Electronic Supplementary Material (ESI) for New Journal of Chemistry.

Remarkable selectivity of the 2-arylquinoline-based acyl hydrazones toward copper salts: Exploration of their catalytic applications in the copper catalysed *N*-arylation of indole derivatives and C1-Alkynylation of Tetrahydroisoquinolines by A^3 Reaction

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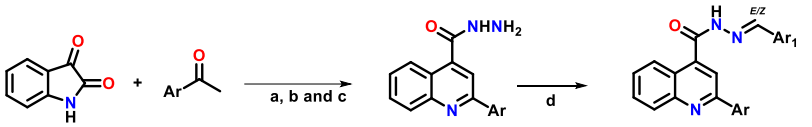
Contenido

1. Synthesis of AC ligands



L1: Ar=Phenyl; Ar_1=py
L2: Ar=Naphtyl; Ar_1=py
L3: Ar=3,4,5-trimethoxyphenyl; Ar_1=py
L4: Ar=Phenyl; Ar_1=2-hydroxyphenyl
L5: Quinoline was replaced by Phenyl; Ar_1=py

Scheme S1. Synthetic Pathway of the novel chelating ligand: a. KOH 33% (ac), EtOH, 78 °C; b. $SOCl_2$, MeOH, 65 °C; c. $NH_2NH_2{\cdot}H_2O$, MeOH, MW (170 °C, 14 bar, normal power), 20 min; and d. EtOH, trifluoracetic acid (TFA), 78 °C. Ligand **L4** and **L5** were synthesised as previously described by Xu and Dijken, respecyively.[1,2]

1.1. General procedure

Experimental section

General. All reagents and solvents were used as purchased. Flash chromatography was performed using silica gel (Merck, Kieselgel 60, 230-240 mesh or Scharlau 60, 230-240 mesh). Analytical thin layer chromatography (TLC) was performed using aluminum coated Merck Kieselgel 60 F254 plates. NMR spectra were recorded on a Bruker Avance 400 (^{1}H: 400 MHz; ^{13}C: 100 MHz) spectrometer at 298 K using partially deuterated solvents as internal standards. Coupling constants (*J*) are denoted in Hz and chemical shifts (δ) in ppm. Multiplicities are denoted as follows: s = singlet, d = doublet, t = triplet, m = multiplet, br = broad. UV-Vis spectra were recorded on a Genesys 10s spectrophotometer using dimethylsulfoxide (DMSO) as solvent. Emission spectra were recorded on a Photon Technology International spectrophotometer using DMSO as solvents. MALDI experiments were carried out in a Bruker ultrafleXtreme MALDI TOF-TOF instrument (Bruker Daltonics, Billerica, MA) equipped with a 1 kHz Smart Beam Nd:YAG laser (355 nm), 6 ns pulse and spot size of 100 μm -according to the manufacturer's specifications-, using the FlexAnalysis software.

Step a, b and c: As shown in Scheme S1, isatine (**1**) (2.0 mmol) and acetophenone (**2a**) (3.6 mmol) were dissolved in ethanol (8 mL). Then, aqueous solution of KOH 33% (28.6 mmol) was added, and the mixture was stirred and refluxed for 12 h. The ethanol was evaporated under reduced pressure and the crude was neutralized with HCl (pH ~5.0) and filtered. The filtered solid (1.33 mmol), without further purification, was dissolved in Methanol (10 mL) and cooled at 0 °C. Then, $SOCl_2$ (1.99 mmol) was added, and the solution was stirred and refluxed for 16 h. The methanol was evaporated under reduced pressure and the crude was neutralized with $NaHCO_3$, the product was extracted using AcOEt without further purification. The ester derivative (1.04 mmol) and hydrazinium hydroxide (6.24 mmol) was stirred and refluxed in ethanol (5 mL) for 4 h. Then, the solution was cooled, and the precipitate was filtered.

Each product was characterized as described previously.[1]

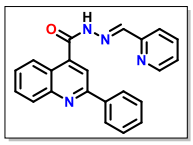
Step d:

Considering the *configurational dynamic* of acylhydrazones (ACs), likewise, although isomer *E* is generally obtained, hydrazides with increased steric interaction led to the formation of significant yields of the *Z* form,[3] we tried to standardized the reaction condition for obtaining only the isomer *E* (Table S1).

Table S1. Optimization of the step d in the synthesis of **L1**

Entry[a]	Heating	Cat.	Solvent (mL)	T (°C)	Time (h)	*E/Z*[e]	Yield (%)	Global yield (%)
1	Conventional	---	EtOH (10 mL)	78	7	3:1	87	41
2[b]	MW	---	EtOH (3 mL)	170	0.33	3:1	49	23
3[c]	Conventional	TFA	EtOH (10 mL)	78	0.16	3.3:1	90	43
4[d]	grinding	---	H_2O/AcOH (3:3 drops)	r.t.	0.16	3.3:1	67	32

[a] All entries were performed using 2-phenylquinoline-4-carbohydrazine (**3a**) (0.2 mmol) and 2-pyridincarbaldehyde (**4a**) (0.4 mmol).; [b] MW conditions: (120 °C, 9-10 bar, low power).; [c] It was used five drops of trifluoroacetic acid (TFA).[2]; [d] the reaction was performed in an agate mortar as previously described.[4]; [e] *E/Z* ratio was determined by NMR ^{1}H.



L1: Beige solid (90%). Mp. 190-193 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 12.46 (s, 1H), 8.66 (dd, J = 4.8, 0.7 Hz, 1H), 8.42 (d, *J* = 2.4 Hz, 2H), 8.41 – 8.37 (m, 2H), 8.37 – 8.34 (m, 1H), 8.28 – 8.23 (m, 1H), 8.21 – 8.17 (m, 1H), 8.11 – 8.06 (m, 1H), 7.98 – 7.85 (m, 2H), 7.73 – 7.69 (m, 1H), 7.62 – 7.55 (m, 3H), 7.49 – 7.46 (m, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.5, 156.3, 153.4, 150.1, 149.5, 148.4, 141.5, 138.5, 137.5, 130.9, 130.5, 130.2, 129.4, 128.0, 127.8, 127.7, 125.5, 125.3, 123.8, 120.6, 117.8.ppm. Calculated for $C_{22}H_{16}N_4O$ m/z 352.1324; found: : [M-H] m/z 351.1239.

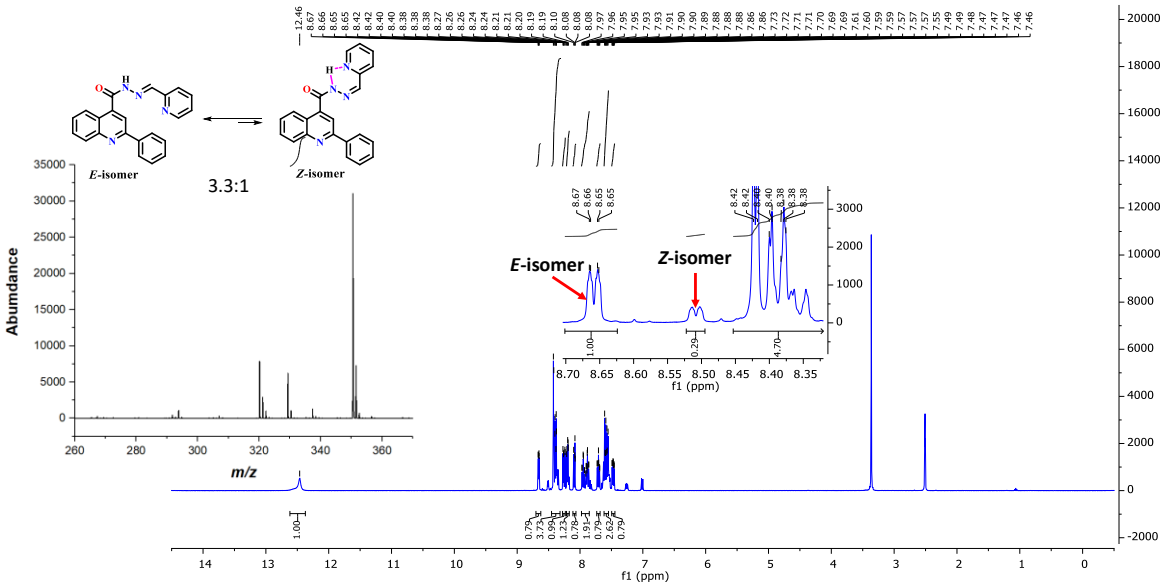
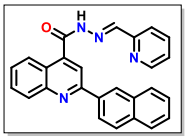


Figure S1. ^{1}H spectrum ($CDCl_3$) and MS characterization of **L1**



L2 was synthesised using the general procedure described for **L1**. Beige solid (88%). Mp. 220-223 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 12.52 (s, 1H), 9.00 (s, 1H), 8.67 – 8.56 (m, 16.8, 6.5 Hz, 3H), 8.45 (d, *J* = 9.7 Hz, 1H), 8.26 – 8.21 (m, 2H), 8.12 (dd, *J* = 12.3, 8.1 Hz, 3H), 8.04 – 7.87 (m, 3H), 7.72 (t, *J* = 7.6 Hz, 1H), 7.67 – 7.58 (m, 2H), 7.48 (t, *J* = 6.4 Hz, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.6, 156.1, 153.4, 150.1, 149.6, 148.5, 137.5, 135.8, 134.2, 133.6, 131.0, 130.2, 129.3, 129.0, 128.1, 128.1, 127.2, 125.6, 125.2, 125.0, 123.9, 120.7, 117.9 ppm. Calculated for $C_{26}H_{18}N_4O$ m/z 402.1481; found: [M-H] m/z 401.1482.

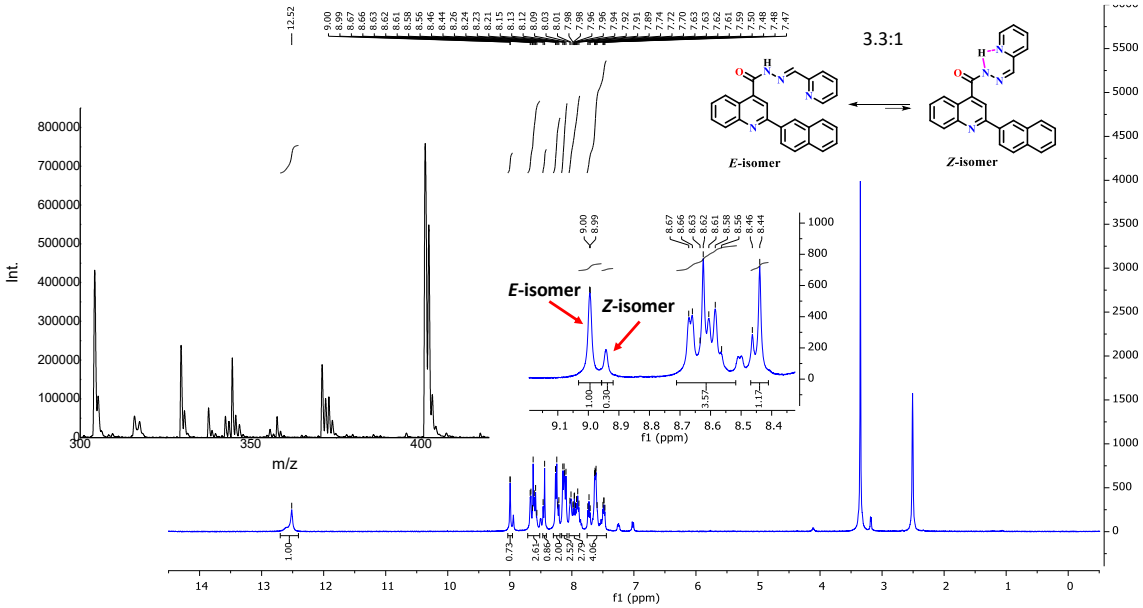
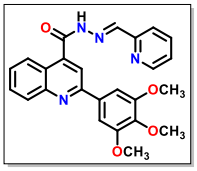


Figure S2. ^{1}H spectrum ($CDCl_3$) and MS characterization of **L2**



L3 was synthesised using the general procedure described for **L1.** Yellow solid (78%). Mp. 228-230 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 12.47 (s, 1H), 8.65 (d, *J* = 4.0 Hz, 1H), 8.50 (s, 1H), 8.40 (s, 1H), 8.20 – 8.16 (m, 2H), 8.08 (d, *J* = 7.9 Hz, 1H), 7.97 – 7.93 (m, 1H), 7.89 – 7.85 (m, 1H), 7.71 – 7.66 (m, 3H), 7.47 (dd, *J* = 7.5, 5.0 Hz, 1H), 3.96 (s, 6H), 3.77 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.6, 156.0, 153.8, 153.4, 150.1, 149.6, 148.2, 141.7, 140.0, 137.5, 134.0, 130.8, 130.1, 127.8, 125.4, 125.2, 123.7, 120.6, 117.8, 105.5, 105.3, 60.7, 56.7 ppm. Calculated for $C_{25}H_{22}N_4O_4$ m/z 442.1641; found: [M-H] m/z m/z 441.1605.

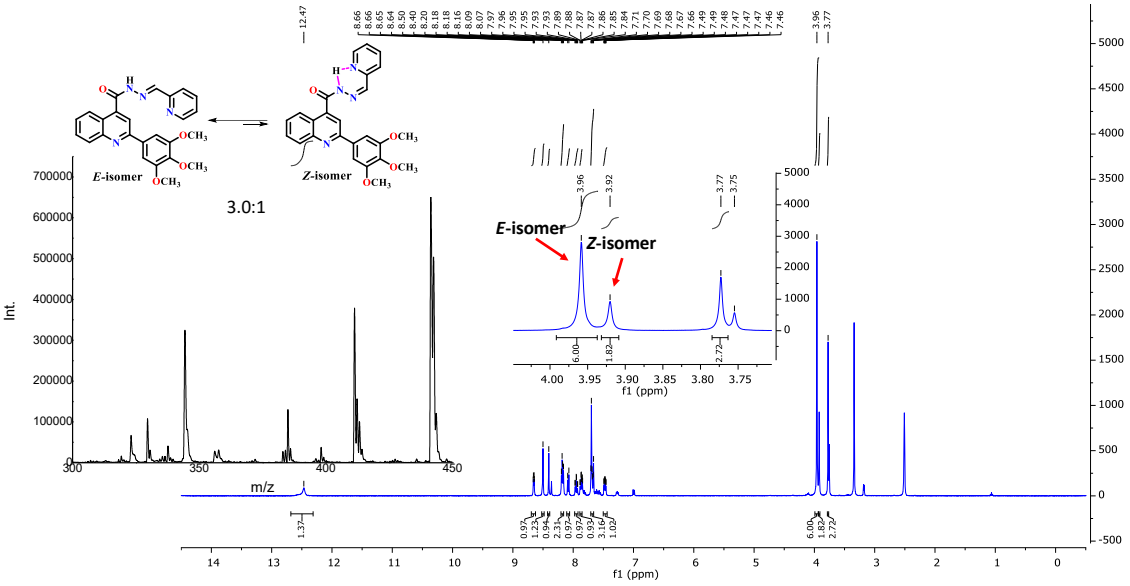
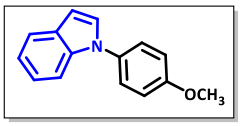


Figure S3. ^{1}H spectrum ($CDCl_3$) and MS characterization of **L3**

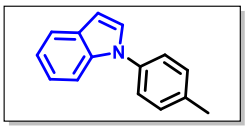
2. Catalysis of Ullmann *N*-arylation of Heterocycles

2.1. General procedure:

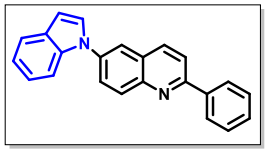
Aryl halide (0.5 mmol), indole (0.7 mmol), K_2CO_3 (0.7 mmol), CuI (0.05 mmol), and ligand (0.05 mmol) were dissolved in 2 mL of DMSO and heated at 110 °C for 24 h. The cooled solution was partitioned between H_2O and EtOAc. The aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude was purified by SiO_2 using Dichloromethane/Petroleum ether (2/1).



3 was synthesised using the general procedure described above. White solid (99%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.76 (d, *J* = 8.0 Hz, 1H), 7.45 (d, *J* = 8.0 Hz, 1H), 7.37 (d, *J* = 12.0 Hz, 2H), 7.25 (d, *J* = 3.2 Hz, 1H), 7.21 – 7.12 (m, 2H), 7.00 (d, *J* = 8.0 Hz, 2H), 6.64 (dd, *J* = 3.2, 0.9 Hz, 1H), 3.84 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ: 158.3, 136.4, 132.9, 129.0, 128.3, 126.0, 122.2, 121.1, 120.1, 114.8, 110.43, 102.9, 55.6 ppm. Calculated for $C_{15}H_{13}NO$ m/z 223.0997; found: m/z 223.2992.

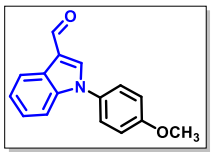


4 was synthesised using the general procedure described above. White solid (93%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.67 (d, *J* = 8.0 Hz, 1H), 7.52 (d, *J* = 8.2, 1H), 7.37 (d, *J* = 8.0 Hz, 2H), 7.31 – 7.28 (m, 3H), 7.22 – 7.13 (m, 2H), 6.65 (dd, *J* = 3.2, 0.9 Hz, 1H), 2.42 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ: 137.3, 136.4, 136.0, 130.2, 130.2, 129.2, 128.1, 124.4, 122.2, 121.1, 110.5, 103.2, 21.1 ppm. Calculated for $C_{15}H_{13}N$ m/z 207.1048; found: m/z 207.1052.

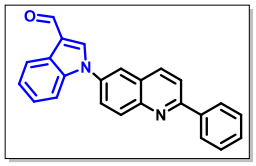


5 was synthesised using the general procedure described above. Beige solid (99%). Mp. 145-147 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.30 (d, *J* = 8.0 Hz, 1H), 8.23 (d, *J* = 8.7 Hz, 1H), 8.20 – 8.17 (m, 2H), 7.95 – 7.89 (m, 3H), 7.73 (d, *J* = 7.7 Hz, 1H), 7.67 (dd, *J* = 8.2, 1.0 Hz,

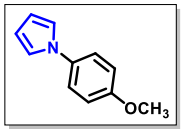
1H), 7.57 – 7.53 (m, 2H), 7.50 – 7.46 (m, 1H), 7.45 (d, *J* = 4.0 Hz, 1H), 7.29 – 7.25 (m, 1H), 7.23 – 7.19 (m, 1H), 6.75 (dd, J = 3.2, 0.9 Hz, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ: 157.4, 146.7, 139.4, 137.6, 136.5, 136.0, 131.5, 129.5, 129.0, 128.0, 127.7, 127.6, 126.8, 122.7, 121.3, 121.0, 120.7, 119.9, 110.5, 104.3 ppm. Calculated for $C_{23}H_{16}N_2$ m/z 320.1313; found: m/z 320.1308.



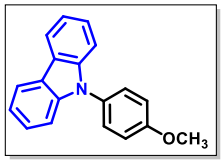
6 was synthesised using the general procedure described above. Beige solid (69%). Mp. 105-107 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 10.09 (s, 1H), 7.40 (d, *J* = 8.0 Hz, 1H), 7.85 (s, 1H), 7.46 – 7.38 (m, 3H), 7.37 – 7.30 (m, 2H), 7.07 (d, *J* = 8.0 Hz, 2H), 3.90 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ: 184.9, 159.5, 138.5, 138.0, 131.0, 126.4, 125.3, 124.5, 123.3, 122.2, 119.3, 115.1, 111.0, 55.7 ppm. Calculated for $C_{16}H_{13}NO_2$ m/z 251.0946; found: m/z 251.0944.



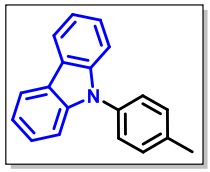
7 was synthesised using the general procedure described above. Beige solid (99%). Mp. 141-143 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 10.15 (s, 1H), 8.44 – 8.40 (m, 1H), 8.36 (d, *J* = 8.9 Hz, 1H), 8.28 (d, *J* = 8.6 Hz, 1H), 8.21 (d, *J* = 7.0 Hz, 2H), 8.02 (s, 1H), 8.00 (d, *J* = 8.6 Hz, 1H), 7.96 (d, *J* = 2.4 Hz, 1H), 7.88 (dd, *J* = 8.9, 2.4 Hz, 1H), 7.58 – 7.55 (m, 3H), 7.53 - 7.59 (m, 1H), 7.42 – 7.36 (m, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ: 185.0, 158.4, 147.4, 139.1, 138.1, 137.6, 136.7, 135.8, 132.0, 129.9, 129.0, 127.6, 127.5, 126.5, 125.7, 124.9, 123.7, 122.5, 122.4, 120.3, 120.1, 111.0 ppm. Calculated for $C_{24}H_{16}N_2O$ m/z 348.1263; found: m/z 348.1259.



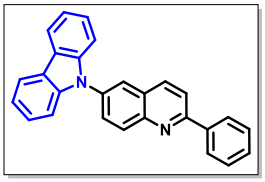
8 was synthesised using the general procedure described above. Beige solid (70%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.30 (d, *J* = 9.0 Hz, 2H), 6.99 (t, *J* = 2.2 Hz, 2H), 6.94 (d, *J* = 9.0 Hz, 2H), 6.32 (t, *J* = 2.2 Hz, 2H), 3.82 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ: 157.7, 134.5, 122.2, 119.7, 114.6, 109.9, 55.6 ppm. Calculated for $C_{11}H_{11}NO$ m/z 173.0841; found: m/z 173.084.



9 was synthesised using the general procedure described above. Beige solid (98%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.13 (d, *J* = 8.0 Hz, 2H), 7.44 (d, *J* = 9.0 Hz, 2H), 7.39 (t, *J* = 2.2 Hz, 2H), 7.33 – 7.31 (m, 2H), 7.28 – 7.24 (m, 2H), 7.10 (d, *J* = 9.0 Hz, 2H), 3.82 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ: 158.9, 141.4, 130.3, 128.6, 125.9, 123.1, 120.3, 119.7, 115.1, 109.7, 55.6 ppm. Calculated for $C_{19}H_{15}NO$ m/z 273.1154; found: m/z 273.1156

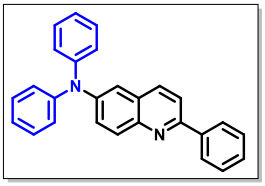


10 was synthesised using the general procedure described above. Beige solid (95%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.13 (d, *J* = 7.8 Hz, 2H), 7.43 (d, *J* = 8.4 Hz, 2H), 7.40 – 7.35 (m, 6H), 7.30 – 7.22 (m, 2H), 2.48 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ: 141.1, 137.4, 135.0, 130.5, 127.0, 125.9, 123.3, 120.3, 119.7, 109.8, 21.3 ppm. Calculated for $C_{19}H_{15}N$ m/z 257.1204; found: m/z 257.1206



11 was synthesised using the general procedure described above. Beige solid (95%). Mp. 168-171 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.38 (d, *J* = 8.9 Hz, 1H), 8.27 – 8.14 (m, 5H), 7.99 (d, *J* = 2.3 Hz, 1H), 7.94 (d, *J* = 8.6 Hz, 1H), 7.91 (dd, *J* = 8.9, 2.3 Hz, 1H), 7.60 – 7.52 (m, 2H), 7.52 – 7.44 (m, 3H), 7.44 – 7.40 (m, 2H), 7.33 – 7.29 (m, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ:

157.9, 147.2, 140.9, 139.4, 136.6, 135.5, 131.7, 129.6, 129.0, 127.8, 127.6, 126.2, 124.7, 123.6, 120.5, 120.3, 119.8, 109.8 ppm. Calculated for $C_{27}H_{18}N_2$ m/z 370.1470; found: m/z 370.1465.



12 was synthesised in high yield using the general procedure for Buchwald reaction. Briefly, Aryl iodide (0.5 mmol), diphenylamine (0.7 mmol), *t*-BuOK (0.7 mmol), x-Phos-Pd-G2 (0.005 mmol) were dissolved in 1 mL of 1,4-dioxane and heated at 110 °C for 24 h. The cooled solution was partitioned between H_2O and EtOAc. The aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude was purified by SiO_2 using Dichlorometane/Petroleum ether (2/1). Yellow solid (96%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.15 – 8.10 (m, 2H), 8.02 (d, *J* = 9.1 Hz, 1H), 7.94 (dd, *J* = 8.7, 0.8 Hz, 1H), 7.78 (d, *J* = 8.6 Hz, 1H), 7.55 – 7.49 (m, 3H), 7.47 – 7.41 (m, 1H), 7.36 – 7.28 (m, 5H), 7.20 – 7.15 (m, 4H), 7.12 – 7.07 (m, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ: 155.6, 147.5, 145.9, 135.5, 130.5, 129.5, 129.0, 128.8, 128.2, 127.4, 127.3, 124.8, 123.5, 119.3, 118.1 ppm. Calculated for $C_{27}H_{20}N_2$ m/z 372.1626; found: m/z 372.1622.

3. Catalysis of A^3 redox-neutral coupling reaction

3.1. General procedure:

A crimper vial equipped with a magnetic stir bar was charged with 1,2,3,4-tetrahydroisoquinoline **13** (1.4 mmol), aldehyde (1.4 mmol) and alkyne (1 mmol), CuI (10 mol%), Ligand 1 (10 mol%) and 4 Å molecular sieves. The vial was sealed and was purged three times with argon and degassed toluene (0.2 M) was added. Then, the reaction mixture was heated over 24 hours at 100°C. After cooling to room temperature, the crude mixture was loaded directly onto celite; then, purified by column chromatography (silica gel) using hexane/ethyl acetate mixtures as the eluent.

Previous reports have shown the formation of the *endo*- and *exo*- isomers, however, when using ligand, it was observed in the ^{1}H NMR spectrum a complete isomerization of the *exo*- to *endo*- intermediate (Figure S4). This indicates a regioselectivity of the CuI /**L1** catalytic system and the determining role that ligands have on the activation of the catalytic system.

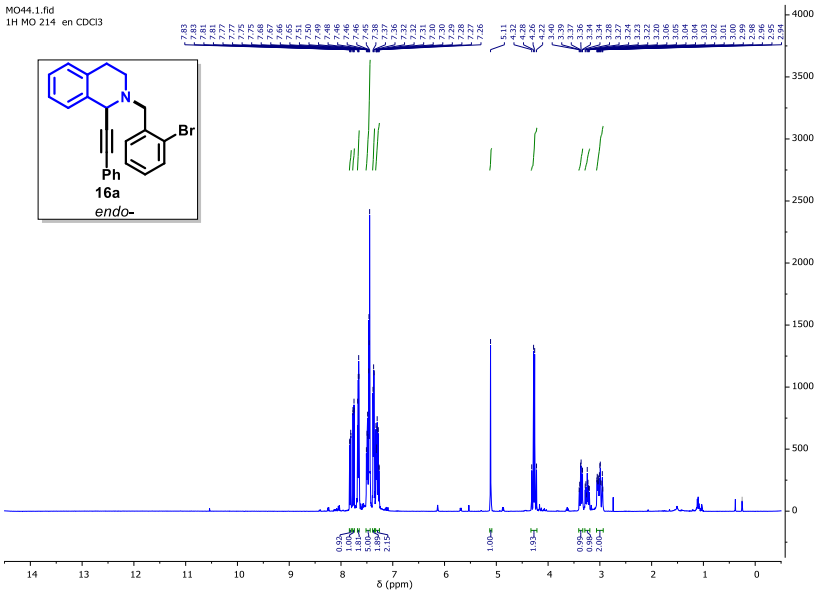
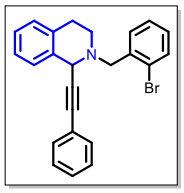
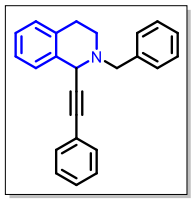


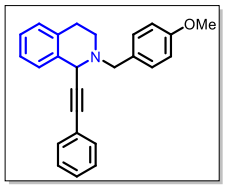
Figure S4. ^{1}H NMR spectrum of crude of reaction for compound **16a**



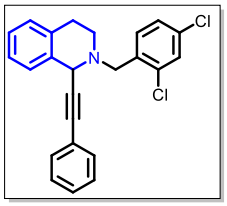
16a: yellow liquid (100%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.69 (dd, *J*= 7.7, 1.5 Hz, 1H), 7.64 (dd, *J* = 8.0, 1.1 Hz, 1H), 7.56–7.51 (m, 2H), 7.37 (m, 5H), 7.27–7.24 (m, 2H), 7.23–7.17 (m, 2H), 4.97 (s, 1H), 4.16 (d, *J* = 15.4 Hz, 1H), 4.10 (d, *J* = 15.4, 1H), 3.28–3.08 (m, 2H), 2.89-2.83 (m, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ: 137.8, 135.5, 134.1, 132.9, 131.8 (2C), 130.7, 129.1, 128.5, 128.2, 128.1 (2C), 127.8, 127.3, 127.0, 125.9, 124.9, 123.2, 87.7, 86.8, 58.9, 54.7, 45.8, 29.2 ppm. ESI Calculated for $C_{24}H_{20}BrN$ $(M+H)^+$: 402.0852, Found: 402.0901.



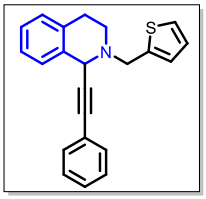
19a: color-less oil (85%). ^{1}H NMR (400 MHz, $CDCl_3$) δ : 7.55–7.49 (m, 4H), 7.40 (t, *J* = 7.3 Hz, 3H), 7.37–7.30 (m, 4H), 7.24–7.18 (m, 3H), 4.86 (s, 1H), 4.03 (d, *J* = 13.3 Hz, 1H), 3.98 (d, *J* = 13.3 Hz, 1H), 3.21–3.02 (m, 2H), 2.94–2.78 (m, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ: 138.3, 135.5, 134.1, 131.8 (2C), 129.3 (2C), 129.0, 128.3 (2C), 128.2 (2C), 128.0, 127.8, 127.2, 126.9, 125.8, 123.3, 87.5, 86.9, 59.6, 54.4, 45.8, 29.0 ppm. ESI Calculated for $C_{24}H_{21}N$ $(M+H)^+$: 324.1747, Found: 324.1756.



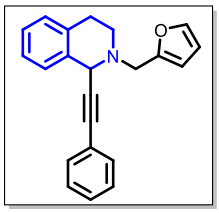
20a: yellow liquid (98%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.51–7.47 (m, 2H), 7.43 (d, *J* = 8.6 Hz, 2H), 7.35–7.28 (m, 4H), 7.22–7.15 (m, 3H), 6.92 (d, *J* = 8.7 Hz, 2H), 4.81 (s, 1H), 3.93 (d, *J* = 12.9 Hz, 1H), 3.89 (d, *J* = 12.8 Hz, 1H), 3.85 (s, 3H), 3.17–3.01 (m, 2H), 2.91–2.80 (m, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ: 158.8, 135.4, 134.1, 131.8 (2C), 130.5 (2C), 130.2, 129.0, 128.2 (2C), 128.0, 127.8, 126.9, 125.8, 123.2, 113.7 (2C), 87.5, 86.9, 58.9, 55.3, 54.1, 45.7, 29.0 ppm. ESI calculated for $C_{25}H_{23}NO$ $(M+H)^+$: 354.1852, Found: 354.1907.



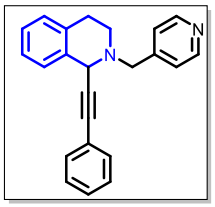
21a: yellow liquid (75%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.51–7.47 (m, 2H), 7.40–7.32 (m, 6H), 7.29–7.21 (m, 4H), 4.90 (s, 1H), 4.06 (d, *J* = 3.7 Hz, 2H), 3.20–3.03 (m, 2H), 2.89–2.82 (m, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ: 133.3, 131.9 (C2), 131.5, 129.4, 129.1 (2C), 128.3 (2C), 128.2 (2C), 127.8, 127.6, 127.1, 127.1, 126.7, 126.0, 123.1, 87.5, 86.9, 55.9, 54.8, 45.9, 29.2 ppm. Full characterization can be consulted at the reference.[5]



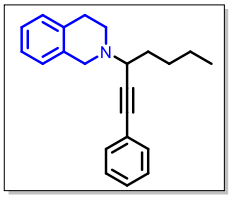
22a: yellow oil (100%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.58 (dd, *J* = 6.6, 3.0 Hz, 2H), 7.40 (dd, *J* = 4.0, 2.6 Hz, 4H), 7.37 (dd, *J* = 5.1, 1.0 Hz, 1H), 7.31–7.27 (m, 2H), 7.25 (q, *J* = 5.6 Hz, 1H), 7.20 (d, *J* = 3.3 Hz, 1H), 7.10 (dd, *J* = 5.0, 3.5 Hz, 1H), 5.04 (s, 1H), 4.28 (q, *J* = 13.8 Hz, 2H), 3.26–3.11 (m, 2H), 3.06–2.89 (m, 2H) ppm.^{13}C NMR (100 MHz, $CDCl_3$) δ: 141.9, 135.2, 134.0, 131.8 (C2), 129.0, 128.2 (C2), 128.1, 127.8, 127.0, 126.5, 126.3, 125.9, 125.2, 123.1, 87.3, 86.9, 54.3, 54.0, 45.6, 29.1 ppm. ESI calculated for $C_{22}H_{19}NS$ $(M+H)^+$: 330.1311, Found: 330.1347.



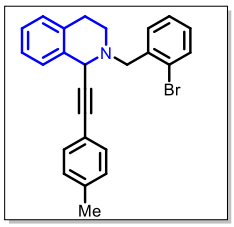
23a: yellow oil (80%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.50–7.46 (m, 2H), 7.46–7.42 (m, 1H), 7.34–7.31 (m, 4H), 7.21–7.17 (m, 2H), 7.14 (dd, *J* = 6.3, 2.7 Hz, 1H), 6.39 (d, *J* = 1.6 Hz, 2H), 4.85 (s, 1H), 4.00 (q, *J* = 14.0 Hz, 2H), 3.17–3.01 (m, 2H), 2.94–2.84 (m, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ: 151.7, 142.4, 135.1, 133.8, 131.8 (C2), 128.9, 128.2 (C2), 128.1, 127.8, 126.9, 125.8, 123.1, 110.1, 109.0, 87.1, 86.9, 54.3, 51.9, 45.9, 28.9 ppm. ESI calculated for $C_{22}H_{19}NO$ $(M+H)^+$: 314.1539, Found: 314.1595.



24a: yellow oil (65%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.57 (d, *J* = 2.2 Hz, 2H), 7.45–7.41 (m, 2H), 7.40 (d, *J* = 5.6 Hz, 2H), 7.29 (ddt, *J* = 7.0, 5.7, 2.1 Hz, 4H), 7.21–7.17 (m, 2H), 7.14 (dd, *J* = 6.9, 2.1 Hz, 1H), 4.79 (s, 1H), 3.93 (d, *J* = 1.8 Hz, 2H), 3.14–3.00 (m, 2H), 2.85–2.75 (m, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ: 149.8 (C2), 147.8, 135.1, 133.7, 131.7 (C2), 129.0, 128.2 (2C), 128.2, 127.7, 127.1 (2C), 125.9, 124.0, 122.9, 86.9, 86.9, 58.5, 54.6, 45.9, 29.0 ppm. ESI calculated for $C_{23}H_{20}N_2$ $(M+H)^+$: 325.1699, Found: 325.1718.

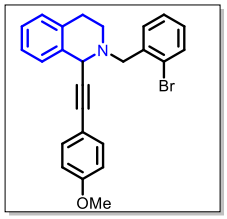


25b: yellow oil (45%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: δ 7.48–7.44 (m, 2H), 7.33–7.30 (m, 3H), 7.16 (d, *J* = 3.8 Hz, 3H), 7.10 (dd, *J* = 6.3, 2.2 Hz, 1H), 3.98 (d, *J* = 14.7 Hz, 1H), 3.86–3.75 (m, 2H), 3.10–3.04 (m, 1H), 3.02–2.95 (m, 1H), 2.87–2.81 (m, 1H), 1.92–1.85 (m, 2H), 1.67–1.41 (m, 5H), 0.99 (t, *J*= 7.2 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ: 135.3, 134.5, 131.8 (2C), 128.7, 128.3 (2C), 128.0, 126.8, 126.0, 125.6, 123.4, 87.4, 86.1, 58.0, 52.1, 47.5, 33.4, 29.7, 29.1, 22.6, 14.2 ppm. ESI calculated for $C_{22}H_{25}N$ $(M+H)^+$: 304.2060, Found: 304.2091.

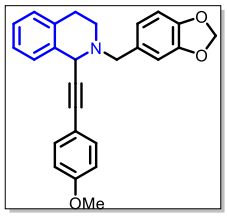


26a: yellow oil (91%).^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.69 (dd, *J* = 7.6, 1.3 Hz, 1H), 7.65–7.62 (m, 1H), 7.43 (d, *J* = 8.1 Hz, 2H), 7.38–7.35 (m, 2H), 7.27–7.23 (m, 2H), 7.22–7.18 (m, 2H), 7.16 (d, *J*= 7.9 Hz, 2H), 4.96 (s, 1H), 4.18–4.06 (m, 2H), 3.28–3.07 (m, 2H), 2.94–2.83 (m, 2H), 2.40 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ: 138.1, 137.9, 135.7, 134.1, 132.9, 131.8 (2C), 130.7,

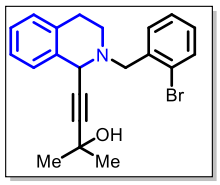
129.1, 129.0 (2C), 128.5, 127.9, 127.3, 127.0, 125.9, 124.9, 120.2, 87.0, 86.8, 58.9, 54.8, 45.8, 29.3, 21.5 ppm. (ESI): m/z calculated for $C_{25}H_{22}BrN$ $[M + H]^+$: 416.1008; found: 416.0993.



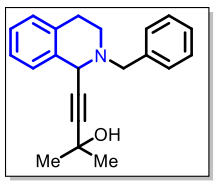
27a: yellow oil (65%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.75 (dd, *J* = 7.6, 1.4 Hz, 1H), 7.69 (dd, *J* = 7.9, 1.0 Hz, 1H), 7.53 (d, *J* = 8.9 Hz, 2H), 7.44–7.37 (m, 2H), 7.34–7.26 (m, 2H), 7.26–7.20 (m, 2H), 6.93 (d, **J** = 8.9 Hz, 2H), 5.02 (s, 1 H), 4.20–4.13 (m, 2H), 3.86 (s, 3H), 3.33–3.12 (m, 2H), 2.98–2.88 (m, 2H) ppm.^{13}C NMR (100 MHz, $CDCl_3$) δ: 159.4, 137.8, 135.7, 134.0, 133.2 (2C), 132.8, 130.6, 129.0, 128.5, 127.8, 127.3, 126.9, 125.8, 124.8, 115.3, 113.8 (2C), 86.6, 86.1, 58.9, 55.2, 54.8, 45.8, 29.2 ppm. ESI calculated for $C_{25}H_{22}BrNO$ $[M + H]^+$: 432.0958, Found:432.0940.



28a: colorless oil (50%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.44–7.39 (m, 2H), 7.31–7.27 (m, 1H), 7.21–7.13 (m, 3H), 7.02 (d, *J* = 1.4 Hz, 1H), 6.94 (dd, *J* = 8.0, 1.3 Hz, 1H), 6.87–6.83 (m, 2H), 6.81 (d, *J* = 7.9 Hz, 1H), 5.97 (d, *J* = 2.2 Hz, 2H), 4.79 (s, 1H), 3.86 (d, *J* = 3.7 Hz, 2H), 3.83 (s, 3 H), 3.13–3.01 (m, 2H), 2.88–2.79 (m, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ: 159.4, 147.6, 146.7, 135.7, 134.0, 133.1 (2C), 132.3, 128.9, 127.8, 126.8, 125.8, 122.3, 115.3, 113.8 (2C), 109.6, 107.9, 100.8, 86.6, 85.9, 59.3, 55.3, 54.2, 45.6, 29.0 ppm. ESI calculated for $C_{26}H_{23}NO_3$ $[M + H]^+$: 398.1751, Found: 398.1473.



29a: yellow oil (30%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.59 (ddd, J= 7.9, 3.2, 1.5 Hz, 2H), 7.31 (td, J= 7.6, 1.4 Hz, 1H), 7.24–7.12 (m, 5H), 4.71 (s, 1H), 3.96 (s, 2H), 3.12–2.97 (m, 2H), 2.87–2.73 (m, 2H), 1.98 (s, 1H),1.57 (d, J= 2.0 Hz, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ: 137.7, 135.3, 134.0, 132.8, 130.5, 128.9, 128.4, 127.6, 127.3, 126.9, 125.7, 124.7, 91.3, 80.0, 65.3, 58.7, 54.0, 45.6, 31.7, 31.7, 29.1 ppm. ESI calculated for $C_{21}H_{22}BrNO$ $(M+H)^+$: 384.0958, Found: 384.0985.



30a: yellow oil, (25%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.48–7.45 (m, 2H), 7.39–7.34 (m, 3H), 7.19-7.11 (m, 4H) , 4.61 (s, 1H), 3.92 (d, *J* = 13.1 Hz, 1H), 3.82 (d, *J* = 13.1 Hz, 1H), 3.02–2.96 (m, 2H), 2.83–2.75 (m, 2H), 2.02 (s, 1H), 1.57 (s, 6H) ppm.^{13}C NMR (100 MHz, $CDCl_3$) δ: 138.2, 135.4, 134.0, 129.2 (2C), 128.9, 128.3 (2C), 127.7, 127.2, 126.8, 125.7, 91.4, 79.9, 65.3, 59.5, 53.7, 45.7, 31.7, 31.7, 28.9 ppm. ESI calculated for $C_{21}H_{23}NO$ $(M+H)^+$: 306.1852, Found: 306.1883.

4. ^{1}H and ^{13}C NMR spectra and MS characterization

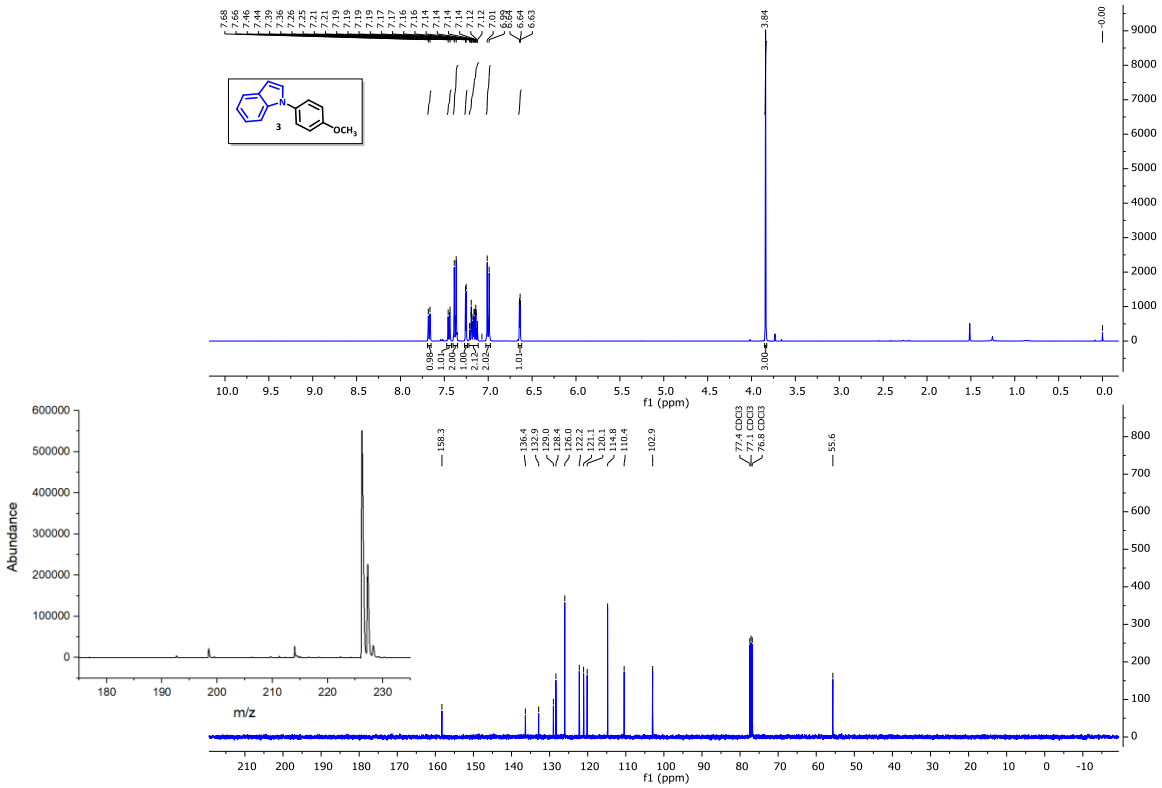


Fig S5. ^{1}H and ^{13}C NMR spectra ($CDCl_3$) and MS characterization of the compound **3.**

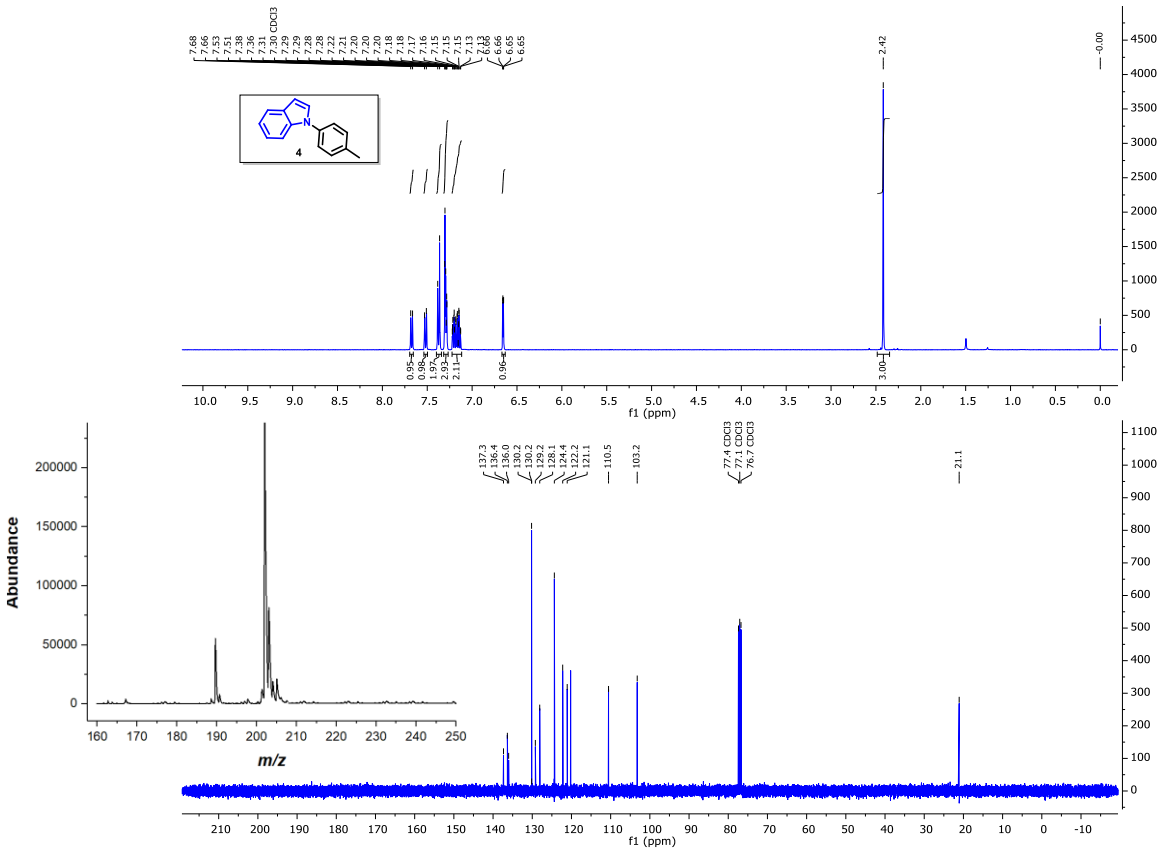


Fig S6. ^{1}H and ^{13}C NMR spectra ($CDCl_3$) of the compound **4.**

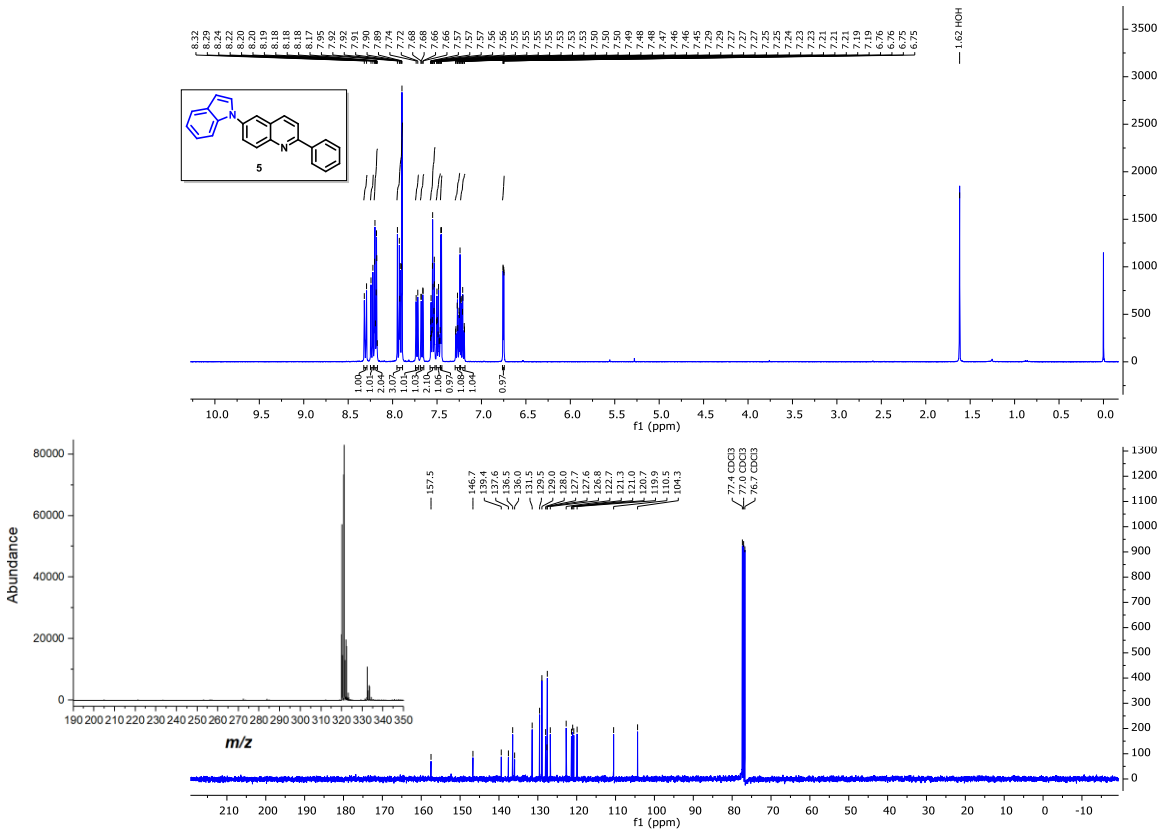


Fig S7. ^{1}H and ^{13}C NMR spectra ($CDCl_3$) and MS characterization of the compound **5.**

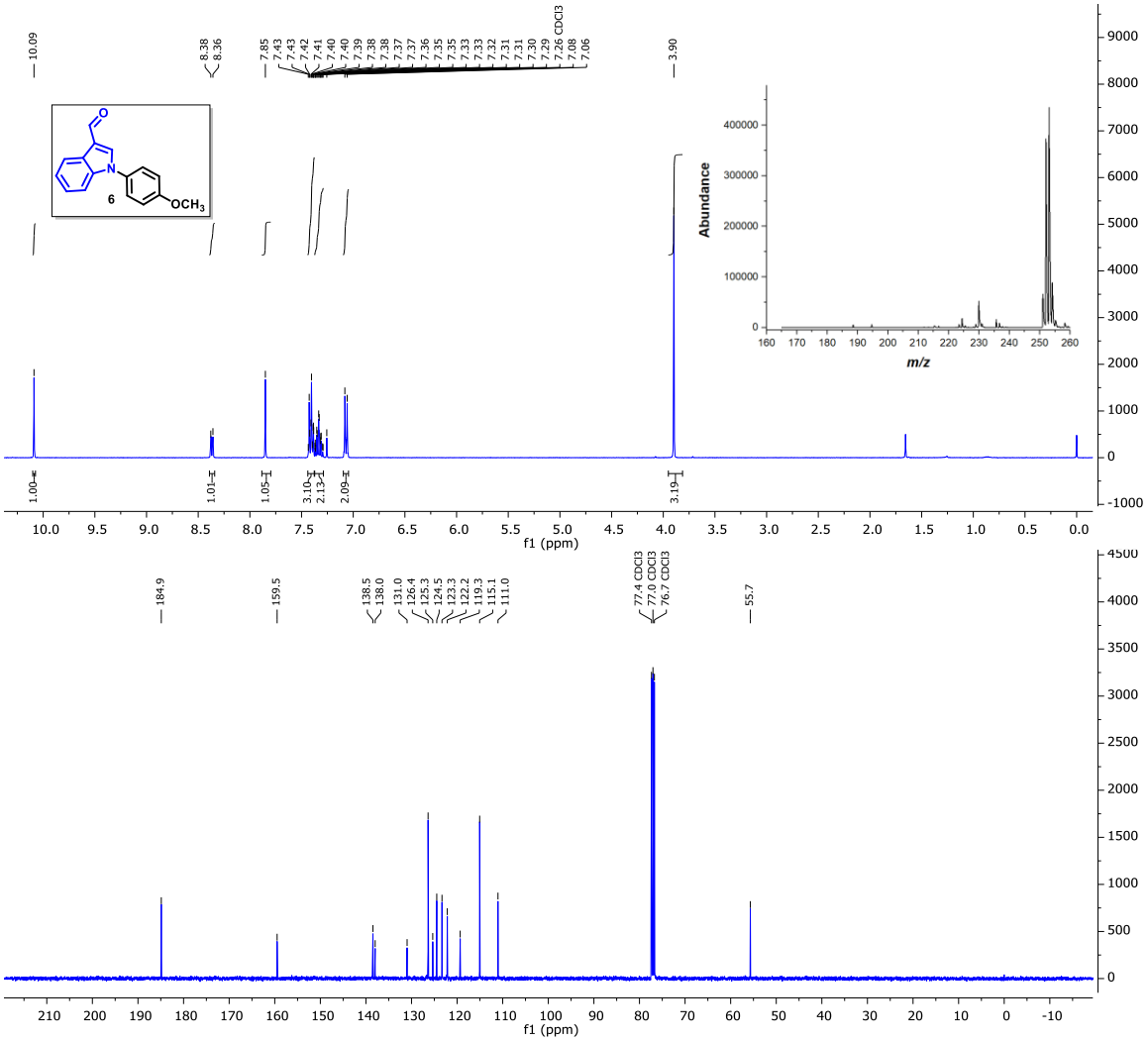


Fig S8. ^{1}H and ^{13}C NMR spectra ($CDCl_3$) and MS characterization of the compound **6.**

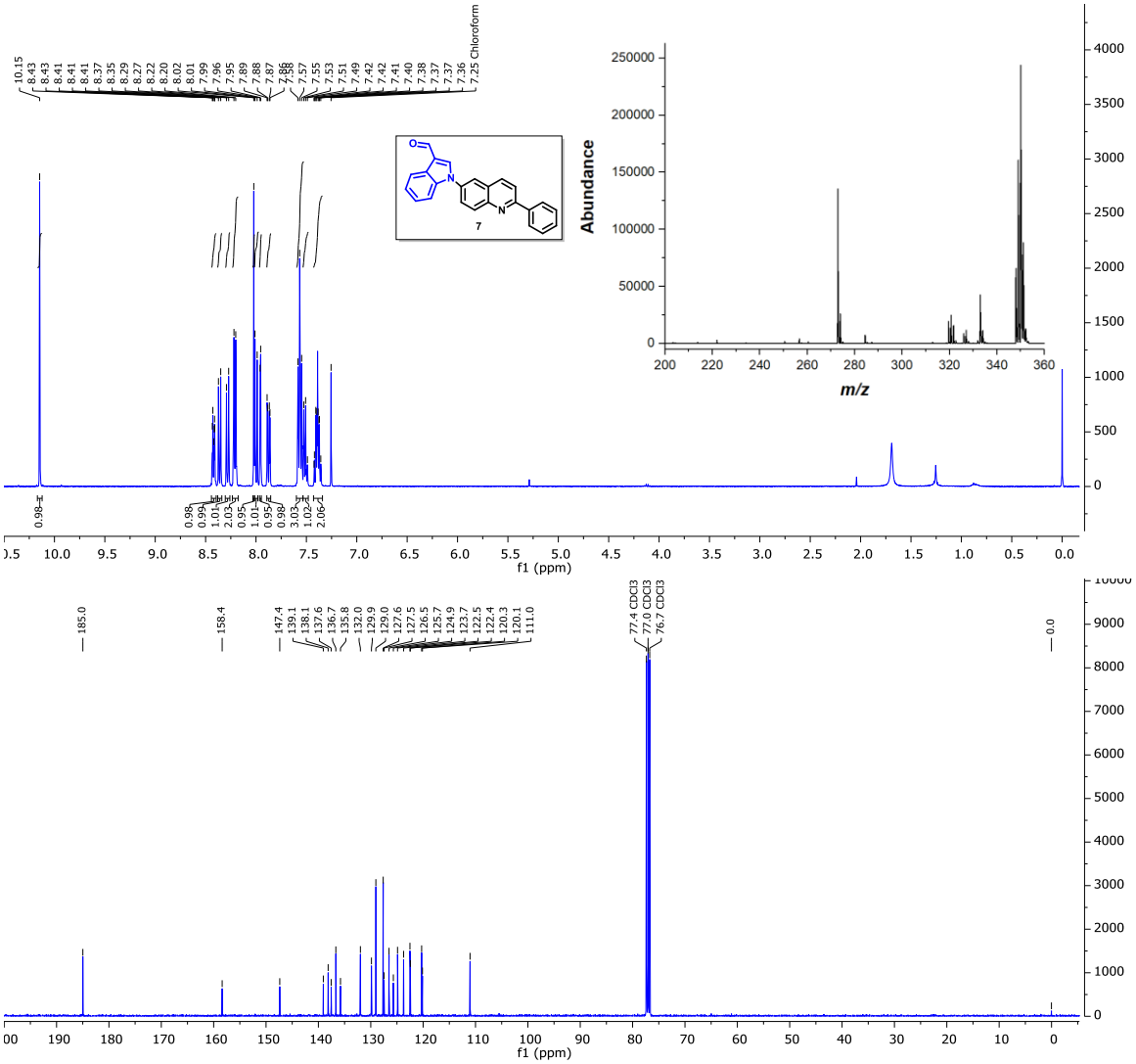


Fig S9. ^{1}H and ^{13}C NMR spectra ($CDCl_3$) and MS characterization of the compound **7.**

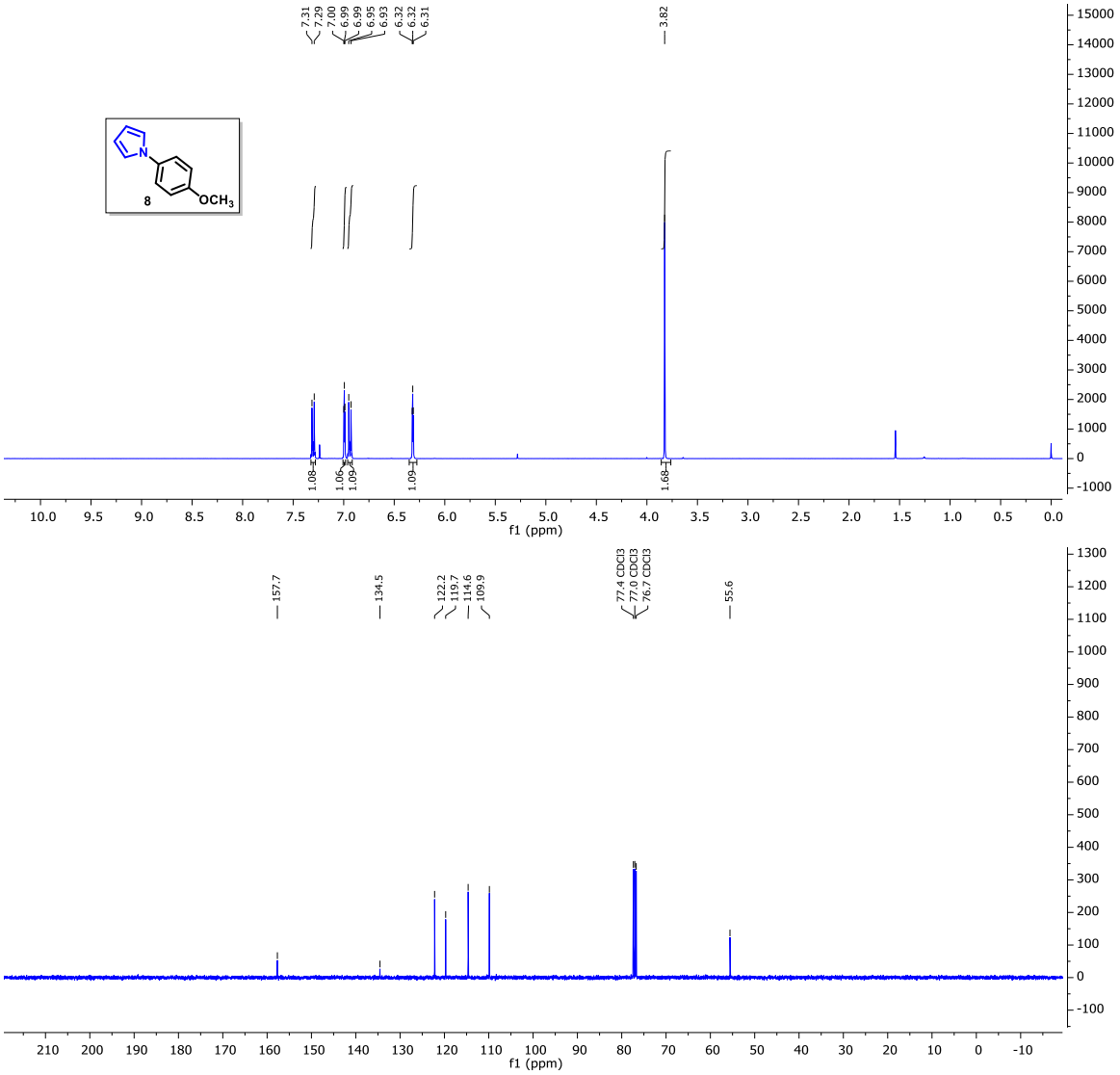


Fig S10. ^{1}H and ^{13}C NMR spectra ($CDCl_3$) and MS characterization of the compound **8.**

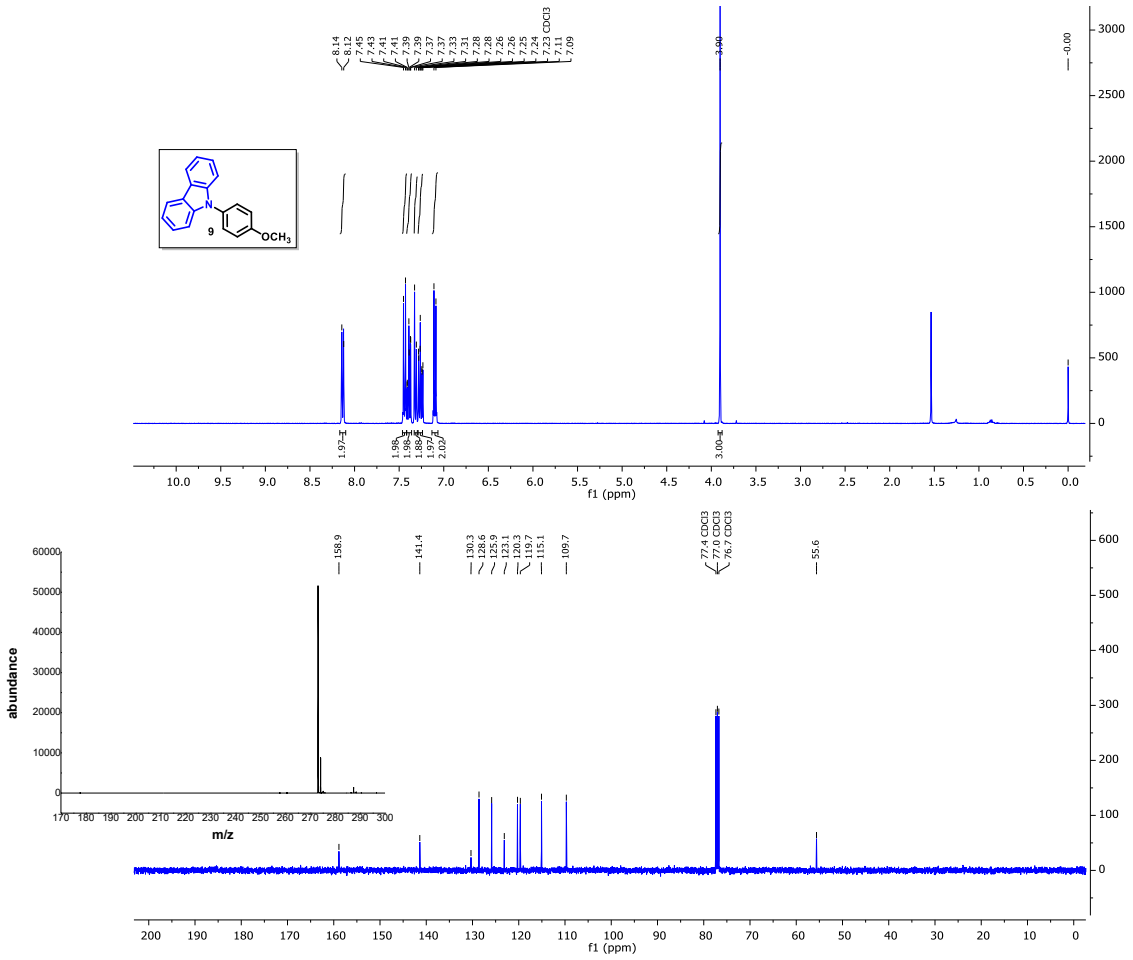


Fig S11. ^{1}H and ^{13}C NMR spectra ($CDCl_3$) and MS characterization of the compound **9.**

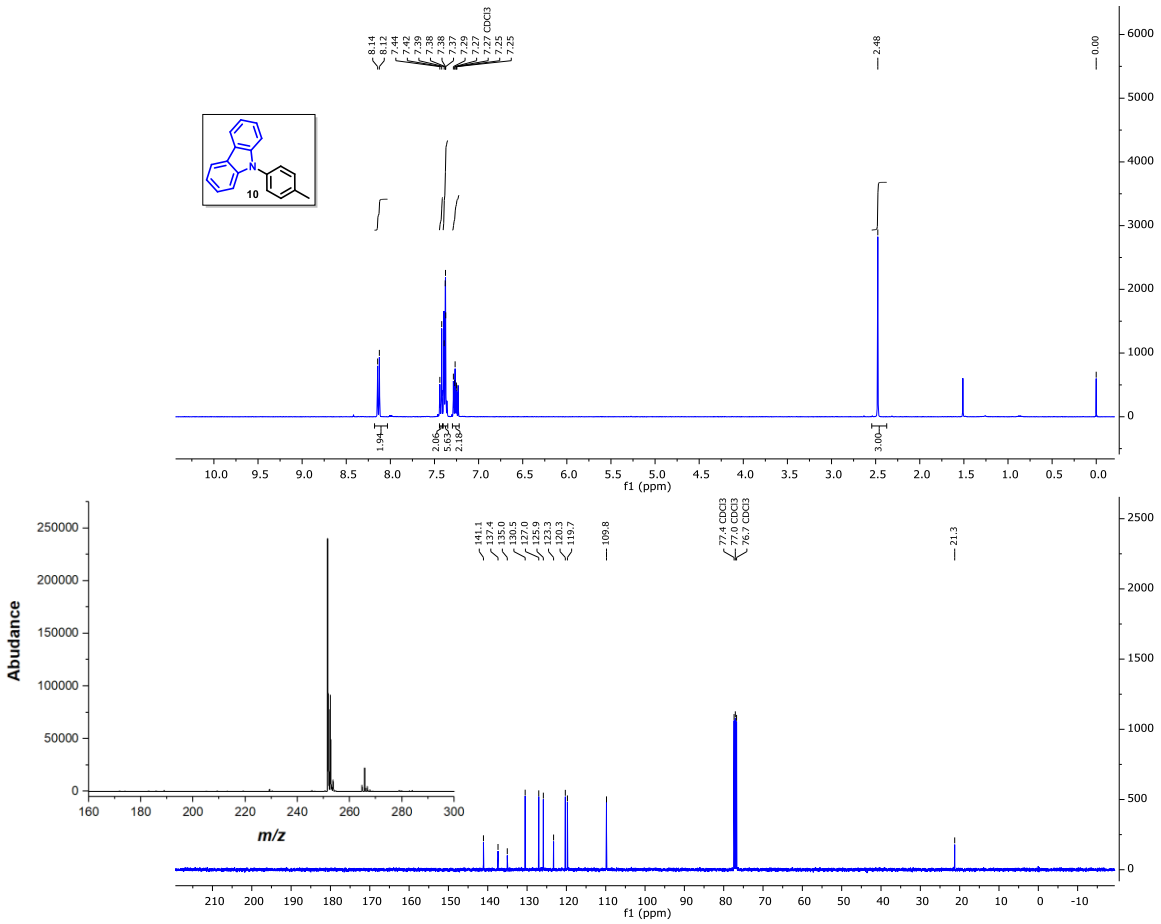


Fig S12. ^{1}H and ^{13}C NMR spectra ($CDCl_3$) and MS characterization of the compound **10.**

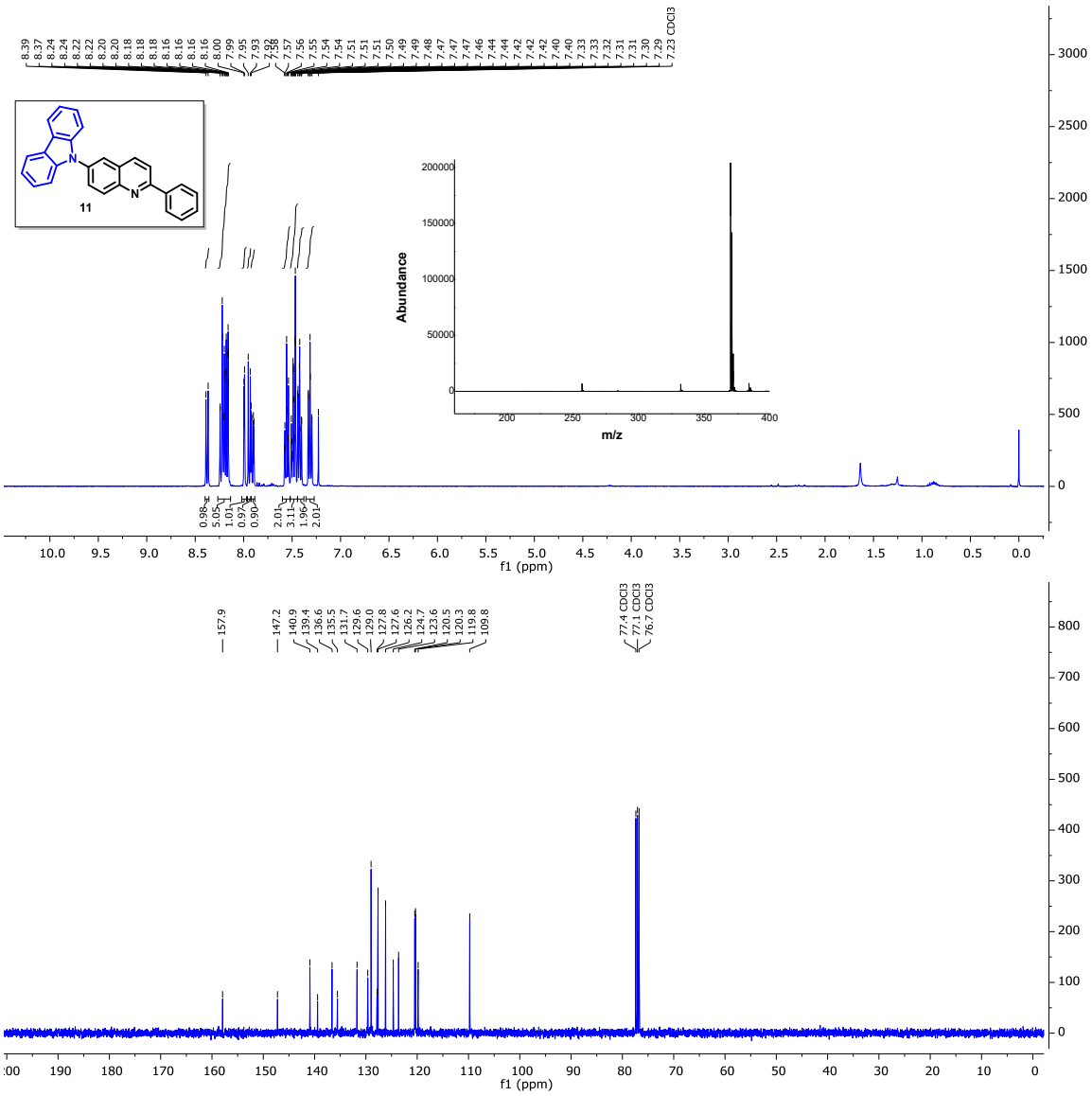


Fig S13. ^{1}H and ^{13}C NMR spectra ($CDCl_3$) and MS characterization of the compound **11.**

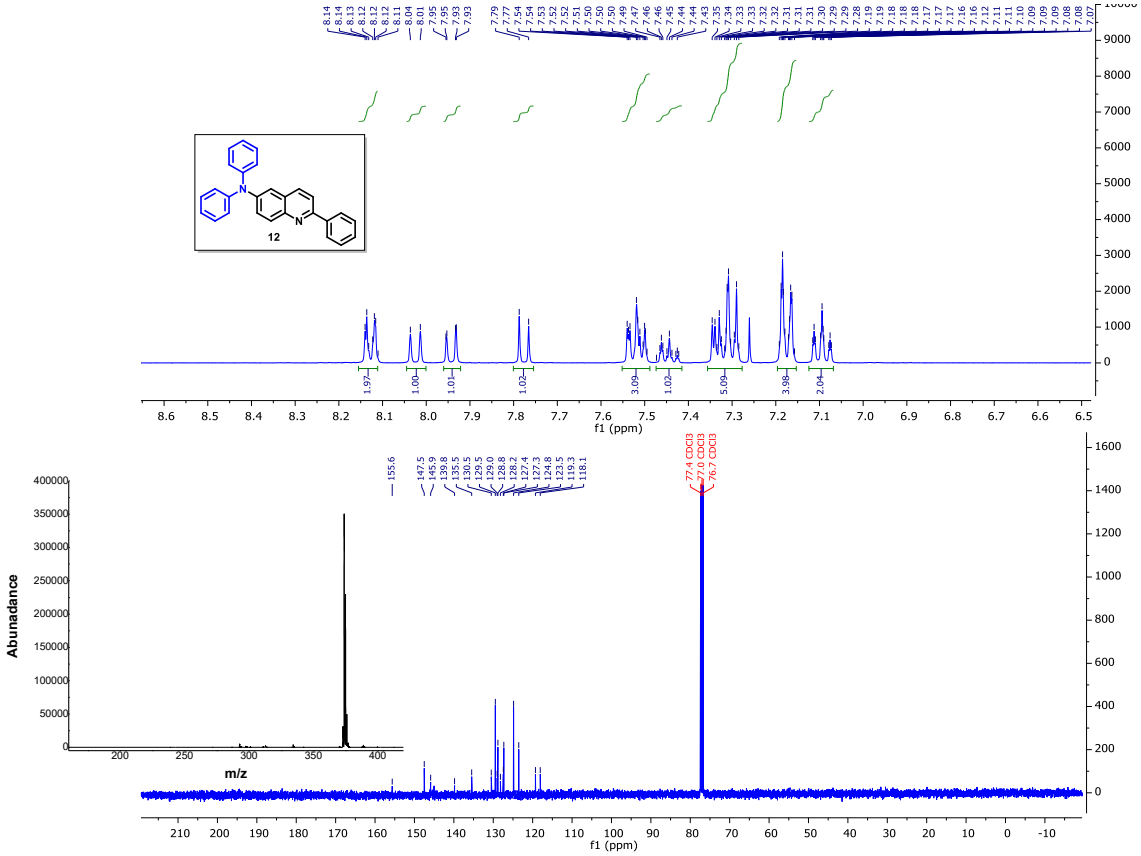


Fig S14. ^{1}H and ^{13}C NMR spectra ($CDCl_3$) and MS characterization of the compound **12.**

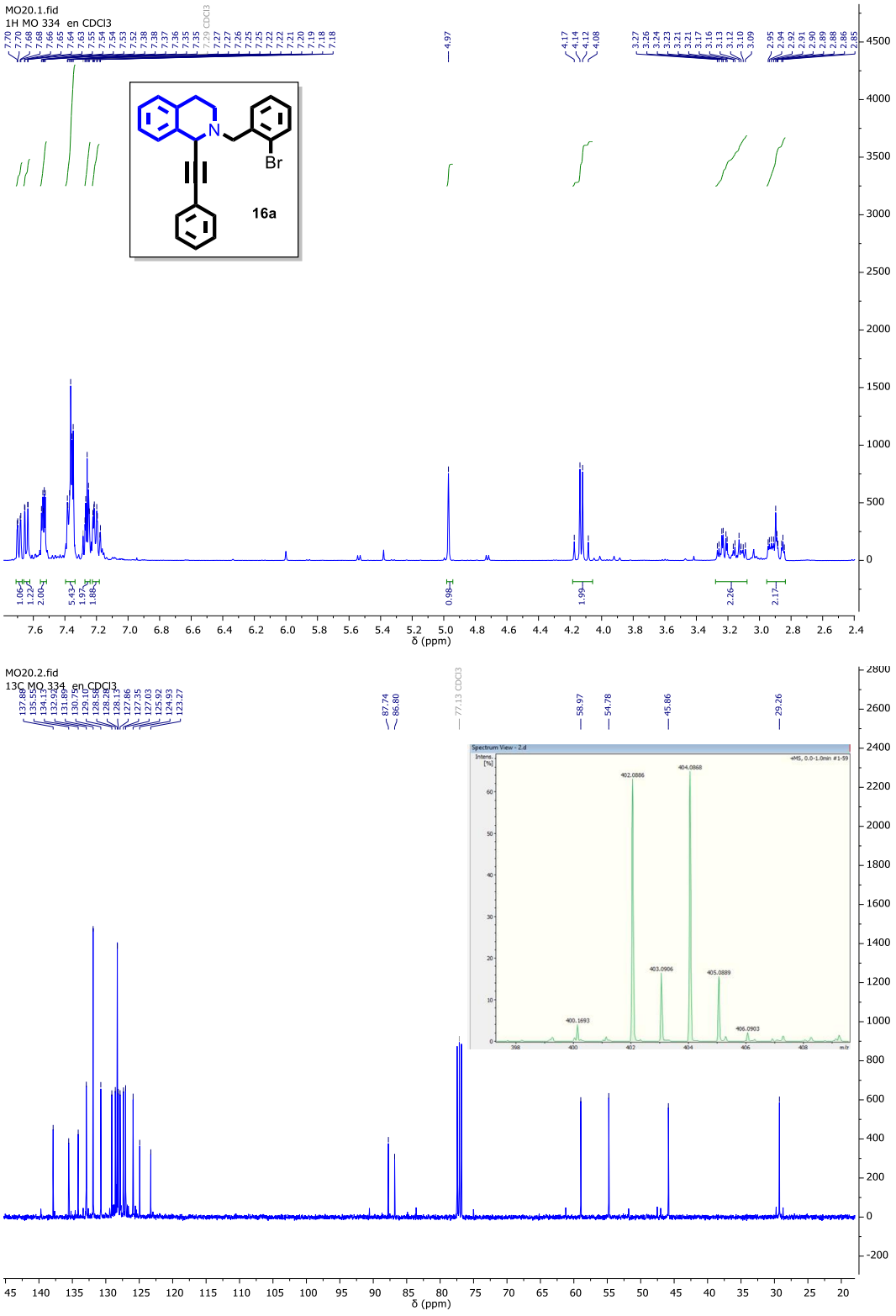


Fig S15. ^{1}H and ^{13}C NMR spectra ($CDCl_3$) and MS characterization of the compound **16a.**

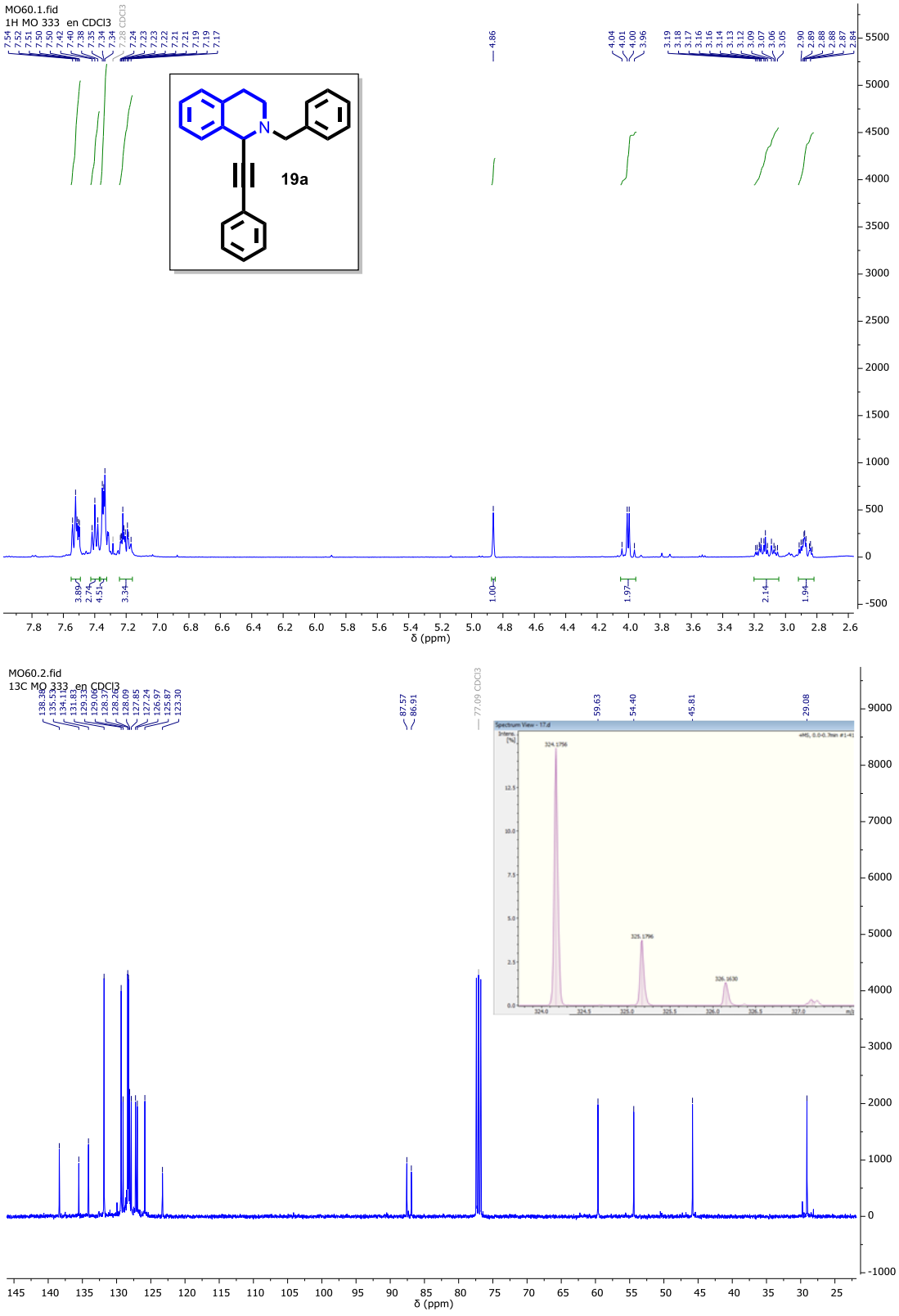


Fig S16. ^{1}H and ^{13}C NMR spectra ($CDCl_3$) and MS characterization of the compound **19a.**

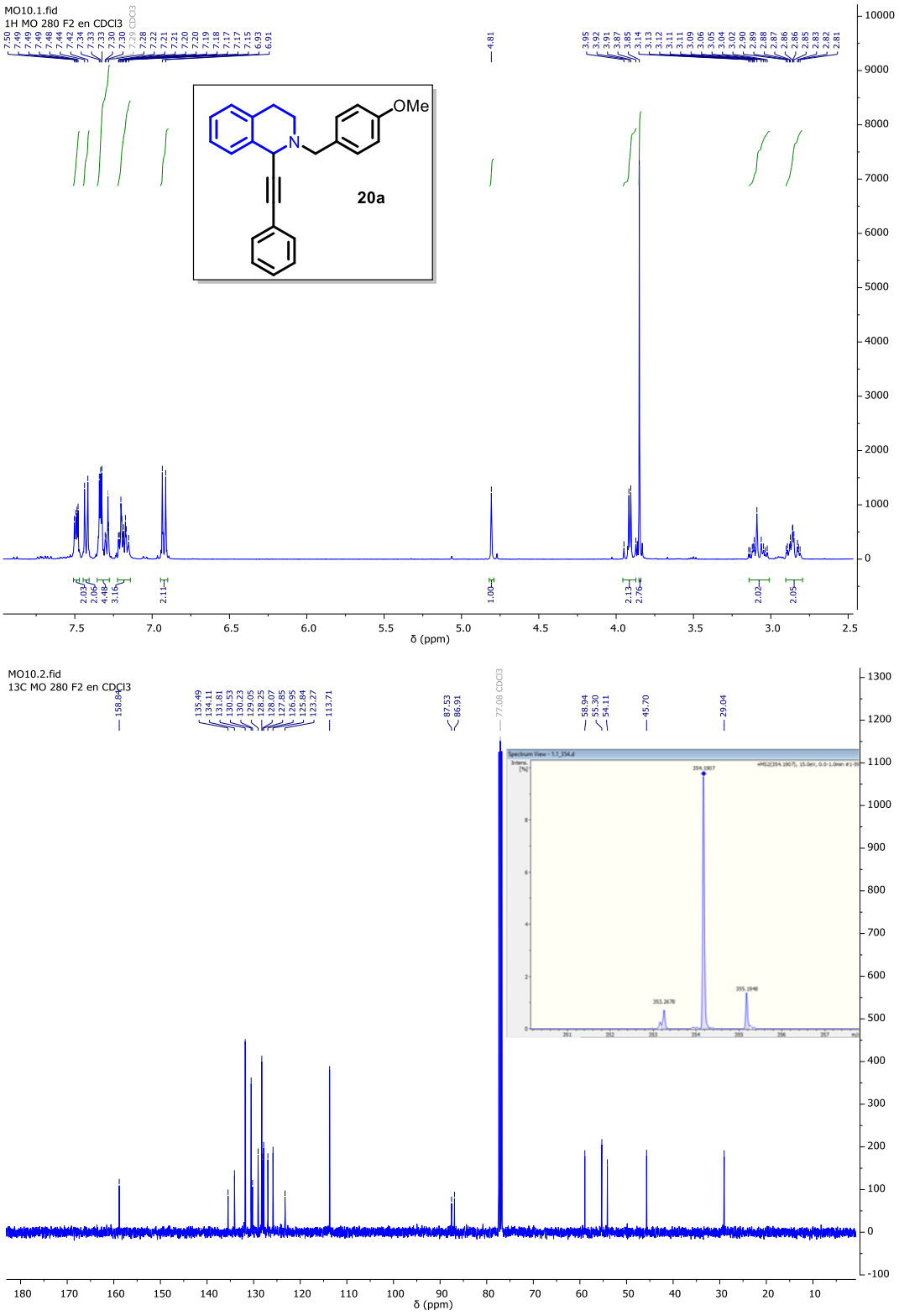


Fig S17. ^{1}H and ^{13}C NMR spectra ($CDCl_3$) and MS characterization of the compound **20a.**

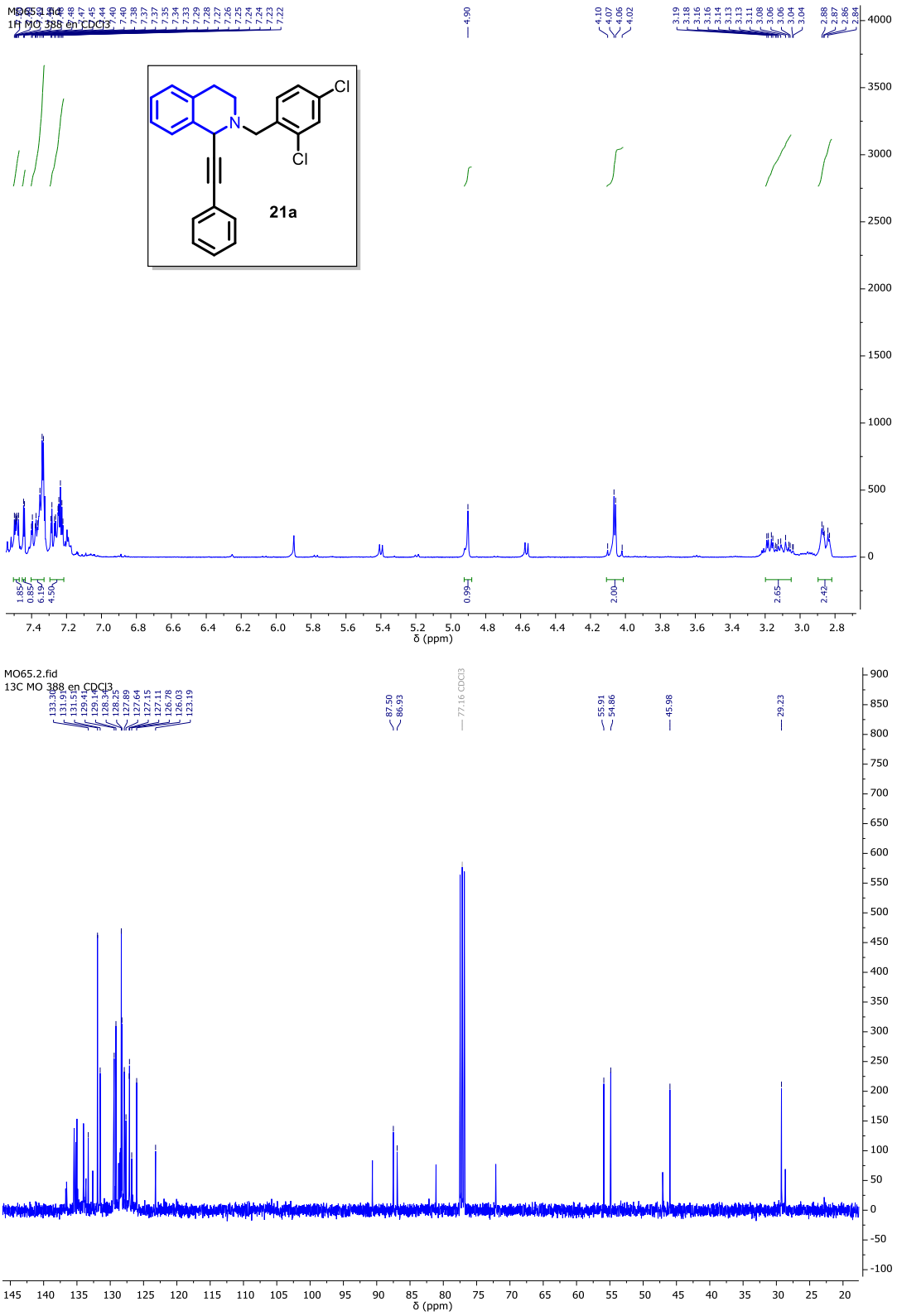


Fig S18. ^{1}H and ^{13}C NMR spectra ($CDCl_3$) of the compound **21a.**

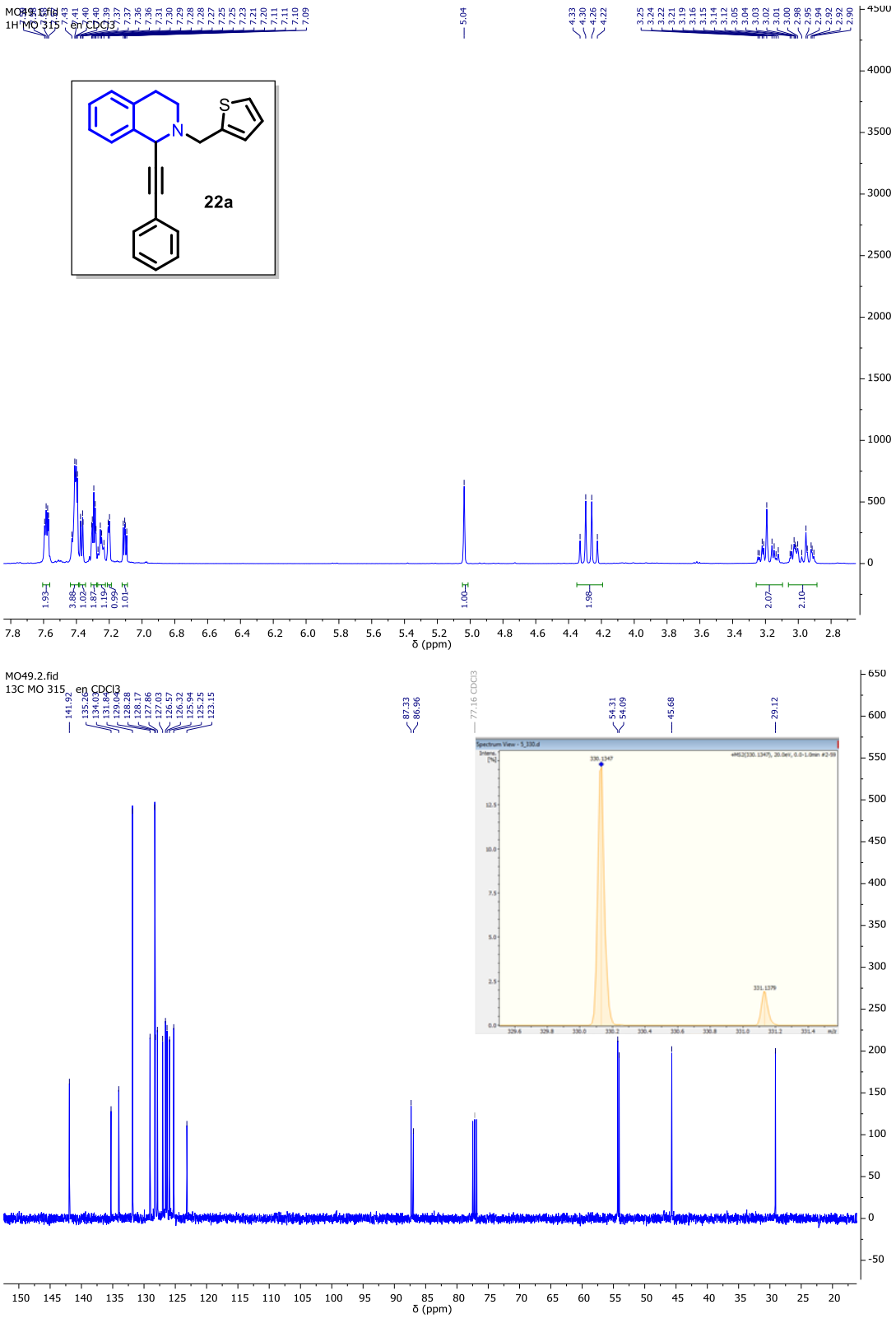


Fig S19. ^{1}H and ^{13}C NMR spectra ($CDCl_3$) and MS characterization of the compound **22a.**

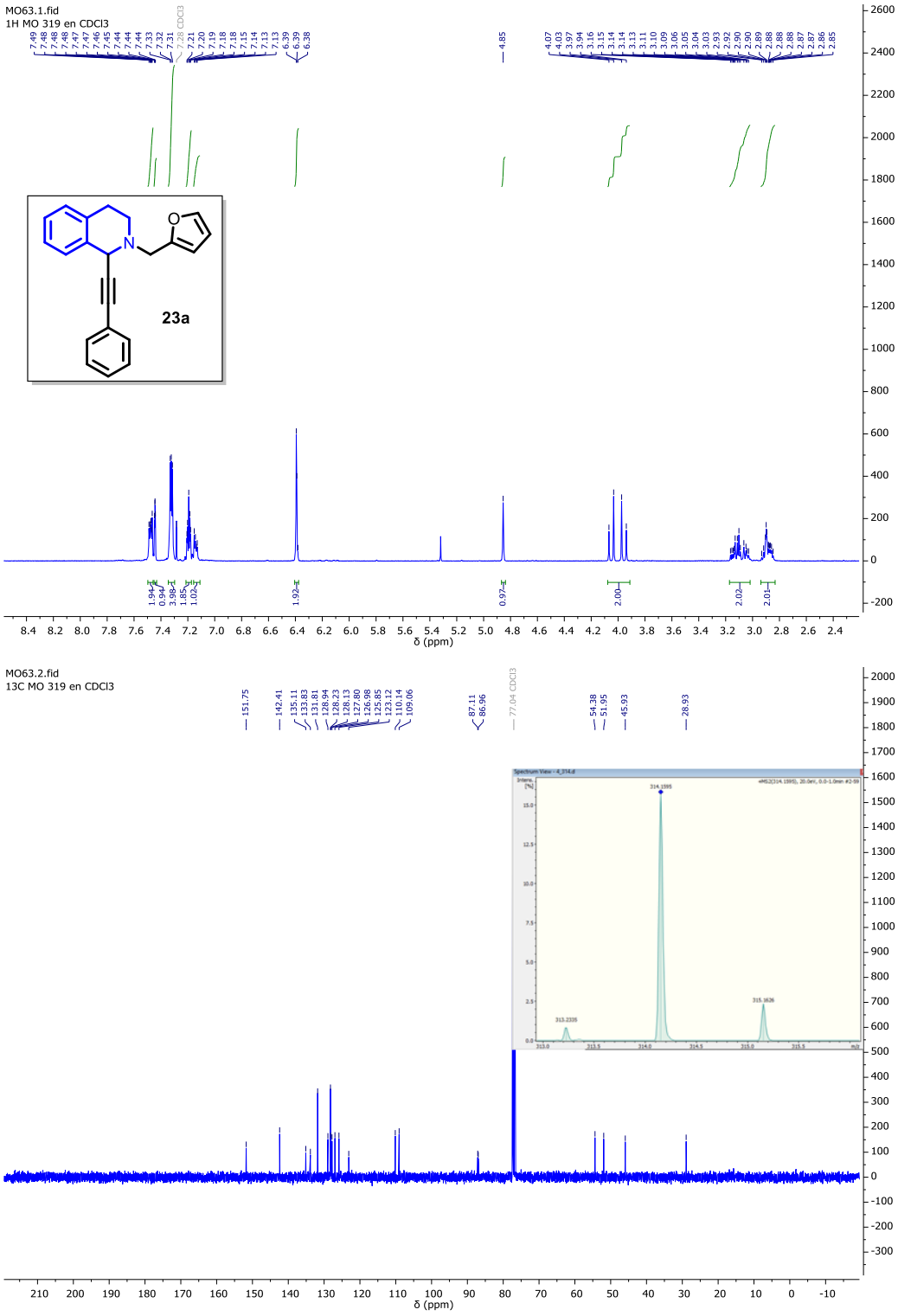


Fig S20. ^{1}H and ^{13}C NMR spectra ($CDCl_3$) and MS characterization of the compound **23a.**

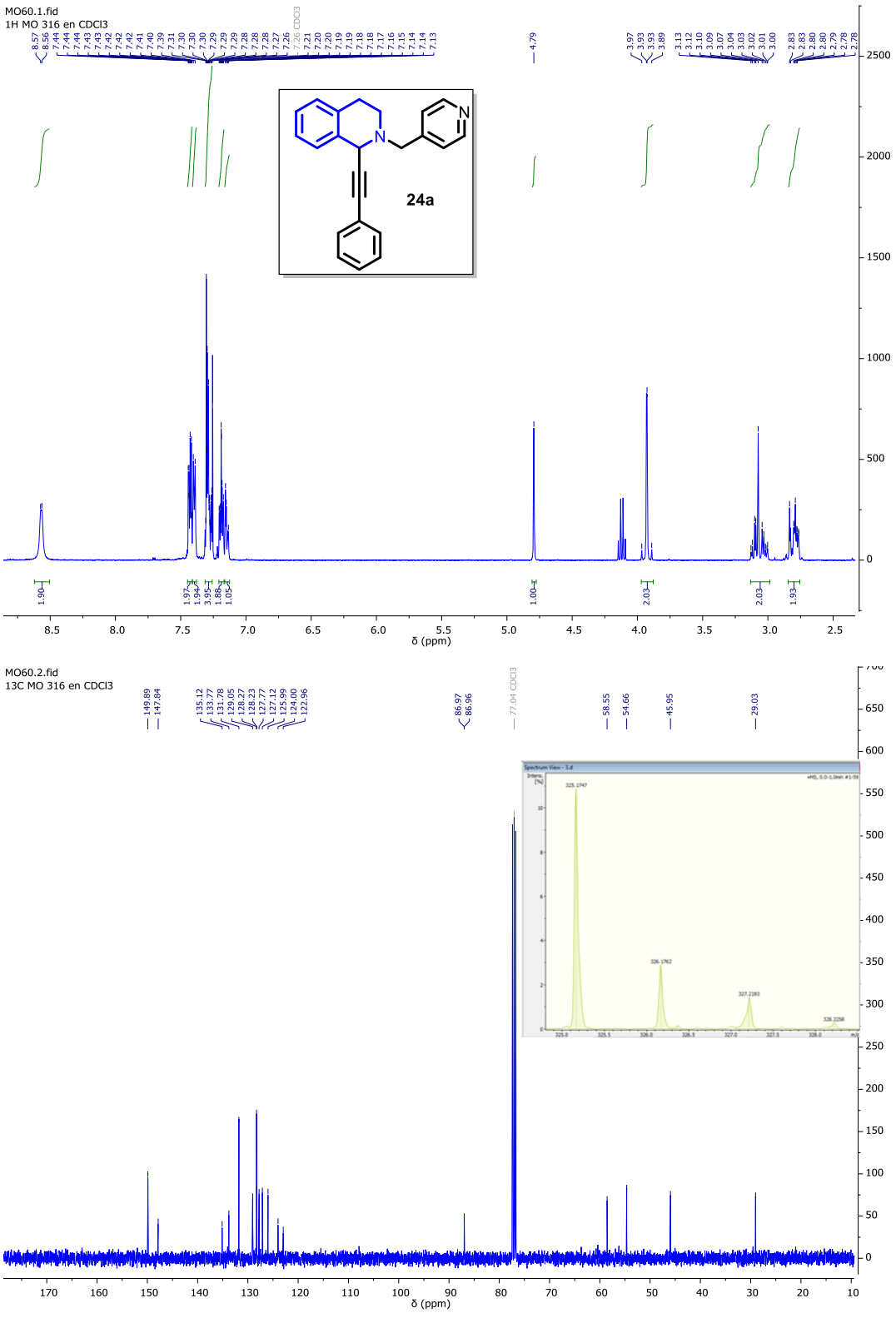


Fig S21. ^{1}H and ^{13}C NMR spectra ($CDCl_3$) and MS characterization of the compound **24a.**

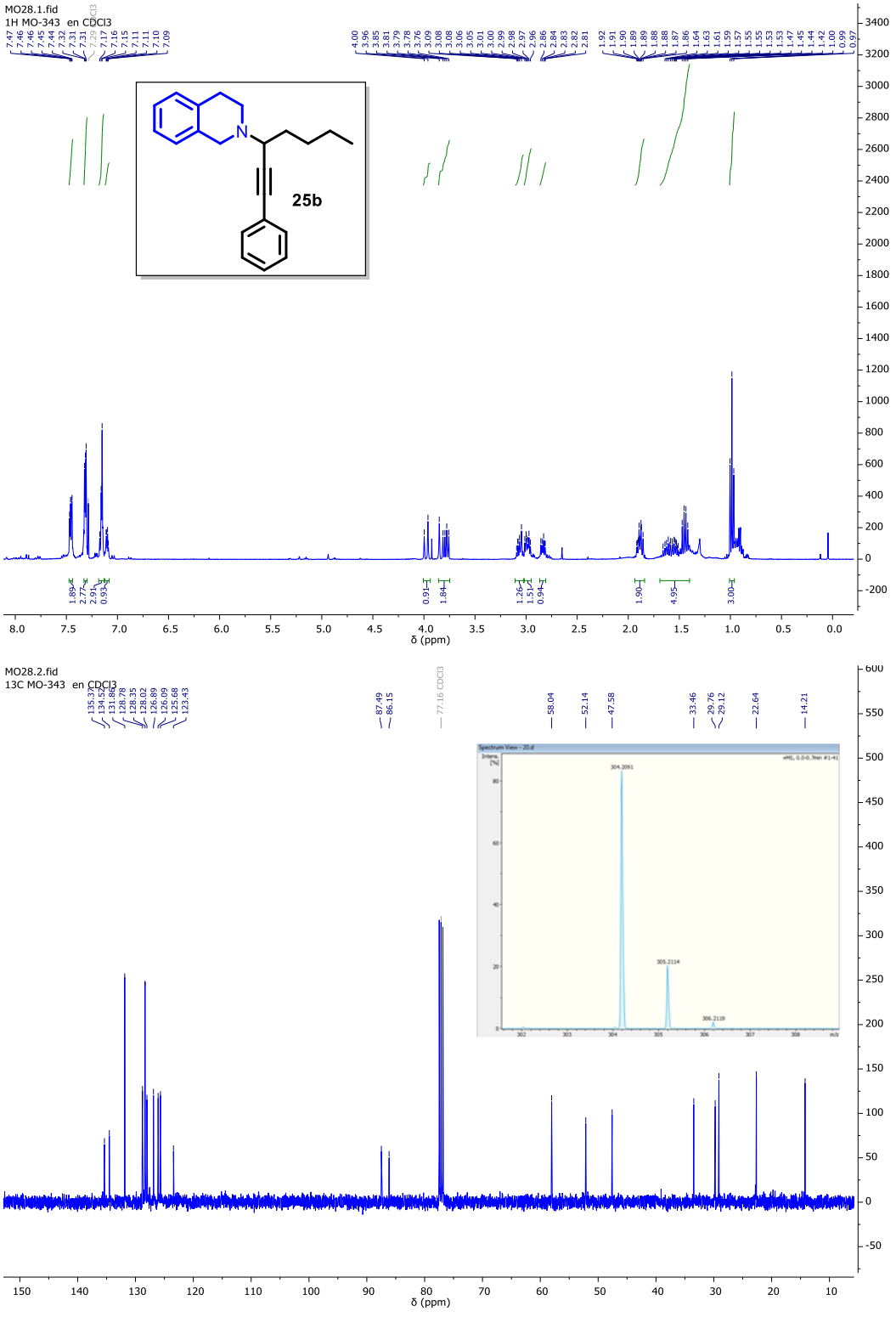


Fig S22. ^{1}H and ^{13}C NMR spectra ($CDCl_3$) and MS characterization of the compound **25b.**

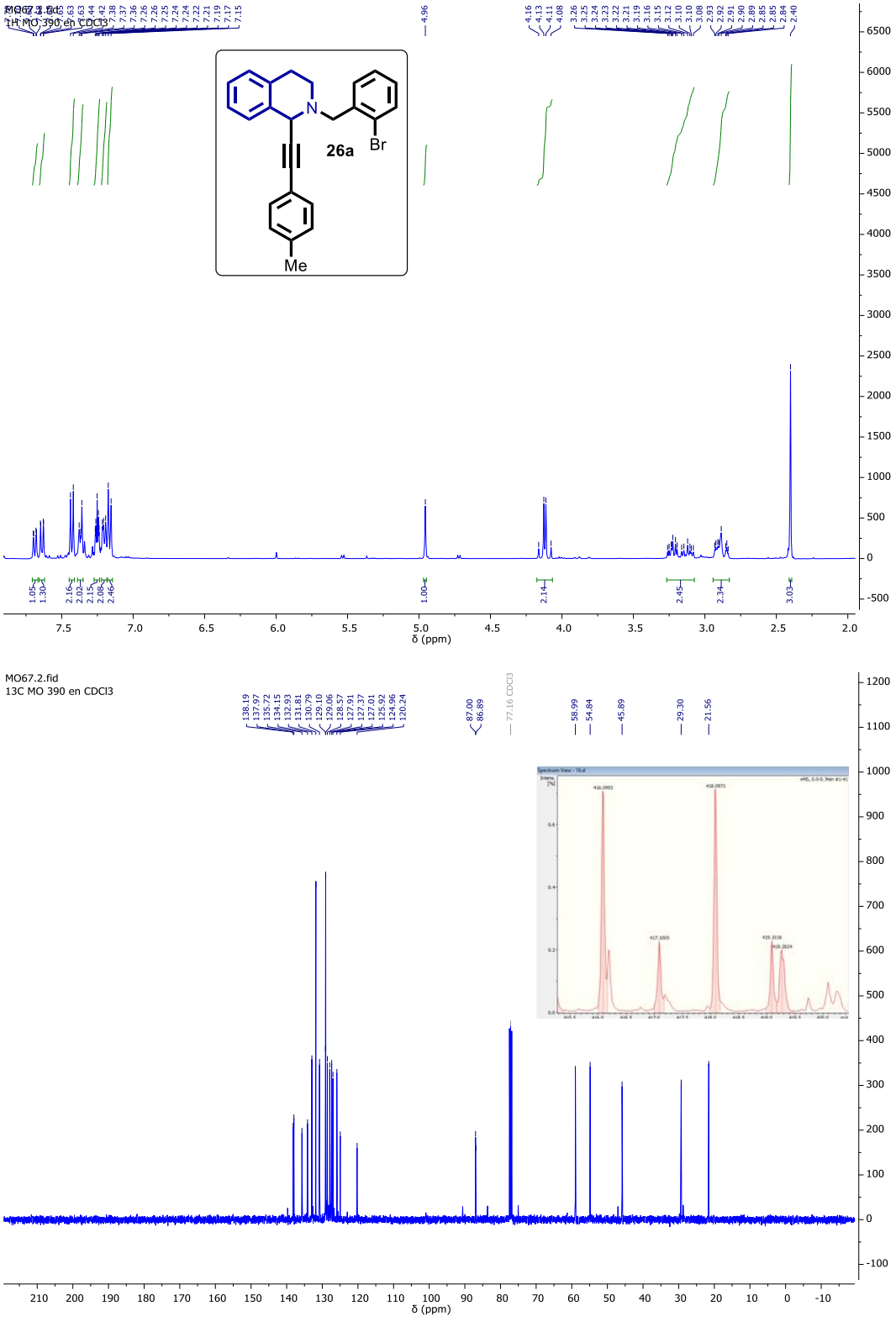


Fig S23. ^{1}H and ^{13}C NMR spectra ($CDCl_3$) and MS characterization of the compound **26a.**

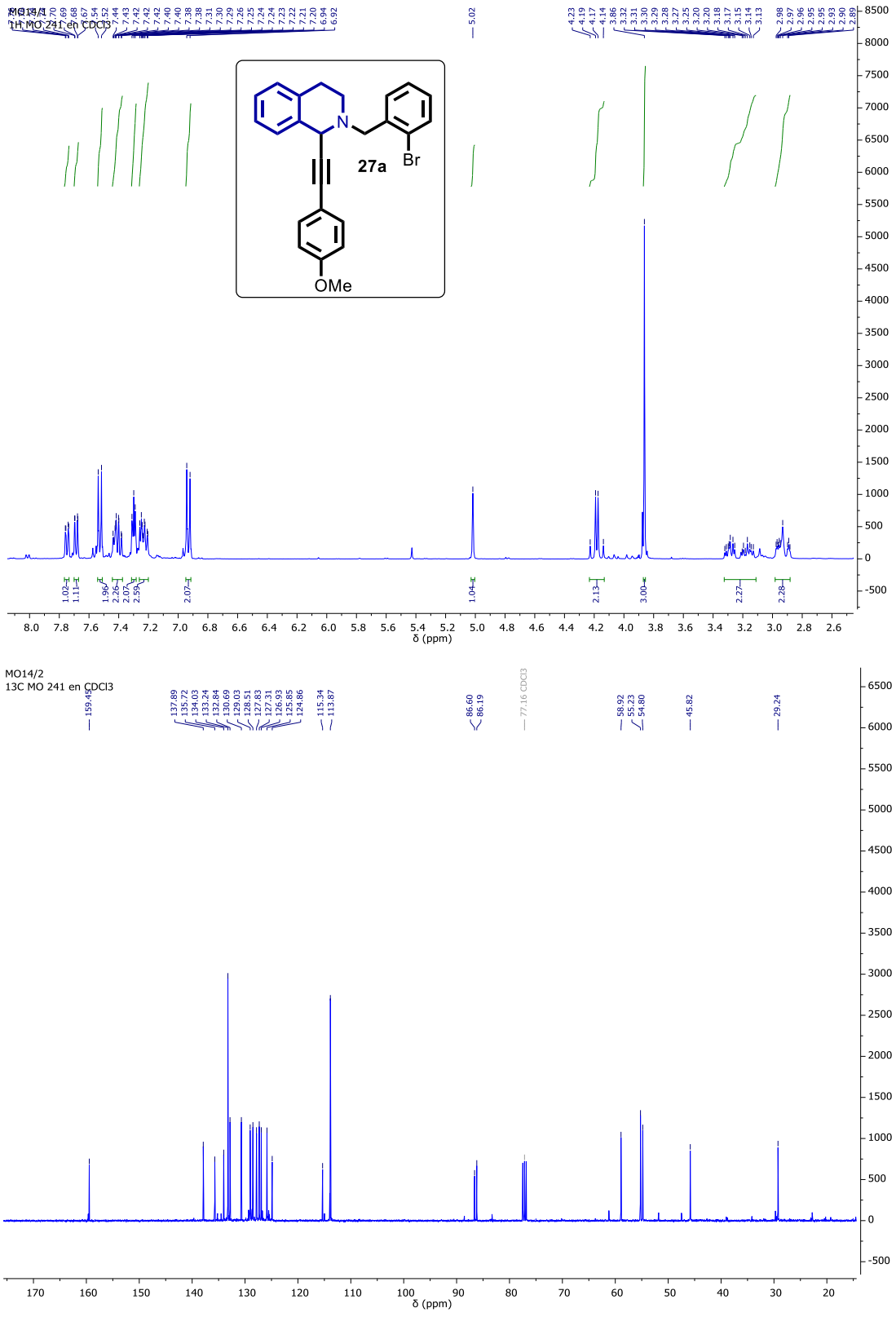


Fig S24. ^{1}H and ^{13}C NMR spectra ($CDCl_3$) of the compound **27a.**

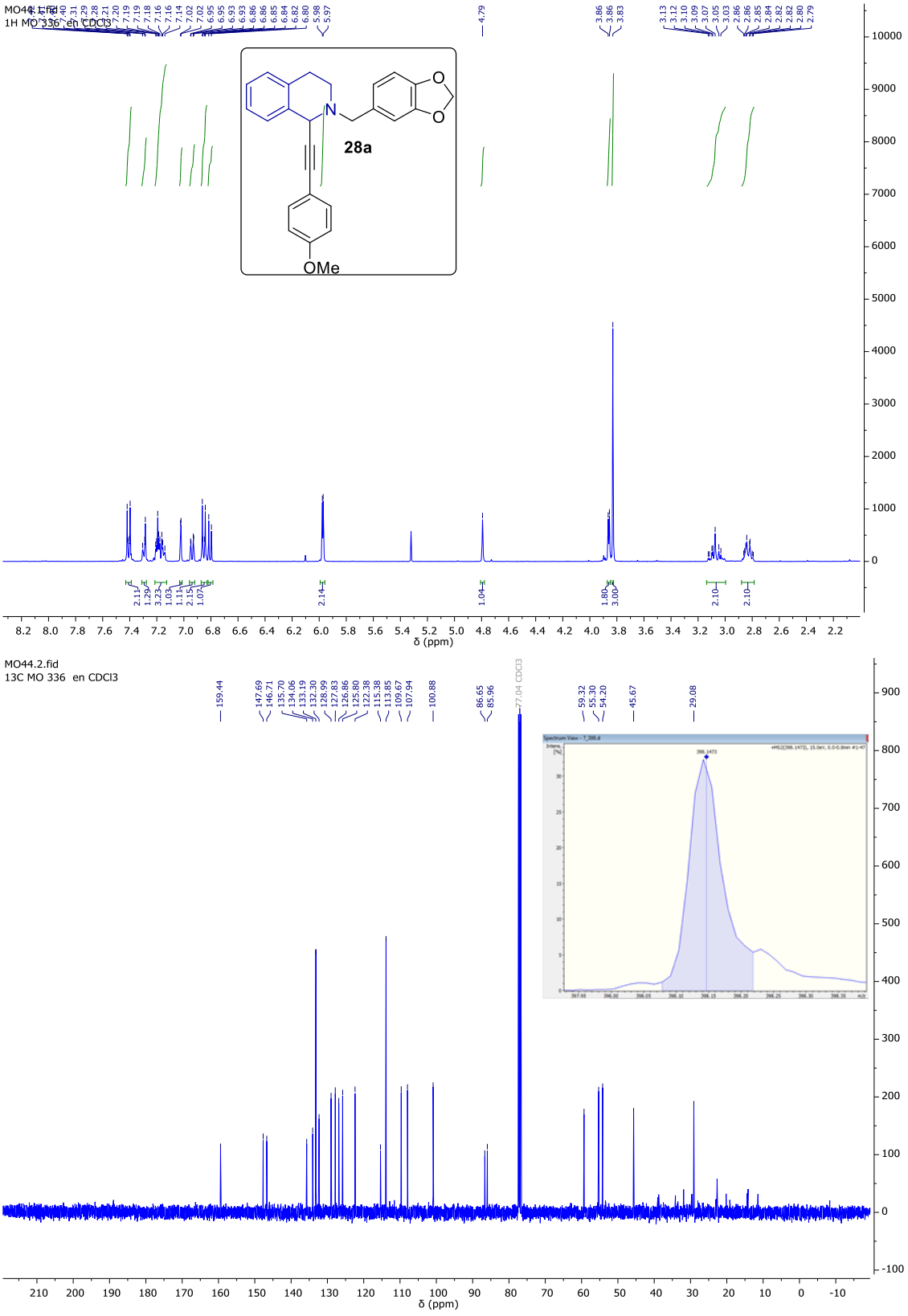


Fig S25. ^{1}H and ^{13}C NMR spectra ($CDCl_3$) and MS characterization of the compound **28a.**

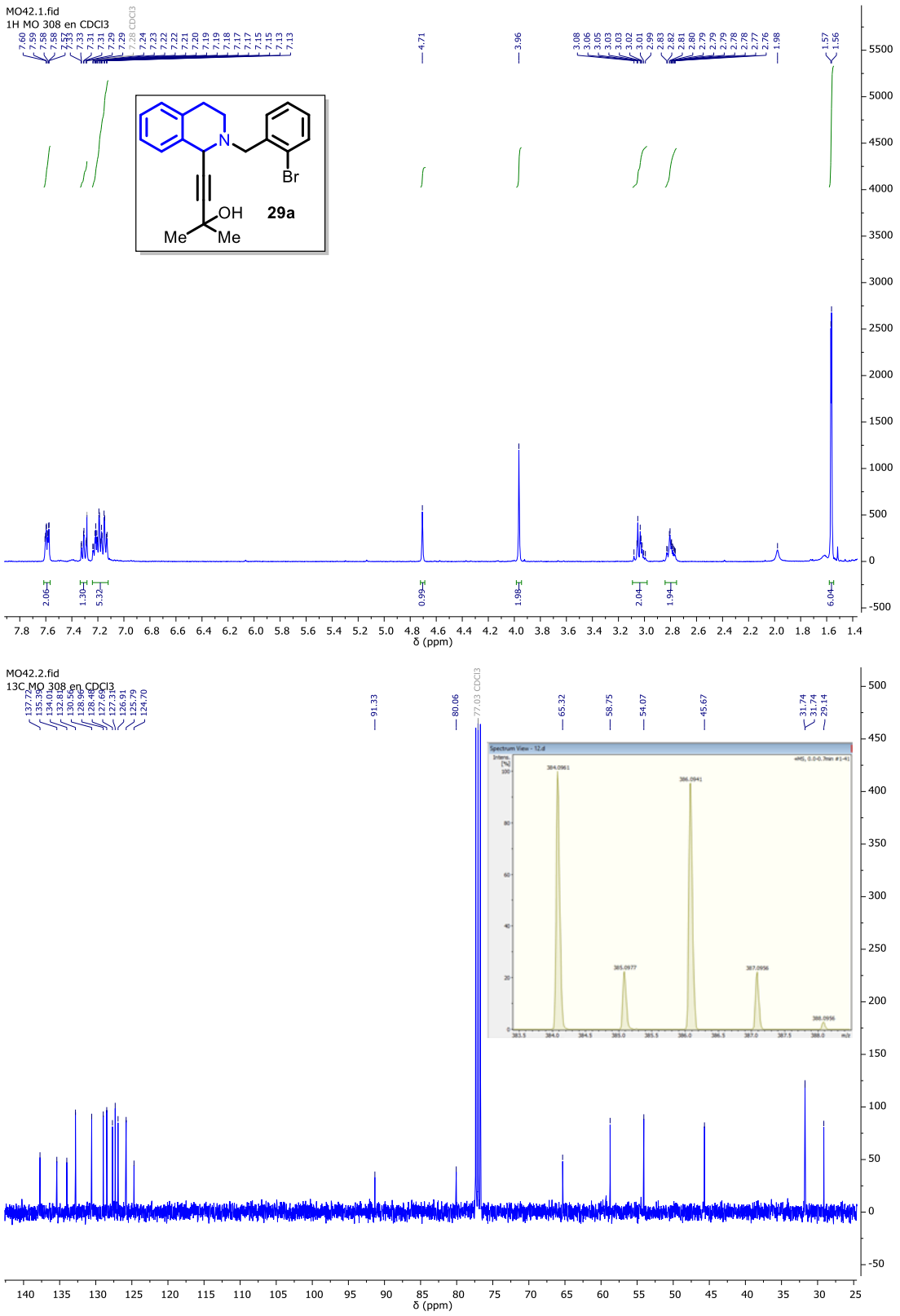


Fig S26. ^{1}H and ^{13}C NMR spectra ($CDCl_3$) and MS characterization of the compound **29a.**

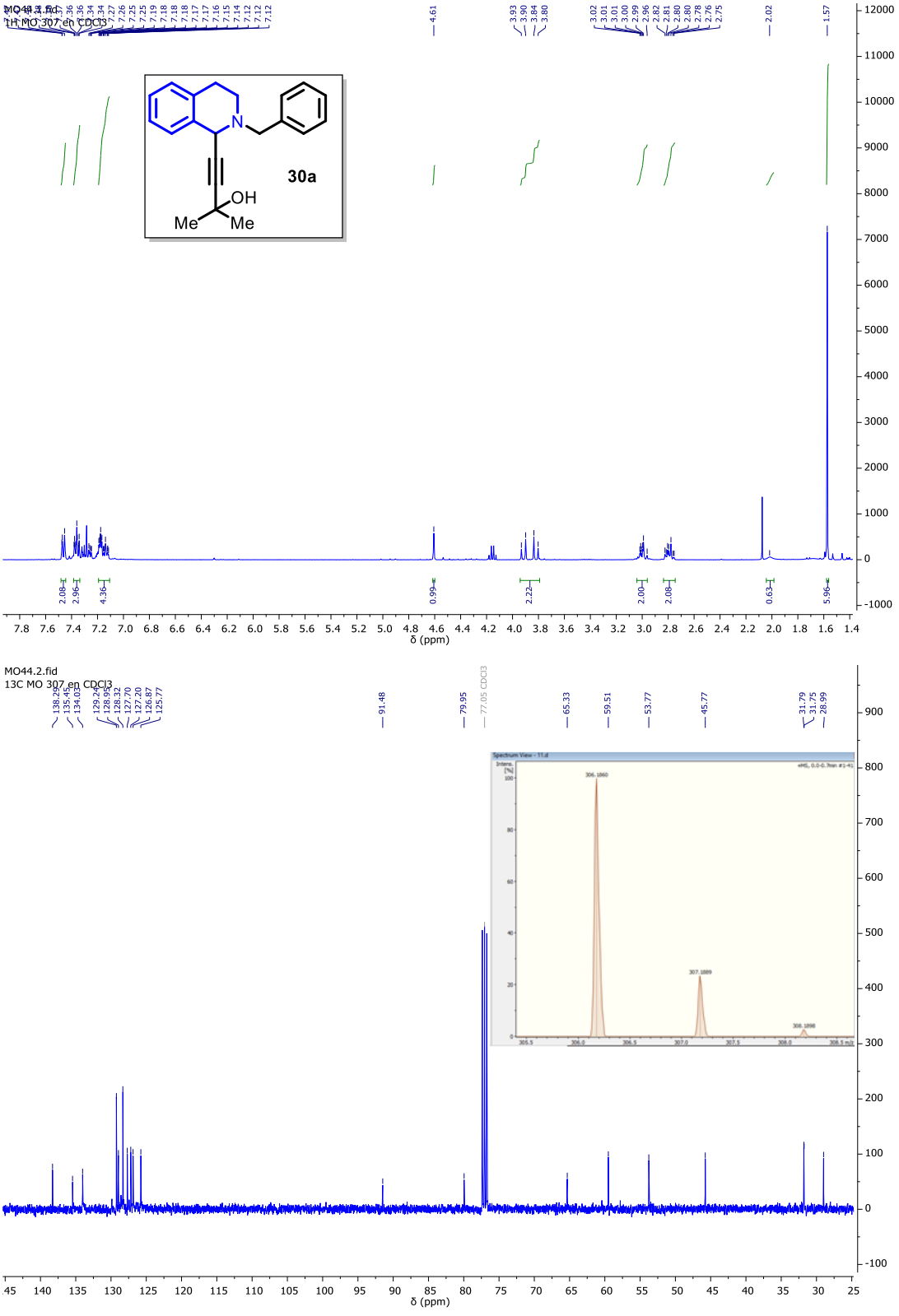


Fig S27. ^{1}H and ^{13}C NMR spectra ($CDCl_3$) and MS characterization of the compound **30a.**

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