Metal-Free Tandem Dehydrogenative *α*-Arylation Reaction of Propargylic Alcohols with 2-Alkynylbenzaldoximes toward the Synthesis of *α*-(4-Bromo-isoquinolin-1-yl)-propenone Skeletons

Khalil Alatat,[a] Alireza Abbasi Kejani,[a] Ali Nikbakht,[a] Hamid Reza Bijanzadeh,*[b] Saeed Balalaie*[a,c]

[a] Peptide Chemistry Research Center, K. N. Toosi University of Technology,P. O. Box 15875-4416, Tehran, Iran

[b] Department of Environmental Sciences, Faculty of Natural Resources and Marine Sciences, Tarbiat Modares University, Tehran, Iran

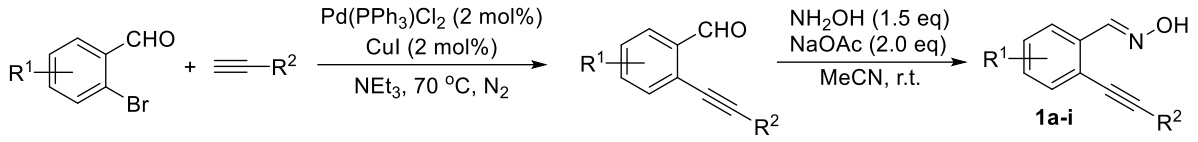
[c] Medical Biology Research Center, Kermanshah University of Medical Sciences, Kermanshah, Iran

Table of content

1. General methods

Commercially available reagents were purchased in reagent grades and used with no purification. Reaction progress was monitored by thin layer chromatography (TLC) using aluminum coated plates of silica gel 60-F254 detecting at 254 nm. Products 3 were purified via flash column chromatography using silica gel 63-200 mesh. Melting points were found by Electerothermal 9100 apparatus and are uncorrected. ^{1}H NMR spectra were recorded on Bruker 300 MHz, and ^{13}C NMR spectra were obtained by Bruker of 75 MHz. Chemical shifts are given parts per million (δ, ppm) and coupling constants are reported in Hertz (J, Hz). High resolution mass (ESI-HRMS) was obtained by Apex LCT Premier^{TM} XE spectrometer.

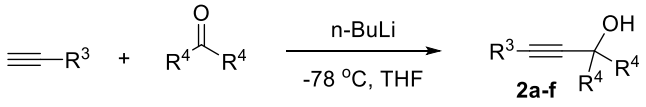
2. General Procedure for the Preparation of Substrates 1a-i[1]



Step 1: To a solution of the 2- bromobenzaldehyde S1 (10 mmol, 1 equiv.), $PdCl_2(PPh_3)_2$ (0.2 mol%), and CuI (0.2 mol%) in Et_3N (50 mL), the appropriate acetylene (1.5 equiv.) was added at room temperature under N_2 atmosphere. The reaction mixture was heated at 70 °C for 6-18 h, and monitored by TLC. After the reaction was completed, the mixture was cooled to room temperature, and filtered by celite, washed with acetone. The filtrate was concentrated under vacuum. The residue was purified by column chromatography on silica gel to afford the product S2 in almost 90% yield.

Step 2: A solution of 2-alkynylbenzaldehyde (2.0 mmol), hydroxylamine hydrochloride (3 mmol, 1.5 equiv), sodium acetate (4.0 mmol, 2.0 equiv) in ACN (10 mL) was stirred at room temperature for 12 hours. The solvent was evaporated and then quenched with water (10 mL), extracted with EtOAc (2×30 mL), dried by anhydrate Na_2SO_4. Evaporation of the solvent followed by purification on silica gel provided the corresponding 2-alkynylbenzaldoximes **1a-i**.

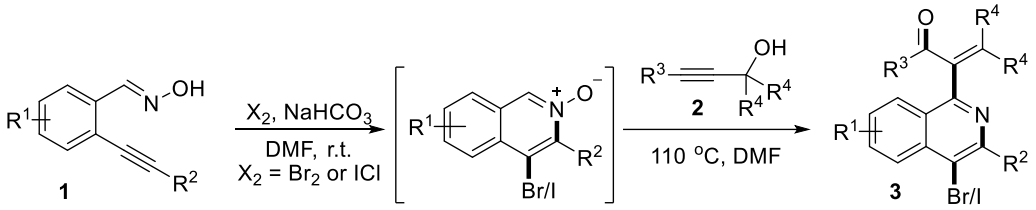
3. General Procedure for the Preparation of Substrates 2a-f[1]



To a stirring solution of aryl acetylene (5 mmol) in THF (1.0 M) was added dropwise *n*-BuLi (1.0 M in THF, 1.1 equiv) at −78 °C. Then, benzophenone derivatives (5 mmol) were added dropwise with stirring after 0.5 h. The solution was warming to room temperature after 1.0 h. After the reaction was completed as determined by TLC, the reaction mixture was quenched by addition of saturated aqueous ammonium chloride (10 mL) and extracted with ethyl acetate (3 × 15 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and

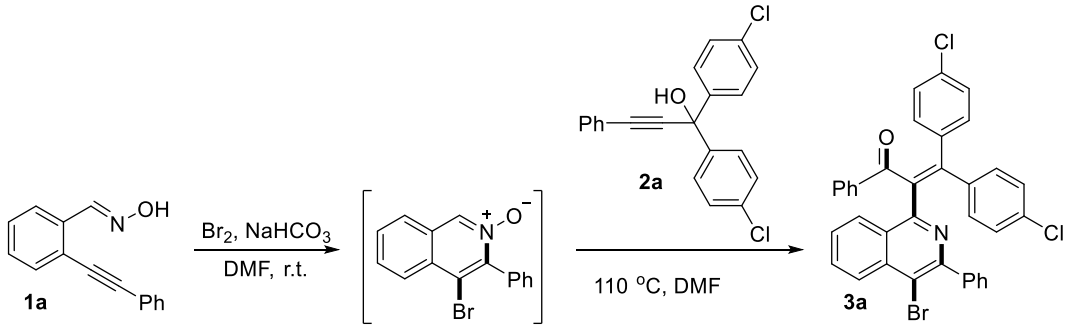
concentrated under reduced pressure. The crude material was purified by column chromatography on silica gel using petroleum ether/ethyl acetate to obtain the pure product propargylic alcohols **2a-f**.

4. Tandem reaction of 2-alkynylbenzaldoximes with propargylalcohols and Br_2 (or ICl)



2-Alkynylbenzaldoximes **1** (0.2 mmol) was added to a solution of $NaHCO_3$ (1.5 equiv.) and Br_2 (or ICl) (2.0 equiv.) in DMF (2 mL). Following 1 hour of stirring at room temperature and the formation of 4-bromoisoquinoline-*N*-oxides, propargyl alcohols **2** (0.2 mmol) was added, and the mixture was stirred at 110 °C. After completion of reaction as indicated by TLC, the mixture was diluted with ethyl acetate (5 mL) and quenched with water (5 mL). The organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash column chromatograph on silica gel (EtOAc /hexane = 1/20) to afford the product **3**.

5. Typical Procedure for the Synthesis of 3a on 1.0 mmol Scale



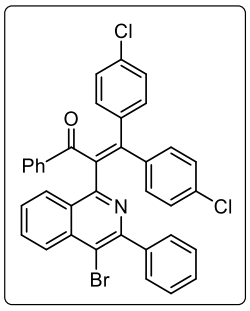
2-Alkynylbenzaldoximes **1a** (1.0 mmol) was added to a solution of $NaHCO_3$ (1.5 mmol, 126.0 mg) and Br_2 (2.0 mmol, 320.0 mg) in DMF (10 mL). Following 1 hour of stirring at room temperature and the formation of 4-bromoisoquinoline-N-oxides, propargyl alcohols **2a** (1.0 mmol, 352.0 mg) was added, and the mixture was stirred at 110 °C. After completion of reaction as indicated by TLC, the mixture was diluted with ethyl acetate (25 mL) and quenched with water (25 mL). The organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash column chromatograph on silica gel (EtOAc /hexane = 1/20) to afford the product **3a** (69% yield, 437 mg).

6. References

[1] 13 A. Nikbakht, S. Balalaie and B. Breit, *Org. Lett.*, 2019, **21**, 7645–7648.

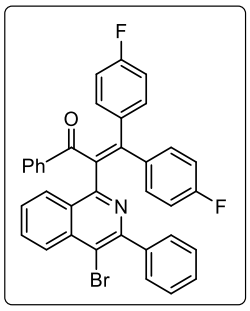
7. The spectroscopic data (1H, 13C NMR, and HRMS) of compounds

3a: 2-(4-bromo-3-phenylisoquinolin-1-yl)-3,3-bis(4-chlorophenyl)-1-phenylprop-2-en-1-one



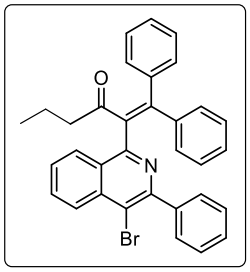
Yellow solid, m.p. 125-128 ℃, (95 mg, yield 75%), (silica gel, *n*-hexane/EtOAc = 20:1); **^{1}H NMR** (300 MHz, $CDCl_3$): δ_H (ppm) = 8.29 (d, *J* = 8.4 Hz, 1H), 8.24 (d, *J* = 8.2 Hz, 1H), 8.07 (dd, *J* = 8.3, 1.2 Hz, 2H), 7.72 (ddd, *J* = 8.4, 6.9, 1.3 Hz, 1H), 7.62 – 7.52 (m, 3H), 7.46 – 7.37 (m, 4H), 7.32 – 7.26 (m, 2H), 7.22 (d, *J* = 8.7 Hz, 2H), 7.16 (d, *J* = 8.7 Hz, 2H), 7.04 (s, 4H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ_C (ppm) = 197.3, 156.9, 151.1, 146.6, 140.3, 138.5, 138.5, 137.7, 137.2, 136.5, 134.8, 134.3, 132.9, 131.5, 131.5, 131.4, 130.2, 130.0, 128.5, 128.2, 128.2, 128.2, 127.6, 127.4, 127.3, 126.9, 117.9; **HRMS-ESI** (m/z): calcd. for $C_{36}H_{23}BrCl_2NO$ $[M+H]^+$ 634.0340, found 634.0334.

3b: 2-(4-bromo-3-phenylisoquinolin-1-yl)-3,3-bis(4-fluorophenyl)-1-phenylprop-2-en-1-one



Yellow solid, m.p. 115-118 ℃, (102 mg, yield 85%), (silica gel, *n*-hexane/EtOAc = 20:1); **^{1}H NMR** (300 MHz, $CDCl_3$): δ_H (ppm) = 8.28 (d, *J* = 8.5 Hz, 1H), 8.23 (d, *J* = 8.3 Hz, 1H), 8.05 (dd, *J* = 8.3, 1.3 Hz, 2H), 7.70 (ddd, *J* = 8.4, 6.9, 1.2 Hz, 1H), 7.66 – 7.61 (m, 2H), 7.53 (ddd, *J* = 8.1, 6.9, 1.1 Hz, 1H), 7.47 – 7.36 (m, 4H), 7.30 – 7.23 (m, 4H), 7.11 – 7.06 (m, 2H), 6.87 (t, *J* = 8.6 Hz, 2H), 6.74 (t, *J* = 8.7 Hz, 2H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ_C (ppm) = 197.8, 162.8 (d, $^1J_{C\text{-}F}$ = 249.5 Hz), 162.3 (d, $^1J_{C\text{-}F}$ = 249.4 Hz), 157.5, 151.0, 147.0, 140.4, 137.4, 137.0, 136.5, 136.3 (d, $^3J_{C\text{-}F}$ = 7.6), 136.3 (d, $^3J_{C\text{-}F}$ = 7.6), 132.7, 132.2, 132.1, 131.9, 131.4, 130.2, 129.9, 128.2, 128.1, 128.0, 127.3, 127.2, 127.0, 117.7, 115.3 (d, $^2J_{C\text{-}F}$ = 21.8 Hz), 115.0 (d, $^2J_{C\text{-}F}$ = 21.8 Hz); **HRMS-ESI** (m/z): calcd. for $C_{36}H_{23}BrF_2NO$ $[M+H]^+$ 602.0931, found 602.0923.

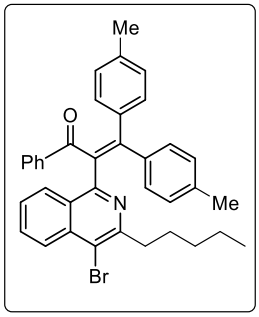
3c: 2-(4-bromo-3-phenylisoquinolin-1-yl)-1-phenyl-3,3-di-*p*-tolylprop-2-en-1-one



Yellow solid, m.p. 146-148 ℃, (92 mg, yield 86%), (silica gel, *n*-hexane/EtOAc = 20:1); **^{1}H NMR** (300 MHz, $CDCl_3$): δ_H (ppm) = 8.23 (d, *J* = 8.5 Hz, 1H), 8.08 (d, *J* = 8.3 Hz, 1H), 7.75 – 7.61 (m, 4H), 7.53 – 7.44 (m, 4H), 7.43 – 7.39 (m, 4H), 6.99 (s, 5H), 2.52 (brs, 2H), 1.52 (brs, 2H), 0.70 (t, *J* = 7.4 Hz, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ_C (ppm) = 207.3, 158.1, 151.0, 147.5, 140.6, 140.3, 138.8, 136.3, 131.3, 130.1, 130.1, 128.9, 128.5, 128.2,

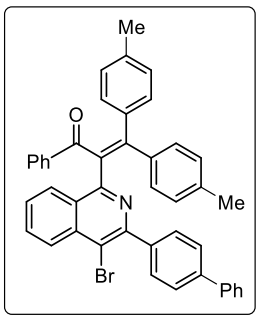
128.1, 127.9, 127.7, 127.6, 127.4, 127.2, 127.0, 127.0, 125.9, 117.6, 45.6, 17.4, 13.5; **HRMS-ESI** (m/z): calcd. for $C_{33}H_{27}BrNO$ $[M+H]^+$ 532.1276, found 532.1272.

3d: 2-(4-bromo-3-pentylisoquinolin-1-yl)-1-phenyl-3,3-di-*p*-tolylprop-2-en-1-one



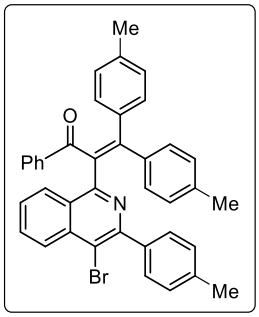
Yellow solid, m.p. 155-157 ℃, (99 mg, yield 81%), (silica gel, *n*-hexane/EtOAc = 20:1); **^{1}H NMR** (300 MHz, $CDCl_3$): δ_H (ppm) = 8.21 (d, *J* = 8.4 Hz, 1H), 8.12 – 8.02 (m, 3H), 7.57 (t, *J* = 7.1 Hz, 1H), 7.42 – 7.33 (m, 2H), 7.31 – 7.24 (m, 2H), 7.19 (d, J = 8.1 Hz, 2H), 6.96 (t, *J* = 8.7 Hz, 4H), 6.79 (d, *J* = 7.9 Hz, 2H), 3.11 (brs, 1H), 2.25 (s, 3H), 2.13 (s, 3H), 1.75 – 1.64 (m, 2H), 1.42 – 1.22 (m, 5H), 0.88 (t, J = 6.6 Hz, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ_C (ppm) = 198.4, 157.9, 153.5, 149.2, 138.5, 138.1, 138.0, 137.8, 136.0, 135.9, 132.2, 130.4, 130.2, 130.1, 130.0, 129.8, 129.7, 128.7, 128.5, 128.3, 127.8, 127.0, 126.9, 118.2, 37.4, 31.3, 28.2, 22.6, 21.3, 21.1, 14.1; **HRMS-ESI** (m/z): calcd. for $C_{37}H_{35}BrNO$ $[M+H]^+$ 558.1902, found 558.1895.

3e: 2-(3-([1,1'-biphenyl]-4-yl)-4-bromo-6-chloroisoquinolin-1-yl)-1-phenyl-3,3-di-p-tolylprop-2-en-1-one



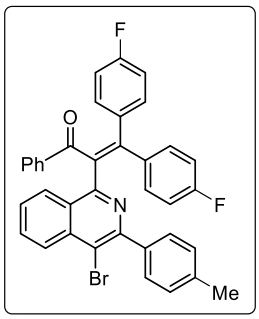
Yellow solid, m.p. 215-217 ℃, (93 mg, yield 69%), (silica gel, *n*-hexane/EtOAc = 20:1); **^{1}H NMR** (300 MHz, $CDCl_3$): δ_H (ppm) = 8.29 (t, *J* = 7.6 Hz, 2H), 8.08 (d, *J* = 7.8 Hz, 2H), 7.77 – 7.64 (m, 7H), 7.53 (d, *J* = 8.6 Hz, 1H), 7.49 (t, *J* = 7.8 Hz, 2H), 7.40 (d, *J* = 7.0 Hz, 1H), 7.34 (d, *J* = 6.8 Hz, 1H), 7.26 (t, *J* = 7.6 Hz, 2H), 7.20 (d, *J* = 7.7 Hz, 2H), 7.03 (d, *J* = 7.8 Hz, 2H), 6.98 (d, *J* = 7.8 Hz, 2H), 6.86 (d, *J* = 7.8 Hz, 2H), 2.25 (s, 3H), 2.19 (s, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ_C (ppm) = 198.4, 158.5, 150.5, 149.9, 140.9, 139.7, 138.6, 138.0, 138.0, 137.9, 136.6, 135.6, 132.3, 131.2, 130.8, 130.6, 130.5, 130.4, 130.0, 130.2, 128.8, 128.5, 128.3 127.9, 127.8, 127.6, 127.4, 127.4, 127.2, 127.1, 126.3, 117.4, 21.2, 21.1; **HRMS-ESI** (m/z): calcd. for $C_{44}H_{33}BrNO$ $[M+H]^+$ 670.1746, found 670.1738.

3f: 2-(4-bromo-3-(p-tolyl)isoquinolin-1-yl)-1-phenyl-3,3-di-p-tolylprop-2-en-1-one



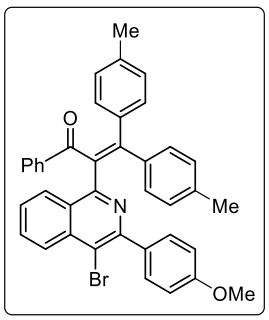
Yellow solid, m.p. 191-193 ℃, (85 mg, yield 70%), (silica gel, *n*-hexane/EtOAc = 20:1); **^{1}H NMR** (300 MHz, $CDCl_3$): δ_H (ppm) = 8.29 (d, *J* = 8.3 Hz, 1H), 8.25 (d, *J* = 8.5 Hz, 1H), 8.06 (d, *J* = 7.1 Hz, 2H), 7.65 (ddd, *J* = 8.4, 6.9, 1.3 Hz, 1H), 7.55 (d, *J* = 8.1 Hz, 2H), 7.53 – 7.46 (m, 1H), 7.36 – 7.31 (m, 1H), 7.30 – 7.19 (m, 4H), 7.19 (d, *J* = 8.0 Hz, 2H), 7.02 (d, *J* = 8.1 Hz, 2H), 6.97 (d, *J* = 7.9 Hz, 2H), 6.84 (d, *J* = 7.9 Hz, 2H), 2.44 (s, 3H), 2.25 (s, 3H), 2.17 (s, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ_C (ppm) = 198.4, 158.3, 150.9, 149.7, 138.5, 138.0, 137.9, 137.8, 136.5, 135.7, 132.2, 131.1, 130.4, 130.3, 130.2, 130.1, 129.9, 128.7, 128.5, 128.4, 128.4, 128.3, 127.8, 127.6, 127.5, 127.4, 127.0, 117.2, 21.4, 21.2, 21.1; **HRMS-ESI** (m/z): calcd. for $C_{39}H_{31}BrNO$ $[M+H]^+$ 608.1589, found 608.1586.

3g: 2-(4-bromo-3-(*p*-tolyl)isoquinolin-1-yl)-3,3-bis(4-fluorophenyl)-1-phenylprop-2-en-1-one



Yellow solid, m.p. 207-210 ℃, (99 mg, yield 81%), (silica gel, *n*-hexane/EtOAc = 20:1); **^{1}H NMR** (300 MHz, $CDCl_3$): δ_H (ppm) = 8.27 (d, *J* = 8.5 Hz, 1H), 8.22 (d, *J* = 8.3 Hz, 1H), 8.05 (d, *J* = 7.1 Hz, 2H), 7.69 (ddd, *J* = 8.4, 6.9, 1.3 Hz, 1H), 7.58 – 7.49 (m, 3H), 7.42 – 7.36 (m, 1H), 7.31 – 7.23 (m, 6H), 7.12 – 7.06 (m, 2H), 6.87 (t, *J* = 8.6 Hz, 2H), 6.74 (t, *J* = 8.7 Hz, 2H), 2.43 (s, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ_C (ppm) = 197.8, 162.8 (d, $^1J_{C\text{-}F}$ = 249.7 Hz), 162.3 (d, $^1J_{C\text{-}F}$ = 249.2 Hz), 157.4, 151.0, 146.8, 138.1, 137.6, 137.4, 136.6, 136.5 (d, $^3J_{C\text{-}F}$ = 8.8 Hz), 136.5 (d, $^3J_{C\text{-}F}$ = 8.8 Hz), 132.7, 132.2, 132.1, 131.9, 131.4, 130.1, 129.9, 128.4, 128.1, 127.9, 127.3, 127.1, 127.0, 117.5, 115.3 (d, $^2J_{C\text{-}F}$ = 21.8 Hz), 115.0 (d, $^2J_{C\text{-}F}$ = 21.8 Hz), 21.4; **HRMS-ESI** (m/z): calcd. for $C_{37}H_{25}BrF_2NO$ $[M+H]^+$ 616.1088, found 616.1084.

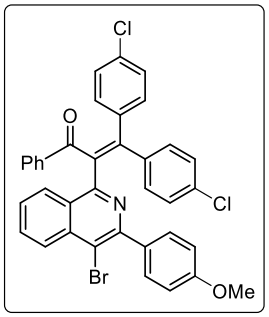
3h: 2-(4-bromo-3-(4-methoxyphenyl)isoquinolin-1-yl)-1-phenyl-3,3-di-p-tolylprop-2-en-1-one



Yellow solid, m.p. 203-206 ℃, (111 mg, yield 89%), (silica gel, *n*-hexane/EtOAc = 20:1); **^{1}H NMR** (300 MHz, $CDCl_3$): δ_H (ppm) = 8.26 (t, *J* = 9.3 Hz, 2H), 8.07 (d, *J* = 7.1 Hz, 2H), 7.70 – 7.58 (m, 3H), 7.48 (t, *J* = 7.7 Hz, 1H), 7.35 (t, *J* = 7.3 Hz, 1H), 7.29 – 7.17 (m, 4H), 7.05 – 6.93 (m, 6H), 6.84 (d, *J* = 7.9 Hz, 2H), 3.86 (s, 3H), 2.25 (s, 3H), 2.17 (s, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ_C (ppm) = 198.4, 159.5, 158.3,

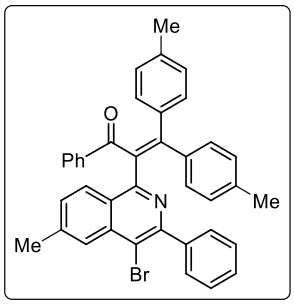
150.5, 149.6, 138.5, 138.0, 137.9, 137.8, 136.6, 135.6, 133.1, 132.2, 131.7, 131.1, 130.4, 130.3, 129.9, 128.7, 128.4, 127.9, 127.6, 127.4, 127.3, 127.0, 117.0, 112.9, 55.2, 21.2, 21.1; **HRMS-ESI** (m/z): calcd. for $C_{39}H_{31}BrNO_2$ $[M+H]^+$ 624.1538, found 624.1538.

3i: 2-(4-bromo-3-(4-methoxyphenyl)isoquinolin-1-yl)-3,3-bis(4-chlorophenyl)-1-phenylprop -2-en-1-one



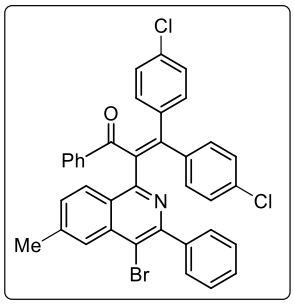
Yellow solid, m.p. 196-198 ℃, (121 mg, yield 91%), (silica gel, *n*-hexane/EtOAc = 20:1); **^{1}H NMR** (300 MHz, $CDCl_3$): δ_H (ppm) = 8.27 (d, *J* = 8.5 Hz, 1H), 8.21 (d, *J* = 8.2 Hz, 1H), 8.07 (d, *J* = 7.2 Hz, 2H), 7.69 (ddd, *J* = 8.4, 6.9, 1.3 Hz, 1H), 7.60 (d, *J* = 8.8 Hz, 2H), 7.52 (ddd, *J* = 8.2, 6.9, 1.2 Hz, 1H), 7.41 (t, *J* = 6.8 Hz, 1H), 7.29 (t, *J* = 7.7 Hz, 12H), 7.22 (d, *J* = 8.6 Hz, 2H), 7.16 (d, *J* = 8.7 Hz, 2H), 7.03 (s, 4H), 6.97 (d, *J* = 8.8 Hz, 2H), 3.87 (s, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ_C (ppm) = 197.5, 159.6, 156.8, 150.6, 146.4, 138.6, 138.5, 137.7, 137.2, 136.7, 134.8, 134.3, 132.9, 132.7, 131.6, 131.5, 131.5, 130.0, 128.5, 128.2, 128.2, 127.9, 127.4, 127.3, 127.0, 126.8, 117.5, 113.0, 55.3; **HRMS-ESI** (m/z): calcd. for $C_{37}H_{25}BrCl_2NO_2$ $[M+H]^+$ 664.0446, found 664.0438.

3j: 2-(4-bromo-6-methyl-3-phenylisoquinolin-1-yl)-1-phenyl-3,3-di-p-tolylprop-2-en-1-one



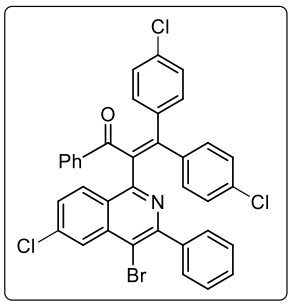
Yellow solid, m.p. 168-170 ℃, (89 mg, yield 73%), (silica gel, *n*-hexane/EtOAc = 20:1); **^{1}H NMR** (300 MHz, $CDCl_3$): δ_H (ppm) = 8.17 (d, *J* = 8.6 Hz, 1H), 8.08 – 8.01 (m, 3H), 7.63 – 7.54 (m, 2H), 7.44 – 7.29 (m, 5H), 7.23 (t, *J* = 7.5 Hz, 2H), 7.16 (d, *J* = 8.1 Hz, 2H), 7.00 (d, *J* = 8.1 Hz, 2H), 6.96 (d, *J* = 7.8 Hz, 2H), 6.85 (d, *J* = 7.9 Hz, 2H), 2.53 (s, 3H), 2.24 (s, 3H), 2.19 (s, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ_C (ppm) = 198.3, 157.9, 151.0, 149.7, 141.7, 140.8, 138.4, 138.0, 137.9, 137.9, 137.9, 136.6, 135.9, 132.2, 130.4, 130.3, 130.3, 130.0, 129.9, 129.1, 128.7, 128.4, 127.9, 127.8, 127.5, 127.2, 126.1, 116.8, 22.2, 21.2, 21.1; **HRMS-ESI** (m/z): calcd. for $C_{39}H_{31}BrNO$ $[M+H]^+$ 608.1589, found 608.1586.

3k: 2-(4-bromo-6-methyl-3-phenylisoquinolin-1-yl)-3,3-bis(4-chlorophenyl)-1-phenylprop -2-en-1-one



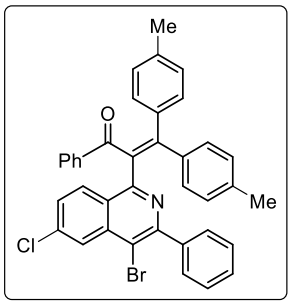
Yellow solid, m.p. 154-157 ℃, (96 mg, yield 74%), (silica gel, *n*-hexane/EtOAc = 20:1); **^{1}H NMR** (300 MHz, $CDCl_3$): δ_H (ppm) = 8.11 (d, *J* = 8.6 Hz, 1H), 8.08 – 8.02 (m, 3H), 7.63 – 7.51 (m, 3H), 7.43 – 7.36 (m, 3H), 7.36 – 7.24 (m, 3H), 7.20 (d, *J* = 8.8 Hz, 2H), 7.15 (d, *J* = 8.8 Hz, 2H), 7.03 (s, 4H), 2.55 (s, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ_C (ppm) = 197.4, 156.5, 151.1, 146.4, 142.2, 140.5, 138.6, 137.9, 137.2, 136.7, 134.8, 134.2, 132.9, 131.4, 131.4, 130.4, 130.1, 129.9, 128.5, 128.4, 128.2, 128.1, 127.6, 127.4, 126.7, 126.4, 125.7, 117.3, 22.2; **HRMS-ESI** (m/z): calcd. for $C_{37}H_{25}BrCl_2NO$ $[M+H]^+$ 648.0497, found 648.0496.

3l: 2-(4-bromo-6-chloro-3-phenylisoquinolin-1-yl)-3,3-bis(4-chlorophenyl)-1-phenylprop -2-en-1-one



Yellow solid, m.p. 135-137 ℃, (122 mg, yield 91%), (silica gel, *n*-hexane/EtOAc = 20:1); **^{1}H NMR** (300 MHz, $CDCl_3$): δ_H (ppm) = 8.30 (d, *J* = 2.1 Hz, 1H), 8.18 (d, *J* = 8.9 Hz, 1H), 8.05 (d, *J* = 8.4 Hz, 2H), 7.94 (d, *J* = 8.7 Hz, 1H), 7.62 – 7.56 (m, 2H), 7.45 – 7.40 (m, 4H), 7.37 – 7.27 (m, 4H), 7.19 – 7.13 (m, 4H), 7.07 – 7.03 (m, 4H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ_C (ppm) = 197.3, 157.0, 152.3, 146.6, 140.0, 138.3, 137.9, 137.1, 135.7, 135.0, 133.1, 131.4, 131.4, 131.0, 130.1, 129.9, 129.8, 128.8, 128.7, 128.5, 128.5, 128.3, 128.2, 127.7, 126.6, 125.5, 124.4, 116.4; **HRMS-ESI** (m/z): calcd. for $C_{36}H_{22}BrCl_3NO$ $[M+H]^+$ 667.9950, found 667.9947.

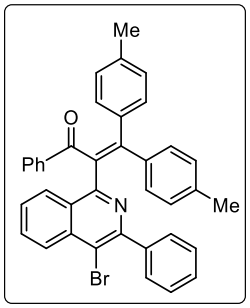
3m: 2-(4-bromo-6-chloro-3-phenylisoquinolin-1-yl)-1-phenyl-3,3-di-p-tolylprop-2-en-1-one



Yellow solid, m.p. 196-198 ℃, (101 mg, yield 80%), (silica gel, *n*-hexane/EtOAc = 20:1); **^{1}H NMR** (300 MHz, $CDCl_3$): δ_H (ppm) = 8.26 (d, *J* = 2.0 Hz, 1H), 8.20 (d, *J* = 8.9 Hz, 1H), 8.04 – 7.95 (m, 3H), 7.65 – 7.61 (m, 2H), 7.44 – 7.37 (m, 3H), 7.23 (t, *J* = 7.5 Hz, 2H), 7.17 – 7.07 (m, 3H), 6.98 (d, *J* = 8.2 Hz, 2H), 6.95 (d, *J* = 7.9 Hz, 2H), 6.85 (d, *J* = 8.0 Hz, 2H), 2.23 (s, 3H), 2.19 (s, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ_C (ppm) = 198.3, 158.5, 152.0, 149.9, 140.2, 138.7, 138.2, 137.8, 137.5, 137.4, 132.9, 132.4, 132.3, 130.4, 130.3, 130.2, 129.9, 129.3, 128.7, 128.6, 128.6, 128.4, 128.3,

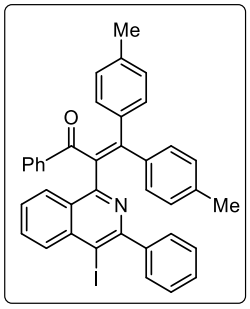
127.9, 127.6, 126.3, 125.7, 115.9, 21.2, 21.1; **HRMS-ESI** (m/z): calcd. for $C_{38}H_{28}BrClNO$ $[M+H]^+$ 628.1043, found 628.1035.

3n: 2-(4-bromo-3-phenylisoquinolin-1-yl)-1-phenyl-3,3-di-*p*-tolylprop-2-en-1-one



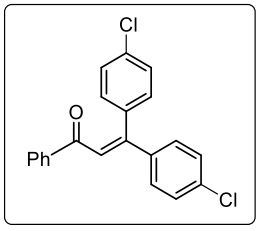
Yellow solid, m.p. 198-200 ℃, (84 mg, yield 71%), (silica gel, *n*-hexane/EtOAc = 20:1); **^{1}H NMR** (300 MHz, $CDCl_3$): δ_H (ppm) = 8.30 – 8.22 (m, 2H), 8.07 – 8.00 (m,2H), 7.67 – 7.54 (m, 3H), 7.46 – 7.31 (m, 5H), 7.27 – 7.13 (m, 4H), 7.01 – 6.91 (m, 4H), 6.84 (d, *J* = 8.6 Hz, 2H), 2.24 (s, 3H), 2.18 (s, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ_C (ppm) = 198.3, 158.4, 150.9, 149.9, 140.6, 138.5, 137.9, 137.8, 136.4, 135.6, 132.2, 131.1, 130.4, 130.3, 130.1, 129.9, 129.7, 129.2, 129.1, 128.7, 128.4, 128.0, 127.8, 127.8, 127.5, 127.4, 127.0, 117.3, 21.2, 21.1; **HRMS-ESI** (m/z): calcd. for $C_{38}H_{29}BrNO$ $[M+H]^+$ 594.1433, found 594.1425.

3n′: 2-(4-iodo-3-phenylisoquinolin-1-yl)-1-phenyl-3,3-di-p-tolylprop-2-en-1-one



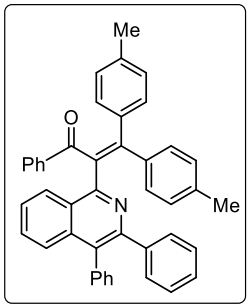
Yellow solid, m.p. 204-206 ℃, (83 mg, yield 65%), (silica gel, *n*-hexane/EtOAc = 20:1); **^{1}H NMR** (300 MHz, $CDCl_3$): δ_H (ppm) = 8.27 (d, *J* = 8.3 Hz, 1H), 8.16 (d, *J* = 8.5 Hz, 1H), 8.05 (dd, *J* = 7.1, 1.6 Hz, 2H), 7.64 (ddd, *J* = 8.4, 6.9, 1.4 Hz, 1H), 7.55 – 7.48 (m, 3H), 7.46 – 7.39 (m, 3H), 7.33 (t, *J* = 7.3 Hz, 1H), 7.27 – 7.16 (m, 4H), 7.04 – 6.95 (m, 4H), 6.85 (d, *J* = 7.9 Hz, 2H), 2.24 (s, 3H), 2.18 (s, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ_C (ppm) = 198.3, 159.3, 155.8, 150.0, 143.6, 139.0, 138.6, 138.0, 137.9, 137.9, 135.6, 132.7, 132.2, 131.5, 130.4, 130.3, 130.2, 130.0, 129.9, 129.7, 128.8, 128.7, 128.4, 128.0, 127.9, 127.5, 127.2, 97.4, 21.3, 21.2; **HRMS-ESI** (m/z): calcd. for $C_{38}H_{29}INO$ $[M+H]^+$ 642.1294, found 642.1287.

4a: 2-(4-bromo-6-chloro-3-phenylisoquinolin-1-yl)-1-phenyl-3,3-di-p-tolylprop-2-en-1-one



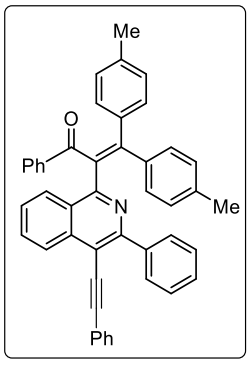
Yellow solid, mp 101-103 ℃, (51 mg, yield 80%), (silica gel, *n*-hexane/EtOAc = 20:1); **^{1}H NMR** (300 MHz, $CDCl_3$): δ_H (ppm) = 7.92 (d, *J* = 7.0 Hz, 2H), 7.54 (t, *J* = 7.4 Hz, 1H), 7.46 – 7.38 (m, 3H), 7.36 – 7.26 (m, 5H), 7.15 – 7.09 (m, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ_C (ppm) = 192.0, 152.3, 139.4, 137.8, 136.9, 135.7, 134.6, 133.0, 131.0, 129.7, 128.8, 128.6, 128.5, 128.5, 124.4; **HRMS-ESI** (m/z): calcd. for $C_{21}H_{15}Cl_2O$ $[M+H]^+$ 353.0500, found 353.0495.

5c: 2-(3,4-diphenylisoquinolin-1-yl)-1-phenyl-3,3-di-p-tolylprop-2-en-1-one



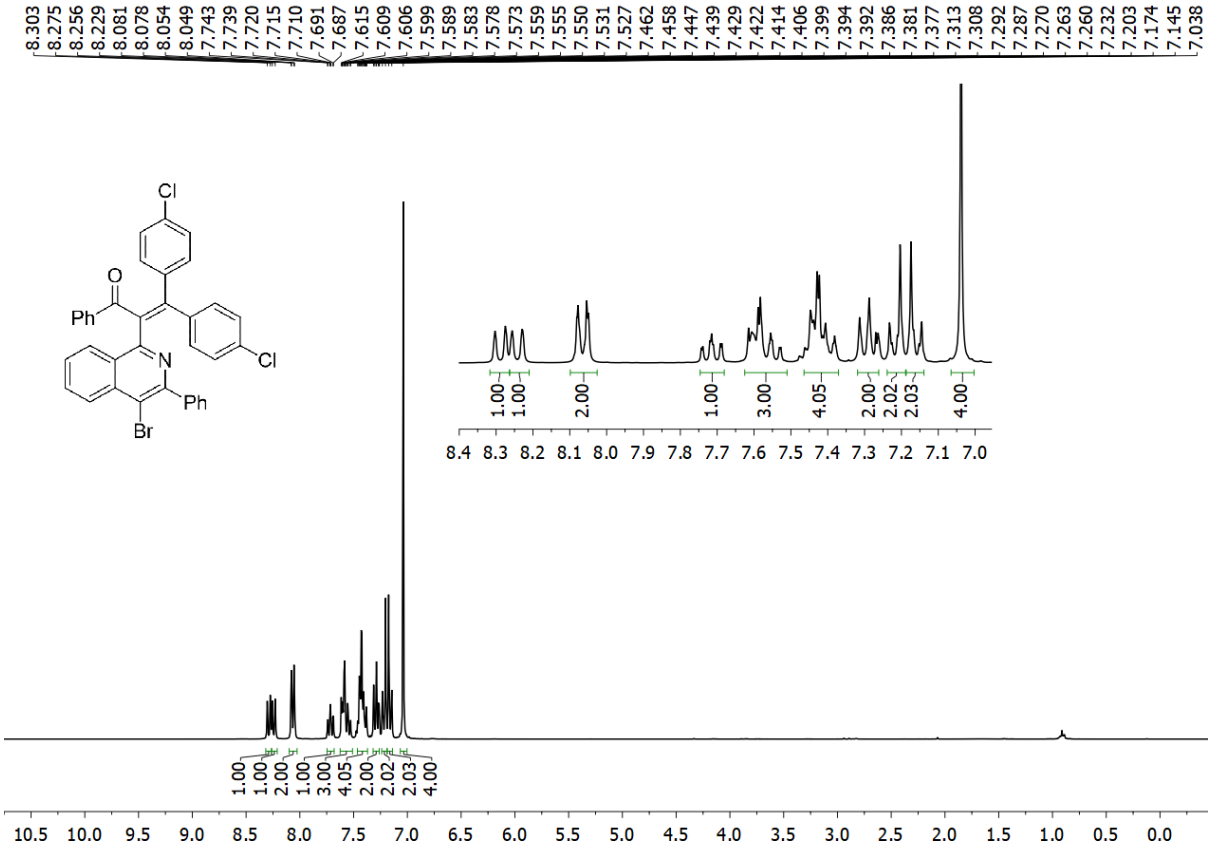
Yellow solid, m.p. 93-95 ℃, (68 mg, yield 58%), (silica gel, *n*-hexane/EtOAc = 30:1); **^{1}H NMR** (300 MHz, $CDCl_3$): δ_H (ppm) = 8.36 – 8.26 (m, 1H), 8.15 – 8.08 (m, 2H), 7.56 – 7.50 (m, 1H), 7.47 – 7.38 (m, 3H), 7.38 – 7.30 (m, 4H), 7.30 – 7.22 (m, 3H), 7.21 – 7.17 (m, 4H), 7.17 – 7.09 (m, 3H), 7.05 (d, *J* = 8.1 Hz, 2H), 6.97 (d, *J* = 7.8 Hz, 2H), 6.85 (d, *J* = 8.0 Hz, 2H), 2.25 (s, 3H), 2.19 (s, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ_C (ppm) = 198.9, 158.6, 150.5, 148.9, 140.6, 138.3, 138.2, 138.1, 137.7, 137.6, 136.8, 136.4, 132.1, 131.3, 130.5, 130.1, 130.0, 129.9, 129.7, 128.7, 128.6, 128.3, 128.2, 127.8, 127.3, 127.2, 127.0, 126.8, 126.7, 126.1, 125.7, 125.3, 21.2, 21.2; **HRMS-ESI** (m/z): calcd. for $C_{44}H_{34}NO$ $[M+H]^+$ 592.2640, found 592.2631.

5c′: 1-phenyl-2-(3-phenyl-4-(phenylethynyl)isoquinolin-1-yl)-3,3-di-p-tolylprop-2-en-1-one

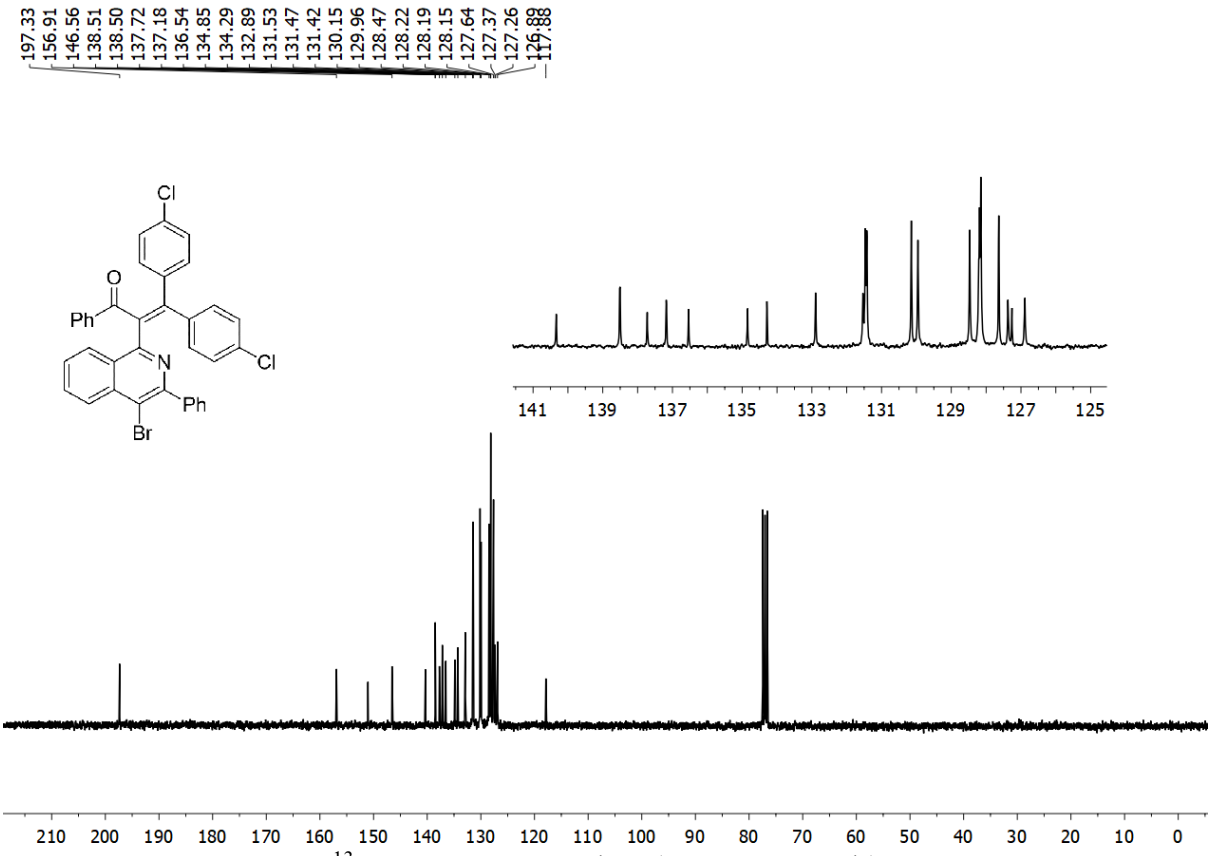


Yellow solid, m.p. 95-98 ℃, (76 mg, yield 62%), (silica gel, *n*-hexane/EtOAc = 30:1); **^{1}H NMR** (300 MHz, $CDCl_3$): δ_H (ppm) = 8.44 (d, *J* = 7.8 Hz, 1H), 8.30 (d, *J* = 8.1 Hz, 1H), 8.14 – 8.07 (m, 4H), 7.67 (ddd, *J* = 8.4, 6.8, 1.3 Hz, 1H), 7.59 – 7.54 (m, 2H), 7.51 – 7.42 (m, 4H), 7.41 – 7.35 (m, 4H), 7.30 (d, J = 7.8 Hz, 2H), 7.23 (d, *J* = 8.1 Hz, 2H), 7.02 (t, *J* = 8.3 Hz, 4H), 6.85 (d, *J* = 7.9 Hz, 2H), 2.27 (s, 3H), 2.17 (s, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ_C (ppm) = 198.6, 158.8, 152.9, 149.6, 139.9, 138.5, 138.2, 138.1, 138.0, 137.5, 136.2, 132.2, 131.5, 131.4, 130.5, 130.2, 130.0, 129.9, 129.7, 128.8, 128.7, 128.6, 128.5, 128.4, 127.9, 127.6, 127.4, 127.4, 125.8, 125.4, 123.3, 111.5, 99.3, 86.5, 21.3, 21.1; **HRMS-ESI** (m/z): calcd. for $C_{46}H_{34}NO$ $[M+H]^+$ 616.2640, found 616.2631.

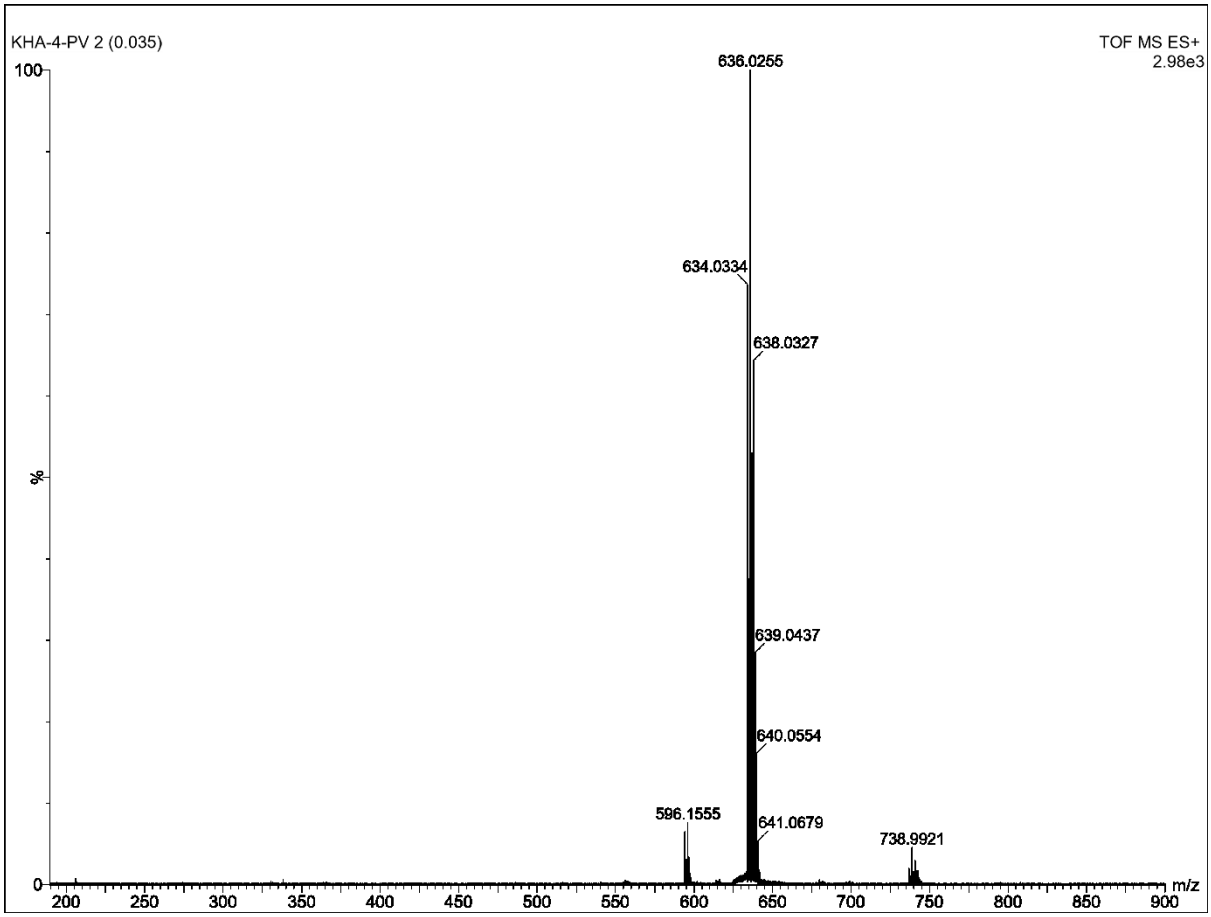
8. ^{1}H, ^{13}C NMR, and HRMS spectra



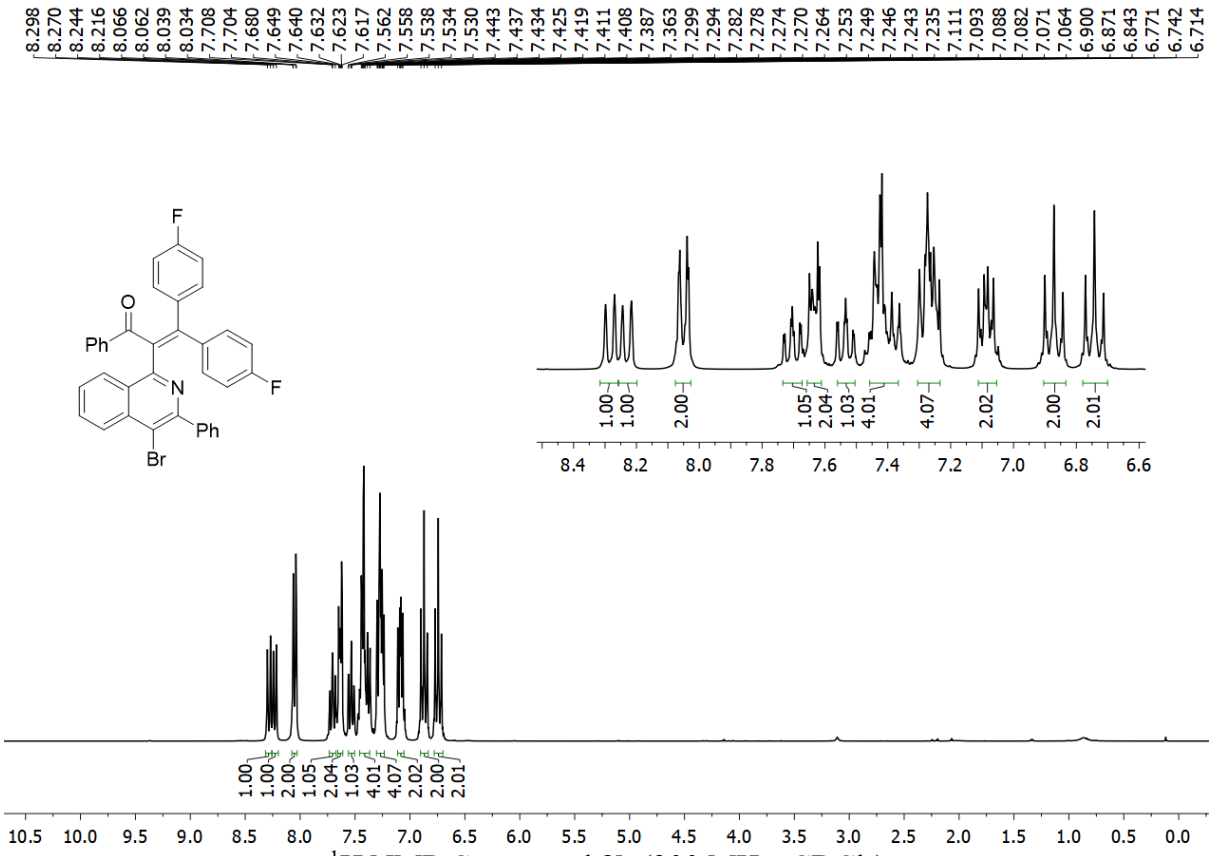
^{1}H NMR Compound **3a** (300 MHz, $CDCl_3$)



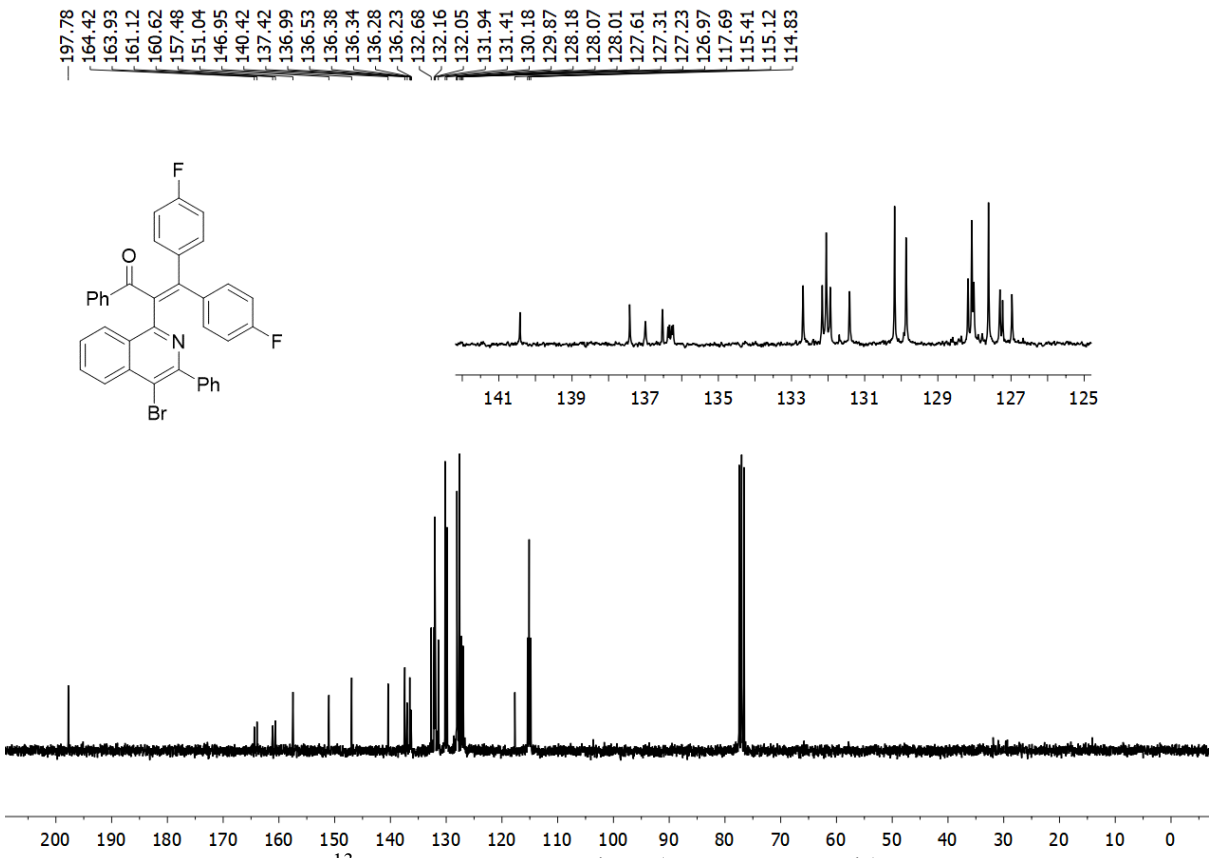
^{13}C NMR Compound **3a** (75 MHz, $CDCl_3$)



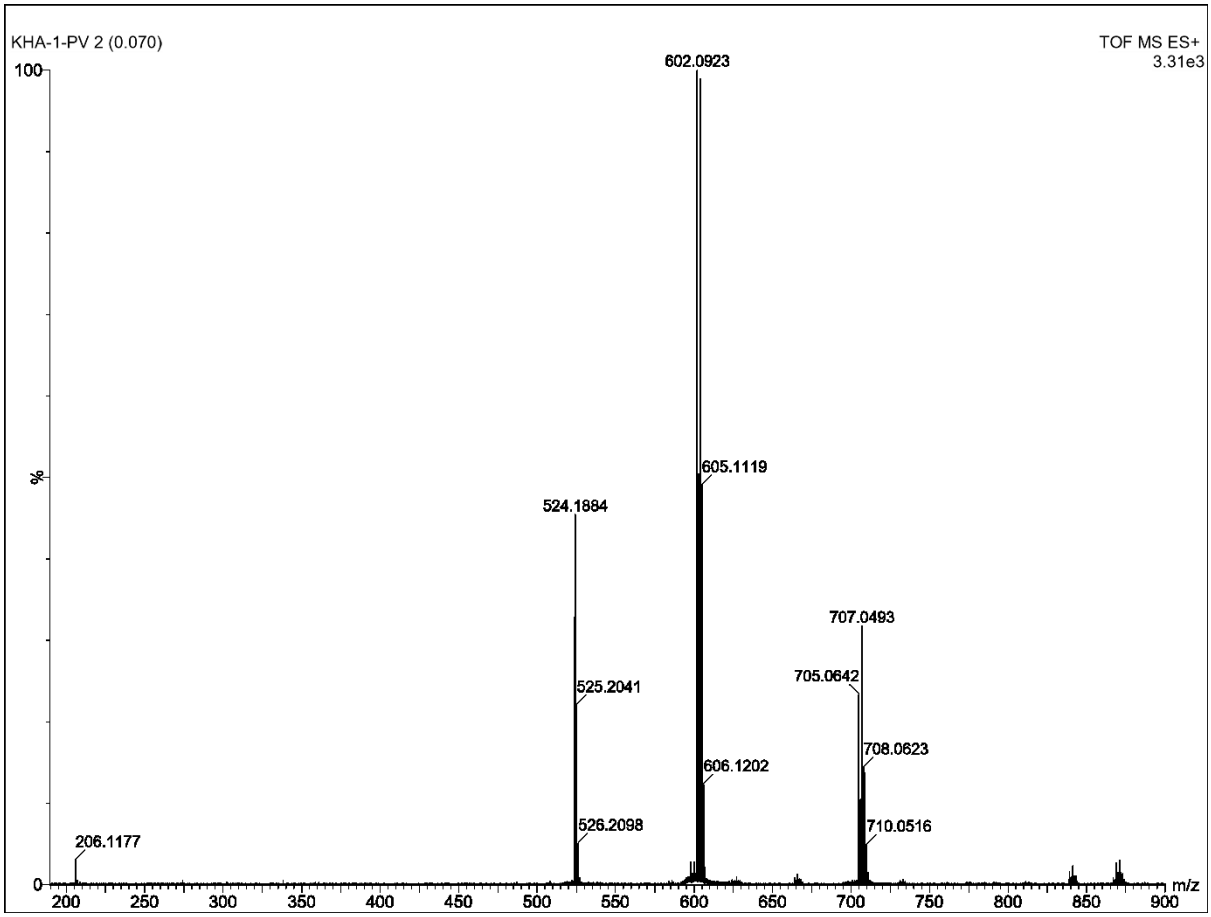
HRMS-ESI Compound **3a**



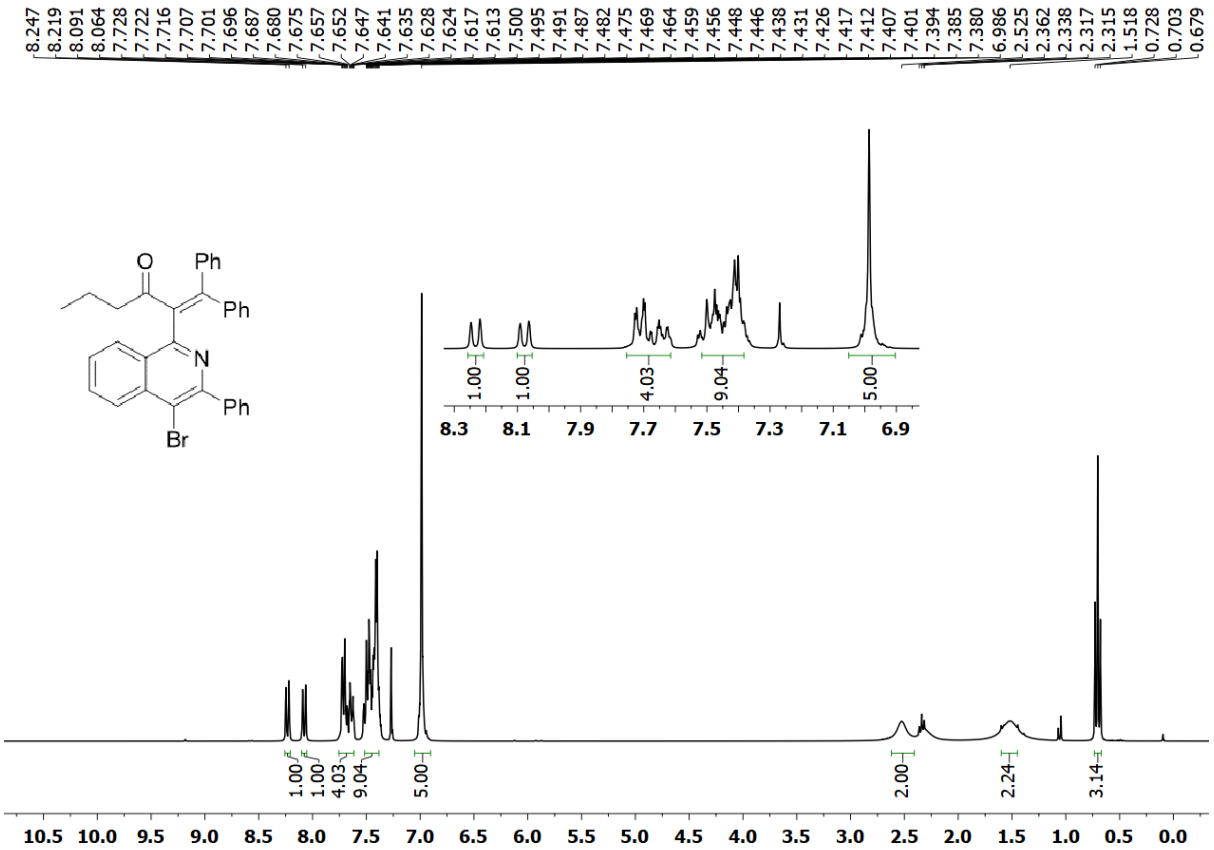
^{1}H NMR Compound **3b** (300 MHz, $CDCl_3$)



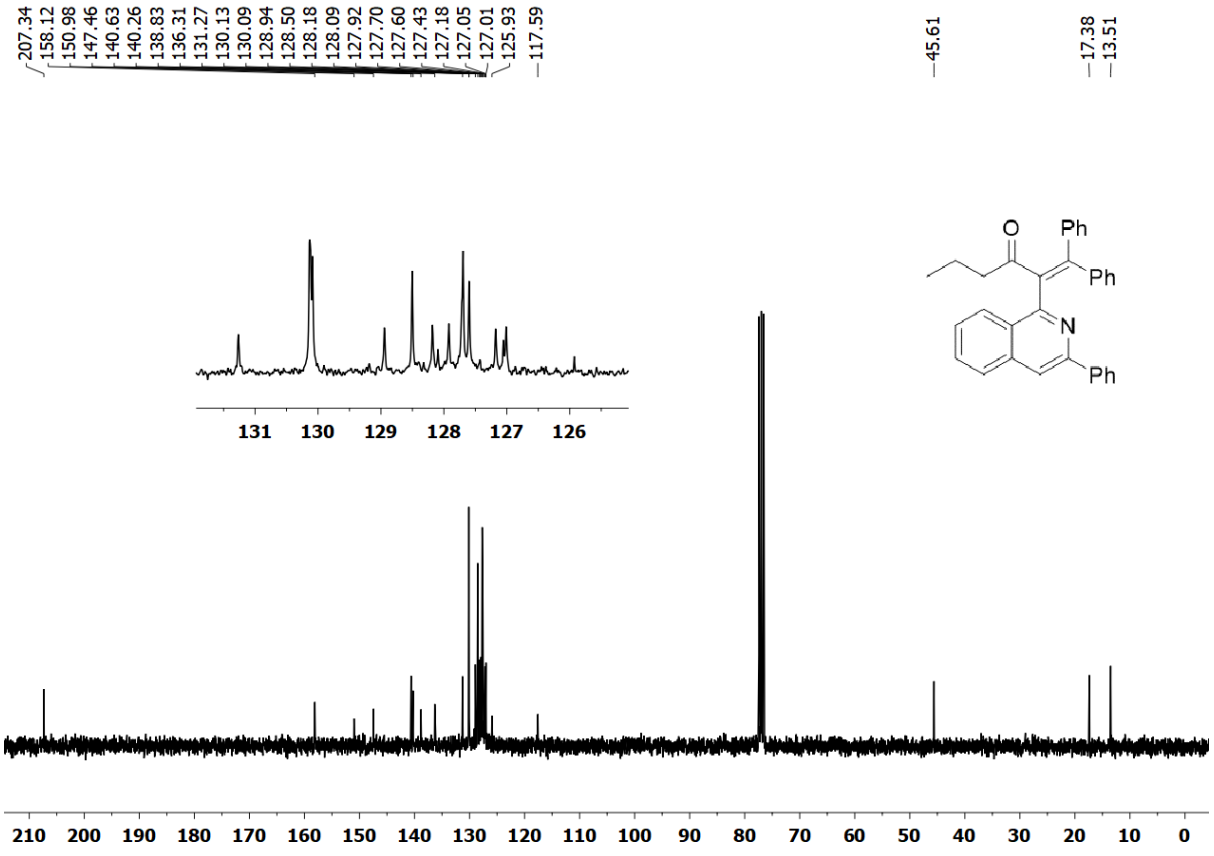
^{13}C NMR Compound **3b** (75 MHz, $CDCl_3$)



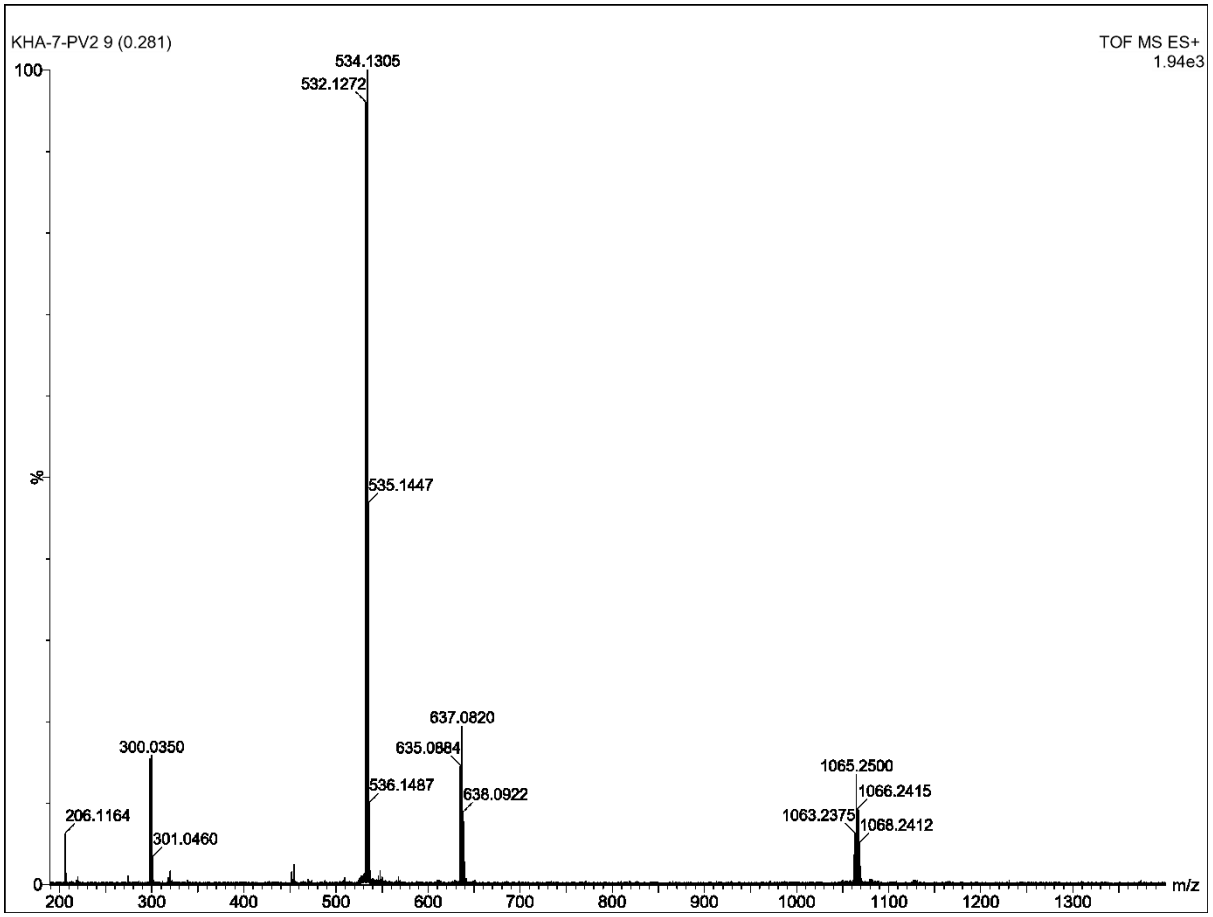
HRMS-ESI Compound **3b**



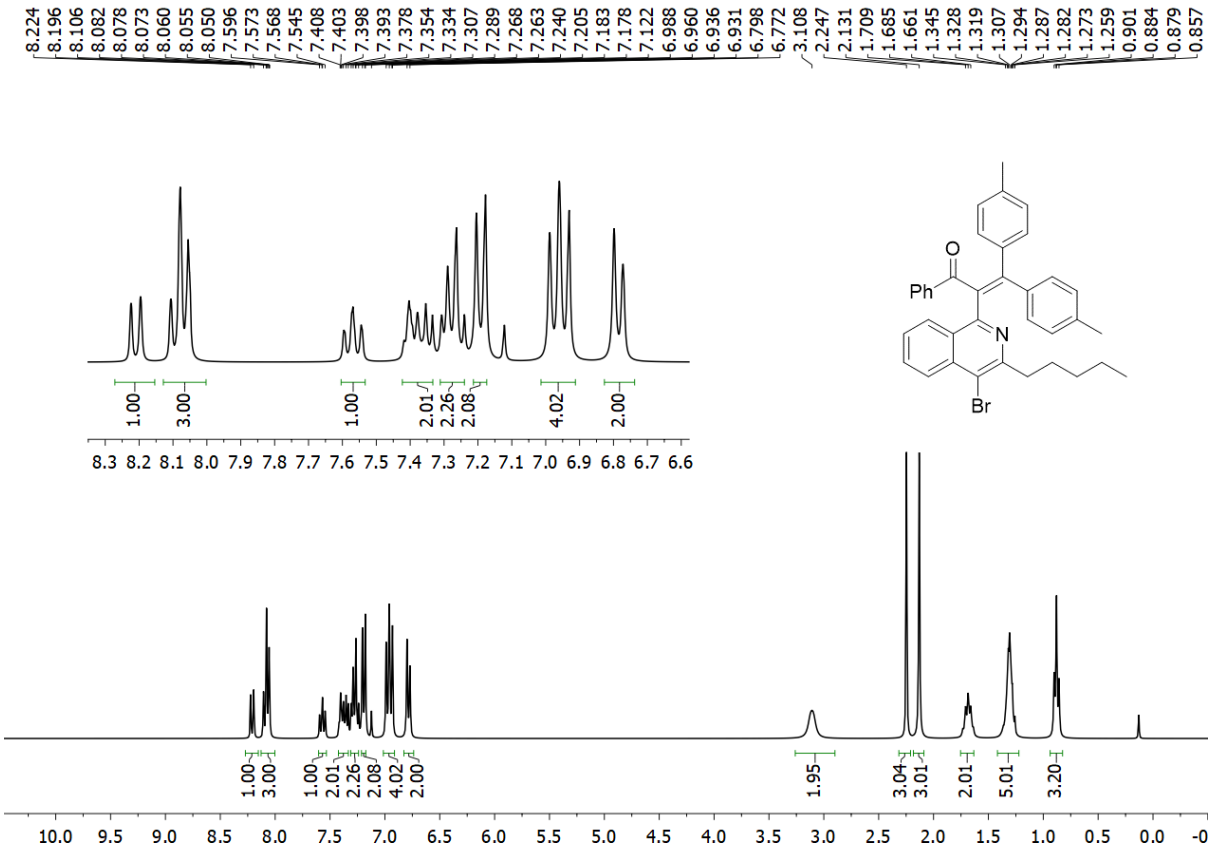
^{1}H NMR Compound **3c** (300 MHz, $CDCl_3$)



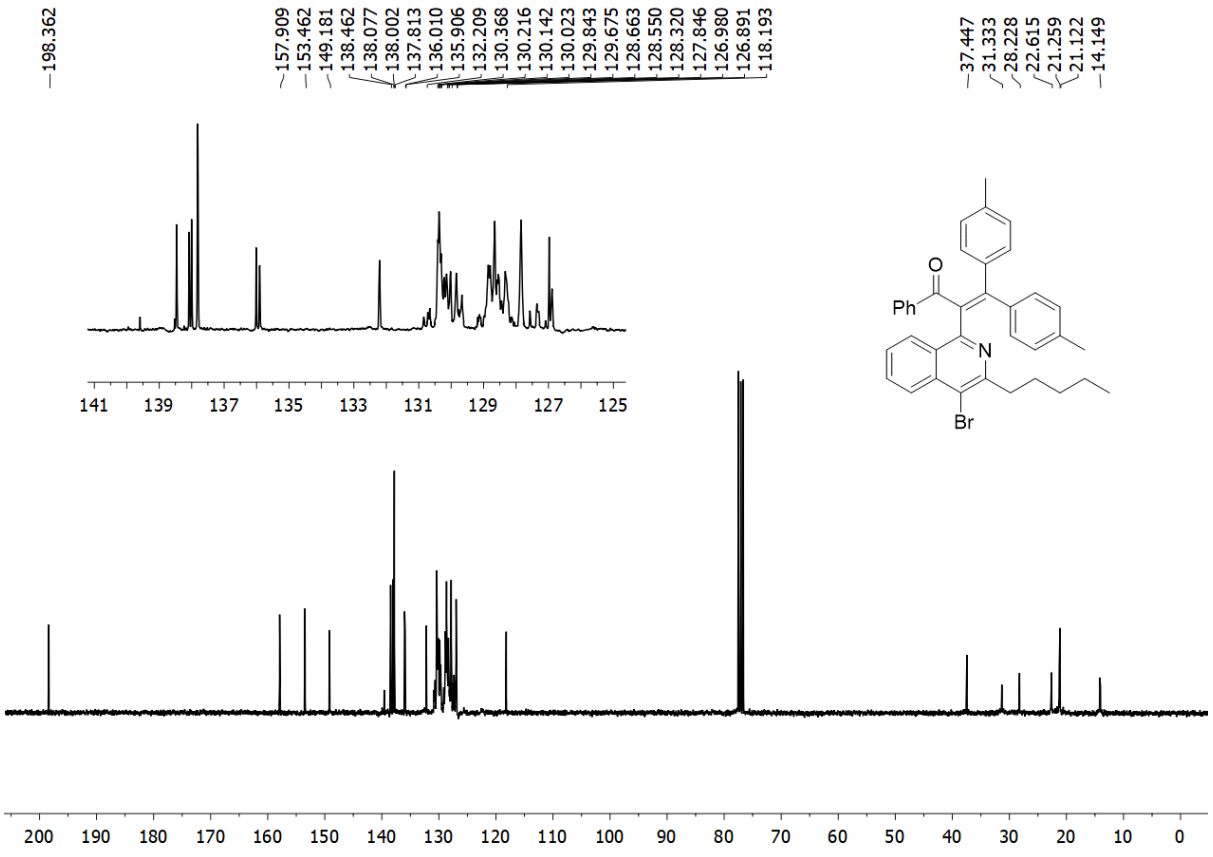
^{13}C NMR Compound **3c** (75 MHz, $CDCl_3$)



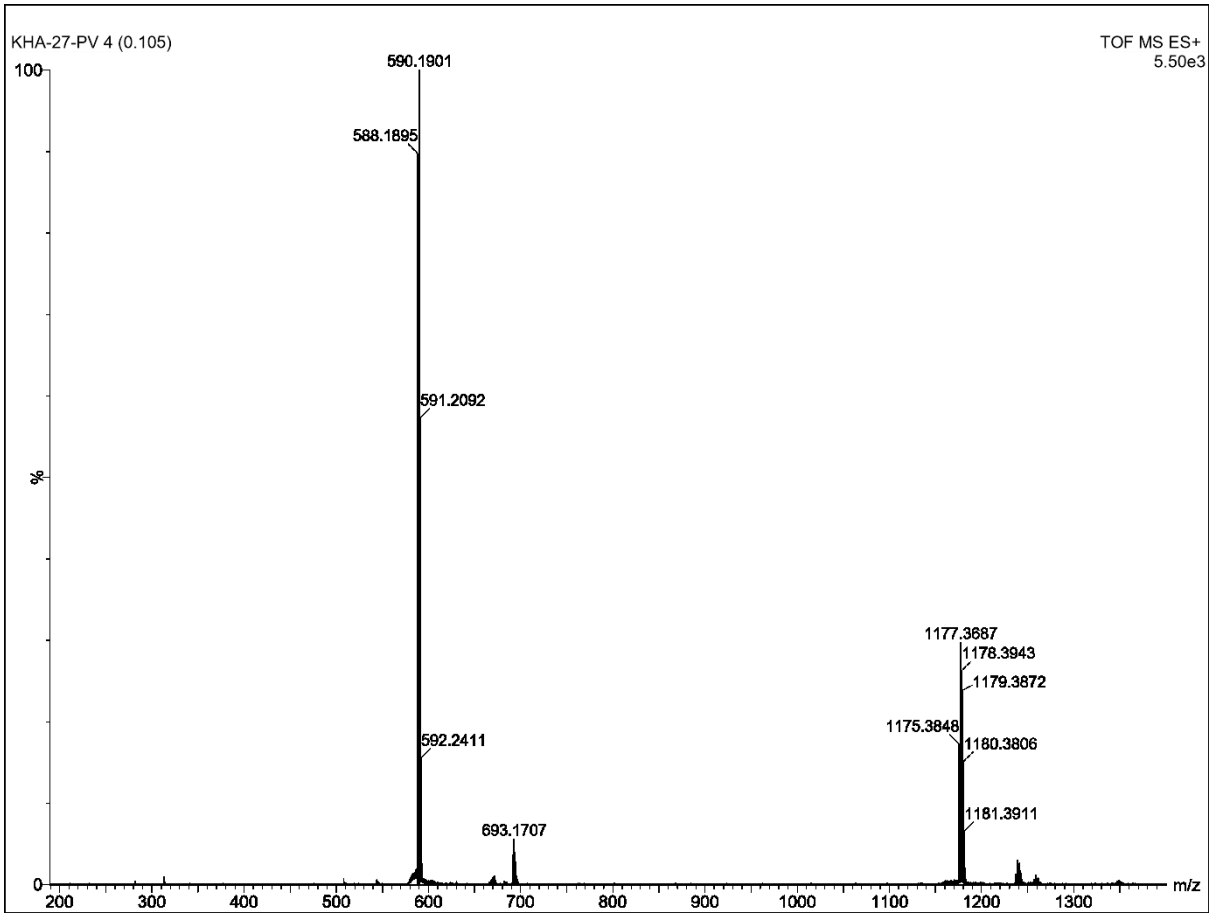
HRMS-ESI Compound **3c**



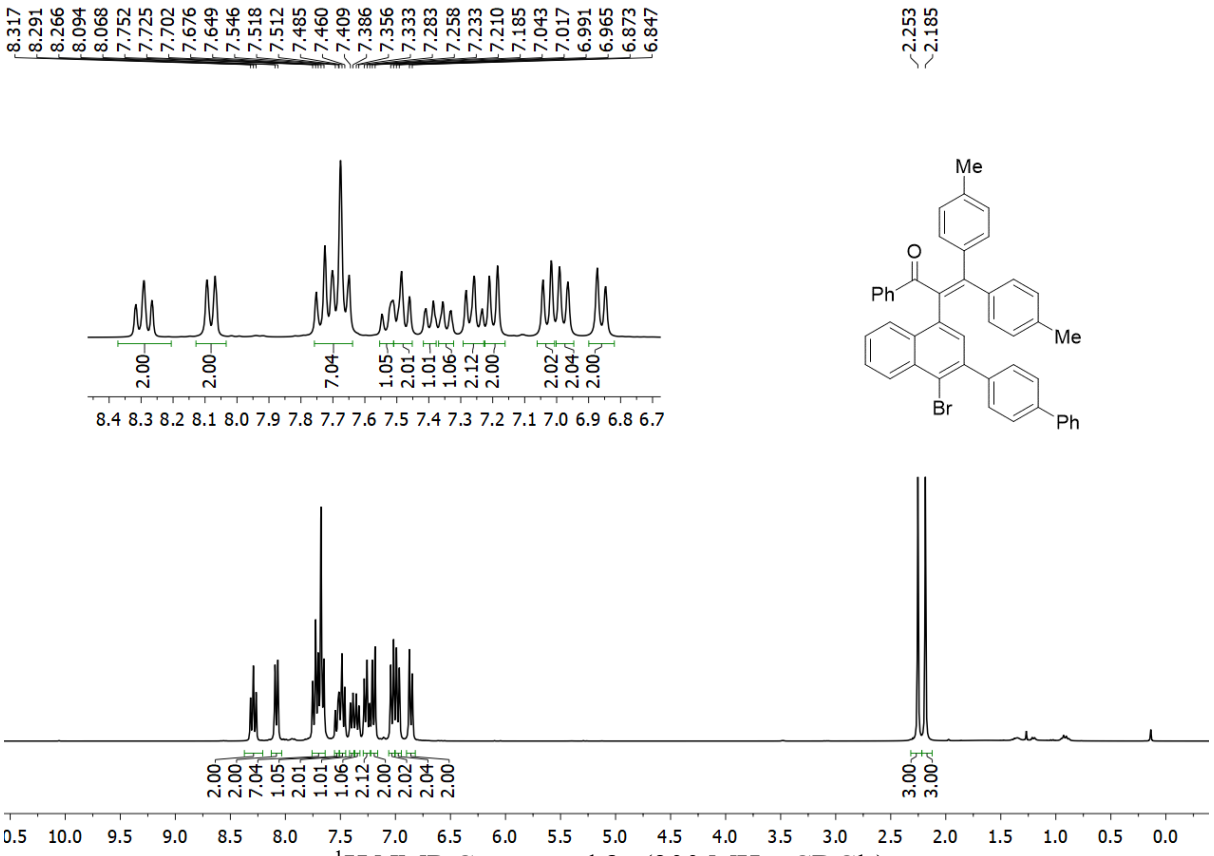
^{1}H NMR Compound **3d** (300 MHz, $CDCl_3$)



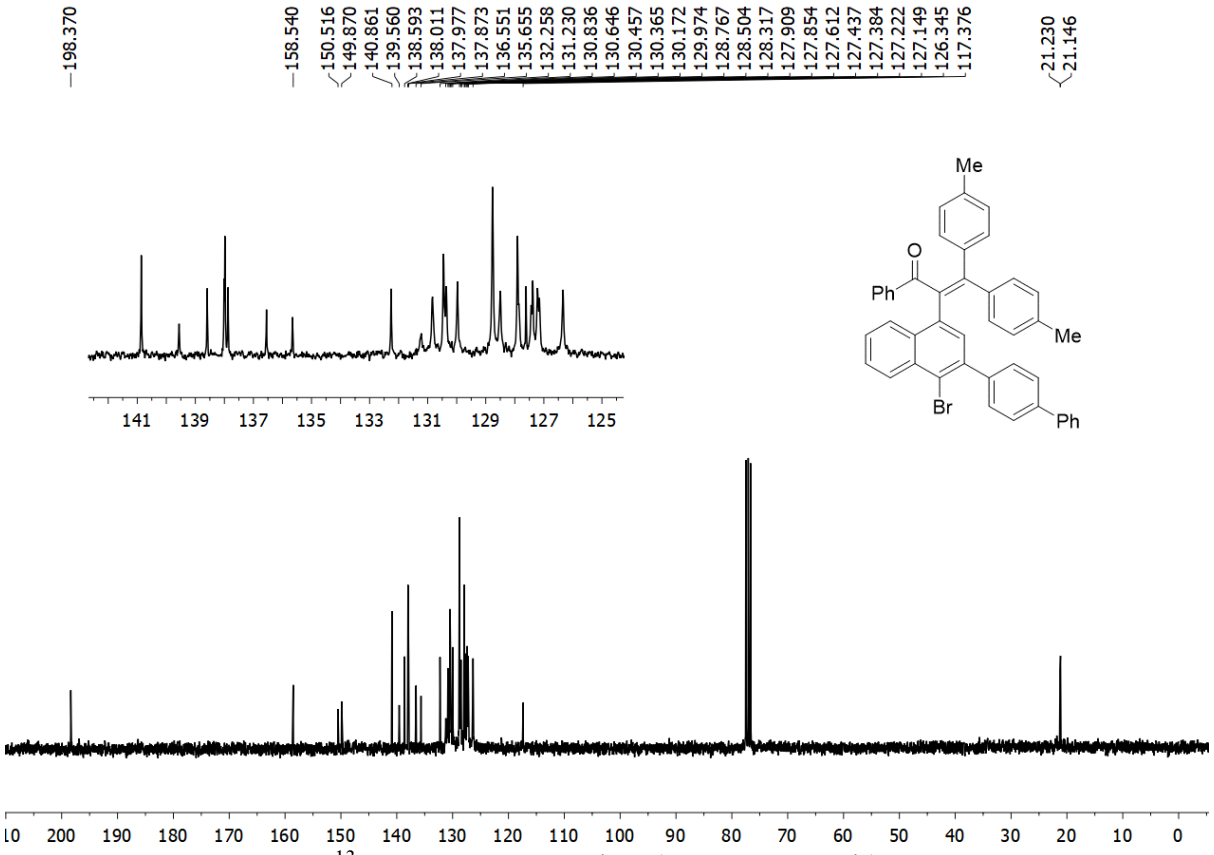
^{13}C NMR Compound **3d** (75 MHz, $CDCl_3$)



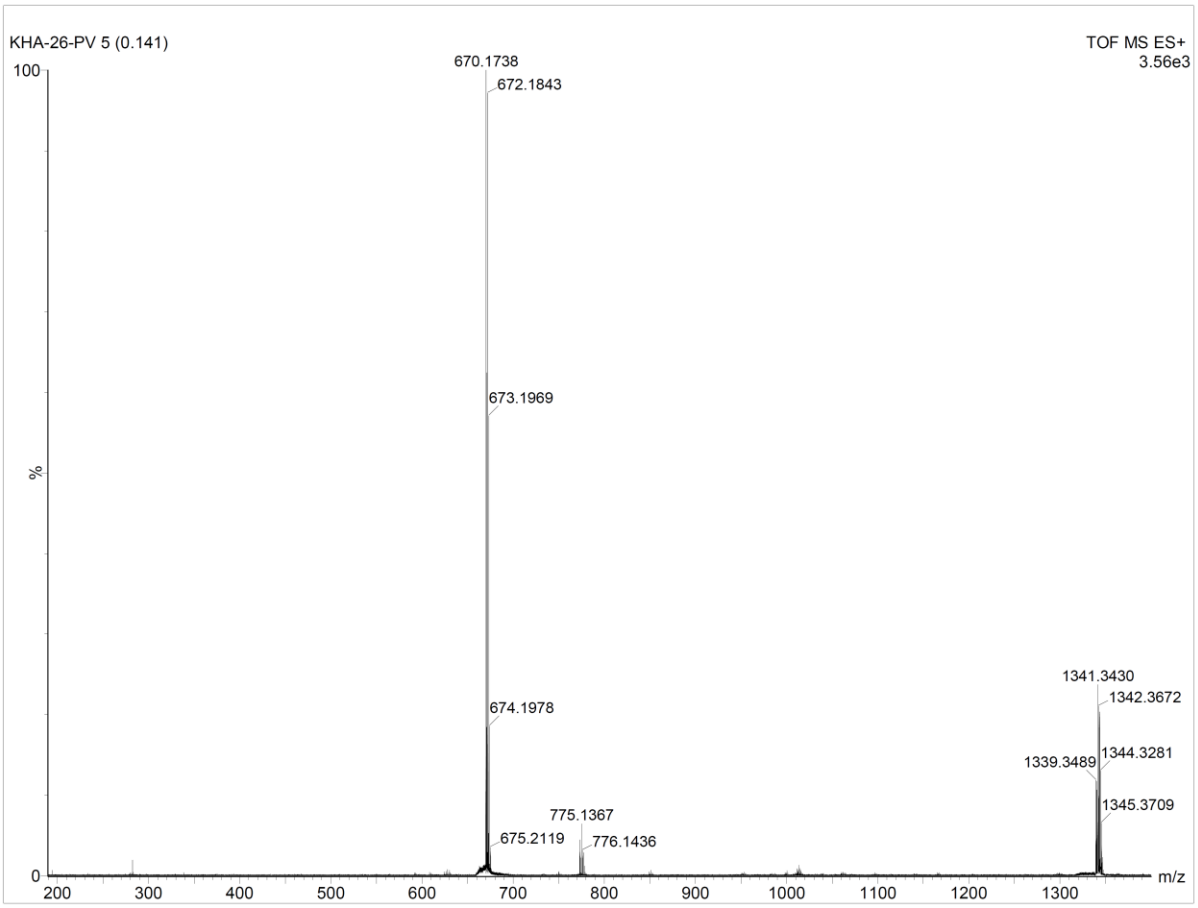
HRMS-ESI Compound **3d**



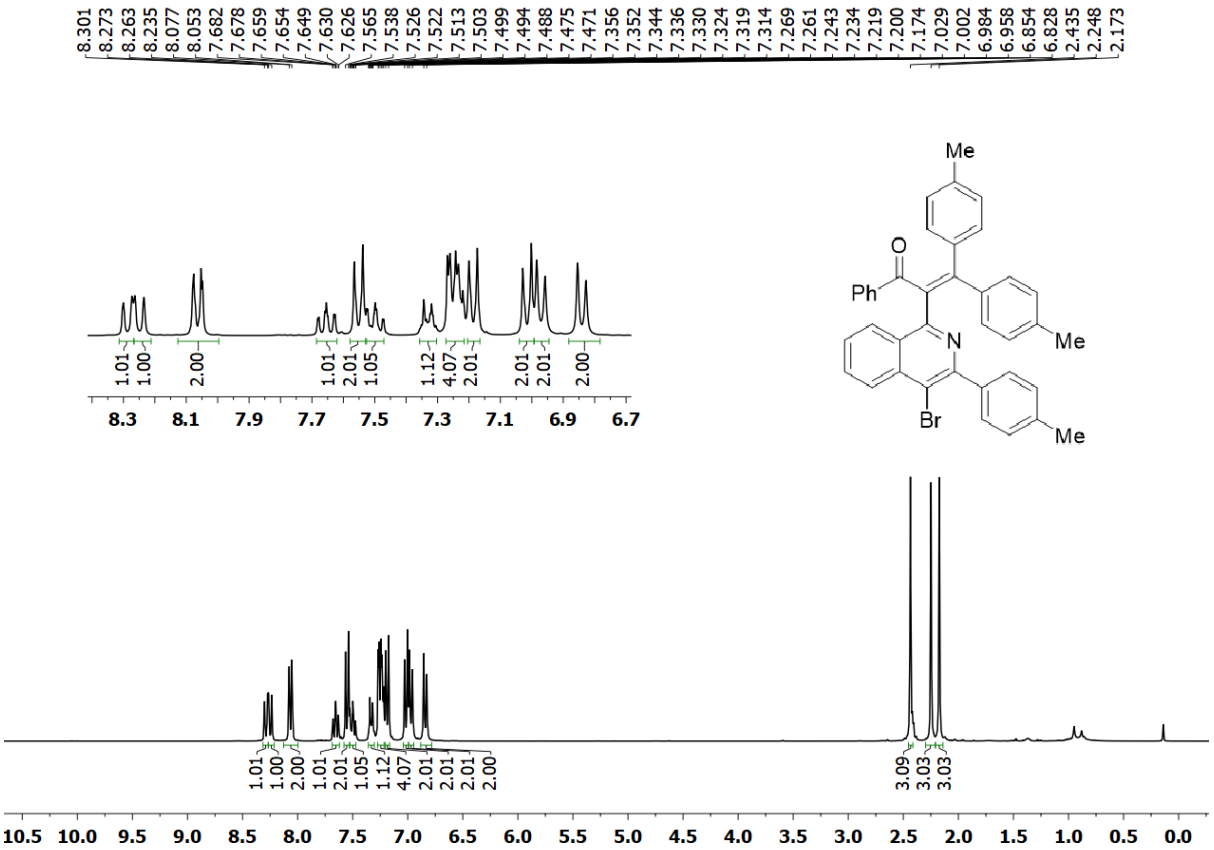
^{1}H NMR Compound **3e** (300 MHz, $CDCl_3$)



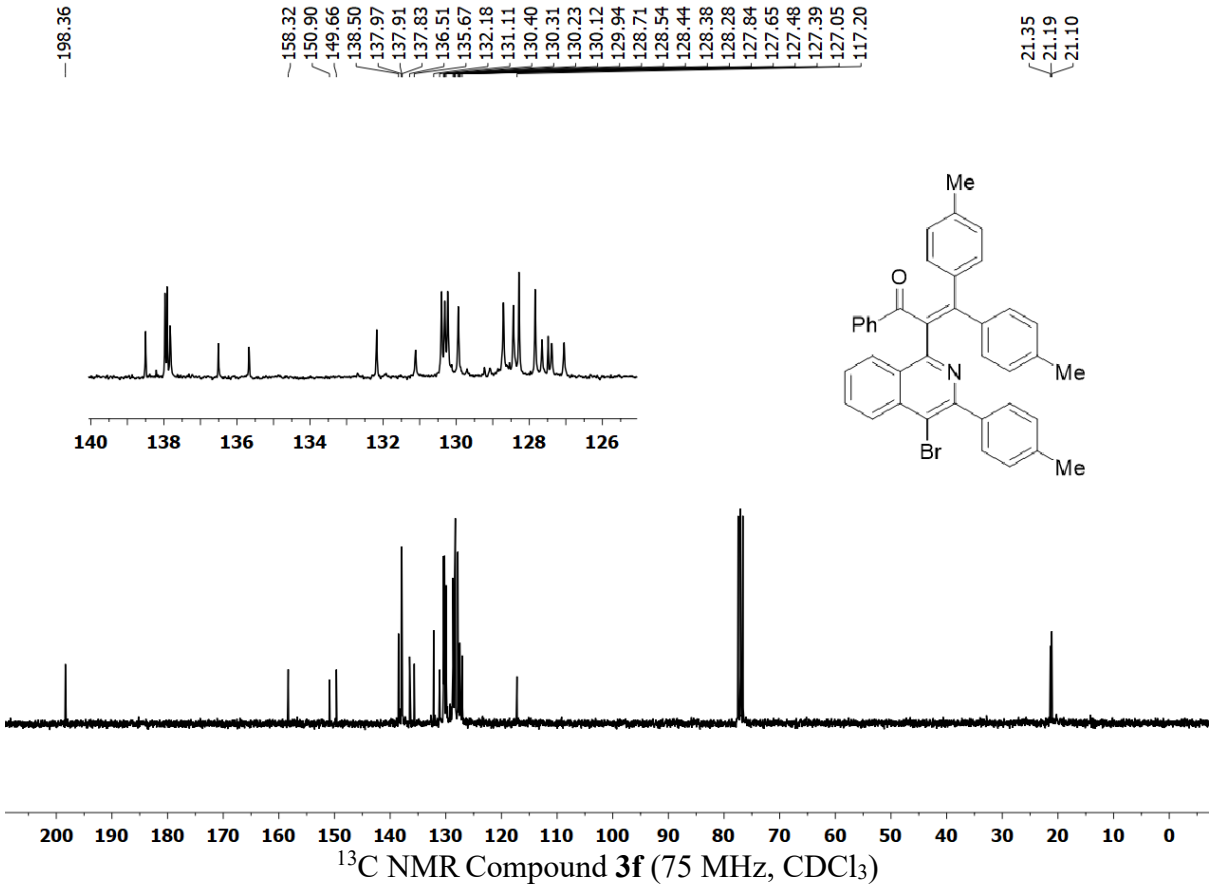
^{13}C NMR Compound **3e** (75 MHz, $CDCl_3$)



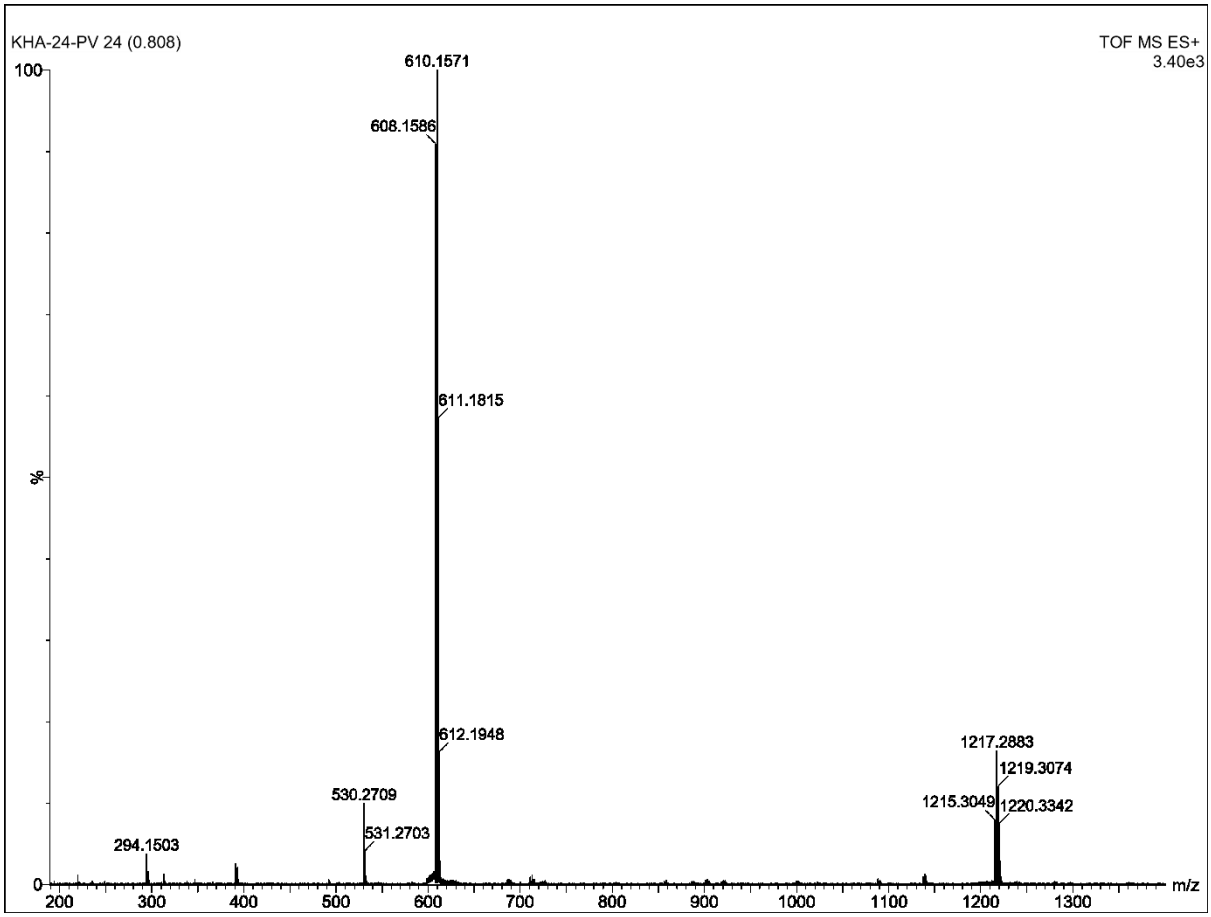
HRMS-ESI Compound **3e**



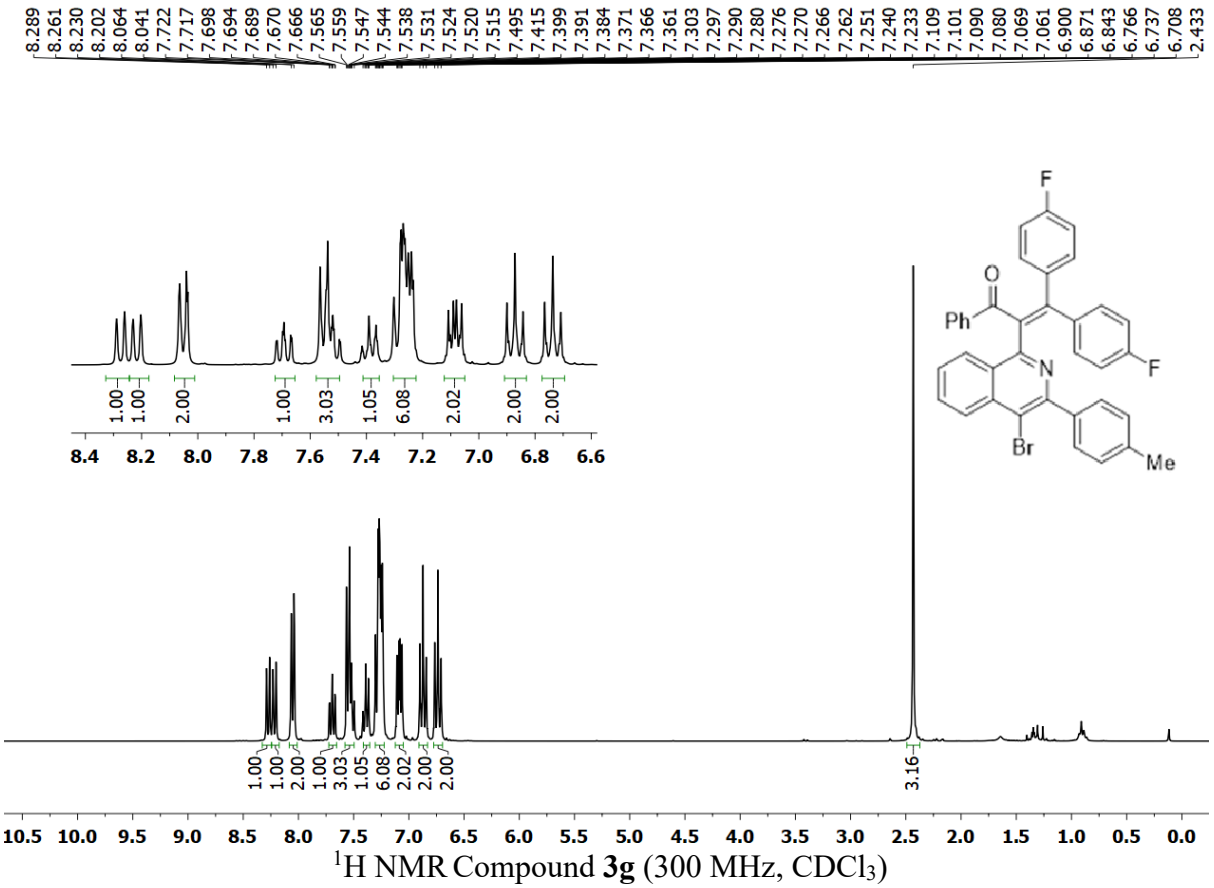
^{1}H NMR Compound **3f** (300 MHz, $CDCl_3$)



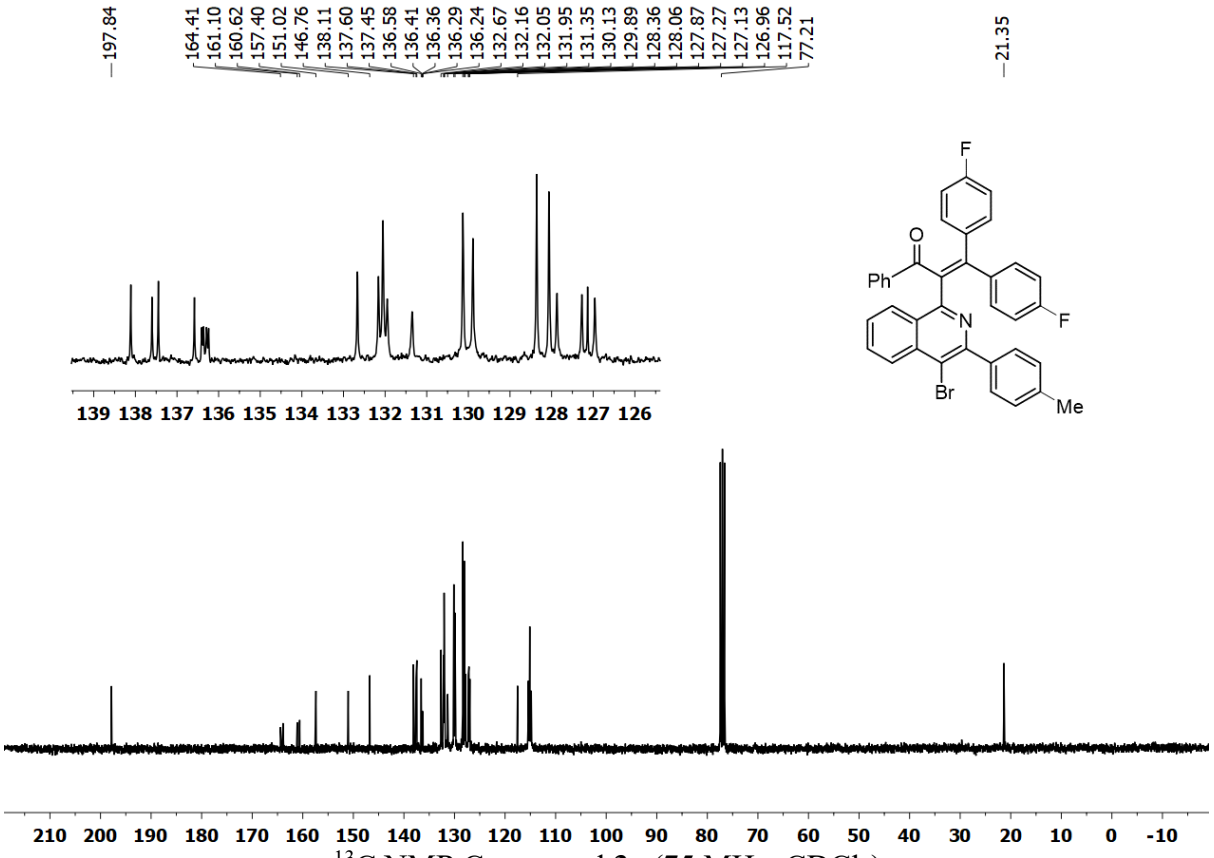
^{13}C NMR Compound **3f** (75 MHz, $CDCl_3$)



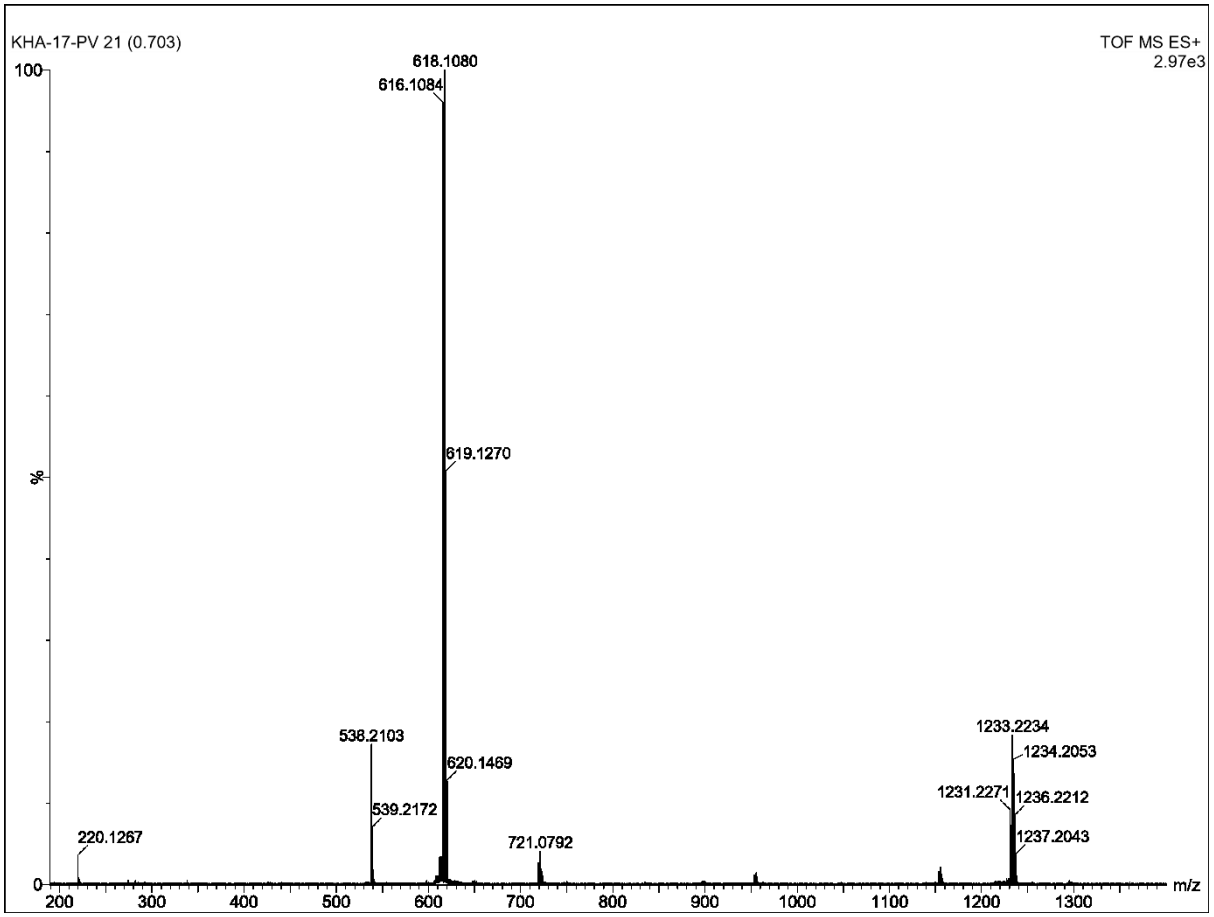
HRMS-ESI Compound **3f**



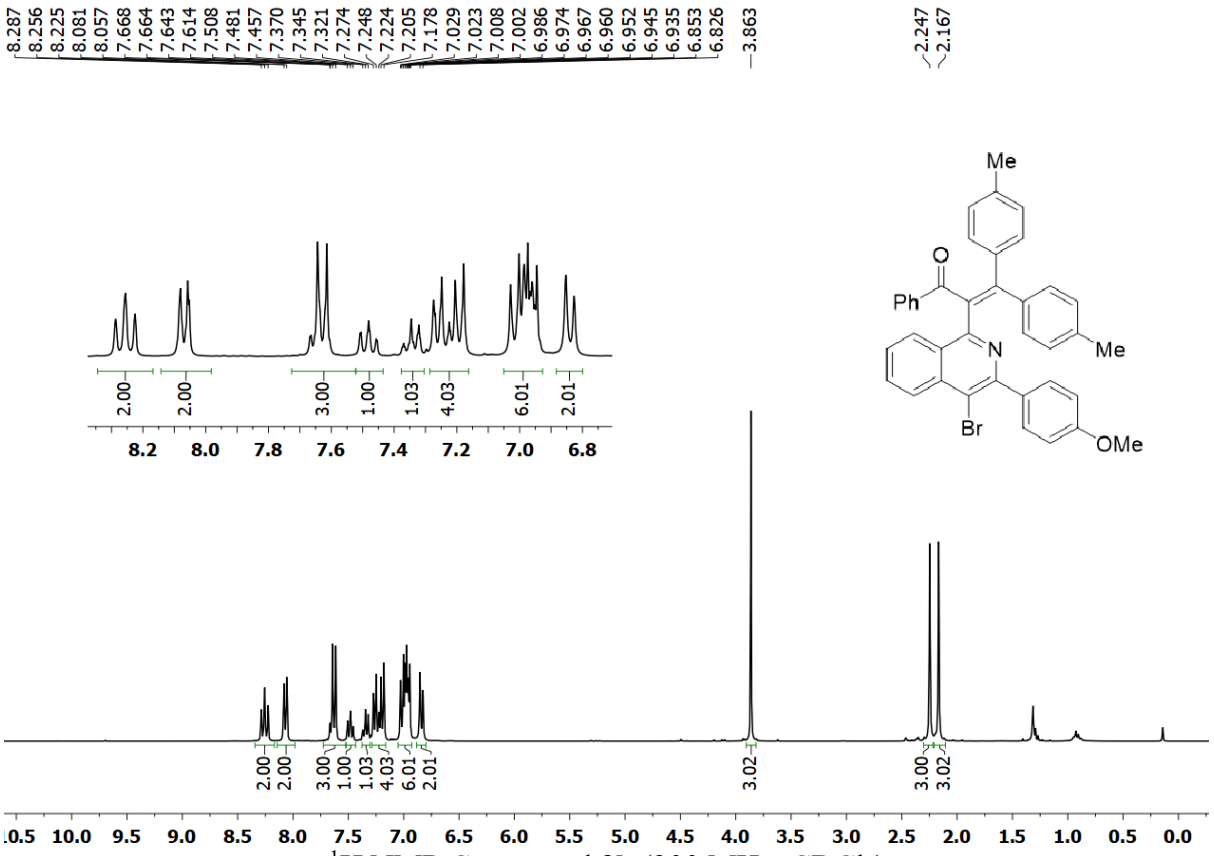
^{1}H NMR Compound **3g** (300 MHz, $CDCl_3$)



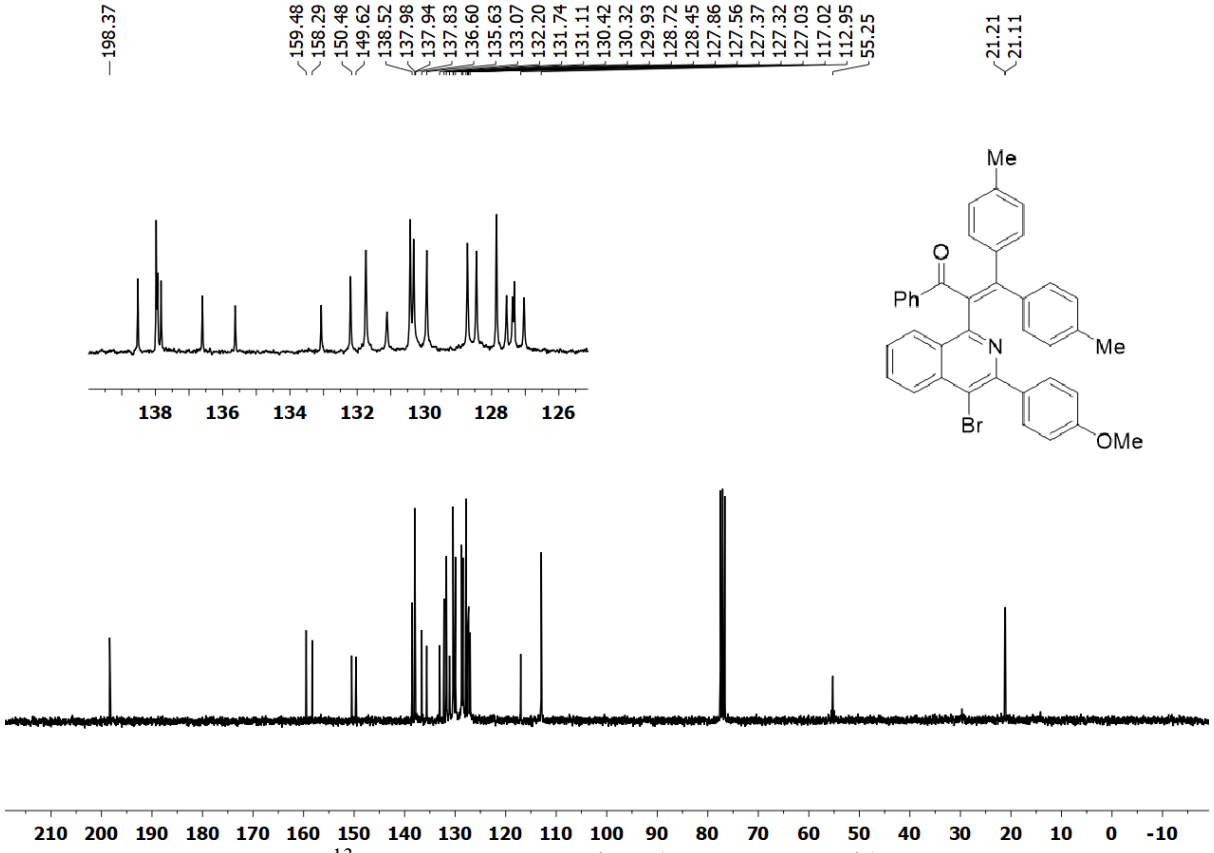
^{13}C NMR Compound **3g** (75 MHz, $CDCl_3$)



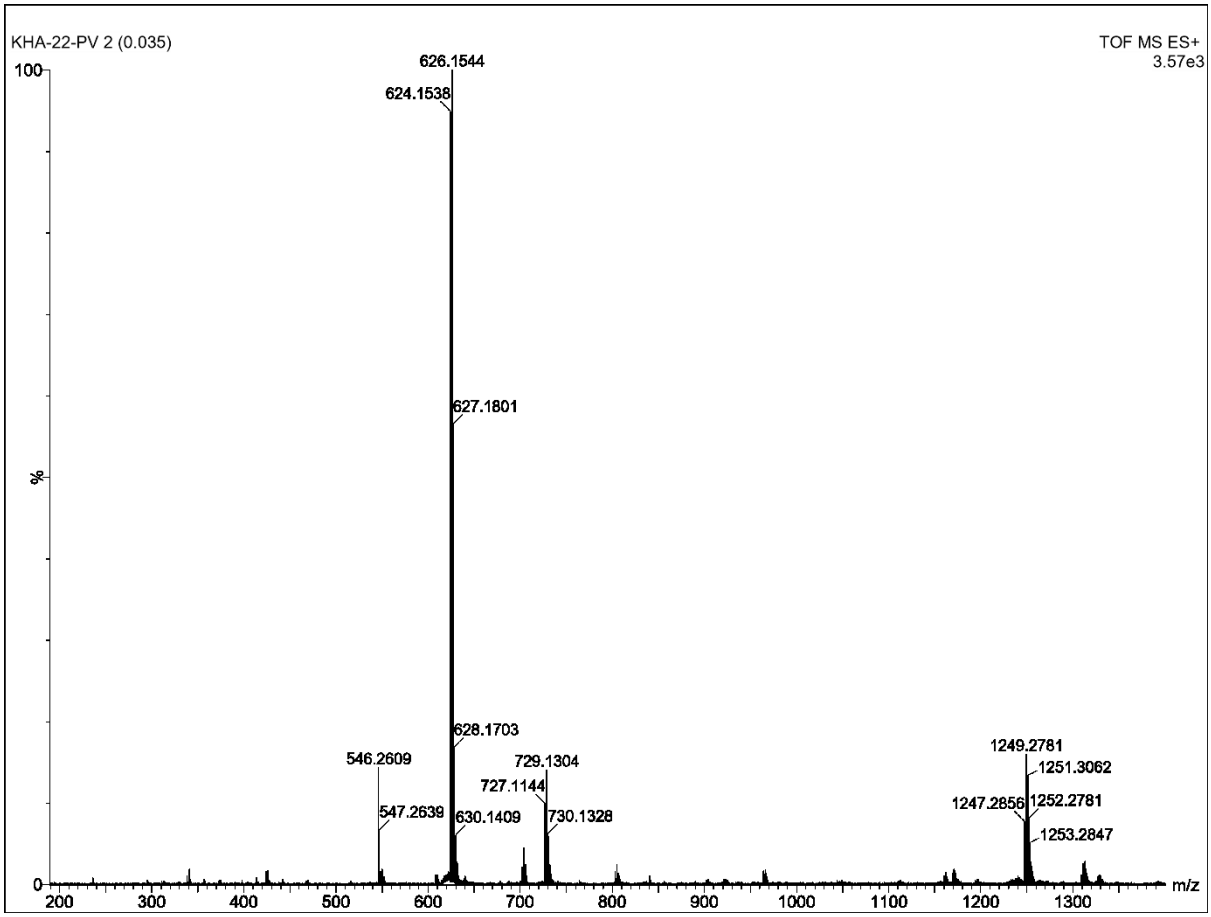
HRMS-ESI Compound **3g**



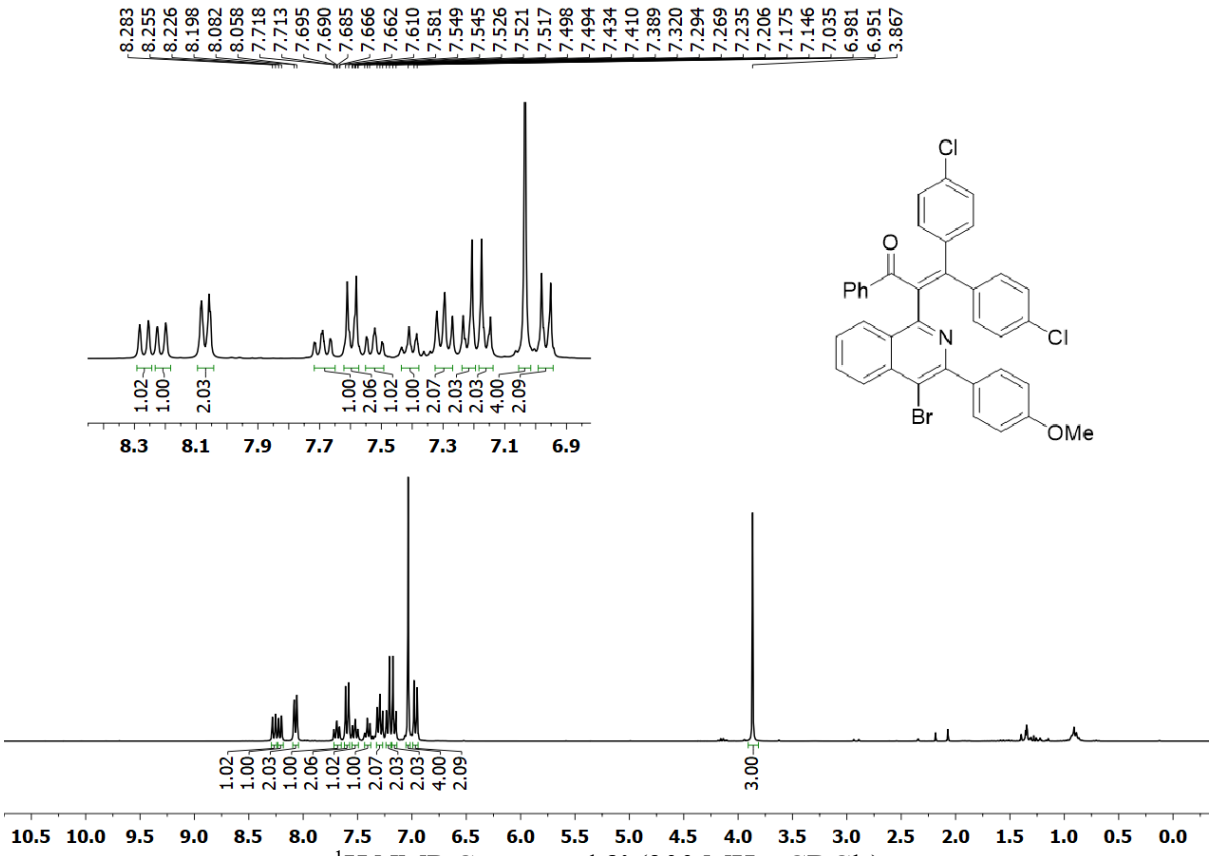
^{1}H NMR Compound **3h** (300 MHz, $CDCl_3$)



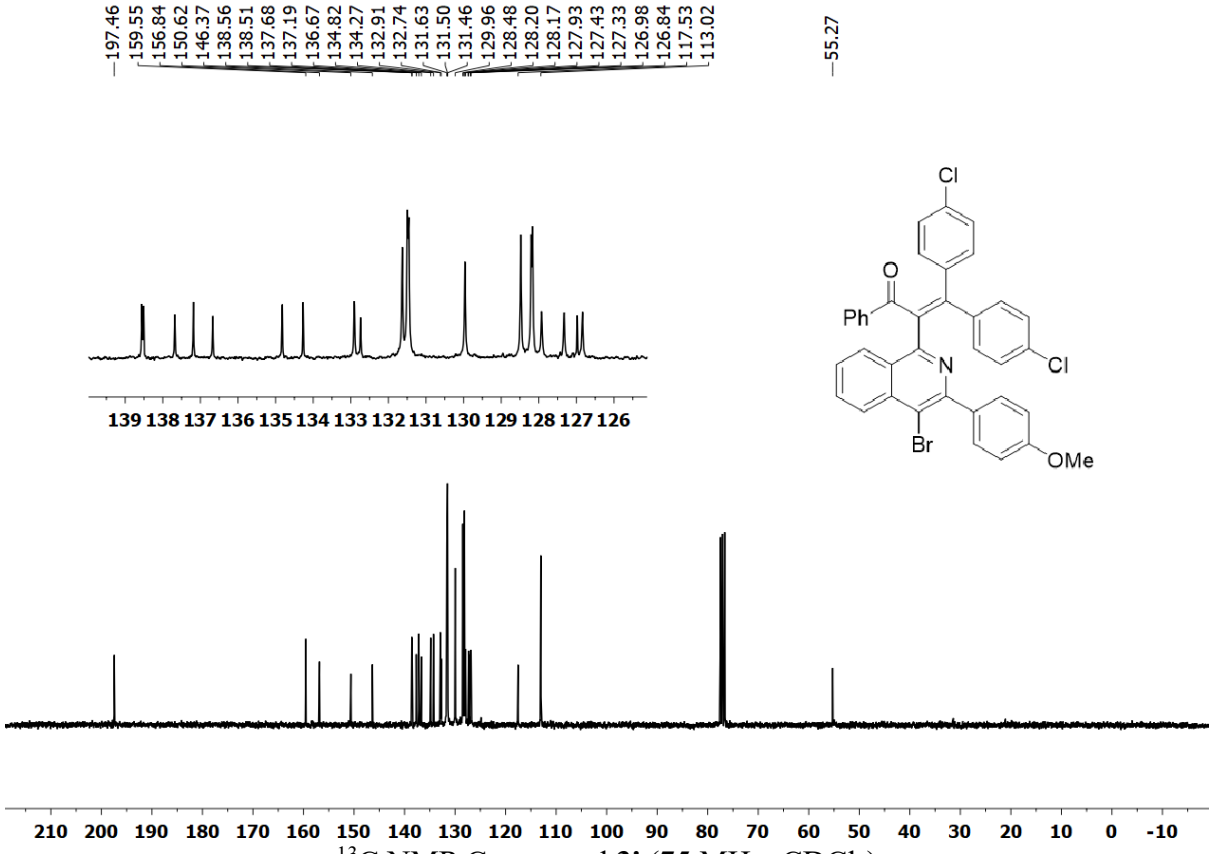
^{13}C NMR Compound **3h** (75 MHz, $CDCl_3$)



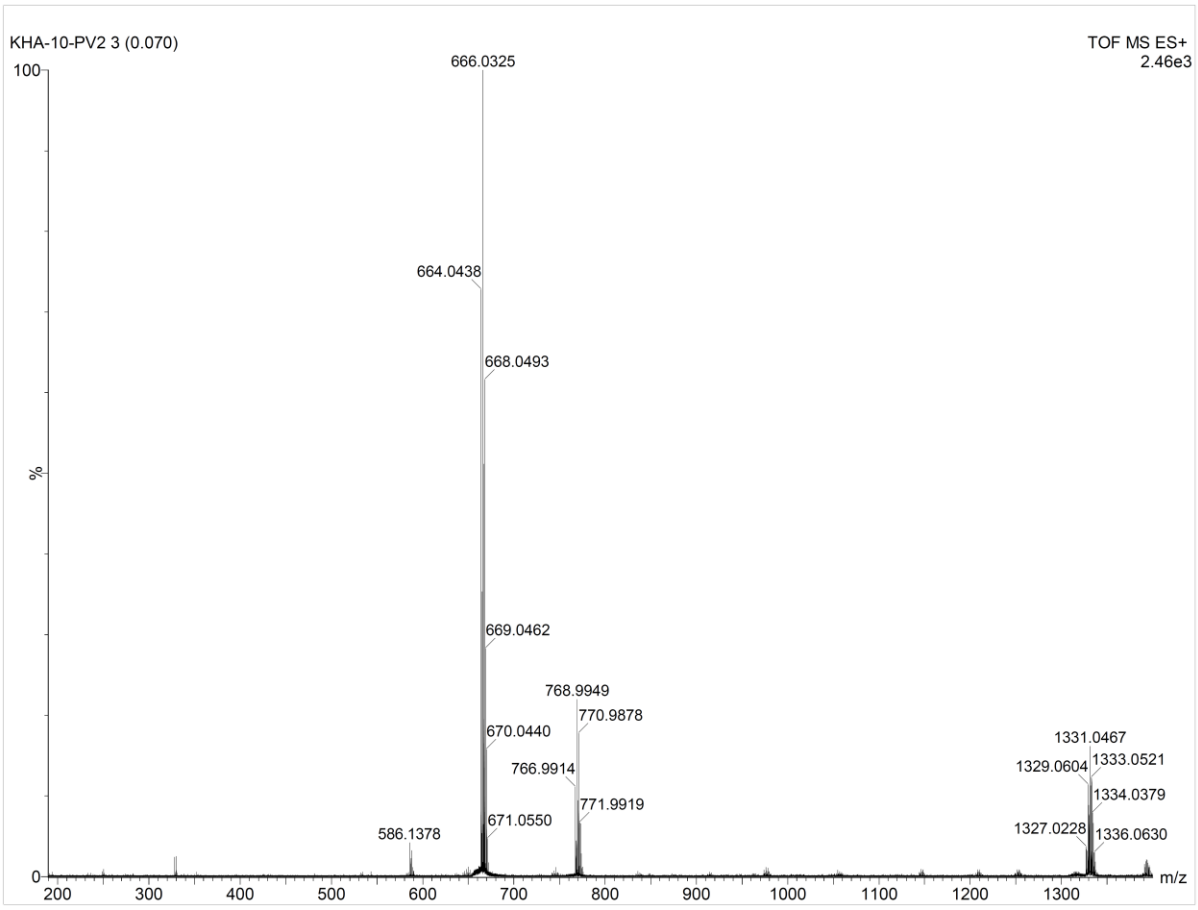
HRMS-ESI Compound **3h**



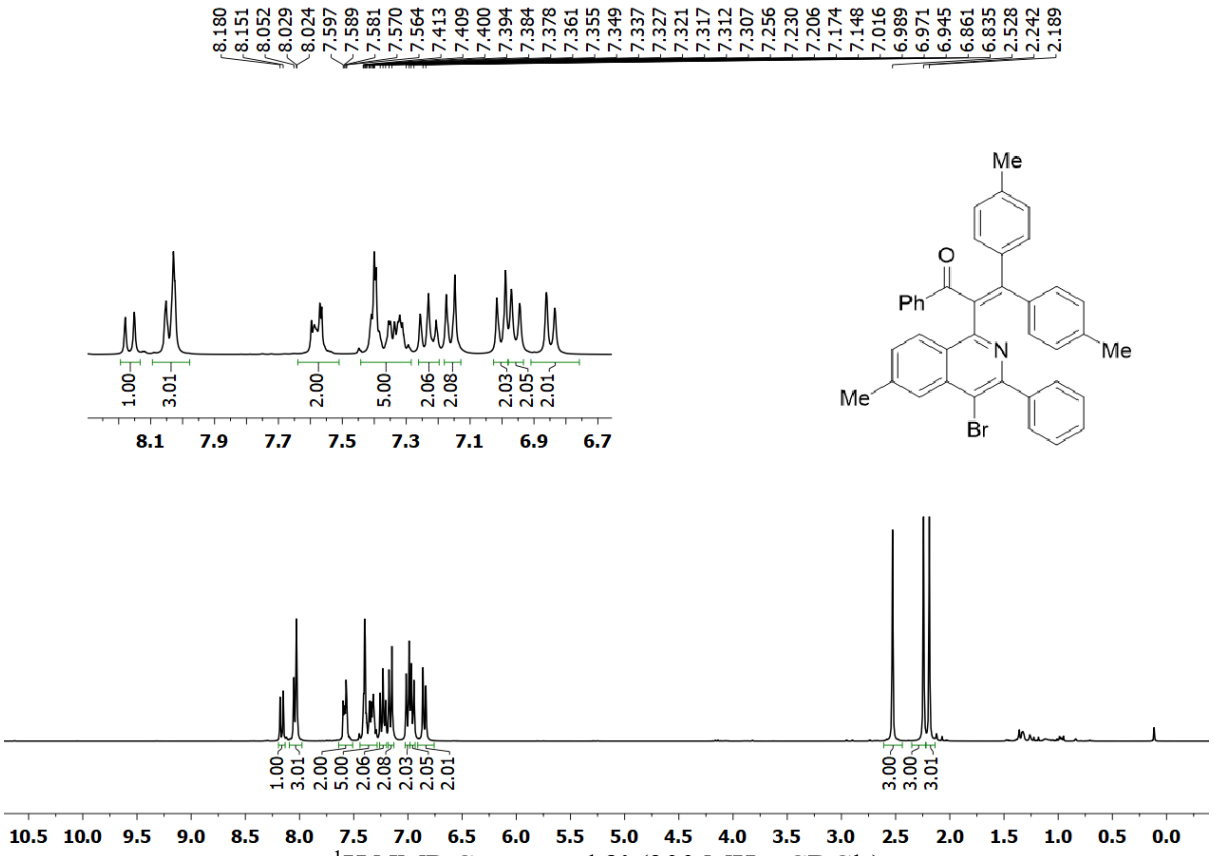
^{1}H NMR Compound **3i** (300 MHz, $CDCl_3$)



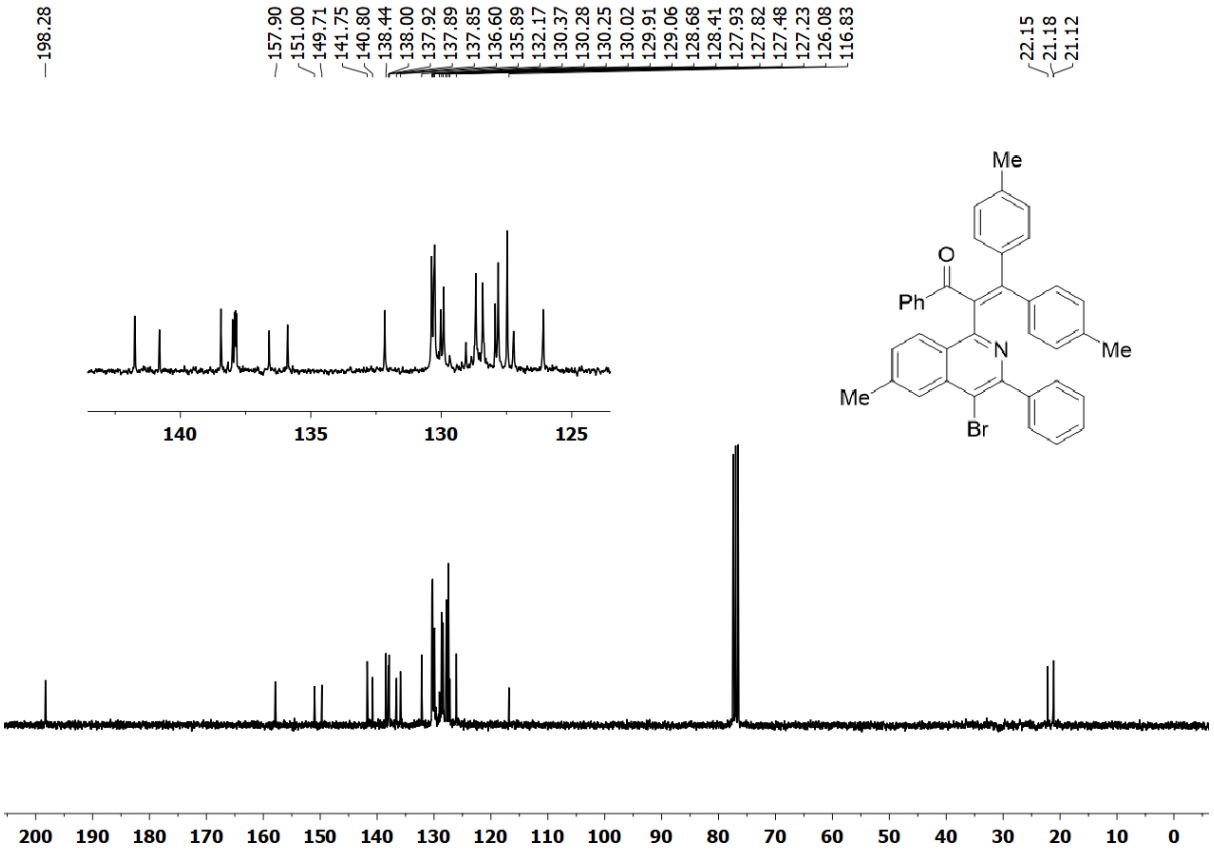
^{13}C NMR Compound **3i** (75 MHz, $CDCl_3$)



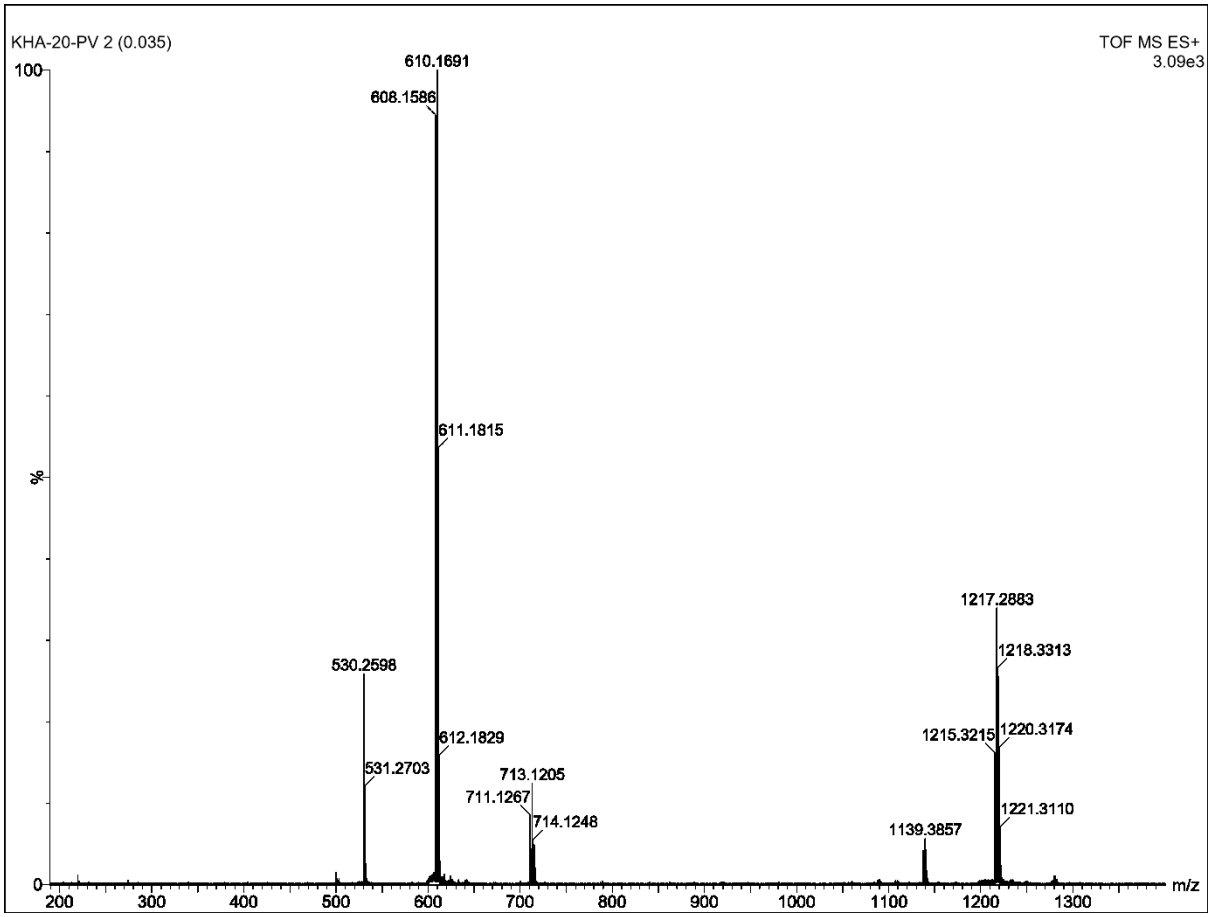
HRMS-ESI Compound **3i**



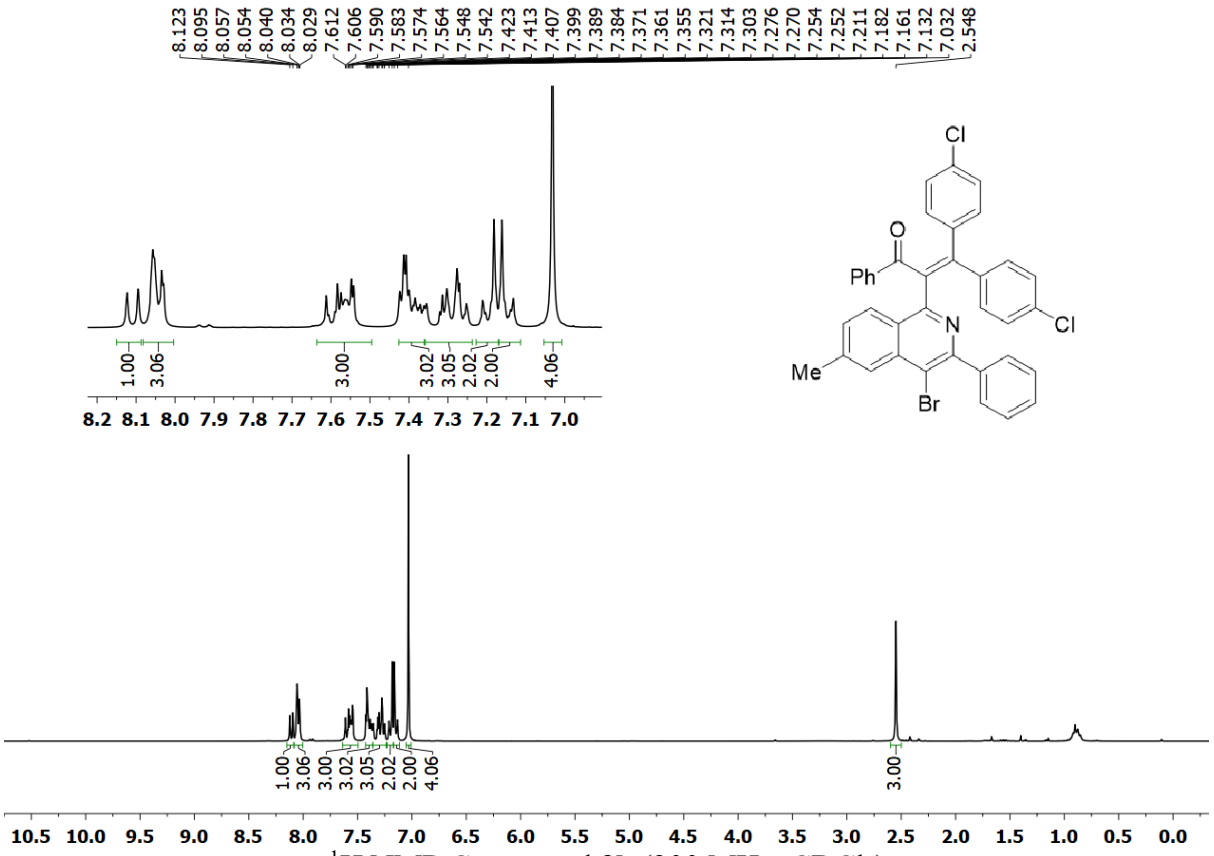
^{1}H NMR Compound **3j** (300 MHz, $CDCl_3$)



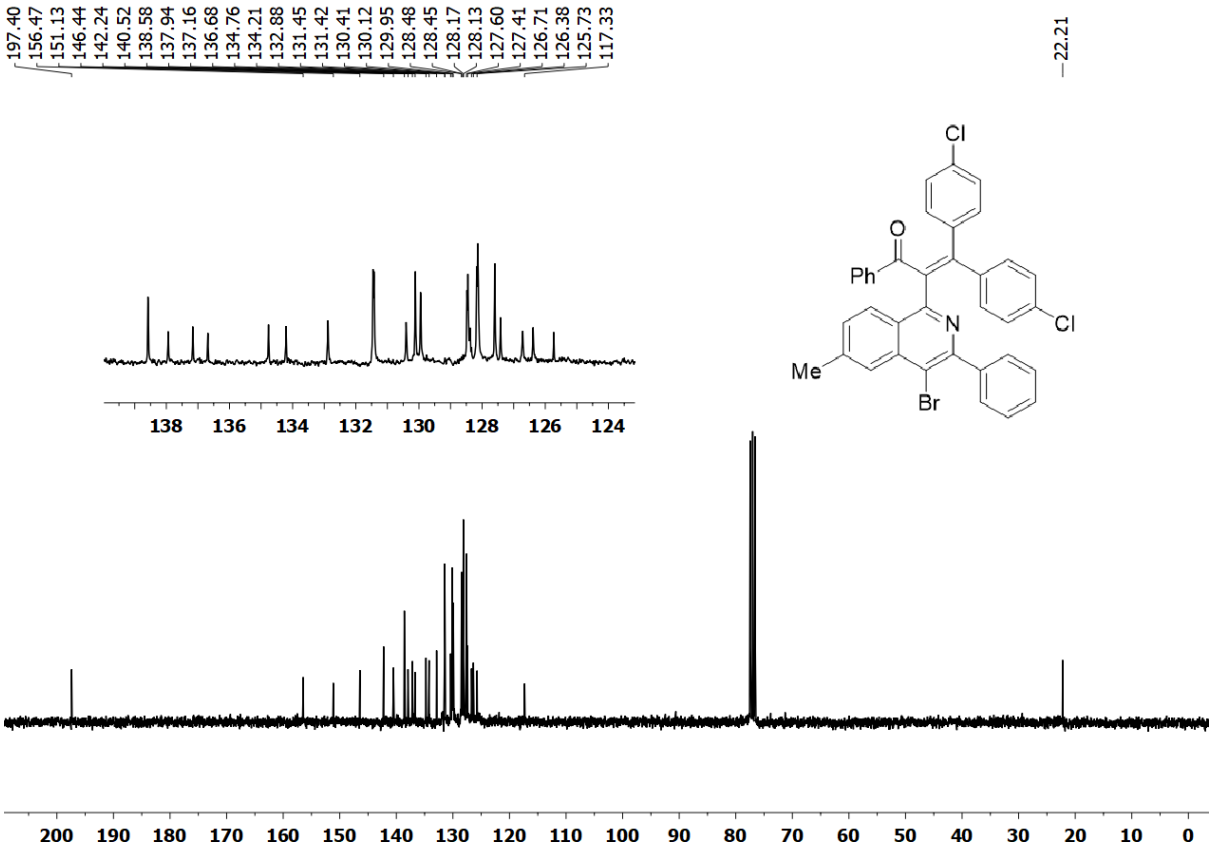
^{13}C NMR Compound **3j** (75 MHz, $CDCl_3$)



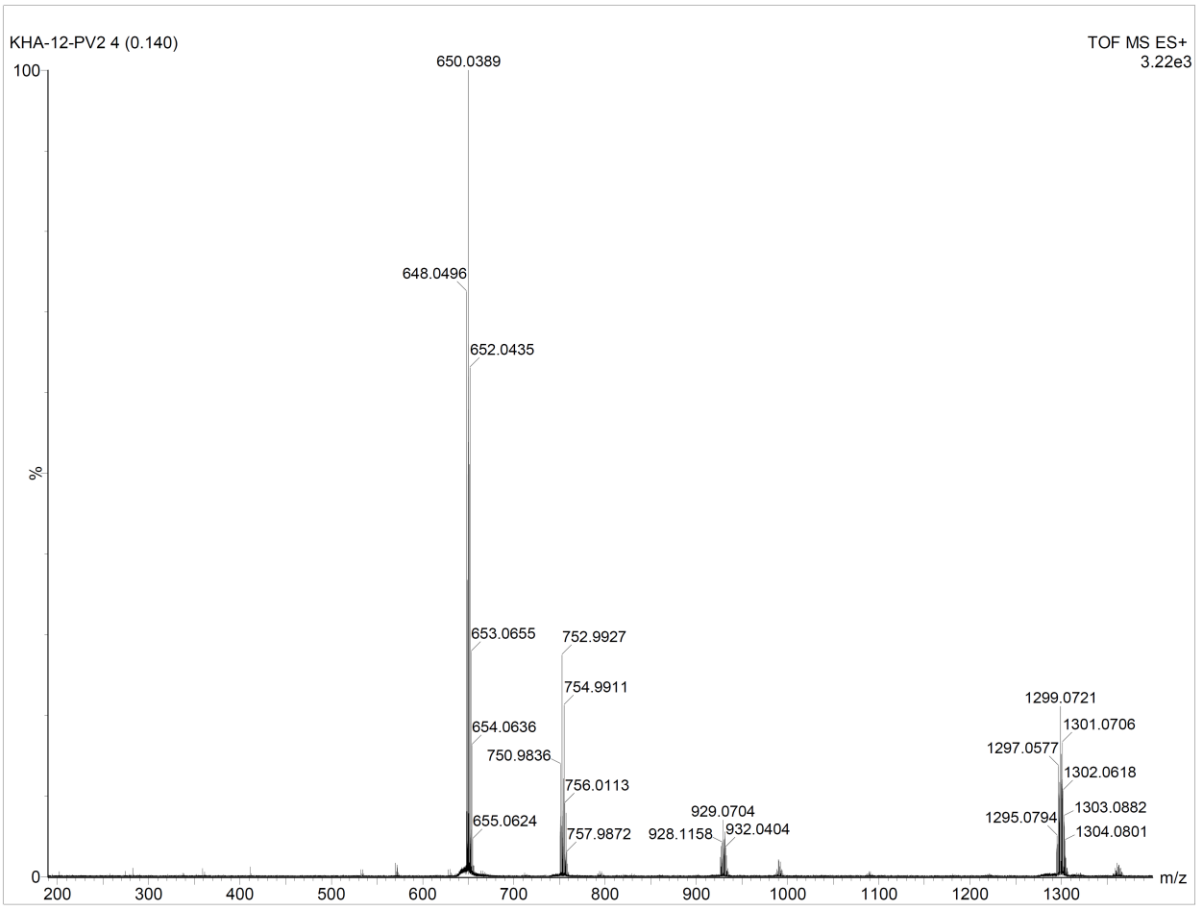
HRMS-ESI Compound **3j**



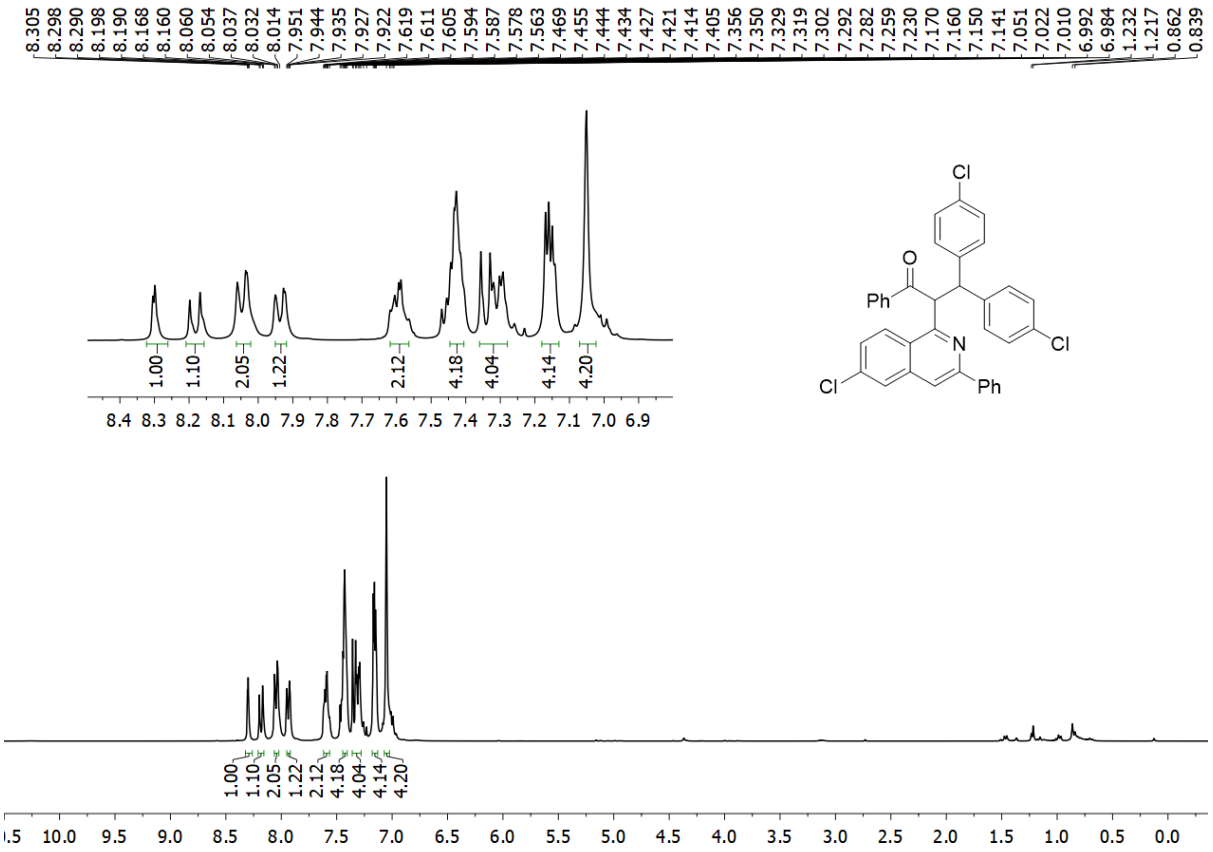
^{1}H NMR Compound **3k** (300 MHz, $CDCl_3$)



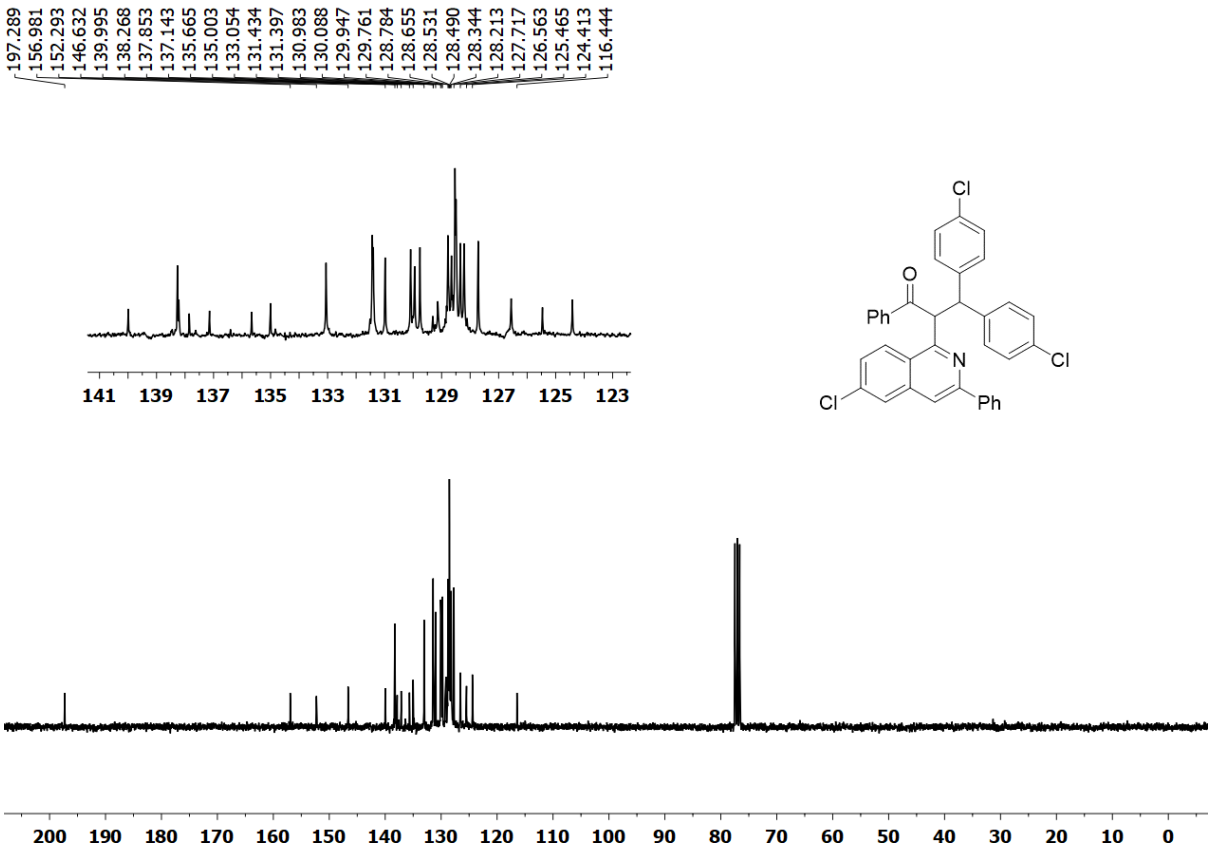
^{13}C NMR Compound **3k** (75 MHz, $CDCl_3$)



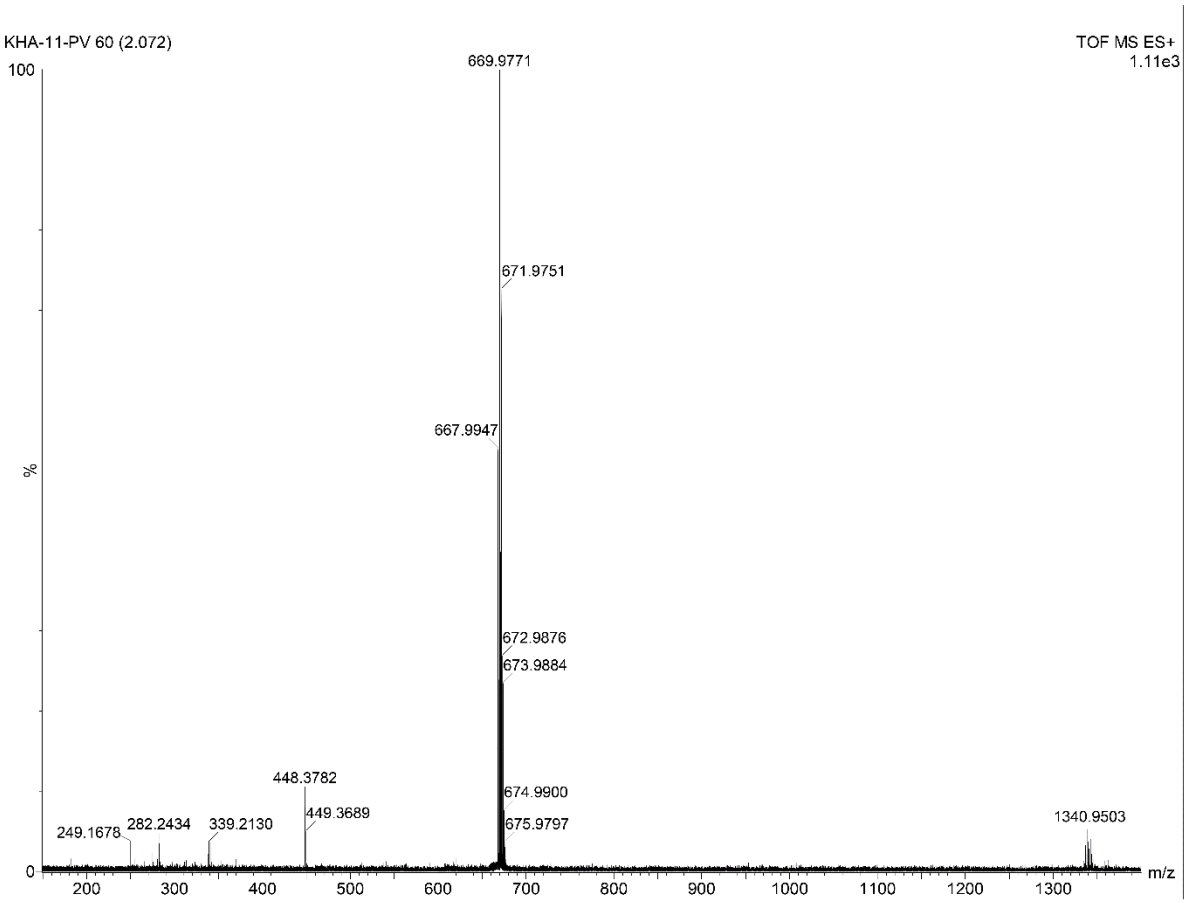
HRMS-ESI Compound **3k**



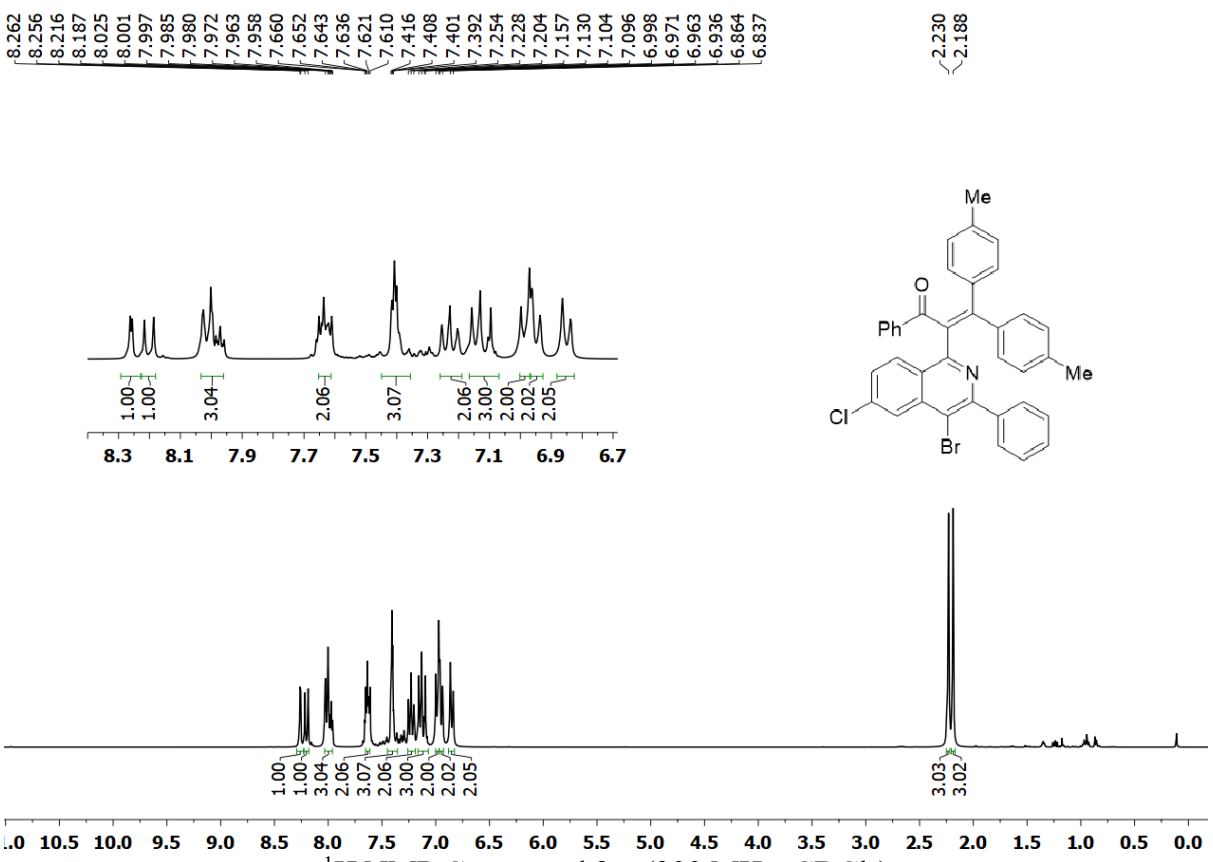
^{1}H NMR Compound **3l** (300 MHz, $CDCl_3$)



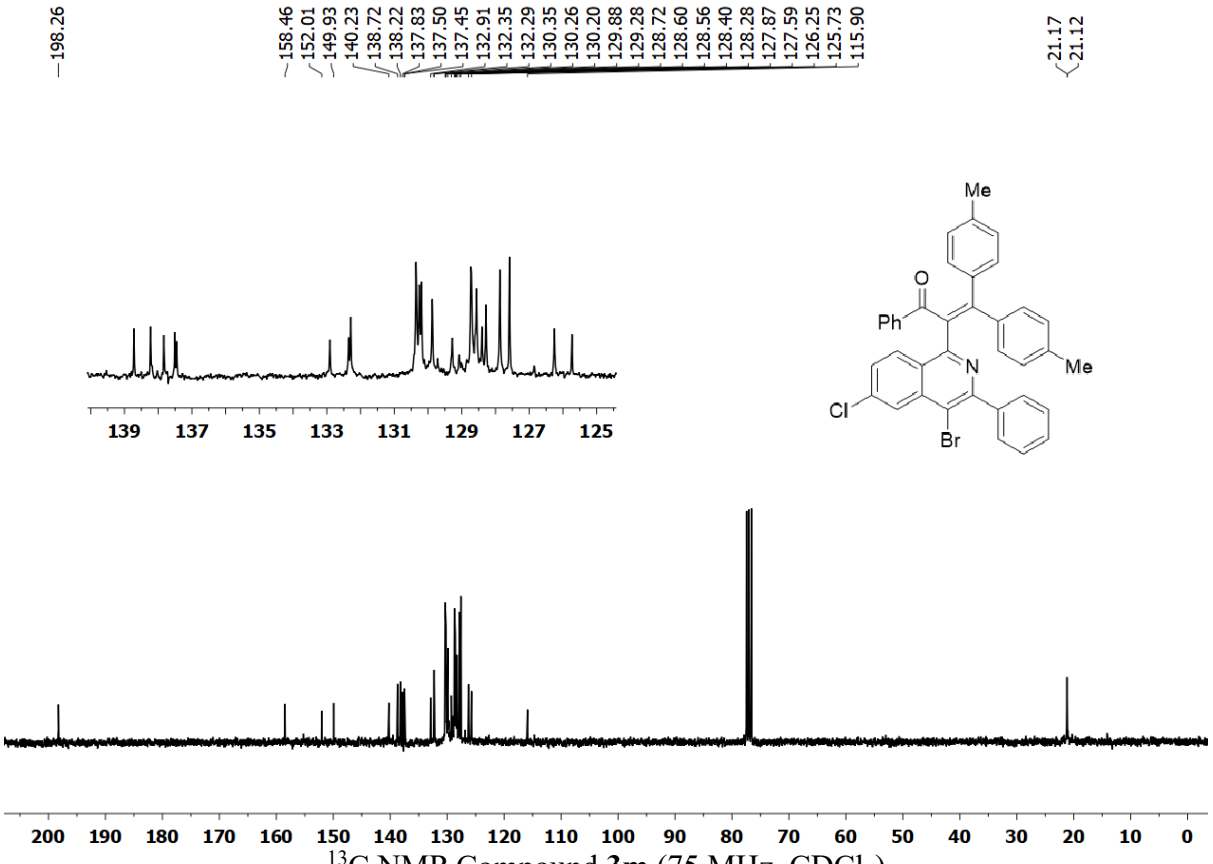
^{13}C NMR Compound **3l** (75 MHz, $CDCl_3$)



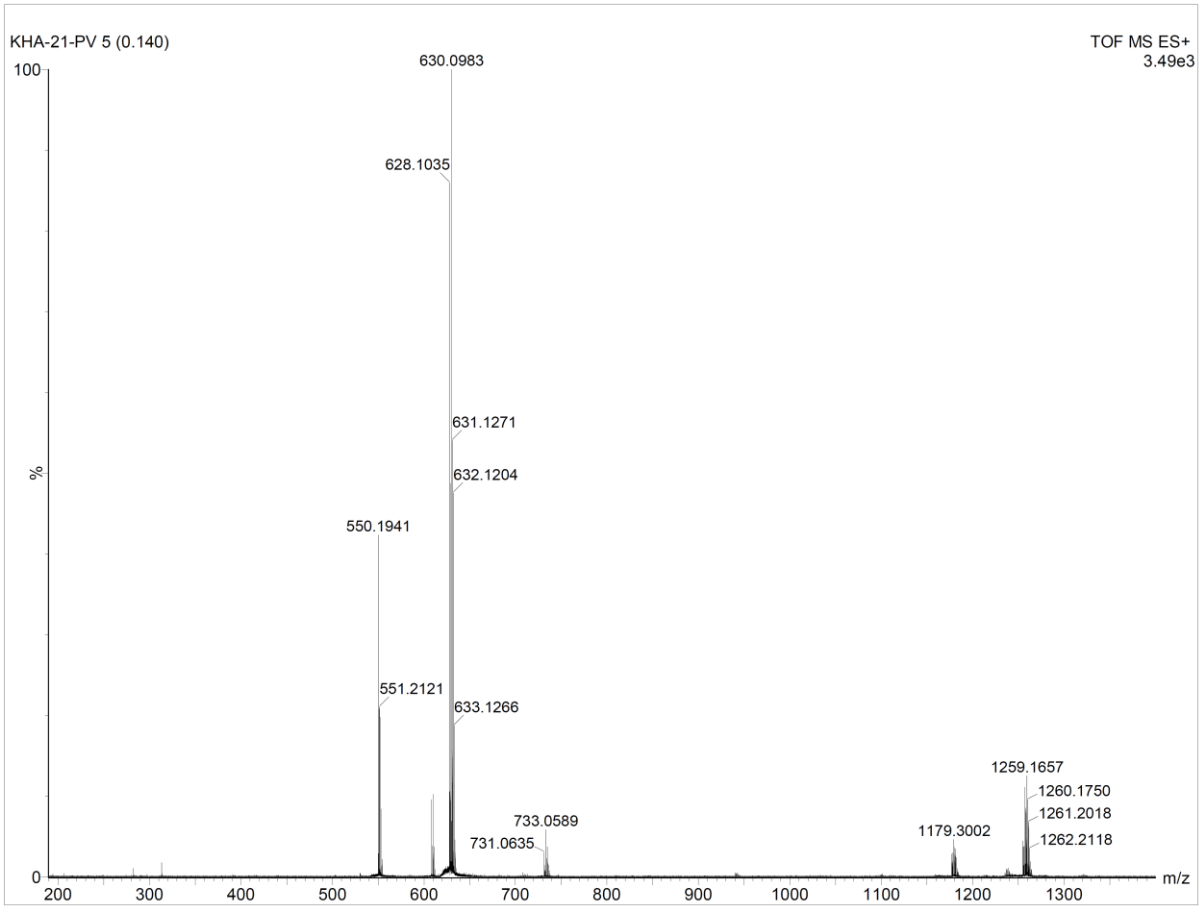
HRMS-ESI Compound **3l**



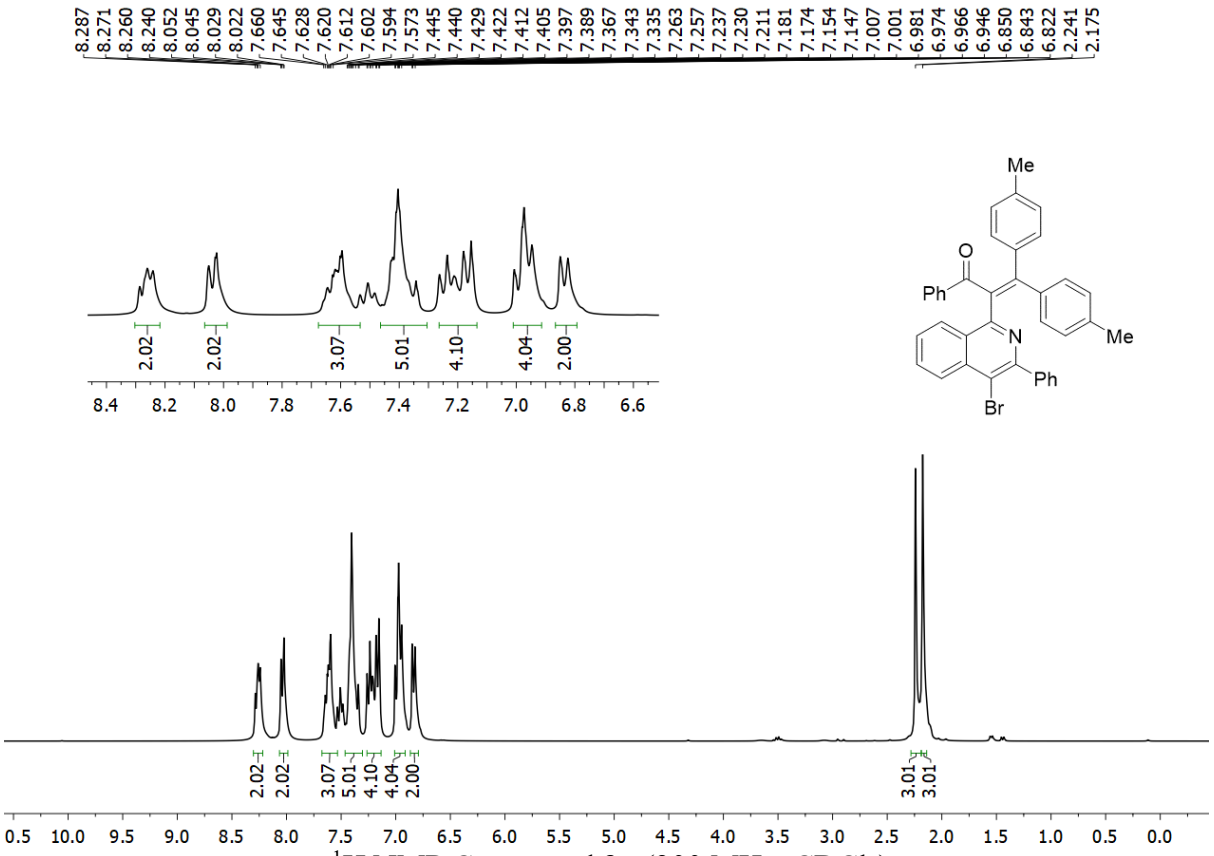
^{1}H NMR Compound **3m** (300 MHz, $CDCl_3$)



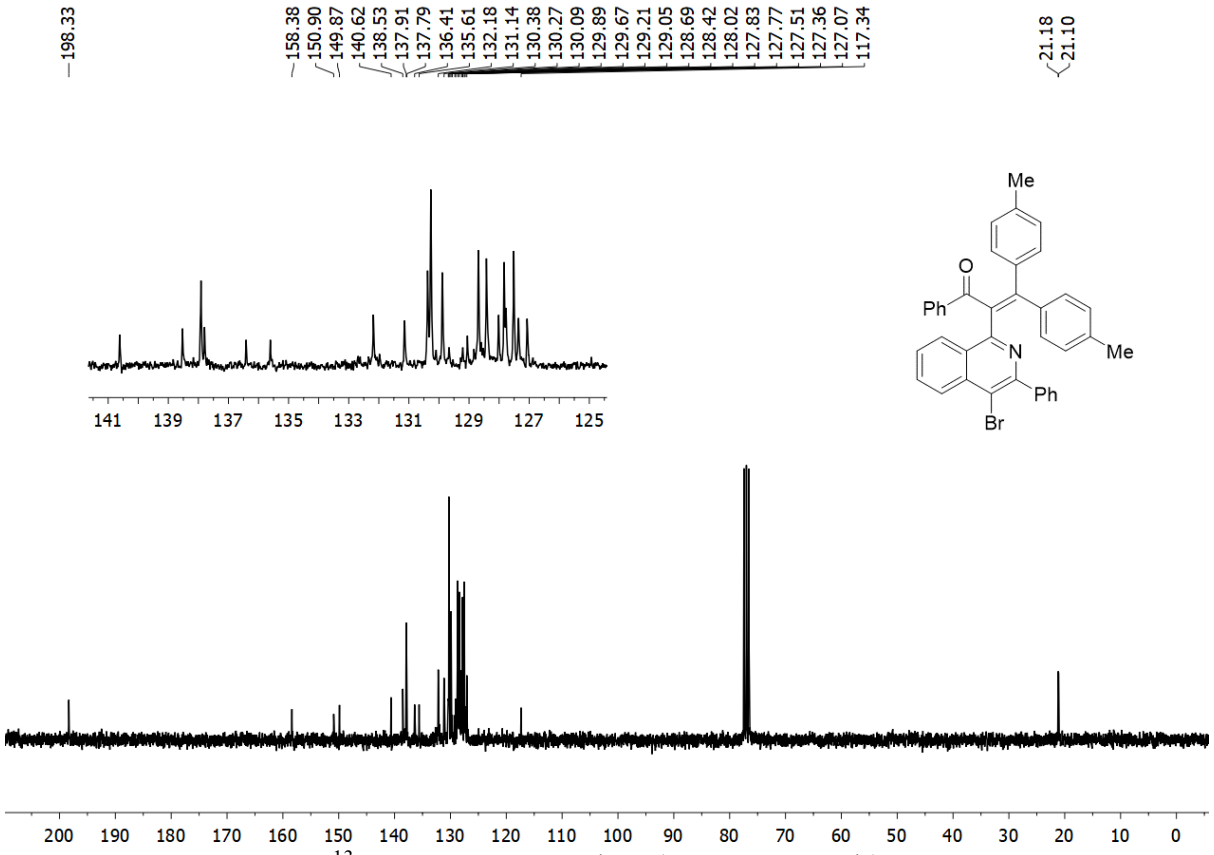
^{13}C NMR Compound **3m** (75 MHz, $CDCl_3$)



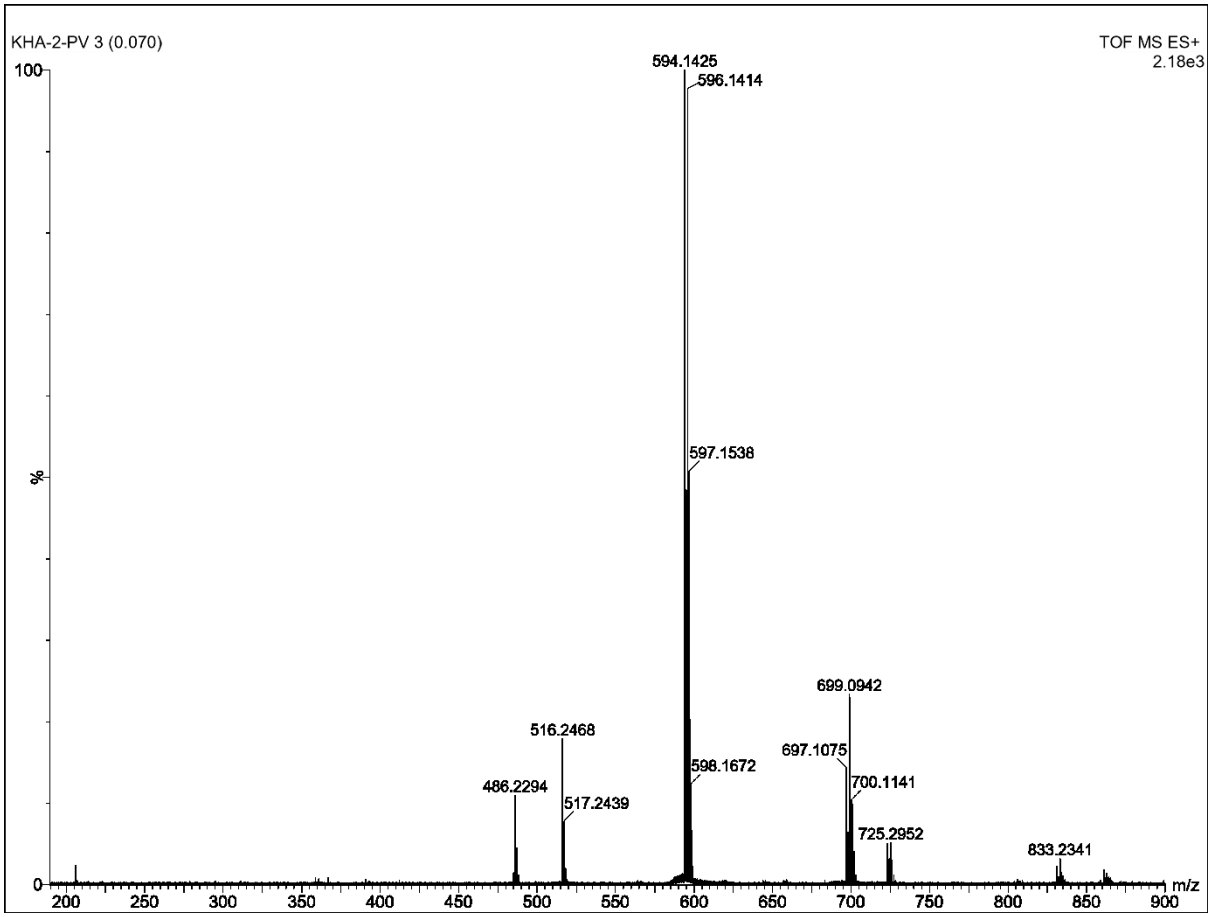
HRMS-ESI Compound **3m**



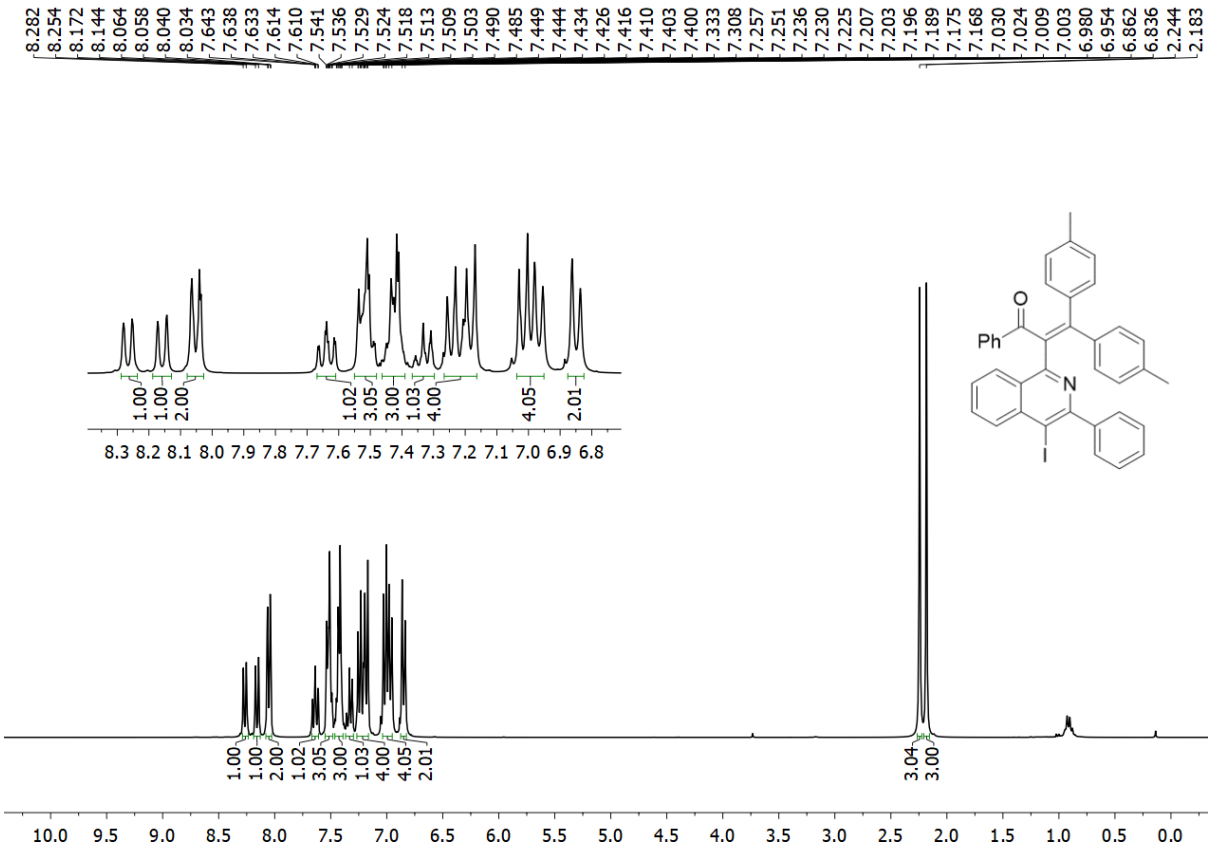
^{1}H NMR Compound **3n** (300 MHz, $CDCl_3$)



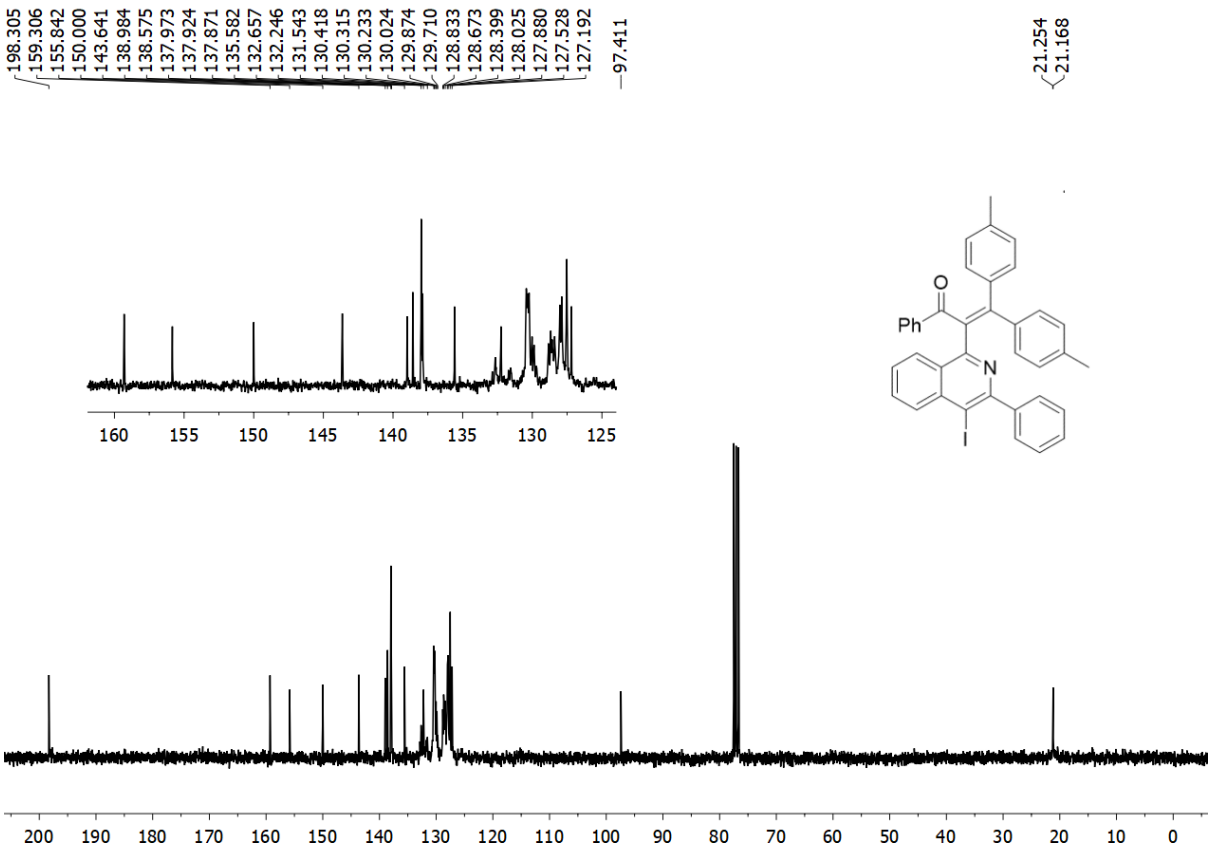
^{13}C NMR Compound **3n** (75 MHz, $CDCl_3$)



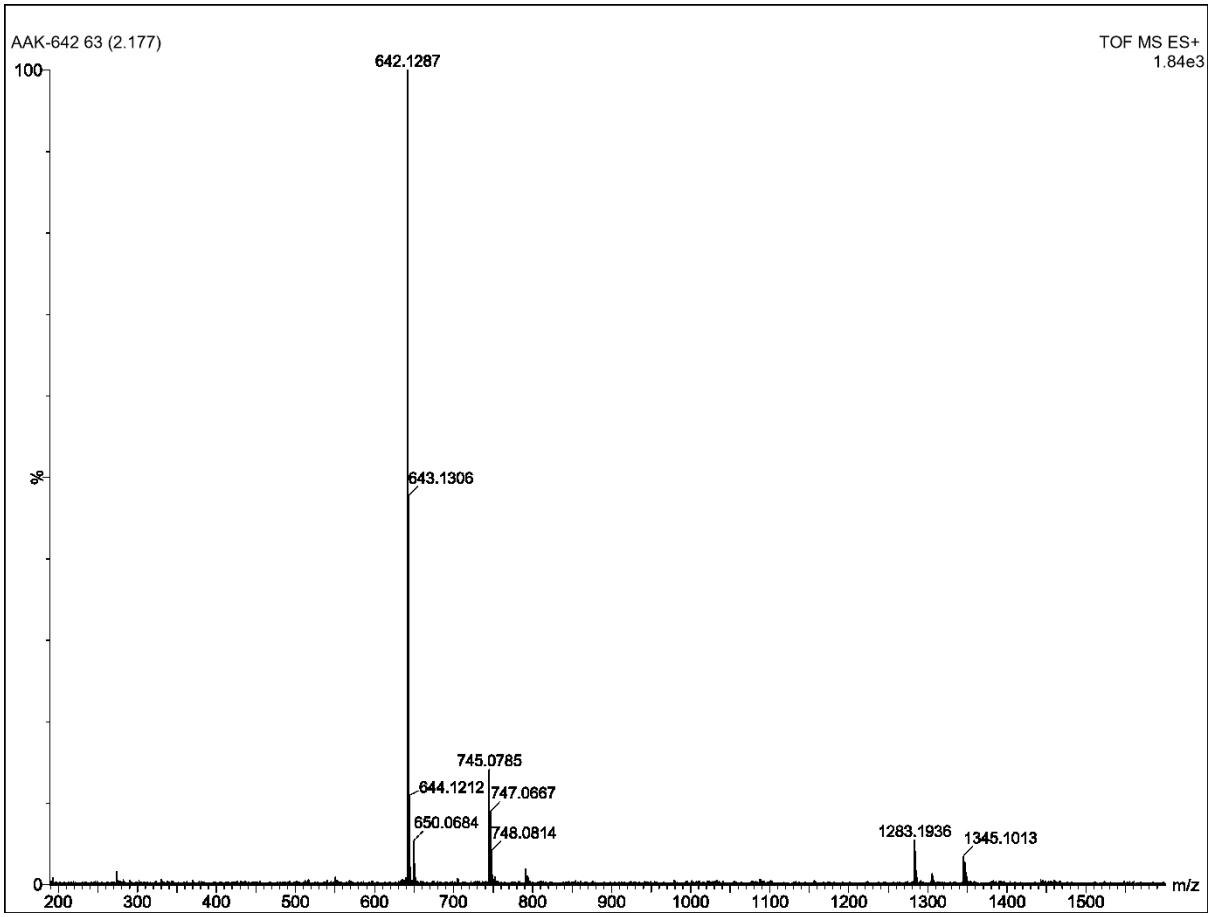
HRMS-ESI Compound **3n**



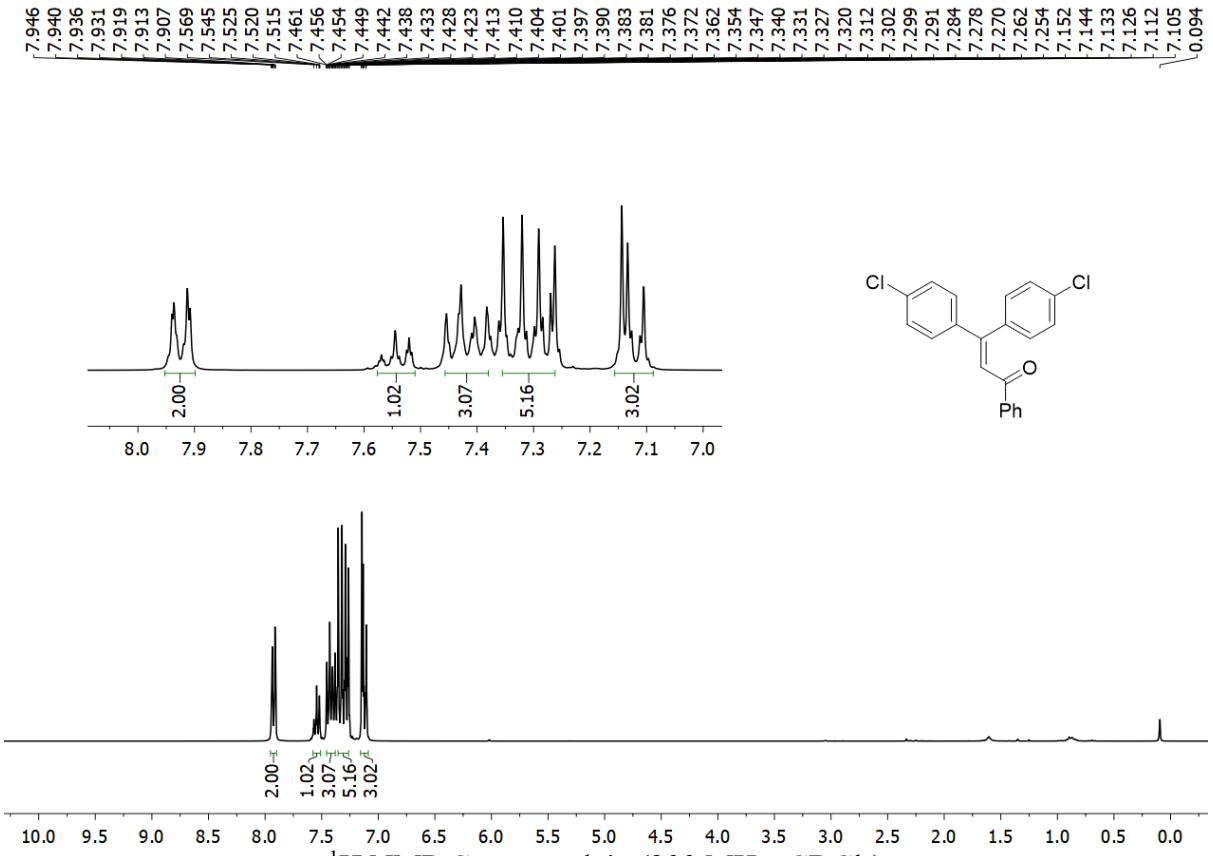
^{1}H NMR Compound **3n´** (300 MHz, $CDCl_3$)



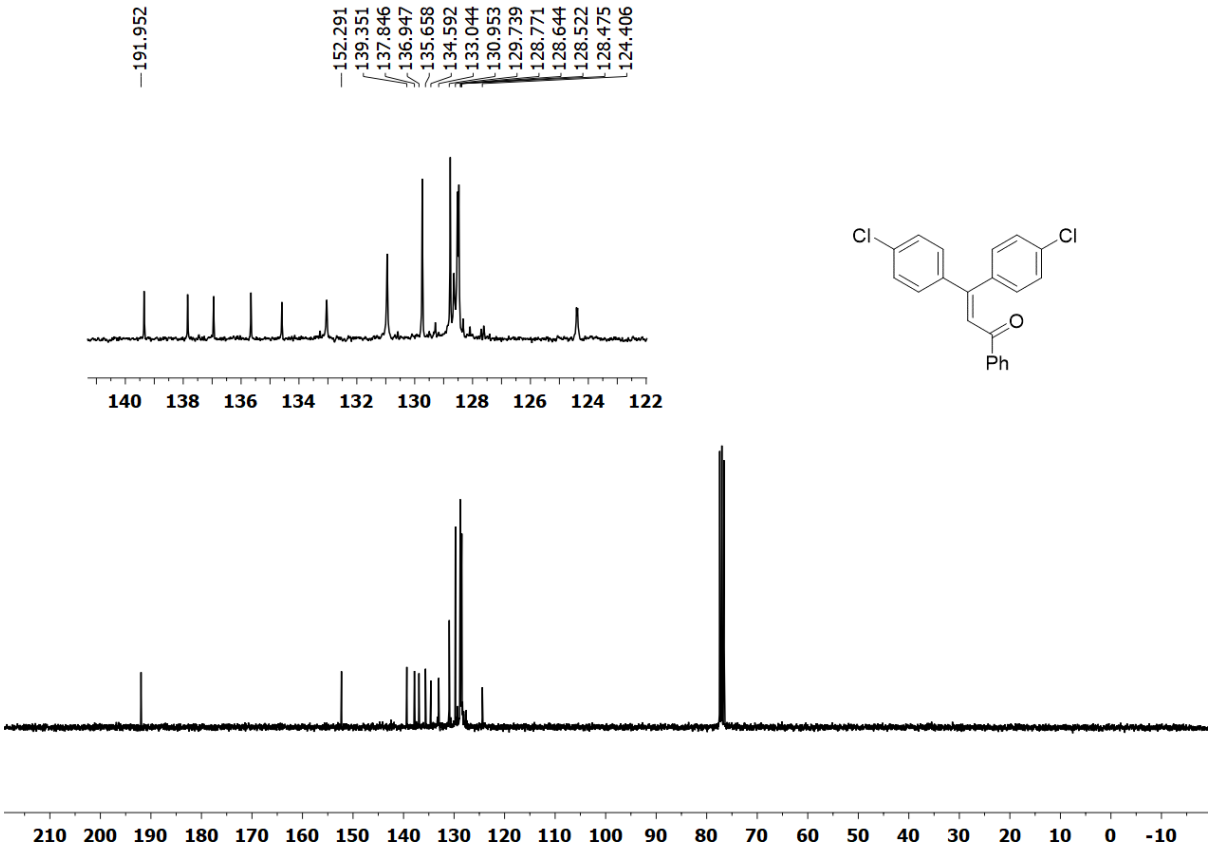
^{13}C NMR Compound **3n´** (75 MHz, $CDCl_3$)



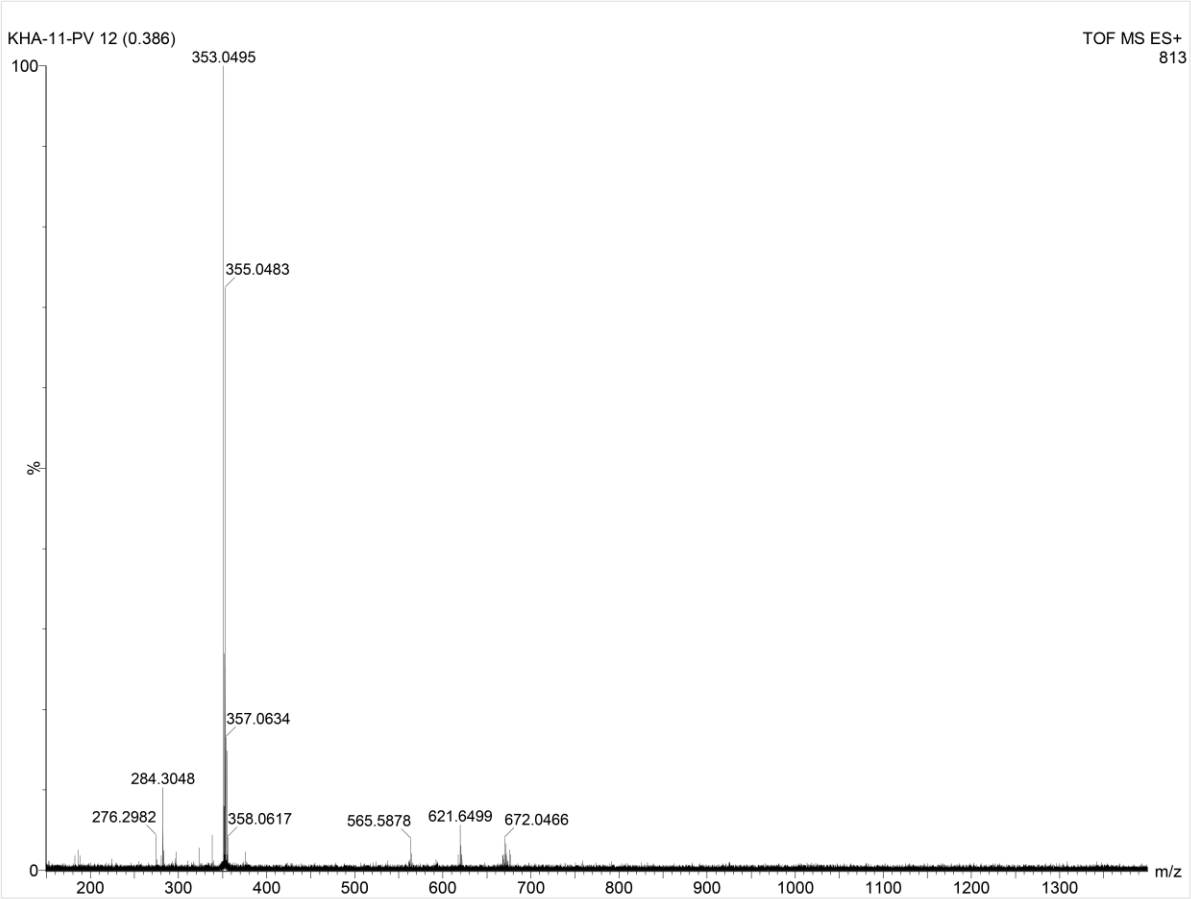
HRMS-ESI Compound **3n´**



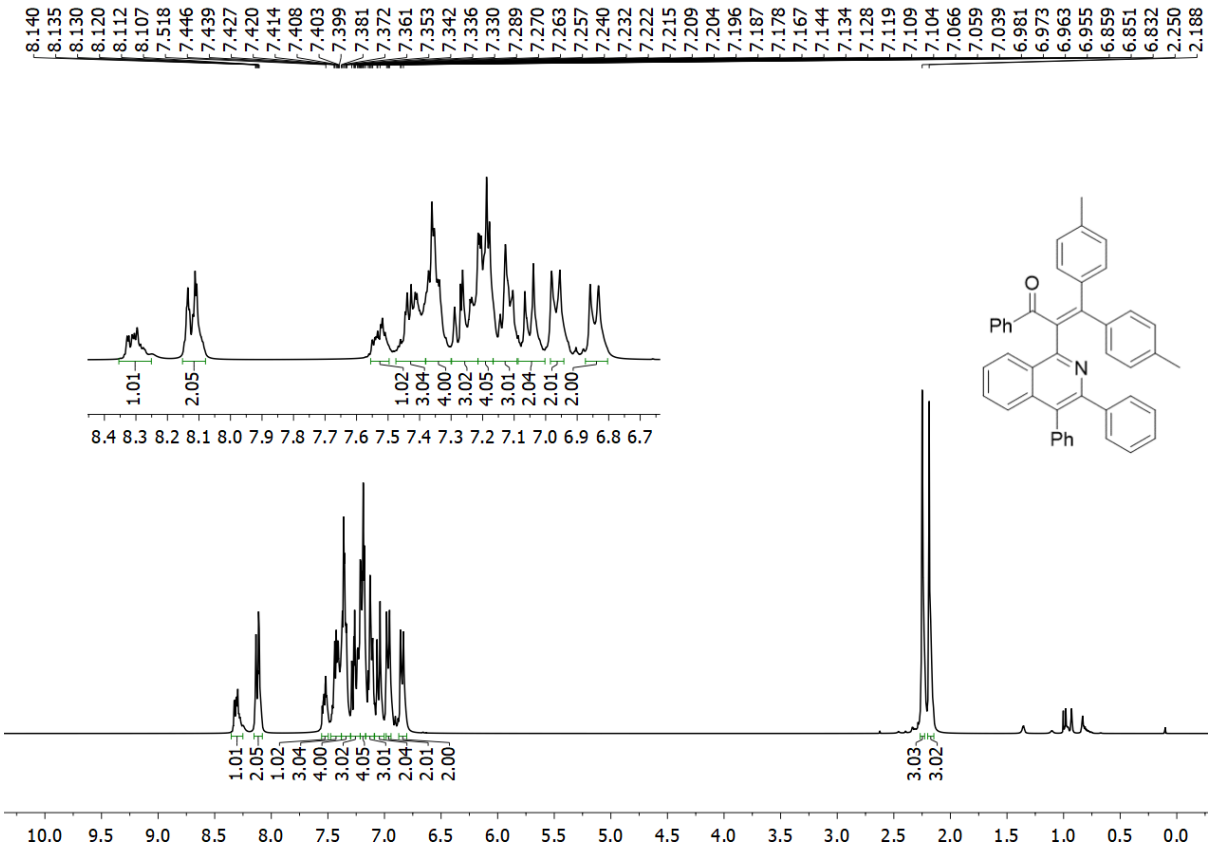
^{1}H NMR Compound **4a** (300 MHz, $CDCl_3$)



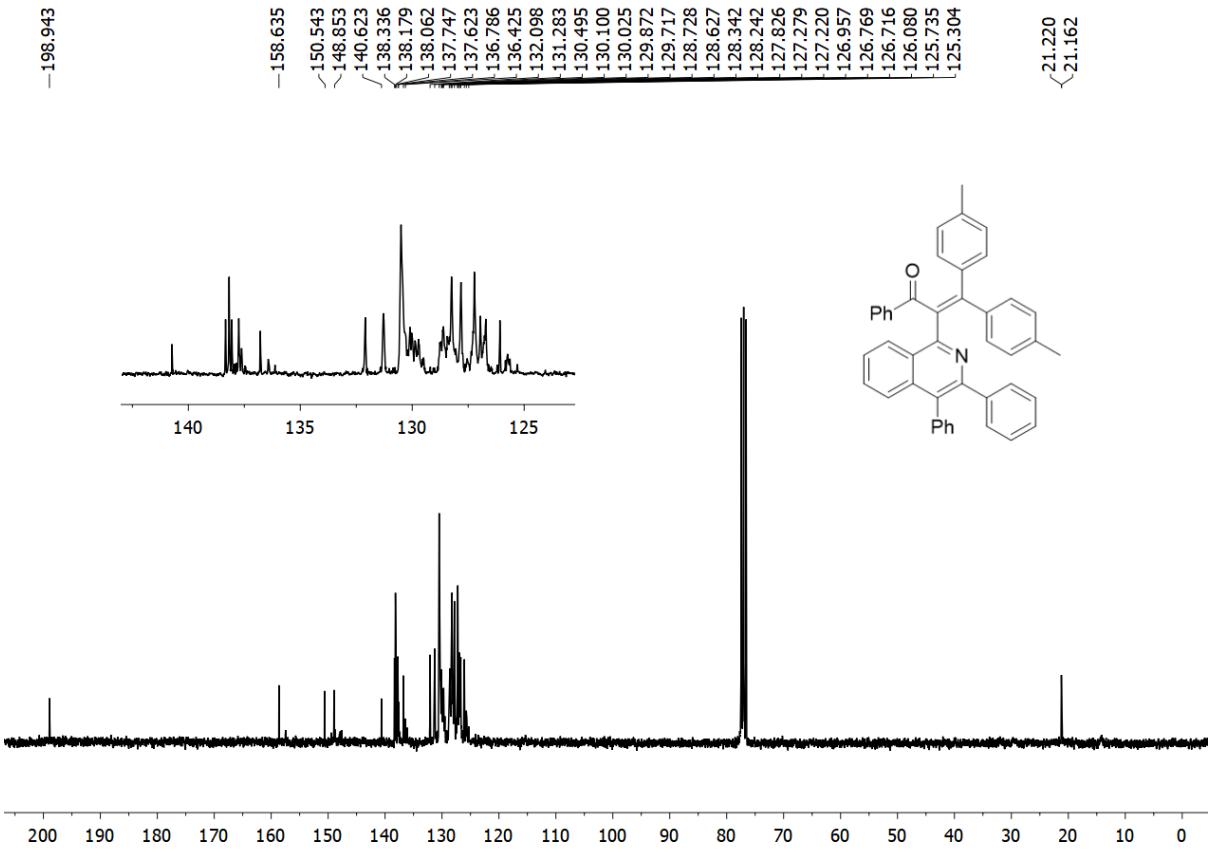
^{13}C NMR Compound **4a** (75 MHz, $CDCl_3$)



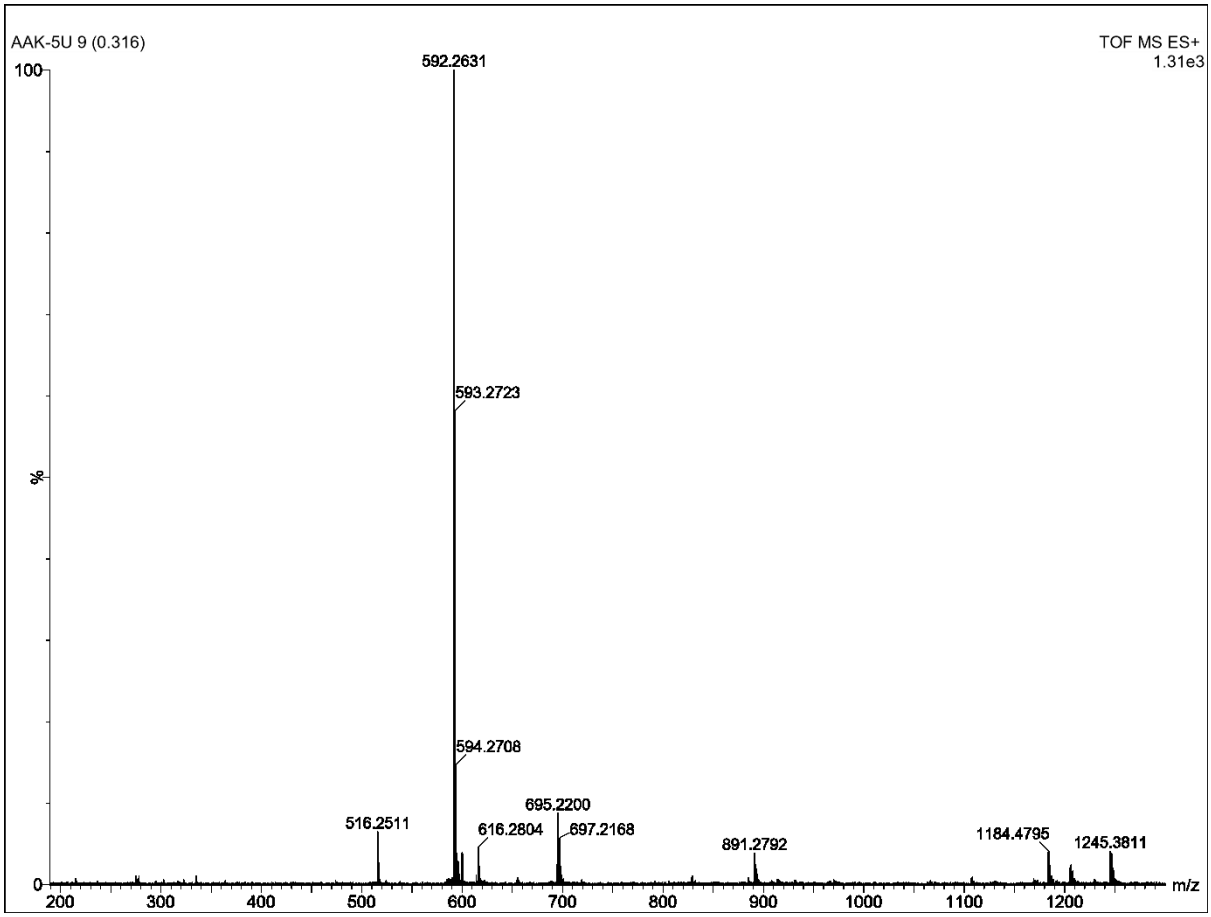
HRMS-ESI Compound **3n**



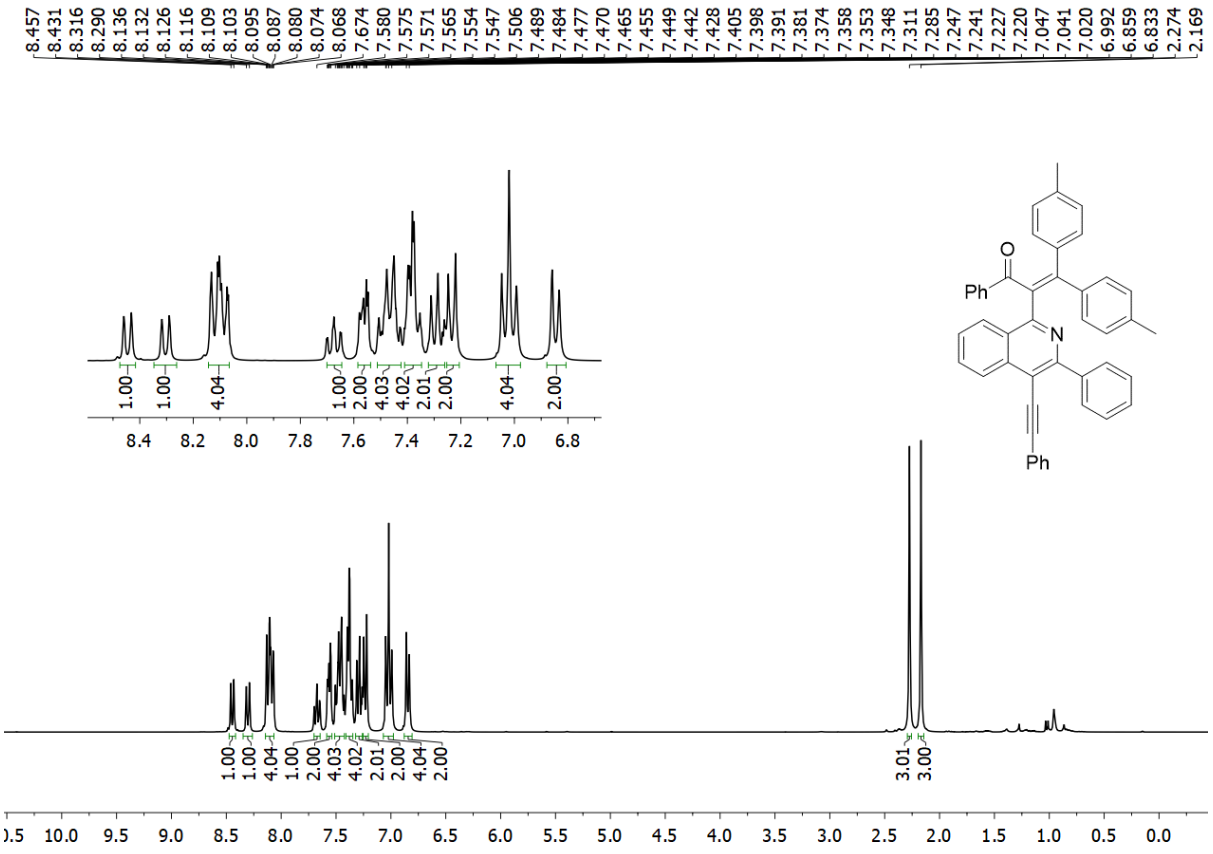
^{1}H NMR Compound **5c** (300 MHz, $CDCl_3$)



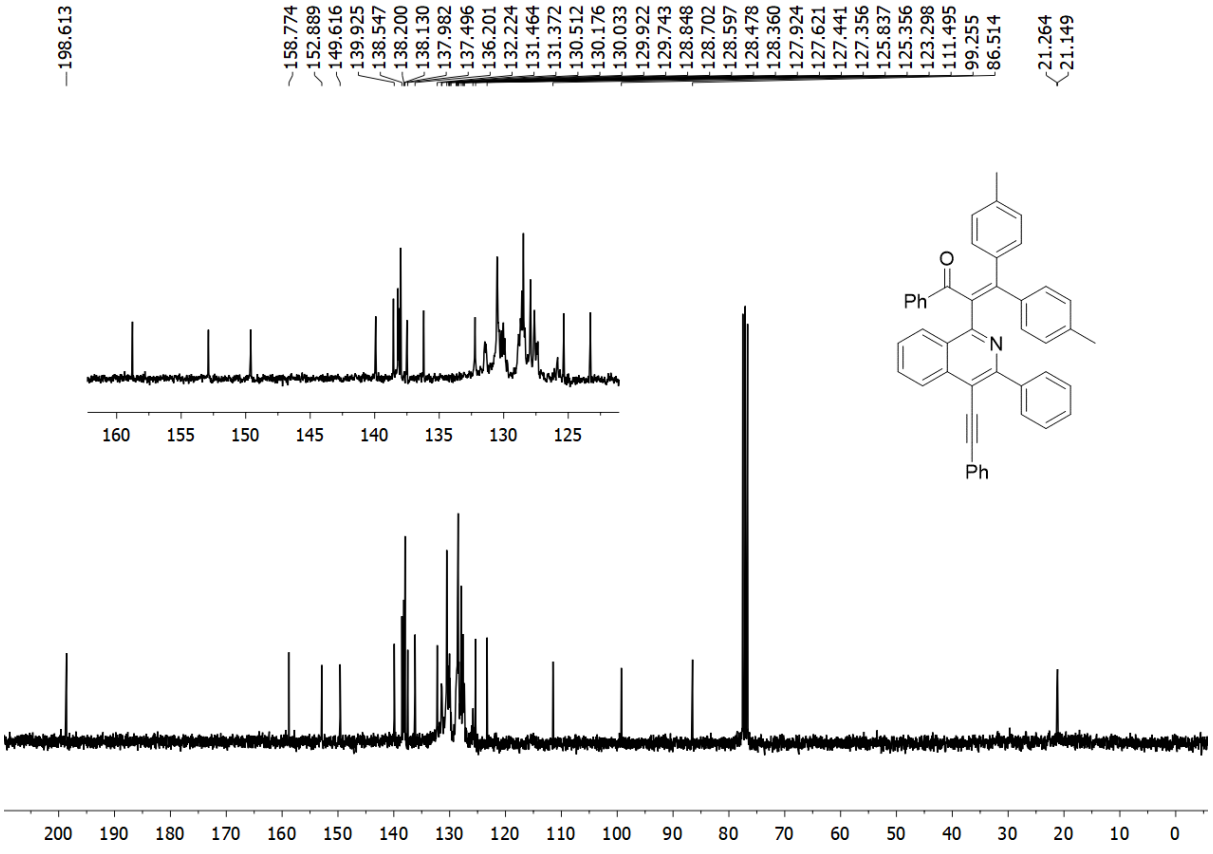
^{13}C NMR Compound **5c** (75 MHz, $CDCl_3$)



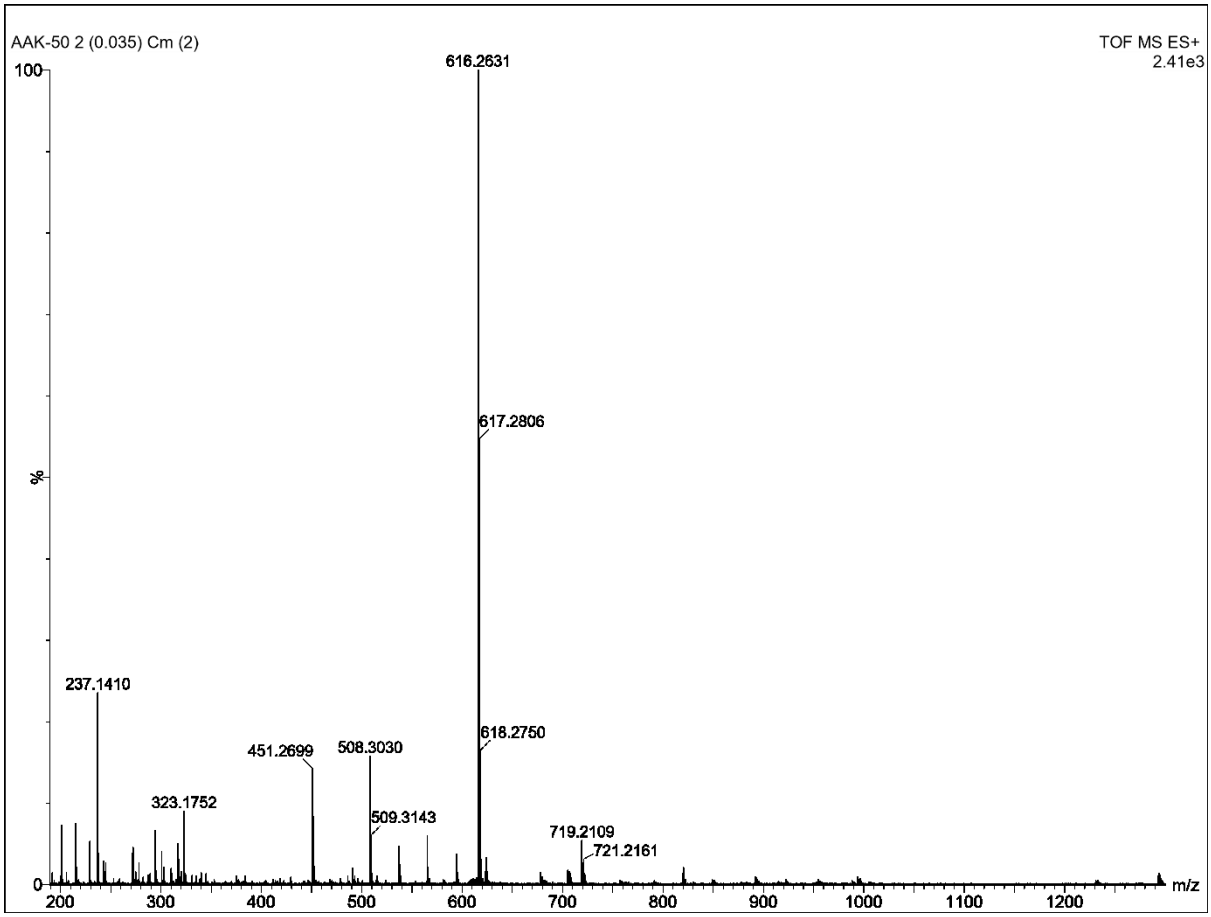
HRMS-ESI Compound **5c**



^{1}H NMR Compound **5c´** (300 MHz, $CDCl_3$)



^{13}C NMR Compound **5c´** (75 MHz, $CDCl_3$)



HRMS-ESI Compound **5c´**