Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry.

Supporting Information

Synthesis of highly functionalized 1,6-dihydropyridines via $Zn(OTf)_2$-catalysed three-component cascade reaction of aldimines and two alkynes (IA^2-coupling)

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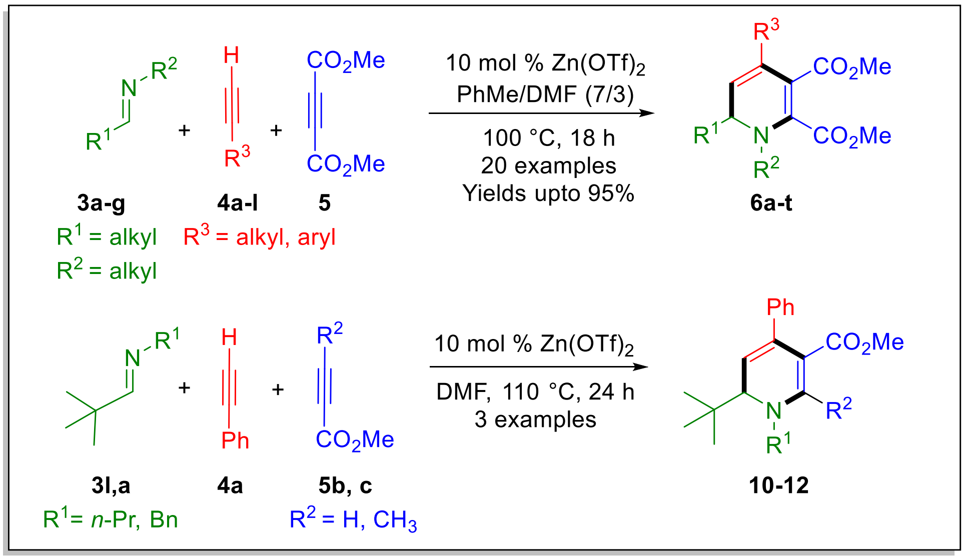

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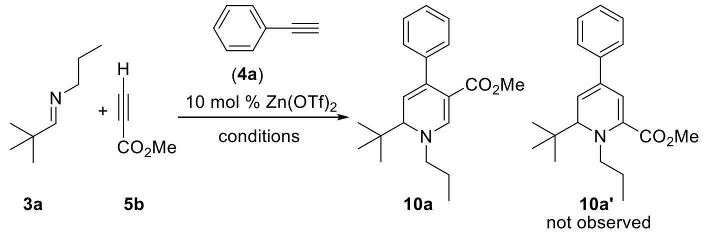
1. General remarks and instrumentation

All reactions were carried out under air, in an oven dried 10 mL microwave vial. Solvents used in extraction and purification were distilled prior to use. All acetylenes, pivaldehyde, *iso*butyraldehyde, *n*-butyraldehyde, benzaldehyde, primary amines, DMAD, methyl propiolate, ethyl 2-butynoate and ethyl phenylpropiolate were purchased from commercial suppliers (Sigma-Aldrich, Acros Organics, Alfa-Aesar, and TCI. Imines **3a-h** were prepared using a previously reported method.[1] The final products were purified by flash column chromatography using silica gel pore 60 Å, 40-63 μm mesh size, as an adsorbent while the procedure included the subsequent evaporation of solvents in vacuo. For thin layer chromatography (TLC) silica gel plates with fluorescence indicator 254 nm were used and compounds were visualized by irradiation with UV light. ^{1}H (^{13}C) NMR spectra were recorded at 400 (100) MHz on a Bruker type spectrometer using $CDCl_3$ as solvent with TMS as the internal standard for both ^{1}H and ^{13}C NMR. Assignments were made either on the basis of unambiguous chemical shifts, coupling patterns or 2D NMR experiments (COSY, HMQC and HMBC). Coupling constants (*J* values) are given in hertz (Hz), chemical shifts are given in parts per million (ppm). For high resolution mass spectrometric analysis (HRMS), samples were dissolved in CH_3OH and diluted to a concentration of approximately 10^{-5} mol/L and measurements were performed on a microTOF spectrometer equipped with orthogonal electrospray interface (ESI). The parent ions [M+H$^+$] are quoted.

2. Extra optimization experiments for the synthesis of dihydropyridine monocarboxylate

Table S1. Optimization of the synthesis of dihydropyridine monocarboxylate (**10a**).



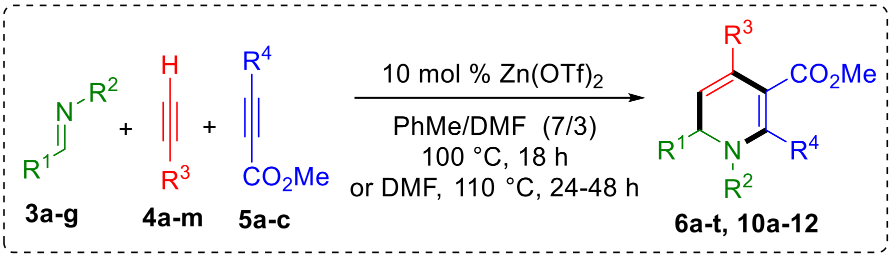
Entry	Amount of **5b** (equiv)	*T*/*t* (°C/h)	Solvent (1 mL)	Yield **10a** (%)^a
1	1.0	100/18	PhMe/DMF (7/3)	45
2	1.5	100/24	PhMe/DMF (7/3)	50
3	1.5	110/24	PhMe/DMF (7/3)	52
4	1.5	110/24	PhMe/DMF (1/1)	78
5	**1.5**	**110/24**	**DMF**	**89**
6	1.1	110/24	PhMe	35^b

^{a} Crude yields. ^{b} xx% propargylamine **7** was detected

3. General experimental procedure for the synthesis of 1,6-dihydropyridines

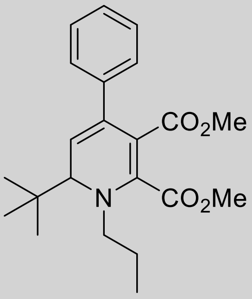
In an oven dried 10 mL vial containing a stirring bar, the appropriate imine (**3**) (0.5 mmol), acetylene (**4**) (0.5 mmol, 1 equiv), dimethyl 2-butynedioate (DMAD) (**5a**) (71.06 mg 0.5 mmol) and $Zn(OTf)_2$ (0.018 g, 0.050 mmol, 10 mol %) were added successively and the vial was sealed under air. Then, 1 mL of toluene/DMF (7/3) was added and the reaction mixture was stirred at 100 °C for 18-24 h. Afterwards the reaction mixture was diluted with CH_2Cl_2 (10 mL) washed with 0.5 N NaOH (10 mL). The aqueous phase was extracted with CH_2Cl_2, dried over anhydrous $MgSO_4$ and the solvent was evaporated under reduced pressure. The crude reaction mixture was purified over silica gel by column chromatography using EtOAc:*n*-Heptane (10:90) as eluent.

4. Synthesis and characterization data of dihydropyridines



Dimethyl 6-(*tert*-butyl)-4-phenyl-1-propyl-1,6-dihydropyridine-2,3-dicarboxylate (6a)

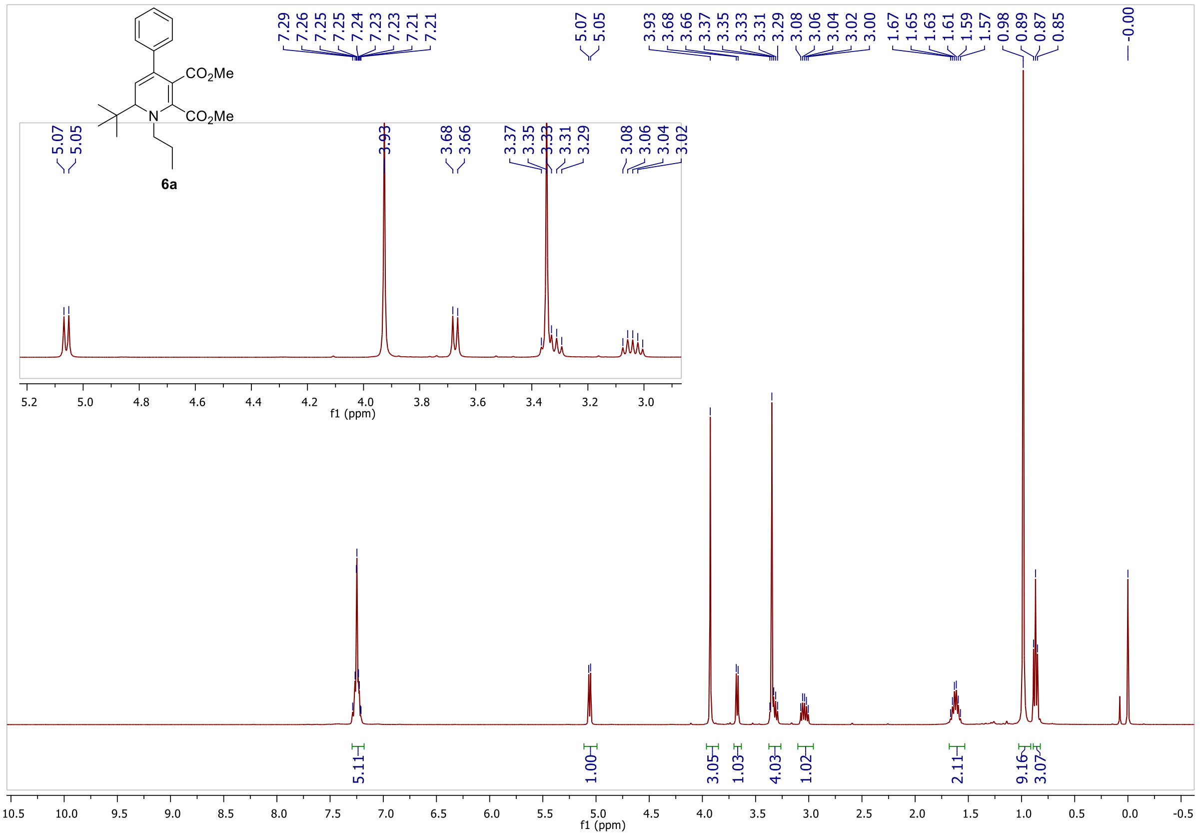
sas-2-116pure



6a

According to the general procedure *N*-(2,2-dimethylpropylidene)propan-1-amine (**3a**) (0.5 mmol, 0.071 g), phenylacetylene (**4a**) (0.5 mmol, 0.051 g), dimethyl 2-butynedioate (**5a**) (0.5 mmol, 0.071 g) and $Zn(OTf)_2$ (0.05 mmol, 0.018 g) were reacted in 1 mL of of toluene/DMF (7/3) at 100 ºC for 18 h. Alkaline work up and column chromatography over silica gel afforded 176 mg (95%) of dimethyl 6-(*tert*-butyl)-4-phenyl-1-propyl-1,6-dihydropyridine-2,3-dicarboxylate **(6a)** as a viscous yellow oil. R_f = 0.55 (Heptane/EtOAc: 90/10). This reaction could be scaled up using 5 mmol of the starting imine **3a**. In this case a yield of 89% was obtained.

^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.27 – 7.22 (m, 5H, aromatic), 5.06 (d, *J* = 6.9 Hz, 1H, **H**C=C), 3.93 (s, 3H, OC**H**$_3$), 3.67 (d, *J* = 6.9 Hz, 1H, **H**CHC=C), 3.37 – 3.28 (m, 4H, overlapped signal OC**H**$_3$ and NC(H)**H**), 3.07 – 3.00 (m, 1H, NC(**H**)H), 1.65 – 1.59 (m, 2H, C**H**$_2$CH$_3$), 0.98 (s, 9H, C(C**H**$_3$)$_3$), 0.87 (t, *J* = 7.5 Hz, 3H, CH$_2$C**H**$_3$). **^{13}C NMR** (100 MHz, $CDCl_3$): *δ* 166.5 (NC(**C**O$_2$CH$_3$)=CCO$_2$CH$_3$), 166.1 (NC(CO$_2$CH$_3$)=C**C**O$_2$CH$_3$), 150.3 (N**C**(CO$_2$CH$_3$)=CCO$_2$CH$_3$), 141.5 (NC(CO$_2$CH$_3$)=**C**CO$_2$CH$_3$), 138.0 (**C**$_{ipso}$), 127.5, 127.4, 126.7 (C$_{para}$), 112.8 (HCH**C**=C), 103.8 (HCHC=**C**), 67.3 (H**C**HC=C), 56.9 (NCH$_2$), 52.8 (OCH$_3$ close to N), 50.6 (OCH$_3$), 40.7 (**C**(CH$_3$)$_3$), 25.2 (C(**C**H$_3$)$_3$), 23.7 (NCH$_2$**C**H$_2$), 10.9 (CH$_2$*C*H$_3$). **HRMS** (ESI) *m/z* calculated for $C_{22}H_{29}NO_4+H^+$: 372.2175; found 372.2175.



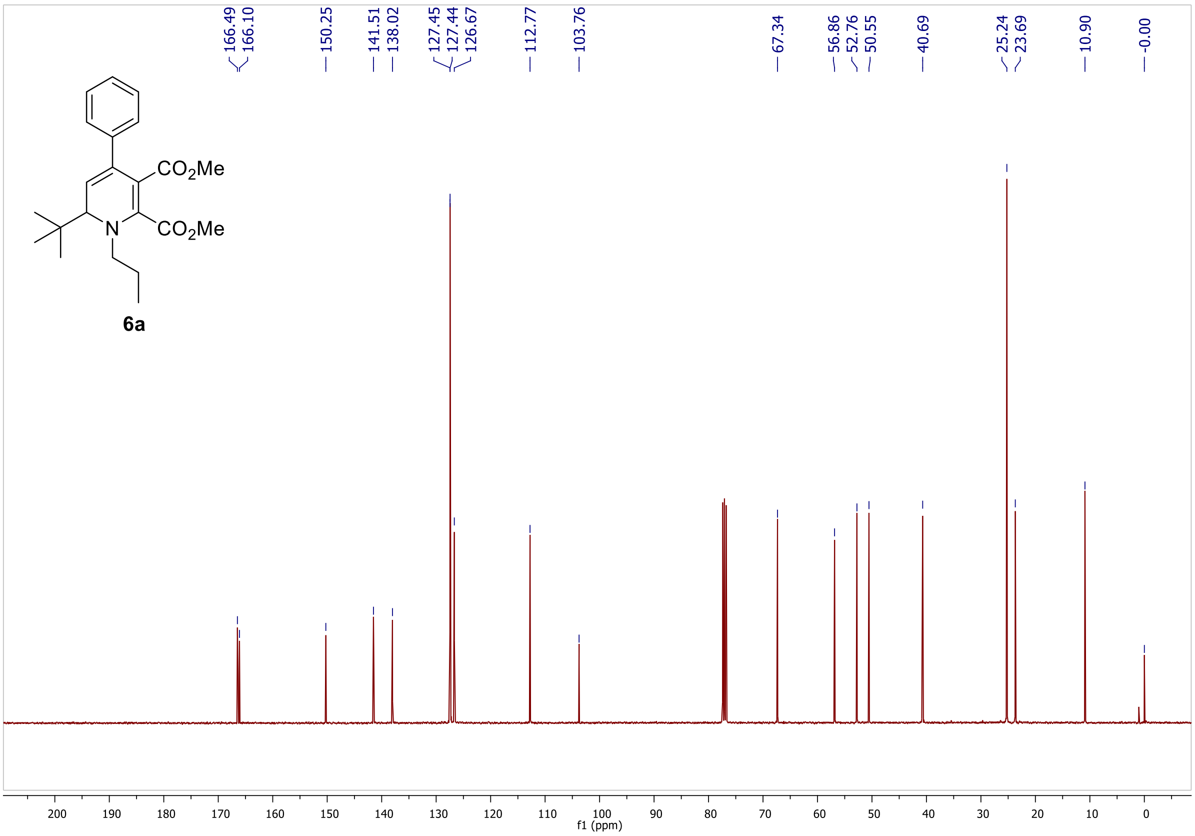
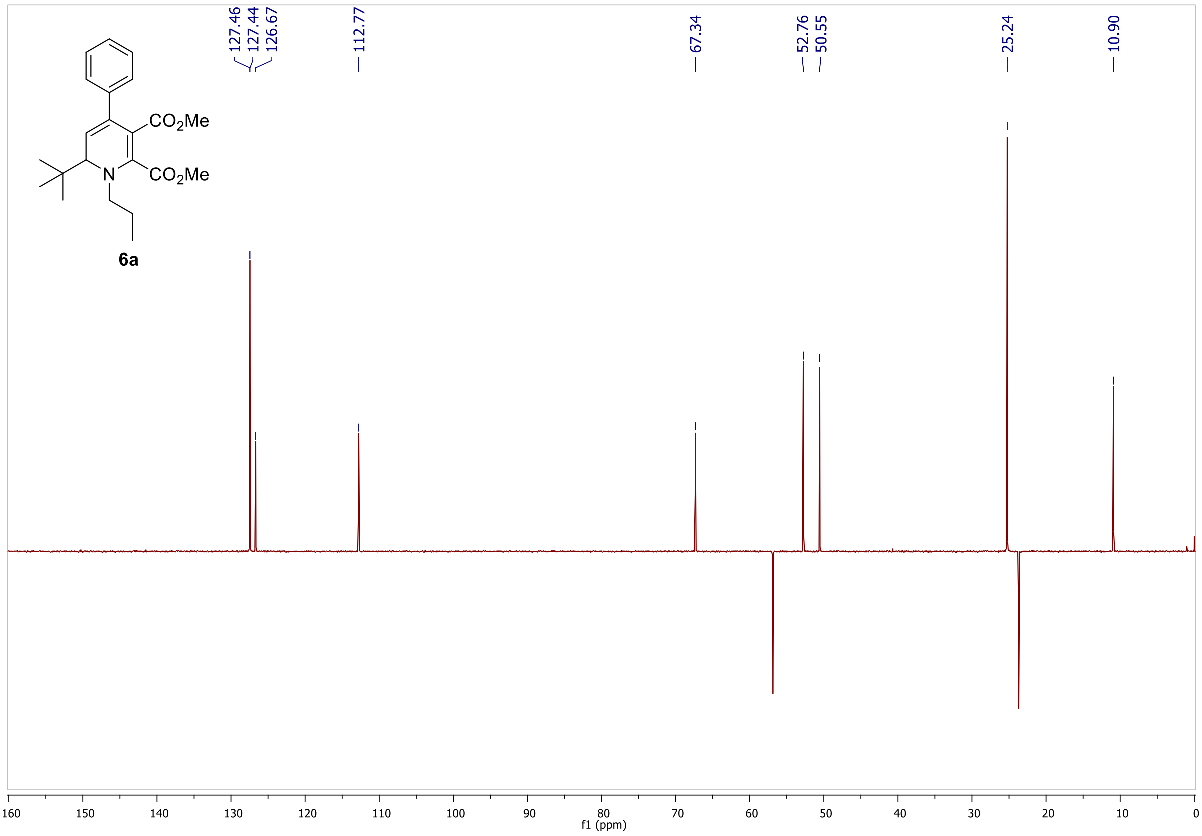


Figure 1. ^{1}H (400 MHz) and ^{13}C (100 MHz) NMR spectra of **6a** in $CDCl_3$.



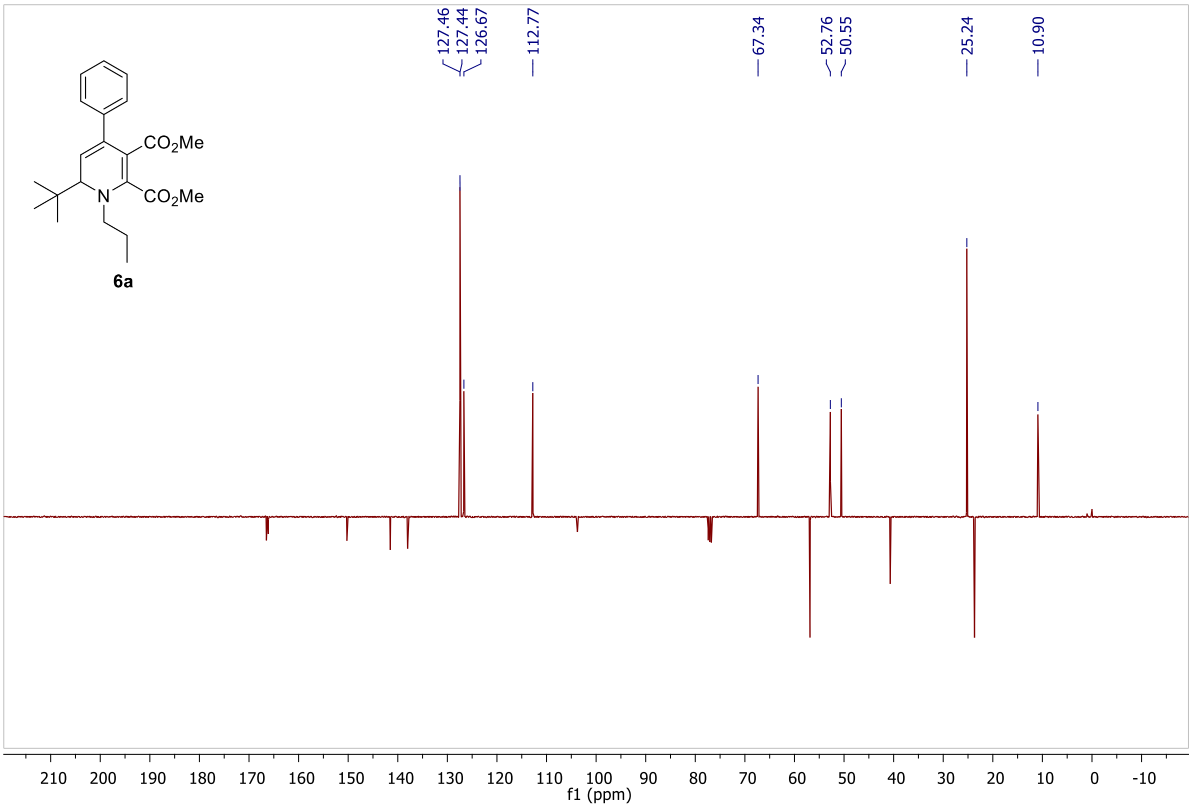
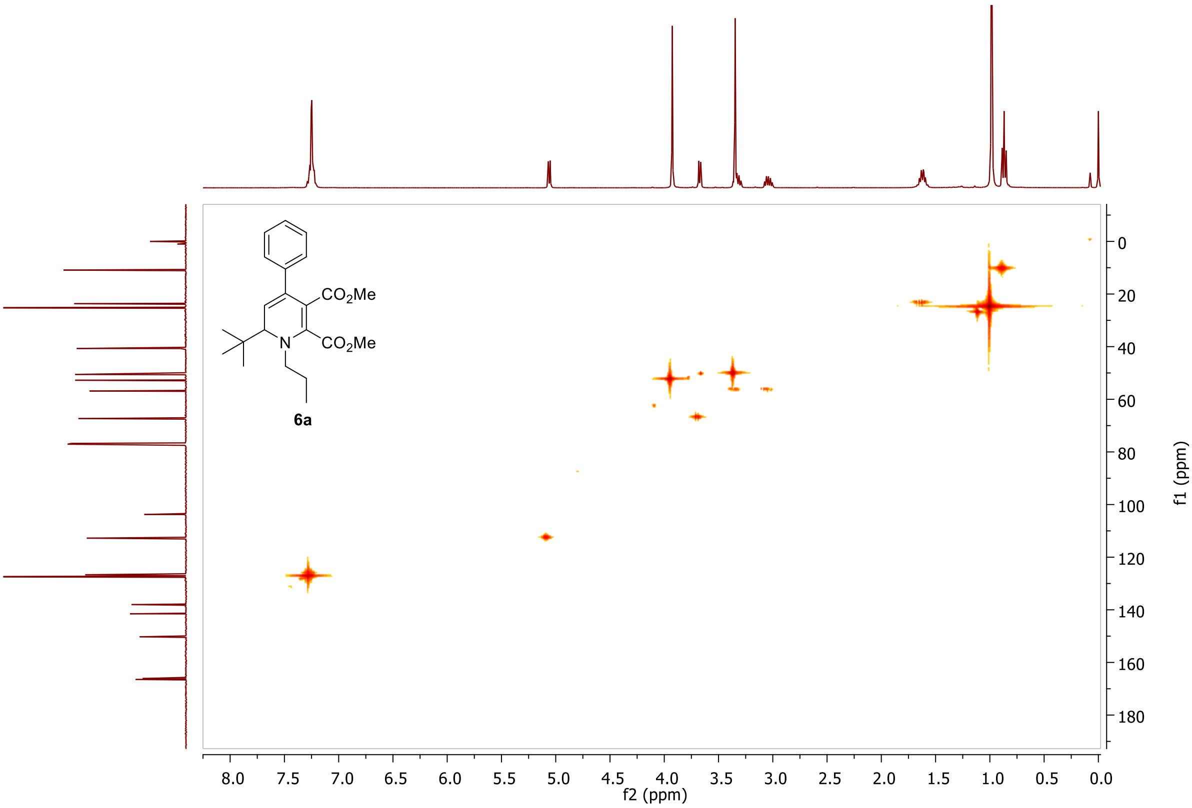


Figure 2. ^{13}C-DEPT 135 and ^{13}C-APT spectra of **6a** in $CDCl_3$.



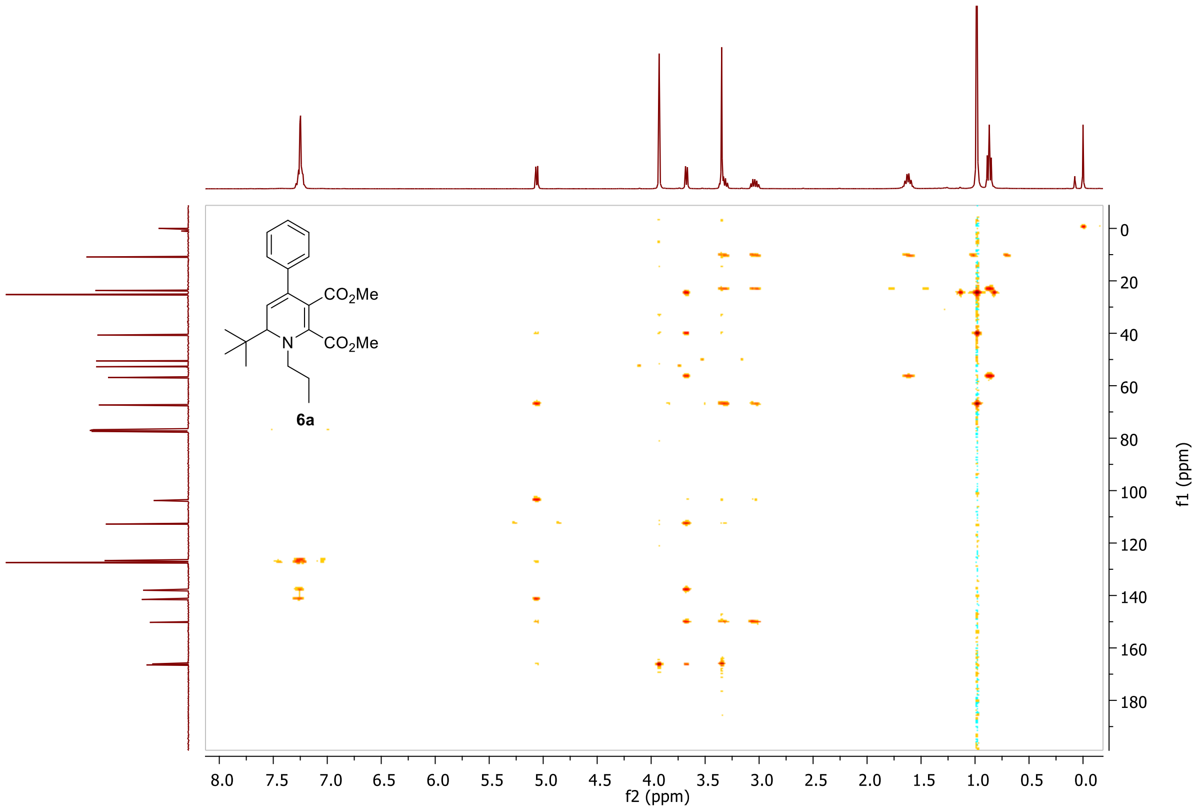


Figure 3. HMQC and HMBC spectra of **6a** in $CDCl_3$.

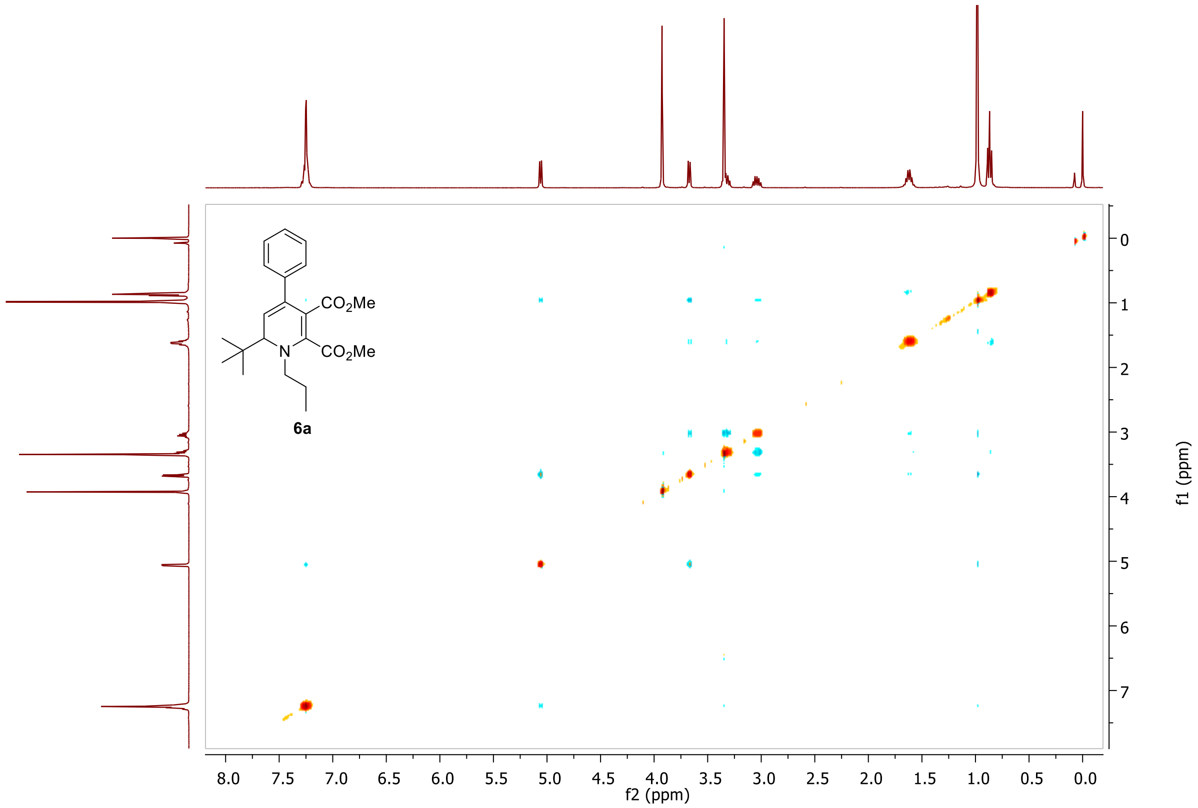
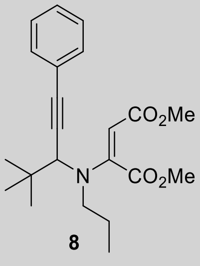
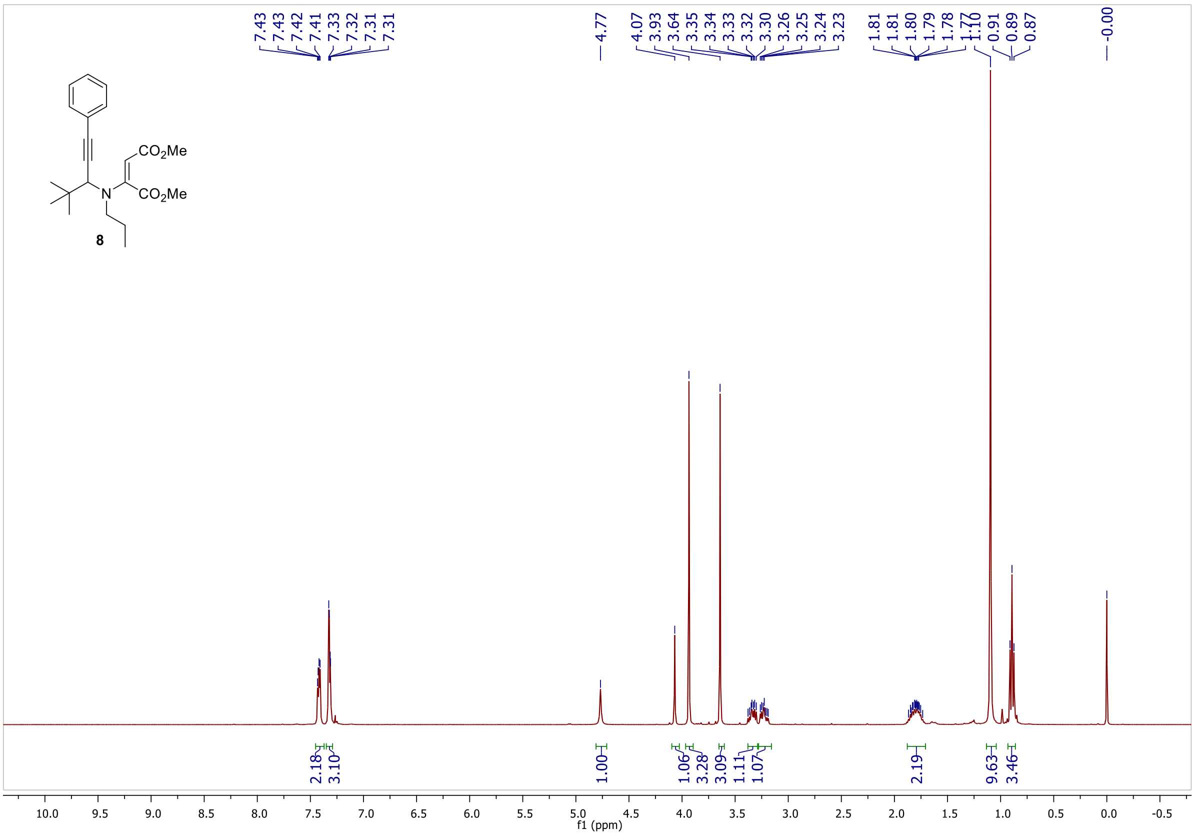


Figure 4. NOESY spectrum of **6a** in $CDCl_3$.

Dimethyl 2-((4,4-dimethyl-1-phenylpent-1-yn-3-yl)(propyl)amino)maleate (8) SAS-2-117Pure



R$_f$ = 0.50 (Heptane/EtOAc: 90/10). **^{1}H NMR** (400 MHz, CDCl$_3$): δ 7.43 – 7.41 (m, 2H, aromatic), 7.33 – 7.31 (m, 3H, aromatic), 4.77 (s, 1H, C=C**H**CO$_2$Me), 4.07 (s, 1H, NC**H**), 3.93 (s, 3H, C=CHCO$_2$C**H**$_3$), 3.64 (s, 3H, HC=CCO$_2$C**H**$_3$), 3.38 – 3.32 (m, 1H, NC(H)**H**), 3.27 – 3.16 (m, 1H, NC(**H**)H), 1.88 – 1.71 (m, 2H, NCH$_2$C**H**$_2$), 1.10 (s, 9H, C(C**H**$_3$)$_3$), 0.89 (t, J = 7.5 Hz, 3H, CH$_2$C**H**$_3$). **^{13}C NMR** (100 MHz, CDCl$_3$): δ 167.9 (C=O), 166.0 (C=CH**C**O$_2$Me), 154.0 (**C**=CHCO$_2$Me), 131.6 (aromatic), 128.5 (C$_{para}$), 128.4 (aromatic), 122.6 (C$_{ipso}$), 87.9 (C=**C**HCO$_2$Me), 87.1 (C≡CPh), 84.9 (C≡CPh), 63.0 (N**C**(H)C≡C), 52.9 (C=CHCO$_2$**C**H$_3$), 50.8 (HC=CCO$_2$**C**H$_3$), 49.9 (NCH$_2$), 38.6 (**C**(CH$_3$)$_3$), 27.5 (C(**C**H$_3$)$_3$), 19.5 (**C**H$_2$CH$_3$), 11.3 (CH$_2$**C**H$_3$). **HRMS** (ESI) *m/z* calculated for C$_{22}$H$_{29}$NO$_4$+H$^+$: 372.2169; found 372.2178.



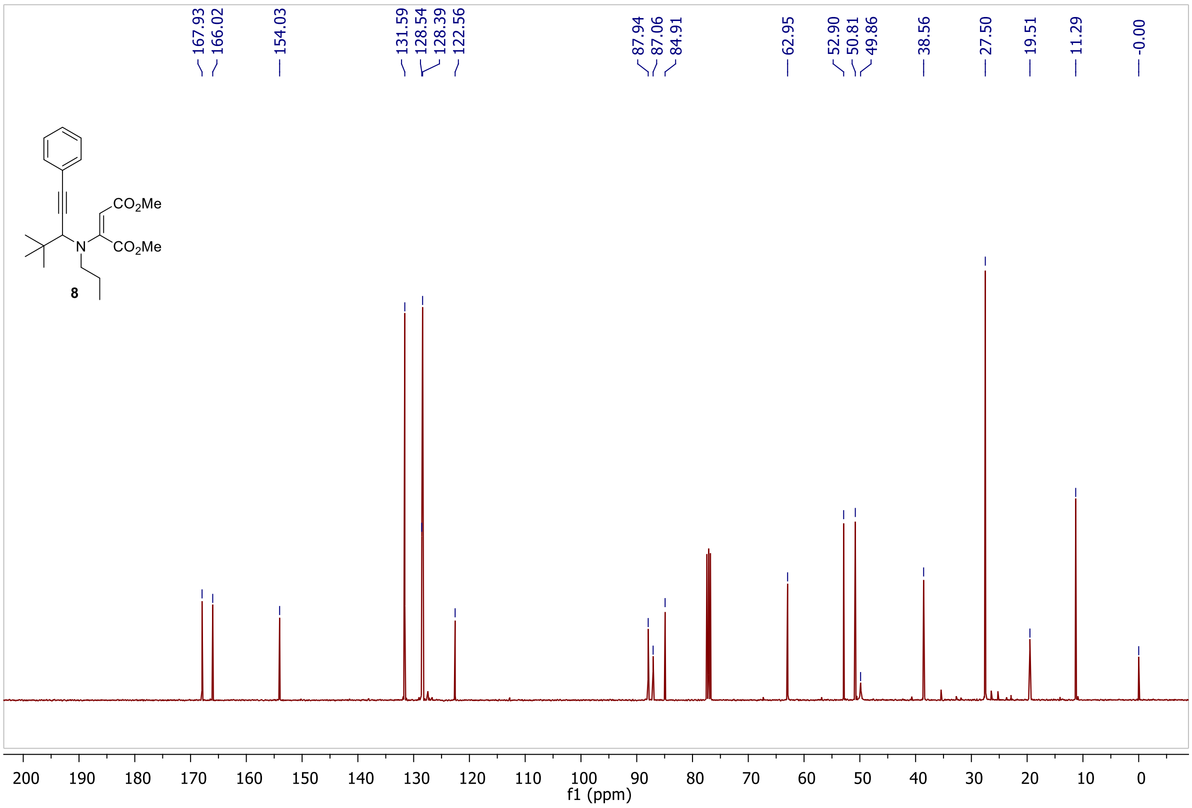


Figure 5. ^{1}H (400 MHz) and ^{13}C (100 MHz) NMR spectra of **8** in CDCl$_3$.

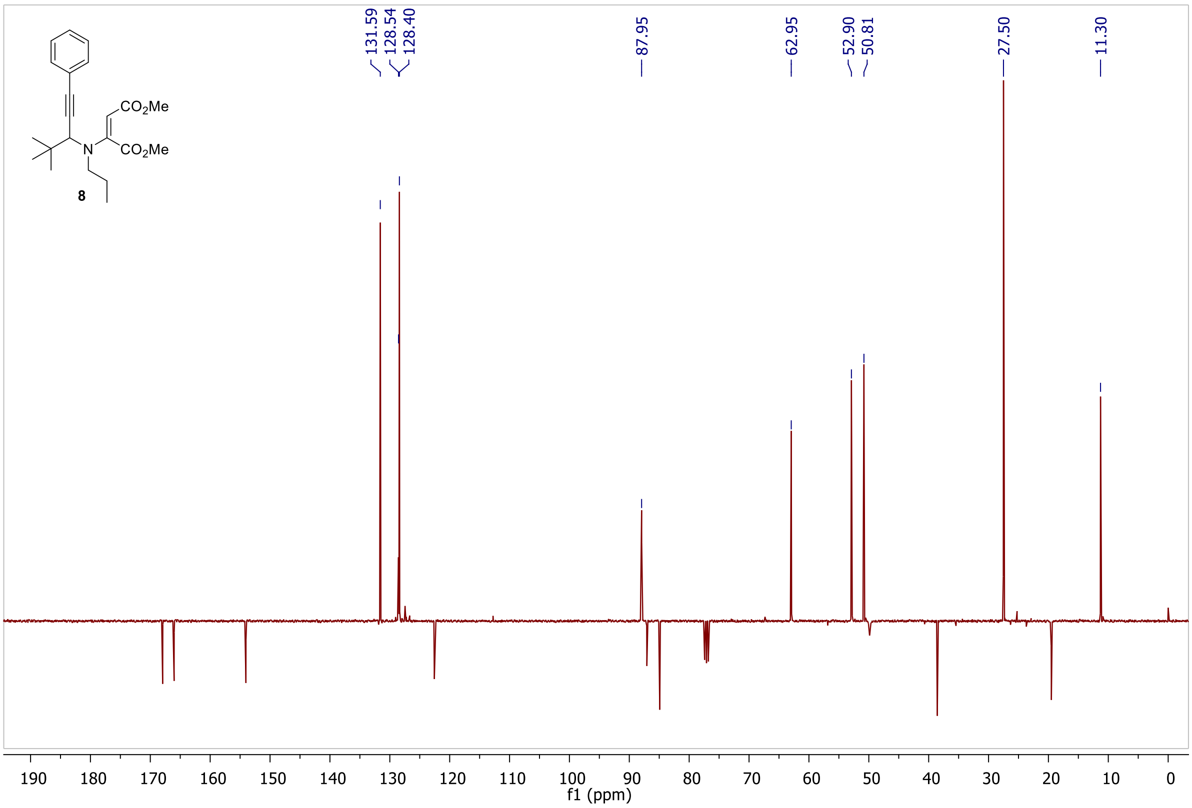


Figure 6. ^{13}C APT spectrum of **8** in CDCl$_3$.

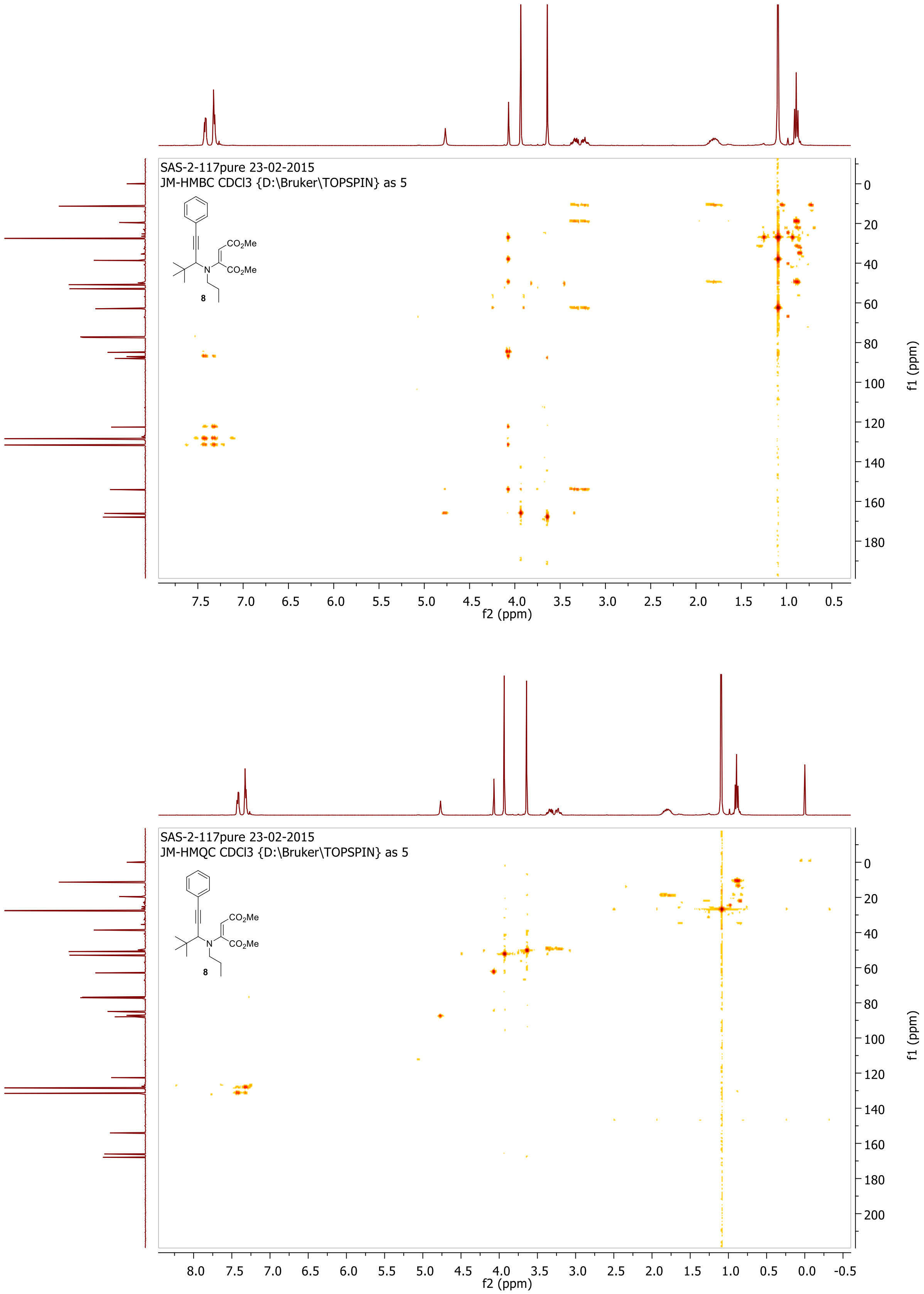
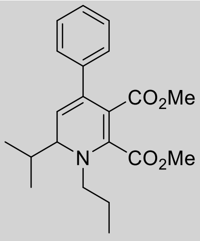


Figure 7. HMBC and HMQC spectra of **8** in CDCl$_3$.

Dimethyl 6-isopropyl-4-phenyl-1-propyl-1,6-dihydropyridine-2,3-dicarboxylate (6b) sas-5-21



6b

According to the general procedure *N*-(2-methylpropylidene)propan-1-amine (**3b**) (0.5 mmol, 0.057 g), phenylacetylene (**4a**) (0.5 mmol, 0.051 g), dimethyl 2-butynedioate (**5a**) (0.5 mmol, 0.071 g) and $Zn(OTf)_2$ (0.05 mmol, 0.018 g) were reacted in 1 mL of toluene/DMF (7/3) at 100 ºC for 18 h. Alkaline work up and column chromatography afforded 155 mg (87%) of dimethyl 6-isopropyl-4-phenyl-1-propyl-1,6-dihydropyridine-2,3-dicarboxylate **(6b)** as a yellow viscous oil. R_f = 0.52 (Heptane/EtOAc: 90/10).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28 – 7.22 (m, 5H, aromatic), 5.12 (d, *J* = 6.7 Hz, 1H, **H**C=C), 3.94 (s, 3H, $OC\mathbf{H}_3$), 3.60 (dd, *J* = 8.2, 6.8 Hz, 1H, C**H***i*-Pr), 3.36 (s, 3H, $OC\mathbf{H}_3$), 3.29 (dt, *J* = 14.7, 7.5 Hz, 1H, NC(**H**)H), 3.15 – 3.08 (m, 1H, NC(H)**H**), 2.09 – 2.00 (m, 1H, $\mathbf{H}C(CH_3)_2$), 1.64 – 1.58 (m, 2H, $C\mathbf{H}_2CH_3$), 0.99 (d, *J* = 6.7 Hz, 3H, $HC(C\mathbf{H}_3)CH_3$), 0.97 (d, *J* = 6.8 Hz, 3H, $HC(CH_3)C\mathbf{H}_3$), 0.86 (t, *J* = 7.4 Hz, 3H, $CH_2C\mathbf{H}_3$). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 166.3 (C=O), 166.2 (C=O), 149.2, 141.5, 137.2, 127.5, 127.5, 126.7, 112.8, 101.2, 64.2, 55.4, 52.8, 50.5, 31.7, 23.5, 18.5, 17.4, 10.9. **HRMS** (ESI) *m/z* calculated for $C_{21}H_{27}NO_4+H^+$: 358.2018; found 358.2024.

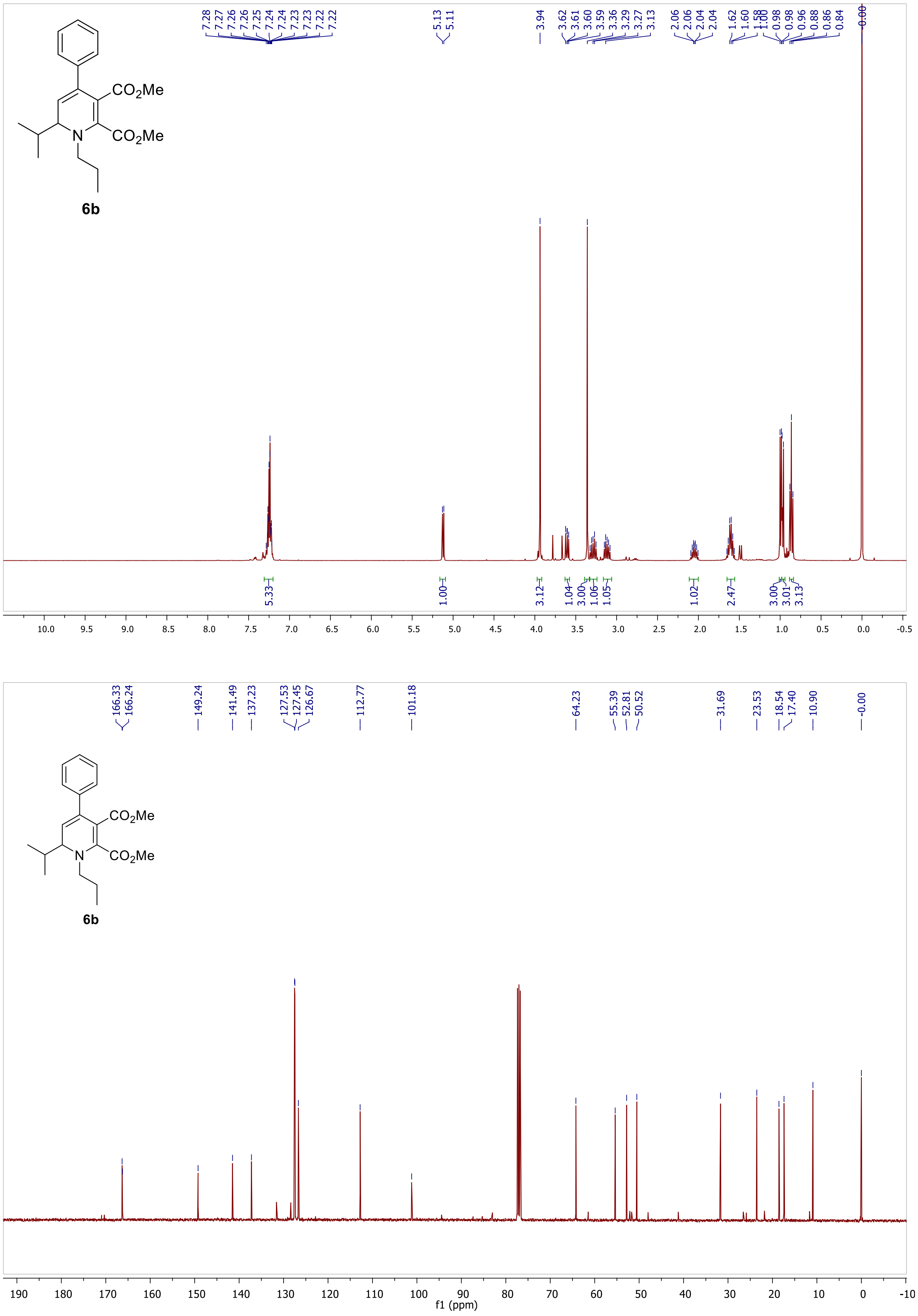
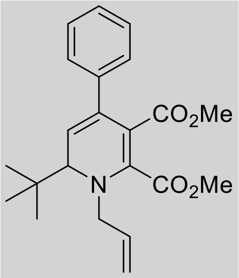


Figure 8. ^{1}H (400 MHz) and ^{13}C (100 MHz) NMR spectra of **6b** in $CDCl_3$.

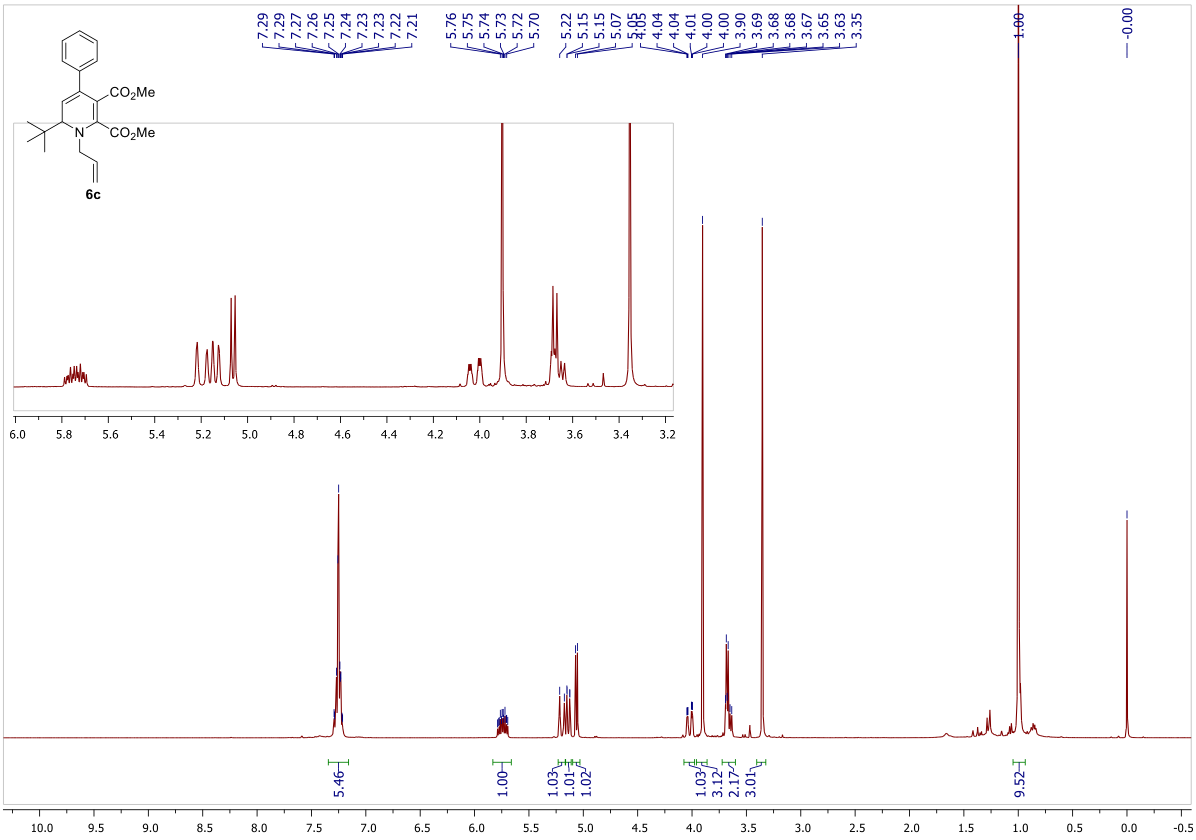
Dimethyl 1-allyl-6-(*tert*-butyl)-4-phenyl-1,6-dihydropyridine-2,3-dicarboxylate (6c) sas-5-14



6c

According to the general procedure *N*-(2,2-dimethylpropylidene)prop-2-en-1-amine (**3c**) (0.5 mmol, 0.063 g), phenylacetylene (**4a**) (0.5 mmol, 0.051 g), dimethyl 2-butynedioate (**5a**) (0.5 mmol, 0.071 g) and $Zn(OTf)_2$ (0.05 mmol, 0.018 g) were reacted in 1 mL of toluene/DMF (7/3) at 100 ºC for 18 h. Alkaline work up and column chromatography afforded 151 mg (82%) of dimethyl 1-allyl-6-(*tert*-butyl)-4-phenyl-1,6-dihydropyridine-2,3-dicarboxylate **(6c)** as yellow viscous oil, which became square shaped crystals on standing; mp = 94-96 ºC. R_f = 0.53 (Heptane/EtOAc: 90/10).

^{1}**H NMR** (400 MHz, $CDCl_3$): δ 7.29 – 7.21 (m, 5H, aromatic), 5.79 – 5.69 (m, 1H, **H**C=CH_2), 5.22 – 5.12 (m, 2H, HC=C**H**$_2$), 5.06 (d, *J* = 6.8 Hz, 1H, **H**C=C), 4.05 – 3.99 (m, 1H, **H**CHC=C), 3.90 (s, 3H, OC**H**$_3$), 3.69 – 3.63 (m, 2H, NC**H**$_2$), 3.35 (s, 3H, OC**H**$_3$), 1.00 (s, 9H, C(C**H**$_3$)$_3$). ^{13}**C NMR** (100 MHz, $CDCl_3$): δ 166.3 (C=O), 166.1 (C=O), 149.8, 141.4, 137.8, 133.4, 127.5, 127.4, 126.7, 117.0, 113.4, 104.3, 66.8, 57.3, 52.8, 50.6, 40.6, 25.3. **HRMS** (ESI) *m/z* calculated for $C_{22}H_{27}NO_4+H^+$: 370.2013; found 370.2015.



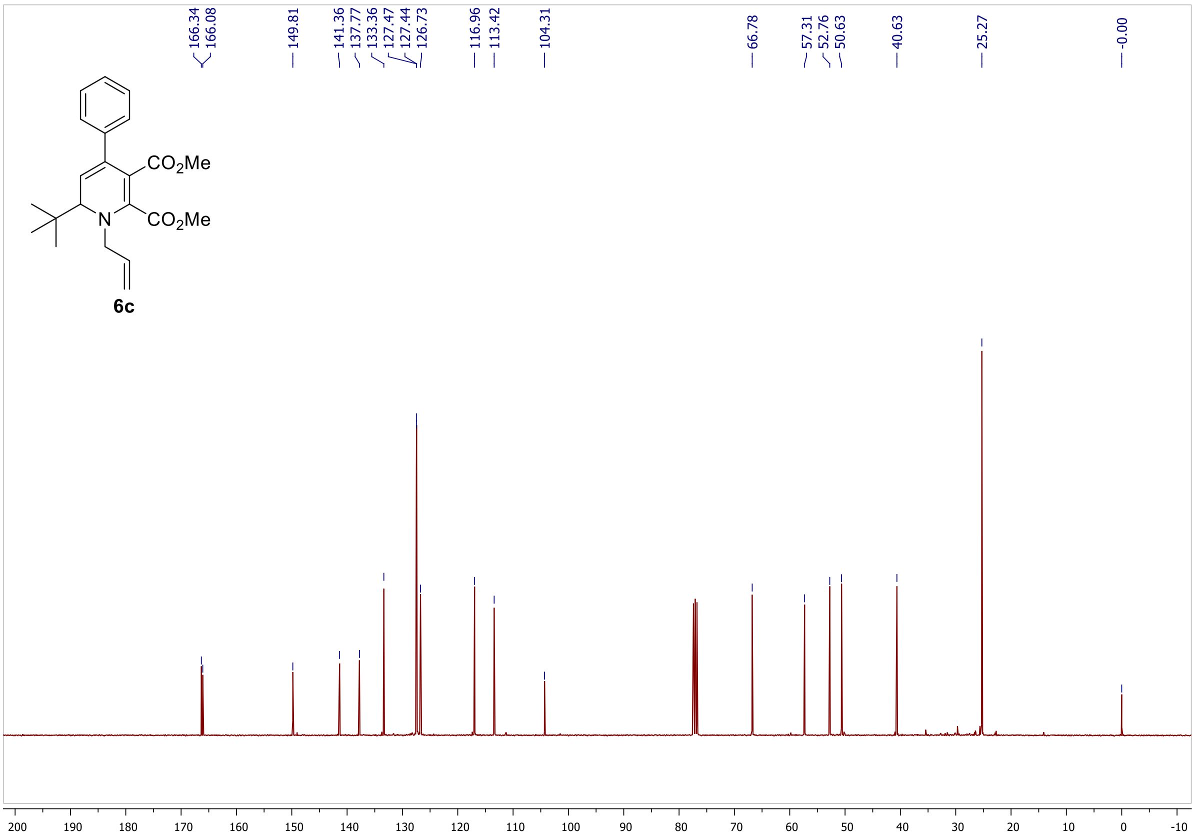
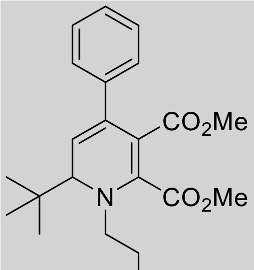


Figure 9. ^{1}H (400 MHz) and ^{13}C (100 MHz) NMR spectra of **6c** in $CDCl_3$.

Dimethyl 6-(*tert*-butyl)-1-isopentyl-4-phenyl-1,6-dihydropyridine-2,3-dicarboxylate (6d) sas-5-40pure



6d

According to the general procedure *N*-(2,2-dimethylpropylidene)-3-methylbutan-1-amine (**3d**) (0.5 mmol, 0.078 g), phenylacetylene (**4a**) (0.5 mmol, 0.051 g), dimethyl 2-butynedioate (**5a**) (0.5 mmol, 0.071 g) and $Zn(OTf)_2$ (0.05 mmol, 0.018 g) were reacted in 1 mL of toluene/DMF (7/3) at 100 ºC for 18 h. Alkaline work up and column chromatography afforded 179 mg (90%) of dimethyl 6-(*tert*-butyl)-1-isopentyl-4-phenyl-1,6-dihydropyridine-2,3-dicarboxylate **(6d)** as shiny crystals; mp = 100 ºC sharp. R_f = 0.60 (Heptane/EtOAc: 90/10).

^{1}**H NMR** (400 MHz, $CDCl_3$): δ 7.32 – 7.24 (m, 5H, aromatic), 5.07 (d, *J* = 6.9 Hz, 1H, **H**C=C), 3.92 (s, 3H, OC**H**$_3$), 3.70 (d, *J* = 6.9 Hz, 1H, **H**CHC=C), 3.40 – 3.37 (m, 4H, overlapped signal OCH_3 & NC(**H**)H), 3.09 – 3.03 (m, 1H, NC(H)**H**), 1.55 – 1.52 (m, 3H, overlapped signal NCH_2C**H**$_2$C**H**), 1.02 (s, 9H, C(C**H**$_3$)$_3$), 0.87 (d, *J* = 6.1 Hz, 6H, HC(C**H**$_3$)$_2$).

^{13}**C NMR** (100 MHz, $CDCl_3$): δ 166.6 (C=O), 166.1 (C=O), 150.01, 141.5, 138.0, 127.5, 127.4, 126.7, 112.8, 103.8, 67.4, 53.8, 52.7, 50.5, 40.7, 39.4, 25.8, 25.2, 22.6, 22.2. **HRMS** (ESI) *m/z* calculated for $C_{24}H_{33}NO_4+H^+$: 400.2488; found 400.2490.

Single crystals of **6d** were recrystallized from ethyl acetate, mounted in inert oil and transferred to the cold gas stream of the diffractometer.

Crystal structure determination of **6d** (CSD1814906):

Crystal data:

$C_{24}H_{33}NO_4$, $M = 399.51$

a =18.3692(7), b = 13.9179(5), c = 18.6682(9) Å

β = 107.269(5)° V = 4557.6(3) Å^3

T = 101(2) K

Space group, crystal system: $P2_1/n$ (no.14), monoclinic

$Z = 8$, 20926 reflections measured, 8932 unique ($R^{\text{int}} = 0.0518$), which were used in all calculations. The final $R1(F^2)$ was 0.0543 (I > 2σ(I)), w$R(F^2)$ was 0.1524 (all data), GoOF 1.018.

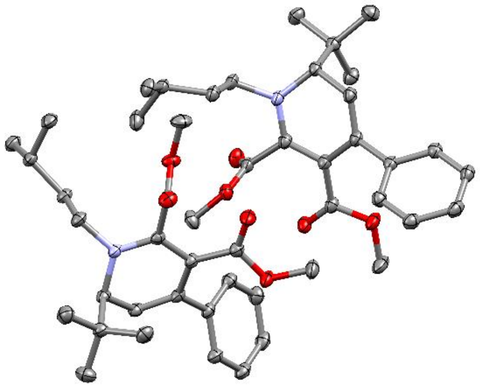
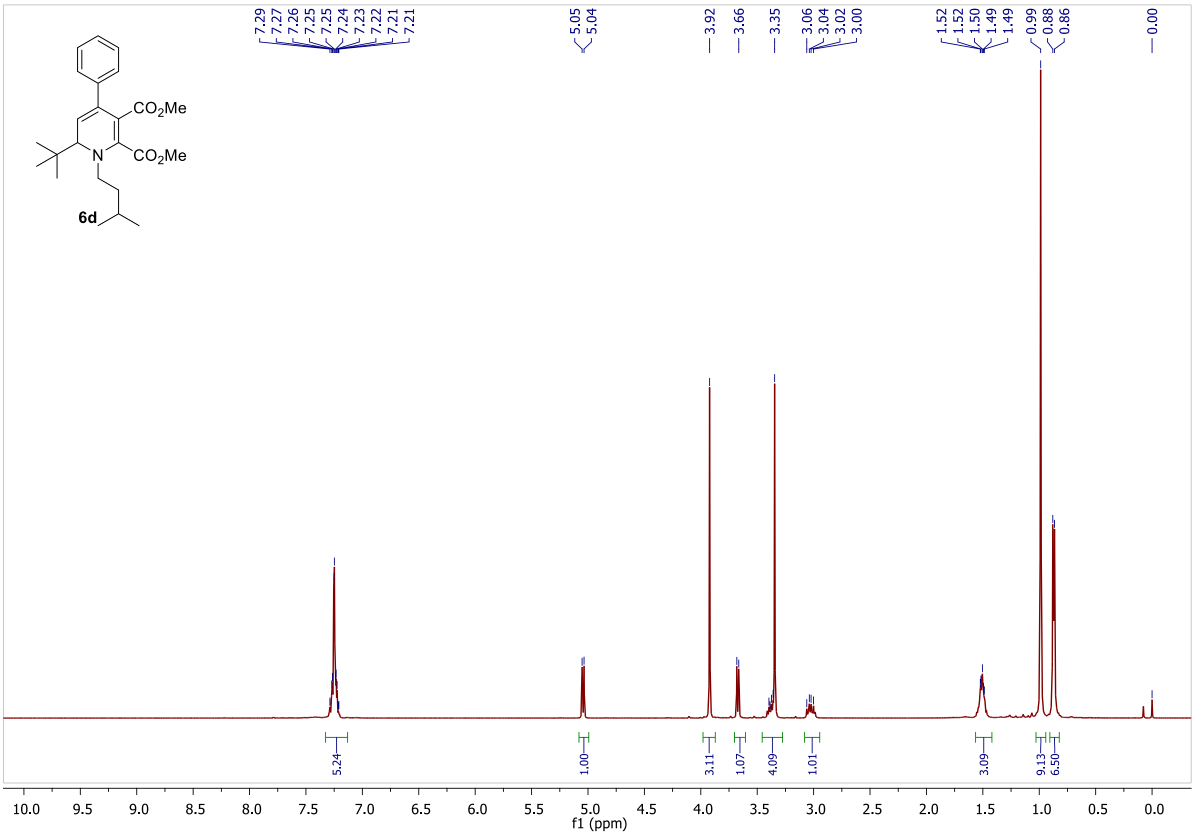


Figure 10. Single-crystal X-ray structure of **6d**. The asymmetric unit is shown (Z’=2). Displacement ellipsoids are at the 50% level, H atoms have been omitted for clarity.



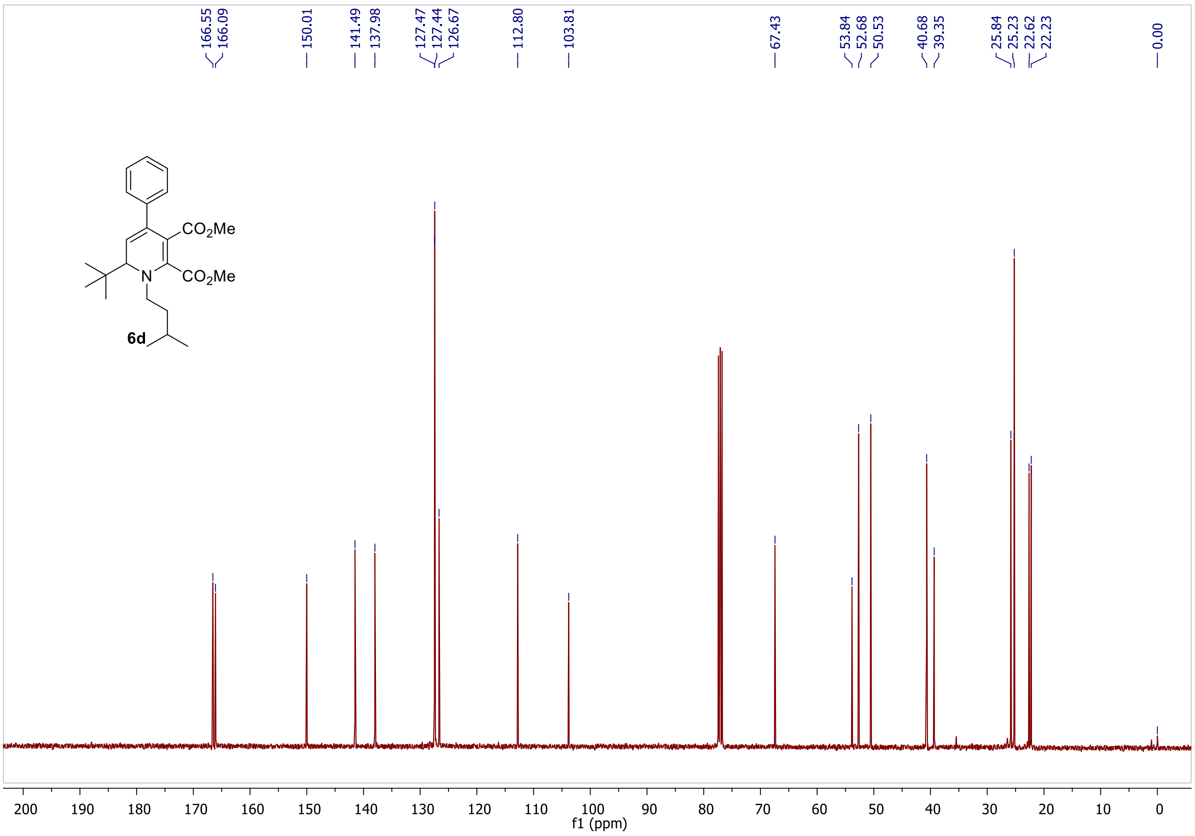
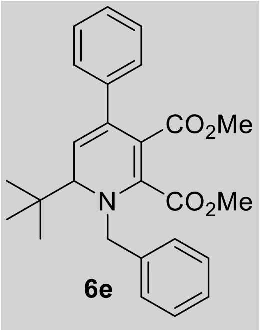


Figure 11. ^{1}H (400 MHz) and ^{13}C (100 MHz) NMR spectra of **6d** in $CDCl_3$.

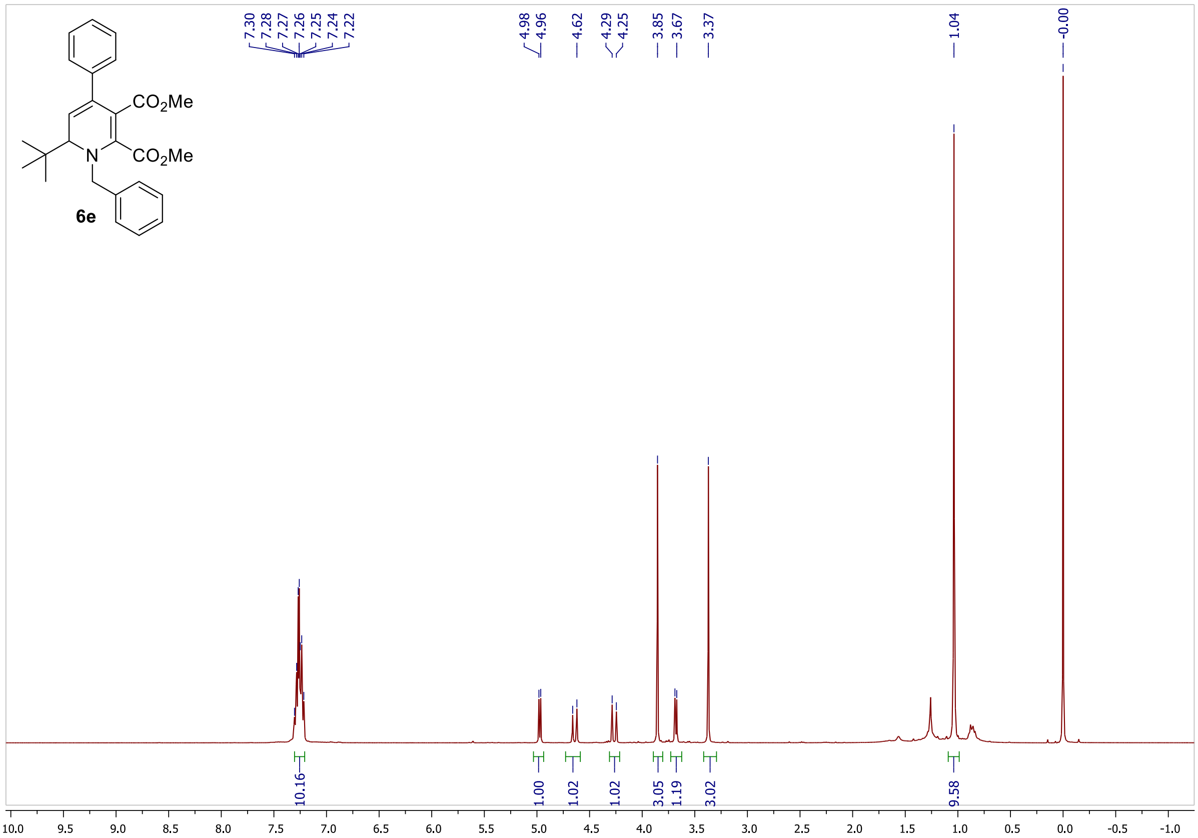
Dimethyl 1-benzyl-6-(*tert*-butyl)-4-phenyl-1,6-dihydropyridine-2,3-dicarboxylate (6e) sas-5-12



6e

According to the general procedure *N*-(2,2-dimethylpropylidene)-1-phenylmethanamine (**3e**) (0.5 mmol, 0.088 g), phenylacetylene (**4a**) (0.5 mmol, 0.051 g), dimethyl 2-butynedioate (**5a**) (0.5 mmol, 0.071 g) and $Zn(OTf)_2$ (0.05 mmol, 0.018 g) were reacted in 1 mL of toluene/DMF (7/3) at 100 ºC for 18 h. Alkaline work up and column chromatography afforded 128 mg (61%) of dimethyl 1-benzyl-6-(*tert*-butyl)-4-phenyl-1,6-dihydropyridine-2,3-dicarboxylate (**6e**) as a yellow viscous oil. R_f = 0.62 (Heptane/EtOAc: 90/10).

^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.30 – 7.22 (m, 10H, aromatic), 4.97 (d, *J* = 6.9 Hz, 1H, **H**C=C), 4.65 (d, *J* = 16.1 Hz, 1H, NC(**H**)H), 4.28 (d, *J* = 16.1 Hz, 1H, NC(H)**H**), 3.85 (s, 3H, OC**H**$_3$), 3.68 (d, *J* = 6.9 Hz, 1H, **H**CHC=C), 3.37 (s, 3H, OC**H**$_3$), 1.04 (s, 9H, C(C**H**$_3$)$_3$). **^{13}C NMR** (100 MHz, $CDCl_3$): *δ* 166.5 (C=O), 166.1 (C=O), 150.2, 141.4, 137.8, 137.7, 128.8, 127.8, 127.5, 126.8, 126.7, 113.8, 104.6, 66.8, 58.4, 52.8, 50.7, 40.8, 25.4. **HRMS** (ESI) *m/z* calculated for $C_{26}H_{29}NO_4+H^+$: 420.2175; found 420.2179.



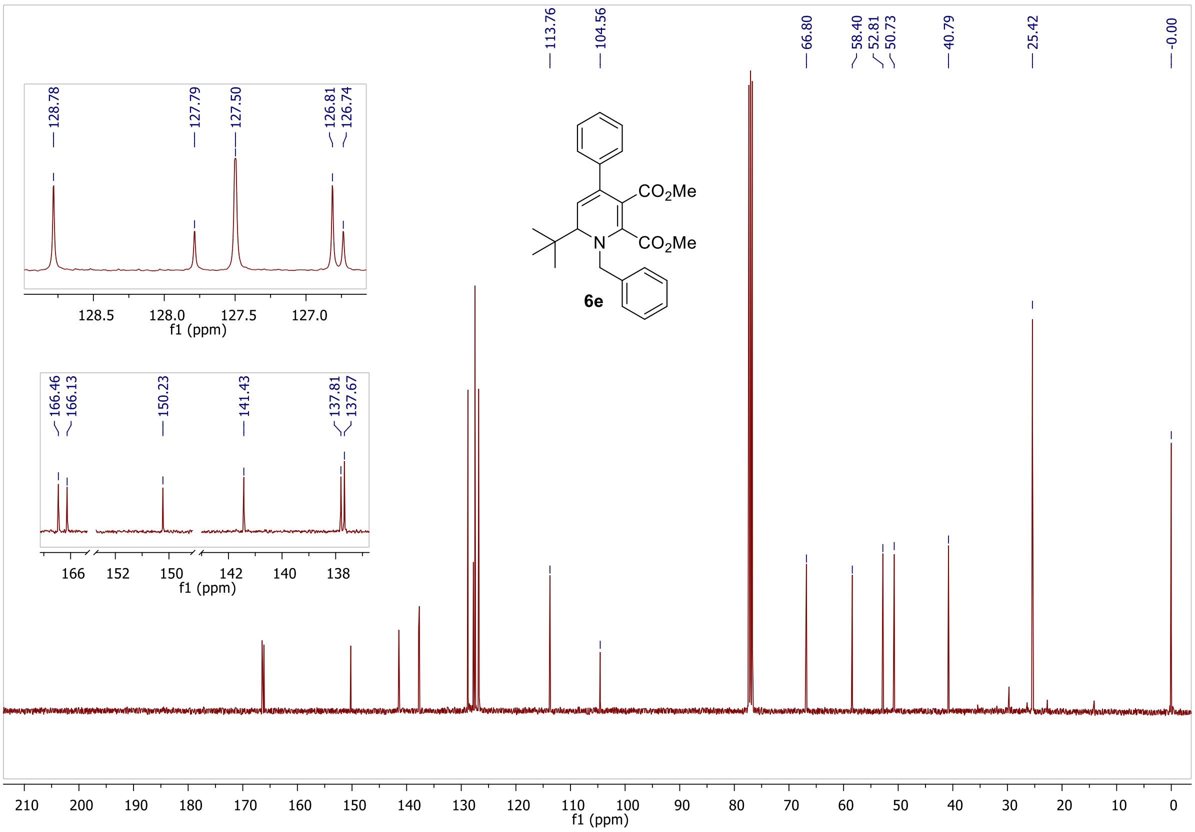
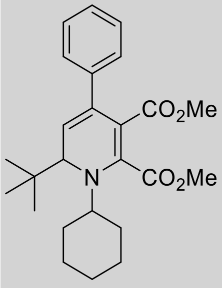


Figure 12. ^{1}H (400 MHz) and ^{13}C (100 MHz) NMR spectra of **6e** in $CDCl_3$.

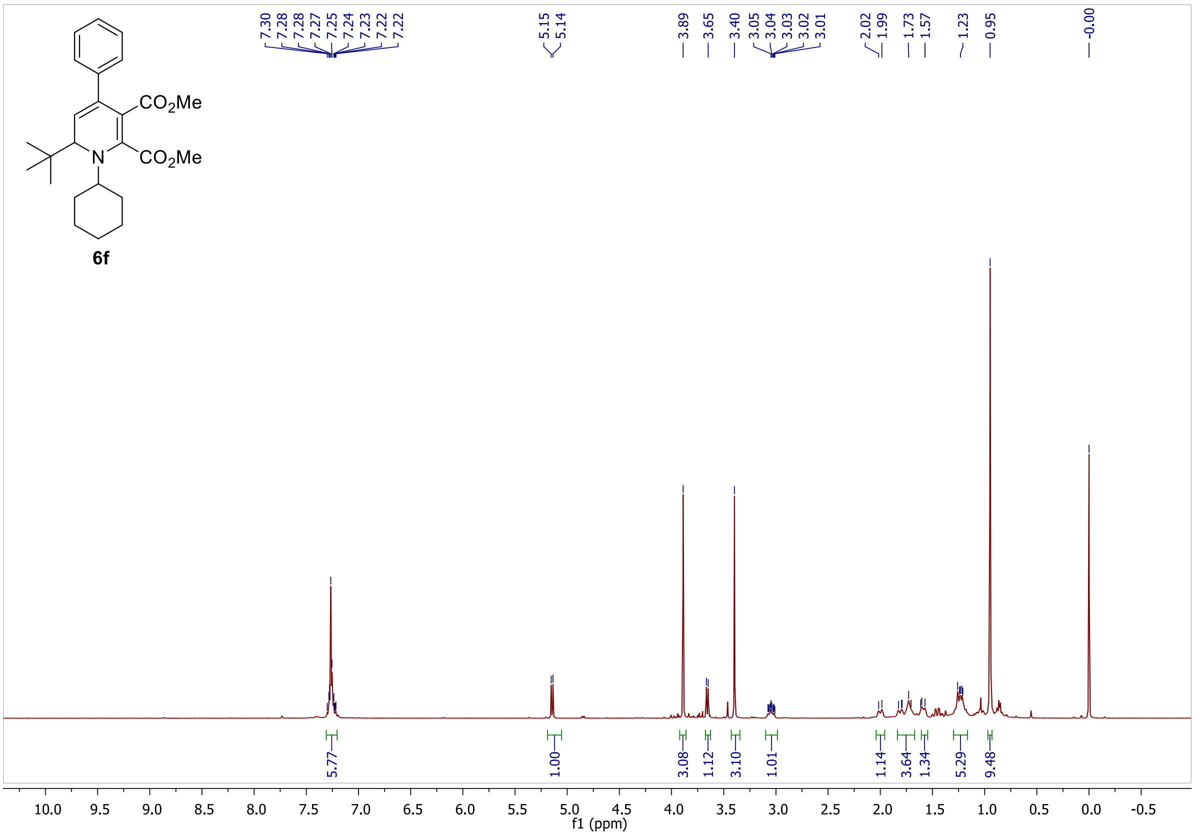
Dimethyl 6-(*tert*-butyl)-1-cyclohexyl-4-phenyl-1,6-dihydropyridine-2,3-dicarboxylate (6f) (sas-5-15)



6f

According to the general procedure *N*-(2,2-dimethylpropylidene) cyclohexanamine (**3f**) (0.5 mmol, 0.084 g), phenylacetylene (**4a**) (0.5 mmol, 0.051 g), dimethyl 2-butynedioate (**5a**) (0.5 mmol, 0.071 g) and $Zn(OTf)_2$ (0.05 mmol, 0.018 g) were reacted together in 1 mL of toluene/DMF (7/3) at 100 ºC for 18 h. Alkaline work up and column chromatography afforded 182 mg (89%) of dimethyl 6-(*tert*-butyl)-1-cyclohexyl-4-phenyl-1,6-dihydropyridine-2,3-dicarboxylate (**6f**) as a yellow viscous oil which became light yellow solid on long standing; mp = 82-84 ºC. R_f = 0.59 (Heptane/EtOAc: 90/10).

^{1}H NMR (400 MHz, CDCl$_3$): *δ* 7.30 – 7.22 (m, 5H, aromatic), 5.13 (d, *J* = 7.0 Hz, 1H, **H**C=C), 3.89 (s, 3H, OC**H**$_3$), 3.66 (d, *J* = 7.0 Hz, 1H, **H**CHC=C), 3.40 (s, 3H, OC**H**$_3$), 3.05 – 3.01 (m, 1H, *Cy*), 2.02 – 1.21 (m, 10 H, *Cy*), 0.95 (s, 9H, C(C**H**$_3$)$_3$). **^{13}C NMR** (100 MHz, CDCl$_3$): *δ* 167.3 (C=O), 166.4 (C=O), 147.5, 140.7, 137.4, 127.8, 127.5, 126.8, 115.8, 112.5, 64.1, 61.5, 52.7, 51.0, 38.4, 33.2, 32.6, 26.4, 26.1, 25.9, 25.3. **HRMS** (ESI) *m/z* calculated for $C_{25}H_{33}NO_4+H^+$: 402.1700; found 402.1705.



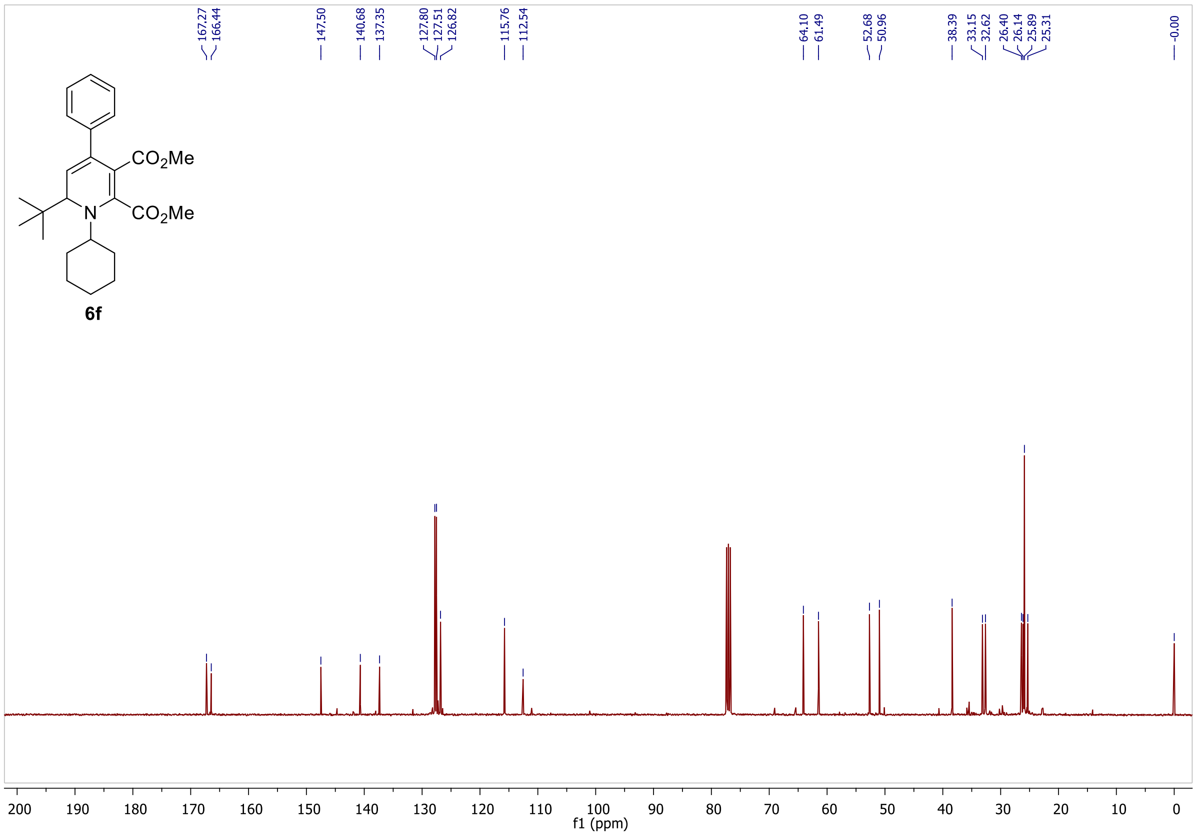
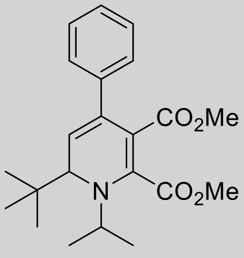


Figure 13. ^{1}H (400 MHz) and ^{13}C (100 MHz) NMR spectra of **6f** in $CDCl_3$.

Dimethyl 6-(*tert*-butyl)-1-isopropyl-4-phenyl-1,6-dihydropyridine-2,3-dicarboxylate (6g) sas-5-10

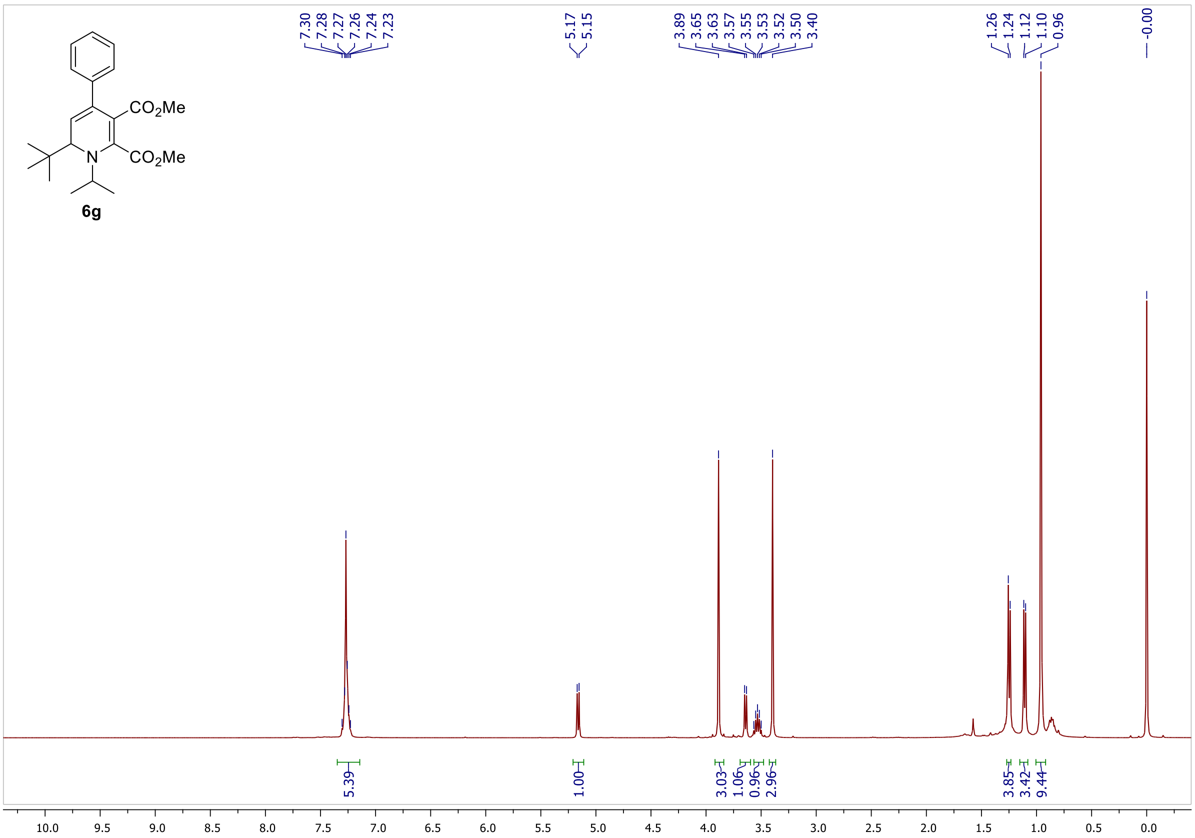


6g

According to the general procedure *N*-(2,2-dimethylpropylidene)propan-2-amine (**3g**) (0.5 mmol, 0.064 g), phenylacetylene (**4a**) (0.5 mmol, 0.051 g), dimethyl 2-butynedioate (**5a**) (0.5 mmol, 0.071 g) and $Zn(OTf)_2$ (0.05 mmol, 0.018 g) were reacted in 1 mL of toluene/DMF (7/3) at 100 ºC for 18 h. Alkaline work up and column chromatography afforded 148 mg (80%) of dimethyl 6-(*tert*-butyl)-1-cyclohexyl-4-phenyl-1,6-dihydropyridine-2,3-dicarboxylate **(6g)** as a yellow viscous oil. R_f = 0.54 (Heptane/EtOAc: 90/10).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30 – 7.23 (m, 5H, aromatic), 5.16 (d, J = 6.9 Hz, 1H, **H**C=C), 3.89 (s, 3H, OC**H**$_3$), 3.64 (d, J = 7.0 Hz, 1H, **H**CHC=C), 3.57 – 3.50 (m, 1H,

HC(CH$_3$)$_2$), 3.40 (s, 3H, OC**H**$_3$), 1.25 (d, *J* = 6.8 Hz, 3H, HC(C**H**$_3$)CH$_3$), 1.11 (d, *J* = 6.7 Hz, 3H, HC(CH$_3$)C**H**$_3$), 0.96 (s, 9H, C(C**H**$_3$)$_3$). **^{13}C NMR** (100 MHz, CDCl$_3$): *δ* 167.3 (C=O), 166.4 (C=O), 147.4, 140.7, 137.3, 127.8, 127.5, 126.8, 115.9, 112.3, 61.1, 55.5, 52.7, 51.0, 38.5, 25.9, 22.4, 22.0. **HRMS** (ESI) *m/z* calculated for $C_{22}H_{29}NO_4$+H^+: 372.2175; found 372.2170.



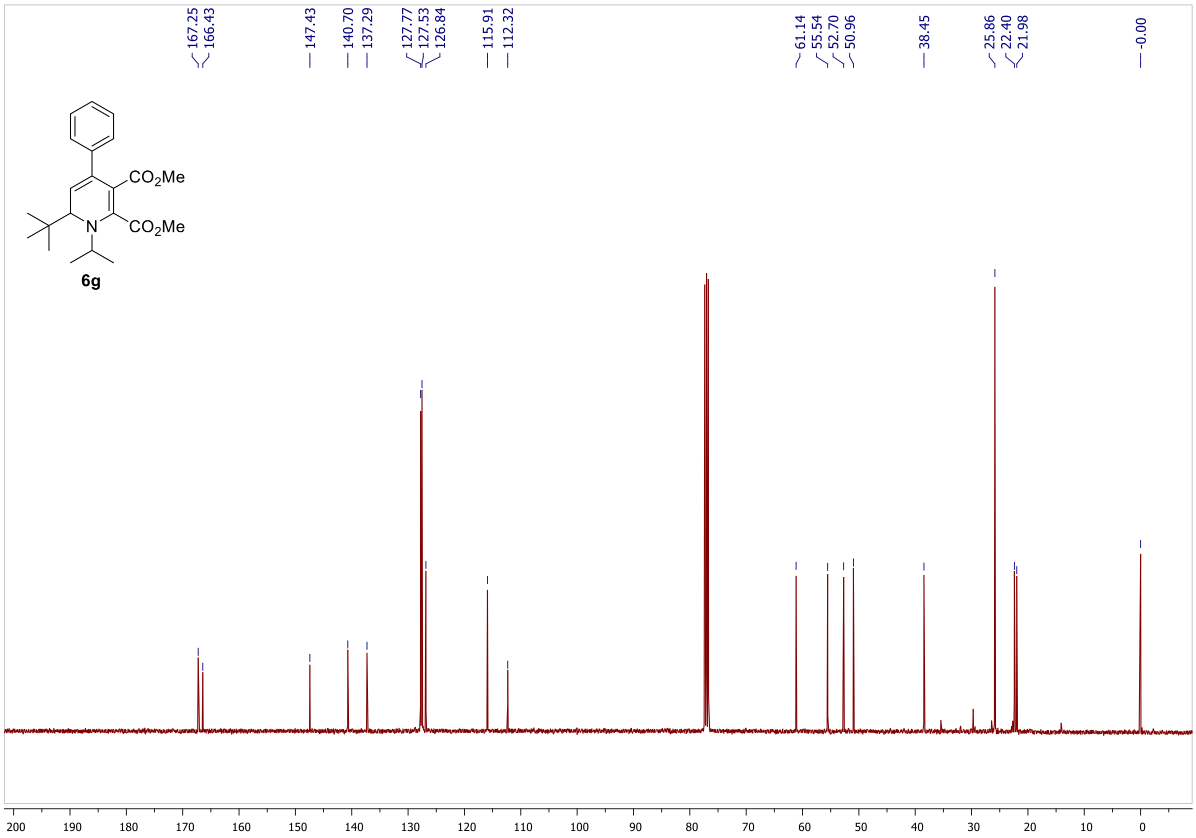
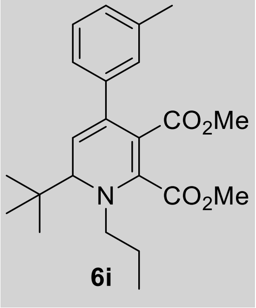


Figure 14. ^{1}H (400 MHz) and ^{13}C (100 MHz) NMR spectra of **6g** in CDCl$_3$.

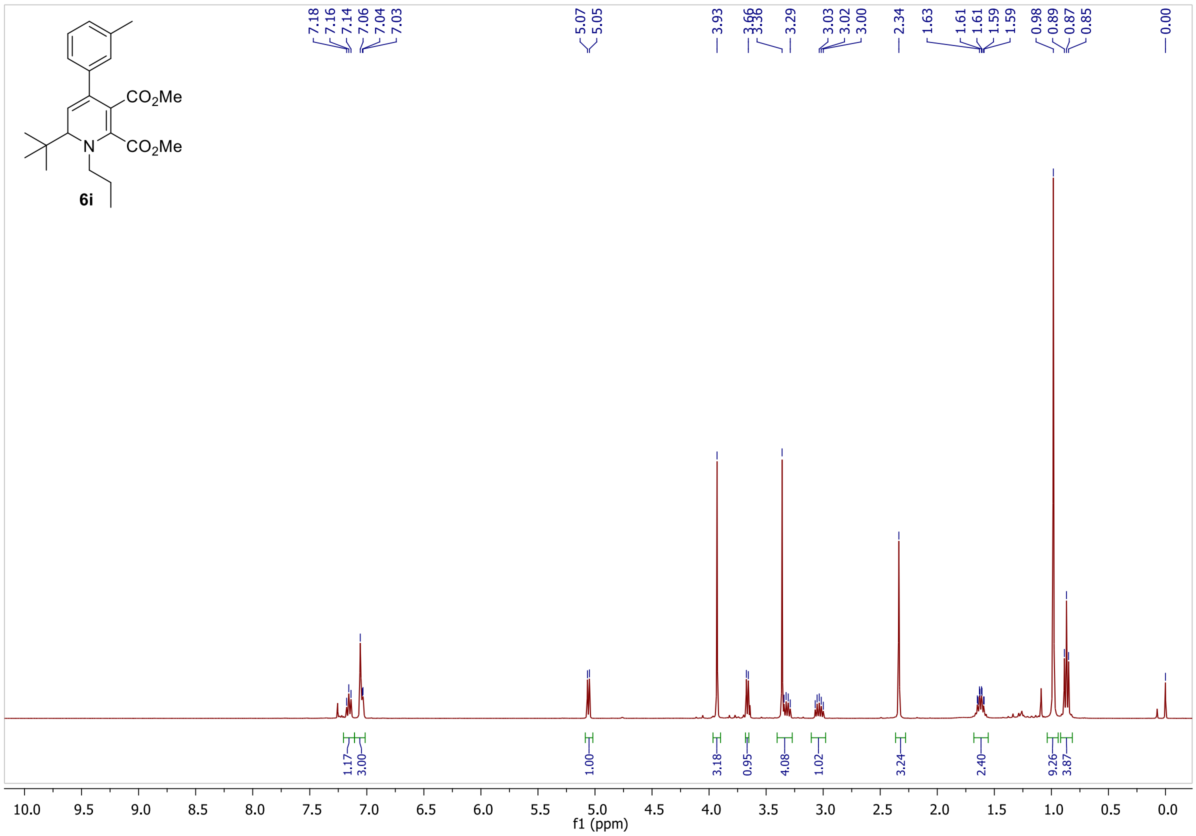
Dimethyl 6-(*tert*-butyl)-1-propyl-4-(*m*-tolyl)-1,6-dihydropyridine-2,3-dicarboxylate (6i) sas-5-24



According to the general procedure *N*-(2,2-dimethylpropylidene)propan-1-amine (**3a**) (0.5 mmol, 0.064 g), 3-methylphenylacetylene (**4b**) (0.5 mmol, 0.058 g), dimethyl 2-butynedioate (**5a**) (0.5 mmol, 0.071 g) and Zn(OTf)$_2$ (0.05 mmol, 0.018 g) were reacted in 1 mL of toluene/DMF (7/3) at 100 ºC for 18 h. Alkaline work up and column chromatography afforded 68 mg (70%) of dimethyl 6-(*tert*-butyl)-1-propyl-4-(*m*-tolyl)-1,6-dihydropyridine-2,3-dicarboxylate **(6i)** as a yellow viscous oil. R$_f$ = 0.56 (Heptane/EtOAc: 90/10).

^{1}H NMR (400 MHz, CDCl$_3$): δ 7.18 – 7.14 (t, J = 7.2, 1H, aromatic), 7.06 – 7.03 (m, 3H, aromatic), 5.06 (d, J = 6.9 Hz, 1H, **H**C=C), 3.93 (s, 3H, OC**H**$_3$), 3.67 (d, J = 6.9 Hz, 1H,

HCHC=C), 3.36 – 3.29 (m, 4H, overlapped signal OC**H**$_3$ & NC(**H**)H), 3.07 – 3.00 (m, 1H, NC(H)**H**), 2.34 (s, 3H, C**H**$_3$Ph), 1.65 – 1.59 (m, 2H, C**H**$_2$CH$_3$), 0.98 (s, 9H, C(C**H**$_3$)$_3$), 0.87 (t, *J* = 7.4 Hz, 3H, CH$_2$C**H**$_3$). **^{13}C NMR** (100 MHz, CDCl$_3$): *δ* 166.6 (C=O), 166.2 (C=O), 150.1, 141.4, 138.0, 137.0, 128.1, 127.5, 127.4, 124.6, 112.7, 103.9, 67.4, 56.9, 52.8, 50.6, 40.7, 25.3, 23.7, 21.4, 10.9. **HRMS** (ESI) *m/z* calculated for $C_{23}H_{31}NO_4$+H$^+$: 386.2326; found 386.2331.



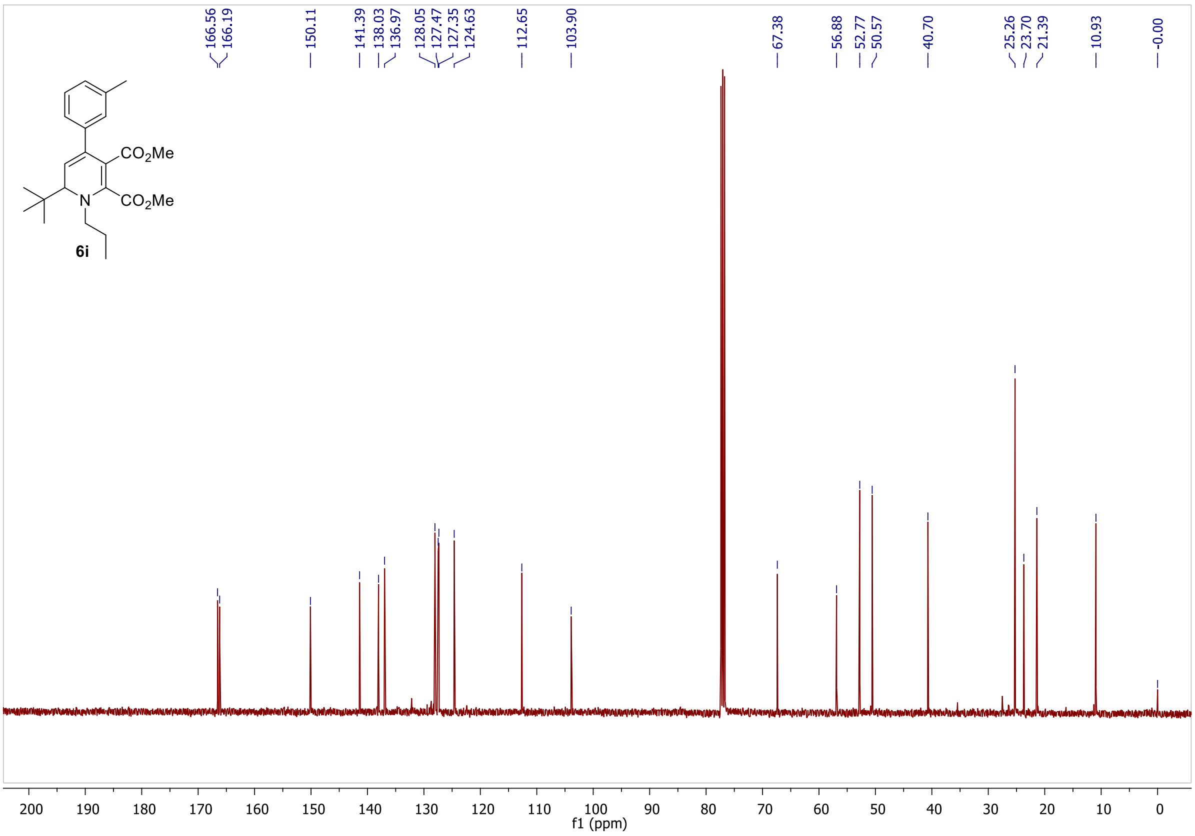
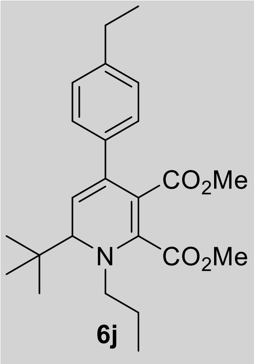


Figure 15. ^{1}H (400 MHz) and ^{13}C (100 MHz) NMR spectra of **6i** in $CDCl_3$.

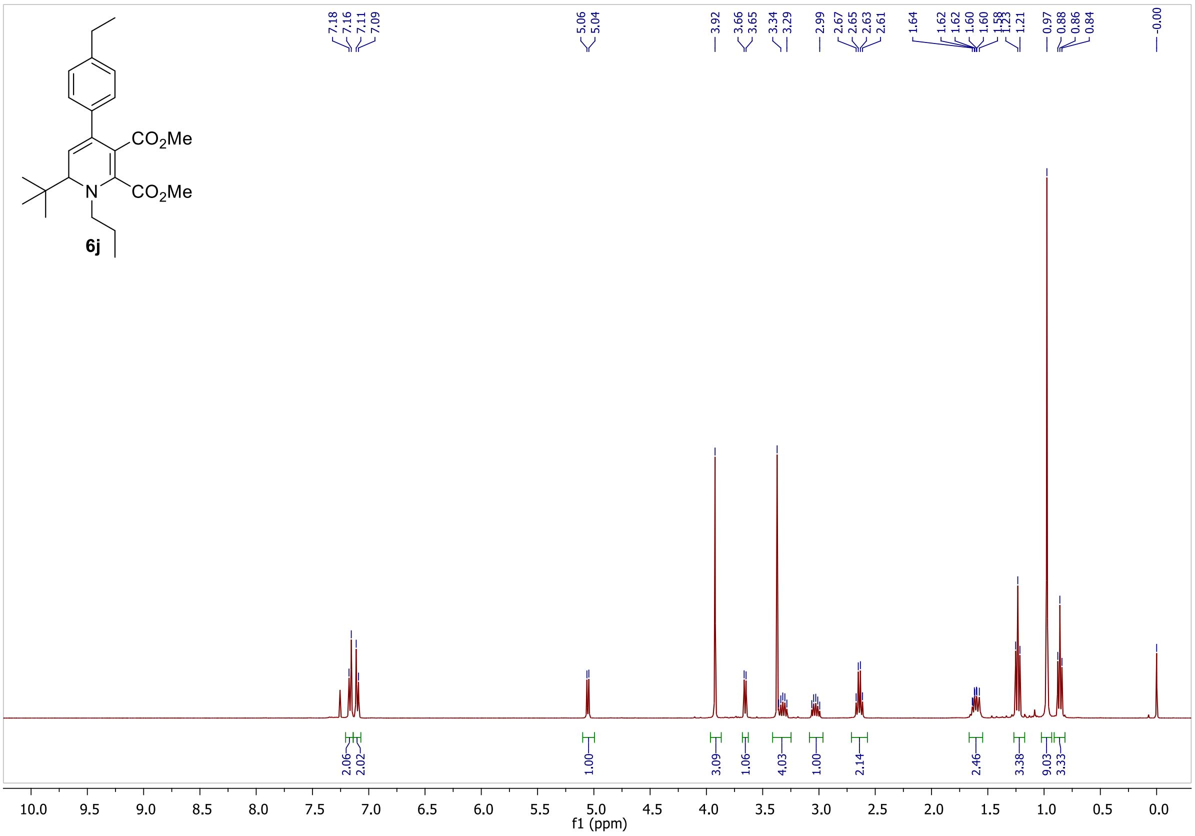
Dimethyl 6-(*tert*-butyl)-4-(4-ethylphenyl)-1-propyl-1,6-dihydropyridine-2,3-dicarboxylate (6j) sas-5-26



6j

According to the general procedure *N*-(2,2-dimethylpropylidene)propan-1-amine (**3a**) (0.5 mmol, 0.064 g), 1-ethyl-4-ethynyl-benzene (**4c**) (0.5 mmol, 0.065 g) , dimethyl 2-butynedioate (**5a**) (0.5 mmol, 0.071 g) and $Zn(OTf)_2$ (0.05 mmol, 0.018 g) were reacted in 1 mL of toluene/DMF (7/3) at 100 ºC for 18 h. Alkaline work up and column chromatography afforded 179 mg (90%) of dimethyl 6-(*tert*-butyl)-4-(4-ethylphenyl)-1-propyl-1,6-dihydropyridine-2,3-dicarboxylate (**6j)** as a yellow viscous oil. R_f = 0.56 (Heptane/EtOAc: 90/10).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.17 (d, J = 8.1 Hz, 2H, aromatic), 7.10 (d, J = 8.1 Hz, 2H, aromatic), 5.05 (d, J = 6.9 Hz, 1H, **H**C=C), 3.92 (s, 3H, OC**H**$_3$), 3.66 (d, J = 6.9 Hz, 1H, **H**CHC=C), 3.37 (s, 3H, OC**H**$_3$) 3.32 (dt, J = 14.5, 7.3 Hz, 1H, NC(**H**)H), 3.05 – 2.99 (m, 1H, NC(H)**H**), 2.64 (q, J = 7.6 Hz, 2H, PhC**H**$_2$CH$_3$), 1.64 – 1.56 (m, 2H, C**H**$_2$CH$_3$), 1.23 (t, J = 7.6 Hz, 3H, PhCH$_2$C**H**$_3$), 0.97 (s, 9H, C(C**H**$_3$)$_3$), 0.86 (t, J = 7.4 Hz, 3H, CH$_2$CH$_2$C**H**$_3$). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 166.6 (C=O), 166.2 (C=O), 150.1, 142.7, 138.7, 137.8, 127.4, 126.9, 112.5, 104.0, 67.4, 56.9, 52.7, 50.6, 40.7, 28.6, 25.3, 23.7, 15.6, 10.9. **HRMS** (ESI) *m/z* calculated for $C_{24}H_{33}NO_4+H^+$: 400.2488; found 400.2501.



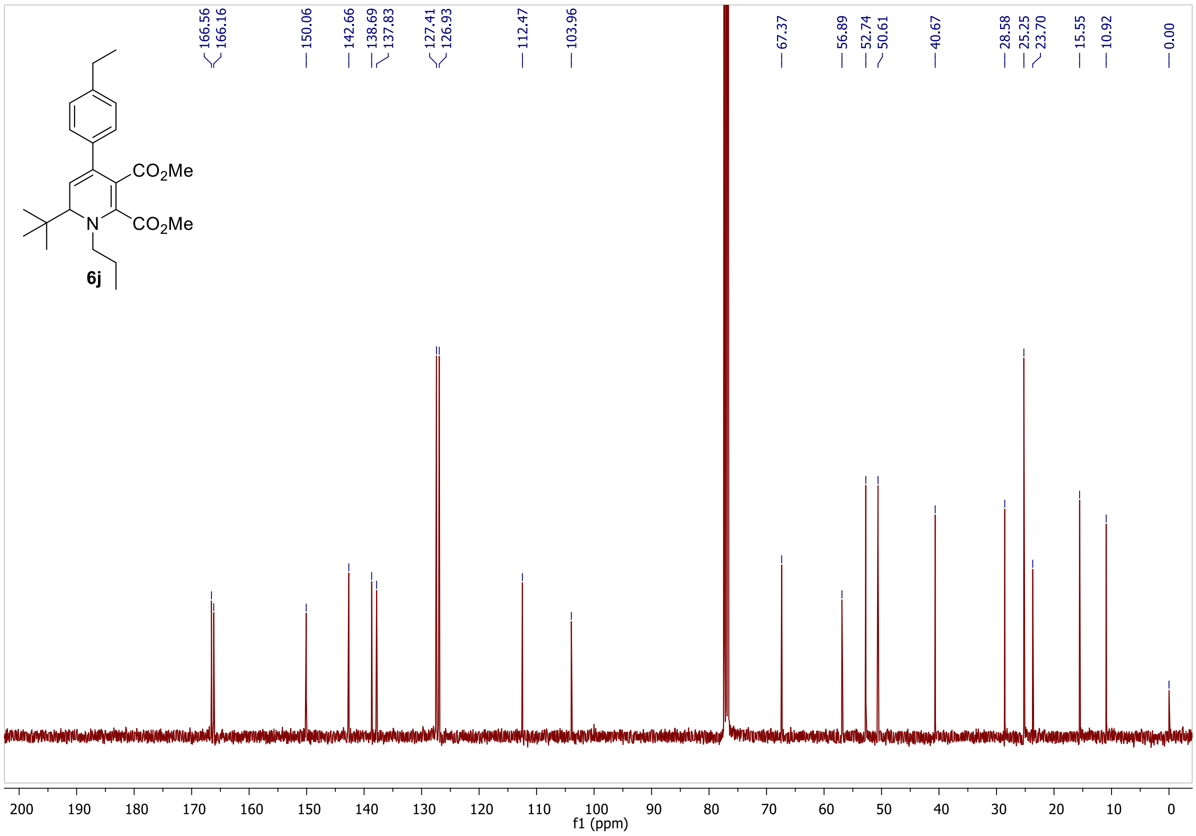
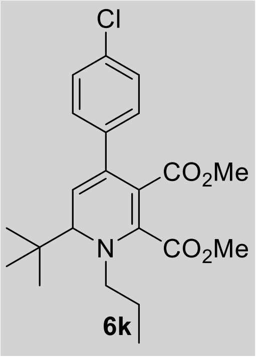


Figure 16. ^{1}H (400 MHz) and ^{13}C (100 MHz) NMR spectra of **6j** in CDCl$_3$.

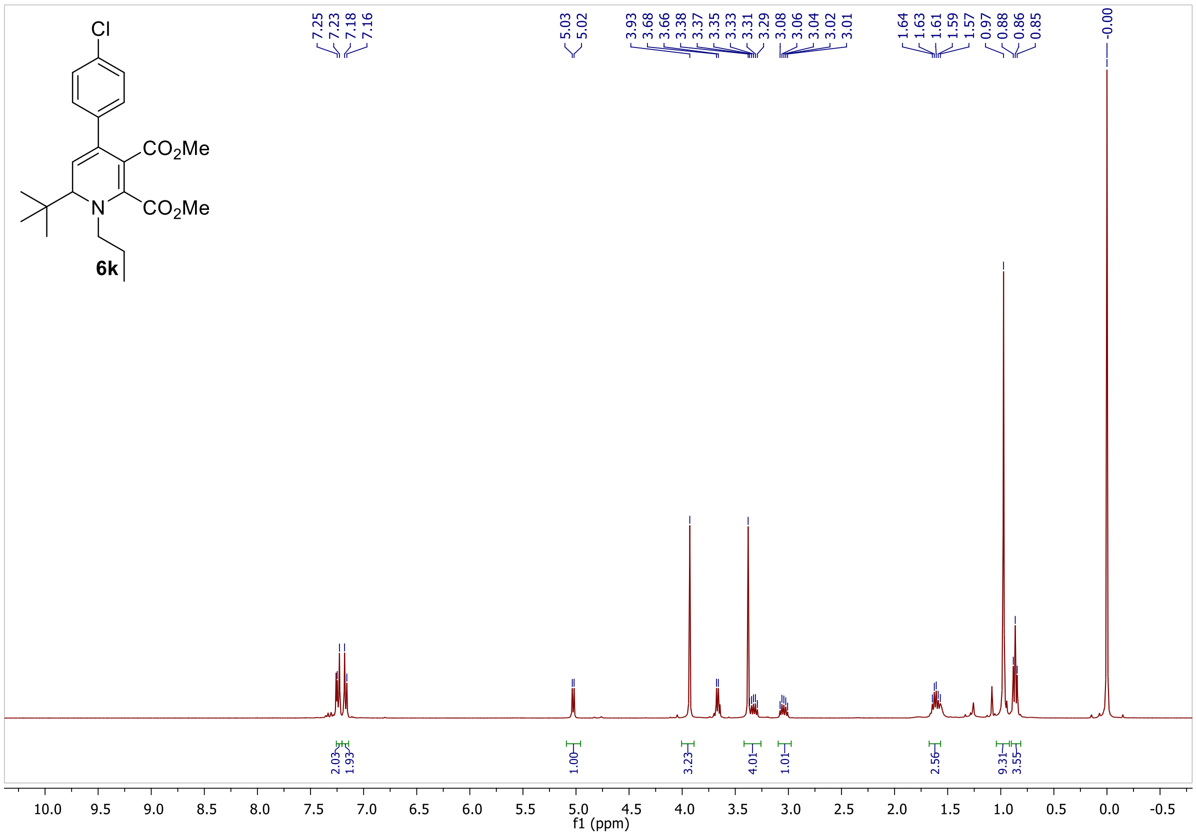
Dimethyl 6-(*tert*-butyl)-4-(4-chlorophenyl)-1-propyl-1,6-dihydropyridine-2,3-dicarboxylate (6k) sas-5-27



6k

According to the general procedure *N*-(2,2-dimethylpropylidene)propan-1-amine (**3a**) (0.5 mmol, 0.064 g), 1-chloro-4-ethynylbenzene (**4d**) (0.5 mmol, 0.068 g), dimethyl 2-butynedioate (**5a**) (0.5 mmol, 0.071 g) and Zn(OTf)$_2$ (0.05 mmol, 0.018 g) were reacted in 1 mL of toluene/DMF (7/3) at 100 ºC for 48 h. Alkaline work up and column chromatography afforded 111 mg (55%) of dimethyl 6-(*tert*-butyl)-4-(4-chlorophenyl)-1-propyl-1,6-dihydropyridine-2,3-dicarboxylate **(6k)** as a yellow viscous oil. R$_f$ = 0.48 (Heptane/EtOAc: 90/10).

^{1}H NMR (400 MHz, CDCl$_3$): δ 7.24 (d, J = 8.4 Hz, 2H, aromatic), 7.17 (d, J = 8.4 Hz, 2H, aromatic), 5.03 (d, J = 6.9 Hz, 1H, HC**H**C=CPh), 3.93 (s, 3H, OC**H**$_3$), 3.67 (d, J = 6.9 Hz, 1H, **H**CHC=C), 3.38 (s, 3H, OC**H**$_3$), 3.37 – 3.29 (m, 1H, NC(**H**)H), 3.04 (dt, J = 14.2, 6.9 Hz, 1H, NC(H)**H**), 1.64 – 1.57 (m, 2H, C**H**$_2$CH$_3$), 0.97 (s, 9H, C(C**H**$_3$)$_3$), 0.86 (t, J = 7.4 Hz, 3H, CH$_2$C**H**$_3$). **^{13}C NMR** (100 MHz, CDCl$_3$): δ 166.3 (C=O), 165.9 (C=O), 150.6 (N**C**=C), 140.0, 137.1, 132.4, 128.8 (aromatic), 127.6 (aromatic), 113.0 (HCH**C**=CPh), 103.3 (HCHC=**C**Ph), 67.3 (H**C**HC=CPh), 56.9 (N**C**H$_2$), 52.8 and 50.7 (2 × OCH$_3$), 40.7 (**C**(CH$_3$)$_3$), 25.2 (C(**C**H$_3$)$_3$), 23.7 (**C**H$_2$CH$_3$), 10.9 (CH$_2$**C**H$_3$). **HRMS** (ESI) *m/z* calculated for $C_{22}H_{28}ClNO_4+H^+$: 406.1785; found 406.1772.



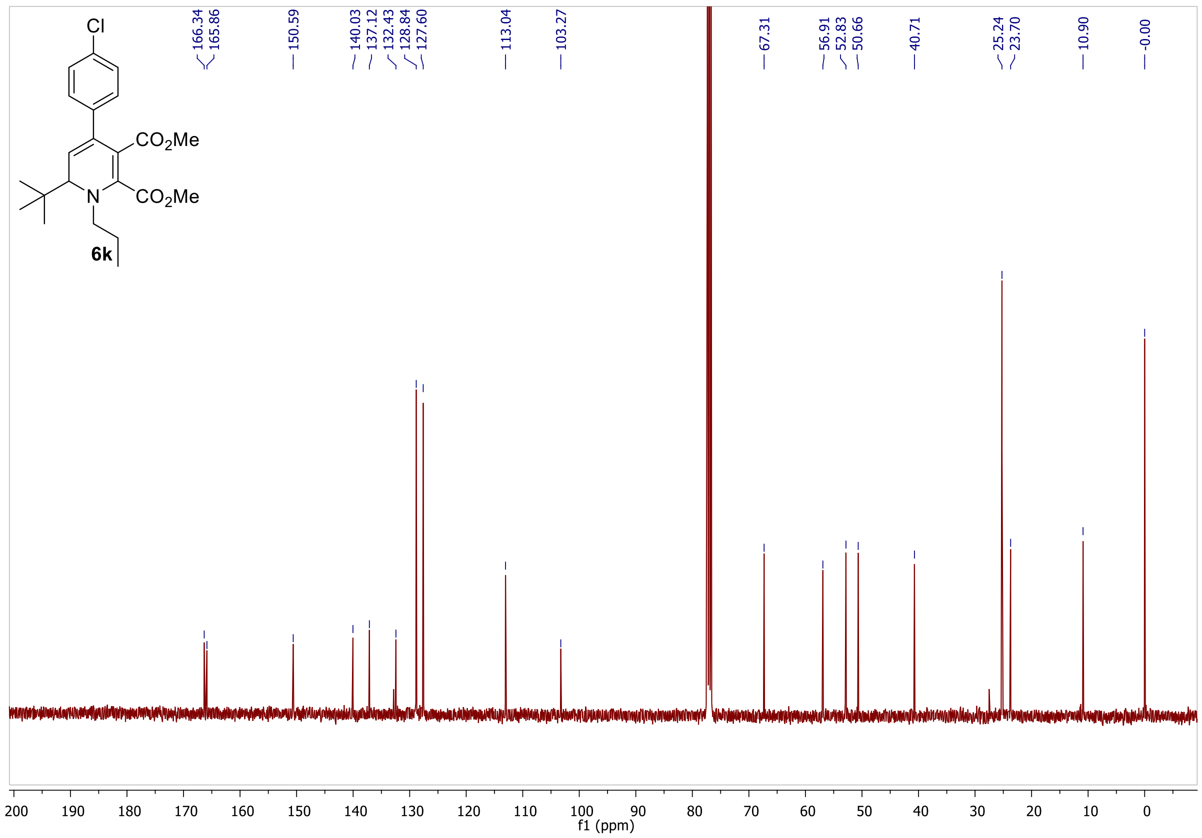
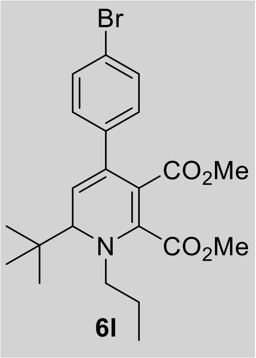


Figure 17. ^{1}H (400 MHz) and ^{13}C (100 MHz) NMR spectra of **6k** in $CDCl_3$.

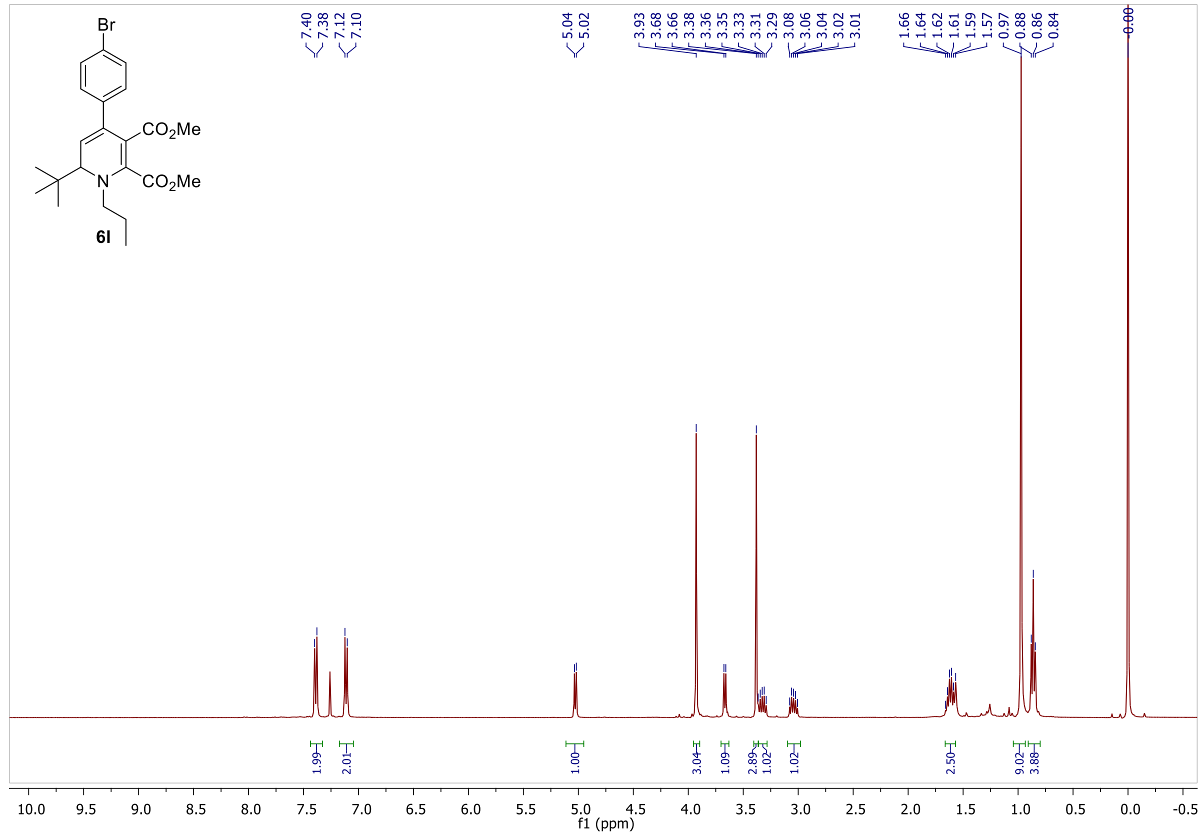
Dimethyl 4-(4-bromophenyl)-6-(*tert*-butyl)-1-propyl-1,6-dihydropyridine-2,3 dicarboxylate (6l) sas-5-28



According to the general procedure *N*-(2,2-dimethylpropylidene)propan-1-amine (**3a**) (0.5 mmol, 0.064 g), 1-bromo-4-ethynylbenzene (**4e**) (0.5 mmol, 0.091 g), dimethyl 2-butynedioate (**5a**) (0.5 mmol, 0.071 g) and $Zn(OTf)_2$ (0.05 mmol, 0.018 g) were reacted in 1 mL of toluene/DMF (7/3) at 100 °C for 48 h. Alkaline work up and column chromatography afforded 112 mg (50%) of dimethyl 4-(4-bromophenyl)-6-(tert-butyl)-1-propyl-1,6-dihydropyridine-2,3-dicarboxylate **(6l)** as a yellow viscous oil. $R_f = 0.49$ (Heptane/EtOAc: 90/10).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39 (d, J = 8.3 Hz, 2H, aromatic), 7.11 (d, J = 8.3 Hz, 2H, aromatic), 5.03 (d, J = 6.9 Hz, 1H, **H**C=C), 3.93 (s, 3H, OC**H**$_3$), 3.67 (d, J = 6.9 Hz, 1H,

HCHC=C), 3.38 (s, 3H, OC**H**$_3$), 3.35 – 3.29 (m, 1H, NC(**H**)H), 3.08 – 3.01 (m, 1H, NC(H)**H**), 1.66 – 1.57 (m, 2H, C**H**$_2$CH$_3$), 0.97 (s, 9H, C(C**H**$_3$)$_3$), 0.86 (t, *J* = 7.4 Hz, 3H, CH$_2$C**H**$_3$). **^{13}C NMR** (100 MHz, CDCl$_3$): δ 166.3 (C=O), 165.8 (C=O), 150.6 (N**C**=C), 140.5, 137.2, 130.5 (aromatic), 129.2 (aromatic), 120.5, 113.1 (HCH**C**=CPh), 103.2 (HCHC=**C**Ph), 67.3 (H**C**HC=CPh), 56.9 (NCH$_2$), 52.8 and 50.7 (2 × OCH$_3$), 40.7 (**C**(CH$_3$)$_3$), 25.2 (C(**C**H$_3$)$_3$), 23.7 (**C**H$_2$CH$_3$), 10.9 (CH$_2$**C**H$_3$). **HRMS** (ESI) *m/z* calculated for $C_{22}H_{28}BrNO_4+H^+$: 450.1280; found 450.1276.



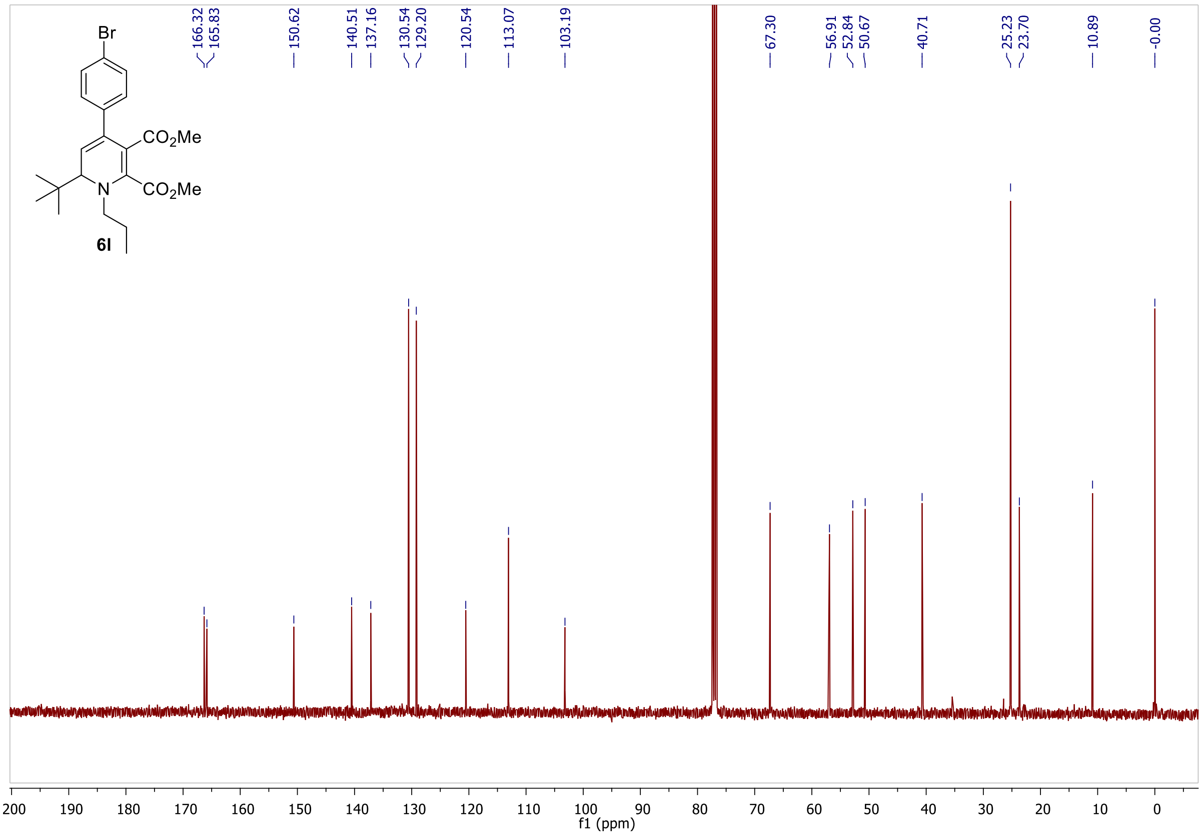
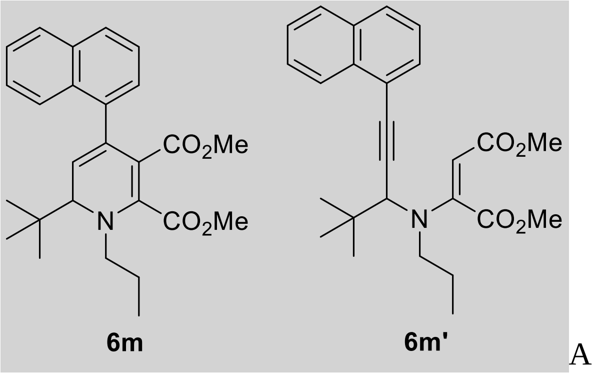


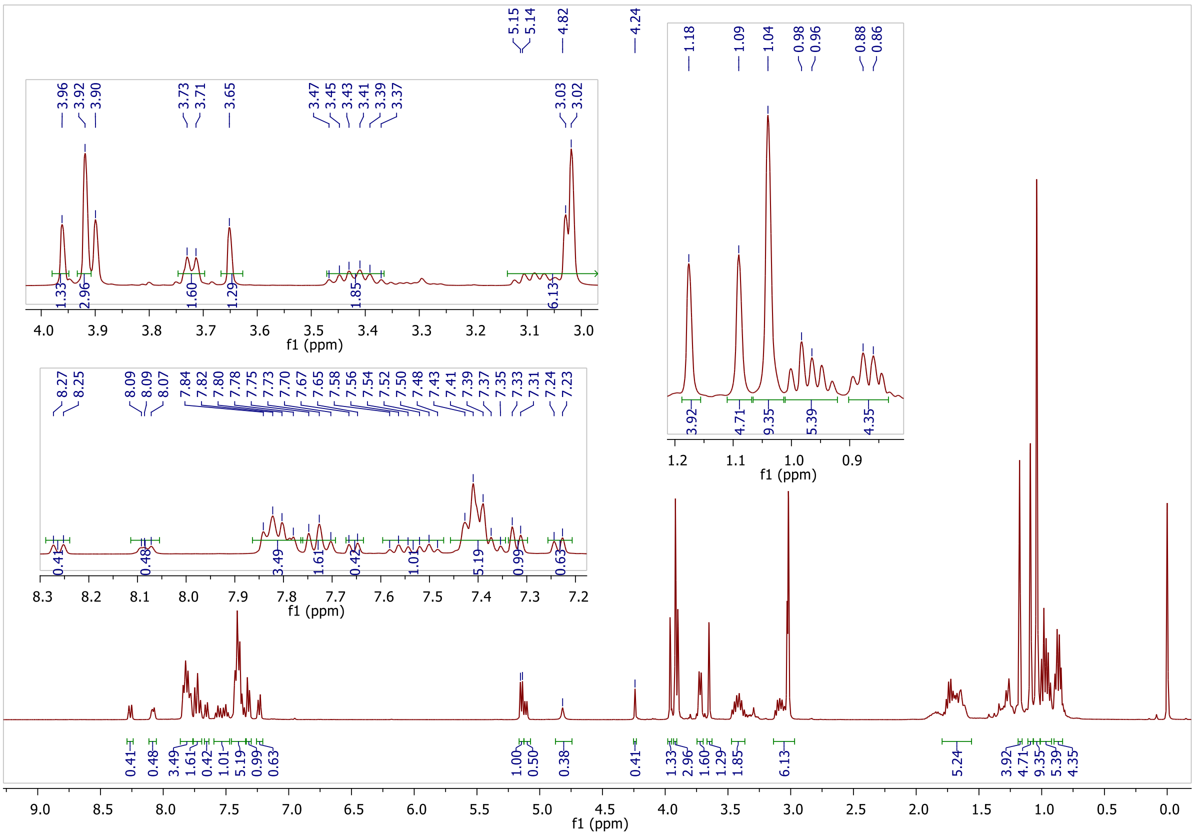
Figure 18. ^{1}H (400 MHz) and ^{13}C (100 MHz) NMR spectra of **6l** in CDCl$_3$.

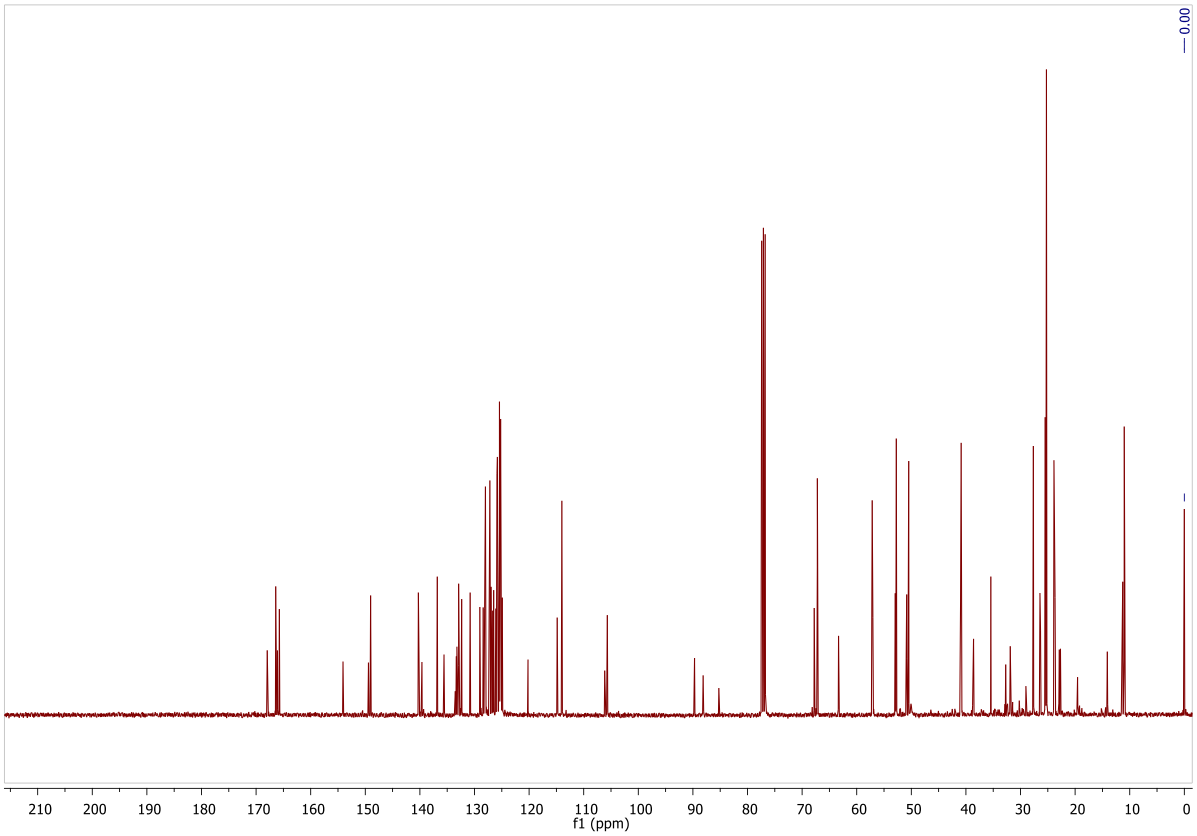
Dimethyl 6-(*tert*-butyl)-4-(2-naphthyl)-1-propyl-1,6-dihydropyridine-2,3-dicarboxylate (6m)



6m **6m'**

According to the general procedure *N*-(2,2-dimethylpropylidene)propan-1-amine (**3a**) (0.5 mmol, 0.064 g), 1-ethynylnapthalene (**4f**) (0.5 mmol, 0.076 g), dimethyl 2-butynedioate (**5a**) (0.5 mmol, 0.071 g) and Zn(OTf)$_2$ (0.05 mmol, 0.018 g) were reacted in 1 mL of toluene/DMF (7/3) at 100 °C for 24 h. Alkaline work up afforded 139 mg of a complex mixture in which the major compounds dimethyl 6-(*tert*-butyl)-4-(2-naphthyl)-1-propyl-1,6-dihydropyridine-2,3-dicarboxylate (**6m**) and its corresponding enamine **6m'** could be distinguished. Besides **6m** and **6m'**, another compound was present which could not be identified. These compounds could not be separated by means of column chromatography. Therefore no yield could be determined.




0.00
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

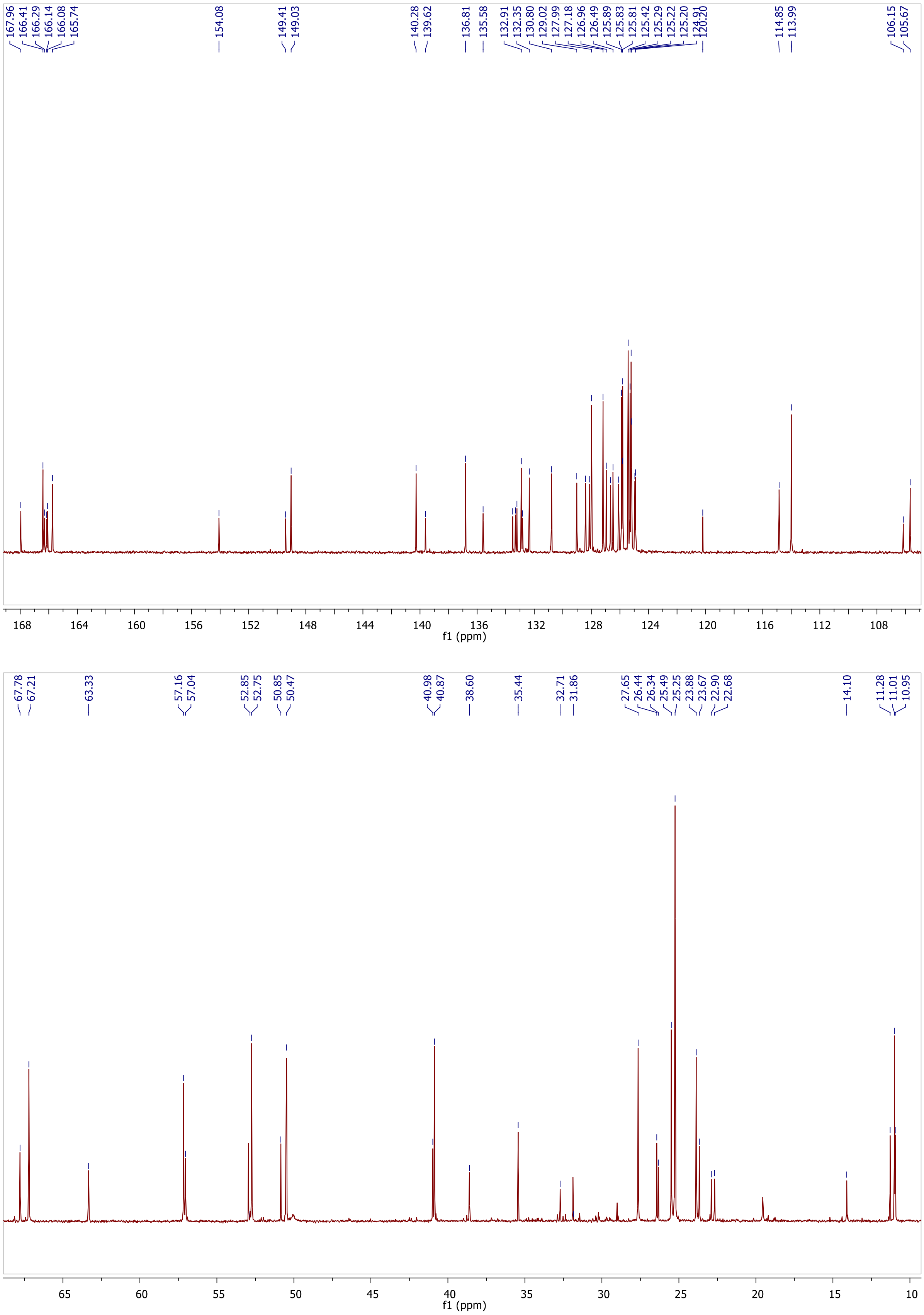
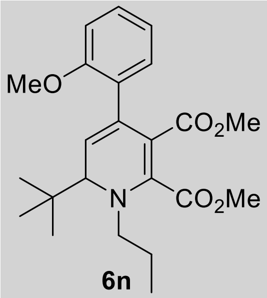


Figure 19. ^{1}H (400 MHz) and ^{13}C (100 MHz) NMR spectra of **6m/6m’** in CDCl$_3$.

Dimethyl 6-(*tert*-butyl)-4-(2-methoxyphenyl)-1-propyl-1,6-dihydropyridine-2,3-dicarboxylate (6n) sas-5-23



6n

According to the general procedure *N*-(2,2-dimethylpropylidene)propan-1-amine (**3a**) (0.5 mmol, 0.064 g), 1-ethynyl-2-methoxybenzene (**4g**) (0.5 mmol, 0.066 g), dimethyl 2-butynedioate (**5a**) (0.5 mmol, 0.071 g) and Zn(OTf)$_2$ (0.05 mmol, 0.018 g) were reacted in 1 mL of toluene/DMF (7/3) at 100 °C for 18 h. Alkaline work up and column chromatography afforded 61 mg (60%) of dimethyl 6-(*tert*-butyl)-4-(2-methoxyphenyl)-1-propyl-1,6-dihydropyridine-2,3-dicarboxylate **(6n)** as a yellow viscous oil. R$_f$ = 0.50 (Heptane/EtOAc: 90/10).

^{1}H NMR (400 MHz, CDCl$_3$): δ 7.20 – 7.16 (m, 1H, aromatic), 6.85 – 6.78 (m, 3H, aromatic), 5.08 (d, *J* = 6.9 Hz, 1H, **H**C=C), 3.93 (s, 3H, OC**H**$_3$), 3.80 (s, 3H, OC**H**$_3$), 3.66 (d, *J* = 6.9 Hz, 1H, **H**CHC=C), 3.37 (s, 3H, OC**H**$_3$) 3.35 – 3.29 (m, 1H, NC(**H**)H), 3.07 – 3.00 (m, 1H, NC(H)**H**), 1.67 – 1.57 (m, 2H, C**H**$_2$CH$_3$), 0.98 (s, 9H, C(C**H**$_3$)$_3$), 0.87 (t, *J* = 7.4 Hz, 3H, CH$_2$C**H**$_3$). **^{13}C NMR** (100 MHz, CDCl$_3$): δ 166.5 (C=O), 166.1 (C=O), 159.0, 150.2, 143.0, 137.9, 128.3, 120.3, 113.4, 112.8, 112.0, 103.8, 67.3, 56.9, 55.3, 52.8, 50.6, 40.7, 25.2, 23.7, 10.9. **HRMS** (ESI) *m/z* calculated for $C_{23}H_{31}NO_5+H^+$: 402.2280; found 402.2265.

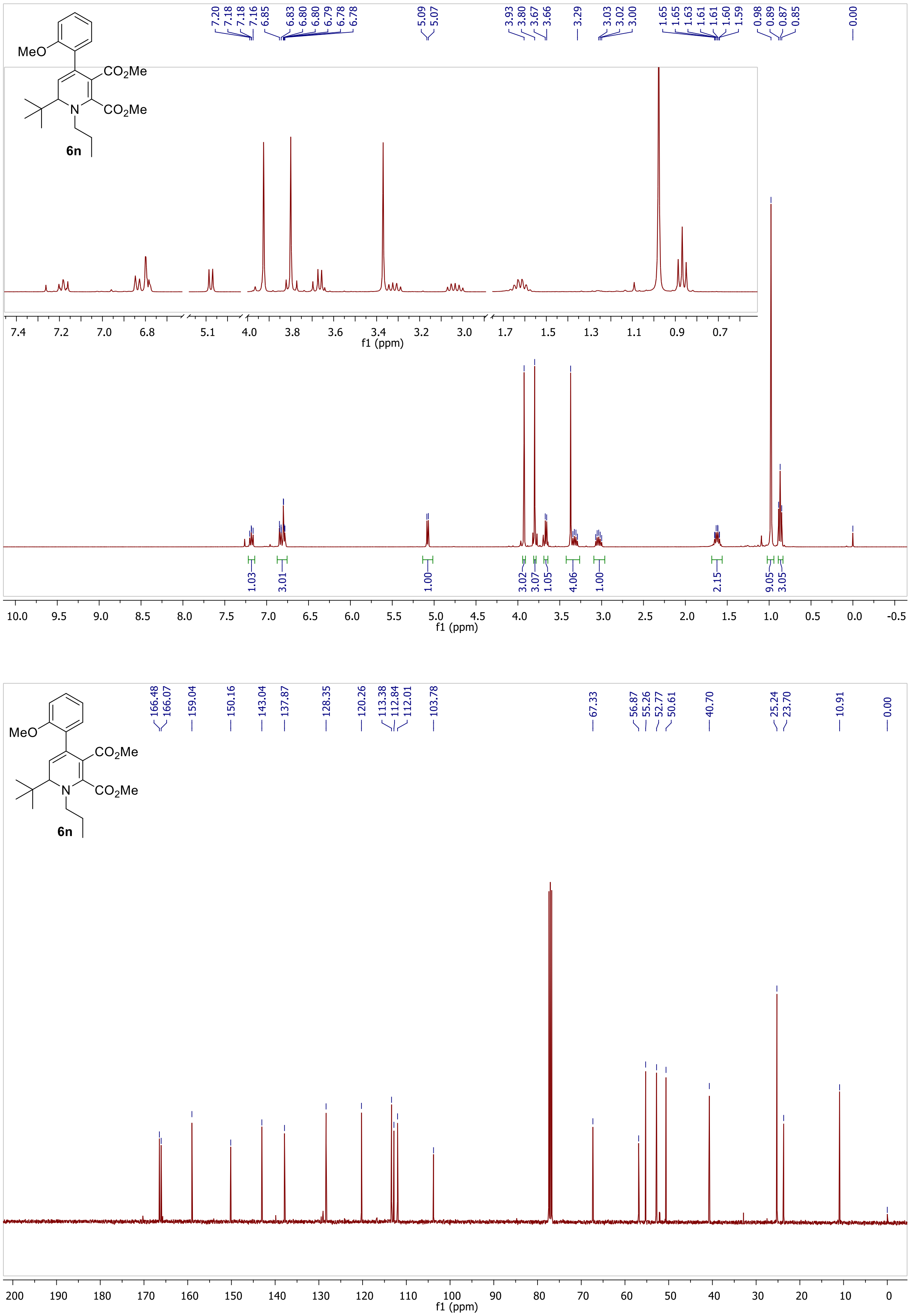
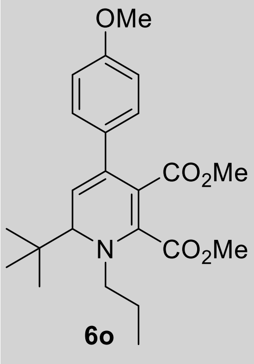


Figure 20. ^{1}H (400 MHz) and ^{13}C (100 MHz) NMR spectra of **6n** in $CDCl_3$.

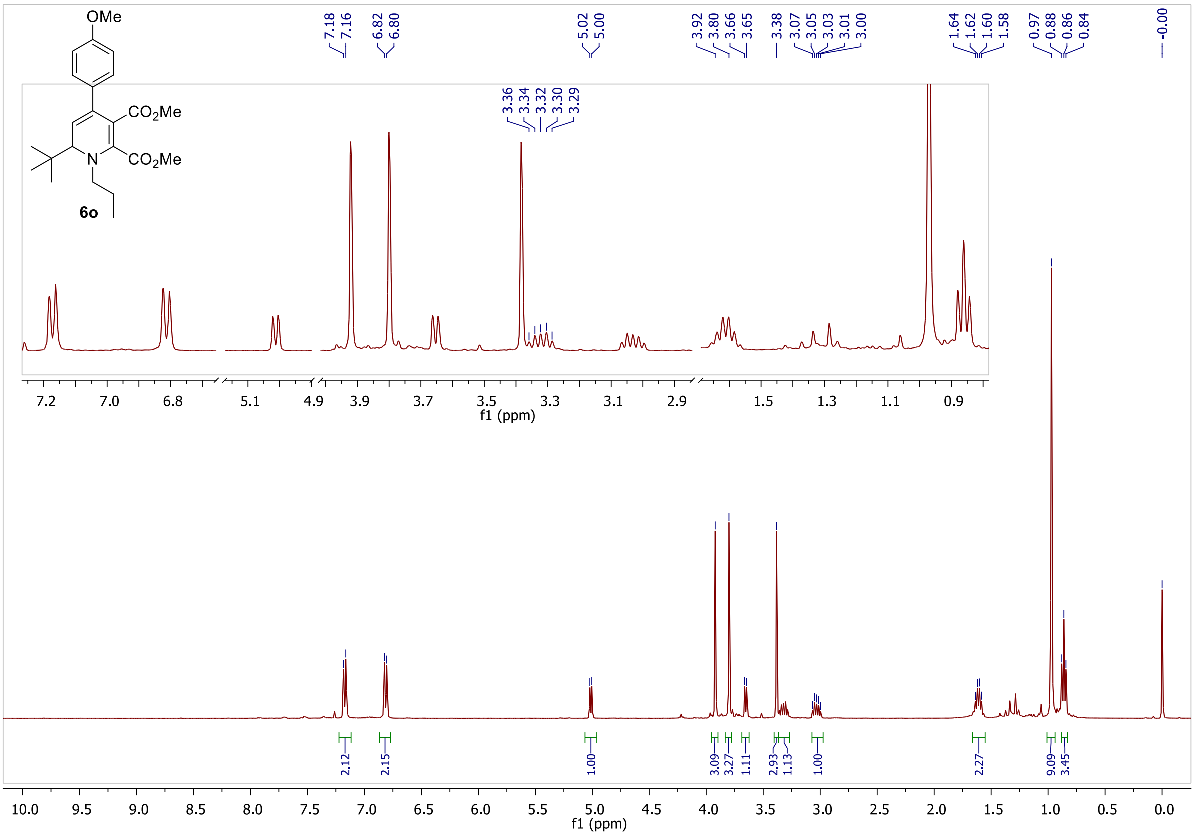
Dimethyl 6-(*tert*-butyl)-4-(4-methoxyphenyl)-1-propyl-1,6-dihydropyridine-2,3 dicarboxylate (6o) sas-5-31



6o

According to the general procedure *N*-(2,2-dimethylpropylidene)propan-1-amine (**3a**) (0.5 mmol, 0.064 g), 1-ethynyl-4-methoxybenzene (**4h**) (0.5 mmol, 0.066 g), dimethyl 2-butynedioate (**5a**) (0.5 mmol, 0.071 g) and $Zn(OTf)_2$ (0.05 mmol, 0.018 g) were reacted in 1 mL of toluene/DMF (7/3) at 100 °C for 18 h. Alkaline work up and column chromatography afforded 110 mg (55%) of dimethyl 6-(*tert*-butyl)-4-(4-methoxyphenyl)-1-propyl-1,6-dihydropyridine-2,3-dicarboxylate **(6o)** as a yellow viscous oil. R_f = 0.50 (Heptane/EtOAc: 90/10).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.17 (d, *J* = 7.5 Hz, 2H, aromatic), 6.81 (d, *J* = 7.5 Hz, 2H, aromatic), 5.01 (d, *J* = 6.8 Hz, 1H, **H**C=C), 3.92 (s, 3H, OC**H**$_3$), 3.80 (s, 3H, OC**H**$_3$), 3.66 (d, *J* = 6.9 Hz, 1H), 3.38 (s, 3H, OC**H**$_3$) 3.36 – 3.29 (m, 1H, NC(**H**)H), 3.07 – 3.00 (m, 1H, NC(H)**H**), 1.64 – 1.58 (m, 2H, C**H**$_2$CH$_3$), 0.97 (s, 9H, C(C**H**$_3$)$_3$), 0.86 (t, *J* = 7.3 Hz, 3H, CH$_2$C**H**$_3$). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 166.6 (C=O), 166.2 (C=O), 158.6, 150.1, 137.4, 134.0, 128.6, 112.9, 112.0, 103.9, 67.4, 56.9, 55.2, 52.7, 50.7, 40.7, 25.2, 23.7, 10.9. **HRMS** (ESI) *m/z* calculated for $C_{23}H_{31}NO_5+H^+$: 402.2280; found 402.2261.



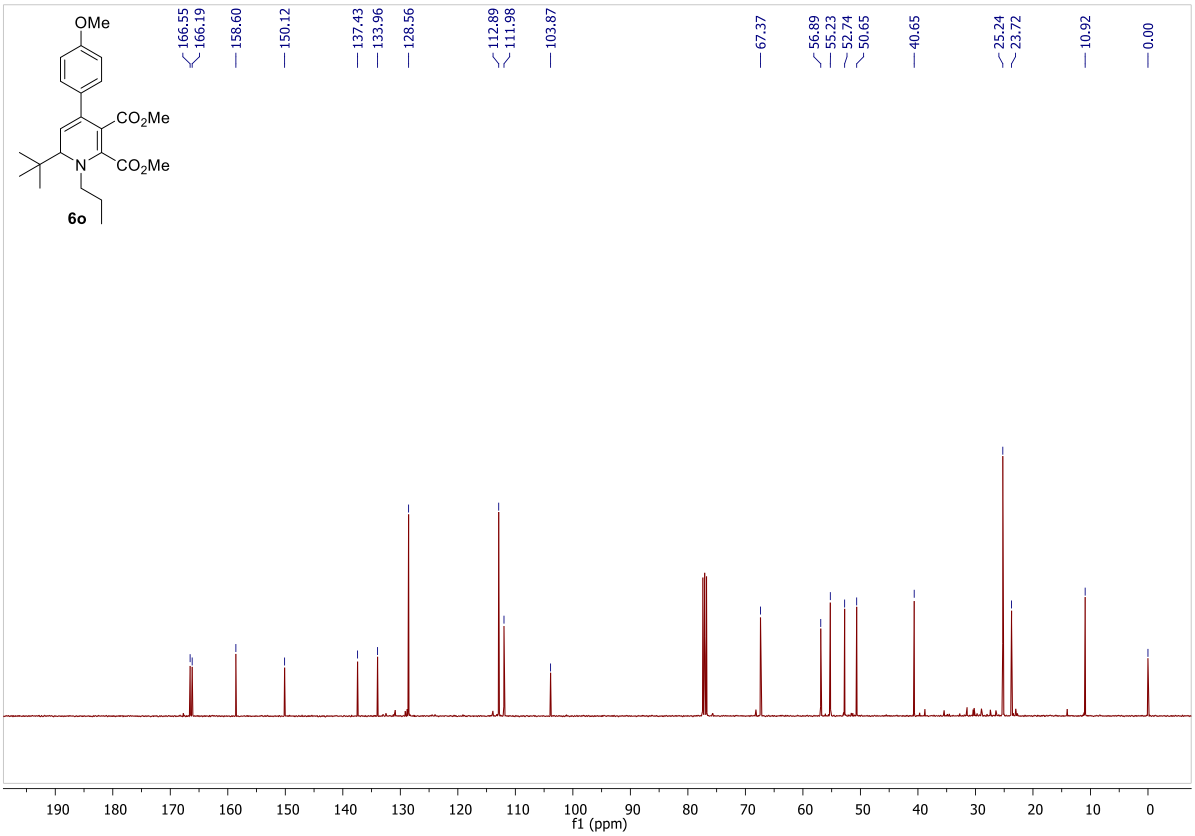
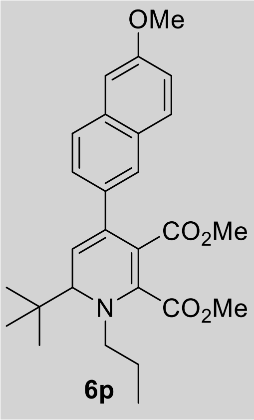


Figure 21. ^{1}H (400 MHz) and ^{13}C (100 MHz) NMR spectra of **6o** in $CDCl_3$.

Dimethyl 6-(*tert*-butyl)-4-(6-methoxynaphthalen-2-yl)-1-propyl-1,6-dihydropyridine-2,3-dicarboxylate (6p) SAS-5-39



6p

According to the general procedure *N*-(2,2-dimethylpropylidene)propan-1-amine (**3a**) (0.5 mmol, 0.064 g), 2-ethynyl-6-methoxynaphthalene (**4i**) (0.5 mmol, 0.091 g), dimethyl 2-butynedioate (**5a**) (0.5 mmol, 0.071 g) and $Zn(OTf)_2$ (0.05 mmol, 0.018 g) were reacted in 1 mL of toluene/DMF (7/3) at 100 °C for 18 h. Alkaline work up and column chromatography afforded 146 mg (59%) of dimethyl 6-(*tert*-butyl)-4-(6-methoxynaphthalen-2-yl)-1-propyl-1,6-dihydropyridine-2,3-dicarboxylate **(6p)** as a brown oil, which became solid upon long standing; mp = 104-106 ºC. R_f = 0.53 (Heptane/EtOAc: 90/10).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.71 (d, J = 9.6 Hz, 1H, aromatic), 7.63 (dd, J = 9.3, 4.9 Hz, 2H, aromatic), 7.33 (dd, J = 8.5, 1.8 Hz, 1H, aromatic), 7.13 – 7.08 (m, 2H, aromatic), 5.14 (d, J = 6.9 Hz, 1H, **H**C=C), 3.95 (s, 3H, OC**H**$_3$), 3.91 (s, 3H, OC**H**$_3$), 3.71 (d, J = 6.9 Hz, 1H, **H**CHC=C), 3.39 – 3.32 (m, 1H, NC(**H**)H), 3.31 (s, 3H, OC**H**$_3$), 3.07 – 3.00 (m, 1H, NC(H)**H**), 1.67 – 1.61 (m, 2H, C**H**$_2$CH$_3$), 1.02 (s, 9H, C(C**H**$_3$)$_3$), 0.88 (t, J = 7.4 Hz, 3H, CH$_2$C**H**$_3$). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 166.6 (C=O), 166.3 (C=O), 157.4, 150.4, 138.0, 137.1, 133.7, 129.4, 128.8, 127.2, 125.5, 125.2, 118.5, 112.8, 105.8, 103.7, 67.5, 57.0, 55.3, 52.8, 50.6, 40.8, 25.3, 23.7, 10.9. **HRMS** (ESI) *m/z* calculated for $C_{27}H_{33}NO_5+H^+$: 452.2437; found 452.2454.

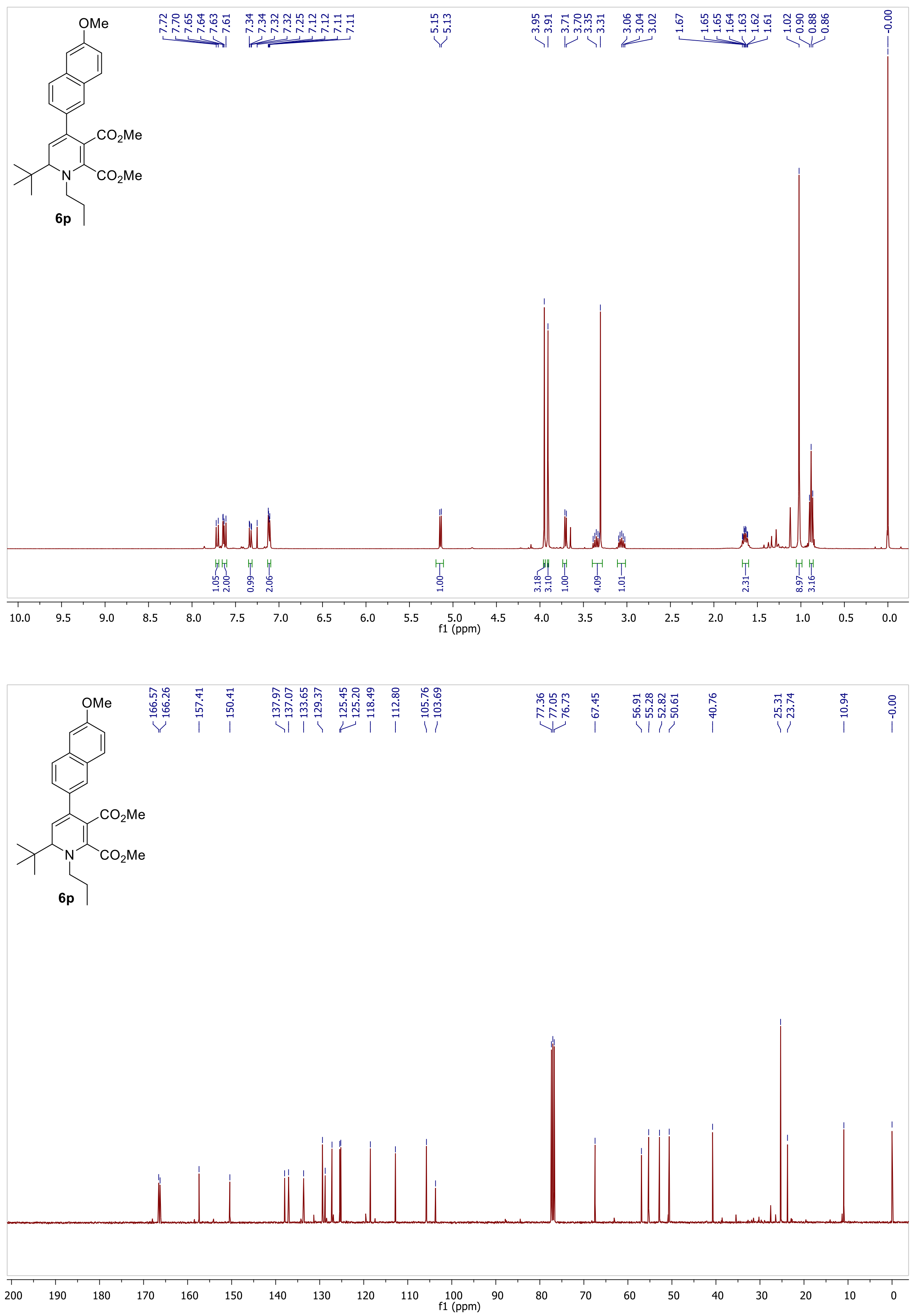
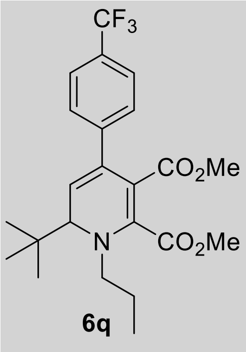


Figure 22. ^{1}H (400 MHz) and ^{13}C (100 MHz) NMR spectra of **6p** in CDCl$_3$.

Dimethyl 6-(*tert*-butyl)-1-propyl-4-(4-(trifluoromethyl)phenyl)-1,6-dihydropyridine-2,3-dicarboxylate (6q) sas-5-30



6q

According to the general procedure *N*-(2,2-dimethylpropylidene)propan-1-amine (**3a**) (0.5 mmol, 0.064 g), 1-ethynyl-4-(trifluoromethyl)benzene (**4j**) (0.5 mmol, 0.085 g), dimethyl 2-butynedioate (**5a**) (0.5 mmol, 0.071 g) and Zn(OTf)$_2$ (0.05 mmol, 0.018 g) were reacted in 1 mL of toluene/DMF (7/3) at 100 °C for 24 h. Alkaline work up and column chromatography afforded 96 mg (44%) of dimethyl 6-(*tert*-butyl)-1-propyl-4-(4-(trifluoromethyl)phenyl)-1,6-dihydropyridine-2,3-dicarboxylate **(6q)** as a yellow viscous oil. R$_f$ = 0.45 (Heptane/EtOAc: 90/10).

^{1}H NMR (400 MHz, CDCl$_3$): δ 7.52 (d, J = 8.0 Hz, 2H, aromatic), 7.34 (d, J = 8.0 Hz, 2H, aromatic), 5.07 (d, J = 6.9 Hz, 1H, **H**C=C), 3.94 (s, 3H, OC**H**$_3$), 3.70 (d, J = 6.9 Hz, 1H, **H**CHC=C), 3.36 (s, 3H, OC**H**$_3$), 3.38 – 3.31 (m, 1H, overlapping signal NC(**H**)H), 3.10 – 3.02 (m, 1H, NC(H)**H**), 1.65 – 1.60 (m, 2H, C**H**$_2$CH$_3$), 0.99 (s, 9H, C(C**H**$_3$)$_3$), 0.87 (t, J = 7.4 Hz, 3H, CH$_2$C**H**$_3$). **^{13}C NMR** (100 MHz, CDCl$_3$): δ 166.2 (C=O), 165.7 (C=O), 150.8 (N**C**=C), 145.3 (q, $^4J_{C\text{-}F}$ = 1.2 Hz), 137.3 (C$_{ipso}$), 128.8 (q, $^2J_{C\text{-}F}$ = 32.3 Hz,), 127.8, 124.42 (q, $^3J_{C\text{-}F}$ = 3.7 Hz,) 124.43 (q, $^1J_{C\text{-}F}$ = 271.8 Hz, CF$_3$), 113.9 (HCH**C**=CPh), 103.1 (HCHC=**C**Ph), 67.3 (H**C**HC=CPh), 57.0 (NCH$_2$), 52.9 and 50.7 (2 × OCH$_3$), 40.8 (**C**(CH$_3$)$_3$), 25.3 (C(**C**H$_3$)$_3$), 23.7 (**C**H$_2$CH$_3$), 10.9 (CH$_2$*C*H$_3$). **HRMS** (ESI) *m/z* calculated for $C_{23}H_{28}F_3NO_4$+H$^+$: 440.2049; found 440.2037.

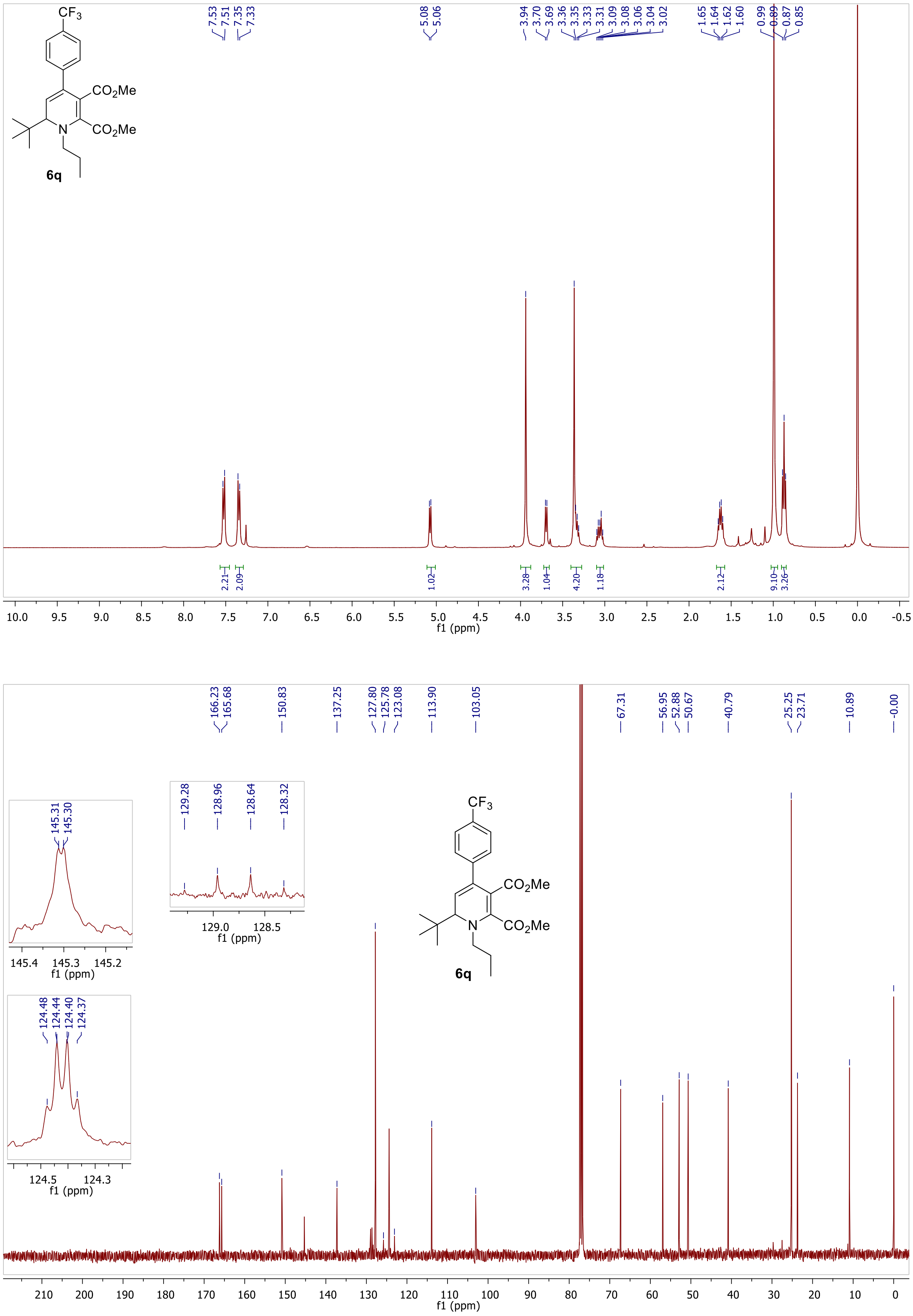


Figure 23. ^{1}H (400 MHz) and ^{13}C (100 MHz) NMR spectra of **6q** in $CDCl_3$.

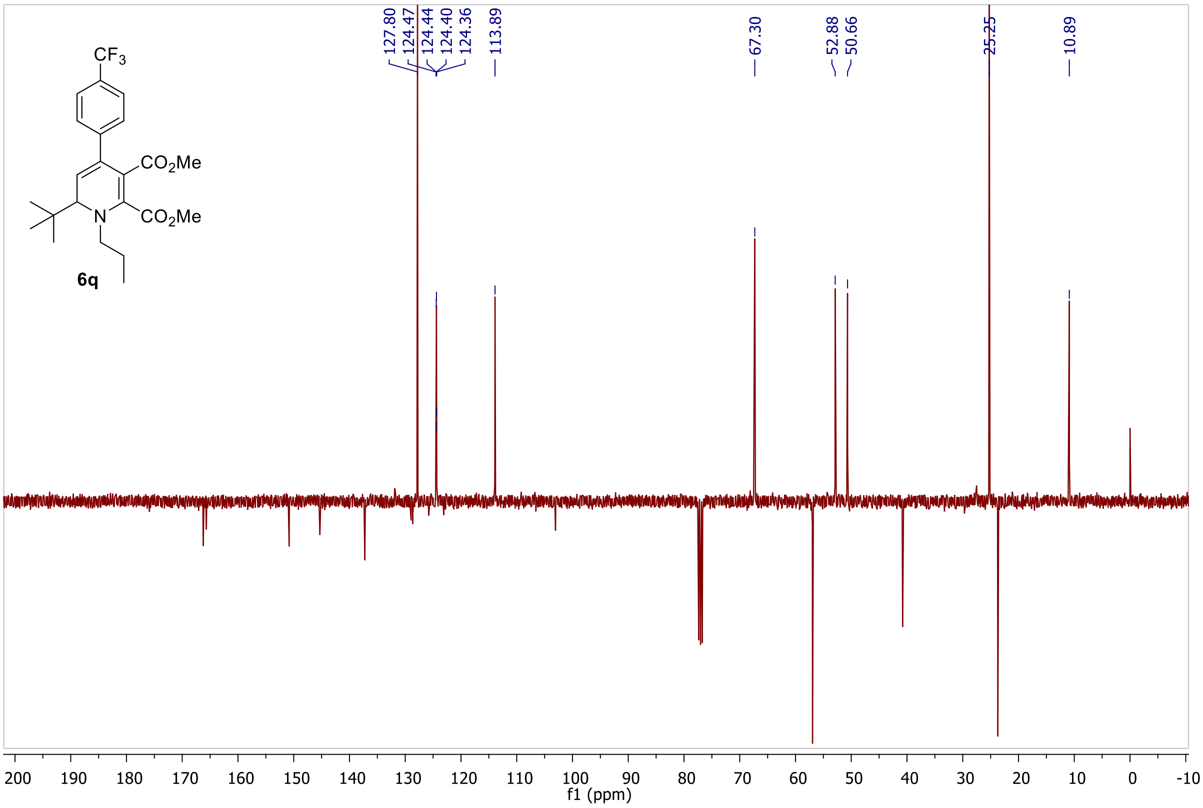
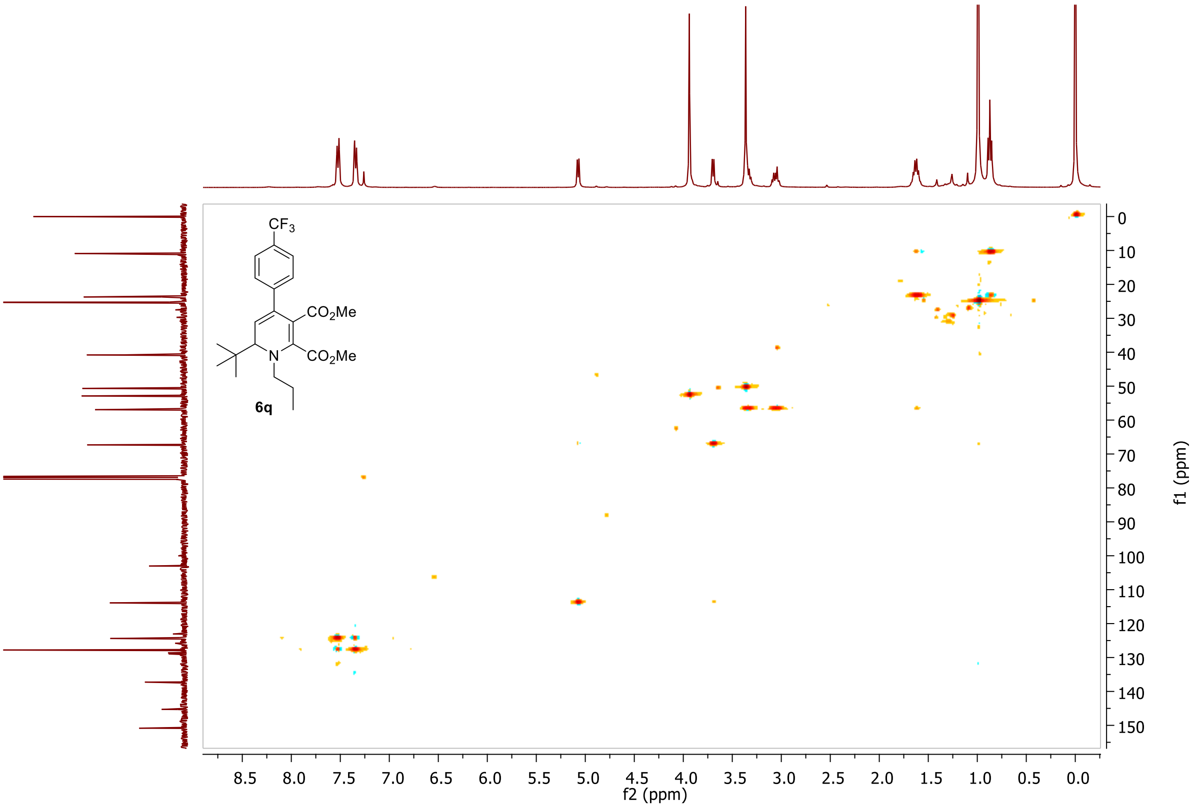


Figure 24. ^{13}C-APT (100 MHz) spectrum of **6q** in CDCl$_3$.



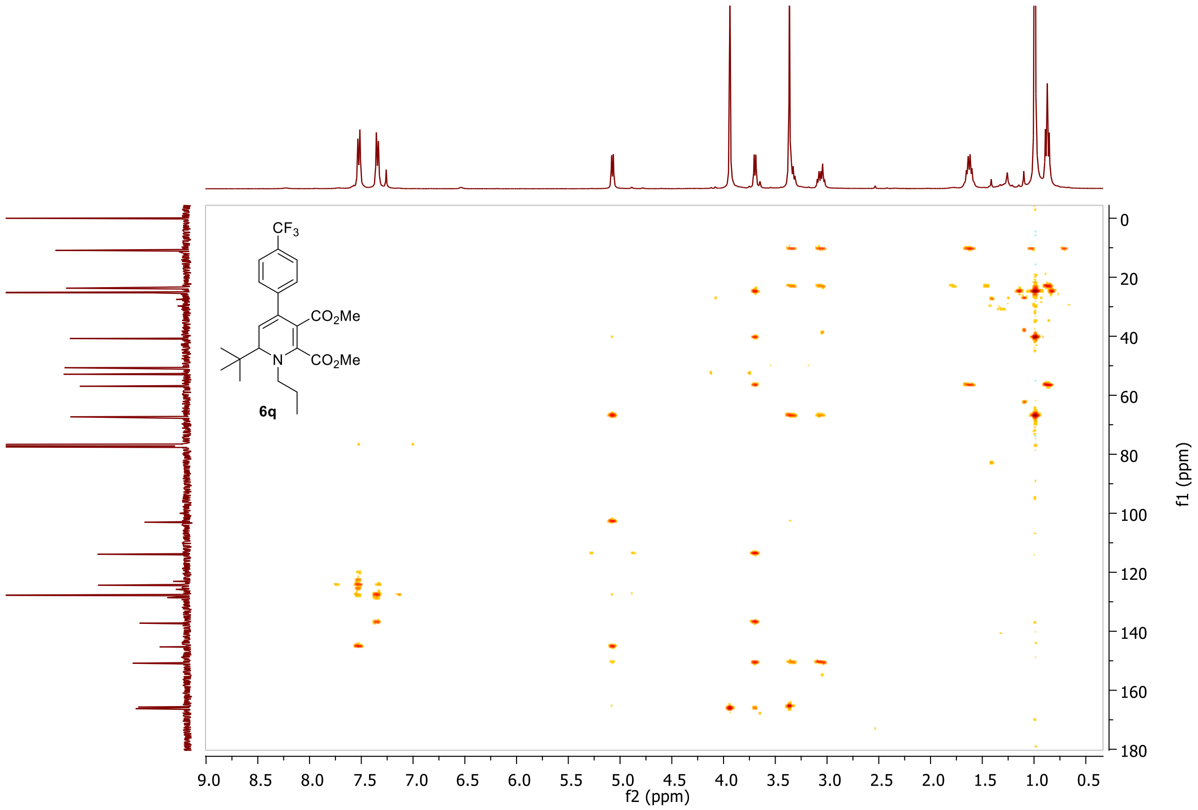
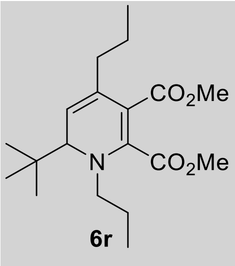


Figure 25. HSQC and HMBC spectra of **6q** in $\mathrm{CDCl_3}$.

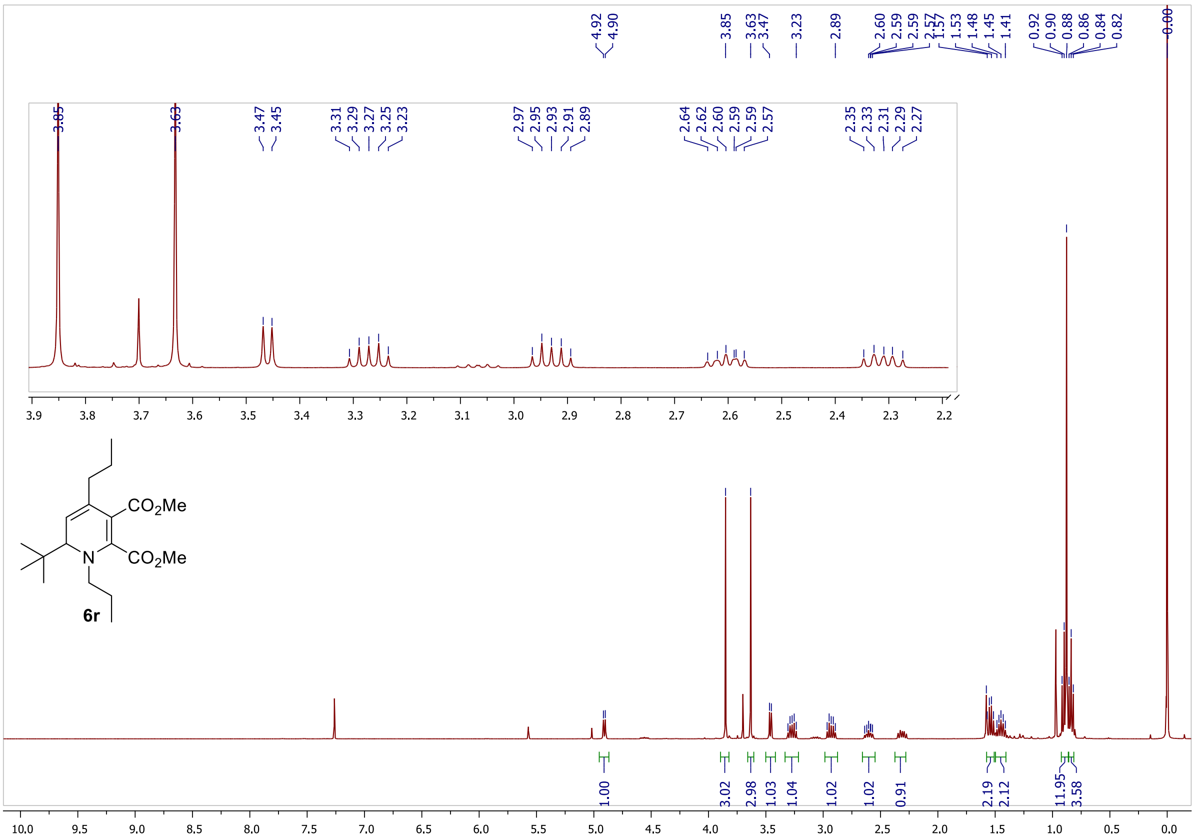
Dimethyl 6-(*tert*-butyl)-1,4-dipropyl-1,6-dihydropyridine-2,3-dicarboxylate (6r) sas-5-34



According to the general procedure *N*-(2,2-dimethylpropylidene)propan-1-amine (**3a**) (0.5 mmol, 0.064 g), 1-pentyne (**4k**) (0.5 mmol, 0.034 g), dimethyl 2-butynedioate (**5a**) (0.5 mmol, 0.071 g) and $\mathrm{Zn(OTf)_2}$ (0.05 mmol, 0.018 g) were reacted in 1 mL of toluene/DMF (7/3) at 100 °C for 18 h. Alkaline work up and column chromatography afforded 112 mg (67%) of dimethyl 6-(*tert*-butyl)-1,4-dipropyl-1,6-dihydropyridine-2,3-dicarboxylate **(6r)** as a yellow viscous oil. R_f = 0.60 (Heptane/EtOAc: 90/10).

^{1}**H NMR** (400 MHz, $\mathrm{CDCl_3}$): δ 4.91 (d, J = 6.6 Hz, 1H, **H**C=C), 3.85 (s, 3H, OC**H**$_3$), 3.63 (s, 3H, OC**H**$_3$), 3.46 (d, J = 6.6 Hz, 1H, **H**CHC=C), 3.27 (dt, J = 14.5, 7.2 Hz, 1H, N(C**H**)H), 2.93 (dt, J = 14.4, 7.1 Hz, 1H, NC(H)**H**), 2.61 (ddd, J = 13.9, 7.9, 6.2 Hz, 1H, C=CC(**H**)H), 2.35 – 2.27 (m, 1H, C=CC(H)**H**), 1.54 (q, J = 7.3 Hz, 2H, C**H**$_2$CH$_3$), 1.50 – 1.41 (m, 2H, C**H**$_2$CH$_3$), 0.90 (d, J = 7.3 Hz, 3H, CH$_2$C**H**$_3$), 0.88 (s, 9H, C(C**H**$_3$)$_3$), 0.84 (t, J = 7.4 Hz, 3H,

$CH_2C\mathbf{H_3}$). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 166.8 (C=O), 166.7 (C=O), 149.2, 136.1, 110.6, 105.4, 99.3, 88.8, 67.2, 57.1, 52.5, 50.9, 40.4, 35.9, 25.1, 24.2, 23.7, 23.1, 13.9, 11.0. **HRMS** (ESI) *m/z* calculated for $C_{19}H_{31}NO_4+H^+$: 338.2331; found 338.2315.



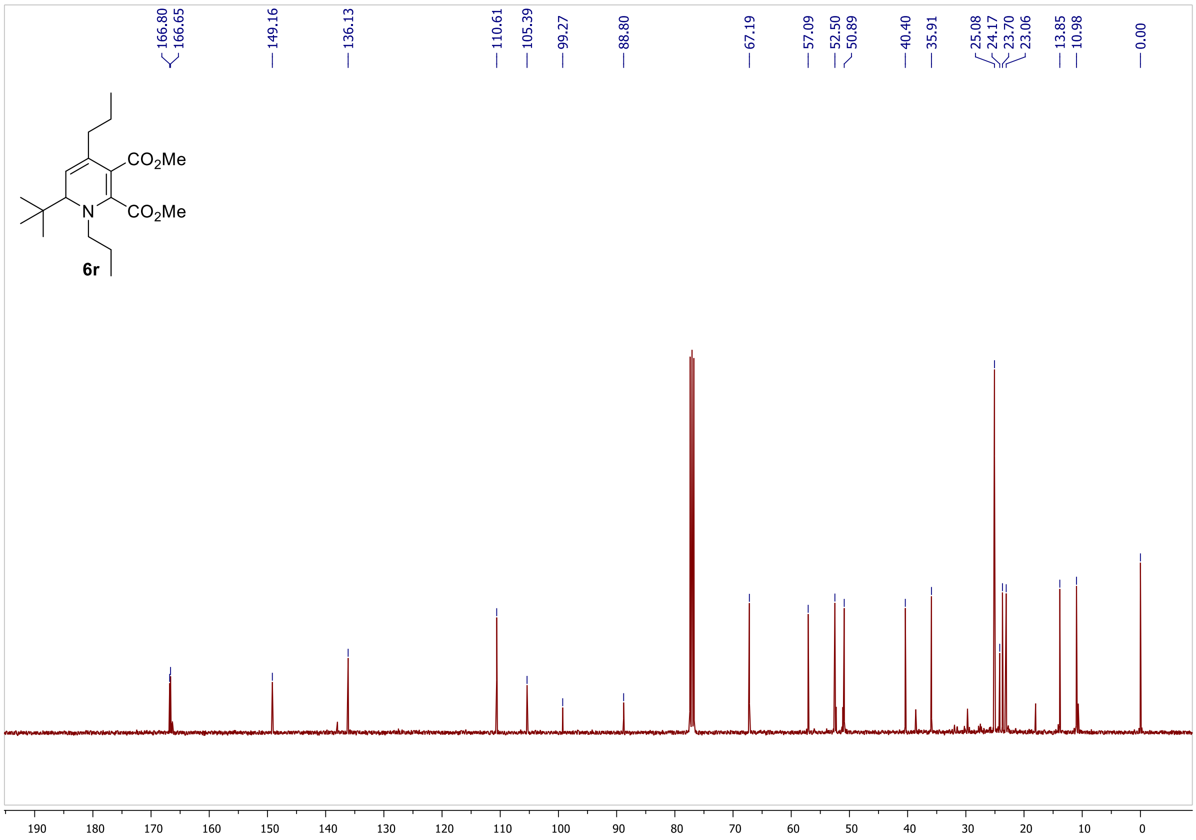
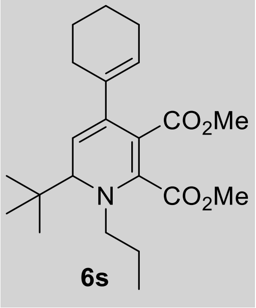


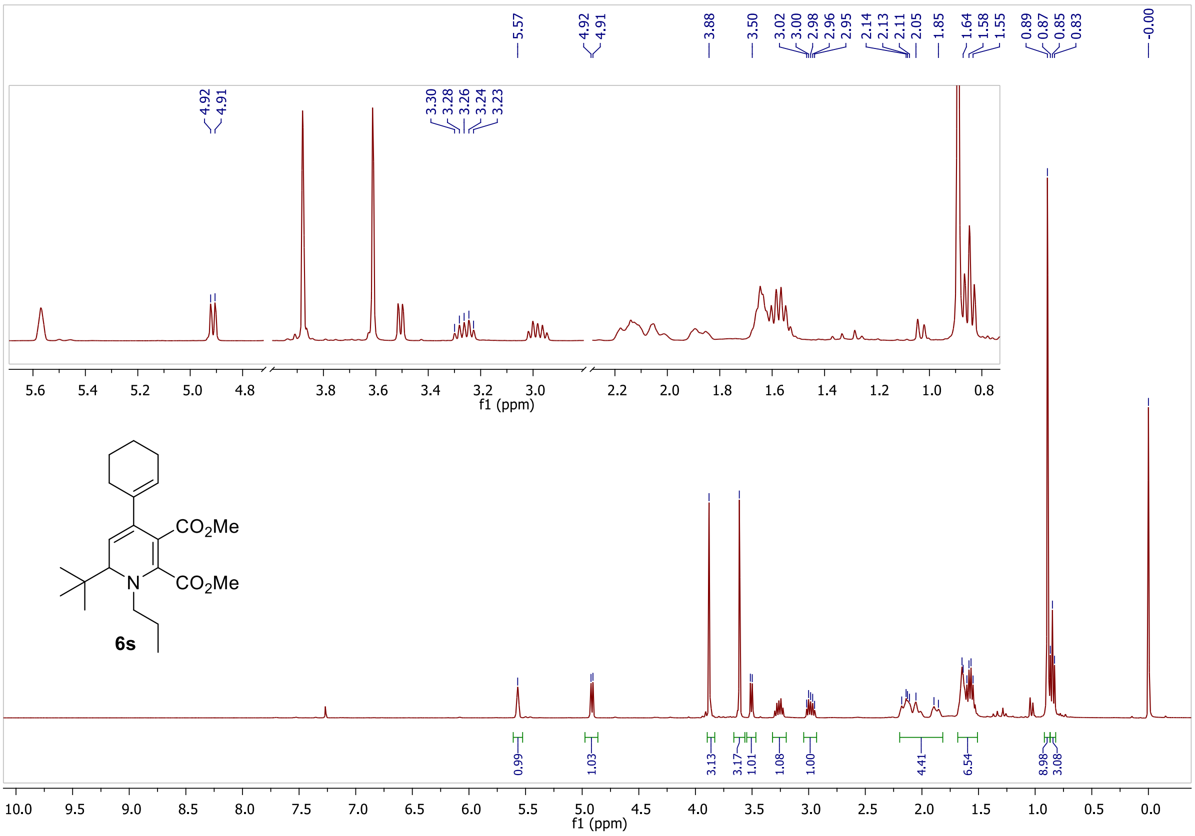
Figure 26. ^{1}H (400 MHz) and ^{13}C (100 MHz) NMR spectra of **6r** in CDCl$_3$.

Dimethyl 6-(*tert*-butyl)-4-(cyclohex-1-en-1-yl)-1-propyl-1,6-dihydropyridine-2,3-dicarboxylate (6s) sas-5-37



According to the general procedure *N*-(2,2-dimethylpropylidene)propan-1-amine (**3a**) (0.5 mmol, 0.064 g), 1-ethynylcyclohex-1-ene (**4l**) (0.5 mmol, 0.053 g), dimethyl 2-butynedioate (**5a**) (0.5 mmol, 0.071 g) and Zn(OTf)$_2$ (0.05 mmol, 0.018 g) were reacted in 1 mL of toluene/DMF (7/3) at 100 °C for 18 h. Alkaline work up and column chromatography afforded 165 mg (88%) of dimethyl 6-(*tert*-butyl)-4-(cyclohex-1-en-1-yl)-1-propyl-1,6-dihydropyridine-2,3-dicarboxylate **(6s)** as a yellow viscous oil. R$_f$ = 0.61 (Heptane/EtOAc: 90/10).

^{1}H NMR (400 MHz, CDCl$_3$): δ 5.57 (bs, 1H, *Cy*C=C**H**), 4.92 (d, *J* = 6.7 Hz, 1H, **H**C=C), 3.88 (s, 3H, OC**H**$_3$), 3.61 (s, 3H, OC**H**$_3$), 3.51 (d, *J* = 6.7 Hz, 1H, **H**CHC=C), 3.30 – 3.23 (m, 1H, NC(**H**)H), 3.02 – 2.95 (m, 1H, NC(H)**H**), 2.18 – 2.05 (m, 4H, *Cy*), 1.65 – 1.53 (m, 6H, *Cy*), 0.89 (s, 9H, C(C**H**$_3$)$_3$), 0.85 (t, *J* = 7.4 Hz, 3H, CH$_2$C**H**$_3$). ^{13}**C NMR** (100 MHz, CDCl$_3$): *δ* 166.7 (C=O), 166.3 (C=O), 149.9, 140.3, 140.1, 122.3, 109.8, 103.9, 67.0, 56.8, 52.6, 50.9, 40.5, 29.5, 25.6, 25.1, 23.7, 23.1, 22.4, 10.9. **HRMS** (ESI) *m/z* calculated for $C_{22}H_{33}NO_4+H^+$: 376.2488; found 376.2488.



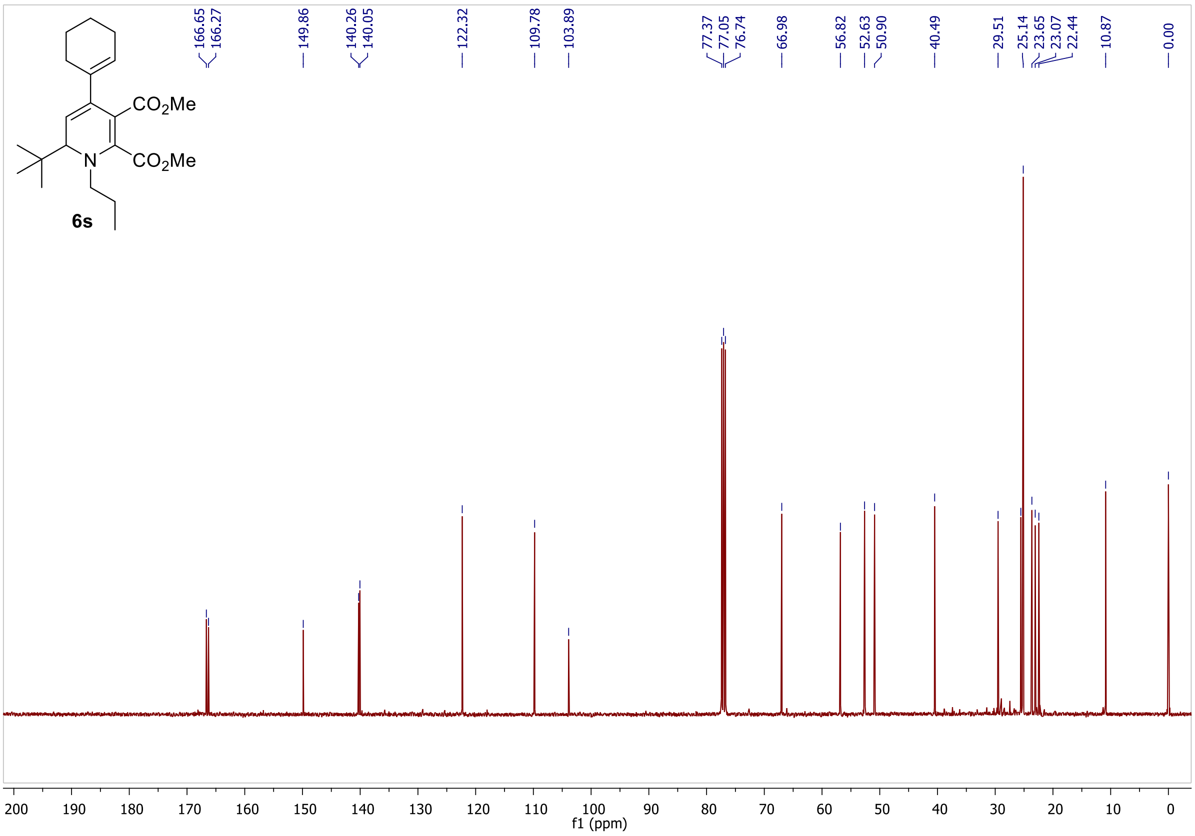
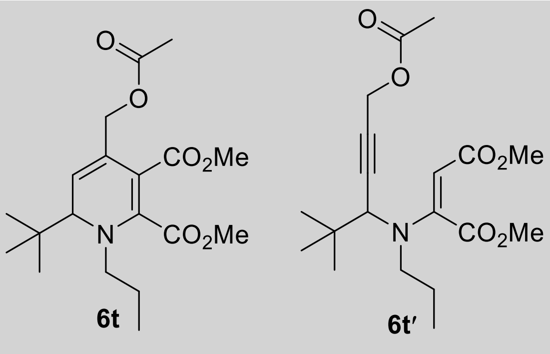


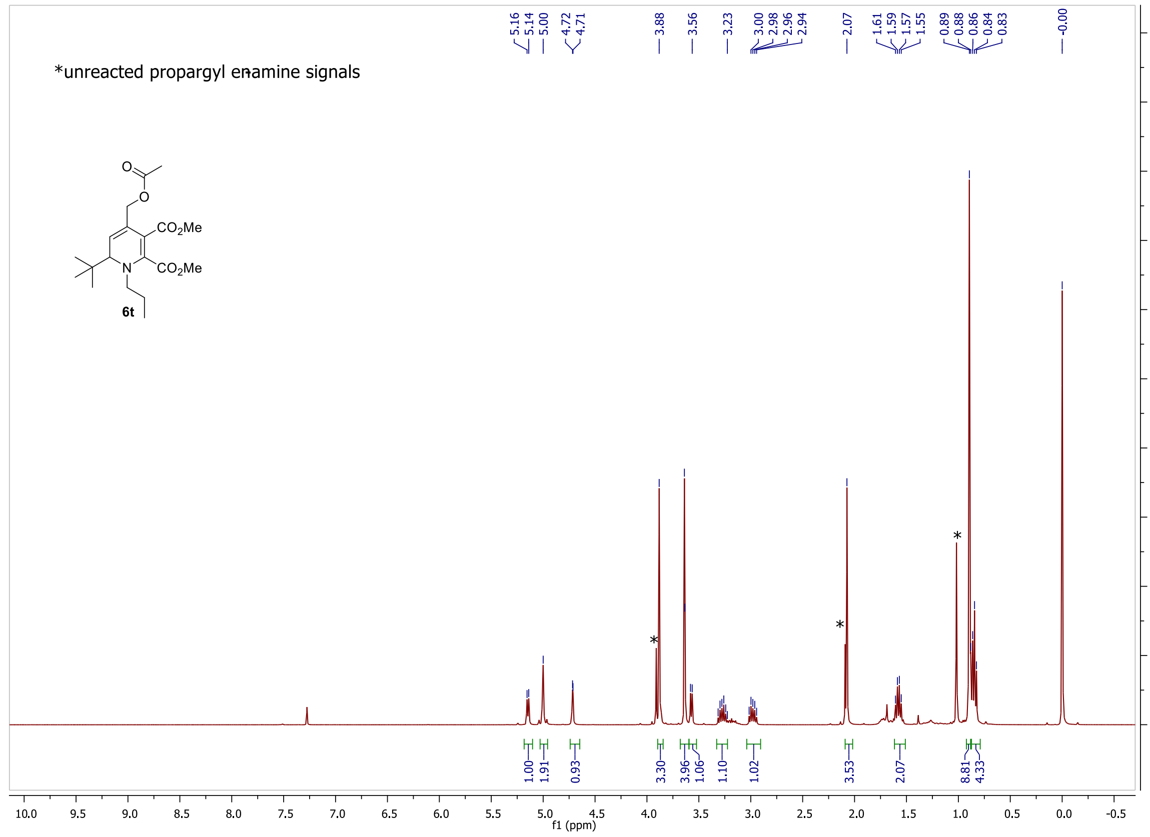
Figure 27. ^{1}H (400 MHz) and ^{13}C (100 MHz) NMR spectra of **6s** in CDCl$_3$.

Dimethyl 4-(acetoxymethyl)-6-(*tert*-butyl)-1-propyl-1,6-dihydropyridine-2,3-dicarboxylate (6t) sas-5-35



According to the general procedure *N*-(2,2-dimethylpropylidene)propan-1-amine (**3a**) (0.5 mmol, 0.064 g), prop-2-yn-1-yl acetate (**4m**) (0.5 mmol, 0.049 g), dimethyl 2-butynedioate (**5a**) (0.5 mmol, 0.071 g) and Zn(OTf)$_2$ (0.05 mmol, 0.018 g) were reacted in 1 mL of toluene/DMF (7/3) at 100 °C for 18 h. Alkaline work up and column chromatography afforded 176 mg (96%) of dimethyl 4-(acetoxymethyl)-6-(*tert*-butyl)-1-propyl-1,6-dihydropyridine-2,3-dicarboxylate **(6t)** as yellow viscous oil. R$_f$ = 0.59 (Heptane/EtOAc: 90/10). Some unreacted propargyl enamine (**6t'**) was also present, which due to exact same R$_f$ value could not be separated (yield is collective).

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.15 (d, J = 6.4 Hz, 1H, **H**C=C), 5.00 (s, 2H, C**H**$_2$OCOCH$_3$), 3.88 (s, 3H, OC**H**$_3$), 3.64 (s, 3H, OC**H**$_3$), 3.58 (d, J = 6.5 Hz, 1H, **H**CHC=C), 3.30 – 3.24 (m, 1H, NC(**H**)H), 3.02 – 2.95 (m, 1H, NC(H)**H**), 2.07 (s, 3H, CH$_2$OCOC**H**$_3$), 1.61 – 1.55 (m, 2H, C**H**$_2$CH$_3$), 0.90 (s, 9H, C(C**H**$_3$)$_3$), 0.84 (t, J = 7.4 Hz, 3H, CH$_2$C**H**$_3$). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 170.6 (C=O), 166.2 (C=O), 166.1 (C=O), 150.2, 131.0, 111.4, 102.2, 66.9, 64.8, 57.0, 52.7, 51.0, 40.7, 27.4, 25.1, 23.7, 21.0, 10.9. **HRMS** (ESI) m/z calculated for $C_{19}H_{29}NO_6+H^+$: 368.2073; found 368.2079.



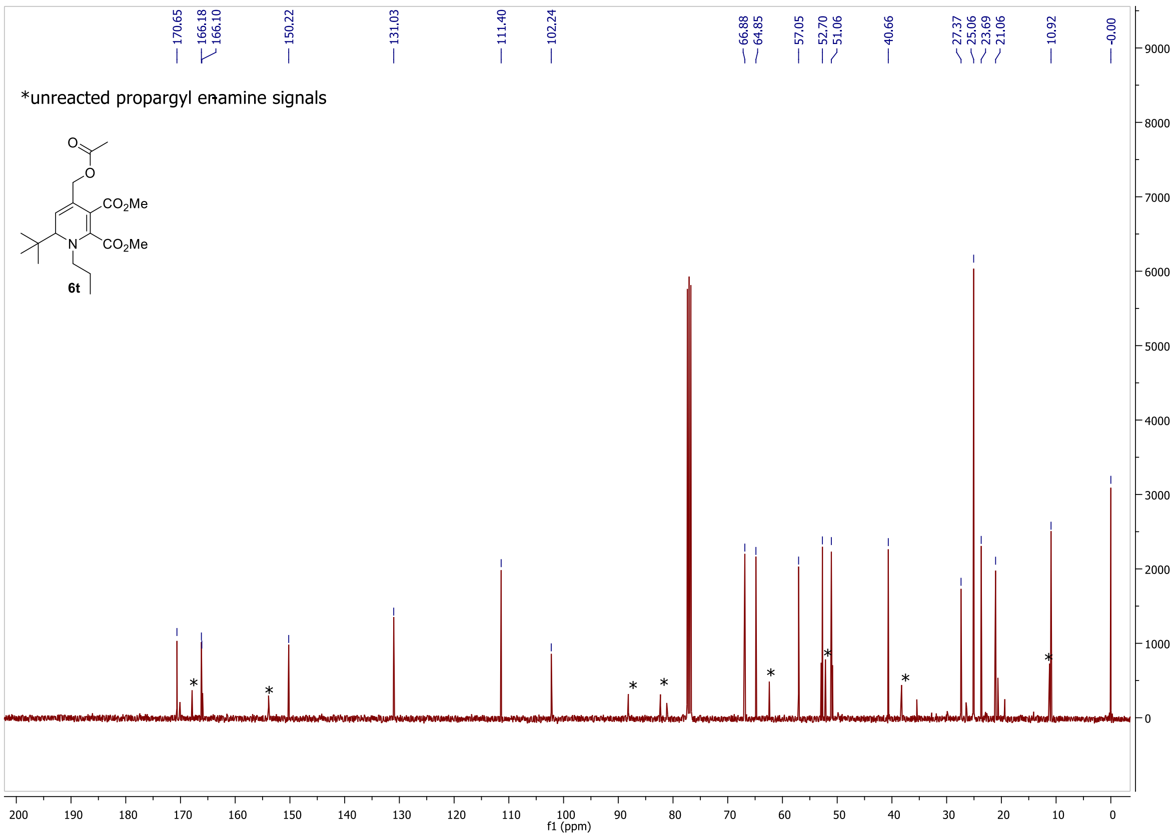
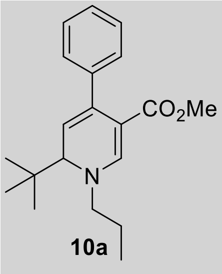


Figure 28. ^{1}H (400 MHz) and ^{13}C (100 MHz) NMR spectra of **6t** in $CDCl_3$.

Methyl 6-(*tert*-butyl)-4-phenyl-1-propyl-1,6-dihydropyridine-3-carboxylate (10a) SAS-5-110C 2D



10a

For the synthesis of **10a,** *N*-(2,2-dimethylpropylidene)propan-1-amine (**3a**) (0.5 mmol, 0.064 g), phenylacetylene (**4a**) (0.5 mmol, 0.051 g), methyl propiolate (**5b**) (0.75 mmol, 0.063 g) and $Zn(OTf)_2$ (0.05 mmol 0.018 g) were reacted in 1 mL of DMF at 110 °C for 24 h. Alkaline work up and column chromatography afforded 139 mg (78%) of methyl 6-(*tert*-butyl)-4-phenyl-1-propyl-1,6-dihydropyridine-3-carboxylate (**10a**) as transparent crystals; mp = 96-98 ºC. $R_f = 0.49$ (Heptane/EtOAc: 90/10).

^{1}H NMR (400 MHz, $CDCl_3$): 7.62 (d, *J* = 1.7 Hz, 1H, **H**C=CCO_2Me), 7.25 – 7.20 (m, 5H, aromatic), 4.86 (d, *J* = 6.4 Hz, 1H, **H**C=C), 3.77 (dd, *J* = 6.4, 1.8 Hz, 1H, **H**CHC=C), 3.47 (s, 3H, OC**H**$_3$), 3.38 (m, 1H), 3.42 – 3.35 (m, 1H, NC(**H**)H), 3.28 – 3.22 (m, 1H, NC(H)**H**), 1.65

(m, 2H, $C\mathbf{H}_2CH_3$), 0.97 (s, 9H, $C(C\mathbf{H}_3)_3$), 0.91 (t, *J* = 7.4 Hz, 3H, $CH_2C\mathbf{H}_3$). **^{13}C NMR** (100 MHz, $CDCl_3$): *δ* 166.5 (C=O), 149.0, 141.9, 138.1, 127.7, 127.3, 126.5, 110.7, 100.8, 67.5, 59.2, 50.2, 41.1, 25.6, 24.0, 11.0. **HRMS** (ESI) *m/z* calculated for $C_{20}H_{27}NO_2+H^+$: 314.2120; found 314.2124.

Single crystals of **10a** were recrystallized from ethyl acetate, mounted in inert oil and transferred to the cold gas stream of the diffractometer.

Crystal structure determination of **10a** (CSD1814907):

Crystal data:

$C_{20}H_{27}NO_2$, $M = 313.42$,

$a = 11.7972(6)$, $b = 12.1131(5)$, $c = 13.4962(7)$ Å

$\alpha = 94.970(4)$, $\beta = 103.881(4)$, $\gamma = 109.494(4)°$

$V = 1762.2(2)$ Å^3

$T = 100.0(1)$K

space group, crystal system: *P*1 (no.2), triclinic

$Z = 4$, 12090 reflections measured, 6966 unique ($R^{\text{int}} = 0.0235$), which were used in all calculations. The final $R1(F^2)$ was 0.0430 ($I > 2\sigma(I)$), $wR(F^2)$ was 0.122 (all data), GoOF 1.023.

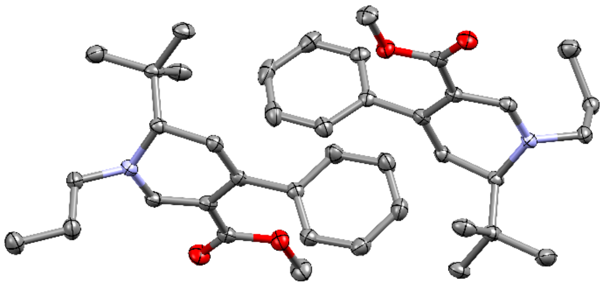


Figure 29. Single-crystal X-ray structure of **10a**. The asymmetric unit is shown (Z’=2). Displacement ellipsoids are at the 50% level, H atoms have been omitted for clarity.

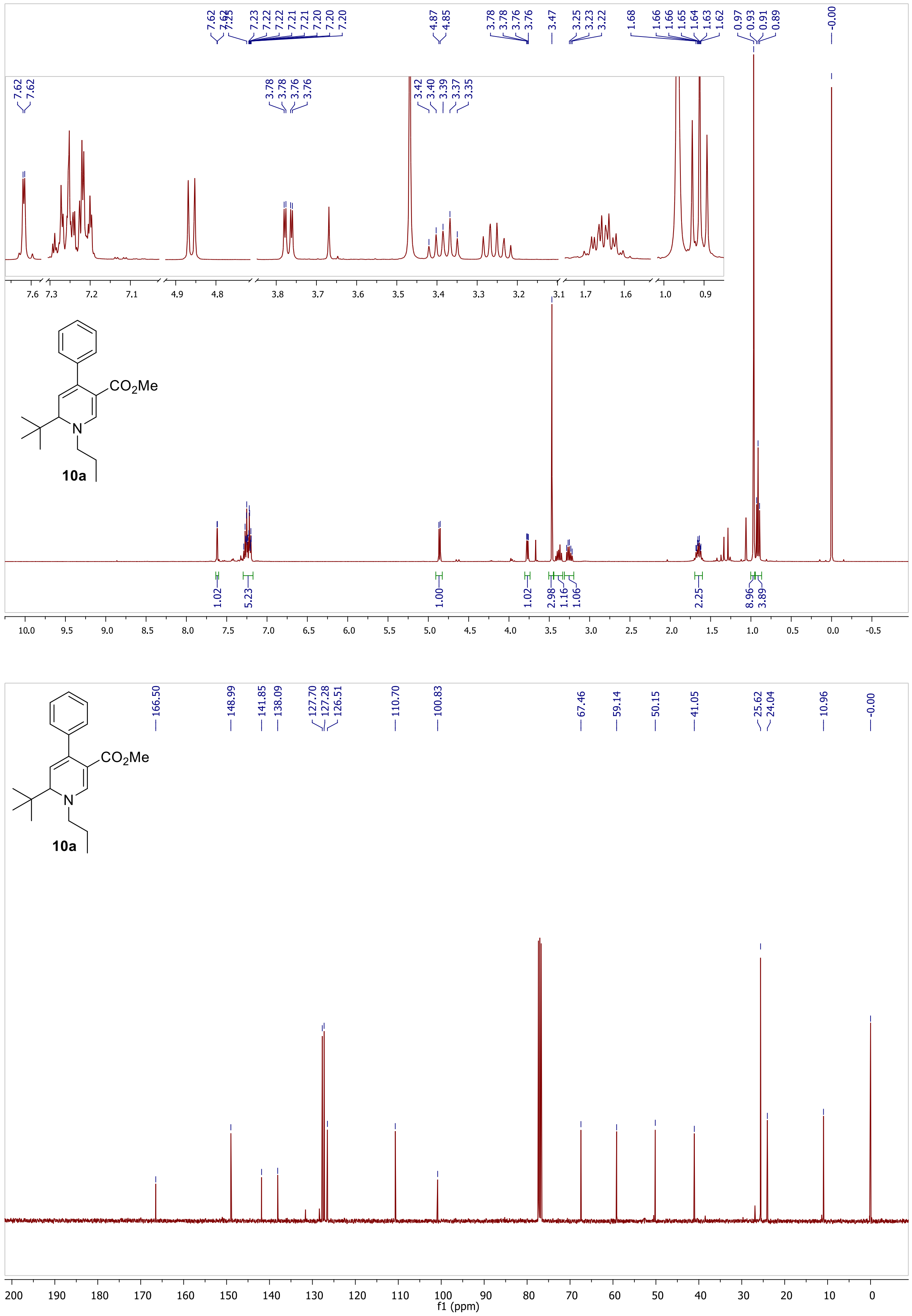


Figure 30. ^{1}H (400 MHz) and ^{13}C (100 MHz) NMR spectra of **10a** in CDCl$_3$.

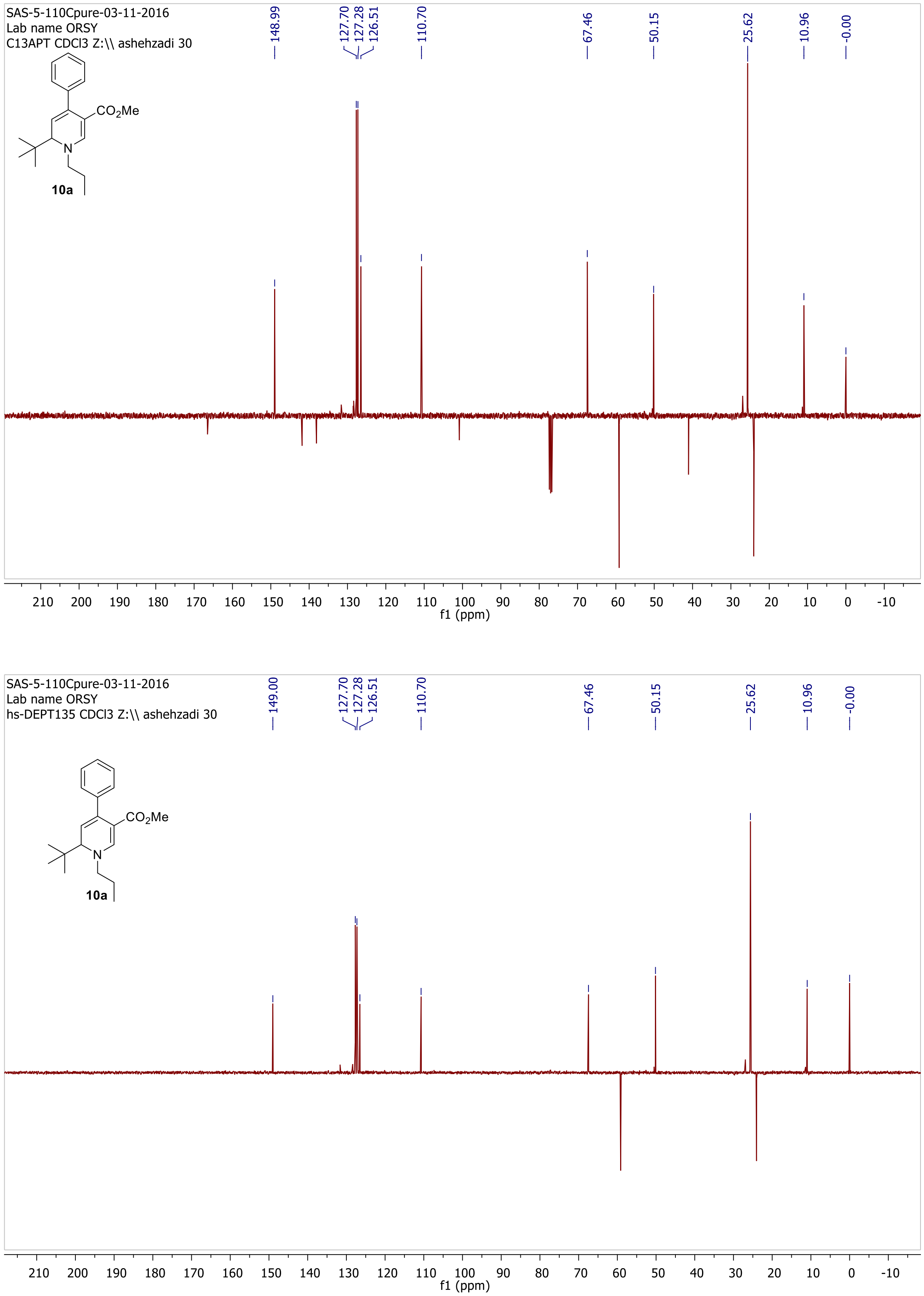


Figure 31. ^{13}C APT and DEPT (100 MHz) spectra of **10a** in $CDCl_3$.

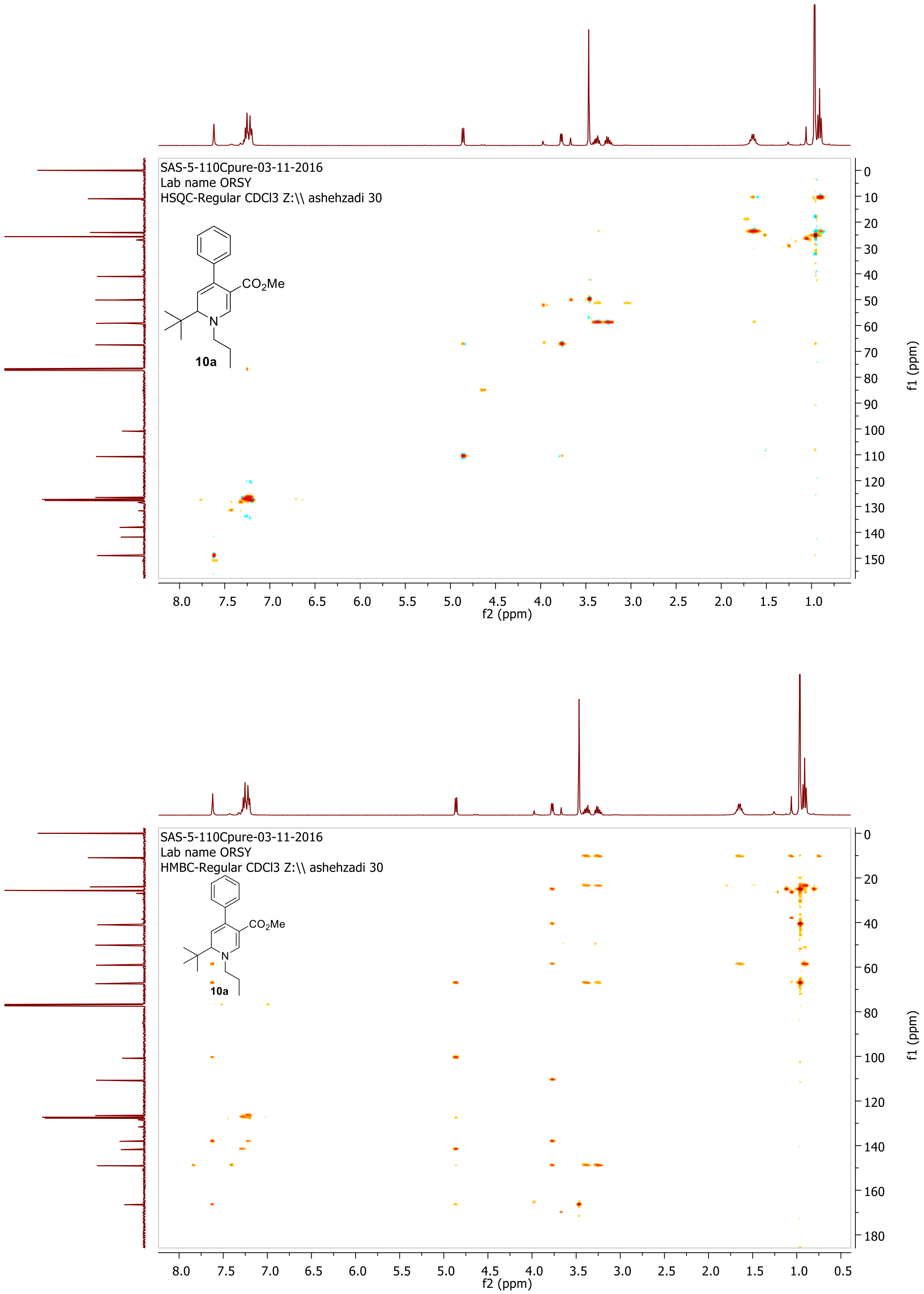
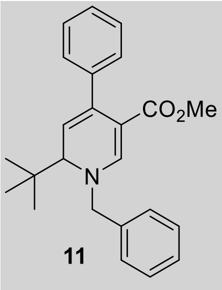


Figure 32. HMQC and HMBC spectra of **10a** in $CDCl_3$.

Methyl 1-benzyl-6-(*tert*-butyl)-4-phenyl-1,6-dihydropyridine-3-carboxylate (11) SAS-5-111A



11

For the synthesis of **11,** *N*-(2,2-dimethylpropylidene)-1-phenylmethanamine (**3l**) (0.5 mmol, 0.088 g), phenylacetylene (**4a**) (0.5 mmol, 0.051 g), methyl propiolate (**5b**) (0.75 mmol, 0.063 g) and $Zn(OTf)_2$ (0.05 mmol 0.018 g) were reacted in 1 mL of DMF at 110 °C for 24 h. Alkaline work up and column chromatography afforded 118 mg (65%) of methyl 1-benzyl-6-(*tert*-butyl)-4-phenyl-1,6-dihydropyridine-3-carboxylate **(11)** as a yellow viscous oil that became solid after long standing; mp = 76-78 ºC; R_f = 0.60 (Heptane/EtOAc: 90/10).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.68 (d, J = 13.3 Hz, 1H, **H**C=CCO_2Me), 7.29 – 7.14 (m, 10H), 4.67 (d, J = 16.4 Hz, 1H, NC(**H)**HPh), 4.48 (d, J = 13.2 Hz, 1H, **H**C=C), 4.28 (d, J = 16.4 Hz, 1H, NC(H)**H**Ph), 4.08 (s, 1H, **H**CHC=C), 3.53 (s, 3H, OC**H**$_3$), 1.04 (s, 9H, C(C**H**$_3$)$_3$). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 169.7, 151.2, 136.3, 131.6, 128.6, 128.5, 128.3, 127.2, 126.7, 122.4, 87.9, 87.4, 85.2, 53.4, 50.5, 38.7, 27.0. **HRMS** (ESI) *m/z* calculated for $C_{20}H_{27}NO_2$+H^+: 362.2115; found 362.2110

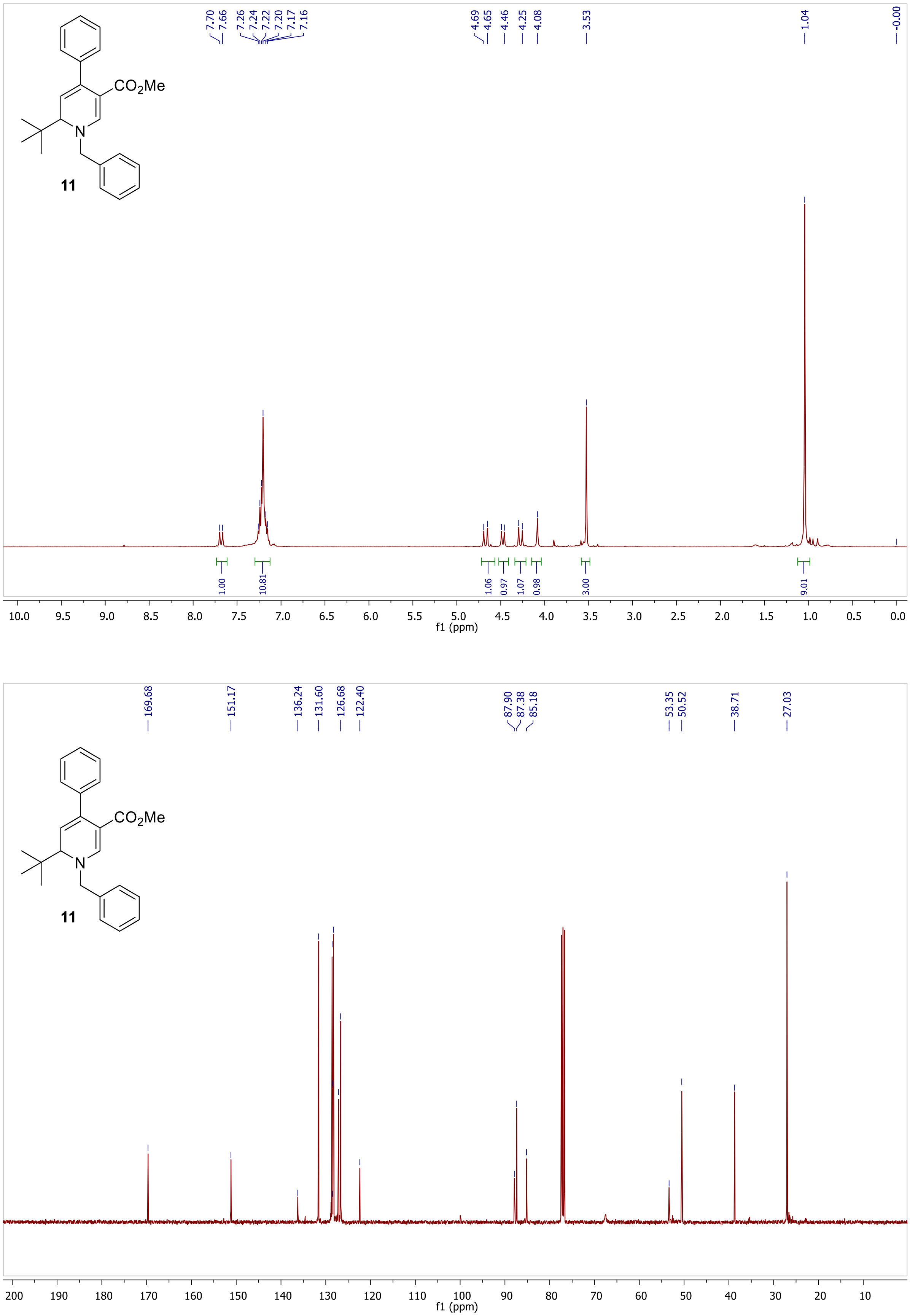
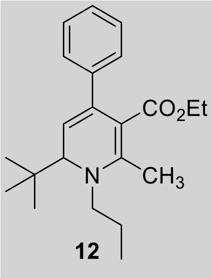


Figure 33. ^{1}H (400 MHz) and ^{13}C (100 MHz) NMR spectra of **11** in CDCl$_3$.

Ethyl 6-(*tert*-butyl)-2-methyl-4-phenyl-1-propyl-1,6-dihydropyridine-3-carboxylate (12)

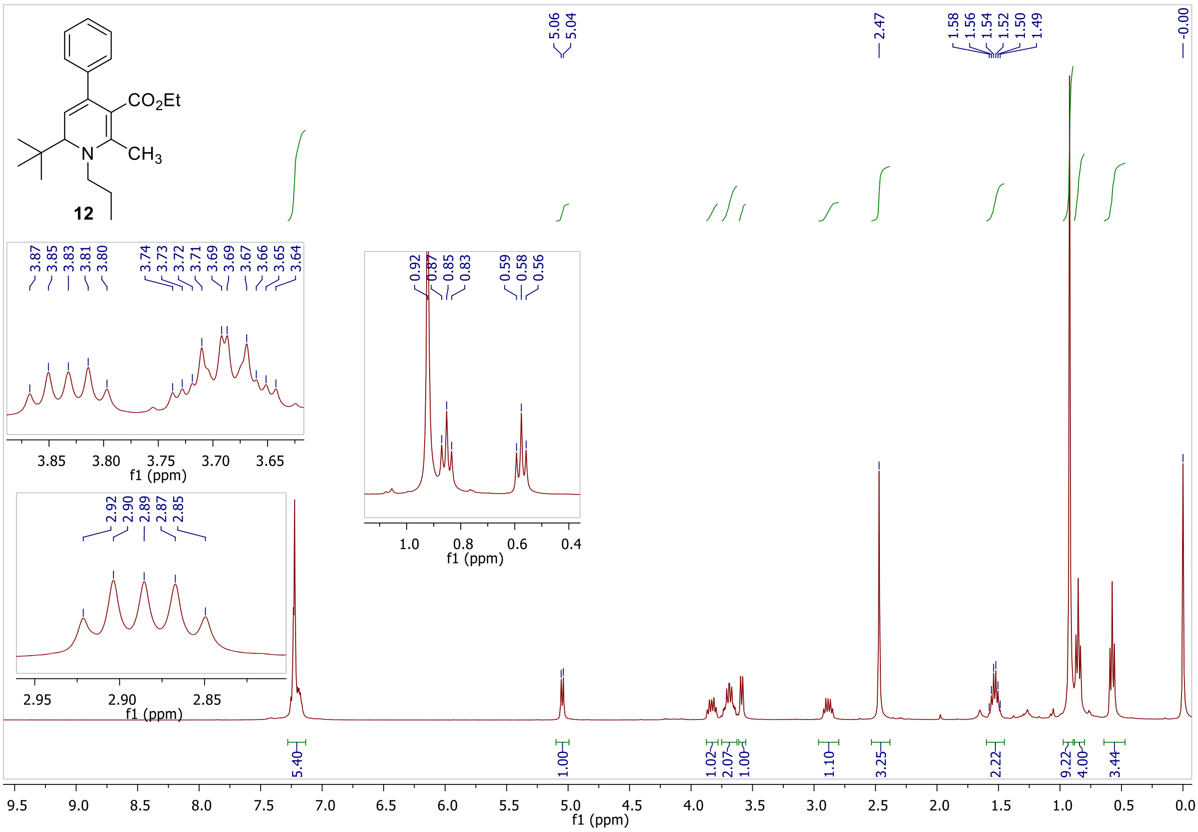
SAS-5-81



12

For the synthesis of **12,** *N*-(2,2-dimethylpropylidene)propan-1-amine (**3a**) (0.5 mmol, 0.064 g), phenylacetylene (**4a**) (0.5 mmol, 0.051 g), ethyl-2-butynoate (**5c**) (0.75 mmol, 0.084 g, 1.5 equiv) and Zn(OTf)$_2$ (0.05 mmol 0.018 g) were reacted together in 1 mL of DMF at 110 °C for 48 h. Alkaline work up and column chromatography over silica gel afforded 107 mg (63%) of ethyl 6-(*tert*-butyl)-2-methyl-4-phenyl-1-propyl-1,6-dihydropyridine-3-carboxylate (**12**) as a yellow viscous oil. R$_f$ = 0.50 (Heptane/EtOAc: 90/10).

^{1}H NMR (400 MHz, CDCl$_3$): δ 7.25 – 7.17 (m, 5H, aromatic), 5.05 (d, J = 7.0 Hz, 1H, **H**C=C), 3.87 – 3.80 (m, 1H, NC(**H**)H), 3.69 (tdd, J = 10.7, 7.2, 3.6 Hz, 2H, OC**H**$_2$CH$_3$), 3.59 (d, J = 7.0 Hz, 1H, **H**CHC=C), 2.89 (dt, J = 14.4, 7.1 Hz, 1H, NC(H)**H**)), 2.47 (s, 3H, C=CC**H**$_3$), 1.60 – 1.45 (m, 2H, NCH$_2$C**H**$_2$), 0.92 (s, 9H, C(C**H**$_3$)$_3$), 0.85 (t, J = 7.3 Hz, 3H, CH$_2$C**H**$_3$), 0.58 (t, J = 7.1 Hz, 3H, OCH$_2$C**H**$_3$). **^{13}C NMR** (100 MHz, CDCl$_3$): δ 168.5 (C=O), 154.5 (CH$_3$**C**=C), 143.6 (HCHC=**C**), 139.4 (**C**$_{ipso}$), 127.7 (Ph$_{para}$), 126.7 (Ph), 126.1 (Ph), 110.9 (HCH**C**=C), 105.4 (CH$_3$C=**C**), 68.7 (H**C**HC=C), 58.8 (O**C**H$_2$CH$_3$), 55.8 (N**C**H$_2$), 40.5 (**C**(CH$_3$)$_3$), 25.5 (C(**C**H$_3$)$_3$, 23.8 (NCH$_2$**C**H$_2$), 17.3 (CH$_3$**C**=C), 13.4 (O**C**H$_2$CH$_3$), 11.0 (CH$_2$**C**H$_3$). **HRMS** (ESI) *m/z* calculated for $C_{22}H_{31}NO_2+H^+$: 342.2428; found 342.2430



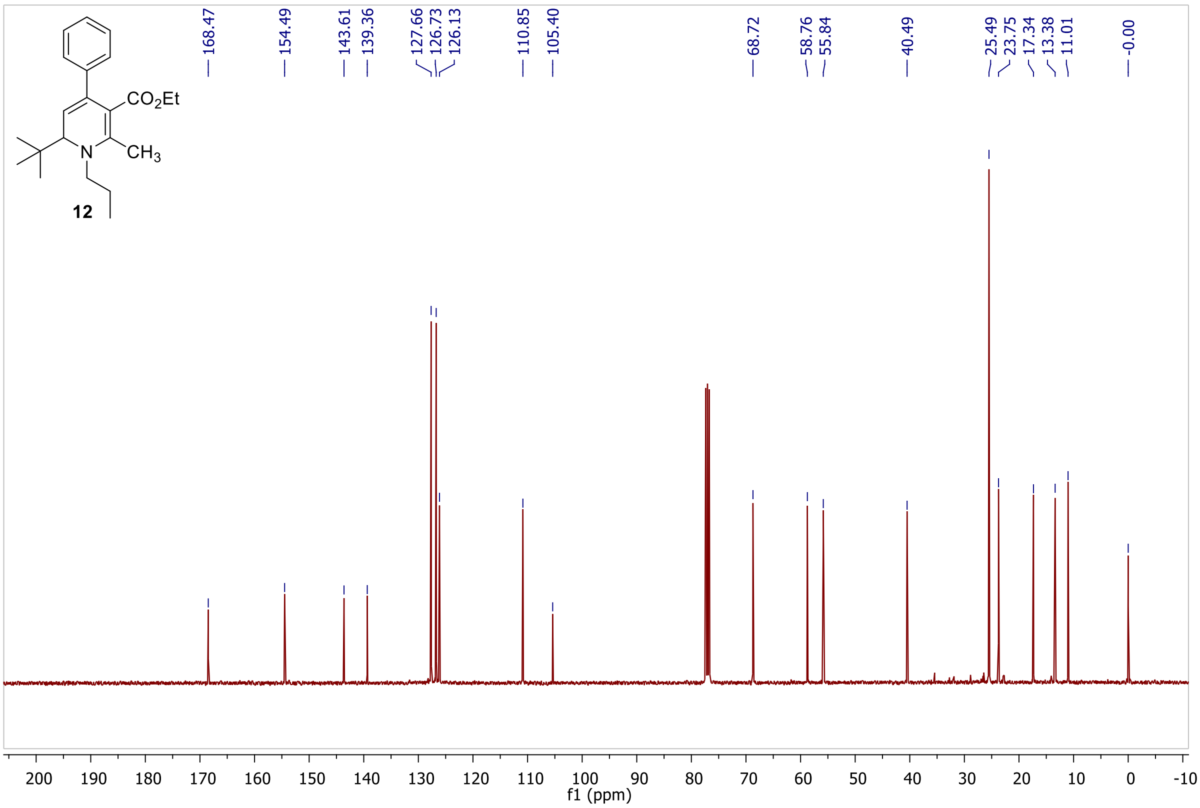


Figure 34. ^{1}H (400 MHz) and ^{13}C (100 MHz) NMR spectra of **12** in $CDCl_3$.

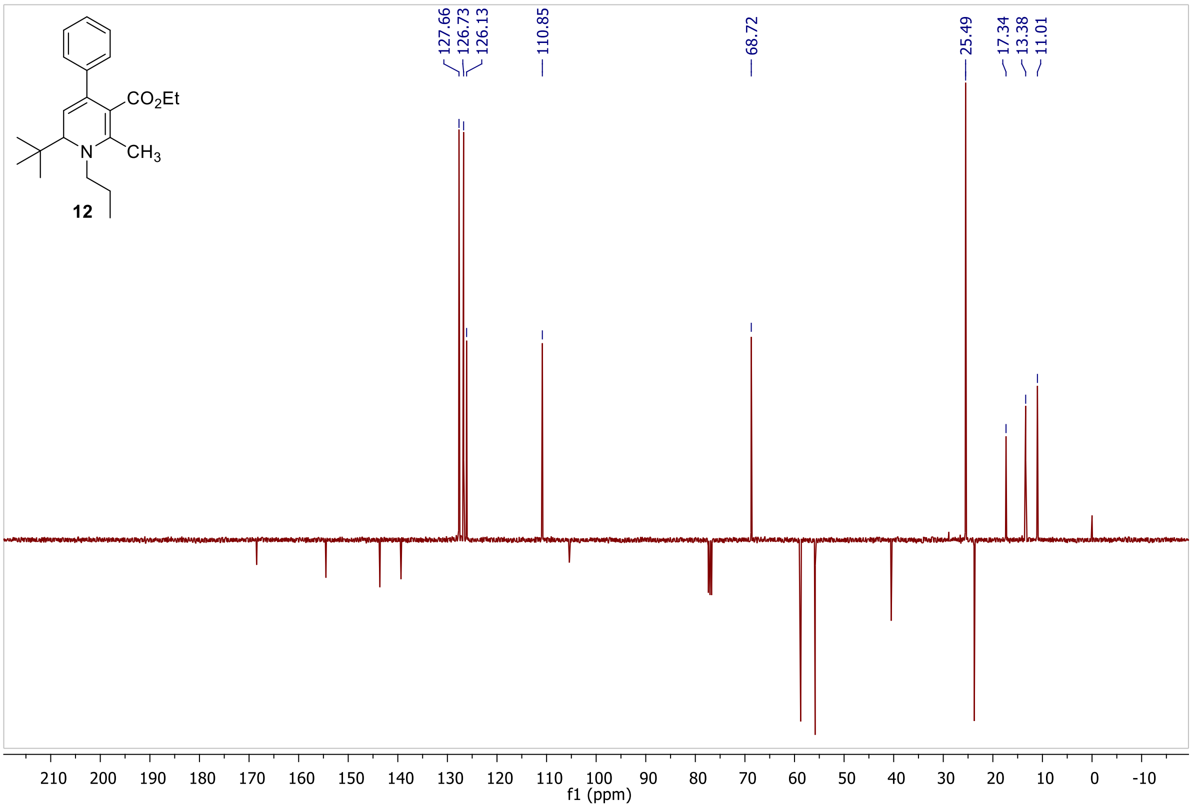
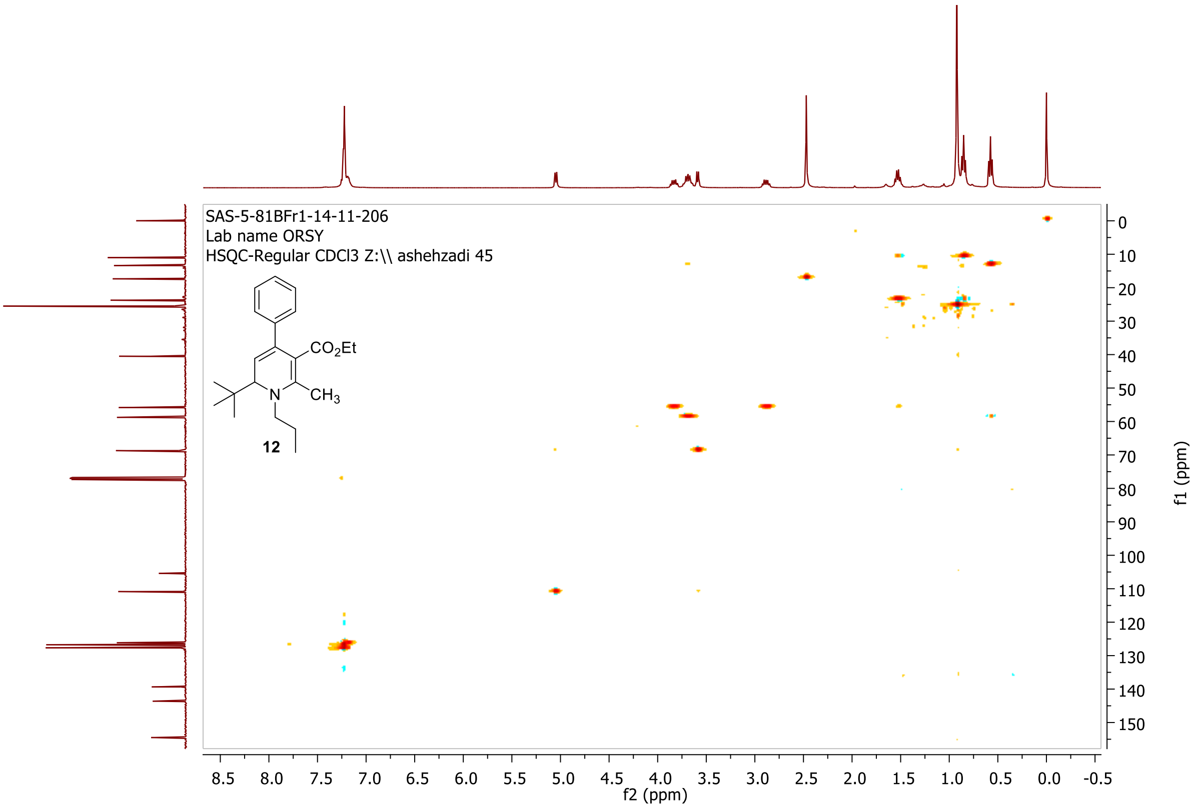


Figure 35. ^{13}C-APT NMR spectrum of **12** in CDCl$_3$.



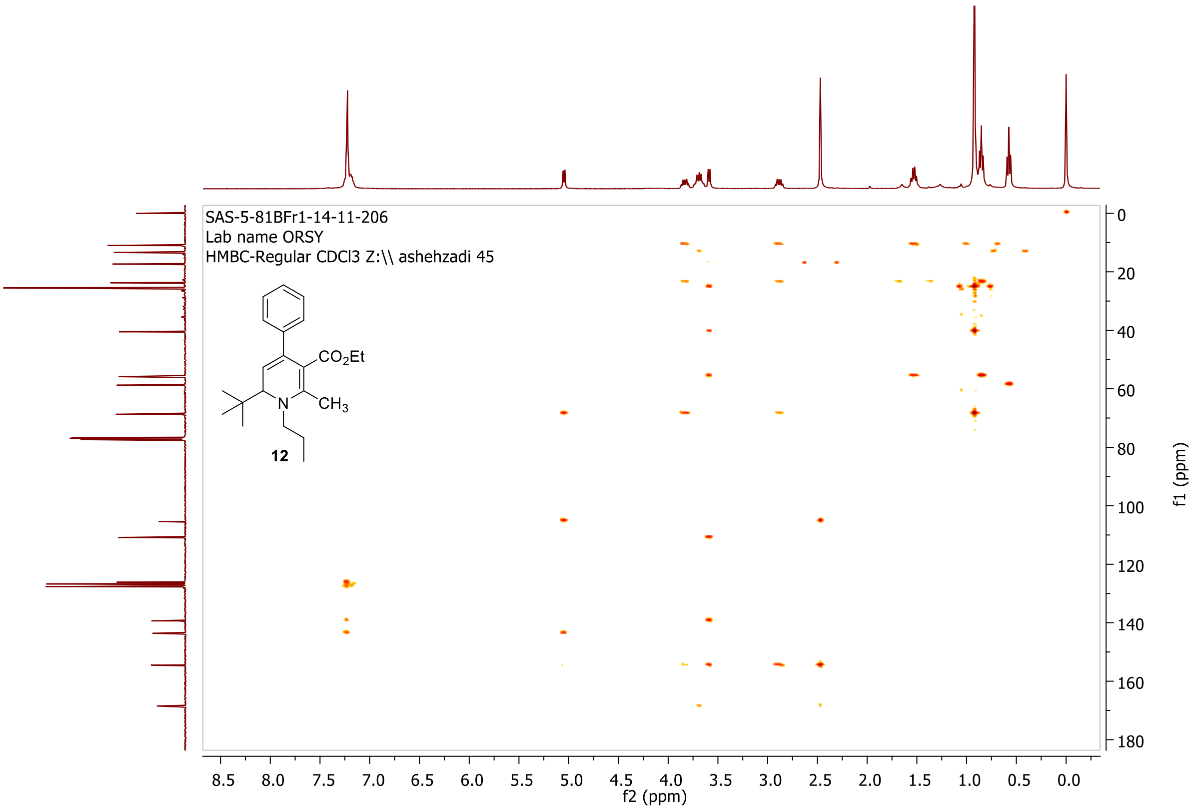


Figure 36. HMQC and HMBC spectra of **12** in $CDCl_3$.

5. References

1. S. Aaliya Shehzadi, Aamer Saeed, F. Lemière, B. U. W. Maes and K. Abbaspour Tehrani, *Eur. J. Org. Chem.*, 2018, 78.