1. Materials and Methods

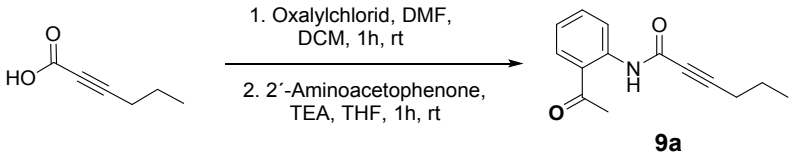
Chemicals and solvents for the synthesis were purchased from Sigma-Aldrich, Acros Organics, Carl Roth or VWR Chemicals and were used without further purification. For silica gel chromatography, distilled technical grade solvents and silica gel 60 A (Carl Roth) was used. Thin layer chromatography (TLC) was performed using aluminum sheets "TLC silica gel 60 F254" from Merck Millipore® and analysed with UV-light or by permanganate staining. NMR spectra were obtained with Bruker Avance-III 400 and Bruker Avance-III 600 NMR spectrometers at ambient temperature. Multiplicities are given as follows: s -singlet, d - doublet, t - triplet, q - quartet, quint. - quintet, m - multiplet. Chemical shifts (δ) are given in parts per million (ppm) relative to the solvent residual signal with $CDCl_3$ δ_H = 7.26 ppm and δ_C = 77.16 ppm, DMSO-d_6 δ_H = 2.50 ppm and δ_C = 39.52 ppm.[1] The data obtained were processed and analyzed with Bruker Topspin 3.5 software. Mass spectrometry data were obtained on an ESI-Orbitrap (Thermo Scientific, LTQ Orbitrap Velos) by direct injection and analyzed with Xcalibur (Thermo Scientific) software. Flash chromatography was performed on a Teledyne ISCO CombiFlash Rf® with Teledyne ISCO RediSep Rf® Normal-phase silica flash columns.

2. Chemical synthesis

Synthesis of 2-alkyl-4-quinolones and 2-alkyl-4-quinolone *N*-oxides 1-8

2-Alkyl-4-quinolones (**1**-**4**) and 2-alkyl-4-quinolone *N*-oxides (**5**-**8**) were synthesized according to the literature. [2]

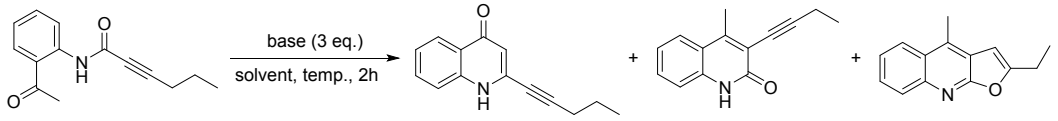
Synthesis of *N*-(2'-acetylphenyl)hex-2-ynamide (9a)



9a

Hex-2-ynoic acid (2.50 g, 22.3 mmol) was dissolved in 45 mL dry DCM and 22.3 mL oxalyl chloride (2 M in DCM, 44.6 mmol) was added. A few drops DMF were added and the reaction was stirred at room temperature for 1 h. The solvent was evaporated under reduced pressure, the residue dissolved in 45 mL dry THF and added to a stirring mixture of 2.73 mL 2´-aminoacetophenone (22.3 mmol) and 6.25 mL TEA (44.6 mmol) in 70 mL dry THF at room temperature. The mixture was stirred at the same temperature for 1 h in which a large amount of precipitate was observed and the color changed to brown. Water was added and extracted with DCM. The combined organic phases were washed with Brine, dried with $MgSO_4$, filtered and the solvent was evaporated. The residue was purified by column chromatography on silica 60 with DCM. The product was obtained as yellow oil (m = 2.91 g, 57%). R_f = 0.7 (DCM). ^{1}H-NMR ($CDCl_3$, 399.79 MHz) δ (ppm): 1.05 (t, 3H, *J* = 7.3 Hz, -CH_2-C**H**$_3$), 1.64 (m, 2H, -C**H**$_2$-CH_3), 2.34 (t, 2H, *J* = 7.0 Hz, ≡C-C**H**$_2$-), 2.66 (s, 3H, -CO-C**H**$_3$), 7.12 (m, 1H, H-4), 7.54 (m, 1H, H-5), 7.89 (dd, 1H, *J* = 7.9 Hz, *J* = 1.0 Hz, H-3), 8.67 (d, 1H, *J* = 8.4 Hz, H-6), 11.89 (s, 1H, N**H**). ^{13}C-NMR ($CDCl_3$, 100.52 MHz) δ (ppm): 13.6 (-CH_2-**C**H$_3$), 20.8 (≡C-**C**H$_2$-), 21.4 (-**C**H$_2$-CH_3), 28.6 (-CO-**C**H$_3$), 76.9 (-**C**≡C-CH_2-), 88.5 (-C≡**C**-CH_2-), 121.8 (C-2), 121.4 (C-6), 123.0 (C-4), 131.7 (C-3), 135.2 (C-5), 140.5 (C-1), 152.0 (-NH-**C**O-C≡), 202.7 (-**C**O-CH_3). ESI-HRMS: m/z = 230.1171 $[M+H]^+$, calc. for $C_{14}H_{15}NO_2 + H^+$ = 230.1176.

Cyclization reactions of 9a



9a **9** **10** **11**

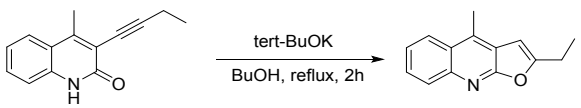
General procedure: Compound **9a** (100 mg, 0.436 mmol) was dissolved in 2.5 mL solvent (see Table S1) and the base (3 eq.) was added. The mixture was placed in a pre-heated oil bath at indicated temperatures and stirred at this temperature for 2 h. After reaching room temperature the mixture was transferred in a 50 mL round-bottom flask with ethanol and the solvents were completely evaporated under reduced pressure. To the residue were added 3 mL water and 30 mL n-hexane and the suspension was sonicated for 2 min. The suspension was neutralized with 1 M HCl solution and the resulting precipitate collected by filtration. The precipitate was washed with 10 mL water and 200 mL n-hexane and dried under vacuum. The collected solid was washed with ethyl acetate (3 x 0.5 mL) by centrifugation, resulting in a pure white or off-white solid which could be identified as the 2-quinolone **10**. The combined washing fractions were purified by flash chromatography (4 g silica gel column, flow: 10 mL/min, gradient from 100% petrol ether to 100% ethyl acetate in 30 min) to obtain the furoquinoline **11**, 2-quinolone **10** and 4-quinolone **9** in this order (see Fig. S1).

2-(Pent-1-yn-1-yl)quinol-4-one (**9**): ^{1}H-NMR ($CDCl_3$, 399.79 MHz) δ (ppm): 0.99 (t, 3H, *J* = 7.4 Hz, -CH_2-C**H**$_3$), 1.58 (m, 2H, -C**H**$_2$-CH_3), 2.34 (t, 2H, *J* = 7.1 Hz, ≡C-C**H**$_2$-), 6.48 (s, 1H, H-3), 7.34 (m, 1H, H-6), 7.53 (d, 1H, *J* = 8.2 Hz, H-8), 7.61 (dd, 1H, *J* = 7.7 Hz, *J* = 1.4 Hz, H-7), 8.36 (dd, 1H, *J* = 8.2 Hz, *J* = 1.1 Hz, H-5). ^{13}C-NMR ($CDCl_3$, 100.52 MHz) δ (ppm): 13.7 (-**C**H_3), 21.4 (≡C-**C**H_2-), 21.6 (-**C**H_2-CH_3), 75.0 (-**C**≡C-CH_2-), 98.0 (-C≡**C**-CH_2-), 113.4 (C-3), 117.8 (C-8), 124.2 (C-6), 125.5 (C-4a), 126.0 (C-5), 132.5 (C-7), 134.0 (C-2), 140.2 (C-8a), 178.5 (C-4). ESI-HRMS: m/z = 212.1068 $[M+H]^+$, calc. for $C_{14}H_{13}NO + H^+$ = 212.1070.

3-(But-1-yn-1-yl)-4-methylquinolin-2(1*H*)-one (**10**): ^{1}H-NMR ($CDCl_3$, 399.79 MHz) δ (ppm): 1.33 (t, 3H, *J* = 7.5 Hz, -CH_2-C**H**$_3$), 2.61 (q, 2H, *J* = 7.5 Hz, -C**H**$_2$-CH_3), 2.69 (s, 3H, -CH_3), 7.23 (m, 1H, H-6), 7.36 (dd, 1H, *J* = 8.2 Hz, *J* = 0.7 Hz, H-8), 7.48 (m, 1H, H-7), 7.70 (dd, 1H, *J* = 8.3 Hz, *J* = 0.9 Hz, H-5), 11.42 (s, br, 1H, NH). ^{13}C-NMR ($CDCl_3$, 100.52 MHz) δ (ppm): 14.0 (-CH_2-**C**H_3), 14.1 (-**C**H_2-CH_3), 17.6 (-C**H**$_3$), 74.9 (-**C**≡C-CH_2-), 102.4 (-C≡**C**-CH_2-), 116.3 (C-3), 116.5 (C-8), 120.4 (C-4a), 122.8 (C-6), 124.9 (C-5), 130.5 (C-7), 136.9 (C-8a), 150.8 (C-4), 162.6 (C-2). ESI-HRMS: m/z = 212.1065 $[M+H]^+$, calc. for $C_{14}H_{13}NO + H^+$ = 212.1070.

2-Ethyl-4-methylfuro[2,3-*b*]quinoline (**11**): ^{1}H-NMR ($CDCl_3$, 399.79 MHz) δ (ppm): 1.41 (t, 3H, *J* = 7.5 Hz, -CH_2-C**H**$_3$), 2.84 (s, 3H, -C**H**$_3$), 2.89 (dq, 2H, *J* = 7.7 Hz, *J* = 0.6 Hz, -C**H**$_2$-CH_3), 6.53 (t, 1H, *J* = 0.6 Hz, H-3), 7.53 (m, 1H, H-6), 7.68 (m, 1H, H-7), 8.07 (d, 1H, *J* = 8.6 Hz, H-5), 8.11 (d, 1H, *J* = 8.5 Hz, H-8). ^{13}C-NMR ($CDCl_3$ 100.52 MHz) δ (ppm): 11.5 (-CH_2-**C**H_3), 15.2 (-**C**H_3), 22.4 (-**C**H_2-CH_3), 99.0 (C-3), 121.5 (C-3a), 123.7 (C-5), 124.4 (C-6), 126.0 (C-4a), 128.1 (C-7), 129.2 (C-8), 136.0 (C-4), 144.4 (C-8a), 161.4 (C-9a), 162.6 (C-2). ESI-HRMS: m/z = 212.1065 $[M+H]^+$, calc. for $C_{14}H_{13}NO + H^+$ = 212.1070.

Synthesis of 2-ethyl-4-methylfuro[2,3-*b*]quinolone (11) from 2-quinolone (10)

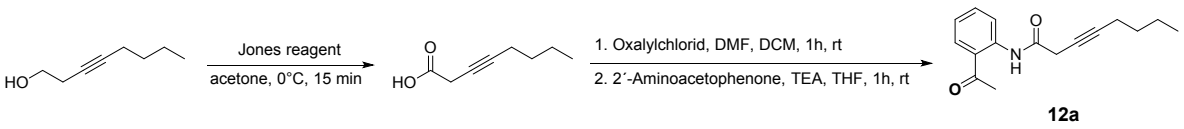


10 **11**

2-Quinolone (**10**) (75.5 mg, 0.357 mmol) was dissolved in 2.5 mL *tert*-BuOH and 120 mg potassium *tert*-butanolate (3 eq.) was added. The reaction mixture was stirred at reflux conditions for 2 h. After the mixture was cooled to room temperature, it was poured in water and extracted with ethyl acetate. The combined organic phases were washed with brine, dried with $MgSO_4$, filtered and the solvent

evaporated leaving the clean product **11** as slightly yellow oil which crystalized later on (m = 48 mg, 0.21 mmol, 64%).

Synthesis of *N*-(2'-acetylphenyl)oct-3-ynamide 12a

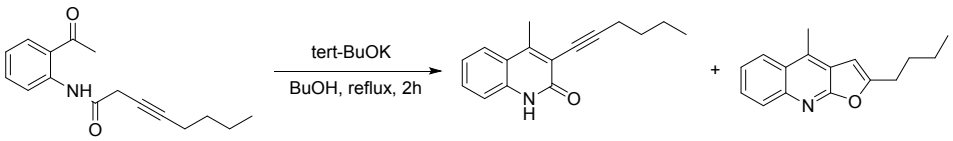


12a

3-Octyn-1-ol (1.55 mL, 97%, 10.5 mmol) was dissolved in 30 mL acetone and cooled to 0 °C with an ice-bath. 15 mL of 2.13 M Jones reagent (32 mmol) was added dropwise and the solution turned orange with a dark precipitate (Jones reagent was produced by dissolving 2.61 g CrO_3 in 2.3 mL conc. H_2SO_4 and 10 mL H_2O). The reaction was stirred at 0°C for 15 min and quenched by the dropwise addition of 4 mL 2-propanol. The reaction was stirred at 0°C for further 15 min until the solution turned colorless and blue precipitate formed. Water was added and the mixture extracted with diethyl ether (3x 25 mL). The combined organic phases were washed once with water and afterwards extracted with 1 M NaOH solution (4x25 mL). The combined aqueous phases acidified with 20 mL 6 M HCl solution. The cloudy solution was extracted with diethyl ether (3x 25 mL). The combined organic phases were washed once with water, dried with $MgSO_4$, filtered and the solvent evaporated. The pure product was received as yellow oil (m = 1.4 g, 95.1%). ^{1}H-NMR ($CDCl_3$, 400.13 MHz) δ (ppm): 0.90 (t, 3H, *J* = 7.3 Hz, -CH_2-C**H**$_3$), 1.40 (m, 2H, -C**H**$_2$-CH_3), 1.48 (m, 2H, -C**H**$_2$-CH_2-CH_3), 2.20 (m, 2H, -C**H**$_2$-CH_2-CH_2-CH_3), 3.31 (t, 2H, *J* = 2.4 Hz, COOH-C**H**$_2$-), 10.40 (s, br, 1H, COOH). ^{13}C-NMR ($CDCl_3$, 100.52 MHz) δ (ppm): 13.7 (-CH_2-**C**H_3), 18.5 (-**C**H_2-CH_2-CH_2-CH_3), 22.1 (-**C**H_2-CH_3), 26.0 (COOH-CH_2-), 30.8 (-**C**H_2-CH_2-CH_3), 70.8 (COOH-CH_2-**C**≡C-),84.7 (COOH-CH_2-C≡**C**-), 174.3 (COOH).

Oct-3-ynoic acid (1.4 g, 9.85 mmol) was dissolved in 30 mL dry DCM and 10 mL oxalyl chloride (2 M in DCM, 20 mmol) was added. 5 drops DMF were added and the reaction stirred at room temperature for 1 h. The solvent was evaporated under reduced pressure. The residue dissolved in 17 mL dry THF and added to a stirring mixture of 1.22 mL 2´-aminaceophenone (10 mmol) and 3 mL TEA (21.2 mmol) in 30 mL dry THF at room temperature. The mixture was stirred at room temperature for 1 h in which a large amount of precipitate was observed and the color changed to brown. Water was added and the mixture extracted with DCM. The combined organic phases were washed with brine, dried with $MgSO_4$, filtered and the solvent was evaporated. The residue was purified by column chromatography on silica 60 with petrol ether/ethyl acetate 5:1. The product was obtained as orange oil (m = 364 mg, 14%). The majority of the product co-eluted with unreacted 2´-aminoacetophenone from the column. ^{1}H-NMR ($CDCl_3$, 400.13 MHz) δ (ppm): 0.93 (t, 3H, *J* = 7.3 Hz, -CH_2-C**H**$_3$), 1.45 (m, 2H, -C**H**$_2$-CH_3), 1.59 (m, 2H, -C**H**$_2$-CH_2-CH_3), 2.41 (m, 2H, -C**H**$_2$-CH_2-CH_2-CH_3), 2.66 (s, 3H, -CO-C**H**$_3$), 3.36 (t, 2H, *J* = 2.4 Hz, -NH-C**H**$_2$-), 7.14 (m, 1H, H-5), 7.55 (m, 1H, H-4), 7.89 (dd, 1H, *J* = 8.0 Hz, *J* = 1.4 Hz, H-6), 8.75 (dd, 1H, *J* = 8.6 Hz, *J* = 1.0 Hz, H-3), 12.20 (s, 1H, N**H**). ^{13}C-NMR ($CDCl_3$, 100.62 MHz) δ (ppm): 13.8 (-CH_2-**C**H_3), 18.8 (≡C-**C**H_2-CH_2-), 22.2 (-**C**H_2-CH_3), 28.7 (-CO-**C**H_3), 29.8 (-NH-CO-**C**H_2-), 30.7 (≡C-CH_2-**C**H_2-), 71.8 (-**C**≡C-CH_2-CH_2-), 87.6 (-C≡**C**-CH_2-CH_2-), 121.2 (C-3), 122.9 (C-5), 123.1 (C-2), 131.5 (C-6), 134.9 (C-4), 140.3 (C-1), 168.1(-NH-**C**O-), 201.8 (-**C**O-CH_3). ESI-HRMS: m/z = 258.1485 $[M+H]^+$, calc. for $C_{16}H_{19}NO_2$ + H^+ = 258.1489.

Cyclization of *N*-(2'-acetylphenyl)oct-3-ynamide (12a)



12a **12** **13**

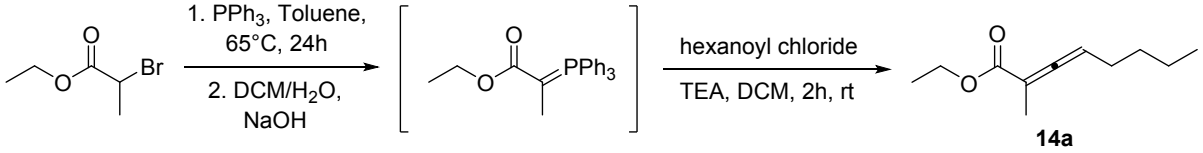
N-(2'-acetylphenyl)oct-3-ynamide **12a** (356.6 mg, 1.356 mmol) was dissolved in 10 mL *tert*-butanol and 440.5 mg potassium tert-butanolate (4.07 mmol, 3 eq.) was added. The reaction mixture was stirred at reflux conditions for 2 h and afterwards neutralized with 1 M HCl and sat. $NaHCO_3$ solution. The mixture was extracted with ethyl acetate and the combined organic phases were washed with brine, dried with $MgSO_4$, filtered and the solvent was evaporated. To the crystallized residue was added petrol ether / ethyl acetate 1:1. The insoluble white solid was filtered off and washed with PE/EA 1:1. The 4-methyl-3-(hept-1-yn-1-yl)quinolin-2(1H)-one (**12**) was obtained as white solid (m = 121 mg, 37%). The filtrate was dried and purified by column chromatography on silica 60 with PE/EE 1:1. The 2-butyl-4-methylfuro[2,3-*b*]XXXuinolone (**13**) was obtained as yellow oil which crystallized after at room temperature (m = 103 mg, 31.7%).

4-Methyl-3-(hept-1-yn-1-yl)quinolin-2(1*H*)-one (**12**): ^{1}H-NMR ($CDCl_3$; 399.79 MHz) δ (ppm): 0.99 (t, 3H, *J* = 7.3 Hz, -CH_2-C**H**$_3$), 1.57 (m, 2H, -C**H**$_2$-CH_3), 1.68 (m, 2H, -C**H**$_2$-CH_2-CH_3), 2.60 (t, 2H, *J* = 7.0 Hz, -C≡C-C**H**$_2$-), 2.71 (s, 3H, -CH_3) 7.26 (m, 1H, H-6), 7.44 (m, 1H, H-8), 7.51 (m, 1H, H-7), 7.72 (dd, 1H, *J* = 8.2 Hz, *J* = 0.8 Hz, H-5), 11.92 (s, br, 1H, N**H**). ^{13}C-NMR ($CDCl_3$, 100.52 MHz) δ (ppm): 13.8 (-CH_2-**C**H$_3$), 17.7 (-**C**H$_3$), 20.0 (-C≡C-C**H**$_2$-), 22.2 (-**C**H$_2$-CH_3), 31.0 (-**C**H$_2$-CH_2-CH_3), 75.2 (-**C**≡C-CH_2-), 101.5 (-C≡**C**-CH_2-), 116.0 (C-3), 116.9 (C-8), 120.6 (C-4a), 123.2 (C-6), 124.9 (C-5), 130.7 (C-7), 136.6 (C-8a), 151.2 (C-4), 162.7 (C-2). ESI-HRMS: m/z = 240.1377 $[M+H]^+$, calc. for $C_{16}H_{17}NO + H^+$ = 240.1383.

2-Butyl-4-methylfuro[2,3-*b*]quinolone (**13**): ^{1}H-NMR ($CDCl_3$, 399.79 MHz) δ (ppm): 0.95 (t, 3H, *J* = 7.3 Hz, -CH_2-C**H**$_3$), 1.43 (m, 2H, -C**H**$_2$-CH_3), 1.77 (m, 2H, -C**H**$_2$-CH_2-CH_3), 2.74 (s, 3H, -CH_3), 2.79 (m, 2H, -C**H**$_2$-CH_2-CH_2-CH_3), 6.44 (s, 1H, H-3), 7.46 (m, 1H, H-6), 7.63 (m, 1H, H-7), 7.98 (m, 1H, H-5), 8.06 (d, 1H, *J* = 8.7 Hz, H-8). ^{13}C-NMR ($CDCl_3$, 100.52 MHz) δ (ppm): 13.9 (-CH_2-**C**H$_3$), 15.4 (-CH_3), 22.4 (-**C**H$_2$-CH_3), 28.7 (-**C**H$_2$-CH_2-CH_2-CH_3), 29.3 (-**C**H$_2$-CH_2-CH_2-CH_3), 99.9 (C-3), 121.7 (C-3a), 123.8 (C-5), 124.5 (C-6), 125.9 (C-4a), 128.4 (C-7), 128.8 (C-8), 136.5 (C-4), 143.9 (C-8a), 161.1 (C-9a), 161.6 (C-2). ESI-HRMS: m/z = 240.1379 $[M+H]^+$, calc. for $C_{16}H_{17}NO + H^+$ = 240.1383.

Synthesis of *N*-(2-acetylphenyl)-2,2-dimethyloct-3-ynamide 14d

Ethyl 2-methyl-octa-2,3-dienoate (14a)

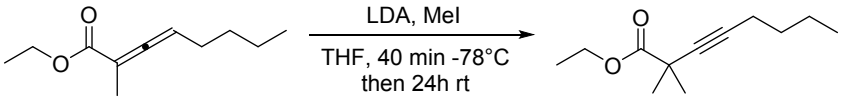


14a

Triphenylphosphine (65.575 g, 250 mmol) was dissolved in 125 mL toluene and 32.5 mL ethyl 2-bromopropionate (250 mmol) was added. The mixture was stirred at 65°C for 16 h, allowed to cool to room temperature, the precipitate collected by filtration, washed with toluene and dried under vacuum. The phosphonium bromide was dissolved in 875 mL water at 50°C and the insoluble parts were removed by filtration of the warm solution. 500 mL DCM and 100 mL 20% NaOH solution was added and the mixture stirred for 1 h at room temperature. The organic phase was separated and the water phase extracted with DCM. The combined organic phases were washed with water (3x250 mL) and afterwards dried with $MgSO_4$, filtered and evaporated leaving the Wittig reagent as yellow solid (m = 51.1 g, 141 mmol, 56.4%). The Wittig reagent was dissolved in 300 mL DCM and 22.5 mL TEA (162.3 mmol) and after 5 min stirring at room temperature, 23.4 mL hexanoyl chloride (97%, 162.5 mmol) in 50 mL DCM was added dropwise. After stirring at room temperature for 2 h the solvent was evaporated under vacuum at 25 °C. To the residue was added 300 mL n-hexane and the mixture stirred in an ice bath for 2 h. The precipitate was collected by filtration and washed with n-hexane. The filtrates were combined and the solvent evaporated under vacuum at 25 °C to approximately one-fourth of the original volume. The precipitated was removed by filtration and the filtrate evaporated leaving the pure product as yellow oil with intensive odor (m = 24.4 g, 134 mmol, 95%). ^{1}H-NMR ($CDCl_3$, 399.79

MHz) δ (ppm): 0.90 (t, 3H, *J* = 7.1 Hz, -CH_2-CH_2-C**H**$_3$), 1.26 (t, 3H, *J* = 7.1 Hz, -COO-CH_2-C**H**$_3$), 1.39 (m, 4H, -C**H**$_2$-C**H**$_2$-CH_3), 1.85 (d, 3H, -CH_3), 2.09 (m, 2H, C=C=CH-C**H**$_2$-), 4.17 (m, 2H, -COO-C**H**$_2$-CH_3), 5.43 (m, 1H, C=C=C**H**-CH_2-). ^{13}C-NMR ($CDCl_3$, 100.52 MHz) δ (ppm): 13.9 (-CH_2-CH_2-**C**H$_3$), 14.4 (-COO-CH_2-**C**H$_3$), 15.4 (-**C**H$_3$), 22.1 (-CH_2-**C**H$_2$-CH_3), 27.8 (C=C=CH-**C**H$_2$-), 31.1 (-**C**H$_2$-CH_2-CH_3), 60.9 (-COO-**C**H$_2$-CH_3), 93.9 (C=C=**C**H-CH_2-), 95.7 (**C**=C=CH-CH_2-), 168.3 (-**C**OO-CH_2-CH_3), 210.2 (C=**C**=CH-CH_2-).

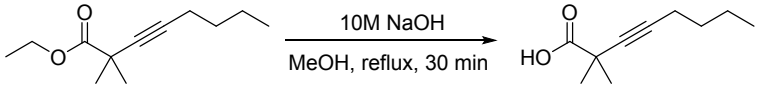
Ethyl 2,2-dimethyloct-3-ynoate (14b)



14a **14b**

Compound **14a** (2.0 g, 11 mmol) was dissolved in 20 mL dry THF and cooled to -78 °C. 8.25 mL LDA (2 M, 16.5 mmol, 1.5 eq.) was added over 5 min and the mixture stirred at -78 °C for 5 min. Afterwards 1.03 mL methyl iodide (16.5 mmol, 1.5 eq.) was added slowly and the mixture stirred for 30 min at -78 °C. The mixture was allowed to warm up to room temperature and stirred for 24 h. Saturated NH_4Cl solution was added and the water phase extracted with ether. The combined organic phases were dried with $MgSO_4$, filtered and the solvent evaporated. The residue was purified by column chromatography on silica 60 using petrol ether / DCM 1:1. The product was received as colorless oil (987.5 mg, 45.7 %). R_f = 0.6 (petrol ether / DCM 1:1). ^{1}H-NMR ($CDCl_3$, 399.79 MHz) δ (ppm): 0.90 (t, 3H, *J* = 7.0 Hz, -CH_2-CH_2-C**H**$_3$), 1.27 (t, 3H, *J* = 7.0 Hz, -COO-CH_2-C**H**$_3$), 1.43 (s, 6H, -C(C**H**$_3$)$_2$), 1.34 – 1.52 (m, 4H, -C**H**$_2$-C**H**$_2$-CH_3), 2.17 (t, 2H, *J* = 6.8 Hz, -C≡C-C**H**$_2$-), 4.17 (q, 2H, *J* = 7.0 Hz, -COO-C**H**$_2$-CH_3). ^{13}C-NMR ($CDCl_3$, 100.52 MHz) δ (ppm): 13.7 (-CH_2-CH_2-**C**H$_3$), 14.2 (-COO-CH_2-**C**H$_3$), 18.5 (-C≡C-**C**H$_2$-), 22.0 (-CH_2-**C**H$_2$-CH_3), 27.6 C-(**C**H$_3$)$_2$), 31.0 (-**C**H$_2$-CH_2-CH_3), 38.3 (2C, -C(**C**H$_3$)$_2$), 61.4 (-COO-**C**H$_2$-CH_3), 82.0 (-C≡**C**-CH_2-), 82.7 (-**C**≡C-CH_2-), 174.5 (-**C**OO-CH_2-CH_3).

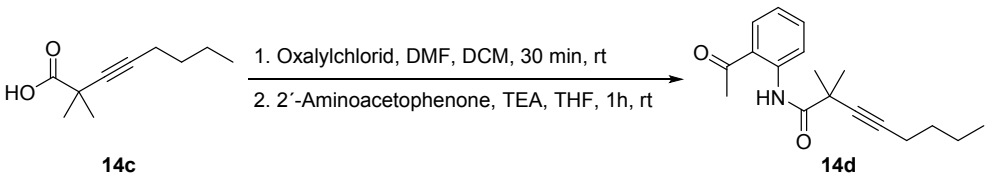
2,2-Dimethyloct-3-ynoic acid (14c)



14b **14c**

Compound **14b** (890 mg, 4.534 mmol) was dissolved in 10 mL MeOH and 2 mL of 10 M NaOH solution was added. The mixture was kept under reflux conditions for 30 min during which the solution turned yellow and a white precipitate occurred. To the reaction was added water and the mixture was washed with ether. The washed aqueous phase was acidified with 6 M HCl solution. The mixture was extracted with ether, the combined organic phases were washed once with water, dried with $MgSO_4$, filtered and the solvent evaporated. NMR of the residue confirmed the clean product. The product was obtained as colorless oil (m = 696.5 mg, 91 %).^{1}H-NMR ($CDCl_3$, 399.79 MHz) δ (ppm): 0.91 (t, 3H, *J* = 7.3 Hz, -CH_2-CH_2-C**H**$_3$), 1.40 (m, 2H, -CH_2-C**H**$_2$-CH_3), 1.48 (s, 6H, -C(C**H**$_3$)$_2$), 1.48 (m, 2H, -C**H**$_2$-CH_2-CH_3), 2.19 (t, 2H, *J* = 7.0 Hz, -C≡C-C**H**$_2$-). ^{13}C-NMR ($CDCl_3$, 100.52 MHz) δ (ppm): 13.7 (-CH_2-CH_2-**C**H$_3$), 18.5 (-C≡C-**C**H$_2$-), 22.0 (-CH_2-**C**H$_2$-CH_3), 27.6 (2C, -C(**C**H$_3$)$_2$), 31.0 (-**C**H$_2$-CH_2-CH_3), 38.4 (-C(**C**H$_3$)$_2$), 81.8 (-C≡**C**-CH_2-), 82.9 (-**C**≡C-CH_2-), 180.3 (-**C**OO-CH_2-CH_3).

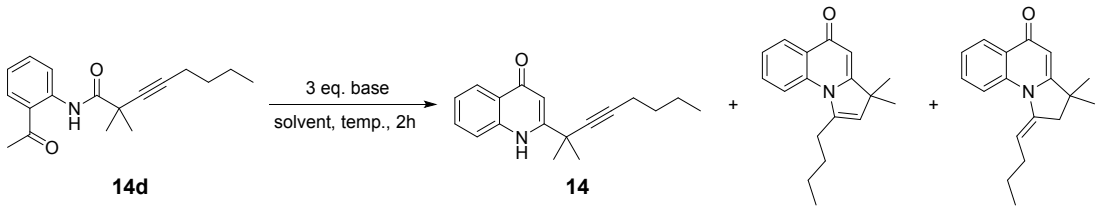
***N*-(2'-Acetylphenyl)-2,2-dimethyloct-3-ynamide (14d)**



14c **14d**

Compound **14c** (696 mg, 4.14 mmol) was dissolved in 16 mL dry DCM and 4.1 mL oxalyl chloride (2 M in DCM, 8.2 mmol) was added. Three drops DMF were added and the reaction stirred at room temperature for 30 min. The solvent was evaporated under reduced pressure. The residue was dissolved in 8.5 mL dry THF and added to a stirring mixture of 0.506 mL 2´-Aminaceophenone (4.14 mmol) and 1.2 mL TEA (8.54 mmol) in 13 mL dry THF at room temperature. The mixture was stirred at room temperature for 1 h in which a large amount of precipitate was observed. Water was added and extracted with DCM. The combined organic phases were washed with brine, dried with $MgSO_4$, filtered and the solvent was evaporated. TLC in PE/EE 5:1 showed no spot from 2´-aminoacetophenone but an intensive product spot which at larger R_f value. The residue was purified by column chromatography on silica 60 with petrol ether/ethyl acetate 5:1. The product was obtained as slightly yellow oil (m = 1.03 g, 87%). ^{1}H-NMR ($CDCl_3$, 399.79 MHz) δ (ppm): 0.93 (t, 3H, *J* = 7.3 Hz, -CH_2-C**H**$_3$), 1.44 (m, 2H, -C**H**$_2$-CH_3), 1.51 (s, 6H, -C(C**H**$_3$)$_2$), 1.60 (m, 2H, -C**H**$_2$-CH_2-CH_3), 2.41 (t, 2H, *J* = 7.1 Hz, ≡C-C**H**$_2$-), 2.65 (s, 3H, -CO-C**H**$_3$), 7.12 (m, 1H, H-4), 7.54 (m, 1H, H-5), 7.88 (dd, 1H, *J* = 8.0 Hz, *J* = 1.5 Hz, H-3), 8.77 (dd, 1H, *J* = 8.6 Hz, *J* = 0.9 Hz, H-6), 12.29 (bs, 1H, N**H**). ^{13}C-NMR ($CDCl_3$, 100.52 MHz) δ (ppm): 13.8 (-CH_2-CH_2-**C**H_3), 18.8 (-C≡C-**C**H_2-), 22.2 (-CH_2-**C**H_2-CH_3), 28.3 (2C, -C(**C**H_3)$_2$), 28.7 (-**C**H_2-CH_2-CH_3), 30.9 (-CO-**C**H_3), 40.3 (**C**-$(CH_3)_2$), 82.2 (-C≡**C**-CH_2-), 86.2 (-**C**≡C-CH_2-), 121.2 (C-6), 12.6 (C-4), 123.3 (C-2), 131.5 (C-3), 134.8 (C-5), 140.7 (C-1), 174.9 (-NH-**C**O-), 201.6 (-**C**O-CH_3). ESI-HRMS: m/z = 286.1793 $[M+H]^+$, calc. for $C_{18}H_{23}NO_2$ + H^+ = 286.1802.

Cyclization of N-(2-acetylphenyl)-2,2-dimethyloct-3-ynamide (14d)



14d **14** **15** **16**

General procedure: compound **14d** (100 mg, 0.436 mmol) was dissolved in 2.5 mL solvent (see Table 1) and the base (3 eq.) was added. The mixture was placed in a pre-heated oil bath at tested temperatures and stirred at this temperature for 2 h. After reaching room temperature the mixture was transferred in a 50 mL round bottom flaks with ethanol and the solvents completely evaporated under reduced pressure. To the residue were added 3 mL water and 30 mL n-hexane and the suspension sonicated for 2 min. The suspension was neutralized with 1 M HCl solution and the resulting precipitate collected by filtration. The precipitate was washed with 10 mL water and 200 mL n-hexane and dried under vacuum. The collected solid was washed with ethyl acetate (3 x 0.5 mL) by centrifugation resulting in a pure white or off-white solid which could be identified as the 4-quinolone **14**. The combined supernatants (including the hexane phase) were purified by flash chromatography (4 g silica gel column, flow: 10 mL/min, gradient from 100% petrol ether to 100% ethyl acetate in 30 min) to receive residual 4-quinolone **14**, saturated pyrroloquinolin-5-one **16**, and unsaturated pyrroloquinolin-5-one **15** in this order (see Fig. S2).

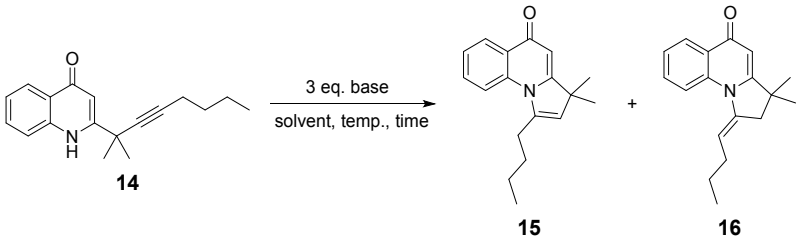
2-(2-Methyloct-3-yn-2-yl)quinol-4(1*H*)-one (14): ^{1}H-NMR ($CDCl_3$, 399.79 MHz) δ (ppm): 0.95 (t, 3H, *J* = 7.3 Hz, -CH_2-C**H**$_3$), 1.46 (m, 2H, -C**H**$_2$-CH_3), 1.56 (m, 2H, -C**H**$_2$-CH_2-CH_3), 1.63 (s, 6H, -C(C**H**$_3$)$_2$), 2.30 (t, 2H, *J* = 7.0 Hz, ≡C-C**H**$_2$-), 6.37 (s, 1H, H-3), 7.33 (m, 1H, H-6), 7.43 (d, 1H, *J* = 8.2 Hz, H-8), 7.60 (m, 1H, H-7), 8.34 (d, 1H, *J* = 8.2 Hz, H-5), 9.41 (s, br, 1H, N**H**). ^{13}C-NMR ($CDCl_3$, 100.52 MHz) δ (ppm): 13.7 (-CH_2-**C**H_3), 18.5 (≡C-**C**H_2-), 22.2 (-**C**H_2-CH_3), 30.6 (2C, -C(**C**H_3)$_2$), 30.9 (-**C**H_2-CH_2-CH_3), 36.8 (-**C**$(CH_3)_2$), 82.1 (-**C**≡C-CH_2-), 86.7 (-C≡**C**-CH_2-), 105.7 (C-3), 117.6 (C-8), 123.9 (C-6), 125.1 (C-4a), 126.1 (C-5), 132.1 (C-7), 139.2 (C-8a), 156.2 (C-2), 179.1 (C-4). ESI-HRMS: m/z = 268.1693 $[M+H]^+$, calc. for $C_{18}H_{21}NO$ + H^+ = 268.1696.

1-Butyl-3,3-dimethylpyrrolo[1,2-*a*]quinol-5-one (15): ^{1}H-NMR ($CDCl_3$, 399.79 MHz) δ (ppm): 1.00 (t, 3H, J = 7.3 Hz, -CH_2-C**H**$_3$), 1.33 (s, 6H, -CH_3), 1.52 (m, 2H, -C**H**$_2$-CH_3), 1.72 (m, 2H, -C**H**$_2$-CH_2-CH_3), 2.98 (m, 2H, -C**H**$_2$-$(CH_2)_2$-CH_3), 5.58 (m, 1H, H-2), 6.39 (s, 1H, H-4), 7.35 (m, 1H, H-7), 7.58 (m, 1H, H-8), 7.96 (d,

1H, J = 8.8 Hz, H-9), 8.48 (dd, 1H, J = 8.2 Hz, J = 1.7 Hz, H-6). ^{13}C-NMR ($CDCl_3$, 100.52 MHz) δ (ppm): 14.0 (-CH_2-**C**H_3), 22.5 (-**C**H_2-CH_3), 26.8 (2C, -C(**C**H_3)$_2$), 30.2 (-**C**H_2-CH_2-CH_3), 31.2 (-**C**H_2-(CH_2)$_2$-CH_3), 45.8 (C-3), 104.9 (C-4), 116.0 (C-9), 123.0 (C-2), 123.5 (C-7), 126.2 (C-5a), 127.6 (C-6), 131.6 (C-8), 138.3 (C-9a), 143.7 (C-1), 166.3 (C-3a), 177.7 (C-5). ESI-HRMS: m/z = 268.1690 $[M+H]^+$, calc. for $C_{18}H_{21}NO + H^+$ = 268.1696.

1-Butylidene-3,3-dimethyl-2,3-dihydropyrrolo[1,2-a]quinol-5-one (16): ^{1}H-NMR (DMSO-d_6, 399.79 MHz) δ (ppm): 0.94 (t, 3H, J = 7.3 Hz, -CH_2-C**H**$_3$), 1.33 (s, 6H, -CH_3), 1.49 (m, 2H, -C**H**$_2$-CH_3), 2.22 (m, 2H, -C**H**$_2$-CH_2-CH_3), 2.67 (s, 2H, H-2), 6.00 (t, 1H, J = 7.7 Hz, =C**H**-(CH_2)$_2$-CH_3), 6.14 (s, 1H, H-4), 7.40 (m, 1H, H-7), 7.72 (m, 1H, H-8), 8.16 (m, overlaying with H-6, 1H, H-9), 8.18 (m, overlaying with H-9, 1H, H-6). ^{13}C-NMR ($CDCl_3$, 100.52 MHz) δ (ppm): 13.6 (-CH_2-**C**H_3), 22.5 (-**C**H_2-CH_3), 26.7 (2C, -C(**C**H_3)$_2$), 30.1 (-**C**H_2-CH_2-CH_3), 40.5 (C-3), 40.7 (C-2), 102.5 (C-4), 113.8 (=**C**H-(CH_2)$_2$-CH_3), 117.6 (C-9), 123.8 (C-7), 126.1 (2C, C-5a and C-6), 132.0 (C-8), 137.0 (C-9a), 137.9 (C-1), 163.7 (C-3a), 176.5 (C-5). ESI-HRMS: m/z = 268.1689 $[M+H]^+$, calc. for $C_{18}H_{21}NO + H^+$ = 268.1696.

Cyclization of 2-(2-methyloct-3-yn-2-yl)quinol-4-one (14)



14 **15** **16**

General procedure: Compound **14** (100 mg, 0.436 mmol) was dissolved in 2.5 mL solvent and the base (3 eq.) was added. The mixture was placed in a pre-heated oil bath at indicated temperatures and stirred at this temperature for the specified time. Depending on the used solvent the purification proceeded as follows.

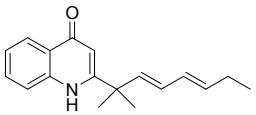
For *tert*-BuOH: After reaching room temperature the mixture was transferred in a 50 mL flask with ethanol and the solvents were completely evaporated under reduced pressure. To the residue were added 30 mL water and 200 mL n-hexane and the suspension was sonicated for 2 min. The suspension was neutralized with 1 M HCl solution and the resulting precipitate collected by filtration. The hexane phase of the filtrate was separated, dried with $MgSO_4$ and evaporated leaving pure compound **15** as white solid. NMR analysis of the washed precipitate showed residual compound **15** which was contaminated with the starting material **14**.

For DMSO: After reaching room temperature the mixture was poured in 20 mL water and a precipitate appeared. The suspension was neutralized with 1 M HCl solution and the suspension extracted with ethyl acetate. The combined organic phases were dried over $MgSO_4$, filtered and the solvent was evaporated under high vacuum to remove residual DMSO. The residue was analyzed by NMR and showed a complex mixture of products.

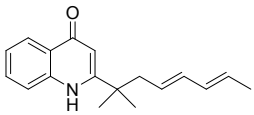
For Ph_2O: After reaching room temperature the mixture was poured in a mixture of hexane and water and sonicated for 2 min. The suspension was neutralized with 1 M HCl solution and the resulting precipitate washed with hexane and water. The dried precipitate was analyzed by NMR and showed the starting material **14**.

For DMF: After reaching room temperature the mixture was poured in 20 mL water and extracted with ethyl acetate (3x 15 mL). The combined organic phases were dried with Na_2SO_4, filtered and the solvent evaporated. To the white solid residue was added 2 mL ethyl acetate/n-hexane 1:1 and the precipitate

treated in an ultrasonic bad. The precipitate was separated by centrifugation and the yellow supernatant collected. The procedure was repeated until the precipitate was free from impurities (monitored by TLC). The precipitate was identified as starting material **14**. The combined supernatants were evaporated to approximately 2 mL and purified by prep. HPLC (A: water + 0.1 % FA and B: MeOH + 0.1 % FA; 5 % B 0-5 min, 5% B to 95% B in 35 min, 95% B 40-45 min). Compound **16** was obtained as slightly yellow oil.



17



18

In some cases, in addition to **16**, the dienes **17** (2-((3*E*,5*E*)-2-methylocta-3,5-dien-2-yl)quinolin-4(1*H*)-one) and **18** (2-((4*E*,6*E*)-2-methylocta-4,6-dien-2-yl)quinolin-4(1*H*)-one) could be identified. Compound **17** could only be obtained in an inseparable mixture with residual **14**.

2-((3*E*,5*E*)-2-Methylocta-3,5-dien-2-yl)quinolin-4(1*H*)-one (17): ^{1}H-NMR ($CDCl_3$, 399.79 MHz) δ (ppm): 0.98 (t, 3H, *J* = 7.4 Hz, -CH_2-C**H**$_3$), 1.49 (s, 6H, -CH_3), 2.07 (m, 2H, -C**H**$_2$-CH_3), 5.70 (dt, 1H, *J* = 15.1 Hz, *J* = 6.6 Hz, -CH=CH-CH=C**H**-CH_2-CH_3), 5.72 (d, 1H, *J* = 15.4 Hz, -C**H**=CH-CH=CH-CH_2-CH_3), 5.99 (m, 1H, -CH=CH-C**H**=CH-CH_2-CH_3), 6.18 (m, 1H, -CH=C**H**-CH=CH-CH_2-CH_3), 6.38 (d, 1H, *J* = 1.4 Hz, H-3), 7.28 (m, 1H, H-6), 7.53 (m, 2H, H-7 and H-8), 8.32 (m, 1H, H-5), 9.42 (s, br, 1H, N**H**). ^{13}C-NMR ($CDCl_3$, 100.52 MHz) δ (ppm): 13.5 (-CH_2-**C**H_3), 25.7 (-**C**H_2-CH_3), 27.1 (2C, -C(**C**H_3)$_2$), 41.2 (-**C**(CH_3)$_2$), 106.9 (C-3), 117.9 (C-8), 123.5 (C-6), 124.9 (C-4a), 125.9 (C-5), 128.6 (-CH=CH-**C**H=CH-CH_2-CH_3), 130.8 (-CH=**C**H-CH=CH-CH_2-CH_3), 131.9 (C-7), 135.8 (-**C**H=CH-CH=CH-CH_2-CH_3), 137.5 (-CH=CH-CH=**C**H-CH_2-CH_3), 140.1 (C-8a), 158.3 (C-2), 179.5 (C-4). ESI-HRMS: m/z = 268.1691 $[M+H]^+$, calc. for $C_{18}H_{21}NO + H^+$ = 268.1696.

2-((4*E*,6*E*)-2-Methylocta-4,6-dien-2-yl)quinolin-4(1*H*)-one (18): ^{1}H-NMR ($CDCl_3$, 399.79 MHz) δ (ppm): 1.38 (s, 6H, -CH_3), 1.68 (d, 3H, *J* = 6.9 Hz, -CH_2-CH=CH-CH=CH-C**H**$_3$), 2.53 (m, 2H, -C**H**$_2$-CH=CH-CH=CH-CH_3), 5.34 (m, 1H, -CH_2-C**H**=CH-CH=CH-CH_3), 5.51 (m, 1H, -CH_2-CH=CH-CH=C**H**-CH_3), 5.90 (m, 1H, -CH_2-CH=CH-C**H**=CH-CH_3), 5.97 (m, 1H, -CH_2-CH=C**H**-CH=CH-CH_3), 6.35 (s, 1H, H-3), 7.31 (m, 1H, H-6), 7.56 (m, 1H, H-7), 7.84 (d, 1H, *J* = 8.4 Hz, H-8), 8.35 (dd, 1H, *J* = 8.1 Hz, *J* = 1.2 Hz, H-5), 10.89 (s, br, 1H, N**H**). ^{13}C-NMR ($CDCl_3$, 100.52 MHz) δ (ppm): 18.1 (-CH_2-CH=CH-CH=CH-**C**H_3), 26.8 (2C, -C(**C**H_3)$_2$), 39.1 (-**C**(CH_3)$_2$), 45.1(-**C**H_2-CH=CH-CH=CH-CH_3), 107.2 (C-3), 118.6 (C-8), 123.6 (C-6), 124.8 (C-4a), 125.5 (C-5), 126.1 (-CH_2-**C**H=CH-CH=CH-CH_3), 128.5 (-CH_2-CH=CH-CH=**C**H-CH_3), 131.3 (-CH_2-CH=CH-**C**H=CH-CH_3), 132.0 (C-7), 134.3 (-CH_2-CH=**C**H-CH=CH-CH_3), 140.8 (C-8a), 160.0 (C-2), 179.3 (C-4). ESI-HRMS: m/z = 268.1690 $[M+H]^+$, calc. for $C_{18}H_{21}NO + H^+$ = 268.1696.

3. Biological experiments

Cell Lines

HuH7 cells were cultured in Dulbecco's modified Eagle's medium (DMEM) (Life Technologies) supplemented with 10% FBS (Sigma) and 1% antibiotic-antimycotic (Life Technologies) and maintained in a standard tissue culture incubator (37 °C, 5% CO_2). Human blood was obtained from Gulf Coast Regional Blood Center. *P. falciparum* 3D7 parasites were obtained through BEI Resources Repository, NIAID, NIH, MRA-102, contributed by Daniel J. Carucci. *P. berghei* ANKA infected *Anopheles stephensi* mosquitoes were purchased from the New York University Langone Medical Center Insectary. *Toxoplasma gondii* (Me49 strain) was a kind gift from John C. Boothroyd.

Anti-*Plasmodium* Liver-Stage Assays

Inhibition of *P. berghei* parasite load in hepatocytes was evaluated as previously described.[3] Briefly, 7,000 HuH7 cells/well were seeded into 384-well plates in the presence or absence of compounds (5

μg/mL) in duplicate before infection with 4,000 luciferase-expressing *P. berghei* ANKA sporozoites. After 45 h, liver cell viability was assessed using CellTiter-Fluor (Promega) and reading florescence with an Envision (PerkinElmer). Relative parasite load was subsequently determined using Bright-Glo (Promega) and reading luminescence with an Envision. A separate liver cell cytotoxicity assay was also completed using CellTiter-Glo (Promega) (Fig. S1). The relative fluorescence and luminescence signal intensity of each well was normalized to the negative control (1% DMSO). The positive control was atovaquone (1 μM). Compounds that inhibited parasite load were evaluated for potency where dose-response analysis was performed with GraphPad Prism. The reported EC_{50} is the average determined from three independent experiments.

Anti-*Plasmodium* Blood-Stage Assays

P. falciparum 3D7 parasites were cultured in complete medium (10.44 g/L RPMI 1640 (ThermoFisher Scientific), 25 mM HEPES (ThermoFisher Scientific), 0.37 mM hypoxanthine (Sigma), 24 mM sodium bicarbonate (Sigma), 0.5% (wt/vol) AlbuMAX II (ThermoFisher Scientific), 25 μg/mL gentamicin (Sigma), pH 7.2) supplemented with washed human red blood cells. The parasite cultures were maintained at 37 °C in a 3% O_2, 5% CO_2, 92% N_2 atmosphere and synchronized with 10 mL of 5% (wt/vol) D-sorbitol (Sigma) at 37 °C for 10 min during the early ring stage. The ring-stage parasites were adjusted to 2% parasitemia and 2% hematocrit, and 100 μl of the culture was added into each well of 96-well black plates (Corning) containing 100 μl complete medium in the presence or absence of compounds (5 μg/mL) in triplicate. Quinacrine dihydrochloride (320 nM; Sigma) was used as the positive control. The plates were incubated at 37 °C for 72 h, followed by adding 40 μl lysis solution (20 mM Tris-HCl, 5 mM EDTA dipotassium salt dihydrate, 0.16% saponin, 1.6% Triton X-100, pH 7.5) containing fresh 10x SYBR Green I (ThermoFisher Scientific) into each well.[4] The plates were incubated in the dark at room temperature for 24 hrs, and the fluorescent signals were measured at 535 nm with excitation at 485 nm using an EnVision to determine the relative parasite loads. The dose-response analysis of the compounds of interest was performed and the EC_{50}s were analyzed using GraphPad Prism. The reported EC_{50} is the average determined from two independent experiments.

Anti-*Toxoplasma* Assays

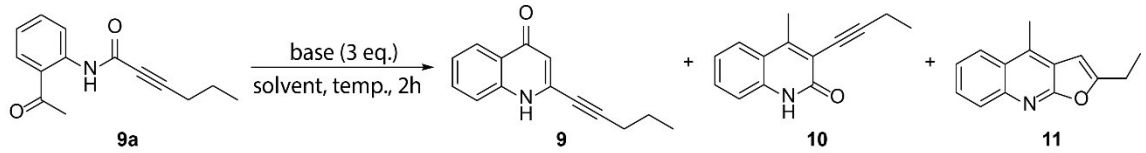
HuH7 cells were seeded at 7,000 cells/well in 384-well plates (Corning). Compounds (5 μg/mL) were added in triplicate 30 min before infection with 6,000 luciferase-expressing *Toxoplasma gondii* tachyzoites. HuH7 viability and *T. gondii* parasite load was assessed 45 hours post infection using the protocol described above. The relative signal intensity of each well was normalized to the negative control (1% DMSO). The positive control was pyrimethamine (10 μM). Compounds that inhibited parasite load were evaluated for potency where dose-response analysis was performed with GraphPad Prism. The reported EC_{50} is the average determined from two independent experiments.

Immunofluorescence Analysis of EEFs

In a 24-well plate, 100,000 HuH7 cells were incubated with compound **15** (100 ng/mL), the electron transport inhibitor atovaquone (1 nM) or DMSO (1%) for 30 min before infection with 60,000 *P. berghei* sporozoites. *P. berghei*-infected HuH7 cells were then fixed at 48 hours post infection and stained with goat anti-*Pb*UIS4 (antibodies-online), donkey anti-goat AlexaFluor 488 (Life Technologies) and DAPI. Images were acquired on a Zeiss Axio Observer widefield fluorescence microscope and ImageJ was used to quantify EEF size.

4. Supporting Tables and Figures

Table S1. Optimization of reaction conditions.

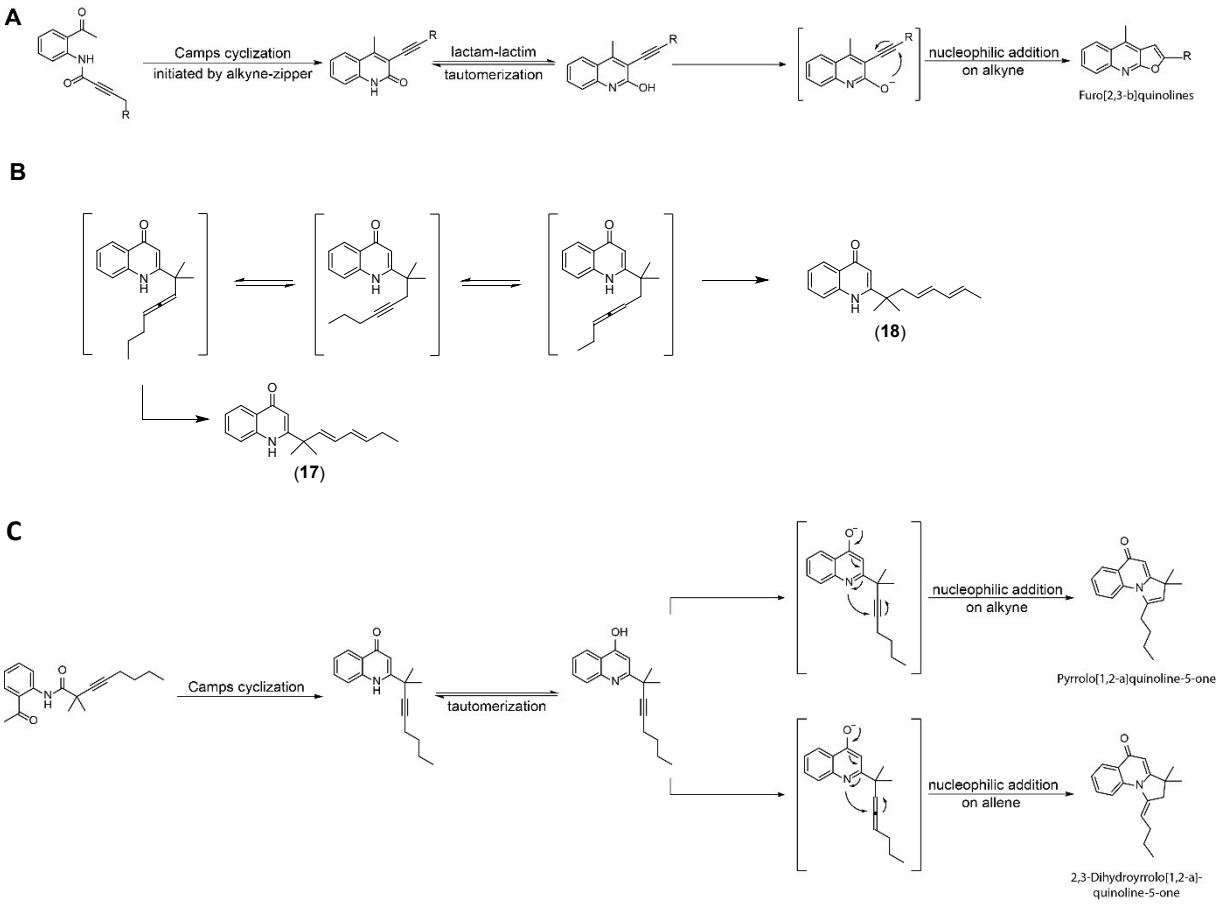


base	solvent	temp.	yield 9 (%)[a]	yield 10 (%)[a]	yield 11 (%)[a]
NaOH	1,4-Dioxan	75 °C	10	3	-
tert-BuOK	1,4-Dioxan	75 °C	4	78	-
$CsCO_3$	1,4-Dioxan	75 °C	-	21	-
NaOH	1,4-Dioxan	reflux	17	5	-
tert-BuOK	1,4-Dioxan	reflux	-	44	-
$CsCO_3$	1,4-Dioxan	reflux	-	63	-
NaOH	*tert*-BuOH	reflux	3	33	-
tert-BuOK	*tert*-BuOH	reflux	-	35	3
$CsCO_3$	*tert*-BuOH	reflux	-	55	3

[a] isolated yields.

Table S2. Inhibitory concentration (50%) of compounds against *Plasmodium*.

Category	Drug	Liver stage *P. berghei*, IC_{50}		Blood stage *P. falciparum* 3D7, IC_{50}	
		μM	μg/mL	μM	μg/mL
ETC inhibitors	Atovaquone [5, 6]	0.0003	0.0001	0.00066	0.00024
	Decoquinate [5, 7]	0.0054	0.0023	0.004	0.0017
	TCMDC-123667 [8]	0.105	0.049	0.109	0.050
	TCMDC-124103 [8]	0.009	0.004	0.127	0.055
	TCMDC-125258 [8]	0.066	0.023	0.386	0.132
	TCMDC-125465 [8]	0.018	0.007	0.171	0.066
	TCMDC-135461 [8]	0.016	0.007	0.005	0.002
	TCMDC-135546 [8]	0.006	0.003	0.026	0.011
	TCMDC-135678 [8]	0.505	0.178	0.099	0.035
	TCMDC-135787 [8]	0.079	0.027	0.516	0.174
	TCMDC-135795 [8]	0.114	0.051	0.212	0.095
	TCMDC-137383 [8]	0.006	0.003	0.031	0.015
	TCMDC-137384 [8]	0.033	0.018	0.131	0.073
	TCMDC-137395 [8]	0.009	0.003	0.021	0.008
	TCMDC-137403 [8]	0.481	0.164	0.969	0.331
	TCMDC-137410 [8]	0.031	0.011	0.038	0.014
	TCMDC-125094 [8]	0.108	0.032	0.389	0.117
	TCMDC-135796 [8]	0.009	0.004	0.016	0.007
	TCMDC-136185 [8]	0.041	0.013	0.171	0.054
	TCMDC-136286 [8]	0.045	0.018	0.661	0.261
	TCMDC-136300 [8]	0.027	0.009	0.075	0.026
	TCMDC-136303 [8]	0.034	0.012	0.186	0.064
	TCMDC-136433 [8]	0.022	0.013	0.217	0.127
	TCMDC-138141 [8]	0.506	0.159	0.44	0.14
	TCMDC-124258 [8]	0.105	0.015	0.13	0.02
	TCMDC-125094 [8]	0.108	0.032	0.389	0.117
	TCMDC-135796 [8]	0.009	0.004	0.016	0.007
	TCMDC-136185 [8]	0.041	0.013	0.171	0.054
Unknown	**15**	0.142	0.038	63.6	17



Scheme S1: Proposed mechanisms of the tandem cyclization reactions of **A**) N-(2´-acetylphenyl)alk-2-ynamides to furo[2,3-*b*]quinolones. **B**) Proposed mechanism leading to dienylquinolones **17** and **18** which suggests **C**) the mechanism for the cyclization of N-(2´-acetylphenyl)-2,2-dimethyloct-3-ynamide to pyrrolo[1,2-*a*]quinoline-5-ones.

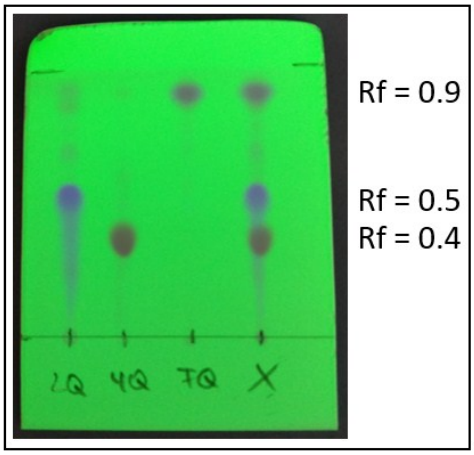


Fig. S1: TLC in petrol ether / ethyl acetate 1:2 of compounds **10** (2Q), **9** (4Q), **11** (FQ) and their mixture under 254 nm wave length.

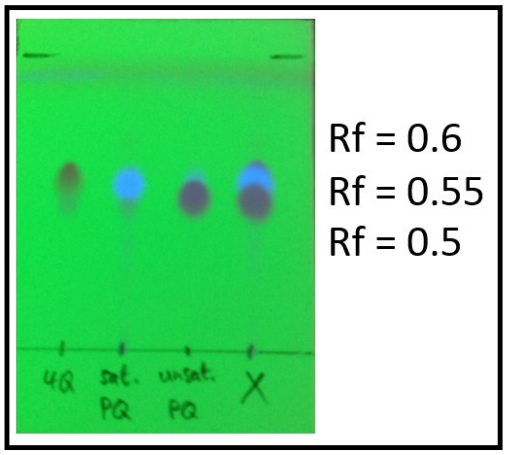


Fig. S2: TLC in ethyl acetate of compounds **14** (4Q, R_f = 0.6), **16** (sat. PQ, R_f = 0.55), **15** (unsat. PQ, R_f = 0.5) and their mixture under 254 nm wave length.

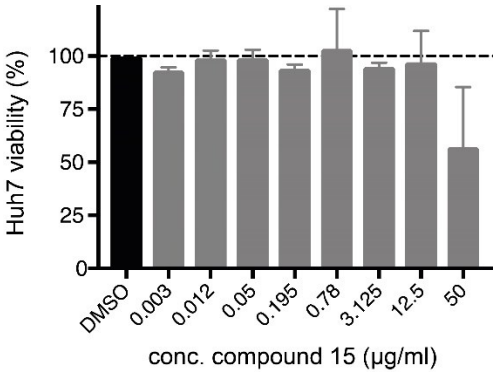


Fig. S3: Cell cytotoxicity assay of compound **15** towards Huh7 viability

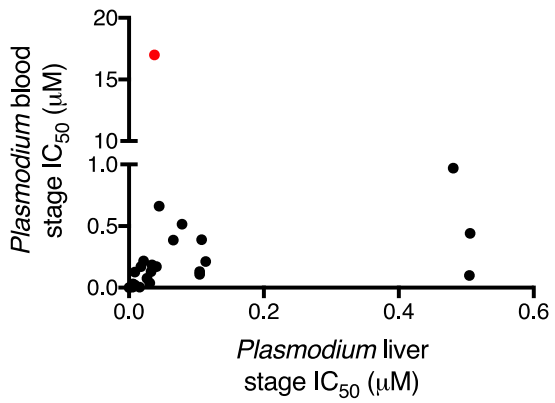


Fig. S4: Potency of various electron transport chain inhibitors for *Plasmodium* blood stage and liver stage in comparison to the unique selectivity of compound **15** (red).

5. NMR spectra

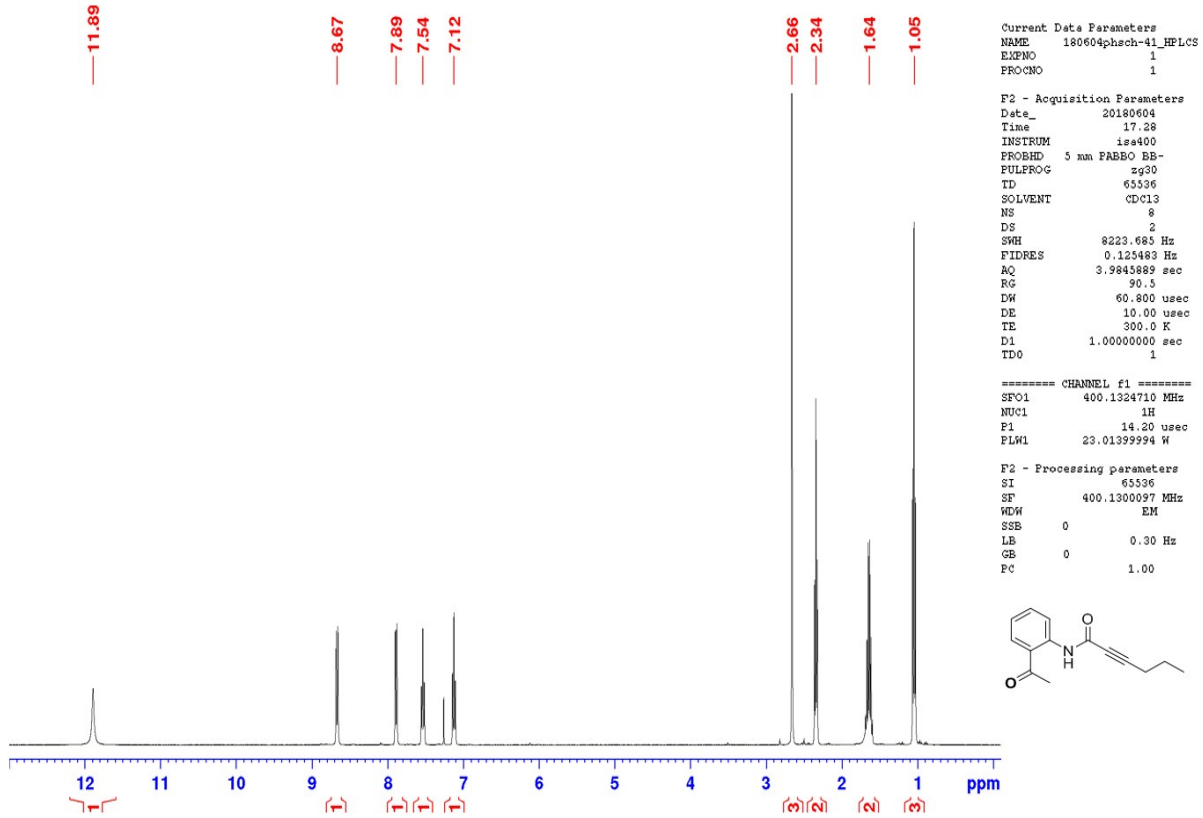


Figure S5. ^{1}H-NMR-spectra of **9a** in $CDCl_3$.

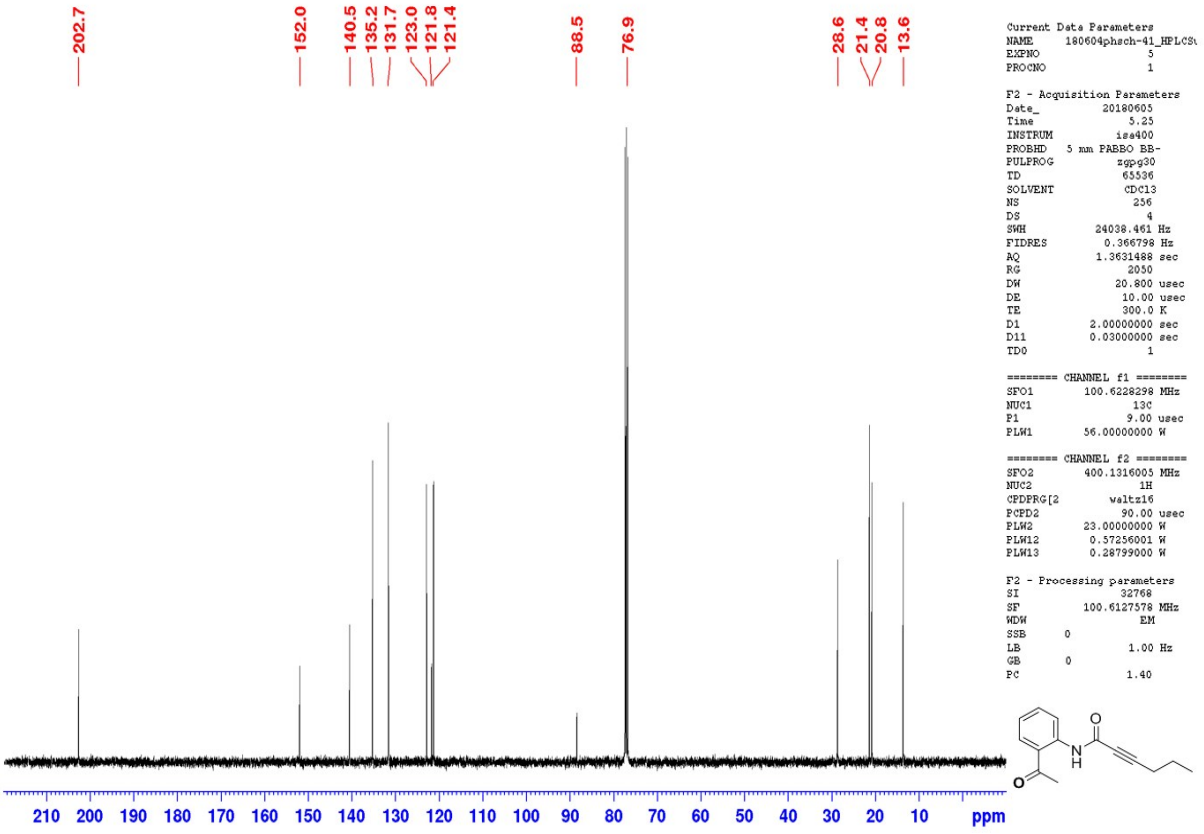


Figure S6. ^{13}C-NMR-spectra of **9a** in $CDCl_3$.

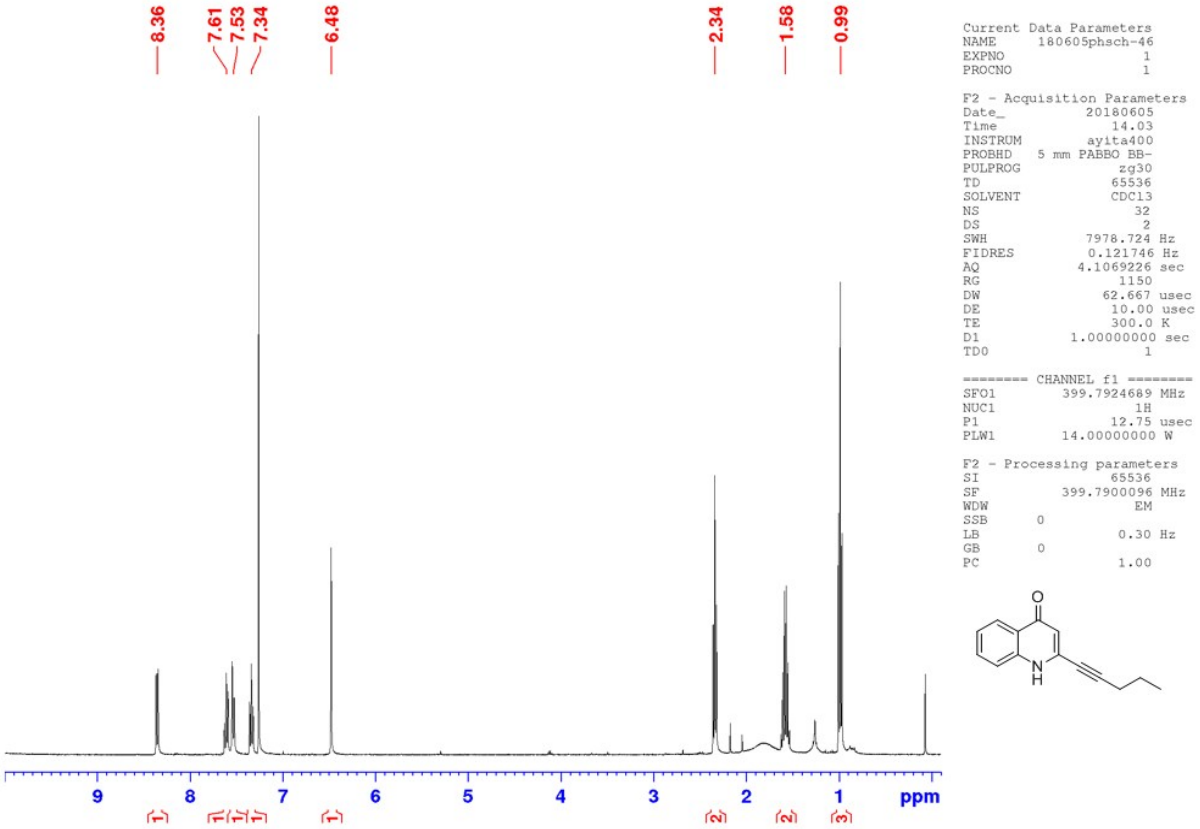


Figure S7. ^{1}H-NMR-spectra of **9** in $CDCl_3$.

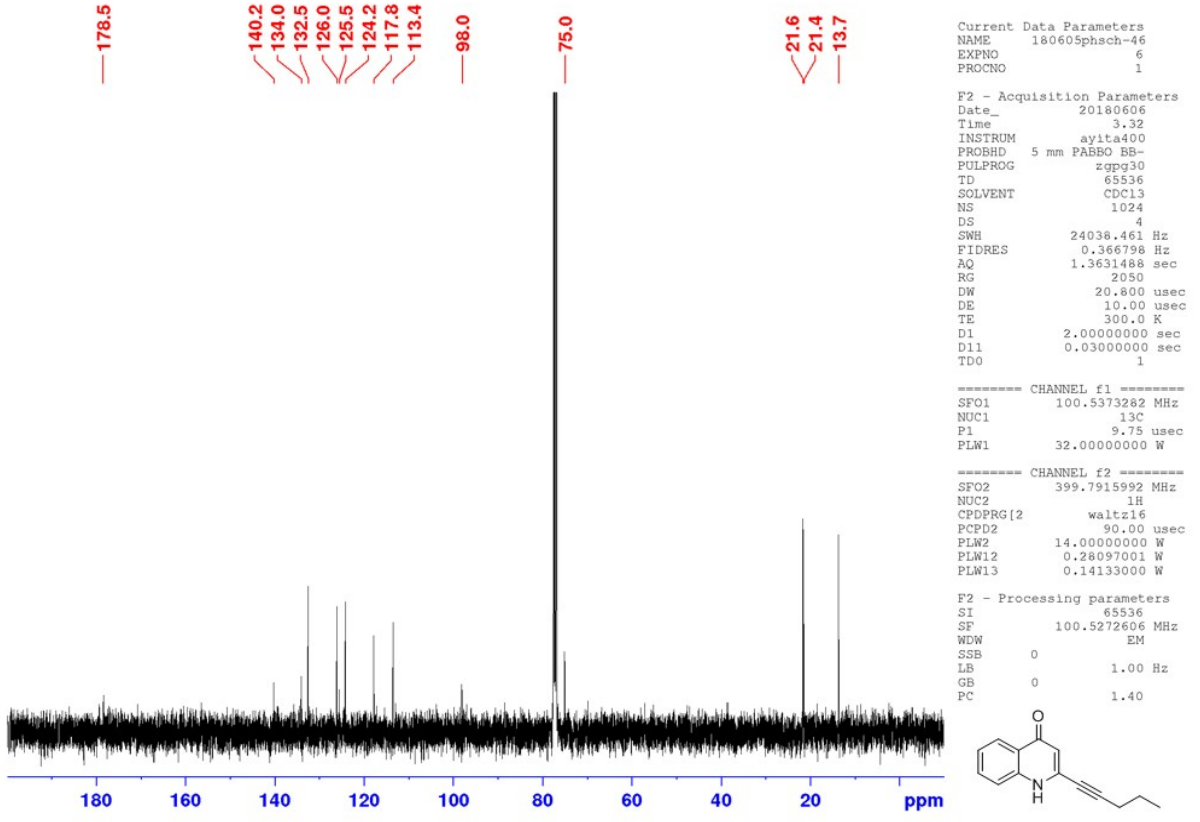


Figure S8. ^{13}C-NMR-spectra of **9** in $CDCl_3$.

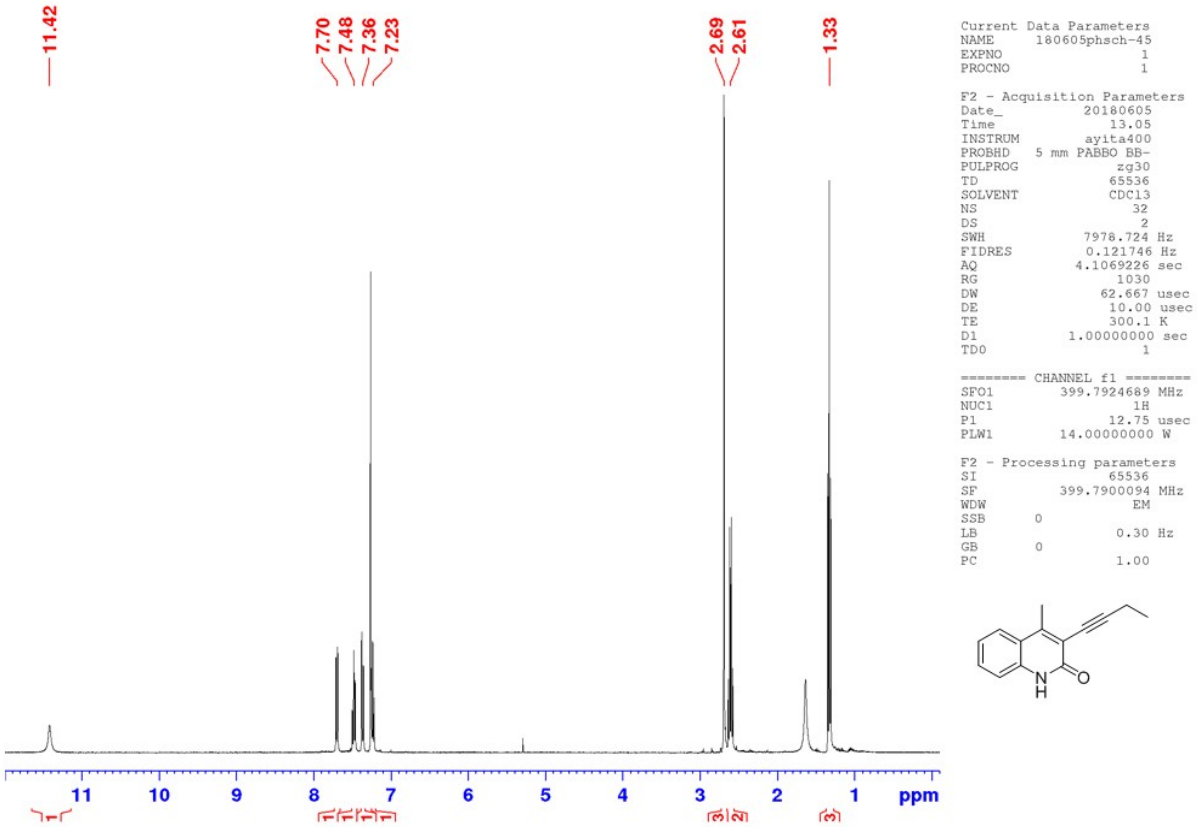


Figure S9. ^{1}H-NMR-spectra of **10** in $CDCl_3$.

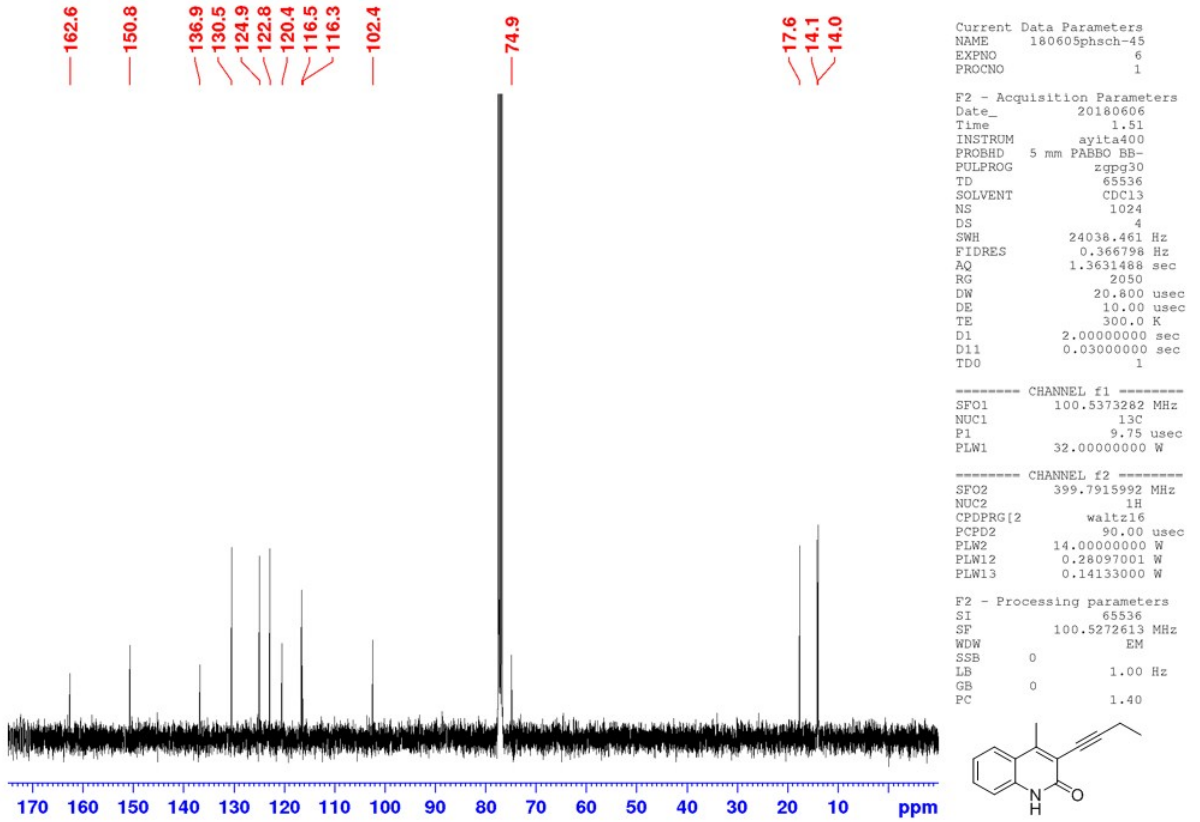


Figure S10. ^{13}C-NMR-spectra of **10** in $CDCl_3$.

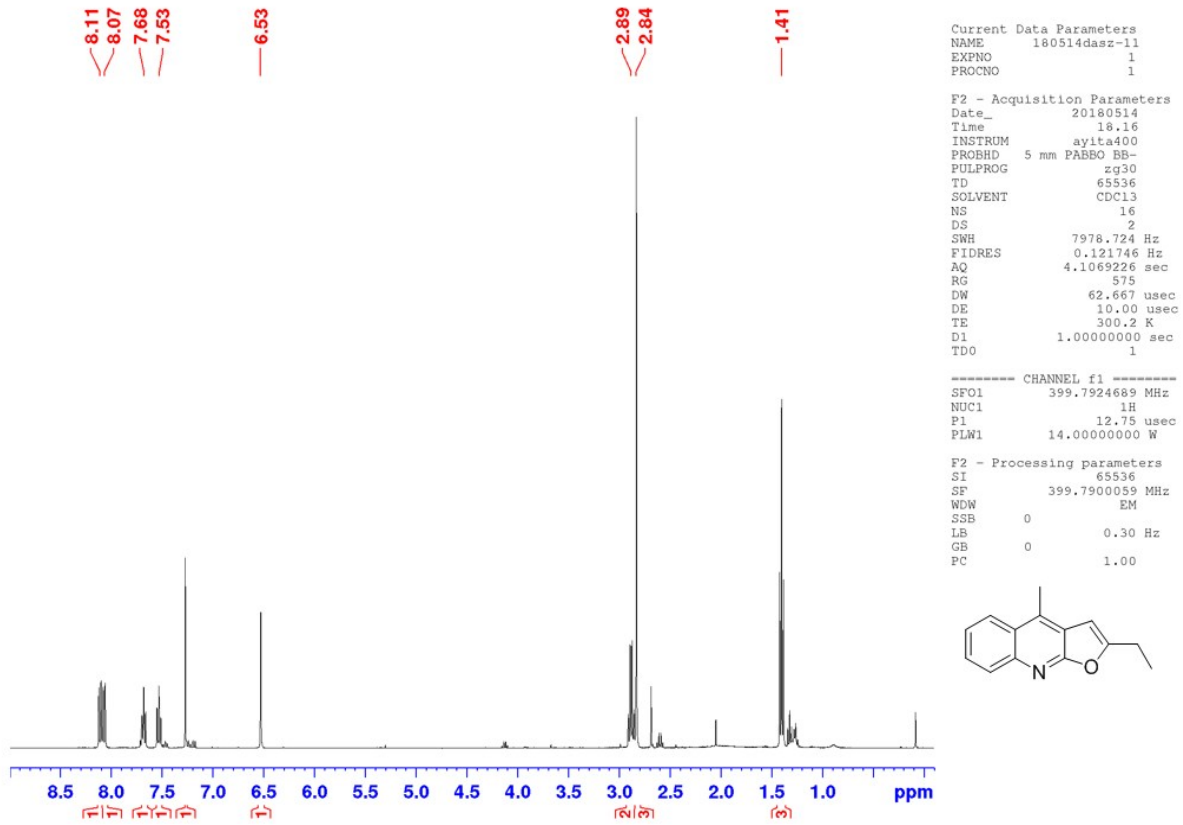


Figure S11. ^{1}H-NMR-spectra of **11** in $CDCl_3$.

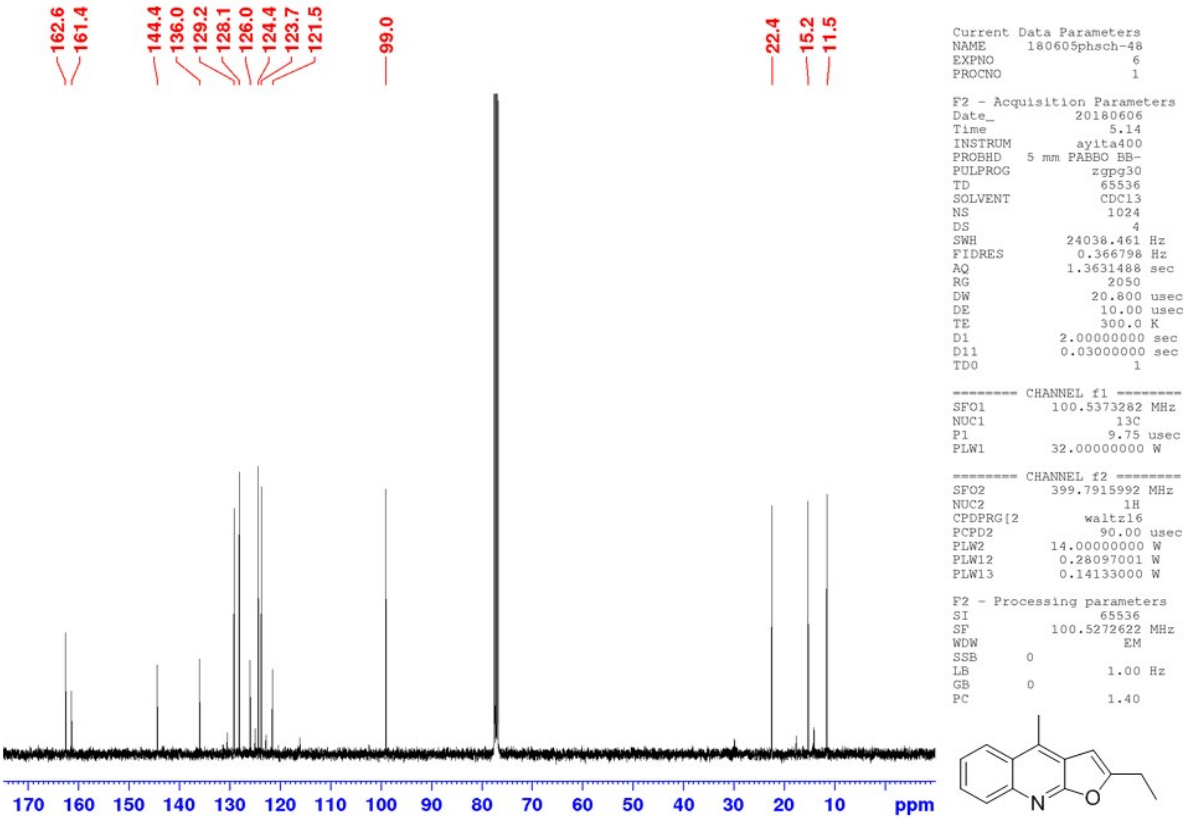


Figure S12. ^{13}C-NMR-spectra of **11** in $CDCl_3$.

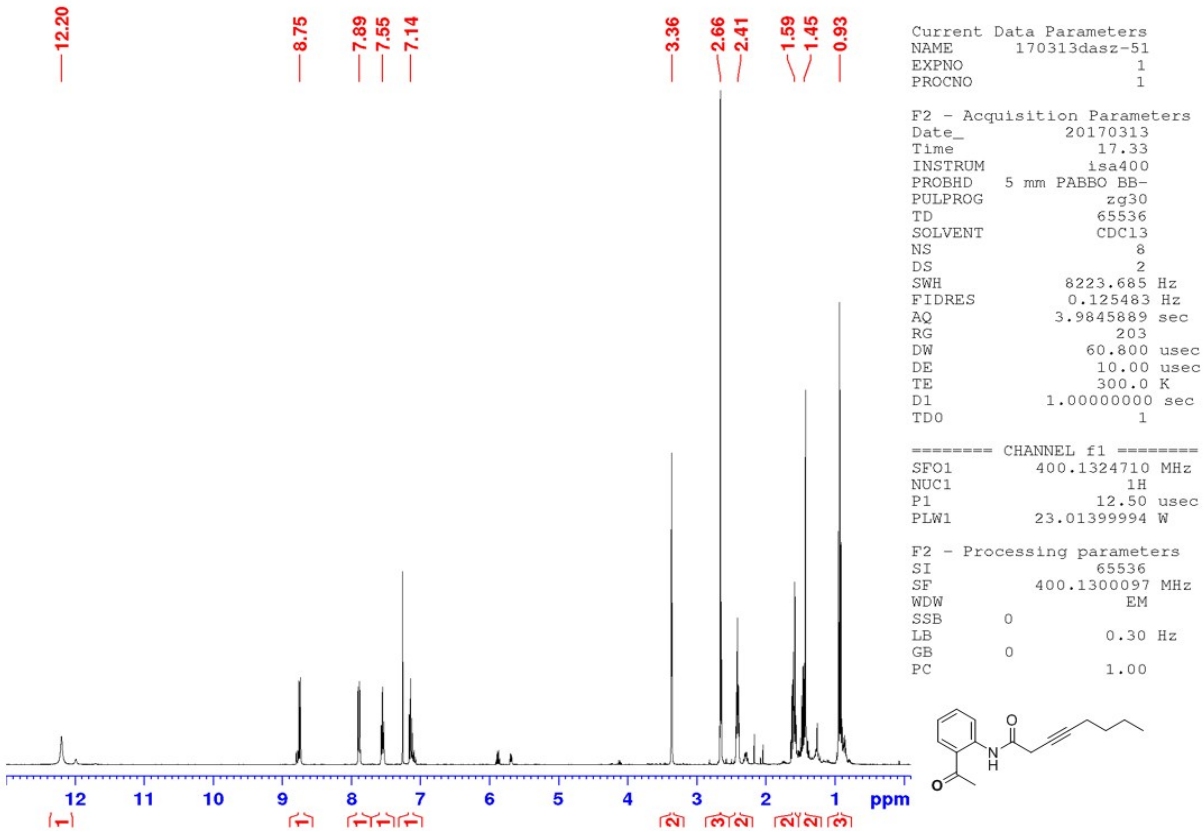


Figure S13. ^{1}H-NMR-spectra of **12a** in $CDCl_3$.

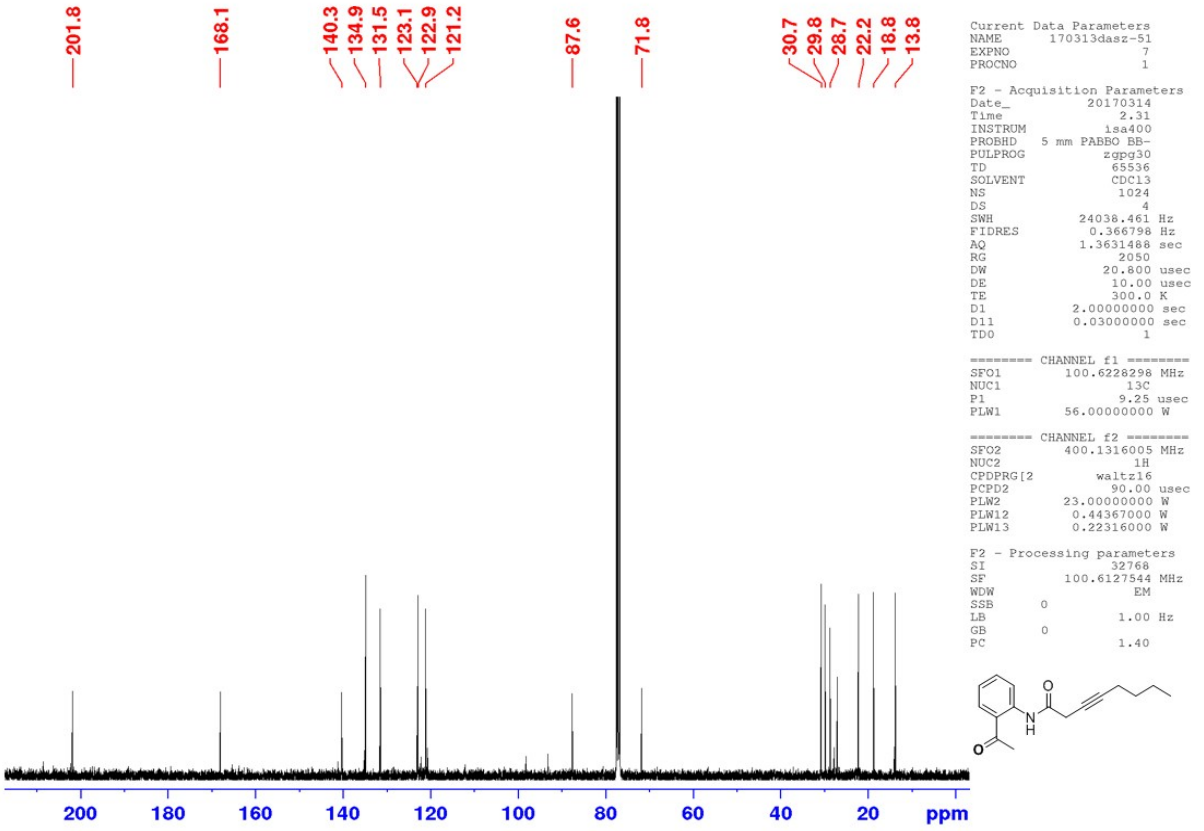


Figure S14. ^{13}C-NMR-spectra of **12a** in $CDCl_3$.

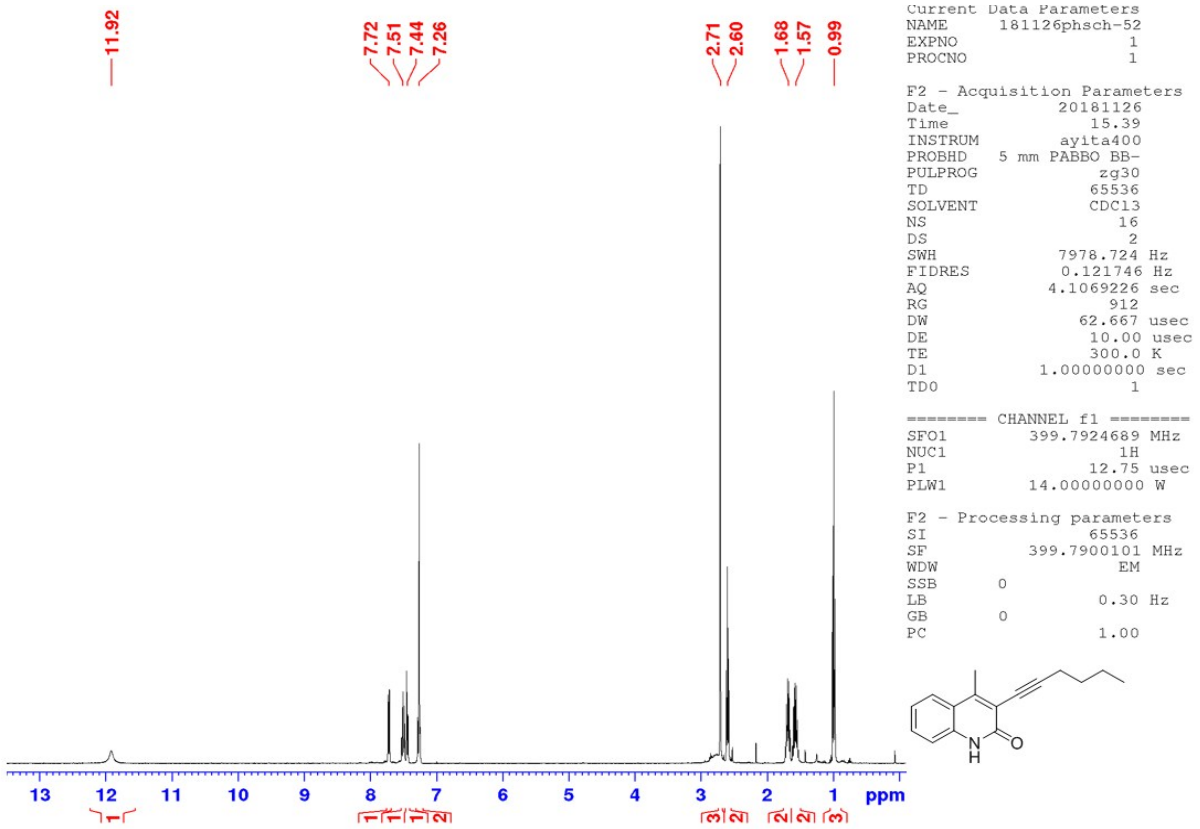


Figure S15. ^{1}H-NMR-spectra of **12** in $CDCl_3$.

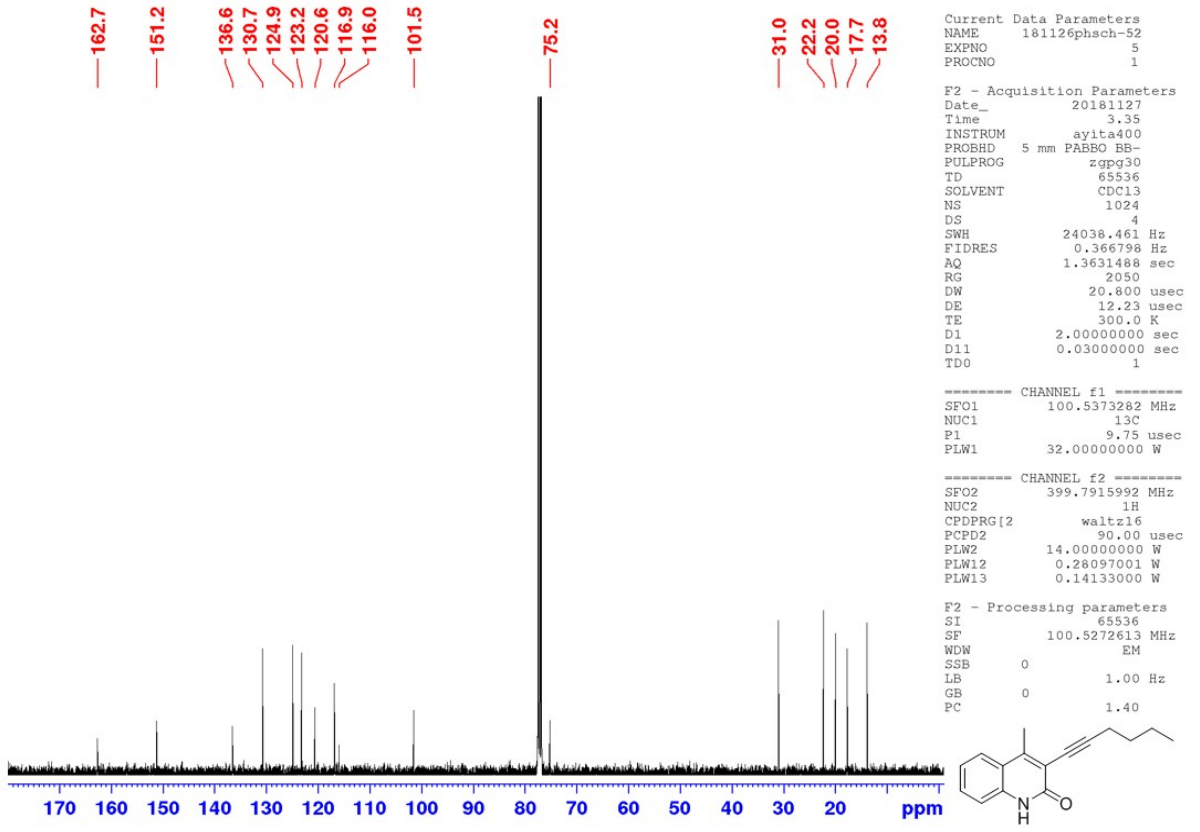


Figure S16. ^{13}C-NMR-spectra of **12** in $CDCl_3$.

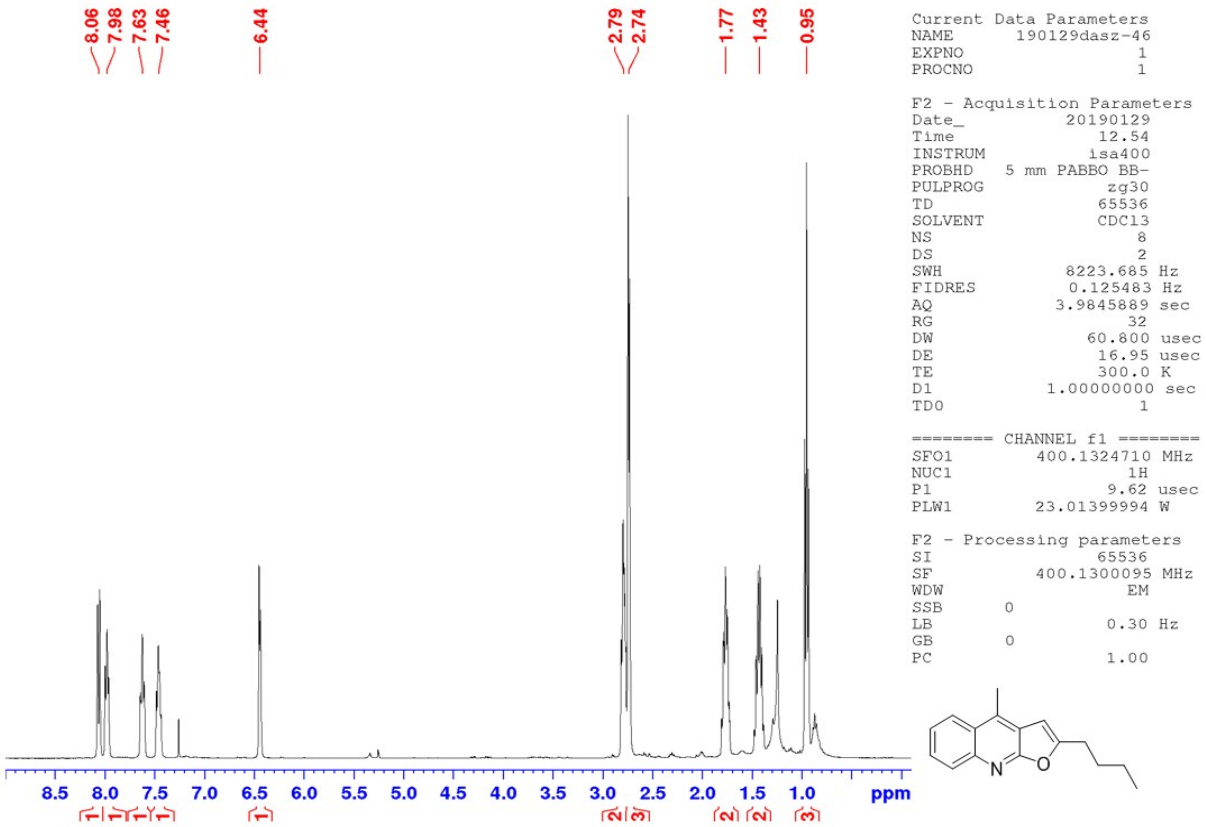


Figure S17. ^{1}H-NMR-spectra of **13** in $CDCl_3$.

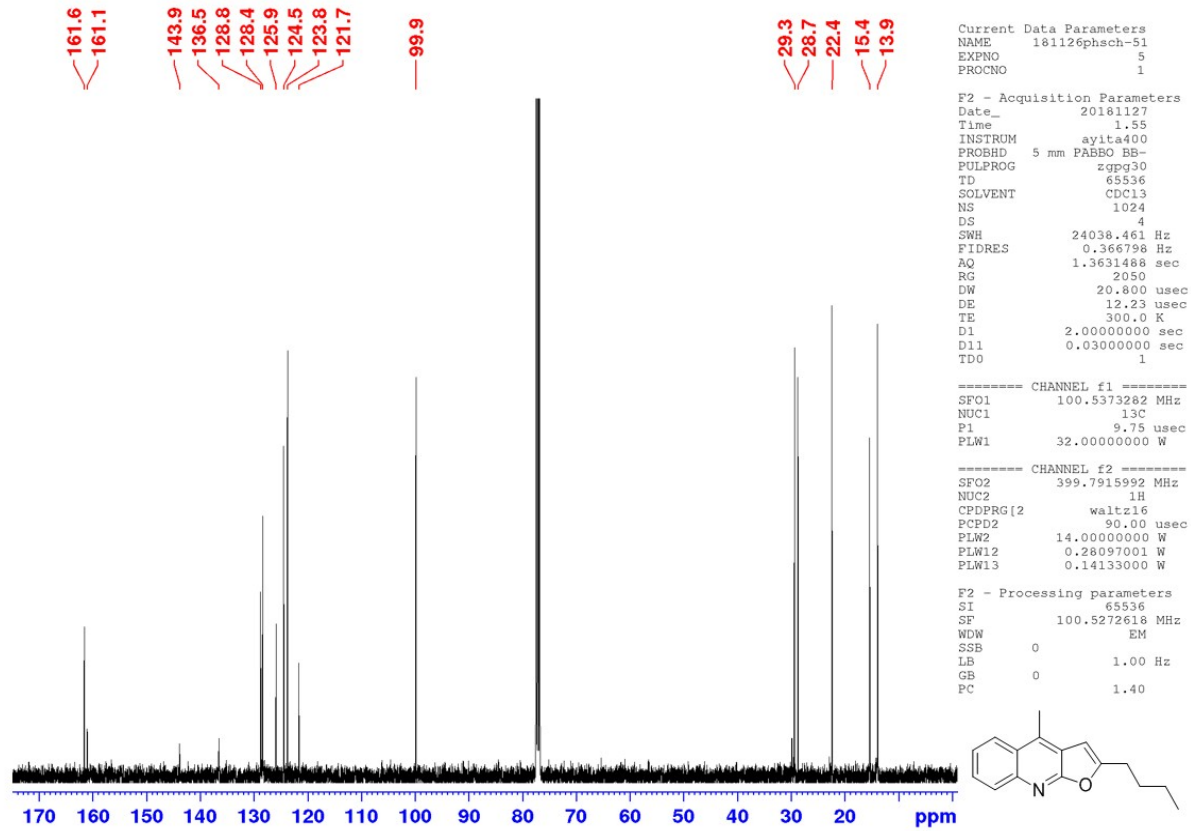


Figure S18. ^{13}C-NMR-spectra of **13** in $CDCl_3$.

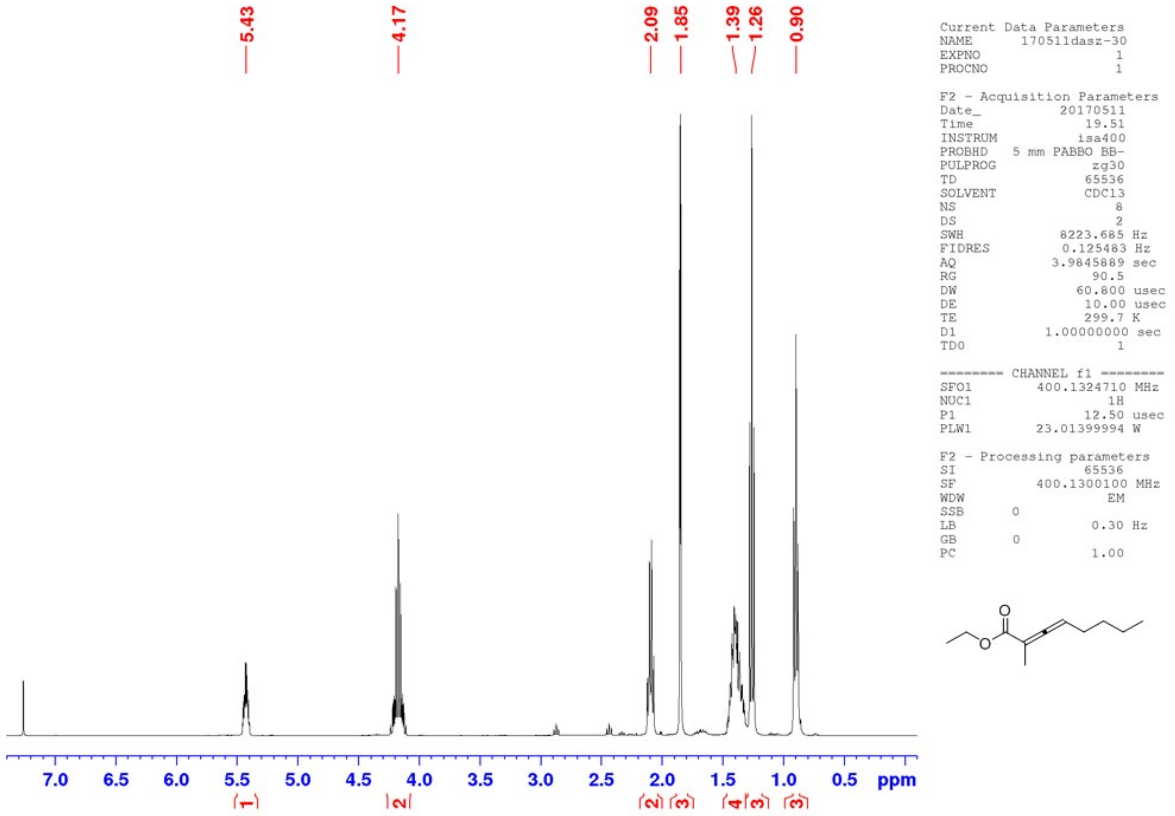


Figure S19. ^{1}H-NMR-spectra of **14a** in $CDCl_3$.

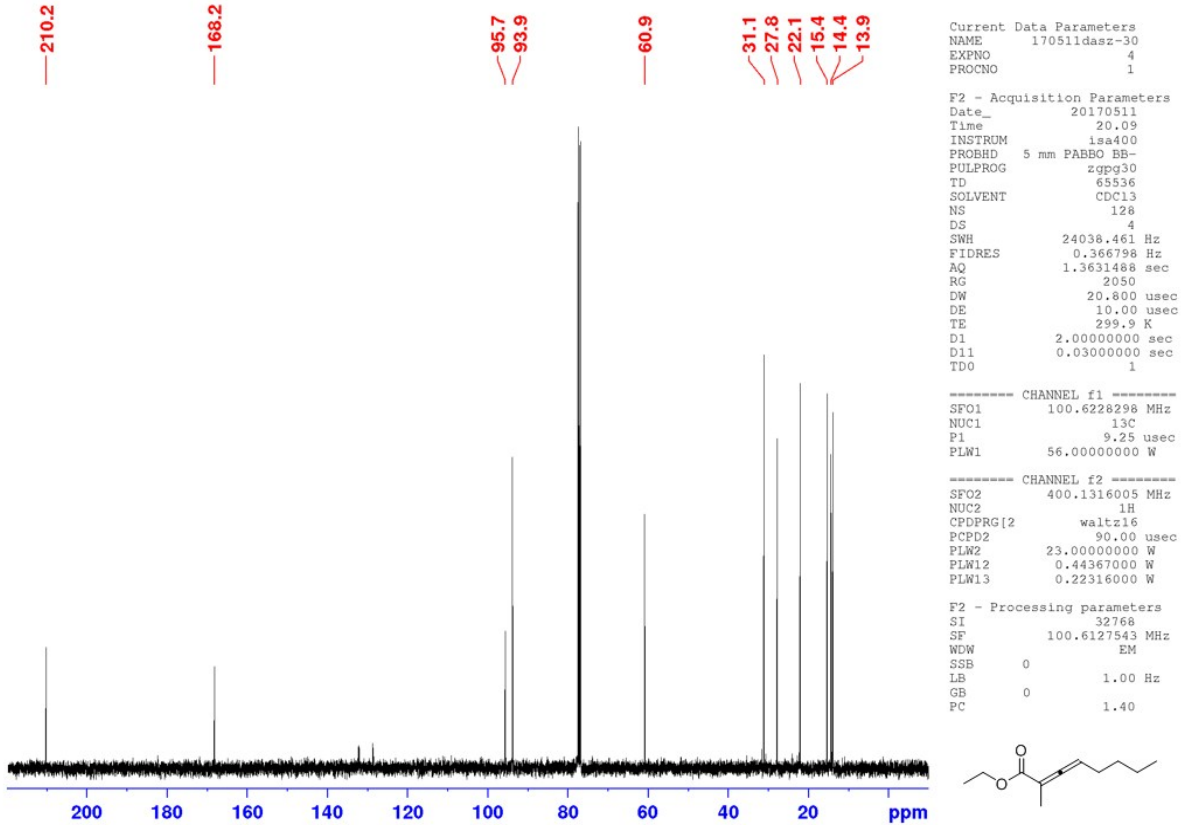


Figure S20. ^{13}C-NMR-spectra of **14a** in $CDCl_3$.

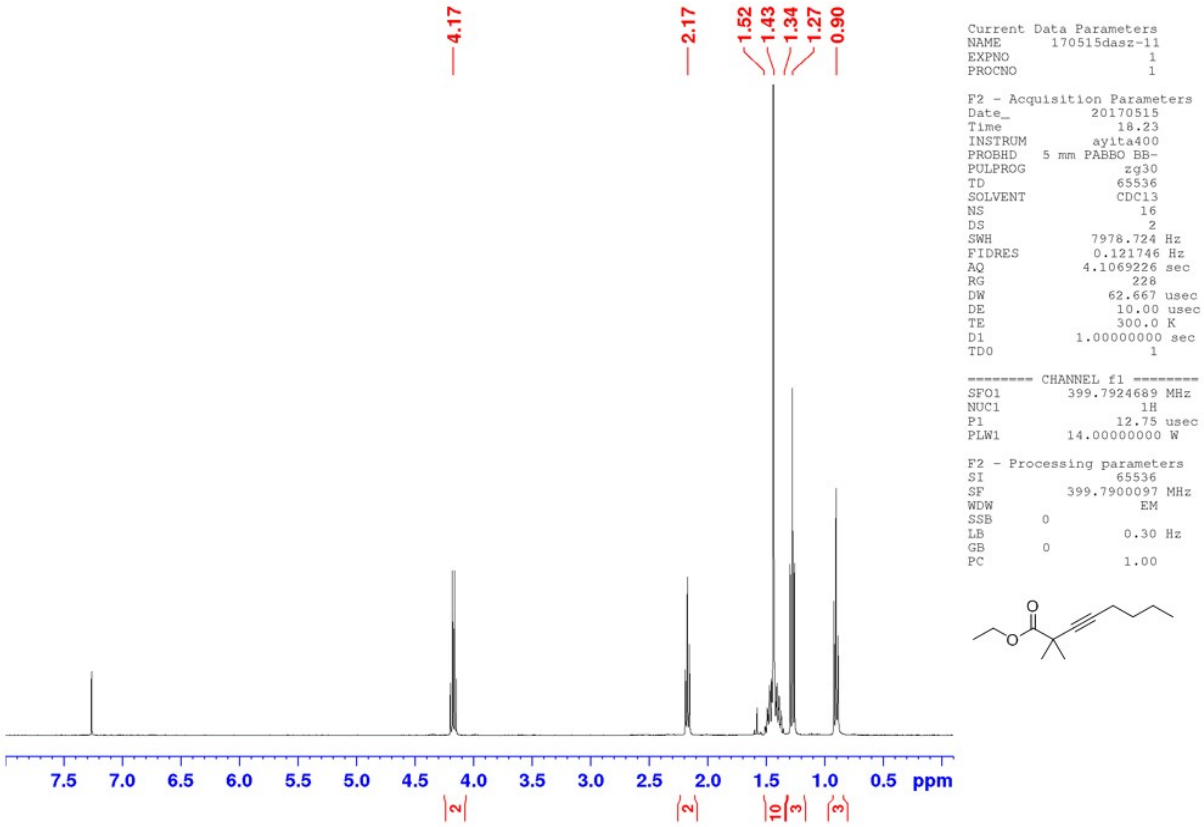


Figure S21. ^{1}H-NMR-spectra of **14b** in $CDCl_3$.

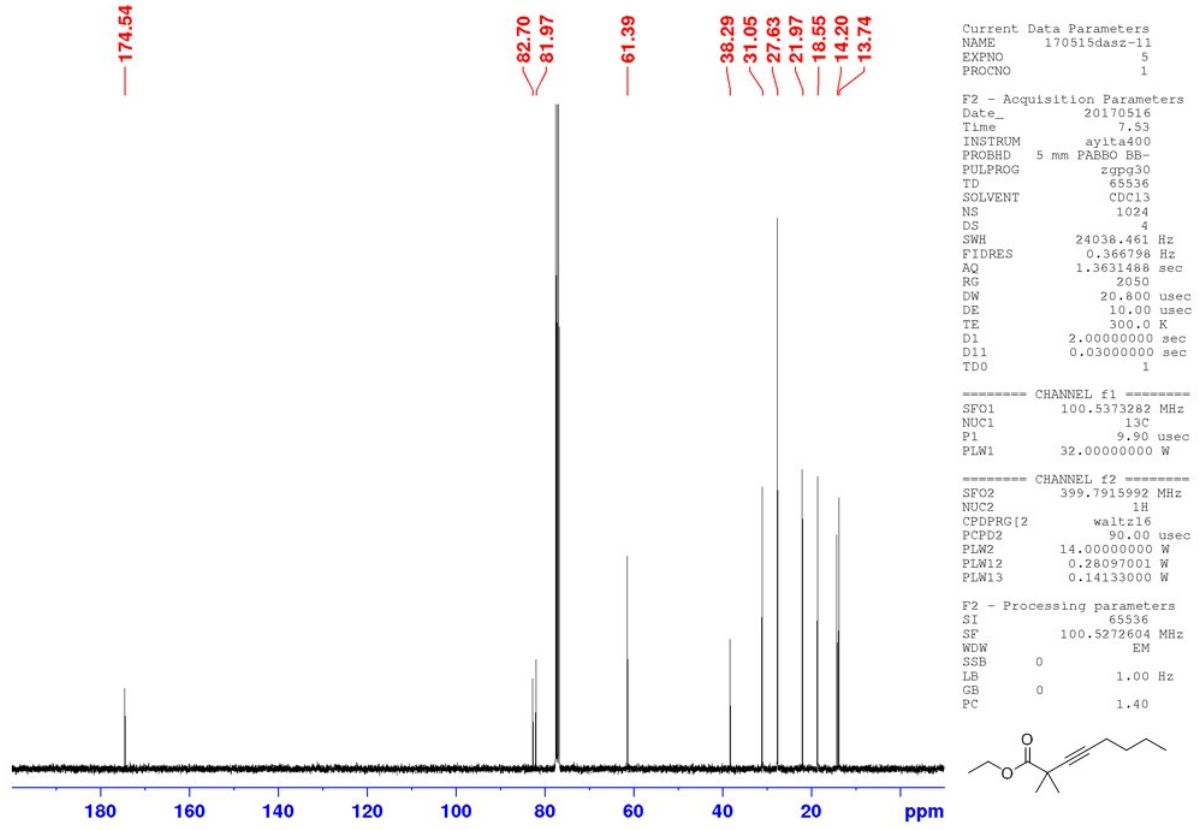


Figure S22. ^{13}C-NMR-spectra of **14b** in $CDCl_3$.

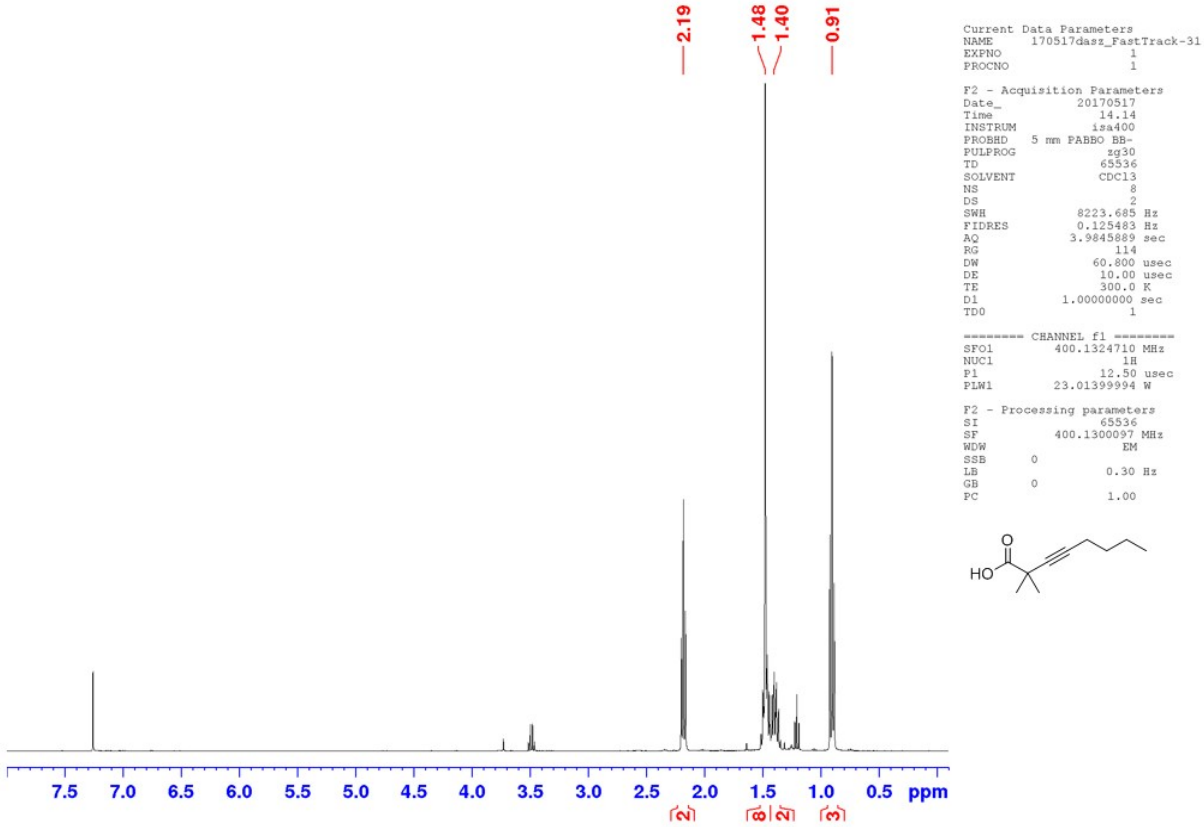


Figure S23. ^{1}H-NMR-spectra of **14c** in $CDCl_3$.

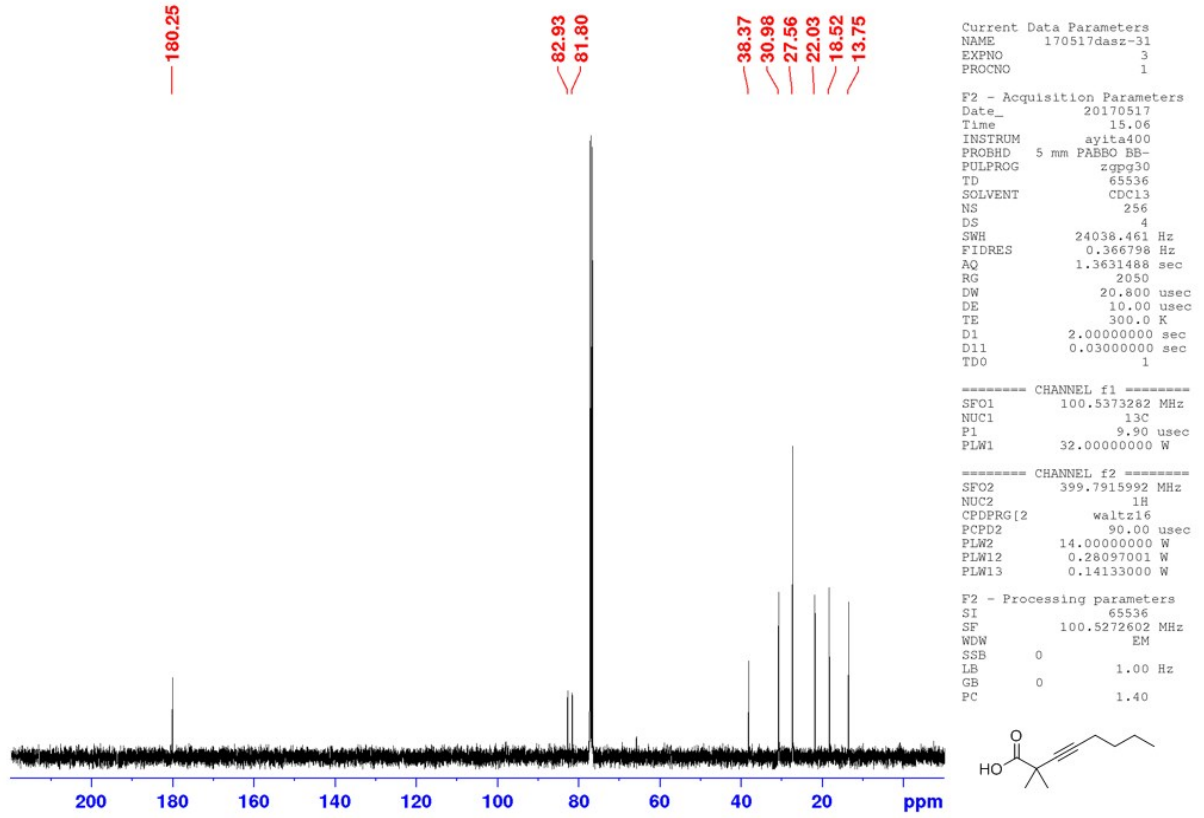


Figure S24. ^{13}C-NMR-spectra of **14c** in $CDCl_3$.

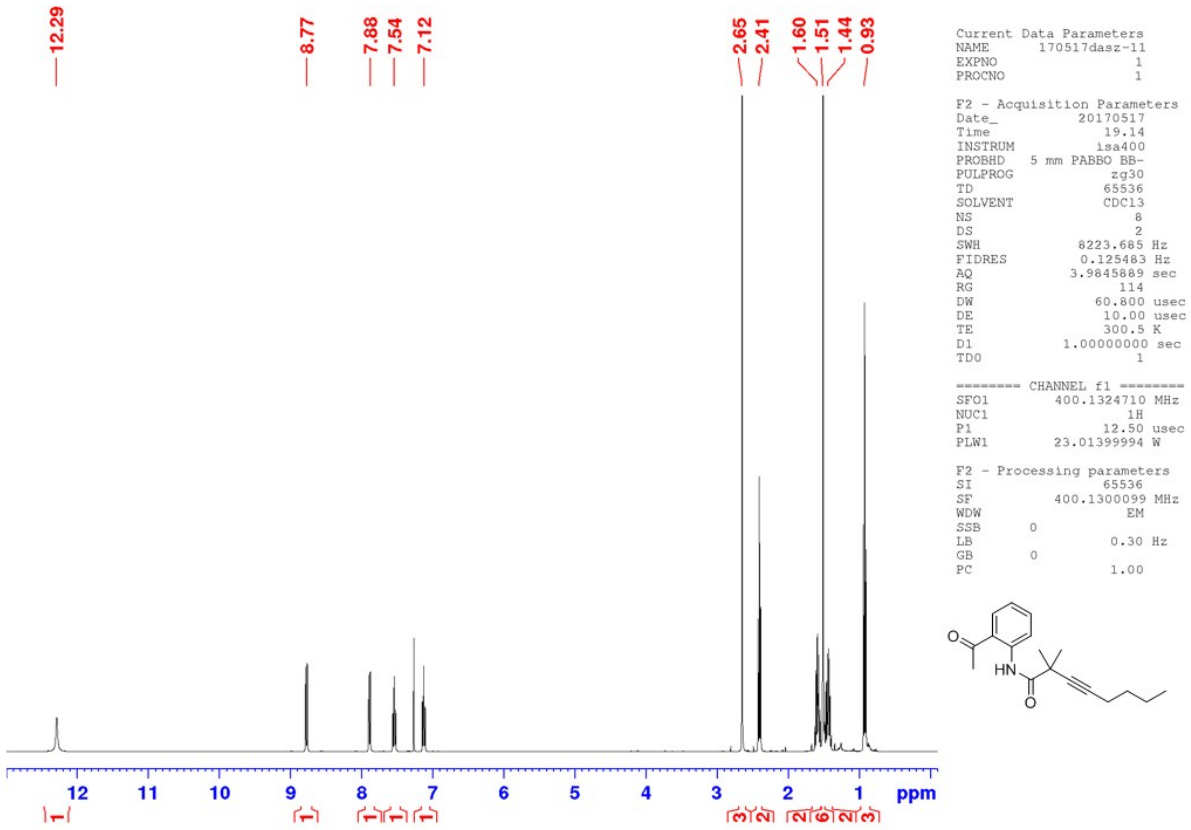


Figure S25. ^{1}H-NMR-spectra of **14d** in $CDCl_3$.

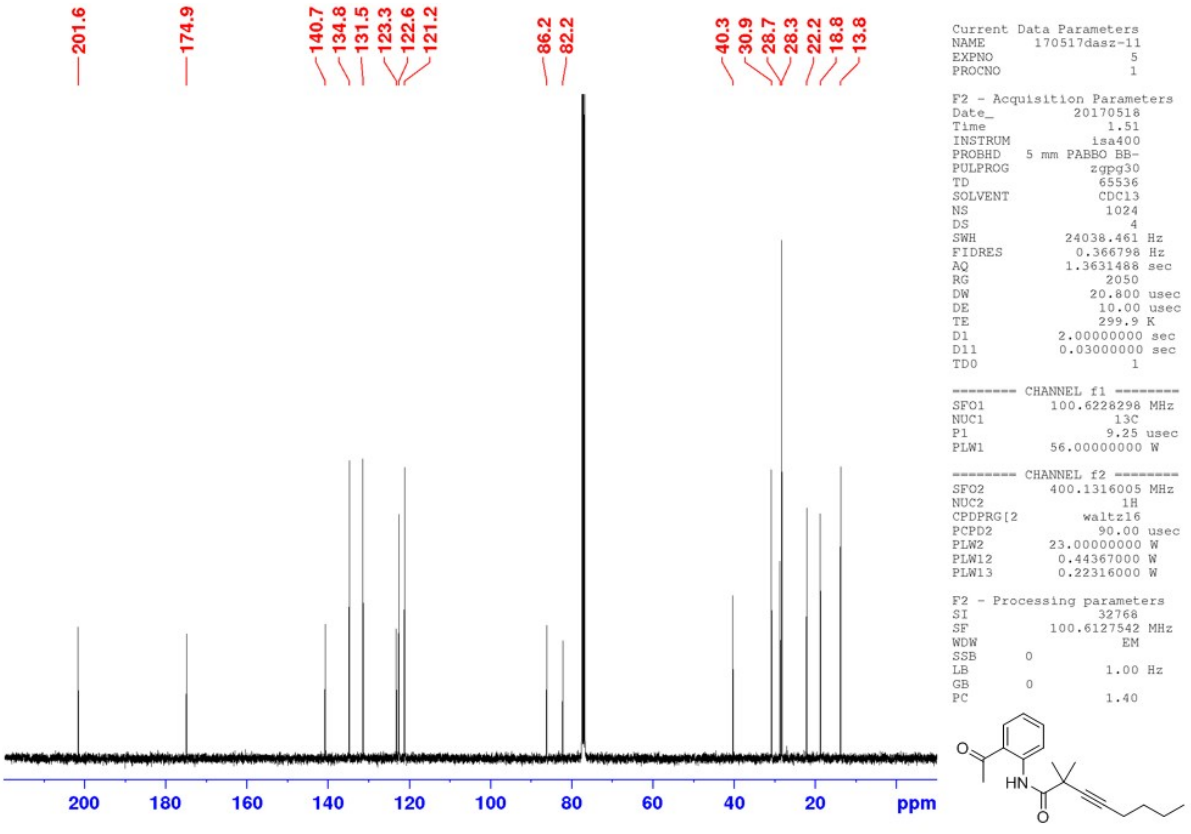


Figure S26. ^{13}C-NMR-spectra of **14d** in $CDCl_3$.

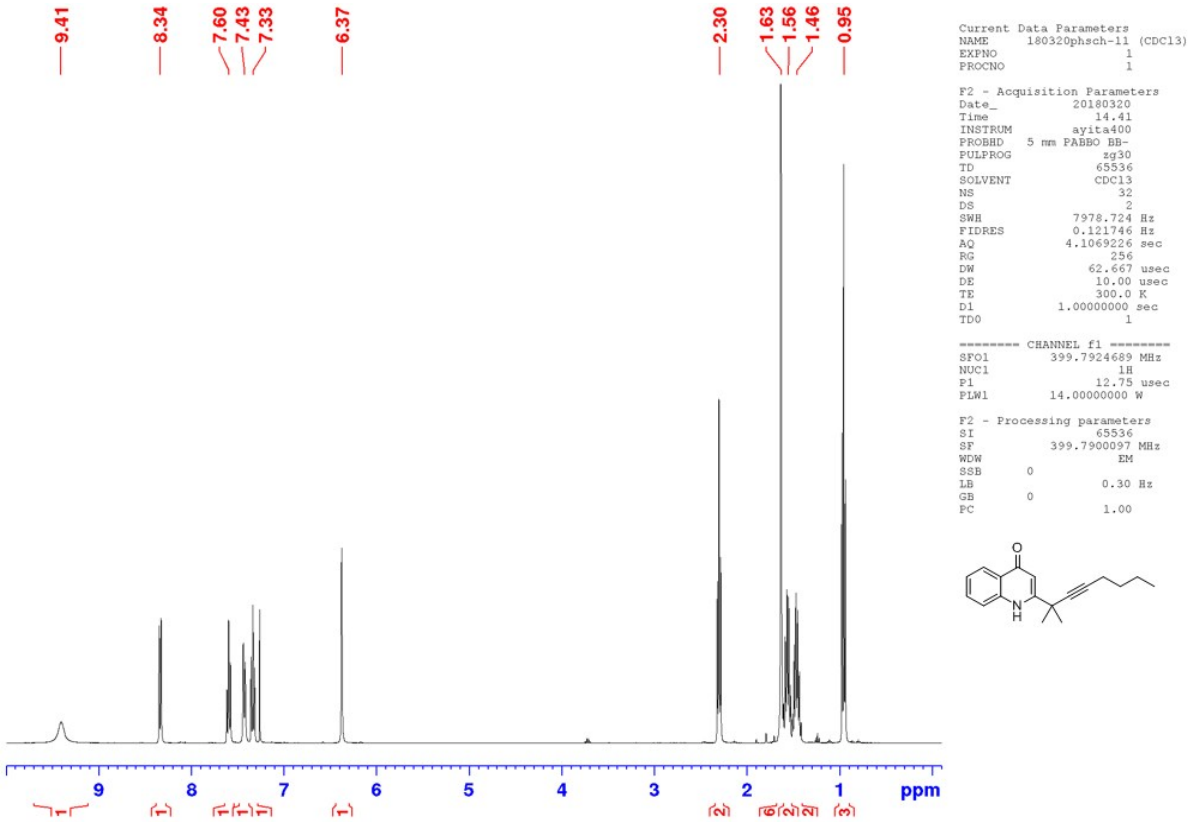


Figure S27. ^{1}H-NMR-spectra of **14** in $CDCl_3$.

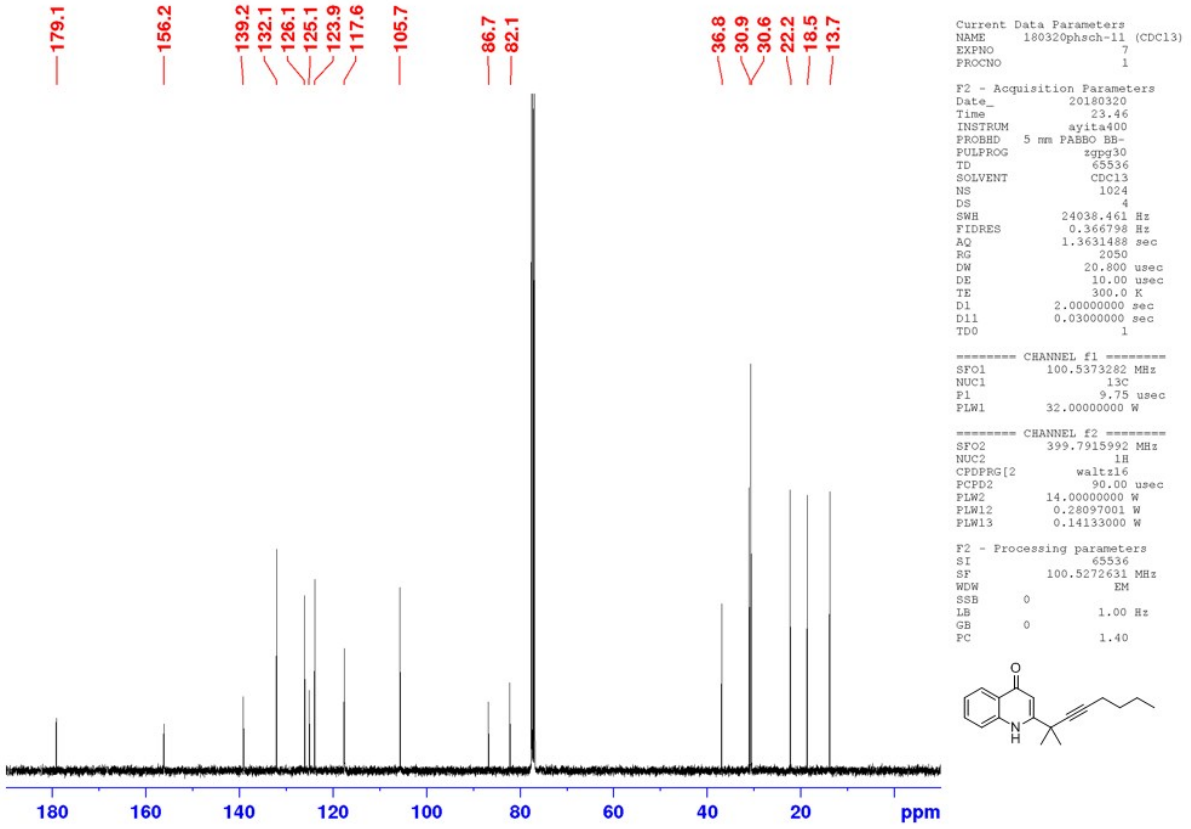


Figure S28. ^{13}C-NMR-spectra of **14** in $CDCl_3$.

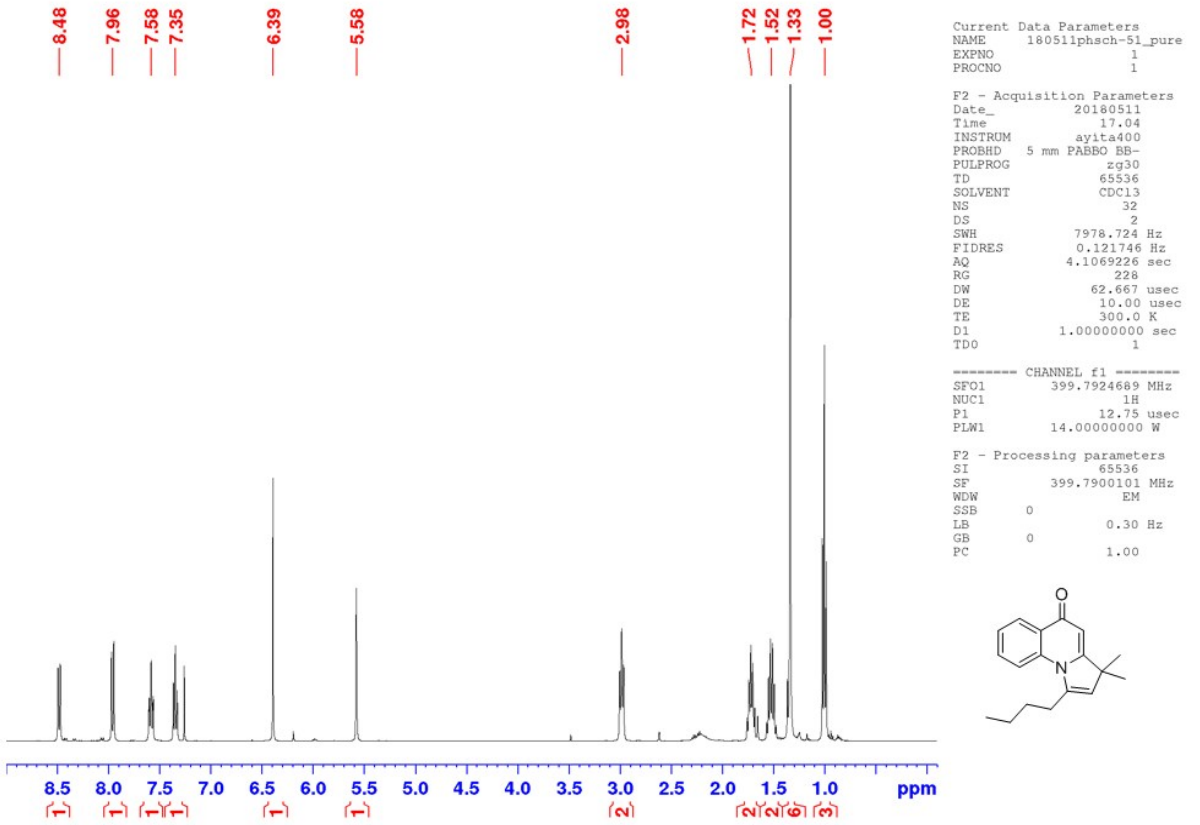


Figure S29. ^{1}H-NMR-spectra of **15** in $CDCl_3$.

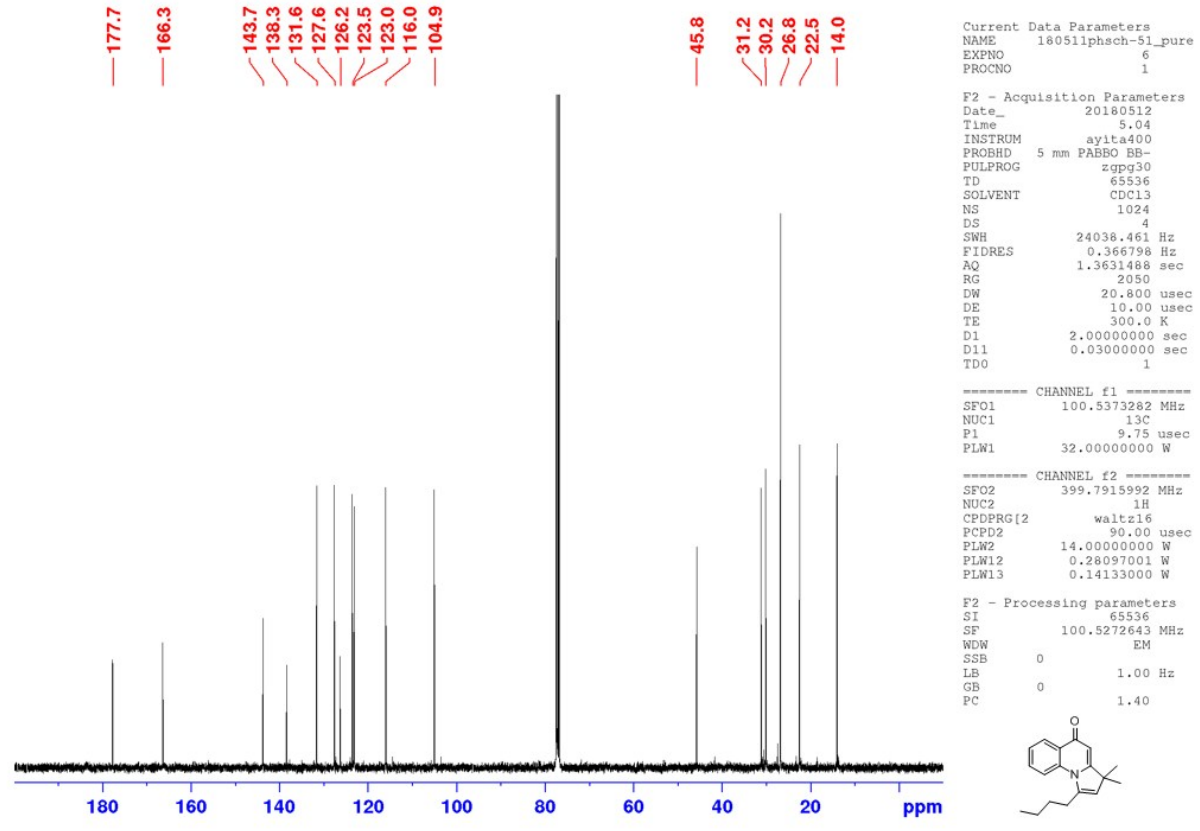


Figure S30. ^{13}C-NMR-spectra of **15** in $CDCl_3$.

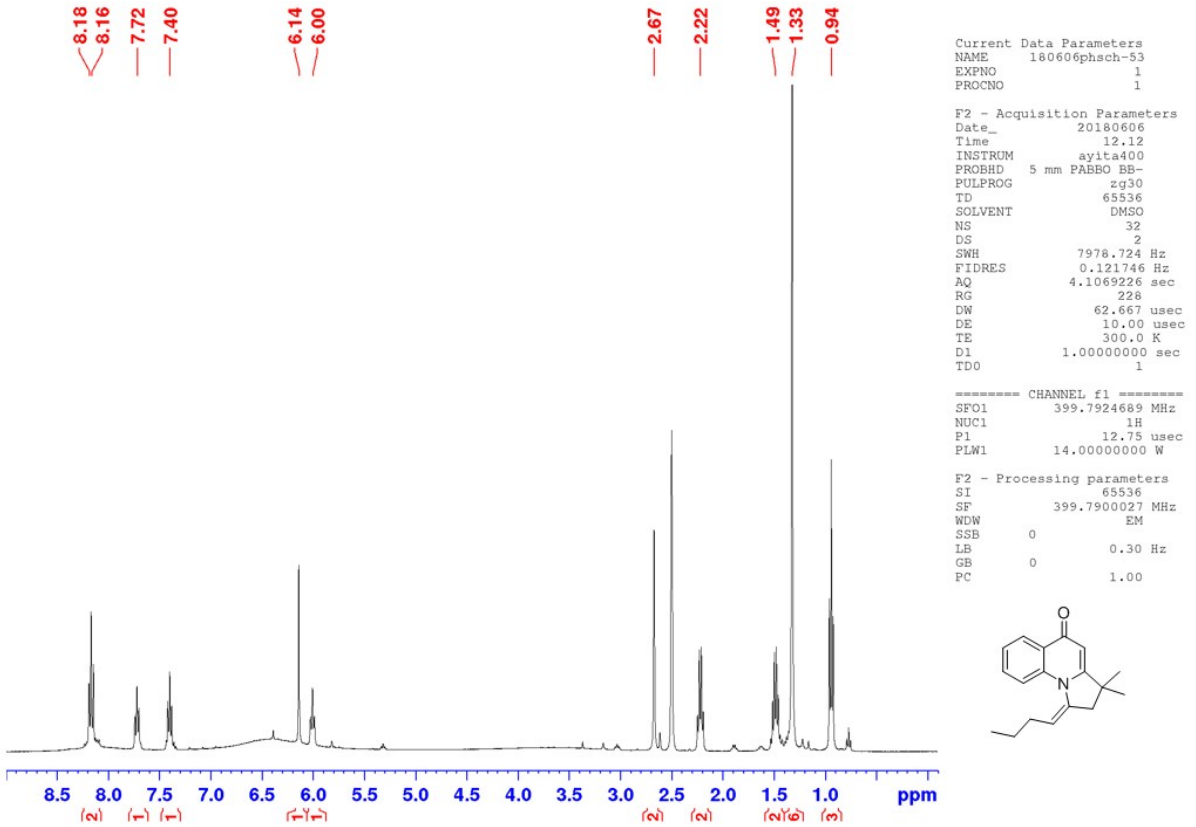


Figure S31. ^{1}H-NMR-spectra of **16** in DMSO-d_6.

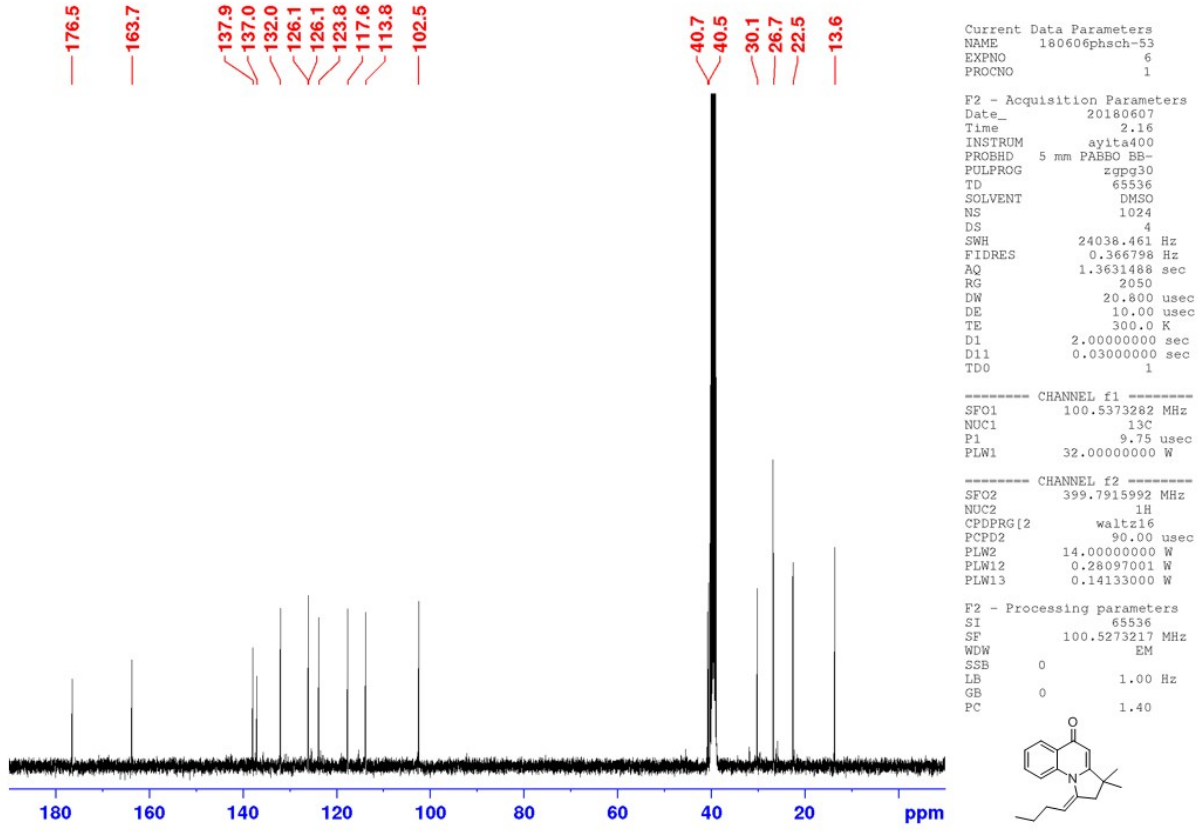


Figure S32. ^{13}C-NMR-spectra of **16** in DMSO-d_6.

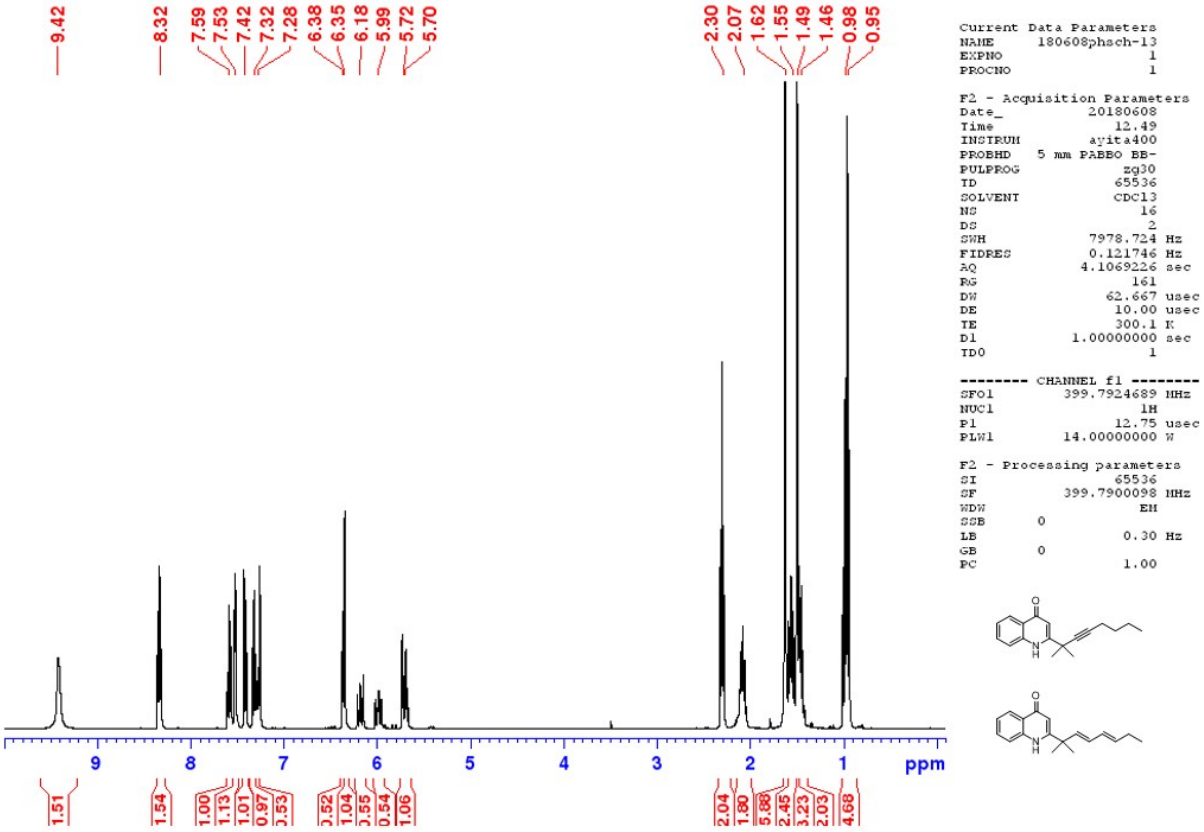


Figure S33. ^{1}H-NMR-spectra of **14 + 17** (1:0.5) in $CDCl_3$.

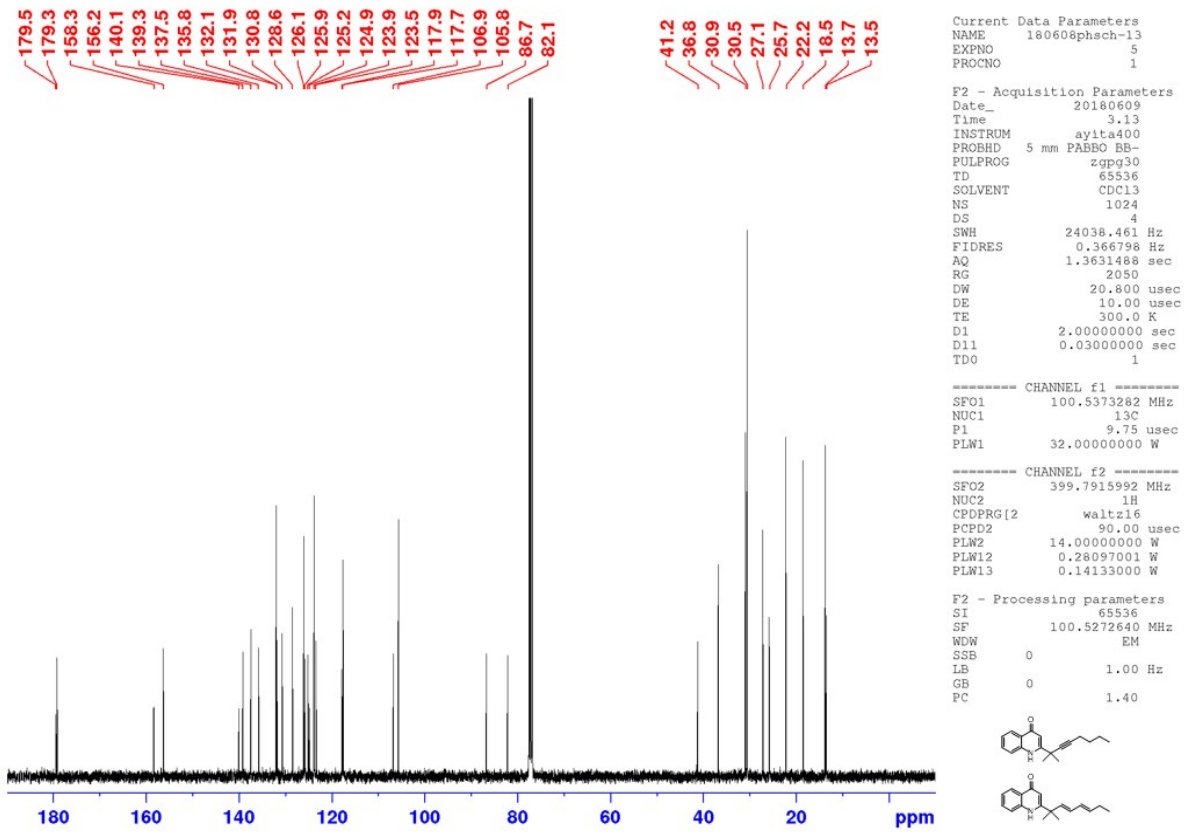


Figure S34. ^{13}C-NMR-spectra of **14 + 17** (1:0.5) in $CDCl_3$.

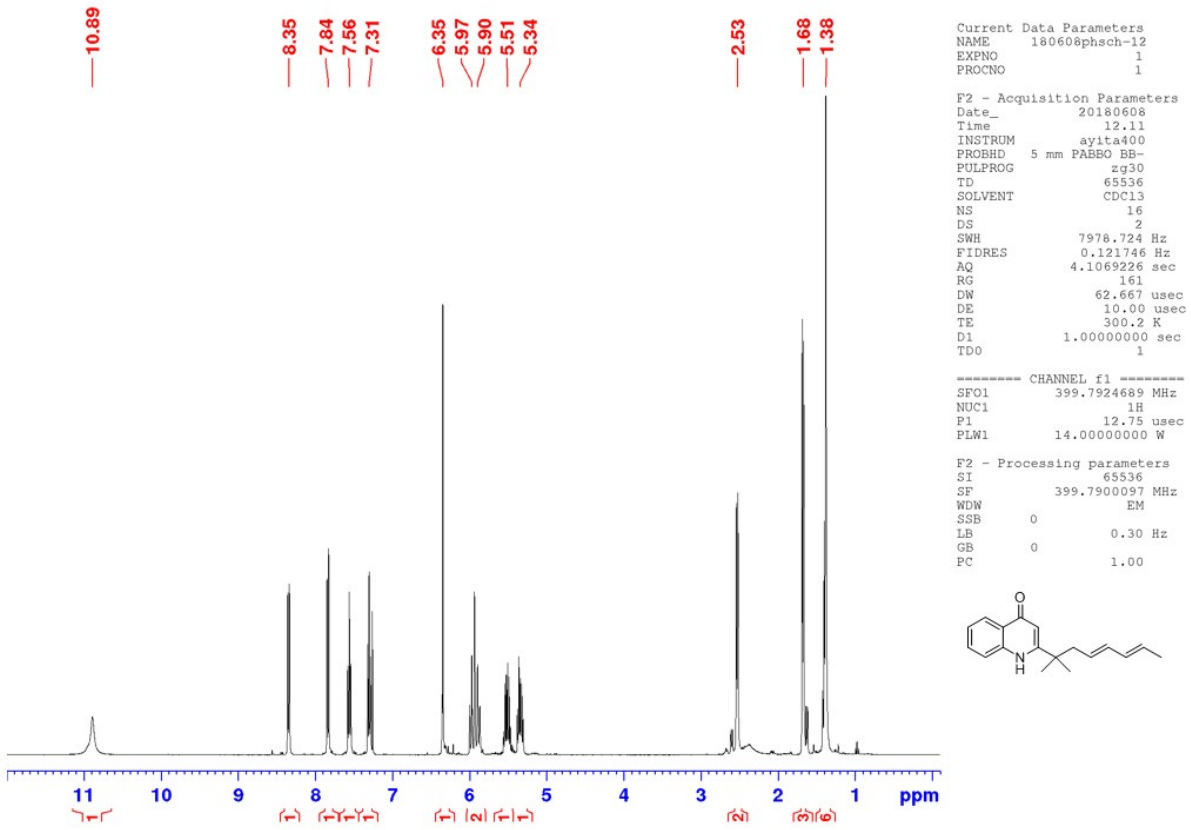


Figure S35. ^{1}H-NMR-spectra of **18** in $CDCl_3$.

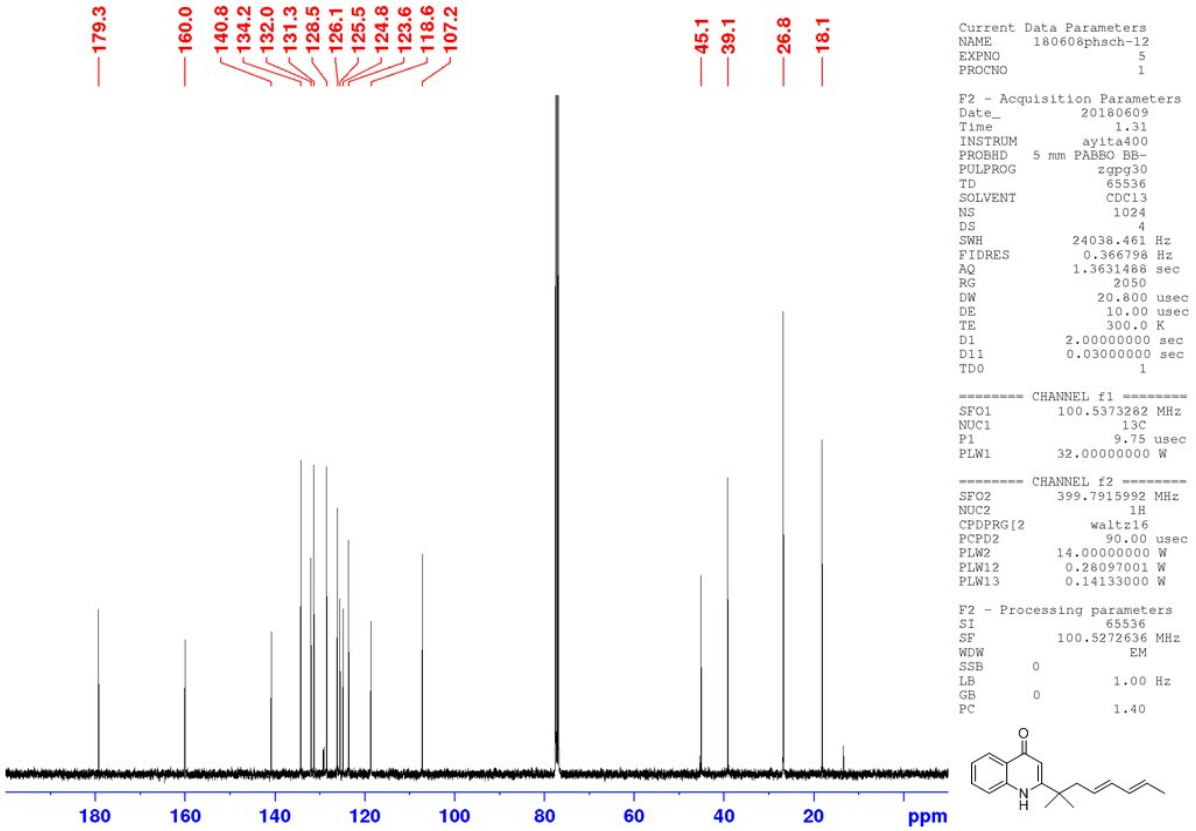


Figure S36. ^{13}C-NMR-spectra of **18** in $CDCl_3$.

6. References

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