Highly solvatochromic and tunable fluorophores based on a 4,5-quinolimide scaffold: Novel CDK5 probes

Juan A. González-Vera,[ab] Francisco Fueyo-González,[a] Ibon Alkorta,[a] Marion Peyressatre,[b] May C. Morris,[b] and Rosario Herranz*[a]

[a]*Instituto de Química Médica (CSIC), Juan de la Cierva 3, 28006 Madrid, Spain.*
[b]*Institut des Biomolécules Max Mousseron, IBMM- UMR 5247, 15 Av. Charles Flahault, 34093 Montpellier, France.*

Supplementary Information

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General Methods: All reagents were of commercial quality. Solvents were dried and purified by standard methods. Analytical TLC was performed on aluminum sheets coated with a 0.2 mm layer of silica gel 60 F_{254}. Silica gel 60 (230-400 mesh) was used for flash chromatography. HPLC-MS was performed on a Sunfire C_{18} (4.6×50 mm, 3.5 μm) column at 30°C, with a flow rate of 1 mL/min and gradient of 0.1% of formic acid in CH_3CN (solvent A) in 0.1% of formic acid in H_2O (solvent B) was used as mobile phase. Electrospray in positive mode was used for ionization. Optical rotations were determined in a Perkin Elmer 141 polarimeter. NMR spectra were recorded using Varian Inova or Mercury 400, and Varian Unity 500 spectrometers. The NMR spectra assignments were based on COSY, HSQC, and HMBC spectra. High resolution mass spectra (HRMS) were recorded on an Agilent 6520 Q-TOF instrument with an ESI source. MW experiments were carried out in sealed vessels in a MW Emrys^{TM} Synthesizer (Biotage AB), with transversal IR sensor for reaction temperature monitoring. UV-visible spectroscopy measurements were made at 25 Cº on a Lambda 35, Perkin Elmer, UV-vis spectrophotometer; Starna Cells (16.100-Q-10) 100 μL sub-micro cuvette, 1 cm path length. Fluorescence spectroscopy measurements were made at 25 Cº on a PerkinElmer LS 50B luminescence spectrometer; Starna Cells (16.100F-Q-10) 100 μL sub-micro cuvette, 1 cm path length.

Synthesis of 7-amino-6-methoxy-2,3-dihydro-1*H*-inden-1-one[1] (1). Iron (10.8 g, 193 mmol) was added to a solution of 6-methoxy-7-nitro-2,3-dihydro-1*H*-inden-1-one (10 g, 48.3 mmol) in acetic acid (150 mL), and this mixture was stirred at 70 ºC for 2 h. The cooled reaction mixture was filtered and the filtrate was concentrated under vacuum. The residue was dissolved in EtOAc (300 mL), and the resulting solution was successively washed with H_2O (100 mL) and brine (100 mL), dried over Na_2SO_4, and evaporated to dryness, to give **1** (8.8 g,100 %) as a brown solid. Mp 64 ºC. This compound was used in the next step without further purification. HPLC-MS (30-95% gradient of A in B for 10 min) t_R = 3.08 min. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 2.59 (m, 2H, 2-H), 2.91 (m, 2H, 3-H), 3.71 (s, 3H, OCH_3), 5.55 (brs, 2H, NH_2), 6.51 (dq, 1H, J = 8 and 1.0 Hz, 4-H), 6.84 (dd, 1H, J = 8 and 1.0 Hz, 5-H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 24.9 (C_3), 37.2 (C_2), 56.2 (OCH_3), 112.0 (C_4), 116.3 (C_5), 120.4 (C_{7a}), 137.5 (C_7), 144.6 (C_6), 146.7 (C_{3a}), 208.1 (C_1). HRMS (ESI) m/z: Calcd. for $C_{10}H_{11}NO_2$ ($[M+H]^+$): 178.0790, found: 178.0788.

Synthesis of diethyl (2-((5-methoxy-3-oxo-2,3-dihydro-1*H*-inden-4-yl)amino)-2-oxoethyl)phosphonate[1] (2). HATU (22.7 g, 59.6 mmol) and DIPEA (21.6 mL, 124 mmol) were added to a solution of **1** (8.8 g, 49.7 mmol) and diethylphosphonoacetic acid (8.8 mL, 54.6 mmol) in dry dichloromethane (300 mL) and the reaction was stirred at room temperature for 3 h. After that time, the transformation was incomplete, therefore, more diethylphosphonoacetic acid (4.0 mL, 24.9 mmol), HATU (9.4 g, 29.4 mmol) and DIPEA (4.3 mL, 29.4 mmol) were added. The mixture was stirred for another 2 h. Then, the reaction mixture was diluted with dichloromethane (300 mL), washed with aqueous 0.2 N HCl (100 mL), aqueous 0.2 N NaOH (100 mL), water (100 mL) and brine (100 mL). The organic phase was dried over Na_2SO_4, filtered and evaporated. The residue was purified by flash chromatography, using 0-20% gradient of MeOH in CH_2Cl_2 as eluent, to give the desired product **2** (16.0 g, 76 % yield) as a pale yellow solid (m.p. 113 ºC). HPLC-MS (30-95% gradient of A in B for 10 min) t_R = 1.30 min. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.29 [t, 6H, J = 7 Hz, CH_3(OEt)], 2.60 (m, 2H, 2-H), 2.95 (m, 2H, 3-H), 3.03 [d, 2H, J = 21 Hz, CH_2P(OEt)$_2$], 3.80 (s, 3H, OCH_3), 4.16 [m, 4H, CH_2(OEt)], 7.12 (d, 1H, J = 8.5 Hz, 5-H), 7.18 (d, 1H, J = 8.5 Hz, 4-H), 8.75 (br s, 1H, NH). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 16.0 and 16.1 [CH_3(OEt)], 24.1 (C_3), 35.3 [d, J = 131 Hz, CH_2P(OEt)$_2$], 37.0 (C_2), 56.2 (OCH_3), 62.3 and 62.4 [CH_2(OEt)], 118.6 (C_5), 122.2 (C_7), 123.8 (C_4), 130.3 (C_{7a}), 146.5 (C_{3a}), 151.6 (C_6), 162.1 (d, J = 4.2 Hz, CONH), 204.7 (C_1) ppm. HRMS (ESI) m/z: Calcd. for $C_{16}H_{22}NO_6P$ ($[M+H]^+$): 356.1185, found: 356.1193.

Synthesis of methyl 3-[(5-methoxy-3-oxo-2,3-dihydro-1*H*-inden-4-yl)amino]-3-oxopropanoate (3). Methyl 3-chloro-3-oxopropanoate (750 μl, 7.02 mmol) was added to a solution of 7-amino-6-methoxy-2,3-

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dihydro-1*H*-inden-1-one (**1**) (830 mg, 4.68 mmol) in anhydrous CH_2Cl_2 (8 mL). Then, DIPEA (1.22 mL, 7.02 mmol) was added to the solution and the mixture was stirred at room temperature for 5 h. The reaction mixture was evaporated to dryness. The residue was dissolved in CH_2Cl_2 (300 mL) and the resulting solution was successively washed with H_2O (100 mL) and brine (100 mL), dried over Na_2SO_4, and evaporated to dryness to give **3** (1.290 g, 100 %) as a brown solid (m.p 138 ºC). HPLC-MS (30-95% gradient of A in B for 10 min) t_R = 1.21 min.^{1}H NMR (400 MHz, $CDCl_3$) δ 2.62 (m, 2H, 2-H), 2.96 (m, 2H, 3-H), 3.49 (s, 2H, *CH*$_2$-CO_2Me), 3.75 (s, 3H, 6-OMe), 3.82 (s, 3H, CO_2Me), 7.14 (d, *J* = 8.5 Hz, 1H, 5-H), 7.19 (dt, 1H, *J* = 8.5, 1 Hz, 4-H), 9.16 (s, 1H, NH). ^{13}C NMR (126 MHz, $CDCl_3$) δ 24.5 (C_3) , 37.8 (*CH*$_2$-CO_2Me), 41.7 (C_2), 52.5 (6-OMe), 56.7 (CO_2Me), 119.2 (C_5) , 122.6 (C_{7a}), 124.1 (C_4), 130.4 (C_7), 147. 0 (C_{3a}), 152.0 (C_6), 163.2 (CONH), 169.3 (CO_2), 205.8 (C_1). HRMS (ESI) *m/z*: Calcd. for $C_{14}H_{15}NO_5$ ([M+H]$^+$): 278.0950 found: 278.1027.

Synthesis of 8-methoxy-4,5-dihydrocyclopenta[*de*]quinolin-2(1*H*)-one[1] (4) and diethyl (8-methoxy-2-oxo-1,2,4,5-tetrahydrocyclopenta[*de*]quinolin-3-yl)phosphonate (5)

Method A: NaH (94.4 mg, 2.8 mmol) was added to a solution of **2** (1.0 g, 2.8 mmol) in dry DMF (18 mL), and this mixture was heated at 180ºC by MW irradiation for 5 min. Afterwards, the solvent was evaporated, the residue was dissolved in CH_2Cl_2 (20 mL) and the resulting solution was successively washed with H_2O (5 mL) and brine (5 mL), dried over Na_2SO_4, and evaporated to dryness. The residue was purified by flash chromatography on silica gel, using (150:1) to (20:1) CH_2Cl_2/MeOH gradient to afford the 4,5-dihydrocyclopenta[*de*]quinolin-2(1*H*)-one **4** (203.5 mg, 36% yield) and the phosphonate **5** (341.2 mg, 36% yield).

*8-Methoxy-4,5-dihydrocyclopenta[*de*]quinolin-2(1*H*)-one* (**4**): White solid (m.p. 275 ºC). HPLC-MS (30-95% gradient of A in B for 10 min) t_R = 1.86 min. ^{1}H NMR (CD_3OD/$CDCl_3$ 1:1, 500 MHz) δ: 3.25 (m, 4H, 4-H and 5-H), 3.95 (s, 3H, OCH_3), 6.37 (s, 1H, 3-H), 7.04 (d, 1H, *J* = 8.0 Hz, 7-H), 7.08 (d, 1H, *J* = 8.0 Hz, 6-H), 7.76 (s, 1H, NH). ^{13}C NMR (CD_3OD/$CDCl_3$ 1:1, 125 MHz) δ: 30.7 (C_5), 31.2 (C_4), 56.7 (OCH_3), 113.8 (C_3), 114.2 (C_7), 118.6 (C_6), 126.2 (C_{8a}), 128.5 (C_{3b}), 138.2 (C_{5a}), 145.2 (C_8), 162.7 (C_2), 167.1 (C_{3a}). HRMS (ESI) *m/z*: Calcd. for $C_{12}H_{11}NO_2$ ([M+H]$^+$): 202.0790, found: 202.0792.

*Diethyl (8-methoxy-2-oxo-1,2,4,5-tetrahydrocyclopenta[*de*]quinolin-3-yl)phosphonate* (**5**): Yellow solid (m.p. 210 ºC). HPLC-MS (30-95% gradient of A in B for 10 min) t_R = 2.31 min. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.34 [t, 6H, *J* = 7 Hz, CH_3(OEt)], 3.19 (t, 2H, *J* = 5.5 Hz, 5-H), 3.55 (m, 2H, 4-H), 3.91 (s, 3H, OCH_3), 4.24 [m, 4H, CH_2(OEt)], 6.96 (d, 1H, *J* = 8 Hz, 6-H), 7.00 (d, 1H, *J* = 8 Hz, 7-H), 9.04 (br s, 1H, NH). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 16.5 and 16.6 [CH_3(OEt)], 30.2 (C_5), 33.8 (C_4), 56.5 (OCH_3), 62.5 and 62.6 [CH_2(OEt)], 114.3 (d, *J* = 197 Hz, C_3), 114.9 (C_7), 117.3 (C_6), 126.6 (d, *J* = 16.5 Hz, C_{3b}), 126.7 (C_{8a}), 139.2 (C_{5a}), 143.2 (C_8), 162.53 (d, *J* = 14 Hz, C_2), 171.13 (d, *J* = 9 Hz, C_{3a}). HRMS (ESI) *m/z*: Calcd. for $C_{16}H_{20}NO_5P$ ([M+H]$^+$): 338.1079, found: 338.1085.

Synthesis of diethyl (8-methoxy-2-oxo-1,2,4,5-tetrahydrocyclopenta[*de*]quinolin-3-yl)phosphonate (5). Method B: LiCl (19.3 mg, 0.45 mmol) and DBU (67.9 µL, 0.45 mmol) were added to a solution of **2** (53.8 mg, 0.15 mmol) in dry THF (3 mL), and this mixture was stirred at room temperature for 24 h. Afterwards, the solvent was evaporated, the residue was dissolved in CH_2Cl_2 (20 mL), and the resulting solution was successively washed with H_2O (5 mL) and brine (5 mL), dried over Na_2SO_4, and evaporated to dryness. The residue was purified by flash chromatography on silica gel to afford **5** (50.6 mg, 100% yield).

Synthesis of methyl 8-methoxy-2-oxo-1,2,4,5-tetrahydrocyclopenta[*de*]quinoline-3-carboxylate (6). K_2CO_3 (707 mg, 5.12 mmol) was added to a solution of compound **3** (1.290 g , 4.65 mmol) in methanol (8 mL). This solution was heated at 70 ºC for 30 min in microwave. The reaction mixture was cooled and the precipitate was filtered to give **6** (1.185 g, 100%) as a yellow solid (m.p 236 ºC). This compound was used in the next step without further purification. HPLC-MS (30-95% gradient of A in B for 10 min) t_R = 2.21 min.

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.18 (m, 2H, 5-H), 3.46 (m, 2H, 4-H), 3.87 (s, 6H, OMe), 6.93 (dt, 1H, J = 8, 1 Hz, 6-H), 6.96 (d, 1H, J = 8 Hz, 7-H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 30.4 (C_5) , 33.5 (C_4), 52.2 (8-OMe), 56.4 (CO_2Me), 114.8 (C_7), 116.6 (C_3), 117.4 (C_6), 126.4(C_{3b}), 126.6 (C_{8a}), 139.3 (C_{5a}), 143.2 (C_8), 161.2 (C_2), 165.8 (CO_2Me), 167.1 (C_{3a}). HRMS (ESI) *m/z*: Calcd. for $C_{14}H_{13}NO_4$([M+H]$^+$): 260.0844, found: 260.0923.

Synthesis of 8-methoxy-2-oxo-1,2,4,5-tetrahydrocyclopenta[*de*]quinoline-3-carboxylic acid (7). 2 M NaOH was added to a suspension of **6** (50 mg, 0.193 mmol) in water (5 mL), and the mixture was stirred at reflux for 3 h. The reaction mixture was diluted with AcOEt (50 mL) and 2 M aquous solution of HCl was added until pH=2 on the aqueous phase. After 30 min, the aqueous phase was washed with AcOEt (3×100 mL). The combined organic phases were dried over Na_2SO_4 and evaporated to give **7** (47 mg, 100 %) as a white solid. M. p. 237ºC. HPLC-MS (30-95% gradient of A in B for 10 min) t_R = 2.4 min. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 3.15 (m, 2H, 5-H), 3.51 (m, 2H, 4-H), 3.85 (s, 3H, OMe), 6.93 (d, 1H, J = 7.5 Hz, 1H, 6-H), 6.98 (d, 1H, J = 7.5 Hz, 7-H).^{13}C NMR (125 MHz, DMSO-d_6) δ: 29. 3 (C_5), 32.5 (C_4) , 55. 5 (OMe) , 112.0 (C_7), 114.7 (C_6), 116.4 (C_3), 130.9 (C_{3b}), 136.3 (C_{8a}), 137.8 (C_{5a}), 149.6 (C_8), 167.6 (C_2), 169.4 (CO_2H), 174.0 (C_{3a}). HRMS (ESI) *m/z*: Calcd. for $C_{13}H_{11}NO_4$([M+H]$^+$): 246.0694, found: 246.0767.

Synthesis of 8-methoxy-4,5-dihydrocyclopenta[*de*]quinolin-2(1*H*)-one (4). Method B: The carboxylic acid **7** (1.012 g, 4.12 mmol) was dissolved in DMF (50 mL) and the solution was heated at 180 ºC for 6 h. Then, the reaction mixture was concentrated under vacuum. The residue was dissolved in CH_2Cl_2 (50 mL) and the solution was successively washed with H_2O (20 mL) and brine (20 mL), dried over Na_2SO_4 and evaporated to dryness to give compound **3** (710 mg, 86%) as brown solid.

Synthesis of 2-chloro-8-methoxy-4,5-dihydrocyclopenta[*de*]quinoline (8). A solution of **4** (1.8 g, 8.9 mmol) in $POCl_3$ (30 mL, 322 mmol) was stirred at 110 ºC for 45 min. Afterwards, the solvent was evaporated, the residue was dissolved in CH_2Cl_2 (100 mL), and the resulting solution was successively washed with 1N NaOH (50 mL), H_2O (50 mL) and brine (50 mL), dried over Na_2SO_4, and evaporated to dryness. The residue was purified by flash chromatography on silica gel (elution with 300:1 to 100:1 CH_2Cl_2/MeOH gradient) yielding **8** (1.9 g, 100 %) as a white solid. M.p. 135 ºC. HPLC-MS (30-95% gradient of A in B for 10 min) t_R = 5.15 min. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 3.13-3.56 (m, 4H, 4-H and 5-H), 4.01 (s, 3H, OCH_3), 7.01 (d, 1H, J = 8 Hz, 7-H), 7.16 (s, 1H, 3-H), 7.22 (d, 1H, J = 8 Hz, 6-H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 29.6 (C_5), 31.3 (C_4), 56.2 (OCH_3), 111.2 (C_7), 117.5 (C_3), 120.5 (C_6), 134.8 (C_{3b}), 136.9 (C_{8a} and C5a), 151.8 (C_2), 151.9 (C_8), 159.3 (C_{3a}). HRMS (ESI) *m/z*: Calcd. for $C_{12}H_{10}NOCl$ ([M+H]$^+$): 220.0451, found: 220.0445.

Synthesis of diethyl (2-chloro-8-methoxy-4,5-dihydrocyclopenta[*de*]quinolin-3-yl)phosphonate (9). A solution of **5** (2.8 g, 8.3 mmol) in $POCl_3$ (28 mL, 300 mmol) was stirred at 110 ºC for 45 min. After that time, the desired phosphonate was partially unprotected, therefore the solvent was evaporated, and the residue was stirred in EtOH (20 mL) at room temperature overnight. Afterwards, the solvent was evaporated to dryness and the residue was purified by flash chromatography on silica gel (elution with 150:1 to 20:1 CH_2Cl_2/EtOH) to afford pure **9** (2.8 g, 96 %) as a yellow solid. M.p. 133 ºC. HPLC-MS (30-95% gradient of A in B for 10 min) t_R = 4.19 min. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.35 [td, 6H, J = 7.1 and 0.6 Hz, CH_3(OEt)], 3.33 (m, 2H, 5-H), 3.79 (m, 2H, 4-H), 4.03 (s, 3H, OCH_3), 4.04-4.35 [m, 4H, CH_2(OEt)], 7.15 (d, 1H, J = 8 Hz, 7-H), 7.33 (d, 1H, J = 8 Hz, 6-H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 16.4 and 16.5 [CH_3(OEt)], 29.8 (C_5), 35.1 (C_4), 56.4 (OCH_3), 62.6 and 62.7 [CH_2(OEt)], 113.5 (C_7), 117.0 (d, J = 195 Hz, C_3) 121.6 (C_6), 134.1 (d, J = 12 Hz, C_{3b}), 137.1 (C_{8a}), 138.6 (C_{5a}), 151.6 (d, J = 12 Hz, C_2), 151.6 (C_8), 169.34 (d, J = 9.5 Hz, C_{3a}). HRMS (ESI) *m/z*: Calcd. for $C_{16}H_{19}NO_4PCl$ ([M+H]$^+$): 356.0740, found: 356.0737.

General procedure for the synthesis of 8-methoxy-4,5-dihydrocyclopenta[*de*]quinoline (10) and diethyl (8-methoxy-4,5-dihydrocyclopenta[*de*]quinolin-3-yl)phosphonate (11). Pd(C) (10% w/w) was added to a solution of the corresponding 2-chloro-derivative (**8** and **9**) (4.5 mmol) in MeOH (20 mL) and the resulting suspension was hydrogenated at room temperature under 20 psi of H_2 for 6 h. Afterwards, the catalyst was

filtered off and washed with MeOH (2×10 mL), the solvent was evaporated to dryness, and the residue was purified by flash chromatography on silica gel (elution with 150:1 to 10:1 CH_2Cl_2/MeOH) to afford **10** and **11**, respectively.

Synthesis of 8-methoxy-4,5-dihydrocyclopenta[*de*]quinoline (10). The general procedure was followed by using **8** as starting material (857 mg, 3.9 mmol) to afford 722 mg of compound **10** (100 %) as a brown solid. M.p. 160 ºC. HPLC-MS (30-95% gradient of A in B for 10 min) t_R = 0.46 min. ^{1}H NMR (CD_3OD, 300 MHz) δ: 3.55 (m, 2H, 5-H), 3.76 (m, 2H, 4-H), 4.18 (s, 3H, OCH_3), 7.64 (d, 1H, *J* = 8 Hz, 7-H), 7.71 (d, 1H, *J* = 8 Hz, 6-H), 7.90 (d, 1H, *J* = 6 Hz, 3-H), 8.92 (d, 1H, *J* = 6 Hz, 2-H). ^{13}C NMR (CD_3OD, 75 MHz) δ = 30.8 (C_5), 34.6 (C_4), 57.6 (OCH_3), 117.1 (C_7), 118.1 (C_3), 125.3 (C_6), 128.0 (C_{8a}), 137.6 (C_{3b}), 140.8 (C_{5a}), 146.0 (C_2), 148.3 (C_8), 172.2 (C_{3a}). HRMS (ESI) *m/z*: Calcd. for $C_{12}H_{11}NO$ ($[M+H]^+$): 186.0841, found: 186.0843.

Synthesis of diethyl (8-methoxy-4,5-dihydrocyclopenta[*de*]quinolin-3-yl)phosphonate (11). The general procedure was followed by using **9** as starting material (926 mg, 2.6 mmol) to afford 836 mg of compound **11** (100 %) as a brown solid. M.p. 82 ºC. HPLC-MS (30-95% gradient of A in B for 10 min) t_R = 2.25 min. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.34 [t, 6H, *J* = 7 Hz, CH_3(OEt)], 3.36 (m, 2H, 5-H), 3.66 (m, 2H, 4-H), 4.07 (s, 3H, OCH_3), 4.07-4.25 [m, 4H, CH_2(OEt)], 7.15 (d, 1H, *J* = 8 Hz, 7-H), 7.35 (d, 1H, *J* = 8 Hz, 6-H), 9.06 (d, 1H, *J* = 5.0 Hz, 2-H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 16.5 [CH_3(OEt)], 29.4 (C_5), 33.0 (C_4), 56.4 (OCH_3), 62.3 [CH_2(OEt)], 112.4 (C_7), 116.9 (d, *J* = 190.5 Hz, C_3), 121.1 (C_6), 134.7 (d, *J* = 13. Hz, C_{3b}), 138.5 (C_{5a}), 139.0 (C_{8a}), 151.8 (d, *J* = 15 Hz, C_2), 152.5 (C_8), 163.21 (d, *J* = 9 Hz, C_{3a}). HRMS (ESI) *m/z*: Calcd. for $C_{16}H_{20}NO_4P$ ($[M+H]^+$): 322.1130, found: 322.1133.

General procedure for the oxidation of the 8-methoxy-4,5-dihydrocyclopenta[*de*]quinolines 8-11. Synthesis of the anhydrides 12-15. The corresponding 8-methoxy-4,5-dihydrocyclopenta[*de*]quinoline **8-11** (0.5 mmol) was dissolved in a 5:1 mixture of acetic anhydride/acetic acid (3 mL) at 110 ºC. CrO_3 (4.0 mmol) was added carefully to the stirred solution over a period of 30 min and the resulting green suspension was stirred at 110 ºC for 30 min. After cooling to room temperature, the solvent was evaporated to dryness and the residue was stirred in CH_2Cl_2 (25 mL) at 40 ºC for 10 min. The resulting green suspension was then filtered through Clarcel® and the solvent was removed under reduced pressure to yield the corresponding anhydrides **12-15** (89-94%), which were taken to the next step without further purification.

9-Methoxypyrano[3,4,5-*de*]quinoline-4,6-dione (12). From **10** (56 mg, 0.30 mmol). Orange solid (89 %). HPLC-MS (30-95% gradient of A in B for 10 min) t_R = 1.68 min. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 4.27 (s, 3H, OCH_3), 7.37 (d,1H, *J* = 8.4 Hz, 8-H), 8.38 (d, 1H, *J* = 4.1 Hz, 3-H), 8.66 (d, 1H, *J* = 8.3 Hz, 7-H), 9.30 (d, 1H, *J* = 4.3 Hz, 2-H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 57.5, 109.8, 125.0, 126.2, 126.7, 136.3,139.4, 151.1, 158.9, 160.3, 162.0, 165.4. HRMS (ESI) *m/z*: Calcd. for $C_{12}H_7NO_4$ ($[M+H]^+$): 230.0375, found: 230.0368.

Diethyl (9-methoxy-4,6-dioxo-4,6-dihydropyrano[3,4,5-*de*]quinolin-3-yl)phosphonate (13). From **11** (36 mg, 0.11 mmol). Orange solid (91 %). HPLC-MS (30-95% gradient of A in B for 10 min) t_R = 2.19 min. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.43 [t, 6H, *J* = 7.0 Hz, CH_3(OEt)], 4.28 (s, 3H, OCH_3), 4.37-4.56 [m, 6H, CH_2(OEt)], 7.42 (d, 1H, *J* = 8.2 Hz, 8-H), 8.70 (d, 1H, *J* = 8.2 Hz, 7-H), 9.72 (d, 1H, *J* = 5.3 Hz, 2-H). HRMS (ESI) *m/z*: Calcd. for $C_{16}H_{16}NO_7P$ ($[M+H]^+$): 366.0664, found: 366.0671.

2-Chloro-9-methoxypyrano[3,4,5-*de*]quinoline-4,6-dione (14). From **8** (92 mg, 0.42 mmol). Orange solid (93 %). HPLC-MS (30-95% gradient of A in B for 10 min) t_R = 3.66 min. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 4.24 (s, 3H, OCH_3), 7.39 (d, 1H, *J* = 8.1 Hz, 8-H), 8.34 (s, 1H, 3-H), 8.62 (d, 1H, *J* = 8.3 Hz, 7-H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 57.4, 110.1, 110.9, 124.9, 126.8, 129.2, 135.9, 138.8, 151.8, 158.2, 158.9, 160.9. HRMS (ESI) *m/z*: Calcd. for $C_{12}H_6NO_4Cl$ ($[M+H]^+$): 263.9985, found: 263.9996.

Diethyl (2-chloro-9-methoxy-4,6-dioxo-4,6-dihydropyrano[3,4,5-*de*]quinolin-3-yl)-phosphonate (15). From **9** (61 mg, 0.17 mmol). Orange solid (90 %). HPLC-MS (30-95% gradient of A in B for 10 min) t_R =

3.39 min. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.40 [t, 6H, J = 7.0 Hz, CH_3(OEt)], 4.24 (s, 3H, OCH_3), 4.27-4.43 [m, 6H, CH_2(OEt)], 7.41 (d,1H, J = 8.3 Hz, 8-H), 8.62 (d, 1H, J = 8.3 Hz, 7-H). HRMS (ESI) *m/z*: Calcd. for $C_{16}H_{15}NO_7PCl$ ($[M+H]^+$): 400.0275, found: 400.0259.

General procedure for the synthesis of imides 16-21, 26 and 27. The corresponding amine (2-aminoethanol, n-butylamine, or *N*-Boc-ethylenediamine, 0.24 mmol) was added to a solution of the corresponding anhydride **12-15** (0.22 mmol) in dry EtOH (3 mL), and this mixture was heated at 120ºC under MW irradiation for 1.5 h. Afterwards, the solvent was evaporated to dryness and the residue was purified by flash chromatography, using 5-25% gradient of MeOH in CH_2Cl_2 as eluent, to give the desired imides **16-21** and **26**.

5-(2-Hydroxyethyl)-9-methoxy-4*H*-benzo[*de*][2,6]naphthyridine-4,6(5*H*)-dione (16). From **12** (39.7 mg, 0.17 mmol). Yellow solid (31 mg, 67 %). M.p. 231 ºC. HPLC-MS (30-95% gradient of A in B for 10 min) t_R = 0.81 min. ^{1}H NMR ($CDCl_3$, 300 MHz) δ :3.97 (t, 2H, J = 5 Hz, 2´-CH_2), 4.21 (s, 3H, OCH_3), 4.41 (t, 2H, J = 5 Hz, 1´-CH_2), 7.23 (d, 1H, J = 8.5 Hz, 8-H), 8.27 (d, 1H, J = 4 Hz, 3-H), 8.53 (d, 1H, J = 8 Hz, 7-H), 9.16 (d, 1H, J = 4 Hz, 2-H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 42.9 (1´-CH_2), 57.0 (OCH_3), 61.5 (2´-CH_2), 108.9 (C_8), 114.3 (C_{6a}), 123.2 (C_3), 124.0 (C_{9b}), 129.5 (C_{3a}), 133.8 (C_7), 138.9 (C_{9a}), 150.5 (C_2), 160.8 (C_9), 163.6 (C_6), 164.1 (C_4). HRMS (ESI) *m/z*: Calcd. for $C_{14}H_{12}N_2O_4$ ($[M+H]^+$): 273.0797, found: 273.0797.

Diethyl (5-(2-hydroxyethyl)-9-methoxy-4,6-dioxo-5,6-dihydro-4*H*-benzo[*de*][2,6]-naphthyridin-3-yl)phosphonate (17). From **13** (26.8 mg, 0.073 mmol). Yellow solid (15.0 mg, 51 %). M.p. 174 ºC. HPLC-MS (30-95% gradient of A in B for 10 min) t_R = 1.17 min. ^{1}H-RMN (500 MHz, $CDCl_3$) δ: 1.30 [t, 6H, J = 7 Hz, CH_3(OEt)], 3.85 (t, 2H, J = 5.5 Hz, 2´-CH_2), 4.11 (s, 3H, OCH_3), 4.18-4.44 [m, 6H, 1´-CH_2 and CH_2(OEt)], 7.23 (d, 1H, J = 8 Hz, 8-H), 8.53 (d, 1H, J = 8 Hz, 7-H), 9.52 (d, 1H, J = 5 Hz, 2-H). ^{13}C-RMN (125 MHz, $CDCl_3$) δ: 15.4 [CH_3(OEt)], 42.0 (1´-CH_2), 56.0 (OCH_3), 60.1 (2´-CH_2), 62.7 [CH_2(OEt)], 108.9 (C_8), 113.4 (C_{6a}), 122.5 (d, J = 11 Hz, C_{9b}), 124.5 (d, J = 190 Hz, C_3), 132.1 (d, J = 5.5 Hz, C_{3a}), 133.5 (C_7), 139.6 (C_{9a}), 152.3 (d, J = 10 Hz, C_2), 159.6 (C_9), 161.6 (d, J = 5 Hz, C_4), 164.1 (C_6). HRMS (ESI) *m/z*: Calcd for $C_{18}H_{21}N_2O_7P$ ($[M+1]^+$): 409.1086, found: 409.1099.

2-Chloro-5-(2-hydroxyethyl)-9-methoxy-4*H*-benzo[*de*][2,6]naphthyridine-4,6(5*H*)-dione (18). From **14** (65.5 mg, 0.25 mmol). Yellow solid (52.0 mg, 68 %). M.p. 240 ºC. HPLC-MS (30-95% gradient of A in B for 10 min) t_R = 1.93 min. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 3.96 (t, 2H, J = 5 Hz, 2´-CH_2), 4.20 (s, 3H, OCH_3), 4.41 (t, 2H, J = 5 Hz, 1´-CH_2), 7.31 (d, 1H, J = 8 Hz, 8-H), 8.32 (s, 1H, 3-H), 8.56 (d, 1H, J = 8 Hz, 7-H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 43.0 (1´-CH_2), 57.1 (OCH_3), 61.5 (2´-CH_2), 110.2 (C_8), 114.3 (C_{6a}), 123.1 (C_{9b}), 125.2 (C_3), 132.3 (C_{3a}), 133.7 (C_7), 138.6 (C_{9a}), 151.5 (C_2), 160.0 (C_9), 163.0 (C_4), 163.3 (C_6). HRMS (ESI) *m/z*: Calcd. for $C_{14}H_{11}N_2O_4Cl$ ($[M+H]^+$): 307.0407, found: 307.0421.

Diethyl (2-chloro-5-(2-hydroxyethyl)-9-methoxy-4,6-dioxo-5,6-dihydro-4*H*-benzo[*de*][2,6]-naphthyridin-3-yl)-phosphonate (19). From **15** (67.2 mg, 0.16 mmol). Yellow solid (34.7 mg, 49 %). M.p. 170 ºC. HPLC-MS (30-95% gradient of A in B for 10 min) t_R = 2.08 min. ^{1}H-RMN (300 MHz, $CDCl_3$) δ: 1.33 [t, 6H, J: 7 Hz, CH_3(OEt)], 3.91 (t, 2H, J = 5 Hz, 2´-CH_2), 4.14 (s, 3H, OCH_3), 4.16-4.33 [m, 4H, CH_2(OEt)], 4.34 (t, 2H, J = 5 Hz, 1´-CH_2), 7.28 (d, 1H, J = 8.5 Hz, 8-H), 8.51 (d, 1H, J = 8.5 Hz, 7-H). ^{13}C-RMN (75 MHz, $CDCl_3$) δ: 16.5 [CH_3(OEt)], 43.6 (1´-CH_2), 57.2 (OCH_3), 61.1 (2´-CH_2), 64.0 and 64.1 [CH_2(OEt)], 111.2 (C_8), 114.4 (C_{6a}), 122.4 (d, J = 9 Hz, C_{9b}), 127.0 (d, J = 193.5 Hz, C_3), 133.8 (C_7), 138.6 (C_{9a}), 140.2 (d, J = 5 Hz, C_{3a}), 152.1 (d, J = 6 Hz, C_2), 159.2 (C_9), 162.5 (d, J = 5 Hz, C_4), 162.7 (C_6). HRMS (ESI) *m/z*: Calcd for $C_{18}H_{20}N_2O_7PCl$ ($[M+1]^+$): 443.0697, found: 443.0689.

5-Butyl-9-methoxy-4*H*-benzo[*de*][2,6]naphthyridine-4,6(5*H*)-dione (20). From **12** (84.4 mg, 0.37 mmol). Yellow solid (68.4 mg, 65 %). M.p. 122 ºC. HPLC-MS (30-95% gradient of A in B for 10 min) t_R = 4.82 min. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 0.90 (t, 3H, J = 7.5 Hz, 4´-CH_3), 1.37 (m, 2H, 3´-CH_2), 1.63 (m, 2H, 2´-CH_2), 4.08 (m, 2H, 1´-CH_2), 4.15 (s, 3H, OCH_3), 7.20 (d, 1H, J = 8.5 Hz, 8-H), 8.26 (d, 1H, J = 4.5 Hz, 3-H),

8.50 (d, 1H, J = 8.5 Hz, 7-H), 9.14 (d, 1H, J = 4.5 Hz, 2-H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 13.9 (4′-CH_3), 20.5 (3′-CH_2), 30.3 (2′-CH_2), 40.5 (1′-CH_2), 56.9 (OCH_3), 108.8 (C_8), 114.8 (C_{6a}), 123.0 (C_3), 124.1 (C_{9b}), 129.8 (C_{3a}), 133.4 (C_7), 138.9 (C_{9a}), 150.5 (C_2), 160.6 (C_9), 162.8 (C_6), 163.4 (C_4). HRMS (ESI) *m/z*: Calcd. for $C_{16}H_{16}N_2O_3$ ($[M+H]^+$): 285.1161, found: 285.1163.

Diethyl (5-butyl-9-methoxy-4,6-dioxo-5,6-dihydro-4*H*-benzo[*de*][2,6]naphthyridin-3-yl)phosphonate (21). From **13** (76.2 mg, 0.21 mmol). Yellow solid (39.5 mg, 45 %). M.p. 124 ºC. HPLC-MS (30-95% gradient of A in B for 10 min) t_R = 4.67 min. ^{1}H-RMN (400 MHz, $CDCl_3$) δ: 0.90 (t, 3H, J = 7.5 Hz, 4′-CH_3), 1.36 [t, 6H, J = 7.5 Hz, CH_3(OEt)], 1.28-1.44 (m, 2H, 3′-CH_2), 1.63 (m, 2H, 2′-CH_2), 4.11 (m, 2H, 1′-CH_2), 4.17 (s, 3H, OCH_3), 4.36 [p, 4H, J = 7 Hz, CH_2(OEt)], 7.28 (d, 1H, J = 8 Hz, 8-H), 8.57 (d, 1H, J = 8 Hz, 7-H), 9.59 (d, 1H, J = 5 Hz, 2-H). ^{13}C-RMN (100 MHz, $CDCl_3$) δ: 13.9 (4′-CH_3), 16.5 and 16.6 [CH_3(OEt)], 20.5 (3′-CH_2), 30.2 (2′-CH_2), 40.8 (1′-CH_2), 57.1 (OCH_3), 63.8 and 63.8 [CH_2(OEt)], 110.0 (C_8), 114.9 (C_{6a}), 123.6 (d, J = 11 Hz, C_{9b}), 125.5 (d, J = 189.5 Hz, C_3), 133.55 (d, J = 6 Hz, C_{3a}), 134.2 (C_7), 140.6 (C_{9a}), 153.54 (d, J = 10 Hz, C_2), 160.3 (C_9), 161.9 (d, J = 5 Hz, C_4), 162.2 (C_6). HRMS (ESI) *m/z*: Calcd for $C_{20}H_{25}N_2O_6P$ ($[M+1]^+$): 421.1450, found: 421.1452.

***tert*-Butyl (2-(9-methoxy-4,6-dioxo-4*H*-benzo[*de*][2,6]naphthyridin-5(6*H*)-yl)ethyl)-carbamate (26).** From **12** (30 mg, 0.13 mmol). Brown solid (35 mg, 81 %). M.p. 215ºC. HPLC-MS (30-95% gradient of A in B for 10 min) t_R = 3.35 min. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.20 (s, 9H), 3.47 (q, 2H, J = 6 Hz, 1′-H), 4.24 (s, 3H, OMe), 4.27 (t, 2H, J = 6 Hz, 2′-H), 4,88 (t, 1H, J=6 Hz, NH-Boc), 7.21 (d, 1H, J = 8.5 Hz, 8-H), 8.27 (d, 1H, J = 4 Hz, 3-H), 8.52 (d, 1H, J = 8.5 Hz, 7-H), 9.14 (d, 1H, J = 4 Hz, 2-H). ^{13}C NMR (126 MHz, $CDCl_3$) δ: 28.5 (Boc), 39.7 ($C_{2'}$), 40.4 ($C_{1'}$), 57.2 (OMe), 79.5 (Boc) , 109.5 (C_8), 114.7 (C_{6a}), 123.4 (C_3), 124.4 (C_{9b}), 129.8 (C_{3a}), 133.9 (C_7), 139.1 (C_{9a}), 150.7 (C_2), 156.4 [CO(Boc)], 160.9 (C_9), 163.4 (C_4), 163.84 (C_6).HRMS (ESI) *m/z*: Calcd. for $C_{19}H_{21}N_3O_5$ ($[M+H]^+$): 372.1494, found: 372.1567.

***tert*-Butyl (2-(2-chloro-3-(diethoxyphosphoryl)-9-methoxy-4,6-dioxo-4*H*-benzo[*de*][2,6]-naphthyridin-5(6*H*)-yl)ethyl)carbamate (27).** From **15** (120 mg, 0.3 mmol). Yellow syrup (65 mg, 40 %). HPLC-MS (30-95% gradient of A in B for 10 min) t_R = 4.68 min. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.24 (s, 9H, Boc), 1.33 (t, 6H, J = 7 Hz, Et), 3.45 (m, 2H, 2′-H), 4.13 (s, 3H, OMe), 4.17-4.38 (m, 6H, 1′-H+ Et), 4,95 (m, 1H, NH-Boc), 7.27 (d, 1H, J = 8.5 Hz, 8-H), 8.50 (d, 1H, J = 8.5 Hz, 7-H. ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.4 [d, J = 7 Hz, CH_3 (Et)], 26.2 (Boc), 37.4 ($C_{1'}$), 38.9 ($C_{2'}$), 55.0 (OMe), 77.2 (Boc) , 109.0 (C_8), 112.3 (C_{6a}), 120.4 (d, J = 9 Hz, C_{9b}), 124.9 (d, J = 193 Hz, C_3), 131.6 (C_7), 136.4 (C_{9a}), 138.0 (d, J = 5 Hz, C_{3a}), 150.7 (d, J = 6 Hz, C_2), 154.0 [CO(Boc)], 157.0 (C_9), 159.9 (d, J = 5 Hz, C_4), 160.2 (C_6).HRMS (ESI) *m/z*: Calcd. for $C_{23}H_{30}C_lN_3O_8P$ ($[M+H]^+$): 542.1454, found: 542.1457.

General procedure for the synthesis of the *N*-Boc-amino acid quinolimide derivatives 22 and 23. A solution of (S)-3-Amino-2-(*N*-Boc-amino)-propionic acid (102.1 mg, 0.50 mmol) and $NaHCO_3$ (209.2 mg, 2.49 mmol) in H_2O (1.5 mL) was slowly added to a solution of the corresponding anhydride **12** or **14** (0.50 mmol) in dioxane (7.5 mL) under Ar_2 atmosphere. The resulting suspension was vigorously stirred at reflux temperature for 30 min. Then, the reaction mixture was cooled to rt, evaporated to dryness, and the residue was diluted with H_2O (50 mL). The aqueous solution was washed with ethyl ether (50 mL), acidified with 6 N HCl and extracted with CH_2Cl_2 (3×100mL). The combined organic layers were dried with Na_2SO_4 and evaporated to dryness. The residue was purified by flash column chromatography, using 2-10% gradient of EtOAc in hexane with 0.5 % of acetic acid as eluant to give the corresponding *N*-Boc-amino acid derivative **22** or **23**.

Synthesis of (*S*)-2-((*tert*-butoxycarbonyl)amino)-3-(9-methoxy-4,6-dioxo-4*H*-benzo-[*de*][2,6]naphthyridin-5(6*H*)-yl)propanoic acid (22). From **12** (114.5 mg, 0.5 mmol). Orange solid (90 mg, 40 %). M.p. 205 ºC. $[\alpha]_D^{20}$= -15.92 (c 1.0, MeOH). HPLC-MS (30-95% gradient of A in B for 10 min) t_R = 2.64 min. ^{1}H-RMN (300 MHz, DMSO-d_6) δ: 1.16 [s, 9H, CH_3(Boc)], 4.13 (s, 3H, OCH_3), 4.35 (m, 3H, α-H and β-H), 7.17 (d, 1H, J = 7 Hz, NH), 7.52 (d, 1H, J = 8.5 Hz, 8-H), 8.29 (d, 1H, J = 4.5 Hz, 3-H), 8.48 (d,

1H, *J* = 8.5 Hz, 7-H), 9.20 (d, 1H, *J* = 4.5 Hz, 2-H). ^{13}C-RMN (100 MHz, DMSO-d_6) δ: 27.9 [CH_3(Boc)], 40.4 (C_β), 50.8 (C_α), 56.7 (OCH_3), 78.2 [C(Boc)], 109.7 (C_8), 113.8 (C_{6a}), 122.6 (C_3), 123.3 (C_{9b}), 129.0 (C_{3a}), 133.0 (C_7), 138.1 (C_{9a}), 150.5 (C_2), 155.3 [CO(Boc)], 160.3 (C_9), 162.3 (C_6), 163.1 (C_4), 171.7 (CO_2H). HRMS (ESI) *m/z*: Calcd for $C_{20}H_{21}N_3O_7$ ([M+1]$^+$): 416.1380, found: 416.1380.

Synthesis of (*S*)-2-((*tert*-butoxycarbonyl)amino)-3-(2-chloro-9-methoxy-4,6-dioxo-4*H*-benzo[*de*][2,6]naphthyridin-5(6*H*)-yl)propanoic acid (23). From **14** (113 mg, 0.42 mmol). Orange solid (54,8 mg, 29%). M.p. 152 ºC. HPLC-MS (2-95% gradient of A in B for 10 min) t_R = 9.09 min. ^{1}H-RMN (400 MHz, $CDCl_3$) δ: 1.16 and 1.18 [2s, 9H, CH_3(Boc)], 4.06 (s, 3H, OCH_3), 4.30-4.59 (m, 2H, β-H), 4.71 (m, 1H, α-H), 5.38 (d, 1H, *J* = 8 Hz, NH), 7.17 (d, 1H, *J* = 8.5 Hz, 8-H), 8.18 (s, 1H, 3-H), 8.42 (d, 1H, *J* = 8.5 Hz, 7-H). ^{13}C-RMN (100 MHz, Cl_3CD) δ: 28.1 [CH_3(Boc)], 41.6 (C_β), 52.2 (C_α), 57.1 (OCH_3), 80.6 [C(Boc)], 110.2 (C_8), 114.0 (C_{6a}), 123.0 (C_{9b}), 125.3 (C_3), 132.0 (C_{3a}), 133.9 (C_7), 138.5 (C_{9a}), 151.5 (C_2), 156.0 [CO(Boc)], 159.9 (C_9), 162.7 (C_4), 162.9 (C_6), 173.4 (CO_2H). HRMS (ESI) *m/z*: Calcd for $C_{20}H_{20}N_3O_7Cl$ ([M+1]$^+$): 450.0990, found: 450.0990.

General procedure for the synthesis of the *N*-Fmoc-amino acid derivatives 24 and 25. TFA (4 mL) was added to a solution of the corresponding *N*-Boc-derivative **22** or **23** (0.21 mmol) in dioxane (2 mL) and this mixture was stirred at room temperature for 16 h. The reaction mixture was evaporated to dryness, dissolved in H_2O (2 mL), and the solution was lyophilized to remove residual TFA. The crude was redissolved in H_2O (1 mL) with $NaHCO_3$ (1.06 mmol), and the pH was checked to ensure that the solution was basic. A solution of *N*-(9-fluorenylmethoxycarbonyloxy) succinimide (77.6 mg, 0.23 mmol) was then prepared in dioxane (5 mL) and slowly added to the stirring solution of the amino acid. The reaction was allowed to proceed for 3 h before concentrating to remove most of the dioxane and re-diluted to a total volume of 10 mL in H_2O. The solution was washed with diethyl ether (50 mL) to remove excess Fmoc-OSu. The aqueous layer was acidified with 6 N HCl and the product extracted into CH_2Cl_2 (50 mL). The organic layers were combined, dried with Na_2SO_4 and evaporated to dryness. The residue was purified by flash chromatography on silica gel, using 1-10% gradient of MeOH into CH_2Cl_2 as eluant to afford the corresponding Fmoc-amino acids **24** and **25**.

Synthesis of (*S*)-2-[(((9*H*-fluoren-9-yl)methoxy)carbonyl)amino]-3-(9-methoxy-4,6-dioxo-4*H*-benzo[*de*][2,6]-naphthyridin-5(6*H*)-yl)propanoic acid (24). From **22** (87.2 mg, 0.21 mmol). Yellow solid (88 mg, 78%). M.p. 180 ºC. $[\alpha]_D^{20}$= -19.74 (c 0.9, MeOH). HPLC-MS (30-95% gradient of A in B for 10 min) t_R = 5.06 min. ^{1}H-RMN (400 MHz, DMSO-d_6) δ: 3.97-4.23 [m, 3H, 9-H (Fmoc) and CH_2 (Fmoc)], 4.10 (s, 3H, OCH_3), 4.41 (s, 3H, α-H and β-H), 7.22 (td, 1H, *J* = 1 and 7.5 Hz, Fmoc), 7.27 (td, 1H, *J* = 1 and 7.5 Hz, Fmoc), 7.39 (t, 2H, *J* = 7.5 Hz, Fmoc), 7.44 (d, 1H, *J* = 8.5 Hz, 8-H), 7.55 (d, 1H, *J* = 7.5 Hz, Fmoc), 7.62 (d, 1H, *J* = 7.5 Hz, Fmoc), 7.77 (br s, 1H, NH), 7.85 (d, 2H, *J* = 7.5 Hz, Fmoc), 8.22 (d, 1H, *J* = 4.5 Hz, 3-H), 8.39 (d, 1H, *J* = 8 Hz, 7-H), 9.15 (d, 1H, *J* = 4.5 Hz, 2-H). ^{13}C-RMN (100 MHz, DMSO-d_6) δ: 39.9 (C_β), 46.5 [aliphatic-CH(Fmoc)], 51.3 (C_α), 56.6 (OCH_3), 65.8 [aliphatic-CH_2(Fmoc)], 109.6 (C_8), 113.7 (C_{6a}), 120.0 [CH(Fmoc)], 122.6 (C_3), 123.3 (C_{9b}), 125.1 [CH(Fmoc)], 125.2 [CH(Fmoc)], 127.0 [CH(Fmoc)], 127.1 [CH(Fmoc)], 127.6 [CH(Fmoc)], 128.9 (C_{3a}), 133.1 (C_7), 138.1 (C_{9a}), 140.6 [C(Fmoc)], 143.7 [C(Fmoc)], 150.4 (C_2), 155.9 [CO(Fmoc)], 160.3 (C_9), 162.3 (C_6), 163.2 (C_4), 171.5 (CO_2H). HRMS (ESI) *m/z*: Calcd for $C_{30}H_{23}N_3O_7$ ([M+1]$^+$): 538.1536, found: 538.1523.

Synthesis of (*S*)-2-[(((9*H*-fuoren-9-yl)methoxy)carbonyl)amino]-3-(2-chloro-9-methoxy-4,6-dioxo-4*H*-benzo[*de*]-[2,6]naphthyridin-5(6*H*)-yl)propanoic acid (25). From **23** (120 mg, 0.26 mmol). Yellow solid (108.5 mg, 71%). M.p. 151 ºC. $[\alpha]_D^{20}$= -34.09 (c 1.1, MeOH). HPLC-MS (30-95% gradient of A in B for 10 min) t_R = 6.69 min. ^{1}H-RMN (400 MHz, DMSO-d_6) δ: 3.89 [t, 3H, *J* = 7 Hz, CH(Fmoc)], 3.96-4.11 [m, 2H, CH_2(Fmoc)], 4.06 (s, 3H, OCH_3), 4.33-4.46 (m, 3H, α-H and β-H), 7.22 (t, 1H, *J* = 7.5 Hz, Fmoc), 7.27 (t, 1H, *J* = 7.5 Hz, Fmoc), 7.37-7.40 (m, 3H, NH and Fmoc), 7.45 (m, 2H, 8-H and Fmoc), 7.56 (d, 1H, *J* = 7.5 Hz, Fmoc), 7.85 (d, 2H, *J* = 8 Hz, Fmoc), 8.10 (s, 1H, 3-H), 8.35 (d, 1H, *J* = 8 Hz, 7-H). ^{13}C-RMN (100 MHz, DMSO-d_6) δ = 41.2 (C_β), 46.5 [aliphatic-CH(Fmoc)], 51.9 (C_α), 56.7 (OCH_3), 65.7 [CH_2(Fmoc)],

110.9 (C_8), 113.9 (C_{6a}), 120.1 [CH(Fmoc)], 122.6 (C_{9b}), 123.7 (C_3), 125.0 [CH(Fmoc)], 125.2 [CH(Fmoc)], 127.0 [CH(Fmoc)], 127.6 [CH(Fmoc)], 132.6 (C_{3a}), 133.0 (C_7), 137.5 (C_{9a}), 140.6 [C(Fmoc)], 143.6 [C(Fmoc)], 143.8 [C(Fmoc)], 149.7 (C_2), 155.9 [CO(Fmoc)], 159.0 (C_9), 162.0 (C_4), 162.1 (C_6), 171.2 (CO_2H). HRMS (ESI) *m/z*: Calcd for $C_{30}H_{22}N_3O_7Cl$([M+1]$^+$): 572.1146, found: 572.1153.

Synthesis of 2-bromo-*N*-(2-(9-methoxy-4,6-dioxo-4*H*-benzo[*de*][2,6]naphthyridin-5(6*H*)-yl)ethyl)acetamide (28). Trifluoroacetic acid (154 µl, 2.02 mmol) was added to a solution of *tert*-butyl (2-(9-methoxy-4,6-dioxo-4H-benzo[*de*][2,6]naphthyridin-5(6H)-yl)ethyl)carbamate (**26**) (30 mg, 0.08 mmol) in CH_2Cl_2 (2 ml). The solution was stirred at room temperature for 2 h in Ar_2 atmosphere. The stirred reaction mixture was concentrated under vacuum and the residue was dissolved in CH_2Cl_2 (50 mL). The resulting solution was successively washed with H_2O (20 mL) and brine (20 mL), dried over Na_2SO_4, and evaporated to dryness, to give of 5-(2-aminoethyl)-9-methoxy-4*H*-benzo[*de*][2,6]naphthyridine-4,6(5*H*)-dione trifluoroacetate (15 mg, 93 %) as a yellow-brown solid. M.p. 137 ºC **(**HPLC-MS (30-95% gradient of A in B for 10 min) t_R = 0.40 min. R=93%. ^{1}H NMR (400 MHz, Methanol-d_4) δ: 3.27 (t, 2H, *J* = 5.5 Hz, 2'-H), 4.10 (s, 3H, OMe), 4.36 (t, 2H, *J* = 5.5, 1'-H), 7.33 (d, 1H, *J* = 8.5 Hz, 8-H), 8.15 (d, 1H, *J* = 4.5 Hz, 3-H), 8.38 (d, 1H, *J* = 8.5 Hz, 7-H), 8.96 (d, 1H, *J* = 4.5 Hz, 2-H). ^{13}C NMR (100 MHz, Methanol-d_4) δ: 38.91 , 39.85, 57.50, 110.64, 115.20, 124.17, 125.06, 130.95, 134.94, 139.23, 151.28, 161.65, 164.43, 165.08. HRMS (ESI) m/z: Calcd. For $C_{14}H_{13}N_3O_3$ ([M+H]$^+$): 272.0957, found: 272.1029.

5-(2-Aminoethyl)-9-hydroxy-4*H*-benzo[*de*][2,6]naphthyridine-4,6(5*H*)-dione trifluoroacetate (15 mg, 0.055 mmol) was dissolved in anhydrous CH_2Cl_2 (2 mL). The solution was stirred at -15ºC for 30 minutes. Then, 2-bromoacetyl bromide (7.1 µl, 0.08 mmol) and DIPEA (10.2 µl, 0.06 mmol) were added to the solution. The reaction mixture was stirred for 1.5 h at rt. Afterwards, the residue was dissolved in CH_2Cl_2 (50 mL) and the resulting solution was successively washed with H_2O (20 mL) and brine (20 mL), dried over Na_2SO_4, and evaporated to dryness, to give **28** (6.7 mg, 32 %) as a yellow foam. HPLC-MS (30-95% gradient of A in B for 10 min) t_R = 1.32 min. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.63 (q, 2H, *J* = 5.5 Hz, 2'-H), 3.71 (s, 2H, CH_2Br), 4.17 (s, 3H, OMe), 4.37 (m, 2H, 1'-H), 6.96 (brs, 1H, NH), 7.23 (d, 1H, *J* = 8.5 Hz, 8-H), 8.30 (d, 1H, *J* = 4.5 Hz, 3-H), 8.55 (d, 1H, *J* = 8.5 Hz, 7-H), 9.17 (d, 1H, *J* = 4.5 Hz, 2-H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 27.9 (CH_2Br), 38.0 ($C_{1'}$), 38.8 ($C_{2'}$), 55.9 (OMe), 107.9 (C_8), 113.1 (C_{6a}), 122.2 (C_3), 123.1 (C_{9b}), 128.3 (C_{3a}), 132.9 (C_7), 137.9 (C_{9a}), 149.4 (C_2), 160.0 (C_9), 162.2 (C_6), 163.0 (C_4), 165.1 (CONH). HRMS (ESI) *m/z*: Calcd. for $C_{16}H_{14}BrN_3O_4$ ([M+H]$^+$): 392.0167, found: 392.0220.

Synthesis of diethyl (5-(2-(2-bromoacetamido)ethyl)-2-chloro-9-methoxy-4,6-dioxo-5,6-dihydro-4*H*-benzo[*de*][2,6]naphthyridin-3-yl)phosphonate (29). Trifluoroacetic acid (71 µL, 0.63 mmol) was added to a solution of *tert*-butyl (2-(2-chloro-3-(diethoxyphosphoryl)-9-methoxy-4,6-dioxo-4*H*-benzo[*de*][2,6]naphthyridin-5(6*H*)-yl)ethyl)carbamate (**27**) (14 mg, 0.025 mmol) in CH_2Cl_2 (2 mL). The solution was stirred at room temperature overnight in Ar_2 atmosphere. Afterwards, the stirred mixture was concentrated under vacuum and the residue was dissolved in CH_2Cl_2 (50 mL). The resulting solution was successively washed with H_2O (20 mL) and brine (20 mL), dried over Na_2SO_4, and evaporated to dryness, to give diethyl (5-(2-aminoethyl)-2-chloro-9-methoxy-4,6-dioxo-5,6-dihydro-4*H*-benzo[*de*][2,6]naphthyridin-3-yl)phosphonate trifluoroacetate (14 mg, 100 %) as a yellow syrup. HPLC-MS (30-95% gradient of A in B for 10 min) t_R = 0.81 min. ^{1}H NMR (500 MHz, CD_3OD) δ: 1.29 (t, 3H, *J* = 7 Hz, Et), 3.25 (t, 2H, *J* = 6 Hz, 2'-H), 4.11 (s, 3H, OMe), 4.20 (m, 4H, Et), 4.35 (t, 2H, *J* = 6, 1'-H), 7.52 (d, 1H, *J* = 8.5 Hz, 8-H), 8.52 (d, 1H, *J* = 8.5 Hz, 7-H). ^{13}C NMR (125 MHz, CD_3OD) δ: 18.1 (d, *J* = 6.5 Hz, Et), 41.0 and 41.2 ($C_{1'}$ and $C_{2'}$), 59.1 (OMe), 66.9 (d, *J* = 7 Hz, Et), 114.6 (C_8), 116.8 (C_{6a}), 125.3 (d, *J* = 9.5 Hz, C_{9b}), 127.8 (d, *J* =196 Hz, C_3), 136.7 (C_7), 141.4 (C_{9a}), 142.9 (d, *J* =5 Hz, C_{3a}), 153.6 (d, *J* = 6 Hz, C_2), 162.2 (C_9), 165.1 (C_6), 165.3 (d, *J* = 5 Hz, C_4). HRMS (ESI) *m/z*: Calcd. For $C_{18}H_{22}C_lN_3O_6P$ ([M+H]$^+$): 442.0929, found: 442.0942. This trifluoroacetate (12 mg, 0.021 mmol) was dissolved in anhydrous CH_2Cl_2 (5 mL). The solution was stirred at -15ºC for 30 minutes. Then, 2-bromoacetyl bromide (3.7 µL, 0.042 mmol) and DIPEA (7.14 µL, 0.042 mmol) were added to the solution. The reaction mixture was stirred for 1.5 h at rt. Afterwards, the residue

was dissolved in CH_2Cl_2 (50 mL) and the resulting solution was successively washed with H_2O (20 mL) and brine (20 mL), dried over Na_2SO_4, and evaporated to dryness, to give **29** (3.5 mg, 30 %) as a yellow syrup. HPLC-MS (30-95% gradient of A in B for 10 min) t_R = 2.92 min. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.35 (t, 3H, *J* = 7 Hz, Et), 3.64 (m, 2H, 2'-H), 3.77 (s, 2H, CH_2Br), 4.14 (s, 3H, OMe), 4.17-4.47 (m, 6H, 1'-H and Et), 7.09 (m, 1H, NH), 7.29 (d, 1H, *J* = 8.5 Hz, 8-H), 8.51 (d, 1H, *J* = 8.5 Hz, 7-H). HRMS (ESI) *m/z*: Calcd. for $C_{20}H_{23}BrClN_3O_7P$ ($[M+H]^+$): 564.0120, found: 564.0148.

Fluorescence experiments. Excitation and emission spectra of compounds were determined for 7.5 μM, 12 μM or 44 μM solutions in solvents of diverse polarity. The spectra were recorded between 300 and 690 nm (0.5 nm increments and 0.1 s integration time) with excitation set at the appropriate excitation wavelength. Slit widths were set to 15 nm for excitation and to 6 or 20 nm for emission, depending on the observed emission intensity. All the spectra were corrected for background fluorescence by subtracting a blank scan of the solvent solution. Data are summarized in Table 1.

Fluorescence quantum yield determination. Fluorescence quantum yields (Φ) were determined in solvents of different polarity, and calculated with reference to a standard, which was selected depending on the photophysical properties of the corresponding fluorophore.[2] Quinine sulphate dihydrate in 0.1 M H_2SO_4 (Φ = 0.55) was used as reference, except for **17**, **19**, **20**, **21**, **24**, **25**, and **26** that were calculated with reference to a C-102 standard (in EtOH). A 12 μM solution of the corresponding fluorophore was compared to a 12 μM solution of the standard to assure that the absorbance is less than 0.1 at identical excitation wavelengths. The following equation was used to calculate the quantum yield:

$$\Phi = \frac{I_x A_r n^2_x \Phi_r}{A_x I_r n^2_r}$$

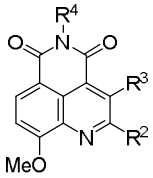
where x and r denote the sample and standard, respectively, A is the absorption at the excitation wavelength, I is the integrated fluorescence intensity, and n is the refractive index of the solvent. Cross-calibration between standards yielded less than 10% error for this method and instrumentation.

Photostability assay. A 12 μM solution of the corresponding cromophore in dioxane (**A1** and **16**) was illuminated at their maximum absorption wavelength (**A1**: 360 nm, **16**: 372 nm) by light of the Xenon lamp of the spectrofluorometer (slits widths were set to 15 nm for excitation and the emission). During the time of illumination (1 h; data interval: 2 seconds), the fluorescence maximum (**A1**: 425 nm, **16**: 460 nm) was recorded as a function of time.

Determination of the kinetic solubility of the naphthalimide A1 and the quinolimide 16 in buffer pH 7.4/DMSO (1%). Kinetic solubility was determined according to the previously reported methods.[3] The solubility of naphthalimide **A1** was: 610±10 μM. The solubility of quinolimide **16** was: 2000±10 μM.

[2] (a) C. Wuerth, M. Grabolle, J. Pauli, M. Spieles and U. Resch-Genger, *Nat. Protoc.*, 2013, **8**, 1535-1550, 1516 pp; (b) A. M. Brouwer, *Pure Appl. Chem.*, 2011, **83**, 2213-2228; (c) K. Rurack and M. Spieles, *Anal. Chem.* , 2011, **83**, 1232-1242.
[3] (a) B. Bard, S. Martel and P.-A. Carrupt, *Eur. J. Pharm. Sci.*, 2008, **33**, 230-240; (b) J. Alsenz and M. Kansy, *Adv. Drug Delivery Rev.*, 2007, **59**, 546-567; (c) L. Di, P. V. Fish and T. Mano, *Drug Discovery Today*, 2012, **17**, 486-495.

Table S1. Photophysical properties of the naphthalimide A1 and quinolimide derivatives 16-26



Compd[a]	R^1	R^2	R^3	solvent	λ_{max}^{abs} (nm)	ε ($M^{-1}cm^{-1}$)	λ_{max}^{em} (nm)	Φ_F [b]
A1			$(CH_2)_2OH$	toluene	362	12251	425	0.64
				dioxane	360	12085	425	0.61
				MeOH	366	12794	442	0.57
				DMSO	368	11898	442	0.47
				H_2O	377	6770	457	0.61
				In vacuum[c]	346		390	
16	H	H	$(CH_2)_2OH$	toluene	377	7873	455	0.90
				dioxane	372	8649	460	0.67
				MeOH	375	6760	490	0.28
				DMSO	377	6849	490	0.03
				H_2O	381	8776	503	0.04
				In vacuum[c]	365		434	
17	$PO(OEt)_2$	H	$(CH_2)_2OH$	toluene	395	4939	484	0.46
				dioxane	390	4252	487	0.54
				MeOH	397	5157	514	0.06
				DMSO	397	4325	510	0.01
				H_2O	403	3752	525	0.01
				In vacuum[c]	382		463	
18	H	Cl	$(CH_2)_2OH$	toluene	381	7555	467	0.83
				dioxane	376	7023	470	0.67
				MeOH	379	7562	500	0.12
				DMSO	382	4399	504	0.01
				H_2O	385	2740	510	0.03
				In vacuum[c]	371		446	
19	$PO(OEt)_2$	Cl	$(CH_2)_2OH$	toluene	401	4476	494	0.52
				dioxane	404	5280	503	0.31
				MeOH	411	3997	525	0.007
				DMSO	395	3725	527	0.0003
				H_2O	402	3435	536	0.001
				In vacuum[c]	391		483	

Table 1. (Continuation)

Compd[a]	R^1	R^2	R^3	solvent	λ_{max}^{abs} (nm)	ε ($M^{-1}cm^{-1}$)	λ_{max}^{em} (nm)	Φ_F [b]
20	H	H	n-Bu	toluene	373	10166	454	0.99
				dioxane	370	10640	461	0.79
				MeOH	373	6961	495	0.38
				DMSO	378	9898	492	0.05
				H_2O	379	2889	510	0.10
21	$PO(OEt)_2$	H	n-Bu	toluene	393	4618	475	0.98
				dioxane	387	5814	485	0.62
				MeOH	396	4981	515	0.06
				DMSO	396	4924	516	0.01
				H_2O	406	3830	518	0.02
24	H	H	$CH_2CH(NHFmoc)CO_2H$	toluene	376	2394	460	0.93
				dioxane	373	7242	461	0.71
				MeOH	373	6873	493	0.07
				DMSO	374	8781	483	0.04
				H_2O	382	2227	498	0.02
25	H	Cl	$CH_2CH(NHFmoc)CO_2H$	toluene	385	3509	474	0.60
				dioxane	376	10268	473	0.58
				MeOH	379	6099	502	0.06
				DMSO	380	7682	510	0.01
				H_2O	394	2341	512	0.02
26	H	H	$(CH_2)_2NHBoc$	toluene	374	5089	455	0.71
				dioxane	370	5125	461	0.59
				MeOH	372	4778	490	0.28
				H_2O	379	2897	500	0.13

[a]Measured in duplicate at a 12 μM concentration, except for **A1** that was measured at a 7.5 μM. [b]Quantum yields calculated with reference to quinine sulfate (in 0.1 M H_2SO_4), except for **17**, **19**, **20**, **21**, **24**, **25**, and **26** that were calculated with reference to a C-102 standard (in EtOH).). [c]TD-DFT calculations in vacuum.

Figure S1.- Photostability assay

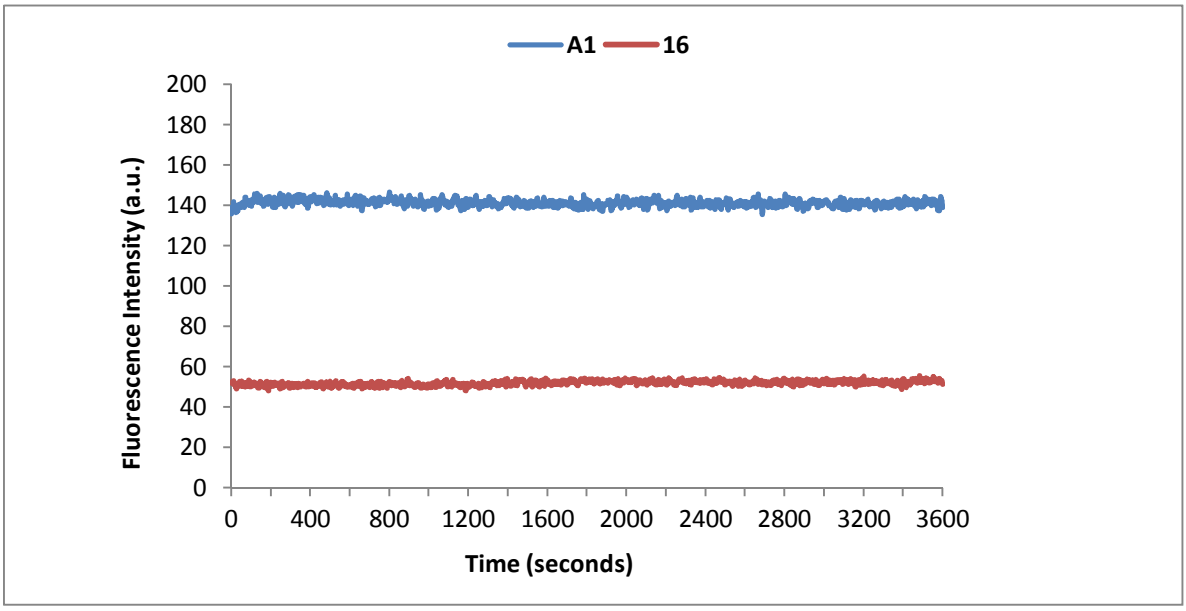


Figure S1. Variation of fluorescence maxima with excitation time

TD-DFT CALCULATIONS

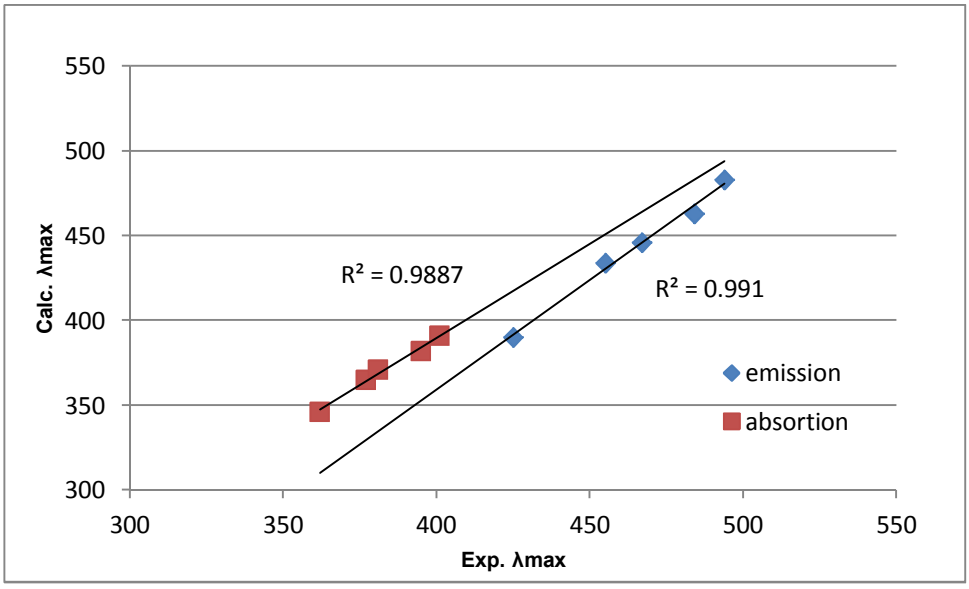


Figure S2. Linear correlations between calculated λ_{max}^{abs} and λ_{max}^{em} in vacuum and experimental values in toluene.

Computational methods The photophysical properties of the naphthalimide **A1** and quinolimides **16-19** have been modelled by means of TD-DFT calculations at the PBE0/6-31+G(d,p) computational level[4] within the Gaussian-09 program.[5] The geometry of the ground (S_0) and first singlet excited electronic (S_1) states of all systems has been optimized at the PBE0/6-31+G(d,p) level and they have been confirmed to be energetic minima by frequency calculations at the same computational level.

Table S2. Calculated HOMO and LUMO energetic values (au) for A1 and the quinolimides 16-19.

	S_0			S_1		
Compd	**HOMO**	**LUMO**	**LUMO-HOMO**	**HOMO**	**LUMO**	**LUMO-HOMO**
A1	-0.24599	-0.09329	0.15270	-0.23822	-0.10073	0.13749
16	-0.25422	-0.10570	0.14852	-0.24491	-0.11539	0.12952
17	-0.25578	-0.11238	0.14340	-0.24747	-0.12380	0.12367
18	-0.25908	-0.11252	0.14656	-0.24989	-0.12290	0.12699
19	-0.25612	-0.11486	0.14126	-0.24904	-0.12910	0.11994

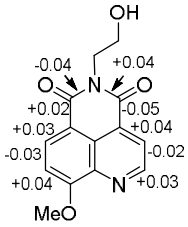


Figure S3. Bond length differences between the S_1 and S_0 states in the quinolimide scaffold of **16**.

[4] (a) C. Adamo and V. Barone, *J. Chem. Phys.*, 1999, **110**, 6158-6170; (b) P. C. Hariharan and J. A. Pople, *Theor. Chim. Acta*, 1973, **28**, 213-222.

[5] M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H. P. Hratchian, A. F. Izmaylov, J. Bloino, G. Zheng, J. L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J. A. Montgomery Jr., J. E. Peralta, F. Ogliaro, M. J. Bearpark, J. Heyd, E. N. Brothers, K. N. Kudin, V. N. Staroverov, R. Kobayashi, J. Normand, K. Raghavachari, A. P. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, N. Rega, N. J. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, R. L. Martin, K. Morokuma, V. G. Zakrzewski, G. A. Voth, P. Salvador, J. J. Dannenberg, S. Dapprich, A. D. Daniels, Ö. Farkas, J. B. Foresman, J. V. Ortiz, J. Cioslowski and D. J. Fox, *Gaussian 09*, Gaussian, Inc., Wallingford, CT, USA, 2009.

Geometry (Å), Total energy (hartree), and number of imaginary frequencies of the optimized S_0 and S_1 electronic configurations of A1 and the quinolimides 16-19.

A1(S_0), Total Energy= -934.120469394 Hartree, NIMAG= 0
C,-2.3613252496,1.9464412143,-2.1441054249
C,-0.9595863409,2.0076114903,-2.1868666403
C,-0.2353776638,2.5685629563,-1.1543949039
C,-0.9143793874,3.0879560958,-0.0265354276
C,-2.3309483865,3.0354543056,0.0446266869
C,-3.0444683301,2.450305193,-1.0486389387
C,1.2298291713,2.6094845742,-1.2240824279
C,-0.1888915982,3.6584638934,1.0433939994
C,1.286313888,3.7265376202,0.9862876022
C,-0.8499670079,4.1607697397,2.1483464355
C,-2.2521436209,4.1092412778,2.2166644301
H,-2.7623762484,4.5064068284,3.0887010759
H,-2.8940857067,1.4998755797,-2.975002009
H,-0.4197921767,1.6094018708,-3.0407017639
H,-0.2607633636,4.5911881412,2.9523350833
O,-4.3824038613,2.4360521516,-0.9140813481
C,-5.1625509191,1.8649478856,-1.9484666436
H,-6.1990491242,1.9588519691,-1.6245760785
H,-5.0242109726,2.4054867899,-2.8919699672
H,-4.9176306246,0.8057901968,-2.088324295
O,1.8620664285,2.145959613,-2.1695049478
O,1.9578144938,4.2147354185,1.8818465824
C,3.3561067669,3.3027253997,-0.2467581346
H,3.6014366193,3.4584660605,-1.3004148588
H,3.6628291161,4.1765266045,0.3315253587
C,4.067495023,2.0679765602,0.2895001551
H,5.1487252887,2.2276152235,0.1483046533
H,3.8849231823,1.9710459088,1.3650673817
O,3.6482432862,0.8639973863,-0.3105420255
H,3.3564561146,1.0521961711,-1.2133421106
N,1.8984225249,3.2110919082,-0.1591888085
C,-2.9824387767,3.5566054569,1.1839980827
H,-4.0652863643,3.5138439553,1.2332465374

A1(S_1), Total Energy= -934.112912158 Hartree, NIMAG= 0
C,-2.3224764608,1.9359201224,-2.1691570543
C,-0.949849258,2.0000394169,-2.2176528307
C,-0.2422534609,2.5860838892,-1.1378588768
C,-0.9174825386,3.1048807452,-0.0035596919
C,-2.3330768171,3.0471941454,0.0650751789
C,-3.0171194291,2.4531549558,-1.0372935849
C,1.2284613453,2.6239057403,-1.209004561
C,-0.1758856602,3.6775938964,1.0539943429

C,1.266748719,3.7434262187,0.9950869607
C,-0.8647471502,4.1967309976,2.187314687
C,-2.2444637282,4.1347830991,2.240205042
H,-2.7640680324,4.532190629,3.1075843202
H,-2.8732340715,1.4910371342,-2.9893762455
H,-0.3804861905,1.6138203801,-3.055673838
H,-0.2774859721,4.6317138446,2.9883127538
O,-4.3421021161,2.4174990345,-0.9313184434
C,-5.138638083,1.8401006753,-1.9577230544
H,-6.1677486446,1.9366244256,-1.614119848
H,-5.013293101,2.3821201805,-2.9007386963
H,-4.8931805125,0.7817597325,-2.0928401927
O,1.8207021667,2.1375996622,-2.1819774764
O,1.9659098384,4.2365505751,1.8811959329
C,3.3471243392,3.291621922,-0.2464952189
H,3.6007191753,3.4674577781,-1.2959818332
H,3.6537348104,4.1503390783,0.3538837854
C,4.045327168,2.0416920399,0.2694013013
H,5.1292380056,2.1973367041,0.1456490016
H,3.8471363272,1.9232149461,1.3400657949
O,3.6291129043,0.8527428777,-0.3647847397
H,3.3292521345,1.0667817926,-1.2592766588
N,1.8895375603,3.2100887239,-0.1645293079
C,-3.0007908705,3.5677421218,1.1961047222
H,-4.0816362167,3.5278679552,1.2518356394

16(S_0), Total Energy= -950.137771623 Hartree, NIMAG= 0
C,-2.3662694124,1.961934033,-2.1225758548
C,-0.9650550888,2.0165699449,-2.1870603103
C,-0.223979762,2.5723164769,-1.1634886457
C,-0.8953132296,3.0873801747,-0.0324128977
C,-2.3090044747,3.0454060981,0.0679115524
C,-3.0472582225,2.4632318925,-1.0209990544
C,1.2399166894,2.6169160768,-1.2355848194
C,-0.1747466197,3.6550529474,1.0373966746
C,1.3055180925,3.7271752348,0.9815815461
C,-0.8639015328,4.1416591695,2.125332407
C,-2.2707116176,4.0511899624,2.1209615671
H,-2.8380474917,4.4295092818,2.9691030309
H,-2.9095137233,1.5188862832,-2.9486066768
H,-0.4418543611,1.6175963849,-3.0508515377
H,-0.3245819937,4.5810847569,2.9582275188
O,-4.373450534,2.4508278753,-0.8767719623
C,-5.1623435582,1.8860408302,-1.9073536672
H,-6.1950705615,1.9827027973,-1.5729657216
H,-5.0309605061,2.429749822,-2.8503474807
H,-4.9227917177,0.8262557201,-2.0536998152
O,1.8742919293,2.159973654,-2.1801205883
O,1.9671760576,4.2129909612,1.8838641894
N,-2.9760459305,3.5266272518,1.1377853453
C,3.3692718372,3.3071521623,-0.2527076993
H,3.6152353452,3.4472839113,-1.3080709098

H,3.6802176952,4.1877872681,0.3131032668
C,4.0714692975,2.0742780124,0.3016934608
H,5.1531620723,2.2159025513,0.1465255069
H,3.8983439498,1.9993179797,1.3801257949
O,3.6250401585,0.8651262432,-0.2664588573
H,3.3897729165,1.0232631201,-1.1906105183
N,1.9112164468,3.2208565118,-0.165763454

16(S_1), Total Energy= -950.127328098 Hartree, NIMAG= 0
C,-2.32093181,1.9539530022,-2.1499723597
C,-0.9460147402,2.0150380447,-2.2175453389
C,-0.2345230904,2.5921359639,-1.1493920001
C,-0.9040772071,3.1088437023,-0.0015012693
C,-2.3030959928,3.0613084149,0.096082405
C,-3.0077594849,2.4668387444,-1.0084262439
C,1.2467732192,2.6378380209,-1.2251417707
C,-0.1547163458,3.6812211679,1.0533267384
C,1.2789791122,3.7548611807,0.993102226
C,-0.894165918,4.1748863853,2.1572636159
C,-2.2772859097,4.0709346278,2.1402884436
H,-2.8493530638,4.447180896,2.986335913
H,-2.8834193261,1.5137959129,-2.9649874984
H,-0.3895504904,1.6311462821,-3.0652605059
H,-0.371557294,4.6231444096,2.9946378118
O,-4.3172026136,2.4302265239,-0.8904584841
C,-5.1363765842,1.8620826329,-1.9062200916
H,-6.1565148334,1.9646702054,-1.5397507376
H,-5.0244860239,2.4096957423,-2.8473358074
H,-4.898961239,0.8032739751,-2.0493611535
O,1.8250600721,2.157068626,-2.2045080149
O,1.9905596299,4.2435123741,1.8690039611
N,-3.0140920469,3.5335117164,1.1500111331
C,3.3604630423,3.2926167926,-0.2580913663
H,3.6225178693,3.4491272114,-1.3084907302
H,3.6717995132,4.158351197,0.3296633277
C,4.0421014375,2.043726518,0.2842392195
H,5.1279549432,2.1753591999,0.1511863758
H,3.8464151874,1.9518878236,1.3572294037
O,3.5941958677,0.8475948847,-0.3145891499
H,3.3837418103,1.02431125,-1.2407638969
N,1.9032544599,3.2219019606,-0.183412765

17(S_0), Total Energy= -1674.52432988 Hartree, NIMAG= 0
C,-2.2427854067,1.7611534,-1.843847769
C,-0.8540789396,1.8858277181,-1.9984656974
C,-0.0813087093,2.5410418484,-1.0617414285
C,-0.6965327375,3.0957601604,0.0863076683
C,-2.0987278618,2.9818819202,0.2688659789
C,-2.8744764492,2.296186628,-0.7315570531
C,1.3652648181,2.6452520373,-1.2559880684
C,0.0620399697,3.7656708137,1.0763693337
C,1.5348231399,3.8872831585,0.8836154938

C,-0.5984749181,4.2833756859,2.1851537905
C,-2.0070145906,4.1089997103,2.2485419473
H,-2.5318660412,4.51475157,3.1095409915
H,-2.8113491812,1.2403382488,-2.604922311
H,-0.3599452769,1.4634709873,-2.8681895166
O,-4.1848791975,2.2295782406,-0.4942555218
C,-5.0094034618,1.5673185289,-1.4351971342
H,-6.0217960522,1.6359329011,-1.0378839907
H,-4.9663105267,2.0588915641,-2.4142633202
H,-4.7265383311,0.5129153297,-1.5365064189
O,1.9491822369,2.1555334448,-2.2171911569
O,2.2571437163,4.4393155855,1.6927098567
N,-2.7328430805,3.4900311079,1.3416759111
C,3.5158477565,3.5008223595,-0.4866493758
H,3.6749851137,3.5702211348,-1.5653114489
H,3.8202724004,4.4360912998,-0.0129396768
C,4.3209944583,2.3476981938,0.0989410271
H,5.3792066767,2.5255154498,-0.151696264
H,4.2334452839,2.3472686947,1.1900793316
O,3.8934548647,1.0807238349,-0.3436732499
H,3.5883473301,1.1569452463,-1.2578257397
N,2.0746949276,3.3491513855,-0.2838379553
P,0.0807791021,5.1708711525,3.6291730882
O,-1.0185815867,5.4627255573,4.5859628795
O,0.803842887,6.4270806345,2.9693780764
O,1.2667839437,4.3054871537,4.2797444989
C,1.9409662625,7.0637558807,3.5798043223
H,1.6764815552,7.3720464576,4.5980064206
H,2.7538173063,6.3331494276,3.626044023
C,1.0408542985,3.5555044655,5.4902259855
H,0.2409297012,4.0324292287,6.0646408926
H,1.9772653999,3.6374050298,6.04960926
C,2.3105347982,8.2551678942,2.7301281062
H,3.178608067,8.762550425,3.1630804259
H,2.5656554944,7.937737821,1.7152294393
H,1.4833134152,8.9683983872,2.6760935867
C,0.7176064955,2.1115928814,5.1760177938
H,1.5041723619,1.6590567219,4.565282823
H,0.6304807218,1.5403609927,6.1063104009
H,-0.2329151449,2.0270607701,4.639895964

17(S_1), Total Energy= -1674.51348724 Hartree, NIMAG= 0
C,-2.1998271459,1.7587128613,-1.8776153742
C,-0.8397529949,1.8920735007,-2.0347750793
C,-0.0905189466,2.5637500617,-1.0504290547
C,-0.6991003134,3.1108550338,0.119190326
C,-2.0818245145,2.9838579781,0.3011662378
C,-2.830609524,2.2964468274,-0.7178157513
C,1.3733742176,2.6707516159,-1.2519364692
C,0.0886691162,3.7858232368,1.0919853426
C,1.511529967,3.9170020176,0.8952473722
C,-0.6206529732,4.2986243187,2.2277010835

C,-2.0092987516,4.0968610634,2.280818093
H,-2.5383563809,4.4905564553,3.1457904527
H,-2.7882208889,1.2462860932,-2.6295344539
H,-0.3137937806,1.4947551558,-2.8958420118
O,-4.1226026407,2.2032757963,-0.5018029593
C,-4.9835946634,1.5497450468,-1.4291600377
H,-5.9789313555,1.6260933515,-0.9947937112
H,-4.9625395733,2.0554414895,-2.3994173009
H,-4.7065542169,0.4967875733,-1.5389906208
O,1.8988805854,2.1550461359,-2.2425015276
O,2.2820281964,4.476638102,1.6674938973
N,-2.758292379,3.4690664926,1.3738702494
C,3.5098956946,3.4870837985,-0.4941488082
H,3.6840474177,3.5659289078,-1.5709504971
H,3.8194119509,4.4118967249,-0.0042225513
C,4.2913480204,2.3179701797,0.0909788587
H,5.3561262738,2.480230154,-0.1410778321
H,4.1837378386,2.3091435898,1.1798342506
O,3.850700133,1.0593931324,-0.3689125321
H,3.5978334719,1.139470103,-1.2976068407
N,2.0679875278,3.3525402944,-0.3034473023
P,0.0359331028,5.1925249771,3.6467594945
O,-1.0501976754,5.4950350274,4.6196006981
O,0.7713031443,6.4501066059,2.990389604
O,1.2457442309,4.3554208193,4.3093834466
C,1.9328099116,7.0535313793,3.5803574771
H,1.6956095664,7.3706784142,4.6030150504
H,2.7274587615,6.3026394404,3.6140793474
C,1.0176389993,3.5768353405,5.4950847375
H,0.2004614982,4.0245056594,6.0697454667
H,1.9428149121,3.6613877426,6.0735767953
C,2.3222854224,8.2341308436,2.7232235641
H,3.2109505982,8.7189180809,3.1406422835
H,2.5517384464,7.9062184123,1.7054194915
H,1.513923042,8.9697293538,2.6795477486
C,0.7268225762,2.1322075718,5.1479777164
H,1.5321917984,1.7086430814,4.5407033368
H,0.6346649466,1.5395693088,6.0646142187
H,-0.2112856404,2.0431399192,4.5912702948

18(S_0), Total Energy= -1409.57537870 Hartree, NIMAG= 0
C,-2.3544949625,1.9510778175,-2.1418696469
C,-0.9539448695,2.0086366867,-2.2094699427
C,-0.2128554679,2.5665758892,-1.1861806873
C,-0.8853105357,3.0781034602,-0.0563728483
C,-2.2959440916,3.0330367745,0.0443507206
C,-3.0368998072,2.4513060189,-1.0398592475
C,1.2517552918,2.6178144917,-1.2573690399
C,-0.1679727489,3.6475048385,1.0168606256
C,1.3146935718,3.7211381487,0.9640413348
C,-0.8479862522,4.1342433922,2.1069843765
C,-2.2573541754,4.034227759,2.0856645954

Cl,-3.1311302004,4.6501946339,3.4574696374
H,-2.8990454446,1.5064618453,-2.9662999447
H,-0.4314096345,1.6110614162,-3.07416679
H,-0.3158707187,4.5742951323,2.9426120625
O,-4.3619530451,2.4386030663,-0.8919936609
C,-5.154075327,1.8773488356,-1.9230663924
H,-6.1858790576,1.9767358154,-1.5871412613
H,-5.0211838926,2.422658361,-2.8647798114
H,-4.9172967756,0.8172129262,-2.0705846268
O,1.8873394749,2.1671969064,-2.2026390013
O,1.971325674,4.2025861682,1.8712183189
N,-2.9585828016,3.5158191978,1.1182412449
C,3.3794309223,3.3047767981,-0.2645415808
H,3.630275633,3.4379021224,-1.3195048917
H,3.6904624805,4.1879201045,0.2973077351
C,4.072379659,2.070765231,0.3002166686
H,5.1552637906,2.2019849242,0.1452056239
H,3.8972906207,2.0041113497,1.3786471884
O,3.6135815544,0.862133073,-0.2585564483
H,3.4146031777,1.0068439323,-1.1929854369
N,1.9205201076,3.2217682728,-0.1842774831

18(S_1), Total Energy= -1409.56469482 Hartree, NIMAG= 0
C,-2.3112628774,1.9424033584,-2.1697886033
C,-0.9374715446,2.0079489277,-2.2371381914
C,-0.2233921541,2.5876530915,-1.1697110951
C,-0.8900927756,3.1001387861,-0.0252284307
C,-2.2866095819,3.0478496669,0.0724538933
C,-2.9973665385,2.4538861484,-1.0292081538
C,1.259393315,2.6373042374,-1.2464151283
C,-0.143796201,3.6748014241,1.0335606365
C,1.290129138,3.751038736,0.9740563379
C,-0.8760441202,4.1658870898,2.1404571624
C,-2.2601199412,4.048837441,2.1028096123
Cl,-3.1652693795,4.6509408049,3.4598078293
H,-2.8735793878,1.4997391963,-2.9835074683
H,-0.3801853042,1.6252105372,-3.0849397137
H,-0.3621139899,4.6145860661,2.9809257411
O,-4.3052975041,2.4202799334,-0.9042108971
C,-5.1311570964,1.8581571358,-1.9191752411
H,-6.1494624593,1.9664540302,-1.5497025659
H,-5.0166992719,2.4069971262,-2.8590988666
H,-4.8991380089,0.7984418176,-2.0635928734
O,1.836814764,2.1604763928,-2.2266198084
O,1.9987710156,4.2380213374,1.8521515008
N,-2.9954756576,3.5185746094,1.129218531
C,3.3719298835,3.2900589214,-0.2727919446
H,3.6386857997,3.435695106,-1.3233896402
H,3.6838559929,4.16048313,0.3077008357
C,4.0444201938,2.0423700747,0.2843744224
H,5.131536317,2.1639312888,0.1531655569
H,3.8446182622,1.9617259036,1.3572657442

O,3.5862548819,0.8445266876,-0.3028928341
H,3.4136964878,1.0046634327,-1.2394750959
N,1.9141598923,3.2229629502,-0.2038998616

19(S_0), Total Energy= -2133.94540925 Hartree, NIMAG= 0
C,-2.3049148978,2.4442104171,-2.2258161095
C,-0.915935639,2.6175268896,-2.3294564153
C,-0.1432013912,2.9034185258,-1.2225578464
C,-0.7679935636,3.0396340118,0.0390879995
C,-2.1663684813,2.8835136757,0.1677358131
C,-2.9422867989,2.5714890172,-1.0001869258
C,1.3034177165,3.0929989218,-1.3633848226
C,-0.0290140702,3.3868134344,1.1952021219
C,1.4622644781,3.3198654715,1.0963260367
C,-0.6931804666,3.6702481356,2.3853227552
C,-2.089344065,3.3506276147,2.3981677885
Cl,-2.9616120282,3.3340779075,3.8932576399
H,-2.8727027746,2.2125168331,-3.119075662
H,-0.4241276857,2.5310906371,-3.2935010622
O,-4.2527930628,2.4303643994,-0.7987268375
C,-5.0770161186,2.1136576051,-1.905553105
H,-6.0886633201,2.0422840327,-1.5069992779
H,-5.0377565467,2.9023282978,-2.6661317746
H,-4.7895896932,1.1535794961,-2.3499773009
O,1.8829813696,3.042690795,-2.4417903766
O,2.1751454661,3.2269193711,2.0742541115
N,-2.7839970447,2.9838638097,1.3583836045
C,3.4726519736,3.3720452721,-0.2797588304
H,3.7035980017,3.8621271612,-1.2285665001
H,3.8370062357,3.9878635984,0.5454695936
C,4.1268624448,1.9965585406,-0.2110903259
H,5.2096567926,2.1398815081,-0.3569110537
H,3.9774516972,1.5622307554,0.7812092817
O,3.5984533822,1.0741300411,-1.1354202369
H,3.4300470854,1.5293702164,-1.970382594
N,2.0136022986,3.3193595701,-0.1845414512
P,0.0410562896,4.629005443,3.7704413207
O,-0.9525852527,5.4882959051,4.4578471133
O,1.2305384826,5.502682798,3.124888278
O,0.7683916776,3.5059752749,4.6280756172
C,1.0108542669,6.8980599246,2.8356962887
H,0.5002461265,6.9737312544,1.8673841534
H,0.3579126562,7.32492839,3.6020252335
C,1.4890992506,3.8670594428,5.8242748639
H,0.8443391039,4.4907121526,6.4532341977
H,2.3706423242,4.4474382129,5.5299887716
C,2.3566043867,7.5819377639,2.7921266267
H,2.2243039696,8.6412947047,2.5495587973
H,2.8598874517,7.5105092854,3.7606176731
H,3.0031846555,7.1323022548,2.0329852031
C,1.8823804066,2.5908399408,6.5270010053
H,2.509278049,1.9719649685,5.8793394135

H,2.4464392265,2.8280783594,7.4346878284
H,0.9967526449,2.0152270316,6.8097255972

19(S_1), Total Energy= -2133.93392953 Hartree, NIMAG= 0
C,-2.2350015925,2.6084473864,-2.2892712091
C,-0.868585452,2.7388337796,-2.3624771778
C,-0.1204752433,2.9618879083,-1.1863858568
C,-0.7452611419,3.0762190496,0.0802887528
C,-2.1307041086,2.912171252,0.1843478559
C,-2.880322516,2.6819518741,-1.021938461
C,1.355103353,3.0478696805,-1.3010260952
C,0.0156632116,3.3507448824,1.2499764737
C,1.4578950449,3.2551389865,1.1776112401
C,-0.7157090561,3.6109811035,2.4605851682
C,-2.0855023837,3.2470182449,2.4292658014
Cl,-2.9865780696,3.1470408069,3.9007274357
H,-2.8159995836,2.4365208779,-3.18746458
H,-0.3307663695,2.6672898328,-3.301684962
O,-4.1761474798,2.5374657148,-0.8636094517
C,-5.0324093197,2.2956628931,-1.9762525209
H,-6.0327900382,2.2194612457,-1.5537430242
H,-4.9904186951,3.1288254933,-2.6844386123
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N,-2.7912036132,2.911410082,1.3663007146
C,3.5002332931,3.1908687298,-0.2079659081
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H,5.1838158417,1.881881289,-0.267539984
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P,-0.044547529,4.5693333497,3.8404935546
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C,1.6060336415,3.9271978659,5.7821810119
H,1.0014036152,4.5234020206,6.4754353807
H,2.4106656635,4.554290069,5.3821308984
C,2.0664227512,7.6385459837,2.7227988746
H,1.853183228,8.6708431898,2.4263703091
H,2.5931327651,7.6568900857,3.6813580447
H,2.7287505943,7.1928419447,1.9748246198
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H,2.7436043539,2.1016031631,5.7430006713
H,2.8067630808,2.9804011437,7.2868811104

H,1.3491900416,2.0679487697,6.8423201399

Cytotoxicity ressults. Taking into account the literature precedent on the antitumor activity of quinolimide derivatives,[6] compounds **16**-**27** were included in a HTS for cytotoxicity in non-small cell lung cancer (A549), colon (HT29), breast (MDA-MD-231), and pancreas (PSN1) human cancer cell lines, using doxorubicin as positive control and according to the National Cancer Institute (NCI) protocols. As shown in Table S2, none of our quinolimide derivatives showed cytotoxicity at a concentration below 10^{-5} M.

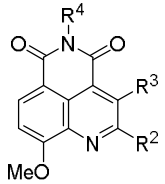
Cytotoxicity assays. A colorimetric assay, using the sulforhodamine B (SRB) reaction, was adapted for a quantitative measurement of cell growth and viability, following the technique described by Skehan, P. A. *et al*.[7] Cells (MDA-MB-231, A549, HT-29 and PSN1) were seeded in 96 well microtiter plates, at 5×10^3 cells per well in aliquots of 195 μL of RPMI medium, and they were allowed to attach to the plate surface by growing in drug free medium for 18 h. Afterwards, samples were added in aliquots of 5 μL [dissolved in (3:7) DMSO/H_2O]. After 48 h exposure, cells were fixed by adding 50 μL of cold 50% (wt/vol) trichloroacetic acid, and incubating at 4 ºC for 60 min. Then, the plates were washed with deionized H_2O and dried. 100 μL of SRB solution (0.4% wt/vol in 1% acetic acid) was added to each microtiter well and these were incubated at room temperature for 10 min. Unbound SRB was removed by washing with 1% acetic acid, the plates were air dried, and the bound stain was solubilized with Tris buffer. Optical densities were read on an automated spectrophotometer plate reader at a single wavelength of 490 nm. Data analysis was automatically generated by the high throughput screening LIMS implemented at the laboratory. The three response parameters GI_{50} (50% cell growth inhibition), LC_{50} (50% lethal concentration), and TGI (total growth inhibition) were extracted from concentration-response curves by linear interpolation, according to the National Cancer Institute (NCI) protocols.[8]

[6] M. F. Braña, A. Gradillas, A. Gómez, N. Acero, F. Llinares, D. Muñoz-Mingarro, C. Abradelo, F. Rey-Stolle, M. Yuste, J. Campos, M. A. Gallo and A. Espinosa, *J. Med. Chem.*, 2004, **47**, 2236-2242.

[7] P. Skehan, R. Storeng, D. Scudiero, A. Monks, J. McMahon, D. Vistica, J. T. Warren, H. Bokesch, S. Kenney and M. R. Boyd, *J. Natl. Cancer. Inst.*, 1990, **82**, 1107-1112.

[8] R. H. Shoemaker, *Nat. Rev. Cancer*, 2006, **6**, 813-823.

Table S2. Cytotoxicity HTS results of quinolimides **16-27**



Compd	R^2	R^3	R^4	Chemical Formula	MW(g/mol)	GI_{50} (µM)			
						Lung A549	Colon HT29	Breast MDA-MD-231	Pancreas PSN1
16	H	H	$(CH_2)_2OH$	$C_{14}H_{12}N_2O_4$	272.26	>36.7	>36.7	>36.7	>36.7
17	H	$PO(OEt)_2$	$(CH_2)_2OH$	$C_{18}H_{21}N_2O_7P$	408.35	>24.5	>24.5	>24.5	>24.5
18	Cl	H	$(CH_2)_2OH$	$C_{14}H_{11}ClN_2O_4$	306.70	>32.6	>32.6	>32.6	>32.6
19	Cl	$PO(OEt)_2$	$(CH_2)_2OH$	$C_{18}H_{20}ClN_2O_7P$	442.79	>22.6	>22.6	>22.6	>22.6
20	H	H	n-Bu	$C_{16}H_{16}N_2O_3$	284.32	>35.2	>35.2	>35.2	>35.2
21	H	$PO(OEt)_2$	n-Bu	$C_{20}H_{25}N_2O_6P$	420.40	>23.8	>23.8	>23.8	>23.8
24	H	H	$CH_2CH(NHFmoc)CO_2H$	$C_{30}H_{23}N_3O_7$	537.53	>18.6	>18.6	>18.6	>18.6
25	Cl	H	$CH_2CH(NHFmoc)CO_2H$	$C_{30}H_{22}ClN_3O_7$	571.97	>17.5	>17.5	>17.5	>17.5
26	H	H	$(CH_2)_2NHBoc$	$C_{19}H_{21}N_3O_5$	371.39	>26.9	>26.9	>26.9	>26.9
27	Cl	$PO(OEt)_2$	$(CH_2)_2NHBoc$	$C_{23}H_{29}ClN_3O_8P$	541.92	>18.5	>18.5	>18.5	>18.5
Doxorubicin[a]						0.07	0.10	0.09	

[a]Reference drug

Peptide synthesis and labelling. Peptides used in this study were purchased from GL Biochem, (Shanghai, China), labelled on their unique cysteine with the bromomethyl acetamide **29** in a 5-10 fold excess dye overnight, then purified from free dye on NAP-5 columns (GE Healthcare). CDK5 peptide: GVPSSALREICLLK; PEP-CDK5 peptide: KETWWETWWTEKK GVPSSALREICLLK; P25 peptide: KEAFWDRCLSVINLM; CTL peptide VESSDTIDNVKSKIQDKEGC.

Fluorescence titration experiments. Fluorescence titration assays were performed in 96-well plates in 200µL 50 mM potassium phosphate (50 mM KH_2PO_4/K_2PO_4, pH 7.4) 150mM NaCl using a Clariostar spectrofluorimeter (BMG). Bromomethyl acetamide **29** fluorescently-labelled peptides or proteins were excited at 390 nm and emission signal acquired at between 405 and 605 nm unless stated otherwise. Data analysis was performed using the GraFit Software (Erathicus Ltd). Experiments were performed in triplicate, and error bars indicate standard deviation from average.

Cell culture, internalization and microscopy. Cell culture media, serum and antibiotics were purchased from Invitrogen. U87 cells were cultured in DMEM + Glutamax supplemented with 10% FCS, 100 units/mL penicillin (G sodium salt) and 100 µg/mL streptomycin at 37°C in an atmosphere containing 5% CO_2. 2µM **29**-Labelled CDK5 peptide or Pep-CDK5 peptide was overlaid onto U87 cells grown to 50-60% confluency in DMEM complemented with 10% of glucose, for 3 hours. Cells were then fixed with formalin in PBS for 10min, washed in PBS and nuclei stained with Hoechst. Indirect immunofluorescence was performed with rabbit polyclonal anti-p25 (C-19 from Santa Cruz) at 1:250 dilution in blocking buffer (4% BSA,4% goat serum and 0,1% Triton) overnight, washed and then incubated with Alexa647-conjugated secondary antibodies at 1:500 dilution for 1h, washed again in PBS, and nuclei were stained with Hoechst, washed in water and mounted on glass slides in Mowiol. Fluorescent cells were observed with a Zeiss microscope equipped with a CoolSnap Camera and images were acquired using MetaMorph software. Excitation band/dichroic/emission band filters for imaging fluorescent signals were as follows: Hoechst: 340-380/400/450-490 nm; Alexa647-conjugated antibodies were imaged using the Cy5 filters: 590-650/ 660/662-737 nm; **29** fluorescence was imaged using the GFP filters: 450-490/495</500-550nm.

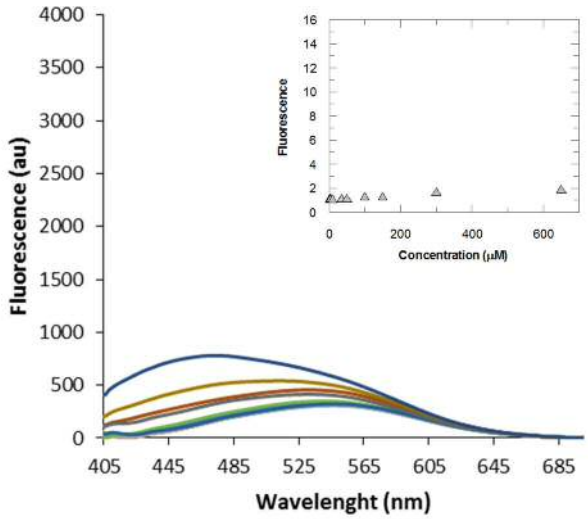


Figure S4. Titration of 5 µM **29**-labelled K5 peptide with an irrelevant peptide (Ctrl)

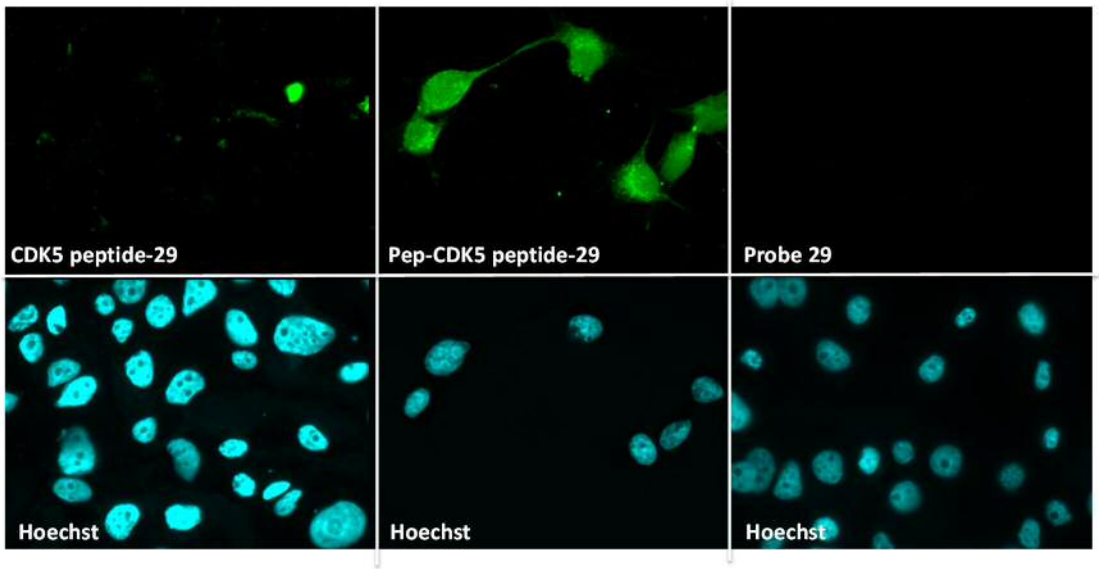
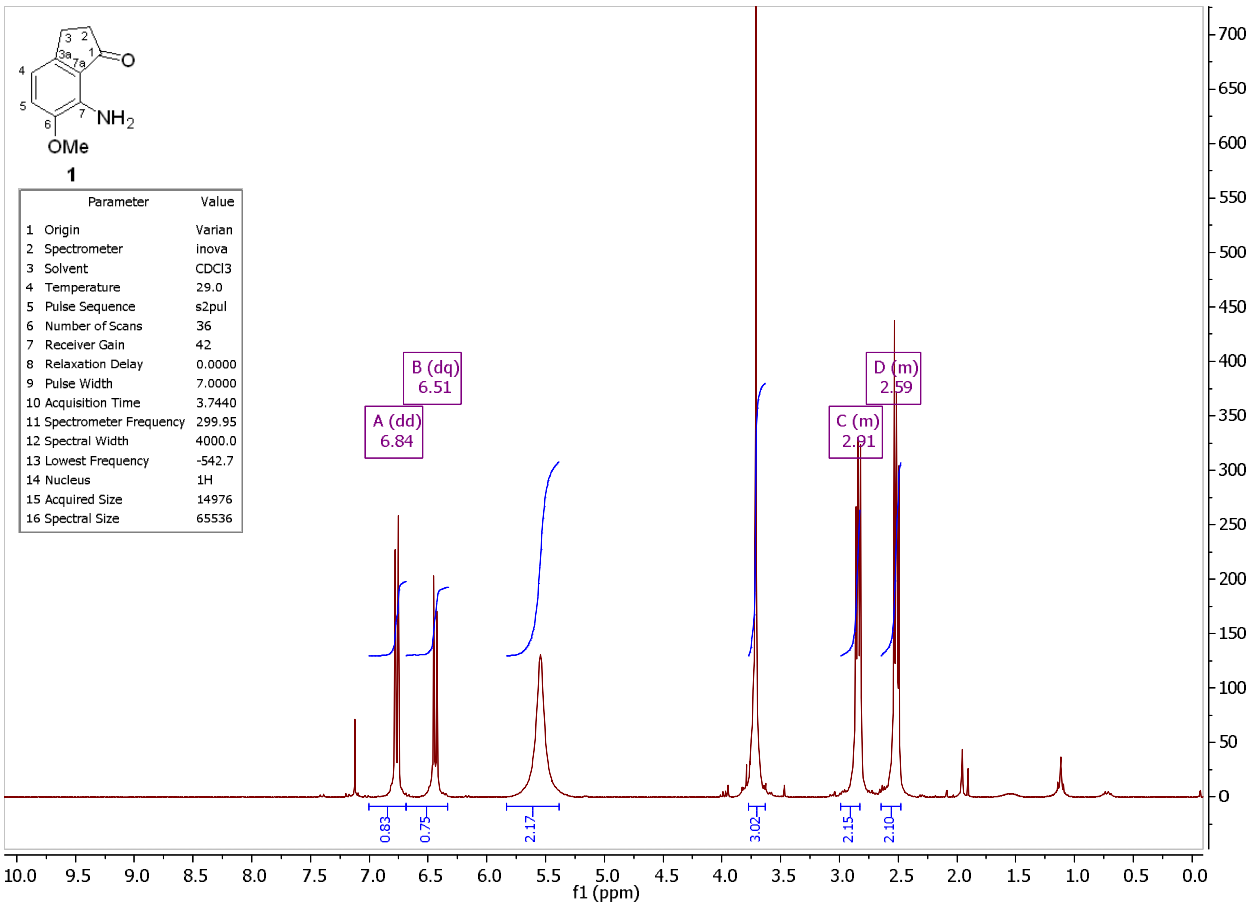


Figure S5. 2 μM **29**-labelled Pep-CDK5 peptide penetrates readily into U87 cells, whereas neither the CDK5 peptide alone, nor **29** alone were observed upon observation through the GFP filter. Nuclear staining with Hoechst is shown in the lower panels, whereas upper panels represent fluorescence emission of **29** through the GFP filter of the microscope.

^{1}H NMR and ^{13}C NMR spectra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9 Pulse Width 7.0000
10 Acquisition Time 3.7440
11 Spectrometer Frequency 299.95
12 Spectral Width 4000.0
13 Lowest Frequency -542.7
14 Nucleus 1H
15 Acquired Size 14976
16 Spectral Size 65536
A (dd) 6.84
B (dq) 6.51
C (m) 2.91
D (m) 2.59
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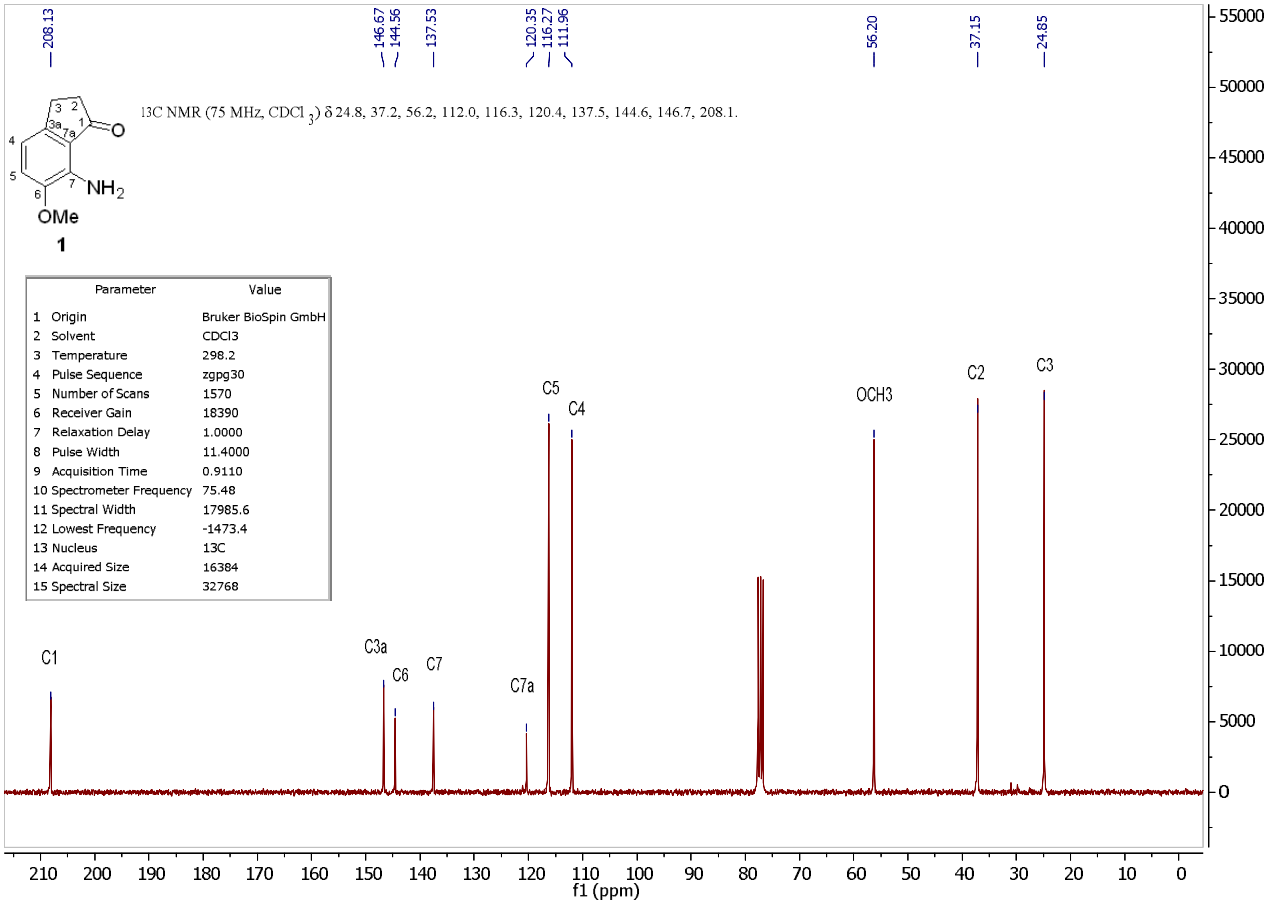
0.75
2.17
3.02
2.15
2.10
f1 (ppm)


208.13
146.67
144.56
137.53
120.35
116.27
111.96
56.20
37.15
24.85
13C NMR (75 MHz, CDCl 3) δ 24.8, 37.2, 56.2, 112.0, 116.3, 120.4, 137.5, 144.6, 146.7, 208.1.
OMe
1
Parameter Value
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2 Solvent CDCl3
3 Temperature 298.2
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7 Relaxation Delay 1.0000
8 Pulse Width 11.4000
9 Acquisition Time 0.9110
10 Spectrometer Frequency 75.48
11 Spectral Width 17985.6
12 Lowest Frequency -1473.4
13 Nucleus 13C
14 Acquired Size 16384
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C1
C3a
C6
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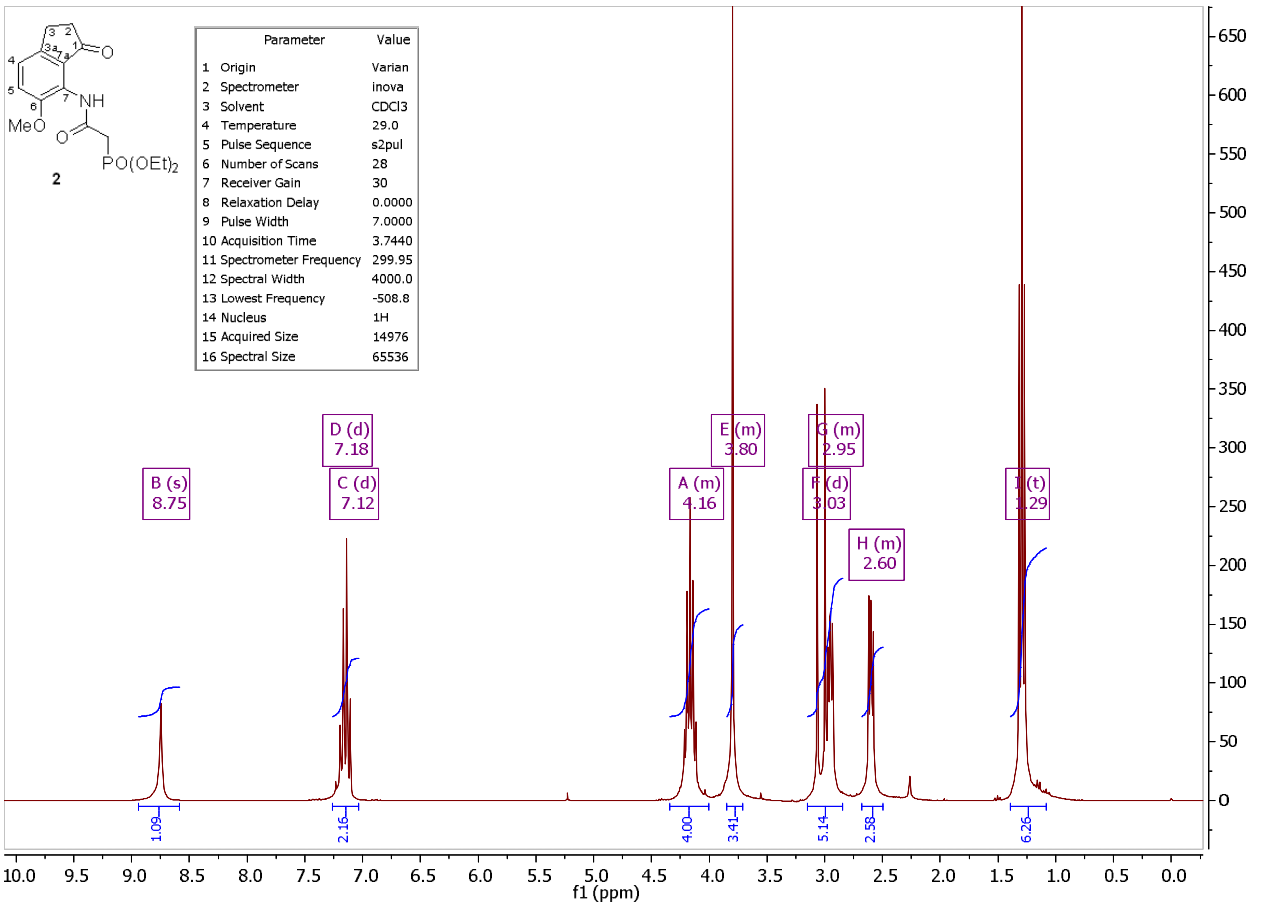
C7a
C5
C4
OCH3
C2
C3
f1 (ppm)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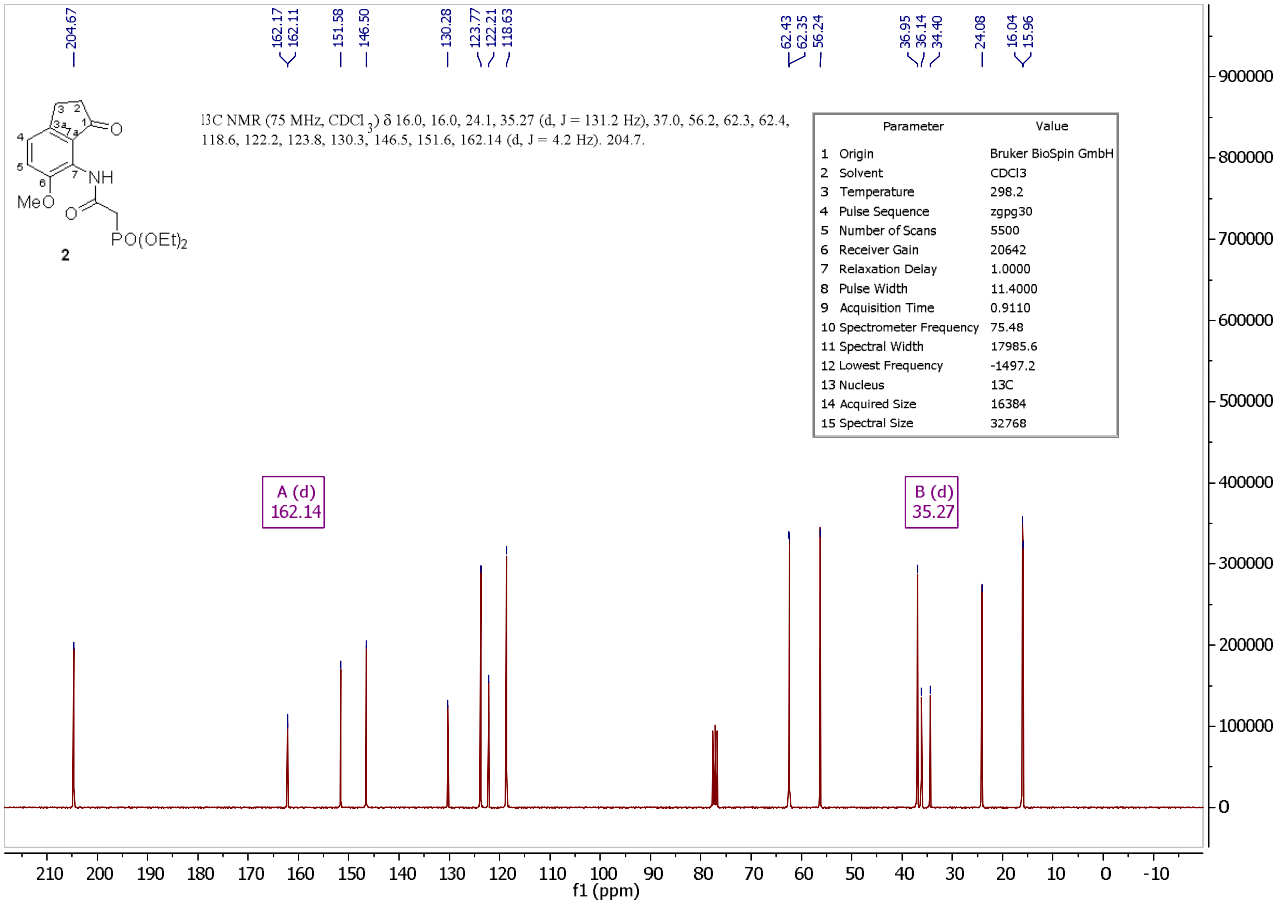
9 Pulse Width 7.0000
10 Acquisition Time 3.7440
11 Spectrometer Frequency 299.95
12 Spectral Width 4000.0
13 Lowest Frequency -508.8
14 Nucleus 1H
15 Acquired Size 14976
16 Spectral Size 65536
B (s) 8.75
D (d) 7.18
C (d) 7.12
A (m) 4.16
E (m) 3.80
G (m) 2.95
F (d) 3.03
H (m) 2.60
I (t) 1.29
1.09
2.16
4.00
3.41
5.14
2.58
6.26
f1 (ppm)


204.67
162.17
162.11
151.58
146.50
130.28
123.77
122.21
118.63
62.43
62.35
56.24
36.95
36.14
34.40
24.08
16.04
15.96
2
13C NMR (75 MHz, CDCl3) δ 16.0, 16.0, 24.1, 35.27 (d, J = 131.2 Hz), 37.0, 56.2, 62.3, 62.4, 118.6, 122.2, 123.8, 130.3, 146.5, 151.6, 162.14 (d, J = 4.2 Hz). 204.7.
Parameter Value
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3 Temperature 298.2
4 Pulse Sequence zgpg30
5 Number of Scans 5500
6 Receiver Gain 20642
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8 Pulse Width 11.4000
9 Acquisition Time 0.9110
10 Spectrometer Frequency 75.48
11 Spectral Width 17985.6
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13 Nucleus 13C
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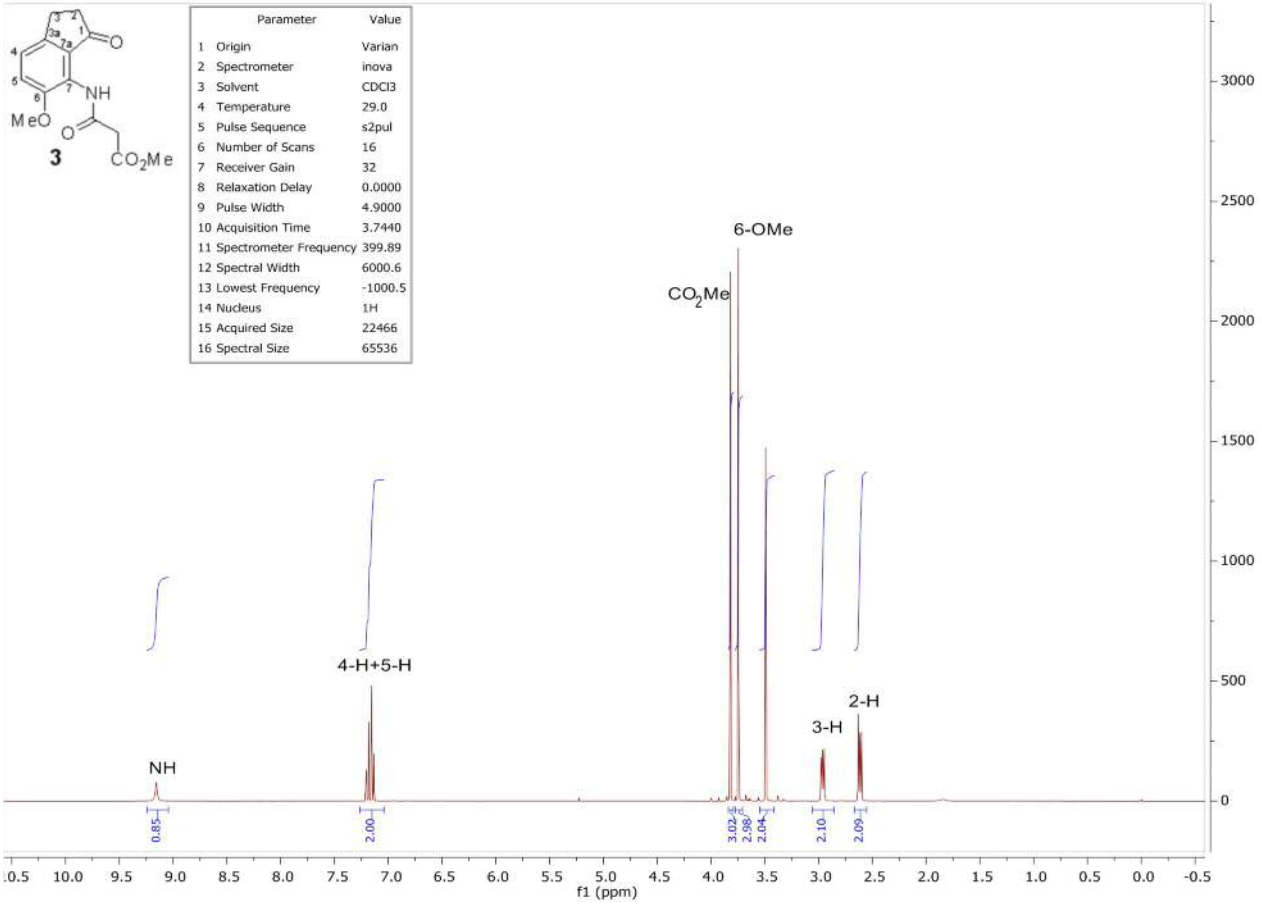
B (d) 35.27
f1 (ppm)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O
CO2Me
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15 Acquired Size 22466
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6-OMe
CO2Me
4-H+5-H
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3-H
NH
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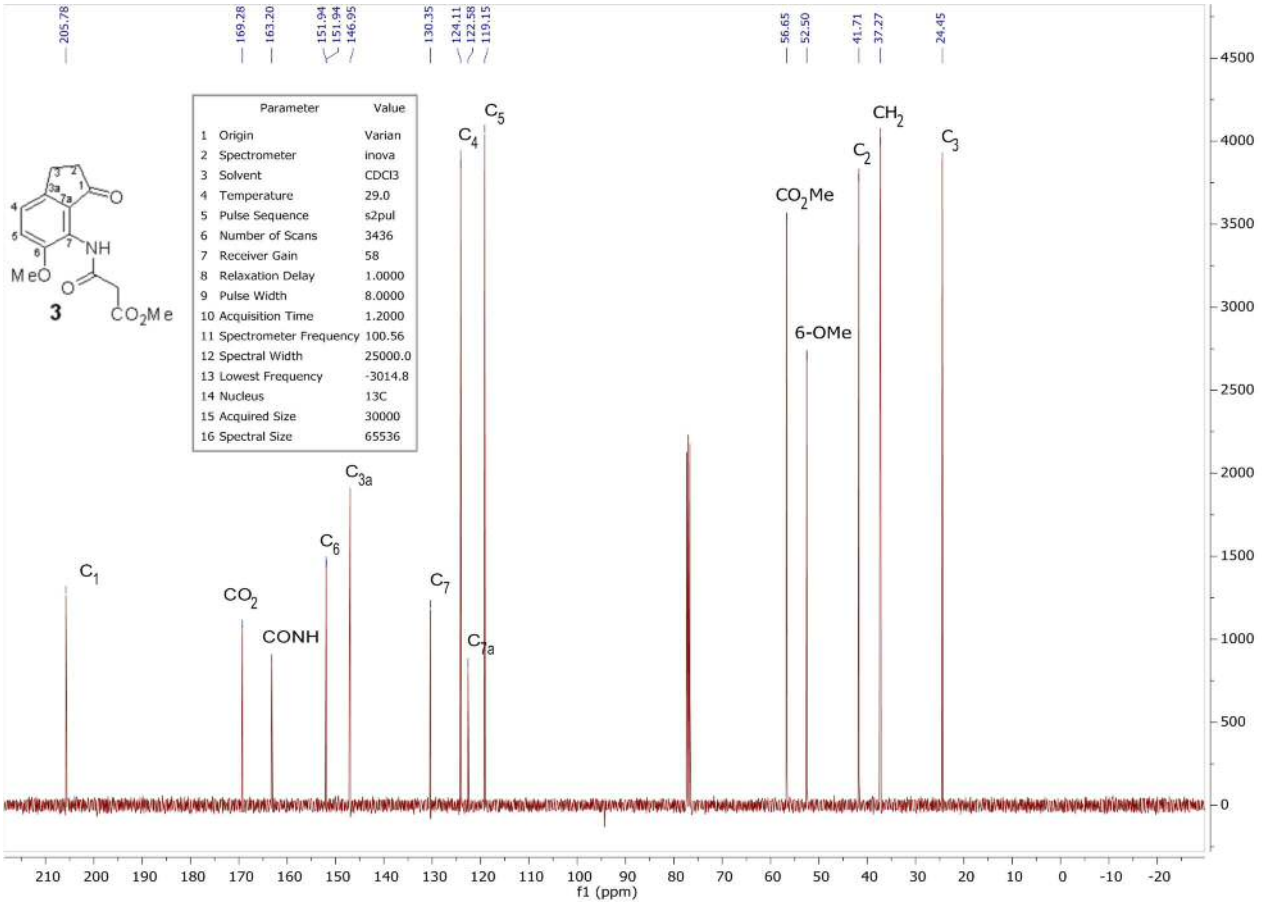
2.98
2.04
2.10
2.09
f1 (ppm)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151.94
146.95
130.35
124.11
122.58
119.15
56.65
52.50
41.71
37.27
24.45
3
MeO
NH
O
CO2Me
Parameter Value
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2 Spectrometer inova
3 Solvent CDCl3
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7 Receiver Gain 58
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9 Pulse Width 8.0000
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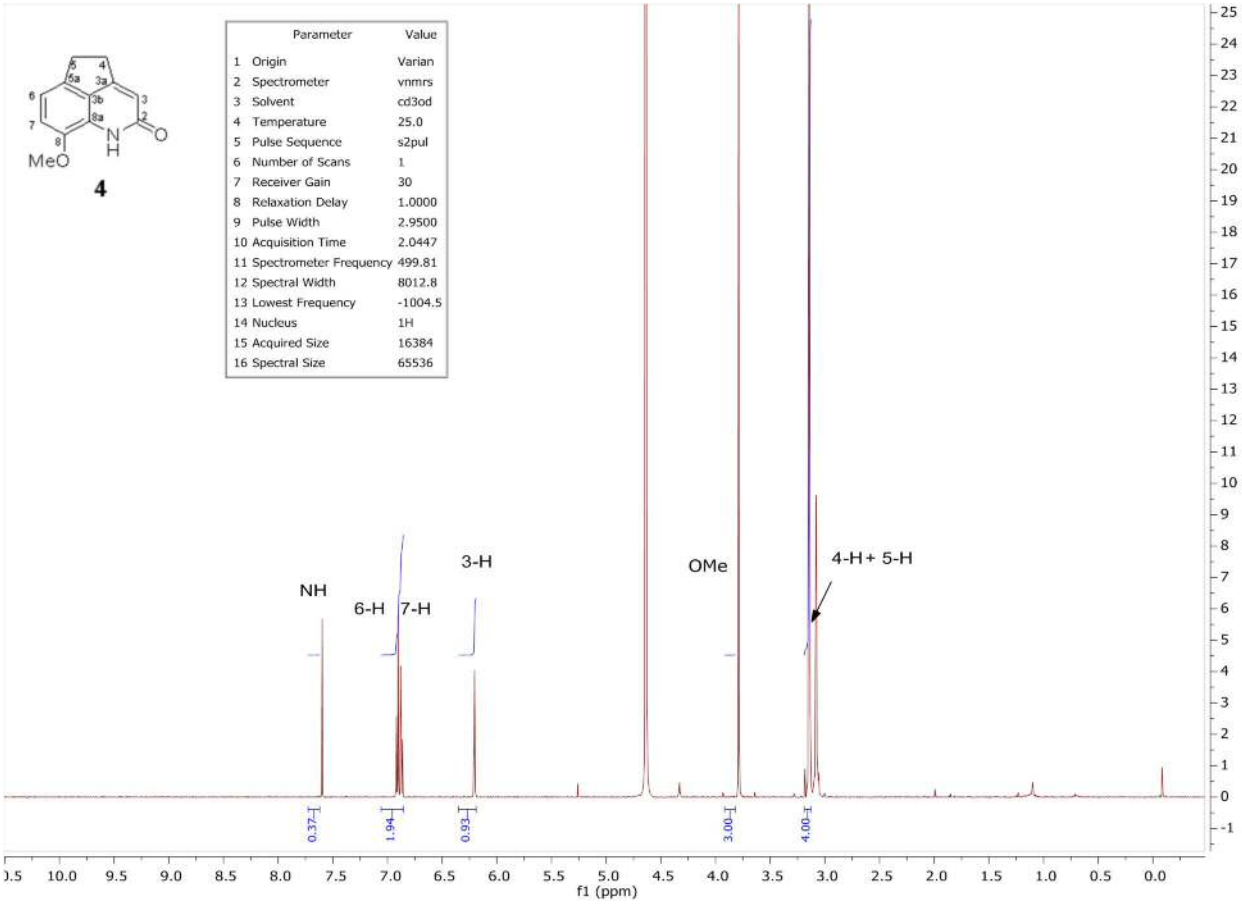
14 Nucleus 13C
15 Acquired Size 30000
16 Spectral Size 65536
C5
C4
CH2
C2
C3
CO2Me
6-OMe
C3a
C6
C1
CO2
C7
CONH
C7a
f1 (ppm)



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9	Pulse Width	2.9500
10	Acquisition Time	2.0447
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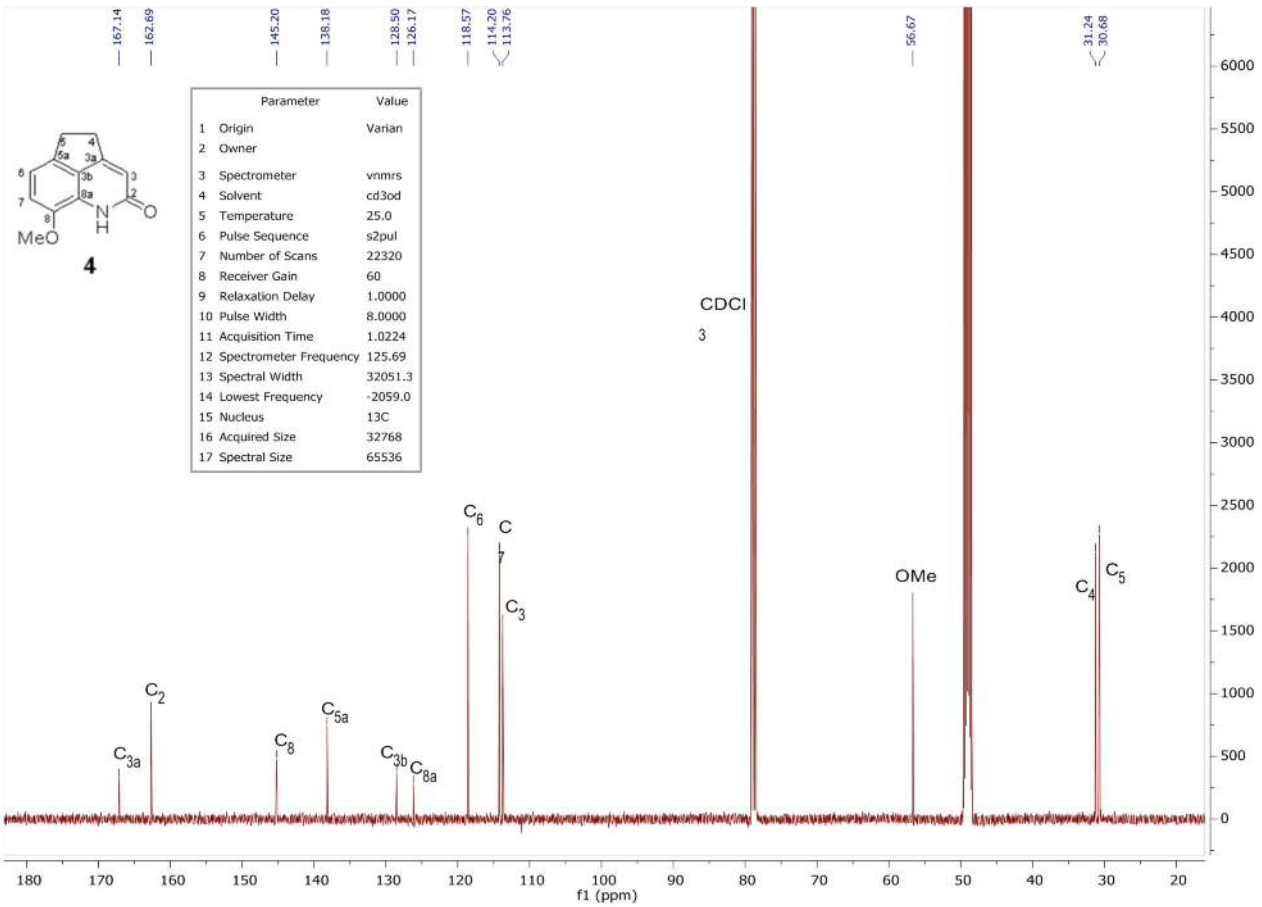

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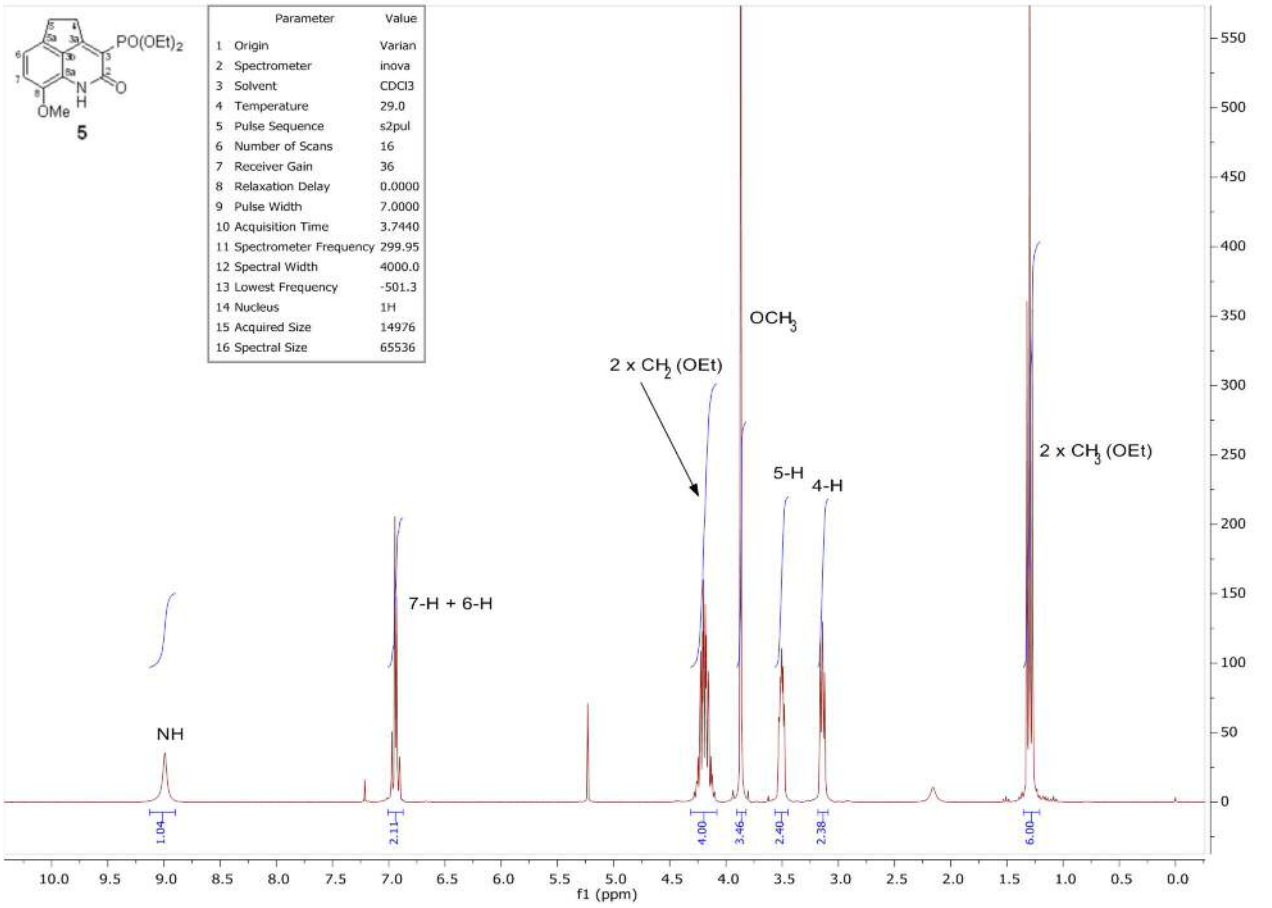
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OMe
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9 Pulse Width 7.0000
10 Acquisition Time 3.7440
11 Spectrometer Frequency 299.95
12 Spectral Width 4000.0
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14 Nucleus 1H
15 Acquired Size 14976
16 Spectral Size 65536
OCH3
2 x CH2 (OEt)
2 x CH3 (OEt)
5-H
4-H
7-H + 6-H
NH
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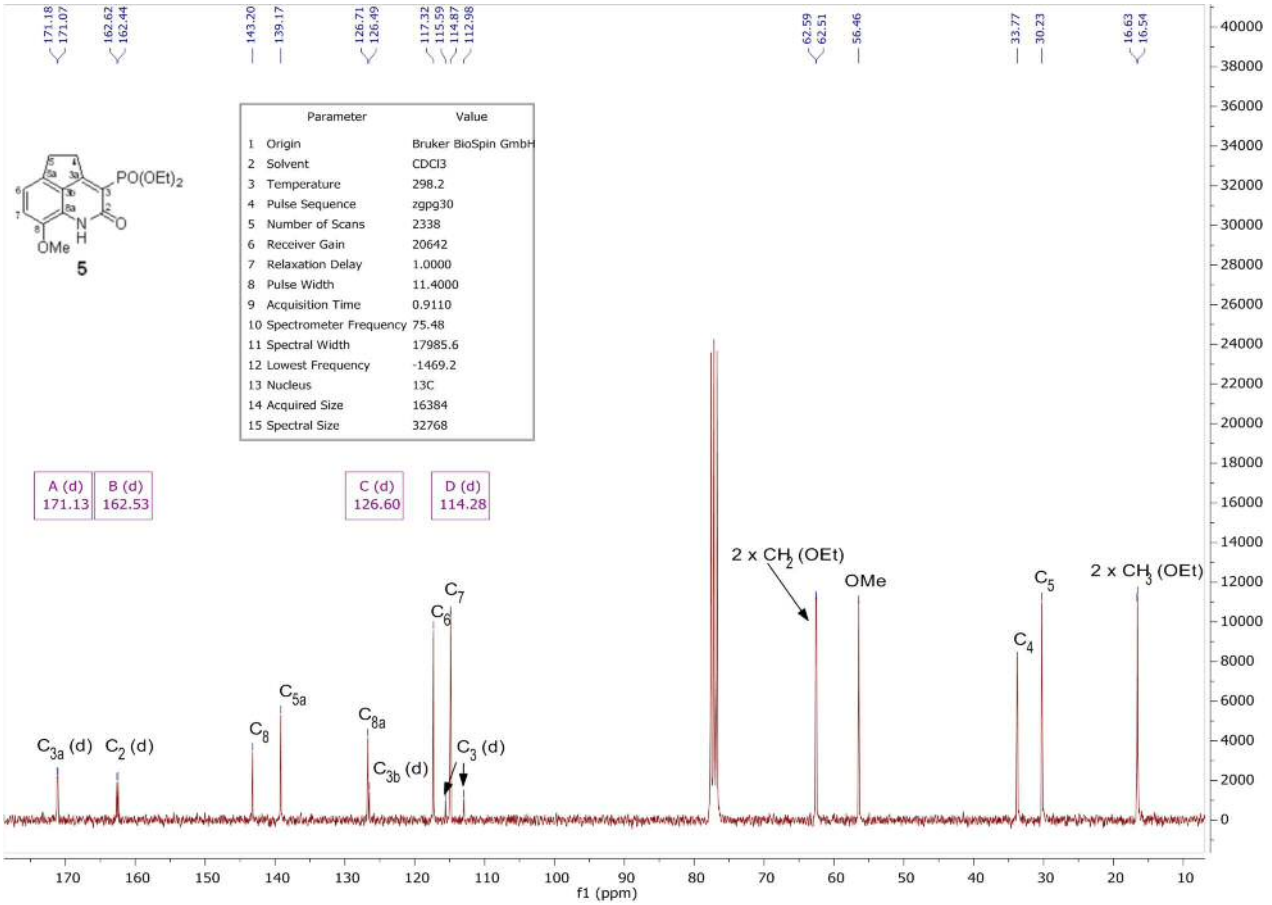
4.00
3.46
2.40
2.38
6.00
f1 (ppm)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62.51
56.46
33.77
30.23
16.63
16.54
PO(OEt)2
OMe
5
Parameter Value
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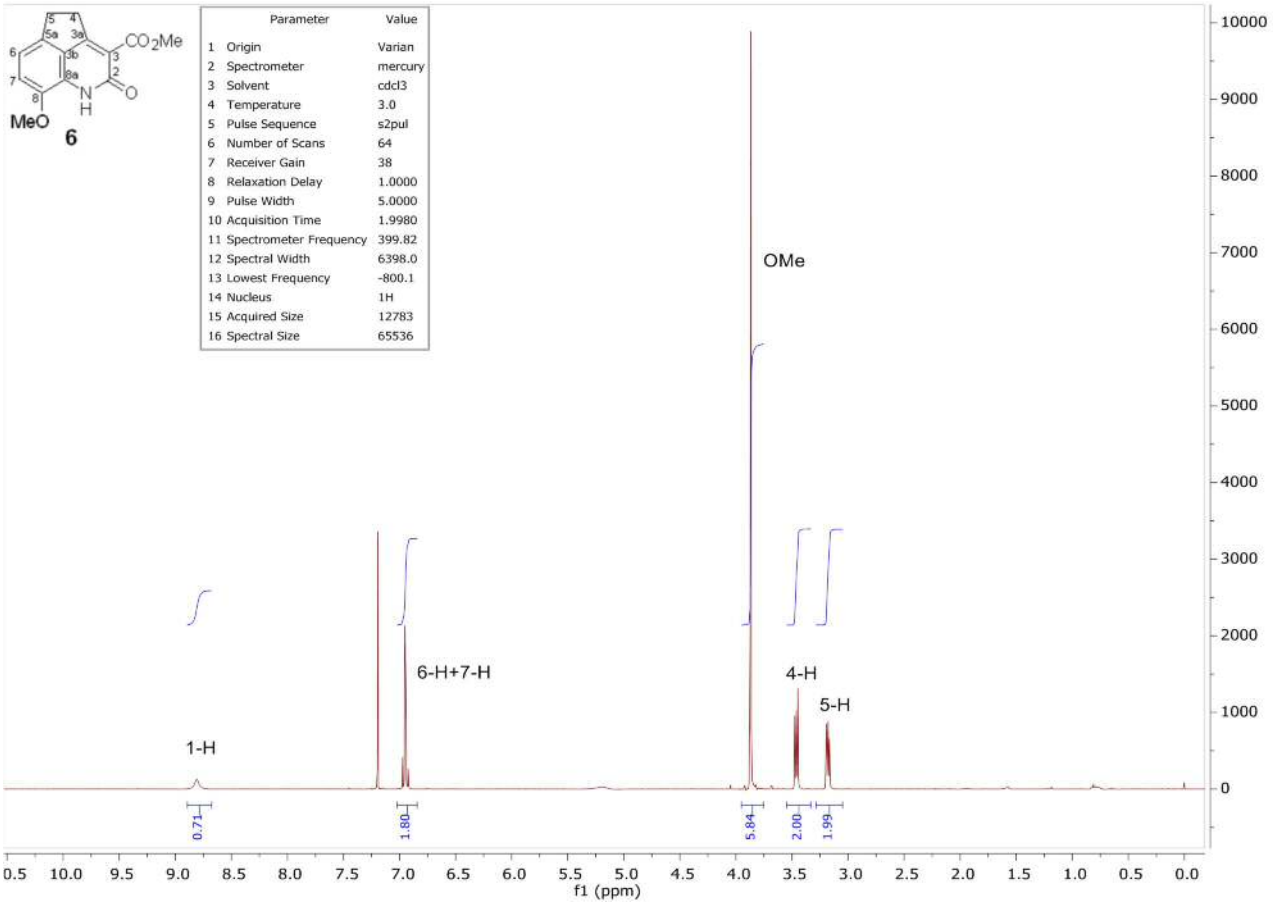
2 Solvent CDCl3
3 Temperature 298.2
4 Pulse Sequence zgpg30
5 Number of Scans 2338
6 Receiver Gain 20642
7 Relaxation Delay 1.0000
8 Pulse Width 11.4000
9 Acquisition Time 0.9110
10 Spectrometer Frequency 75.48
11 Spectral Width 17985.6
12 Lowest Frequency -1469.2
13 Nucleus 13C
14 Acquired Size 16384
15 Spectral Size 32768
A (d) 171.13
B (d) 162.53
C (d) 126.60
D (d) 114.28
2 x CH2 (OEt)
OMe
2 x CH3 (OEt)
C7
C6
C5
C4
C5a
C8a
C8
C3a (d)
C2 (d)
C3b (d)
C3 (d)
f1 (ppm)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9 Pulse Width 5.0000
10 Acquisition Time 1.9980
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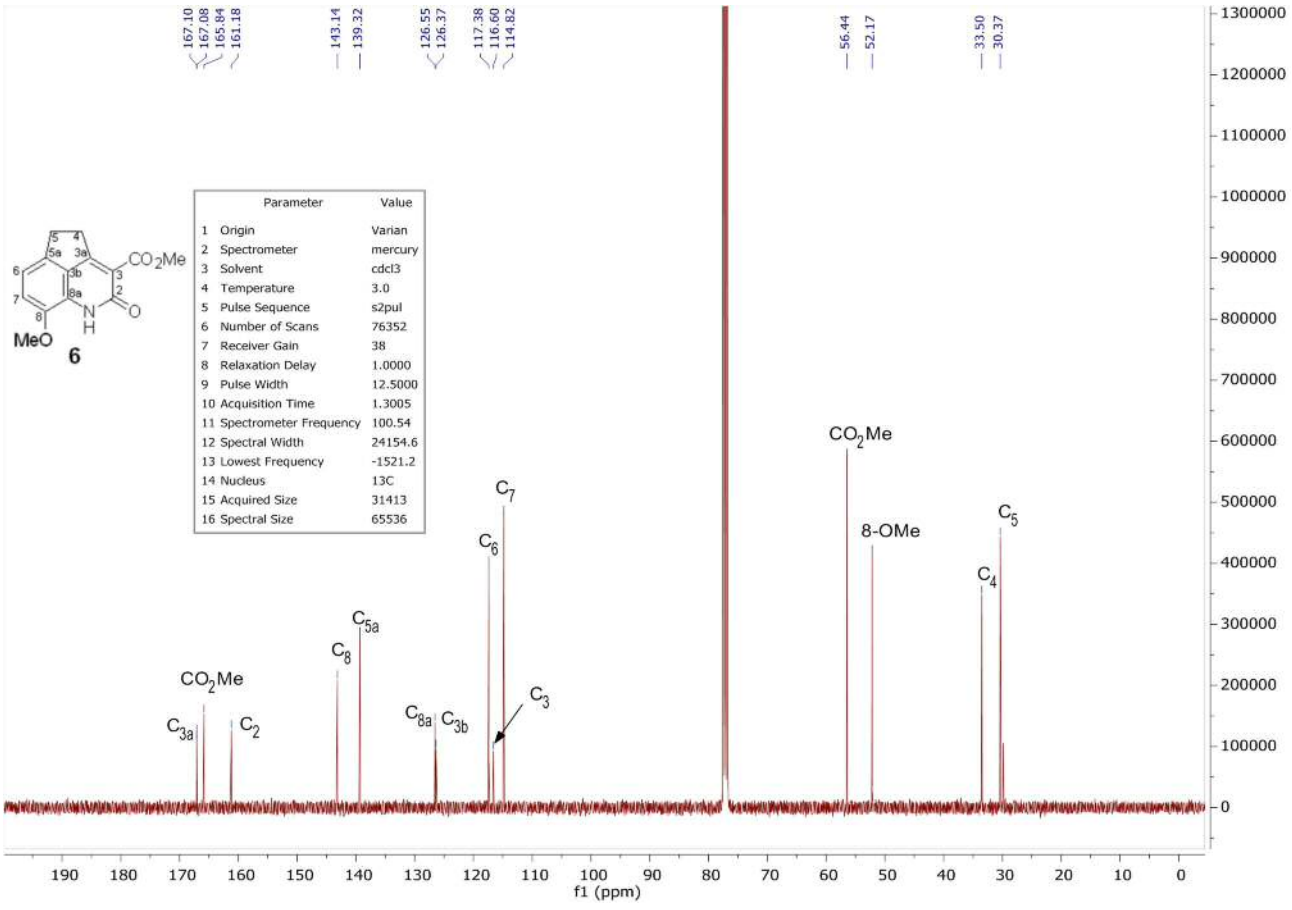
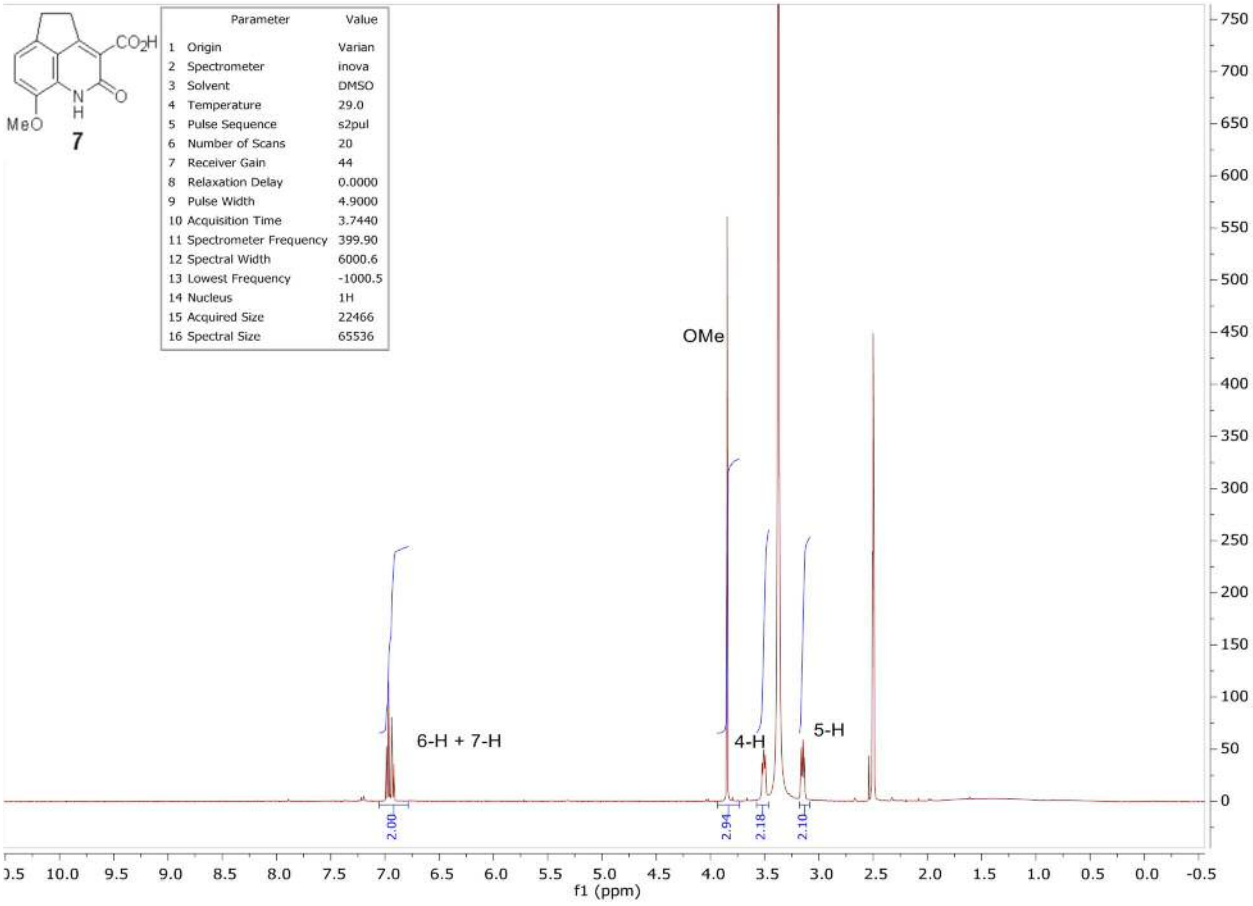
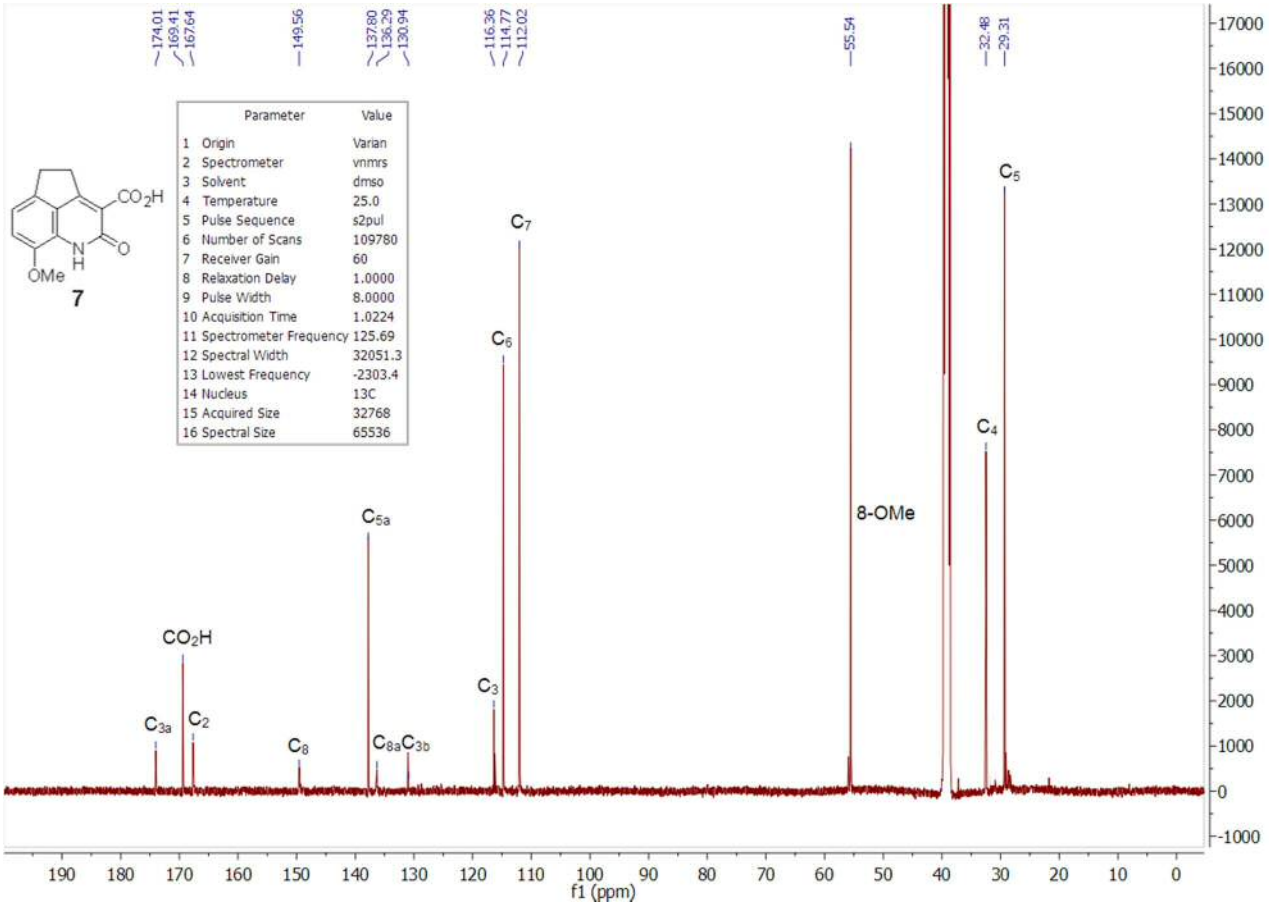
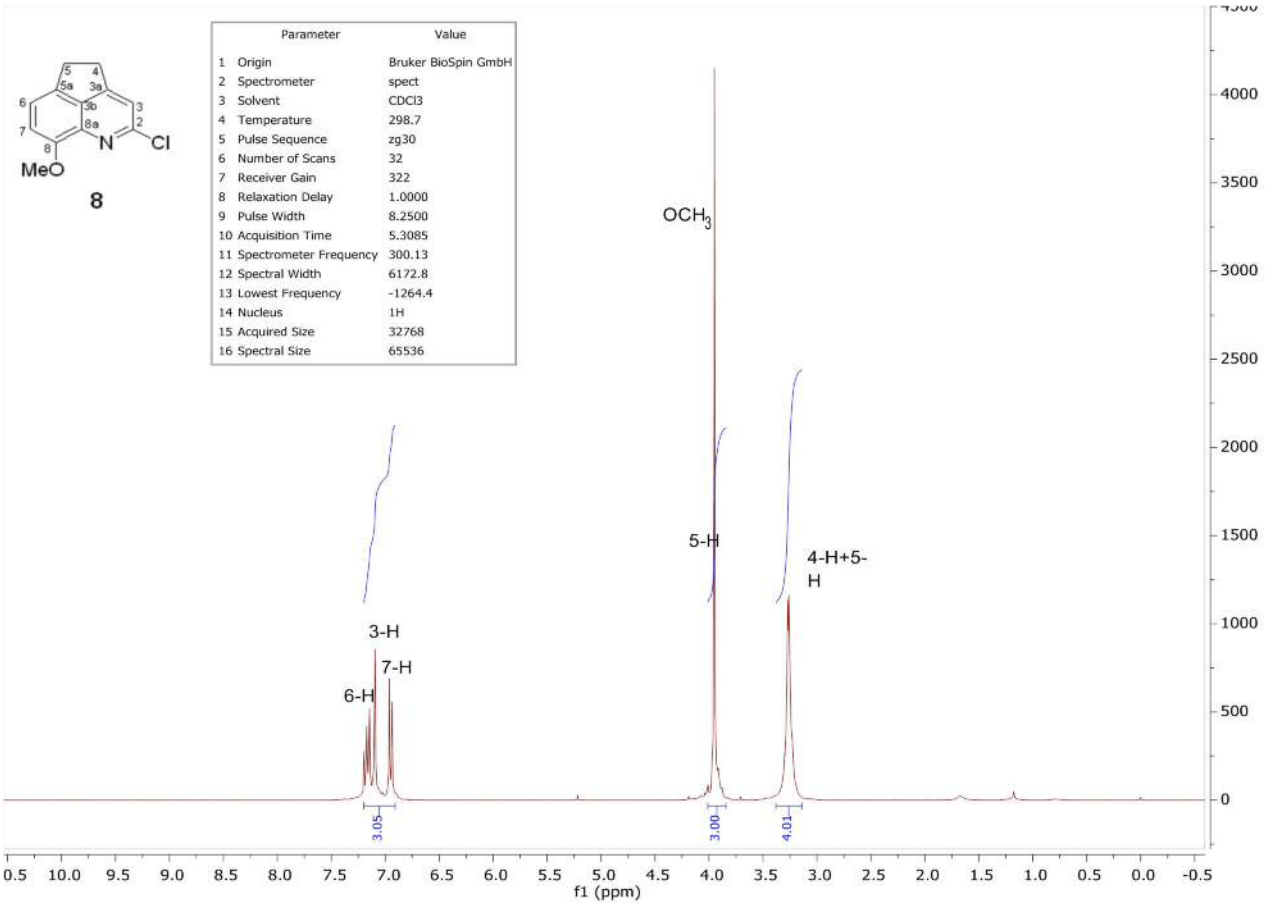
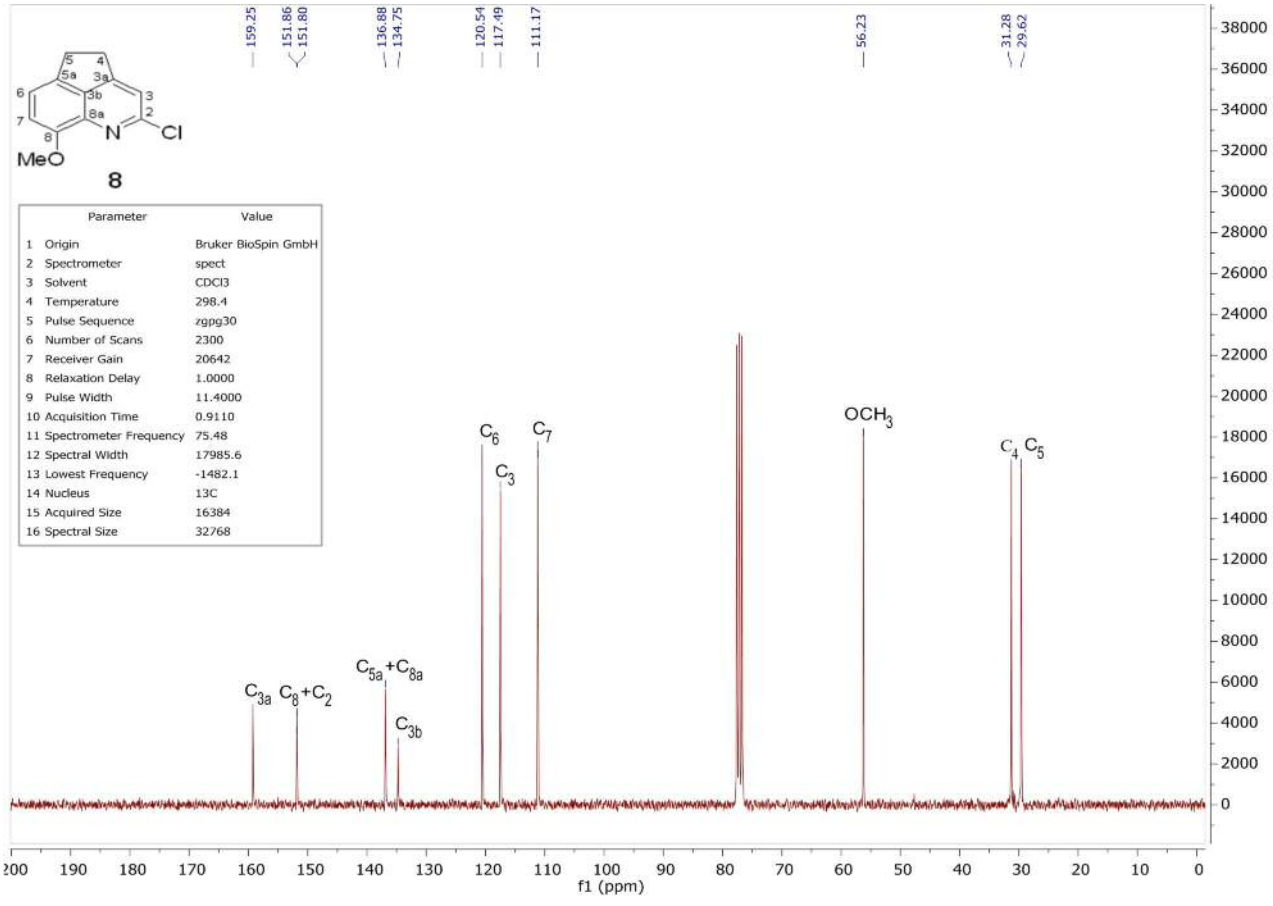
12 Spectral Width 6398.0
13 Lowest Frequency -800.1
14 Nucleus 1H
15 Acquired Size 12783
16 Spectral Size 65536
OMe
6-H+7-H
4-H
5-H
1-H
0.71
1.80
5.84
2.00
1.99
f1 (ppm)

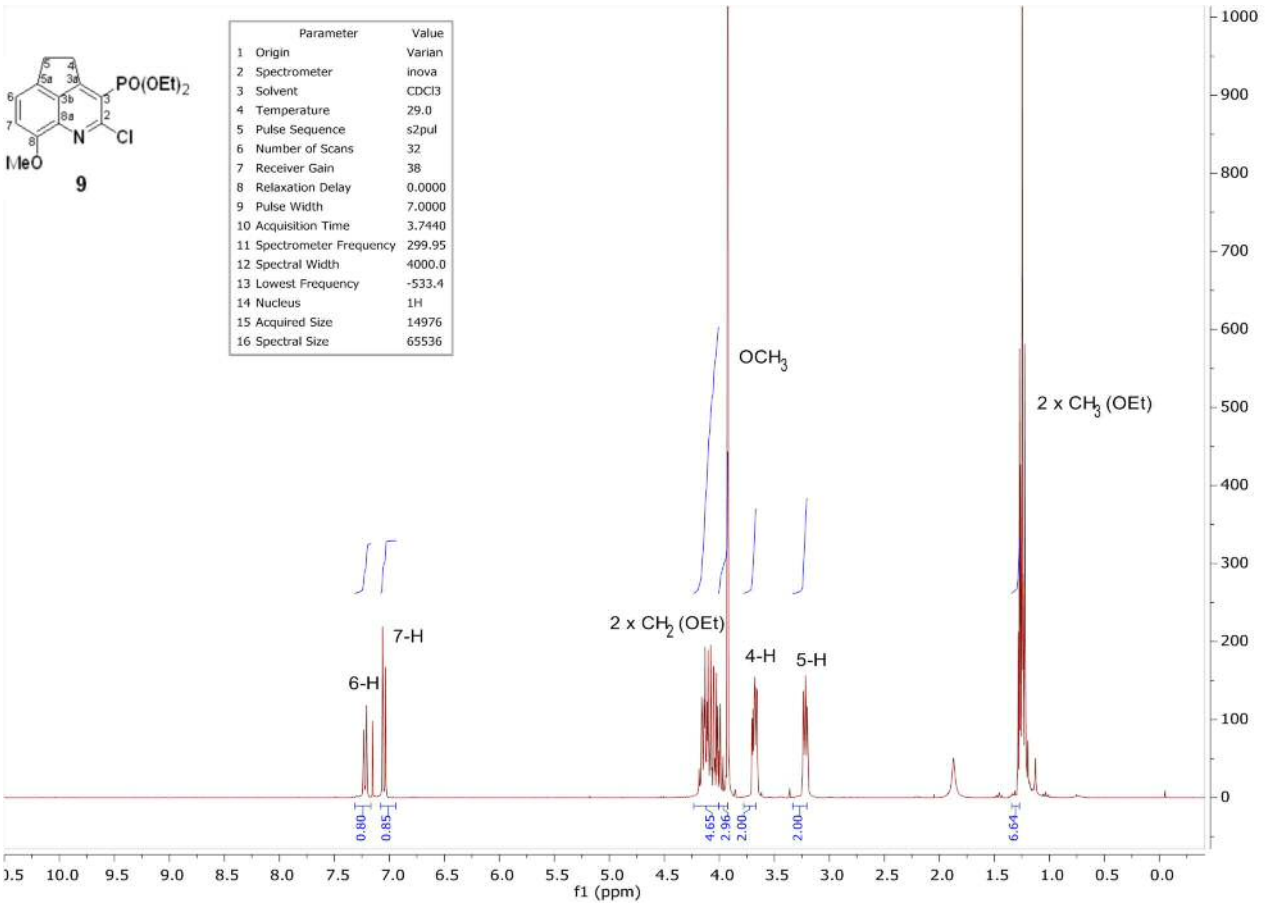

167.10
167.08
165.84
161.18
143.14
139.32
126.55
126.37
117.38
116.60
114.82
56.44
52.17
33.50
30.37
MeO
6
Parameter Value
1 Origin Varian
2 Spectrometer mercury
3 Solvent cdcl3
4 Temperature 3.0
5 Pulse Sequence s2pul
6 Number of Scans 76352
7 Receiver Gain 38
8 Relaxation Delay 1.0000
9 Pulse Width 12.5000
10 Acquisition Time 1.3005
11 Spectrometer Frequency 100.54
12 Spectral Width 24154.6
13 Lowest Frequency -1521.2
14 Nucleus 13C
15 Acquired Size 31413
16 Spectral Size 65536
CO2Me
8-OMe
C7
C6
C5
C4
C5a
C8
C3
C8a
C3b
C3a
C2
f1 (ppm)

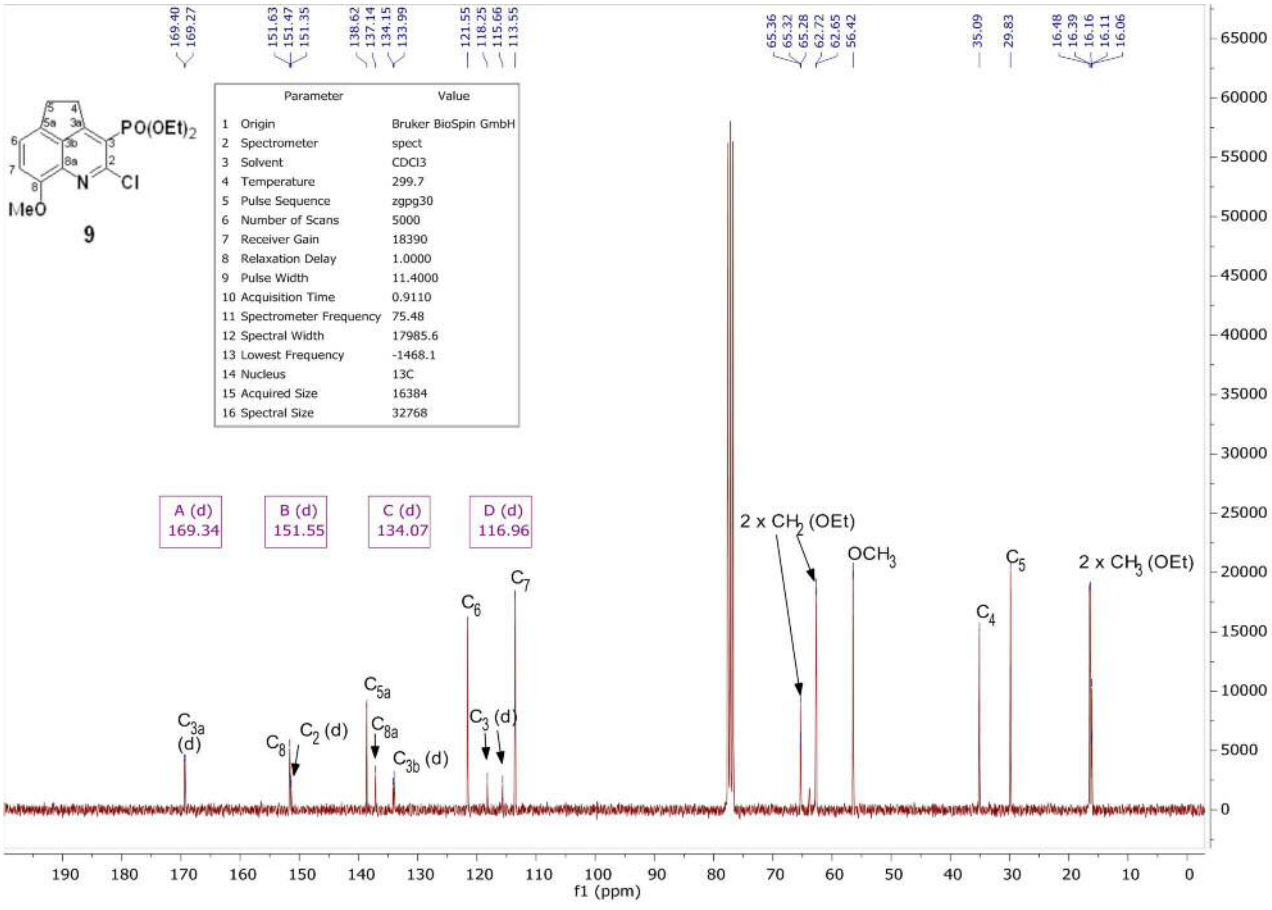

CO2H
MeO
N
H
O
7
Parameter Value
1 Origin Varian
2 Spectrometer inova
3 Solvent DMSO
4 Temperature 29.0
5 Pulse Sequence s2pul
6 Number of Scans 20
7 Receiver Gain 44
8 Relaxation Delay 0.0000
9 Pulse Width 4.9000
10 Acquisition Time 3.7440
11 Spectrometer Frequency 399.90
12 Spectral Width 6000.6
13 Lowest Frequency -1000.5
14 Nucleus 1H
15 Acquired Size 22466
16 Spectral Size 65536
OMe
6-H + 7-H
4-H
5-H
2.00
2.94
2.18
2.10
f1 (ppm)

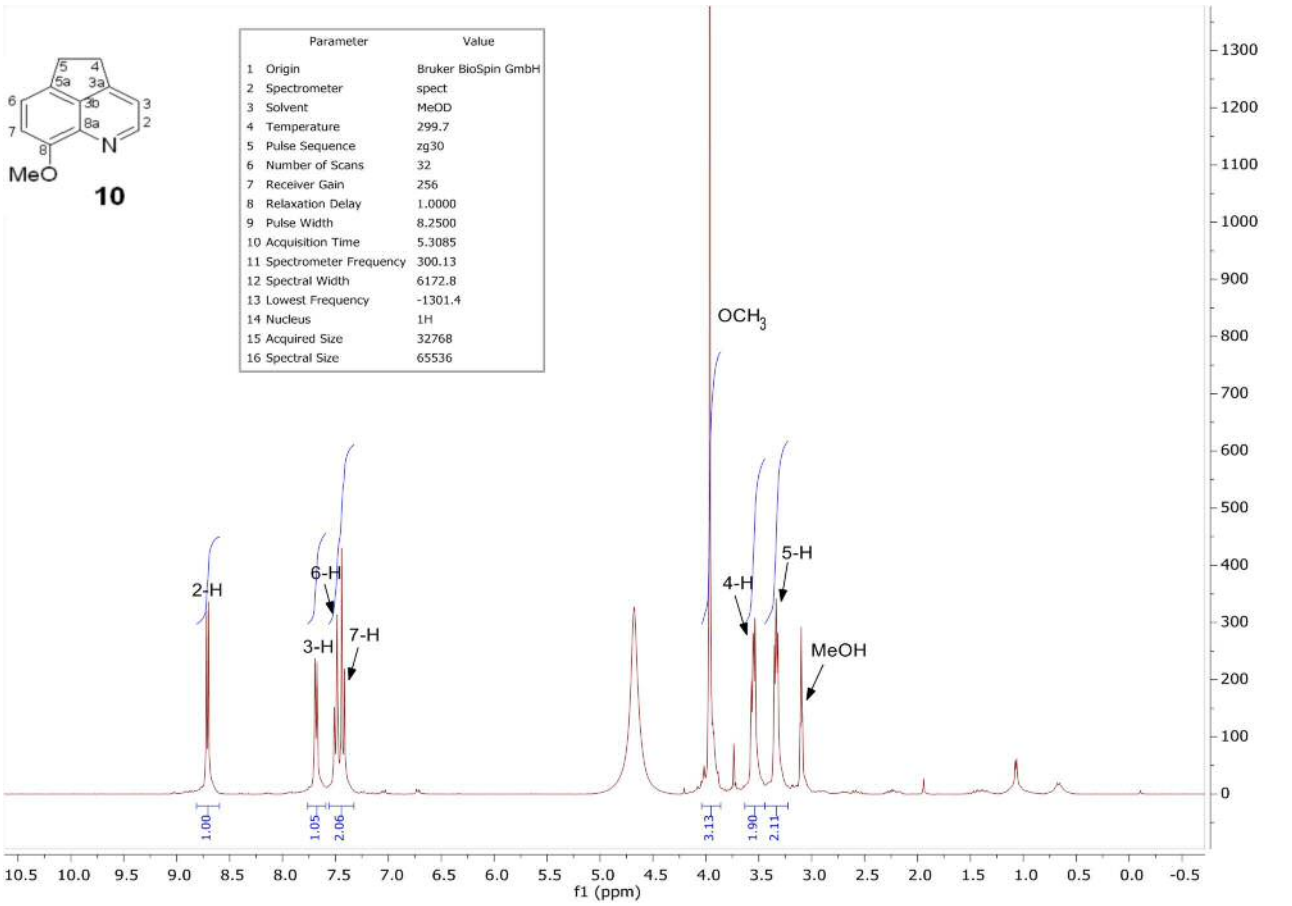

174.01
169.41
167.64
149.56
137.80
136.29
130.94
116.36
114.77
112.02
55.54
32.48
29.31
CO2H
OMe
N
H
O
7
Parameter Value
1 Origin Varian
2 Spectrometer vnmrs
3 Solvent dmso
4 Temperature 25.0
5 Pulse Sequence s2pul
6 Number of Scans 109780
7 Receiver Gain 60
8 Relaxation Delay 1.0000
9 Pulse Width 8.0000
10 Acquisition Time 1.0224
11 Spectrometer Frequency 125.69
12 Spectral Width 32051.3
13 Lowest Frequency -2303.4
14 Nucleus 13C
15 Acquired Size 32768
16 Spectral Size 65536
C7
C6
C5
C4
C5a
8-OMe
CO2H
C3a
C2
C8
C8a
C3b
C3
f1 (ppm)

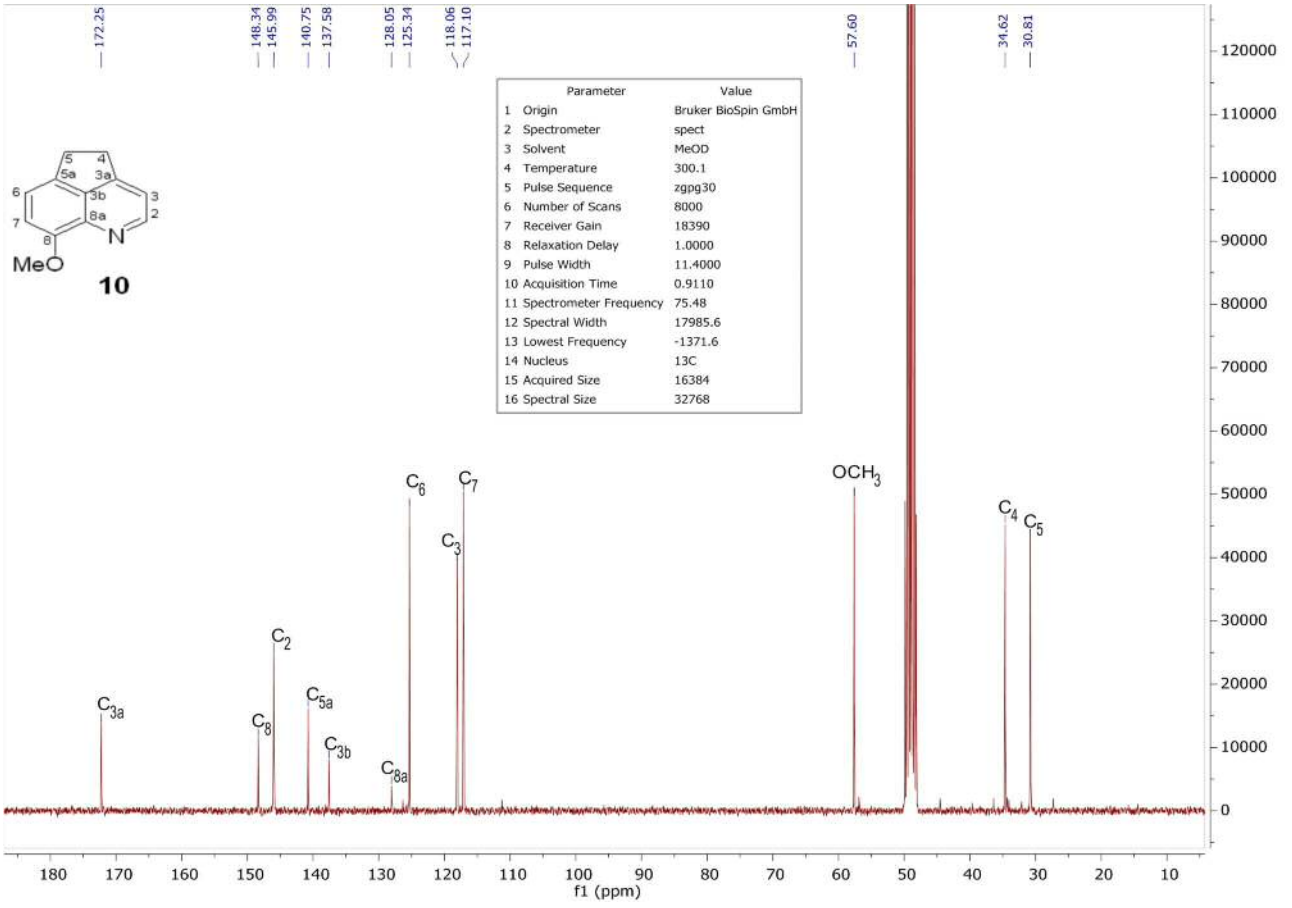

8
Parameter Value
1 Origin Bruker BioSpin GmbH
2 Spectrometer spect
3 Solvent CDCl3
4 Temperature 298.7
5 Pulse Sequence zg30
6 Number of Scans 32
7 Receiver Gain 322
8 Relaxation Delay 1.0000
9 Pulse Width 8.2500
10 Acquisition Time 5.3085
11 Spectrometer Frequency 300.13
12 Spectral Width 6172.8
13 Lowest Frequency -1264.4
14 Nucleus 1H
15 Acquired Size 32768
16 Spectral Size 65536
OCH3
5-H
4-H+5-H
3-H
7-H
6-H
3.05
3.00
4.01
f1 (ppm)

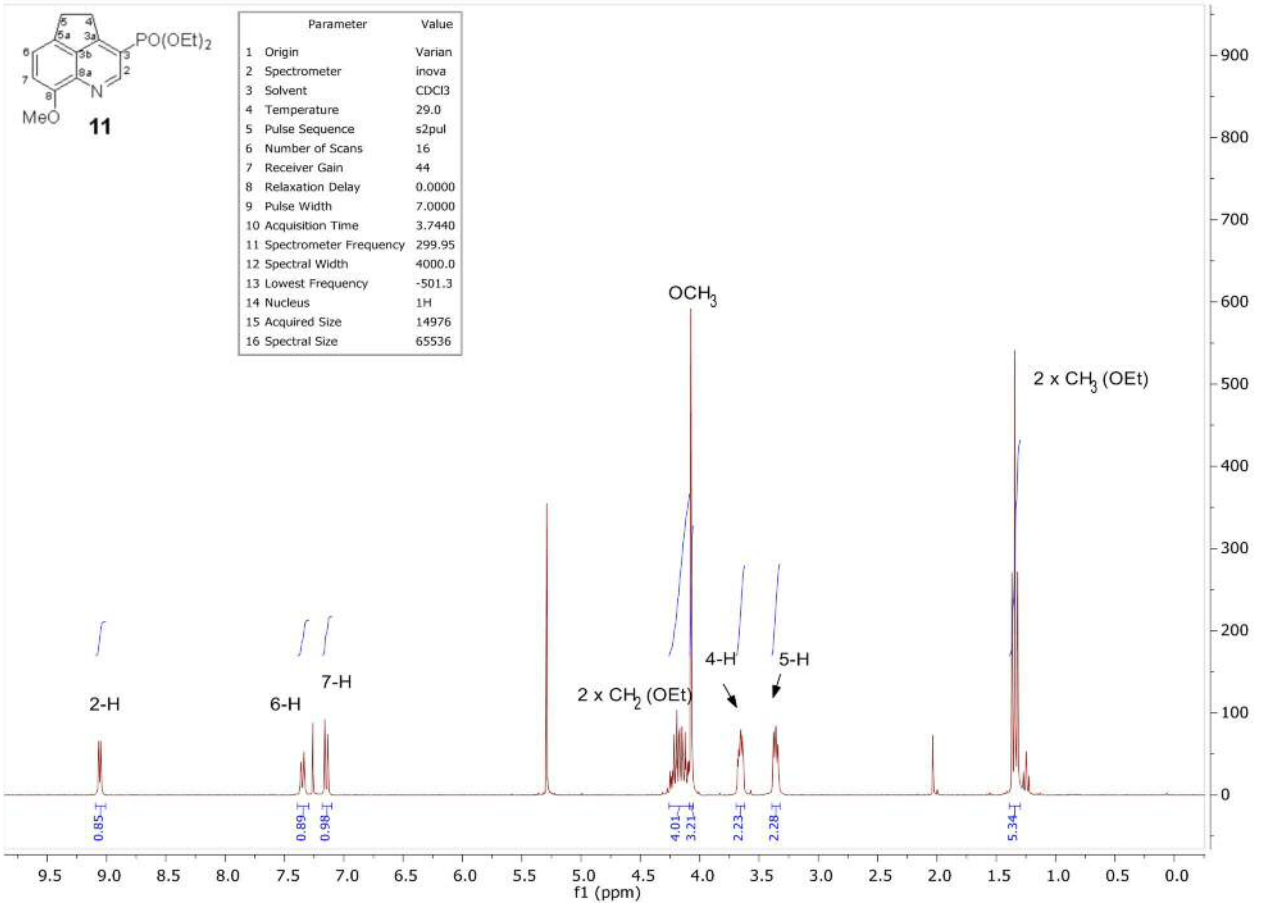

159.25
151.86
151.80
136.88
134.75
120.54
117.49
111.17
56.23
31.28
29.62
8
Parameter Value
1 Origin Bruker BioSpin GmbH
2 Spectrometer spect
3 Solvent CDCl3
4 Temperature 298.4
5 Pulse Sequence zgpg30
6 Number of Scans 2300
7 Receiver Gain 20642
8 Relaxation Delay 1.0000
9 Pulse Width 11.4000
10 Acquisition Time 0.9110
11 Spectrometer Frequency 75.48
12 Spectral Width 17985.6
13 Lowest Frequency -1482.1
14 Nucleus 13C
15 Acquired Size 16384
16 Spectral Size 32768
C6
C3
C7
OCH3
C4 C5
C5a+C8a
C3a
C8+C2
C3b
f1 (ppm)

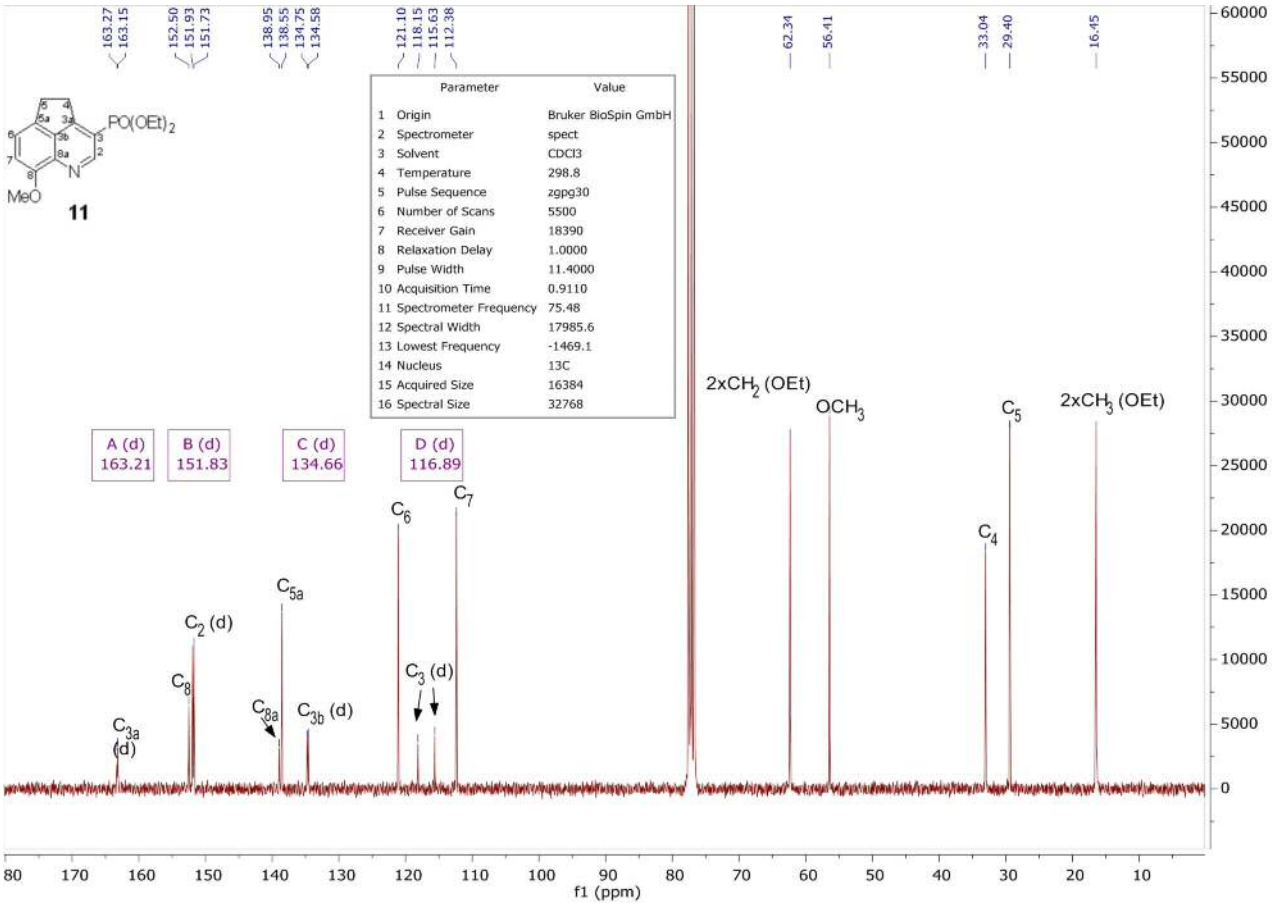

PO(OEt)2
Cl
MeO
9
Parameter Value
1 Origin Varian
2 Spectrometer inova
3 Solvent CDCl3
4 Temperature 29.0
5 Pulse Sequence s2pul
6 Number of Scans 32
7 Receiver Gain 38
8 Relaxation Delay 0.0000
9 Pulse Width 7.0000
10 Acquisition Time 3.7440
11 Spectrometer Frequency 299.95
12 Spectral Width 4000.0
13 Lowest Frequency -533.4
14 Nucleus 1H
15 Acquired Size 14976
16 Spectral Size 65536
OCH3
2 x CH3 (OEt)
2 x CH2 (OEt)
7-H
6-H
4-H
5-H
0.80
0.85
4.65
2.96
2.00
2.00
6.64
f1 (ppm)

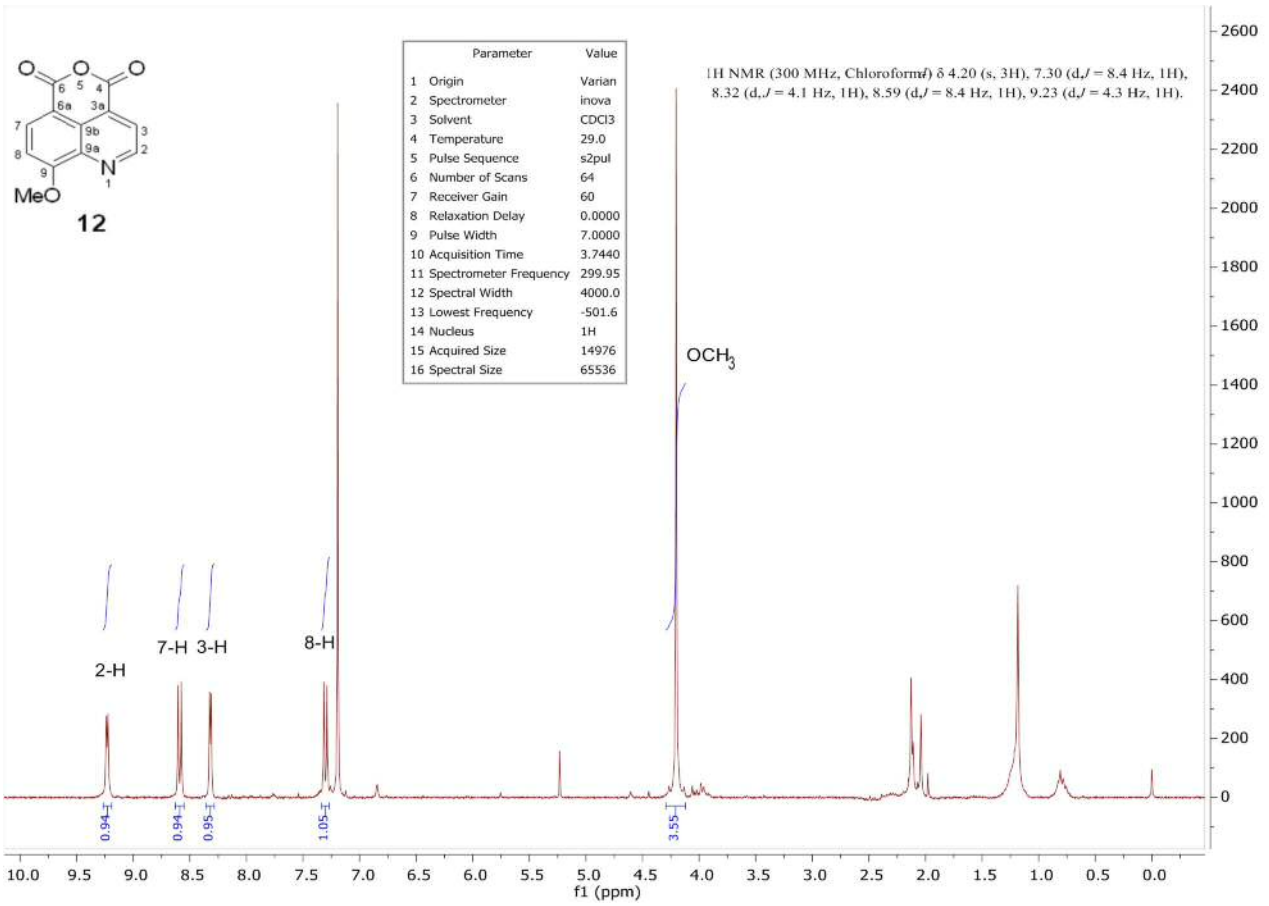

169.40
169.27
151.63
151.47
151.35
138.62
137.14
134.15
133.99
121.55
118.25
115.66
113.55
65.36
65.32
65.28
62.72
62.65
56.42
35.09
29.83
16.48
16.39
16.16
16.11
16.06
PO(OEt)2
Cl
MeO
9
Parameter Value
1 Origin Bruker BioSpin GmbH
2 Spectrometer spect
3 Solvent CDCl3
4 Temperature 299.7
5 Pulse Sequence zgpg30
6 Number of Scans 5000
7 Receiver Gain 18390
8 Relaxation Delay 1.0000
9 Pulse Width 11.4000
10 Acquisition Time 0.9110
11 Spectrometer Frequency 75.48
12 Spectral Width 17985.6
13 Lowest Frequency -1468.1
14 Nucleus 13C
15 Acquired Size 16384
16 Spectral Size 32768
A (d) 169.34
B (d) 151.55
C (d) 134.07
D (d) 116.96
2 x CH2 (OEt)
OCH3
2 x CH3 (OEt)
C5
C4
C7
C6
C5a
C3a (d)
C8
C2 (d)
C8a
C3b (d)
C3 (d)
f1 (ppm)

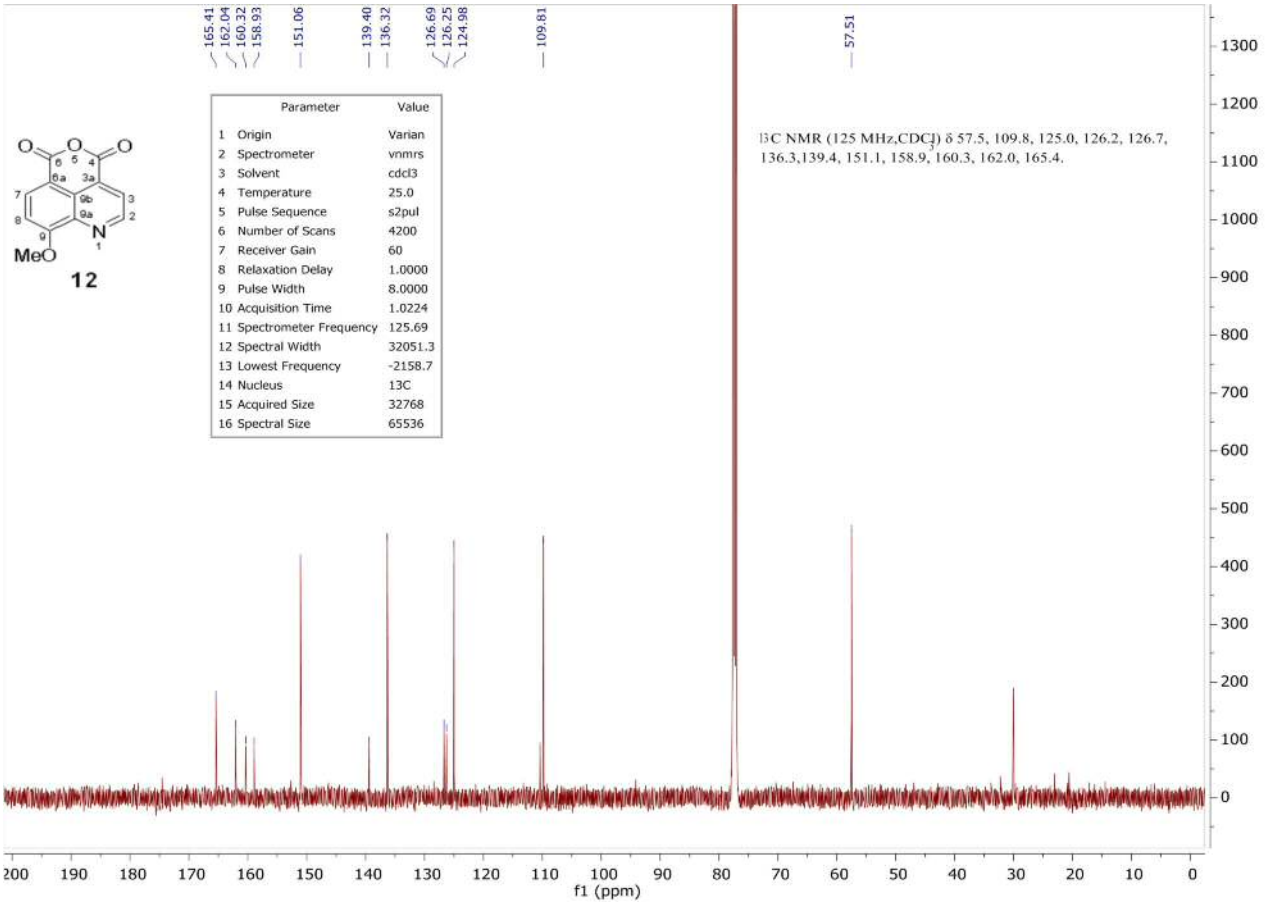

MeO
10
Parameter Value
1 Origin Bruker BioSpin GmbH
2 Spectrometer spect
3 Solvent MeOD
4 Temperature 299.7
5 Pulse Sequence zg30
6 Number of Scans 32
7 Receiver Gain 256
8 Relaxation Delay 1.0000
9 Pulse Width 8.2500
10 Acquisition Time 5.3085
11 Spectrometer Frequency 300.13
12 Spectral Width 6172.8
13 Lowest Frequency -1301.4
14 Nucleus 1H
15 Acquired Size 32768
16 Spectral Size 65536
OCH3
2-H
6-H
3-H
7-H
4-H
5-H
MeOH
1.00
1.05
2.06
3.13
1.90
2.11
f1 (ppm)

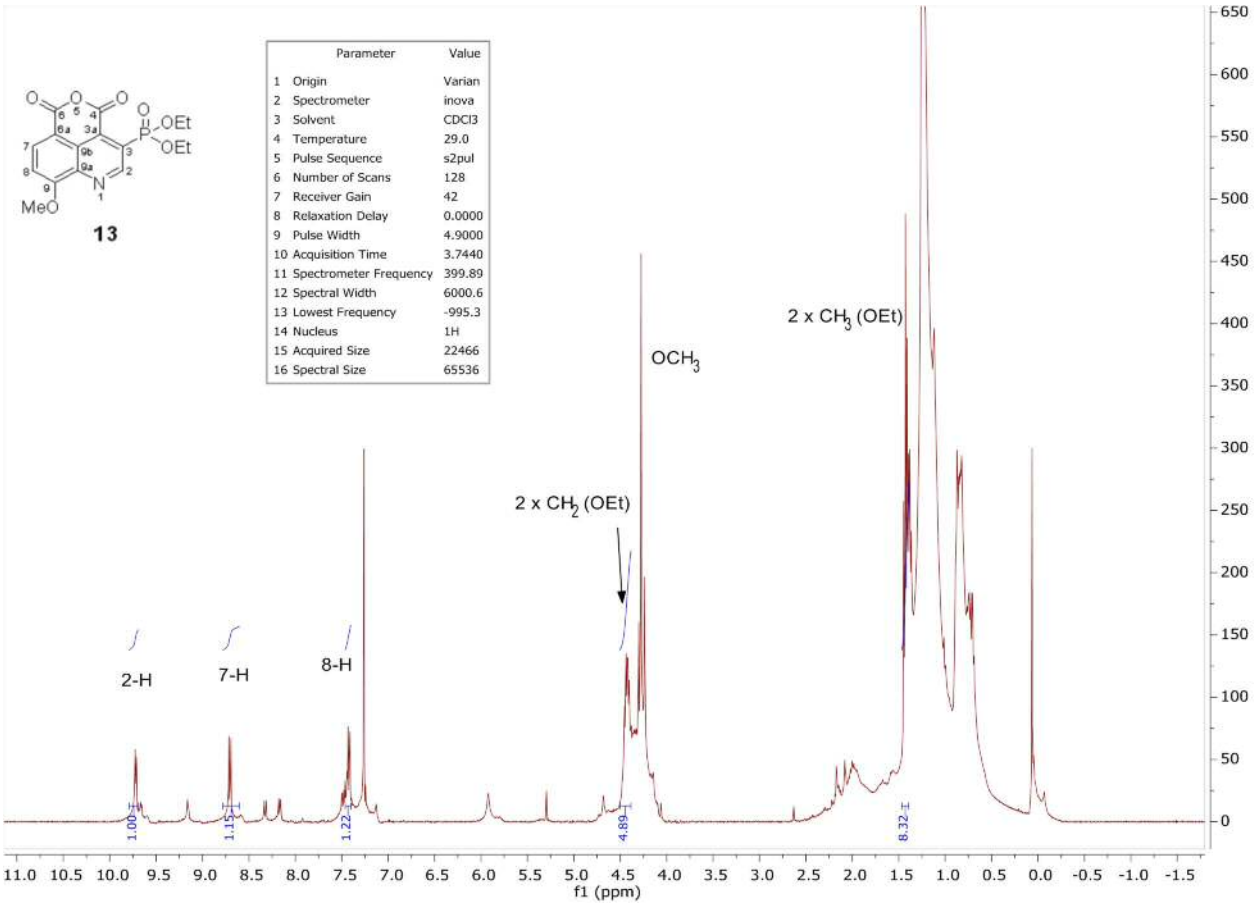

172.25
148.34
145.99
140.75
137.58
128.05
125.34
118.06
117.10
57.60
34.62
30.81
MeO
10
Parameter Value
1 Origin Bruker BioSpin GmbH
2 Spectrometer spect
3 Solvent MeOD
4 Temperature 300.1
5 Pulse Sequence zgpg30
6 Number of Scans 8000
7 Receiver Gain 18390
8 Relaxation Delay 1.0000
9 Pulse Width 11.4000
10 Acquisition Time 0.9110
11 Spectrometer Frequency 75.48
12 Spectral Width 17985.6
13 Lowest Frequency -1371.6
14 Nucleus 13C
15 Acquired Size 16384
16 Spectral Size 32768
C6
C7
C3
OCH3
C4
C5
C2
C3a
C8
C5a
C3b
C8a
f1 (ppm)

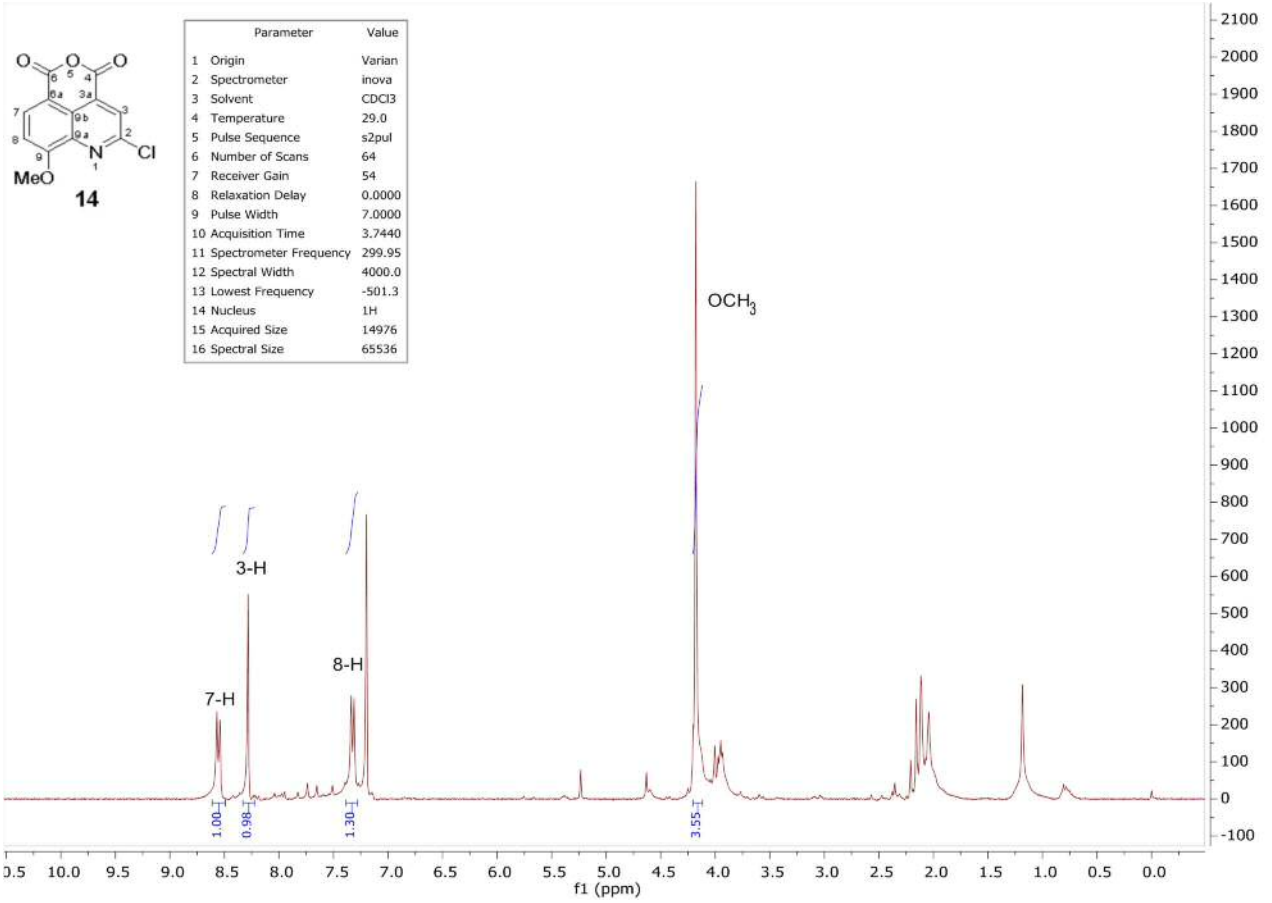

PO(OEt)2
MeO
11
Parameter Value
1 Origin Varian
2 Spectrometer inova
3 Solvent CDCl3
4 Temperature 29.0
5 Pulse Sequence s2pul
6 Number of Scans 16
7 Receiver Gain 44
8 Relaxation Delay 0.0000
9 Pulse Width 7.0000
10 Acquisition Time 3.7440
11 Spectrometer Frequency 299.95
12 Spectral Width 4000.0
13 Lowest Frequency -501.3
14 Nucleus 1H
15 Acquired Size 14976
16 Spectral Size 65536
OCH3
2 x CH3 (OEt)
2-H
6-H
7-H
2 x CH2 (OEt)
4-H
5-H
0.85
0.89
0.98
4.01
3.21
2.23
2.28
5.34
f1 (ppm)


163.27
163.15
152.50
151.93
151.73
138.95
138.55
134.75
134.58
121.10
118.15
115.63
112.38
62.34
56.41
33.04
29.40
16.45
PO(OEt)2
MeO
11
Parameter Value
1 Origin Bruker BioSpin GmbH
2 Spectrometer spect
3 Solvent CDCl3
4 Temperature 298.8
5 Pulse Sequence zgpg30
6 Number of Scans 5500
7 Receiver Gain 18390
8 Relaxation Delay 1.0000
9 Pulse Width 11.4000
10 Acquisition Time 0.9110
11 Spectrometer Frequency 75.48
12 Spectral Width 17985.6
13 Lowest Frequency -1469.1
14 Nucleus 13C
15 Acquired Size 16384
16 Spectral Size 32768
A (d) 163.21
B (d) 151.83
C (d) 134.66
D (d) 116.89
2xCH2 (OEt)
OCH3
C5
2xCH3 (OEt)
C4
C6
C7
C5a
C2 (d)
C8
C3 (d)
C8a
C3b (d)
C3a (d)
f1 (ppm)

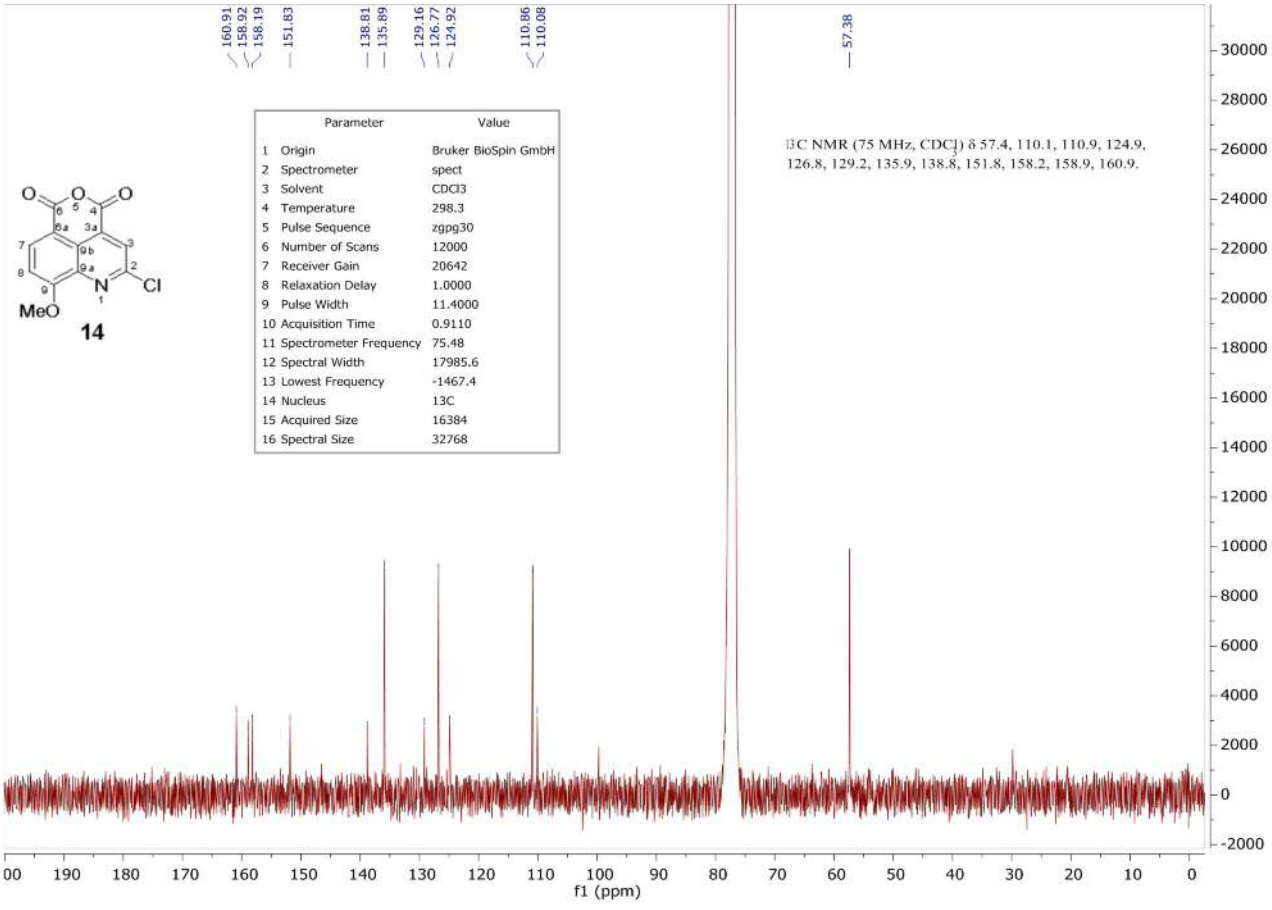

12
MeO
Parameter Value
1 Origin Varian
2 Spectrometer inova
3 Solvent CDCl3
4 Temperature 29.0
5 Pulse Sequence s2pul
6 Number of Scans 64
7 Receiver Gain 60
8 Relaxation Delay 0.0000
9 Pulse Width 7.0000
10 Acquisition Time 3.7440
11 Spectrometer Frequency 299.95
12 Spectral Width 4000.0
13 Lowest Frequency -501.6
14 Nucleus 1H
15 Acquired Size 14976
16 Spectral Size 65536
1H NMR (300 MHz, Chloroform-d) δ 4.20 (s, 3H), 7.30 (d, J = 8.4 Hz, 1H), 8.32 (d, J = 4.1 Hz, 1H), 8.59 (d, J = 8.4 Hz, 1H), 9.23 (d, J = 4.3 Hz, 1H).
OCH3
2-H
7-H 3-H
8-H
0.94 0.94 0.95 1.05 3.55
f1 (ppm)


165.41 162.04 160.32 158.93 151.06 139.40 136.32 126.69 126.25 124.98 109.81 57.51
12
MeO
Parameter Value
1 Origin Varian
2 Spectrometer vnmrs
3 Solvent cdcl3
4 Temperature 25.0
5 Pulse Sequence s2pul
6 Number of Scans 4200
7 Receiver Gain 60
8 Relaxation Delay 1.0000
9 Pulse Width 8.0000
10 Acquisition Time 1.0224
11 Spectrometer Frequency 125.69
12 Spectral Width 32051.3
13 Lowest Frequency -2158.7
14 Nucleus 13C
15 Acquired Size 32768
16 Spectral Size 65536
13C NMR (125 MHz,CDCl3) δ 57.5, 109.8, 125.0, 126.2, 126.7, 136.3,139.4, 151.1, 158.9, 160.3, 162.0, 165.4.
f1 (ppm)


13
Parameter Value
1 Origin Varian
2 Spectrometer inova
3 Solvent CDCl3
4 Temperature 29.0
5 Pulse Sequence s2pul
6 Number of Scans 128
7 Receiver Gain 42
8 Relaxation Delay 0.0000
9 Pulse Width 4.9000
10 Acquisition Time 3.7440
11 Spectrometer Frequency 399.89
12 Spectral Width 6000.6
13 Lowest Frequency -995.3
14 Nucleus 1H
15 Acquired Size 22466
16 Spectral Size 65536
2-H
7-H
8-H
2 x CH2 (OEt)
OCH3
2 x CH3 (OEt)
1.00
1.15
1.22
4.89
8.32
f1 (ppm)

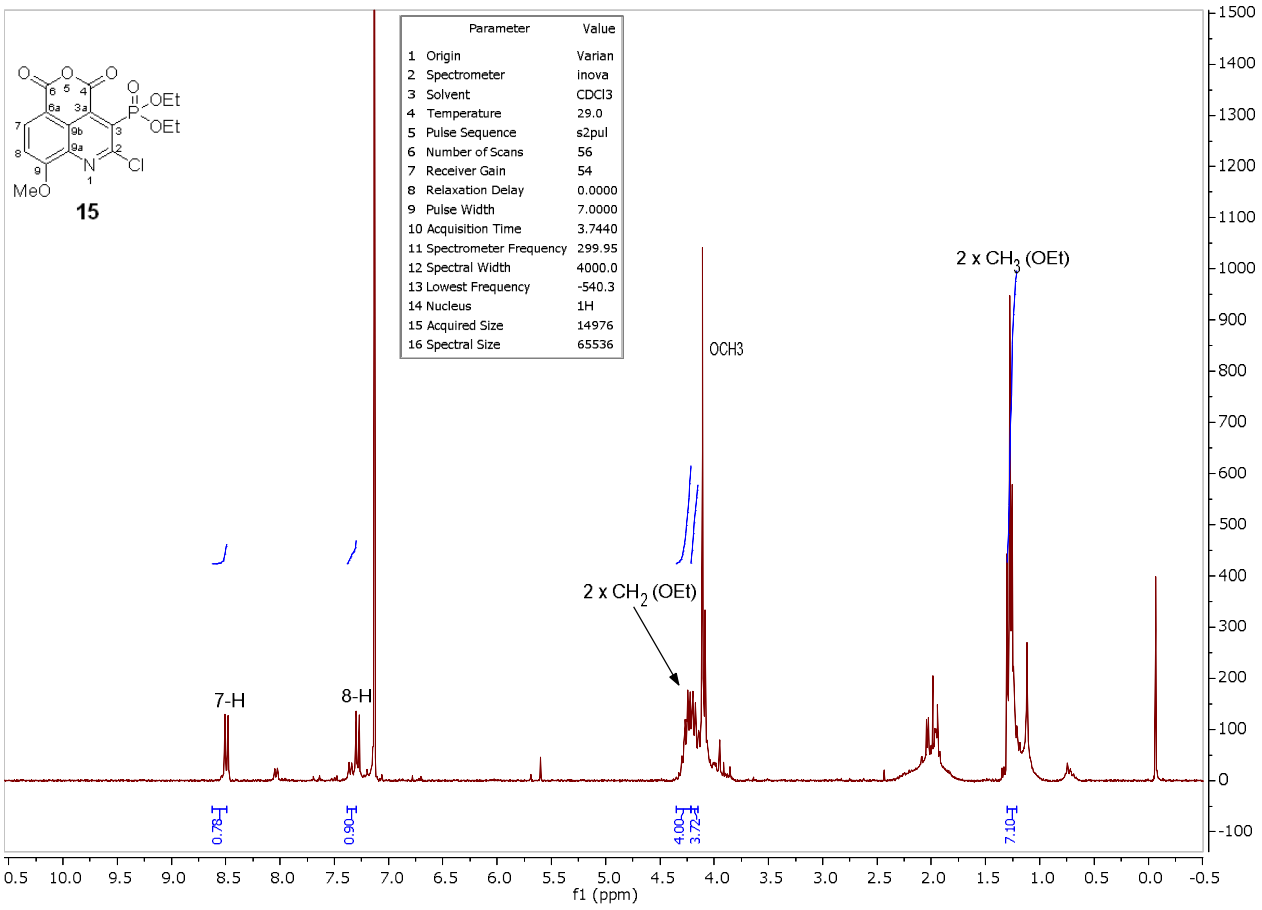


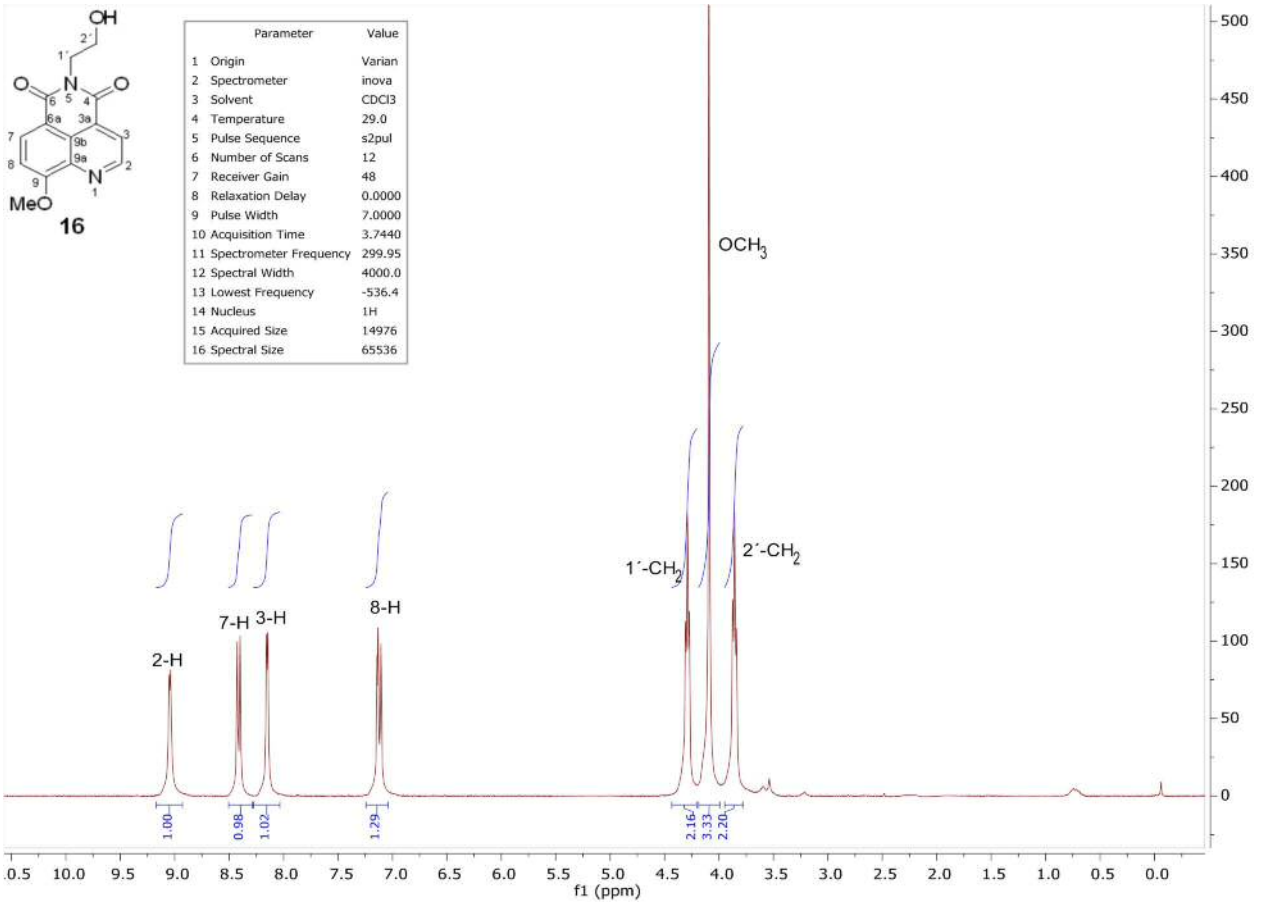
	Parameter	Value
1	Origin	Varian
2	Spectrometer	inova
3	Solvent	CDCl3
4	Temperature	29.0
5	Pulse Sequence	s2pul
6	Number of Scans	64
7	Receiver Gain	54
8	Relaxation Delay	0.0000
9	Pulse Width	7.0000
10	Acquisition Time	3.7440
11	Spectrometer Frequency	299.95
12	Spectral Width	4000.0
13	Lowest Frequency	-501.3
14	Nucleus	1H
15	Acquired Size	14976
16	Spectral Size	65536

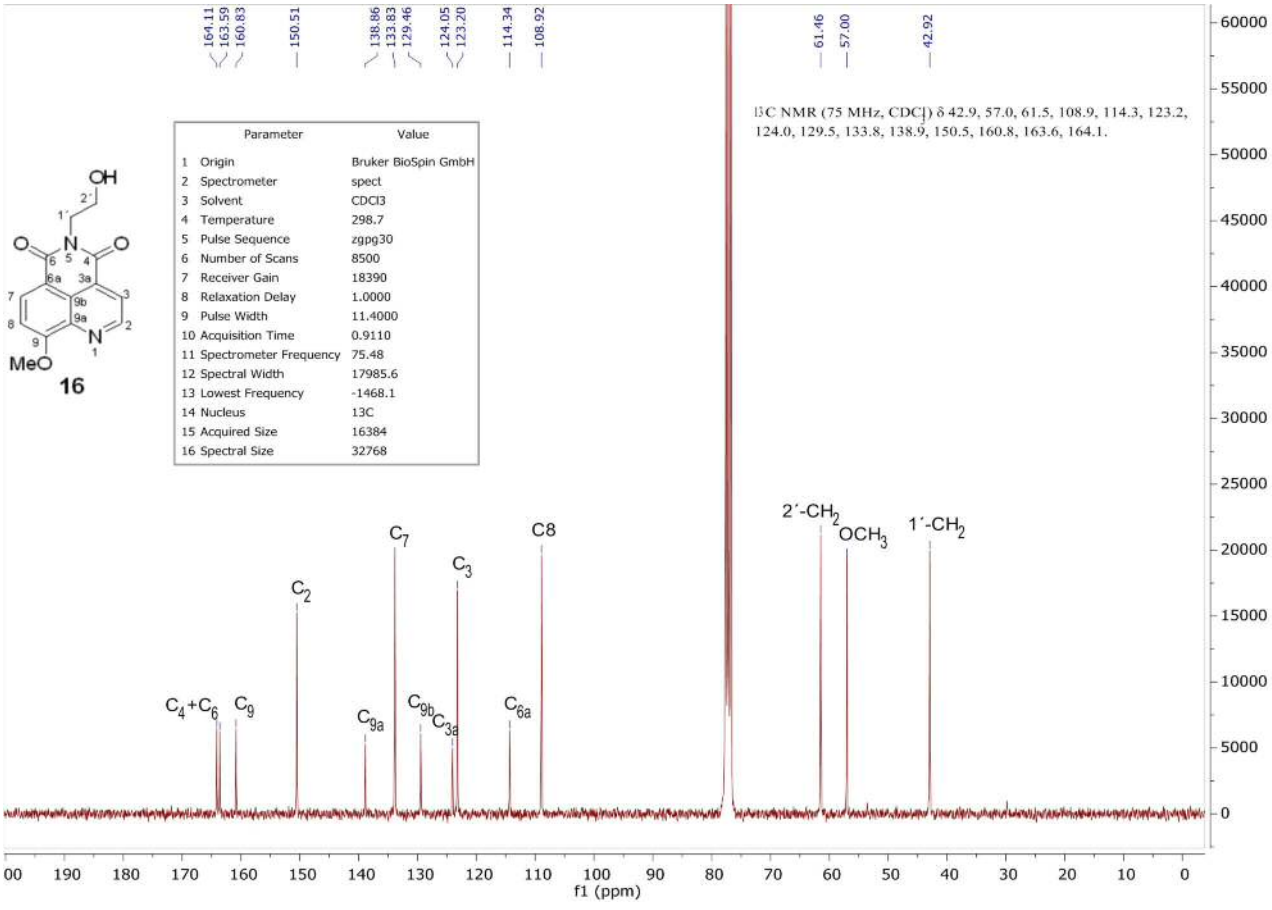


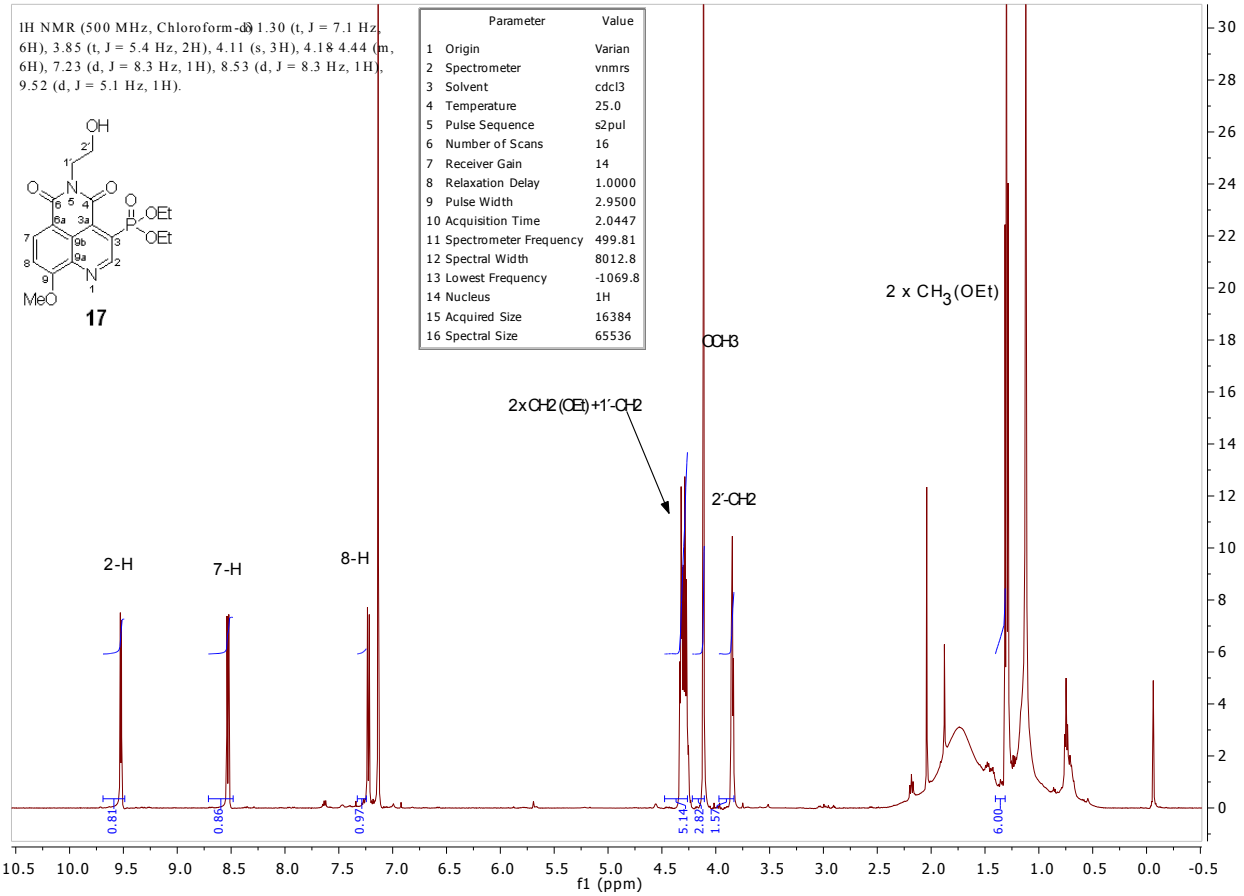
	Parameter	Value
1	Origin	Bruker BioSpin GmbH
2	Spectrometer	spect
3	Solvent	CDCl3
4	Temperature	298.3
5	Pulse Sequence	zgpg30
6	Number of Scans	12000
7	Receiver Gain	20642
8	Relaxation Delay	1.0000
9	Pulse Width	11.4000
10	Acquisition Time	0.9110
11	Spectrometer Frequency	75.48
12	Spectral Width	17985.6
13	Lowest Frequency	-1467.4
14	Nucleus	13C
15	Acquired Size	16384
16	Spectral Size	32768

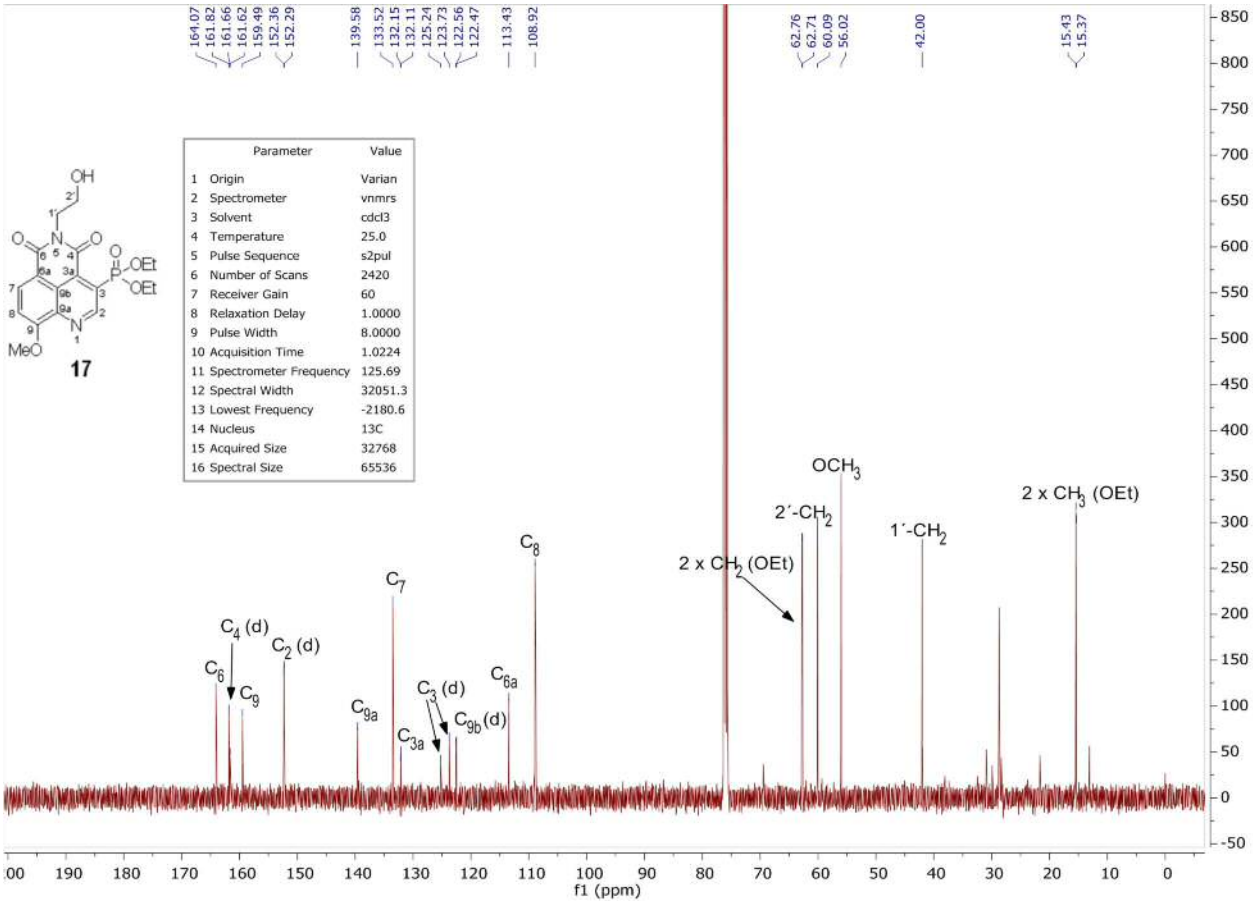
^{13}C NMR (75 MHz, CDCl$_3$) δ 57.4, 110.1, 110.9, 124.9, 126.8, 129.2, 135.9, 138.8, 151.8, 158.2, 158.9, 160.9.

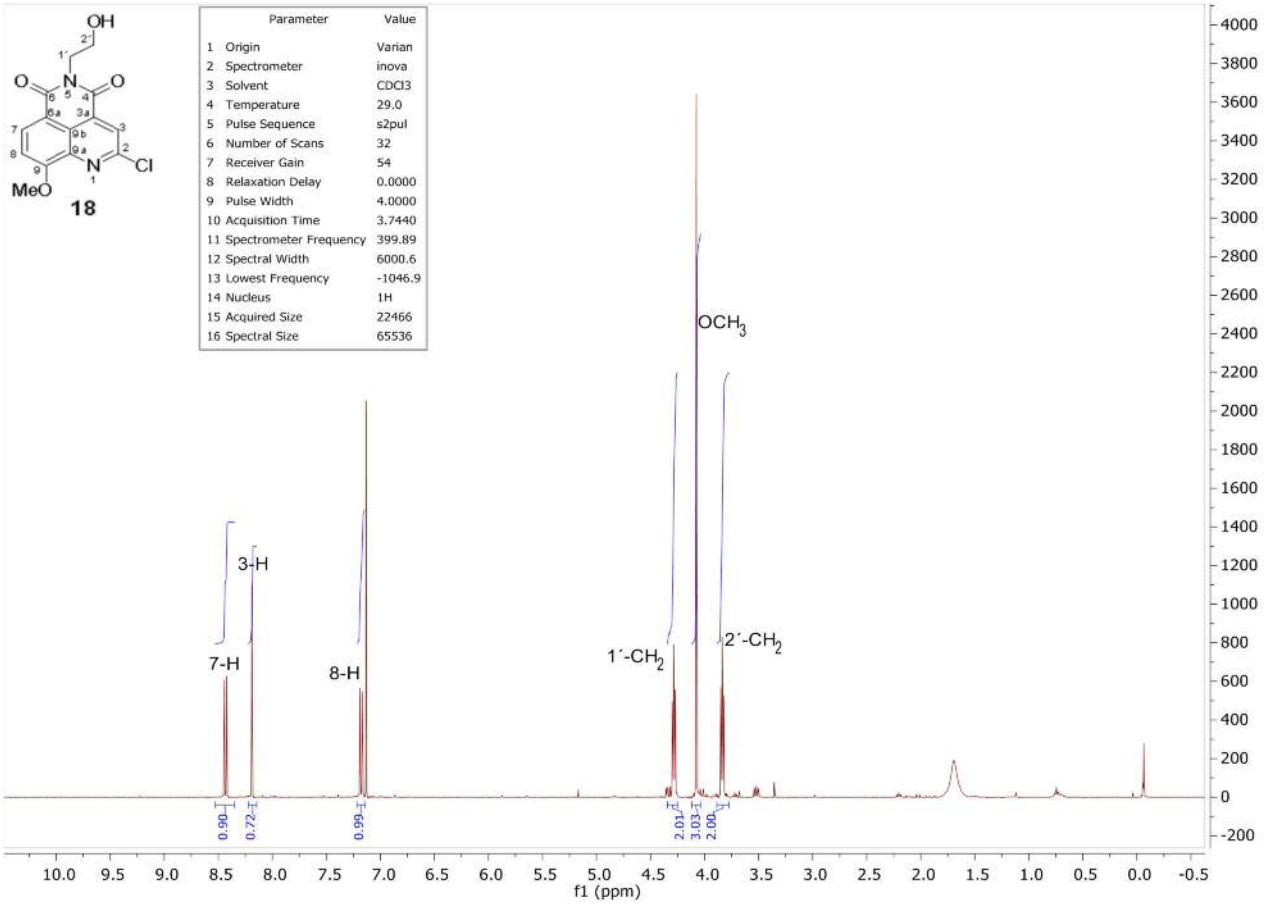

15
Parameter Value
1 Origin Varian
2 Spectrometer inova
3 Solvent CDCl3
4 Temperature 29.0
5 Pulse Sequence s2pul
6 Number of Scans 56
7 Receiver Gain 54
8 Relaxation Delay 0.0000
9 Pulse Width 7.0000
10 Acquisition Time 3.7440
11 Spectrometer Frequency 299.95
12 Spectral Width 4000.0
13 Lowest Frequency -540.3
14 Nucleus 1H
15 Acquired Size 14976
16 Spectral Size 65536
2 x CH3 (OEt)
OCH3
2 x CH2 (OEt)
7-H
8-H
0.78
0.90
4.00
3.72
7.10
f1 (ppm)

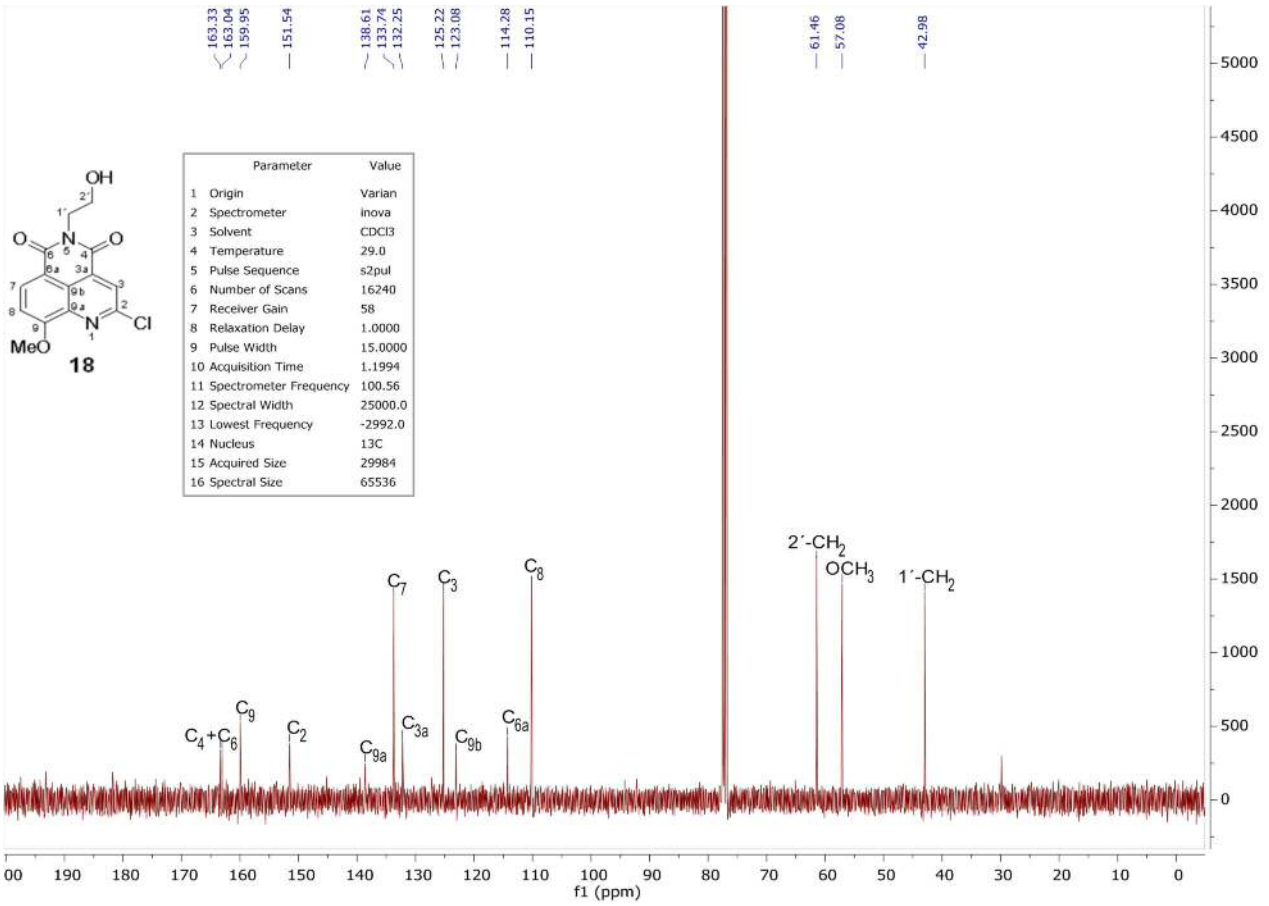

OH
MeO
16
Parameter Value
1 Origin Varian
2 Spectrometer inova
3 Solvent CDCl3
4 Temperature 29.0
5 Pulse Sequence s2pul
6 Number of Scans 12
7 Receiver Gain 48
8 Relaxation Delay 0.0000
9 Pulse Width 7.0000
10 Acquisition Time 3.7440
11 Spectrometer Frequency 299.95
12 Spectral Width 4000.0
13 Lowest Frequency -536.4
14 Nucleus 1H
15 Acquired Size 14976
16 Spectral Size 65536
OCH3
1´-CH2
2´-CH2
2-H
7-H
3-H
8-H
1.00
0.98
1.02
1.29
2.16
3.33
2.20
f1 (ppm)

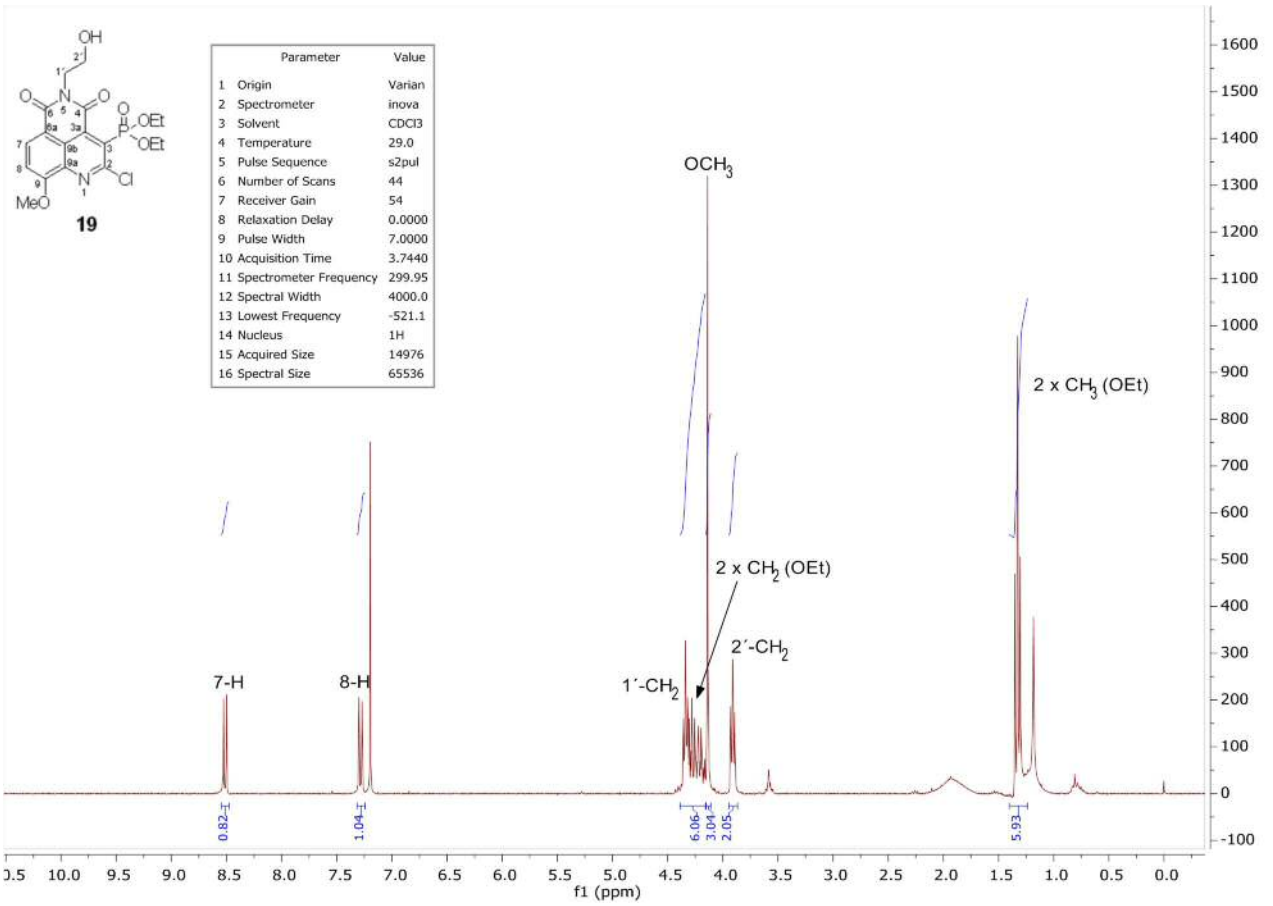

164.11
163.59
160.83
150.51
138.86
133.83
129.46
124.05
123.20
114.34
108.92
61.46
57.00
42.92
13C NMR (75 MHz, CDCl3) δ 42.9, 57.0, 61.5, 108.9, 114.3, 123.2, 124.0, 129.5, 133.8, 138.9, 150.5, 160.8, 163.6, 164.1.
OH
MeO
16
Parameter Value
1 Origin Bruker BioSpin GmbH
2 Spectrometer spect
3 Solvent CDCl3
4 Temperature 298.7
5 Pulse Sequence zgpg30
6 Number of Scans 8500
7 Receiver Gain 18390
8 Relaxation Delay 1.0000
9 Pulse Width 11.4000
10 Acquisition Time 0.9110
11 Spectrometer Frequency 75.48
12 Spectral Width 17985.6
13 Lowest Frequency -1468.1
14 Nucleus 13C
15 Acquired Size 16384
16 Spectral Size 32768
C4+C6
C9
C2
C9a
C7
C9b
C3a
C3
C6a
C8
2´-CH2
OCH3
1´-CH2
f1 (ppm)

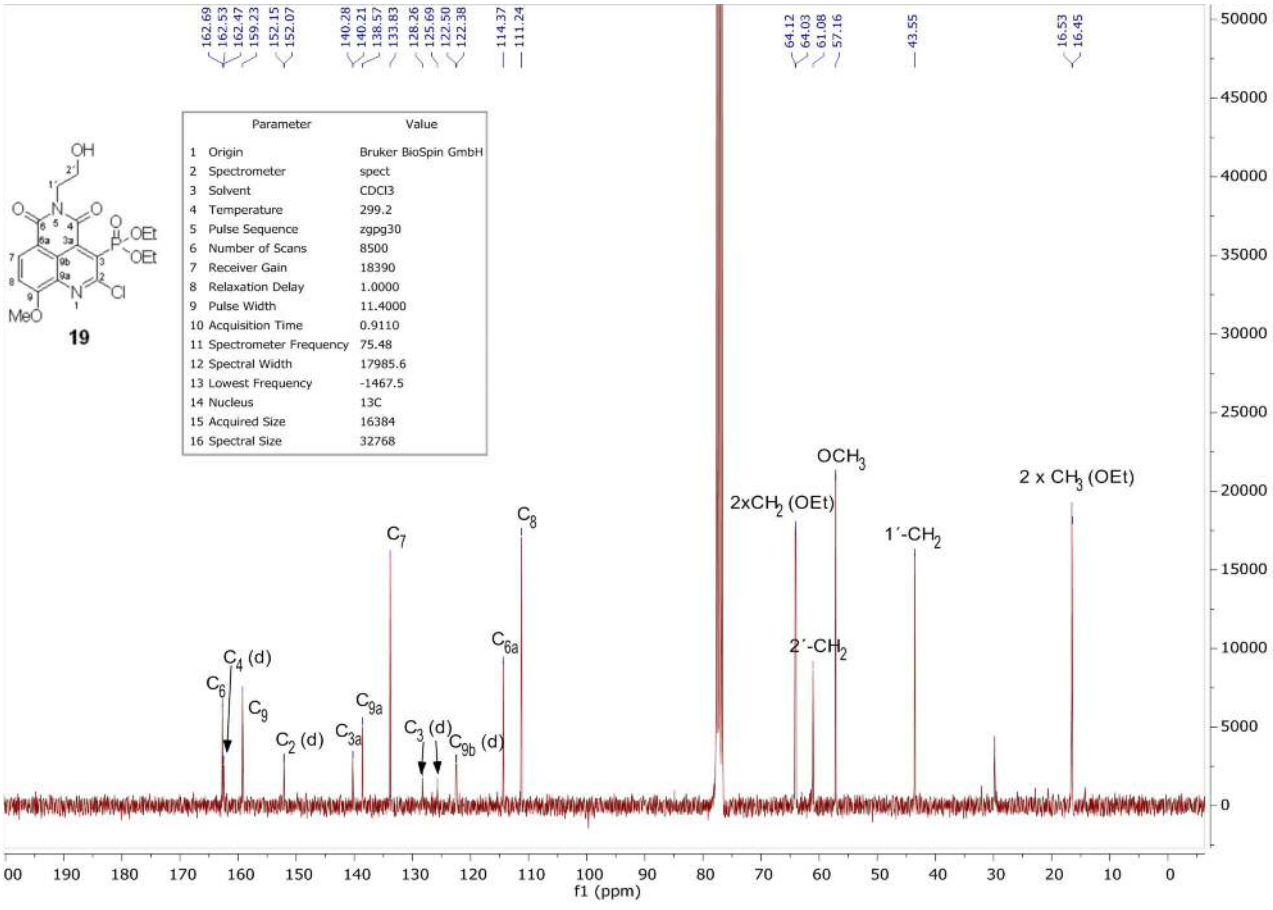

1H NMR (500 MHz, Chloroform-d) δ 1.30 (t, J = 7.1 Hz, 6H), 3.85 (t, J = 5.4 Hz, 2H), 4.11 (s, 3H), 4.18 - 4.44 (m, 6H), 7.23 (d, J = 8.3 Hz, 1H), 8.53 (d, J = 8.3 Hz, 1H), 9.52 (d, J = 5.1 Hz, 1H).
17
Parameter Value
1 Origin Varian
2 Spectrometer vnmrs
3 Solvent cdcl3
4 Temperature 25.0
5 Pulse Sequence s2pul
6 Number of Scans 16
7 Receiver Gain 14
8 Relaxation Delay 1.0000
9 Pulse Width 2.9500
10 Acquisition Time 2.0447
11 Spectrometer Frequency 499.81
12 Spectral Width 8012.8
13 Lowest Frequency -1069.8
14 Nucleus 1H
15 Acquired Size 16384
16 Spectral Size 65536
2 x CH3 (OEt)
OCH3
2xCH2 (OEt) +1´-CH2
2´-CH2
2-H
7-H
8-H
f1 (ppm)

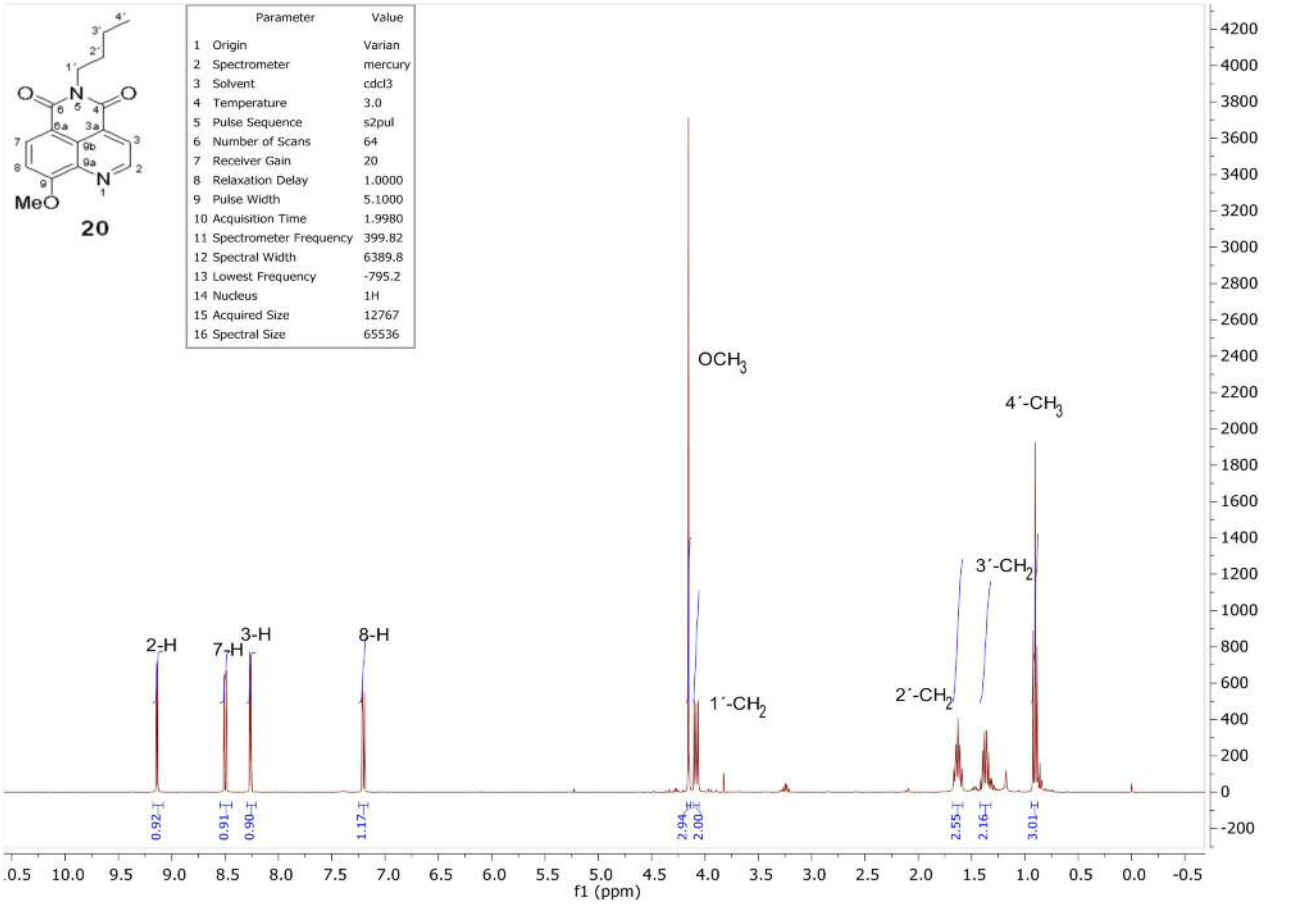

17
Parameter Value
1 Origin Varian
2 Spectrometer vnmrs
3 Solvent cdcl3
4 Temperature 25.0
5 Pulse Sequence s2pul
6 Number of Scans 2420
7 Receiver Gain 60
8 Relaxation Delay 1.0000
9 Pulse Width 8.0000
10 Acquisition Time 1.0224
11 Spectrometer Frequency 125.69
12 Spectral Width 32051.3
13 Lowest Frequency -2180.6
14 Nucleus 13C
15 Acquired Size 32768
16 Spectral Size 65536
OCH3
2´-CH2
1´-CH2
2 x CH2 (OEt)
2 x CH3 (OEt)
C8
C7
C4 (d)
C2 (d)
C6
C9
C9a
C3 (d)
C3a
C9b (d)
C6a
f1 (ppm)


OH
2´
1´
O
N
O
MeO
Cl
18
Parameter Value
1 Origin Varian
2 Spectrometer inova
3 Solvent CDCl3
4 Temperature 29.0
5 Pulse Sequence s2pul
6 Number of Scans 32
7 Receiver Gain 54
8 Relaxation Delay 0.0000
9 Pulse Width 4.0000
10 Acquisition Time 3.7440
11 Spectrometer Frequency 399.89
12 Spectral Width 6000.6
13 Lowest Frequency -1046.9
14 Nucleus 1H
15 Acquired Size 22466
16 Spectral Size 65536
OCH3
3-H
7-H
8-H
1´-CH2
2´-CH2
0.90
0.72
0.99
2.01
3.03
2.00
f1 (ppm)

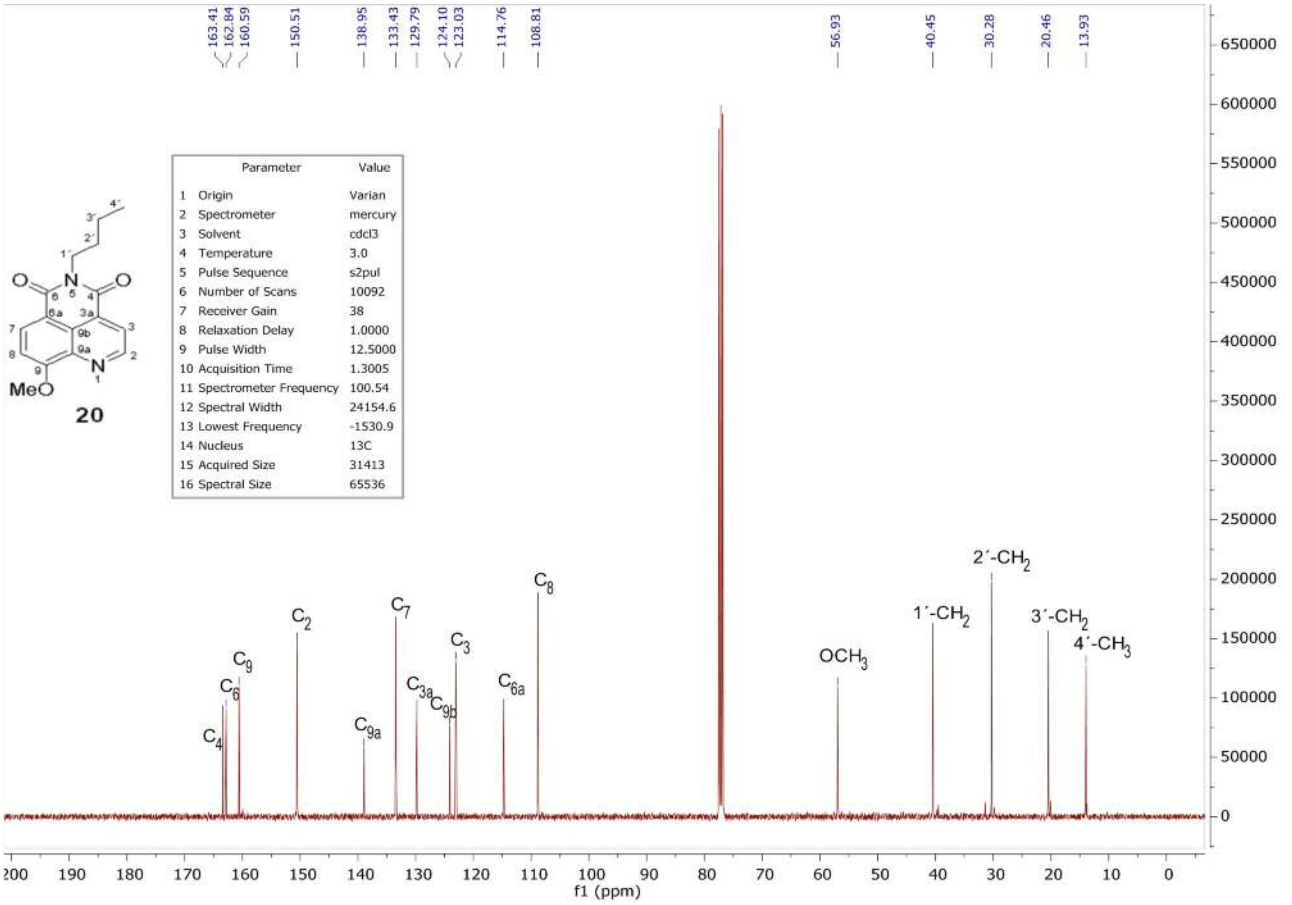

163.33
163.04
159.95
151.54
138.61
133.74
132.25
125.22
123.08
114.28
110.15
61.46
57.08
42.98
OH
2´
1´
O
N
O
MeO
Cl
18
Parameter Value
1 Origin Varian
2 Spectrometer inova
3 Solvent CDCl3
4 Temperature 29.0
5 Pulse Sequence s2pul
6 Number of Scans 16240
7 Receiver Gain 58
8 Relaxation Delay 1.0000
9 Pulse Width 15.0000
10 Acquisition Time 1.1994
11 Spectrometer Frequency 100.56
12 Spectral Width 25000.0
13 Lowest Frequency -2992.0
14 Nucleus 13C
15 Acquired Size 29984
16 Spectral Size 65536
C7
C3
C8
2´-CH2
OCH3
1´-CH2
C9
C4+C6
C2
C9a
C3a
C9b
C6a
f1 (ppm)


19
Parameter Value
1 Origin Varian
2 Spectrometer inova
3 Solvent CDCl3
4 Temperature 29.0
5 Pulse Sequence s2pul
6 Number of Scans 44
7 Receiver Gain 54
8 Relaxation Delay 0.0000
9 Pulse Width 7.0000
10 Acquisition Time 3.7440
11 Spectrometer Frequency 299.95
12 Spectral Width 4000.0
13 Lowest Frequency -521.1
14 Nucleus 1H
15 Acquired Size 14976
16 Spectral Size 65536
OCH3
2 x CH3 (OEt)
2 x CH2 (OEt)
2´-CH2
1´-CH2
7-H
8-H
0.82
1.04
6.06
3.04
2.05
5.93
f1 (ppm)

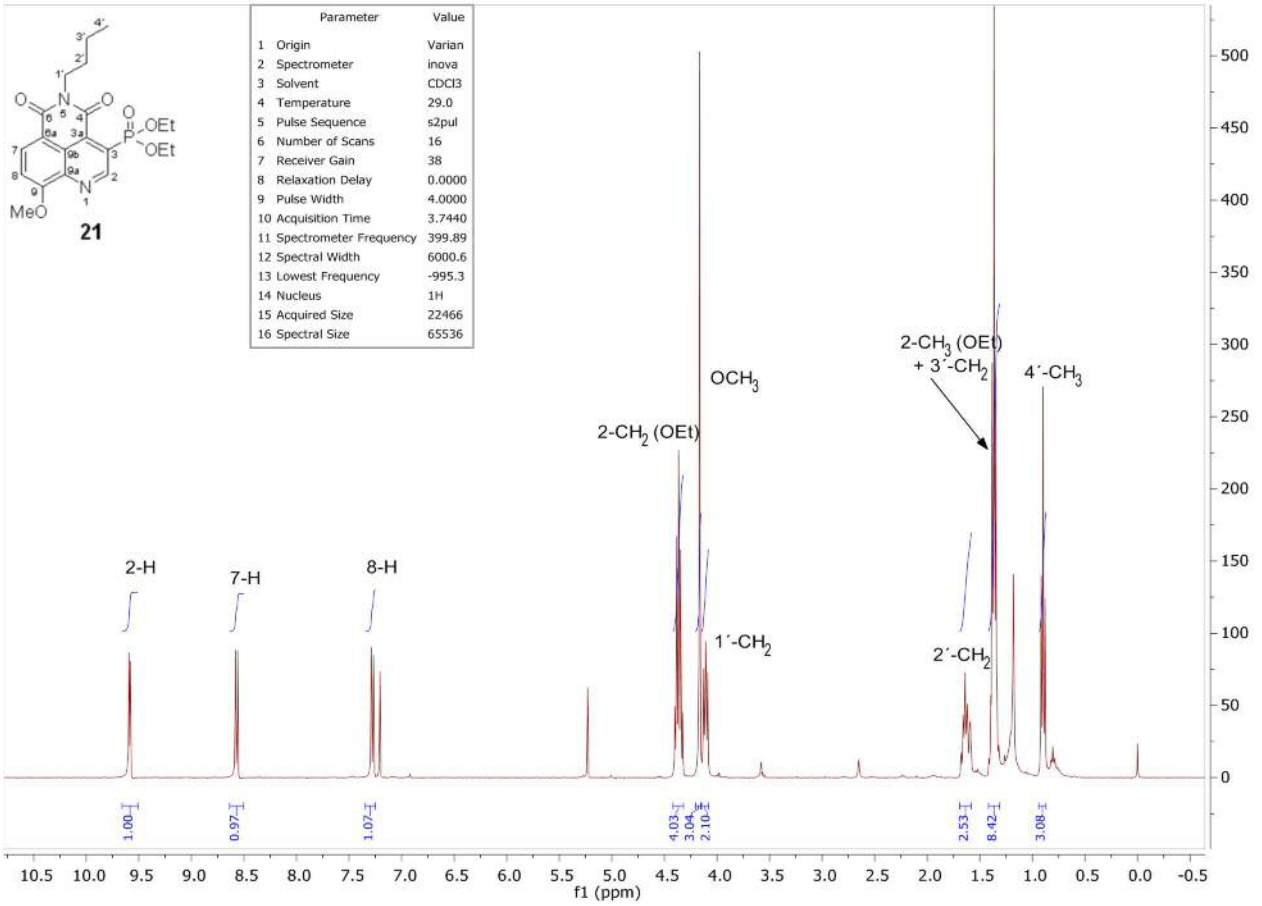

162.69
162.53
162.47
159.23
152.15
152.07
140.28
140.21
138.57
133.83
128.26
125.69
122.50
122.38
114.37
111.24
64.12
64.03
61.08
57.16
43.55
16.53
16.45
19
Parameter Value
1 Origin Bruker BioSpin GmbH
2 Spectrometer spect
3 Solvent CDCl3
4 Temperature 299.2
5 Pulse Sequence zgpg30
6 Number of Scans 8500
7 Receiver Gain 18390
8 Relaxation Delay 1.0000
9 Pulse Width 11.4000
10 Acquisition Time 0.9110
11 Spectrometer Frequency 75.48
12 Spectral Width 17985.6
13 Lowest Frequency -1467.5
14 Nucleus 13C
15 Acquired Size 16384
16 Spectral Size 32768
OCH3
2xCH2 (OEt)
2 x CH3 (OEt)
1´-CH2
2´-CH2
C7
C8
C6a
C4 (d)
C6
C9
C2 (d)
C3a
C9a
C3 (d)
C9b (d)
f1 (ppm)

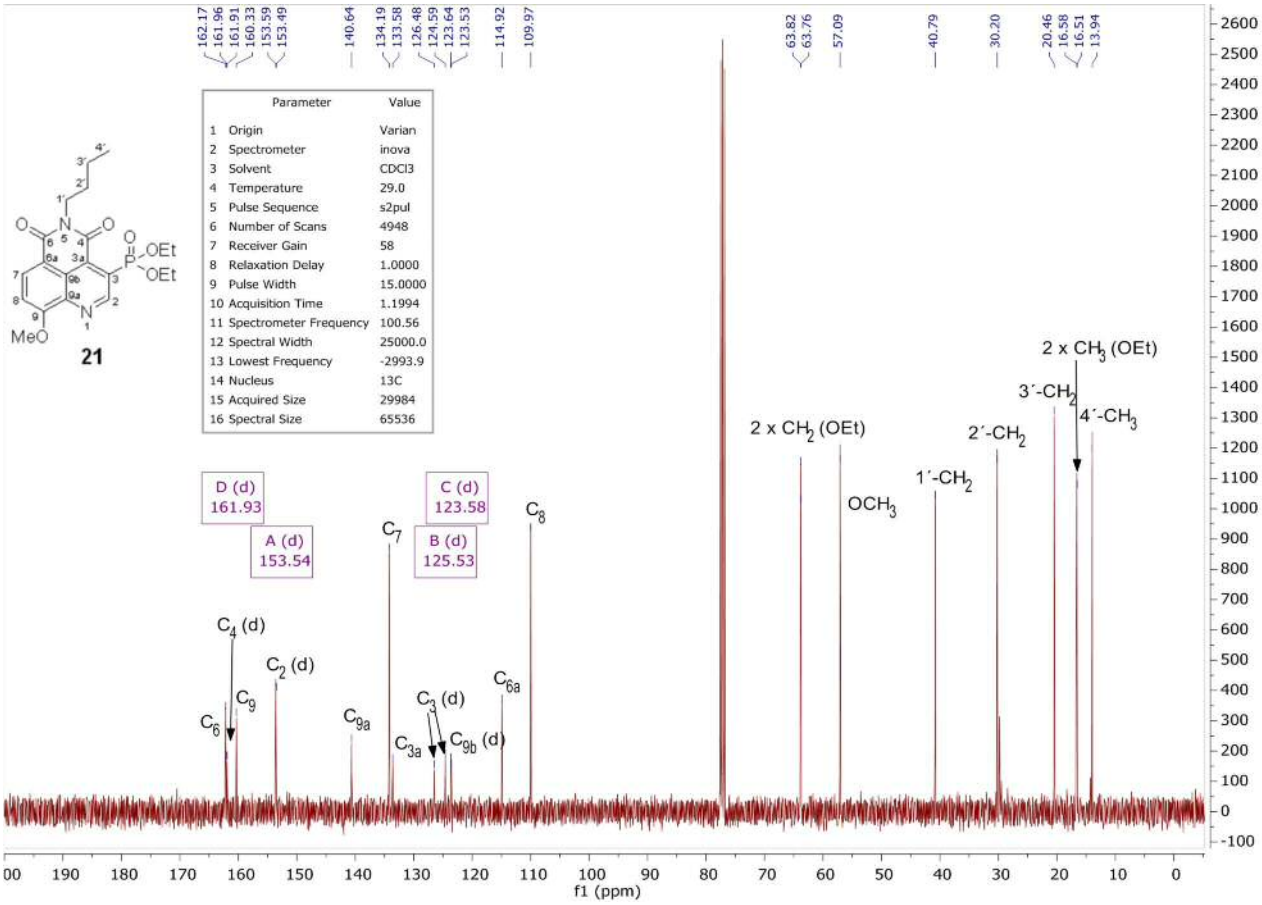


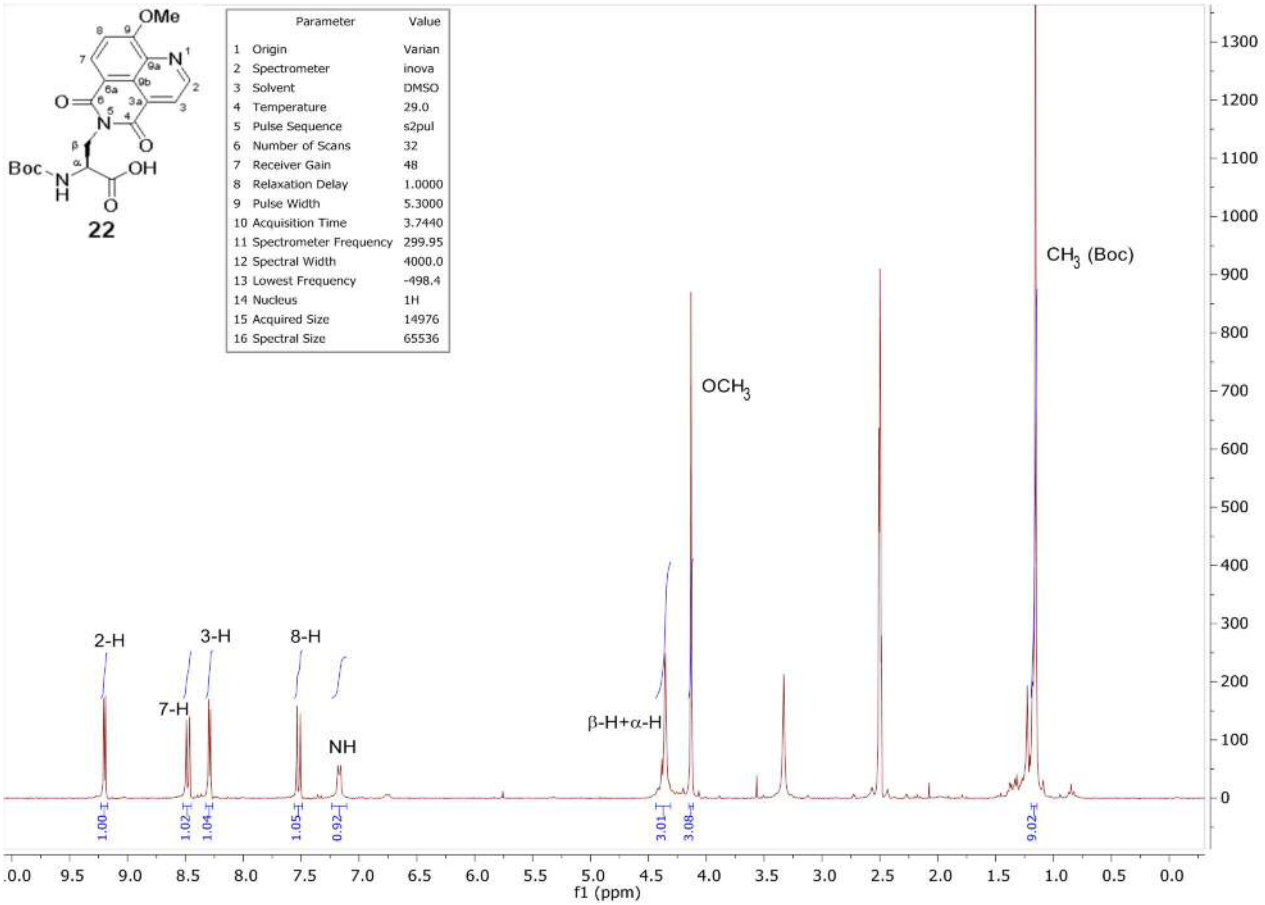
	Parameter	Value
1	Origin	Varian
2	Spectrometer	mercury
3	Solvent	cdcl3
4	Temperature	3.0
5	Pulse Sequence	s2pul
6	Number of Scans	64
7	Receiver Gain	20
8	Relaxation Delay	1.0000
9	Pulse Width	5.1000
10	Acquisition Time	1.9980
11	Spectrometer Frequency	399.82
12	Spectral Width	6389.8
13	Lowest Frequency	-795.2
14	Nucleus	1H
15	Acquired Size	12767
16	Spectral Size	65536

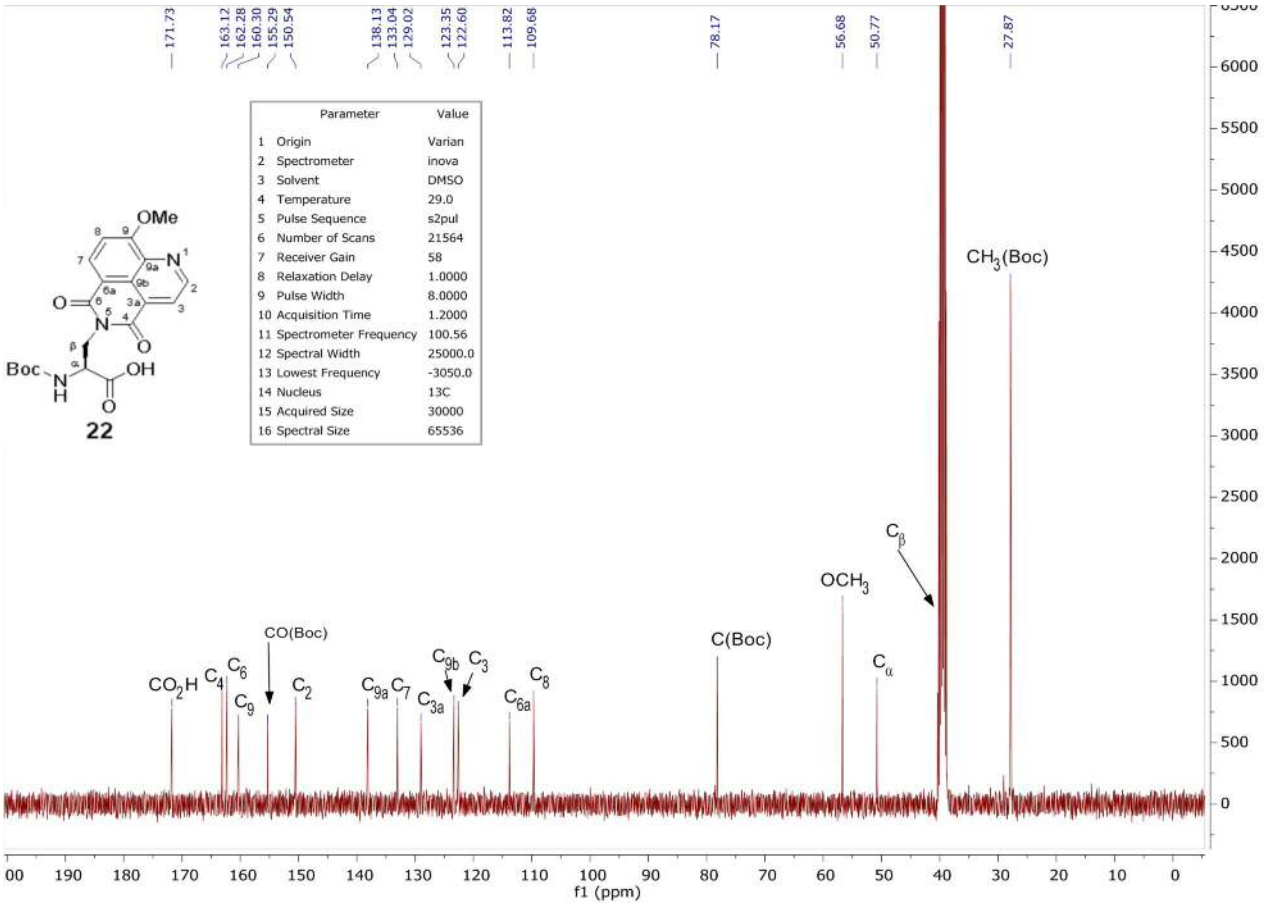


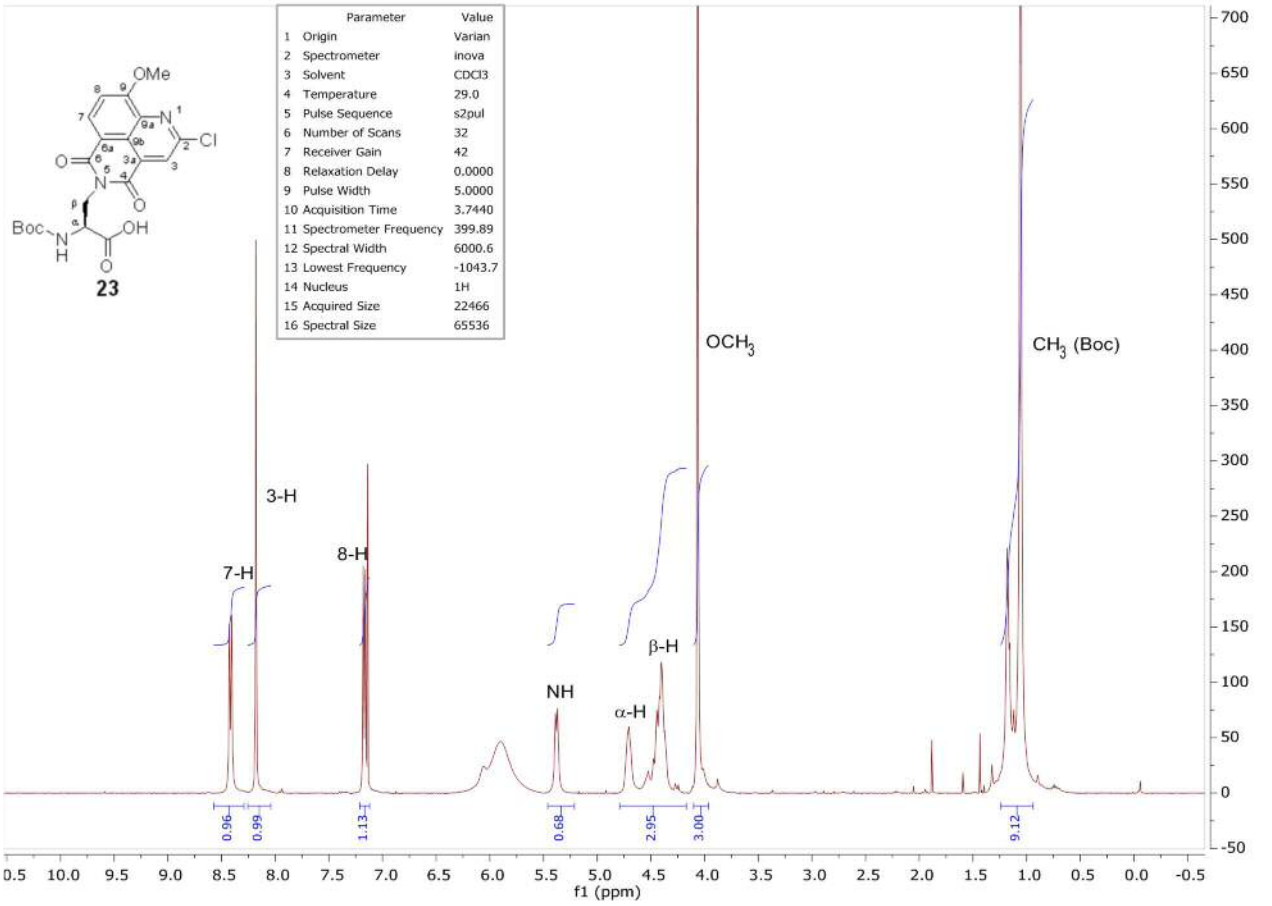
	Parameter	Value
1	Origin	Varian
2	Spectrometer	mercury
3	Solvent	cdcl3
4	Temperature	3.0
5	Pulse Sequence	s2pul
6	Number of Scans	10092
7	Receiver Gain	38
8	Relaxation Delay	1.0000
9	Pulse Width	12.5000
10	Acquisition Time	1.3005
11	Spectrometer Frequency	100.54
12	Spectral Width	24154.6
13	Lowest Frequency	-1530.9
14	Nucleus	13C
15	Acquired Size	31413
16	Spectral Size	65536

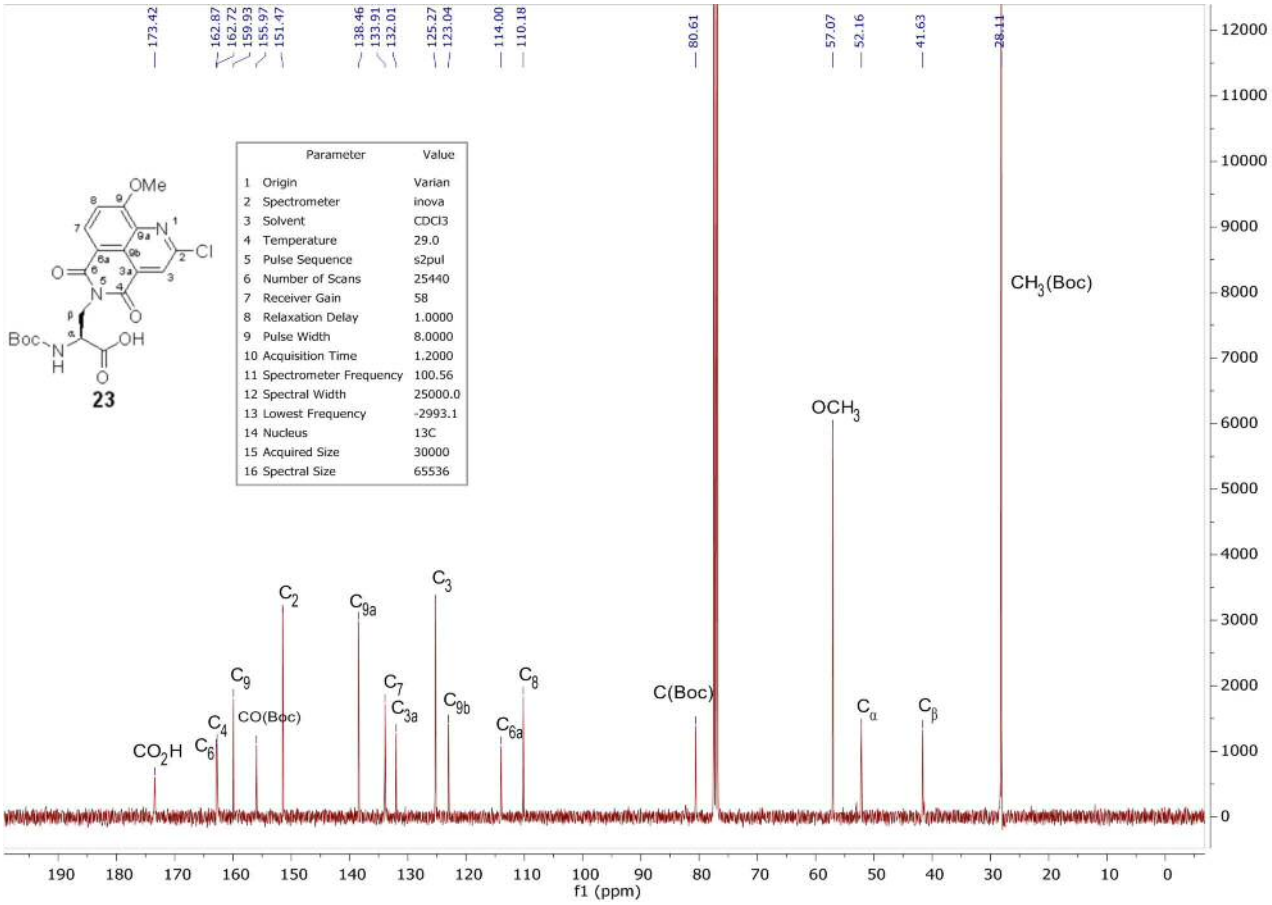

21
Parameter Value
1 Origin Varian
2 Spectrometer inova
3 Solvent CDCl3
4 Temperature 29.0
5 Pulse Sequence s2pul
6 Number of Scans 16
7 Receiver Gain 38
8 Relaxation Delay 0.0000
9 Pulse Width 4.0000
10 Acquisition Time 3.7440
11 Spectrometer Frequency 399.89
12 Spectral Width 6000.6
13 Lowest Frequency -995.3
14 Nucleus 1H
15 Acquired Size 22466
16 Spectral Size 65536
2-H
7-H
8-H
2-CH2 (OEt)
OCH3
1´-CH2
2-CH3 (OEt) + 3´-CH2
2´-CH2
4´-CH3
1.00
0.97
1.07
4.03
3.04
2.10
2.53
8.42
3.08
f1 (ppm)

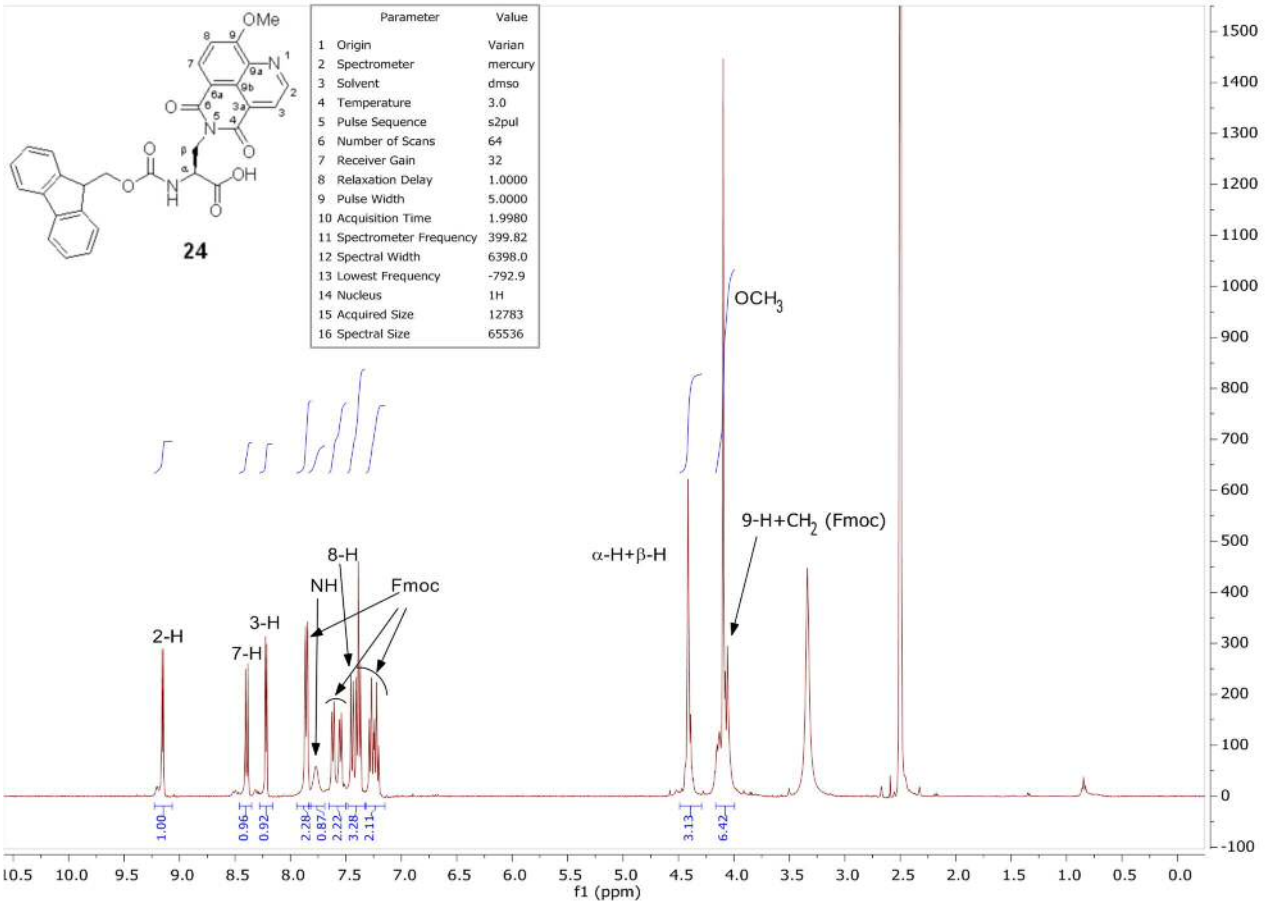

21
Parameter Value
1 Origin Varian
2 Spectrometer inova
3 Solvent CDCl3
4 Temperature 29.0
5 Pulse Sequence s2pul
6 Number of Scans 4948
7 Receiver Gain 58
8 Relaxation Delay 1.0000
9 Pulse Width 15.0000
10 Acquisition Time 1.1994
11 Spectrometer Frequency 100.56
12 Spectral Width 25000.0
13 Lowest Frequency -2993.9
14 Nucleus 13C
15 Acquired Size 29984
16 Spectral Size 65536
162.17
161.96
161.91
160.33
153.59
153.49
140.64
134.19
133.58
126.48
124.59
123.64
123.53
114.92
109.97
63.82
63.76
57.09
40.79
30.20
20.46
16.58
16.51
13.94
D (d) 161.93
A (d) 153.54
C (d) 123.58
B (d) 125.53
C4 (d)
C2 (d)
C9
C6
C9a
C3 (d)
C3a
C9b (d)
C6a
C7
C8
2 x CH2 (OEt)
OCH3
1´-CH2
2´-CH2
3´-CH2
2 x CH3 (OEt)
4´-CH3
f1 (ppm)

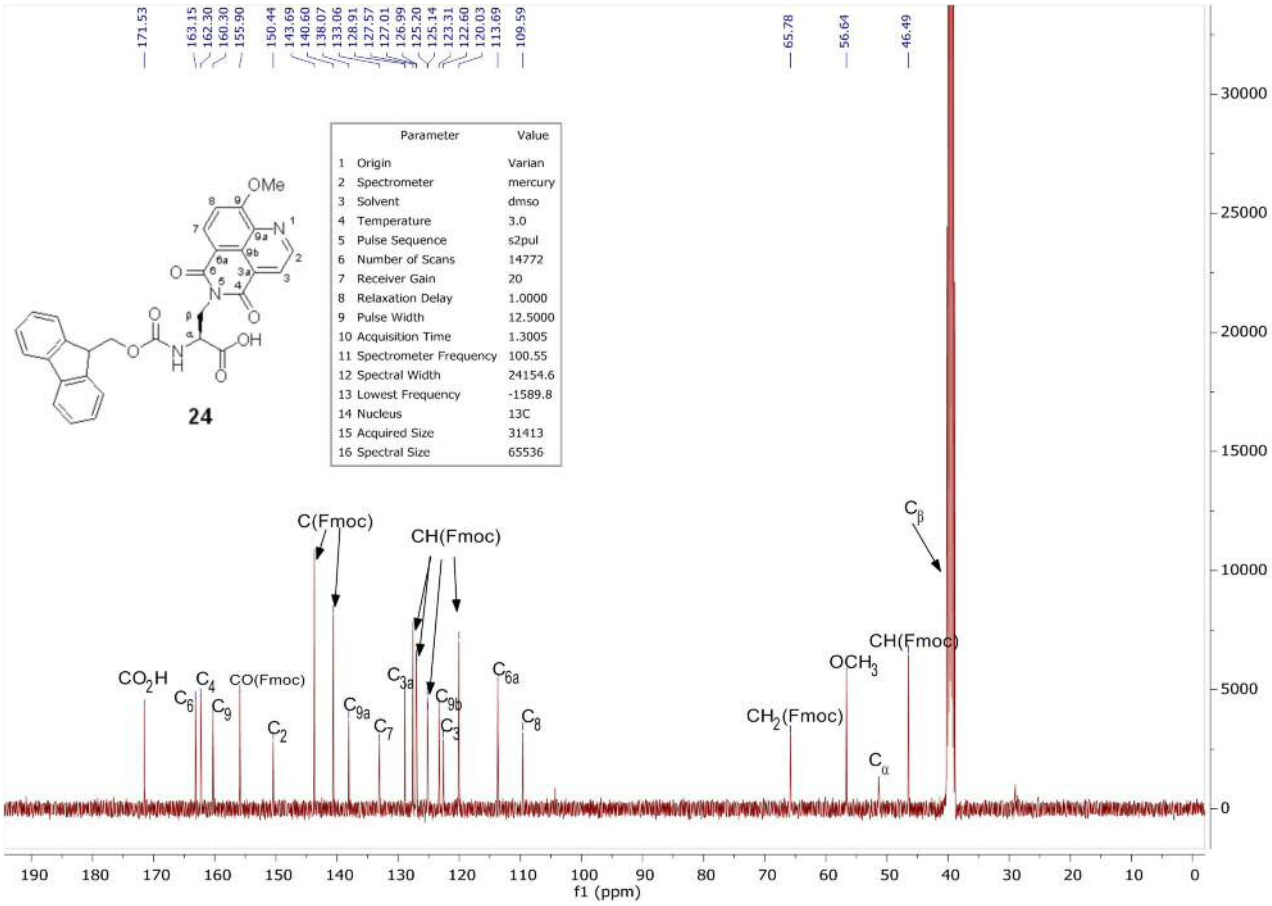

OMe
Boc
OH
22
Parameter Value
1 Origin Varian
2 Spectrometer inova
3 Solvent DMSO
4 Temperature 29.0
5 Pulse Sequence s2pul
6 Number of Scans 32
7 Receiver Gain 48
8 Relaxation Delay 1.0000
9 Pulse Width 5.3000
10 Acquisition Time 3.7440
11 Spectrometer Frequency 299.95
12 Spectral Width 4000.0
13 Lowest Frequency -498.4
14 Nucleus 1H
15 Acquired Size 14976
16 Spectral Size 65536
2-H
3-H
8-H
7-H
NH
β-H+α-H
OCH3
CH3 (Boc)
1.00
1.02
1.04
1.05
0.92
3.01
3.08
9.02
f1 (ppm)

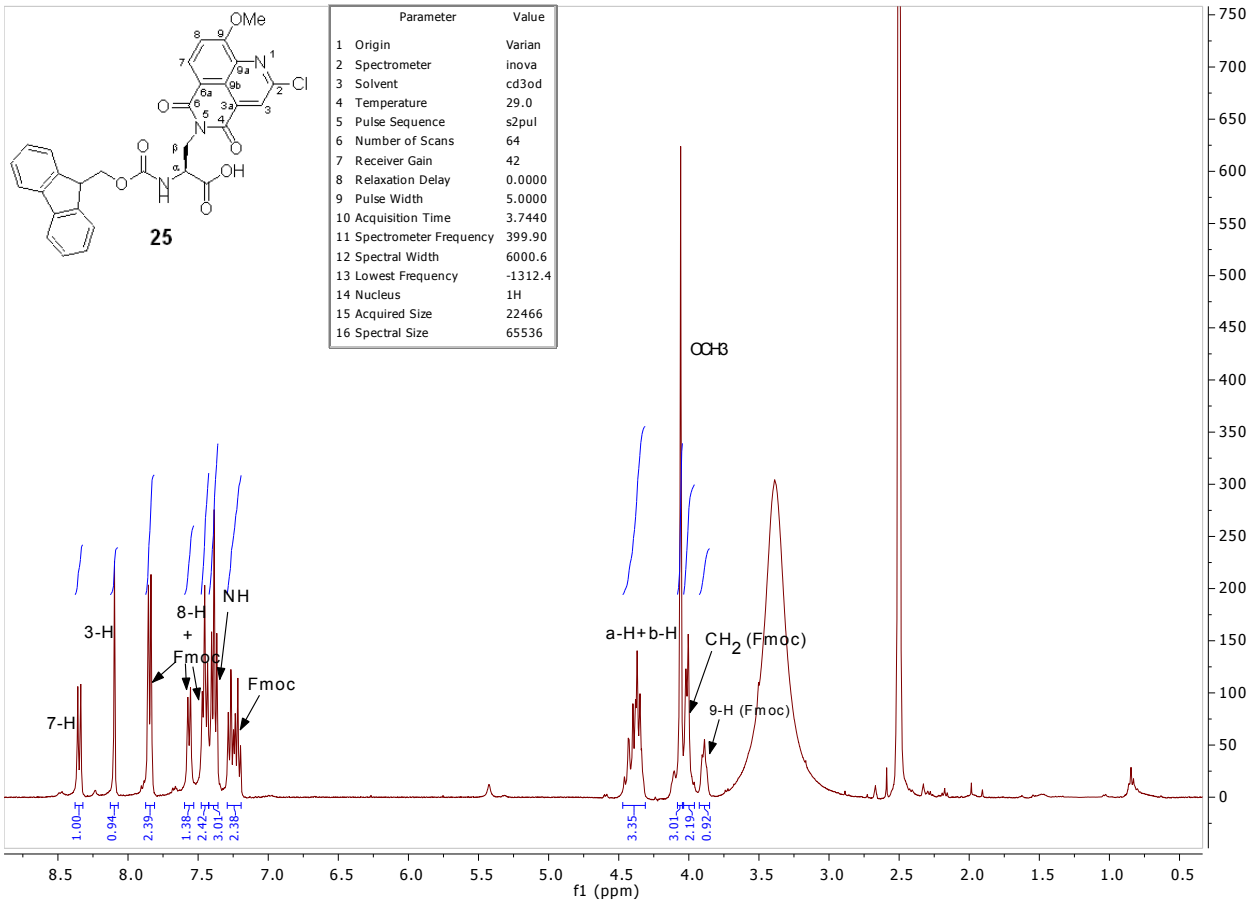

171.73
163.12
162.28
160.30
155.29
150.54
138.13
133.04
129.02
123.35
122.60
113.82
109.68
78.17
56.68
50.77
27.87
OMe
Boc
OH
22
Parameter Value
1 Origin Varian
2 Spectrometer inova
3 Solvent DMSO
4 Temperature 29.0
5 Pulse Sequence s2pul
6 Number of Scans 21564
7 Receiver Gain 58
8 Relaxation Delay 1.0000
9 Pulse Width 8.0000
10 Acquisition Time 1.2000
11 Spectrometer Frequency 100.56
12 Spectral Width 25000.0
13 Lowest Frequency -3050.0
14 Nucleus 13C
15 Acquired Size 30000
16 Spectral Size 65536
CH3(Boc)
Cβ
OCH3
Cα
C(Boc)
CO(Boc)
CO2H
C4
C6
C9
C2
C9a
C7
C3a
C9b
C3
C6a
C8
f1 (ppm)

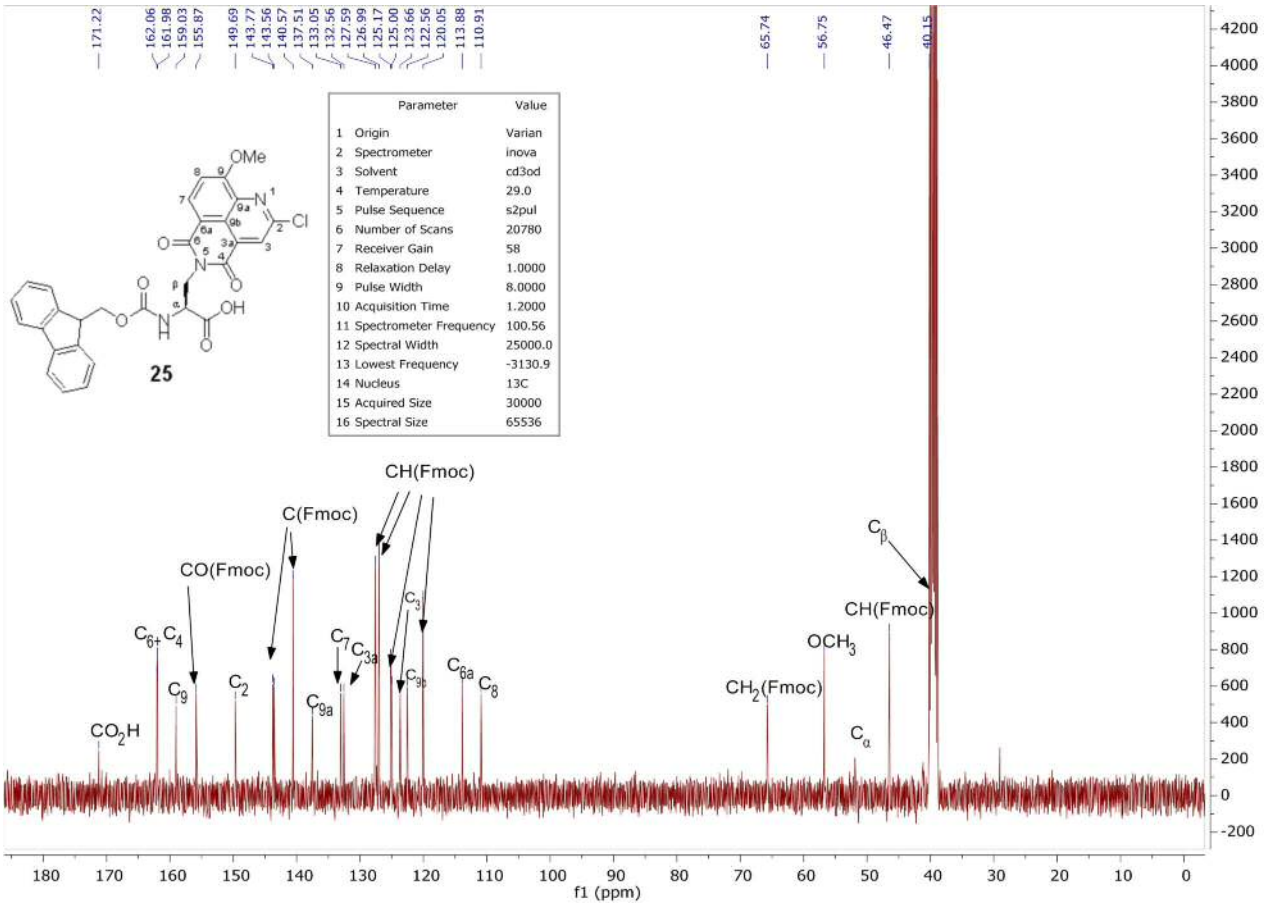

Parameter Value
1 Origin Varian
2 Spectrometer inova
3 Solvent CDCl3
4 Temperature 29.0
5 Pulse Sequence s2pul
6 Number of Scans 32
7 Receiver Gain 42
8 Relaxation Delay 0.0000
9 Pulse Width 5.0000
10 Acquisition Time 3.7440
11 Spectrometer Frequency 399.89
12 Spectral Width 6000.6
13 Lowest Frequency -1043.7
14 Nucleus 1H
15 Acquired Size 22466
16 Spectral Size 65536
23
7-H
3-H
8-H
NH
α-H
β-H
OCH3
CH3 (Boc)
0.96
0.99
1.13
0.68
2.95
3.00
9.12
f1 (ppm)

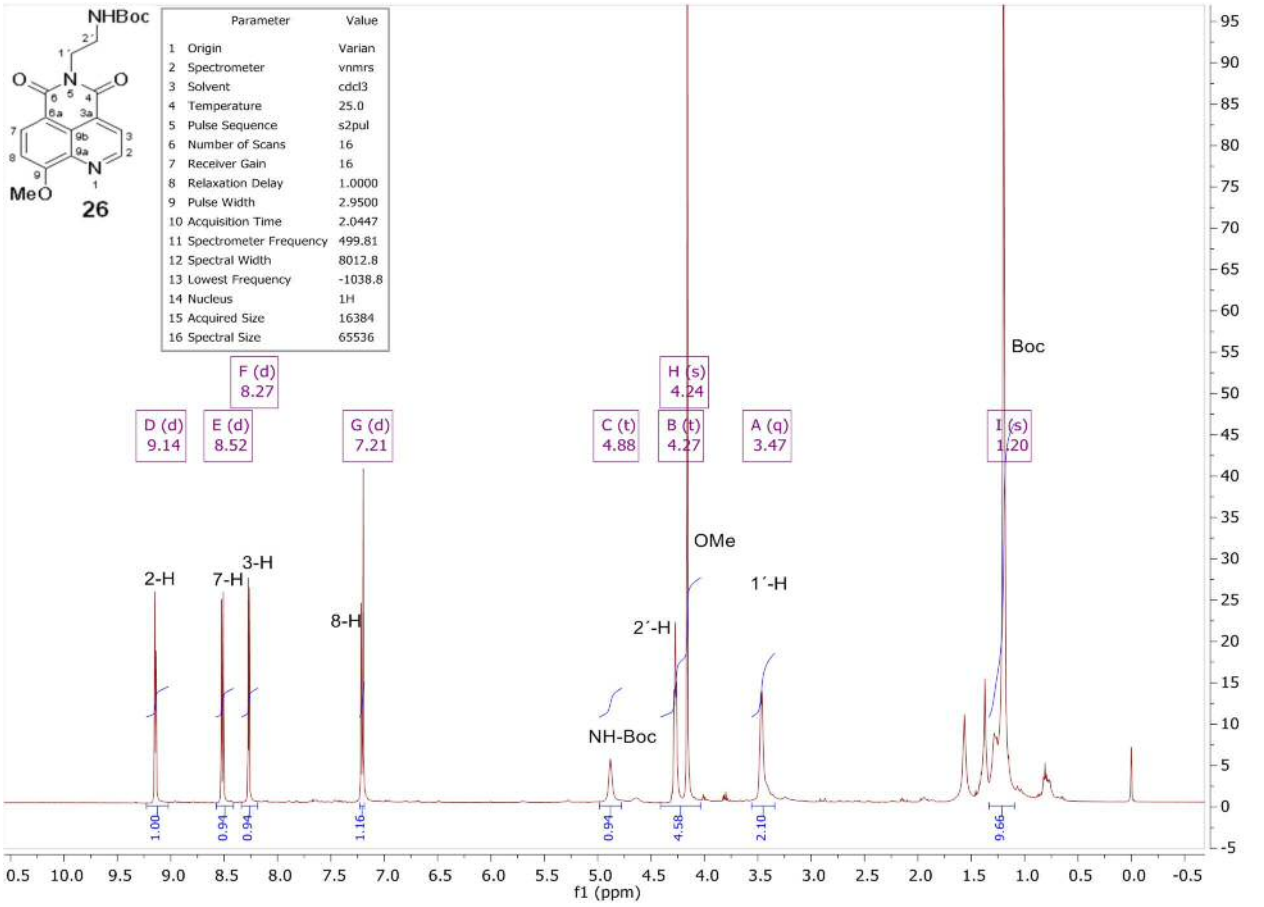

173.42
162.87
162.72
159.93
155.97
151.47
138.46
133.91
132.01
125.27
123.04
114.00
110.18
80.61
57.07
52.16
41.63
28.11
Parameter Value
1 Origin Varian
2 Spectrometer inova
3 Solvent CDCl3
4 Temperature 29.0
5 Pulse Sequence s2pul
6 Number of Scans 25440
7 Receiver Gain 58
8 Relaxation Delay 1.0000
9 Pulse Width 8.0000
10 Acquisition Time 1.2000
11 Spectrometer Frequency 100.56
12 Spectral Width 25000.0
13 Lowest Frequency -2993.1
14 Nucleus 13C
15 Acquired Size 30000
16 Spectral Size 65536
23
CH3(Boc)
OCH3
C2
C9a
C3
C9
C7
C8
C3a
C9b
C6a
C4
C6
CO(Boc)
CO2H
C(Boc)
Cα
Cβ
f1 (ppm)

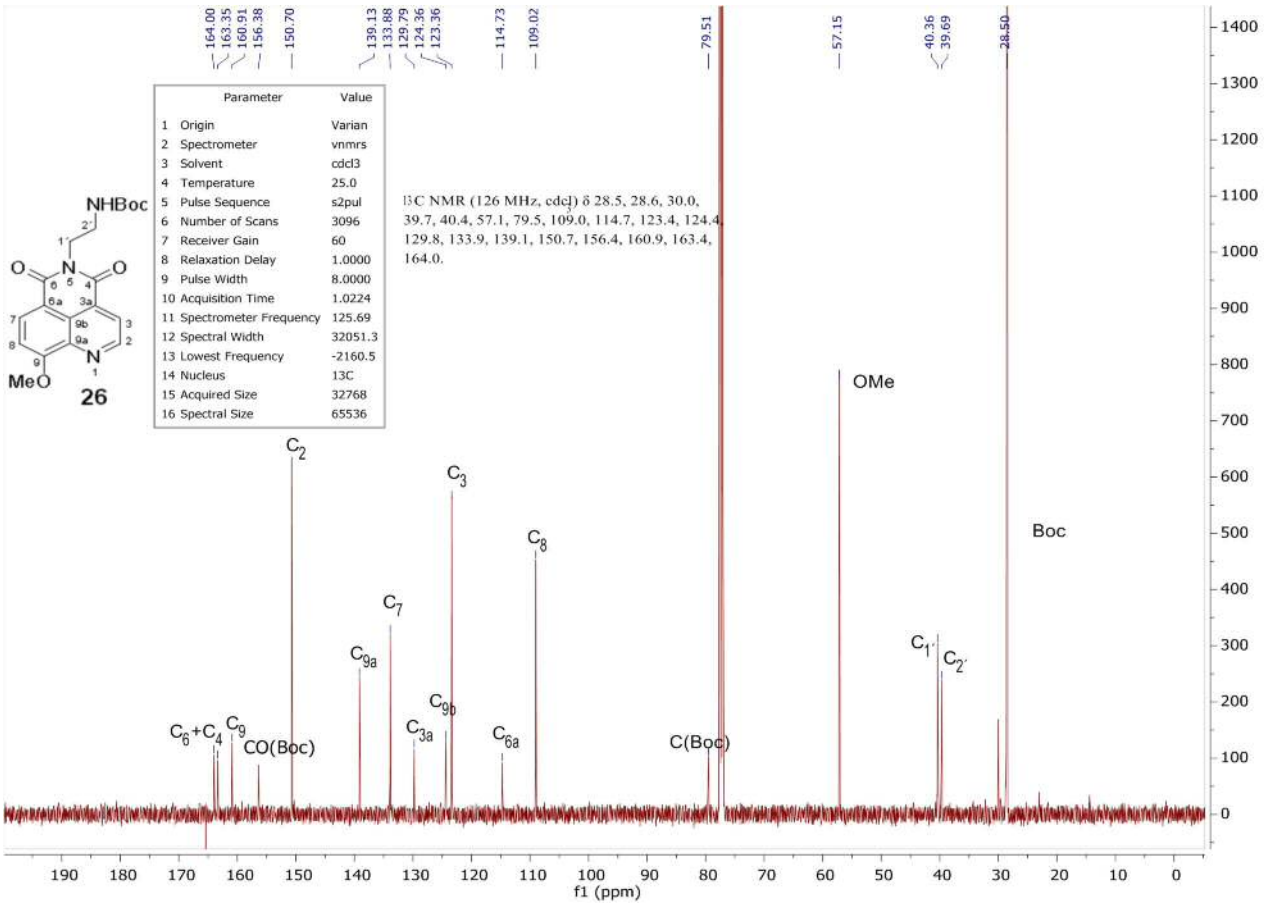

24
Parameter Value
1 Origin Varian
2 Spectrometer mercury
3 Solvent dmso
4 Temperature 3.0
5 Pulse Sequence s2pul
6 Number of Scans 64
7 Receiver Gain 32
8 Relaxation Delay 1.0000
9 Pulse Width 5.0000
10 Acquisition Time 1.9980
11 Spectrometer Frequency 399.82
12 Spectral Width 6398.0
13 Lowest Frequency -792.9
14 Nucleus 1H
15 Acquired Size 12783
16 Spectral Size 65536
OCH3
9-H+CH2 (Fmoc)
α-H+β-H
8-H
NH
Fmoc
3-H
2-H
7-H
1.00
0.96
0.92
2.28
0.87
2.22
3.28
2.11
3.13
6.42
f1 (ppm)

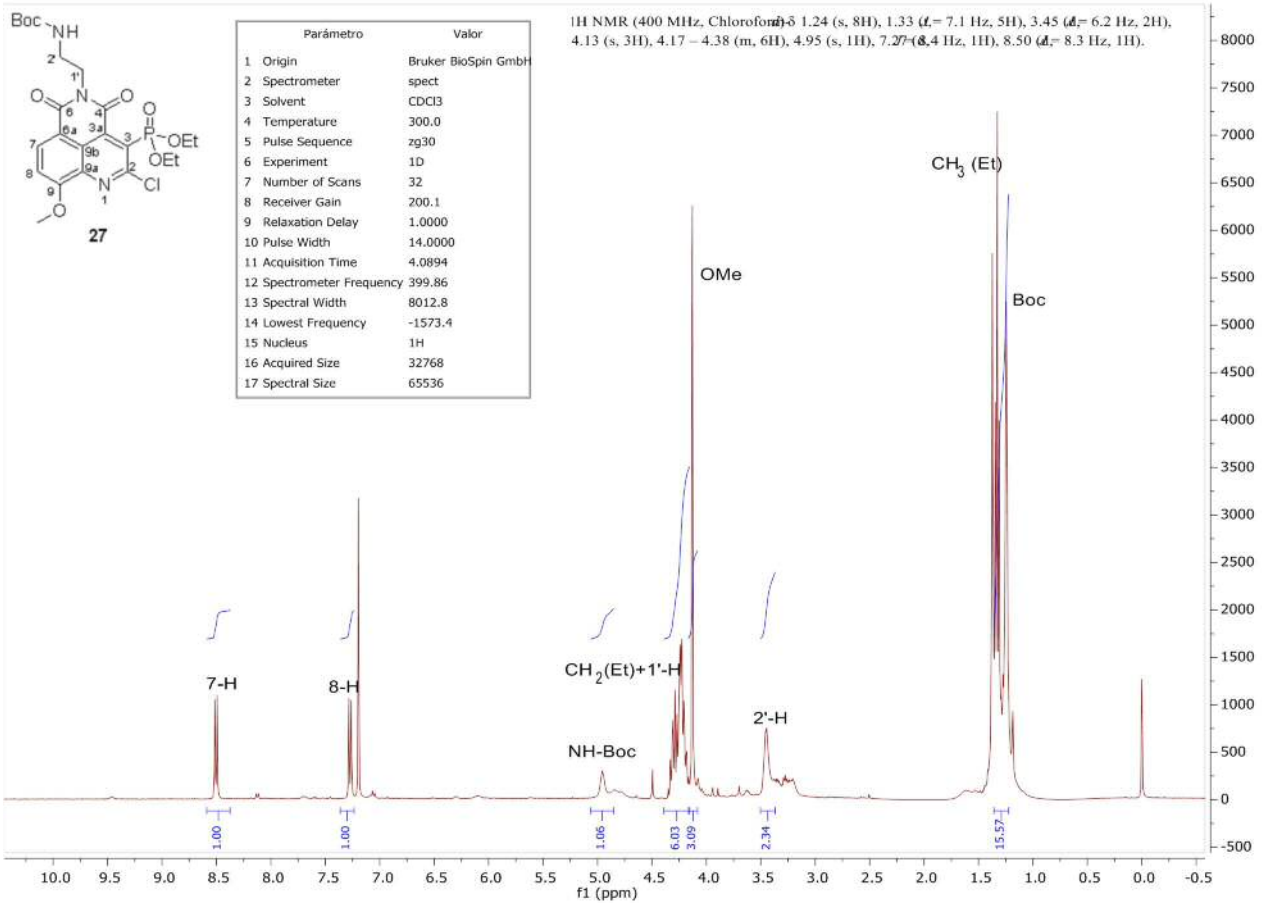

171.53
163.15
162.30
160.30
155.90
150.44
143.69
140.60
138.07
133.06
128.91
127.57
127.01
126.99
125.20
125.14
123.31
122.60
120.03
113.69
109.59
65.78
56.64
46.49
24
Parameter Value
1 Origin Varian
2 Spectrometer mercury
3 Solvent dmso
4 Temperature 3.0
5 Pulse Sequence s2pul
6 Number of Scans 14772
7 Receiver Gain 20
8 Relaxation Delay 1.0000
9 Pulse Width 12.5000
10 Acquisition Time 1.3005
11 Spectrometer Frequency 100.55
12 Spectral Width 24154.6
13 Lowest Frequency -1589.8
14 Nucleus 13C
15 Acquired Size 31413
16 Spectral Size 65536
C(Fmoc)
CH(Fmoc)
Cβ
CH(Fmoc)
OCH3
CO2H
C6
C4
C9
CO(Fmoc)
C2
C9a
C7
C3a
C9b
C3
C6a
C8
CH2(Fmoc)
Cα
f1 (ppm)


OMe
Cl
OH
25
Parameter Value
1 Origin Varian
2 Spectrometer inova
3 Solvent cd3od
4 Temperature 29.0
5 Pulse Sequence s2pul
6 Number of Scans 64
7 Receiver Gain 42
8 Relaxation Delay 0.0000
9 Pulse Width 5.0000
10 Acquisition Time 3.7440
11 Spectrometer Frequency 399.90
12 Spectral Width 6000.6
13 Lowest Frequency -1312.4
14 Nucleus 1H
15 Acquired Size 22466
16 Spectral Size 65536
OCH3
7-H
3-H
8-H
+
Fmoc
NH
Fmoc
a-H+b-H
CH2 (Fmoc)
9-H (Fmoc)
1.00
0.94
2.39
1.38
2.42
3.01
2.38
3.35
3.01
2.19
0.92
f1 (ppm)


171.22
162.06
161.98
159.03
155.87
149.69
143.77
143.56
140.57
137.51
133.05
132.56
127.59
126.99
125.17
125.00
123.66
122.56
120.05
113.88
110.91
65.74
56.75
46.47
40.15
OMe
Cl
OH
25
Parameter Value
1 Origin Varian
2 Spectrometer inova
3 Solvent cd3od
4 Temperature 29.0
5 Pulse Sequence s2pul
6 Number of Scans 20780
7 Receiver Gain 58
8 Relaxation Delay 1.0000
9 Pulse Width 8.0000
10 Acquisition Time 1.2000
11 Spectrometer Frequency 100.56
12 Spectral Width 25000.0
13 Lowest Frequency -3130.9
14 Nucleus 13C
15 Acquired Size 30000
16 Spectral Size 65536
CH(Fmoc)
C(Fmoc)
CO(Fmoc)
C6+C4
C9
C2
C7
C3a
C9a
C3
C9
C6a
C8
CO2H
Cβ
CH(Fmoc)
OCH3
CH2(Fmoc)
Cα
f1 (ppm)


NHBoc
MeO
26
Parameter Value
1 Origin Varian
2 Spectrometer vnmrs
3 Solvent cdcl3
4 Temperature 25.0
5 Pulse Sequence s2pul
6 Number of Scans 16
7 Receiver Gain 16
8 Relaxation Delay 1.0000
9 Pulse Width 2.9500
10 Acquisition Time 2.0447
11 Spectrometer Frequency 499.81
12 Spectral Width 8012.8
13 Lowest Frequency -1038.8
14 Nucleus 1H
15 Acquired Size 16384
16 Spectral Size 65536
D (d) 9.14
E (d) 8.52
F (d) 8.27
G (d) 7.21
C (t) 4.88
B (t) 4.27
H (s) 4.24
A (q) 3.47
I (s) 1.20
2-H
7-H
3-H
8-H
NH-Boc
2´-H
OMe
1´-H
Boc
1.00
0.94
0.94
1.16
0.94
4.58
2.10
9.66
f1 (ppm)

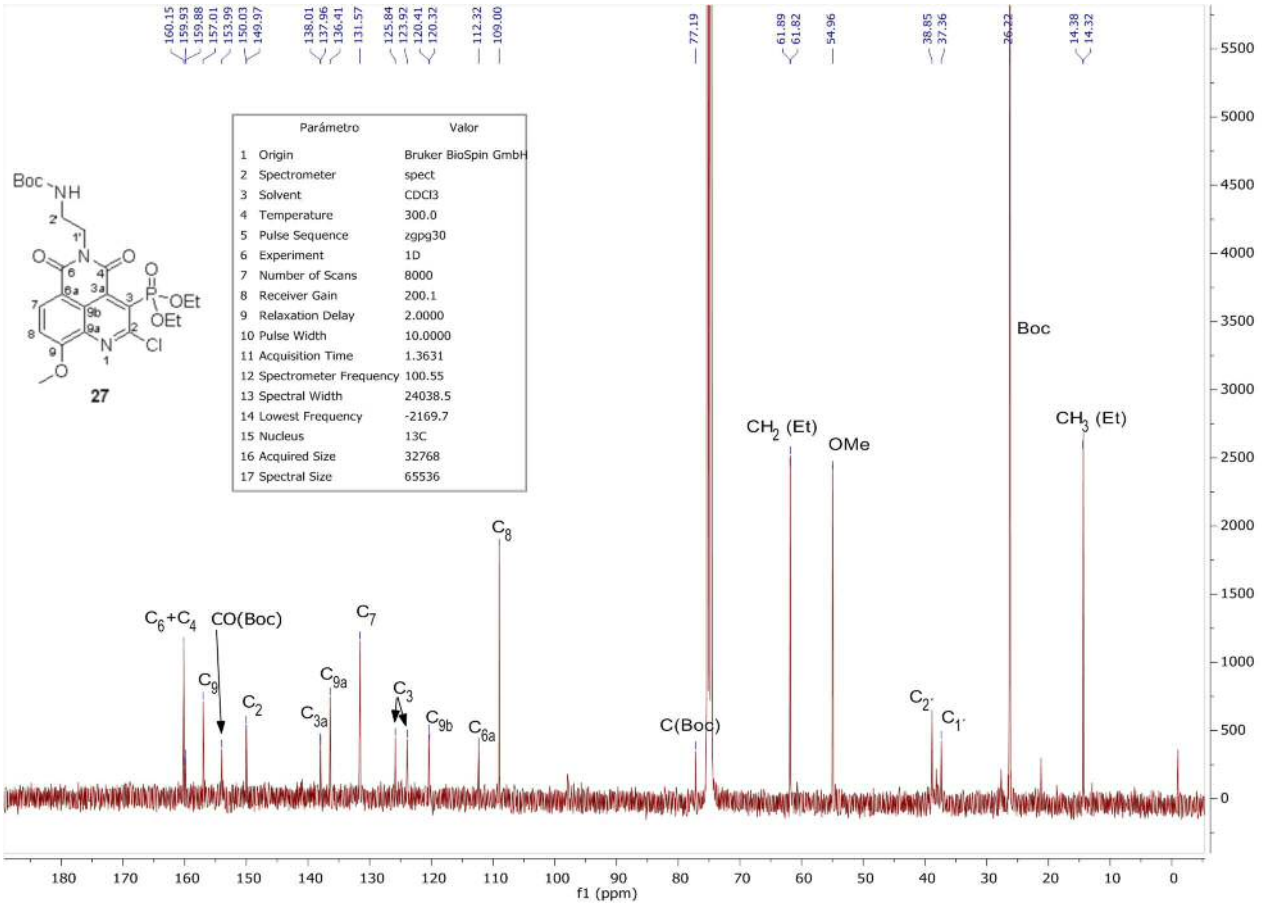

164.00
163.35
160.91
156.38
150.70
139.13
133.88
129.79
124.36
123.36
114.73
109.02
79.51
57.15
40.36
39.69
28.50
NHBoc
MeO
26
Parameter Value
1 Origin Varian
2 Spectrometer vnmrs
3 Solvent cdcl3
4 Temperature 25.0
5 Pulse Sequence s2pul
6 Number of Scans 3096
7 Receiver Gain 60
8 Relaxation Delay 1.0000
9 Pulse Width 8.0000
10 Acquisition Time 1.0224
11 Spectrometer Frequency 125.69
12 Spectral Width 32051.3
13 Lowest Frequency -2160.5
14 Nucleus 13C
15 Acquired Size 32768
16 Spectral Size 65536
13C NMR (126 MHz, cdcl3) δ 28.5, 28.6, 30.0, 39.7, 40.4, 57.1, 79.5, 109.0, 114.7, 123.4, 124.4, 129.8, 133.9, 139.1, 150.7, 156.4, 160.9, 163.4, 164.0.
C2
C3
C8
C7
C9a
C9b
C3a
C6a
C6+C4
C9
CO(Boc)
C(Boc)
OMe
Boc
C1´
C2´
f1 (ppm)



	Parámetro	Valor
1	Origin	Bruker BioSpin GmbH
2	Spectrometer	spect
3	Solvent	CDCl3
4	Temperature	300.0
5	Pulse Sequence	zg30
6	Experiment	1D
7	Number of Scans	32
8	Receiver Gain	200.1
9	Relaxation Delay	1.0000
10	Pulse Width	14.0000
11	Acquisition Time	4.0894
12	Spectrometer Frequency	399.86
13	Spectral Width	8012.8
14	Lowest Frequency	-1573.4
15	Nucleus	1H
16	Acquired Size	32768
17	Spectral Size	65536

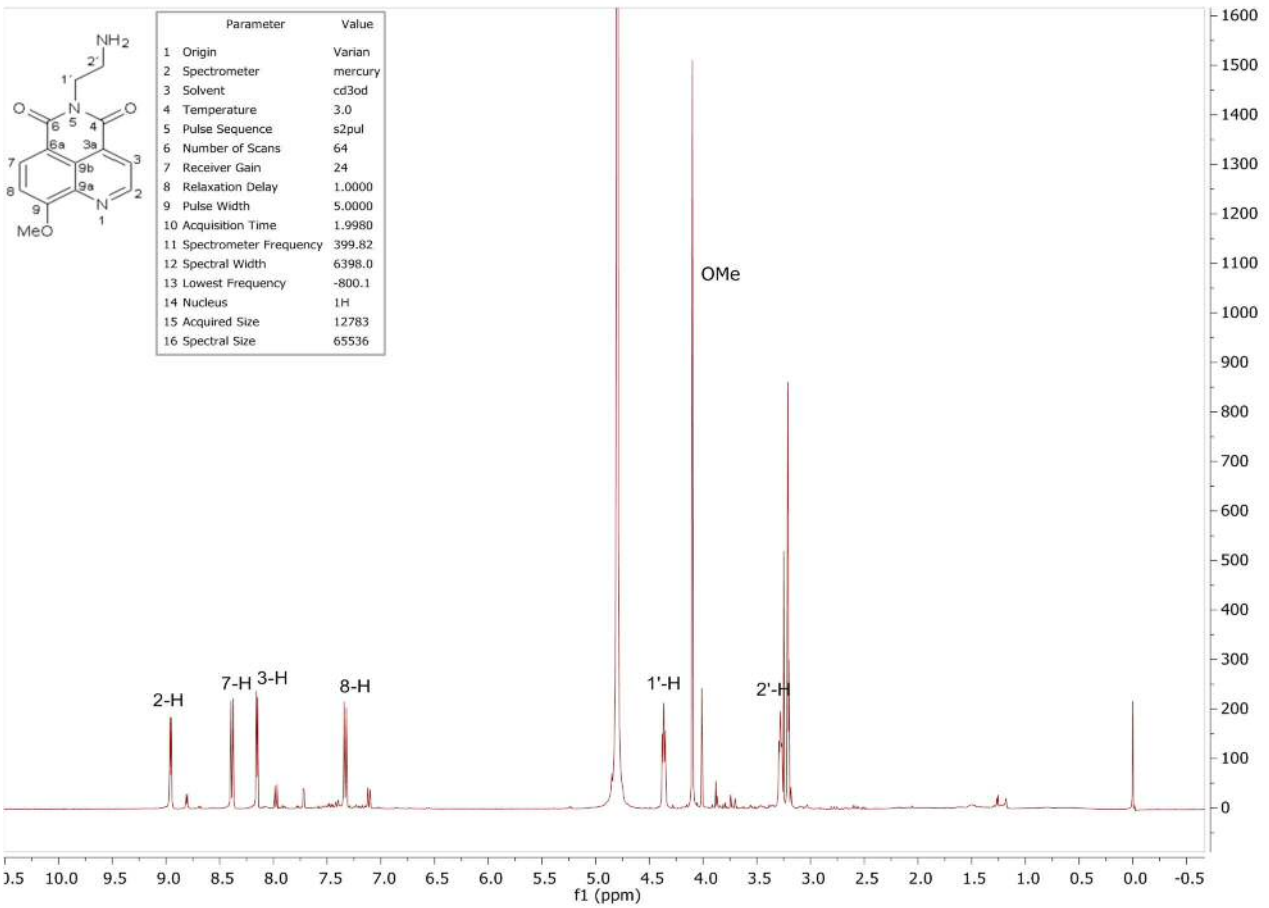
27

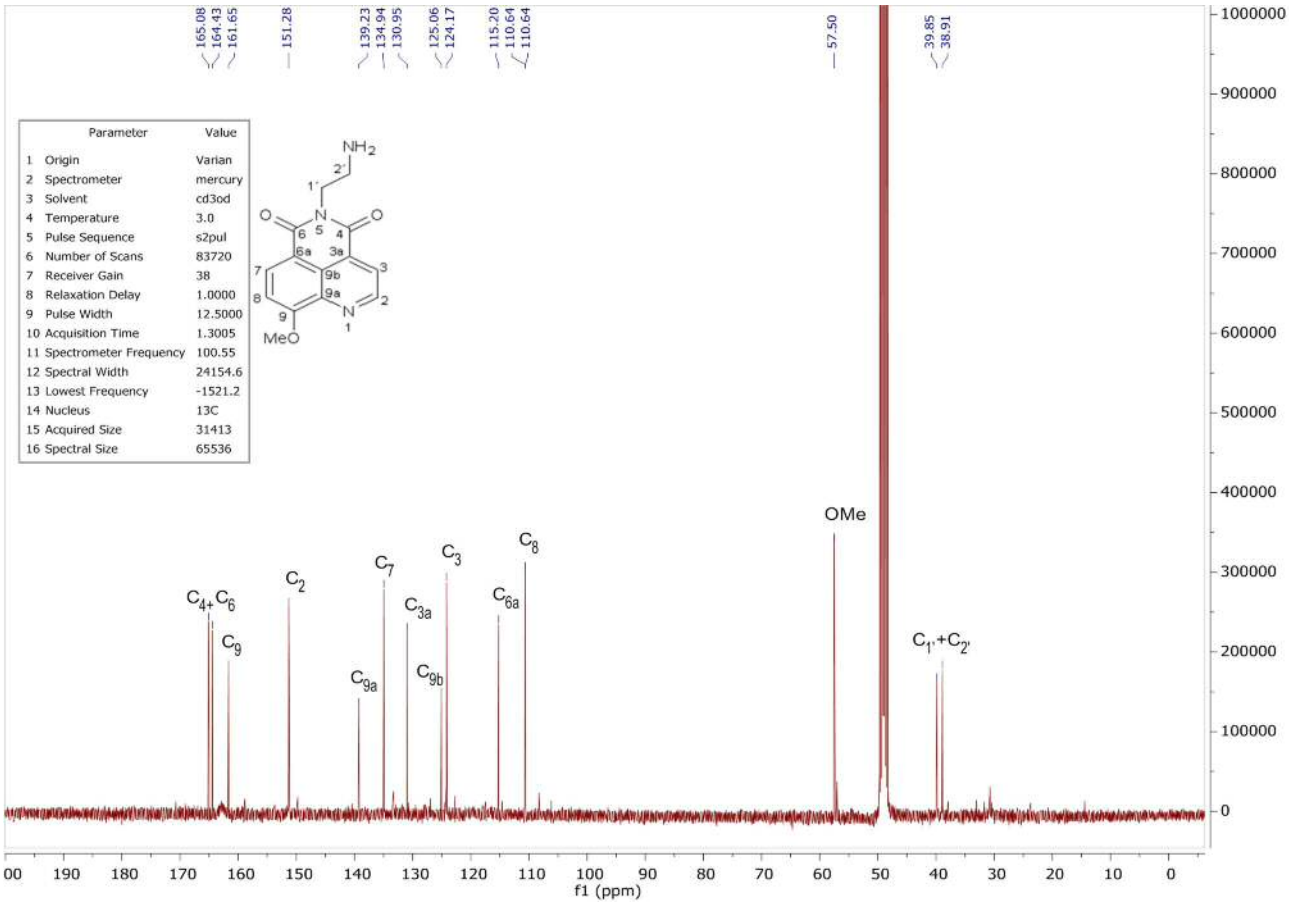
1H NMR (400 MHz, Chloroform-d) δ 1.24 (s, 8H), 1.33 (t, J = 7.1 Hz, 5H), 3.45 (d, J = 6.2 Hz, 2H), 4.13 (s, 3H), 4.17 – 4.38 (m, 6H), 4.95 (s, 1H), 7.27 (s, 1H), 8.50 (d, J = 8.3 Hz, 1H).

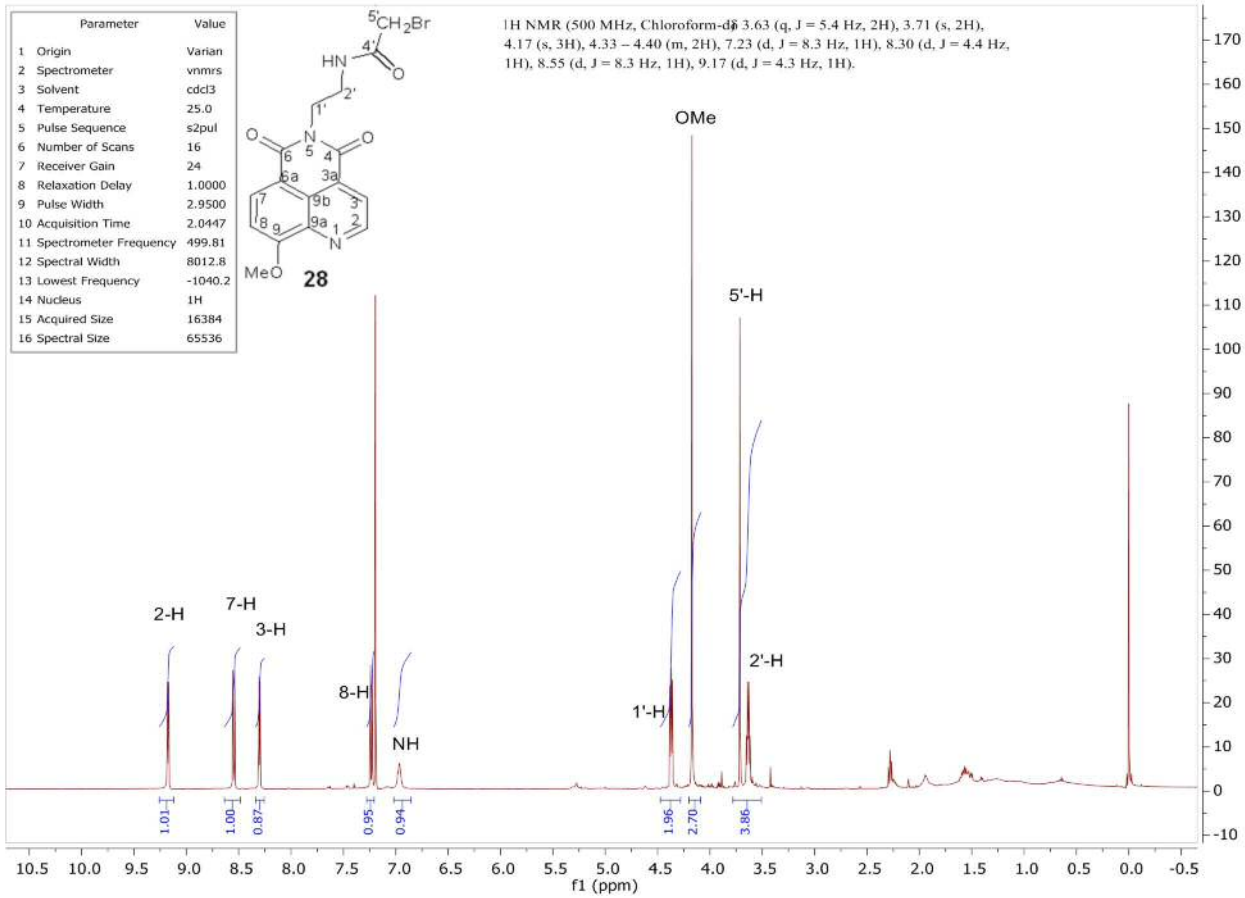


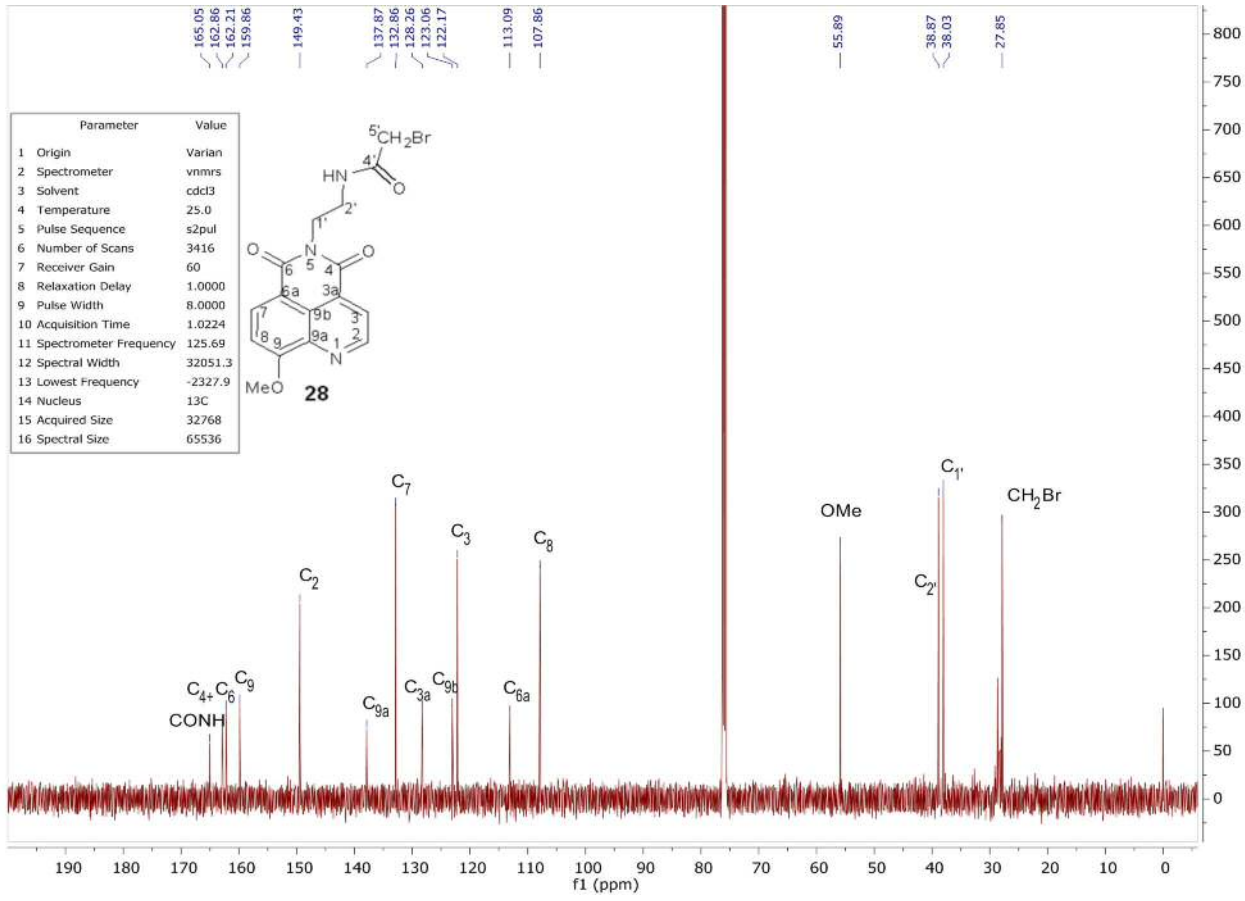
	Parámetro	Valor
1	Origin	Bruker BioSpin GmbH
2	Spectrometer	spect
3	Solvent	CDCl3
4	Temperature	300.0
5	Pulse Sequence	zgpg30
6	Experiment	1D
7	Number of Scans	8000
8	Receiver Gain	200.1
9	Relaxation Delay	2.0000
10	Pulse Width	10.0000
11	Acquisition Time	1.3631
12	Spectrometer Frequency	100.55
13	Spectral Width	24038.5
14	Lowest Frequency	-2169.7
15	Nucleus	13C
16	Acquired Size	32768
17	Spectral Size	65536

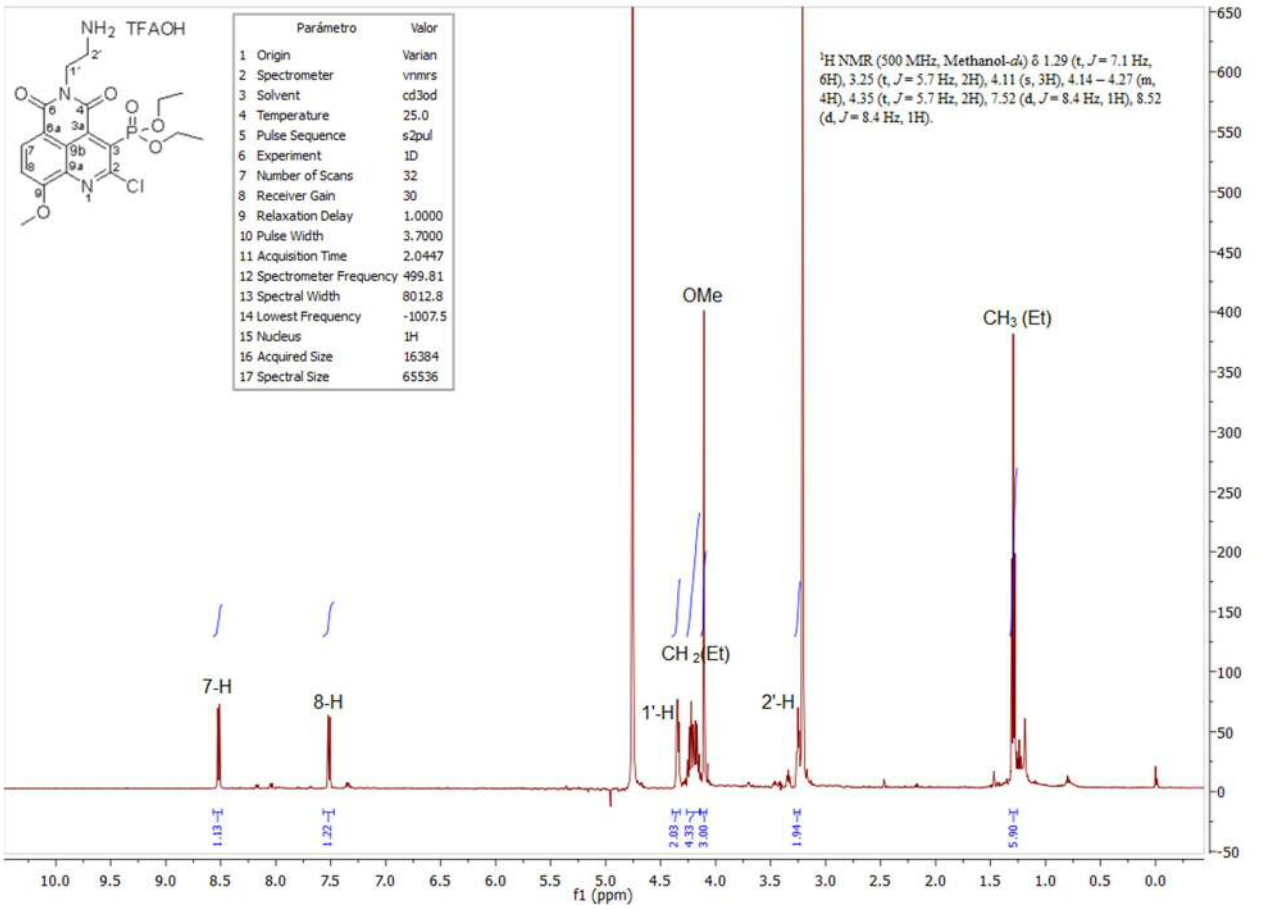
27

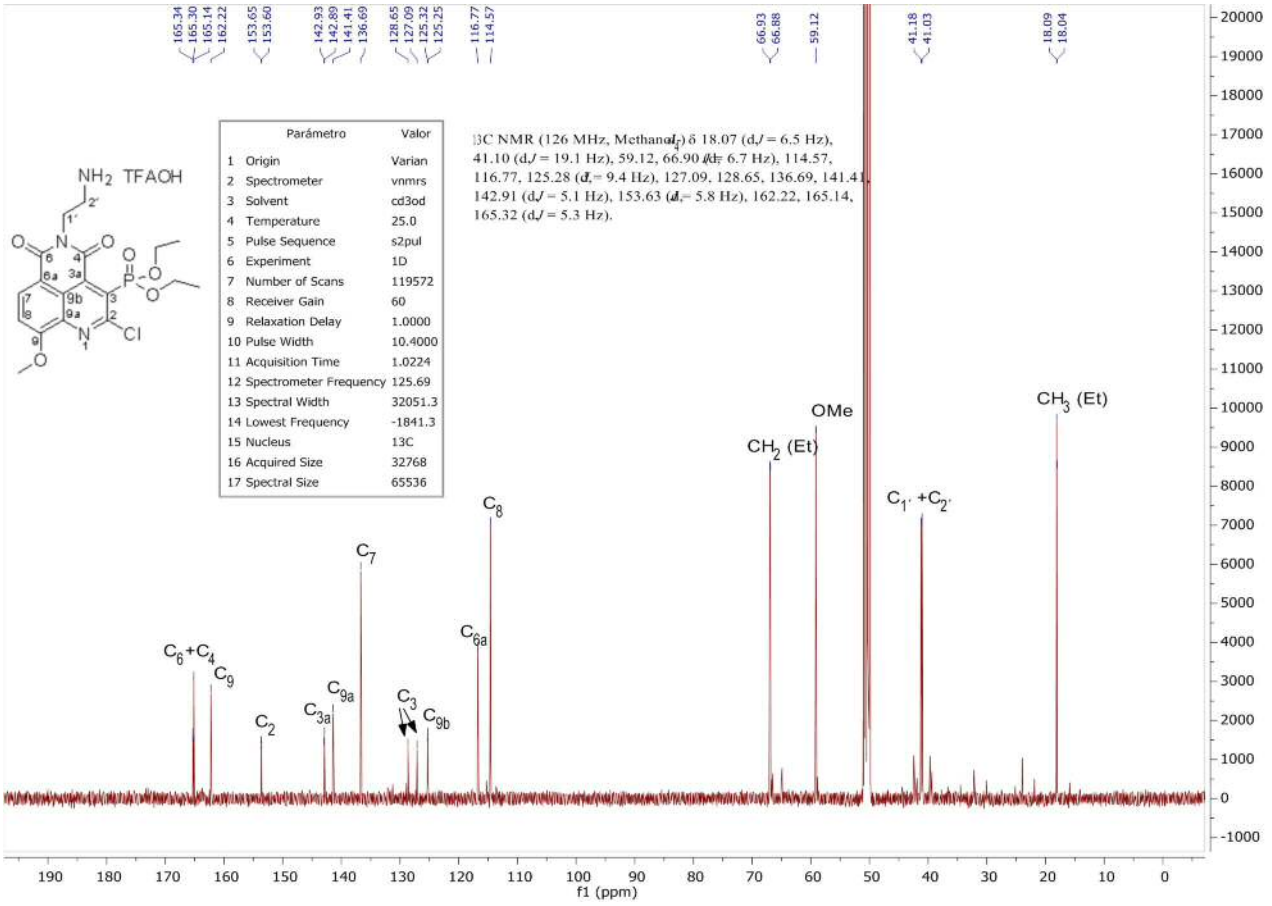

NH2
2'
1'
N
5
O
6
4
O
6a
3a
7
9b
3
8
9a
2
9
N
1
MeO
Parameter Value
1 Origin Varian
2 Spectrometer mercury
3 Solvent cd3od
4 Temperature 3.0
5 Pulse Sequence s2pul
6 Number of Scans 64
7 Receiver Gain 24
8 Relaxation Delay 1.0000
9 Pulse Width 5.0000
10 Acquisition Time 1.9980
11 Spectrometer Frequency 399.82
12 Spectral Width 6398.0
13 Lowest Frequency -800.1
14 Nucleus 1H
15 Acquired Size 12783
16 Spectral Size 65536
OMe
2-H
7-H
3-H
8-H
1'-H
2'-H
f1 (ppm)

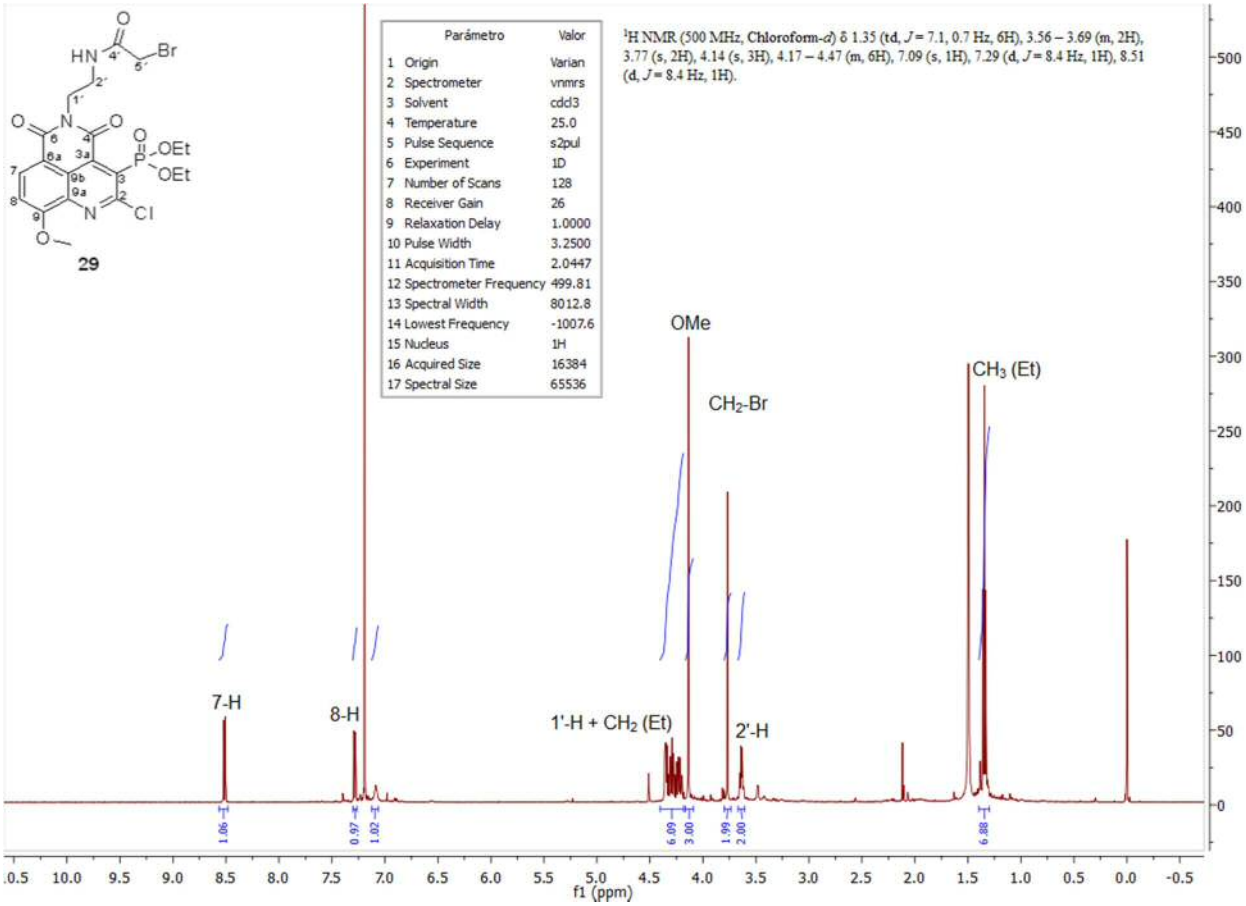

165.08
164.43
161.65
151.28
139.23
134.94
130.95
125.06
124.17
115.20
110.64
110.64
57.50
39.85
38.91
Parameter Value
1 Origin Varian
2 Spectrometer mercury
3 Solvent cd3od
4 Temperature 3.0
5 Pulse Sequence s2pul
6 Number of Scans 83720
7 Receiver Gain 38
8 Relaxation Delay 1.0000
9 Pulse Width 12.5000
10 Acquisition Time 1.3005
11 Spectrometer Frequency 100.55
12 Spectral Width 24154.6
13 Lowest Frequency -1521.2
14 Nucleus 13C
15 Acquired Size 31413
16 Spectral Size 65536
NH2
2'
1'
N
5
O
6
4
O
6a
3a
7
9b
3
8
9a
2
9
N
1
MeO
OMe
C4+C6
C9
C2
C9a
C7
C3a
C9b
C3
C6a
C8
C1'+C2'
f1 (ppm)


Parameter Value
1 Origin Varian
2 Spectrometer vnmrs
3 Solvent cdcl3
4 Temperature 25.0
5 Pulse Sequence s2pul
6 Number of Scans 16
7 Receiver Gain 24
8 Relaxation Delay 1.0000
9 Pulse Width 2.9500
10 Acquisition Time 2.0447
11 Spectrometer Frequency 499.81
12 Spectral Width 8012.8
13 Lowest Frequency -1040.2
14 Nucleus 1H
15 Acquired Size 16384
16 Spectral Size 65536
28
1H NMR (500 MHz, Chloroform-d) δ 3.63 (q, J = 5.4 Hz, 2H), 3.71 (s, 2H), 4.17 (s, 3H), 4.33 – 4.40 (m, 2H), 7.23 (d, J = 8.3 Hz, 1H), 8.30 (d, J = 4.4 Hz, 1H), 8.55 (d, J = 8.3 Hz, 1H), 9.17 (d, J = 4.3 Hz, 1H).
OMe
5'-H
2-H
7-H
3-H
8-H
NH
1'-H
2'-H
1.01
1.00
0.87
0.95
0.94
1.96
2.70
3.86
f1 (ppm)


165.05
162.86
162.21
159.86
149.43
137.87
132.86
128.26
123.06
122.17
113.09
107.86
55.89
38.87
38.03
27.85
Parameter Value
1 Origin Varian
2 Spectrometer vnmrs
3 Solvent cdcl3
4 Temperature 25.0
5 Pulse Sequence s2pul
6 Number of Scans 3416
7 Receiver Gain 60
8 Relaxation Delay 1.0000
9 Pulse Width 8.0000
10 Acquisition Time 1.0224
11 Spectrometer Frequency 125.69
12 Spectral Width 32051.3
13 Lowest Frequency -2327.9
14 Nucleus 13C
15 Acquired Size 32768
16 Spectral Size 65536
28
C7
C3
C8
C2
C1'
CH2Br
OMe
C2'
C4+C6
C9
CONH
C9a
C3a
C9b
C6a
f1 (ppm)


NH2 TFAOH
Parámetro Valor
1 Origin Varian
2 Spectrometer vnmrs
3 Solvent cd3od
4 Temperature 25.0
5 Pulse Sequence s2pul
6 Experiment 1D
7 Number of Scans 32
8 Receiver Gain 30
9 Relaxation Delay 1.0000
10 Pulse Width 3.7000
11 Acquisition Time 2.0447
12 Spectrometer Frequency 499.81
13 Spectral Width 8012.8
14 Lowest Frequency -1007.5
15 Nucleus 1H
16 Acquired Size 16384
17 Spectral Size 65536
¹H NMR (500 MHz, Methanol-d4) δ 1.29 (t, J = 7.1 Hz, 6H), 3.25 (t, J = 5.7 Hz, 2H), 4.11 (s, 3H), 4.14 – 4.27 (m, 4H), 4.35 (t, J = 5.7 Hz, 2H), 7.52 (d, J = 8.4 Hz, 1H), 8.52 (d, J = 8.4 Hz, 1H).
OMe
CH3 (Et)
CH2 (Et)
7-H
8-H
1'-H
2'-H
f1 (ppm)


165.34
165.30
165.14
162.22
153.65
153.60
142.93
142.89
141.41
136.69
128.65
127.09
125.32
125.25
116.77
114.57
66.93
66.88
59.12
41.18
41.03
18.09
18.04
NH2 TFAOH
Parámetro Valor
1 Origin Varian
2 Spectrometer vnmrs
3 Solvent cd3od
4 Temperature 25.0
5 Pulse Sequence s2pul
6 Experiment 1D
7 Number of Scans 119572
8 Receiver Gain 60
9 Relaxation Delay 1.0000
10 Pulse Width 10.4000
11 Acquisition Time 1.0224
12 Spectrometer Frequency 125.69
13 Spectral Width 32051.3
14 Lowest Frequency -1841.3
15 Nucleus 13C
16 Acquired Size 32768
17 Spectral Size 65536
13C NMR (126 MHz, Methanol-d4) δ 18.07 (d, J = 6.5 Hz), 41.10 (d, J = 19.1 Hz), 59.12, 66.90 (d, J = 6.7 Hz), 114.57, 116.77, 125.28 (d, J = 9.4 Hz), 127.09, 128.65, 136.69, 141.41, 142.91 (d, J = 5.1 Hz), 153.63 (d, J = 5.8 Hz), 162.22, 165.14, 165.32 (d, J = 5.3 Hz).
OMe
CH2 (Et)
CH3 (Et)
C1' +C2'
C8
C7
C6a
C6+C4
C9
C2
C3a
C9a
C3
C9b
f1 (ppm)


29
Parámetro Valor
1 Origin Varian
2 Spectrometer vnmrs
3 Solvent cdcl3
4 Temperature 25.0
5 Pulse Sequence s2pul
6 Experiment 1D
7 Number of Scans 128
8 Receiver Gain 26
9 Relaxation Delay 1.0000
10 Pulse Width 3.2500
11 Acquisition Time 2.0447
12 Spectrometer Frequency 499.81
13 Spectral Width 8012.8
14 Lowest Frequency -1007.6
15 Nucleus 1H
16 Acquired Size 16384
17 Spectral Size 65536
¹H NMR (500 MHz, Chloroform-d) δ 1.35 (td, J = 7.1, 0.7 Hz, 6H), 3.56 – 3.69 (m, 2H), 3.77 (s, 2H), 4.14 (s, 3H), 4.17 – 4.47 (m, 6H), 7.09 (s, 1H), 7.29 (d, J = 8.4 Hz, 1H), 8.51 (d, J = 8.4 Hz, 1H).
OMe
CH2-Br
CH3 (Et)
7-H
8-H
1'-H + CH2 (Et)
2'-H
1.06
0.97
1.02
6.09
3.00
1.99
2.00
6.88
f1 (ppm)