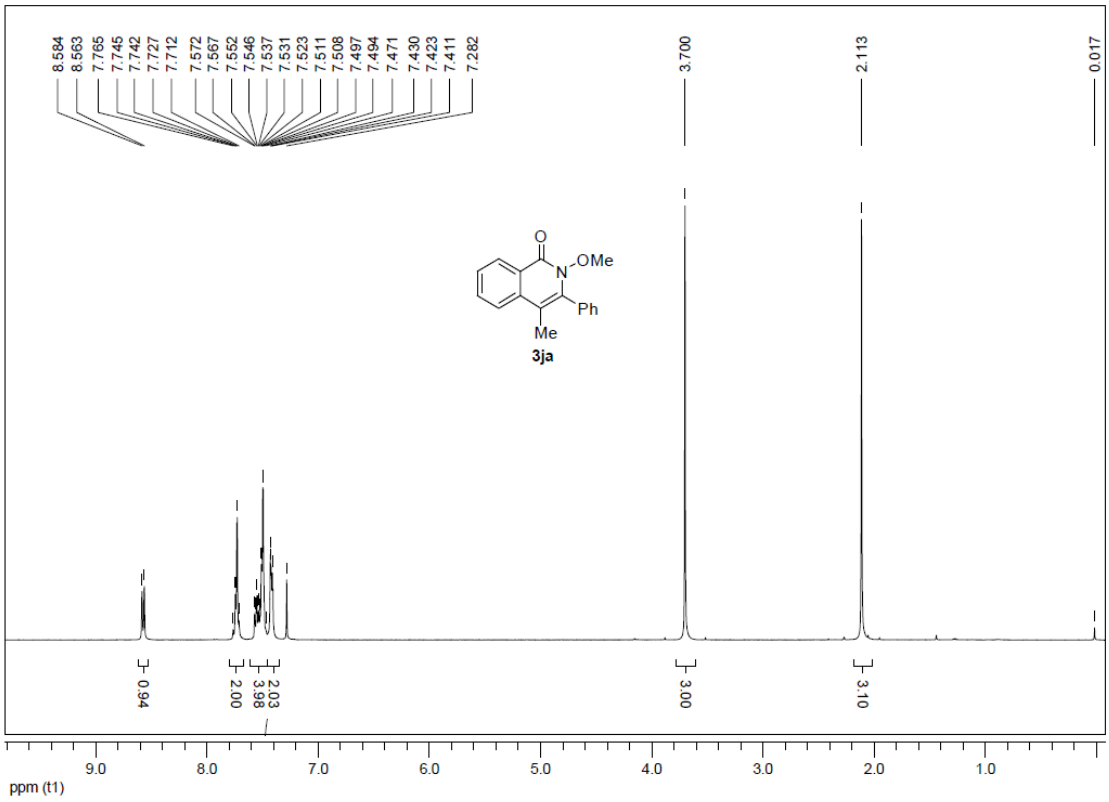
125.711
123.023
113.230
77.379
77.062
76.744
63.710
29.771
29.533
23.659
23.025
14.368
14.284
O
N
OMe
Pr
Pr
3i
150
100
50
0
ppm (t1)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7.766
7.745
7.742
7.727
7.712
7.572
7.567
7.552
7.546
7.537
7.531
7.523
7.511
7.508
7.497
7.494
7.471
7.430
7.423
7.411
7.282
3.700
2.113
0.017
O
N
OMe
Ph
Me
3ja
0.94
2.00
3.98
2.03
3.00
3.10
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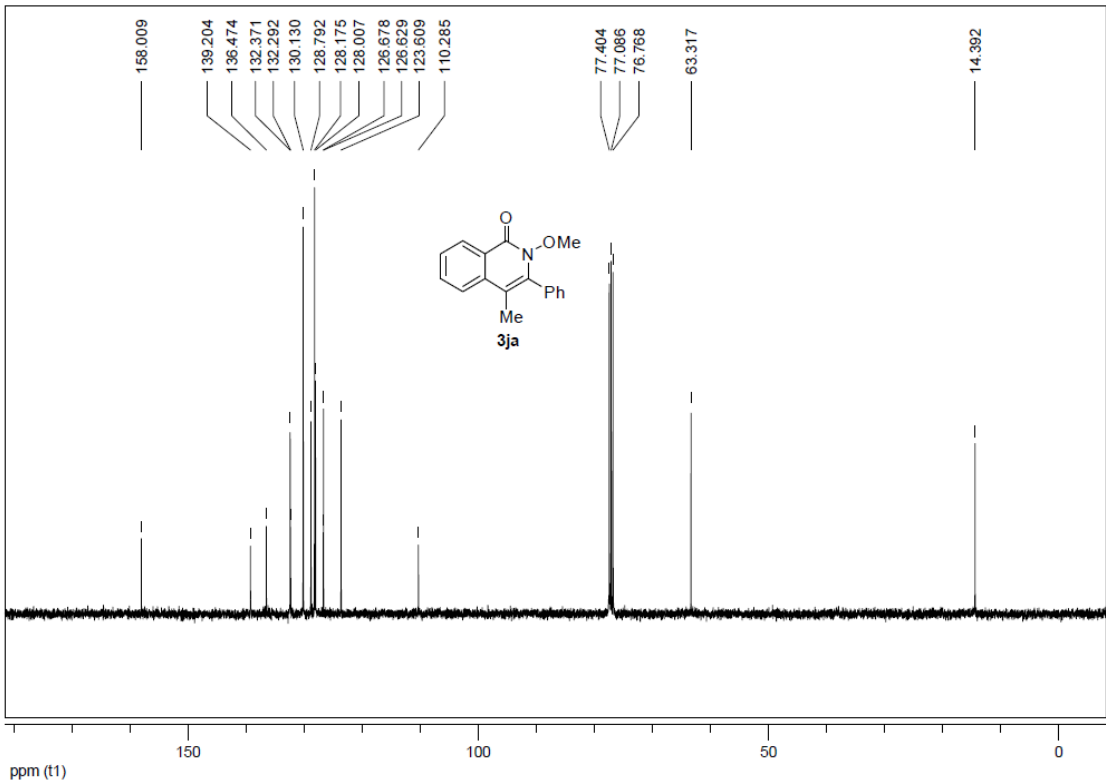
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (t1)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136.474
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130.130
128.792
128.175
128.007
126.678
126.629
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110.285
77.404
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76.768
63.317
14.392
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N
OMe
Ph
Me
3ja
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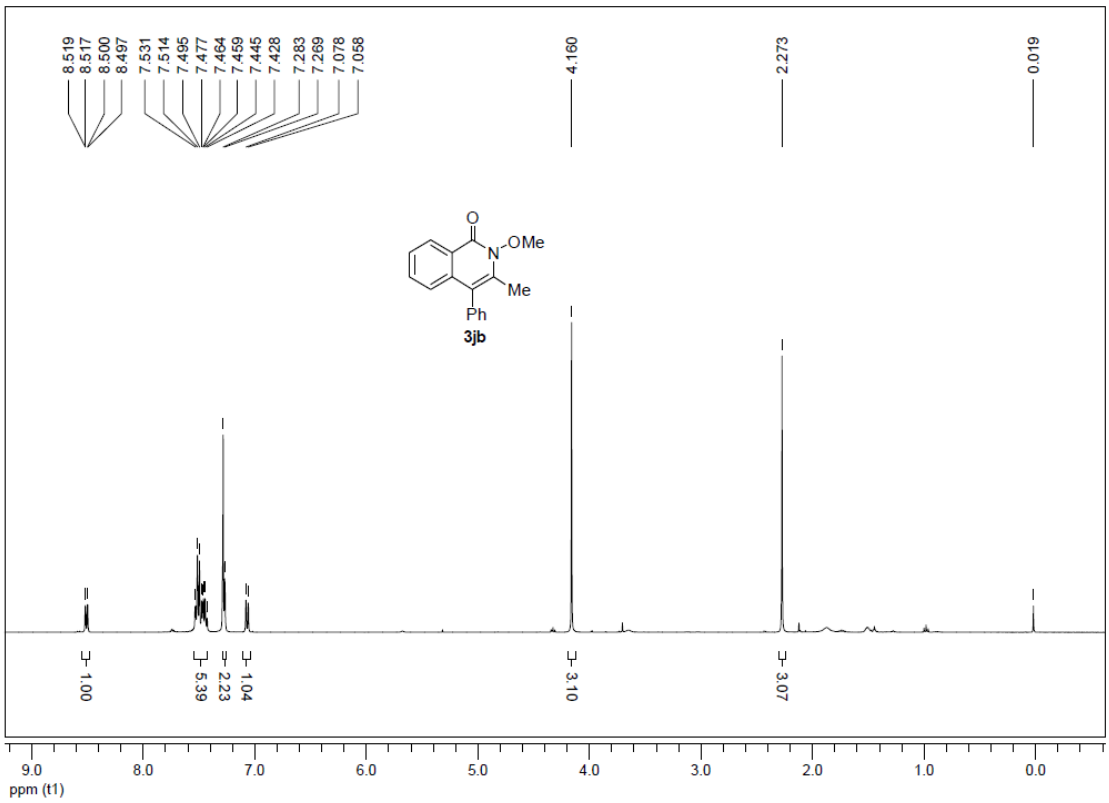
100
50
0
ppm (t1)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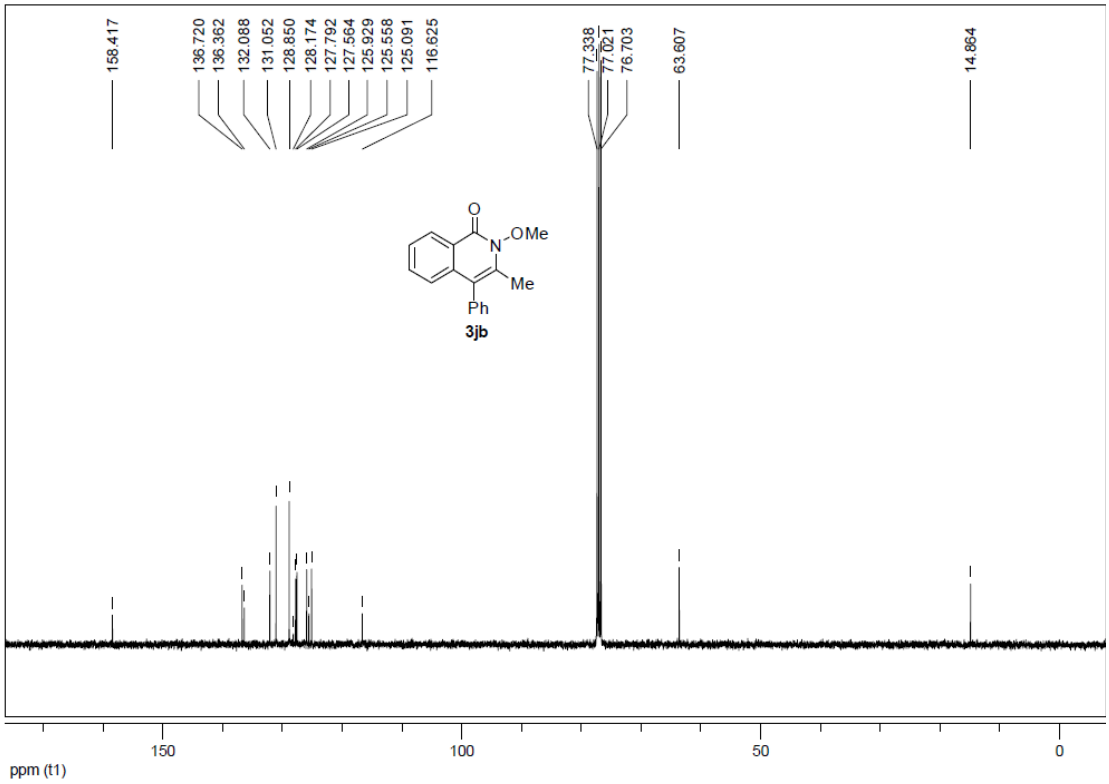
8.517
8.500
8.497
7.531
7.514
7.495
7.477
7.464
7.459
7.445
7.428
7.283
7.269
7.078
7.058
4.160
2.273
0.019
O
N
OMe
Me
Ph
3jb
1.00
5.39
2.23
1.04
3.10
3.07
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)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128.174
127.792
127.564
125.929
125.558
125.091
116.625
77.338
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63.607
14.864
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N
OMe
Me
Ph
3jb
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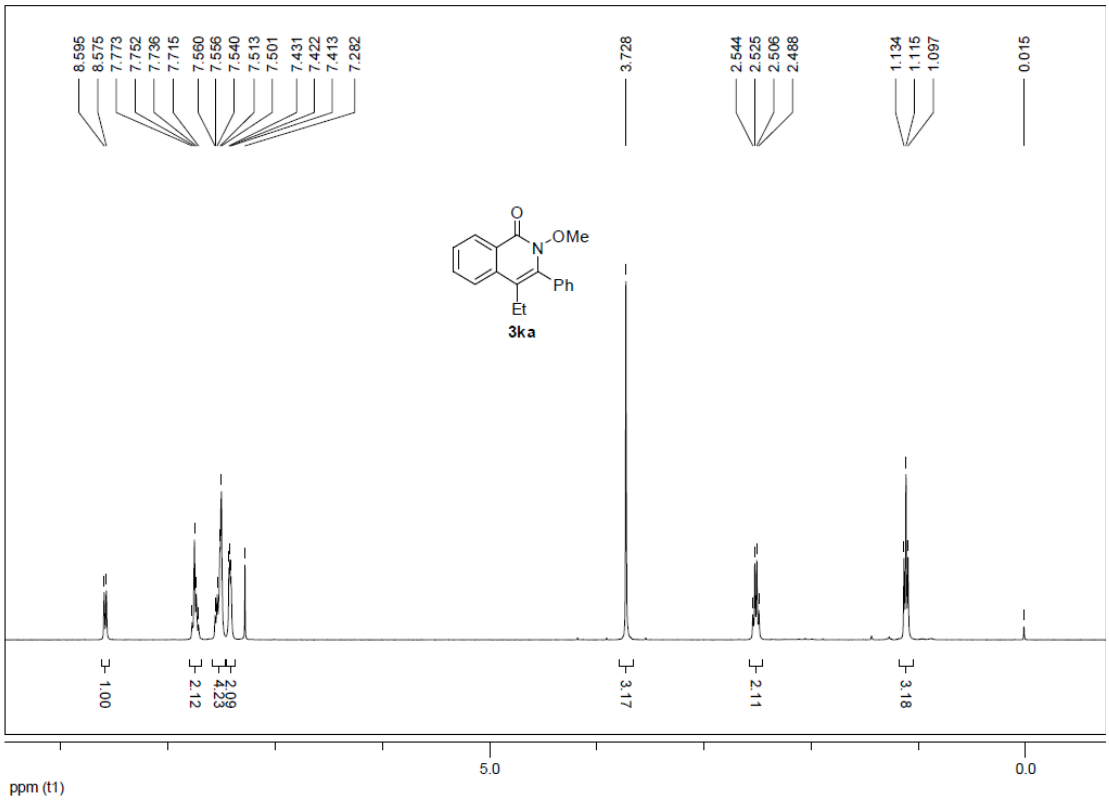
100
50
0
ppm (t1)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8.575
7.773
7.752
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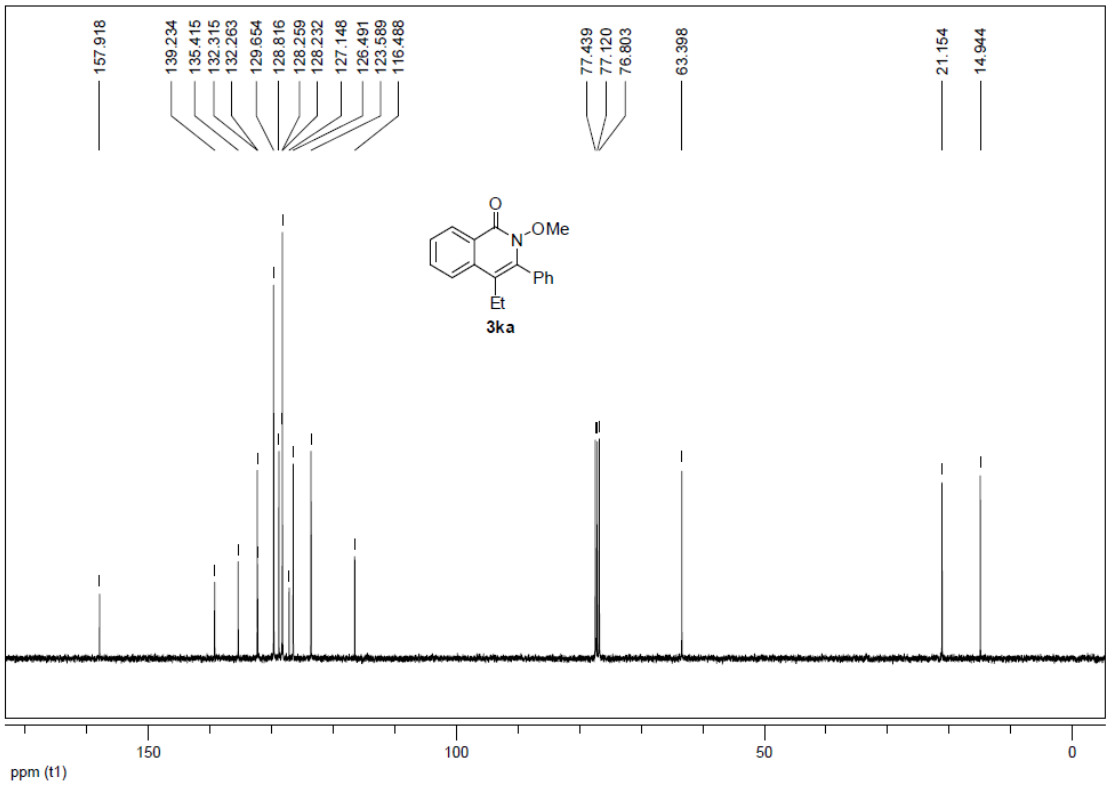
7.560
7.556
7.540
7.513
7.501
7.431
7.422
7.413
7.282
3.728
2.544
2.525
2.506
2.488
1.134
1.115
1.097
0.015
O
N
OMe
Ph
Et
3ka
1.00
2.12
2.09
4.23
3.17
2.11
3.18
5.0
0.0
ppm (t1)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128.259
128.232
127.148
126.491
123.589
116.488
77.439
77.120
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N
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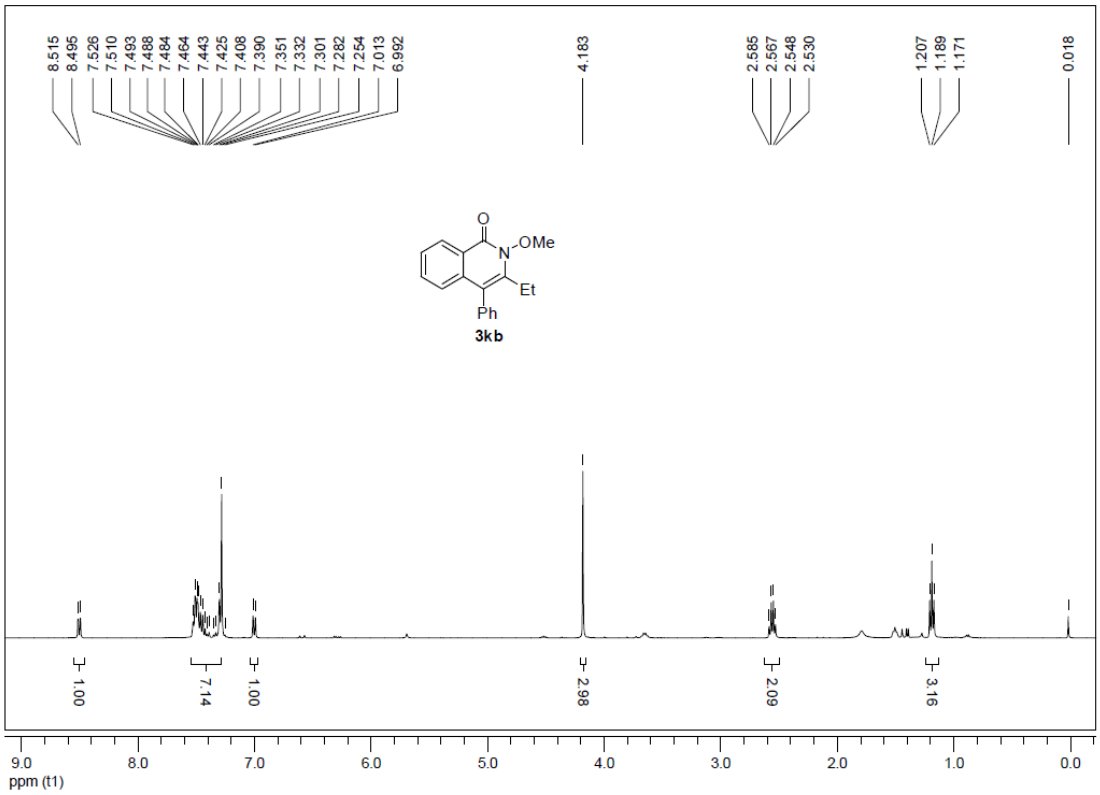
Ph
Et
3ka
150
100
50
0
ppm (t1)


8.515
8.495
7.526
7.510
7.493
7.488
7.484
7.464
7.443
7.425
7.408
7.390
7.351
7.332
7.301
7.282
7.254
7.013
6.992
4.183
2.585
2.567
2.548
2.530
1.207
1.189
1.171
0.018
OMe
Et
Ph
3kb
1.00
7.14
1.00
2.98
2.09
3.16
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8.0
7.0
6.0
5.0
4.0
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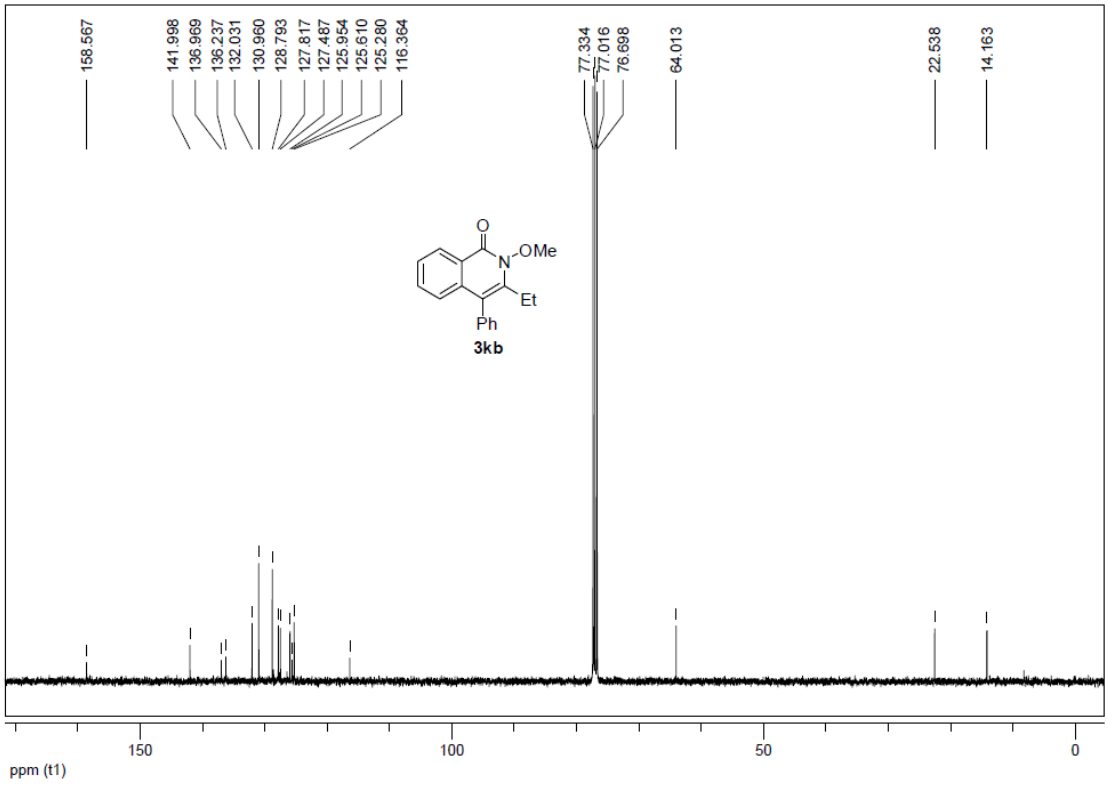
2.0
1.0
0.0
ppm (t1)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136.237
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130.960
128.793
127.817
127.487
125.954
125.610
125.280
116.364
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77.016
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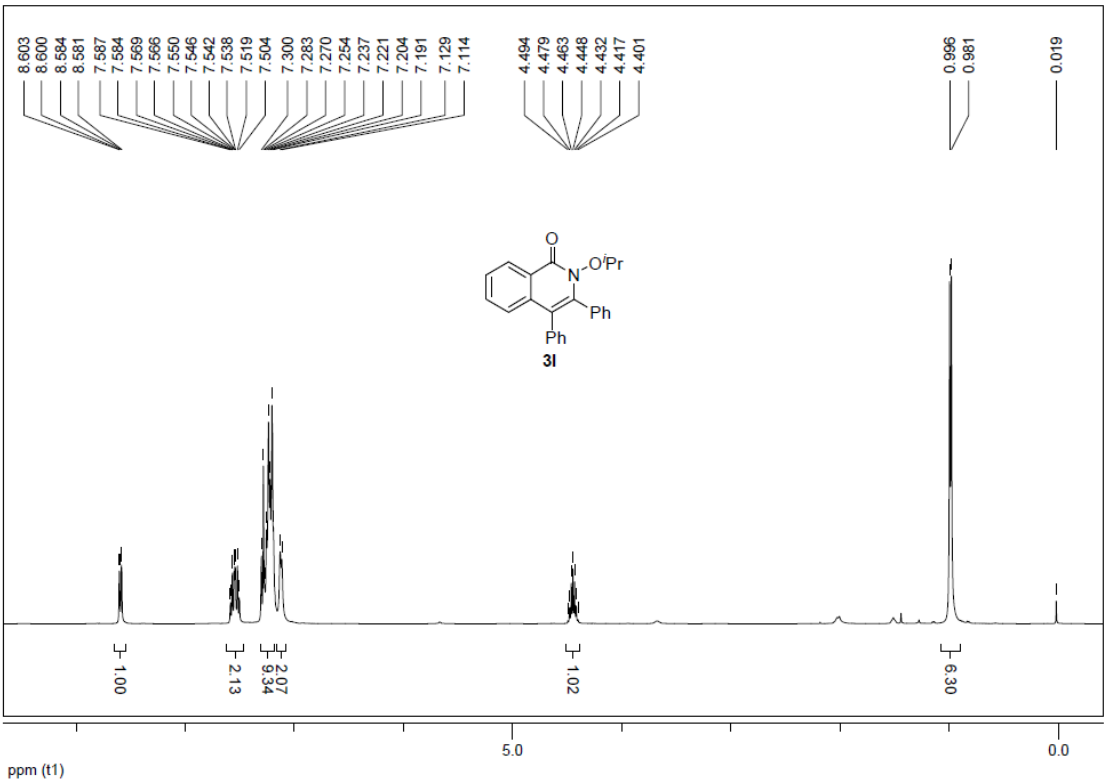
64.013
22.538
14.163
OMe
Et
Ph
3kb
150
100
50
0
ppm (t1)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8.581
7.587
7.584
7.569
7.566
7.550
7.546
7.542
7.538
7.519
7.504
7.300
7.283
7.270
7.254
7.237
7.221
7.204
7.191
7.129
7.114
4.494
4.479
4.463
4.448
4.432
4.417
4.401
0.996
0.981
0.019
O
N
O^{i}Pr
Ph
Ph
3l
1.00
2.13
9.34
2.07
1.02
6.30
5.0
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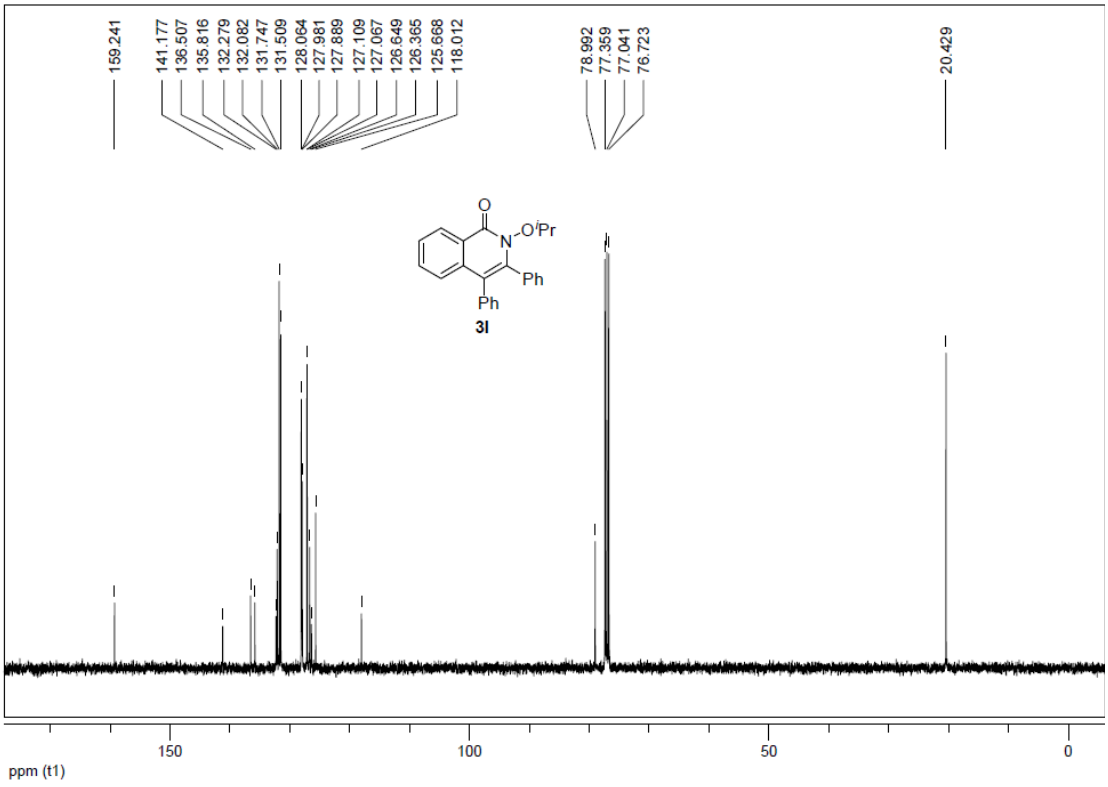
ppm (t1)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132.082
131.747
131.509
128.064
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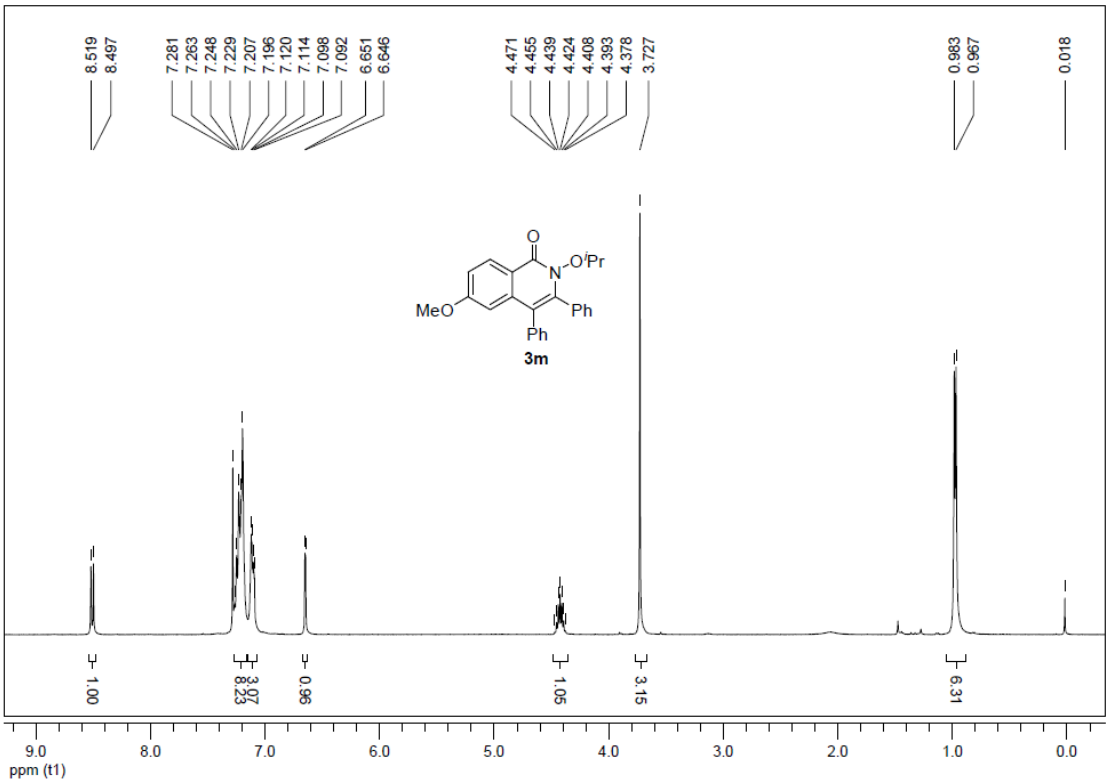
127.889
127.109
127.067
126.649
126.365
125.668
118.012
78.992
77.359
77.041
76.723
20.429
O
N
O^{i}Pr
Ph
Ph
3l
150
100
50
0
ppm (t1)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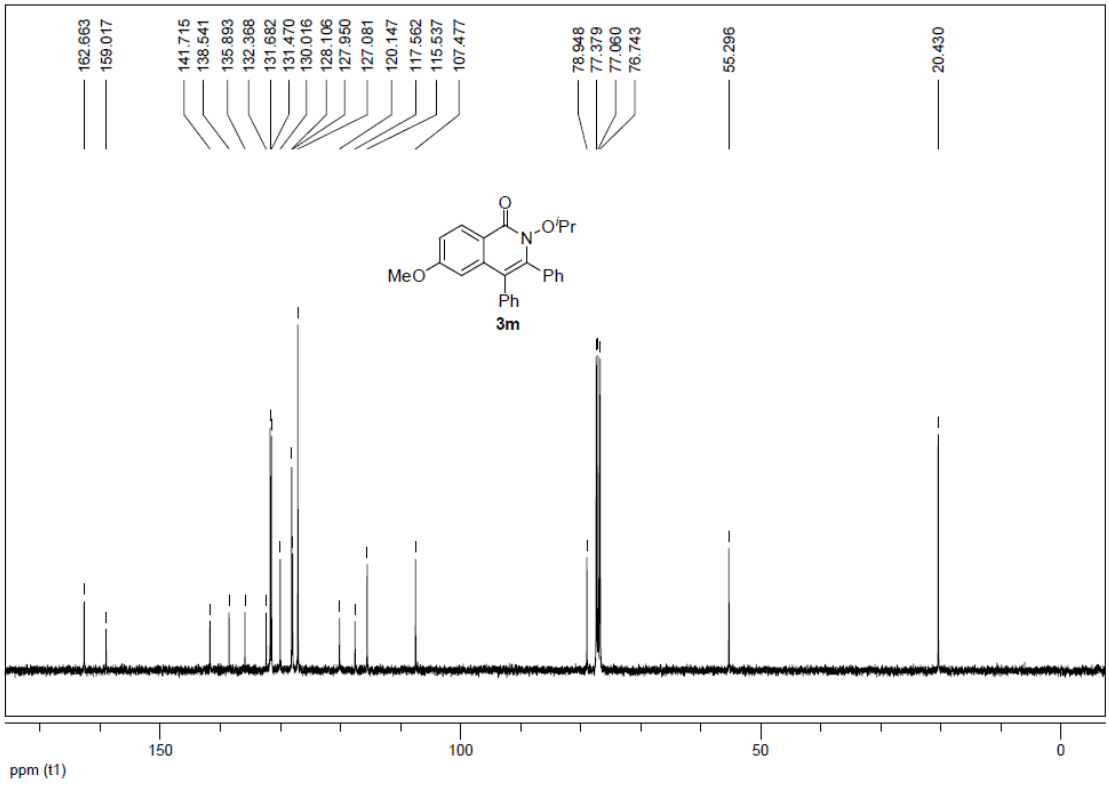
8.497
7.281
7.263
7.248
7.229
7.207
7.196
7.120
7.114
7.098
7.092
6.651
6.646
4.471
4.455
4.439
4.424
4.408
4.393
4.378
3.727
0.983
0.967
0.018
O
N
O^{i}Pr
MeO
Ph
Ph
3m
1.00
3.23
0.96
1.05
3.15
6.31
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)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141.715
138.541
135.893
132.368
131.682
131.470
130.016
128.106
127.950
127.081
120.147
117.562
115.537
107.477
78.948
77.379
77.060
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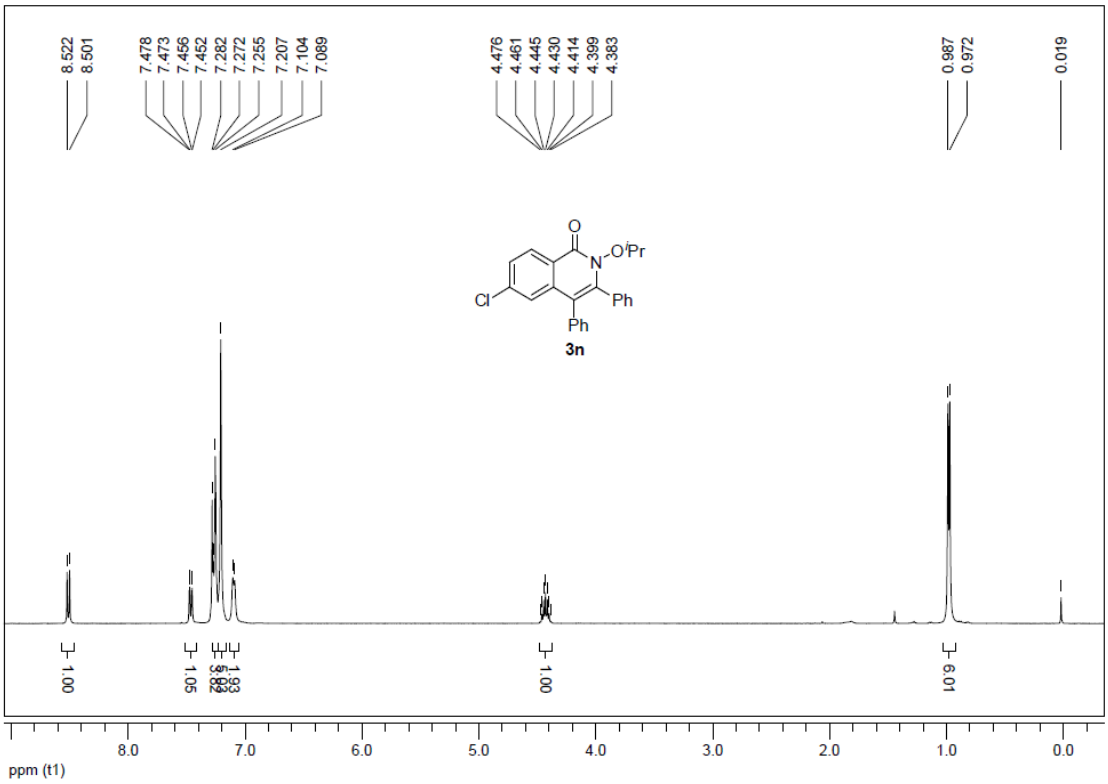
55.296
20.430
O
N
O^{i}Pr
MeO
Ph
Ph
3m
150
100
50
0
ppm (t1)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7.452
7.282
7.272
7.255
7.207
7.104
7.089
4.476
4.461
4.445
4.430
4.414
4.399
4.383
0.987
0.972
0.019
O
N
O^{i}Pr
Cl
Ph
Ph
3n
1.00
1.06
1.93
1.00
6.01
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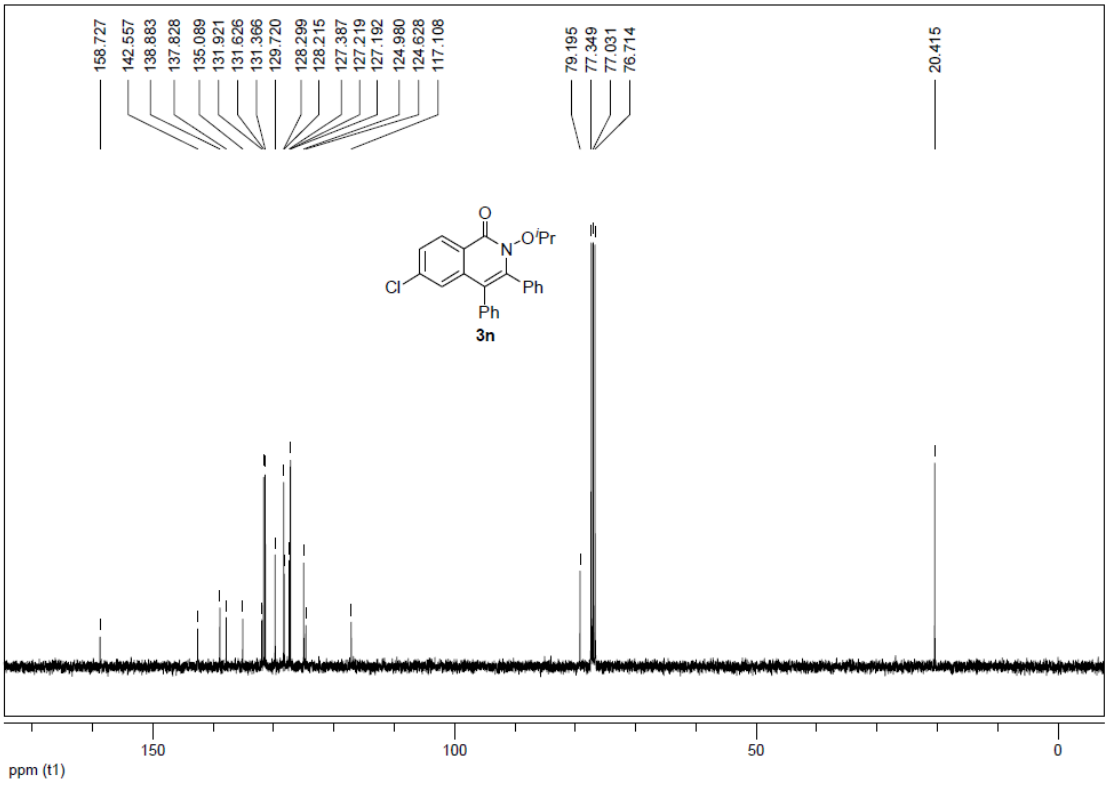
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)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131.366
129.720
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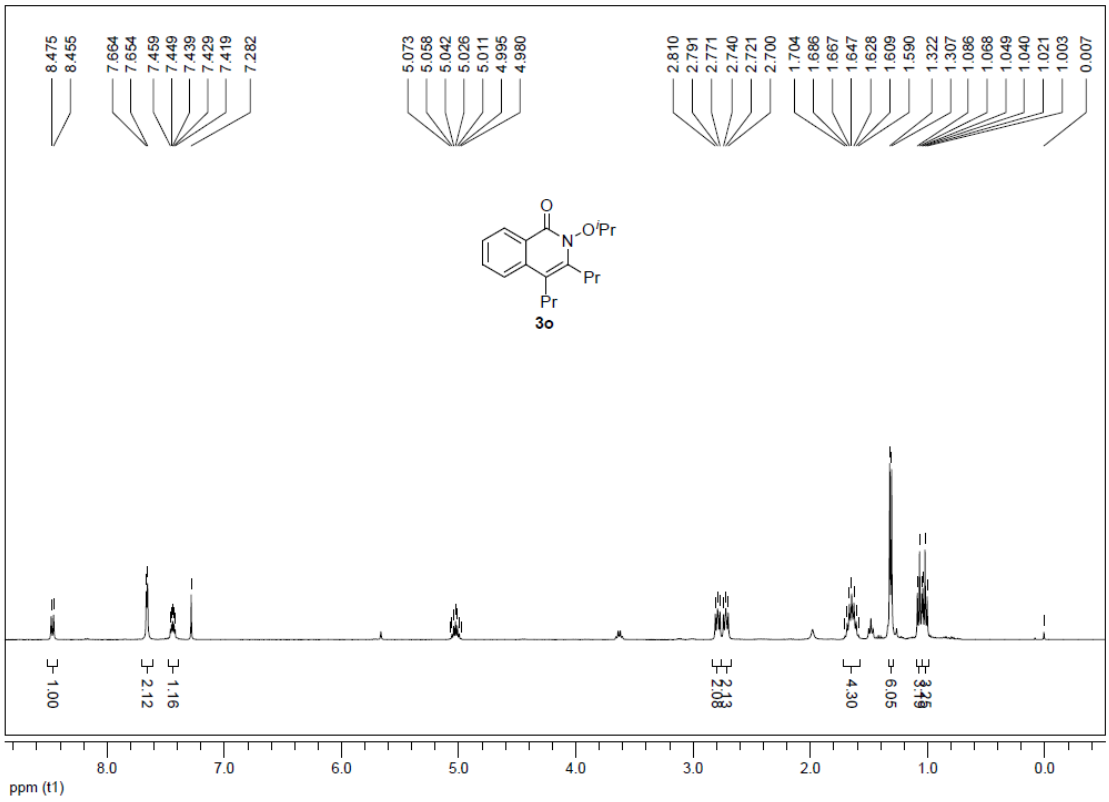
128.215
127.387
127.219
127.192
124.980
124.628
117.108
79.195
77.349
77.031
76.714
20.415
O
N
O^{i}Pr
Cl
Ph
Ph
3n
150
100
50
0
ppm (t1)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7.449
7.439
7.429
7.419
7.282
5.073
5.058
5.042
5.026
5.011
4.995
4.980
2.810
2.791
2.771
2.740
2.721
2.700
1.704
1.686
1.667
1.647
1.628
1.609
1.590
1.322
1.307
1.086
1.068
1.049
1.040
1.021
1.003
0.007
O
N
O^{i}Pr
Pr
Pr
3o
1.00
2.12
1.19
2.13
4.30
9.05
3.19
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7.0
6.0
5.0
4.0
3.0
2.0
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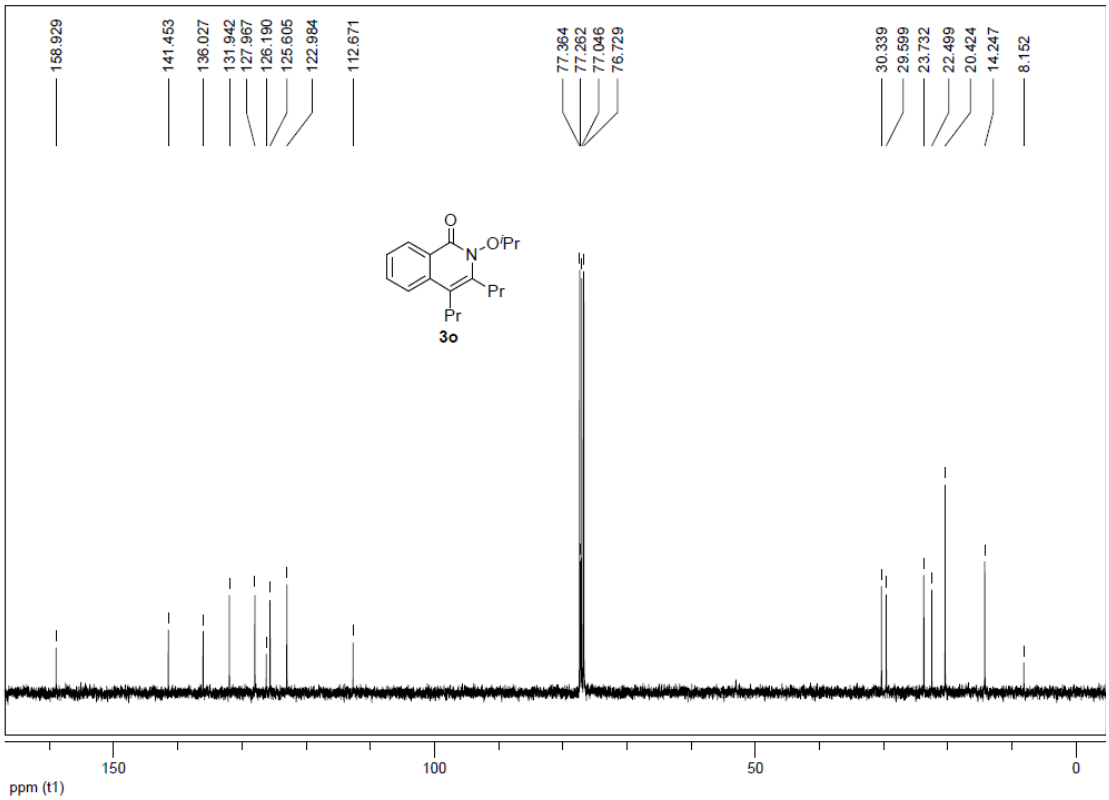
0.0
ppm (t1)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125.605
122.984
112.671
77.364
77.262
77.046
76.729
30.339
29.599
23.732
22.499
20.424
14.247
8.152
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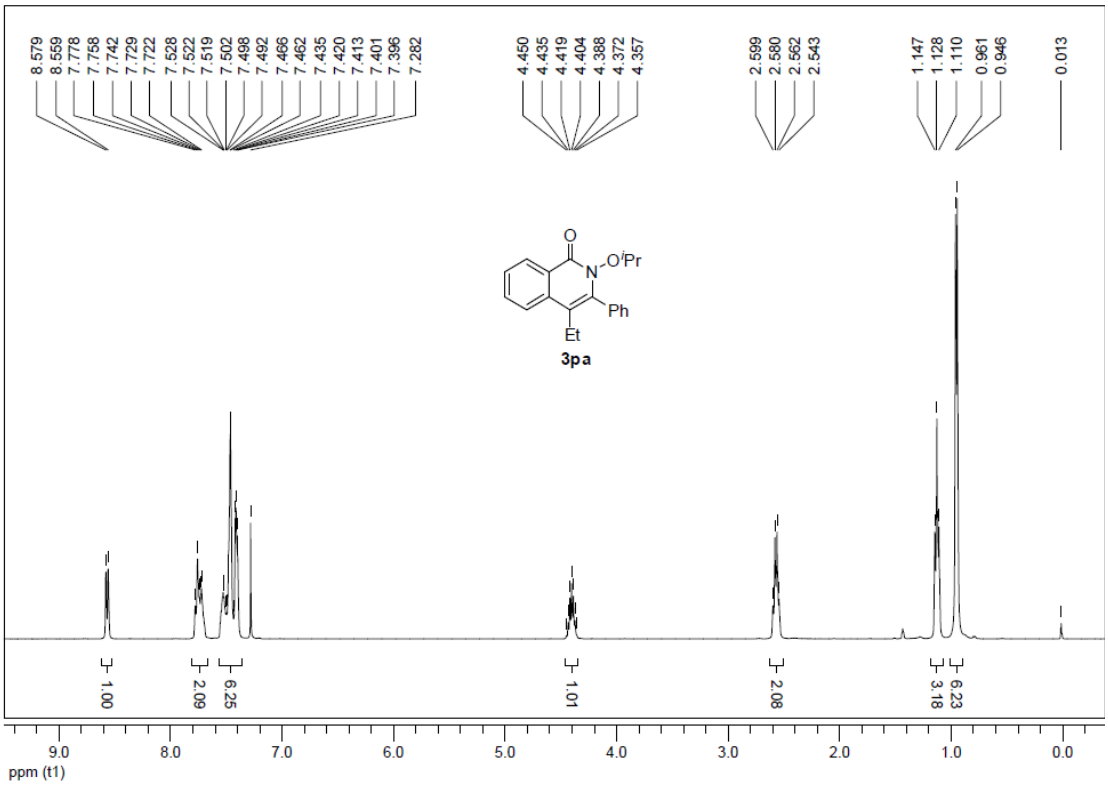
N
O^{i}Pr
Pr
Pr
3o
150
100
50
0
ppm (t1)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7.778
7.758
7.742
7.729
7.722
7.528
7.522
7.519
7.502
7.498
7.492
7.466
7.462
7.435
7.420
7.413
7.401
7.396
7.282
4.450
4.435
4.419
4.404
4.388
4.372
4.357
2.599
2.580
2.562
2.543
1.147
1.128
1.110
0.961
0.946
0.013
O
N
O^{i}Pr
Ph
Et
3pa
1.00
2.09
6.25
1.01
2.08
3.18
6.23
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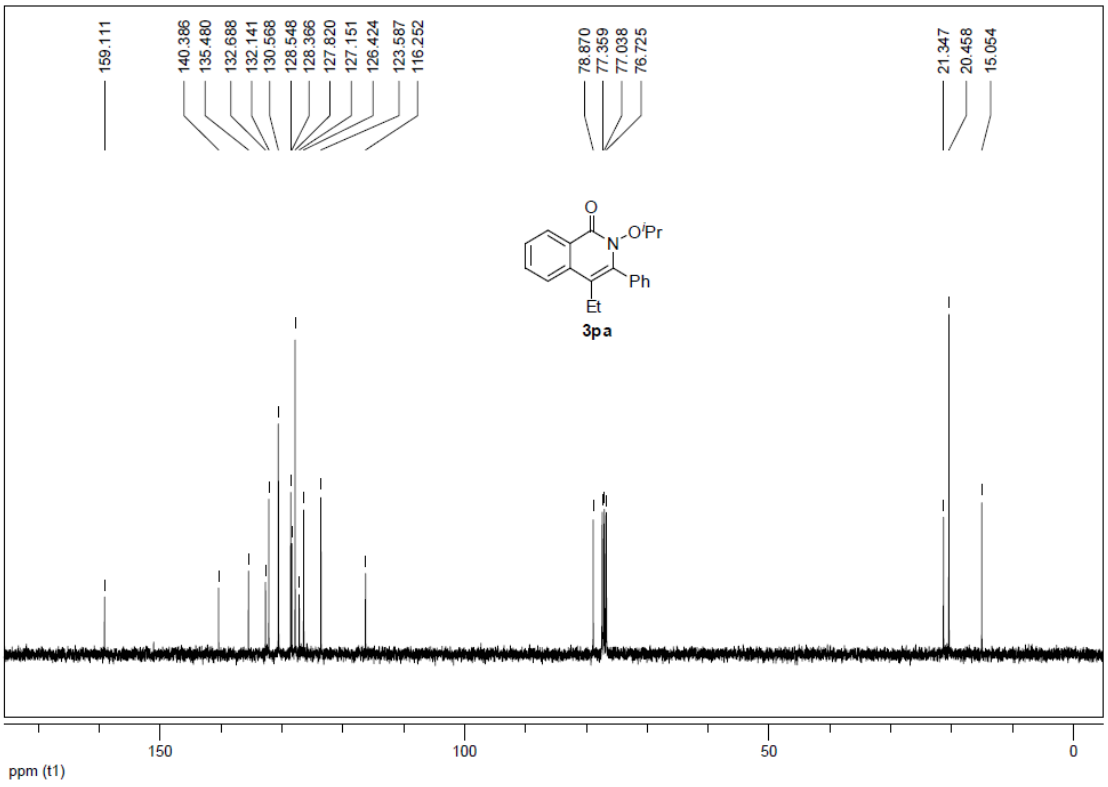
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)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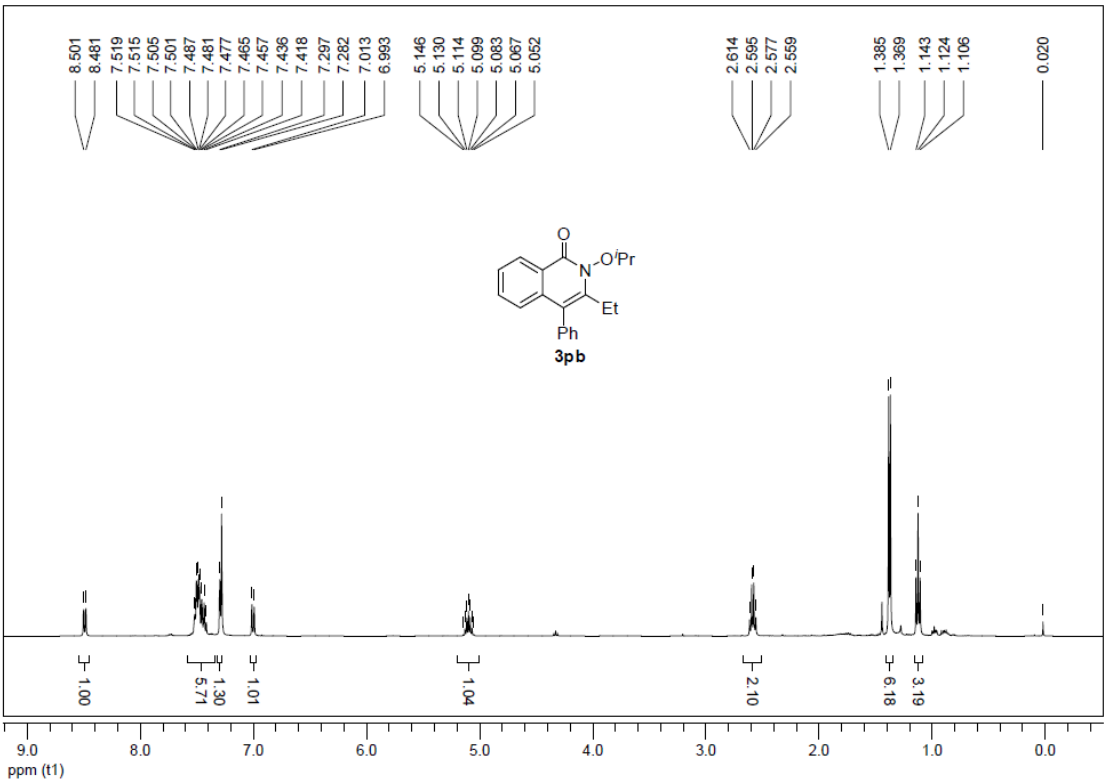
128.548
128.366
127.820
127.151
126.424
123.587
116.252
78.870
77.359
77.038
76.725
21.347
20.458
15.054
O
N
O^{i}Pr
Ph
Et
3pa
150
100
50
0
ppm (t1)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7.515
7.505
7.501
7.487
7.481
7.477
7.465
7.457
7.436
7.418
7.297
7.282
7.013
6.993
5.146
5.130
5.114
5.099
5.083
5.067
5.052
2.614
2.595
2.577
2.559
1.385
1.369
1.143
1.124
1.106
0.020
O
N
O^{i}Pr
Et
Ph
3pb
1.00
5.71
1.30
1.01
1.04
2.10
6.18
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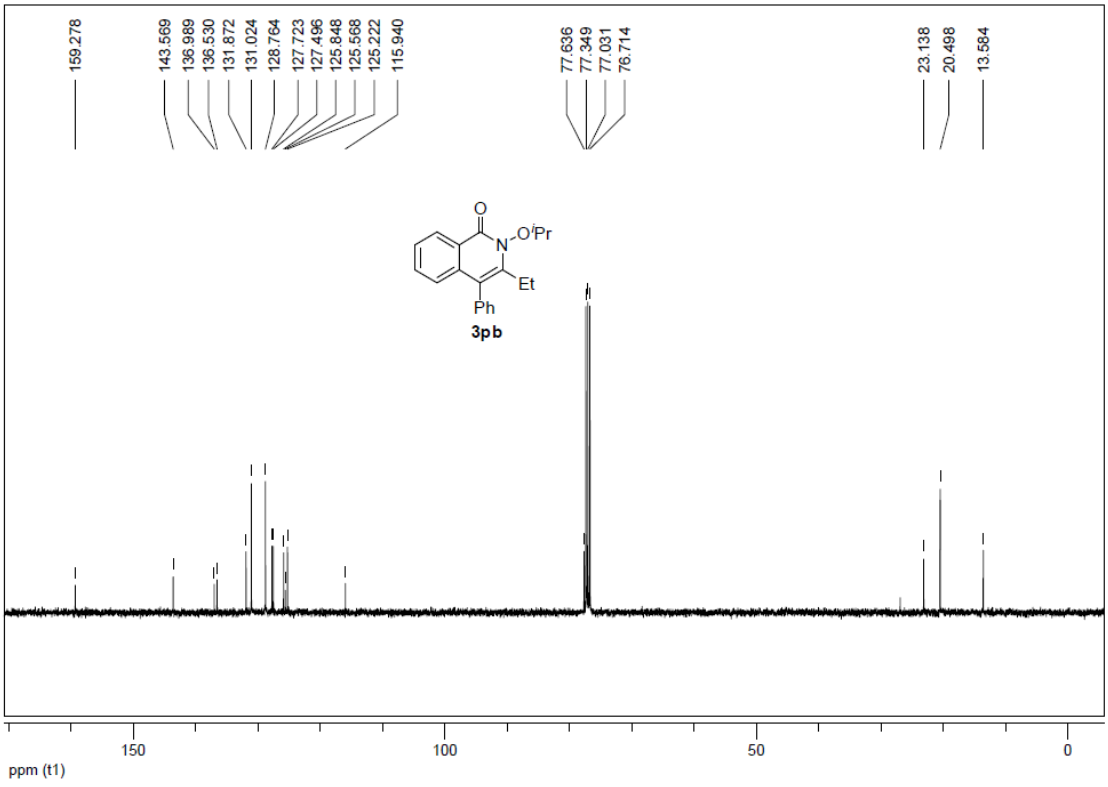
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)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128.764
127.723
127.496
125.848
125.568
125.222
115.940
77.636
77.349
77.031
76.714
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13.584
O
N
O^{i}Pr
Et
Ph
3pb
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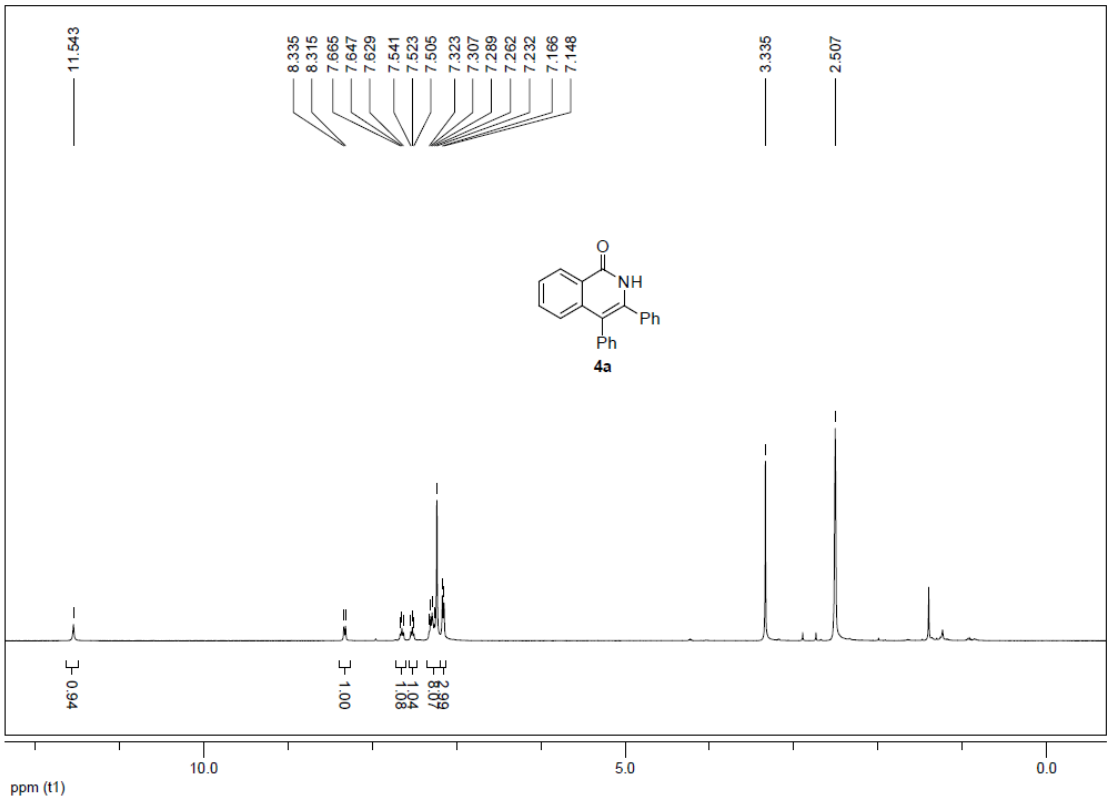
100
50
0
ppm (t1)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7.665
7.647
7.629
7.541
7.523
7.505
7.323
7.307
7.289
7.262
7.232
7.166
7.148
3.335
2.507
O
NH
Ph
Ph
4a
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1.04
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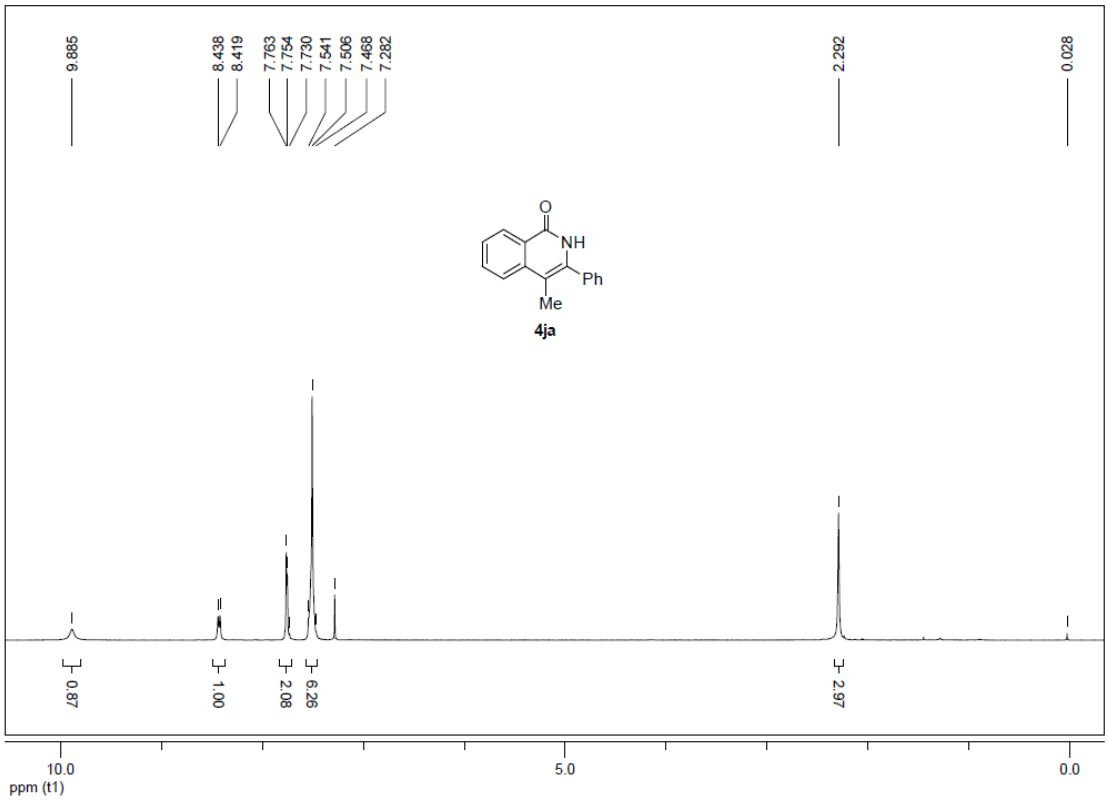
ppm (t1)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7.754
7.730
7.541
7.506
7.468
7.282
2.292
0.028
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NH
Ph
Me
4ja
0.87
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9.26
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5.0
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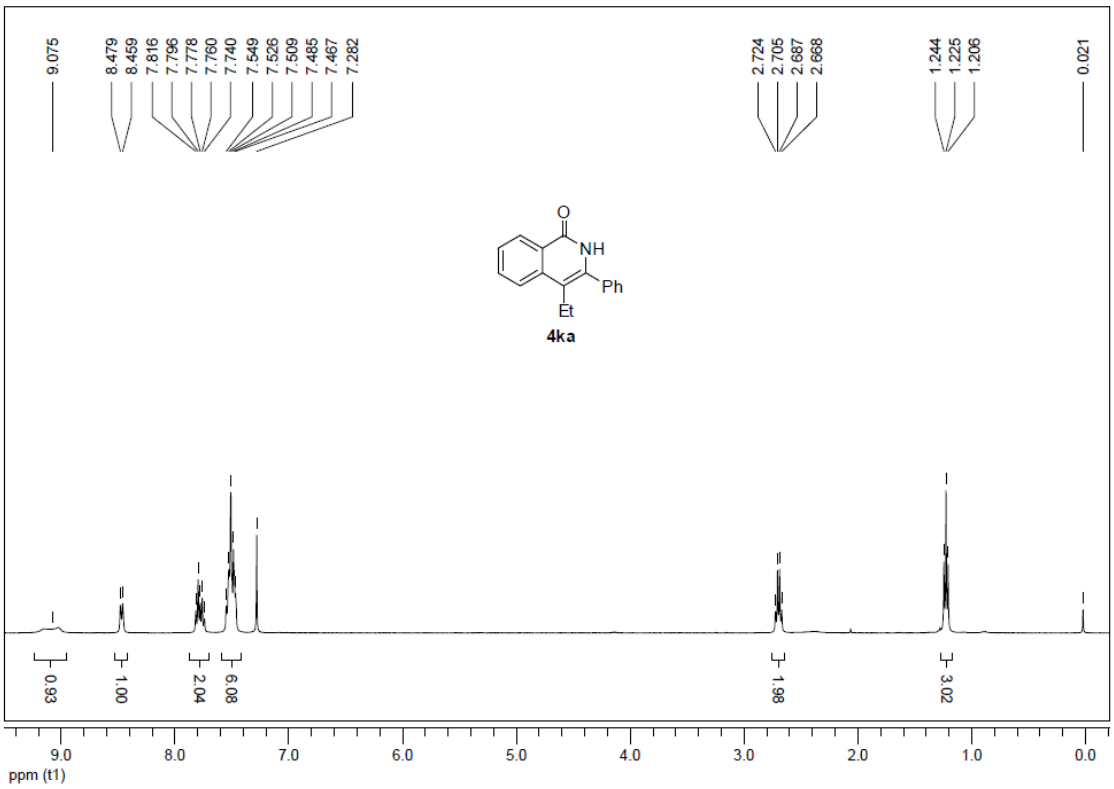
ppm (t1)


9.075
8.479
8.459
7.816
7.796
7.778
7.760
7.740
7.549
7.526
7.509
7.485
7.467
7.282
2.724
2.705
2.687
2.668
1.244
1.225
1.206
0.021
O
NH
Ph
Et
4ka
0.93
1.00
2.04
6.08
1.98
3.02
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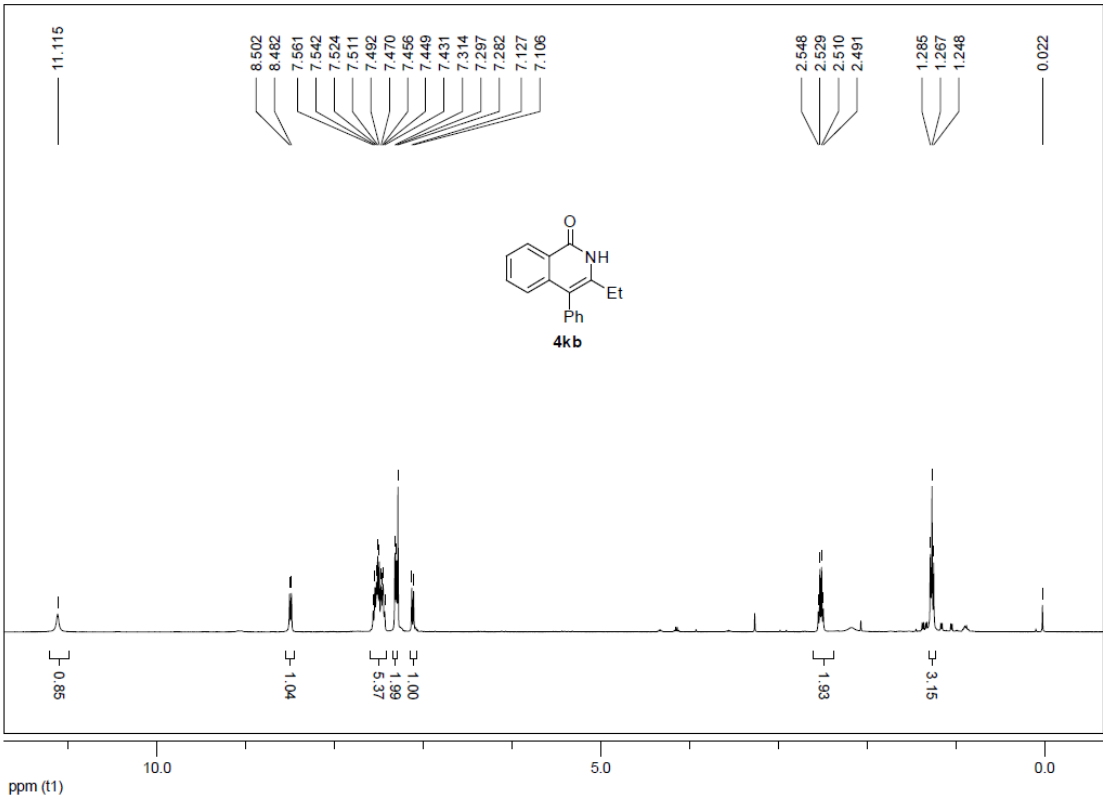
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)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7.524
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7.492
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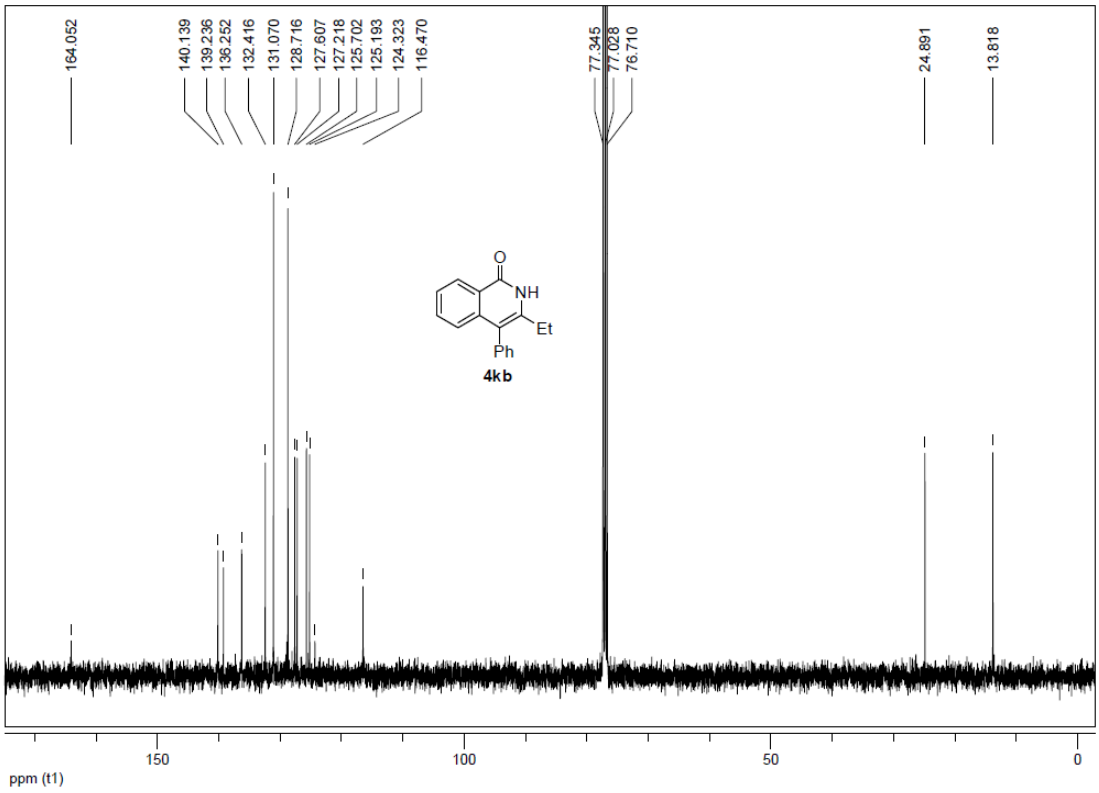
7.456
7.449
7.431
7.314
7.297
7.282
7.127
7.106
2.548
2.529
2.510
2.491
1.285
1.267
1.248
0.022
O
NH
Et
Ph
4kb
0.85
1.04
5.37
1.69
1.00
1.93
3.15
10.0
5.0
0.0
ppm (t1)


164.052
140.139
139.236
136.252
132.416
131.070
128.716
127.607
127.218
125.702
125.193
124.323
116.470
77.345
77.028
76.710
24.891
13.818
O
NH
Et
Ph
4kb
150
100
50
0
ppm (t1)

X-ray structure and data of 3a

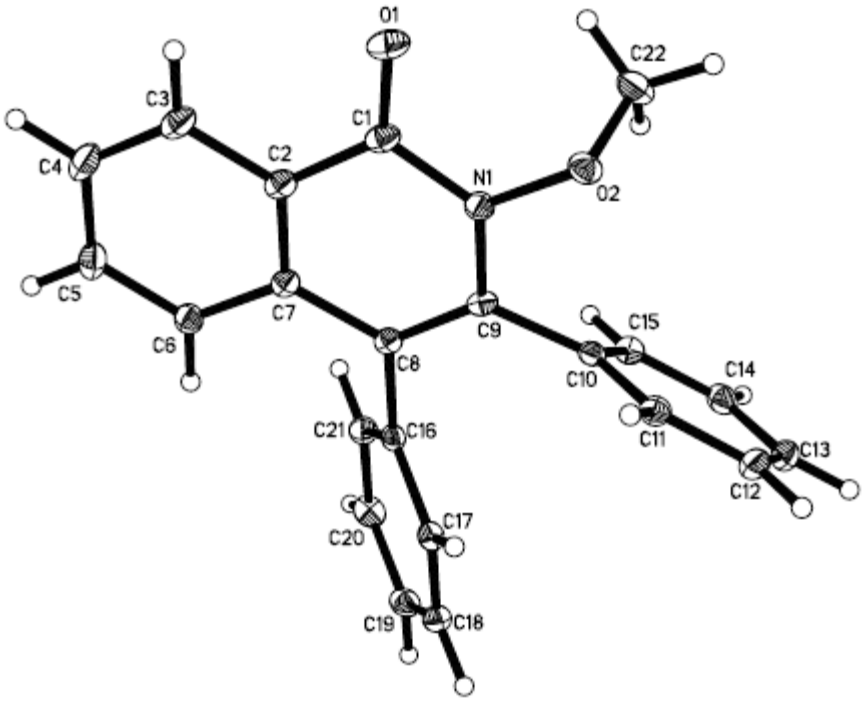


Table 1. Crystal data and structure refinement for **3a**.

Identification code	**3a**
Empirical formula	C22 H17 N O2
Formula weight	327.37
Temperature	113(2) K
Wavelength	0.71073 A
Crystal system, space group	Monoclinic, P2(1)/c
Unit cell dimensions	a = 9.274(4) A alpha = 90 deg.
	b = 19.946(7) A beta = 113.473(5) deg.
	c = 9.644(3) A gamma = 90 deg.
Volume	1636.3(10) A^3
Z, Calculated density	4, 1.329 Mg/m^3
Absorption coefficient	0.085 mm^-1
F(000)	688
Crystal size	0.20 x 0.18 x 0.14 mm
Theta range for data collection	2.04 to 27.88 deg.
Limiting indices	-12<=h<=12, -26<=k<=26, -12<=l<=12
Reflections collected / unique	17061 / 3883 [R(int) = 0.0523]

Completeness to theta = 27.88	99.3 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9882 and 0.9832
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3883 / 0 / 227
Goodness-of-fit on F^2	1.017
Final R indices [I>2sigma(I)]	R1 = 0.0436, wR2 = 0.0805
R indices (all data)	R1 = 0.0708, wR2 = 0.0896
Largest diff. peak and hole	0.190 and -0.227 e.A^-3

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for **3a**.
U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
O(1)	3482(1)	5877(1)	1540(1)	32(1)
O(2)	4625(1)	7099(1)	1593(1)	25(1)
N(1)	3106(1)	7008(1)	1521(1)	20(1)
C(1)	2604(2)	6348(1)	1482(2)	23(1)
C(2)	991(2)	6291(1)	1379(1)	22(1)
C(3)	376(2)	5646(1)	1338(2)	28(1)
C(4)	-1137(2)	5558(1)	1222(2)	32(1)
C(5)	-2087(2)	6117(1)	1109(2)	29(1)
C(6)	-1502(2)	6756(1)	1139(1)	24(1)
C(7)	63(2)	6862(1)	1305(1)	19(1)
C(8)	733(2)	7526(1)	1376(1)	18(1)
C(9)	2238(2)	7586(1)	1497(1)	18(1)
C(10)	3060(2)	8239(1)	1647(1)	19(1)
C(11)	3464(2)	8482(1)	500(2)	22(1)
C(12)	4131(2)	9112(1)	619(2)	28(1)
C(13)	4424(2)	9502(1)	1893(2)	29(1)
C(14)	4039(2)	9261(1)	3047(2)	27(1)
C(15)	3356(2)	8633(1)	2926(2)	23(1)
C(16)	-209(2)	8144(1)	1297(1)	19(1)
C(17)	-449(2)	8623(1)	171(2)	21(1)
C(18)	-1287(2)	9202(1)	120(2)	25(1)
C(19)	-1922(2)	9306(1)	1180(2)	27(1)
C(20)	-1710(2)	8835(1)	2299(2)	28(1)
C(21)	-853(2)	8258(1)	2357(2)	23(1)
C(22)	5739(2)	7079(1)	3151(2)	33(1)

Table 3. Bond lengths [A] and angles [deg] for **3a**.

O(1)-C(1)	1.2294(16)
O(2)-N(1)	1.3946(14)
O(2)-C(22)	1.4460(16)
N(1)-C(1)	1.3915(17)
N(1)-C(9)	1.4012(16)
C(1)-C(2)	1.464(2)
C(2)-C(3)	1.4014(19)
C(2)-C(7)	1.4104(18)
C(3)-C(4)	1.373(2)
C(3)-H(3)	0.9500
C(4)-C(5)	1.397(2)
C(4)-H(4)	0.9500
C(5)-C(6)	1.3808(19)
C(5)-H(5)	0.9500
C(6)-C(7)	1.4114(19)
C(6)-H(6)	0.9500
C(7)-C(8)	1.4533(18)
C(8)-C(9)	1.3585(19)
C(8)-C(16)	1.4946(18)
C(9)-C(10)	1.4874(18)
C(10)-C(11)	1.3887(19)
C(10)-C(15)	1.3938(19)
C(11)-C(12)	1.3857(18)
C(11)-H(11)	0.9500
C(12)-C(13)	1.386(2)
C(12)-H(12)	0.9500
C(13)-C(14)	1.382(2)
C(13)-H(13)	0.9500
C(14)-C(15)	1.3879(19)
C(14)-H(14)	0.9500
C(15)-H(15)	0.9500
C(16)-C(21)	1.3934(19)

C(16)-C(17)	1.3959(18)
C(17)-C(18)	1.3827(18)
C(17)-H(17)	0.9500
C(18)-C(19)	1.384(2)
C(18)-H(18)	0.9500
C(19)-C(20)	1.385(2)
C(19)-H(19)	0.9500
C(20)-C(21)	1.3866(18)
C(20)-H(20)	0.9500
C(21)-H(21)	0.9500
C(22)-H(22A)	0.9800
C(22)-H(22B)	0.9800
C(22)-H(22C)	0.9800

N(1)-O(2)-C(22)	109.70(10)
C(1)-N(1)-O(2)	116.44(11)
C(1)-N(1)-C(9)	126.49(12)
O(2)-N(1)-C(9)	117.07(11)
O(1)-C(1)-N(1)	120.89(14)
O(1)-C(1)-C(2)	125.76(13)
N(1)-C(1)-C(2)	113.35(12)
C(3)-C(2)-C(7)	120.41(14)
C(3)-C(2)-C(1)	117.78(13)
C(7)-C(2)-C(1)	121.81(13)
C(4)-C(3)-C(2)	120.68(14)
C(4)-C(3)-H(3)	119.7
C(2)-C(3)-H(3)	119.7
C(3)-C(4)-C(5)	119.80(14)
C(3)-C(4)-H(4)	120.1
C(5)-C(4)-H(4)	120.1
C(6)-C(5)-C(4)	120.22(15)
C(6)-C(5)-H(5)	119.9
C(4)-C(5)-H(5)	119.9
C(5)-C(6)-C(7)	121.24(14)
C(5)-C(6)-H(6)	119.4

C(7)-C(6)-H(6)	119.4
C(2)-C(7)-C(6)	117.61(13)
C(2)-C(7)-C(8)	119.51(13)
C(6)-C(7)-C(8)	122.88(12)
C(9)-C(8)-C(7)	119.32(12)
C(9)-C(8)-C(16)	119.40(12)
C(7)-C(8)-C(16)	121.27(12)
C(8)-C(9)-N(1)	119.48(12)
C(8)-C(9)-C(10)	123.70(12)
N(1)-C(9)-C(10)	116.80(12)
C(11)-C(10)-C(15)	119.22(13)
C(11)-C(10)-C(9)	121.24(12)
C(15)-C(10)-C(9)	119.45(12)
C(12)-C(11)-C(10)	120.26(13)
C(12)-C(11)-H(11)	119.9
C(10)-C(11)-H(11)	119.9
C(11)-C(12)-C(13)	120.30(13)
C(11)-C(12)-H(12)	119.9
C(13)-C(12)-H(12)	119.9
C(14)-C(13)-C(12)	119.80(14)
C(14)-C(13)-H(13)	120.1
C(12)-C(13)-H(13)	120.1
C(13)-C(14)-C(15)	120.10(13)
C(13)-C(14)-H(14)	119.9
C(15)-C(14)-H(14)	119.9
C(14)-C(15)-C(10)	120.32(13)
C(14)-C(15)-H(15)	119.8
C(10)-C(15)-H(15)	119.8
C(21)-C(16)-C(17)	118.46(13)
C(21)-C(16)-C(8)	120.69(12)
C(17)-C(16)-C(8)	120.85(12)
C(18)-C(17)-C(16)	120.85(13)
C(18)-C(17)-H(17)	119.6
C(16)-C(17)-H(17)	119.6
C(17)-C(18)-C(19)	119.89(13)

C(17)-C(18)-H(18)	120.1
C(19)-C(18)-H(18)	120.1
C(18)-C(19)-C(20)	120.19(14)
C(18)-C(19)-H(19)	119.9
C(20)-C(19)-H(19)	119.9
C(19)-C(20)-C(21)	119.75(14)
C(19)-C(20)-H(20)	120.1
C(21)-C(20)-H(20)	120.1
C(20)-C(21)-C(16)	120.84(13)
C(20)-C(21)-H(21)	119.6
C(16)-C(21)-H(21)	119.6
O(2)-C(22)-H(22A)	109.5
O(2)-C(22)-H(22B)	109.5
H(22A)-C(22)-H(22B)	109.5
O(2)-C(22)-H(22C)	109.5
H(22A)-C(22)-H(22C)	109.5
H(22B)-C(22)-H(22C)	109.5

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters (A^2 x 10^3) for **3a**.

The anisotropic displacement factor exponent takes the form:

-2 pi^2 [h^2 a*^2 U11 + ... + 2 h k a* b* U12]

	U11	U22	U33	U23	U13	U12
O(1)	38(1)	21(1)	36(1)	3(1)	15(1)	10(1)
O(2)	21(1)	28(1)	28(1)	2(1)	12(1)	4(1)
N(1)	19(1)	19(1)	24(1)	0(1)	10(1)	2(1)
C(1)	31(1)	18(1)	17(1)	0(1)	7(1)	2(1)
C(2)	29(1)	20(1)	15(1)	0(1)	7(1)	-1(1)
C(3)	41(1)	18(1)	24(1)	0(1)	10(1)	-2(1)
C(4)	44(1)	22(1)	27(1)	0(1)	12(1)	-11(1)
C(5)	32(1)	31(1)	23(1)	-3(1)	10(1)	-11(1)
C(6)	24(1)	25(1)	19(1)	0(1)	6(1)	-3(1)
C(7)	25(1)	20(1)	12(1)	0(1)	6(1)	-2(1)
C(8)	22(1)	18(1)	13(1)	-1(1)	6(1)	0(1)
C(9)	24(1)	15(1)	14(1)	0(1)	7(1)	3(1)
C(10)	16(1)	19(1)	20(1)	1(1)	5(1)	3(1)
C(11)	22(1)	22(1)	23(1)	0(1)	9(1)	2(1)
C(12)	26(1)	26(1)	33(1)	8(1)	14(1)	1(1)
C(13)	24(1)	19(1)	42(1)	3(1)	11(1)	-1(1)
C(14)	23(1)	24(1)	28(1)	-6(1)	4(1)	0(1)
C(15)	23(1)	23(1)	21(1)	0(1)	8(1)	2(1)
C(16)	17(1)	18(1)	19(1)	-2(1)	5(1)	-2(1)
C(17)	18(1)	23(1)	20(1)	-2(1)	7(1)	-2(1)
C(18)	24(1)	21(1)	26(1)	2(1)	6(1)	1(1)
C(19)	25(1)	23(1)	29(1)	-3(1)	6(1)	4(1)
C(20)	27(1)	33(1)	26(1)	-6(1)	12(1)	4(1)
C(21)	24(1)	25(1)	20(1)	1(1)	9(1)	0(1)
C(22)	22(1)	41(1)	31(1)	4(1)	6(1)	5(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (A^2 x 10^3) for **3a**.

	x	y	z	U(eq)
H(3)	1012	5266	1392	34
H(4)	-1536	5119	1218	38
H(5)	-3139	6056	1012	35
H(6)	-2165	7131	1047	28
H(11)	3283	8215	-369	27
H(12)	4390	9279	-177	33
H(13)	4886	9933	1974	35
H(14)	4243	9526	3923	32
H(15)	3090	8470	3719	27
H(17)	-31	8549	-569	25
H(18)	-1427	9528	-641	30
H(19)	-2506	9703	1140	33
H(20)	-2150	8906	3024	34
H(21)	-704	7937	3129	28
H(22A)	5453	7416	3736	49
H(22B)	6796	7173	3202	49
H(22C)	5723	6633	3571	49

Table 6. Torsion angles [deg] for **3a**.

C(22)-O(2)-N(1)-C(1)	-86.20(13)
C(22)-O(2)-N(1)-C(9)	93.80(13)
O(2)-N(1)-C(1)-O(1)	1.48(18)
C(9)-N(1)-C(1)-O(1)	-178.51(11)
O(2)-N(1)-C(1)-C(2)	-178.93(10)
C(9)-N(1)-C(1)-C(2)	1.08(18)
O(1)-C(1)-C(2)-C(3)	-0.2(2)
N(1)-C(1)-C(2)-C(3)	-179.76(11)
O(1)-C(1)-C(2)-C(7)	-179.44(12)
N(1)-C(1)-C(2)-C(7)	1.00(18)
C(7)-C(2)-C(3)-C(4)	0.2(2)
C(1)-C(2)-C(3)-C(4)	-179.09(13)
C(2)-C(3)-C(4)-C(5)	1.4(2)
C(3)-C(4)-C(5)-C(6)	-1.0(2)
C(4)-C(5)-C(6)-C(7)	-0.9(2)
C(3)-C(2)-C(7)-C(6)	-2.04(18)
C(1)-C(2)-C(7)-C(6)	177.18(11)
C(3)-C(2)-C(7)-C(8)	178.91(11)
C(1)-C(2)-C(7)-C(8)	-1.87(19)
C(5)-C(6)-C(7)-C(2)	2.43(19)
C(5)-C(6)-C(7)-C(8)	-178.55(12)
C(2)-C(7)-C(8)-C(9)	0.71(18)
C(6)-C(7)-C(8)-C(9)	-178.29(12)
C(2)-C(7)-C(8)-C(16)	179.83(11)
C(6)-C(7)-C(8)-C(16)	0.83(19)
C(7)-C(8)-C(9)-N(1)	1.22(18)
C(16)-C(8)-C(9)-N(1)	-177.91(11)
C(7)-C(8)-C(9)-C(10)	-177.20(11)
C(16)-C(8)-C(9)-C(10)	3.67(19)
C(1)-N(1)-C(9)-C(8)	-2.24(19)
O(2)-N(1)-C(9)-C(8)	177.77(11)
C(1)-N(1)-C(9)-C(10)	176.29(11)
O(2)-N(1)-C(9)-C(10)	-3.71(16)

C(8)-C(9)-C(10)-C(11)	-112.21(16)
N(1)-C(9)-C(10)-C(11)	69.33(16)
C(8)-C(9)-C(10)-C(15)	64.38(17)
N(1)-C(9)-C(10)-C(15)	-114.08(14)
C(15)-C(10)-C(11)-C(12)	-1.1(2)
C(9)-C(10)-C(11)-C(12)	175.54(12)
C(10)-C(11)-C(12)-C(13)	1.0(2)
C(11)-C(12)-C(13)-C(14)	-0.4(2)
C(12)-C(13)-C(14)-C(15)	-0.3(2)
C(13)-C(14)-C(15)-C(10)	0.3(2)
C(11)-C(10)-C(15)-C(14)	0.4(2)
C(9)-C(10)-C(15)-C(14)	-176.26(12)
C(9)-C(8)-C(16)-C(21)	-122.12(14)
C(7)-C(8)-C(16)-C(21)	58.76(17)
C(9)-C(8)-C(16)-C(17)	57.18(17)
C(7)-C(8)-C(16)-C(17)	-121.93(14)
C(21)-C(16)-C(17)-C(18)	0.93(19)
C(8)-C(16)-C(17)-C(18)	-178.39(12)
C(16)-C(17)-C(18)-C(19)	-1.1(2)
C(17)-C(18)-C(19)-C(20)	0.5(2)
C(18)-C(19)-C(20)-C(21)	0.2(2)
C(19)-C(20)-C(21)-C(16)	-0.4(2)
C(17)-C(16)-C(21)-C(20)	-0.2(2)
C(8)-C(16)-C(21)-C(20)	179.13(12)

Symmetry transformations used to generate equivalent atoms:

Table 7. Hydrogen bonds for **3a** [A and deg.].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)