Supporting Information

Site-selective 1,3-Double Functionalization of Arenes Using *para*-quinol, C-N, and C-C/C-P Three-Component Coupling

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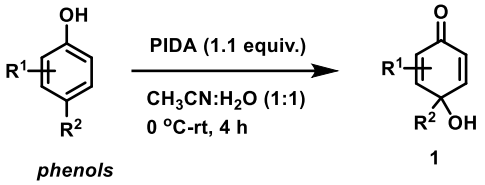
[1] General

^{1}H, ^{13}C, and ^{31}P nuclear magnetic resonance spectra were recorded on Bruker Avance III 400 spectrometer at 25 °C.The chemical shifts in ^{1}H NMR,^{13}C{^{1}H} NMR and ^{31}P{^{1}H} NMR spectra are reported in parts per million (ppm) and are referenced to the residual solvent signal as the internal standard; ^{1}H NMR spectra ($CDCl_3$ δ 7.26 ppm), ^{13}C ($CDCl_3$ δ 77.16). Coupling constants (*J*) are quoted in Hz. Splitting patterns are denoted as "s" for singlet; "d" for doublet; "t" for triplet; "q" for quartet; "sext" for sextet; "sept" for septet; "m"for multiplet, "br" for broad; "dt" for doublet of triplets; "td" for triplet of doublets, and "app" for apparent. Assignment of proton signals was assisted by ^{1}H, ^{1}H COSY, HSQC and HMBC experiments. ^{13}C NMR and ^{31}P NMR spectra were recorded at 100 and 162 MHz, respectively using a Bruker AVANCE 400. High Resolution Mass Spectra (HRMS) were recorded on Q-TOF mass spectrometer at SAIF department in CSIR-CDRI, Lucknow, India. Reactions were performed using borosil sealed tube vial. Column chromatography was done in 60-120Å or 100-200 Å mesh silica gel of Merck Company. All solvents were distilled for purification in column chromatography. Reagents and starting materials were used as received from company. THF and toluene were distilled from sodium benzophenone ketyl and other solvents were distilled under standard procedures. Starting materials were synthesized with the procedure that reported in literature.

[2] Preparation of starting materials

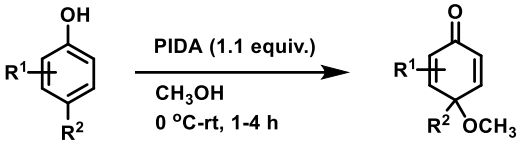
a) *p*-Quinol (1):



phenols 1

The general experimental procedures for the preparation of *p*-quinol were followed as reported previously. (Diacetoxyiodo)benzene (PIDA; 1.1 equiv.) was added portion wise to a stirred solution of 4-substituted phenol (1-10 mmol; 1.0 equiv.) in acetonitrile and water (2:1; 10 mL/mmol) at 0 °C. The solution was allowed to warm to room temperature for 4 h. After the completion of reaction (monitored by TLC), reaction mixture was quenched with saturated aqueous $NaHCO_3$ solution to neutralize the acidic reaction mixture and extracted with EtOAc for three times. The combined organic phases were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (20-30% EtOAc in hexane) to give pure *p*-quinol **1**. Spectral data for these *p*-quinols matched that provided in the literature.[1]

a) *p*-Quinol methyl ether (3):

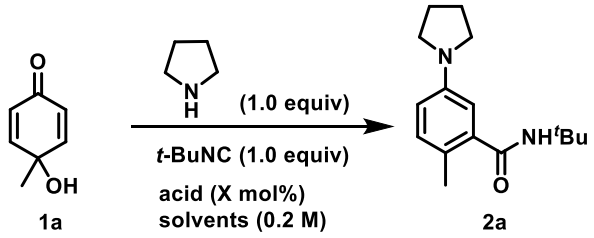


The general experimental procedures for the preparation of *p*-quinol methyl etherwere followed as reported previously. (Diacetoxyiodo)benzene (PIDA, 1.1 equiv) was added portion wise to a stirred solution of 4-substituted phenol (2.0-10 mmol) in methanol (5 mL/mmol) at 0 °C. The solution was allowed to warm to room temperature for 1-4 h. Reaction was quenched with saturated aqueous $NaHCO_3$ solution to neutralize the acidic reaction mixture and extracted with EtOAc for three times. The combined organic phases were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (5-10% EtOAc in hexane) to give pure *p*-quinol **3**. Spectral data for these *p*-quinol methyl ether matched that provided in the literature.[2]

[3] Evaluation of catalytic reaction conditions (Supplementary Table S1)

General Procedure for optimization: To the reaction vial, acid (0.2 to 1.0 equiv.) was added to the mixture of *p*-quinol (**1a**, 0.4 mmol), pyrrolidine (0.4 mmol), and *tert*-butyl isocyanide (0.4 mmol) in solvent (2 mL). After the completion of reaction with reference to *p*-quinol, (monitored by TLC under UV, iodine and $KMnO_4$), solvent was evaporated and re-dissolved in ethyl acetate and extracted with aq. $NaHCO_3$. Aqueous layer was again washed and partitioned with ethyl acetate for two time. Organic extracts were dried over sodium sulfate and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography to receive **2a** as a pale yellow solid (R_f 0.5; 20% EtOAc in hexane, eluted at 10%).

Table S1. Optimization



run	acid (mol%	solvent	temp (^{o} C)	time (h)	yield (%)[b]
1	-	CH_3CN	70	48	0
2	CH_3CO_2H (100)	CH_3CN	rt	10	48
3	CH_3CO_2H (20)	CH_3CN	rt	12	45
4	CH_3CO_2H (20)	MeOH	rt	10	60
5	CH_3CO_2H (20)	THF	rt	16	10
6	CH_3CO_2H (20)	$CHCl_3$	rt	24	trace
7	CH_3CO_2H (20)	Toluene	rt	15	25
8	CH_3CO_2H (20)	DCE	rt	16	trace
9	$PhCO_2H$	MeOH	rt	24	28
10	$PhCH=CHCO_2H$	MeOH	rt	24	20
11	TMSOTf (20)	MeOH	rt	8	0
12	$In(OTf)_2$ (20)	MeOH	rt	10	0
13	$FeCl_3$ (20)	MeOH	rt	10	0
14	TfOH (20)	MeOH	rt	10	0
15	*p*-TSA (20)	MeOH	rt	14	10
16[c]	CH_3CO_2H (20)	MeOH	rt	10	65
17[d]	CH_3CO_2H (20)	MeOH	rt	12	0
18[e]	CH_3CO_2H (20)	MeOH	rt	12	68
19[f]	CH_3CO_2H (20)	MeOH	rt	12	75
20[g]	CH_3CO_2H (20)	MeOH	rt	10	80
21	CH_3CO_2H (10)	MeOH	rt	24	72

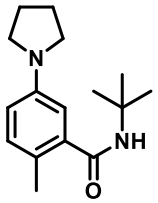
[a]Reaction was carried out at 0.5 mmol scale. [b]Isolated yields were noted. [c]MS (4Å) was added. [d]Reaction was conducted without pyrrolidine [e]1.5 equiv. of isocyanide and pyrrolidine was employed [f]1.5 equiv of *p*-quinone was employed [g]1.2 equiv of *p*-quinone and isocyanide was employed

[4] Synthesis and spectral data of 3-amino benzamide (2)

General Procedure for the synthesis of 3-aminobenzamides (run 20, Table S1):

To the reaction vial, acid (20 mol%) was added to the mixture of *p*-quinol (**1a**, 0.6 mmol), amine (0.5 mmol), and isocyanide (0.6 mmol) in dry methanol (2.5 mL) and MS (4 Å) (200 mg). After the completion of reaction with reference to *p*-quinol, (monitored by TLC), methanol was evaporated and re-dissolved in ethyl acetate and extracted with aq. $NaHCO_3$. Aqueous layer was again washed and partitioned with ethyl acetate for two time. Organic extracts were dried over sodium sulfate and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography as mentioned for individuals. Yields are calculated based on corresponding amines.

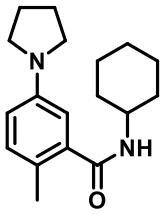
***N*-(tert-butyl)-2-methyl-5-(pyrrolidin-1-yl)benzamide (2a):** General procedure was followed with **1a** (75.0 mg, 0.6 mmol), pyrrolidine (42 µL, 0.5 mmol) and *tert*-butyl isocyanide (68.2 µL, 0.6 mmol) at room temperature for 12 h to furnish **2a** as a pale yellow solid (103 mg, 0.40 mmol, 80% yield).



Purification: Silica gel flash chromatography, eluted with 10% EtOAc in hexane
R_f 0.5 (20% EtOAc in hexane)

^{1}H (400 MHz, $CDCl_3$): δ 7.02 (d, *J* = 8.2 Hz, 1H), 6.53–6.48 (m, 2H), 5.54 (br s, 1H), 3.26 (t, *J* = 6.7 Hz, 4H), 2.29 (s, 3H), 1.99 (tt, *J* = 6.6, 3.4 Hz, 4H), 1.46 (s, 9H).
^{13}C NMR (100 MHz, $CDCl_3$): δ 170.5, 146.2, 138.6, 131.4, 121.0, 112.8, 109.8, 51.6, 47.8, 28.9, 25.4, 18.4.
HRMS (ESI^+): *m/z*: $[M + H]^+$ calculated for $C_{16}H_{25}N_2O$: 261.1967, found 261.1958.

***N*-cyclohexyl-2-methyl-5-(pyrrolidin-1-yl)benzamide (2b):** General procedure was followed with **1a** (75.0 mg, 0.6 mmol), pyrrolidine (42 µL, 0.5 mmol) and cyclohexyl isocyanide (75 µL, 0.6 mmol) at room temperature for 12 h to furnish **2b** as a white solid (116 mg, 0.41 mmol, 82% yield).

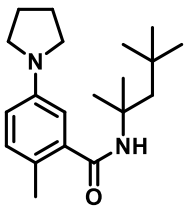


Purification: Silica gel Flash chromatography, eluted with 18% EtOAc in hexane
R_f 0.30 (20% EtOAc in hexane)

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.03 (d, *J* = 8.2 Hz, 1H), 6.56-6.49 (m, 2H), 5.57 (d, *J* = 8.0 Hz, 1H), 4.02–3.93(m, 1H), 3.25(t, *J* = 6.6 Hz, 4H), 2.30 (s, 3H), 2.07–2.01 (m, 2H), 1.99 (tt, *J* = 6.6, 3.4 Hz, 4H), 1.76-1.69(m, 2H), 1.67–1.60 (m, 1H), 1.46–1.40 (m, 2H), 1.24–1.15 (m, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 170.0, 146.2, 137.7, 131.5, 121.2, 113.1,109.9, 48.4, 47.8, 33.2, 29.7, 25.4, 18.4.
HRMS (ESI^+): *m/z*: $[M + H]^+$ Calculated for $C_{18}H_{27}N_2O$: 287.2123, found 287.2118.

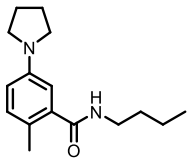
2-Methyl-5-(pyrrolidin-1-yl)-N-(2,4,4-trimethylpentan-2-yl)benzamide (2c): General procedure was followed with **1a** (75.0 mg, 0.6 mmol), pyrrolidine (42 µL, 0.5 mmol) and 1,1,3,3-tetramethylbutyl isocyanide (105 µL, 0.6 mmol) at room temperature for 13 h to furnish **2c** as a white solid (92 mg, 0.29 mmol, 58% yield).



Purification: Silica gel Flash chromatography, eluted with 18% EtOAc in hexane
Rf 0.30 (20% EtOAc in hexane)

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.95 (d, *J* = 8.1 Hz, 1H), 6.43 (d, *J* = 9.4 Hz, 2H), 5.50 (s, 1H), 3.17 (t, *J* = 6.3 Hz, 4H), 2.24 (s, 3H), 1.92 (t, *J* = 6.4 Hz, 4H), 1.77 (s, 2H), 1.44 (s, 6H), 0.99 (s, 9H).
^{13}C NMR (100 MHz, $CDCl_3$): δ 170.0, 146.1, 131.6, 129.8, 121.5, 112.8, 109.6, 55.6, 52.1, 47.7, 31.7, 29.2, 25.4, 18.4.
HRMS (ESI^+): *m/z*: $[M + H]^+$ calculated for $C_{20}H_{33}N_2O$: 317.2593, found 317.2585.

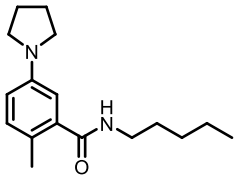
***N*-Butyl-2-methyl-5-(pyrrolidin-1-yl)benzamide (2d):** General procedure was followed with **1a** (75.0 mg, 0.6 mmol), pyrrolidine (41 µL, 0.5 mmol) and *n*-butyl isocyanide (62 mg, 0.6 mmol) at room temperature for 12 h to furnish **2d** as a thick oil (85 mg, 0.32 mmol, 65% yield).



Purification: Silica gel Flash chromatography, eluted with 15% EtOAc in hexane
R_f 0.30 (20% EtOAc in hexane)

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.03 (d, *J* = 8.3 Hz, 1H), 6.54 (d, *J* = 2.6 Hz, 1H), 6.51 (dd, *J* = 8.3, 2.63 Hz, 1H), 5.69 (brs, 1H), 3.44 (q, *J* = 7.1 Hz, 2H), 3.25 (t, *J* = 6.6 Hz, 4H), 2.31 (s, 3H), 1.99 (quint, *J* = 6.6 Hz, 4H), 1.62–1.56 (m, 2H), 1.44–1.38 (m, 2H), 0.96 (t, *J* = 7.3 Hz, 3H).
^{13}C NMR (100 MHz, $CDCl_3$): δ 170.9, 146.1, 137.5, 131.6, 121.4, 113.1, 109.9, 47.8, 39.5, 31.8, 25.4, 20.2, 18.5, 13.8.
HRMS (ESI$^+$): *m/z*: $[M + H]^+$ calculated for$C_{16}H_{25}N_2O$: 261.1967, found 261.1963

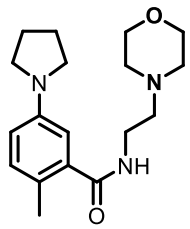
2-Methyl-*N*-pentyl-5-(pyrrolidin-1-yl)benzamide (2e): General procedure was followed with **1a** (75.0 mg, 0.6 mmol), pyrrolidine (43 µL, 0.5 mmol) and 1-pentyl isocyanide (75 µL, 0.6 mmol) at room temperature for 12 h to furnish **2e** as a white solid (98 mg, 0.36 mmol, 71% yield).



Purification: Silica gel Flash chromatography, eluted with 15% EtOAc in hexane
R_f 0.30 (20% EtOAc in hexane)

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.03 (d, *J* = 8.1 Hz, 1H,), 6.54 (d, *J* = 2.6 Hz, 1H), 6.52 (dd, *J* =8.3, 2.6 Hz, 1H), 5.69 (brs, 1H), 3.42 (q, *J* = 7.1 Hz, 2H), 3.25 (t, *J* = 6.6 Hz, 4H), 2.31 (s, 3H), 2.00 (q, *J* =6.6, 3.3 Hz, 4H), 1.63–1.60 (m, 2H), 1.40–1.34 (m, 4H), 0.91 (t, *J* = 7.1 Hz, 3H).
^{13}C NMR (100 MHz, $CDCl_3$): δ 170.9, 146.1, 137.5, 131.6, 121.4, 113.1, 110.0, 47.8, 39.8, 29.4, 29.1, 25.4, 22.4, 18.5, 14.0.
HRMS (ESI$^+$): *m/z*: $[M + H]^+$ calculated for $C_{17}H_{27}N_2O$: 275.2123, found 275.2115.

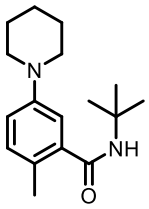
2-Methyl-N-(2-morpholinoethyl)-5-(pyrrolidin-1-yl)benzamide (2f): General procedure was followed with **1a** (76.0 mg, 0.6 mmol), pyrrolidine (42 µL, 0.5 mmol) and 2-morpholinoethyl isocyanide (84 µL, 0.6 mmol) at room temperature for 12 h to furnish **2f** as a pale yellow solid (108 mg, 0.34 mmol, 68% yield).



Purification: Silica gel Flash chromatography, eluted with 30% acetone in hexane
R_f 0.30 (30% Acetone in hexane)

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.05 (d, *J* = 8.3 Hz, 1H), 6.67–6.50 (m, 2H), 6.36 (brs, 1H), 3.69 (t, *J* = 4.6 Hz, 4H), 3.55 (q, *J* = 4.5 Hz, 2H), 3.26 (t, *J* = 6.6 Hz, 4H), 2.58 (t, *J* = 6.0 Hz, 2H), 2.50 (t, *J* = 4.2 Hz, 4H), 2.33 (s, 3H), 2.00 (dt, *J* = 6.6, 3.4 Hz, 4H).
^{13}C NMR (100 MHz, $CDCl_3$): δ 170.8, 146.2, 137.2, 131.7, 121.5, 113.2, 110.3, 66.8, 57.1, 53.5, 53.3, 47.8, 35.8, 25.4, 18.7.
HRMS (ESI$^+$): *m/z*: $[M+H]^+$ calculated for $C_{18}H_{28}N_3O_2$: 318.2182, found 318.2175.

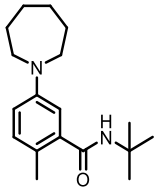
***N*-(*tert*-Butyl)-2-methyl-5-(piperidin-1-yl)benzamide (2g):** General procedure was followed with **1a** (75.0 mg, 0.6 mmol), piperidine (50 µL, 0.5 mmol) and *tert*-butyl isocyanide (68 µL, 0.6 mmol) at 60 °C for 14 h to furnish **2g** as a white solid (89 mg, 0.32 mmol, 65% yield).



Purification: Silica gel Flash chromatograph, eluted with 10% EtOAc in hexane
R_f 0.50 (20% EtOAc in hexane)

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.05 (d, *J* = 8.4 Hz, 1H), 6.90 (d, *J* = 2.6 Hz, 1H), 6.86 (dd, *J* = 8.4, 2.7 Hz, 1H), 5.52 (brs, 1H), 3.10 (t, *J* = 5.6 Hz, 4H), 2.32 (s, 3H), 1.72–1.68 (m, 4H), 1.58–1.54 (m, 2H), 1.45 (s, 9H).
^{13}C NMR (100 MHz, $CDCl_3$): δ 170.0, 138.5, 131.4, 117.9, 115.3, 51.7, 29.7, 28.9, 25.8, 24.1, 18.6.
HRMS (ESI$^+$): *m/z*: $[M + H]^+$ calculated for $C_{17}H_{27}N_2O$: 275.2123, found 275.2116.

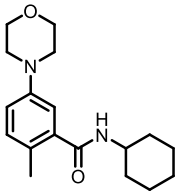
5-(Azepan-1-yl)-*N*-(tert-butyl)-2-methylbenzamide (2h): General procedure was followed with **1a** (75.0 mg, 0.6 mmol), azepane (56 µL, 0.5 mmol) and *tert*-butyl isocyanide (68 µL, 0.6 mmol) at 60 °C for 14 h to furnish **2h** as a white solid (79 mg, 0.27 mmol, 55% yield).



Purification: Silica gel Flash chromatography, eluted with 20% EtOAc in hexane
R_f 0.20 (20% EtOAc in hexane)

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.99 (d, *J* = 8.4 Hz, 1H), 6.64 (d, *J* = 2.7 Hz, 1H), 6.61 (dd, *J* = 8.4, 2.8 Hz, 1H), 5.53 (brs, 1H), 3.42 (t, *J* = 6.0 Hz, 4H), 2.28 (s, 3H), 1.80–1.73 (m, 4H), 1.55–1.50 (m, 4H), 1.46 (s, 9H).
^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 170.5, 147.0, 138.7, 131.6, 120.6, 112.3, 109.3, 51.6, 49.2, 28.9, 27.7, 27.1, 18.3.
HRMS (ESI$^+$): *m/z*: $[M + H]^+$ calculated for $C_{18}H_{29}N_2O$: 289.2280, found 289.2273.

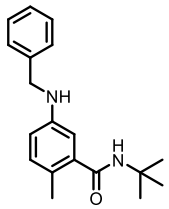
***N*-Cyclohexyl-2-methyl-5-morpholinobenzamide (2i):** General procedure was followed with **1a** (75.0 mg, 0.6 mmol), morpholine (45 µL, 0.5 mmol) and cyclohexyl isocyanide (75 µL, 0.6 mmol) at 60 °C for 14 h to furnish **2i** as pale yellow solid (95 mg, 0.31 mmol, 63% yield).



Purification: Silica gel Flash chromatography, eluted with 10% EtOAc in hexane
R_f 0.50 (20% EtOAc in hexane)

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.10 (d, *J* = 8.4 Hz, 1H), 6.88 (d, *J* = 2.7 Hz, 1H), 6.85 (dd, *J* = 8.3, 2.7 Hz, 1H), 5.57 (brs, 1H), 4.02–3.91 (m, 1H), 3.85 (t, *J* = 4.7 Hz, 4H), 3.11 (t, *J* = 4.9 Hz, 4H), 2.33 (s, 3H), 2.06–2.02 (m, 2H), 1.77–1.71 (m, 2H), 1.65–1.61 (m, 3H), 1.26–1.19 (m, 3H).
^{13}C NMR (100 MHz, $CDCl_3$): δ 169.5, 149.4, 137.8, 131.6, 126.5, 117.2, 114.3, 66.8, 49.6, 48.5, 33.2, 25.5, 24.8, 18.6.
HRMS (ESI$^+$): *m/z*: $[M + H]^+$ calculated for $C_{18}H_{27}N_2O$: 303.2073, found 303.2060.

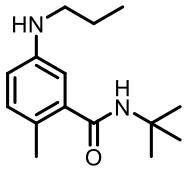
5-(Benzylamino)-*N*-(tert-butyl)-2-methylbenzamide (2j): General procedure was followed with **1a** (75.0 mg, 0.6mmol), benzyl amine (55 µL, 0.5 mmol) and *tert*-butyl isocyanide (68 µL, 0.6 mmol) at room temperature for 12 h to furnish **2j** as a white solid (90 mg, 0.31 mmol, 61% yield).



Purification: Silica gel Flash chromatography, eluted with 10% EtOAc in hexane
R_f 0.50 (20% EtOAc in hexane)

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34–7.28 (m, 5H), 6.97 (d, *J* = 8.2, 1H), 6.59 (d, *J* = 2.58 Hz, 1H), 7.62–7.54 (m, 2H), 5.47 (brs, 1H), 4.31 (s, 2H), 2.29 (s, 3H), 1.43 (s, 9H), 1.26 (brs, 1H).
^{13}C NMR (100 MHz, $CDCl_3$): δ 169.9, 146.0, 139.3, 138.5, 131.6, 128.7, 127.5, 127.3, 123.7, 114.0, 111.2, 51.6, 48.5, 28.9, 18.5.
HRMS (ESI$^+$): *m/z*: $[M + H]^+$ calculated for $C_{19}H_{25}N_2O$: 297.1967, found 297.1962.

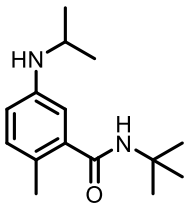
***N*-(*tert*-Butyl)-2-methyl-5-(propylamino)benzamide (2k):** General procedure was followed with **1a** (75.0 mg, 0.6 mmol), propylamine (41 µL, 0.5 mmol) and *tert*-butyl isocyanide (68 µL, 0.6 mmol) at room temperature for 12 h to furnish **2k** as a pale yellow solid (92 mg, 0.38 mmol, 75% yield).



Purification: Silica gel Flash chromatography, eluted with 15% EtOAc in hexane
R_f 0.30 (20% EtOAc in hexane)

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.97 (d, *J* = 8.3 Hz, 1H), 6.57 (d, *J* = 2.6 Hz, 1H), 6.54 (dd, *J* = 8.2, 2.6 Hz, 1H), 5.51 (brs, 1H), 3.06 (t, *J* = 7.3 Hz, 2H), 2.29 (s, 3H), 1.62 (pseudo q, *J* = 7.3, 2H), 1.45 (s, 9H), 1.26 (brs, 1H), 0.99 (t, *J* = 7.3 Hz, 3H).
^{13}C NMR (100 MHz, $CDCl_3$): δ 170.1, 146.4, 138.6, 131.5, 123.0, 113.9, 111.0, 51.6, 46.0, 28.9, 22.7, 18.5, 11.6.
HRMS (ESI$^+$): *m/z*: $[M + H]^+$ calculated for $C_{15}H_{25}N_2O$: 249.1967, found 249.1957.

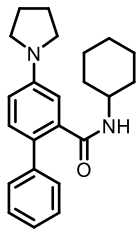
N*-(*tert*-Butyl)-5-(isopropylamino)-2-methylbenzamide (2*l*):** General procedure was followed with **1a** (75.0 mg, 0.6 mmol), isopropyl amine (42.7, 0.5 mmol) and *tert*-butyl isocyanide (68.2 µL, 0.6 mmol) at room temperature for 14 h to furnish ***2l as a white solid (89 mg, 0.36 mmol, 72% yield).



Purification: Silica gel Flash chromatography, eluted with 15% EtOAc in hexane
R_f 0.30 (20% EtOAc in hexane)

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.97 (d, *J* = 8.2 Hz, 1H), 6.57–6.51 (m, 2H), 5.51 (brs, 1H), 3.65–3.56 (m, 1H), 2.28 (s, 3H), 1.45 (s, 9H), 1.26 (brs, 1H), 1.18 (t, *J* = 6.3 Hz, 6H).
^{13}C NMR (100 MHz, $CDCl_3$): δ 170.0, 145.1, 138.7, 131.6, 123.3, 114.7, 112.0, 51.6, 44.7, 28.9, 22.9, 18.5.
HRMS (ESI$^+$): *m/z*: $[M + H]^+$ calculated for $C_{15}H_{25}N_2O$: 249.1967, found 249.1961.

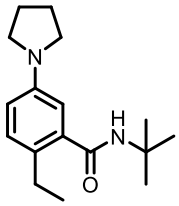
***N*-Cyclohexyl-4-(pyrrolidin-1-yl)-[1,1'-biphenyl]-2-carboxamide (2m):** General procedure was followed with 1-hydroxy-[1,1'-biphenyl]-4(1H)-one (111.6 mg, 0.6 mmol), pyrrolidine (42 µL, 0.5 mmol) and cyclohexylisocyanide (73 µL, 0.6 mmol) at room temperature for 12 h to furnish **2m** as a white solid (101 mg, 0.29 mmol, 58% yield).



Purification: Silica gel Flash chromatography, eluted with 20% EtOAc in hexane
R_f 0.30 (20% EtOAc in hexane).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37–7.29 (m, 5H), 7.21 (d, *J* = 8.5 Hz, 1H), 6.90 (d, *J* = 2.6 Hz, 1H), 6.65 (dd, *J* = 8.5, 2.6 Hz, 1H), 5.04 (brs, 1H), 3.77–3.70 (m, 1H), 3.34 (t, *J* = 6.7 Hz, 4H), 2.02 (quint, *J* = 6.7, 3.3 Hz, 4H), 1.64–1.57 (m, 4H), 1.50–1.42 (m, 3H), 1.24–1.21 (m, 3H).
^{13}C NMR (100 MHz, $CDCl_3$): δ 169.1, 147.3, 136.8, 131.1, 128.9, 128.4, 126.7, 113.1, 111.7, 48.1, 47.7, 32.4, 25.5, 25.4, 24.5.
HRMS (ESI$^+$): *m/z*: $[M+H]^+$ calculated for $C_{23}H_{29}N_2O$: 349.2280, found 249.2271.

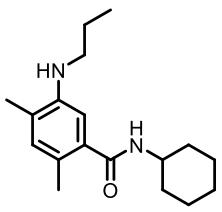
***N*-(*tert*-Butyl)-2-ethyl-5-(pyrrolidin-1-yl)benzamide (2n):** General procedure was followed with 4-ethyl-4-hydroxycyclohexa-2,5-dien-1-one (83 mg, 0.6 mmol), pyrrolidine (42 µL, 0.5 mmol) and *tert*-butylisocyanide (69 µL, 0.6 mmol) at room temperature for 12 h to furnish **2n** as a white solid (103 mg, 0.37 mmol, 75% yield).



Purification: Silica gel Flash chromatography, eluted with 10% EtOAc in hexane
R_f 0.50 (10% EtOAc in hexane)

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.06 (d, *J* = 8.4 Hz, 1H), 6.53 (dd, *J* = 8.4, 2.3 Hz,1H), 6.48 (d, *J* = 2.3 Hz, 1H), 5.56 (brs, 1H), 3.26 (t, *J* = 6.8 Hz, 4H), 2.66 (q, *J* = 7.7 Hz, 2H), 1.99 (quint, *J* = 6.5, 3.3 Hz, 4H), 1.46 (s, 9H), 1.19 (t, *J* = 7.4 Hz, 3H).
^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 170.6, 146.1, 138.3, 130.0, 127.7, 112.9, 109.7, 51.6, 47.8, 29.7, 28.8, 25.4, 16.3.
HRMS (ESI$^+$): *m/z*: $[M + H]^+$ calculated for $C_{17}H_{27}N_2O$: 275.2123, found 275.2115.

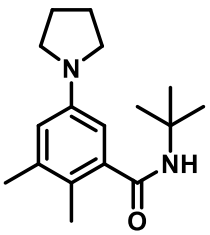
***N*-Cyclohexyl-2,4-dimethyl-5-(propylamino)benzamide (2o):** General procedure was followed with 4-hydroxy-2,4-dimethylcyclohexa-2,5-dien-1-One (83 mg, 0.6 mmol), propyl amine (41 µL, 0.5 mmol) and cyclohexyl isocyanide (73 µL, 0.6 mmol) at 60 °C for 14 h to furnish **2o** as a thick liquid (104 mg, 0.36 mmol, 72% yield).



Purification: Silica gel Flash chromatography, eluted with 10% EtOAc in hexane
R_f 0.50 (20% EtOAc in hexane)

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.87 (s, 1H), 6.60 (s, 1H), 5.57 (d, *J* = 7.4 Hz, 1H), 4.00–3.93 (m, 1H), 3.11 (t, *J* = 7.0 Hz, 2H), 2.29 (s, 3H), 2.11 (s, 3H), 2.07–2.00 (m, 2H), 1.77–1.70 (m, 2H), 1.67 (q, *J* = 7.01 Hz, 2H), 1.46–1.40 (m, 2H), 1.27–1.16 (m, 4H), 1.01 (t, *J* = 7.4 Hz, 3H).
^{13}C NMR (100 MHz, $CDCl_3$): δ 169.9, 144.2, 135.5, 132.6, 123.7, 122.9, 108.4, 48.4, 46.0, 33.2, 25.6, 24.8, 22.7, 18.6, 17.2, 11.6.
HRMS (ESI$^+$): *m/z*: $[M + H]^+$ calculated for $C_{18}H_{29}N_2O$: 289.2280, found 289.2272.

***N*-(tert-butyl)-2,3-dimethyl-5-(pyrrolidin-1-yl)benzamide (2p):** General procedure was followed with 4-hydroxy-3,4-dimethylcyclohexa-2,5-dien-1-One (83 mg, 0.6 mmol), pyrrolidine (42 µL, 0.5 mmol) and cyclohexyl isocyanide (73 µL, 0.6 mmol) at 60 °C for 14 h to furnish **2p** as a thick liquid (97 mg, 0.35 mmol, 71% yield).



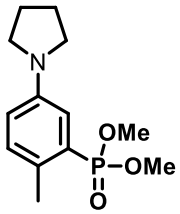
Purification: Silica gel Flash chromatography, eluted with 10% EtOAc in hexane
R_f 0.50 (20% EtOAc in hexane)

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.41 (d, *J* = 2.45 Hz, 1H), 6.34 (d, *J* = 2.55 Hz, 1H), 5.51 (brs, 1H), 3.24 (t, *J* = 6.58 Hz, 4H), 2.23 (s, 3H), 2.18 (s, 3H), 1.98 (dt, *J* = 6.6, 3.4 Hz, 4H), 1.45 (s, 9H).
^{13}C NMR (100 MHz, $CDCl_3$): δ 171.1, 146.0, 139.4, 138.3, 119.5, 114.3, 107.4, 51.6, 47.8, 28.9, 25.4, 20.6, 15.0.
HRMS (ESI$^+$): *m/z*: $[M+H]^+$ calculated for $C_{17}H_{27}N_2O$: 275.2123, found 275.2114.

[5] Synthesis and spectral data of 3-amino arylphosphonates (4)

General Procedure for the synthesis of 3-amino arylphosphonates (run 5, Table 2):
To the reaction vial, acid (20 mol%) was added to the mixture of *p*-quinol-methyl ether (**3a**, 0.6 mmol), amine (0.5 mmol), and trialkyl phosphite (0.6 mmol) in methanol or acetonitrile (2.5 mL). After the completion of reaction with reference to *p*-quinol, (monitored by TLC), solvent was evaporated and re-dissolved in ethyl acetate and extracted with aq. $NaHCO_3$. Aqueous layer was again washed and partitioned with ethyl acetate for two time. Organic extracts were dried over sodium sulfate and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography as mentioned for individuals. Yields are calculated based on corresponding amines.

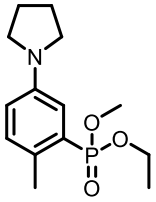
Dimethyl (2-methyl-5-(pyrrolidin-1-yl)phenyl)phosphonate (4a): General procedure was followed with **3a** (83 mg, 0.6 mmol), pyrrolidine (42 µL, 0.5 mmol) and trimethyl phosphite (72 µL, 0.6 mmol) at room temperature for 12 h to furnish **4a** as a thick oil (114 mg, 0.43 mmol, 85% yield).



Purification: Silica gel Flash chromatography, eluted with 30% EtOAc in hexane
R_f 0.30 (30% EtOAc in hexane)

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.15–7.07 (m, 2H), 6.63 (dd, *J* = 8.3, 2.6 Hz, 1H), 3.74 (d, *J* = 11.2 Hz, 6H), 3.29 (t, *J* = 6.6 Hz, 4H), 2.41 (d, *J* = 1.5 Hz, 3H), 2.02–1.98 (m, 4H).
^{13}C NMR (100 MHz, $CDCl_3$): δ 145.7 (d, *J* (C,P) = 17.5 Hz), 132.1 (d, *J* (C,P) = 17.5 Hz), 127.3 (d, *J* (C,P) = 9.8 Hz), 125.2 (d, *J* (C,P) = 179.9 Hz), 117.3 (d, *J* (C,P) = 12.7 Hz), 115.7, 52.3 (d, *J* (C,P) = 5.5 Hz), 47.7, 25.4, 19.8 (d, *J* (C,P) = 3.3 Hz).
^{31}P NMR (162 MHz, $CDCl_3$): δ 24.20.
HRMS (ESI$^+$): *m/z*: $[M + H]^+$ calculated for $C_{13}H_{21}NO_3P$: 270.1259, found 270.1250

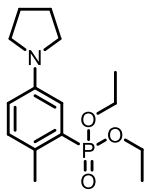
Ethyl methyl (2-methyl-5-(pyrrolidin-1-yl)phenyl)phosphonate (4b): General procedure was followed with **3a** (83 mg, 0.6 mmol), pyrrolidine (42 µL, 0.5 mmol) and triethyl phosphite (103 µL, 0.6 mmol) at room temperature for 11 h to furnish **4b** as a thick oil (108 mg, 0.38 mmol, 76% yield).



Purification: Silica gel Flash chromatography, eluted with 30% EtOAc in hexane
R_f 0.30 (30% EtOAc in hexane)

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.16–7.07 (m, 2H), 6.64–6.61 (m, 1H), 4.17–4.04 (m, 2H), 3.74 (dd, *J* = 11.2, 6.4 Hz, 3H), 3.29 (t, *J* = 6.6 Hz, 4H), 2.42 (td, *J* = 4.5, 1.5 Hz, 3H), 2.00 (quint, *J* = 6.5, 3.3 Hz, 4H), 1.34–1.30 (m, 3H).
^{13}C NMR (100 MHz, $CDCl_3$): δ 145.7 (d, *J* (C,P) = 18.1 Hz), 132.0 (d, *J* (C,P) = 19.2 Hz), 127.3 (d, *J* (C,P) = 9.0 Hz), 125.8 (d, *J* (C,P) = 180.1 Hz), 117.2 (d, *J* (C,P) = 12.4 Hz), 115.5 (d, *J* (C,P) = 3.1 Hz), 61.7 (d, *J* (C,P) = 5.2 Hz), 52.2 (d, *J* (C,P) = 5.7 Hz), 47.7, 25.4, 19.8 (d, *J* (C,P) = 4.0 Hz), 16.3 (d, *J* (C,P) = 6.6 Hz).
^{31}P NMR (162 MHz, $CDCl_3$): δ 22.66.
HRMS (ESI^+): *m/z*: $[M+H]^+$ calculated for $C_{14}H_{23}NO_3P$: 284.1416, found 284.1410

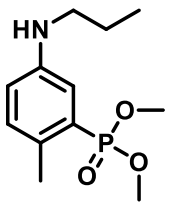
Diethyl (2-methyl-5-(pyrrolidin-1-yl)phenyl)phosphonate (4c): General procedure was followed with **3a** (83.0 mg, 0.6mmol), pyrrolidine (43 µL, 0.5 mmol) and triethyl phosphite (103 mg, 0.6 mmol) in acetonitrile at room temperature for 12 h to furnish **4c** as a thick oil (116 mg, 0.39 mmol, 78% yield).



Purification: Silica gel Flash chromatography, eluted with 30% EtOAc in hexane
R_f 0.20 (30% EtOAc in hexane)

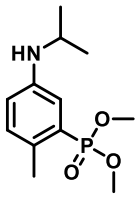
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.08 (dd, *J* = 16.3, 2.8 Hz, 1H), 7.01 (dd, *J* = 7.9, 7.0 Hz, 1H), 6.54 (dd, *J* = 8.3, 2.6 Hz, 1H), 4.16–3.91 (m, 4H), 3.21 (dd, *J* = 7.7, 5.5 Hz, 4H), 2.36 (d, *J* = 1.5 Hz, 3H), 1.96–1.89 (m, 4H), 1.25 (t, *J* = 7.1 Hz, 6H).
^{13}C NMR (100 MHz, $CDCl_3$): δ 145.6 (d, *J* (C,P) = 17.7 Hz), 132.0 (d, *J* (C,P) = 17.2 Hz), 126.6 (d, *J* (C,P) = 180.4 Hz), 119.2, 117.3 (d, *J* (C,P) = 12.8 Hz), 115.5, 61.7 (d, *J* (C,P) = 5.2 Hz), 47.8, 25.4, 19.9 (d, *J* (C,P) = 3.4 Hz), 16.3 (d, *J* (C,P) = 6.6 Hz).
^{31}P NMR (162 MHz, $CDCl_3$): δ 21.08
HRMS (ESI^+):*m/z*: $[M+H]^+$ calculated for $C_{15}H_{25}NO_3P$: 298.1572, found 298.1565

Dimethyl (2-methyl-5-(propylamino)phenyl)phosphonate (4d): General procedure was followed with **3a** (83 mg, 0.6 mmol), propylamine (42 µL, 0.5 mmol) and trimethyl phosphite (72 µL, 0.6 mmol) at room temperature for 15 h to furnish **4d** as a thick oil (96 mg, 0.38 mmol, 75% yield).
Purification: Silica gel Flash chromatography, eluted with 30% EtOAc in hexane
R_f 0.30 (30% EtOAc in hexane)



^{1}H NMR (400 MHz, $CDCl_3$): δ 7.11 (dd, *J* = 16.0, 2.7 Hz, 1H), 7.04–6.92 (m, 1H), 6.60 (dd, *J* = 8.2, 2.5 Hz, 1H), 3.67 (d, *J* = 11.2 Hz, 6H), 3.01 (t, *J* = 7.1 Hz, 2H), 2.32 (d, *J* = 1.5 Hz, 3H), 1.61 – 1.51 (m, 2H), 0.92 (t, *J* = 7.4 Hz, 3H).
^{13}C NMR (100 MHz, $CDCl_3$): δ 146.1 (d, *J* (C,P) = 17.2 Hz), 132.2 (d, *J* (C,P) = 17.4 Hz), 129.3 (d, *J* (C,P) = 9.6 Hz), 125.5 (d, *J* (C,P) = 182.0 Hz), 118.7(d, *J* (C,P) = 11.7 Hz), 116.6(d, *J* (C,P) = 3.1 Hz), 52.3 (d, *J* (C,P) = 5.4 Hz), 45.9, 22.7, 19.9 (d, *J* (C,P) = 3.4 Hz), 11.6.
^{31}P NMR (162 MHz, $CDCl_3$): δ 23.68.
HRMS (ESI^+): *m/z*: $[M+H]^+$ calculated for $C_{12}H_{21}NO_3P$: 258.1259, found 254.1254

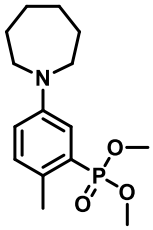
Dimethyl (5-(isopropylamino)-2-methylphenyl)phosphonate (4e): General procedure was followed with **3a** (82.8 mg, 0.6mmol), isopropyl amine (42.7 µL, 0.5 mmol) and trimethyl phosphite (71 mg, 0.6 mmol) at room temperature for 15 h to furnish **4e** as a thick oil (83 mg, 0.32 mmol, 65% yield).



Purification: Silica gel Flash chromatography, eluted with 30% EtOAc in hexane
R_f 0.30 (30% EtOAc in hexane)

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.16 (dd, *J* = 16.0, 2.7 Hz, 1H), 7.08 –7.01 (m, 1H), 6.66 (dd, *J* = 8.2, 2.5 Hz, 1H), 3.74 (d, *J* = 11.2 Hz, 6H), 3.64 (m, 1H), 2.39 (d, *J* = 1.5 Hz, 3H), 1.26 (brs, 1H), 1.19 (d, *J* = 6.3 Hz, 6H).
^{13}C NMR (100 MHz, $CDCl_3$): δ 145.0 (d, *J* (C,P) = 17.5 Hz), 132.2 (d, *J* (C,P) = 17.0 Hz), 129.4 (d, *J* (C,P) = 9.6 Hz), 125.5 (d, *J* (C,P) = 181.8 Hz), 119.5 (d, *J* (C,P) = 12.0 Hz), 117.3 (d, *J* (C,P) = 2.8 Hz), 52.3 (d, *J* (C,P) = 5.4 Hz), 44.5, 22.9, 19.9 (d, *J* (C,P) = 3.3 Hz).
^{31}P NMR (162 MHz, $CDCl_3$): δ 23.54.
HRMS (ESI^+): *m/z*: $[M+H]^+$ calculated for $C_{12}H_{21}NO_3P$: 258.1259, found 258.1251

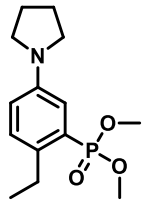
Dimethyl (5-(azepan-1-yl)-2-methylphenyl)phosphonate (4f): General procedure was followed with **3a** (82.8 mg, 0.6mmol), azepane (56 µL, 0.5 mmol) and trimethyl phosphite (72 µL, 0.6 mmol) at room temperature for 14 h to furnish **4f** as a thick oil (94 mg, 0.32 mmol, 63% yield).



Purification: Silica gel Flash chromatography, eluted with 30% EtOAc in hexane
R_f 0.30 (30% EtOAc in hexane)

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.22 (d, *J* = 2.8 Hz, 1H), 7.09–7.05 (m, 1H), 6.75 (dd, *J* = 8.3, 2.4 Hz, 1H), 3.75 (d, *J* = 11.2 Hz, 6H), 3.48–3.43 (m, 4H), 2.39 (s, 3H), 1.78 (s, 4H), 1.57–1.50 (m, 4H).
^{13}C NMR (100 MHz, $CDCl_3$): δ 146.5 (d, *J* (C,P) = 16.5 Hz), 132.3 (d, *J* (C,P) = 17.7 Hz), 127.1, 125.4 (d, *J* (C,P) = 181.8 Hz), 116.6 (d, *J* (C,P) = 12.8 Hz), 115.2, 52.3 (d, *J* (C,P) = 5.4 Hz), 49.1, 30.9, 29.7, 27.3, 19.7.
^{31}P NMR (162 MHz, $CDCl_3$): δ 24.32.
HRMS (ESI^+): *m/z*: $[M+H]^+$ calculated for $C_{15}H_{25}NO_3P$: 298.1572, found 298.1564

Dimethyl (2-ethyl-5-(pyrrolidin-1-yl)phenyl)phosphonate (4g): General procedure was followed with 4-ethyl-4-methoxycyclohexa-2,5-dien-1-one (**3b**, 91 mg, 0.6 mmol), pyrrolidine (42 µL, 0.5 mmol) and trimethyl phosphite (72 µL, 0.6 mmol) at room temperature for 15 h to furnish **4g** as a thick oil (106 mg, 75% yield).

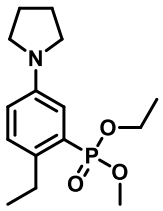


Purification: Silica gel Flash chromatography, eluted with 30% EtOAc in hexane
R_f 0.30 (30% EtOAc in hexane)

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.17 (dd, *J* = 8.4, 7.0 Hz, 1H), 7.10 (dd, *J* = 16.3, 2.7 Hz, 1H), 6.69 (dd, *J* = 8.4, 2.5 Hz, 1H), 3.75 (d, *J* = 11.2 Hz, 6H), 3.29 (dd, *J* = 7.7, 5.5 Hz, 4H), 2.83–2.77 (m, 2H), 2.02–1.98 (m, 4H), 1.19 (t, *J* = 7.5 Hz, 3H).
^{13}C NMR (100 MHz, $CDCl_3$): δ 145.5 (d, *J* (C,P) = 17.1 Hz), 134.0 (d, *J* (C,P) = 10.7 Hz), 130.5 (d, *J* (C,P) = 17.5 Hz), (d, *J* (C,P) = 17.7 Hz), 124.7 (d, *J* (C,P) = 181.1 Hz), 117.0 (d, *J* (C,P) = 12.8 Hz), 116.0 (d, *J* (C,P) = 3.2 Hz), 52.4 (d, *J* (C,P) = 5.7 Hz), 47.7, 26.1 (d, *J* (C,P) = 3.4 Hz), 25.4, 16.1.
^{31}P NMR (162 MHz, $CDCl_3$): δ 24.35.

HRMS (ESI$^+$): *m/z*: $[M+H]^+$ calculated for $C_{14}H_{23}NO_3P$: 284.1416, found 284.1406

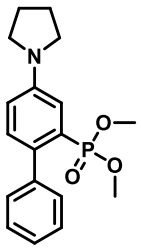
Ethyl methyl (2-ethyl-5-(pyrrolidin-1-yl)phenyl)phosphonate (4h): General procedure was followed with 4-ethyl-4-methoxycyclohexa-2,5-dien-1-one (92 mg, 0.6 mmol), pyrrolidine (42 µL, 0.5 mmol) and triethyl phosphite (103 µL, 0.6 mmol) at room temperature for 13 h to furnish **4h** as a thick oil (111 mg, 0.38 mmol, 75% yield).



Purification: Silica gel Flash chromatography, eluted with 30% EtOAc in hexane
R_f 0.20 (30% EtOAc in hexane)

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.13–6.99 (m, 2H), 6.61 (dt, *J* = 8.1, 2.6 Hz, 1H), 4.11–3.98 (m, 2H), 3.67 (dd, *J* = 11.2, 7.0 Hz, 3H), 3.22 (t, *J* = 6.6 Hz, 4H), 2.76 (dt, *J* = 13.9, 6.9 Hz, 2H), 1.95–1.90 (m, 4H), 1.28–1.23 (m, 3H), 1.13 (tt, *J* = 7.5, 2.0 Hz, 3H).
^{13}C NMR (100 MHz, $CDCl_3$): δ 145.5 (d, *J* (C,P) = 17.1 Hz), 130.5 (d, *J* (C,P) = 17.7 Hz), 130.4 (d, *J* (C,P) = 17.1 Hz), 125.4 (d, *J* (C,P) = 181.4 Hz), 116.9 (d, *J* (C,P) = 12.3 Hz), 115.8 (d, *J* (C,P) = 2.7 Hz), 61.9 (d, *J* (C,P) = 6.1 Hz), 52.2 (d, *J* (C,P) = 5.6 Hz), 47.7, 26.0 (d, *J* (C,P) = 3.8 Hz), 25.4, 16.3 (d, *J* (C,P) = 6.3 Hz), 16.1.
^{31}P NMR (162 MHz, CDCl3): δ 22.86.
HRMS (ESI$^+$): *m/z*: $[M+H]^+$ calculated for $C_{15}H_{25}NO_3P$: 298.1572, found 298.1565

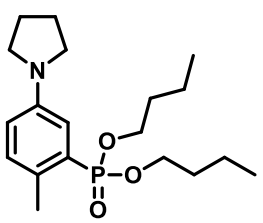
Dimethyl (4-(pyrrolidin-1-yl)-[1,1'-biphenyl]-2-yl)phosphonate (4i): General procedure was followed with 1-methoxy-[1,1'-biphenyl]-4(1H)-one (120 mg, 0.6 mmol), pyrrolidine (42 µL, 0.5 mmol) and trimethyl phosphite (74 µl, 0.6 mmol) at room temperature for 15 h to furnish **4i** as a thick oil (107 mg, 0.33 mmol, 65% yield).



Purification: Silica gel Flash chromatography, eluted with 10% EtOAc in hexane
R_f 0.50 (20% EtOAc in hexane)

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35 (m, 5H), 7.19 (m, 2H), 6.72 (dd, *J* = 8.4, 2.2 Hz, 1H), 3.49 (d, *J* = 11.2 Hz, 6H), 3.35 (t, *J* = 6.6 Hz, 4H), 2.06–2.00 (m, 4H).
^{13}C NMR (100 MHz, $CDCl_3$): δ 146.5 (d, *J* (C,P) = 16.4 Hz), 141.9 (d, *J* (C,P) = 4.2 Hz), 132.4 (d, *J* (C,P) = 9.8 Hz), 132.3 (d, *J* (C,P) = 16.1 Hz), 129.6, 127.4, 126.7, 125.6 (d, *J* (C,P) = 184.5 Hz), 116.8 (d, *J* (C,P) = 12.1 Hz), 114.9 (d, *J* (C,P) = 2.9 Hz), 52.2 (d, *J* (C,P) = 5.8 Hz), 47.7, 25.5.
^{31}P NMR (162 MHz, $CDCl_3$): δ 22.57.
HRMS (ESI$^+$): *m/z*: $[M+H]^+$ calculated for $C_{18}H_{23}NO_3P$: 332.1416, found 332.1408

Dibutyl (2-methyl-5-(pyrrolidin-1-yl)phenyl)phosphonate (4l): General procedure was followed with **3a** (82.8 mg, 0.6mmol), pyrrolidine (42 µL, 0.5 mmol) and tributyl phosphite (150 mg, 0.6 mmol) in acetonitrile at room temperature for 16 h to furnish **4l** as a thick oil (132 mg, 0.38 mmol, 75% yield).

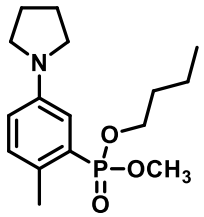


Purification: Silica gel Flash chromatography, eluted with 30% EtOAc in hexane
R_f 0.30 (30% EtOAc in hexane)

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.17-7.06 (m, 2H), 6.61 (dd, *J* = 8.30, 2.4 Hz, 1H), 4.09-4.03 (m, 2H), 4.01-3.95 (m, 2H), 3.28 (t, *J* = 6.5 Hz, 4H), 2.42 (d, *J* = 1.2 Hz, 3H), 2.00 (dt, *J* = 6.5, 3.3 Hz, 4H), 1.69-1.62 (m,

4H), 1.44-1.35 (m, 4H), 0.91 (t, *J* = 7.4, 6H).
^{13}C NMR (101 MHz, $CDCl_3$): δ 145.7 (d, *J* (C,P) = 17.0 Hz), 132.1 (d, *J* (C,P) = 17.0 Hz), 127.3 (d, *J* (C,P) = 9.4 Hz), 126.7 (d, *J* (C,P) = 180.4 Hz), 117.3 (d, *J* (C,P) = 12.5 Hz), 115.3, 65.4 (d, *J* (C,P) = 5.6 Hz), 47.7, 32.5 (d, *J* (C,P) = 6.7 Hz), 25.4, 19.9 (d, *J* (C,P) = 3.0 Hz), 18.8, 13.6.
^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ 21.21.
HRMS (ESI^+): *m/z*: $[M+H]^+$ calculated for $C_{19}H_{33}NO_3P$: 354.2198, found 354.2185.

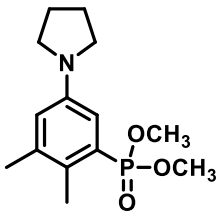
Butyl methyl (2-methyl-5-(pyrrolidin-1-yl)phenyl)phosphonate (4m): General procedure was followed with **3a** (82.8 mg, 0.6mmol), pyrrolidine (42 µL, 0.5 mmol) and tributyl phosphite (150 mg, 0.6 mmol) in methanol at room temperature for 14 h to furnish a mixture of arylphosphonates (**4l:4m:4a** = *ca* 2:2:1**)** as a thick oil. Pure **4m** was isolated as a thick liquid in 38% yield (59 mg, 0.19 mmol).



Purification: Silica gel Flash chromatography, eluted with 8-9% acetone in hexane
R_f 0.30 (30% EtOAc in hexane)

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.17-7.06 (m, 2H), 6.63 (dd, *J* = 8.4, 2.6 Hz, 1H), 4.12-3.97 (m, 2H), 3.72 (d, *J* = 11.2 Hz, 3H), 3.29 (t, *J* = 6.5 Hz, 4H), 2.41 (d, *J* = 1.4 Hz, 3H), 2.00 (dt, *J* = 6.6, 3.3 Hz, 4H), 1.71-1.61 (m, 2H), 1.44-1.36 (m, 2H), 0.91 (t, *J* = 7.3 Hz, 3H).
13C NMR (101 MHz, $CDCl_3$): δ 146.6 (d, *J* (C,P) = 17.0 Hz), 132.1 (d, *J* (C,P) = 17.3 Hz), 127.3 (d, *J* (C,P) = 9.4 Hz), 125.9 (d, *J* (C,P) = 180.5 Hz), 117.3 (d, *J* (C,P) = 12.6 Hz), 115.5, 65.3 (d, *J* (C,P) = 5.5 Hz), 52.1 (d, *J* (C,P) = 5.1 Hz), 47.2, 32.4 (d, *J* (C,P) = 6.6 Hz), 25.4, 19.8, 18.8, 13.6.
^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ 22.70.
HRMS (ESI^+): *m/z*: $[M+H]^+$ calculated for $C_{16}H_{27}NO_3P$: 312.1729, found 312.1716.

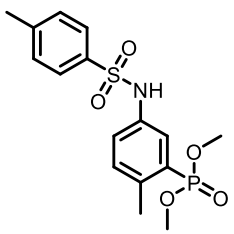
Dimethyl (2,3-dimethyl-5-(pyrrolidin-1-yl)phenyl)phosphonate (4o): General procedure was followed with 4-hydroxy-3,4-dimethylcyclohexa-2,5-dien-1-One (91 mg, 0.6 mmol), pyrrolidine (42 µL, 0.5 mmol) and trimethyl phosphite (74 µl, 0.6 mmol) at room temperature for 15 h to furnish **4o** as a thick oil (110 mg, 0.39 mmol, 78% yield).



Purification: Silica gel Flash chromatography, eluted with 10% EtOAc in hexane
R_f 0.50 (20% EtOAc in hexane)

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.02 (dd, *J* = 16.2, 2.6 Hz, 1H), 6.56 (d, *J* = 2.4 Hz, 1H), 3.74 (d, *J* = 11.3 Hz, 6H), 3.28 (t, *J* = 6.6 Hz, 4H), 2.33 (d, *J* = 1.7 Hz, 3H), 2.26 (s, 3H), 1.99 (dt, *J* = 6.6, 3.4 Hz, 4H).
13C NMR (101 MHz, $CDCl_3$): δ 145.5 (d, *J* (C,P) = 18.4 Hz), 138.8 (d, *J* (C,P) = 17.5 Hz), 126.0 (d, *J* (C,P) = 10.8 Hz), 125.6 (d, *J* (C,P) = 179.8 Hz), 117.6, 115.3 (d, *J* (C,P) = 12.5 Hz), 52.3 (d, *J* (C,P) = 5.2 Hz), 47.7, 25.4, 20.9, 16.2 (d, *J* (C,P) = 4.0 Hz).
^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ 25.02
HRMS (ESI^+): *m/z*: $[M+H]^+$ calculated for $C_{14}H_{23}NO_3P$: 284.1416, found 284.1399.

Dimethyl (2-methyl-5-((4-methylphenyl)sulfonamido)phenyl)phosphonate (4p): General procedure was followed with *N*-(4-methoxy-4-methylcyclohexa-2,5-dien-1-ylidene)-4-methylbenzenesulfonamide (145 mg, 0.5 mmol), synthesized with reported method[3] and trimethyl phosphite (73 µL, 0.6 mmol) in methanol at room temperature for 10 h to furnish **4p** as a thick oil (114 mg, 0.33 mmol, 62% yield).

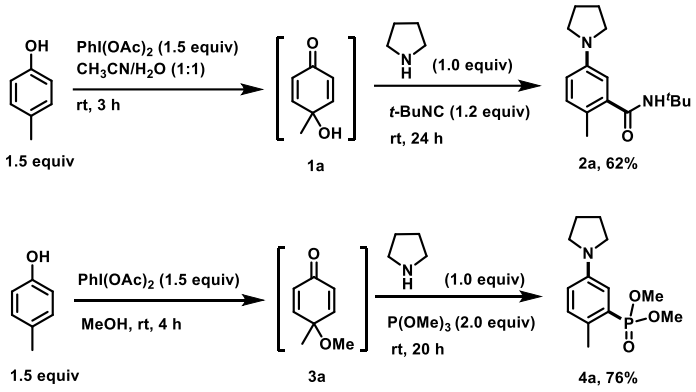


Purification: Silica gel Flash chromatography, eluted with 10% EtOAc in hexane
R_f 0.20 (20% EtOAc: hexane)

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.55 (s, 1H), 7.78 (dd, *J* = 15.9, 2.4 Hz, 1H), 7.74–7.70 (m, 2H), 7.55 (dd, *J* = 8.2, 1.9 Hz, 1H), 7.17 (dd, *J* = 9.5, 1.5 Hz, 2H), 7.16–7.10 (m, 1H), 3.77 (d, *J* = 11.2 Hz, 6H), 2.41 (d, *J* = 1.4 Hz, 3H), 2.34 (s, 3H).
^{13}C NMR (100 MHz, $CDCl_3$): δ 143.4, 136.9 (d, *J* (C,P) = 9.1 Hz), 136.8, 135.8 (d, *J* (C,P) = 19.0 Hz), 132.1 (d, *J* (C,P) = 16.7 Hz), 129.5, 127.2, 126.6 (d, *J* (C,P) = 9.1 Hz), 125.4 (d, *J* (C,P) = 183.7 Hz), 123.7 (d, *J* (C,P) = 2.9 Hz), 52.8 (d, *J* (C,P) = 5.9 Hz), 21.4, 20.3.
^{31}P NMR (162 MHz, $CDCl_3$): δ 21.95.
HRMS (ESI^+): *m/z*: $[M+H]^+$ calculated for $C_{16}H_{21}NO_5PS$: 370.0878, found 370.0867

[6] One-Pot Synthesis of 2a and 4a

Two-step one-pot synthesis of **2a** and **4a** was executed, starting from *p*-cresol by slightly modified conditions as described below (Scheme S1).



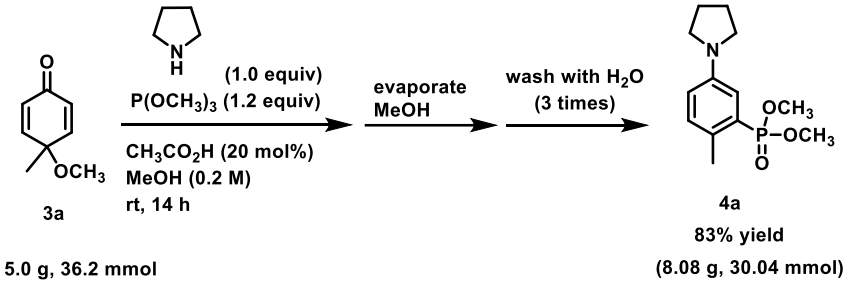
Scheme S1. Two-step one-pot synthesis of **2a** and **4a**

Synthesis of 3a: PIDA (483 mg, 1.5 mmol) was added to solution of *p*-cresol (162 mg, 1.5 mmol) in CH_3CN/H_2O (15 mL, 2:1) at 0 ºC and stirred at room temperature till completion of starting material (3 h). Pyrrolidine (84 µL, 1.0 mmol) followed by *tert*-butyl isocyanide (136 mg, 1.2 mmol) was added to the reaction mixture and the progress of reaction was monitored by TLC. After the completion of starting material (*p*-quinol, **1a**, 16 h), volatile material (CH_3CN) was evaporated and re-diluted with ethyl acetate and quenched with saturated aqueous $NaHCO_3$ solution to neutralize the acidic reaction mixture. Aqueous layer was extracted with ethyl acetate (3 x 20 mL) and combined organic layer was washed with brine and dried over anhyd. $NaSO_4$. Concentration under reduced pressure and purified further with FCC to yield **2a** (162 mg, 0.62 mmol, 62%) as a pure product.

Synthesis of 4a: PIDA (483 mg, 1.5 mmol) was added to solution of *p*-cresol (162 mg, 1.5 mmol) in methanol (10 mL) at 0 °C and stirred at room temperature till completion of starting material, *p*-cresol (4 h). To the stirring reaction mixture, pyrrolidine (85 µL, 1.0 mmol) and trimethyl phosphite (355 µL, 3.0 mmol) were added. After the completion of starting material (*p*-quinol methyl ether, **3a**, 20 h), methanol was evaporated completely and re-diluted with ethyl acetate and quenched with saturated aqueous $NaHCO_3$ solution to neutralize the acidic reaction mixture. Aqueous layer was extracted with ethyl acetate (3 x 20 mL) and combined organic layer was washed with brine and dried over anhyd. $NaSO_4$. Concentration under reduced pressure and purified further with FCC to yield **4a** (204 mg, 76%) as a pure product.

[7] Gram scale synthesis (free from Column Chromatography purification) for 4a

To a round bottom flask, acid (20 mol%) was added to the mixture of *p*-quinol-methyl ether (**3a**, 5.0 gm, 36.2 mmol), pyrrolidine (2.57 g, 1.0 equiv) and trimethylphosphite (5.39 g, 1.2 equiv) in methanol (200 mL). After the completion of reaction (monitored by TLC), methanol was completely distilled off and residue was washed with water (3 x 10 mL) to remove phosphorous materials and acetic acid and dried under high vacuum for 3h. Pure **4a** (8.08 g, 30.04 mmol, 83% yield) was obtained as a thick liquid. Here, we avoided the use of column chromatography.

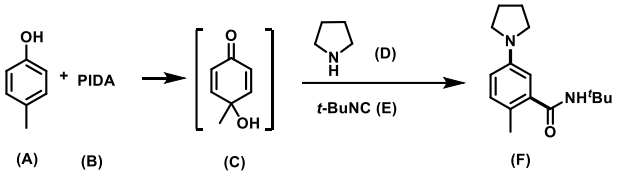


[8] Calculations of Green Chemistry Metrics

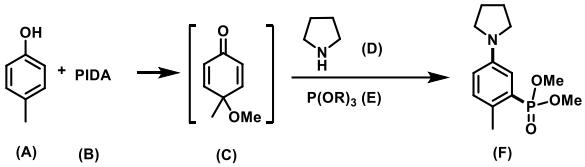
Basic Green Chemistry metrics[4] were calculated for some representative examples of synthesized compounds; 3-amino benzamide (**2a**) and 3-aminodiemthyl arylphosphonate (**4a**).

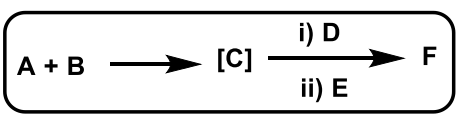
Green metrics calculations: Formulae used

For a **linear synthetic process:**

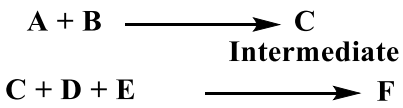


or





Steps involved in this process are:



The reactants and reagents efficiently participate in product formation excluding intermediates are:

1. No. of steps = No. of steps involved in the process
2. Atom economy = [(M.W. of product F)/ (M.W. of A+ M.W. of B+ M.W. of D+ M.W. of E)]x100
3. % yield = (Observed yield/ Calculated yield) x100
4. Atom efficiency = % yield x Atom economy
5. Carbon efficiency = [(no. of moles of product F x no. of carbons in product F)/ {(no. of moles of A x no. of carbons in A) + (no. of moles of B x no. of carbons in B) + (no. of moles of D x no. of carbons in D) + (no. of moles of E x no. of carbons in E)}]x100
6. Process Mass intensity = (Total mass used in the process / Mass of the product)
7. Mass productivity = (1/ Mass intensity) x100
8. E-factor = (Mass intensity – 1)
9. Effective Mass Yield = (1/ E-factor) x100
10. Reaction Mass Efficiency = [(Mass of product F) / (Mass of A + Mass of B + Mass of D + Mass of E)] x 100

a) Green Metrics Calculation for synthesis of 3-aminobenzamide (2a), starting from *p*-quinol (1a):

1. **No. of steps = 1**
2. Atom economy = [(260)/ (124+71.12+ 83.13)]x100 = [(260/338)]x100 = 76.92%
3. % yield = (0.40/ 0.5) x100 = 80%
4. Atom efficiency = (80/100) x 76.92 = 61.53
5. Carbon efficiency = [(0.40 x16)/{(0.6x7) + (0.5x4) + (0.6x5) + (0.1x2)}]x100
   = [(6.4/4.2+2.0+3.0 +0.2)]x100
   = (6.4/9.4) = 68.08%
6. Process mass intensity = (75+35.81+50.23+6.05+16.13 /105)
   = (182.22/105) = 1.74 kg/kg
7. Mass productivity = (1/1.74) x100 = 57.47%
8. E- factor = (1.74 – 1) = 0.74kg/kg
9. Effective Mass Yield = (1/ 0.74) x100 = 135%
10. Reaction Mass Efficiency = [(105) / (75+35.81+50.23+6.05)] x 100
    (105/137.09) x100 = 76.59%

b) Green Metrics Calculation for synthesis of 3-aminobenzamide (2a), starting from *p*-cresol:

1. **No. of steps = 2 (One pot)**
2. Atom economy = [(260)/ (108+ 322+ 71.12+ 83.13)]x100 = [(260/584.25)]x100 = 44.50%
3. % yield = (0.62/ 1.0) x100 = 62%
4. Atom efficiency = (62/100) x 44.50 = 27.59
5. Carbon efficiency = [(0.62 x16)/{(1.5x7) + (1.5x10) + (1.0x4) + (1.2x5)}]x100
   = [(9.92/10.5 + 15.0 + 4.0+6.0)]x100
   = (9.92/35.5) = 27.94%

6. Process mass intensity = (162.0+482.52+71.03+99.63+41.0+18.0 / 162.0)
= (874.18/162) = 5.40 kg/kg
7. Mass productivity = (1/5.40) x100 = 18.51%
8. E- factor = (5.41 – 1) = 4.40 kg/kg
9. Effective Mass Yield = (1/ 4.40) x100 = 22.72%
10. Reaction Mass Efficiency = [(162.0) / (162.0+482.52+71.03+99.63)] x 100
= (162/815.18) x100 = 19.87%

c) Green Metrics Calculation for synthesis of 3-aminoarylphosphonate (4a), starting from *p*-quinol-methylether (3a):

1. **No. of steps = 1**
2. Atom economy = [(269)/ (138+ 71+ 124+ 60)]x100 = [(269/393)]x100 = 68.44%
3. % yield = (0.43/ 0.5) x100 = 85%
4. Atom efficiency = (85/100) x 68.44 = 58.17
5. Carbon efficiency = [(0.43 x 13)/ {(0.60 x 8) +(0.50 x 4)+(0.60 x 3)+ (0.10 x 2)}]x100
= [(5.59/4.8058+2.0024+1.8022+0.20024)]x100
= (5.59/8.81) x100 = 63.45%
6. Process mass intensity = (83.00+35.60+74.54+6.01+16.04 /115)
= (215.19/115) = 1.87 kg/kg
7. Mass productivity = (1/ 1.87) x100 = 53.47%
8. E- factor = (1.87 – 1) = 0.87 kg/kg
9. Effective Mass Yield = (1/ 0.87) x100 = 114.94%
10. Reaction Mass Efficiency = [(115) / (83 + 35.60 + 74.54 + 6.01)] x 100
= (115/199.15) x100 = 57.74%

d) Green Metrics Calculation for synthesis of 3-aminoarylphosphonate (4a), starting from *p*-cresol:

1. **No. of steps = 2 (one pot)**
2. Atom economy = [(269)/ (108+ 322+ 71.12+ 124.08)]x100 = [(269/625.20)]x100 = 43.02%
3. % yield = (0.7575/ 1.0) x100 = 75.75%
4. Atom efficiency = (75.75/100) x 43.02 = 32.58
5. Carbon efficiency = [(0.7575 x13)/{(1.5x7) + (1.5x10)+ (1.0x4)+ (2.0x3)}]x100
= [(9.85/10.5+15.0+4.0+6.0)]x100
= (9.85/35.5) = 27.75%
6. Process mass intensity = (162+482.52+71.03+247.83+32.0/ 204)
= (995.38/204) = 4.88 kg/kg
7. Mass productivity = (1/4.88) x100 = 20.49%
8. E- factor = (4.88 – 1) = 3.88kg/kg
9. Effective Mass Yield = (1/ 3.88) x100 = 25.77%
10. Reaction Mass Efficiency = [(204) / (162 +482.52 + 71.03 +247.83)] x 100
= (204/963.38) x100 = 21.75%

e) Green Metrics Calculation for synthesis of 3-aminoarylphosphonate (4a), starting from *p*-quinol-methyl ether (3a):

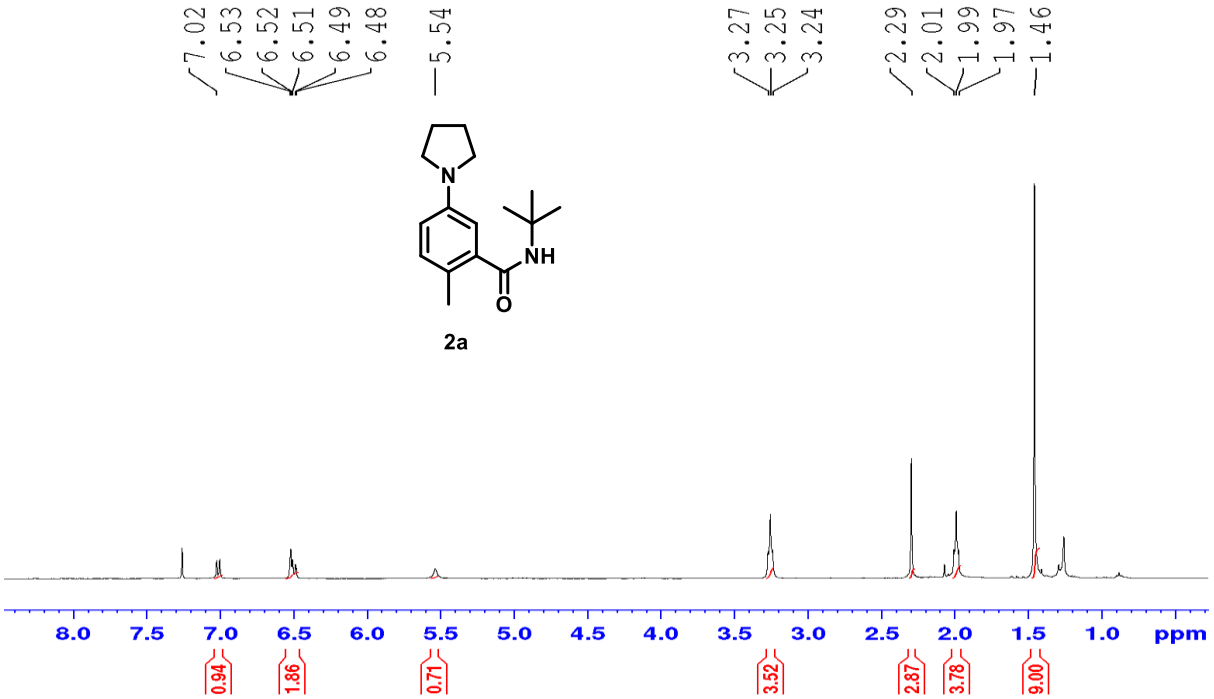
Multi-gram synthesis (5g), Purification without column chromatography
Consideration: *Methanol was distilled off after the reaction and reused. Thus, not included in calculation.*

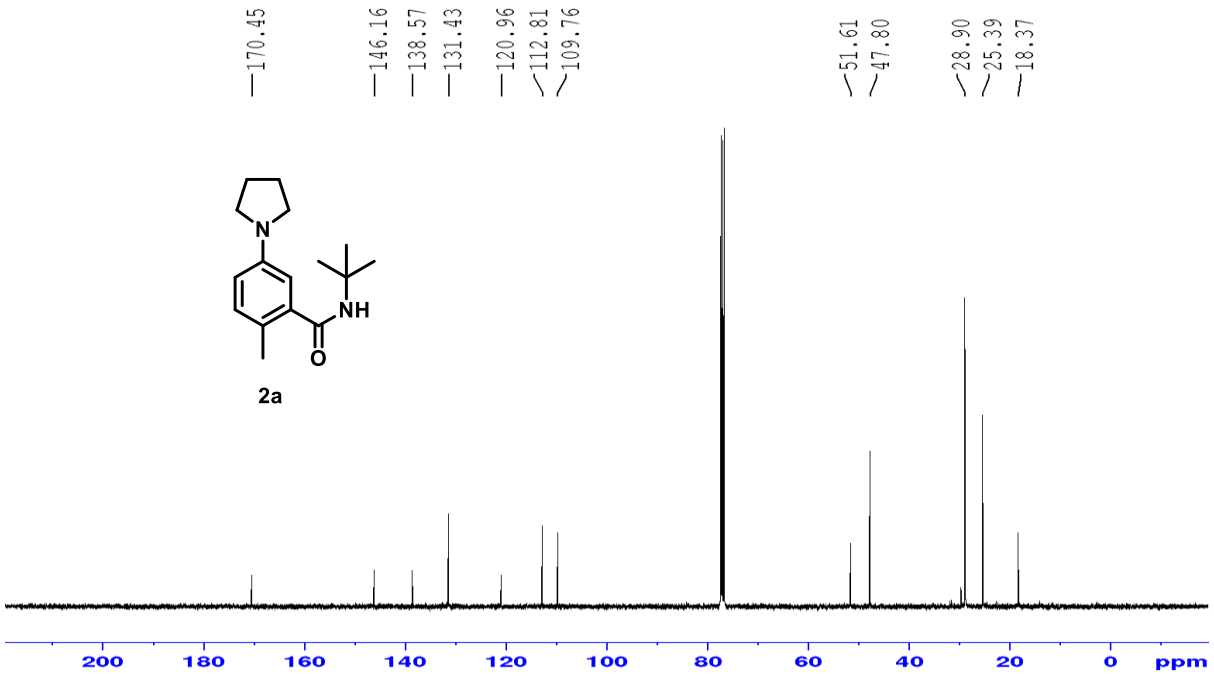
1. **No. of steps = 1**
2. Atom economy = [(269)/ (138+ 71+ 124+ 60)]x100 = [(269/393)]x100 = 68.44%
3. % yield = (30.01/ 36.19) x100 = 83.0%
4. Atom efficiency = (83/100) x 68.44 = 56.80
5. Carbon efficiency = [(30.01 x 13)/ {(36.19 x 8) +(36.19 x 4)+(43.43 x 3)+ (7.24 x 2)}]x100
   = [(390.13/289.52+144.76+130.29+14.48)]x100
   = (390.13/579.05) x100 = 67.37%
6. Process mass intensity = (5.0+2.57+5.39+0.434/8.08)
   = (13.39/8.08) = 1.65kg/kg
7. Mass productivity = (1/ 1.65) x100 = 60.6%
8. E- factor = (1.65 – 1) = 0.65kg/kg
9. Effective Mass Yield = (1/ 0.65) x100 = 154.0%
10. Reaction Mass Efficiency = [(8.08) / (5.0+2.57+5.39+0.434)] x 100
    = (8.08/13.39) x100 = 60.34%

[9] References:

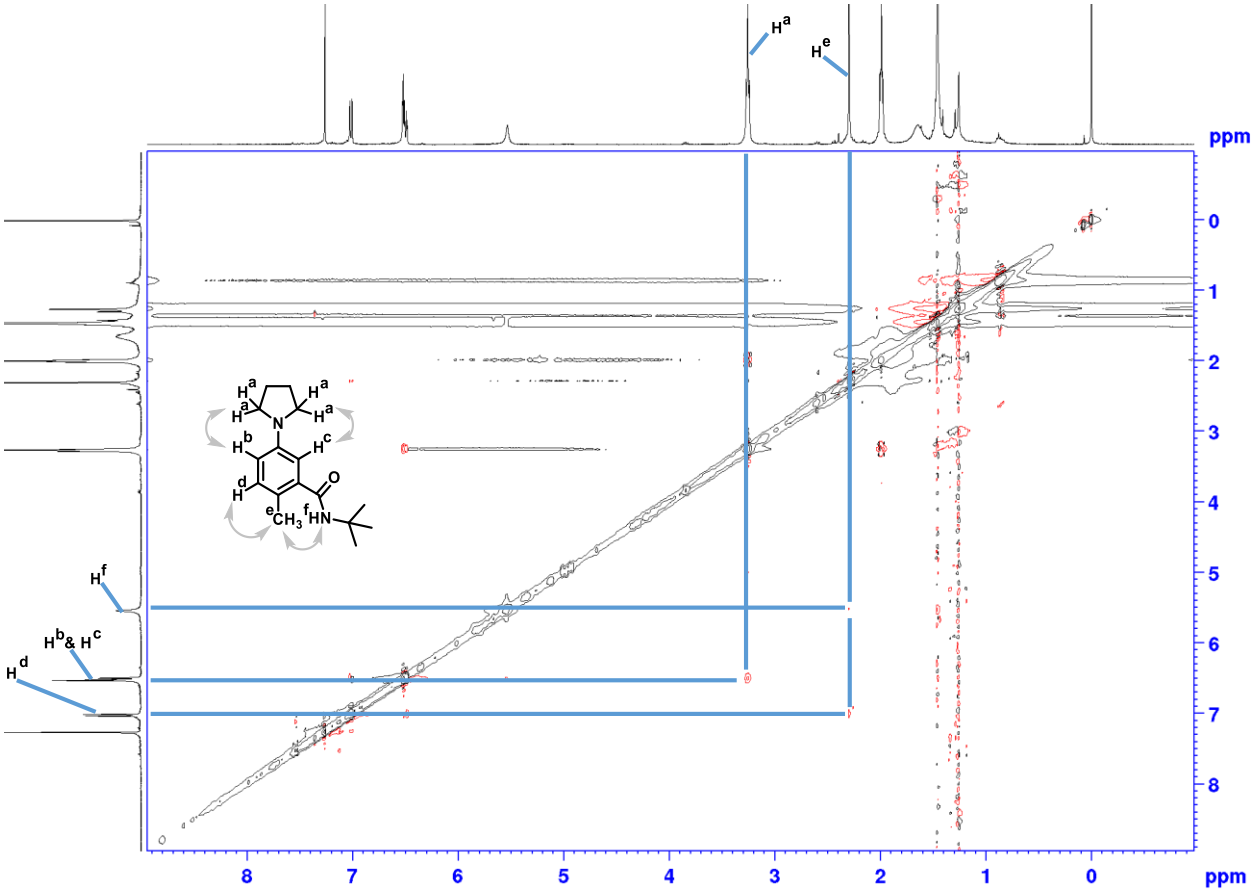
1. a) M. Novak, S. A. Glover, *J. Am. Chem. Soc.***2004**, *126*, 7748–7749; b) N. J. Green, C. A. Connolly, K. P. W. Rietdijk, G. S. Nichol, F. Duarte, A. L. Lawrence, Angew. Chem. Int. Ed. **2018**, *57*, 6198–6202.
2. Z.Xia,J.Hu,Z. Shen, Q. Yao, W.Xie, *RSC Advances*, **2015**, *5*, 38499–38502.
3. T. Liu, Y. Li, F. Cheng, X. Shen, J. Liu, J. Lin, *Green Chem.* **2019**, *21*, 3536–3541
4. a) David J. C. Constable, Alan D. Curzons and Virginia L. Cunningham, *Green Chem.*, **2002**, *4*, 521–527; b) Alan D. Curzons, David J. C. Constable, David N. Mortimer and Virginia L. Cunningham, *Green Chem.*, **2001**, *3*, 1–6.

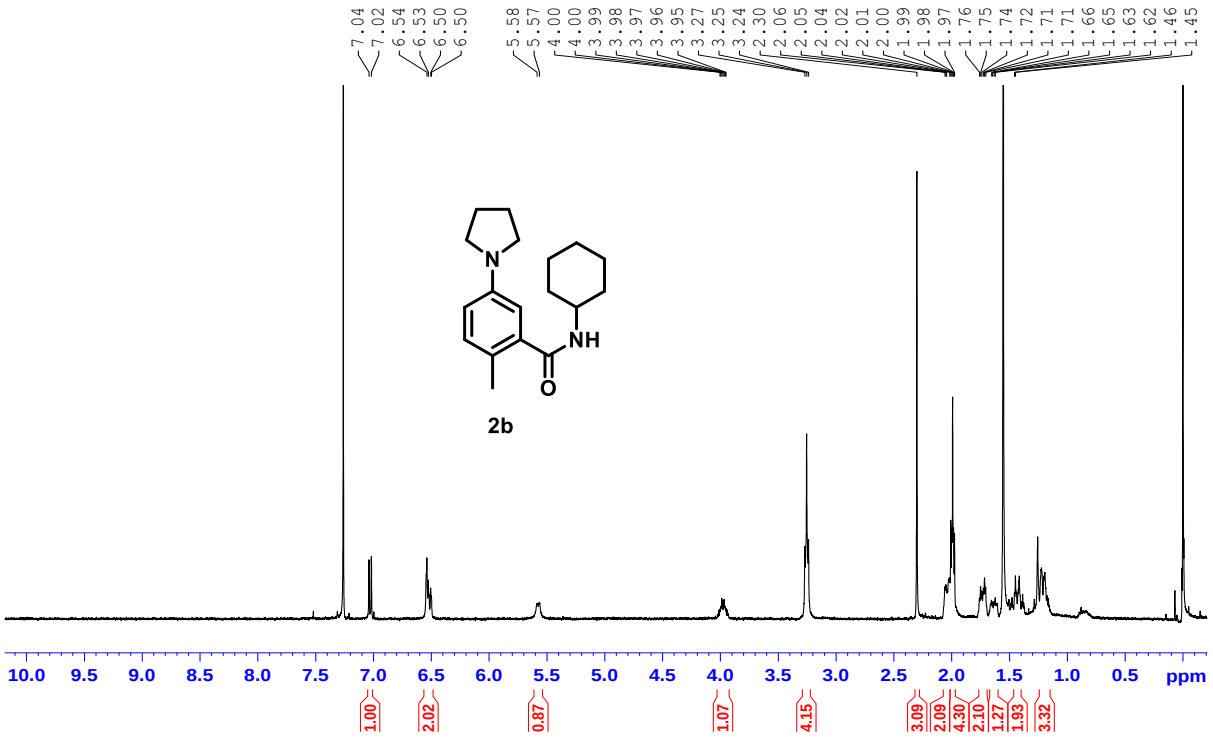
[10] ^{1}H, ^{13}C, and ^{31}P NMR spectra

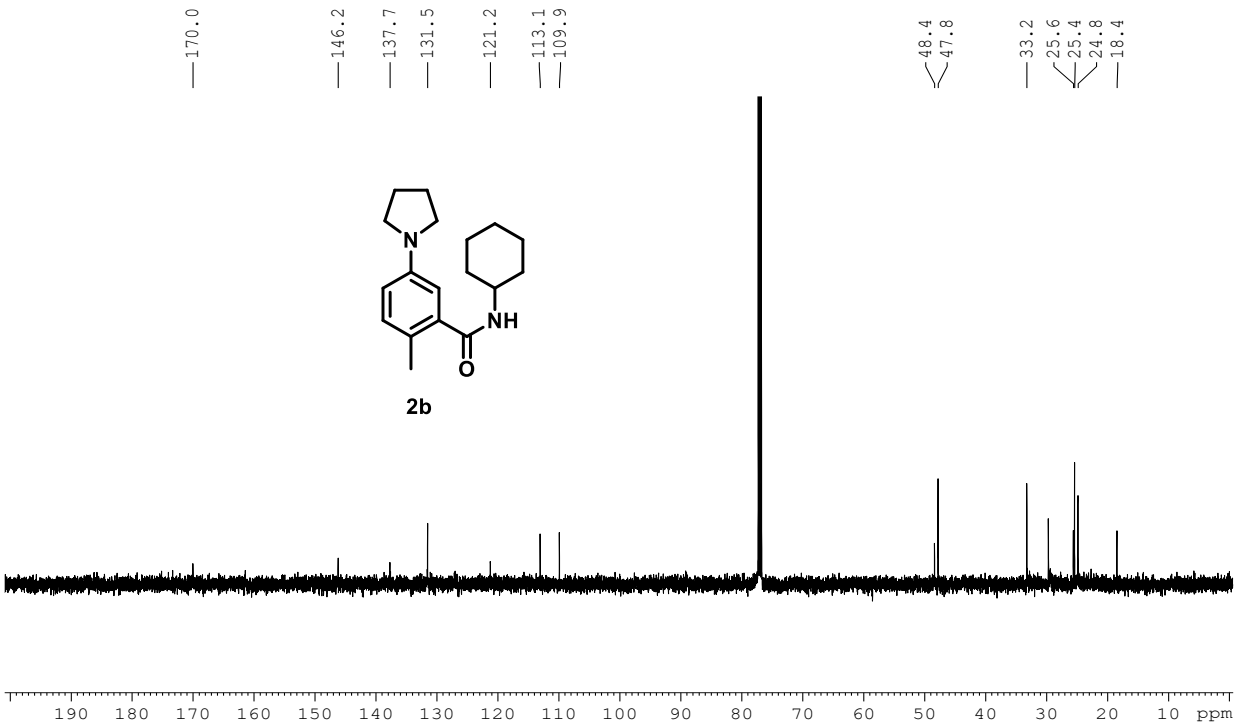




NOESY spectrum of **2a**



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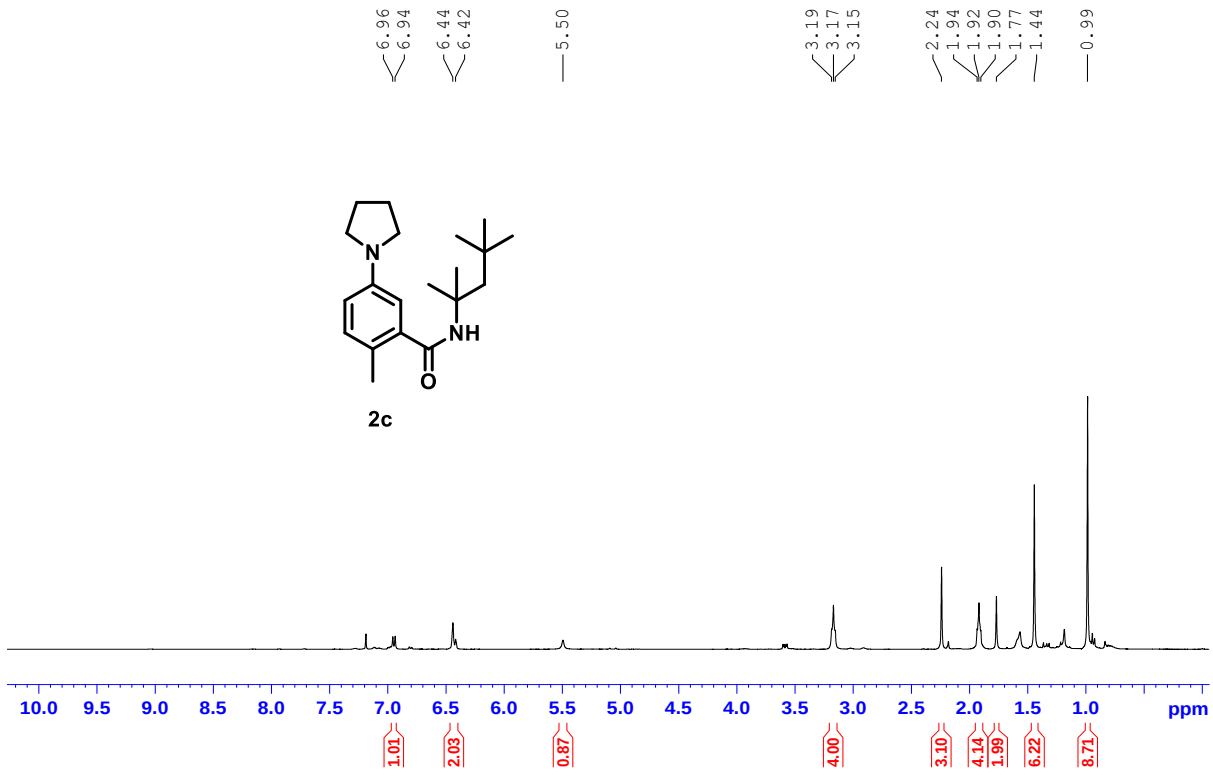
146.2
137.7
131.5
121.2
113.1
109.9
48.4
47.8
33.2
25.6
25.4
24.8
18.4
N
NH
O
2b
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm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3.17
3.15
2.24
1.94
1.92
1.90
1.77
1.44
0.99
N
NH
O
2c
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
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4.14
1.99
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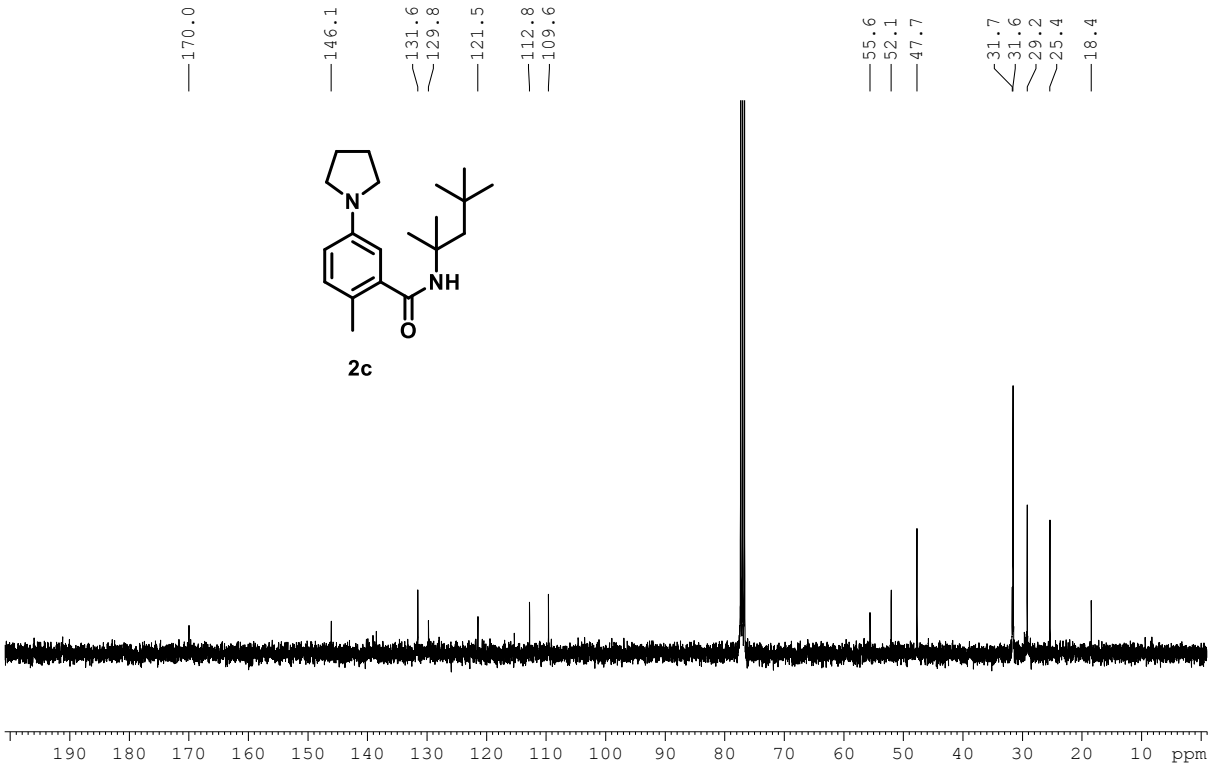
8.71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NH
O
2c
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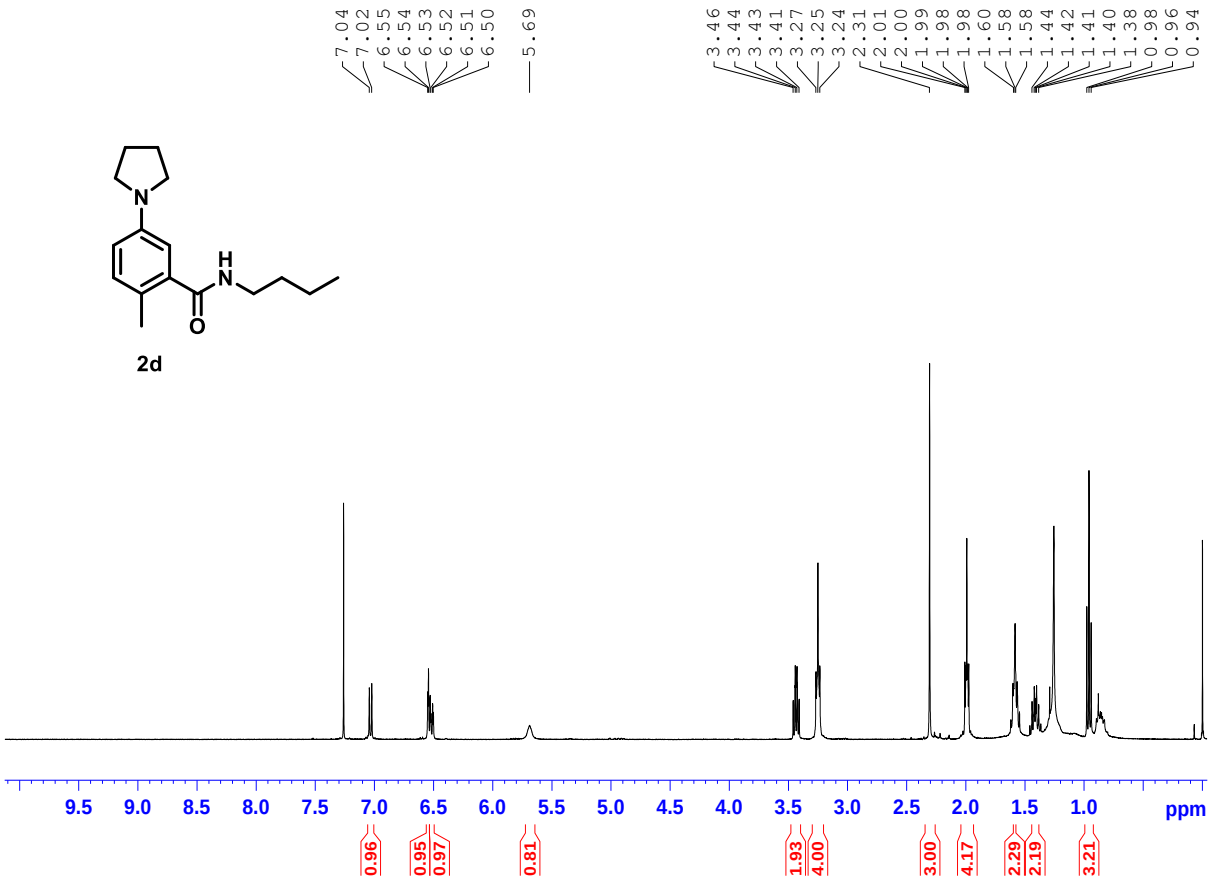
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6.55
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6.53
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6.51
6.50
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3.46
3.44
3.43
3.41
3.27
3.25
3.24
2.31
2.01
2.00
1.99
1.98
1.98
1.60
1.58
1.58
1.44
1.42
1.41
1.40
1.38
0.98
0.96
0.94
N
H
N
O
2d
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
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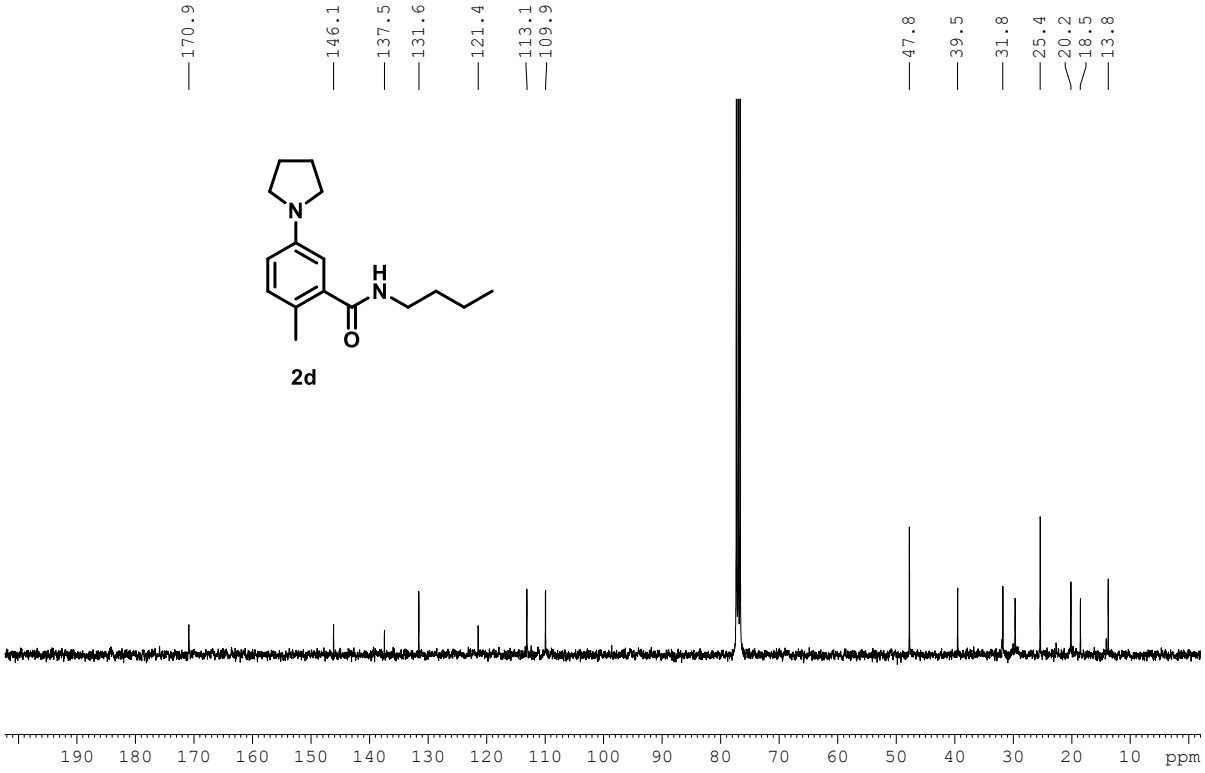
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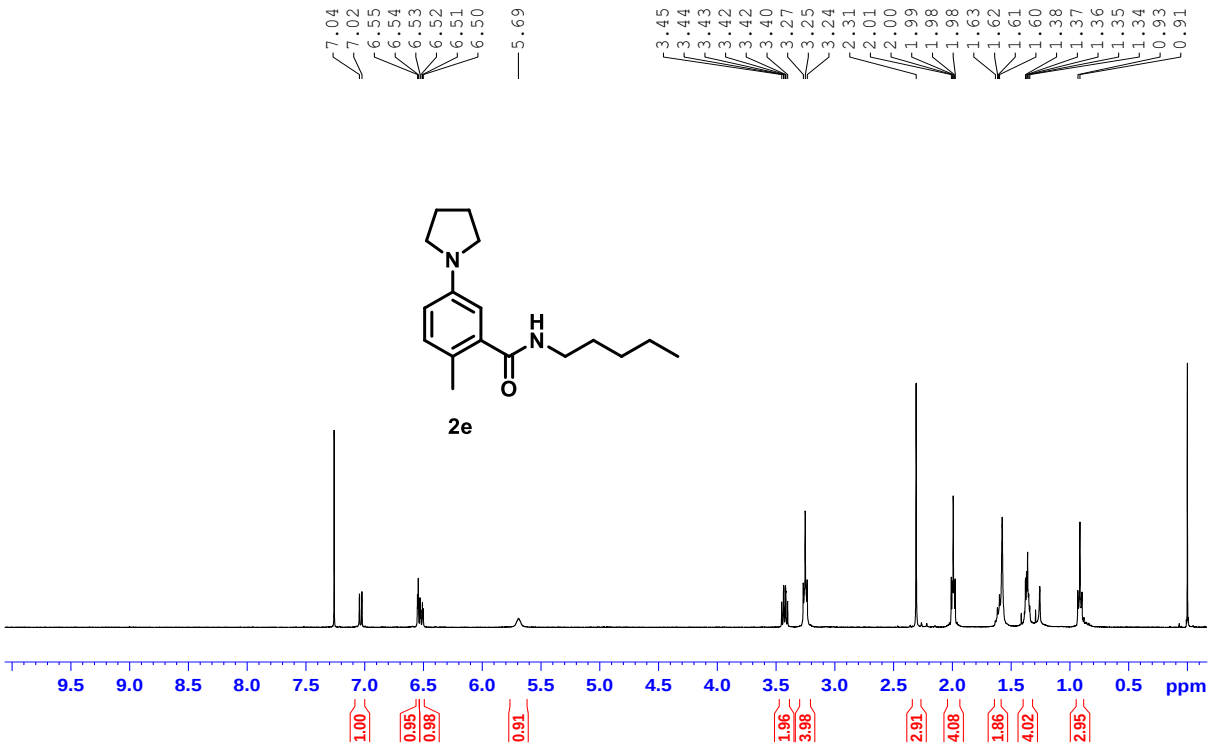
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3.40
3.27
3.25
3.24
2.31
2.01
2.00
1.99
1.98
1.98
1.63
1.62
1.61
1.60
1.38
1.37
1.36
1.35
1.34
0.93
0.91
2e
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
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4.02
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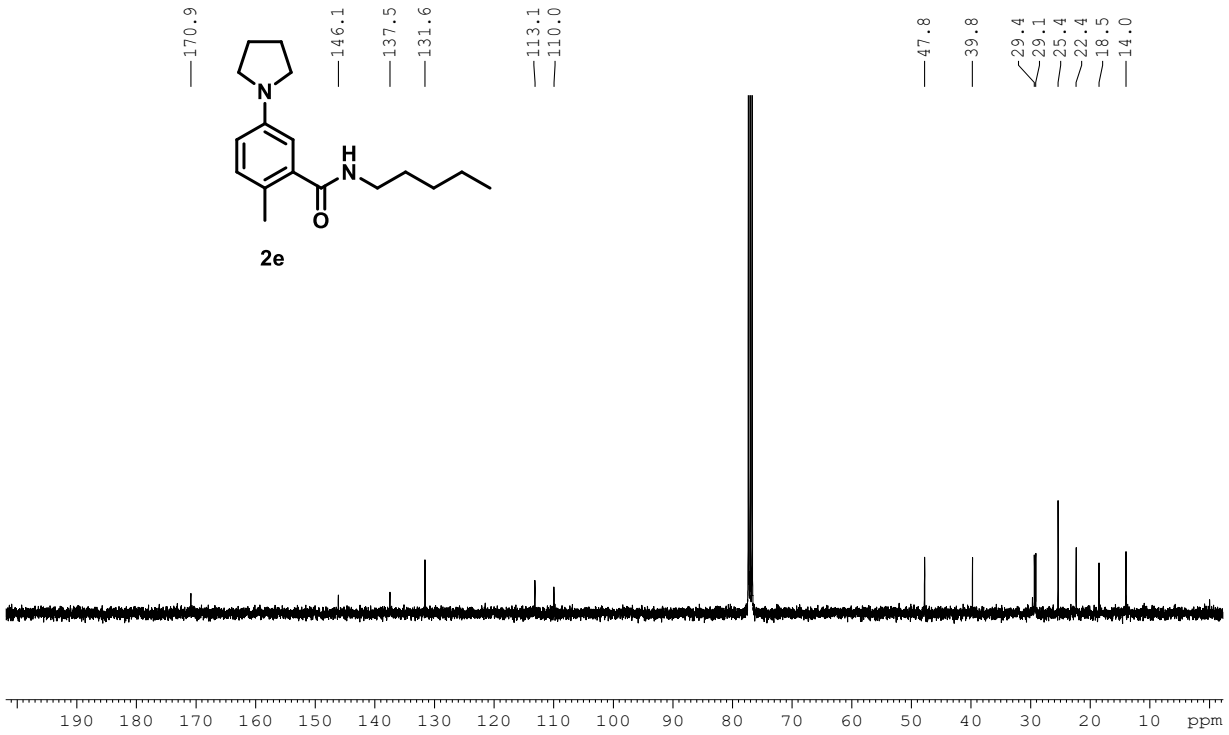
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14.0
2e
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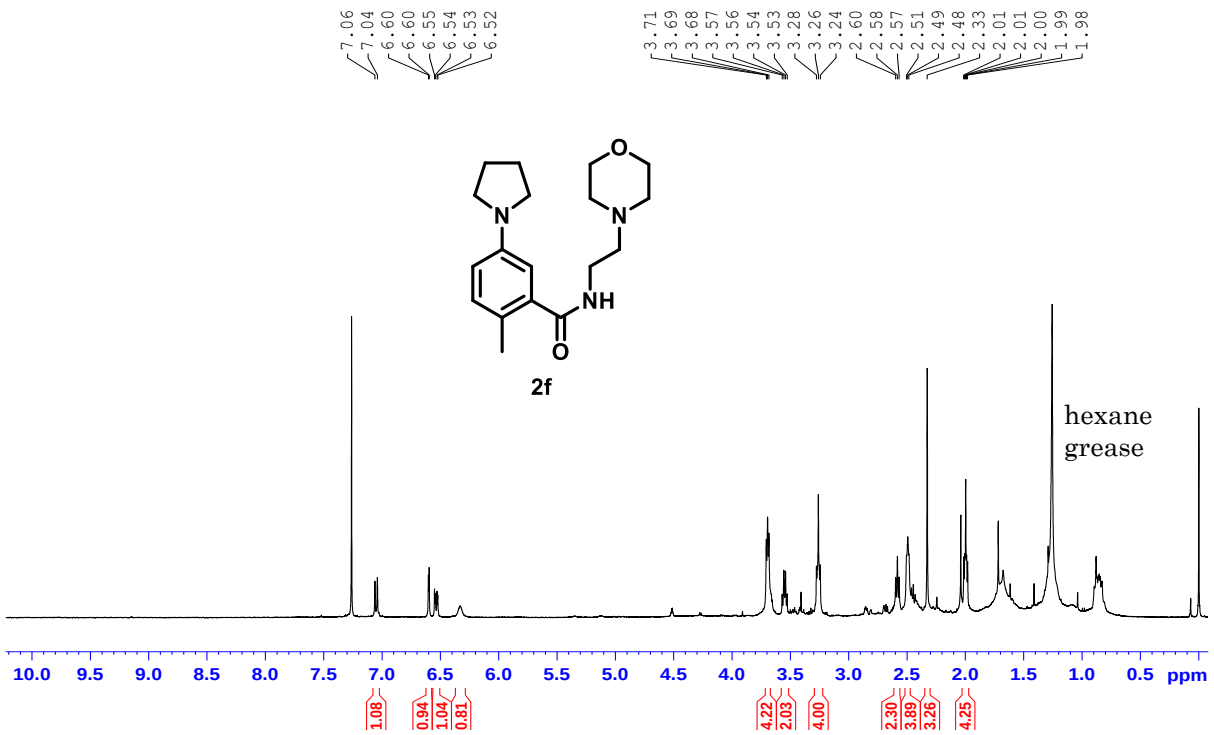
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3.54
3.53
3.28
3.26
3.24
2.60
2.58
2.57
2.51
2.49
2.48
2.33
2.01
2.00
1.99
1.98
2f
hexane
grease
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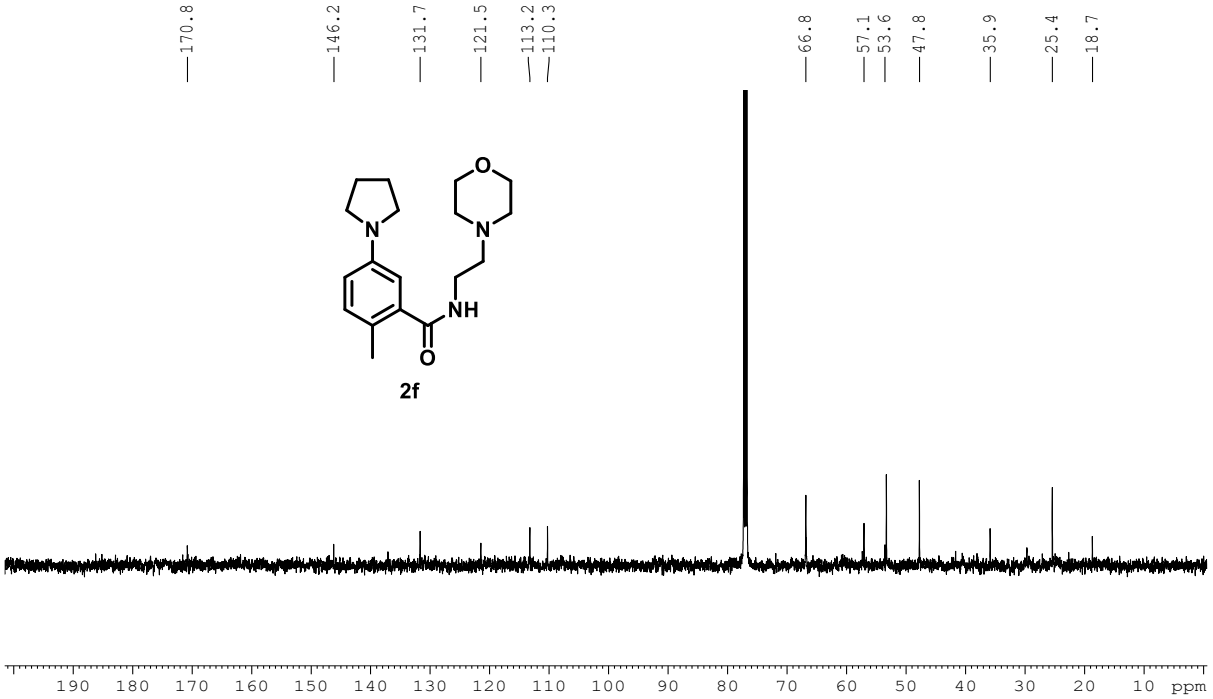
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18.7
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N
N
NH
O
2f
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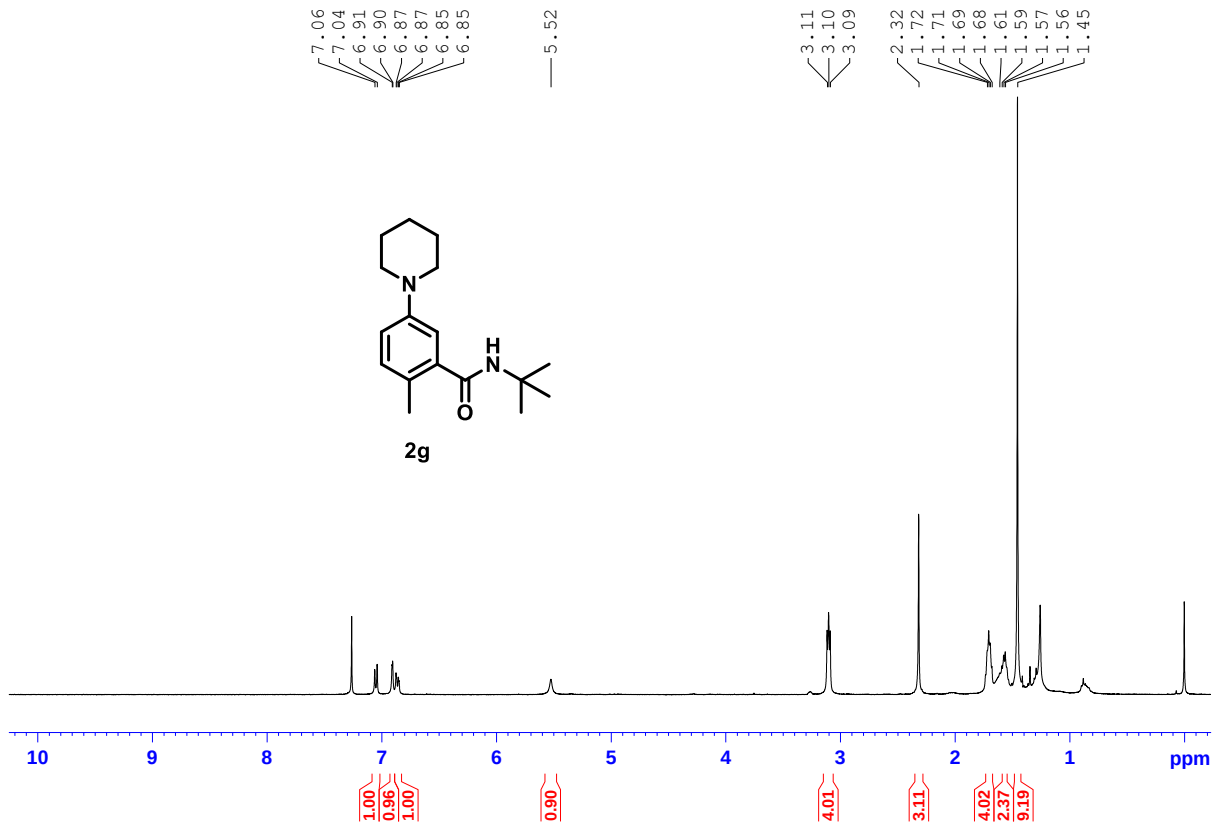
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2.32
1.72
1.71
1.69
1.68
1.61
1.59
1.57
1.56
1.45
N
H
N
O
2g
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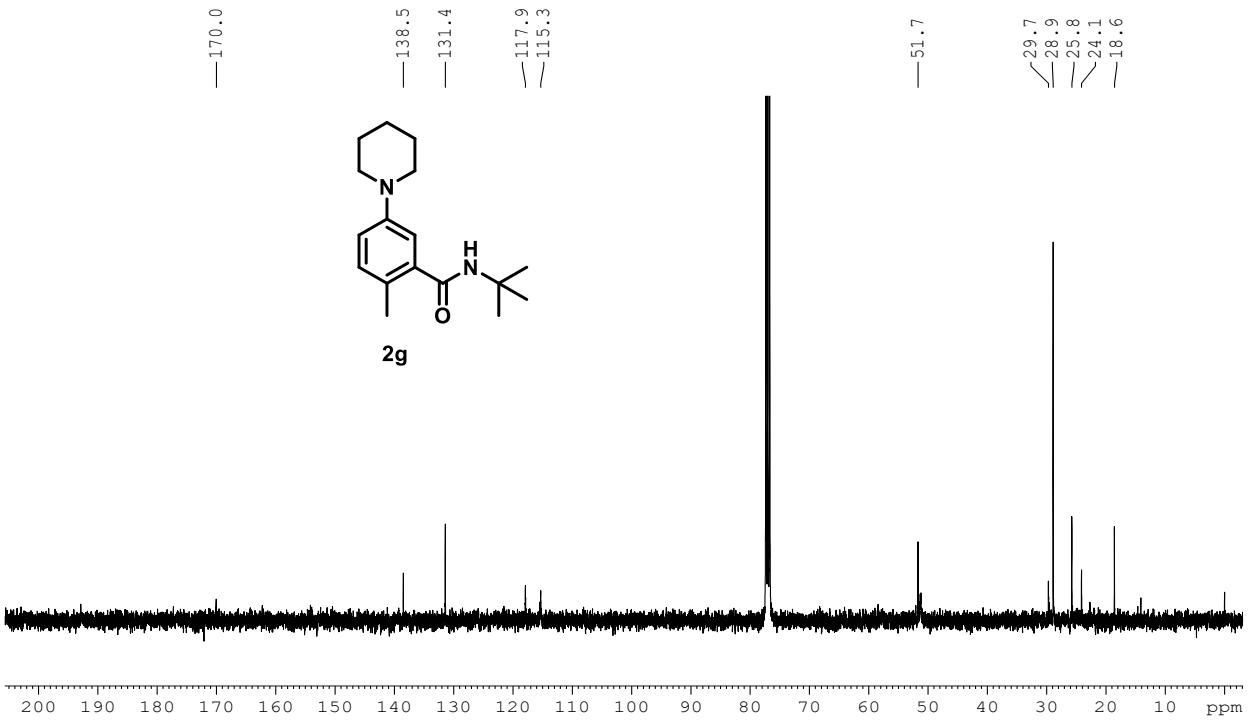
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117.9
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28.9
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24.1
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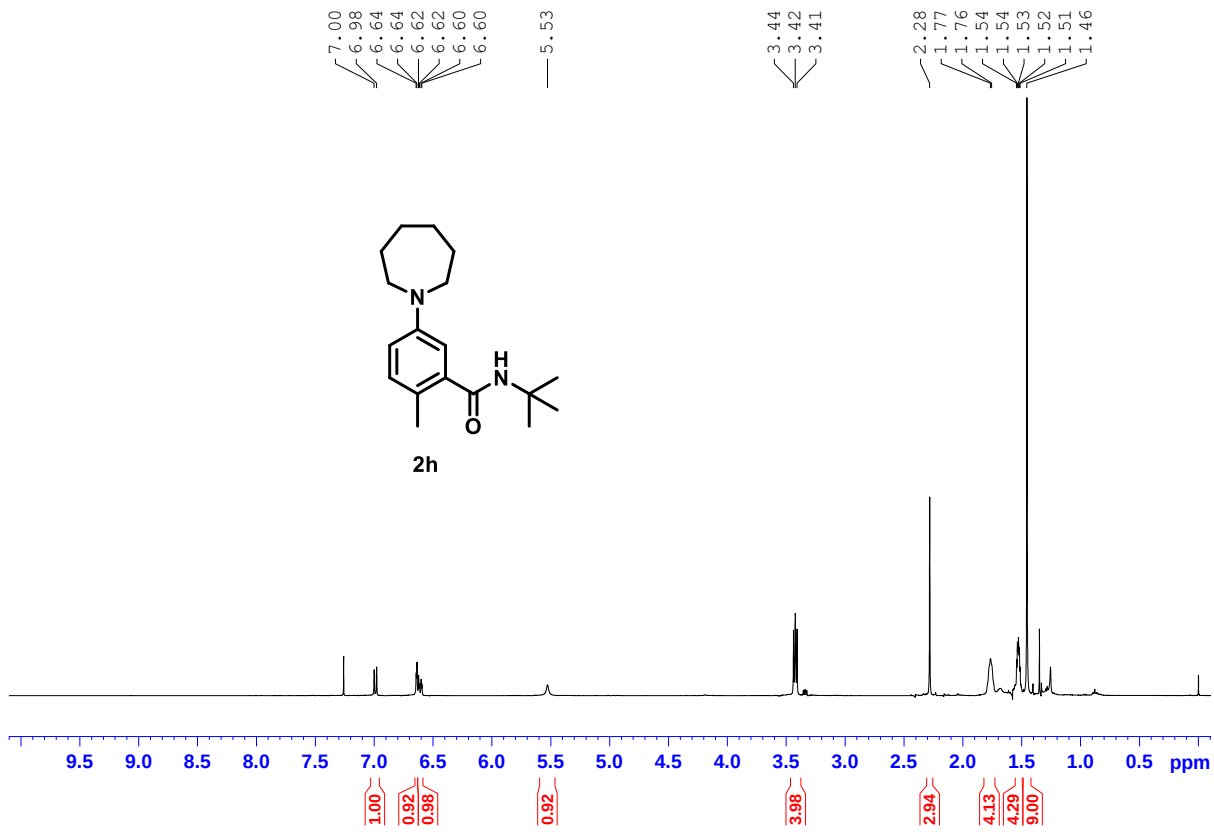
2g
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm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6.60
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2.28
1.77
1.76
1.54
1.54
1.53
1.52
1.51
1.46
2h
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
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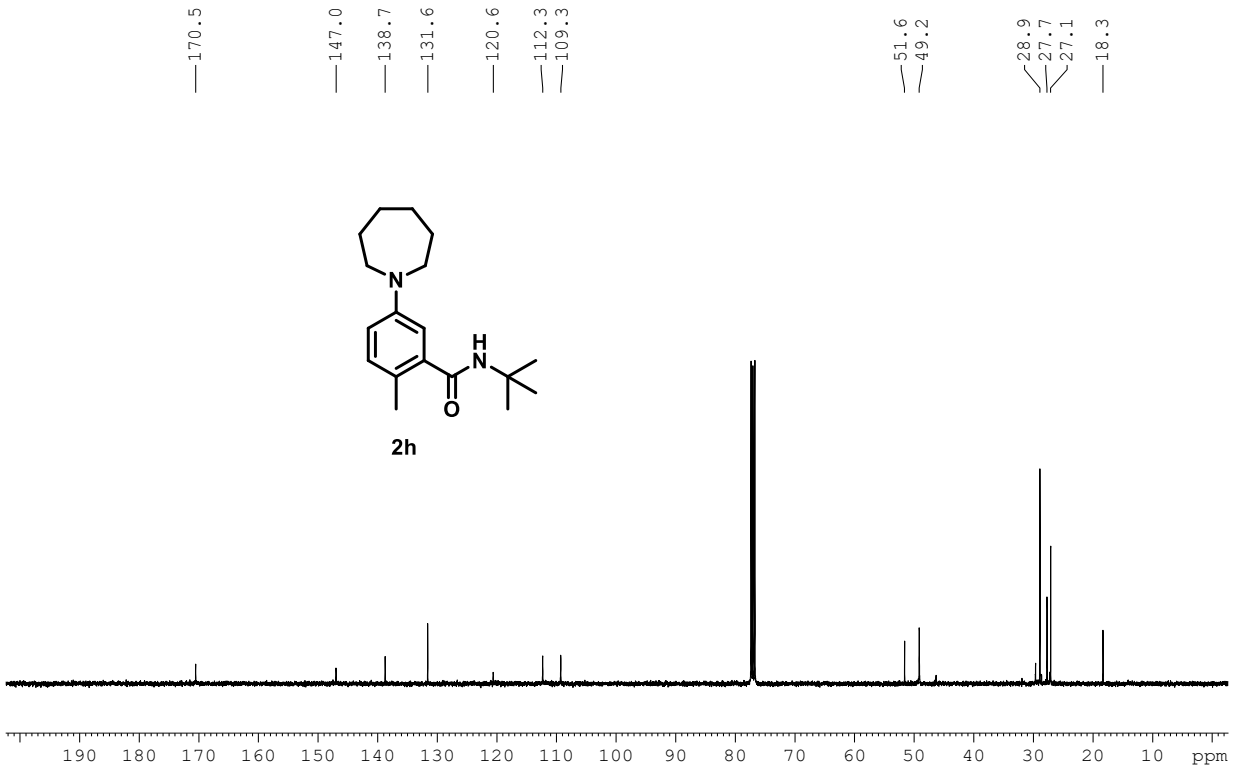
4.13
4.29
9.00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131.6
120.6
112.3
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51.6
49.2
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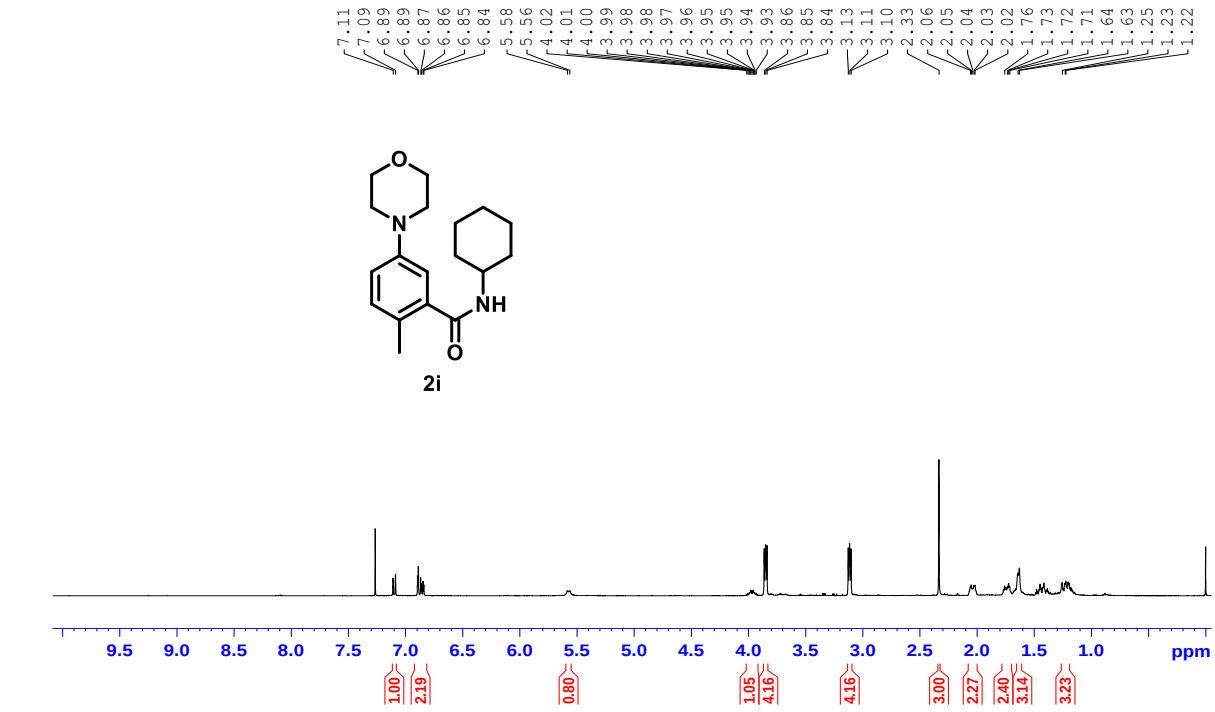
27.1
18.3
N
H
N
O
2h
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm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3.97
3.96
3.95
3.95
3.94
3.93
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3.85
3.84
3.13
3.11
3.10
2.33
2.06
2.05
2.04
2.03
2.02
1.76
1.73
1.72
1.71
1.64
1.63
1.25
1.23
1.22
O
N
NH
O
2i
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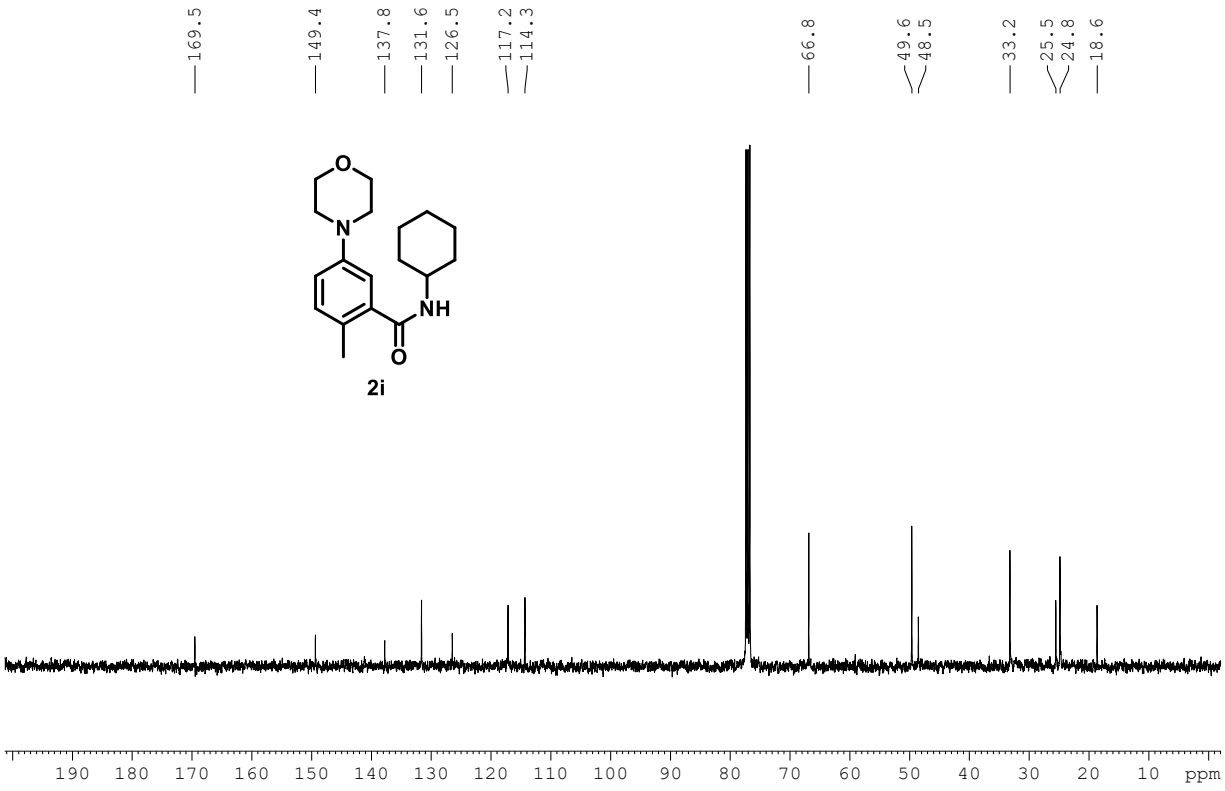
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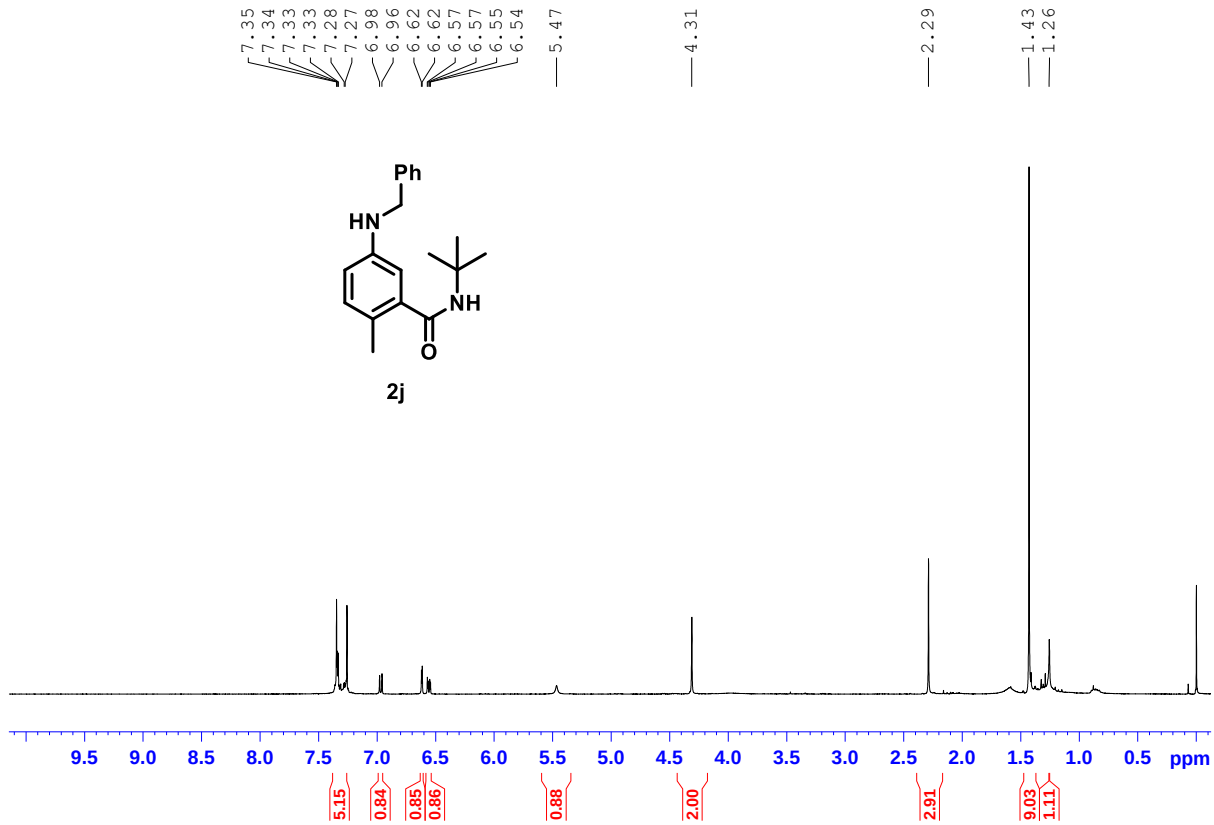
114.3
66.8
49.6
48.5
33.2
25.5
24.8
18.6
O
N
NH
O
2i
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm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6.62
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6.57
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6.54
5.47
4.31
2.29
1.43
1.26
Ph
HN
NH
O
2j
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
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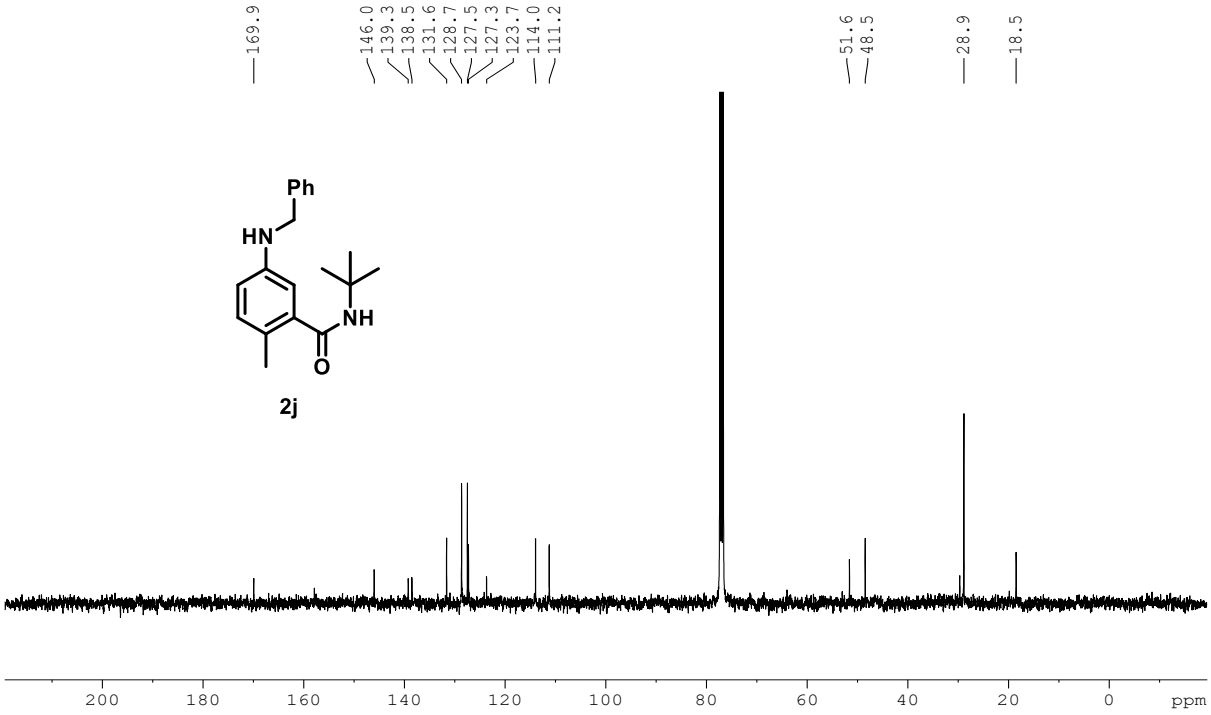
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114.0
111.2
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48.5
28.9
18.5
Ph
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O
2j
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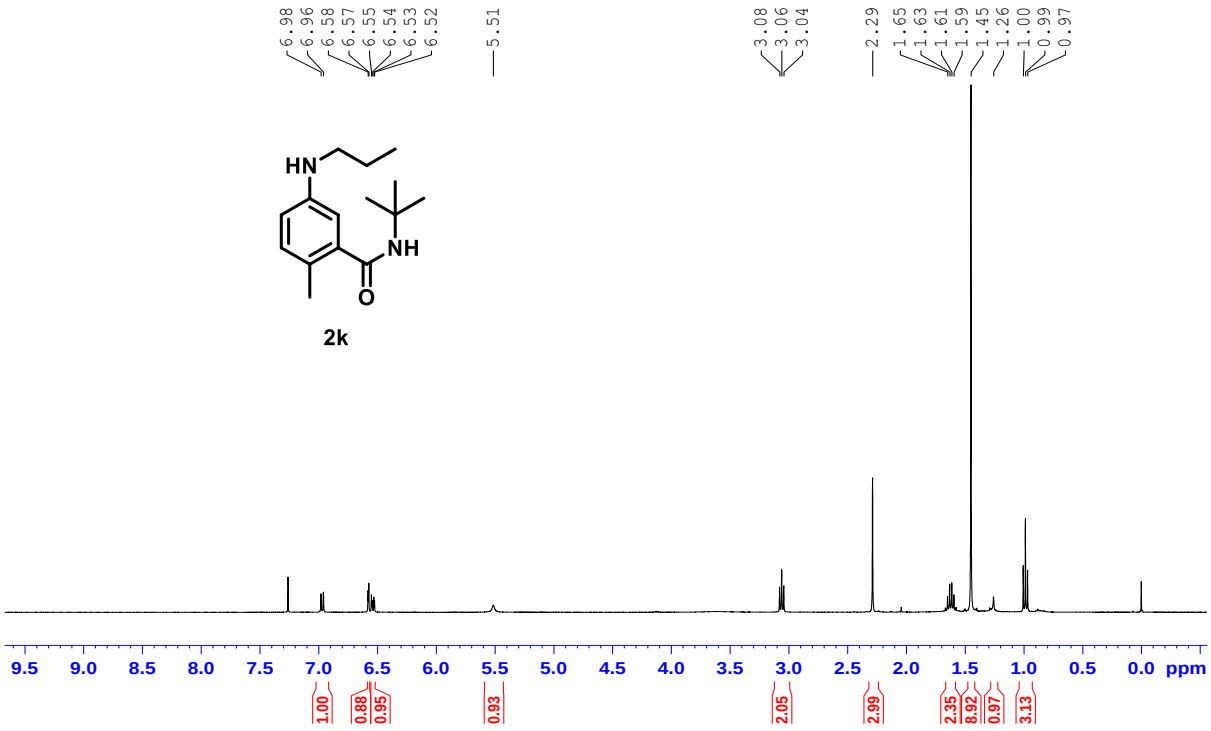
140
120
100
80
60
40
20
0
ppm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6.0
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4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
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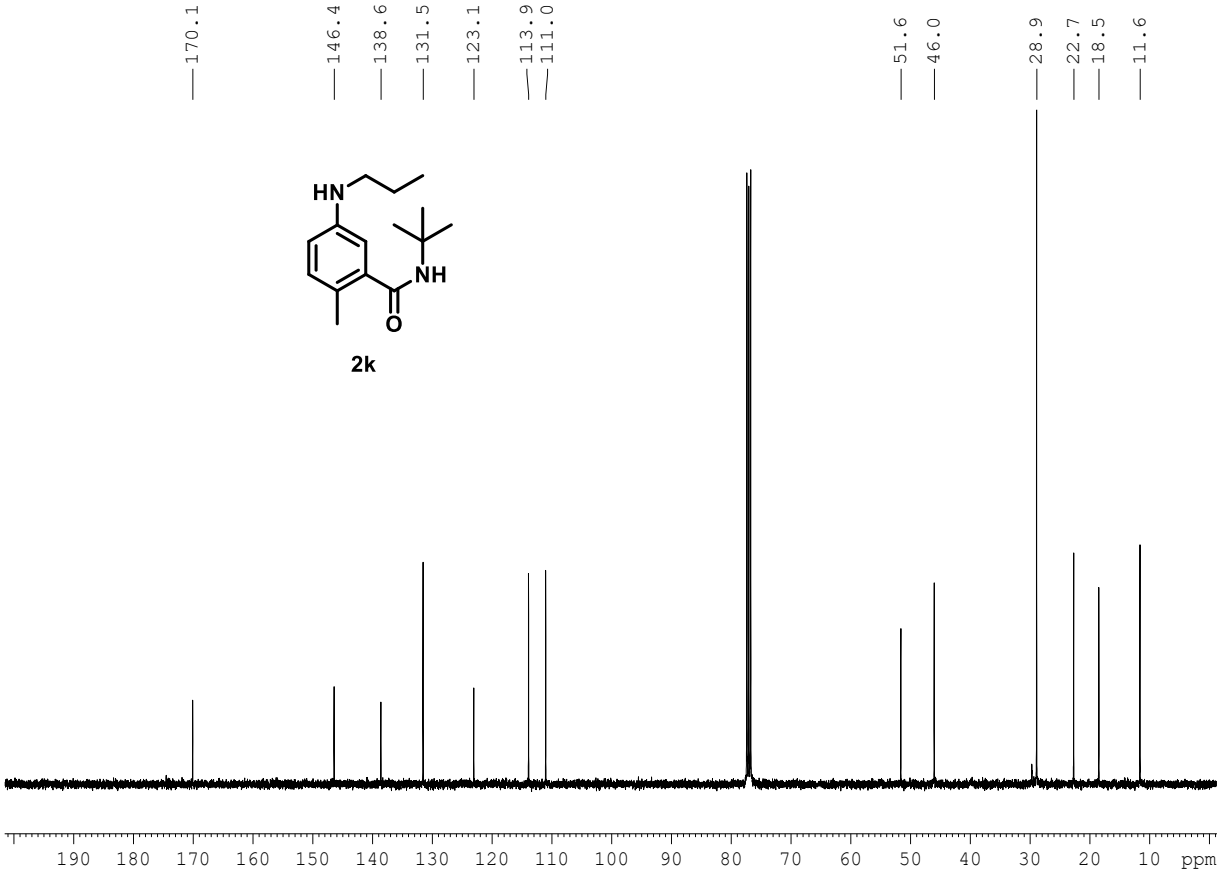
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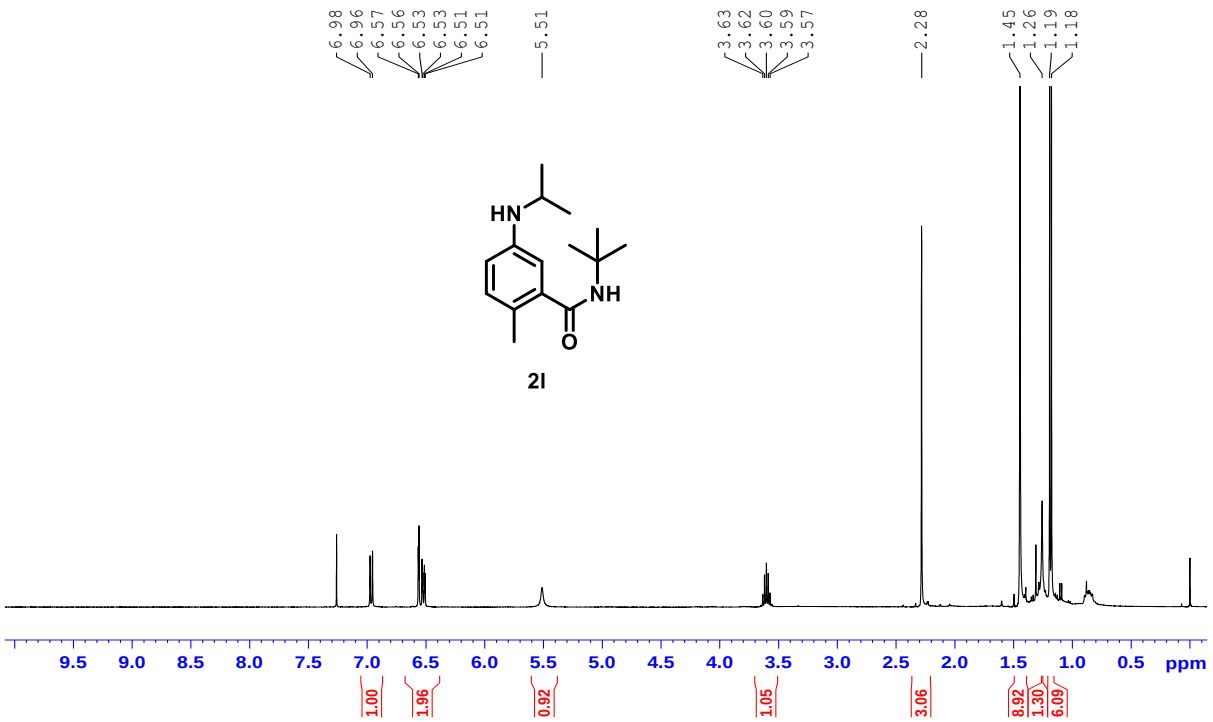
NH
O
2k
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm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6.53
6.51
6.51
5.51
3.63
3.62
3.60
3.59
3.57
2.28
1.45
1.26
1.19
1.18
HN
NH
O
2l
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
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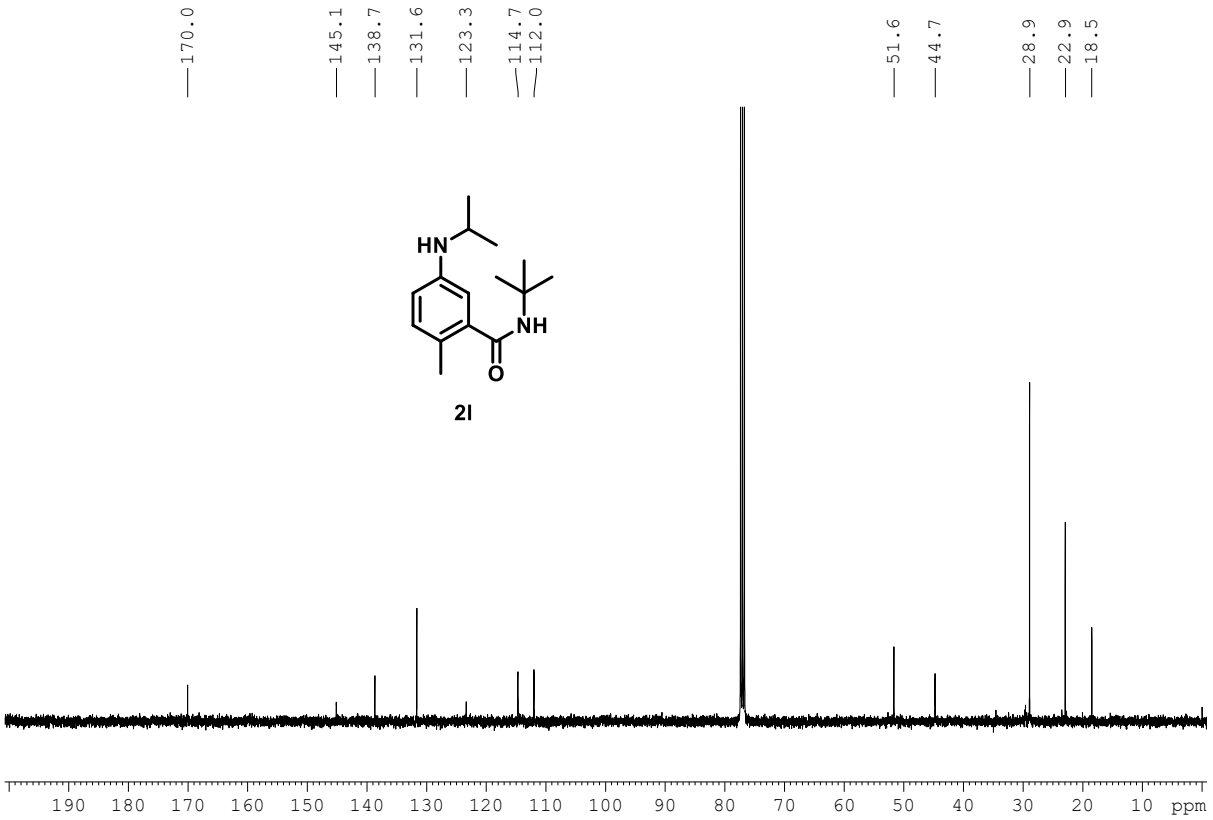
0.92
1.05
3.06
8.92
1.30
6.09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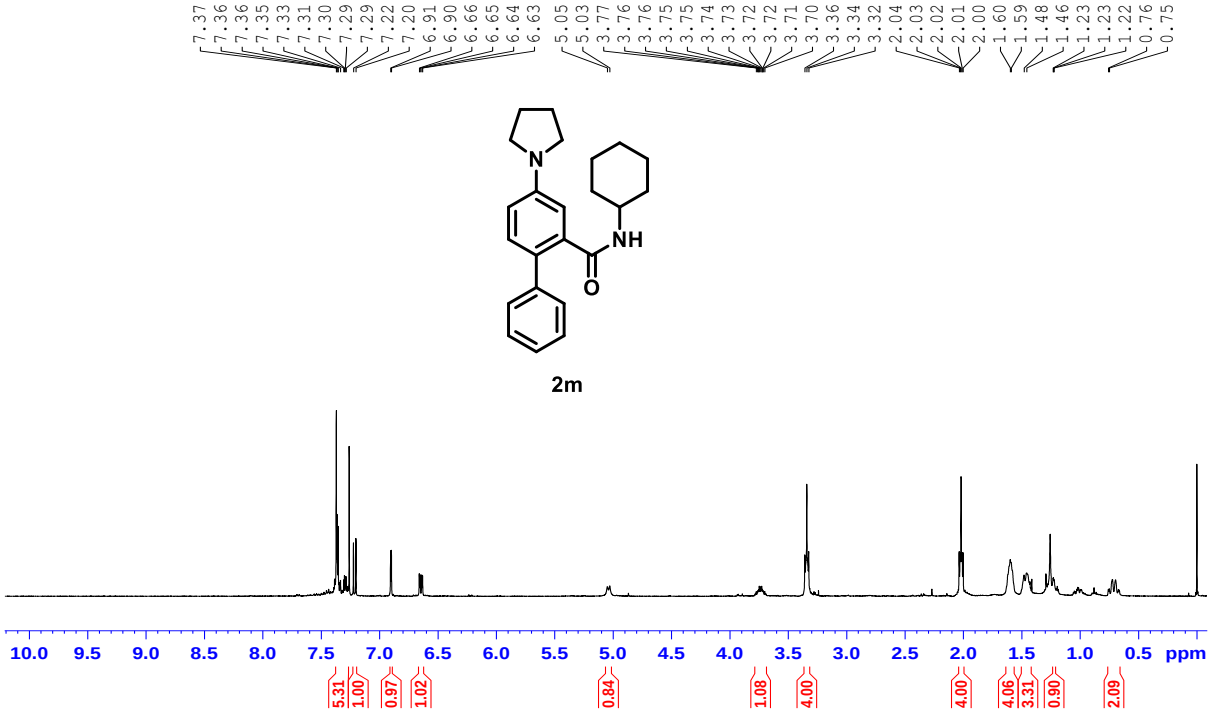
28.9
22.9
18.5
HN
NH
O
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

2l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6.66
6.65
6.64
6.63
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5.03
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3.76
3.76
3.75
3.75
3.74
3.73
3.72
3.72
3.71
3.70
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2.04
2.03
2.02
2.01
2.00
1.60
1.59
1.48
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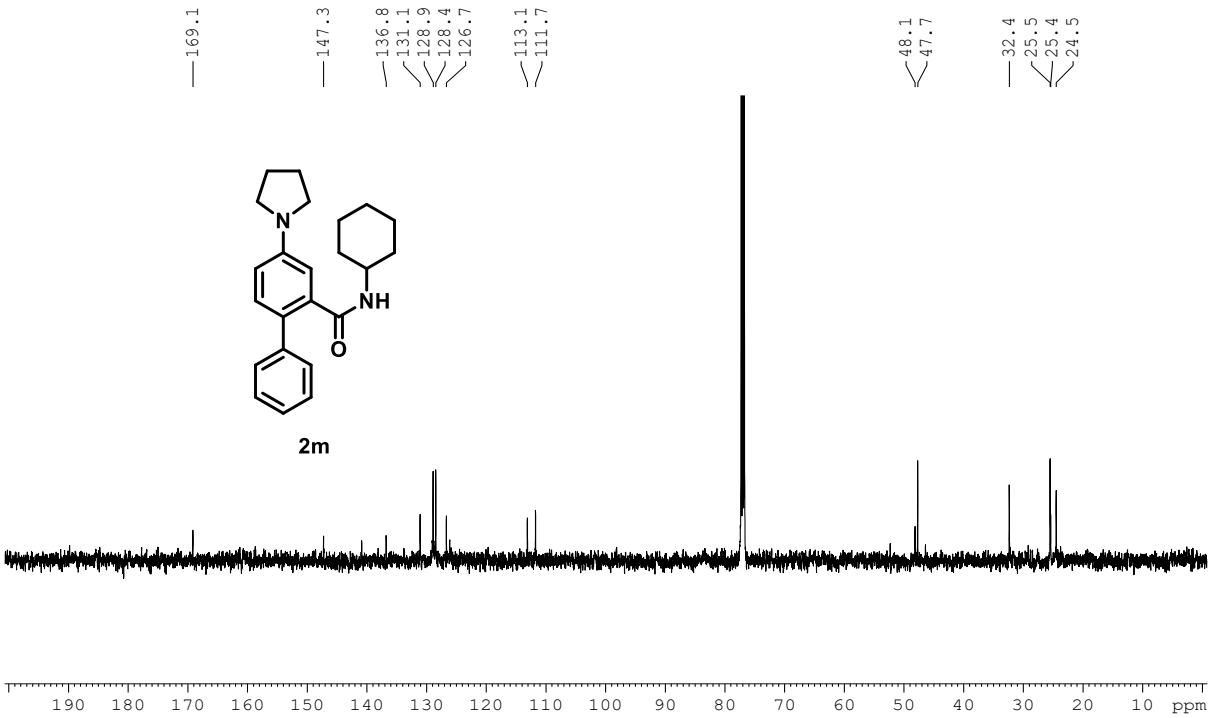
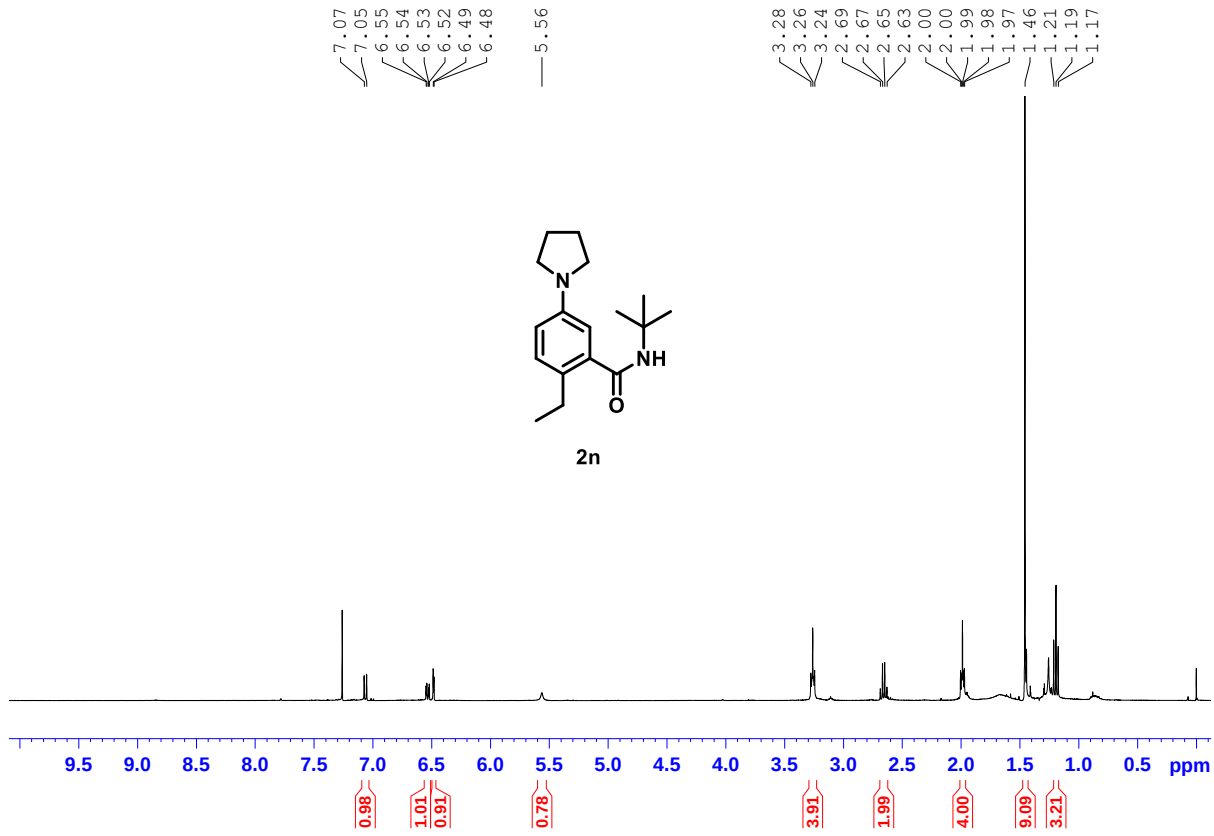
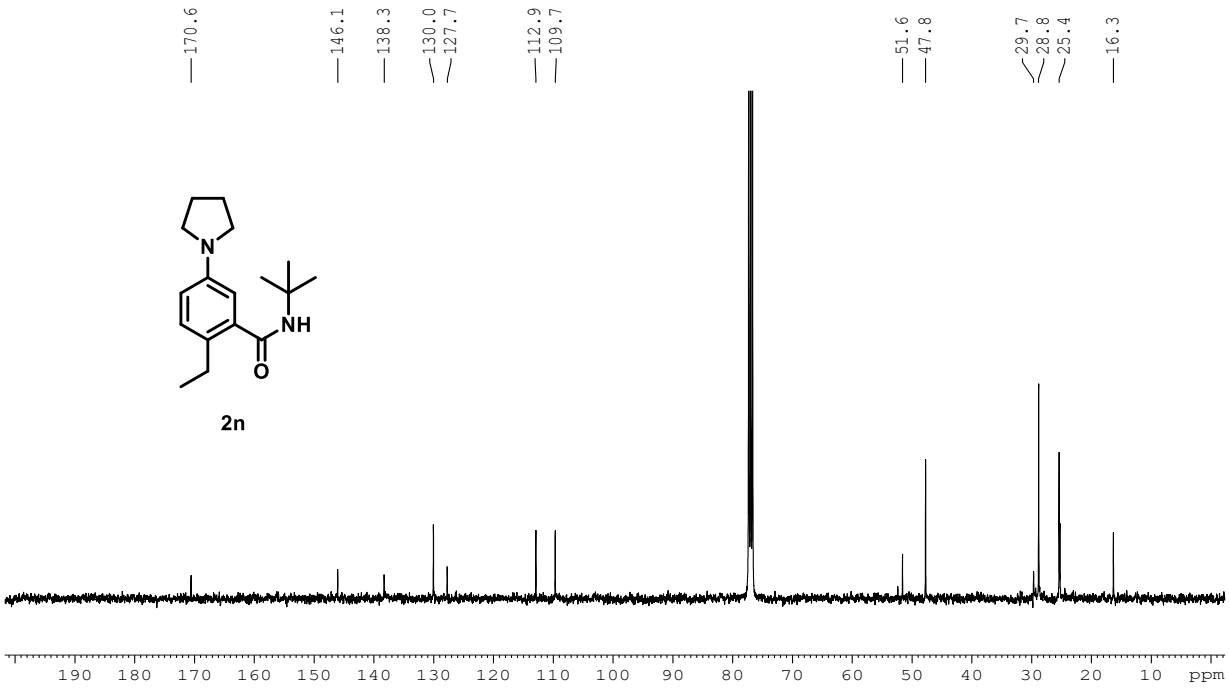
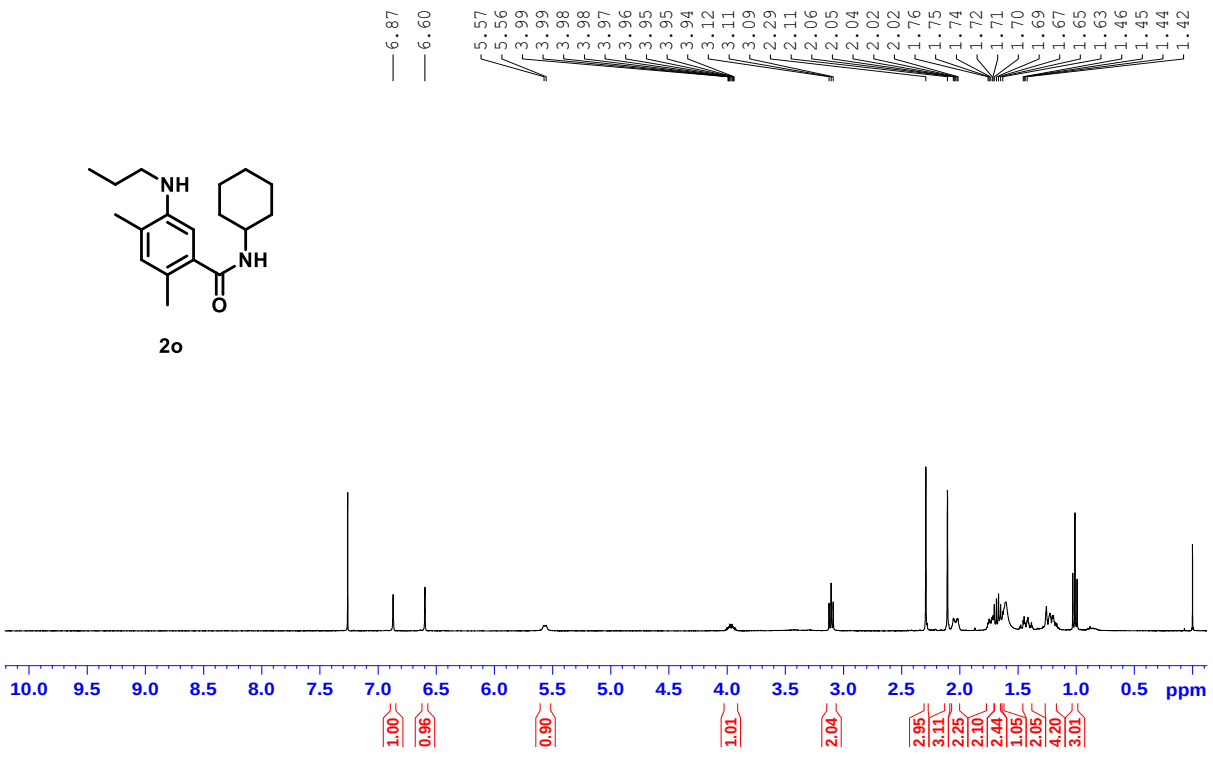
1.23
1.23
1.22
0.76
0.75
N
NH
O
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
5.31
1.00
0.97
1.02
0.84
1.08
4.00
4.00
4.06
3.31
0.90
2.09

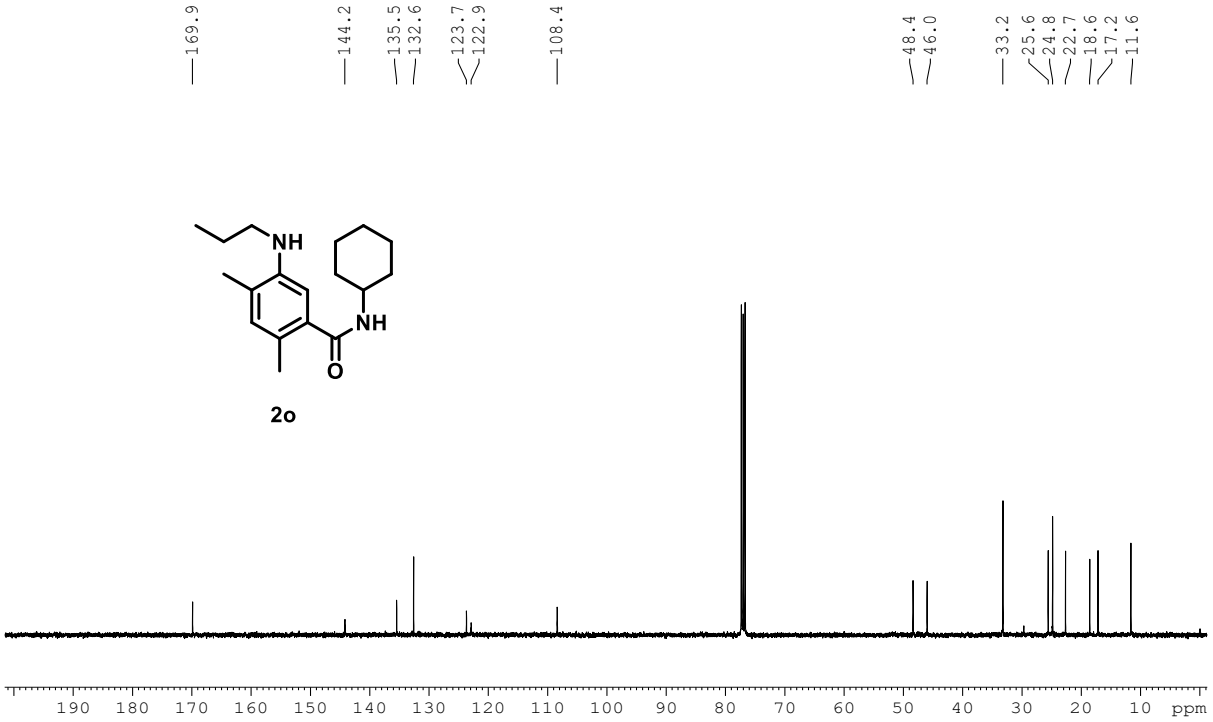
2m

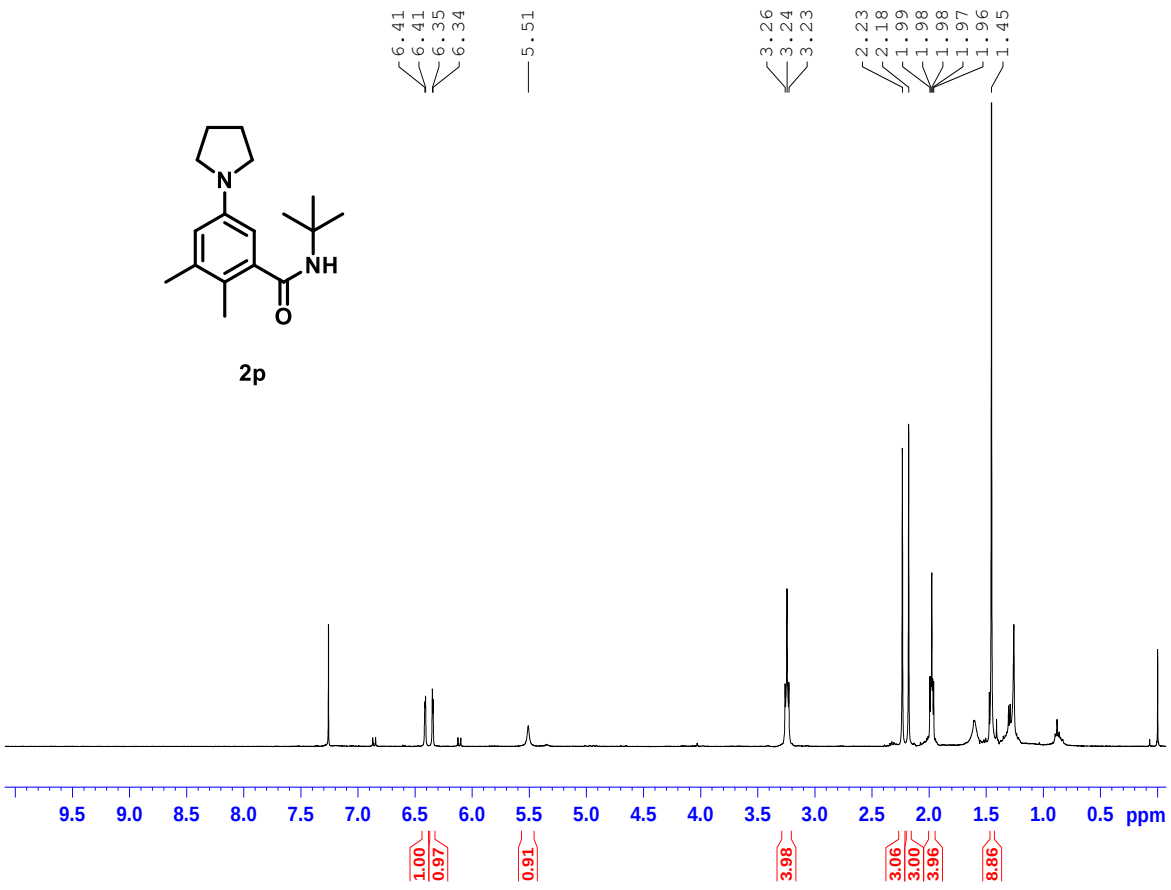

169.1
147.3
136.8
131.1
128.9
128.4
126.7
113.1
111.7
48.1
47.7
32.4
25.5
25.4
24.5
N
NH
O
2m
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

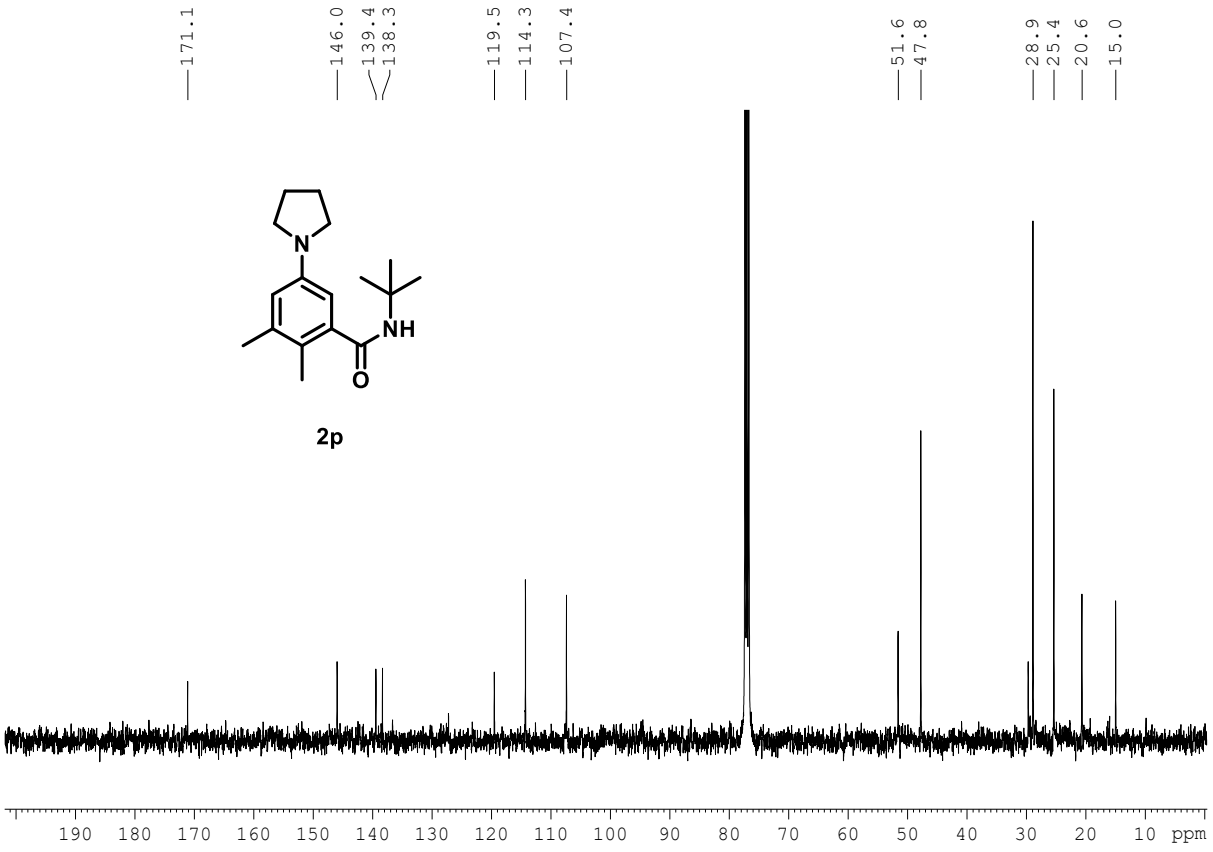

7.07
7.05
6.55
6.54
6.53
6.52
6.49
6.48
5.56
3.28
3.26
3.24
2.69
2.67
2.65
2.63
2.00
2.00
1.99
1.98
1.97
1.46
1.21
1.19
1.17
N
NH
O
2n
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
0.98
1.01
0.91
0.78
3.91
1.99
4.00
9.09
3.21

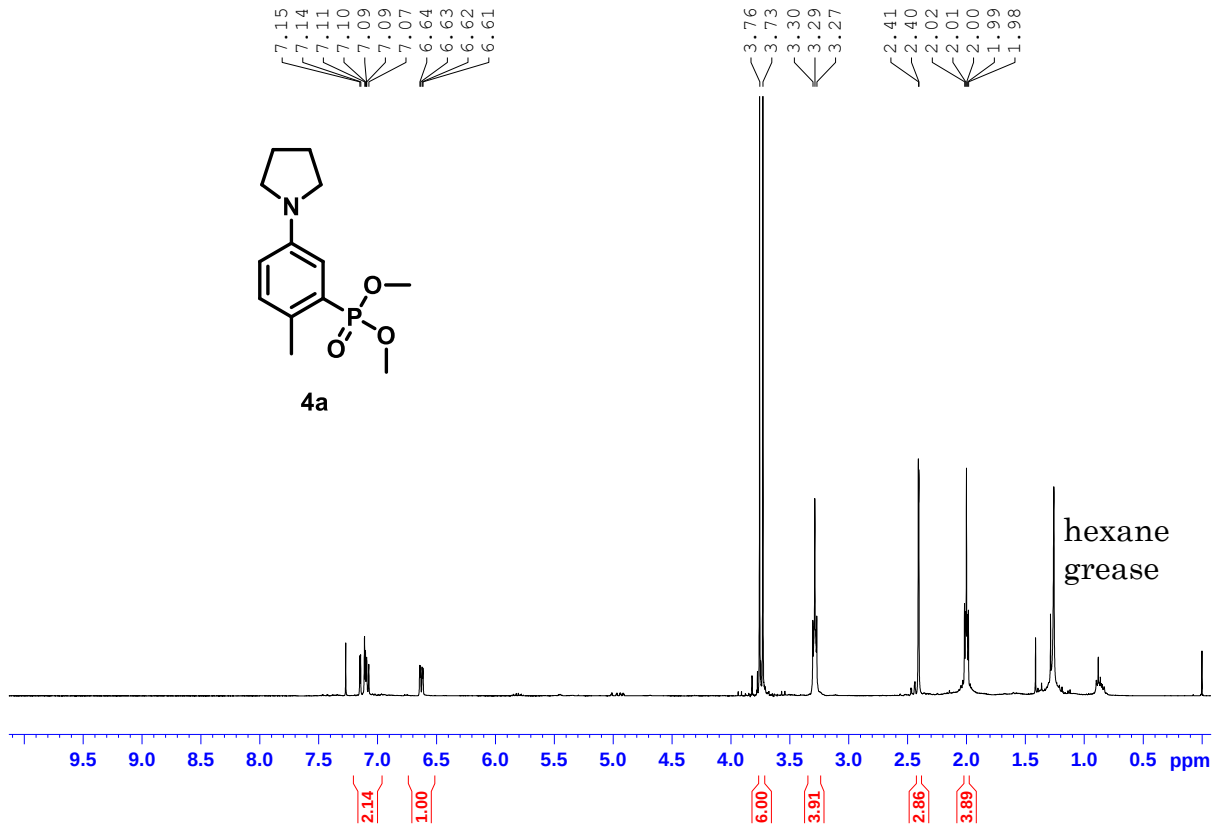

170.6
146.1
138.3
130.0
127.7
112.9
109.7
51.6
47.8
29.7
28.8
25.4
16.3
N
NH
O
2n
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

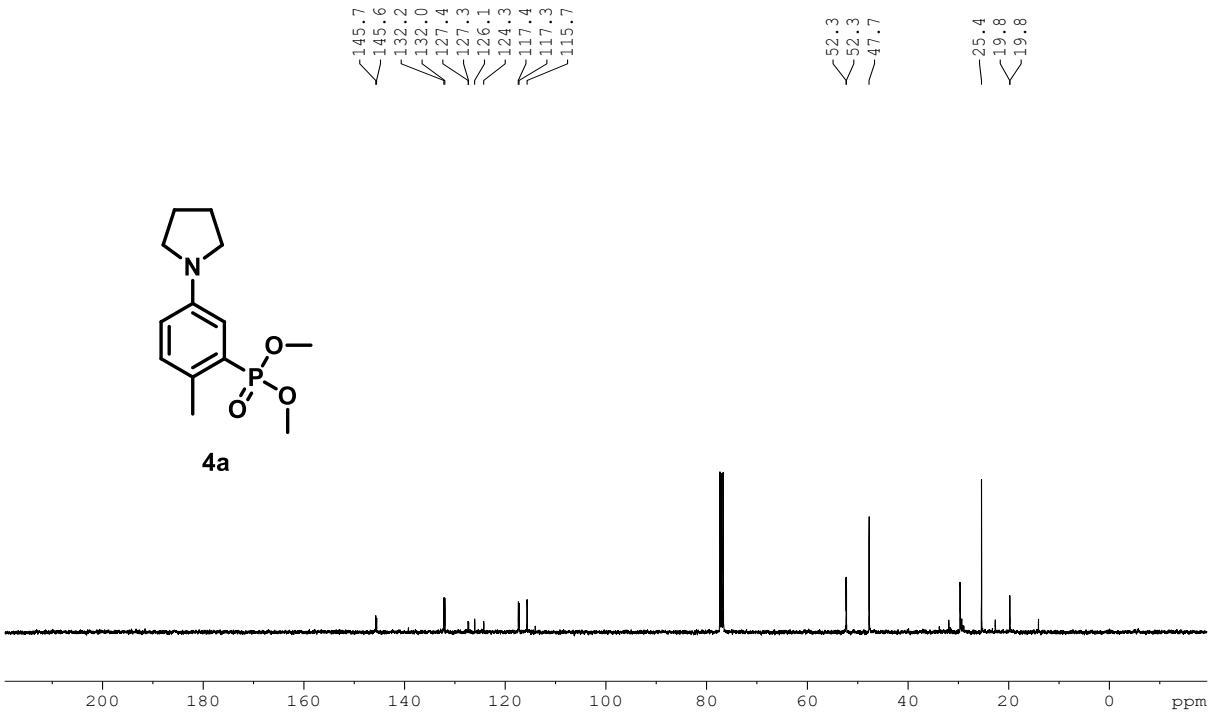

6.87
6.60
5.57
5.56
3.99
3.99
3.98
3.98
3.97
3.96
3.95
3.95
3.94
3.12
3.11
3.09
2.29
2.11
2.06
2.05
2.04
2.02
2.02
1.76
1.75
1.74
1.72
1.71
1.70
1.69
1.67
1.65
1.63
1.46
1.45
1.44
1.42
NH
NH
O
2o
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
1.00
0.96
0.90
1.01
2.04
2.95
3.11
2.25
2.10
2.44
1.05
2.05
4.20
3.01

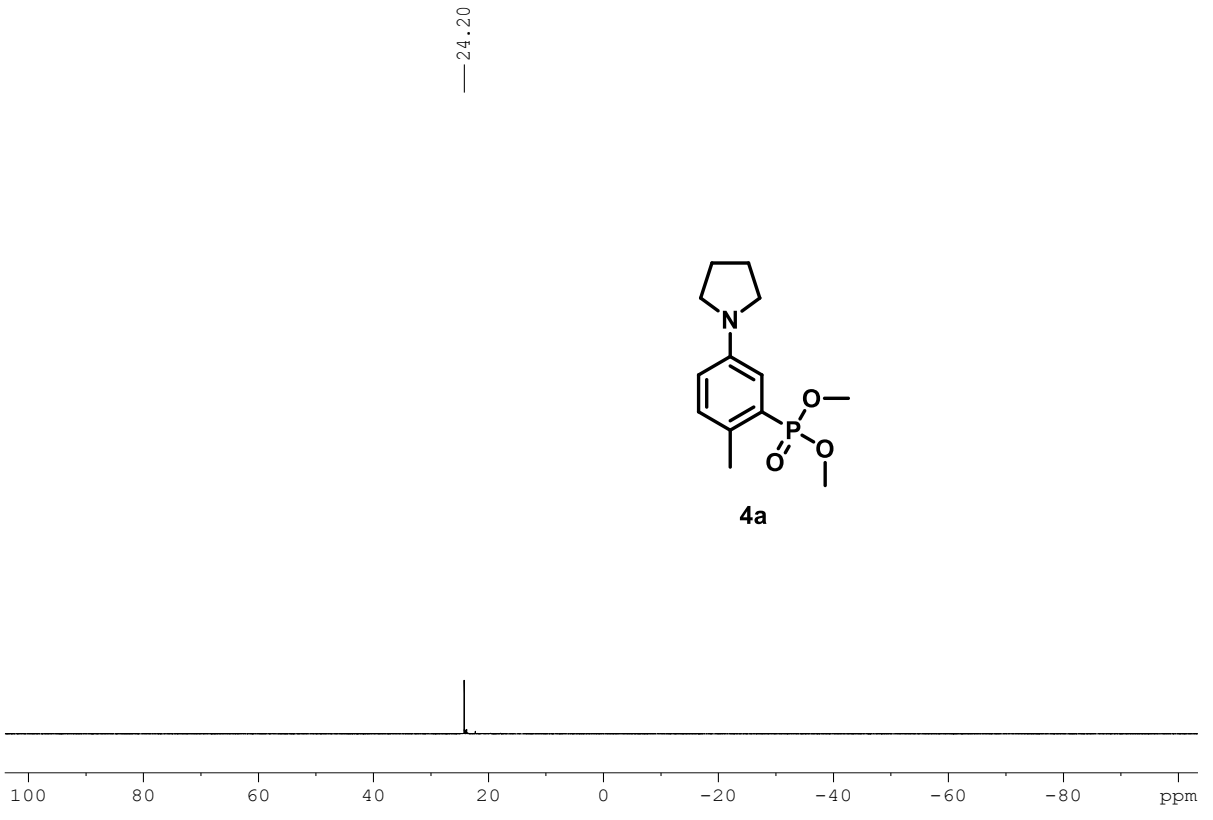

169.9
144.2
135.5
132.6
123.7
122.9
108.4
48.4
46.0
33.2
25.6
24.8
22.7
18.6
17.2
11.6
NH
NH
O
2o
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm


6.41
6.41
6.35
6.34
5.51
3.26
3.24
3.23
2.23
2.18
1.99
1.98
1.98
1.97
1.96
1.45
N
NH
O
2p
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
1.00
0.97
0.91
3.98
3.06
3.00
3.96
8.86

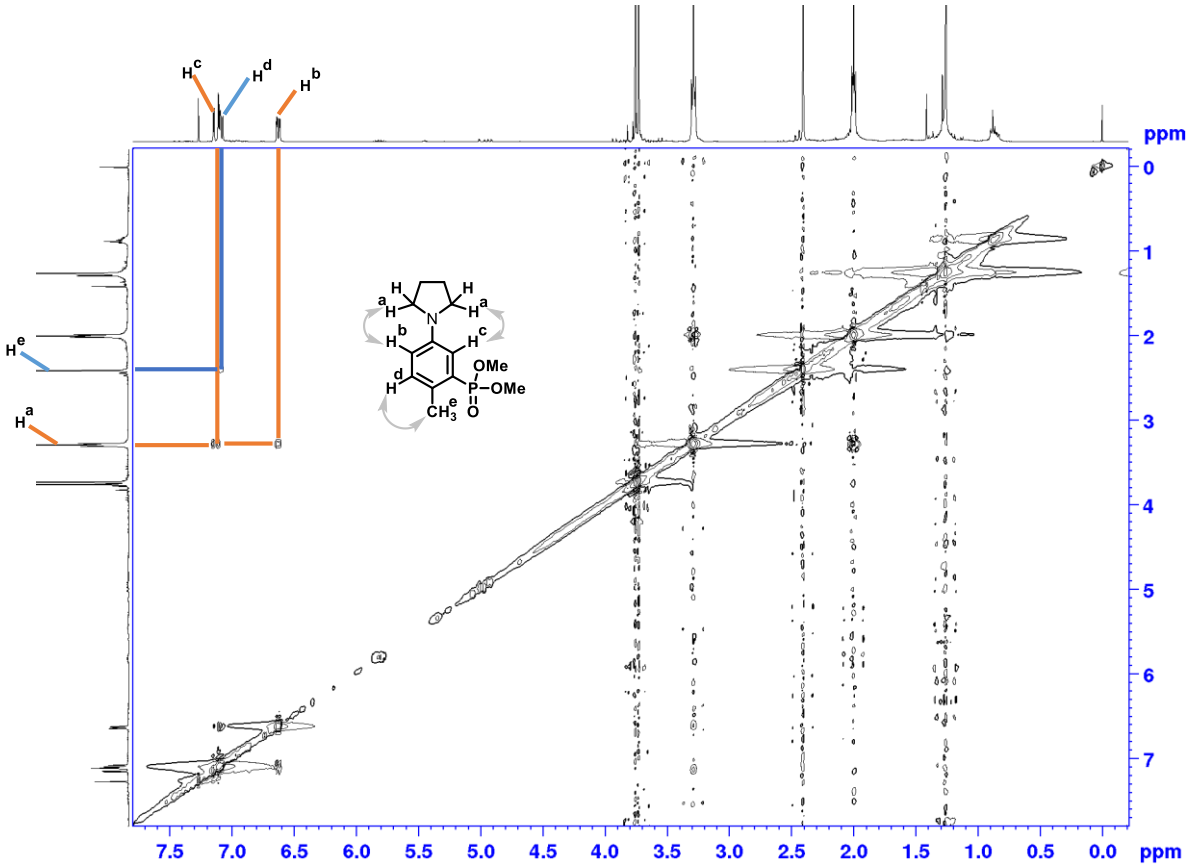

171.1
146.0
139.4
138.3
119.5
114.3
107.4
51.6
47.8
28.9
25.4
20.6
15.0
N
NH
O
2p
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

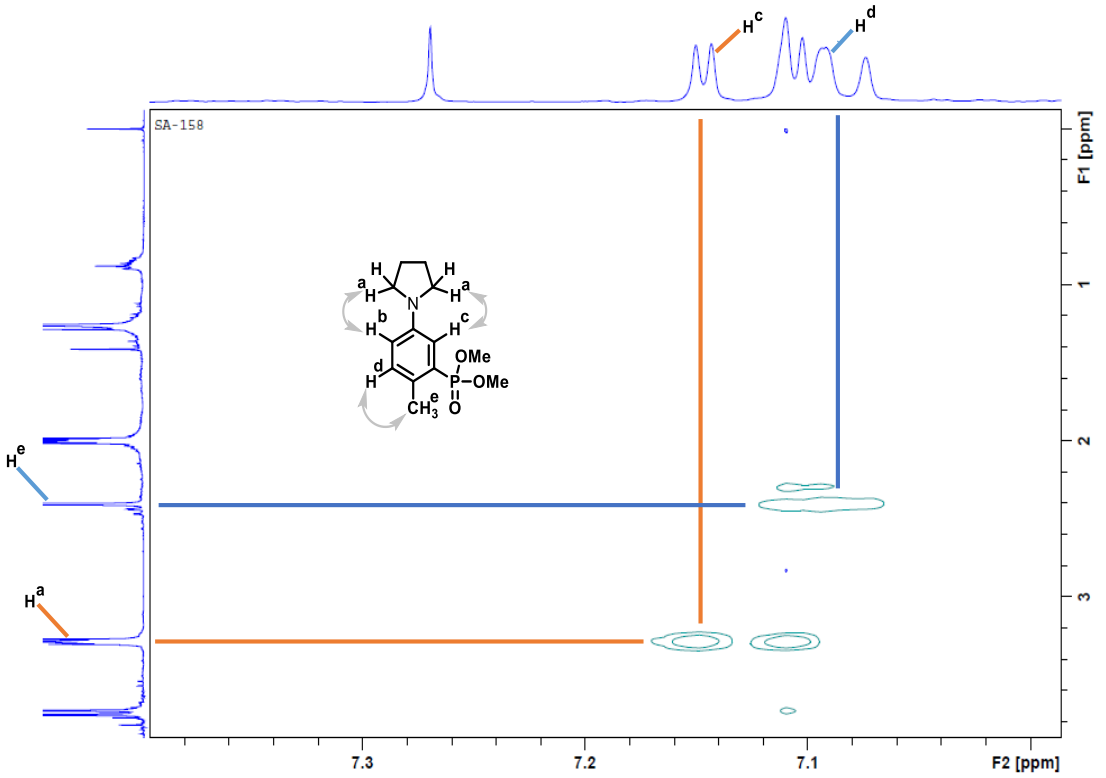

7.15
7.14
7.11
7.10
7.09
7.09
7.07
6.64
6.63
6.62
6.61
3.76
3.73
3.30
3.29
3.27
2.41
2.40
2.02
2.01
2.00
1.99
1.98
N
O
P
O
O
4a
hexane
grease
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
2.14
1.00
6.00
3.91
2.86
3.89

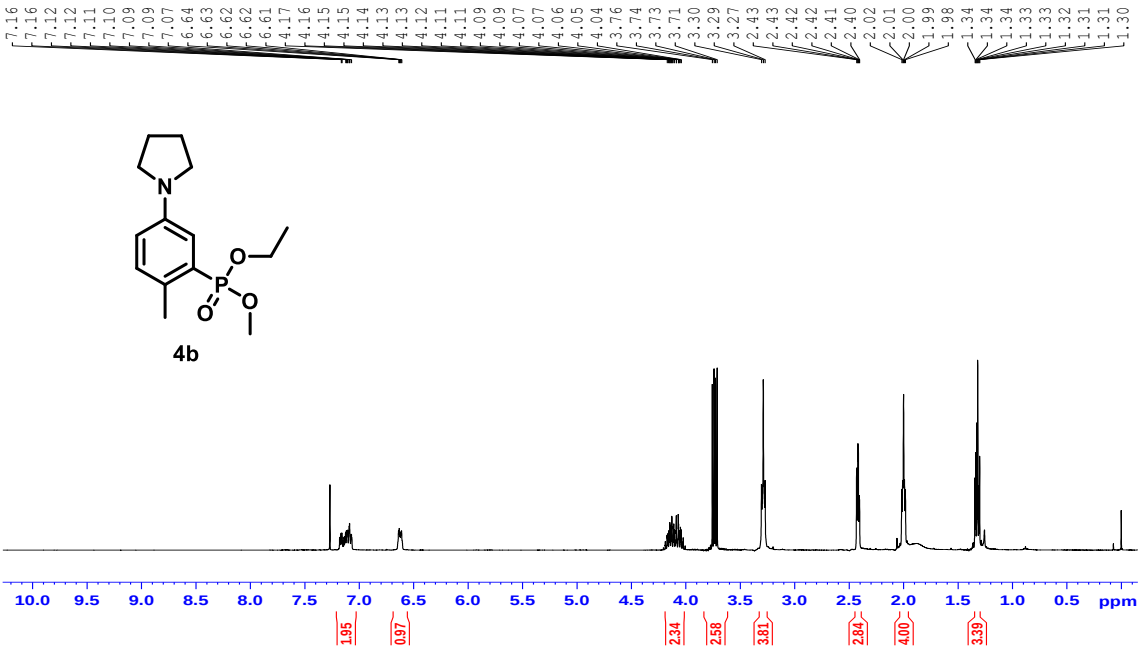

145.7
145.6
132.2
132.0
127.4
127.3
126.1
124.3
117.4
117.3
115.7
52.3
52.3
47.7
25.4
19.8
19.8
N
O
P
O
O
4a
200
180
160
140
120
100
80
60
40
20
0
ppm

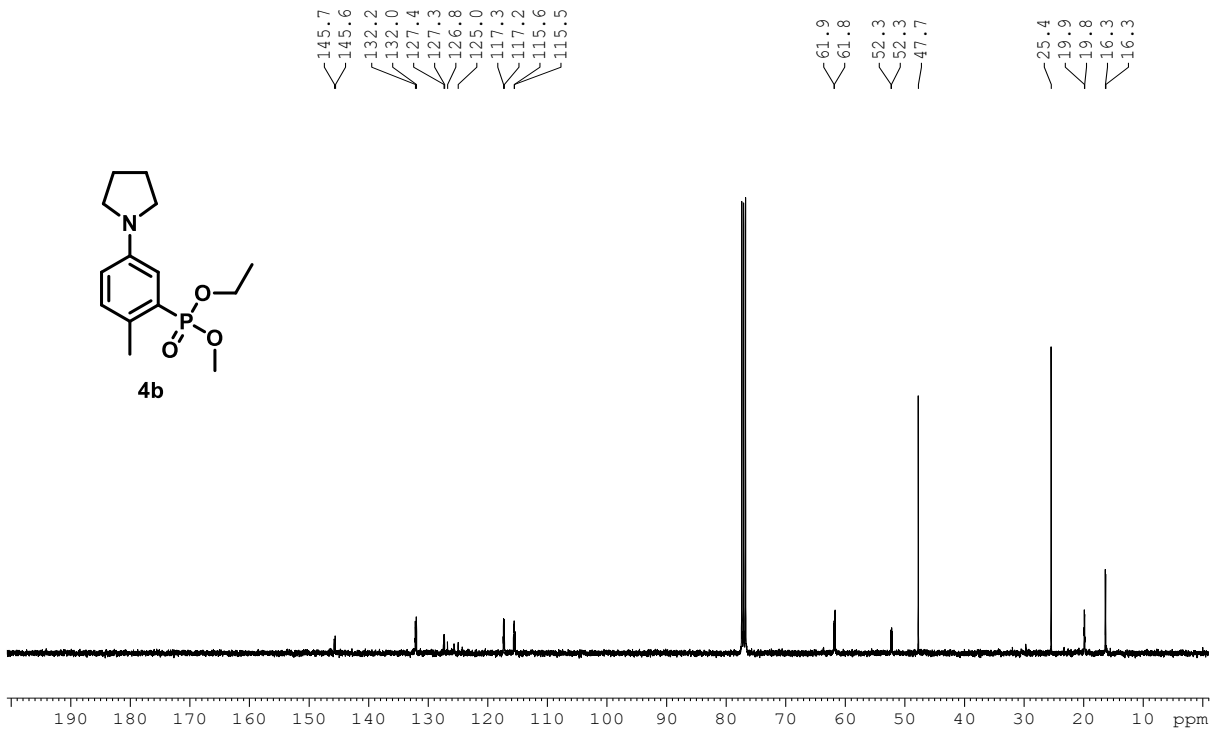

24.20
N
O
P
O
O
4a
100
80
60
40
20
0
-20
-40
-60
-80
ppm

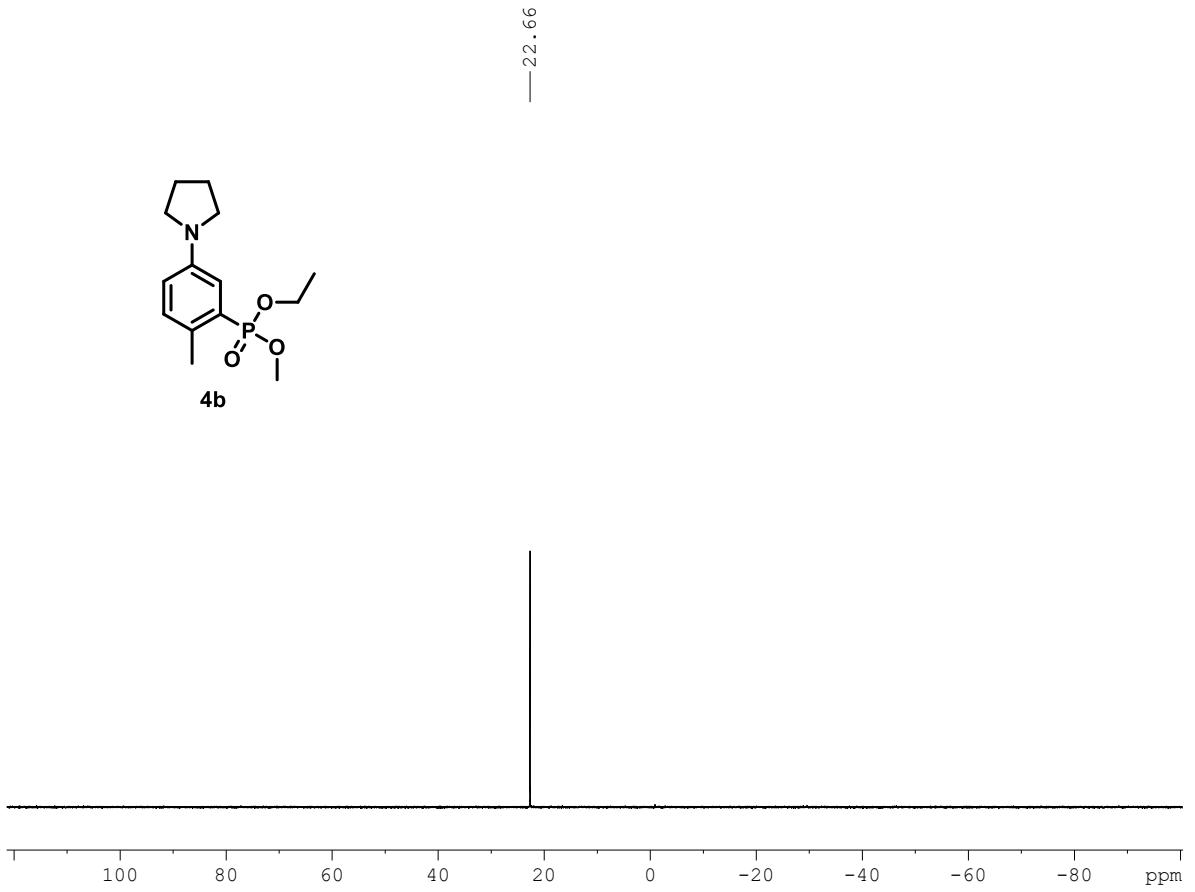
NOESY spectrum of **4a**

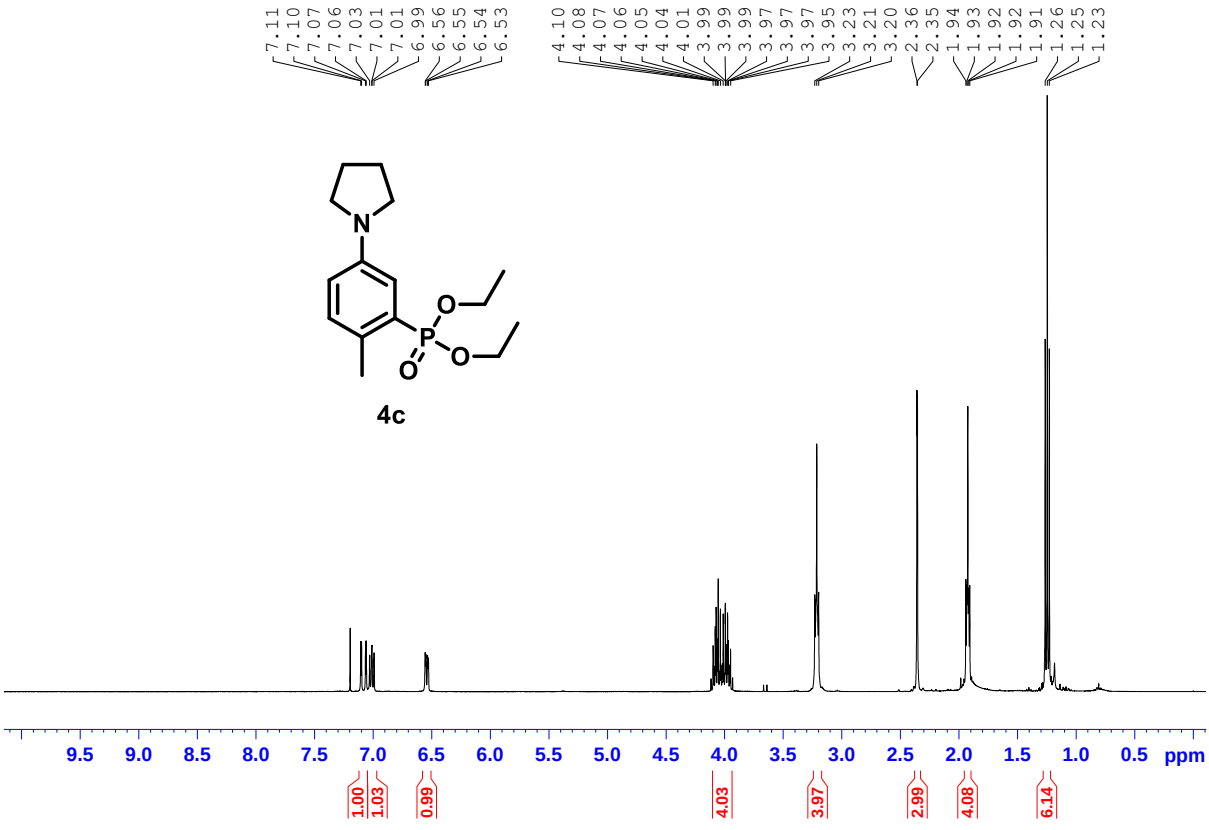


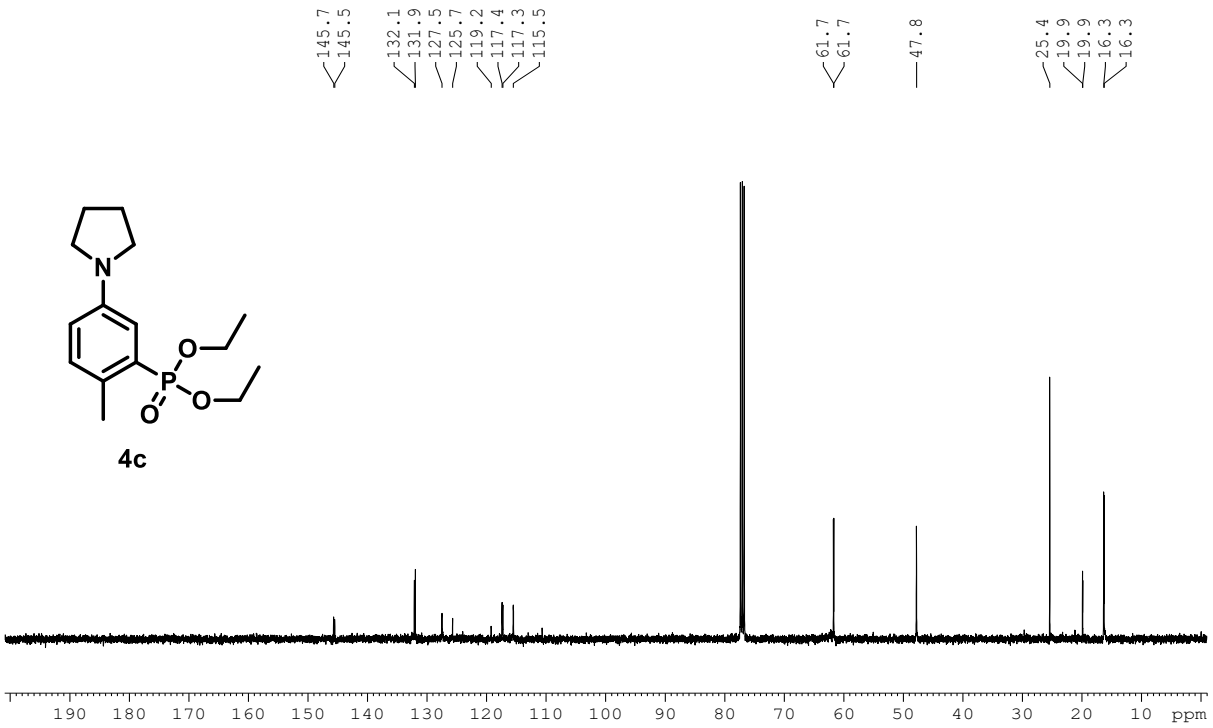



7.16
7.16
7.12
7.12
7.11
7.10
7.09
7.09
7.07
6.64
6.63
6.62
6.62
6.61
4.17
4.16
4.15
4.15
4.14
4.13
4.13
4.12
4.11
4.11
4.09
4.09
4.07
4.07
4.06
4.05
4.04
3.76
3.74
3.73
3.71
3.30
3.29
3.27
2.43
2.42
2.42
2.41
2.40
2.02
2.01
2.00
1.99
1.98
1.34
1.34
1.34
1.33
1.33
1.32
1.31
1.31
1.30
4b
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
1.95
0.97
2.34
2.58
3.81
2.84
4.00
3.39

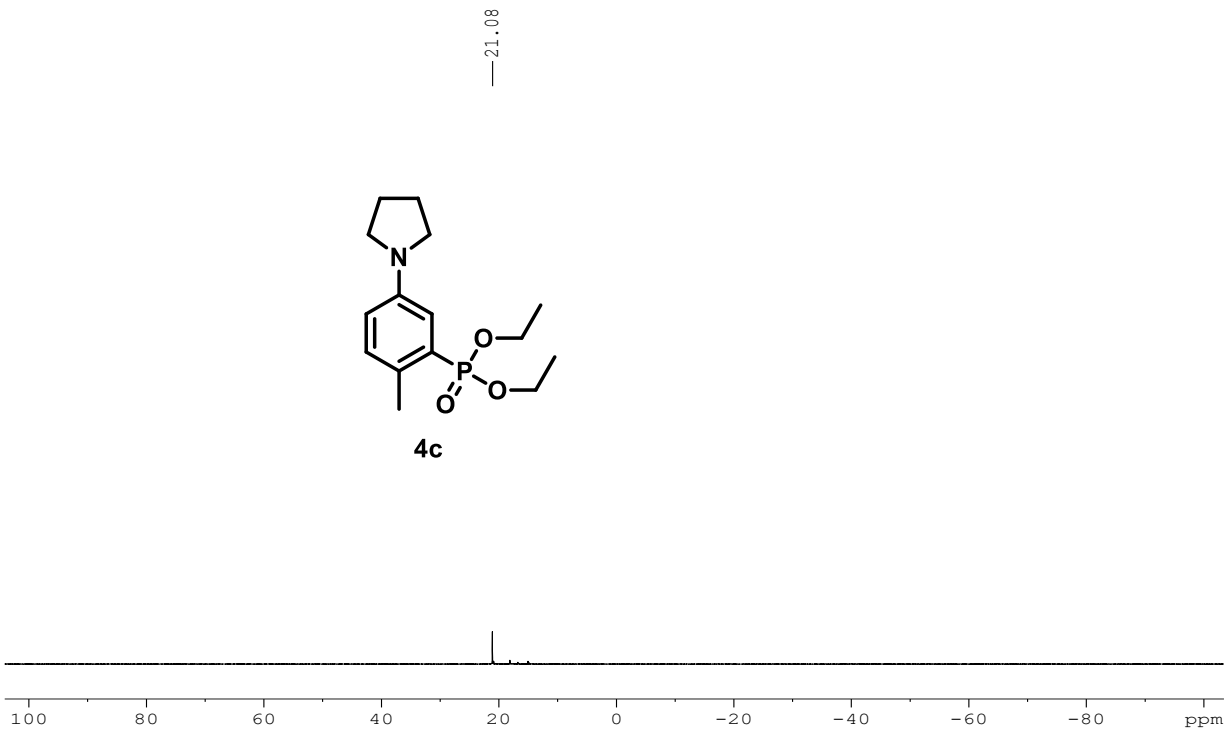

145.7
145.6
132.2
132.0
127.4
127.3
126.8
125.0
117.3
117.2
115.6
115.5
61.9
61.8
52.3
52.3
47.7
25.4
19.9
19.8
16.3
16.3
4b
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm


22.66
4b
100
80
60
40
20
0
-20
-40
-60
-80
ppm

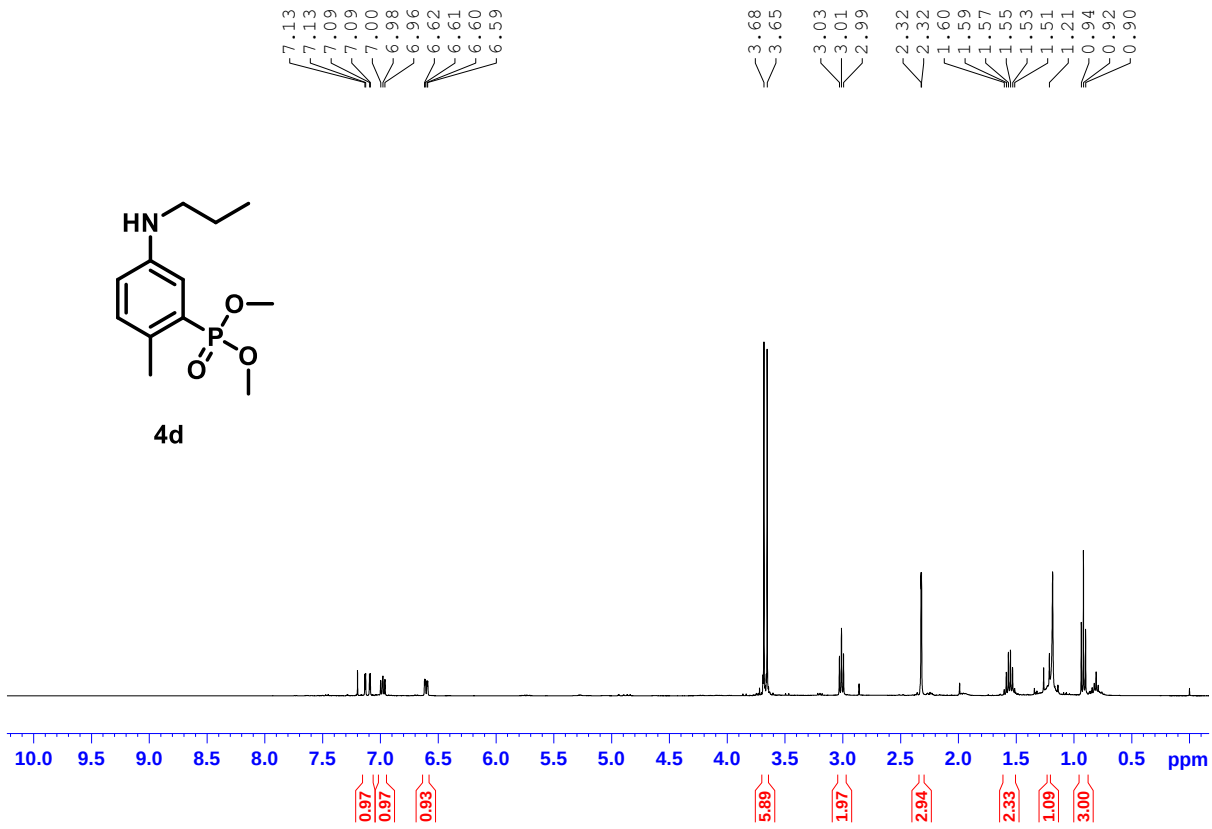

7.11
7.10
7.07
7.06
7.03
7.01
7.01
6.99
6.56
6.55
6.54
6.53
4.10
4.08
4.07
4.06
4.05
4.04
4.01
3.99
3.99
3.99
3.97
3.97
3.97
3.95
3.23
3.21
3.20
2.36
2.35
1.94
1.93
1.92
1.92
1.91
1.26
1.25
1.23
4c
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
1.00
1.03
0.99
4.03
3.97
2.99
4.08
6.14


145.7
145.5
132.1
131.9
127.5
125.7
119.2
117.4
117.3
115.5
61.7
61.7
47.8
25.4
19.9
19.9
16.3
16.3
N
O
P
O
O
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

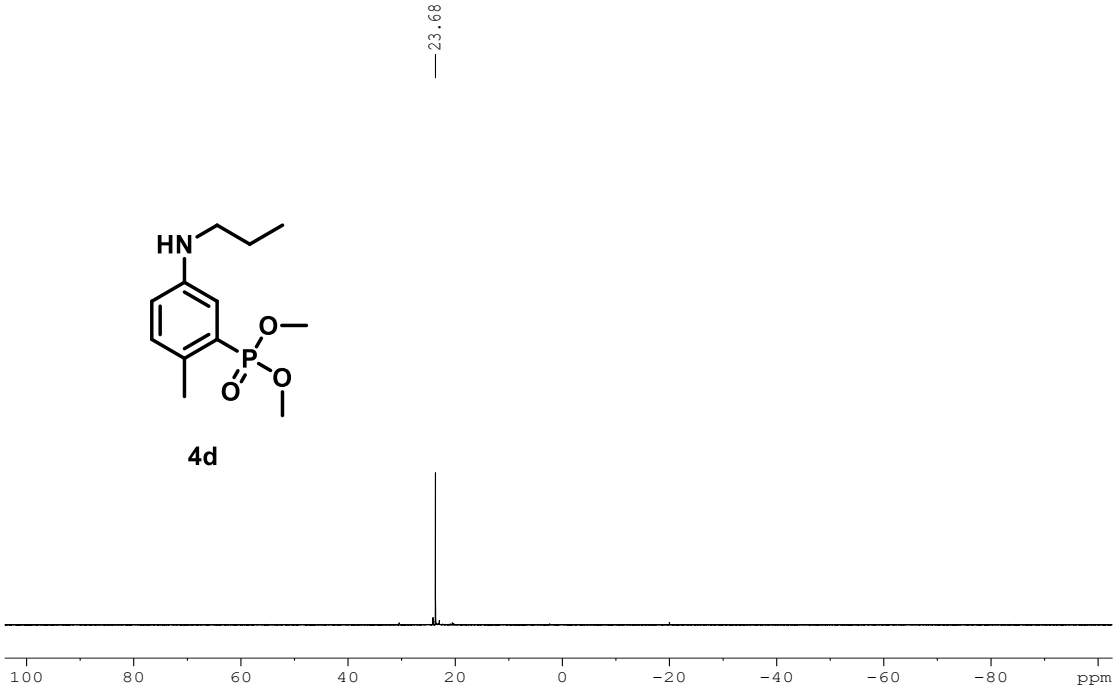
4c

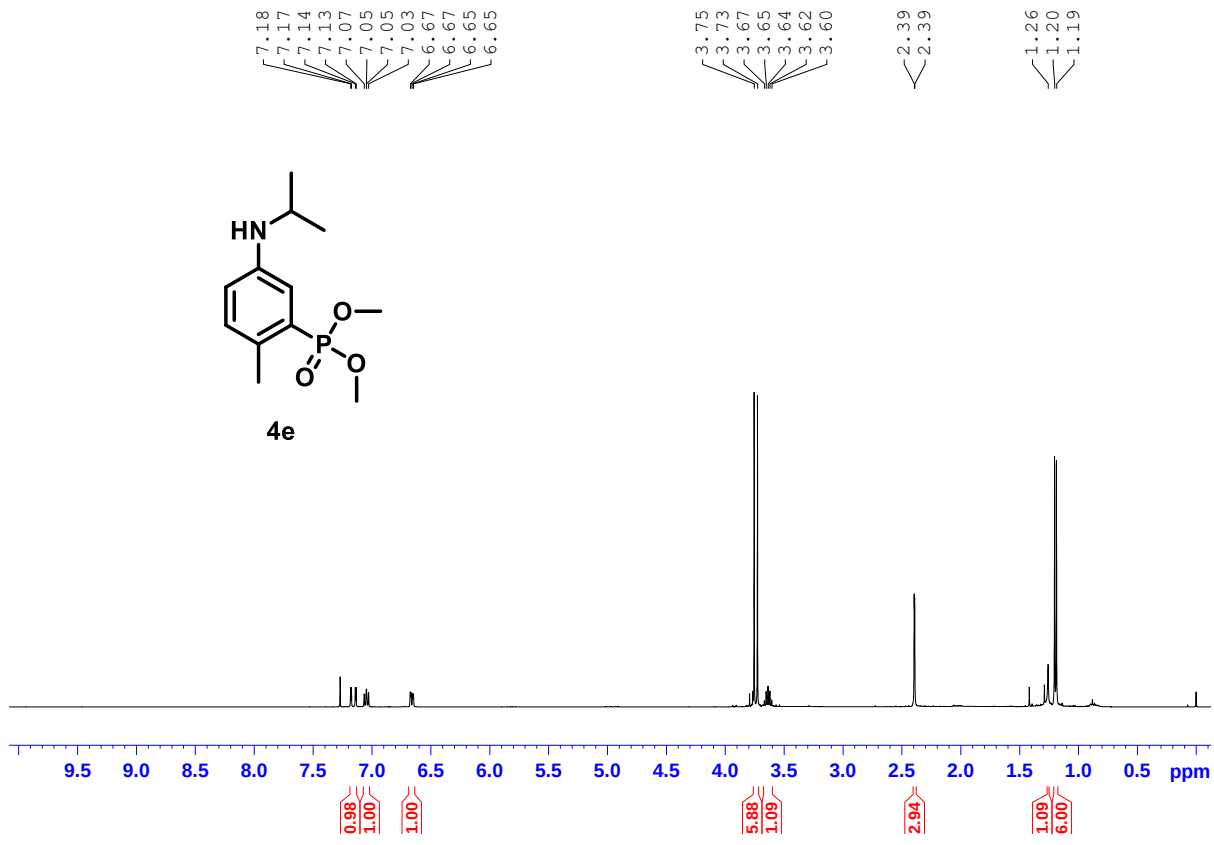

21.08
N
O
P
O
O
100 80 60 40 20 0 -20 -40 -60 -80 ppm

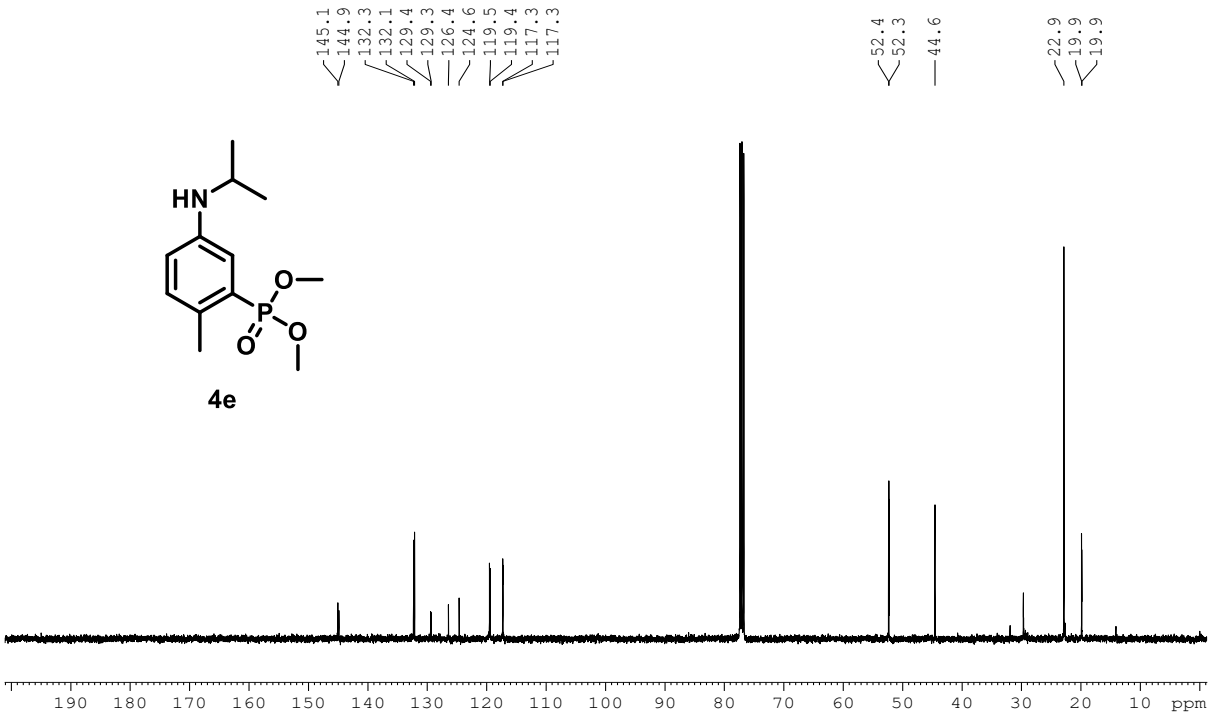
4c

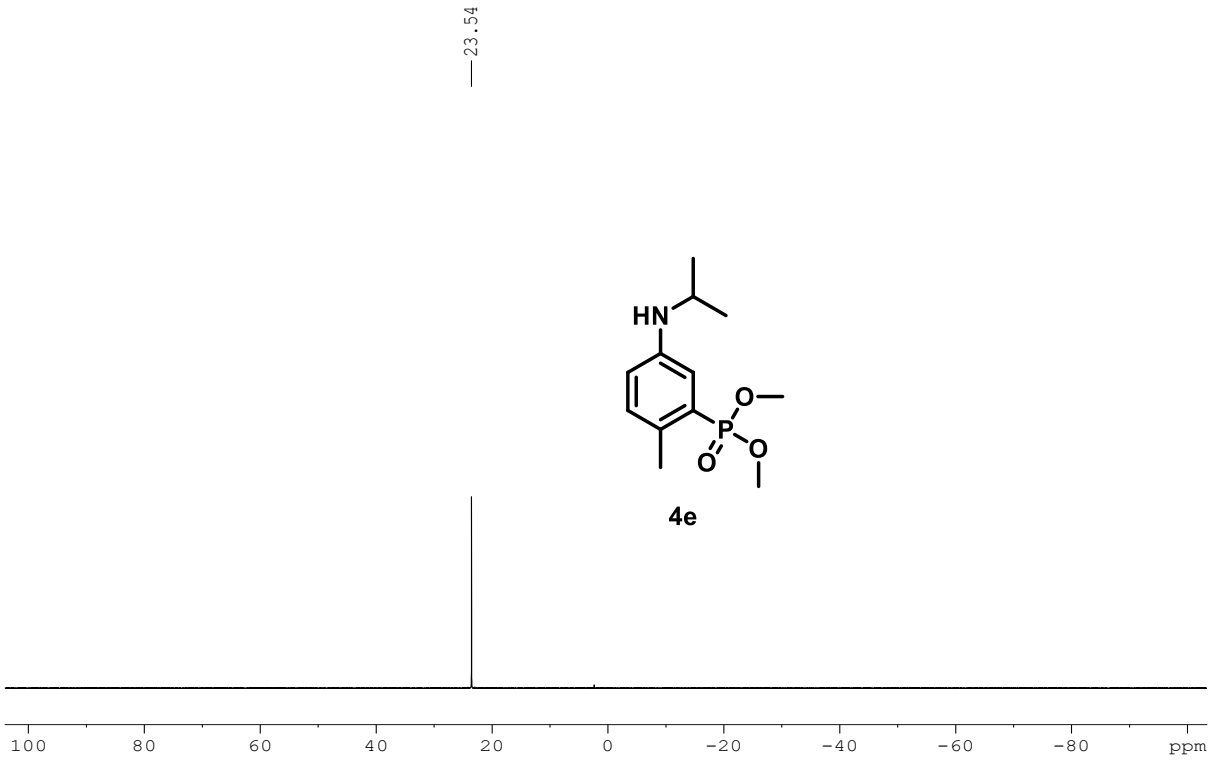

7.13
7.13
7.09
7.09
7.00
6.98
6.96
6.62
6.61
6.60
6.59
3.68
3.65
3.03
3.01
2.99
2.32
2.32
1.60
1.59
1.57
1.55
1.53
1.51
1.21
0.94
0.92
0.90
HN
O
P
O
O
4d
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
0.97
0.97
0.93
5.89
1.97
2.94
2.33
1.09
3.00

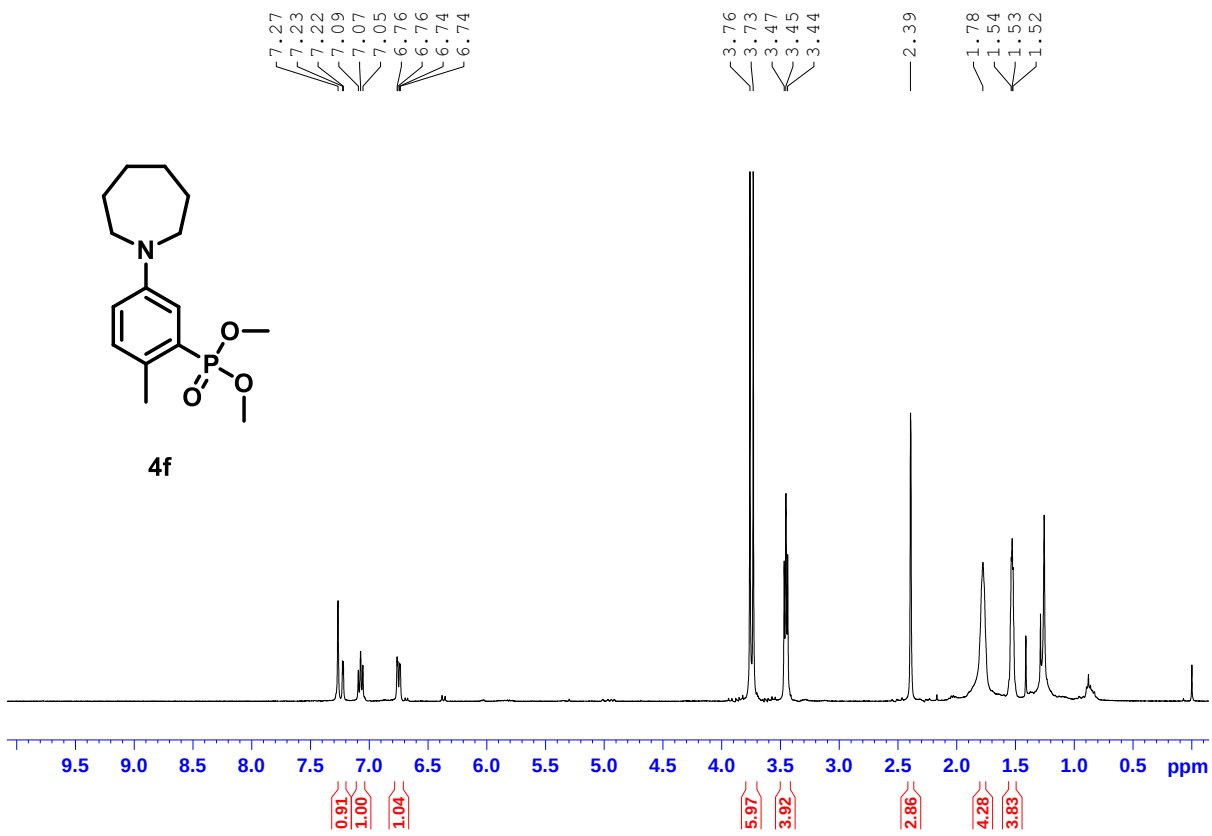

146.2
146.0
132.3
132.1
129.4
129.3
126.4
124.6
118.8
118.7
116.6
116.6
52.4
52.3
45.9
22.7
19.9
19.9
11.6
HN
O
P
O
O
4d
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

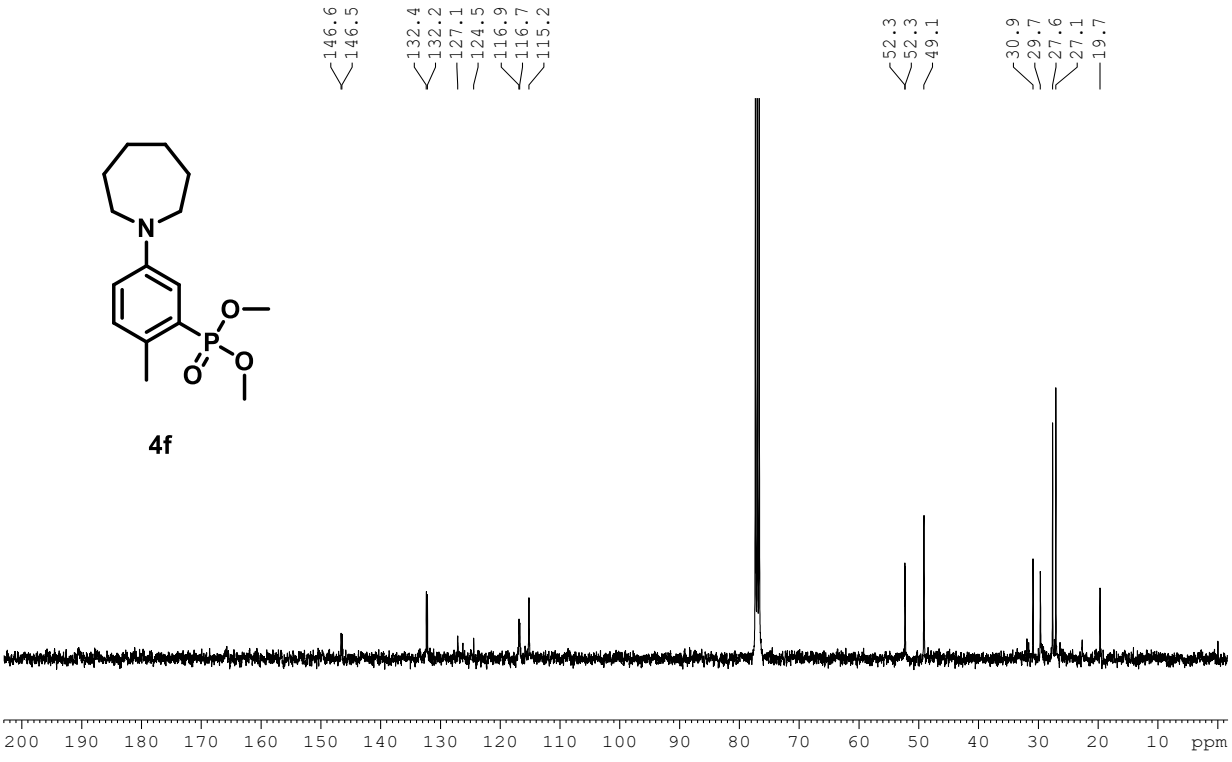

23.68
HN
O
P
O
O
4d
100
80
60
40
20
0
-20
-40
-60
-80
ppm

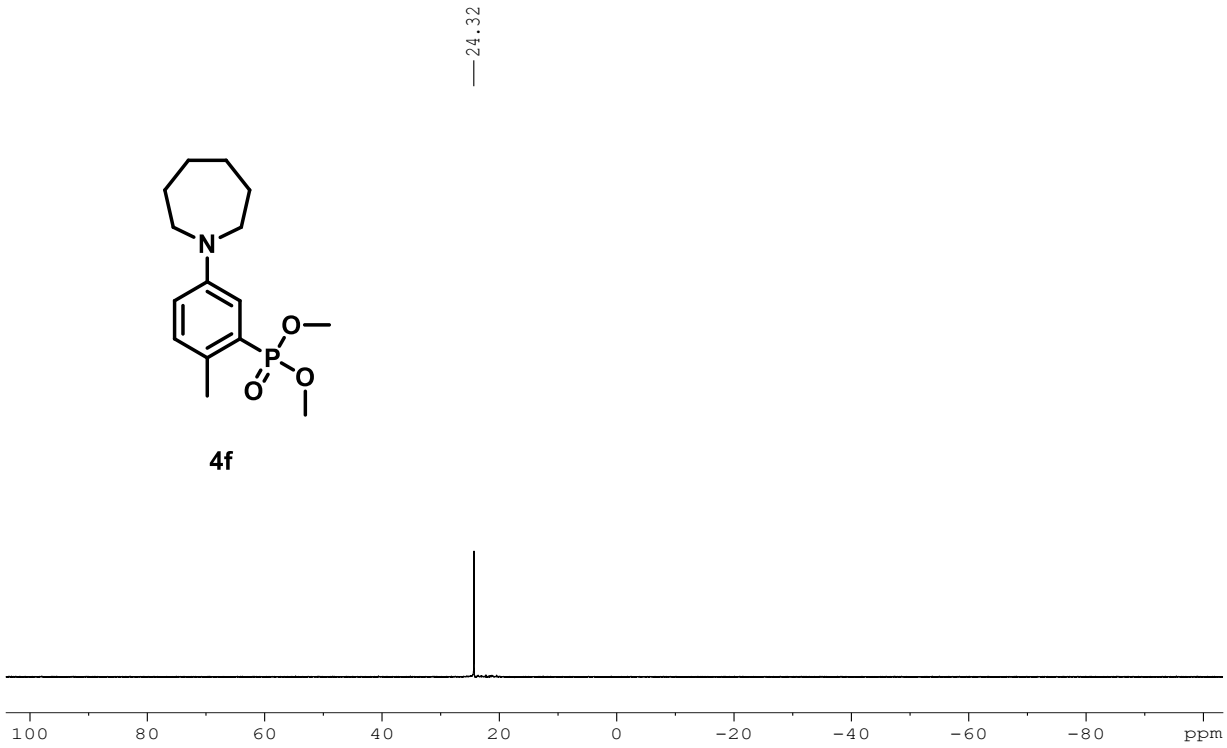

7.18
7.17
7.14
7.13
7.07
7.05
7.05
7.03
6.67
6.67
6.65
6.65
3.75
3.73
3.67
3.65
3.64
3.62
3.60
2.39
2.39
1.26
1.20
1.19
HN
O
P
O
O
4e
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
0.98
1.00
1.00
5.88
1.09
2.94
1.09
6.00

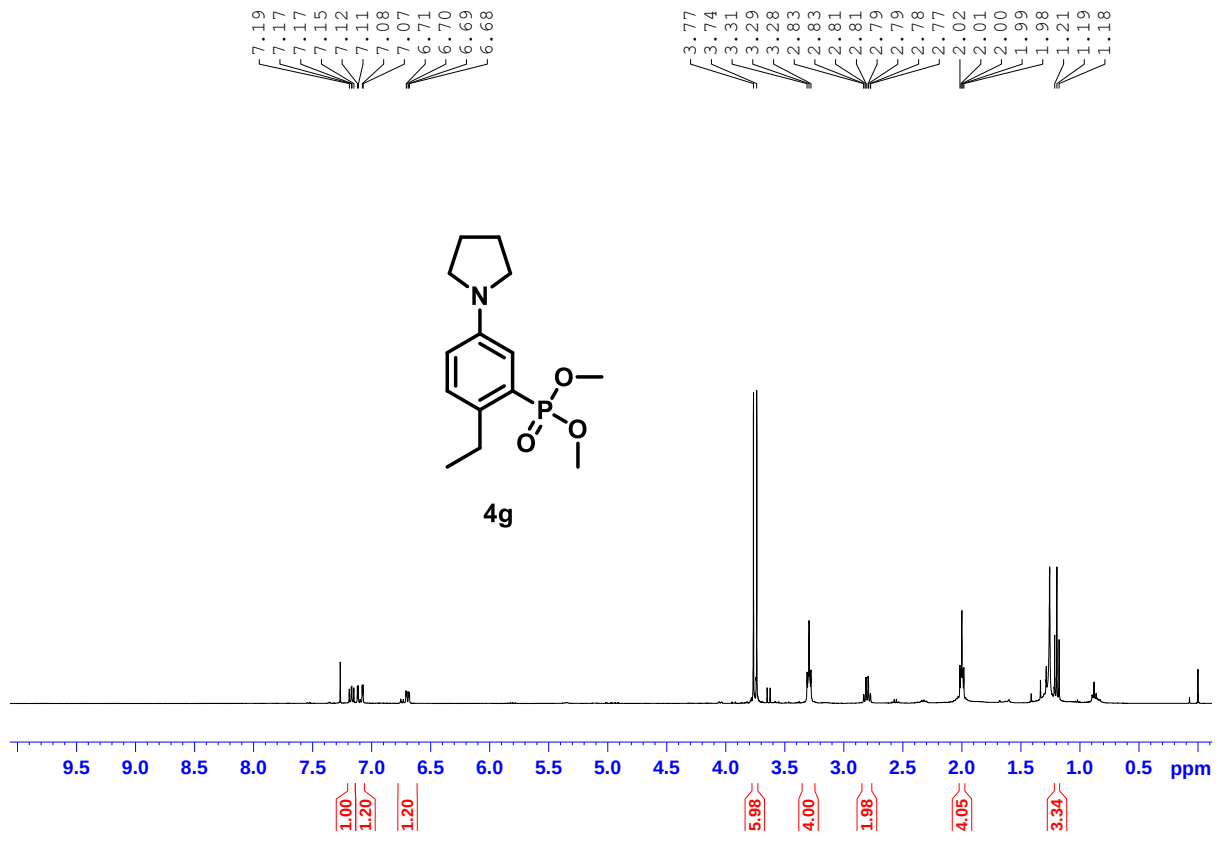

145.1
144.9
132.3
132.1
129.4
129.3
126.4
124.6
119.5
119.4
117.3
117.3
52.4
52.3
44.6
22.9
19.9
19.9
HN
O
P
O
O
4e
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

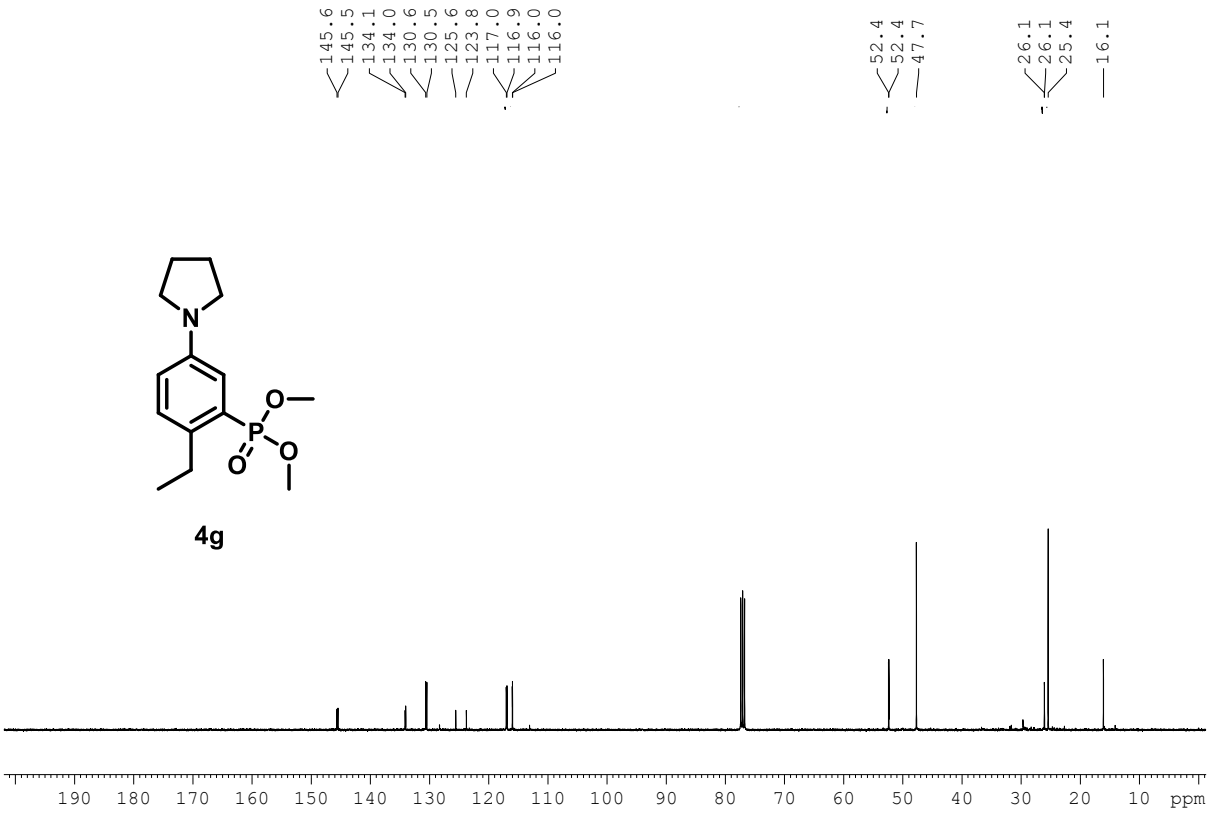

23.54
HN
O
P
O
O
4e
100 80 60 40 20 0 -20 -40 -60 -80 ppm

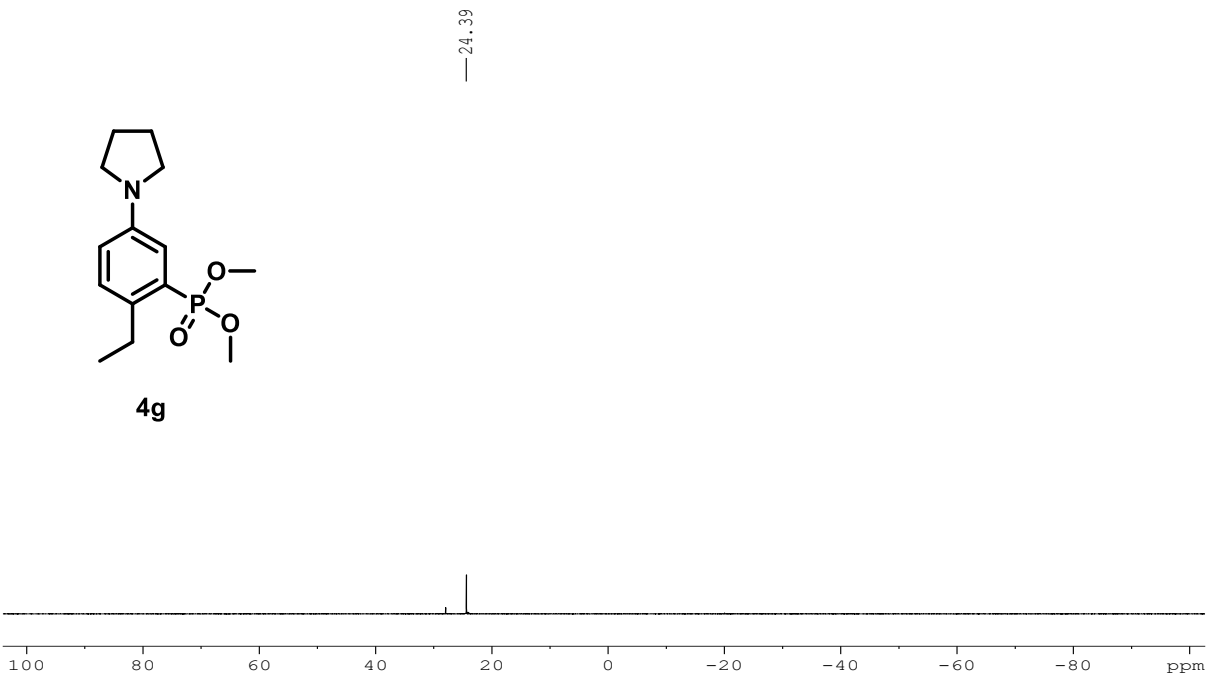

7.27
7.23
7.22
7.09
7.07
7.05
6.76
6.76
6.74
6.74
3.76
3.73
3.47
3.45
3.44
2.39
1.78
1.54
1.53
1.52
4f
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
0.91
1.00
1.04
5.97
3.92
2.86
4.28
3.83

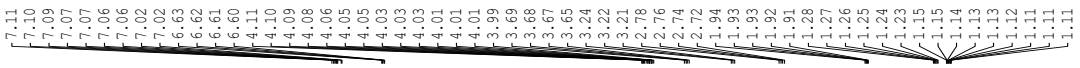

146.6
146.5
132.4
132.2
127.1
124.5
116.9
116.7
115.2
52.3
52.3
49.1
30.9
29.7
27.6
27.1
19.7
4f
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

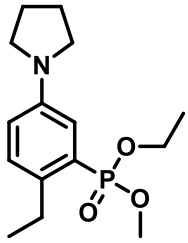

24.32
4f
100
80
60
40
20
0
-20
-40
-60
-80
ppm


7.19
7.17
7.17
7.15
7.12
7.11
7.08
7.07
6.71
6.70
6.69
6.68
3.77
3.74
3.31
3.29
3.28
2.83
2.83
2.81
2.81
2.79
2.79
2.78
2.77
2.02
2.01
2.00
1.99
1.98
1.21
1.19
1.18
4g
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
1.00
1.20
1.20
5.98
4.00
1.98
4.05
3.34

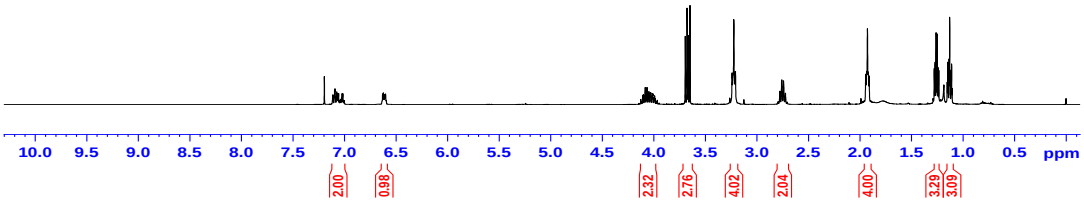

145.6
145.5
134.1
134.0
130.6
130.5
125.6
123.8
117.0
116.9
116.0
116.0
52.4
52.4
47.7
26.1
26.1
25.4
16.1
4g
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

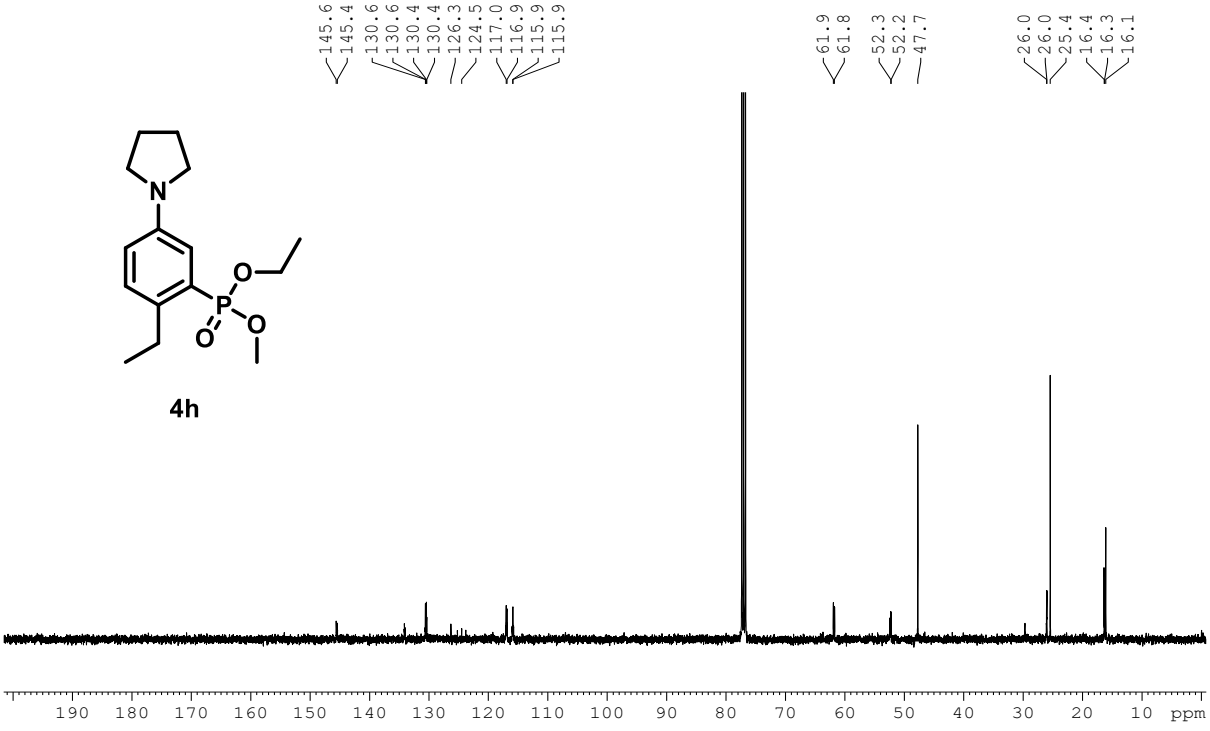

24.39
4g
100 80 60 40 20 0 -20 -40 -60 -80 ppm


7.11
7.10
7.09
7.07
7.07
7.06
7.06
7.02
7.02
6.63
6.62
6.61
6.60
4.11
4.10
4.09
4.08
4.06
4.05
4.05
4.03
4.03
4.03
4.01
4.01
4.01
3.99
3.69
3.68
3.67
3.65
3.24
3.22
3.21
2.78
2.76
2.74
2.72
1.94
1.93
1.93
1.92
1.91
1.28
1.27
1.26
1.25
1.24
1.23
1.15
1.15
1.14
1.13
1.13
1.12
1.11
1.11
1.11


N
O
P
O
O

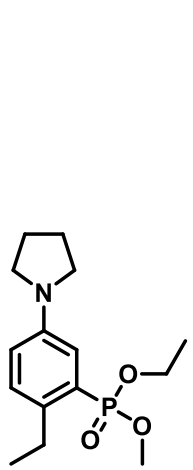
4h


10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
2.00
0.98
2.32
2.76
4.02
2.04
4.00
3.29
3.09

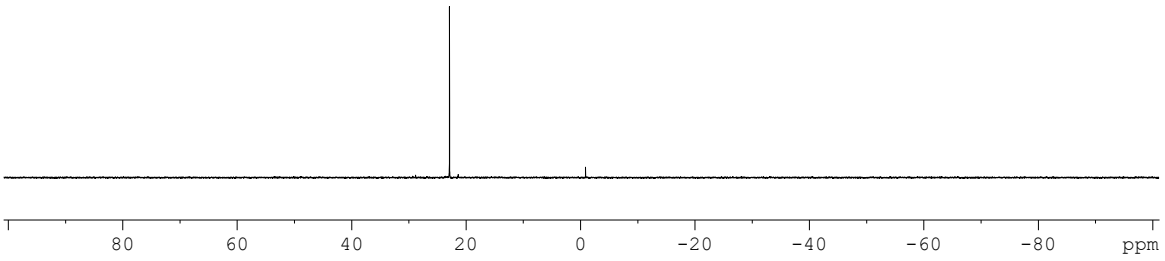

145.6
145.4
130.6
130.6
130.4
130.4
126.3
124.5
117.0
116.9
115.9
115.9
61.9
61.8
52.3
52.2
47.7
26.0
26.0
25.4
16.4
16.3
16.1
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

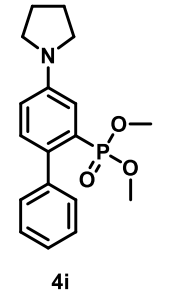
N
O
P
O
O

4h



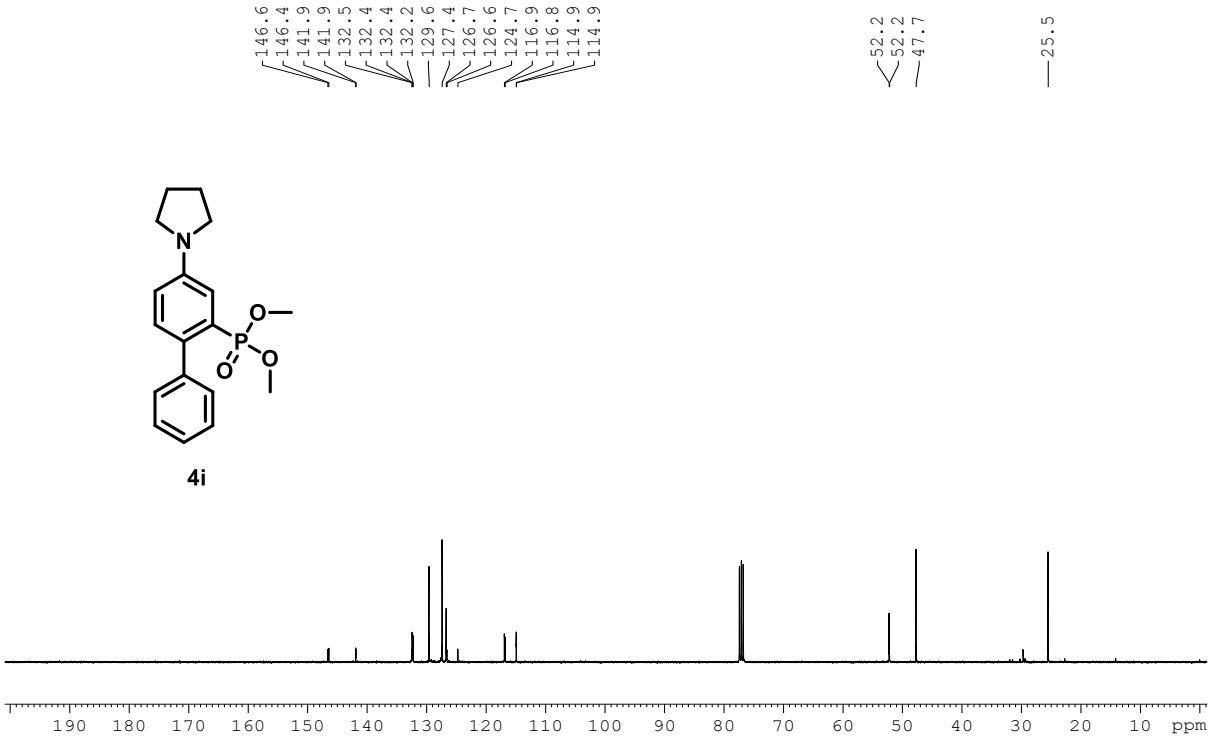
4h

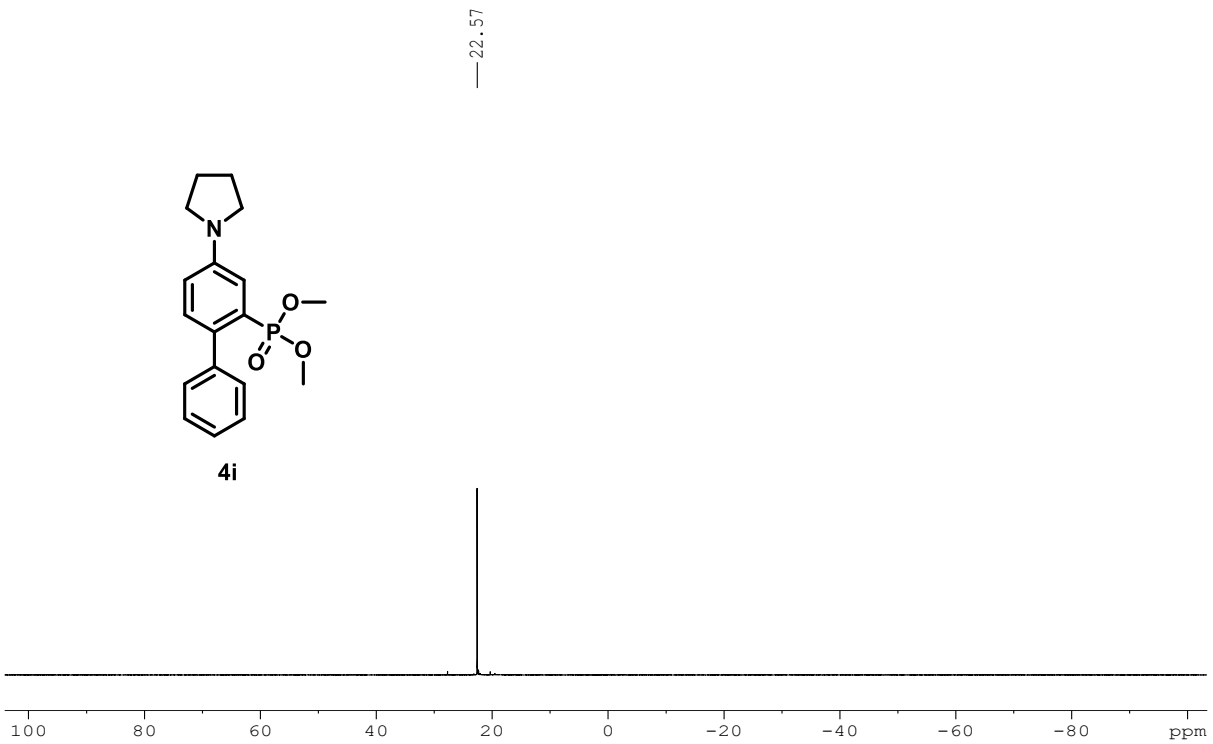

22.86
80
60
40
20
0
-20
-40
-60
-80
ppm

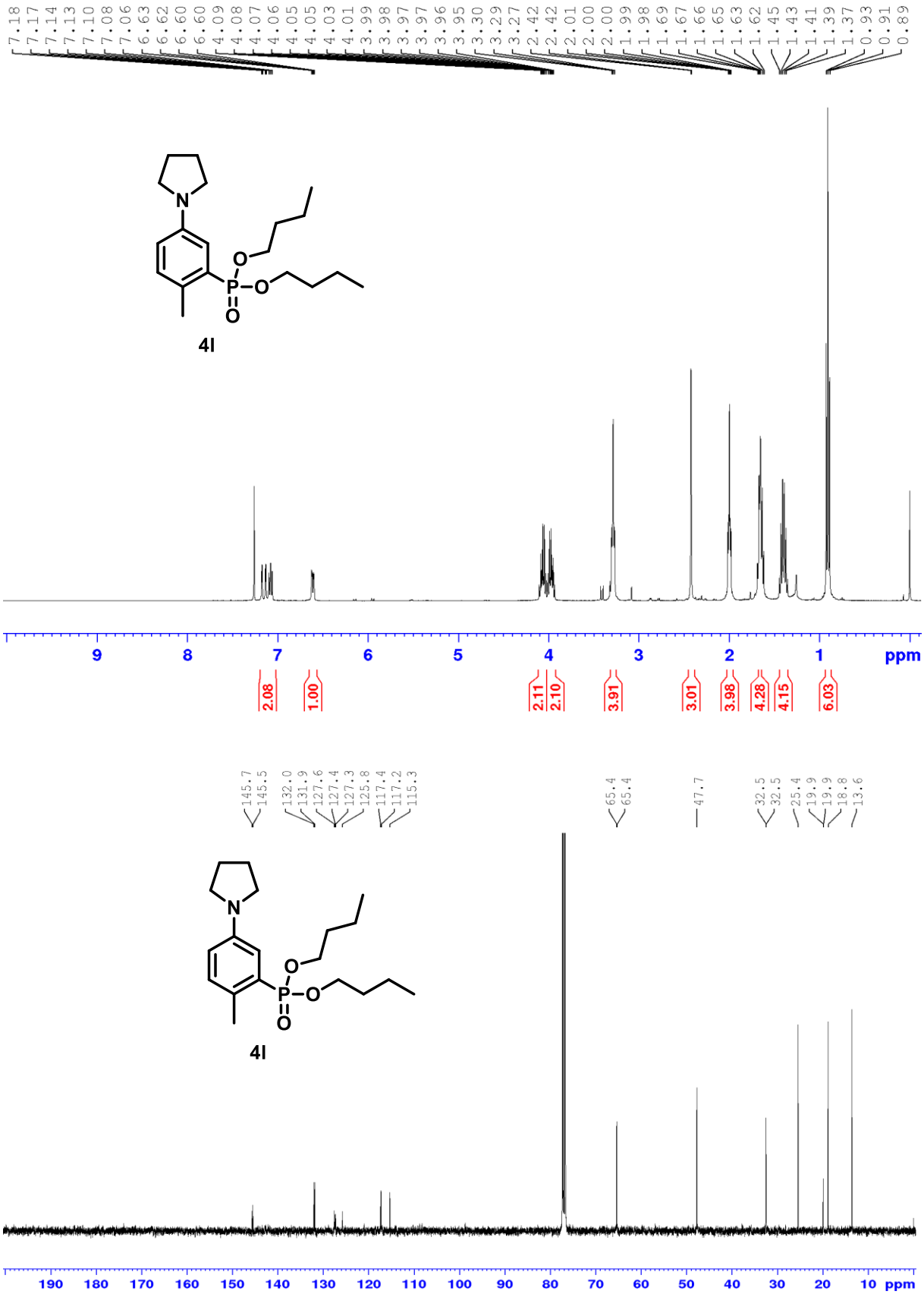


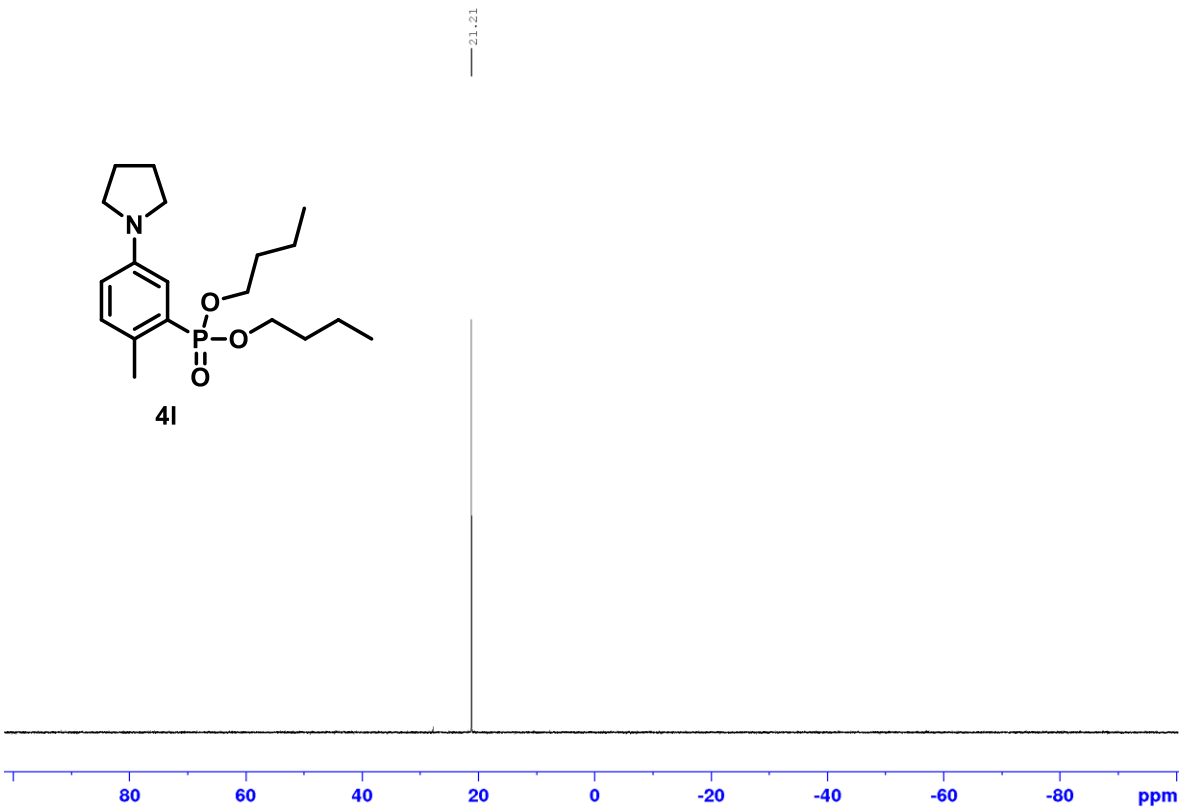
4i

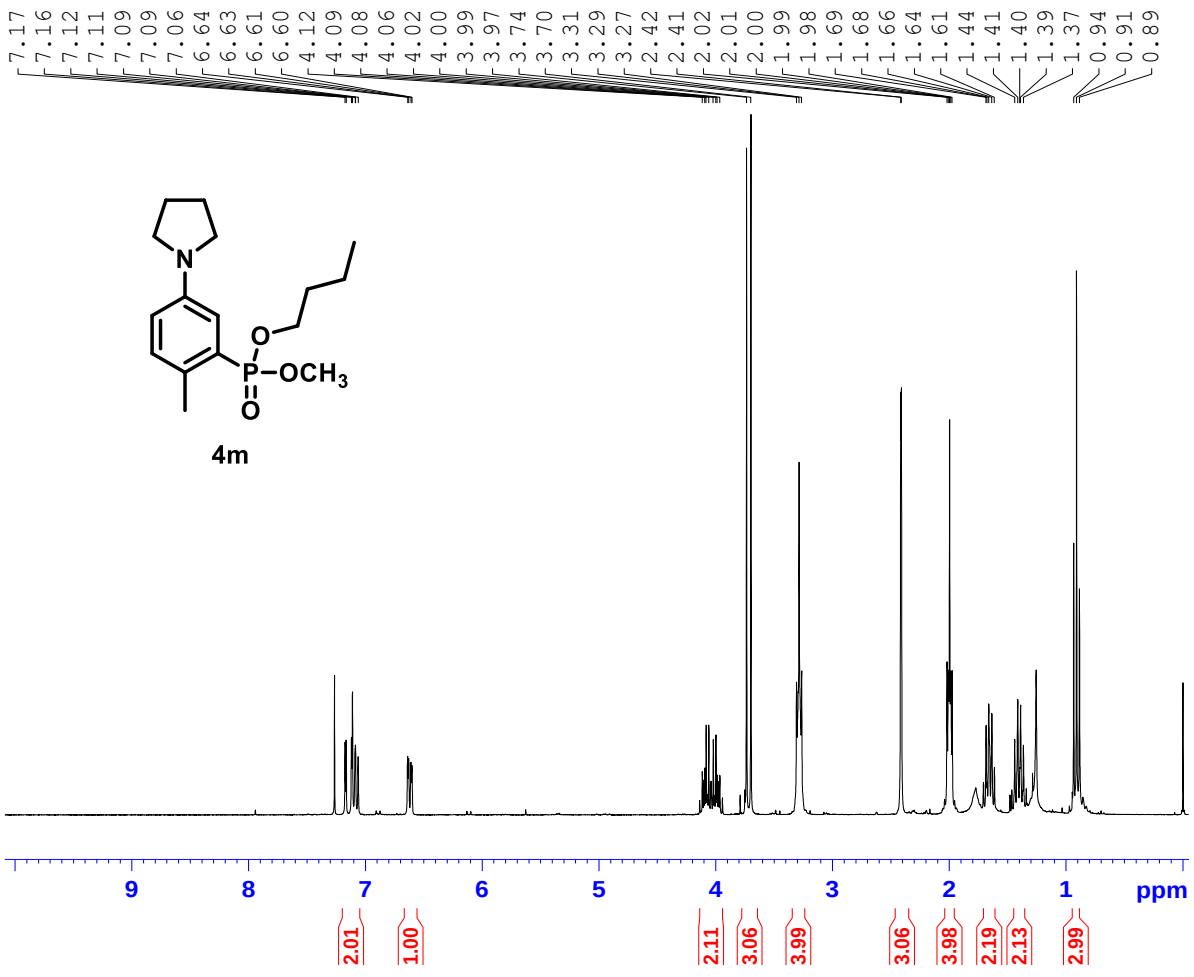
7.40
7.39
7.38
7.37
7.37
7.35
7.35
7.33
7.32
7.32
7.23
7.22
7.19
7.19
7.18
7.17
7.17
7.15
6.73
6.73
6.71
6.71
3.51
3.48
3.37
3.35
3.33
2.05
2.04
2.03
2.02
2.01
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
5.22
2.14
0.99
5.97
4.00
3.97

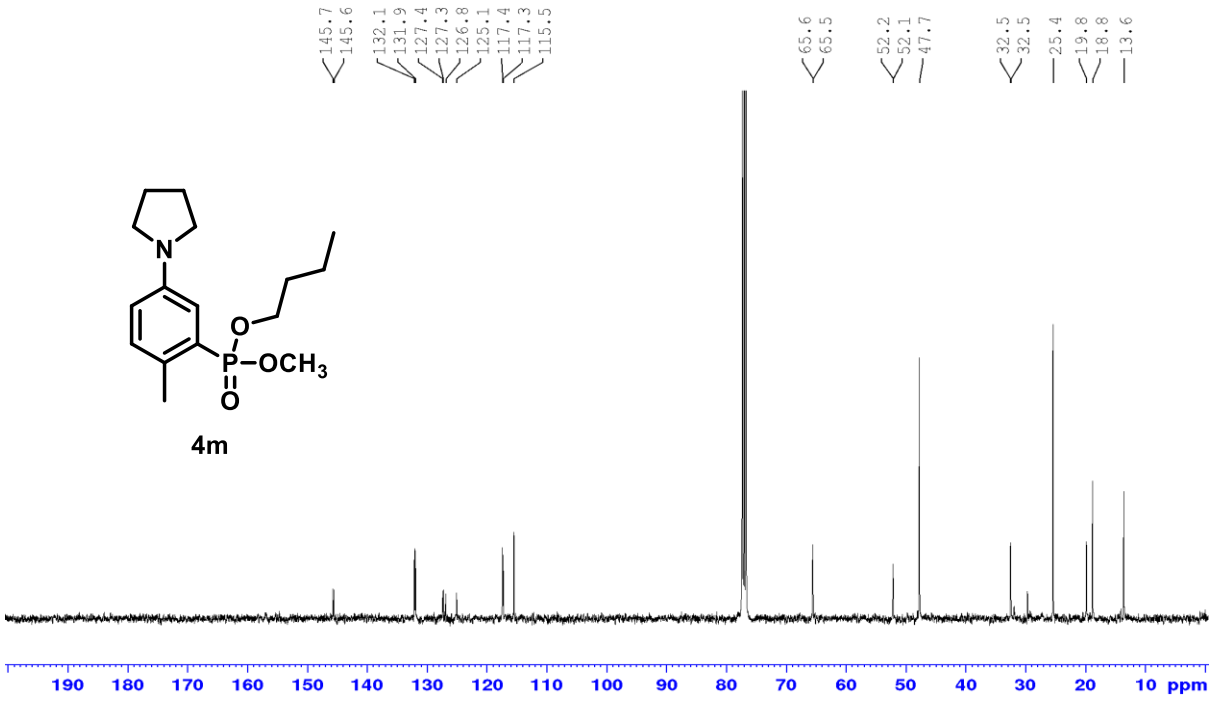

146.6
146.4
141.9
141.9
132.5
132.4
132.4
132.2
129.6
127.4
126.7
126.6
124.7
116.9
116.8
114.9
114.9
52.2
52.2
47.7
25.5
4i
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm


22.57
4i
100 80 60 40 20 0 -20 -40 -60 -80 ppm

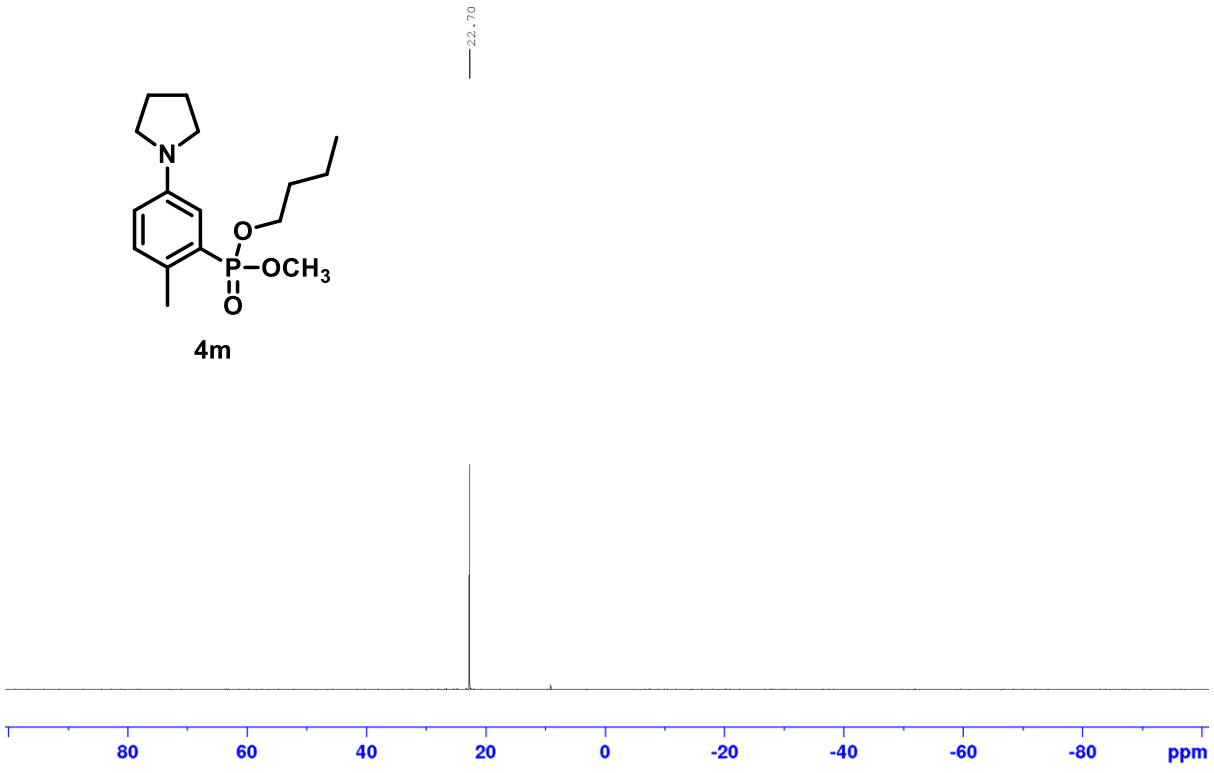

7.18
7.17
7.14
7.13
7.10
7.08
7.06
6.63
6.62
6.60
6.60
4.09
4.08
4.07
4.06
4.05
4.05
4.03
4.01
3.99
3.98
3.97
3.97
3.96
3.95
3.30
3.29
3.27
2.42
2.42
2.01
2.00
2.00
1.99
1.98
1.69
1.67
1.66
1.65
1.63
1.62
1.45
1.43
1.41
1.39
1.37
0.93
0.91
0.89
4l
9
8
7
6
5
4
3
2
1
ppm
2.08
1.00
2.11
2.10
3.91
3.01
3.98
4.28
4.15
6.03
145.7
145.5
132.0
131.9
127.6
127.4
127.3
125.8
117.4
117.2
115.3
65.4
65.4
47.7
32.5
32.5
25.4
19.9
19.9
18.8
13.6
4l
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm


21.21
N
O
P
O
O
4l
80
60
40
20
0
-20
-40
-60
-80
ppm

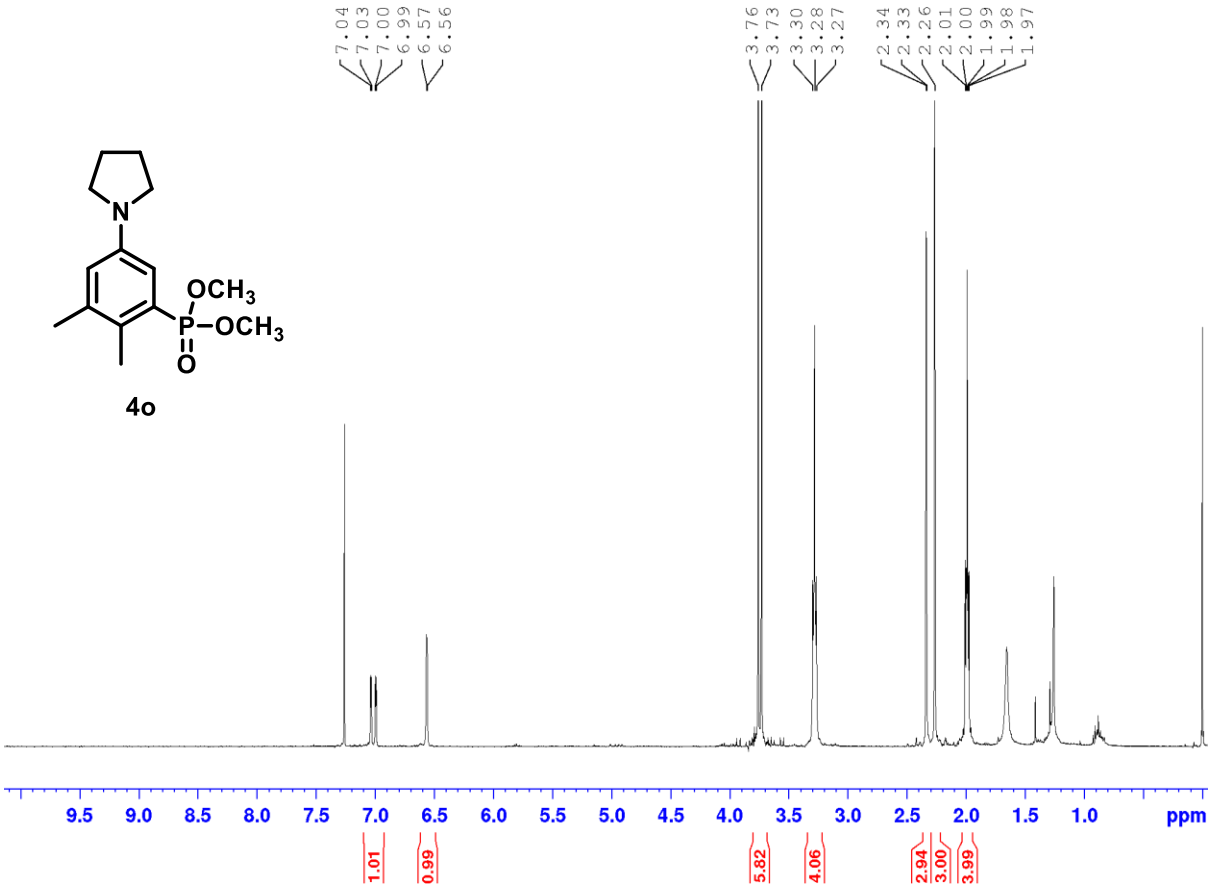

7.17
7.16
7.12
7.11
7.09
7.09
7.06
6.64
6.63
6.61
6.60
4.12
4.09
4.08
4.06
4.02
4.00
3.99
3.97
3.74
3.70
3.31
3.29
3.27
2.42
2.41
2.02
2.01
2.00
1.99
1.98
1.69
1.68
1.66
1.64
1.61
1.44
1.41
1.40
1.39
1.37
0.94
0.91
0.89
N
O
P
OCH3
O
4m
9
8
7
6
5
4
3
2
1
ppm
2.01
1.00
2.11
3.06
3.99
3.06
3.98
2.19
2.13
2.99

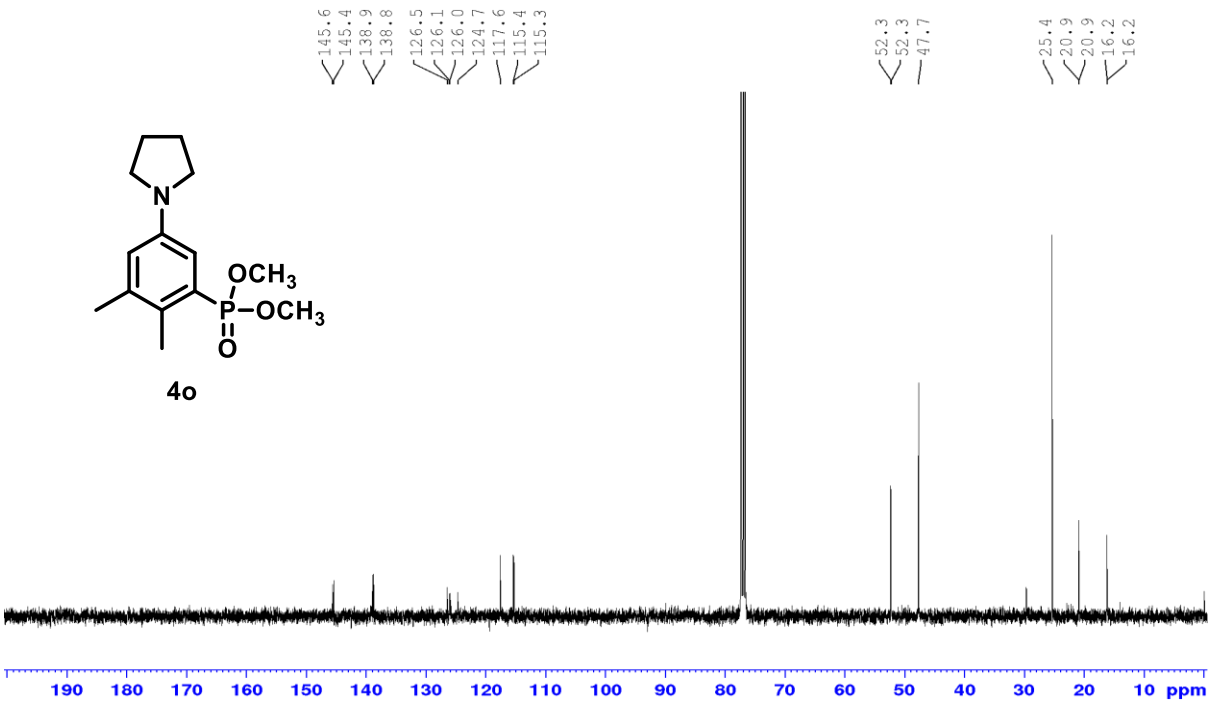

145.7
145.6
132.1
131.9
127.4
127.3
126.8
125.1
117.4
117.3
115.5
65.6
65.5
52.2
52.1
47.7
32.5
32.5
25.4
19.8
18.8
13.6
N
O
P–OCH3
O
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

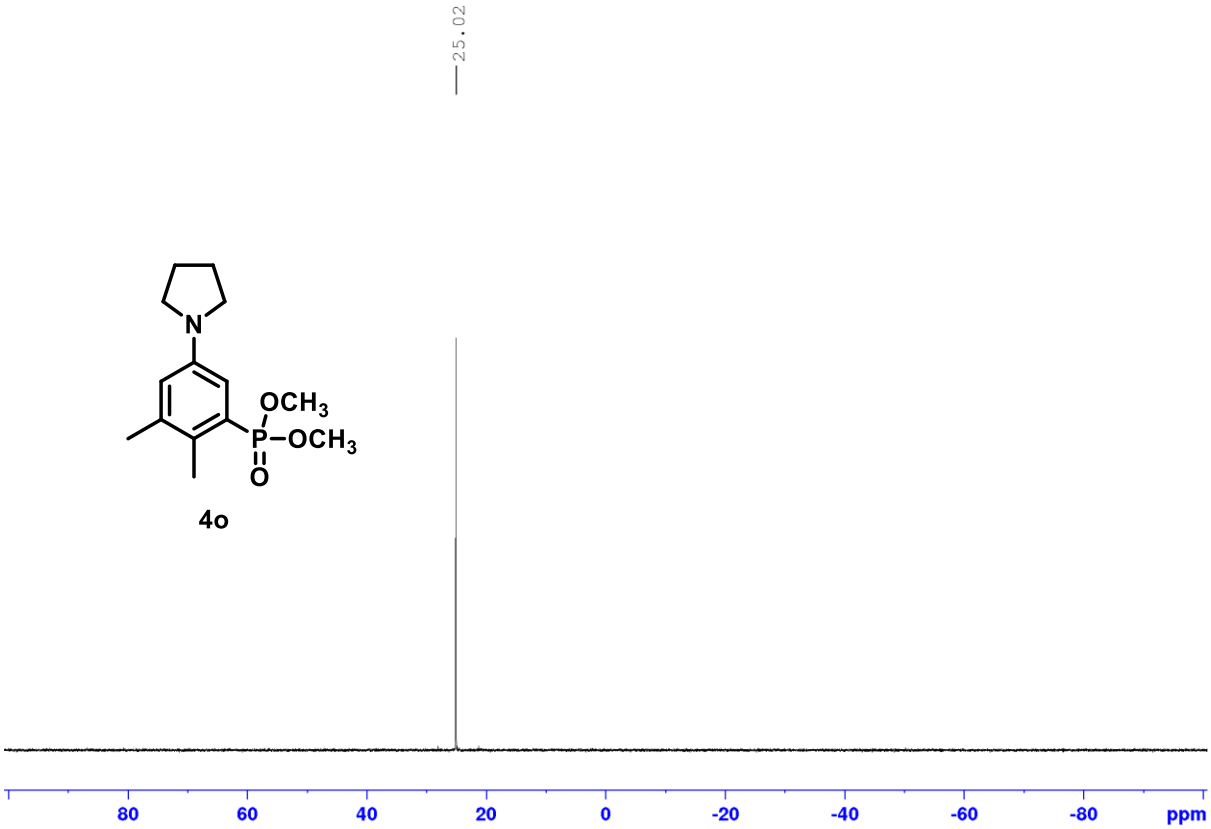
4m

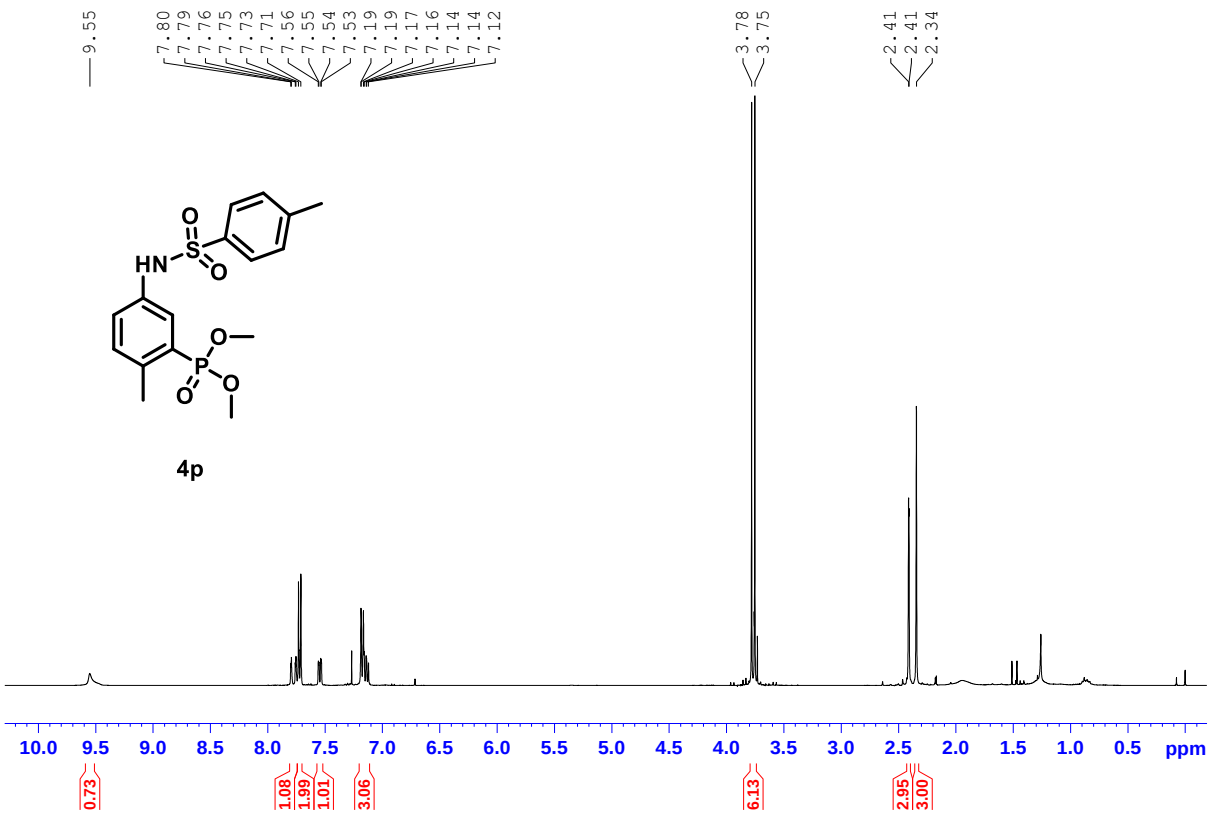

22.70
N
O
P–OCH3
O
80 60 40 20 0 -20 -40 -60 -80 ppm

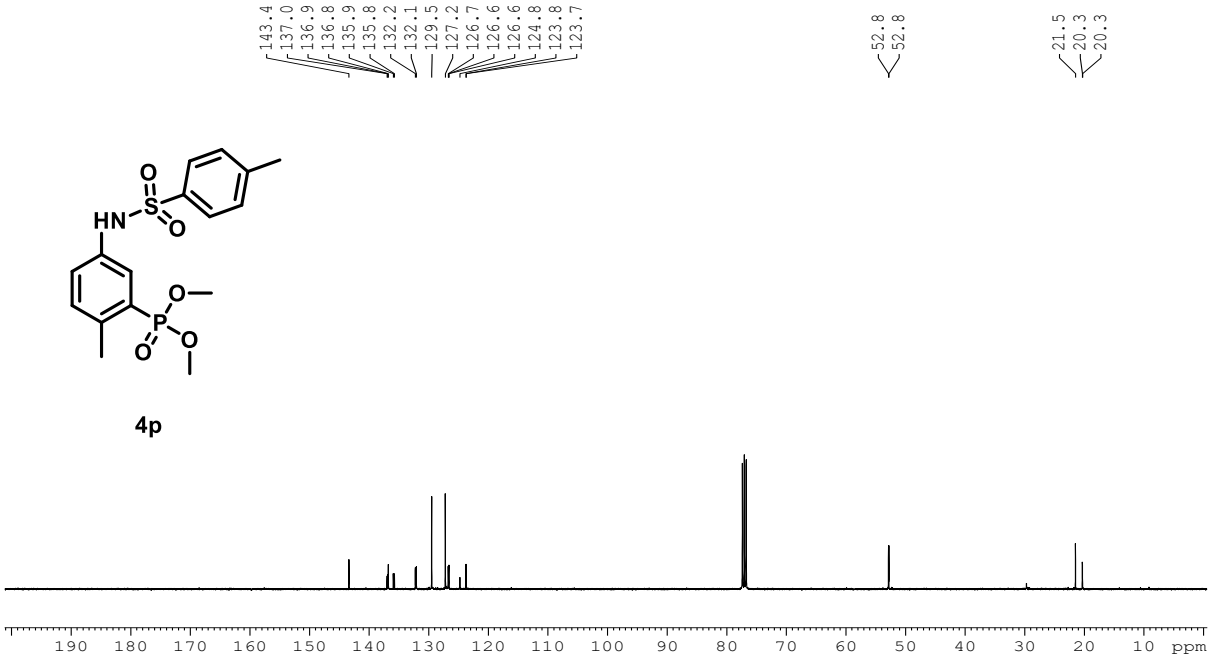
4m


7.04
7.03
7.00
6.99
6.57
6.56
3.76
3.73
3.30
3.28
3.27
2.34
2.33
2.26
2.01
2.00
1.99
1.98
1.97
OCH3
P–OCH3
O
4o
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
1.01
0.99
5.82
4.06
2.94
3.00
3.99

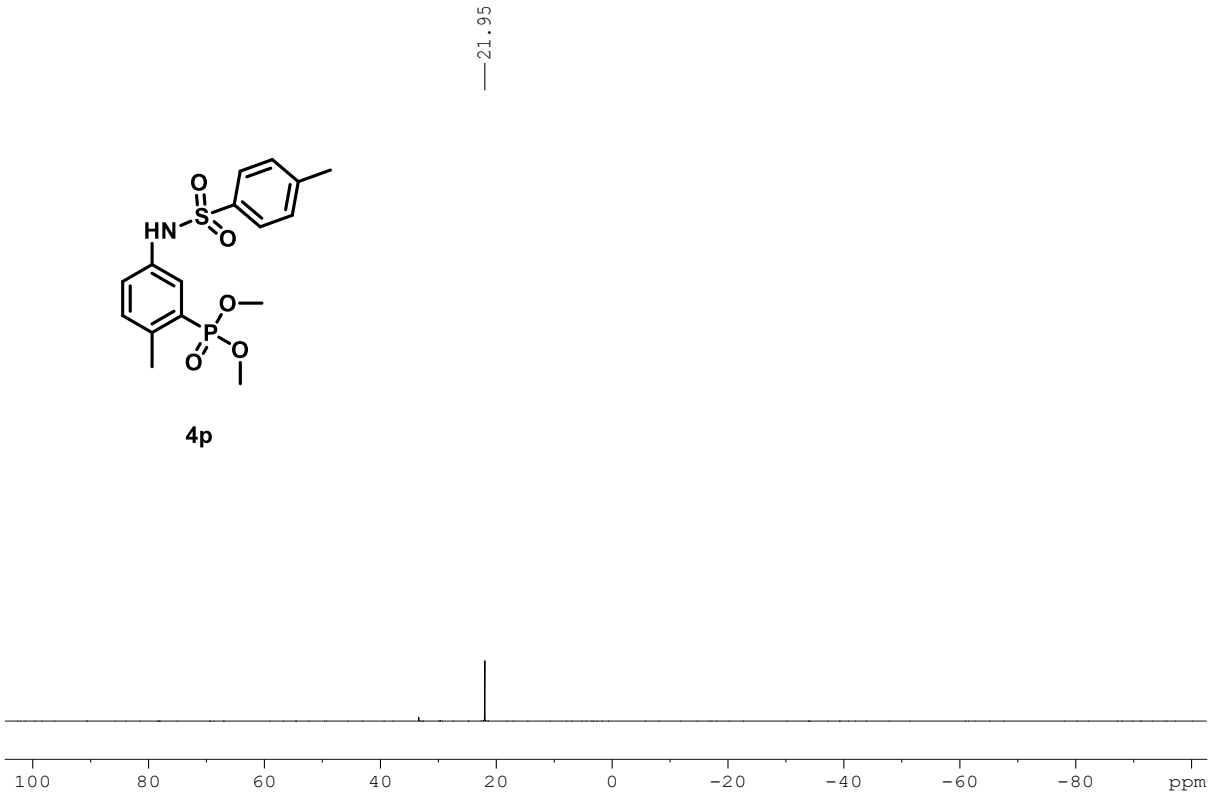

145.6
145.4
138.9
138.8
126.5
126.1
126.0
124.7
117.6
115.4
115.3
52.3
52.3
47.7
25.4
20.9
20.9
16.2
16.2
OCH3
P–OCH3
O
4o
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm


25.02
OCH3
P–OCH3
O
4o
80
60
40
20
0
-20
-40
-60
-80
ppm


9.55
7.80
7.79
7.76
7.75
7.73
7.71
7.56
7.55
7.54
7.53
7.19
7.19
7.17
7.16
7.14
7.14
7.12
3.78
3.75
2.41
2.41
2.34
HN
4p
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
0.73
1.08
1.99
1.01
3.06
6.13
2.95
3.00

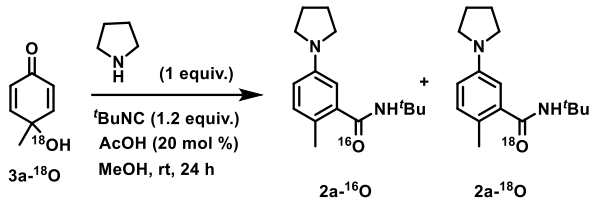

143.4
137.0
136.9
136.8
135.9
135.8
132.2
132.1
129.5
127.2
126.7
126.6
126.6
124.8
123.8
123.7
52.8
52.8
21.5
20.3
20.3
HN
O
S
O
O
P
O
O
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

4p


21.95
HN
O
S
O
O
P
O
O
100 80 60 40 20 0 -20 -40 -60 -80 ppm

4p

Experiment with 2a-^{18}O



3a-^{18}O 2a-^{16}O 2a-^{18}O

HRMS spectrum: Mass distribution of **2a** and **2a-^{18}O** products