

Supporting Information

Visible-Light-Driven Organophotocatalyzed *mono*-, *di*- and *tri*-C(sp³)-H Alkylation of Phosphoramides

Krishna Gopal Ghosh,^a Debabrata Das,^a Palasetty Chandu,^a and Devarajulu Sureshkumar ^{*a}

Department of Chemical Sciences, Indian Institute of Science Education and Research Kolkata Mohanpur-741246, West Bengal, India.

1. Optimization of reaction condition:	S2-S4
2. Reaction setup:	S4
3. Mechanistic investigation:	S5-S6
4. UV-Vis Absorption of Eosin-Y:	S7
5. Luminescence quenching studies of different forms of Eosin-Y with substrate 2a and HMPA:	S8-S9
6. Luminescence quenching studies of Acr-mes ⁺ ClO ₄ ⁻ with substrate 2a and HMPA:	S10
7. Light on/off experiment over time:	S11
8. X-ray crystallographic data:	S12-S14
9. NMR spectra of the products:	S15-S99

^aDepartment of Chemical Sciences

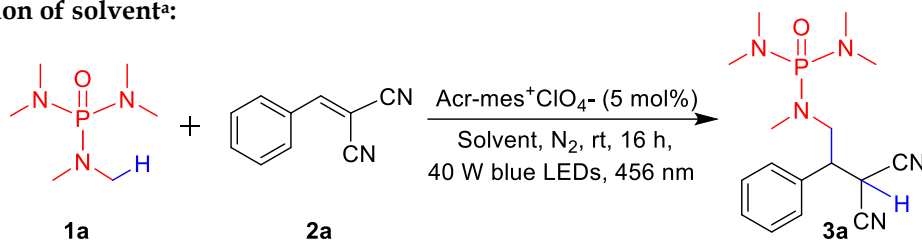
Indian Institute of Science Education and Research Kolkata

Mohanpur 741246, West Bengal, India.

E-mail: suresh@iiserkol.ac.in

Group webpage: <https://www.iiserkol.ac.in/~suresh/>

1. Optimization of reaction conditions:

Table S1. Optimization of solvent^a:

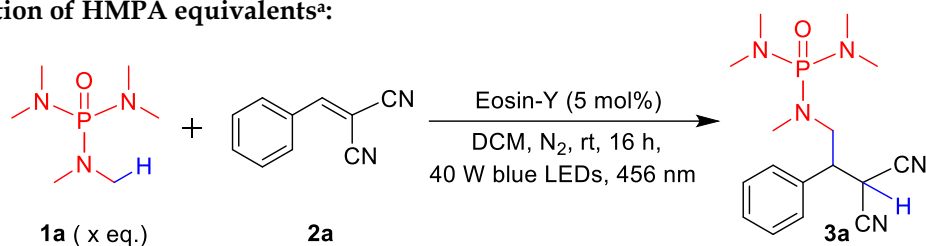
Entry	Solvent	Yield ^b (%)
1	Acetone	56
2	DMSO	35
3	THF	62
4	CH ₃ CN	84
5	CHCl ₃	93
6	DCM	95
7	DCE	92
8	DMF	76
9	Benzene	41
10	NMP	18
11	Chlorobenzene	78
12	EtOAc	52
13	DME	47
14	Dioxane	50

^aReaction condition: **1a** (1.0 mmol), **2a** (0.2 mmol), Acr-mes⁺ClO₄⁻ (5 mol%), solvent (1.0 mL), irradiation with 456 nm, 40 W Blue LED, rt, 16 h, ^b¹H NMR Yield using tetrachloroethane as internal standard.

Table S2. Optimization of photocatalysts^a:

Entry	Photocatalysts	Yield ^b (%)
1	Acr-mes ⁺ ClO ₄ ⁻	97
2	Ru(bpy) ₃ Cl ₂	0
3 ^c	<i>fac</i> -Ir(ppy) ₃	0
4	Ru(phen) ₃ Cl ₂	0
5	Ru(bpm) ₃ PF ₆	0
6	Ru(bpz) ₃ PF ₆	0
7 ^c	Ir[(dFCF ₃)ppy] ₂ (dtbbpy)BF ₄ ⁻	14
8 ^c	Ir(ppy) ₂ (dtbbpy)BF ₄ ⁻	0
9 ^c	Ir(ppy) ₂ (4-Me-bpy)BF ₄ ⁻	0
10	Eosin-B	0
11	Eosin-Y	99
12	Na ₂ Eosin-Y	89
12	Rhodamine B	0
13	Rose Bengal	0
14	Erythrosine B	0
15	T(<i>p</i> -F)PPT	36
16	T(<i>p</i> -CH ₃)PPT	66
17	T(<i>p</i> -Cl)PPT	63

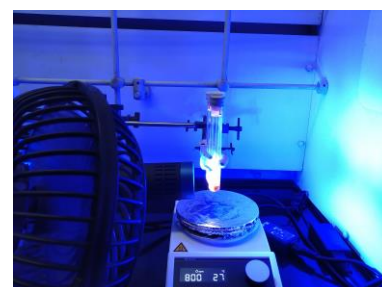
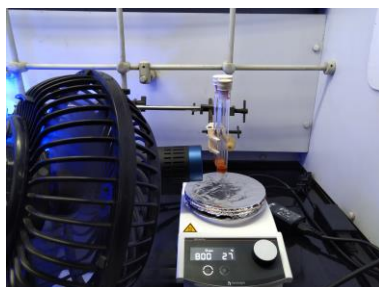
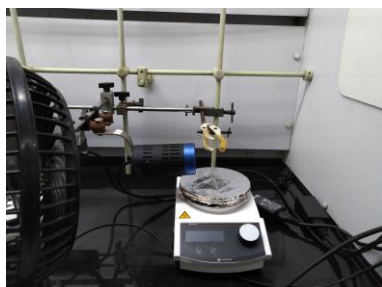
^aReaction condition: **1a** (1.0 mmol), **2a** (0.2 mmol), photocatalysts (5 mol%), DCM (1.0 mL), irradiation with 456 nm, 40 W Blue LED, rt, 16 h, ^b¹H NMR Yield using tetrachloroethane as internal standard. ^c2 mol% of photocatalysts was used.

Table S3. Optimization of HMPA equivalents^a:

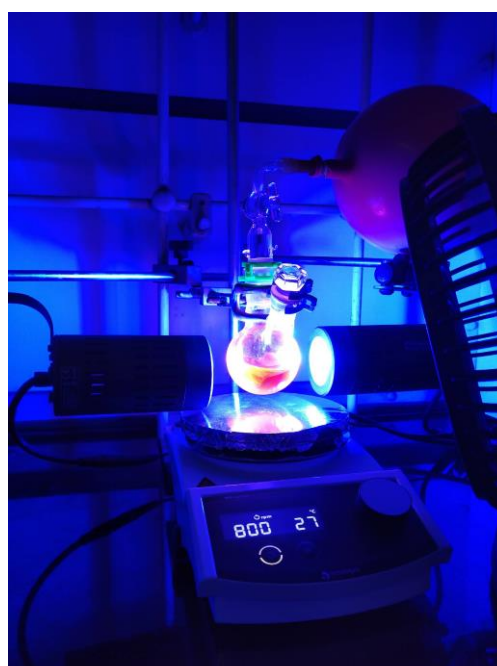
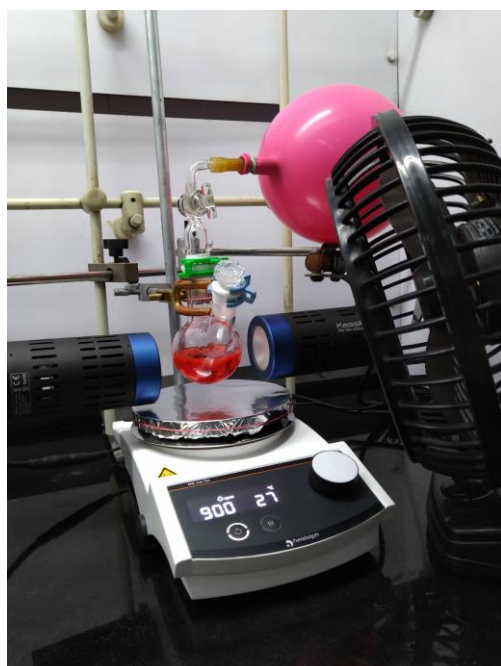
Entry	1a (eq.)	Yield ^b (%)
1	1	52
2	2	72
3	3	81
4	4	89
5	5	99

^aReaction condition: **1a** (x eq.), **2a** (0.2 mmol), Eosin-Y (5 mol%), DCM (1.0 mL), irradiation with 456 nm, 40 W Blue LED, rt, 16 h, ^b¹H NMR Yield using tetrachloroethane as internal standard.

2.1. Reaction setup for synthesis of 3, 4, 5 and 6:

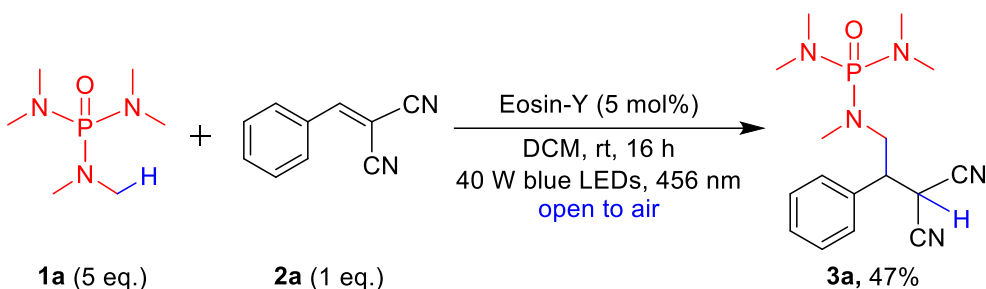


2.2. Reaction setup for gram scale synthesis of 3a:

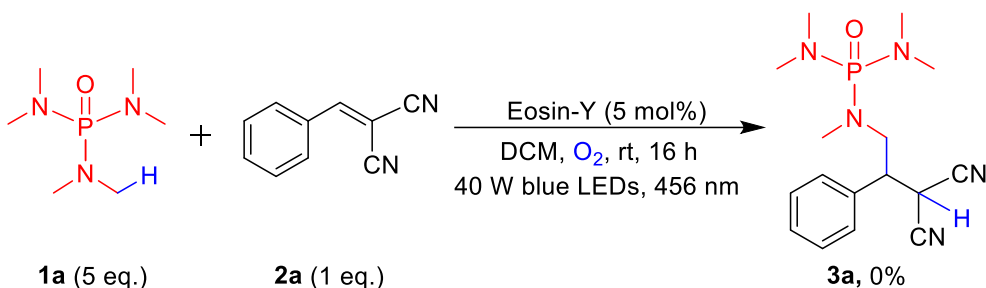


3. Mechanistic investigation:

3.1. Effect of air and O_2 :



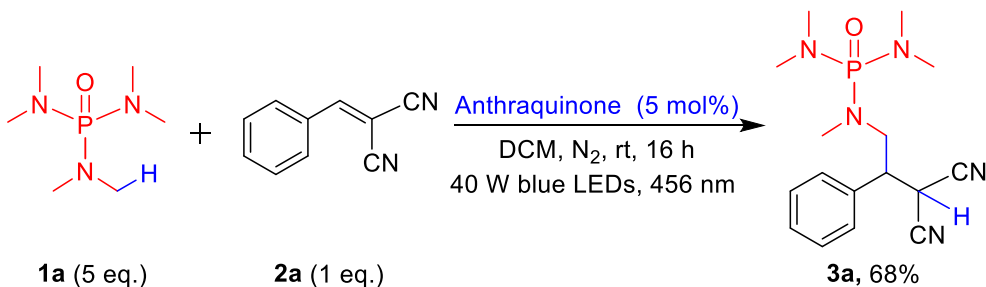
To an oven-dried 20 mL reaction tube equipped with a magnetic stirring bar, 0.2 mmol of **2** (1 eq.), 1 mmol of **1** (5 eq.), and 0.01 mmol of Eosin-Y (5 mol%) was added. Then, 1 mL of dry DCM was added and the reaction tube was placed ~2.5 away cm from a Kessil 40 W 456 nm LED setup and ~30 cm from a cooling fan to maintain room temperature. The reaction was kept open to air. After 16 h of the reaction 10 mL of water was added and extracted with DCM (3 x 20 mL). The combined organic layer was dried over Na_2SO_4 and solvent was evaporated under reduced pressure. 1H NMR showed a decreased yield of 47% using tetrachloroethane as a standard.



To an oven-dried 20 mL reaction tube equipped with a magnetic stirring bar, 0.2 mmol of **2** (1 eq.), 1 mmol of **1** (5 eq.), and 0.01 mmol of Eosin-Y (5 mol%) was added. The reaction tube was vacuumed and backfilled with oxygen (3 times) and sealed with a septum. Then, 1 mL of dry DCM was added through the septum by a syringe and placed ~2.5 away cm from a Kessil 40 W 456 nm LED setup and ~30 cm away from a cooling fan to maintain room temperature. After 16 h of the reaction, 10 mL of water was added and extracted with DCM (3 x 20 mL). The combined organic layer was dried over Na_2SO_4 and solvent was evaporated under reduced pressure. 1H NMR was recorded from the crude which indicated the failure of the reaction.

The above results suggest that oxygen can quench the reaction. Hence, the active catalysts for this reaction is triplet state of Eosin-Y.

3.2. Experiment with Anthraquinone photocatalyst:

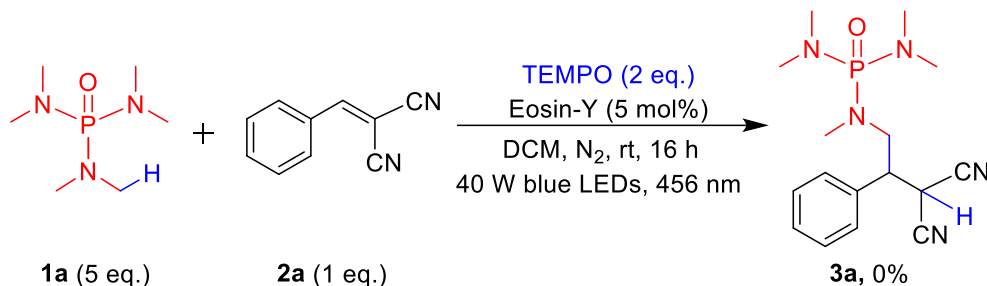


To an oven-dried 20 mL reaction tube equipped with a magnetic stirring bar, 0.2 mmol of **2** (1 eq.), 1 mmol of **1** (5 eq.), and 0.01 mmol of anthraquinone (5 mol%) was added. The reaction tube was vacuumed and backfilled with nitrogen (3 times) and secured with a septum. Then, 1 mL of dry DCM was added using a syringe and the reaction tube was placed ~3 cm away from a Kessil 40 W 456 nm LED setup and ~30 cm away from a cooling fan to maintain room temperature. After 16 h of the reaction, 10 mL of water was added and extracted with DCM (3 x 20 mL). The combined organic layer

was dried over Na_2SO_4 and solvent was evaporated under reduced pressure. ^1H NMR yield of the reaction was 68% based on tetrachloroethane as an internal standard.

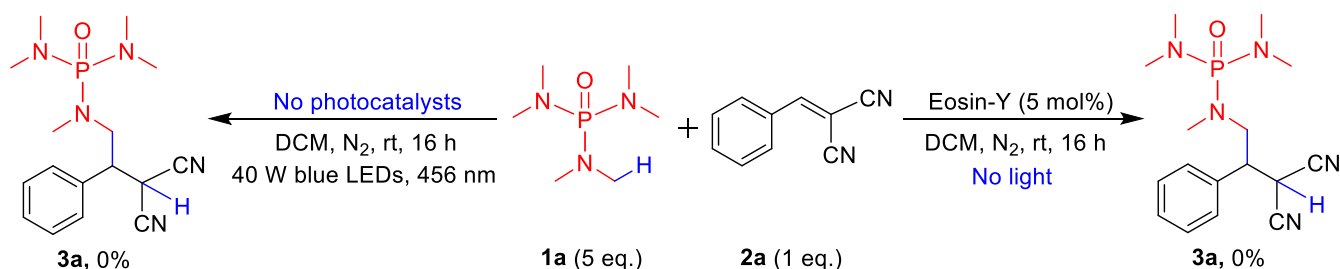
Anthraquinone is a well-known direct HAT photocatalyst. Therefore, the above result suggests that our reaction proceeds through direct HAT mechanism.

3.3. Radical trapping experiment with TEMPO:



To an oven-dried 20 mL reaction tube equipped with a magnetic stirring bar, 0.2 mmol of **2** (1 eq.), 1 mmol of **1** (5 eq.), 0.01 mmol of Eosin-Y (5 mol%) and 0.4 mmol of TEMPO (2 eq.) was added. The reaction tube was vacuumed and backfilled with nitrogen (3 times) and sealed with a septum. Then, 1 mL of dry DCM was added using a syringe and placed ~3 cm away from a Kessil 40 W 456 nm LED setup and ~30 cm away from a cooling fan to maintain temperature. After 16 h of the reaction 10 mL of water was added and extracted with DCM (3 x 20 mL). The combined organic layer was dried over Na_2SO_4 and solvent was evaporated under reduced pressure. ^1H and ^{31}P NMR was recorded from the crude which indicated the complete failure of the reaction. Thus, it indicates that our reaction proceeds through radical mechanism.

3.4. Reaction without photocatalysts or without light:



When our standard reaction was performed in the absence of any photocatalyst or light irradiation source, no trace of desired product was found, which indicates the absolute necessity of photocatalyst and/or light.

4. UV-Vis Absorption of Eosin-Y:

To measure the UV-Vis absorption of the different forms of Eosin-Y, 10 mM of commercially available Eosin-Y, 1 mM of $Na_2Eosin-Y$, 10 mM of TFA and 1 M of HMPA solution in acetonitrile were prepared and used as stock solution and all other solutions with different concentration was prepared by dilution. (1 mM Eosin-Y + 1 mM TFA) solution in acetonitrile was considered as neutral Eosin-Y and (50 μ M Eosin-Y + 50 μ M NaOH aq.) solution in acetonitrile was considered as NaEosin-Y.

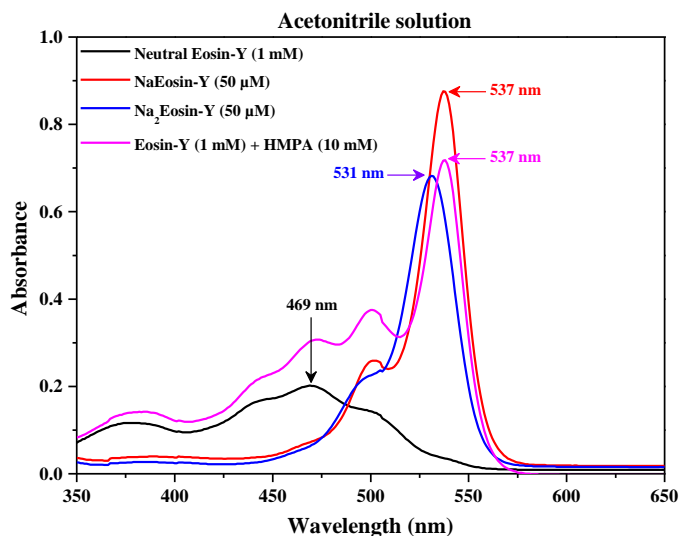


Figure S1. UV-Vis spectrum of different forms of Eosin Y in acetonitrile solution.

Acetonitrile solution: Neutral Eosin-Y (1 mM) (black line); NaEosin-Y (50 μ M) (red line); $Na_2Eosin-Y$ (50 μ M) (blue line); Eosin-Y (1 mM) + HMPA (10 mM) (pink line).

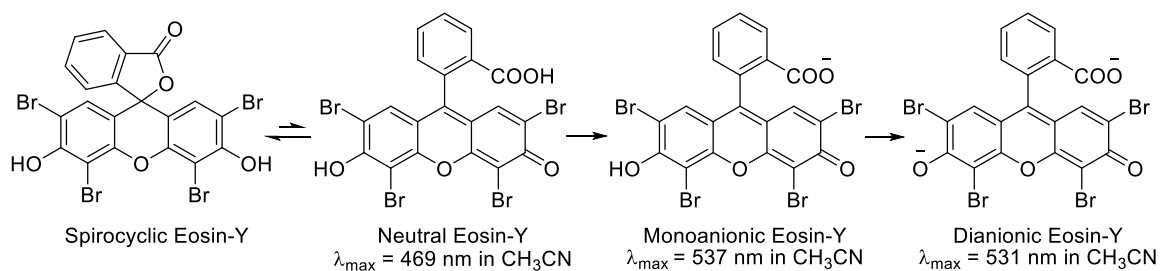


Figure S2. λ_{max} of different forms of Eosin-Y in acetonitrile

We have measured the UV-vis absorption of different forms of Eosin-Y in acetonitrile as depicted in Figure S1. The neutral Eosin-Y has an absorption maximum at 469 nm. The monoanionic Eosin-Y (NaEosin-Y) and dianionic Eosin-Y have absorption maximum at 537 nm and 531 nm respectively. Again, when we measured the absorption maximum of neutral Eosin-Y after addition of HMPA (neutral Eosin-Y + HMPA), we observed an absorption maximum at 537 nm, similar to monoanionic Eosin-Y. Based on UV-Vis studies, we conclude that the active catalyst for our reaction system is the monoanionic form of Eosin-Y.

5. Luminescence quenching studies on different forms of Eosin-Y with substrate **2a** and HMPA:

To perform luminescence quenching studies on different forms of Eosin-Y, 10 mM of commercially available Eosin-Y, 1 mM of $\text{Na}_2\text{Eosin-Y}$, 10 mM of TFA, 1 M of HMPA, and 1 M of substrate **2a** solution in acetonitrile were prepared as stock solution and all other solutions with different concentration was prepared by dilution. (1 mM Eosin-Y + 1 mM TFA) solution in acetonitrile was considered as neutral Eosin-Y and (50 μM Eosin-Y + 50 μM NaOH aq.) solution in acetonitrile was considered as NaEosin-Y.

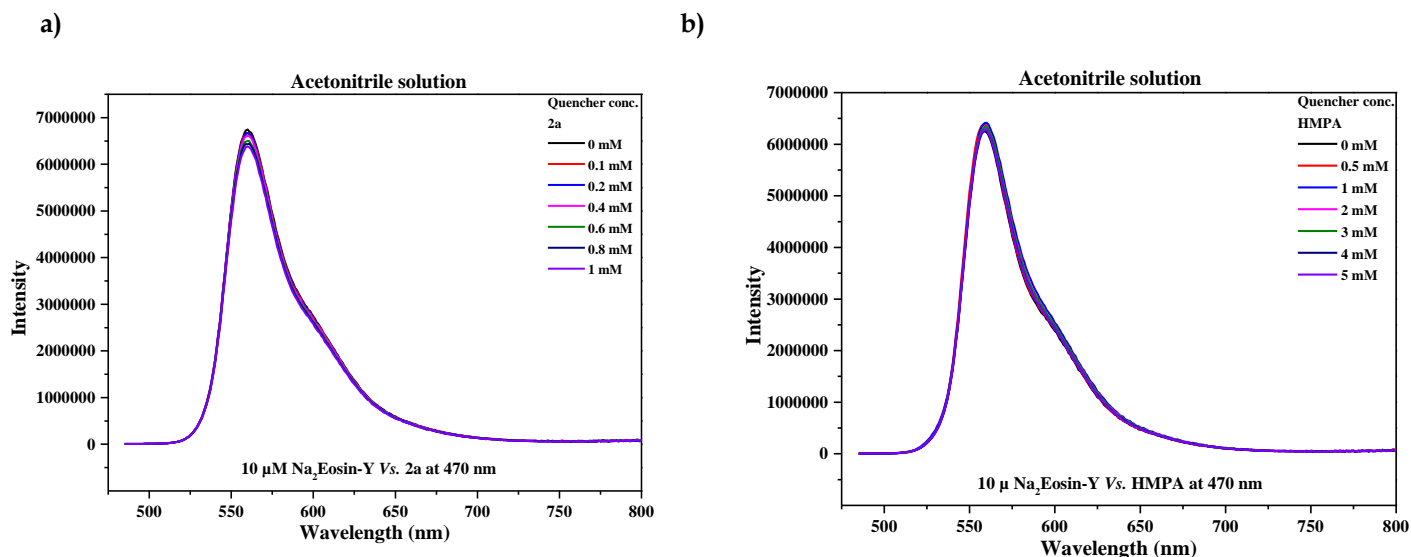


Figure S3. Luminescence quenching spectra of $\text{Na}_2\text{Eosin-Y}$ Vs. **2a** and **HMPA** at λ_{ex} 470 nm

In acetonitrile solution: a) 10 μM $\text{Na}_2\text{Eosin-Y}$ Vs. **2a** at 470 nm; b) 10 μM $\text{Na}_2\text{Eosin-Y}$ Vs. **HMPA** at 470 nm.

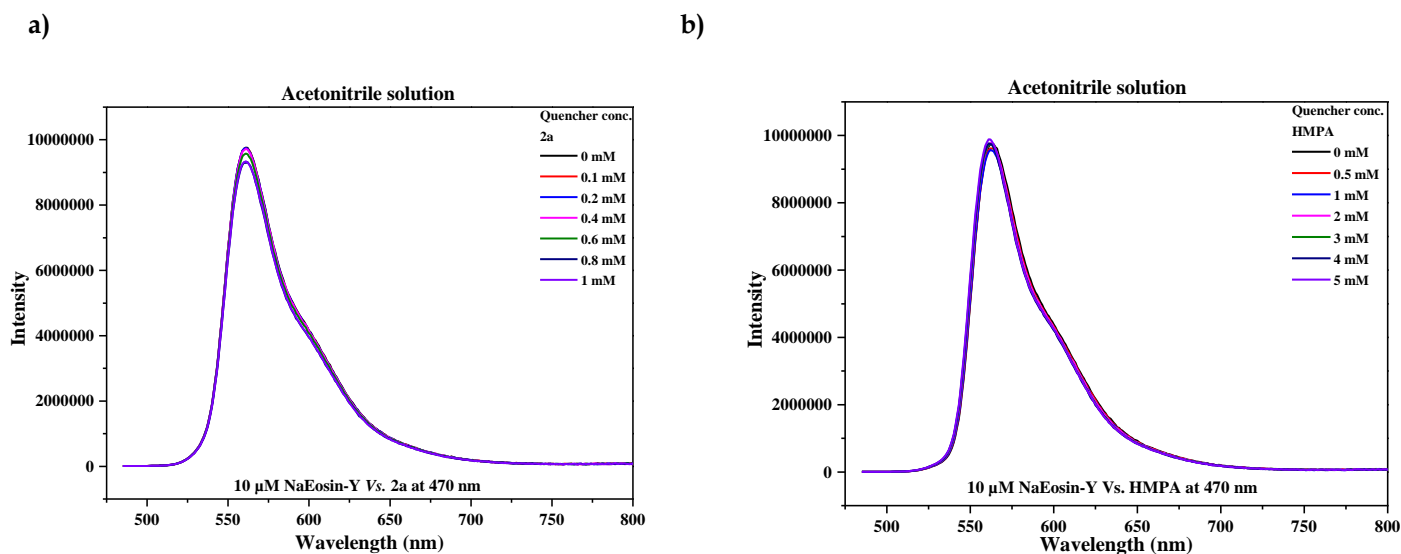


Figure S4. Luminescence quenching spectra of NaEosin-Y Vs. **2a** and **HMPA** at λ_{ex} 470 nm.

In acetonitrile solution: a) 10 μM NaEosin-Y Vs. **2a** at 470 nm; b) 10 μM NaEosin-Y Vs. **HMPA** at 470 nm.

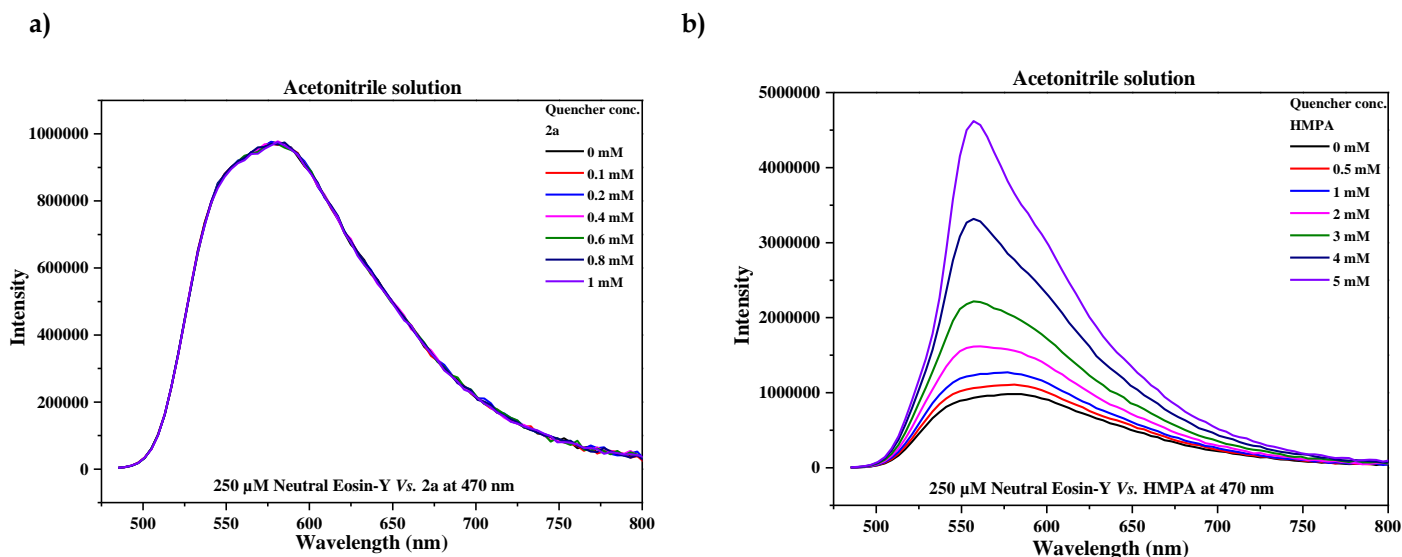


Figure S5. Luminescence quenching spectra of Eosin-Y Vs. **2a** and **HMPA** at λ_{ex} 470 nm.

In acetonitrile solution: a) 250 μ M Eosin-Y Vs. **2a** at 470 nm; b) 250 μ M Eosin-Y Vs. **HMPA** at 470 nm.

Although our active catalyst is the monoanionic form of Eosin-Y, we have performed luminescence quenching experiments on all three forms of Eosin-Y. There was no quenching observed for dianionic Eosin-Y ($\text{Na}_2\text{Eosin-Y}$) and monoanionic Eosin-Y (NaEosin-Y) neither with Michael acceptor nor with HMPA. In the case of neutral Eosin-Y also, no quenching was observed with respect to Michael acceptor. However, an increase in emission value was observed in the case of neutral Eosin-Y with increasing concentration of HMPA. This increase in emission again suggests that the active form of the catalyst is the monoanionic form of Eosin-Y. As there was no quenching observed for monoanionic and dianionic Eosin-Y with respect to HMPA, we believe that our reaction follows a direct hydrogen atom transfer (HAT) mechanism.

6. Luminescence quenching studies of Acr-mes⁺ClO₄⁻ with substrate **2a** and HMPA:

To perform luminescence quenching studies of Acr-mes⁺ClO₄⁻, 10 mM of commercially available Acr-mes⁺ClO₄⁻, 1 M of HMPA, and 1 M of substrate **2a** solution in acetonitrile was prepared as a stock solution and all other solutions with different concentration were prepared by dilution.

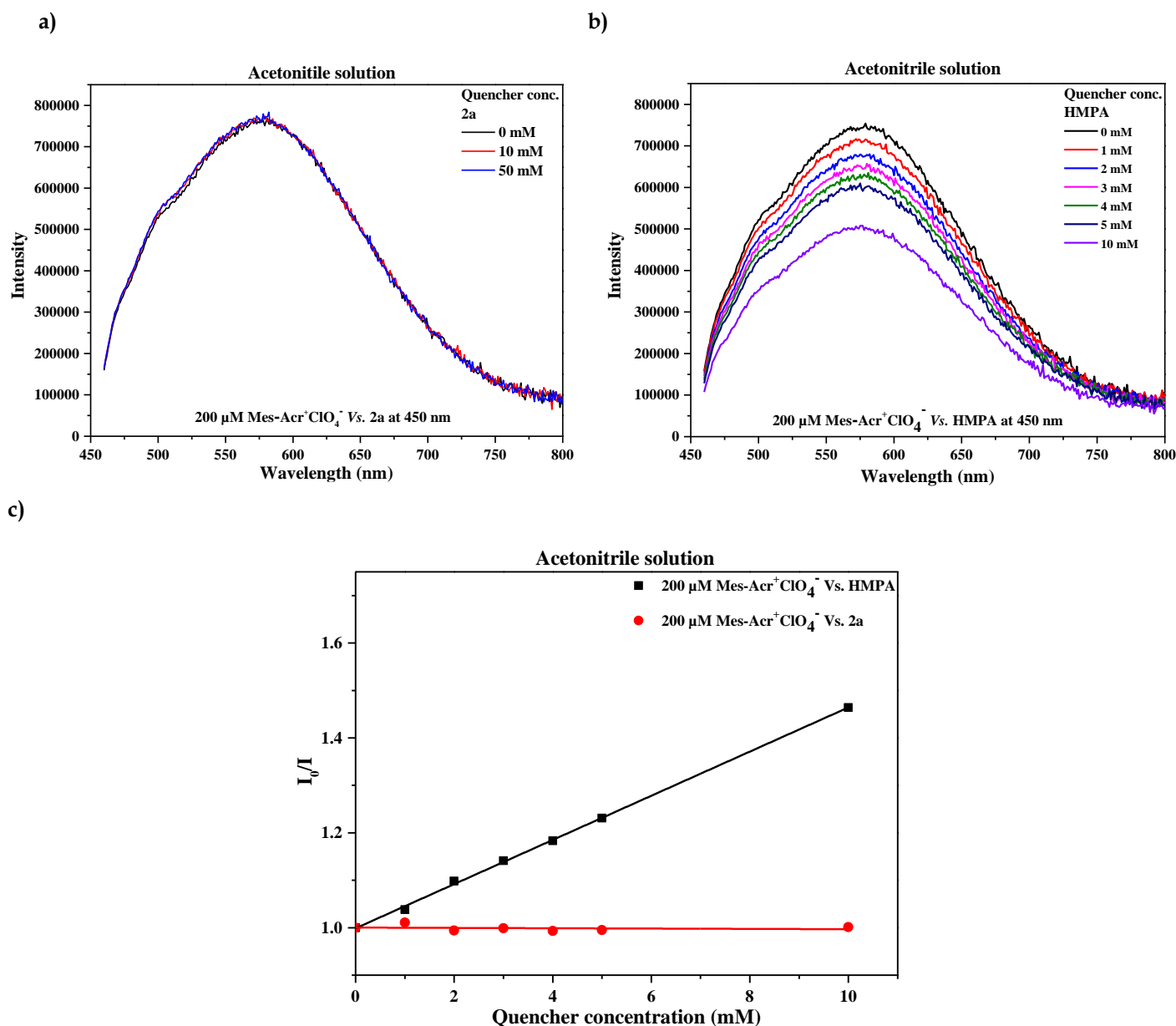
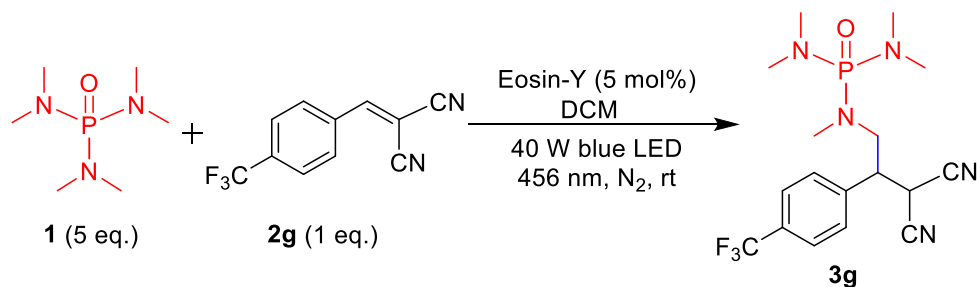


Figure S6. Luminescence quenching spectra of Acr-mes⁺ClO₄⁻ at λ_{ex} 450 nm.

In acetonitrile solution: a) 200 μM Acr-mes⁺ClO₄⁻ Vs. **2a** at 450 nm; b) 200 μM Acr-mes⁺ClO₄⁻ Vs. HMPA at 450 nm; c) Stern-Volmer plot of luminescence quenching of 200 μM Acr-mes⁺ClO₄⁻ Vs. **2a** and HMPA.

In the case of acridinium photocatalyst, as expected, no quenching was observed with respect to Michael acceptor shown in Figure S6a. However, quenching of the acridinium photocatalyst was observed with respect to HMPA, as shown in Figure S6b, as well as in Stern-Volmer plot Figure S6c. Therefore, we can conclude that in the case of acridinium photocatalyst, the reaction follows a single electron transfer (SET) pathway mechanism.

7. Light on/off experiment over time:



To an oven-dried 25 mL two-neck round bottom flask equipped with a magnetic stirring bar, 2.25 mmol of **2g** (1 eq.), 11.25 mmol of **1** (5 eq.) and 0.1125 mmol of Eosin-Y (5 mol%) were added. One neck of the flask was sealed with a septum and an adapter with a stopcock was attached to the other. The flask was vacuumed, backfilled with nitrogen (5 times) and a nitrogen balloon was connected to the adapter. Then, 10 mL of dry DCM and 2.25 mmol of benzonitrile (1 eq.) (was used as an internal standard for ^{19}F NMR) were added using a syringe and the flask was placed ~3 cm away from one Kessil 40 W 456 nm LED setup and ~30 cm away from a cooling fan to maintain room temperature. The light on/off experiment was performed by altering light-dark conditions (light : dark; 2 : 2 h) for up to 30 h. At the end of each light/dark session, the reaction progress was monitored by measuring the yield based on ^{19}F NMR using benzonitrile as an internal standard. The results in Figure S7 show the essential role of light, as the reaction progressed in the presence of light and stopped in the dark. From the experiment, we also speculate that our reaction does not proceed through a chain propagation mechanism.

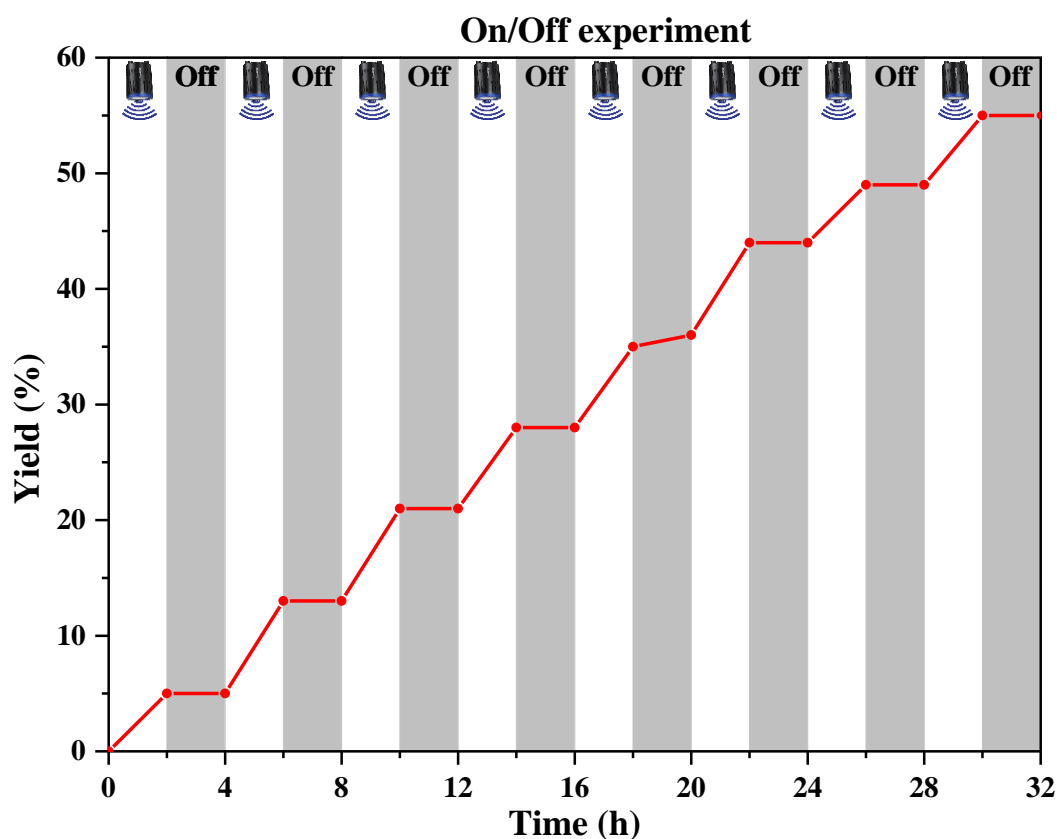
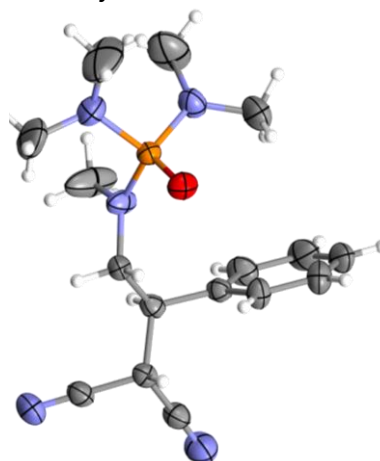
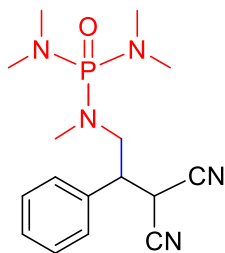
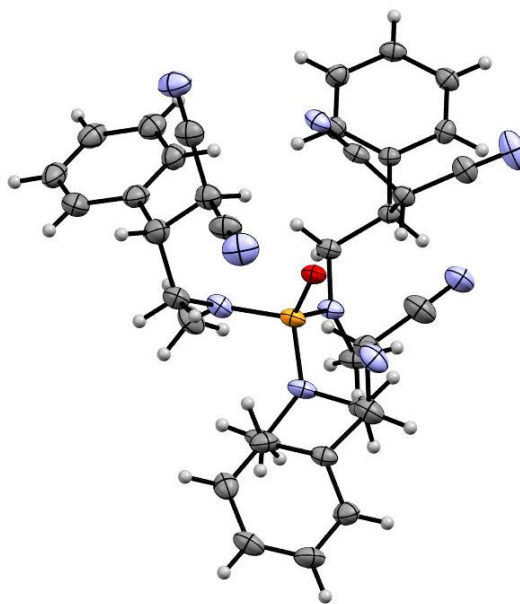
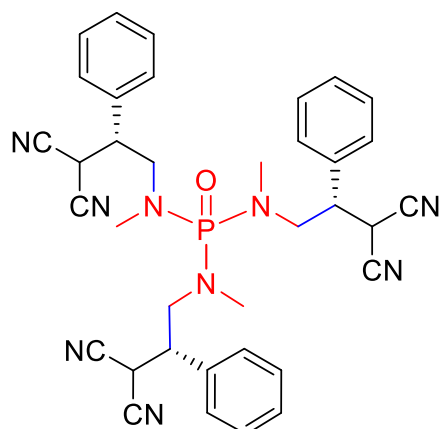


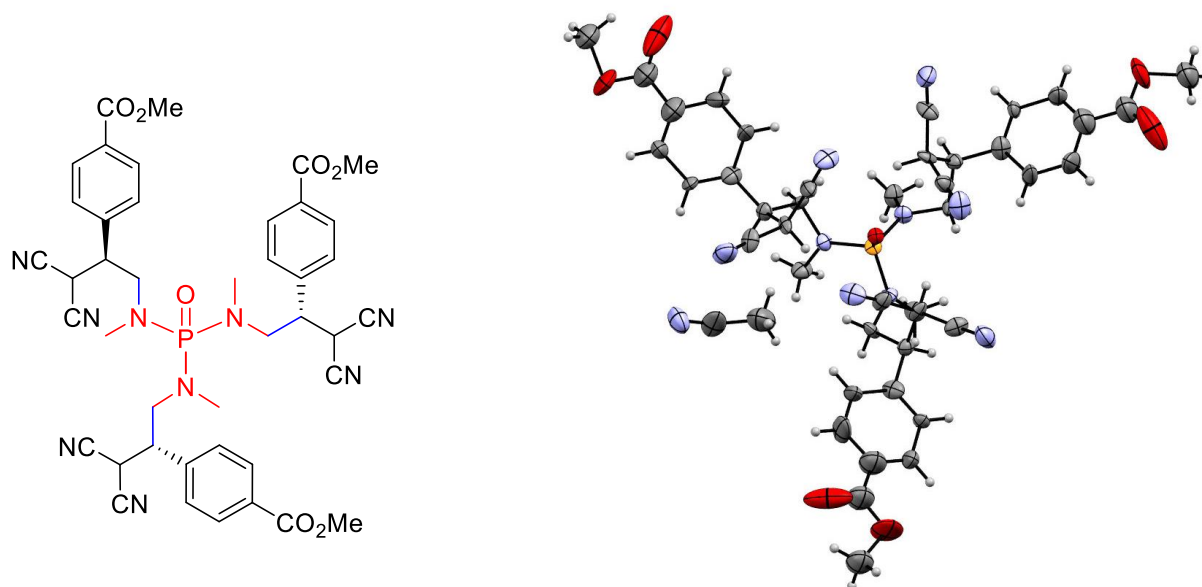
Figure S7. Light On/Off experiment

8. X-ray crystallographic data:**8.1. X-ray crystallographic data of 3a with 50% ellipsoid contour probability:****Table S4 Crystal data and structure refinement for Compound 3a:**

Identification code	Compound 3a
Empirical formula	C ₁₆ H ₂₄ N ₅ OP
CCDC Number	2003244
Formula weight	333.37
Temperature/K	293(2)
Crystal system	monoclinic
Space group	P2 ₁ /n
a/Å	10.6517(2)
b/Å	11.4441(2)
c/Å	16.4948(3)
$\alpha/^\circ$	90.00
$\beta/^\circ$	100.088(2)
$\gamma/^\circ$	90.00
Volume/Å ³	1979.62(6)
Z	4
$\rho_{\text{calc}}/\text{cm}^3$	1.119
μ/mm^{-1}	1.314
F(000)	712.0
Crystal size/mm ³	0.3 × 0.2 × 0.2
Radiation	CuK α (λ = 1.54184)
2 θ range for data collection/ $^\circ$	9.2 to 132.22
Index ranges	-12 ≤ h ≤ 12, -13 ≤ k ≤ 13, -18 ≤ l ≤ 19
Reflections collected	15379
Independent reflections	3438 [R _{int} = 0.0544, R _{sigma} = 0.0368]
Data/restraints/parameters	3438/0/217
Goodness-of-fit on F ²	1.062
Final R indexes [I ≥ 2 σ (I)]	R ₁ = 0.0658, wR ₂ = 0.1804
Final R indexes [all data]	R ₁ = 0.0779, wR ₂ = 0.1889
Largest diff. peak/hole / e Å ⁻³	0.37/-0.30

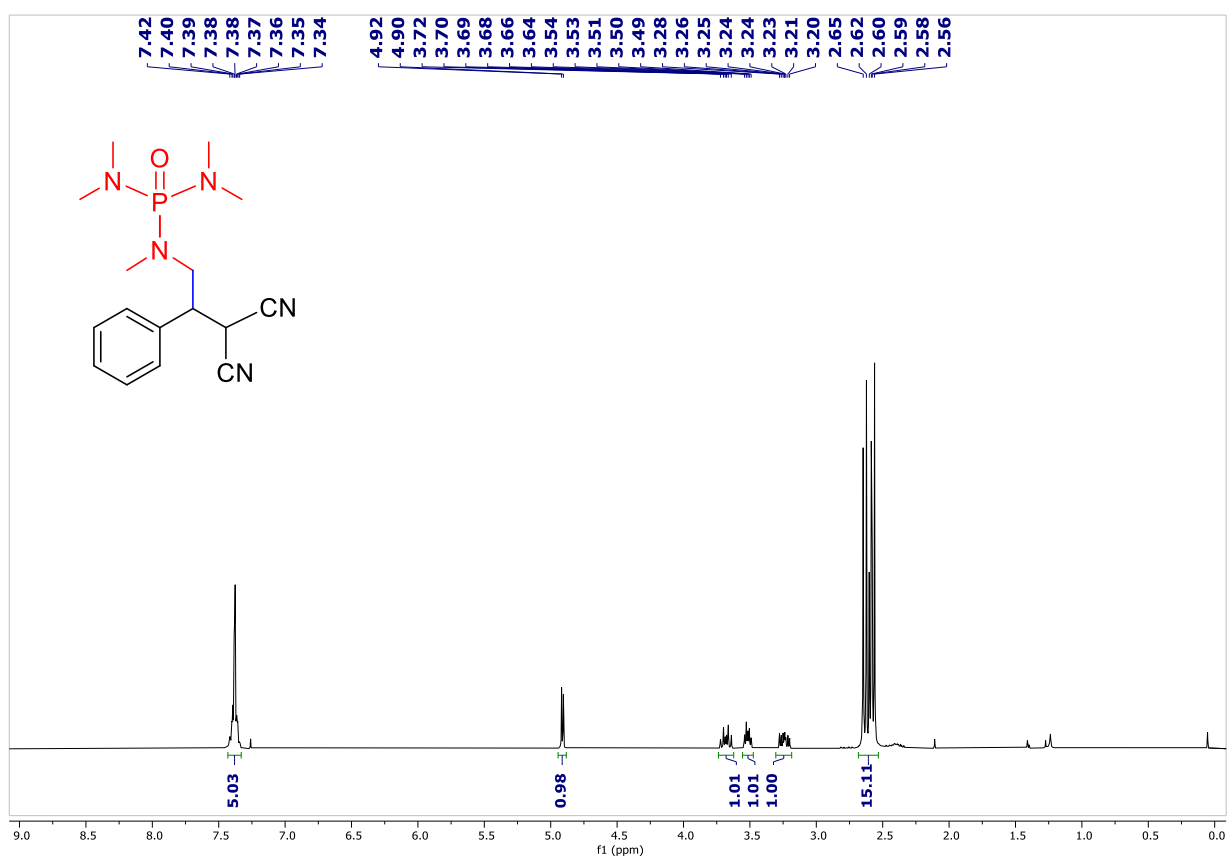
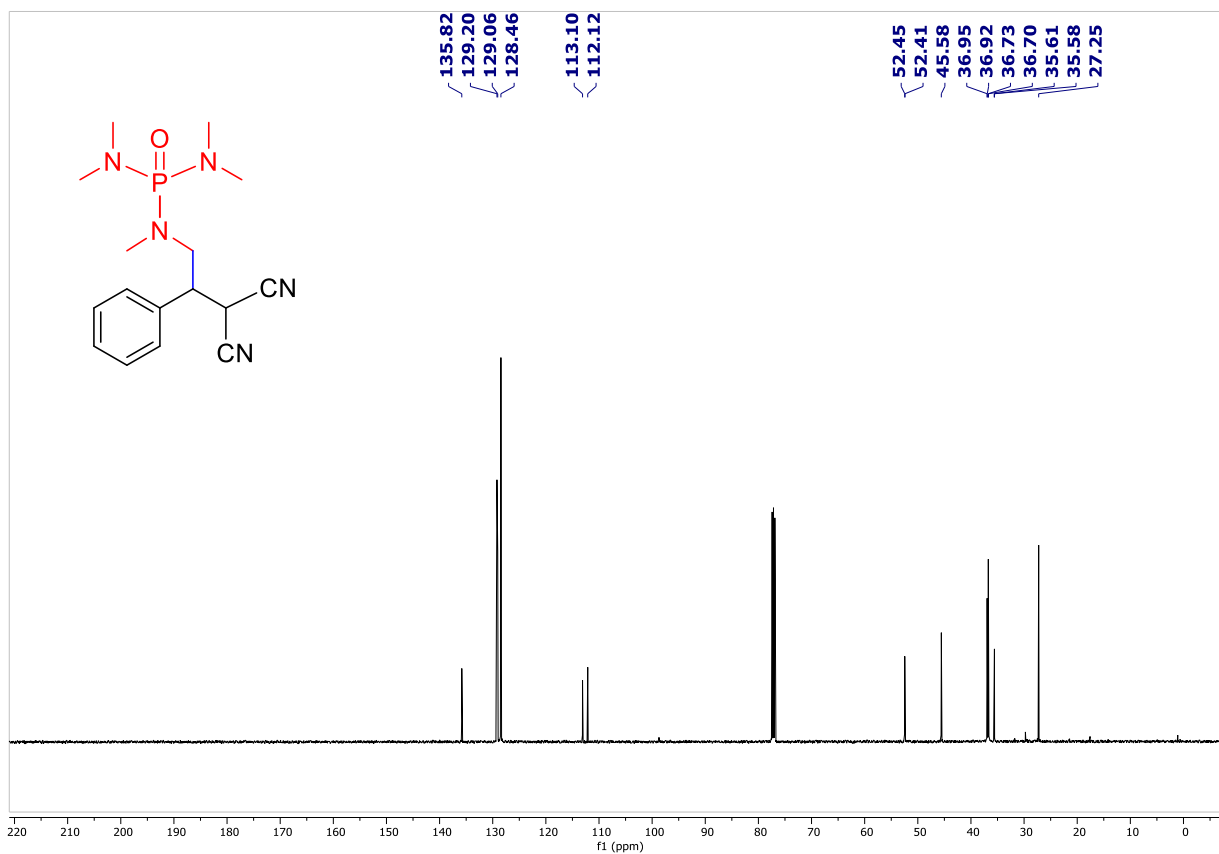
8.2. X-ray crystallographic data of compound major isomer (\pm)-6a' with 50% ellipsoid contour probability:Table S5 Crystal data and structure refinement for Compound (\pm)-6a':

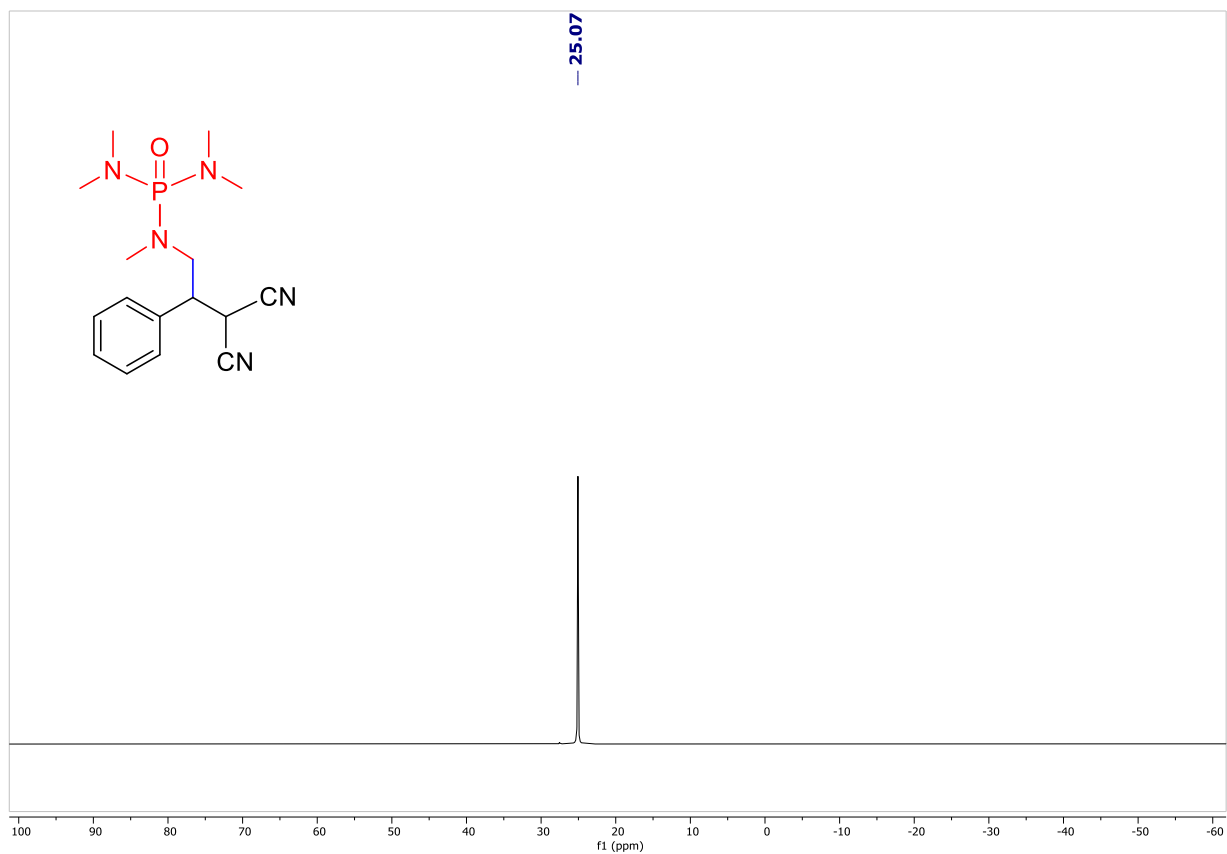
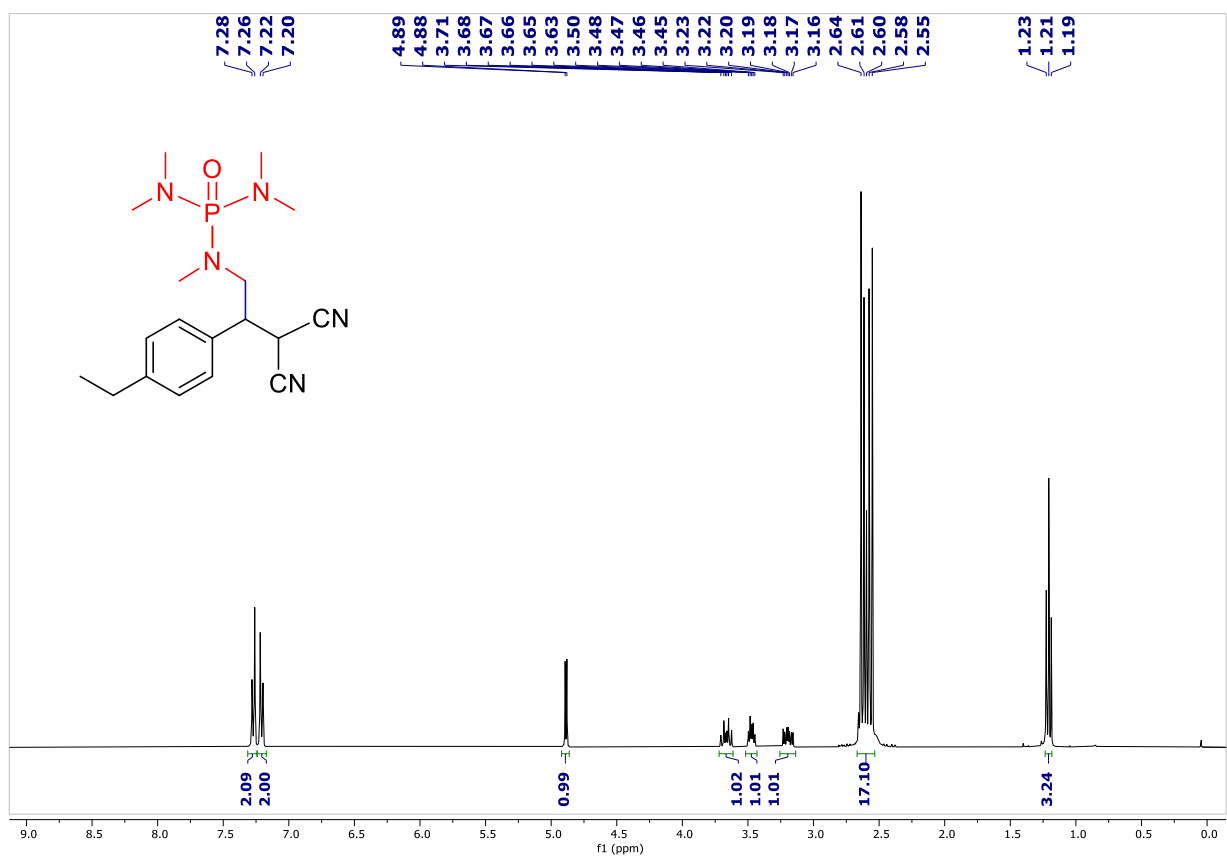
Identification code	major isomer (\pm)-6a'
Empirical formula	C ₃₆ H ₃₆ N ₉ OP
CCDC Number	2003245
Formula weight	641.71
Temperature/K	100.00(10)
Crystal system	Orthorhombic
Space group	P2 ₁ 2 ₁ 2 ₁
a/Å	10.13530(10)
b/Å	16.17310(10)
c/Å	21.1190(2)
$\alpha/^\circ$	90
$\beta/^\circ$	90
$\gamma/^\circ$	90
Volume/Å ³	3461.81(5)
Z	4
$\rho_{\text{calc}}/\text{g/cm}^3$	1.231
μ/mm^{-1}	1.040
F(000)	1352.0
Crystal size/mm ³	0.4 × 0.2 × 0.1
Radiation	CuK α (λ = 1.54184)
2 θ range for data collection/ $^\circ$	6.884 to 132.254
Index ranges	-11 ≤ h ≤ 12, -19 ≤ k ≤ 19, -25 ≤ l ≤ 19
Reflections collected	17178
Independent reflections	5766 [R _{int} = 0.0210, R _{sigma} = 0.0200]
Data/restraints/parameters	5766/0/427
Goodness-of-fit on F ²	1.069
Final R indexes [I ≥ 2 σ (I)]	R ₁ = 0.0359, wR ₂ = 0.0938
Final R indexes [all data]	R ₁ = 0.0365, wR ₂ = 0.0942
Largest diff. peak/hole / e Å ⁻³	0.60/-0.20
Flack parameter	0.013(7)

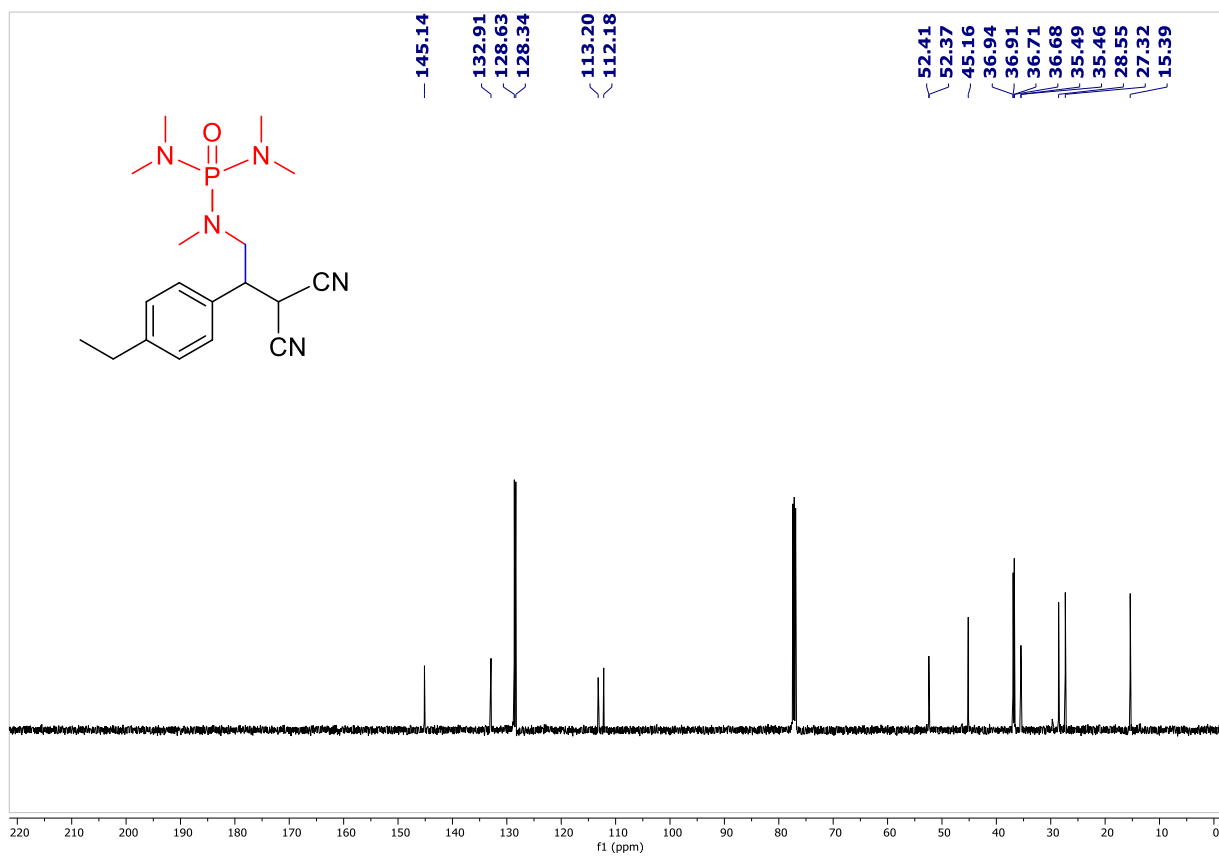
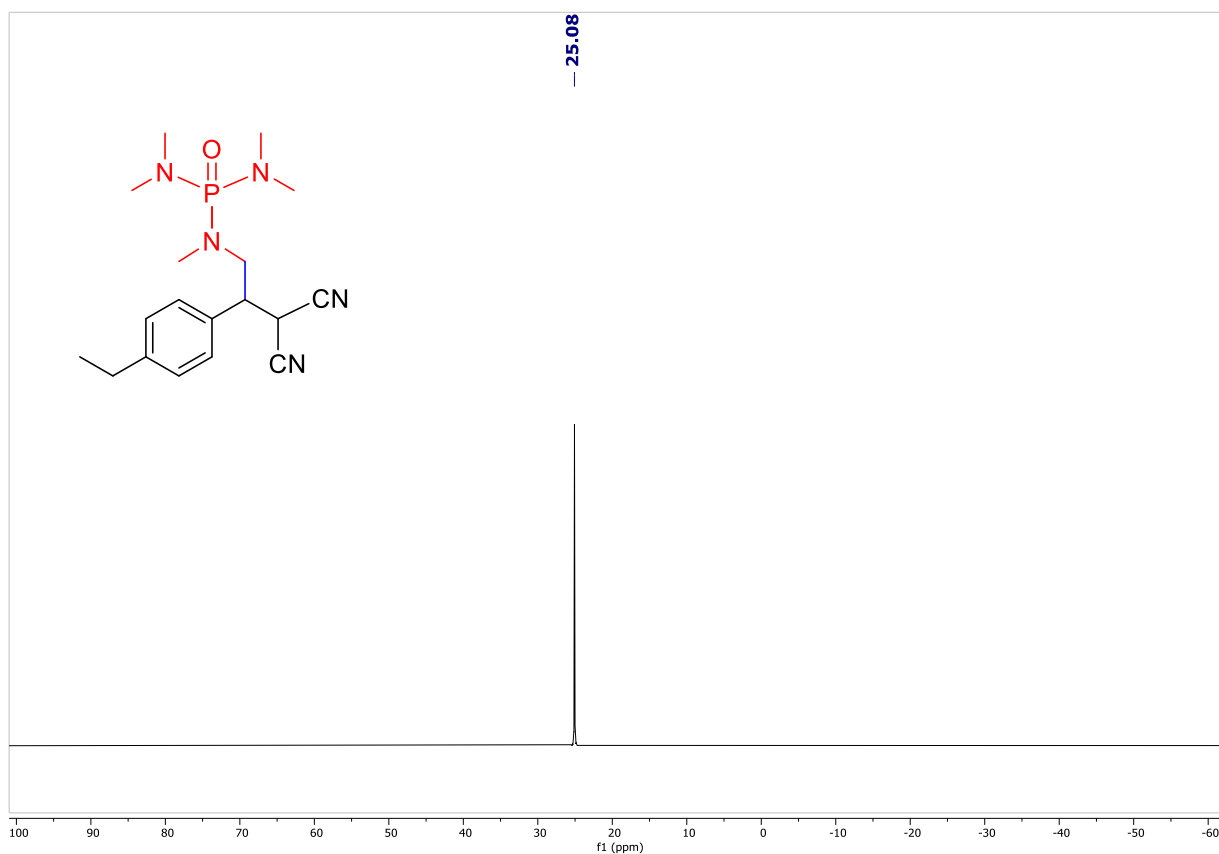
8.3. X-ray crystallographic data of compound (\pm)-6e'' with 50% ellipsoid contour probability:Table S6 Crystal data and structure refinement for compound (\pm)-6e'':

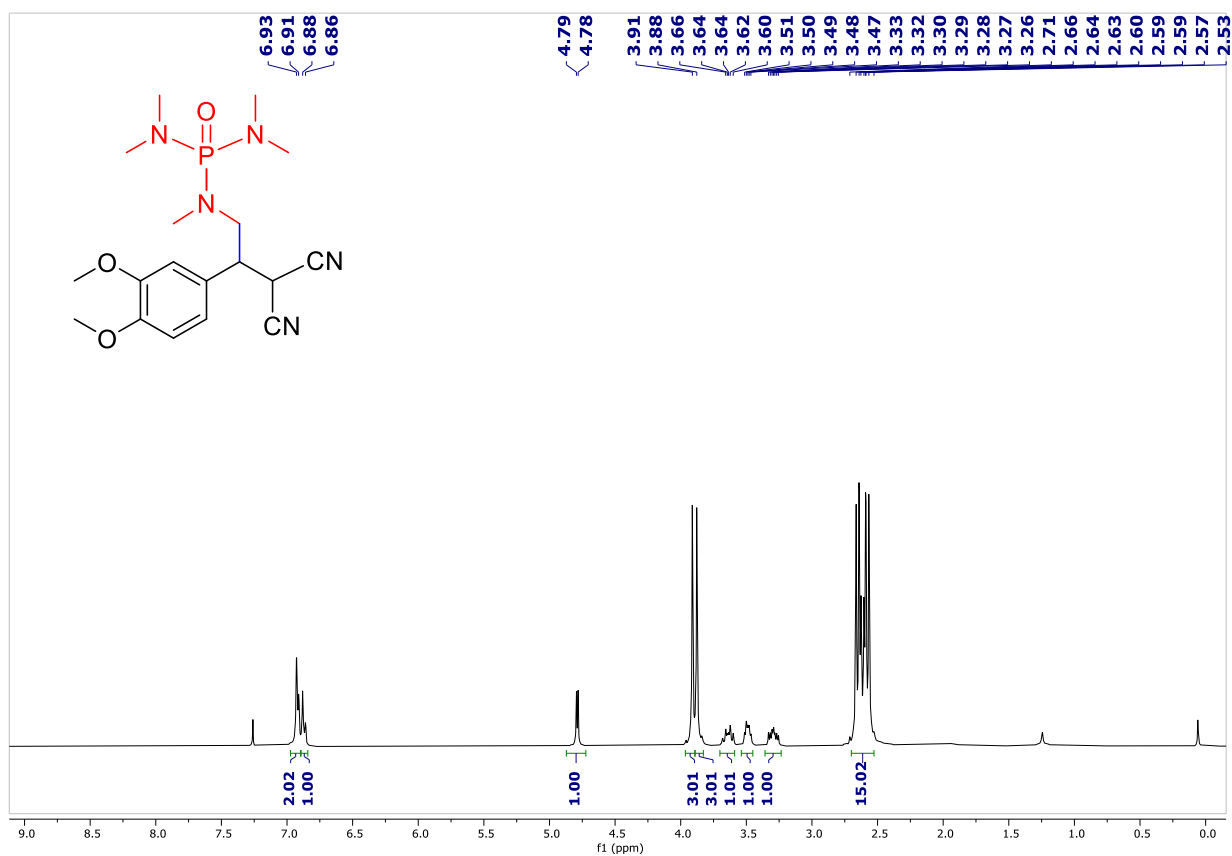
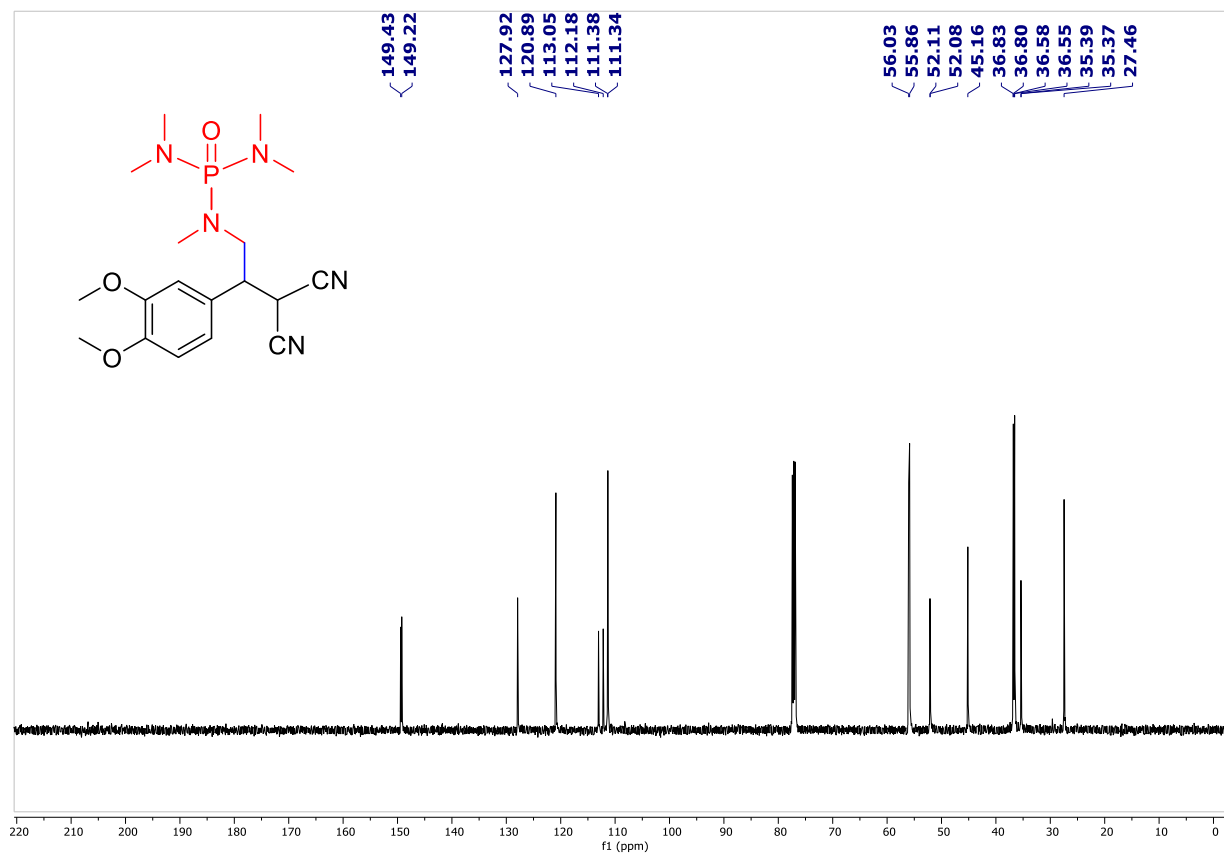
Identification code	minor isomer (\pm)-6e''
Empirical formula	C ₄₄ H ₄₅ N ₁₀ O ₇ P
CCDC Number	2003294
Formula weight	856.88
Temperature/K	100.00(10)
Crystal system	Trigonal
Space group	P31c
a/Å	18.6068(8)
b/Å	18.6068(8)
c/Å	8.2273(3)
$\alpha/^\circ$	90
$\beta/^\circ$	90
$\gamma/^\circ$	120
Volume/Å ³	2466.8(2)
Z	1.99998
$\rho_{\text{calc}}/\text{cm}^3$	1.154
μ/mm^{-1}	0.950
F(000)	900.0
Crystal size/mm ³	0.3 × 0.2 × 0.1
Radiation	CuK α (λ = 1.54184)
2 θ range for data collection/ $^\circ$	9.506 to 132.074
Index ranges	-22 ≤ h ≤ 21, -21 ≤ k ≤ 21, -7 ≤ l ≤ 9
Reflections collected	17046
Independent reflections	2688 [R _{int} = 0.0480, R _{sigma} = 0.0296]
Data/restraints/parameters	2688/1/198
Goodness-of-fit on F ²	2.352
Final R indexes [I ≥ 2 σ (I)]	R ₁ = 0.1711, wR ₂ = 0.4437
Final R indexes [all data]	R ₁ = 0.1716, wR ₂ = 0.4451
Largest diff. peak/hole / e Å ⁻³	1.14/-1.48
Flack parameter	0.24(5)

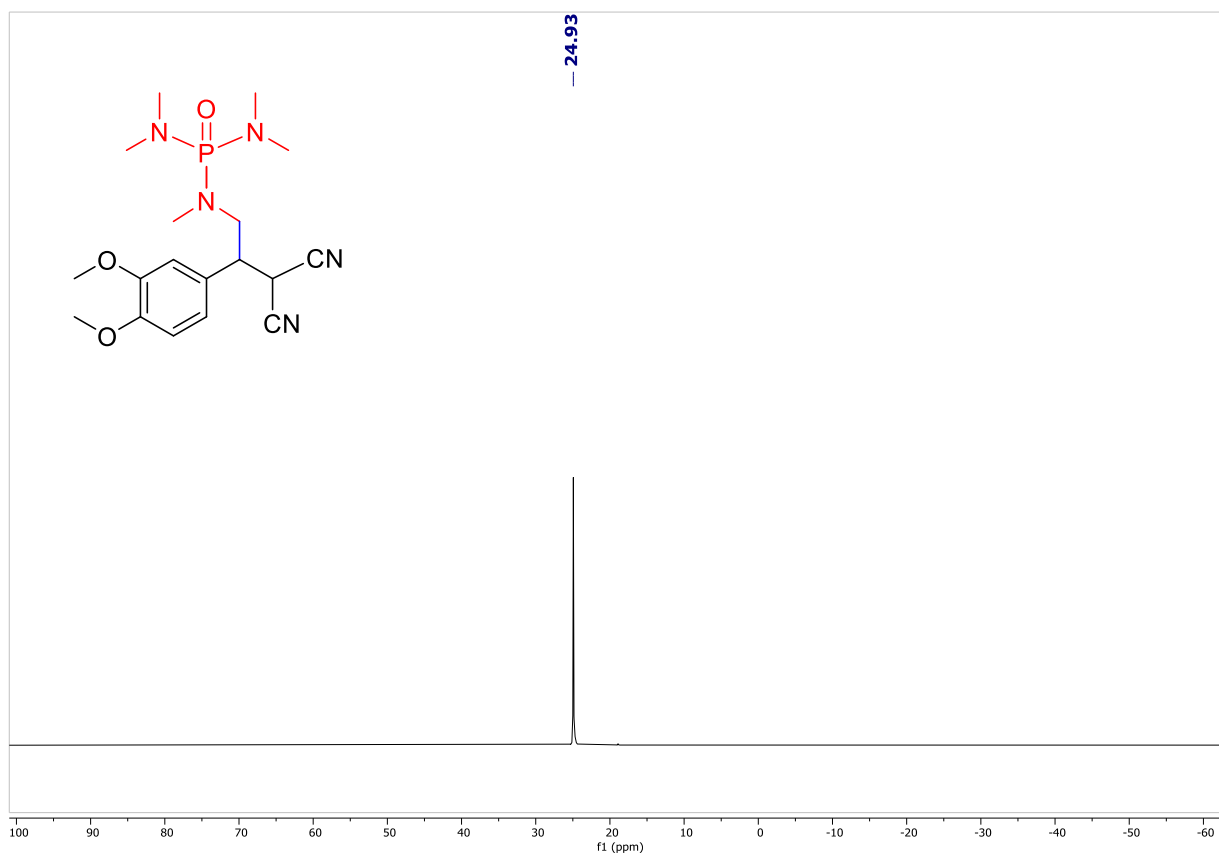
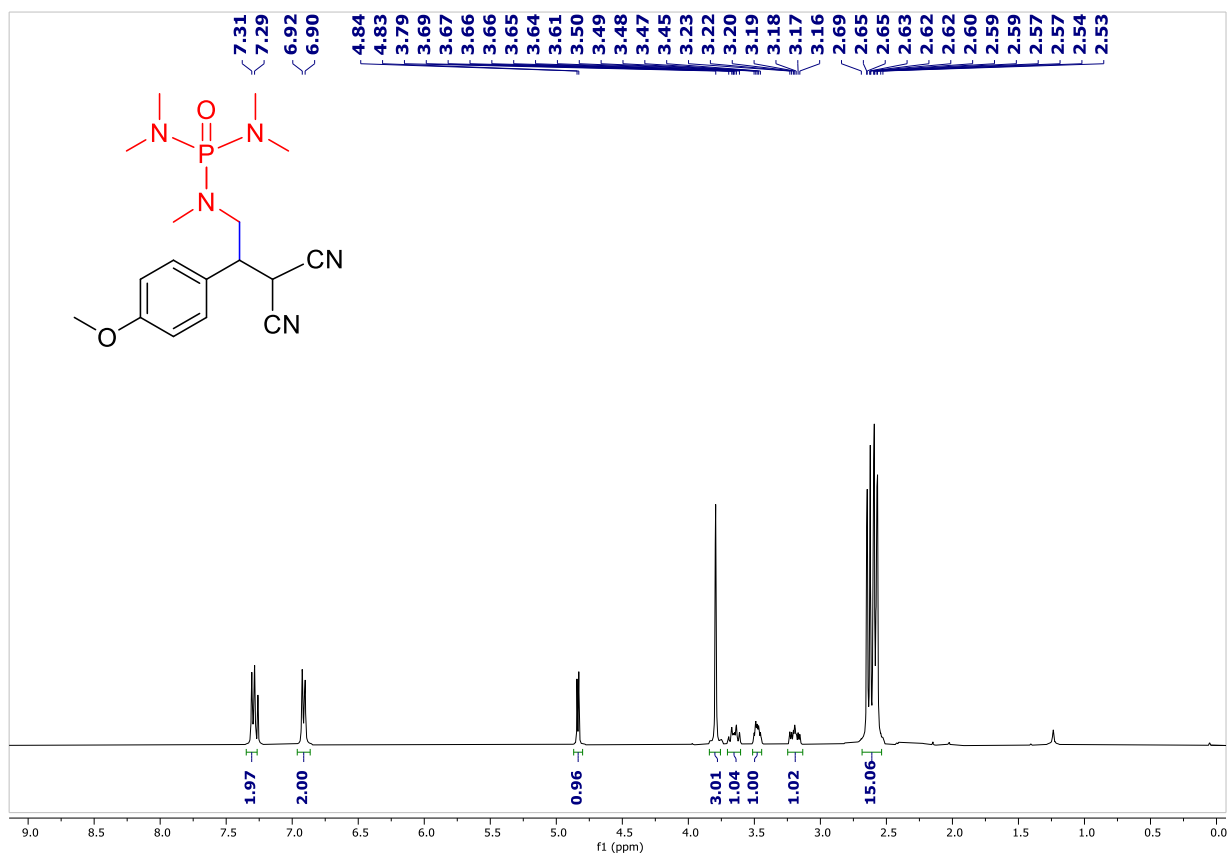
9. NMR spectra of the products:

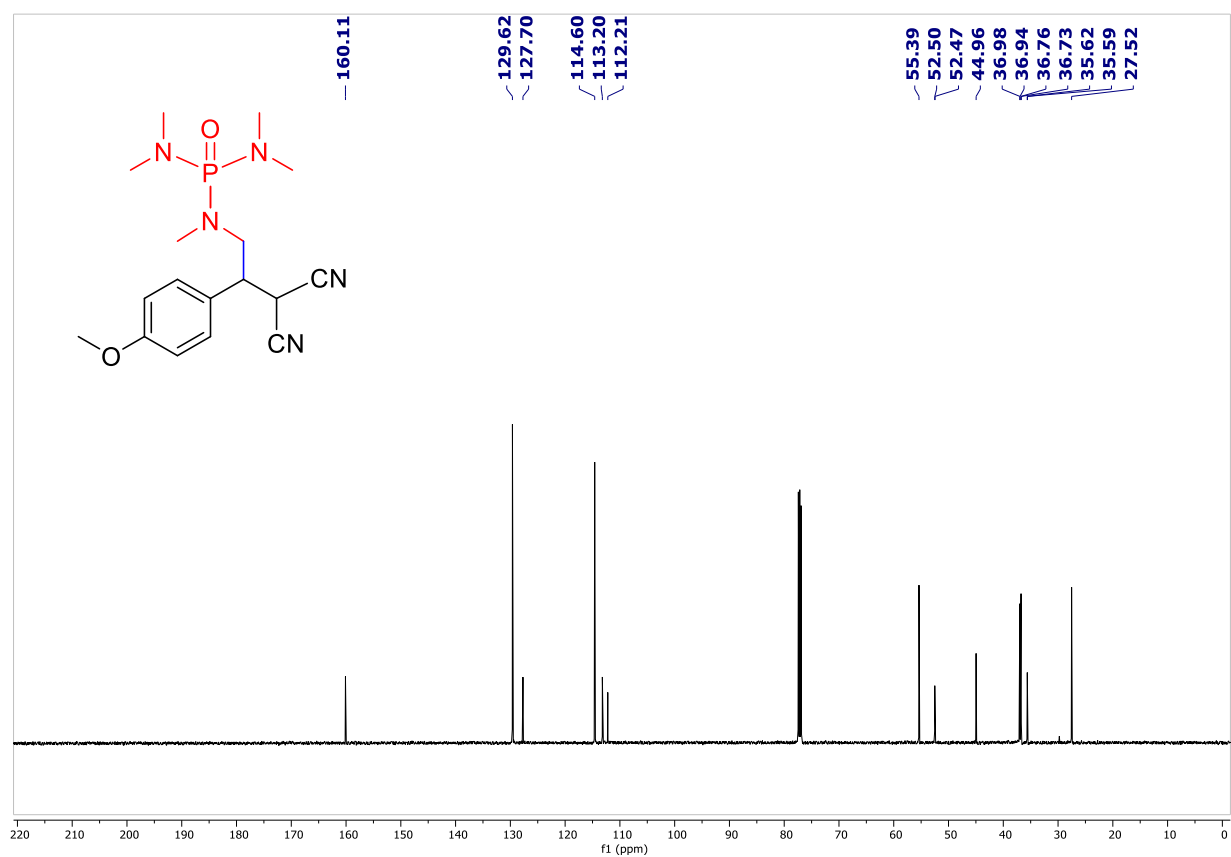
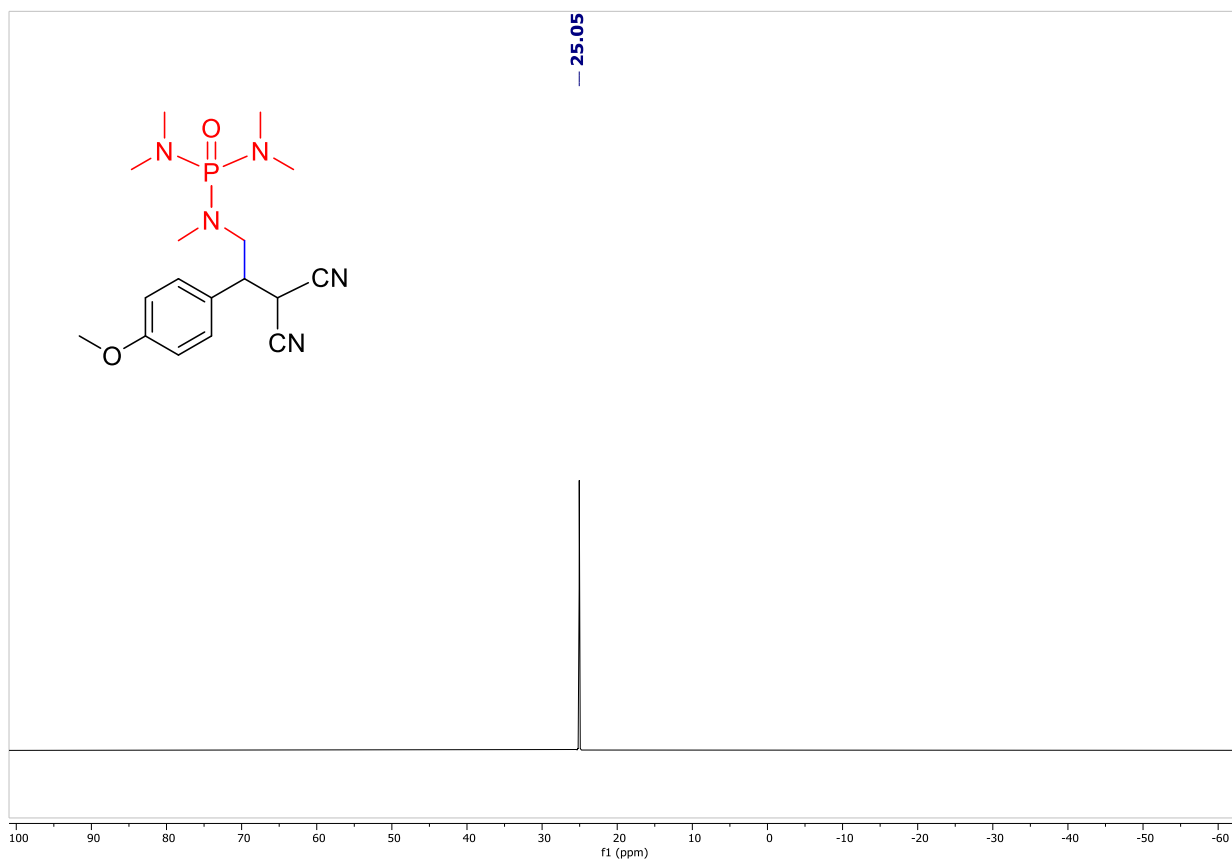
 ^1H NMR (400 MHz, CDCl_3) of compound **3a** $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) of compound **3a**

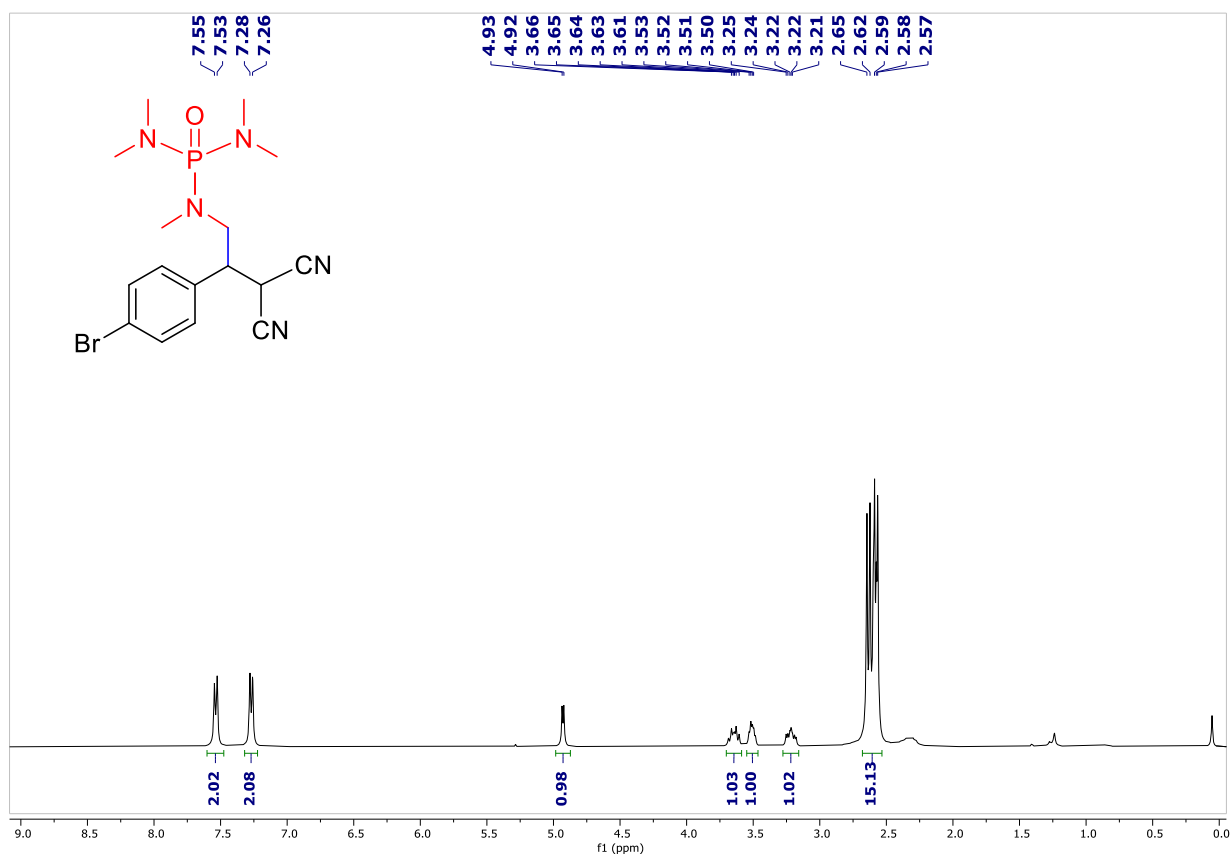
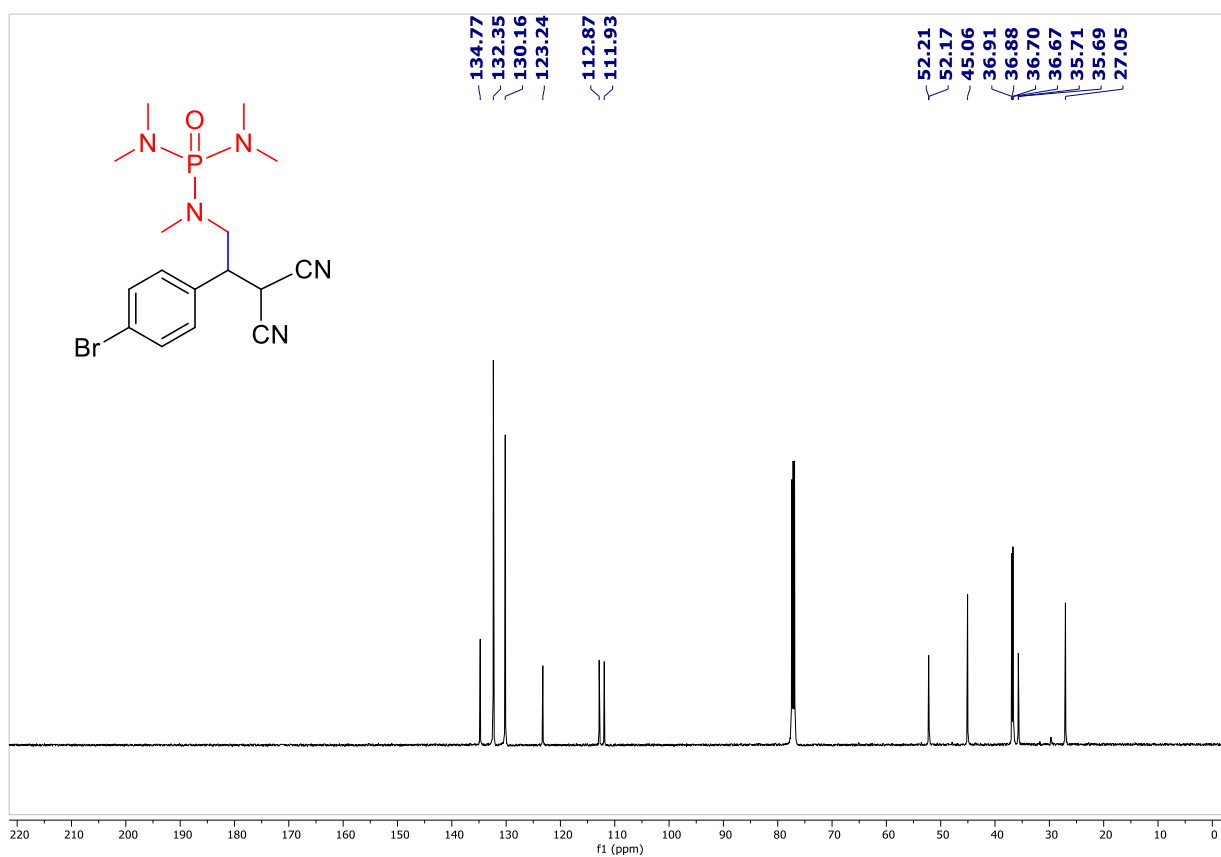
^{31}P NMR (203 MHz, CDCl_3) of compound **3a** ^1H NMR (400 MHz, CDCl_3) of compound **3b**

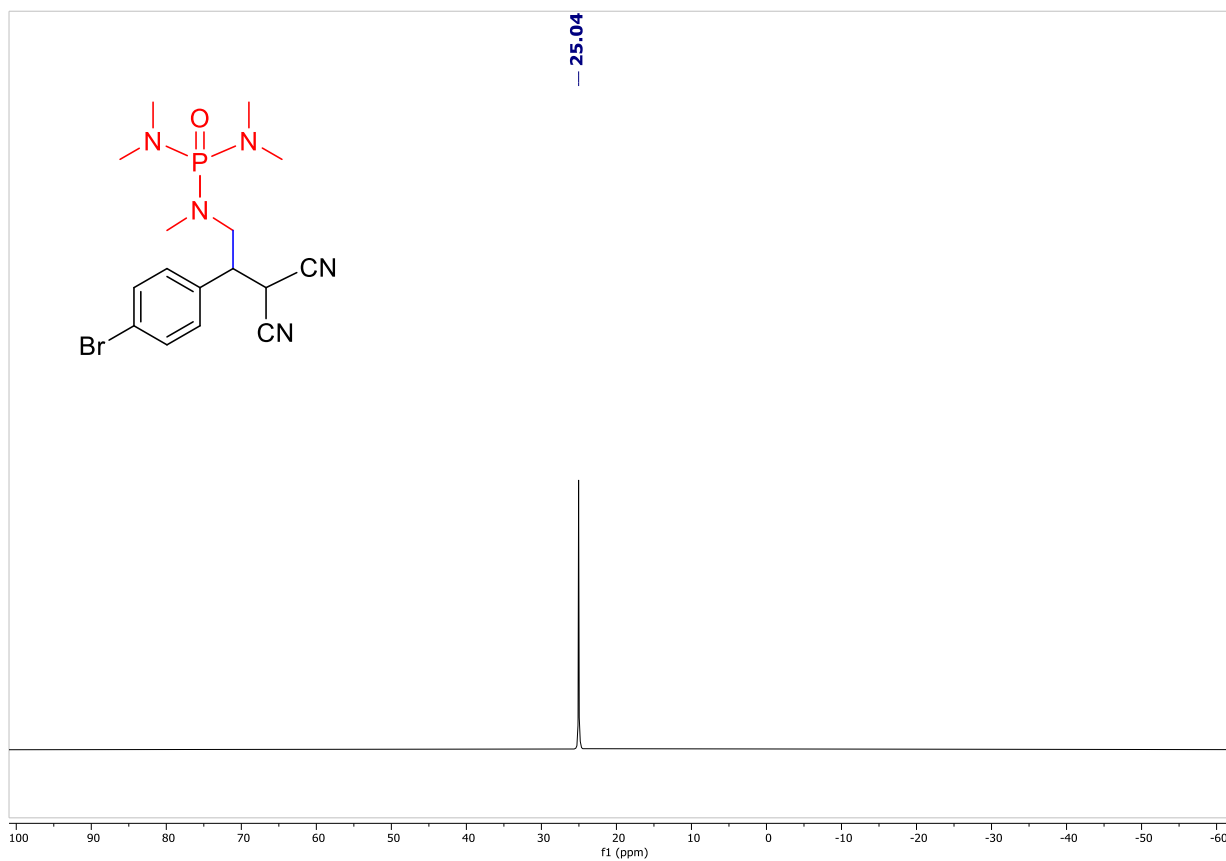
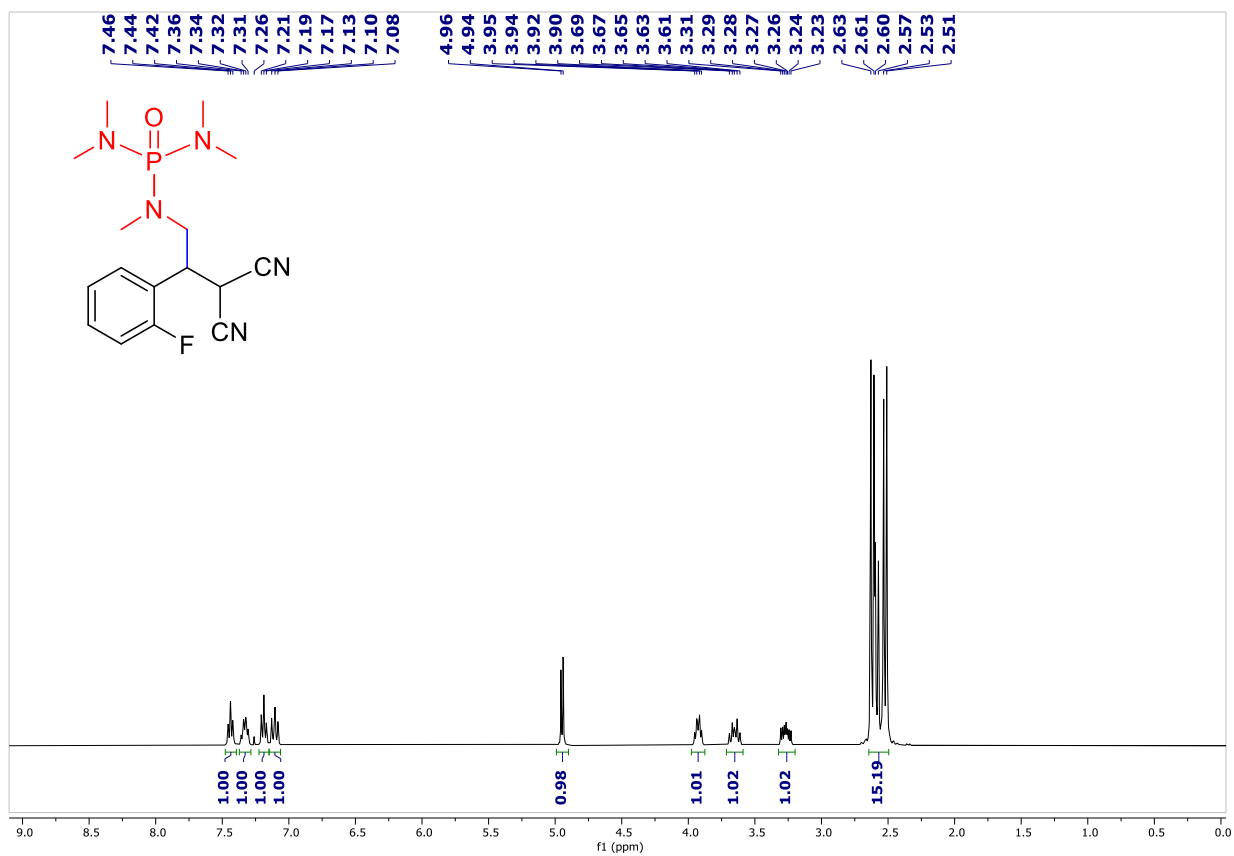
$^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) of compound **3b** ^{31}P NMR (203 MHz, $CDCl_3$) of compound **3b**

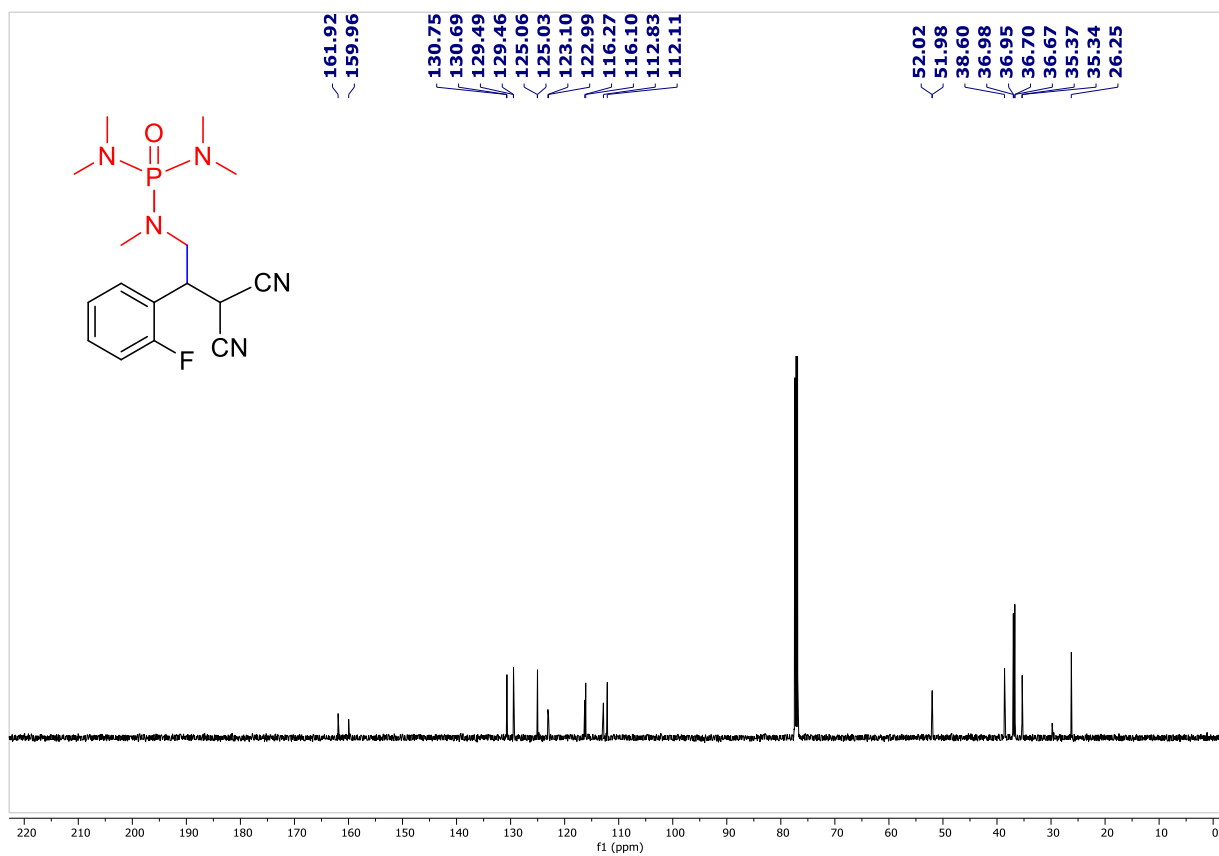
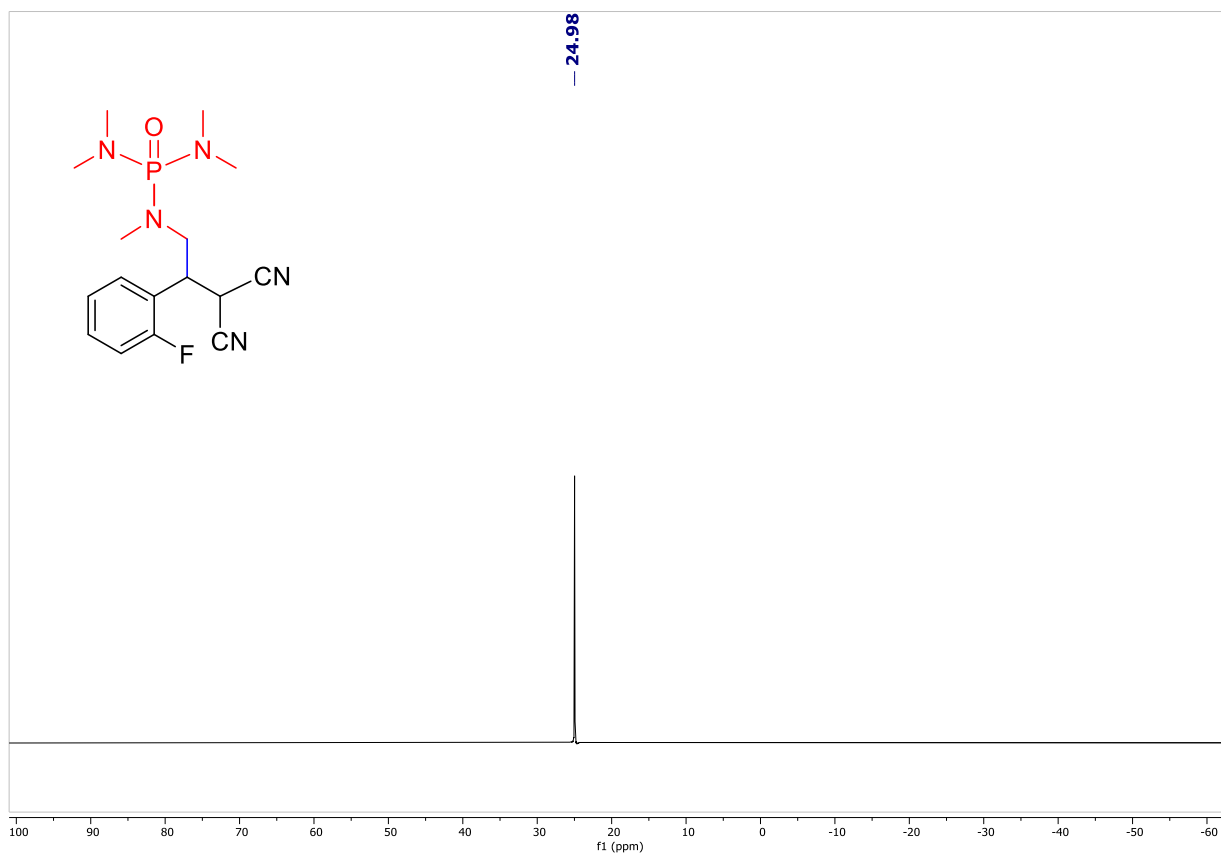
^1H NMR (400 MHz, CDCl_3) of compound **3c** $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) of compound **3c**

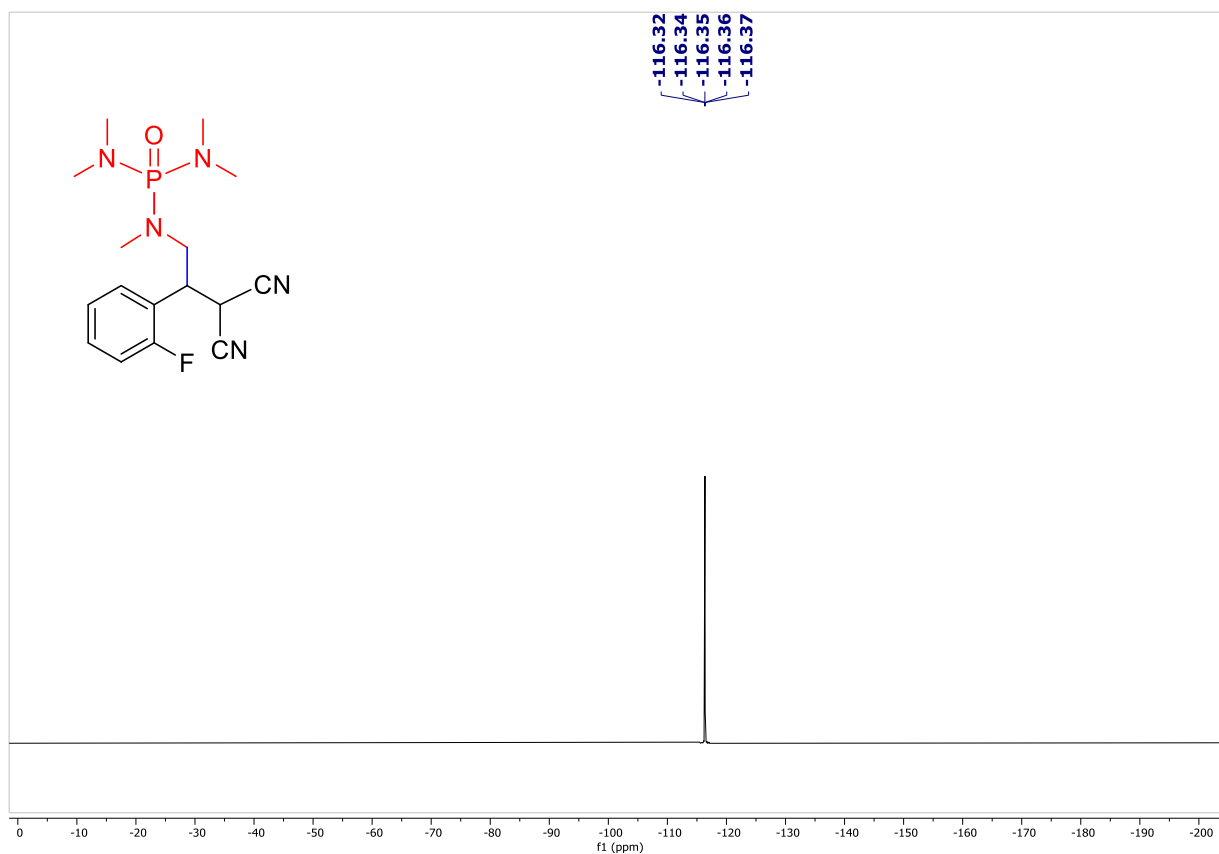
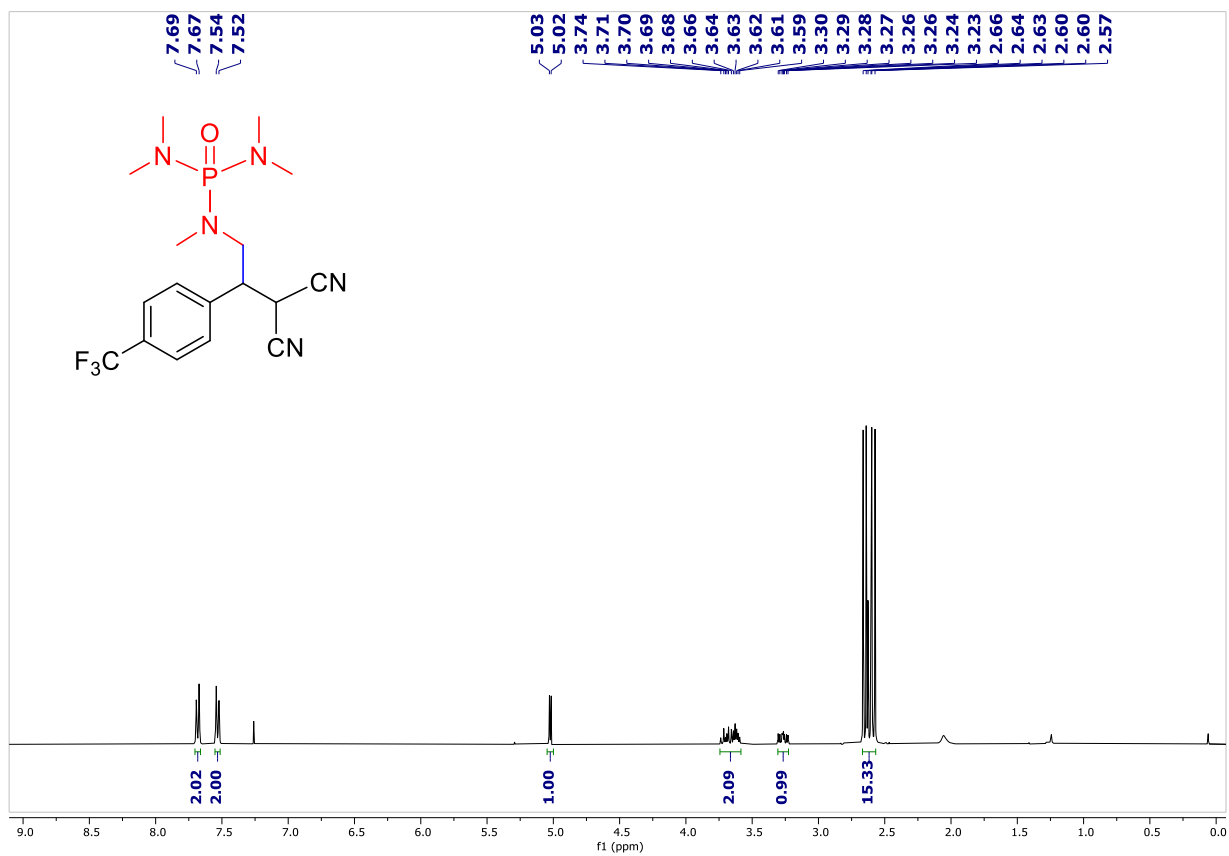
^{31}P NMR (203 MHz, CDCl_3) of compound **3c** ^1H NMR (400 MHz, CDCl_3) of compound **3d**

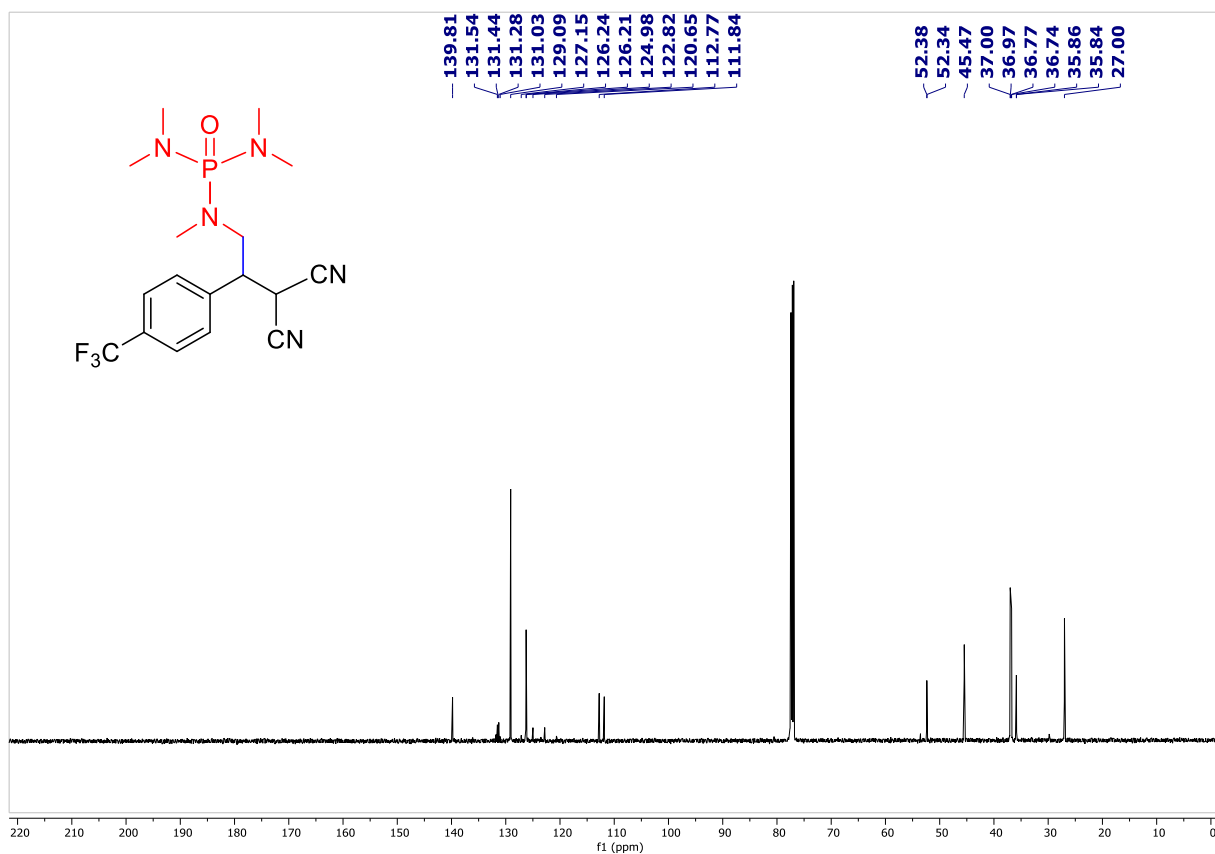
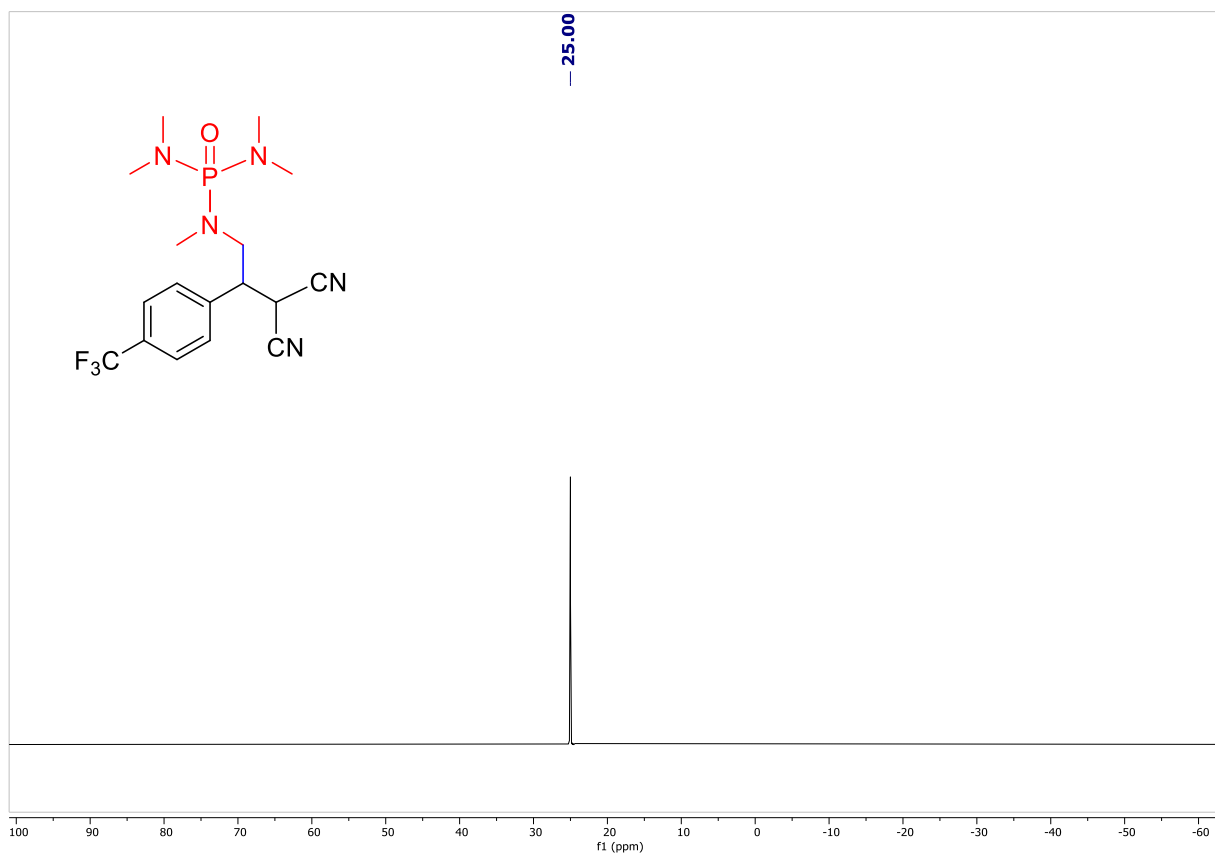
$^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) of compound **3d** ^{31}P NMR (203 MHz, $CDCl_3$) of compound **3d**

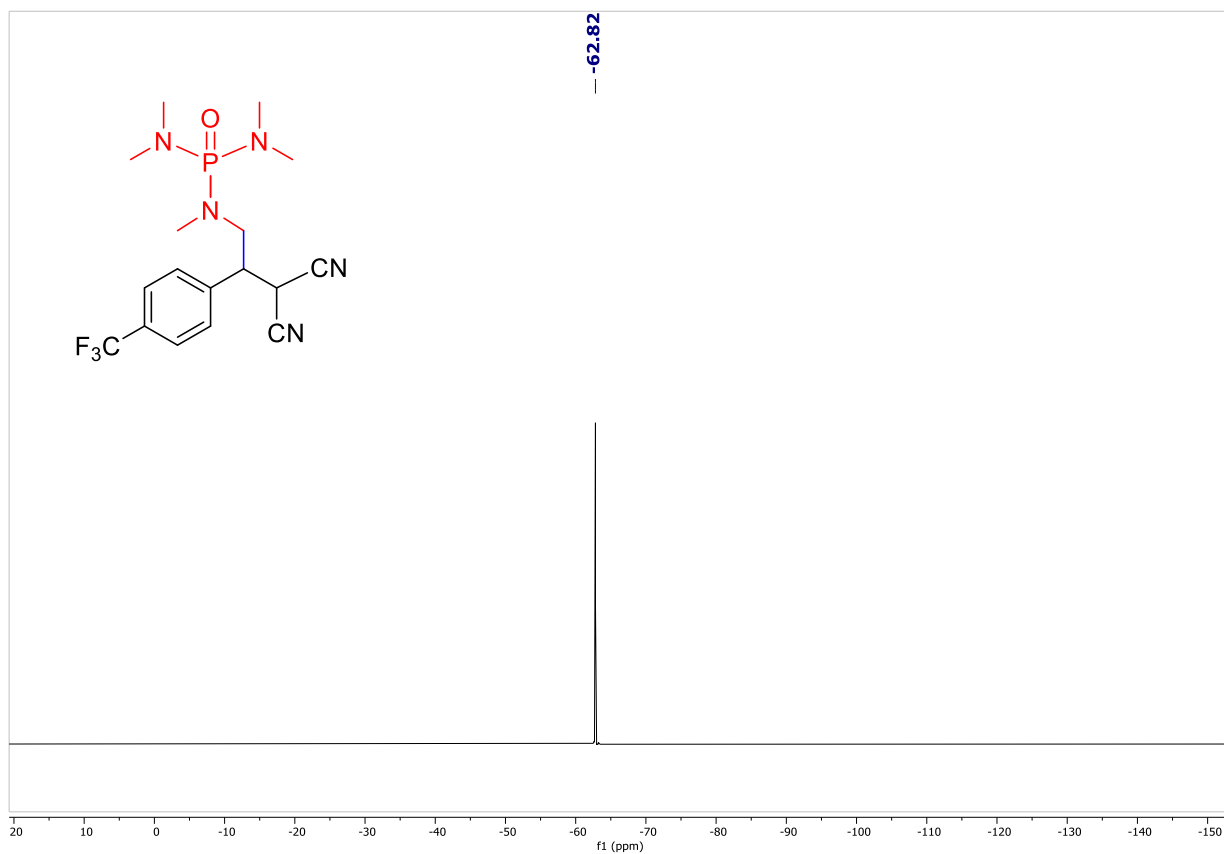
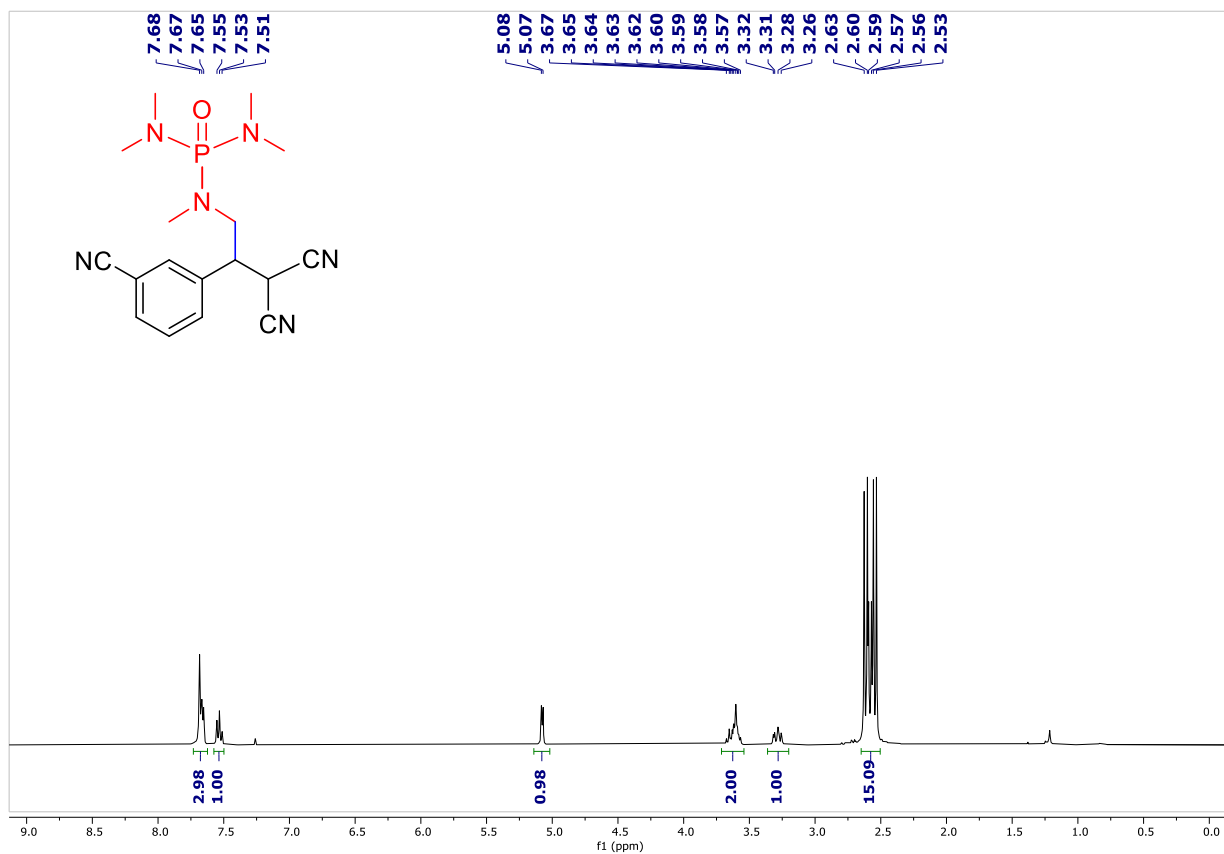
^1H NMR (400 MHz, CDCl_3) of compound **3e** $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) of compound **3e**

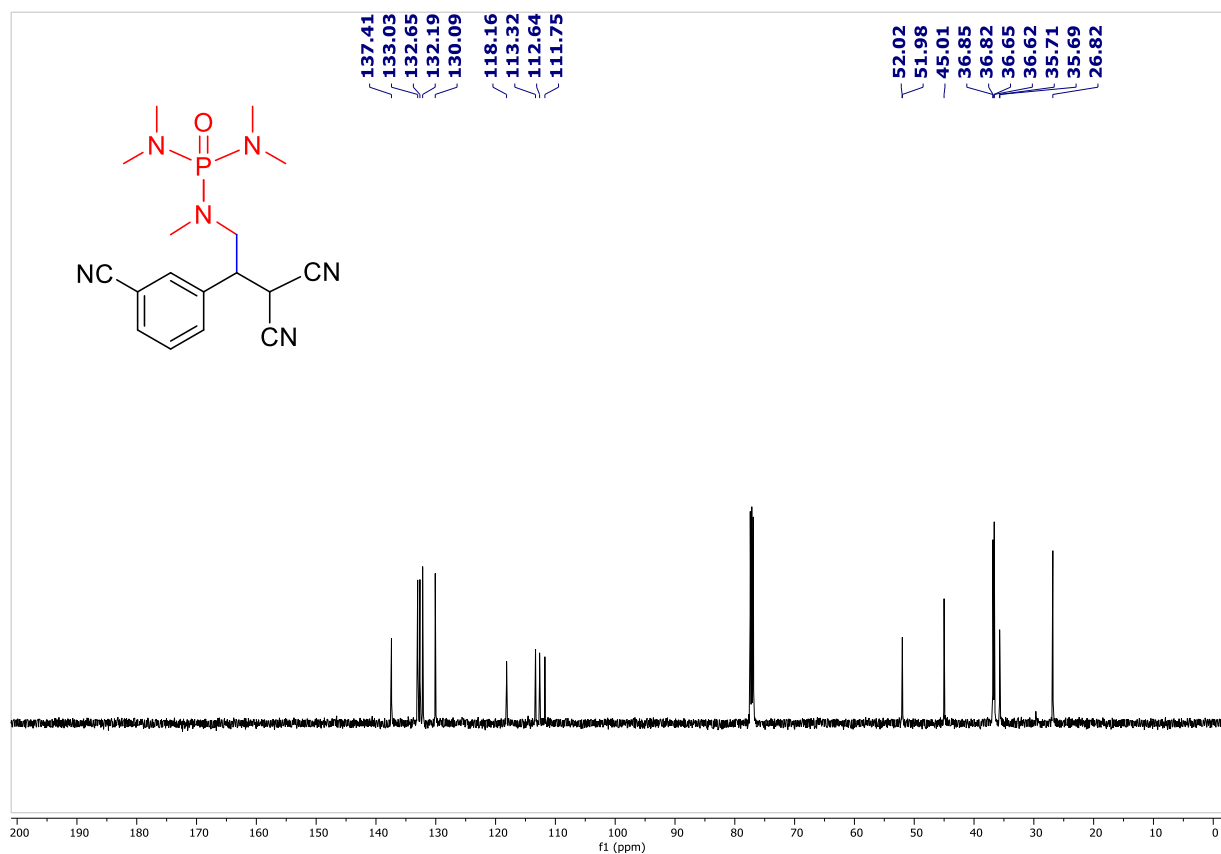
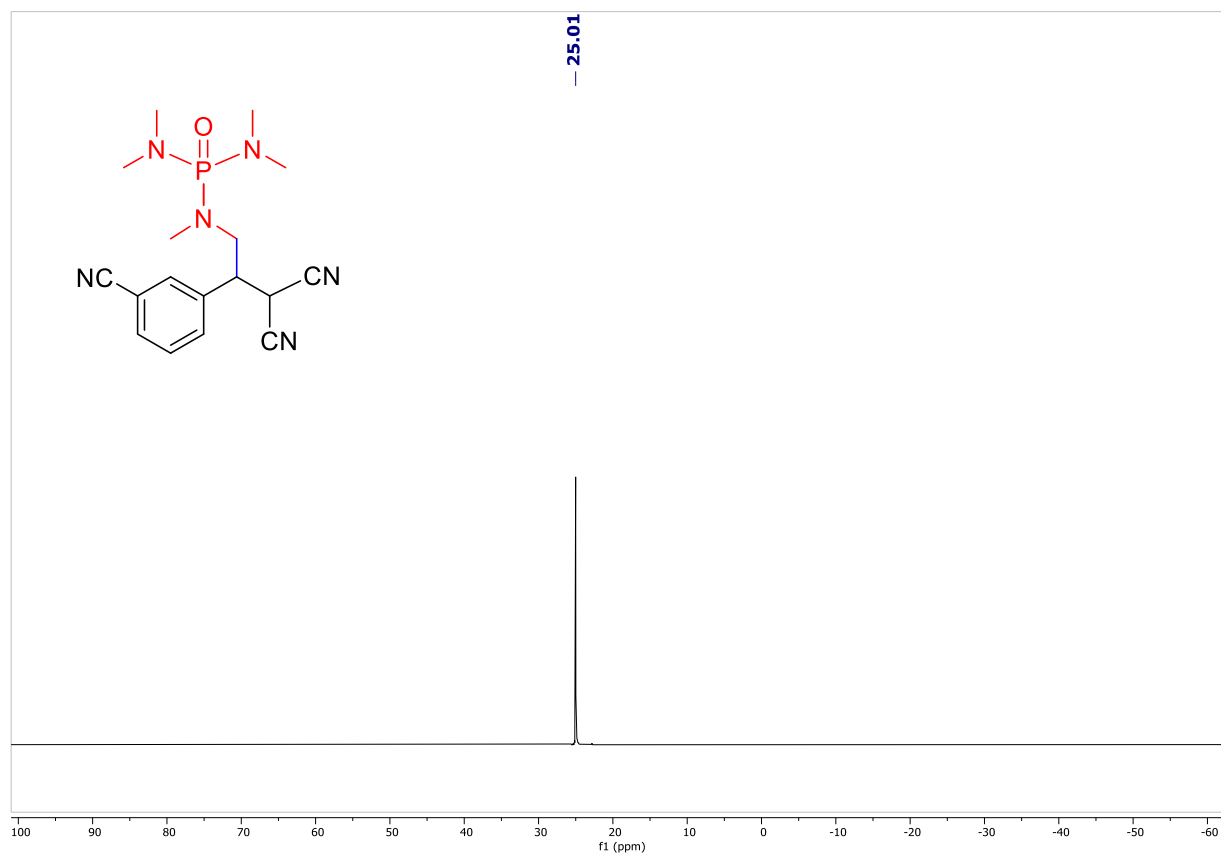
^{31}P NMR (203 MHz, CDCl_3) of compound **3e** ^1H NMR (400 MHz, CDCl_3) of compound **3f**

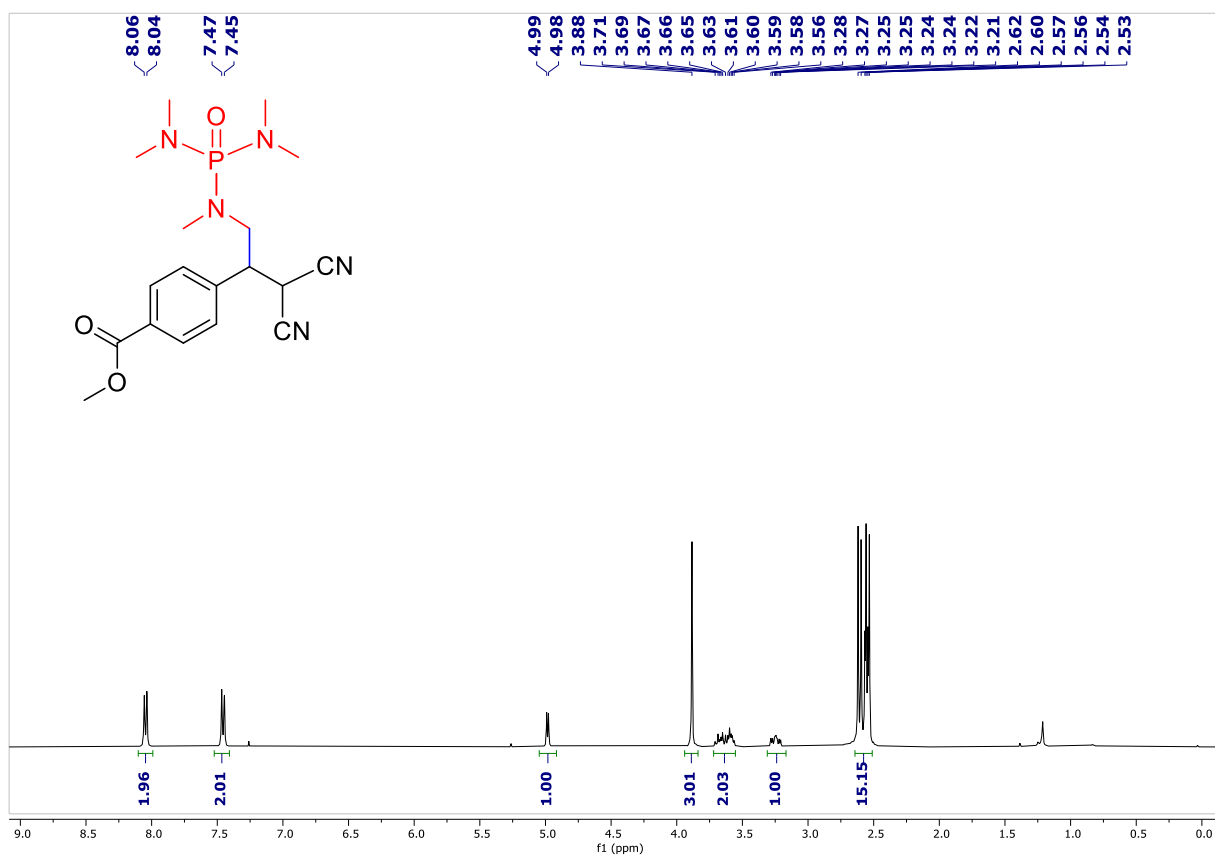
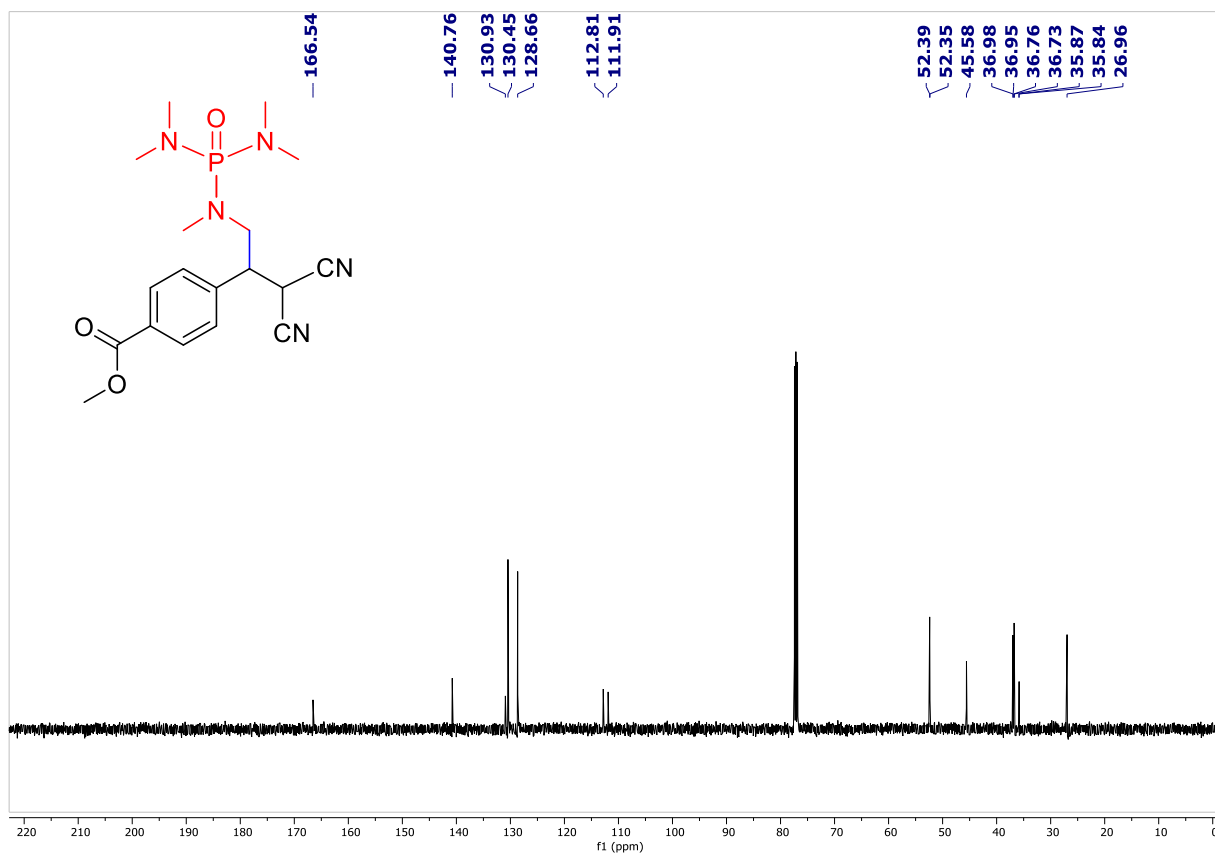
$^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) of compound **3f** ^{31}P NMR (203 MHz, $CDCl_3$) of compound **3f**

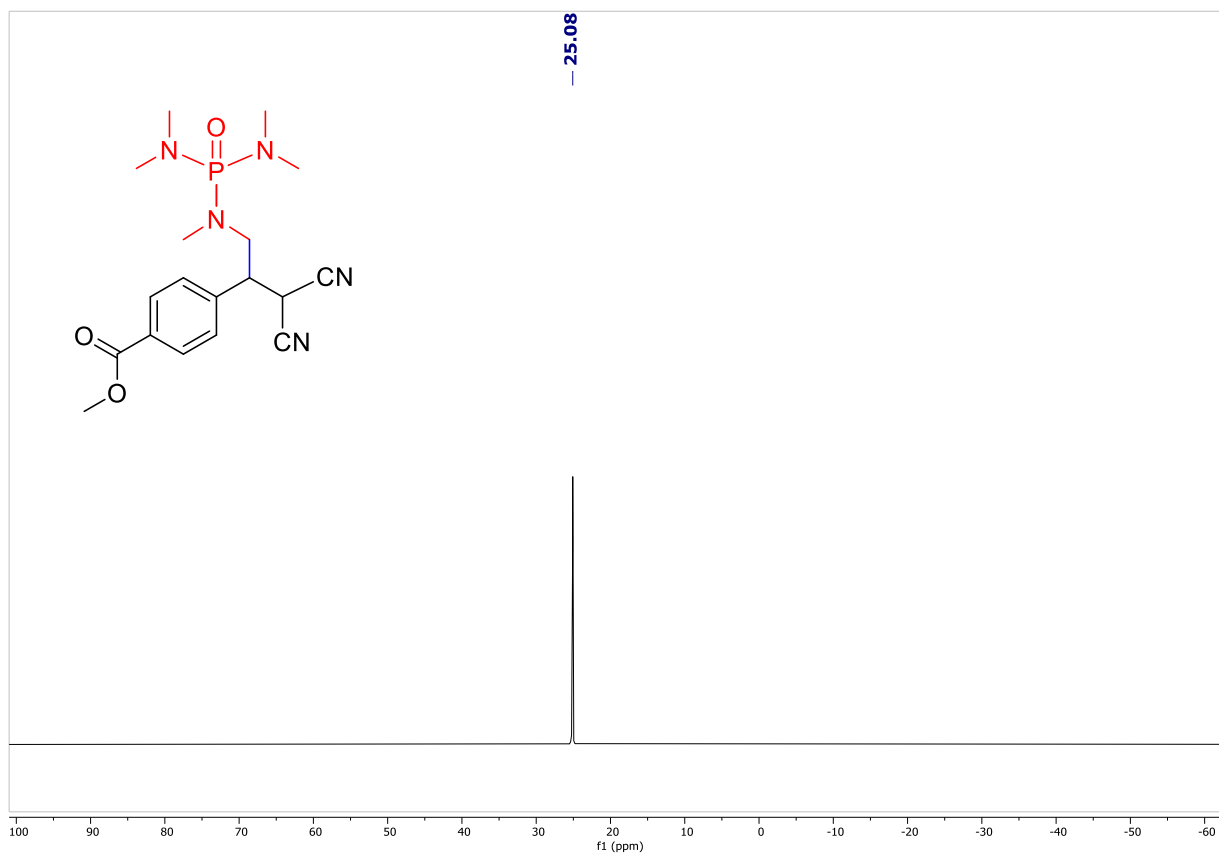
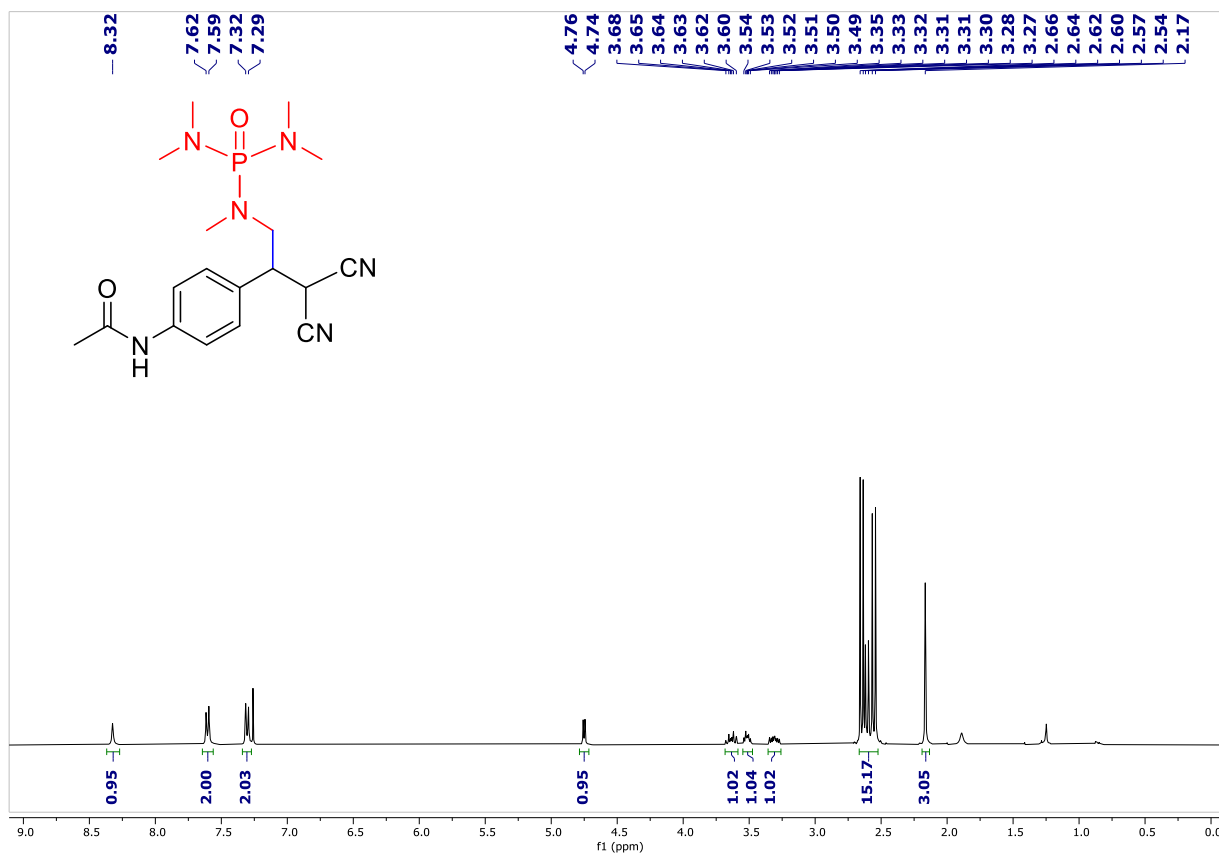
^{19}F NMR (471 MHz, CDCl_3) of compound **3f** ^1H NMR (400 MHz, CDCl_3) of compound **3g**

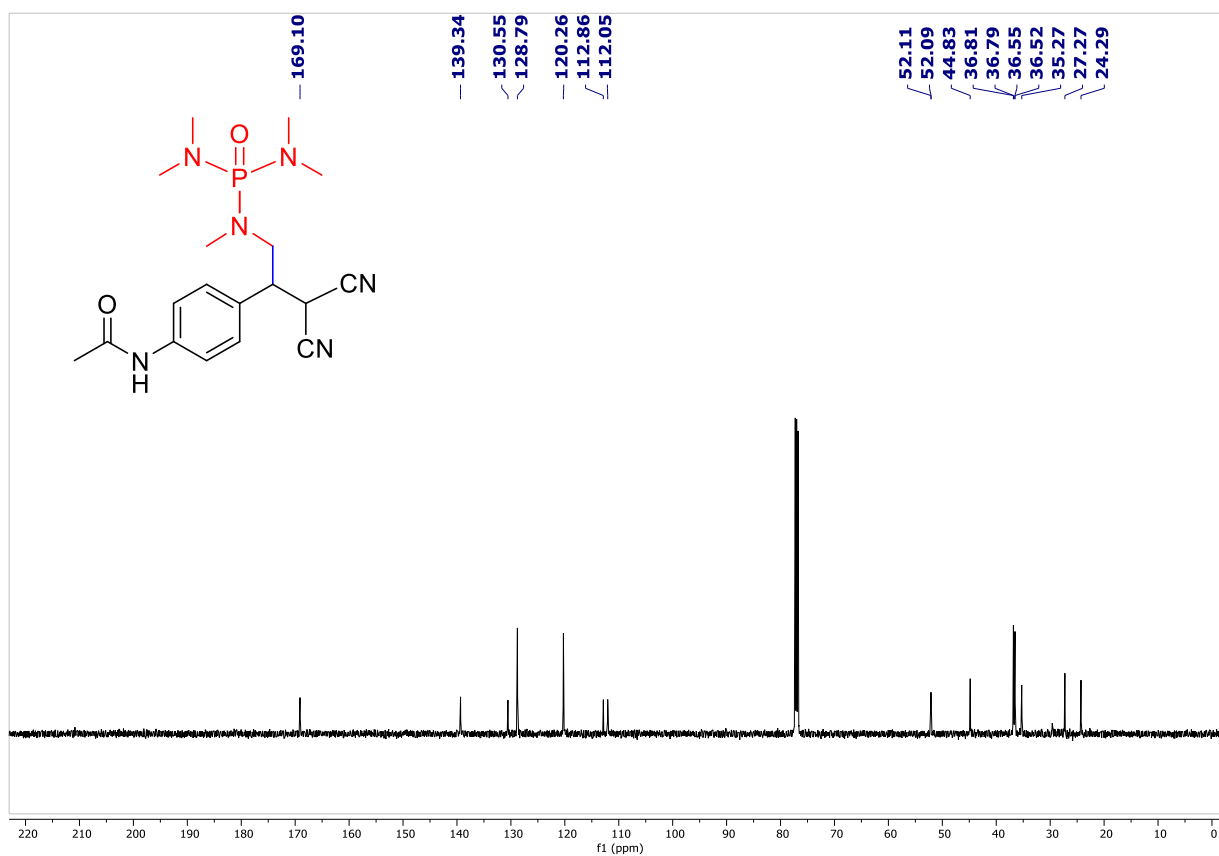
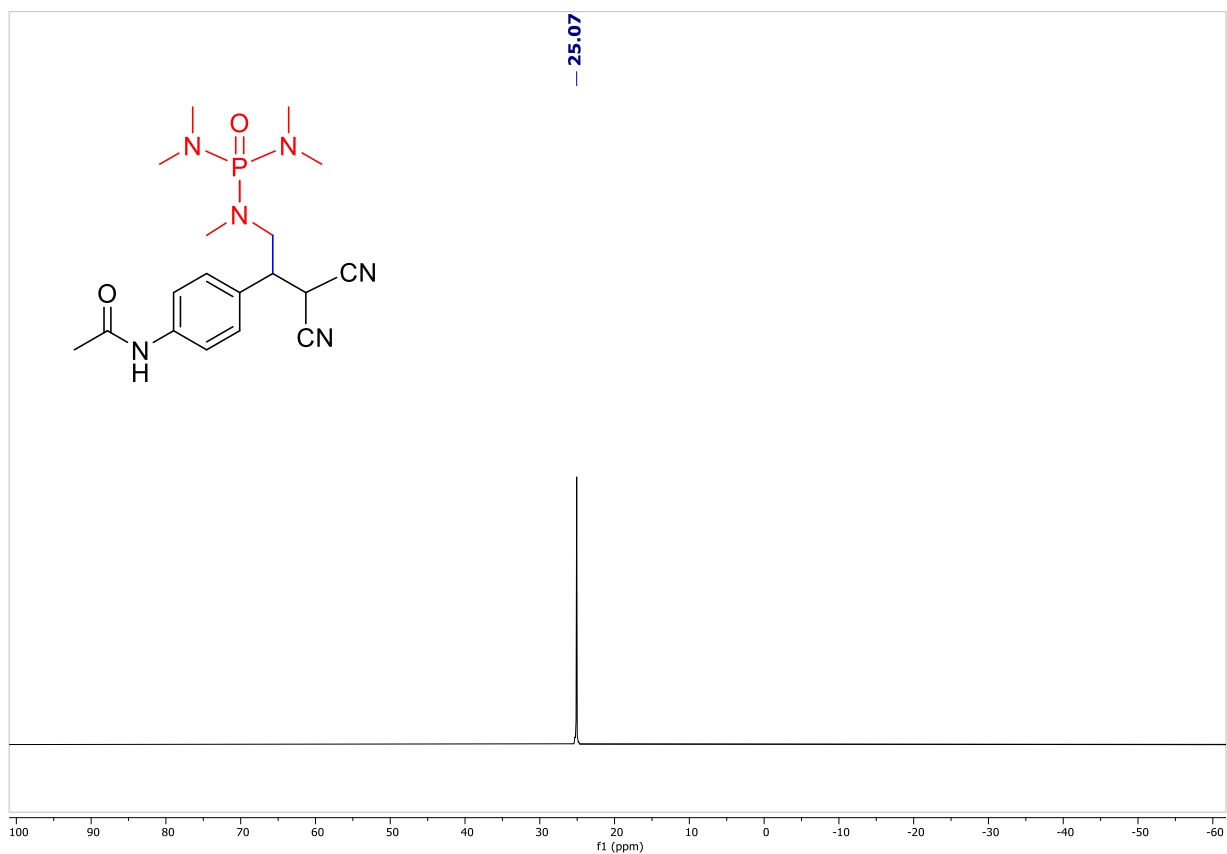
$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) of compound **3g** ^{31}P NMR (203 MHz, CDCl_3) of compound **3g**

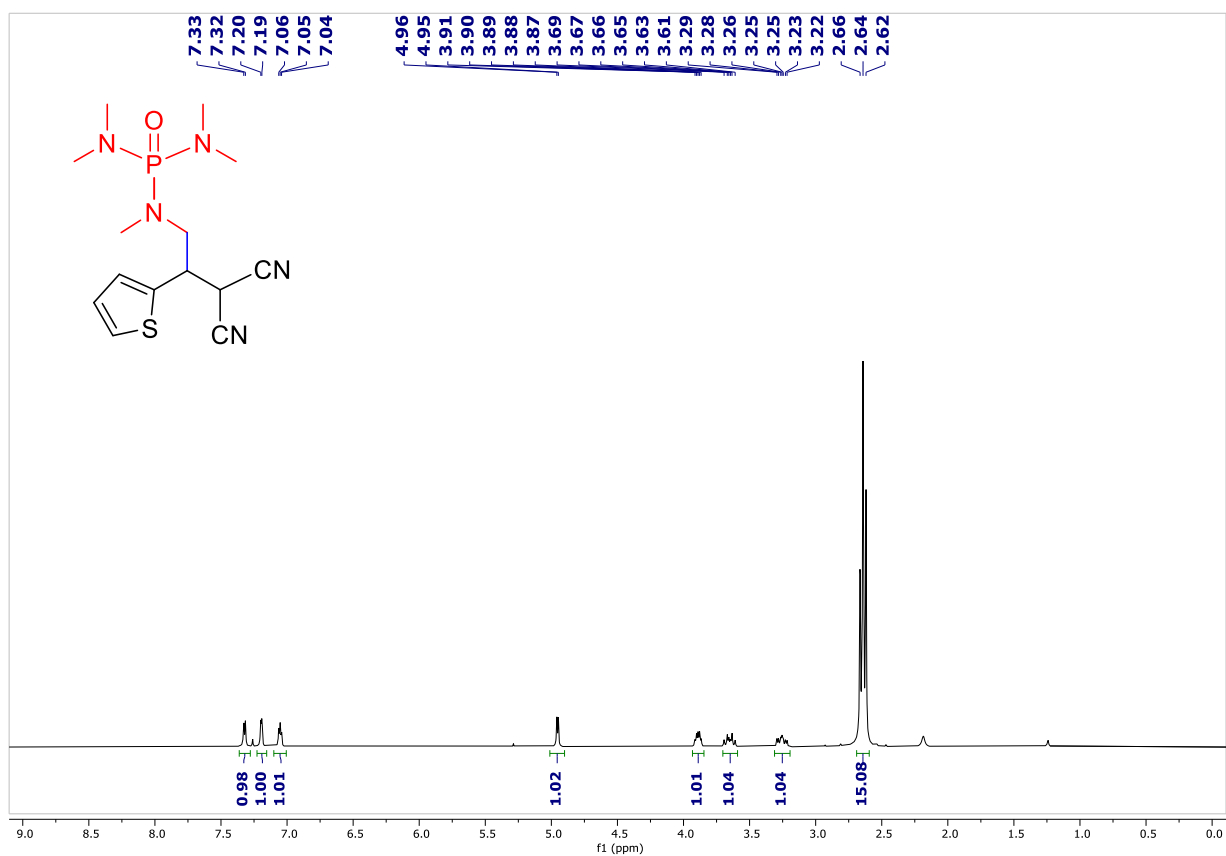
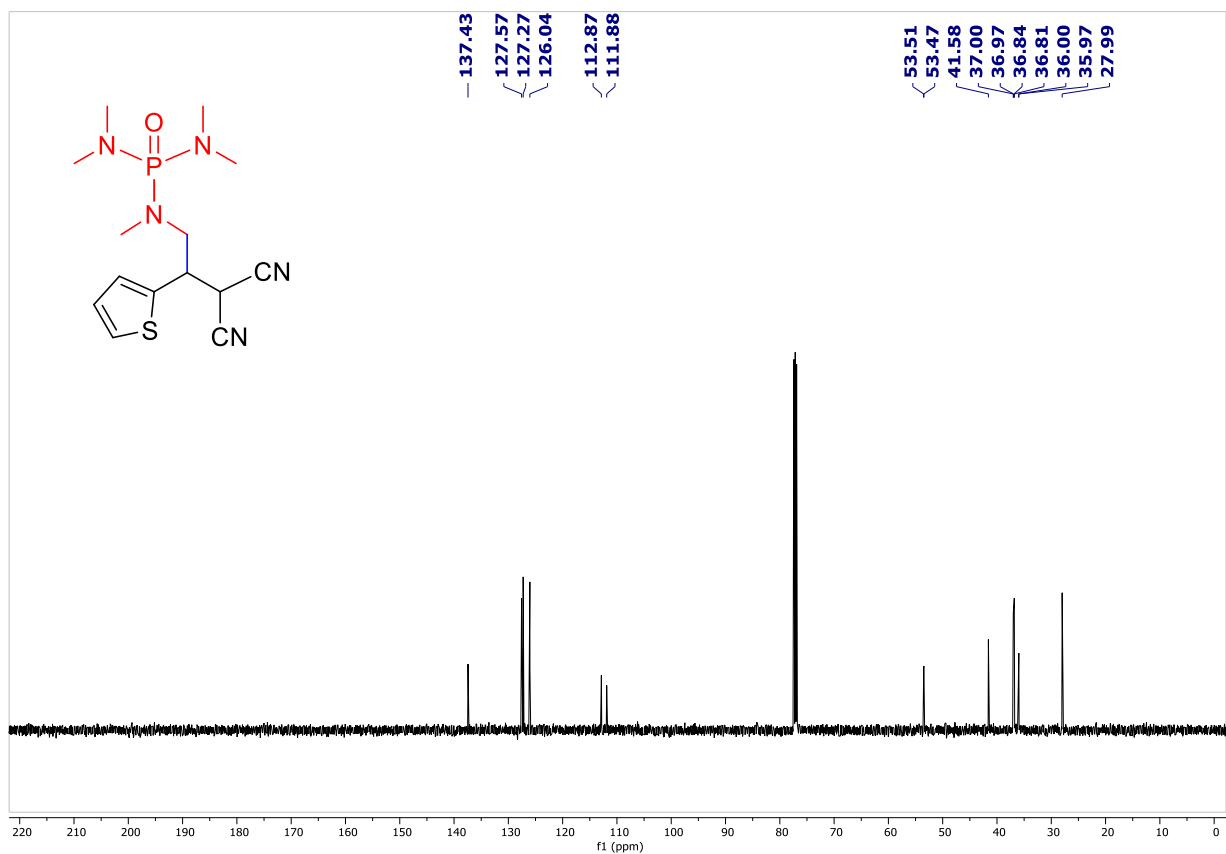
^{19}F NMR (471 MHz, CDCl_3) of compound **3g** ^1H NMR (400 MHz, CDCl_3) of compound **3h**

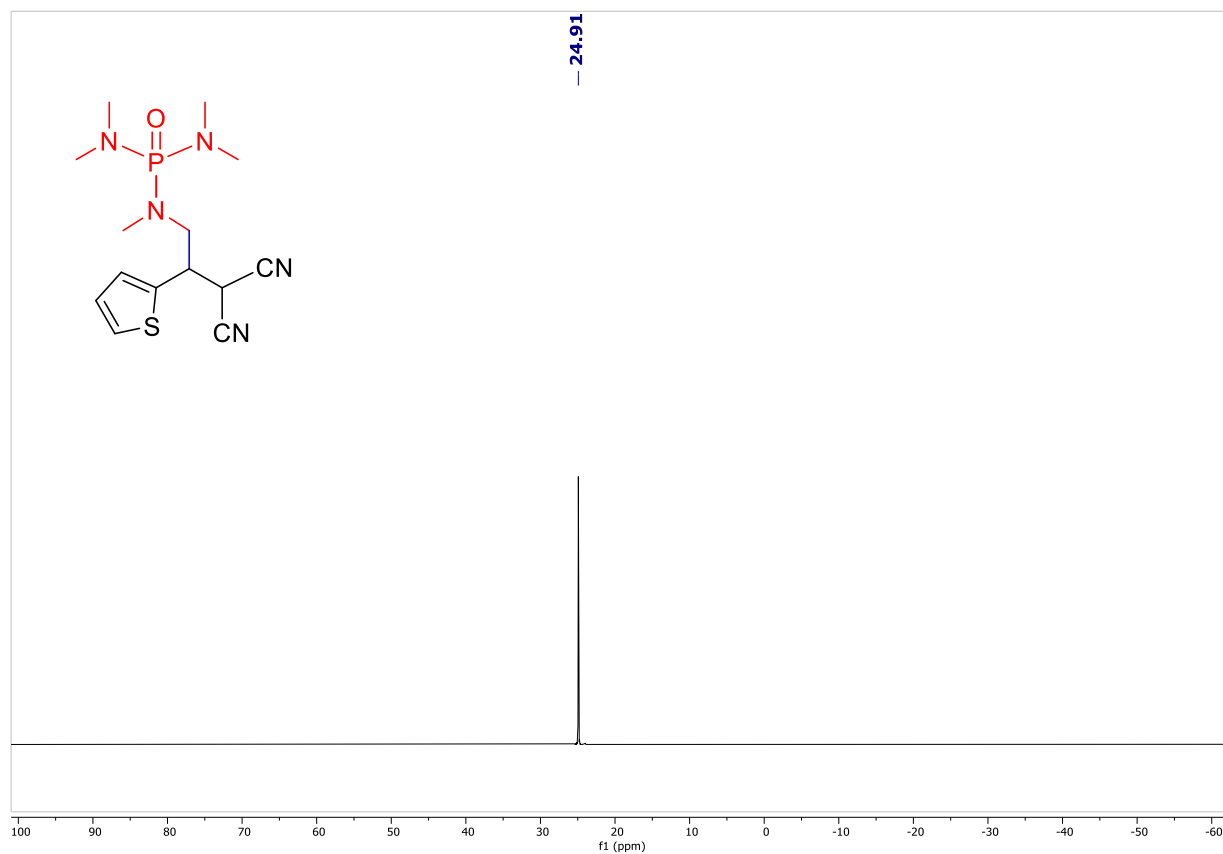
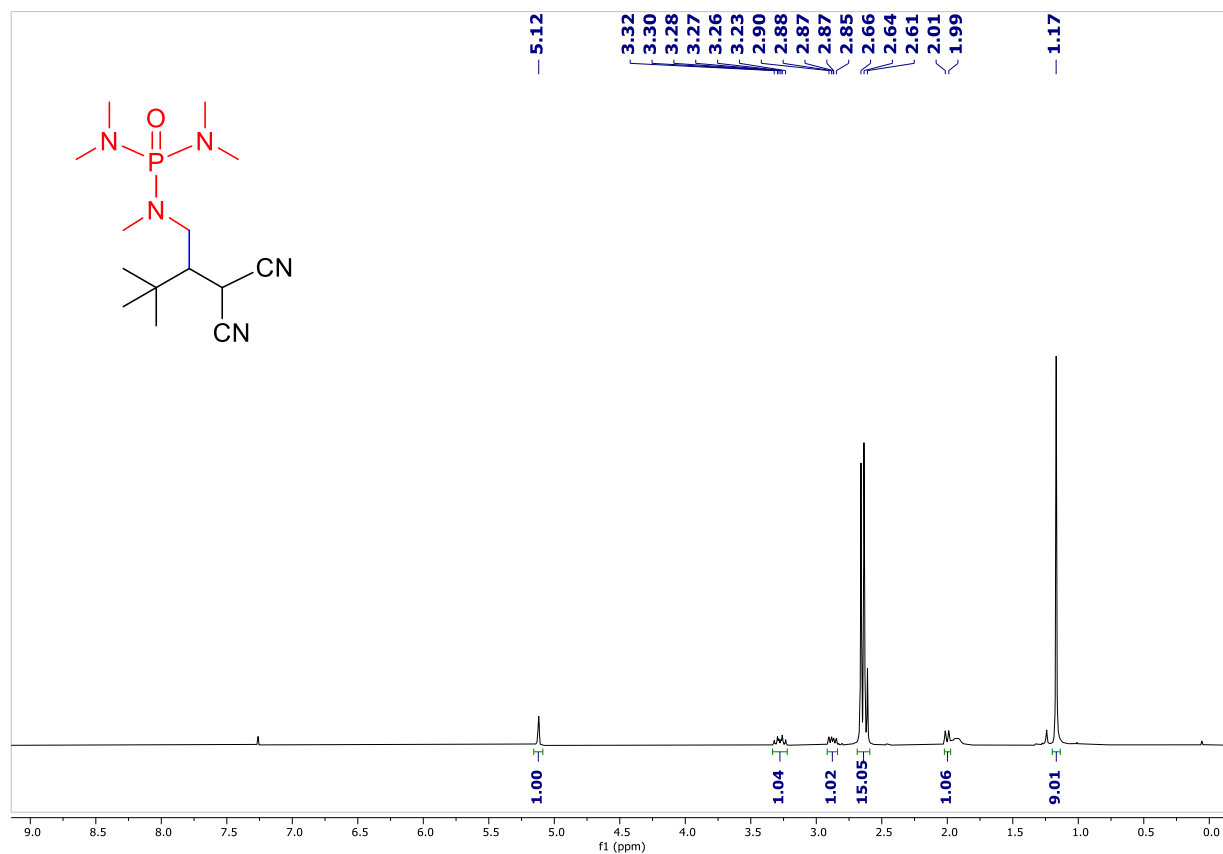
$^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) of compound **3h** ^{31}P NMR (203 MHz, $CDCl_3$) of compound **3h**

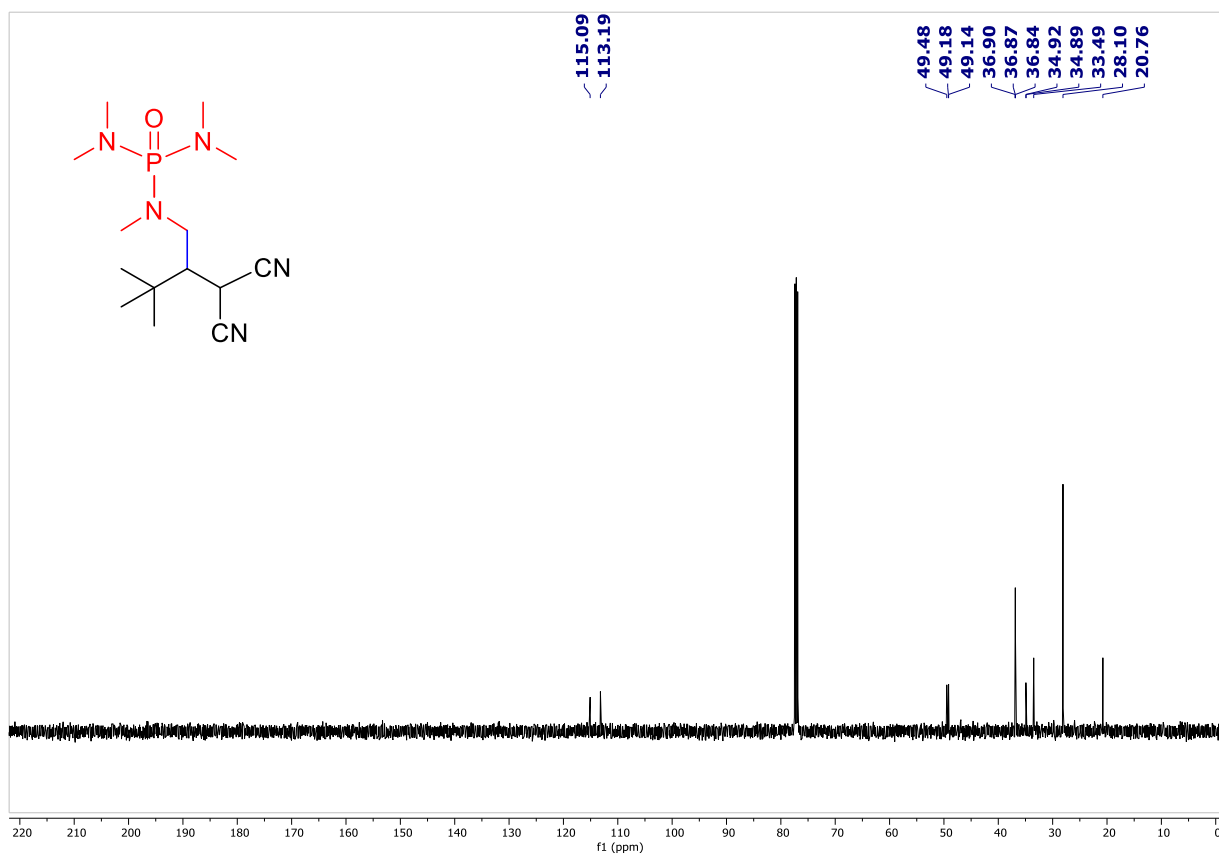
^1H NMR (400 MHz, CDCl_3) of compound **3i** $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) of compound **3i**

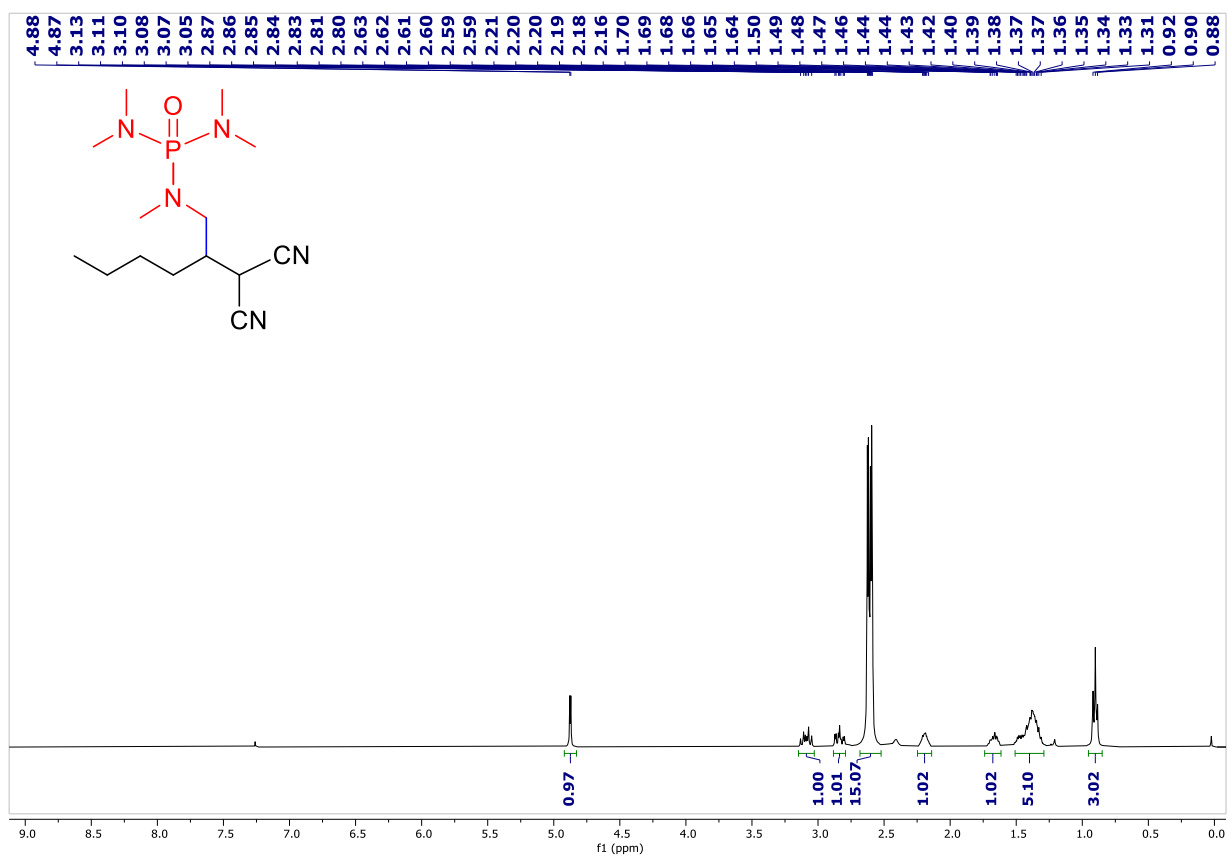
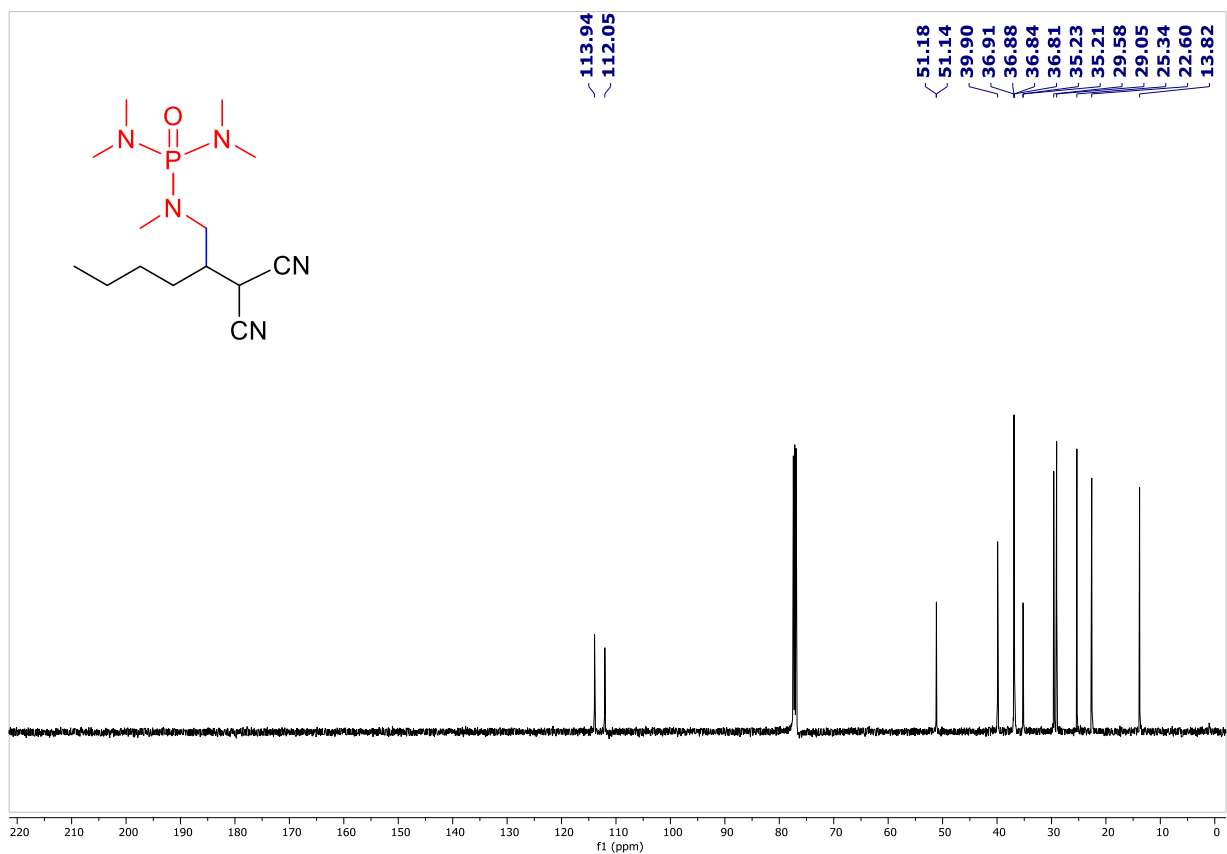
^{31}P NMR (203 MHz, CDCl_3) of compound **3i** ^1H NMR (400 MHz, CDCl_3) of compound **3j**

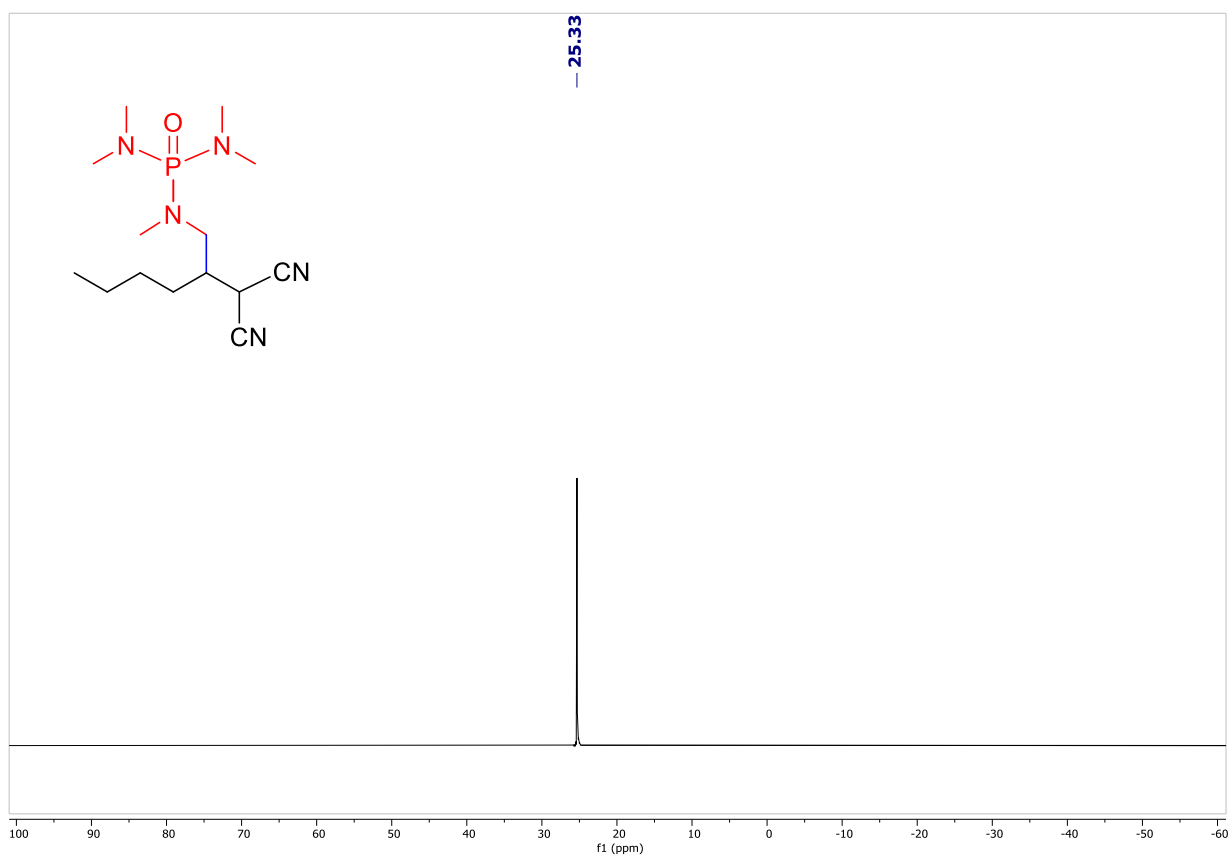
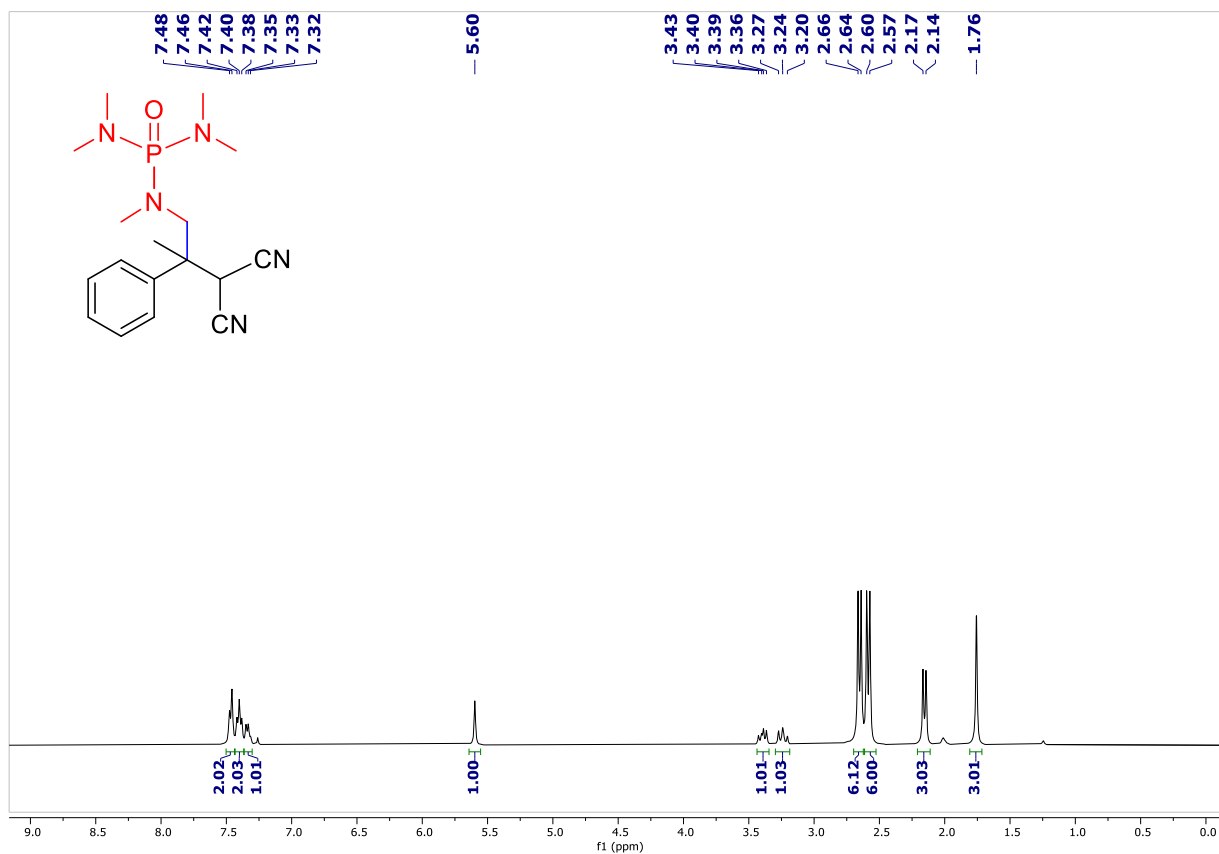
$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) of compound **3j** ^{31}P NMR (203 MHz, CDCl_3) of compound **3j**

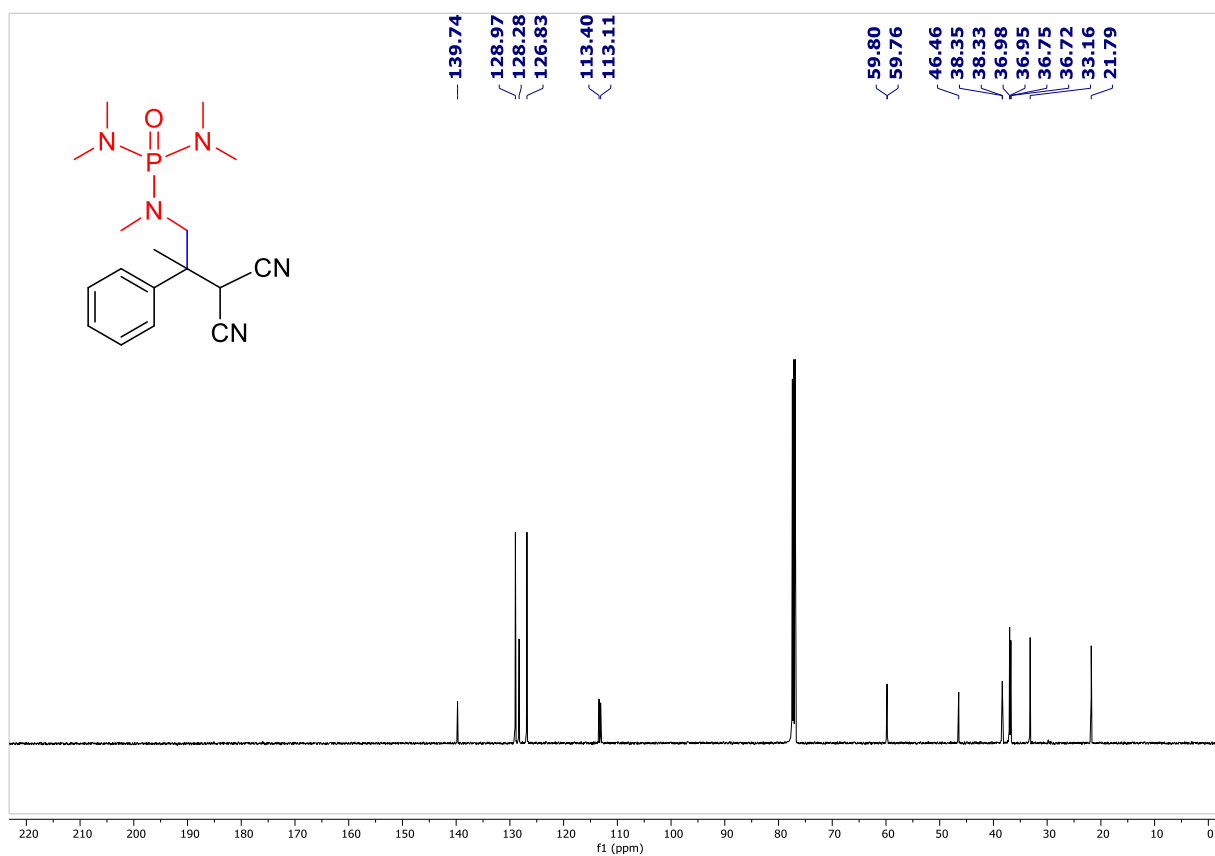
^1H NMR (400 MHz, CDCl_3) of compound **3k** $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) of compound **3k**

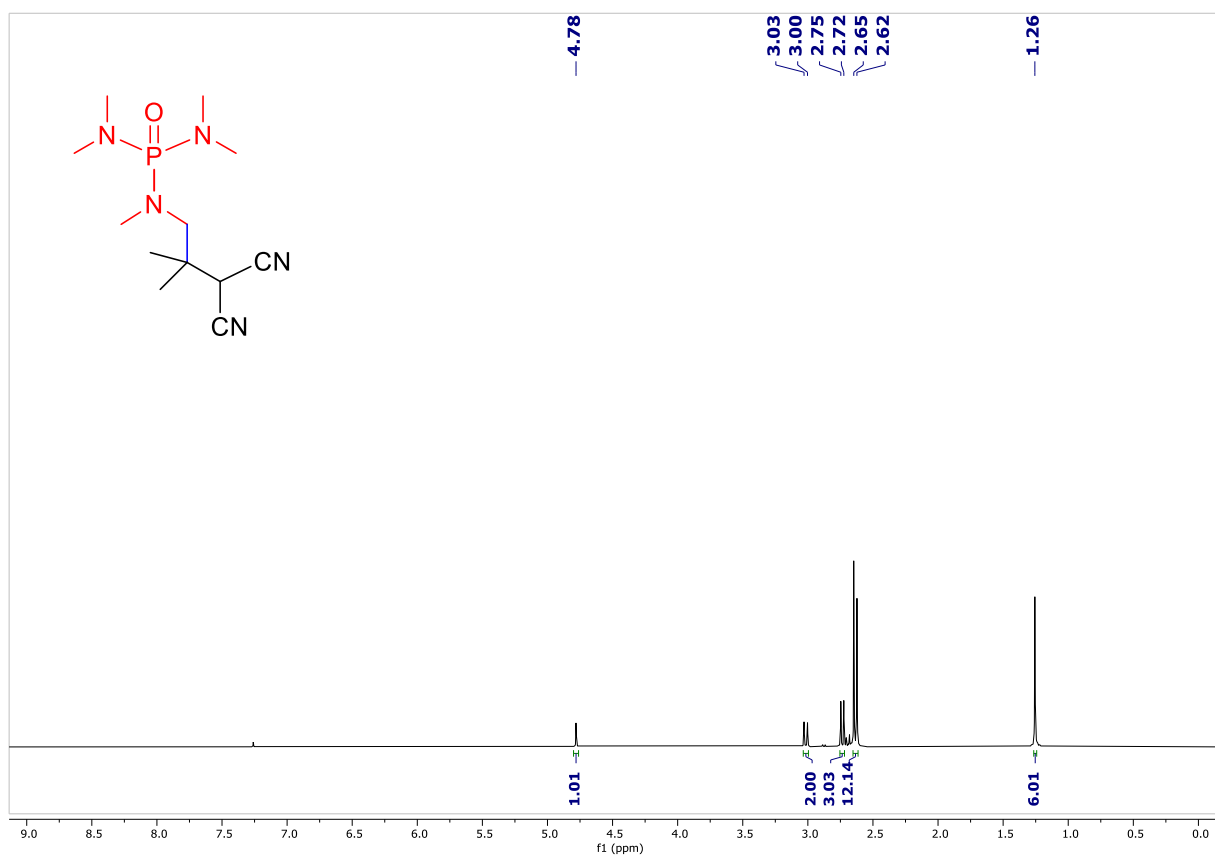
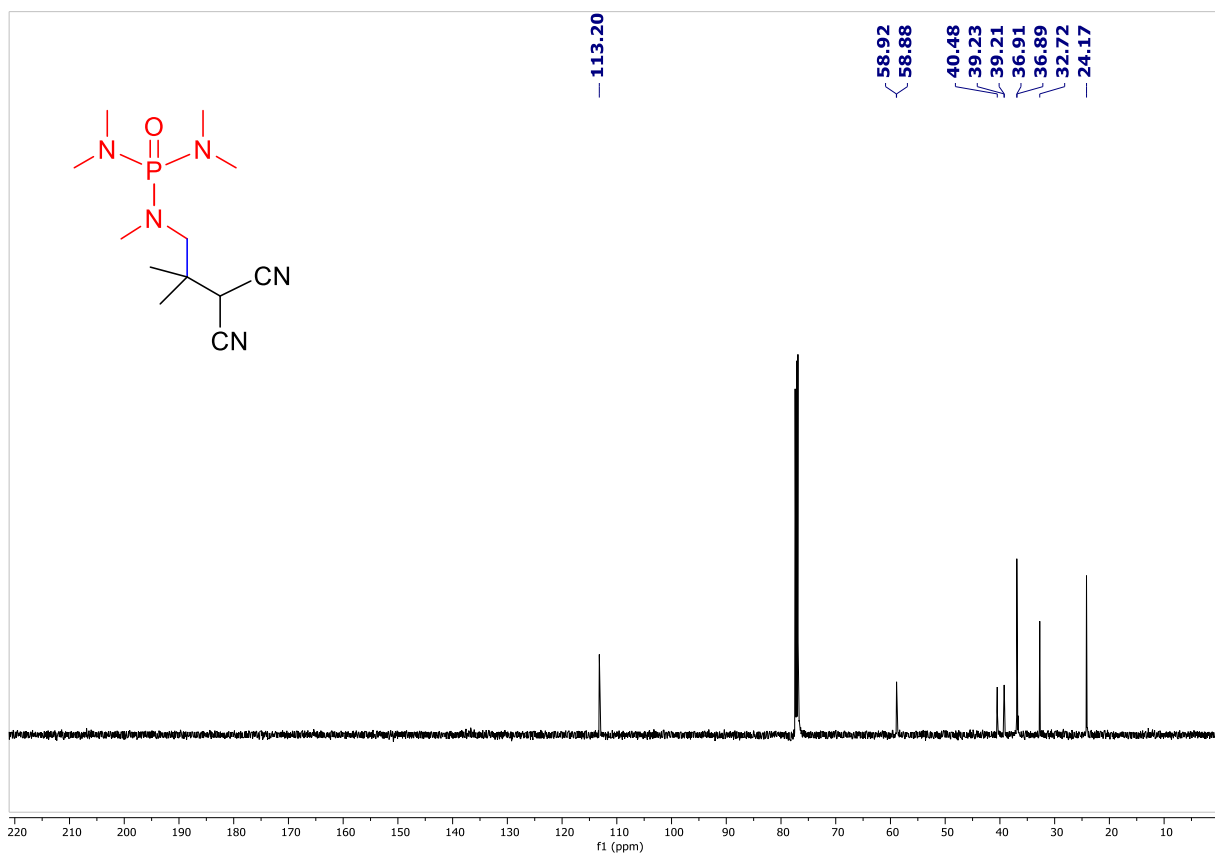
^{31}P NMR (203 MHz, CDCl_3) of compound **3k** ^1H NMR (400 MHz, CDCl_3) of compound **3l**

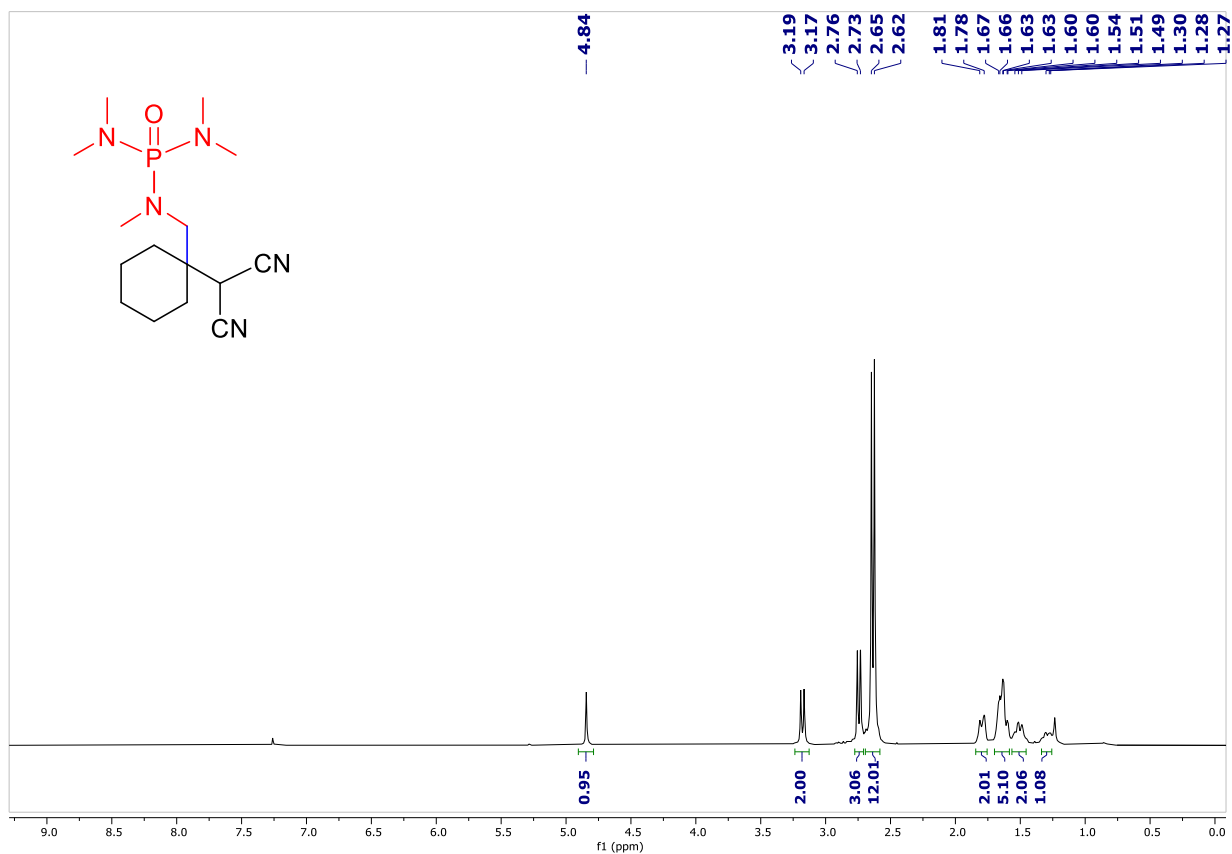
$^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) of compound **31** ^{31}P NMR (203 MHz, $CDCl_3$) of compound **31**

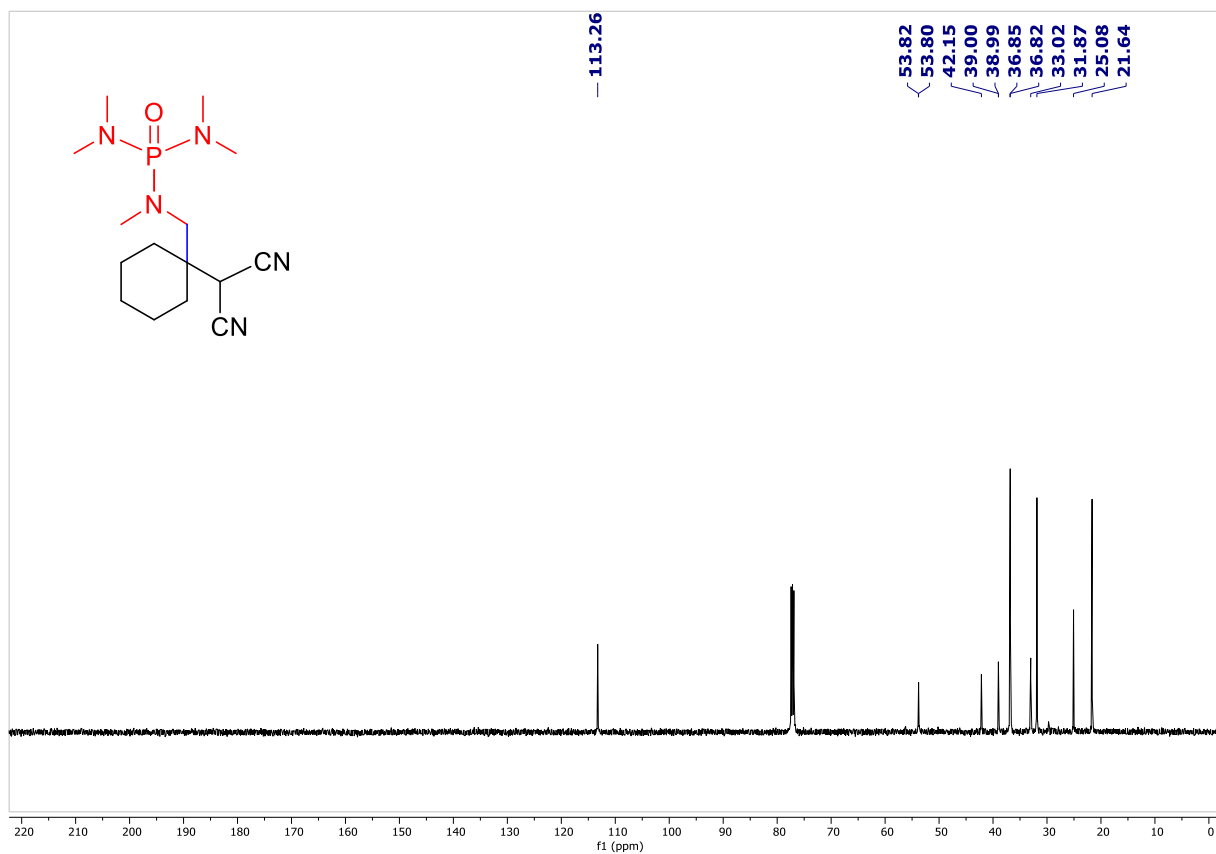
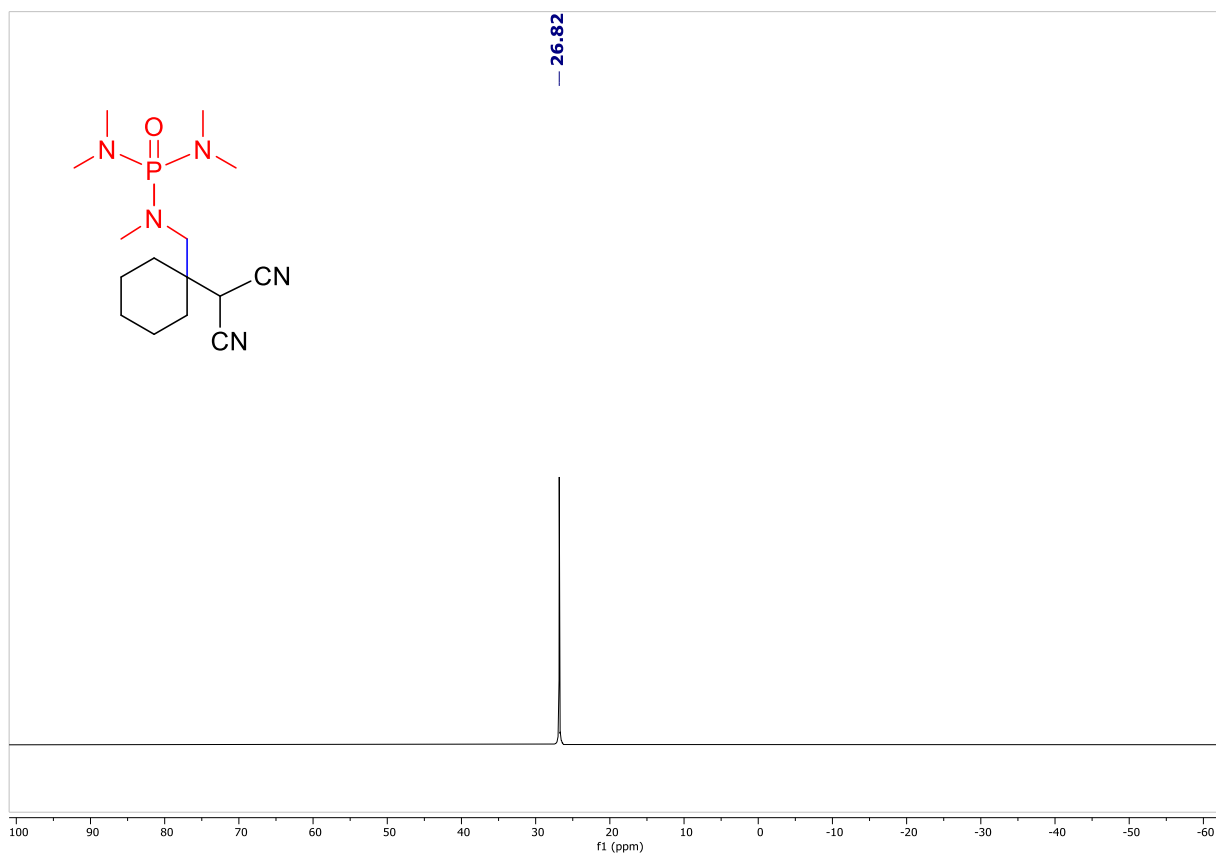
^1H NMR (400 MHz, CDCl_3) of compound **3m** $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) of compound **3m**

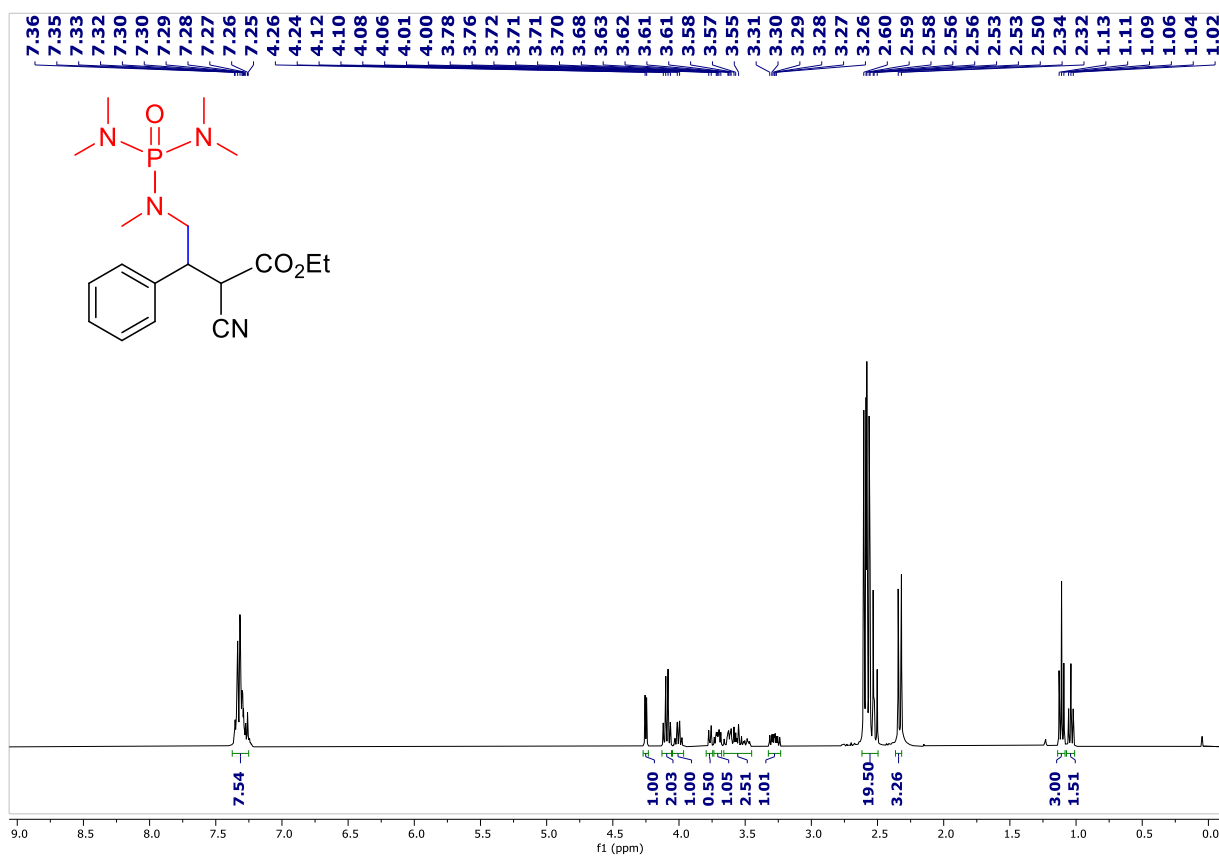
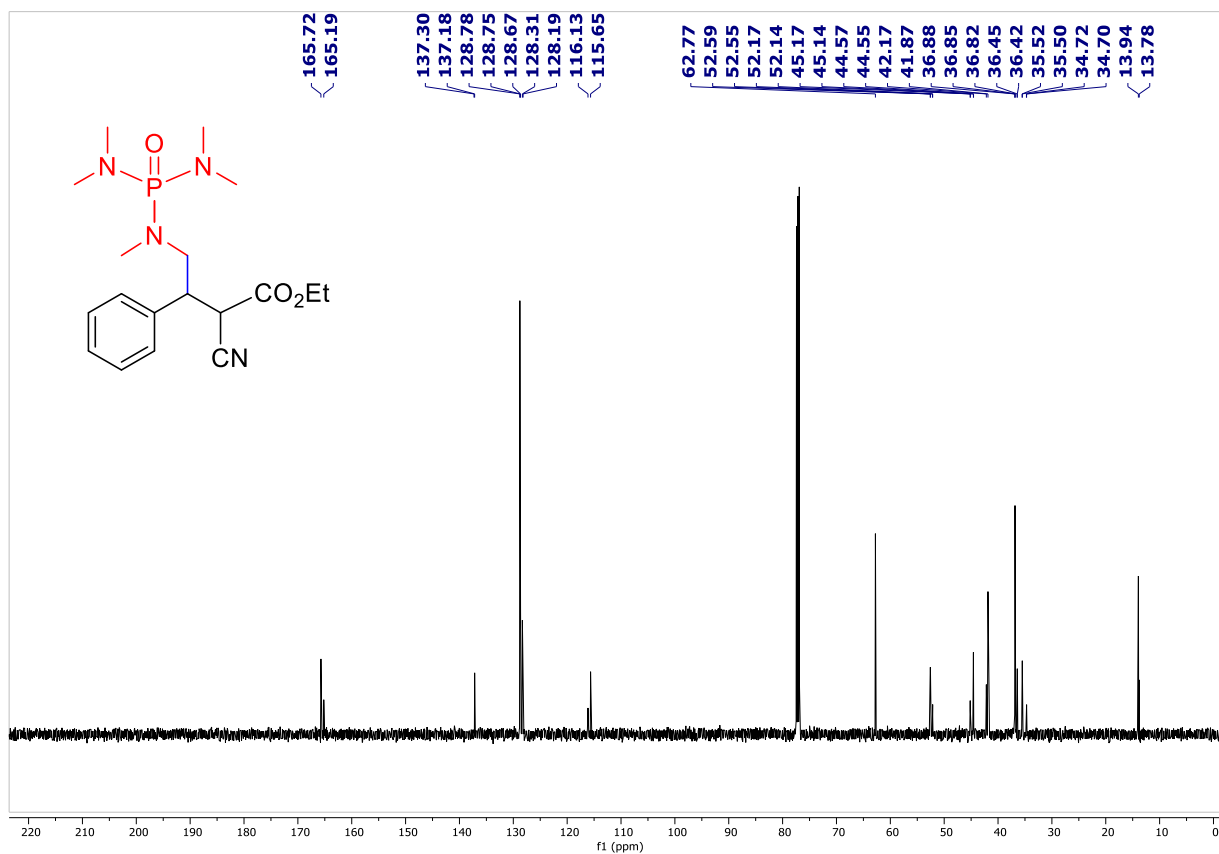
^{31}P NMR (203 MHz, CDCl_3) of compound **3m** ^1H NMR (400 MHz, CDCl_3) of compound **3n**

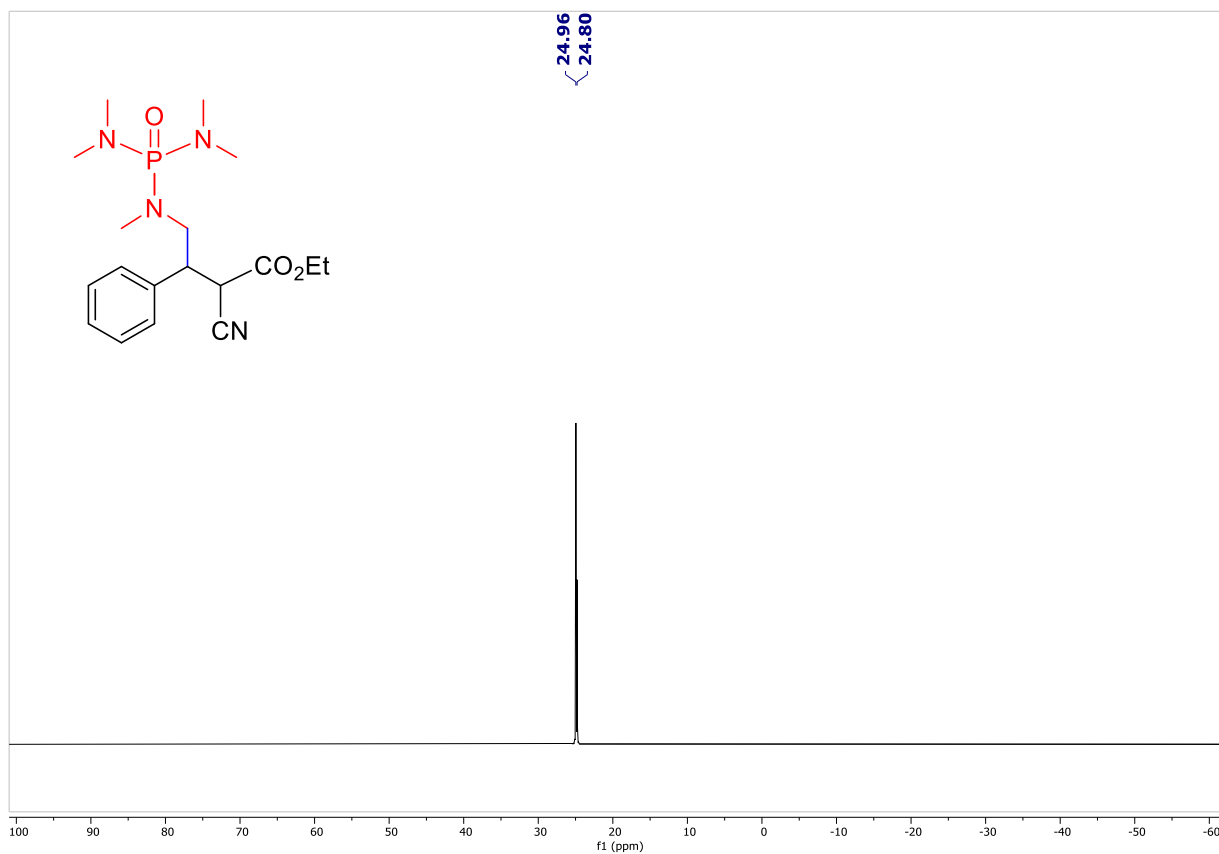
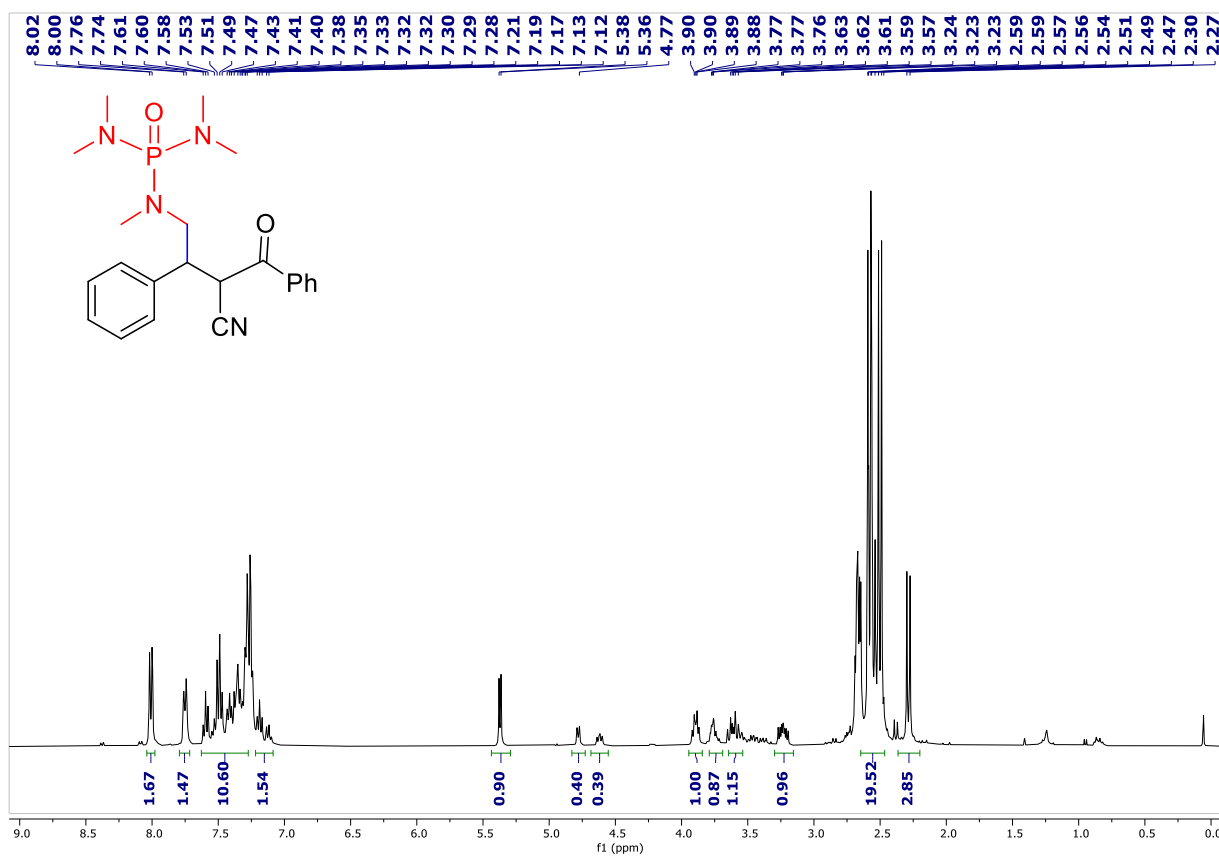
$^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) of compound **3n** ^{31}P NMR (203 MHz, $CDCl_3$) of compound **3n**

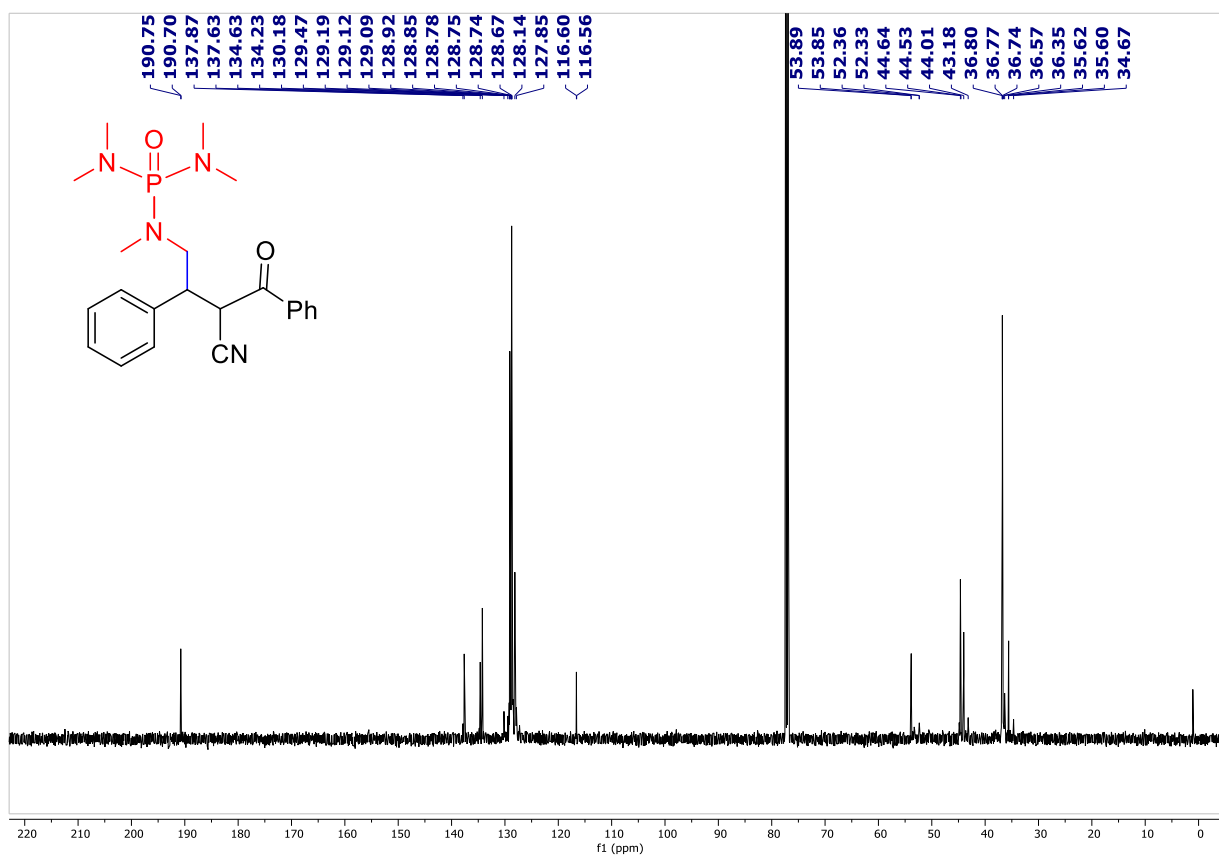
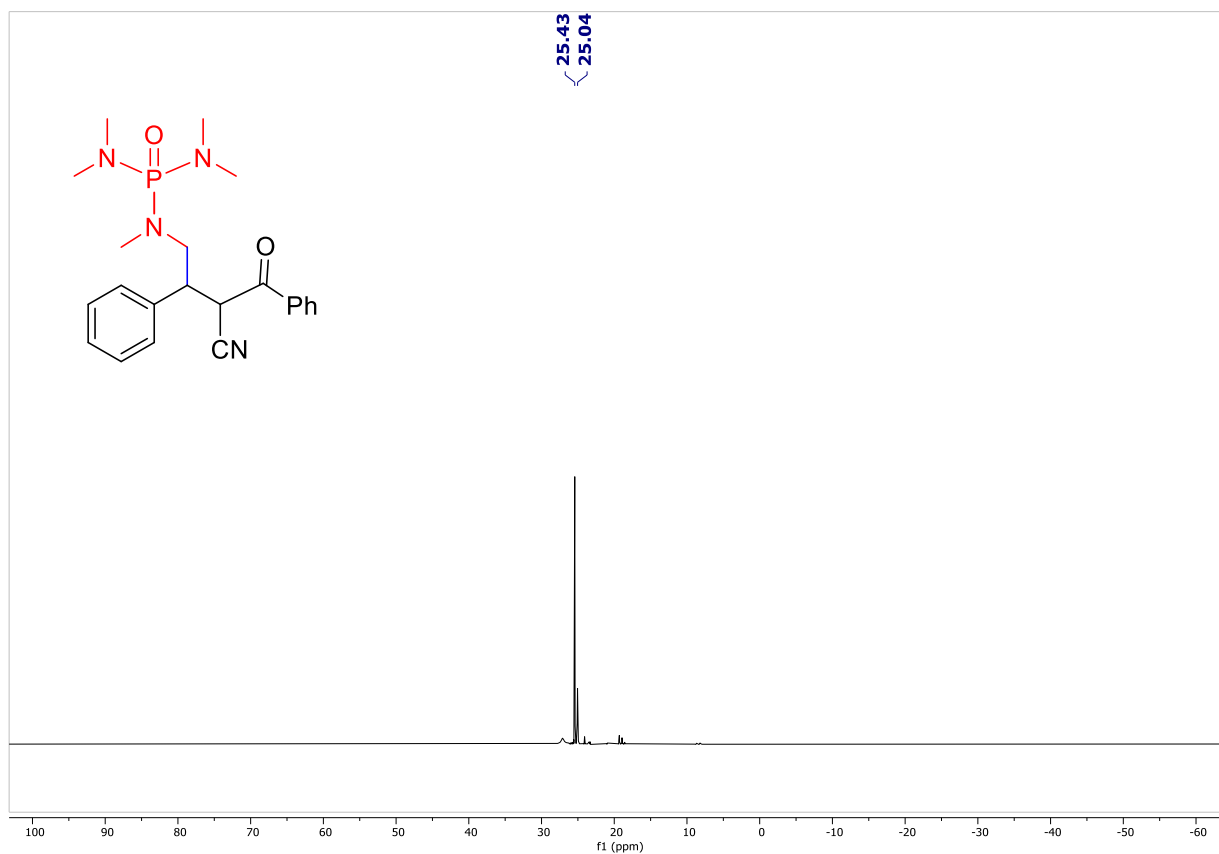
1H NMR (400 MHz, $CDCl_3$) of compound **3o** $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) of compound **3o**

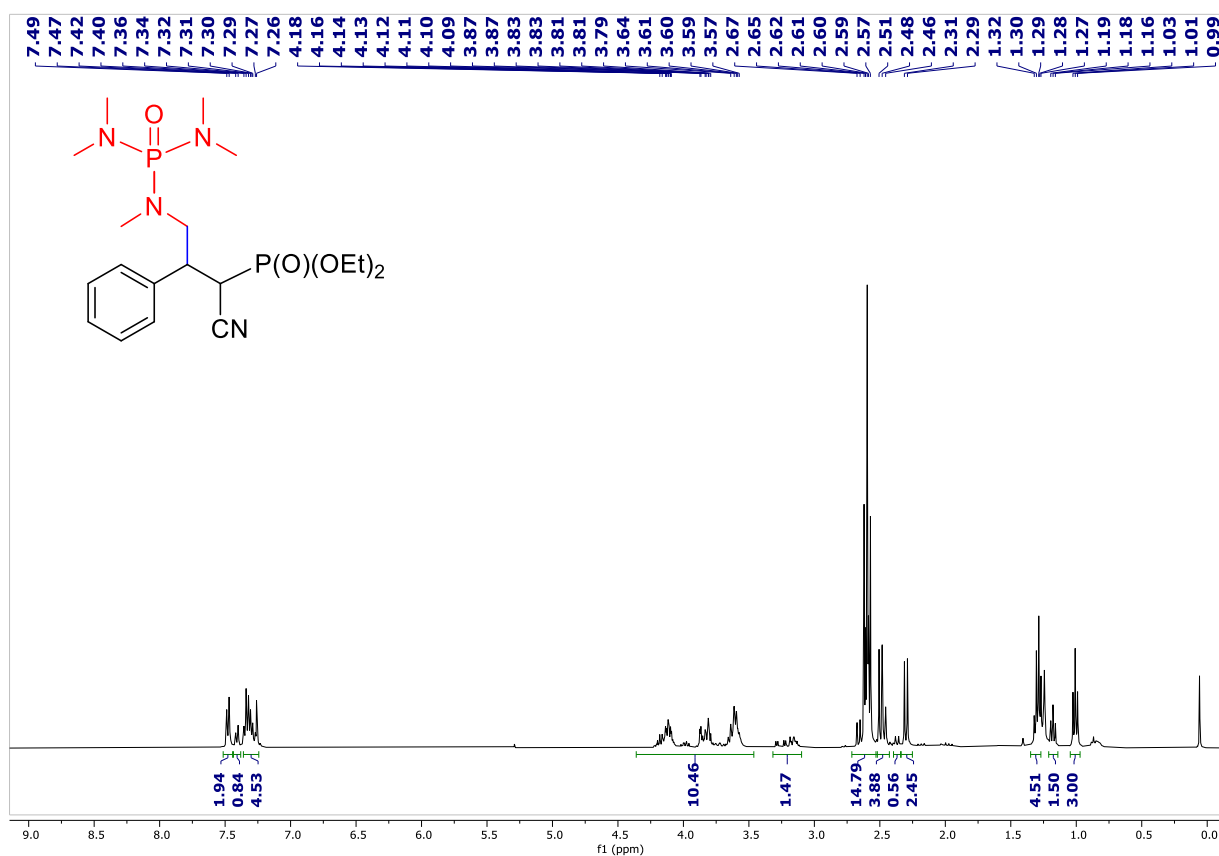
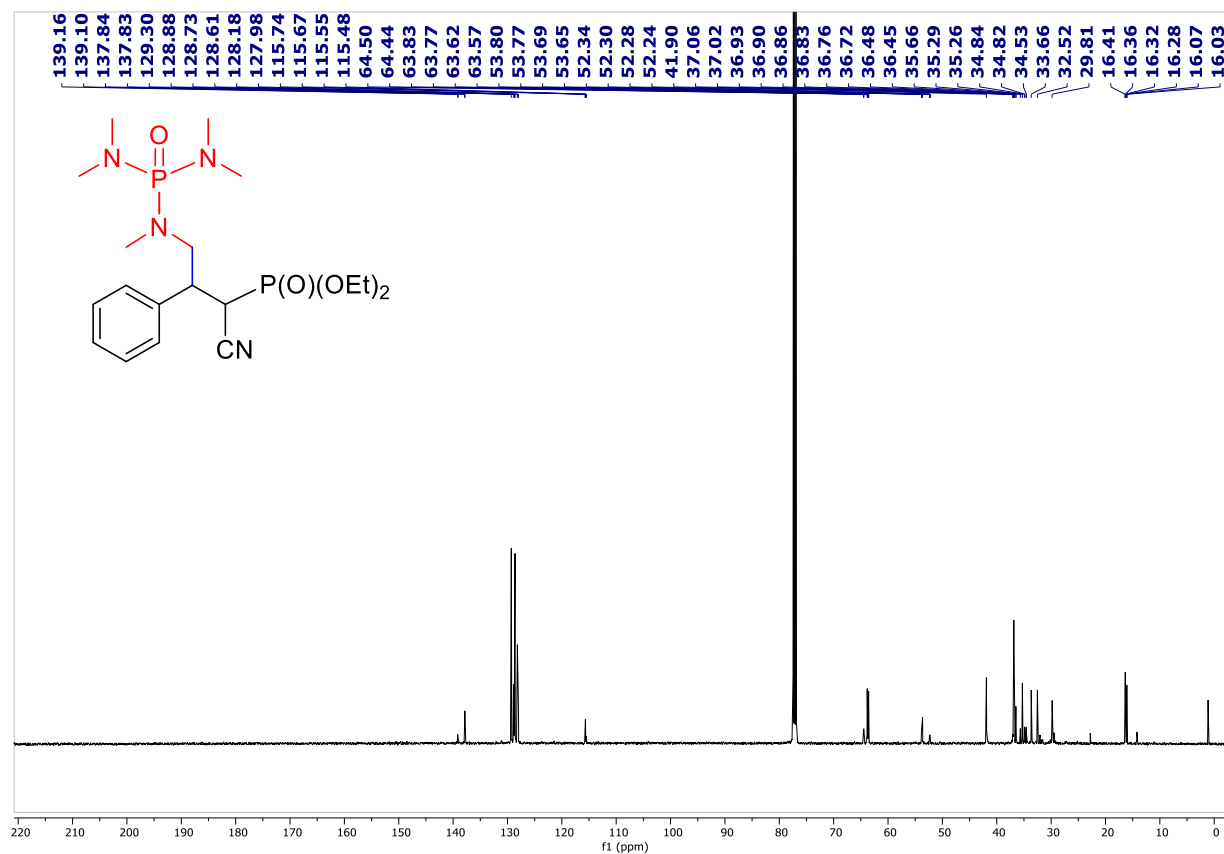
^{31}P NMR (203 MHz, CDCl_3) of compound **3o** ^1H NMR (400 MHz, CDCl_3) of compound **3p**

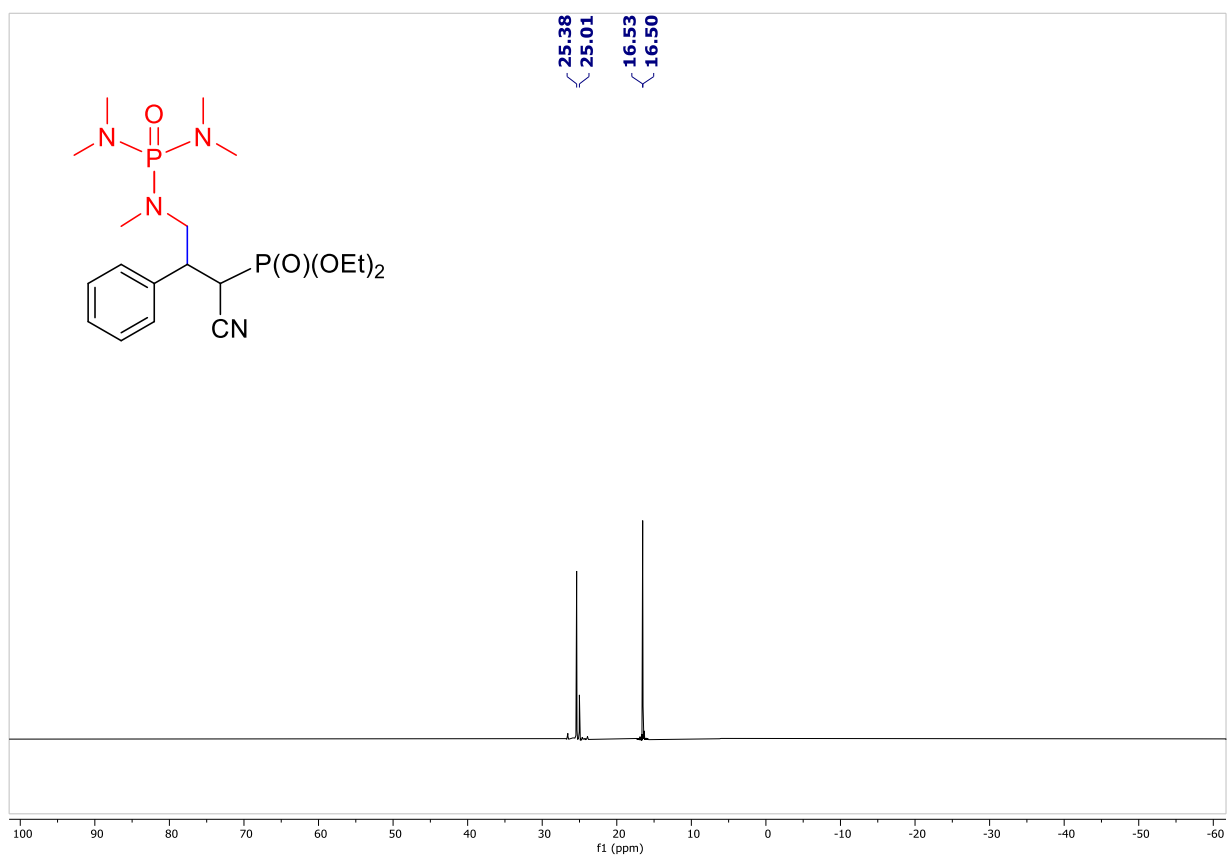
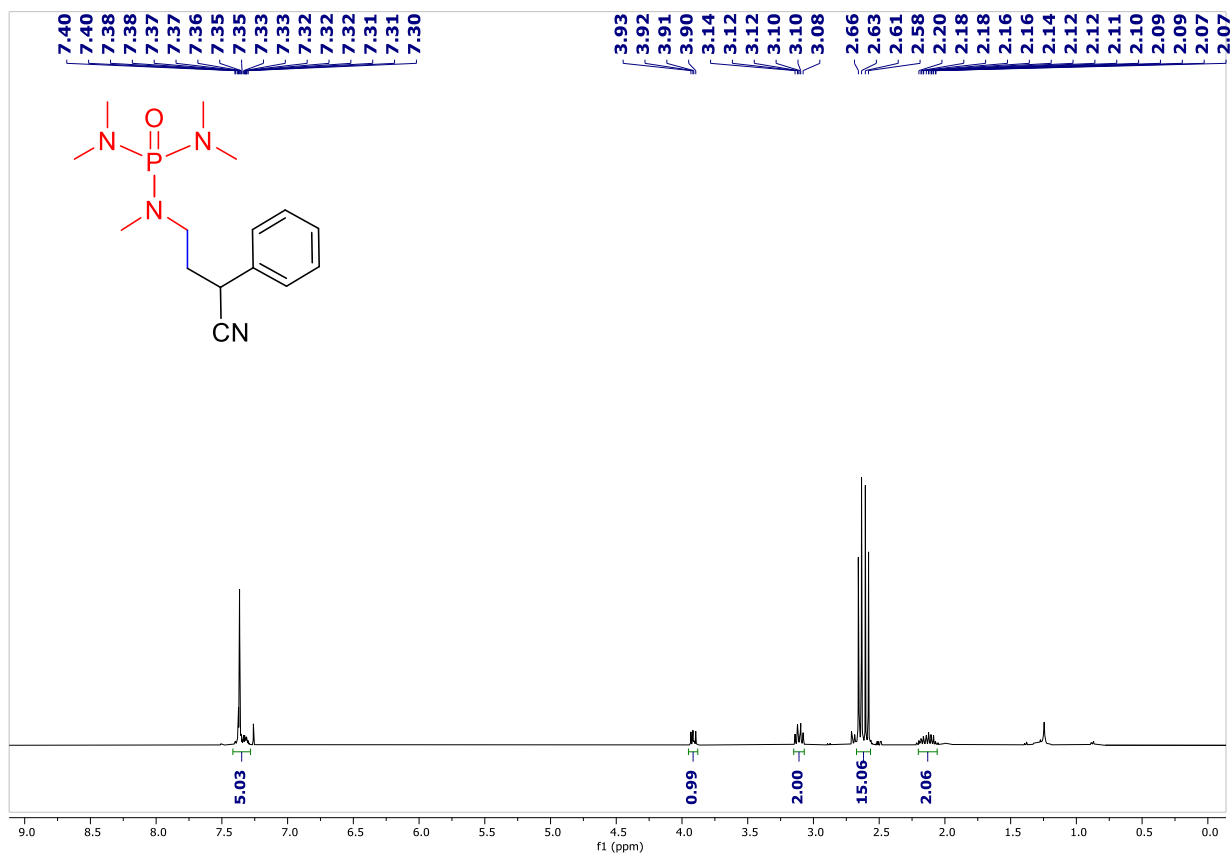
$^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) of compound **3p** ^{31}P NMR (203 MHz, $CDCl_3$) of compound **3p**

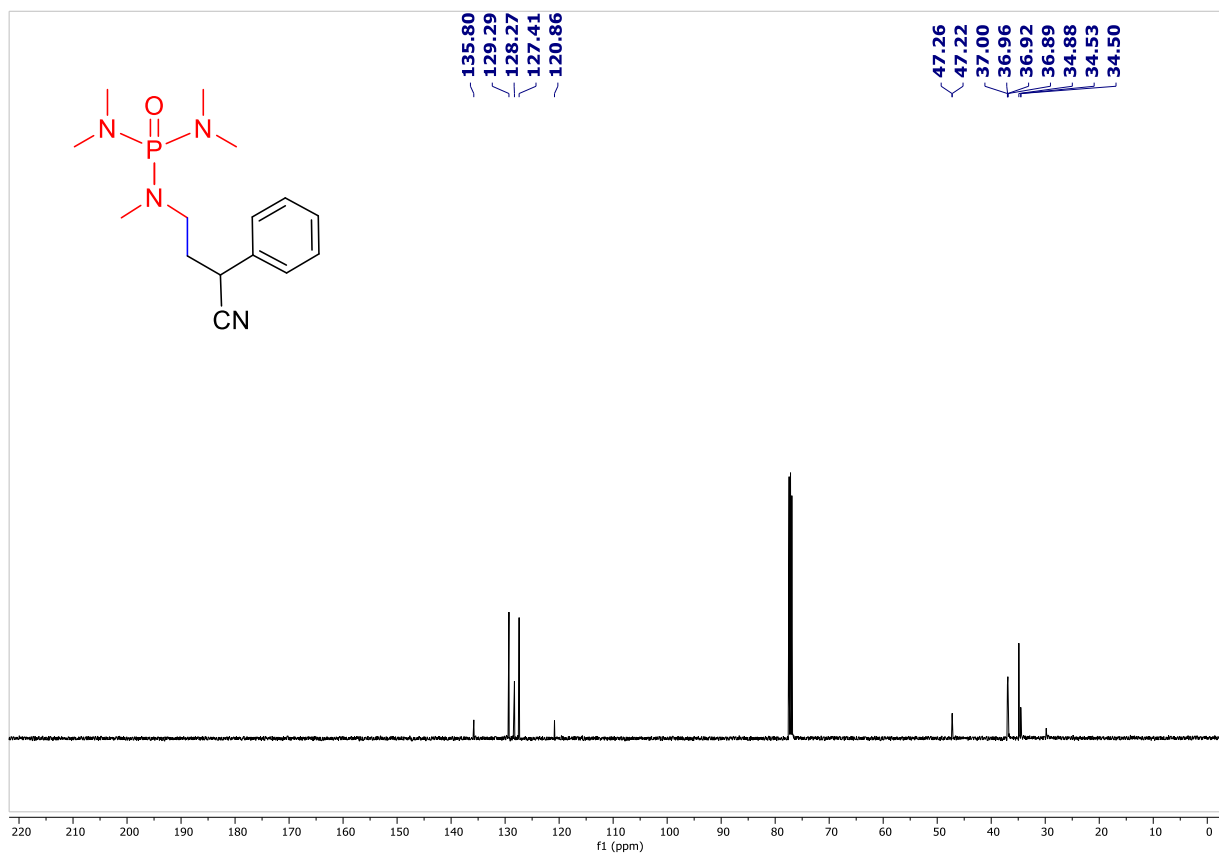
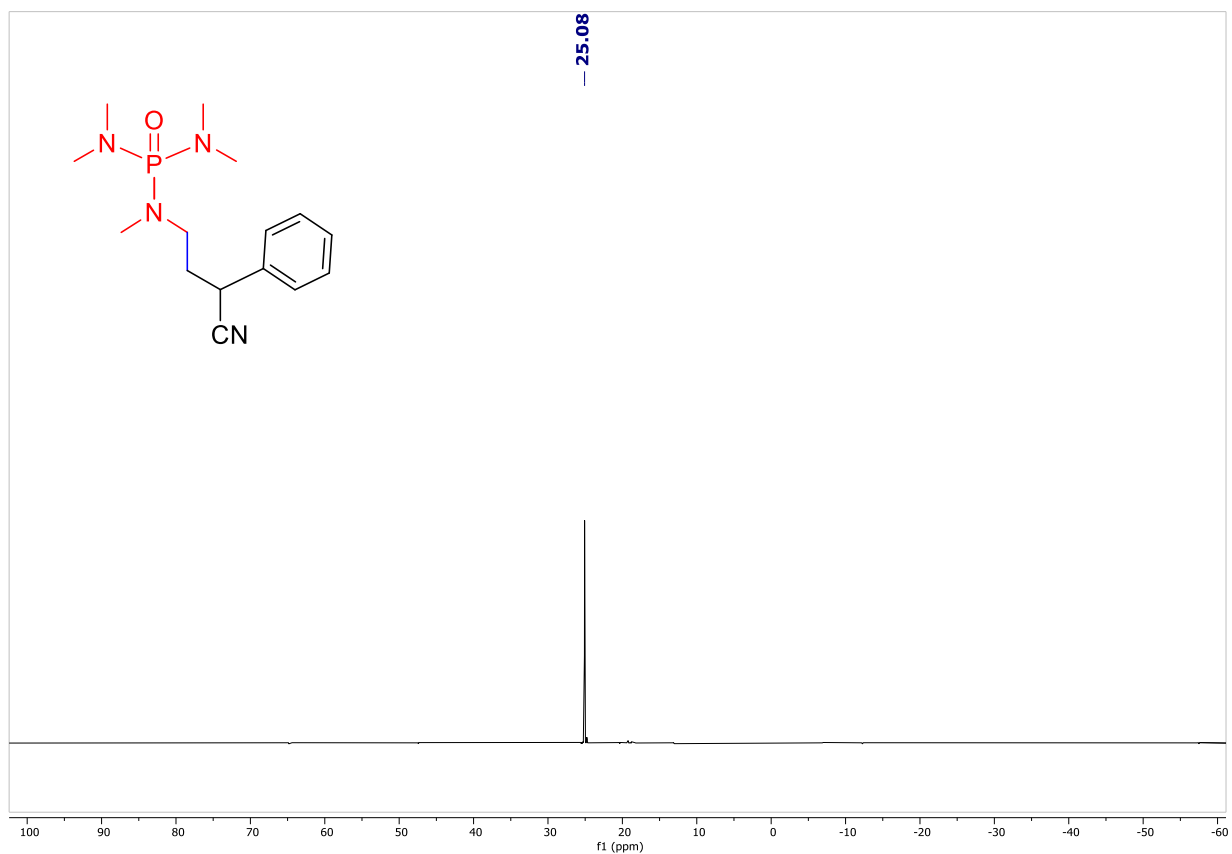
^1H NMR (400 MHz, CDCl_3) of compound **3q** $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) of compound **3q**

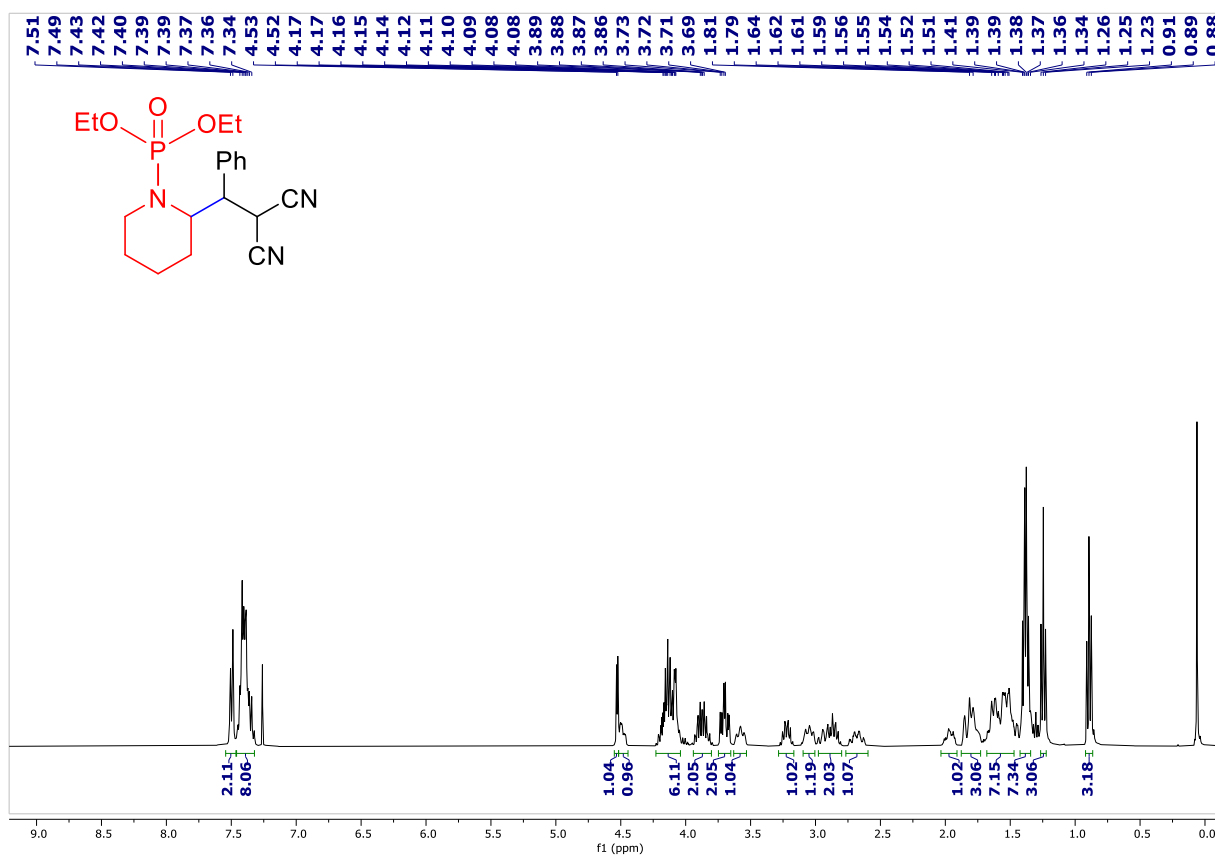
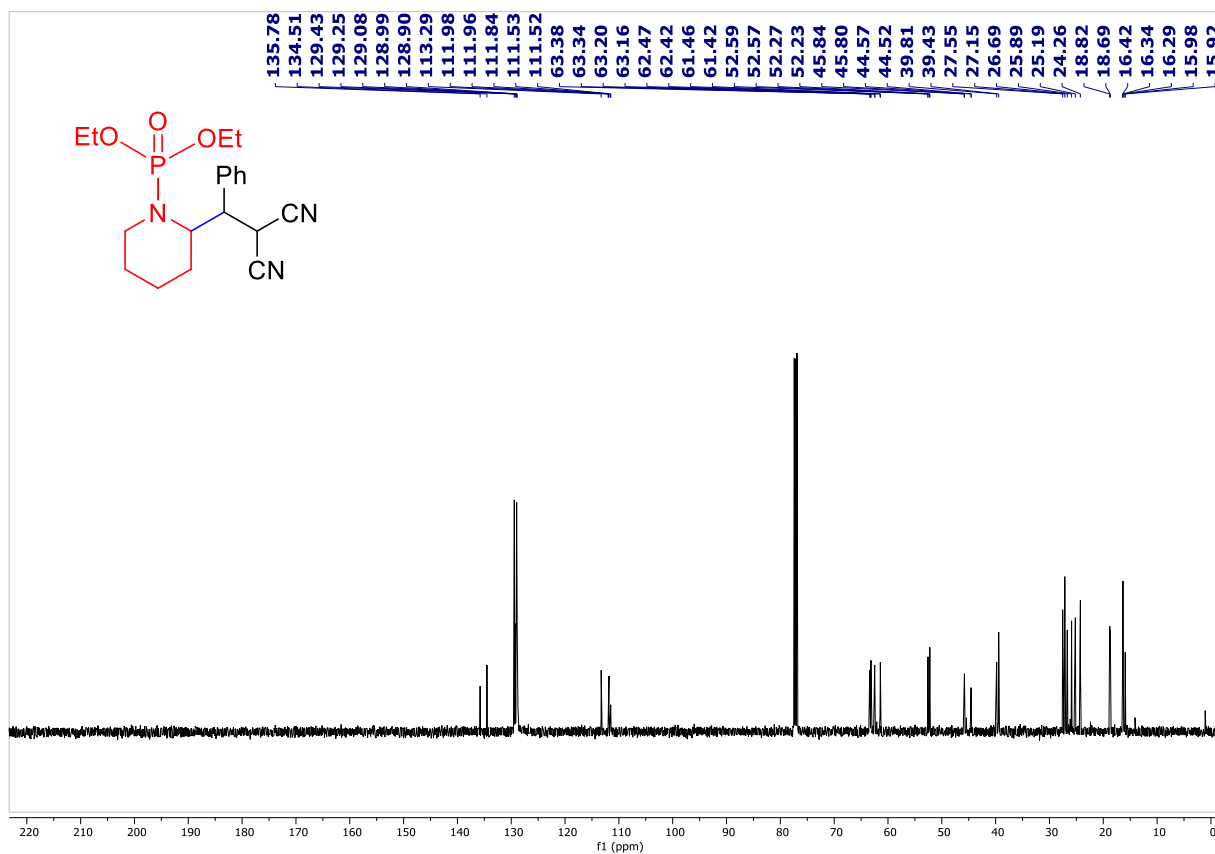
^{31}P NMR (203 MHz, $CDCl_3$) of compound **3q** 1H NMR (400 MHz, $CDCl_3$) of compound **3r**

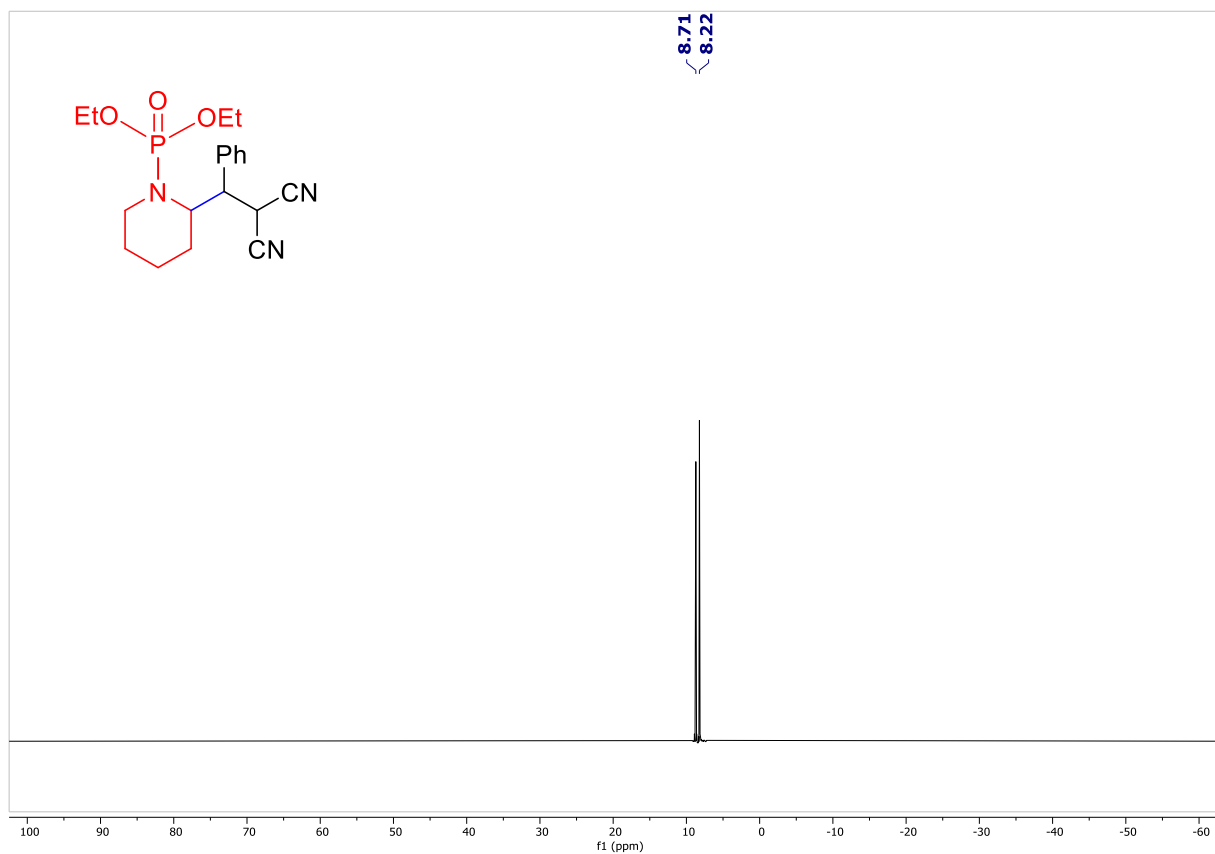
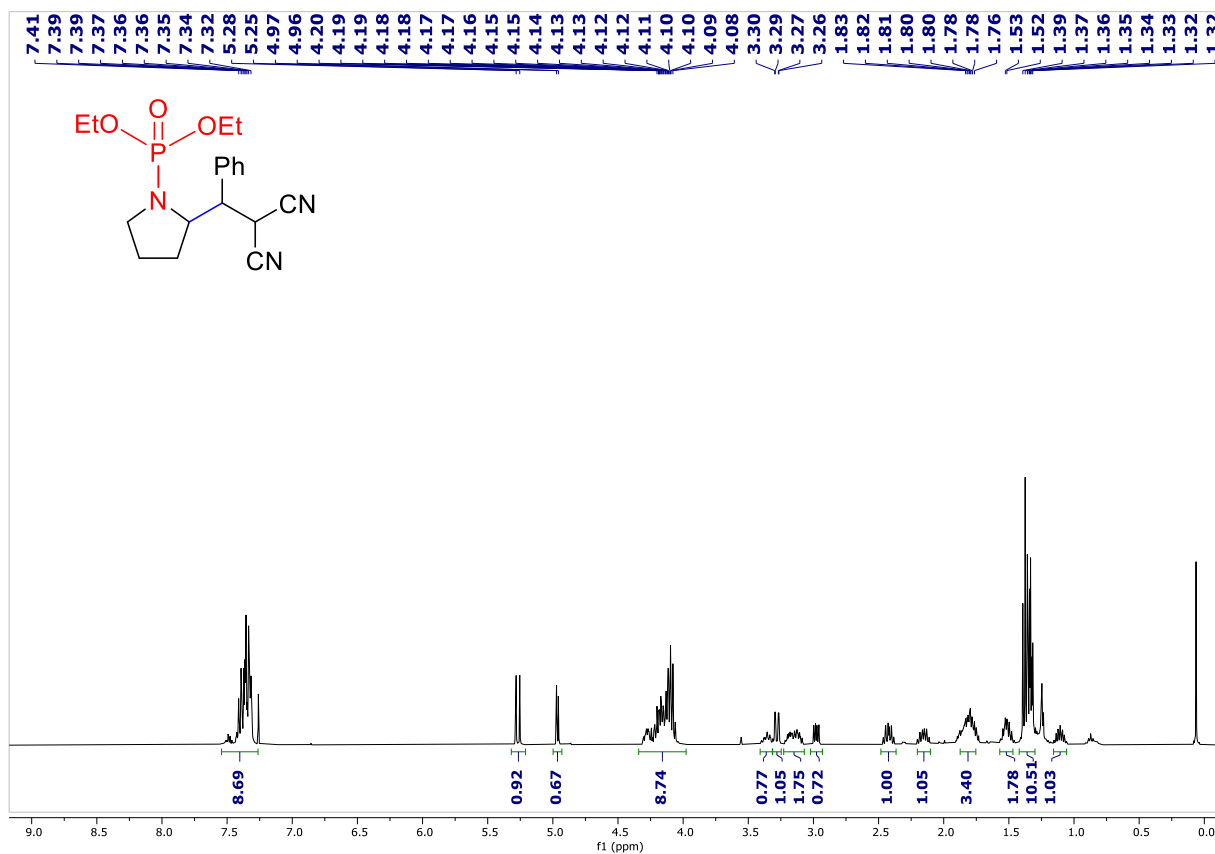
$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) of compound **3r** ^{31}P NMR (203 MHz, CDCl_3) of compound **3r**

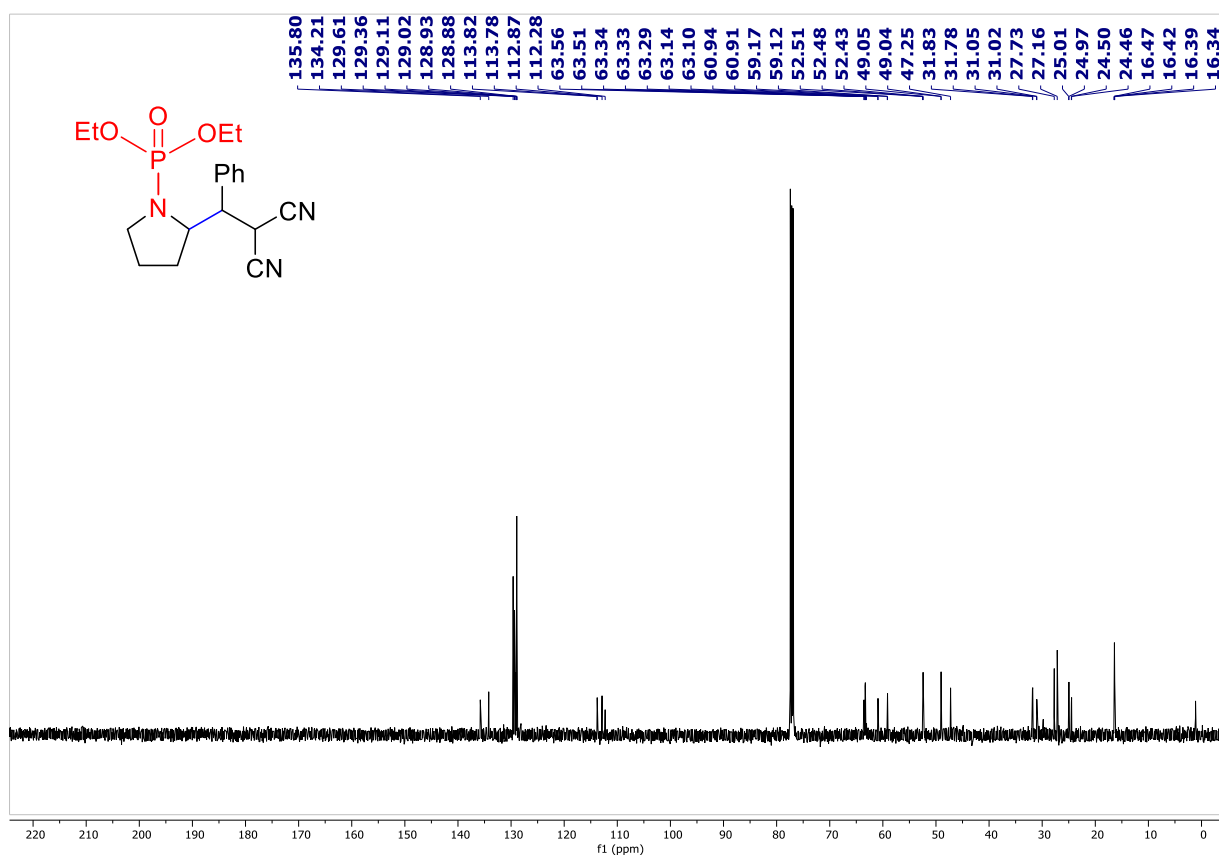
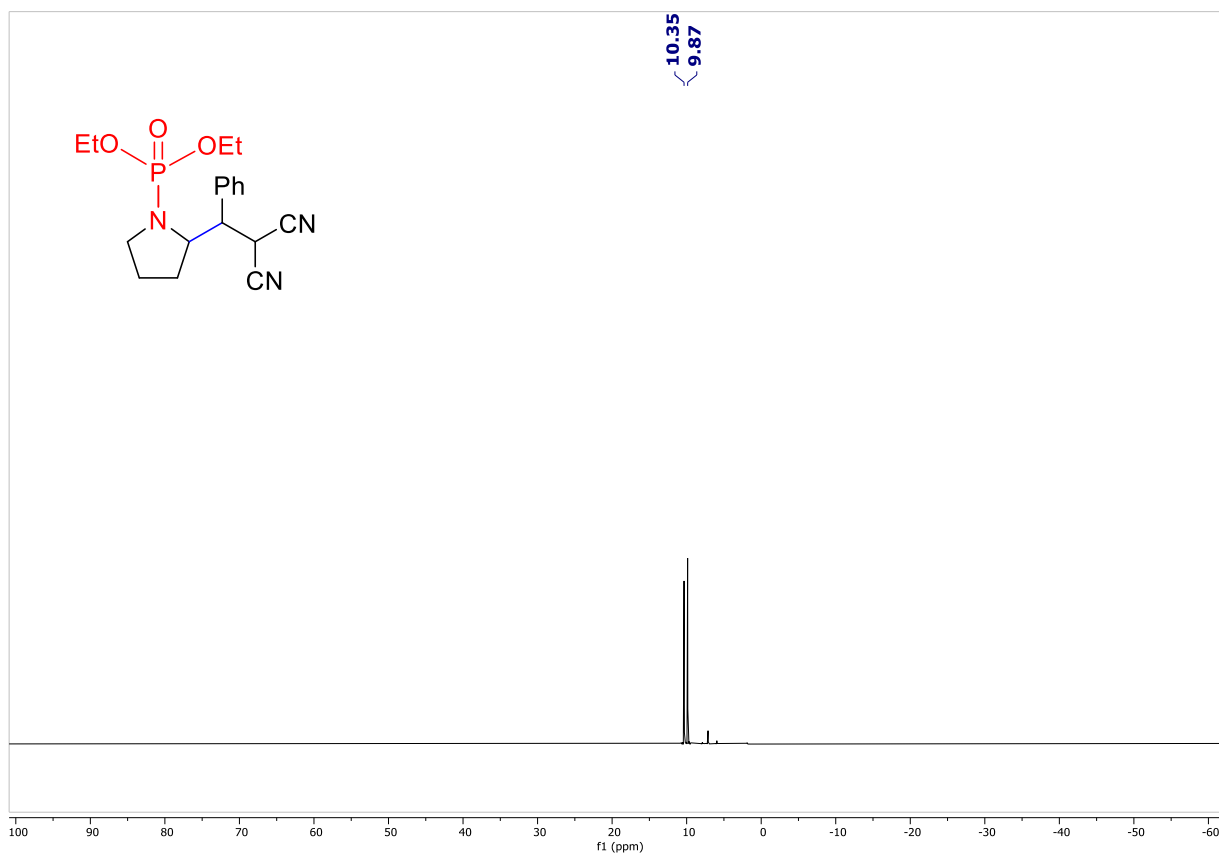
^1H NMR (400 MHz, CDCl_3) of compound **3s** $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) of compound **3s**

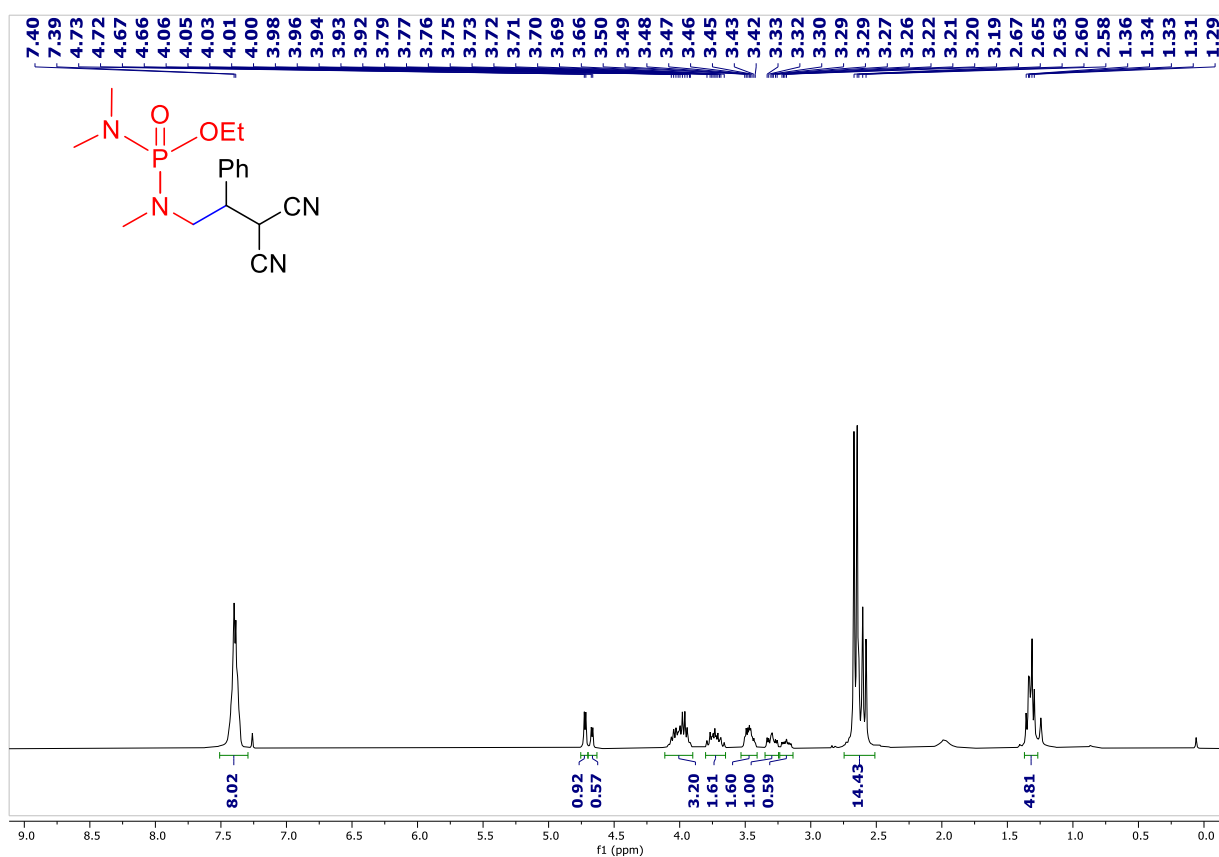
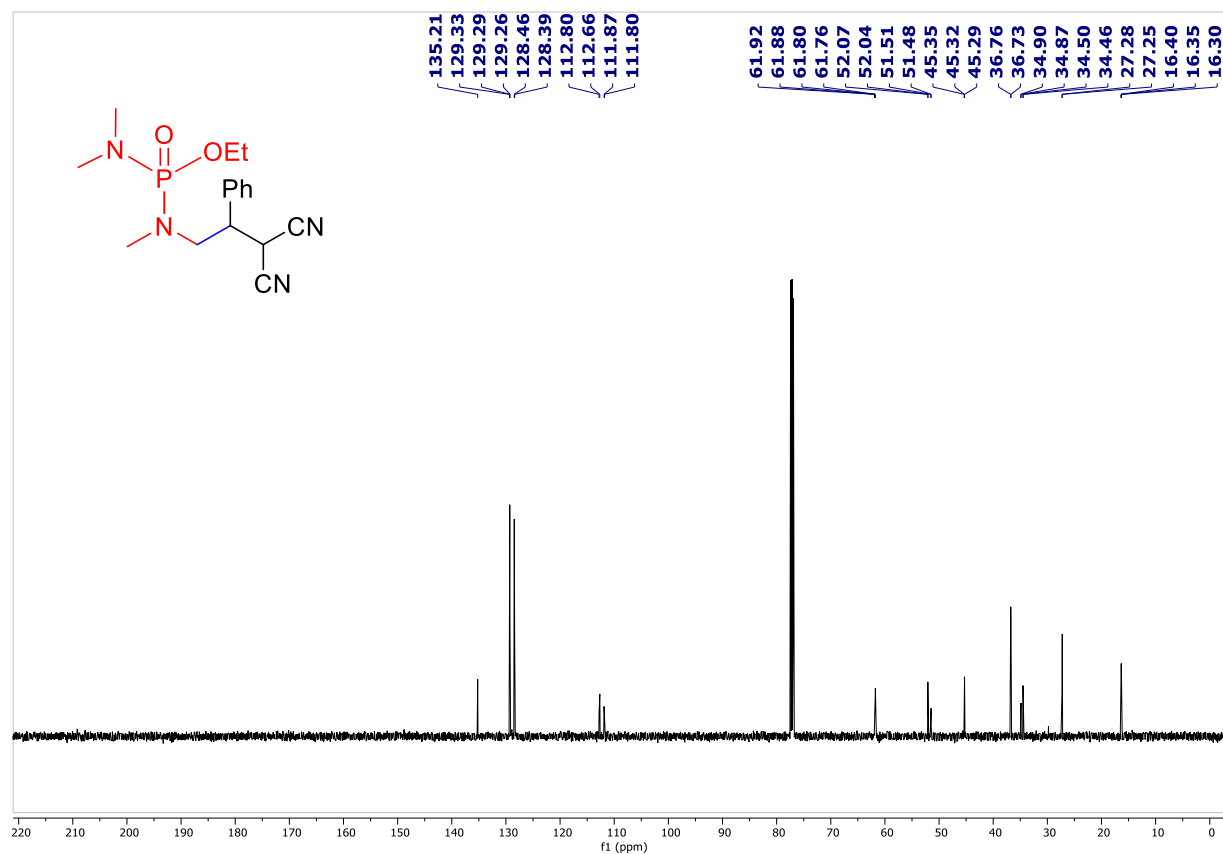
^{31}P NMR (203 MHz, CDCl_3) of compound **3s** ^1H NMR (400 MHz, CDCl_3) of compound **3t**

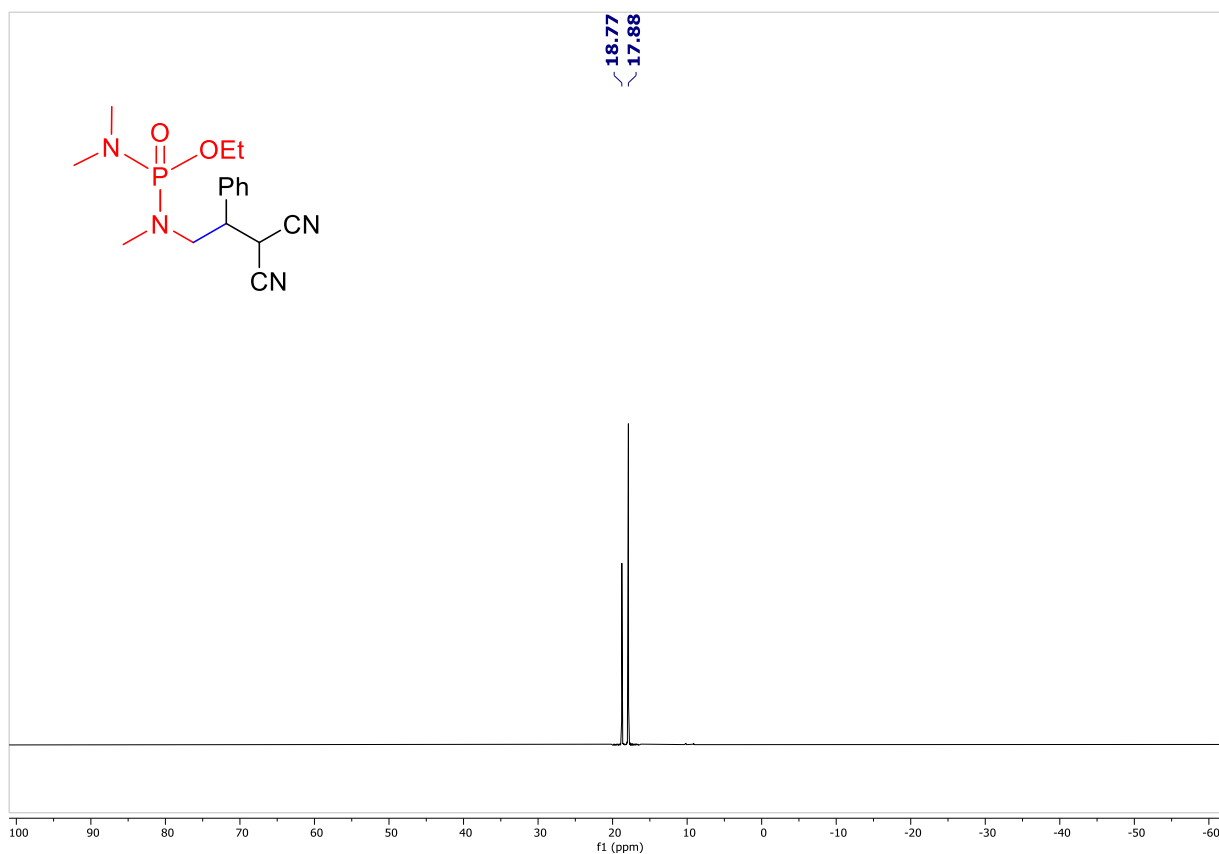
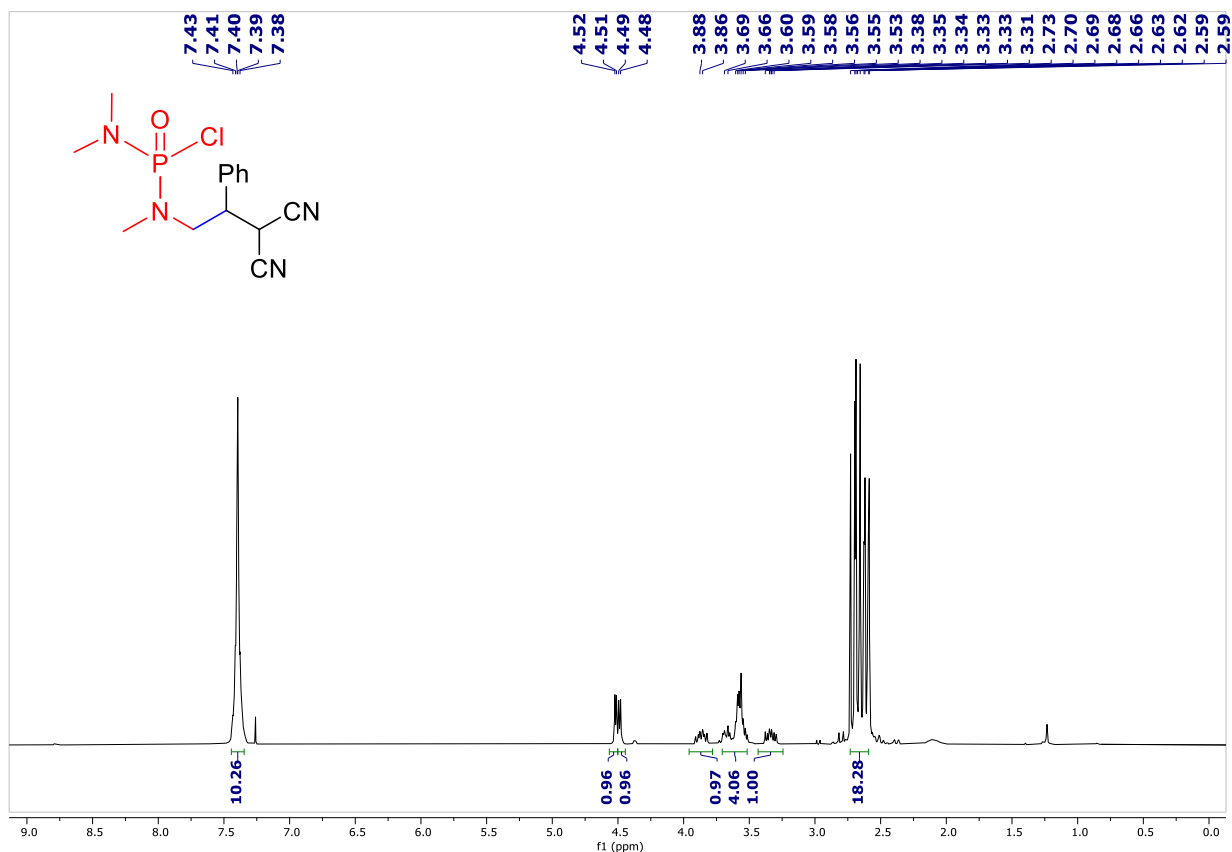
$^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) of compound **3t** ^{31}P NMR (203 MHz, $CDCl_3$) of compound **3t**

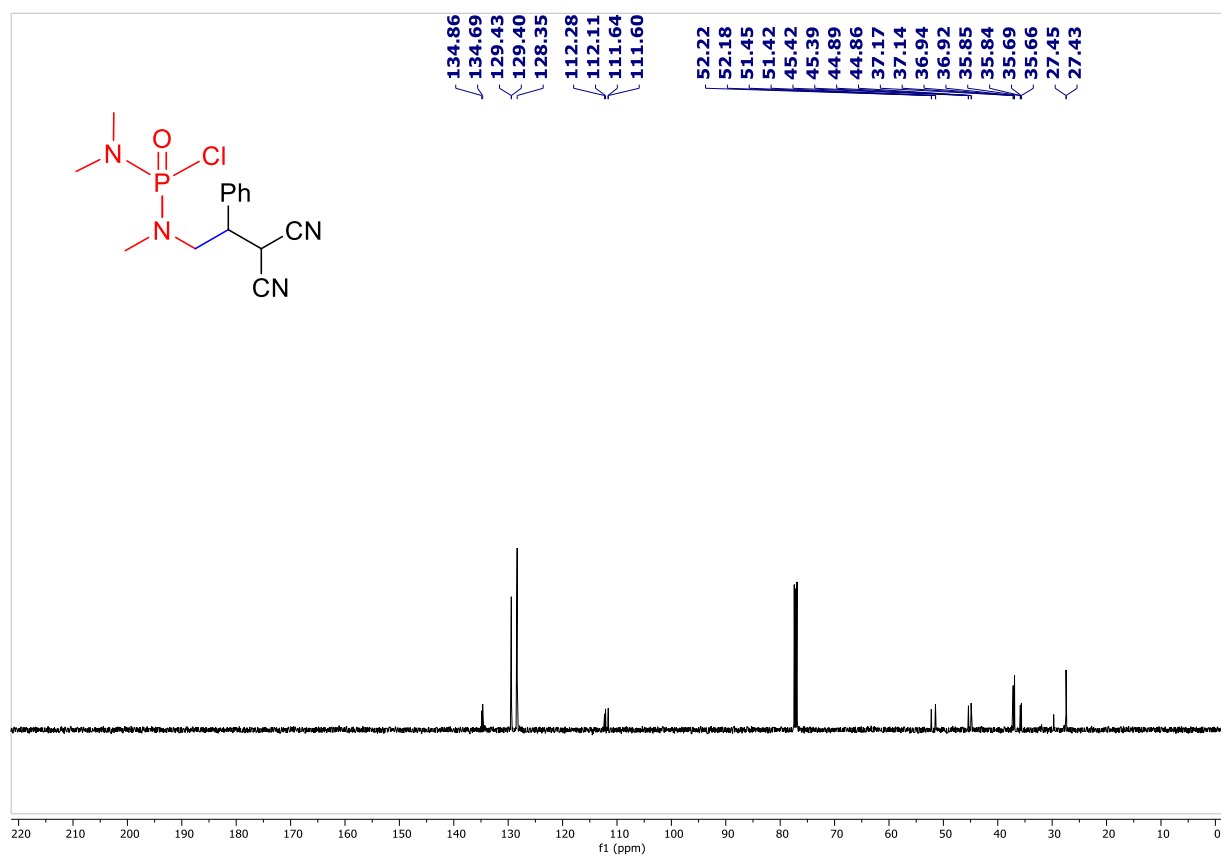
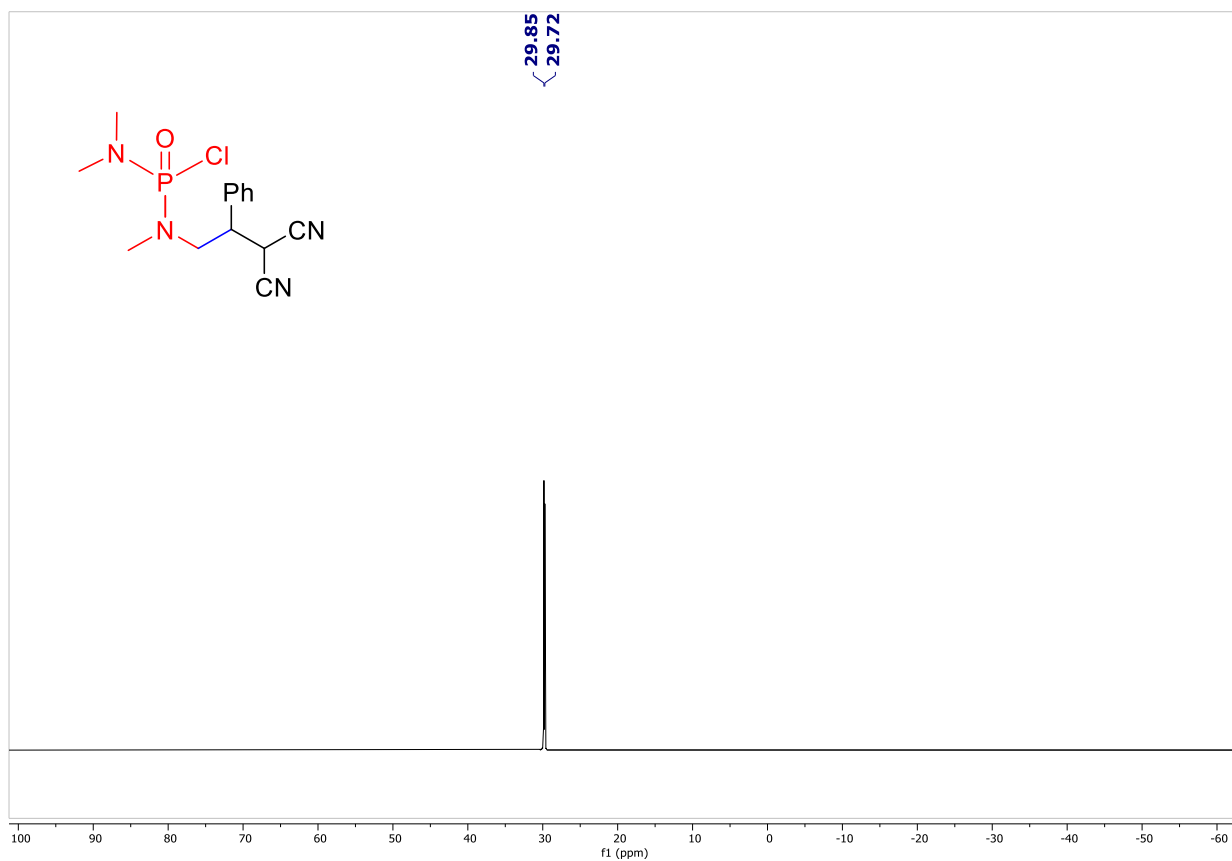
^1H NMR (400 MHz, CDCl_3) of compound **4a** $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) of compound **4a**

^{31}P NMR (203 MHz, CDCl_3) of compound **4a** ^1H NMR (400 MHz, CDCl_3) of compound **4b**

$^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) of compound **4b** ^{31}P NMR (203 MHz, $CDCl_3$) of compound **4b**

^1H NMR (400 MHz, CDCl_3) of compound **4c** $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) of compound **4c**

^{31}P NMR (203 MHz, CDCl_3) of compound **4c** ^1H NMR (400 MHz, CDCl_3) of compound **4d**

$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) of compound **4d** ^{31}P NMR (203 MHz, CDCl_3) of compound **4d**

Chemical structure of compound 10 is shown. The ^1H NMR spectrum (CDCl₃) displays peaks corresponding to the structure, with integration values and chemical shifts (ppm) listed below the spectrum.

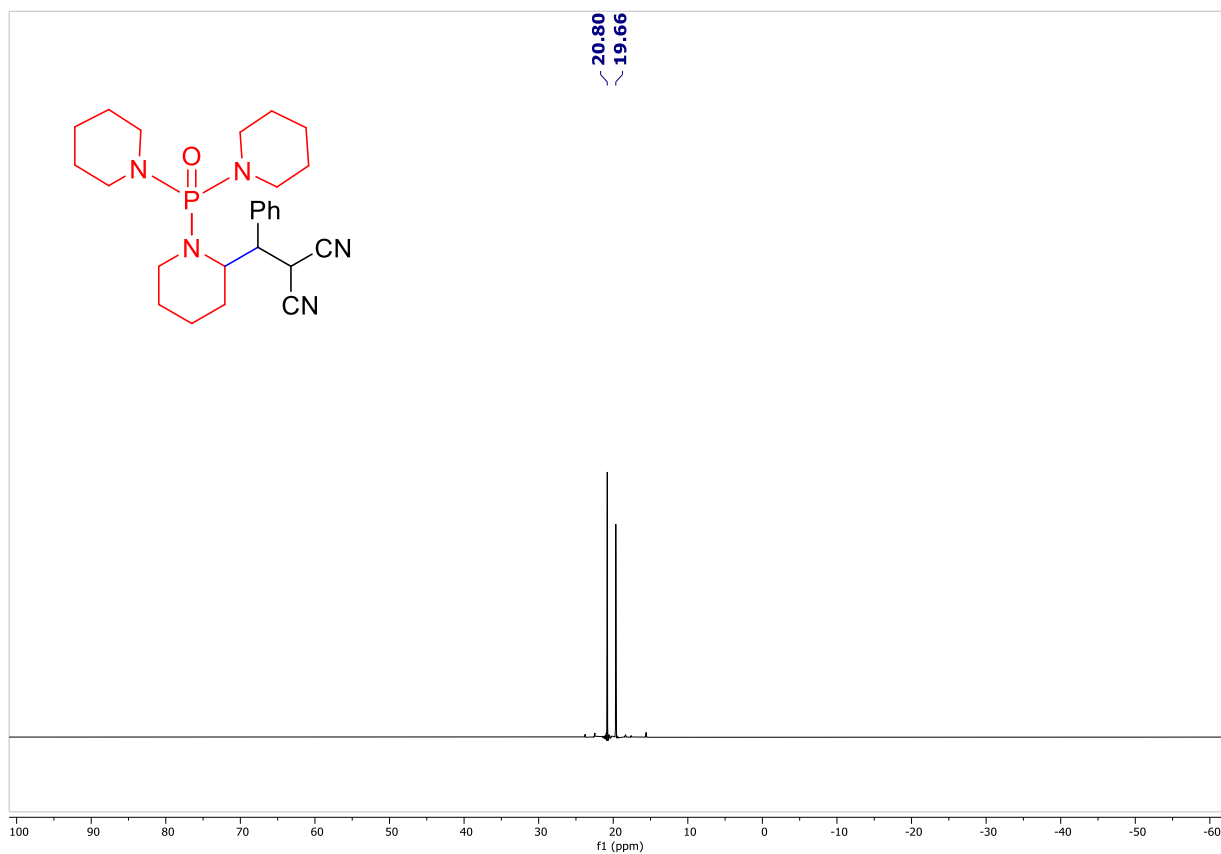
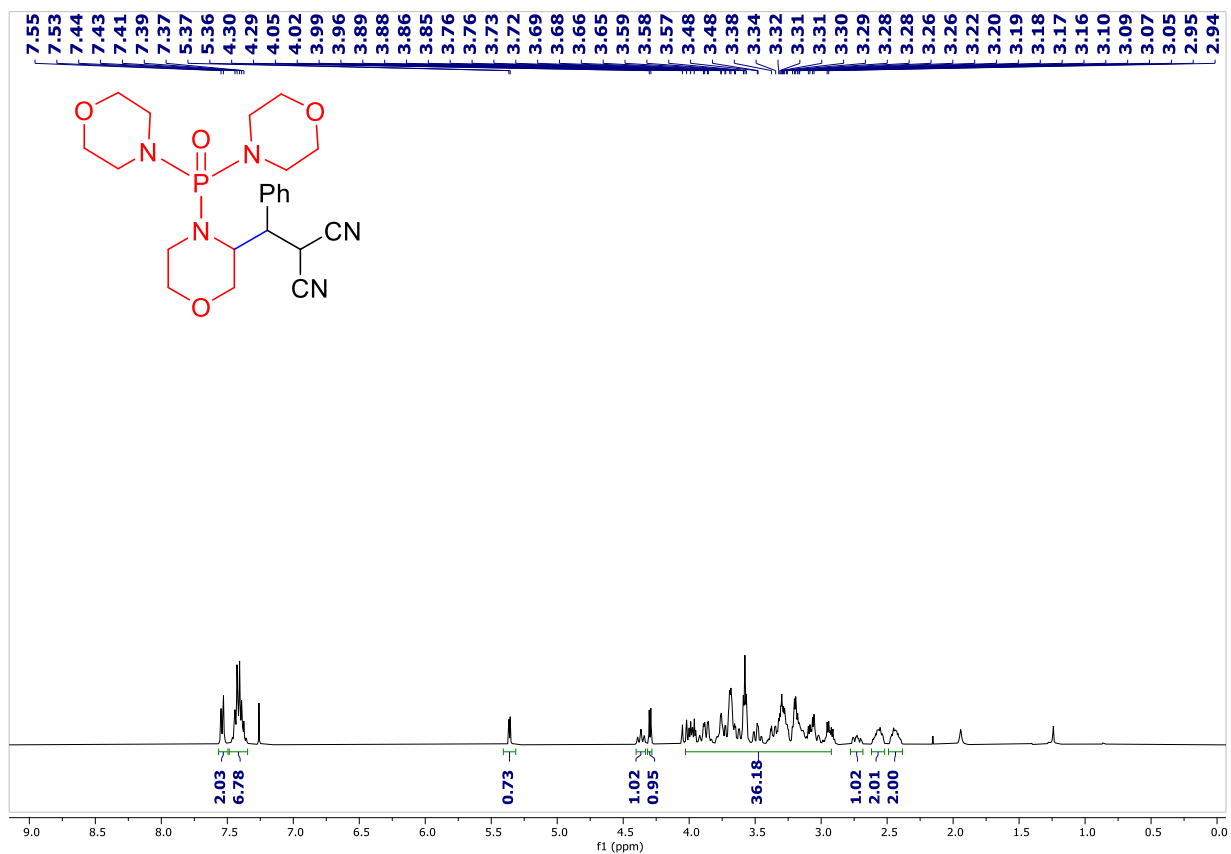
Integration values (from left to right): 1.63, 7.41, 1.02, 1.55, 1.07, 1.80, 1.05, 8.05, 4.82, 2.45, 2.05, 1.59, 27.07, 3.64.

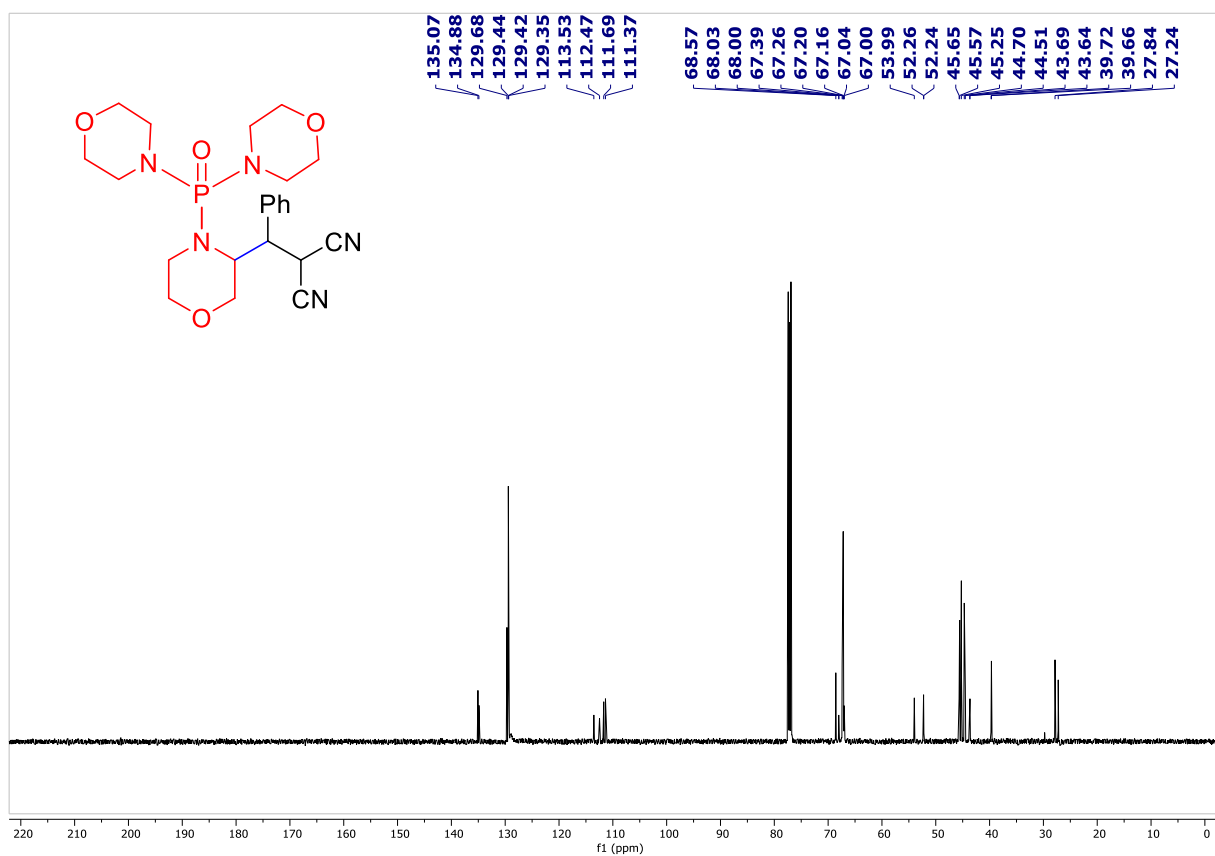
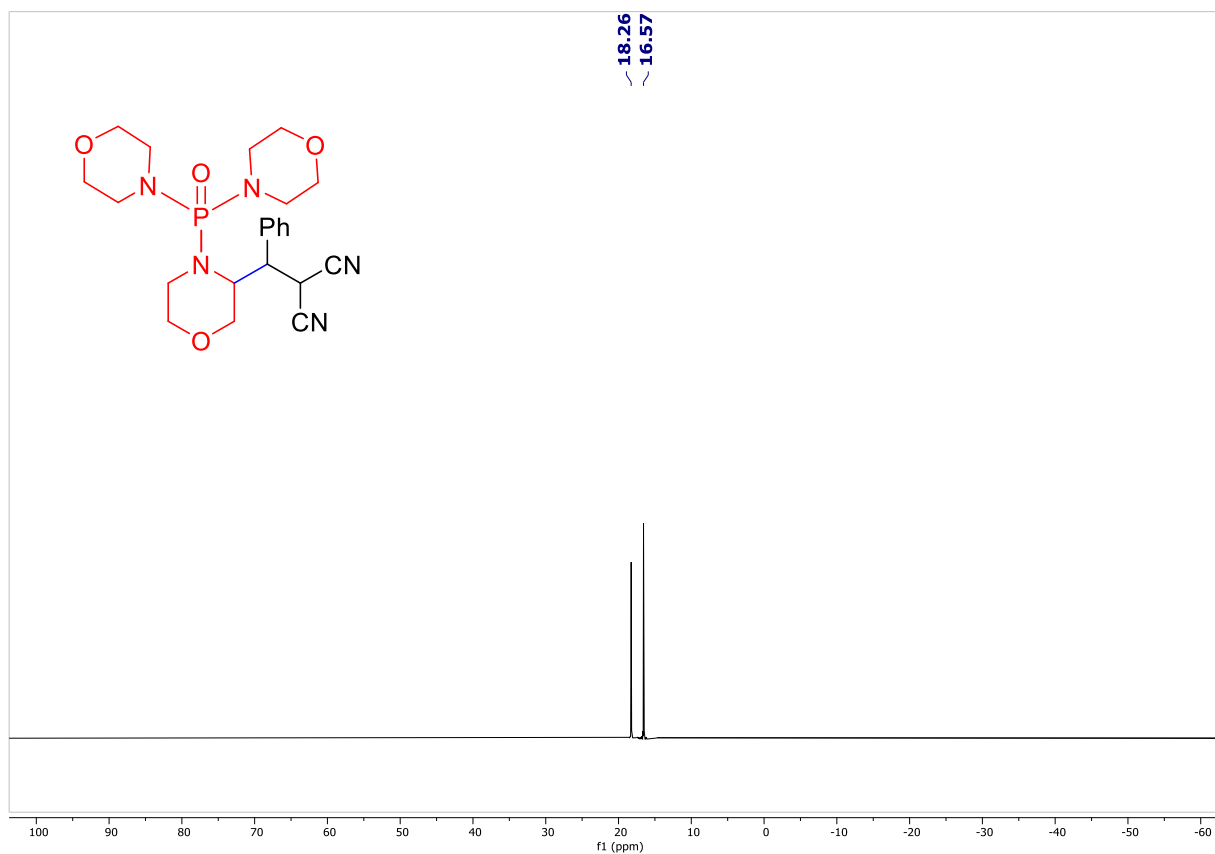
Chemical shifts (ppm) (from left to right): 7.51, 7.49, 7.40, 7.39, 7.36, 7.34, 7.32, 7.30, 5.64, 5.64, 4.41, 4.40, 3.70, 3.69, 3.68, 3.66, 3.65, 3.16, 3.14, 3.12, 3.11, 3.10, 3.08, 3.07, 2.91, 2.89, 2.88, 2.87, 2.86, 2.84, 2.82, 2.56, 2.55, 2.53, 2.52, 2.43, 2.42, 2.40, 1.83, 1.82, 1.82, 1.66, 1.64, 1.61, 1.59, 1.58, 1.52, 1.49, 1.47, 1.41, 1.40, 1.39, 1.25, 1.24, 1.23.

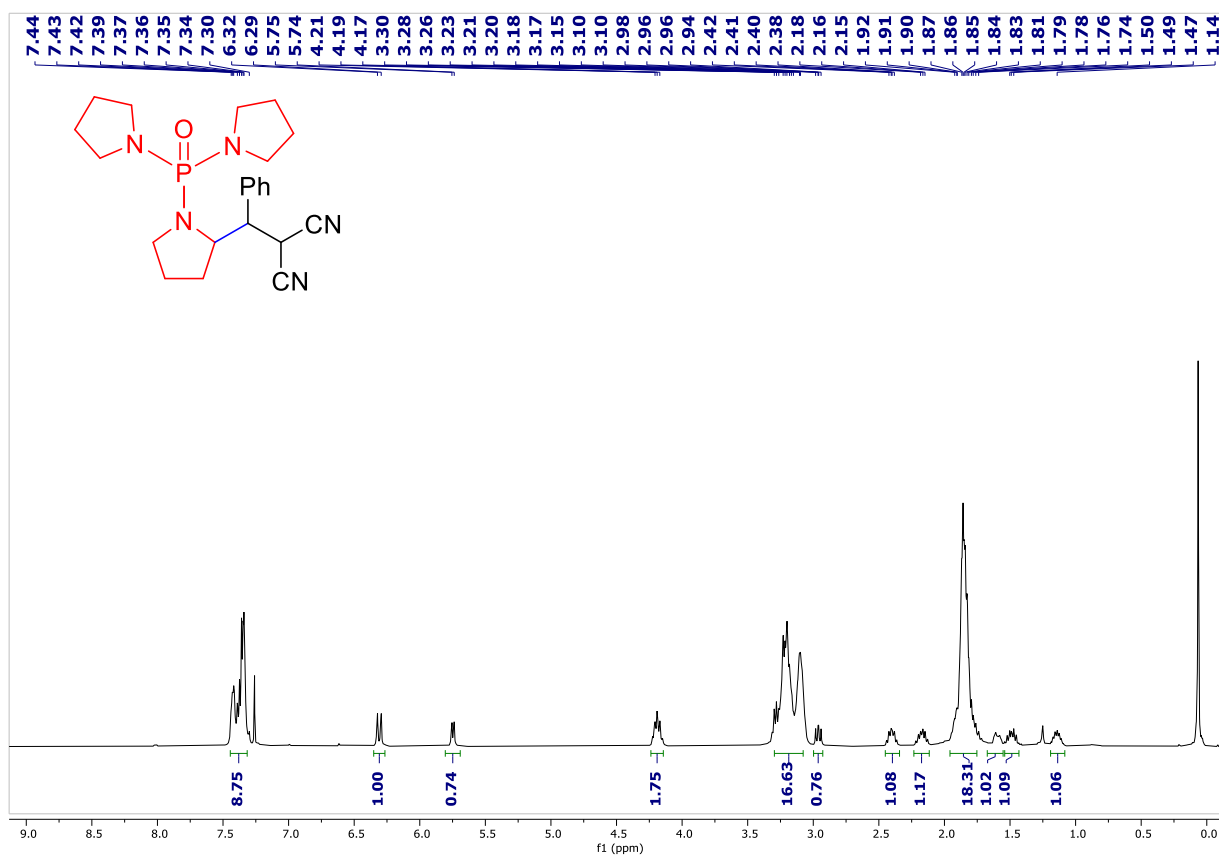
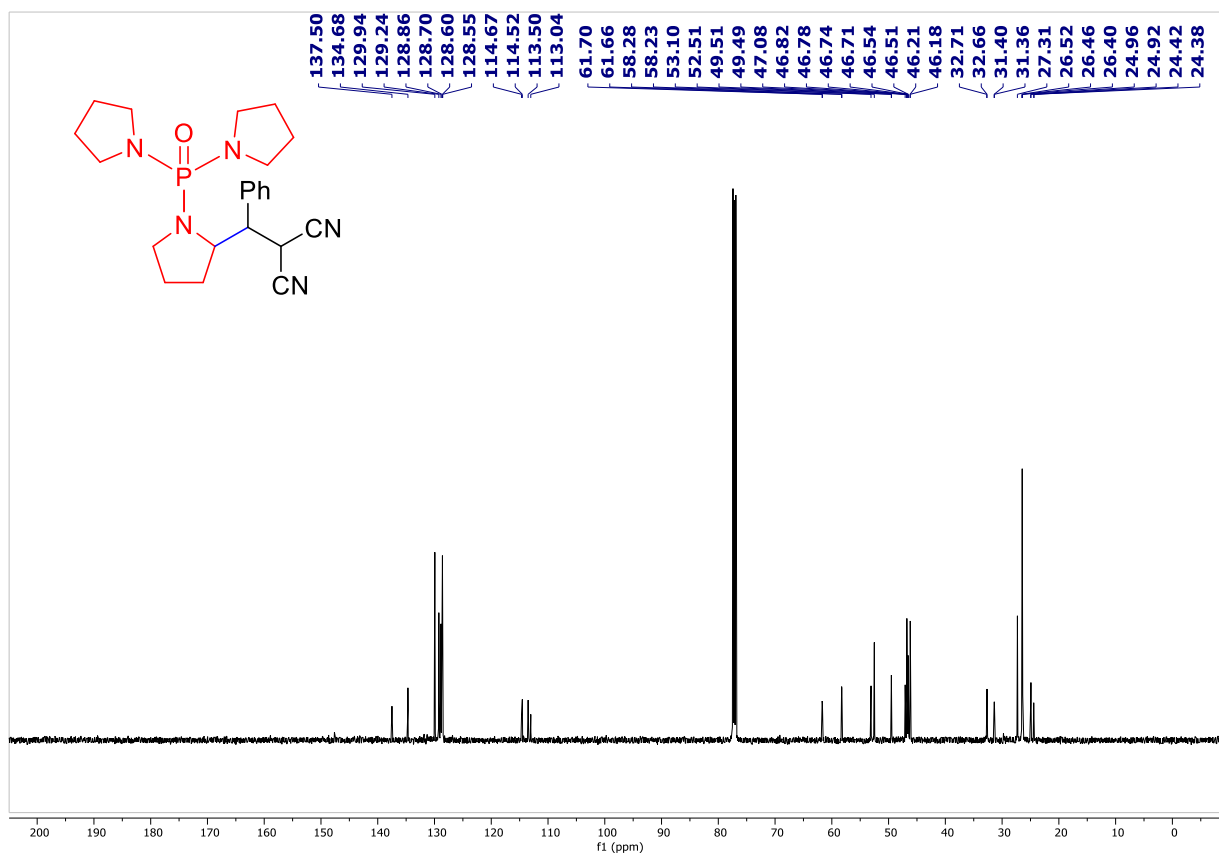
Chemical structure of compound 10 is shown above the ^{13}C NMR spectrum. The structure features a central phosphorus atom double-bonded to an oxygen and single-bonded to three piperidine rings. One piperidine ring is substituted with a 1-phenyl-2,2-dicyanomethyl group.

The ^{13}C NMR spectrum (f1 (ppm)) displays the following chemical shifts (ppm):

- 136.00
- 135.37
- 129.21
- 129.07
- 128.89
- 113.95
- 112.64
- 112.43
- 111.83
- 52.69
- 51.73
- 51.70
- 46.20
- 45.83
- 45.55
- 45.51
- 45.42
- 45.27
- 39.73
- 39.42
- 39.40
- 28.21
- 27.89
- 27.61
- 26.98
- 26.95
- 26.47
- 26.43
- 26.37
- 26.35
- 26.30
- 25.29
- 25.26
- 24.93
- 24.76
- 24.69
- 24.66
- 24.59
- 18.53

^{31}P NMR (203 MHz, $CDCl_3$) of compound **4e** 1H NMR (400 MHz, $CDCl_3$) of compound **4f**

$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) of compound **4f** ^{31}P NMR (203 MHz, CDCl_3) of compound **4f**

^1H NMR (400 MHz, CDCl_3) of compound **4g** $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) of compound **4g**

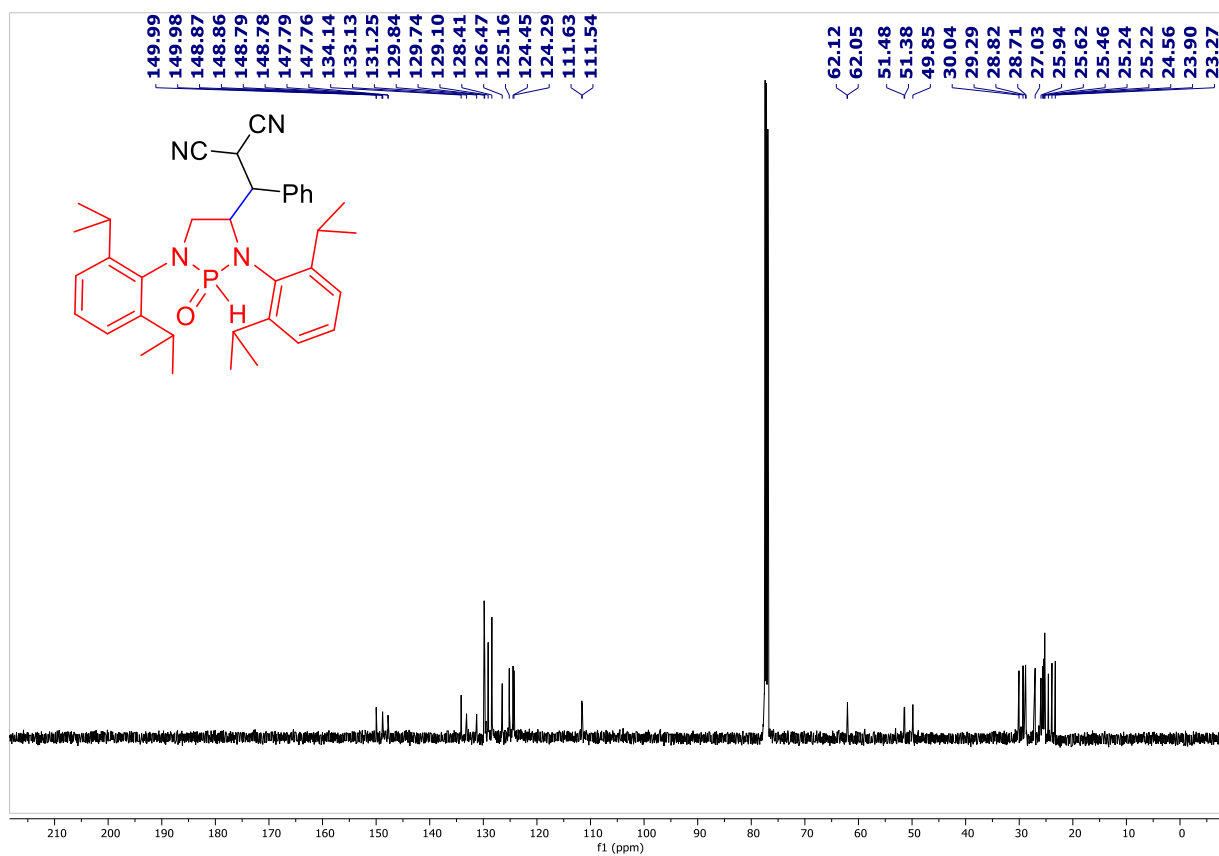
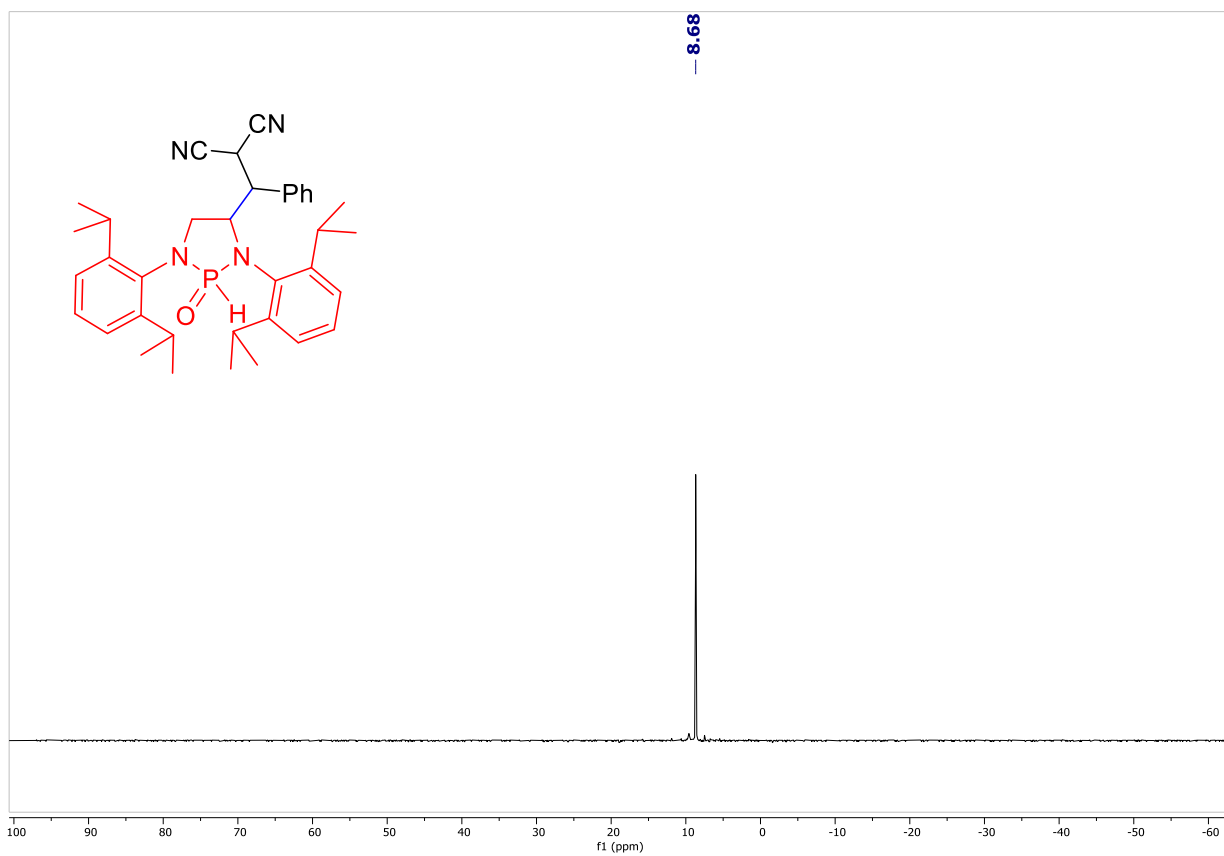
Chemical structure of the compound is shown above the spectrum. The structure is a phosphonate derivative of a substituted pyrrolidine. The phosphorus atom is bonded to two pyrrolidine rings and a carbonyl group. The carbonyl carbon is bonded to a phenyl group (Ph) and a cyano group (CN). The cyano group is further substituted with a methyl group (CH₃).

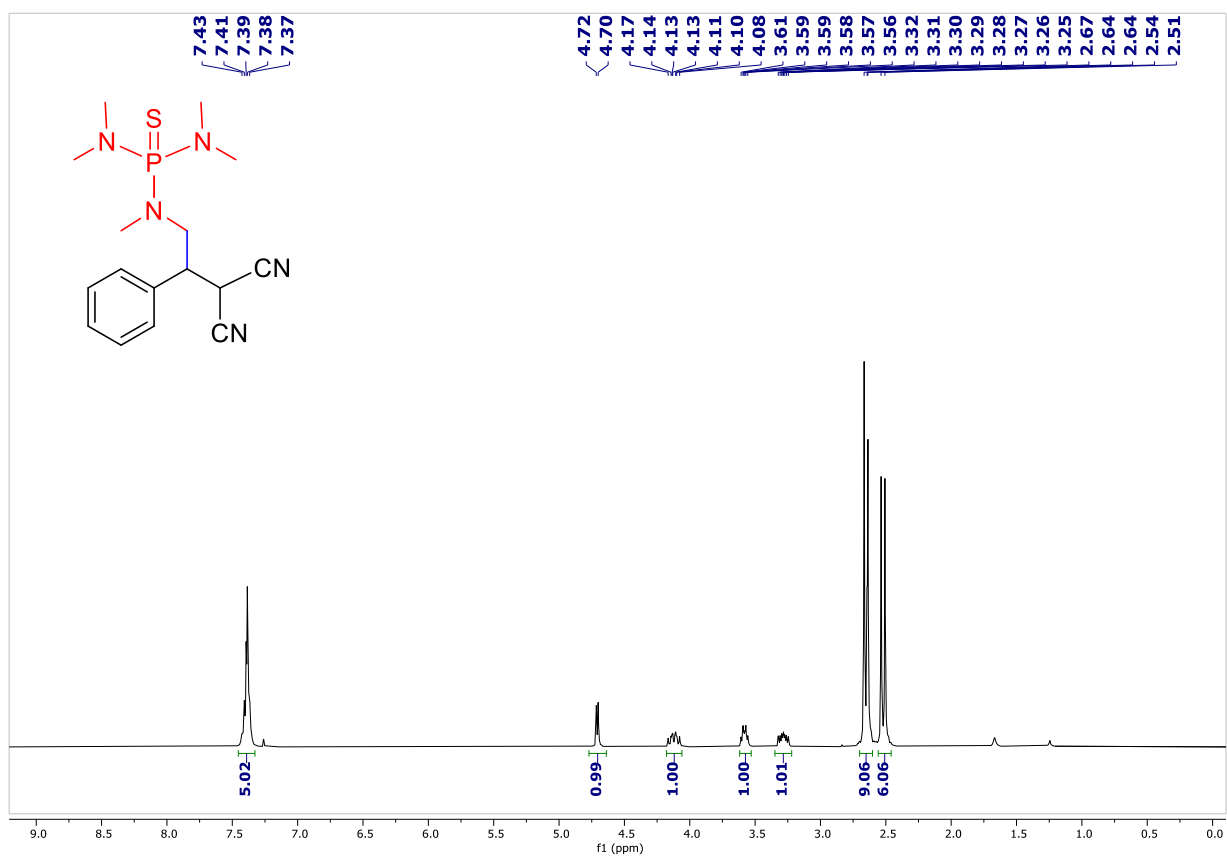
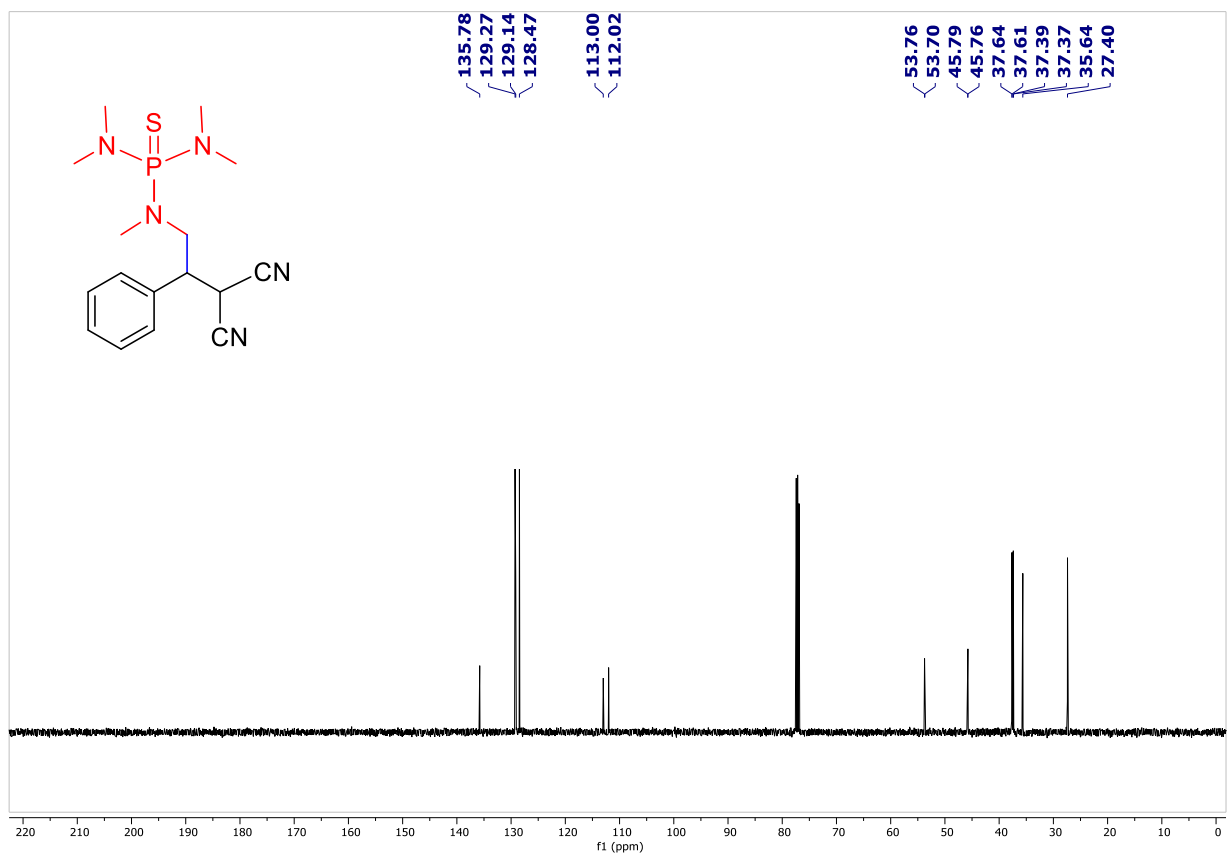
The spectrum shows a single sharp peak at 17.10 ppm, which is characteristic of a carbonyl group in a phosphonate derivative. The x-axis is labeled "f1 (ppm)" and ranges from -60 to 100.

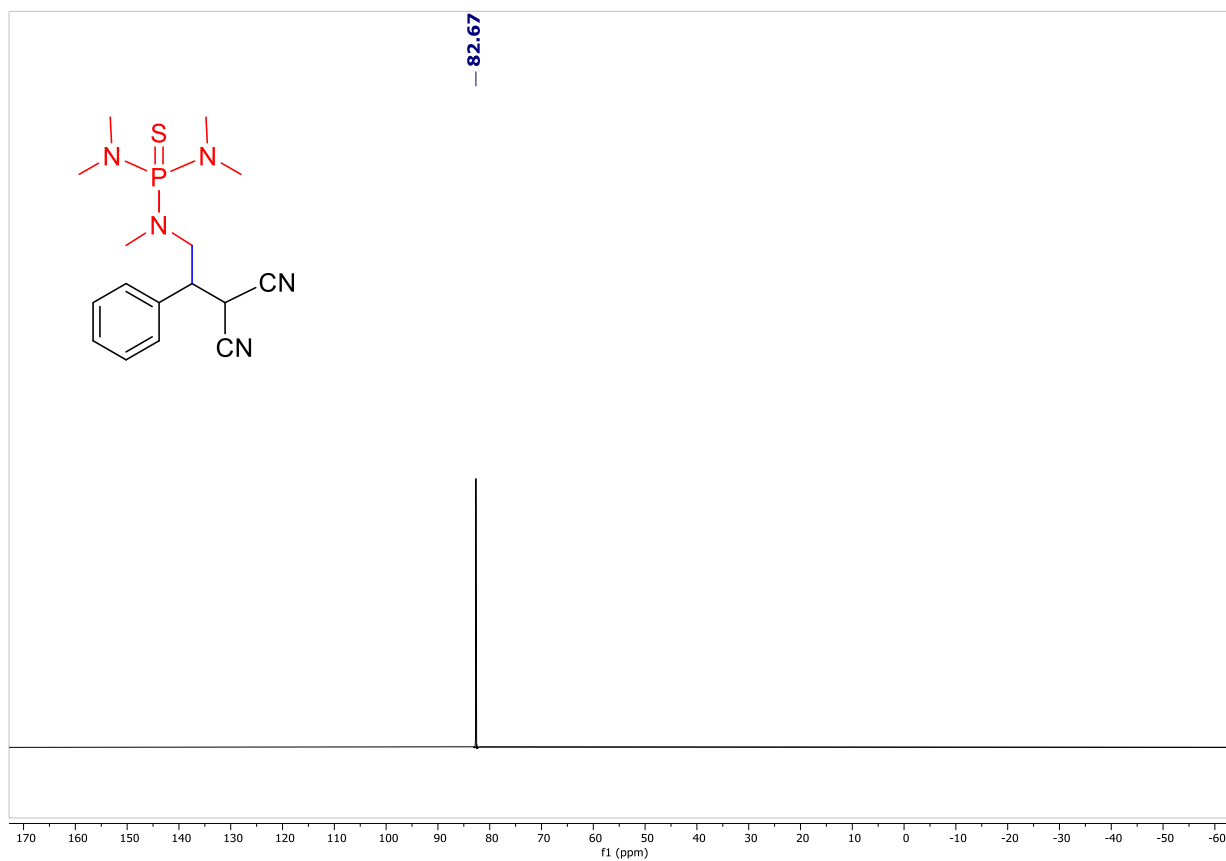
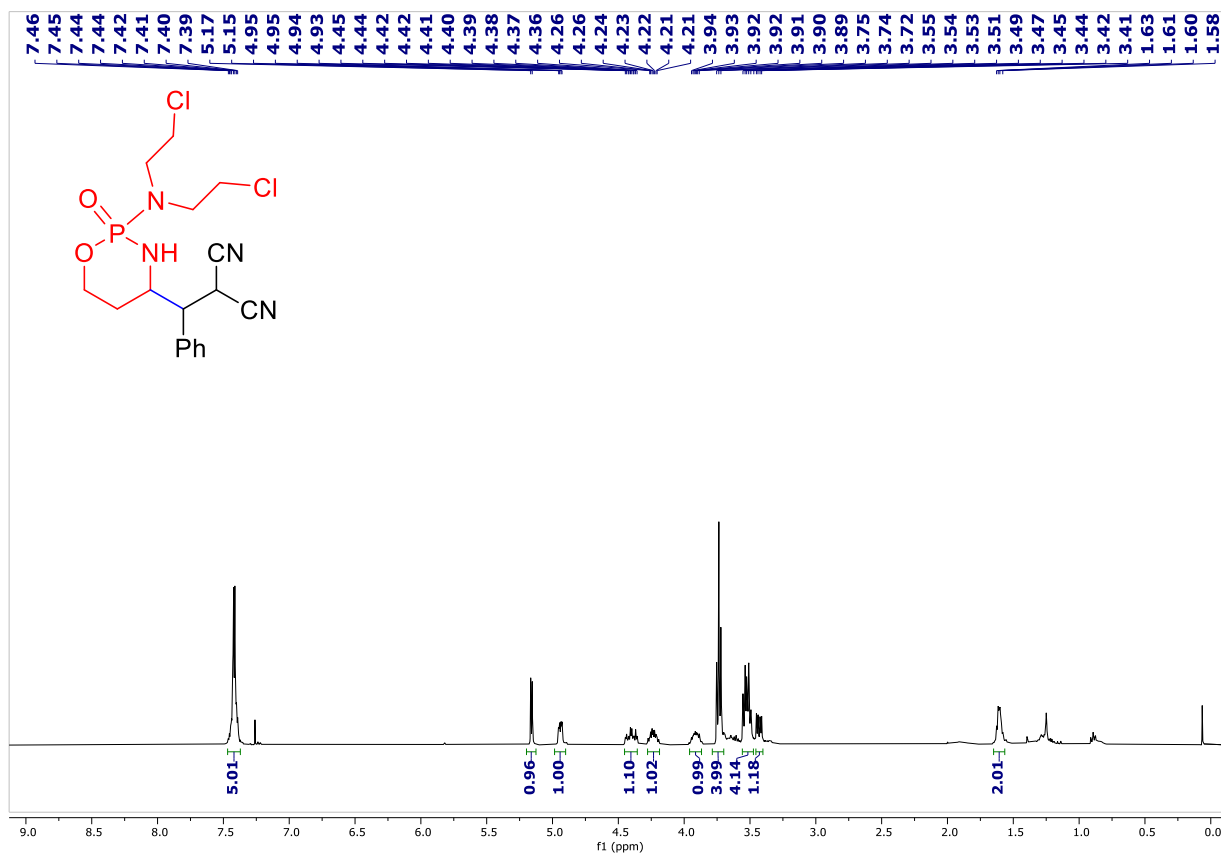
Chemical structure of compound 10 is shown in the top left corner. The structure is a complex molecule with a central phosphorus atom (P) bonded to two nitrogen atoms (N) and an oxygen atom (O). The phosphorus atom is also bonded to a hydrogen atom (H). The nitrogen atoms are part of a ring system that includes two phenyl groups (Ph) and two cyano groups (CN). The structure is drawn in red and blue.

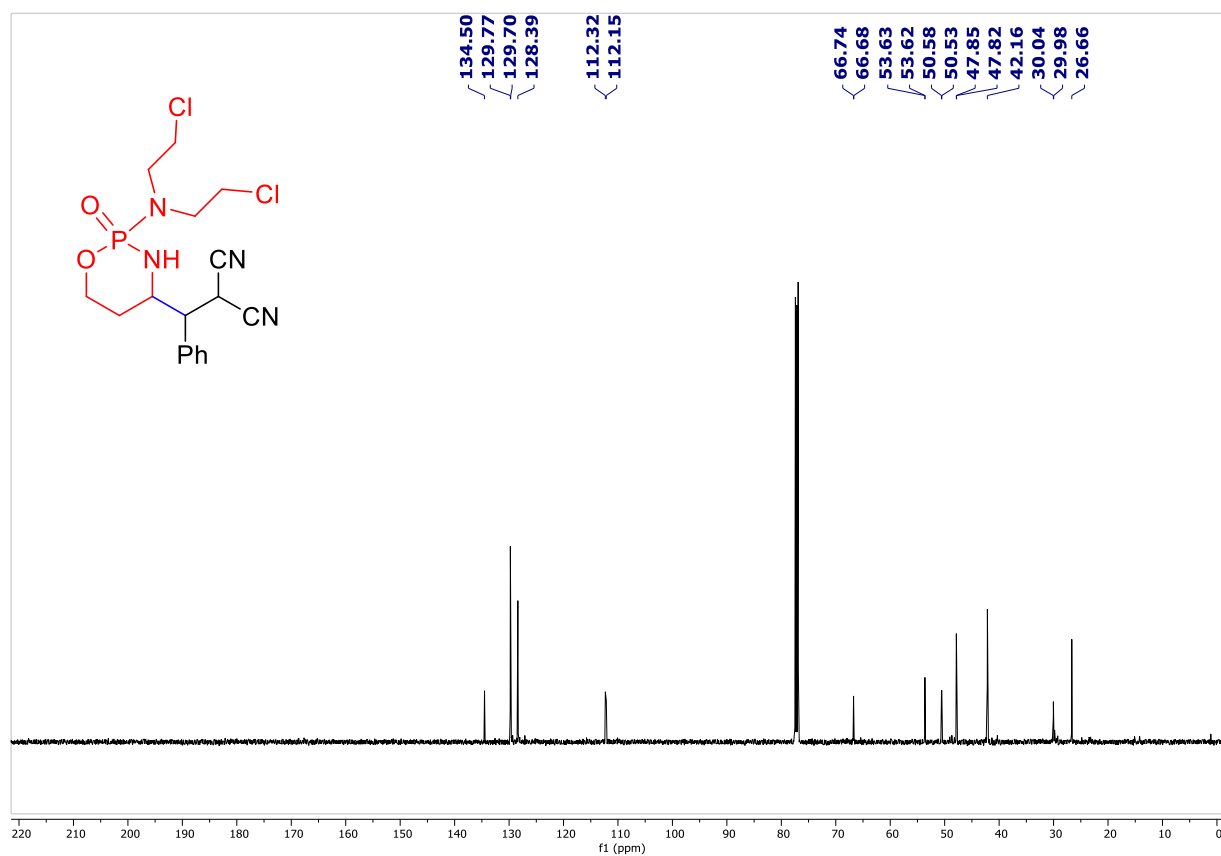
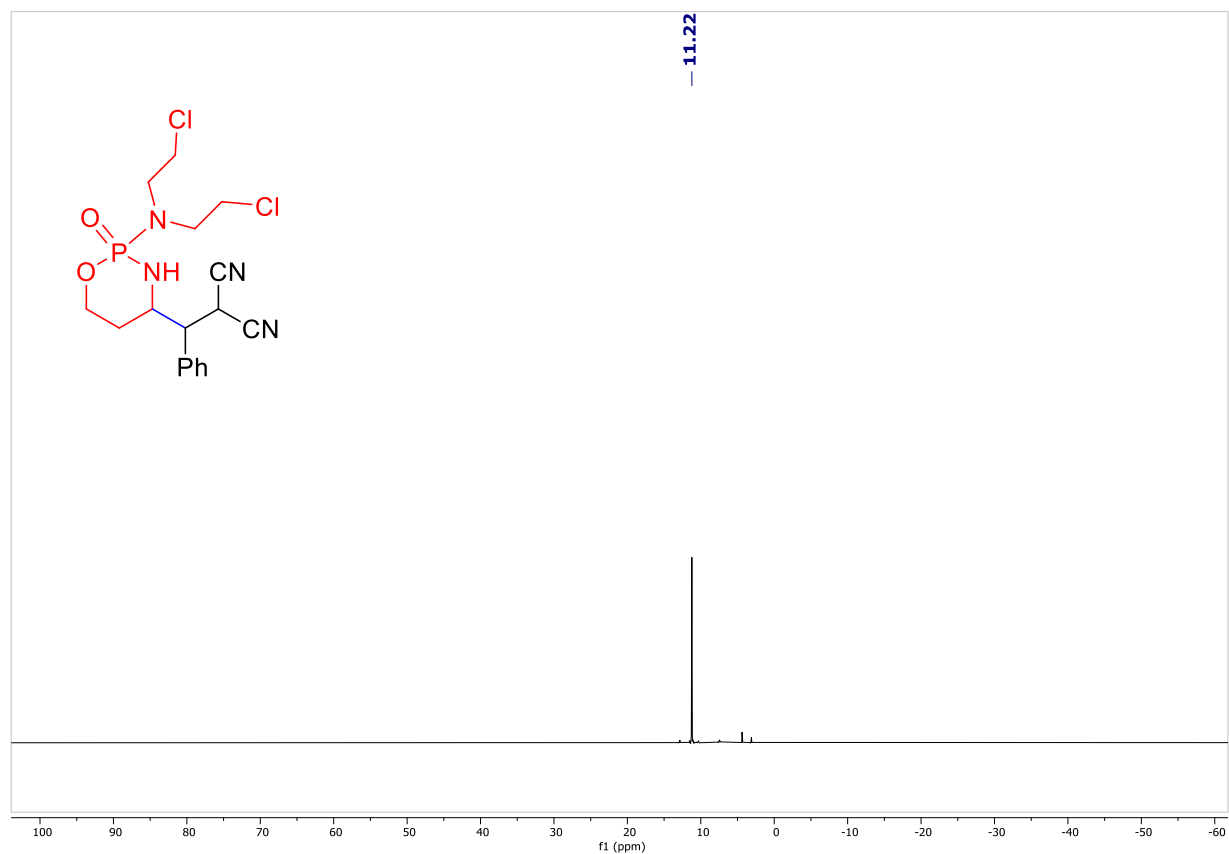
The ^1H NMR spectrum (400 MHz, CDCl_3) shows the following chemical shifts (ppm) and integration values:

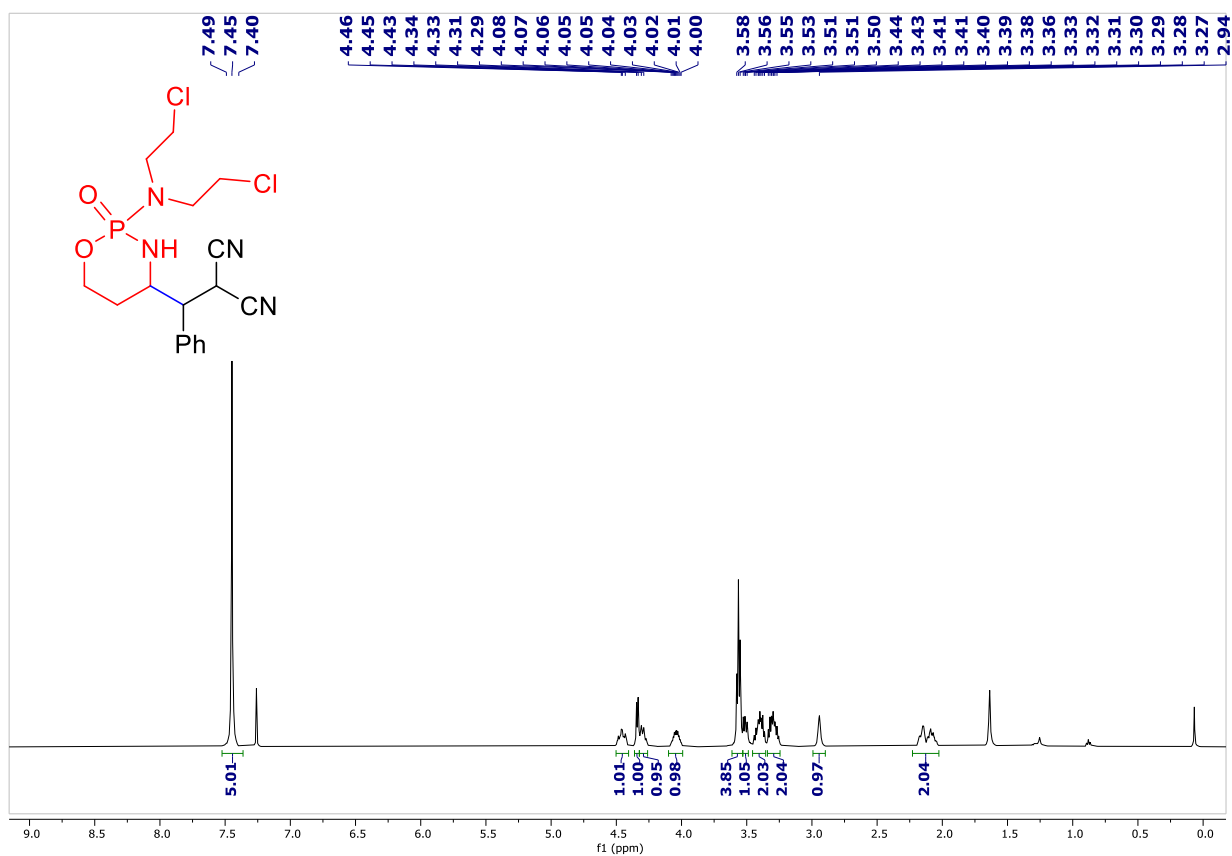
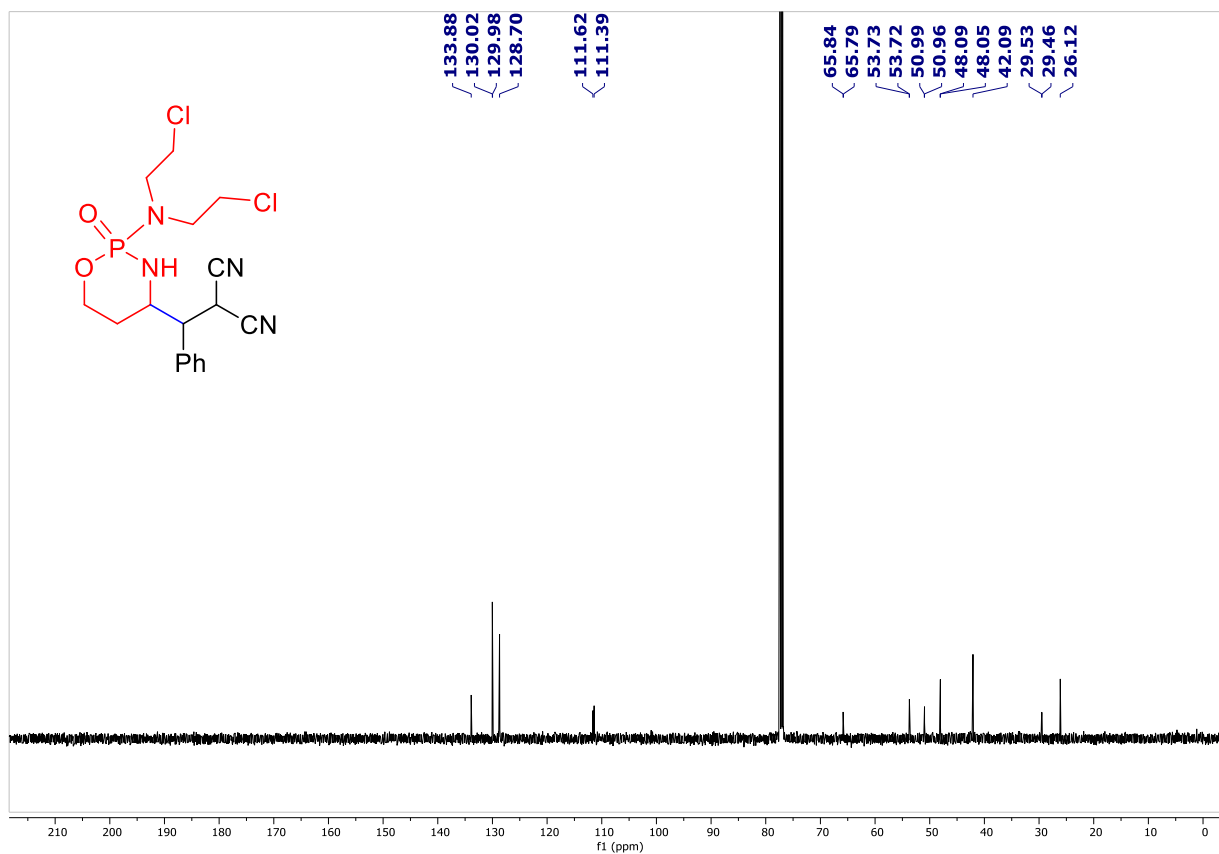
Chemical Shift (ppm)	Integration
8.51, 7.41, 7.40, 7.38, 7.37, 7.37, 7.36, 7.34, 7.32, 7.30, 7.24, 7.24, 7.22, 7.20, 7.19, 7.17, 7.15, 7.13, 7.13, 6.92	0.47
4.71, 4.71, 4.70, 4.20, 4.18, 3.93, 3.91, 3.77, 3.76, 3.75, 3.63, 3.61, 3.59, 3.59, 3.57, 3.35, 3.33, 3.32, 3.31, 3.30	5.10, 6.09, 0.45
1.39, 1.37, 1.36, 1.34, 1.33, 1.31, 1.29, 1.28, 1.27, 1.26, 1.25, 1.23, 1.21, 1.19	0.95, 1.01, 1.01, 1.00, 1.96, 2.07, 0.95
0.0	24.20

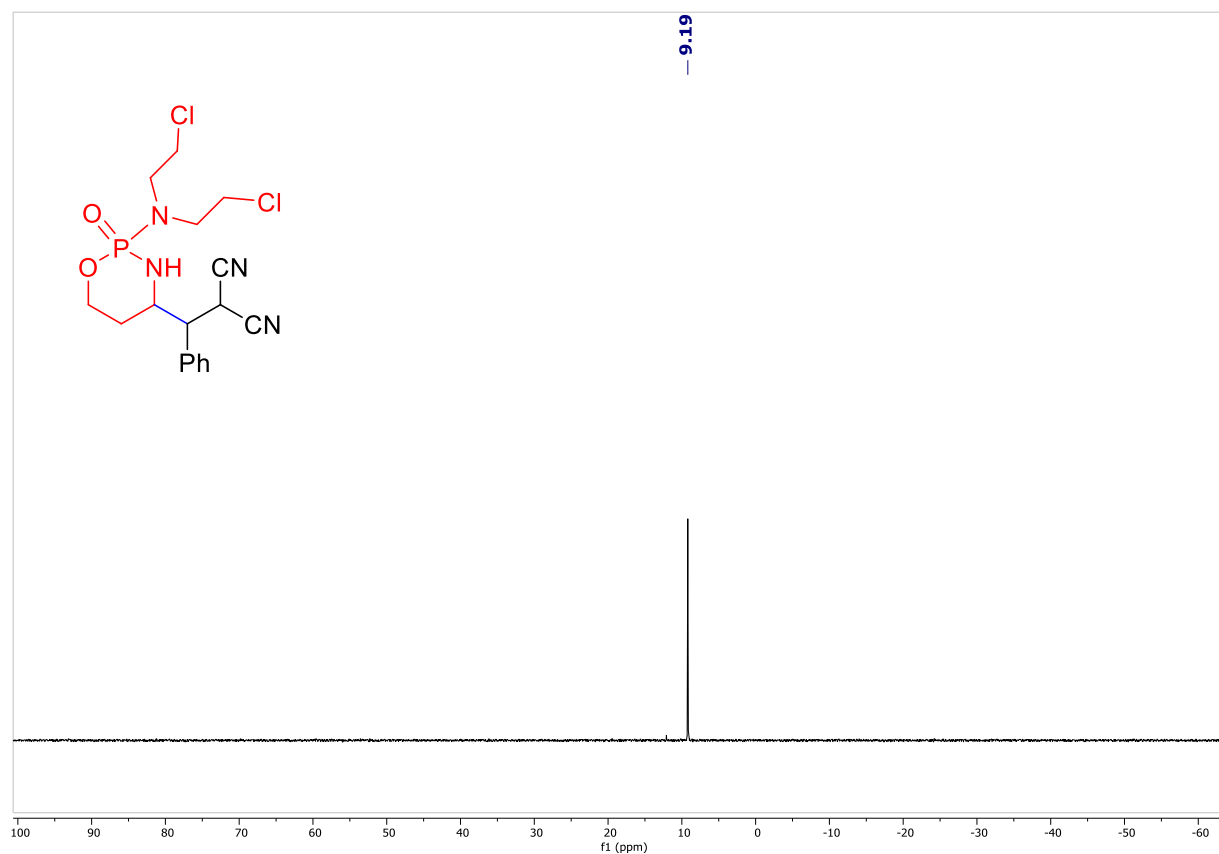
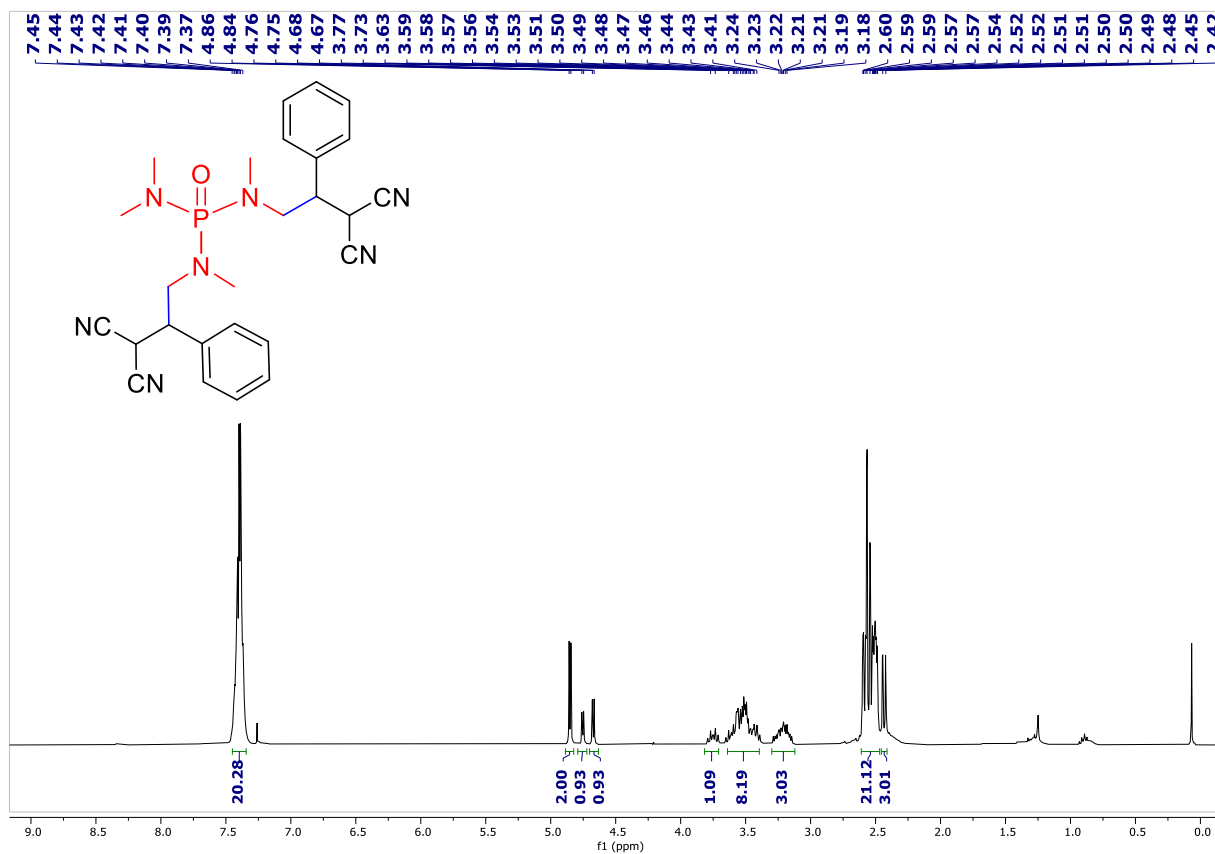
$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) of compound **4h** ^{31}P NMR (203 MHz, CDCl_3) of compound **4h**

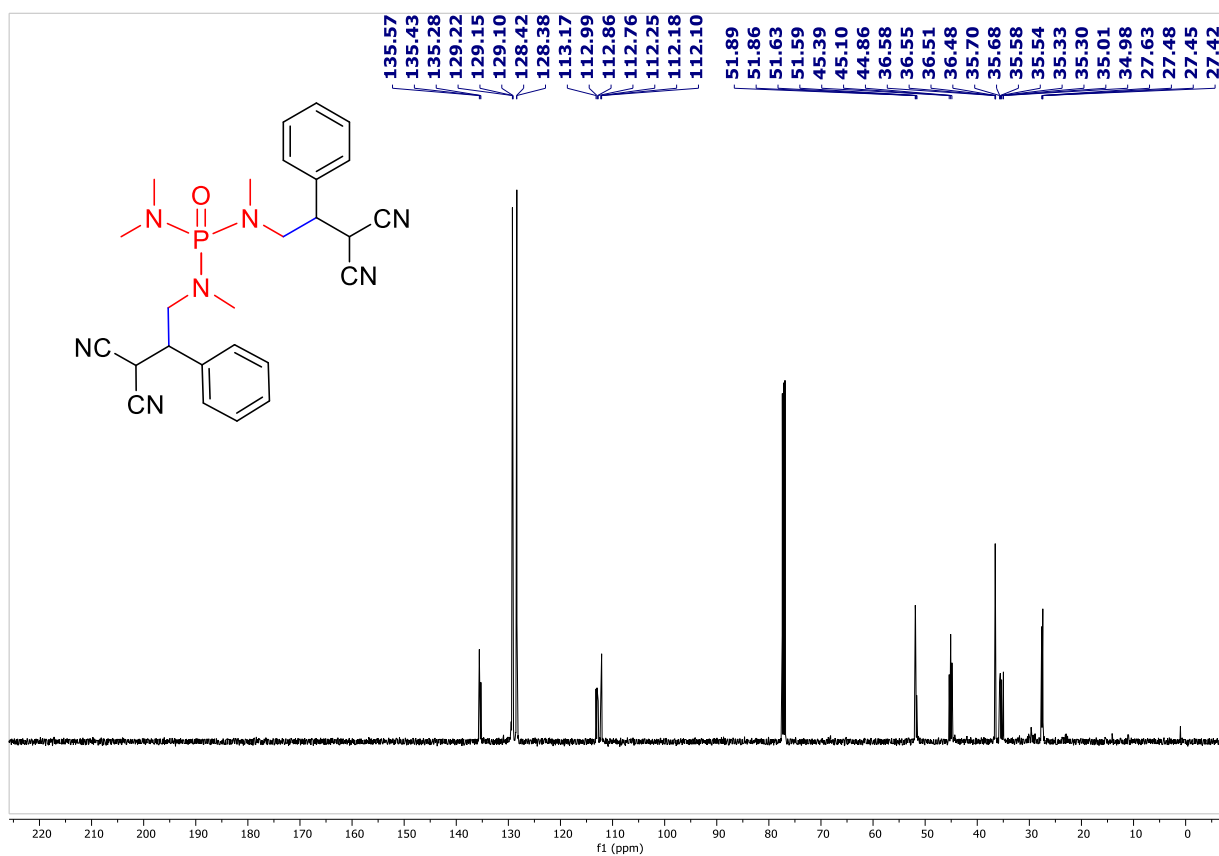
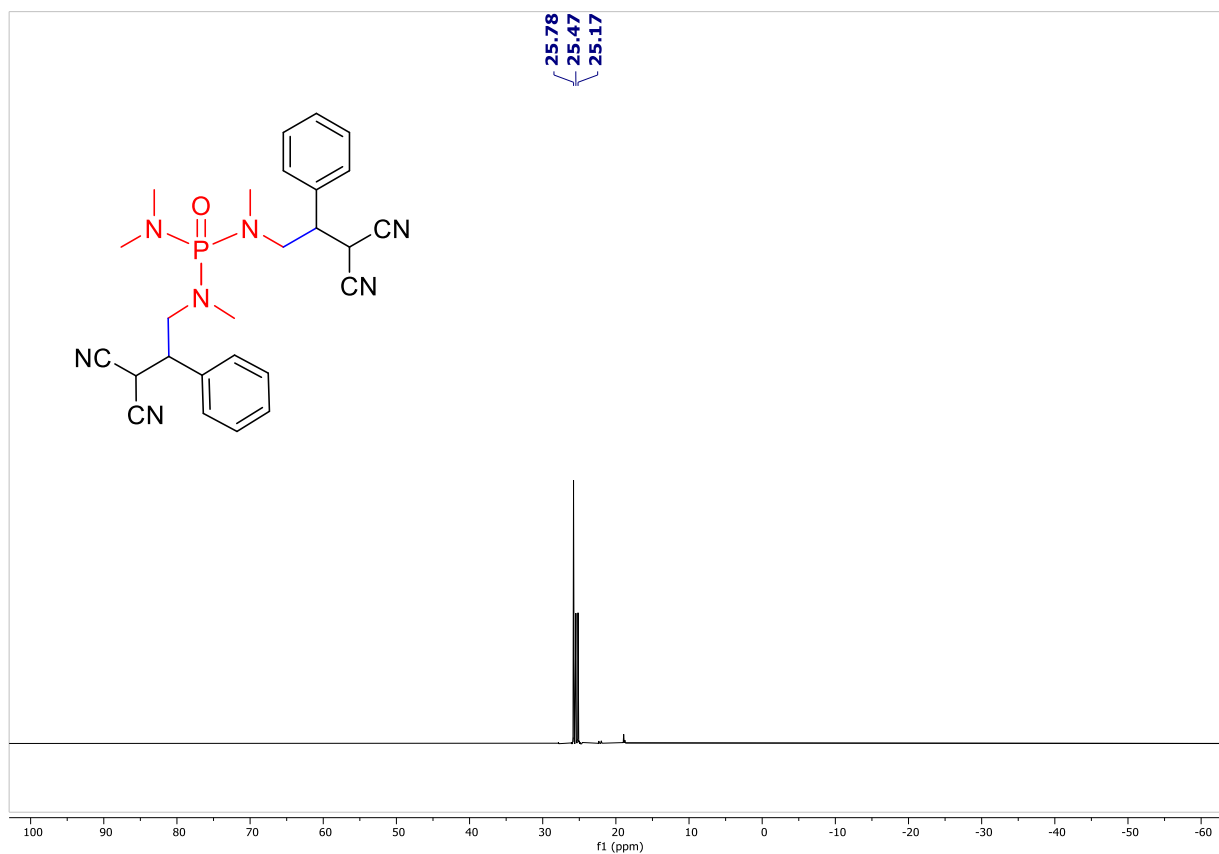
^1H NMR (400 MHz, CDCl_3) of compound **4i** $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) of compound **4i**

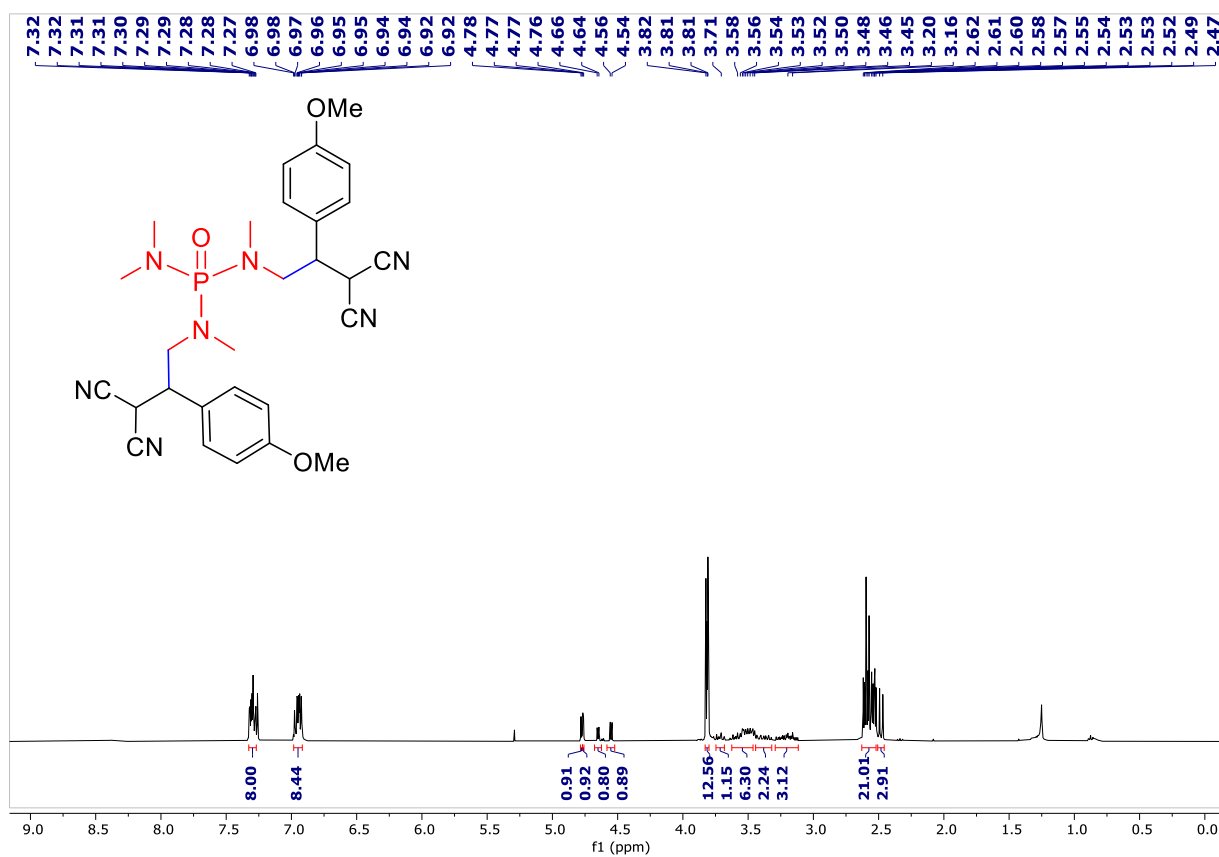
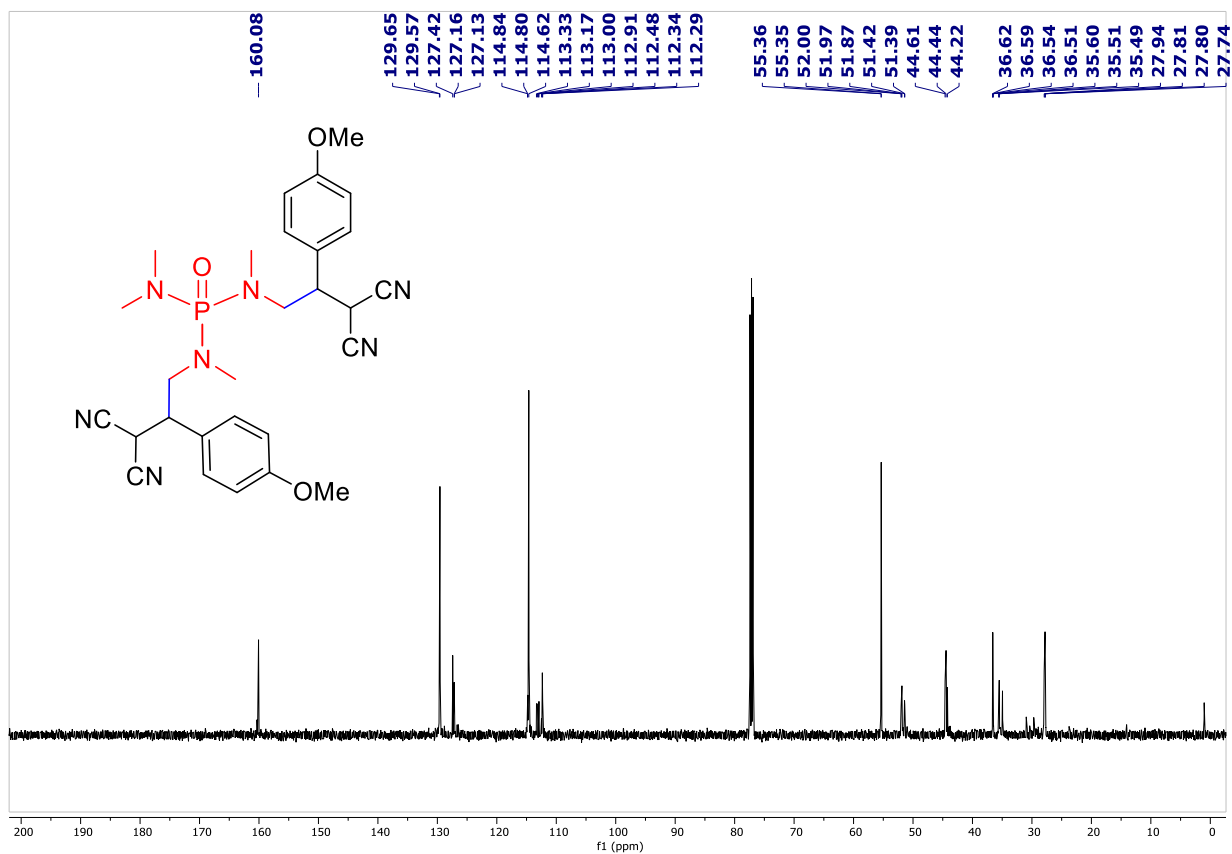
^{31}P NMR (203 MHz, CDCl_3) of compound **4i** ^1H NMR (400 MHz, CDCl_3) of compound **4j'**

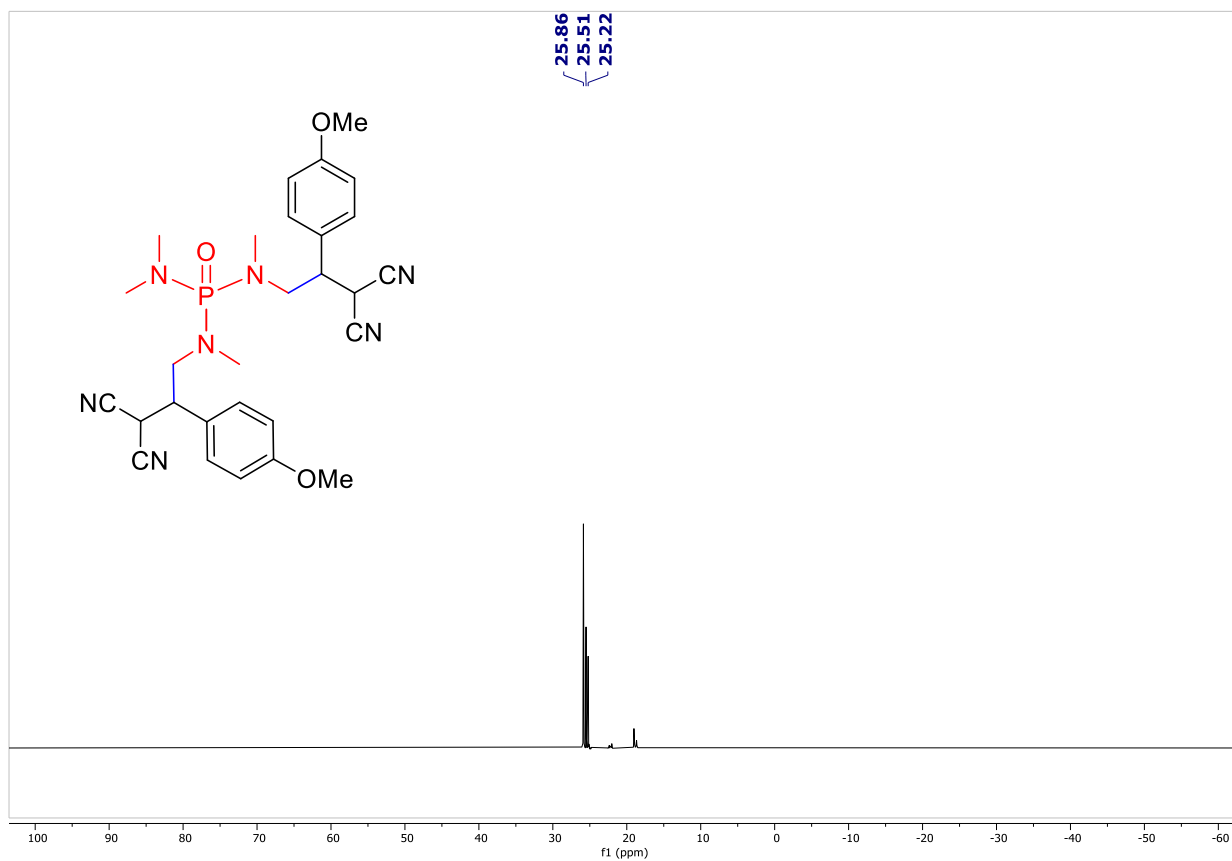
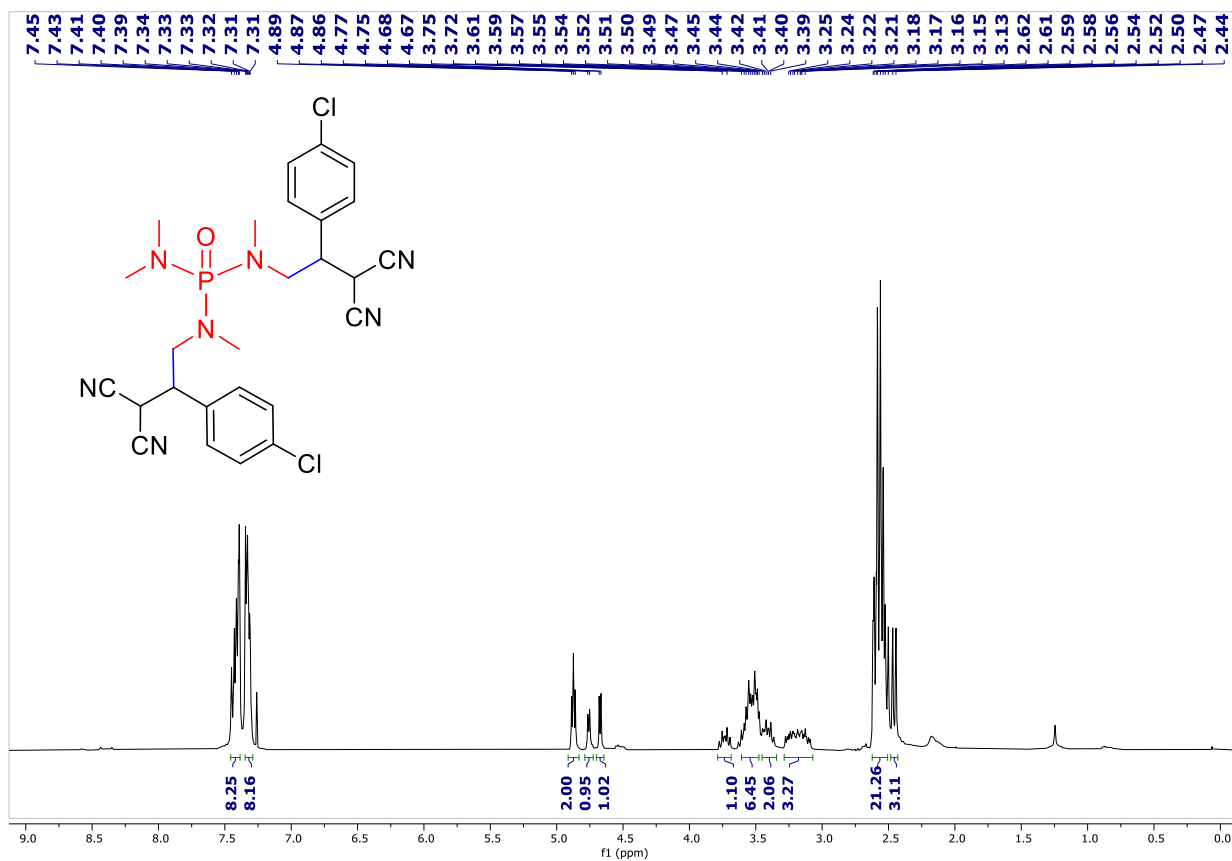
$^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) of compound **4j'** ^{31}P NMR (203 MHz, $CDCl_3$) of compound **4j'**

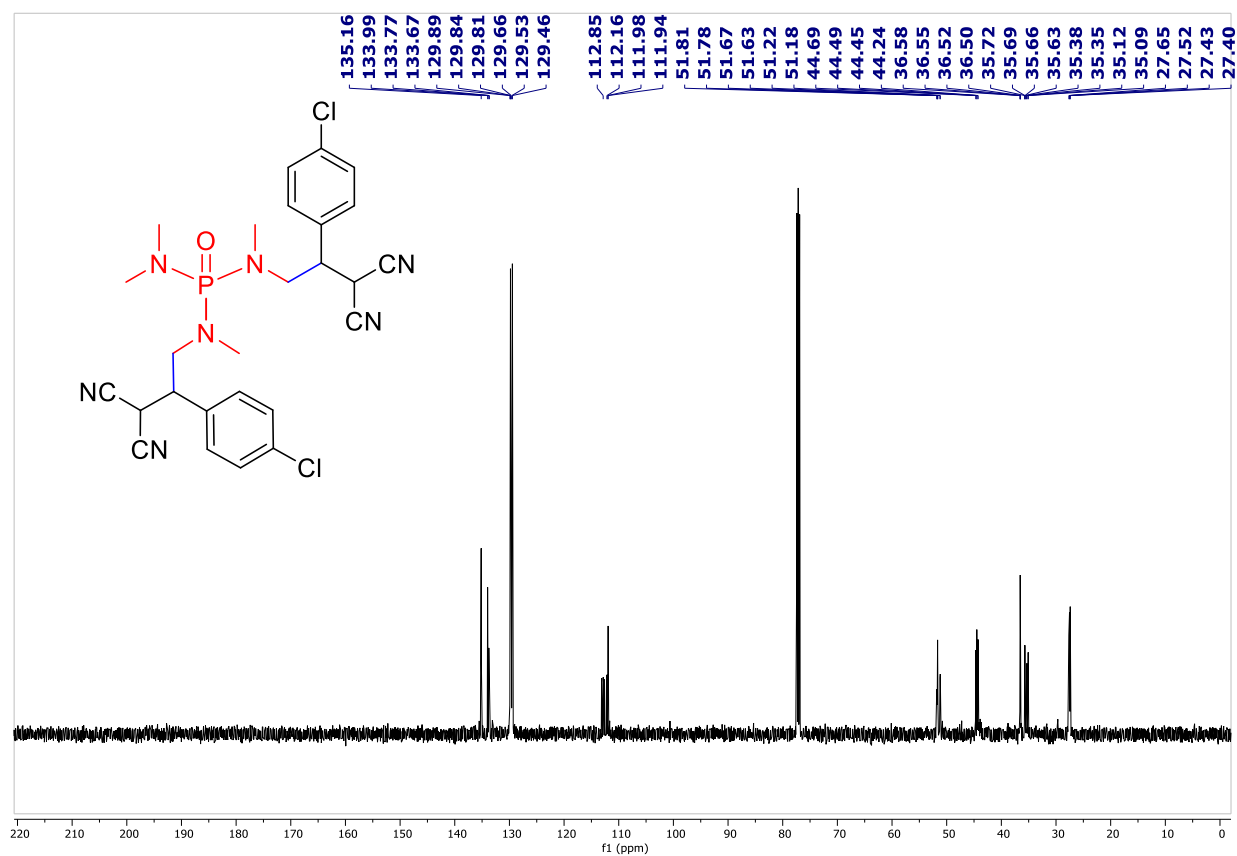
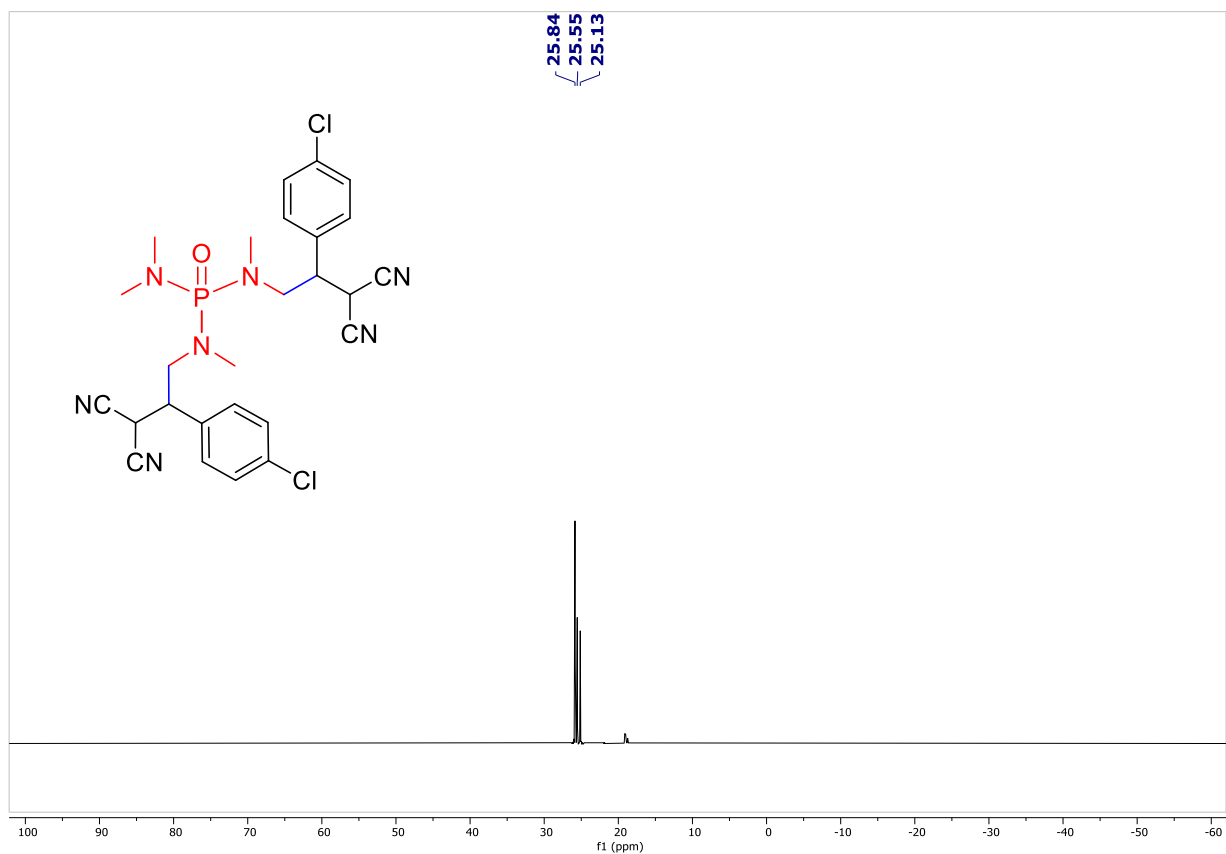
^1H NMR (500 MHz, CDCl_3) of compound **4j''** $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) of compound **4j''**

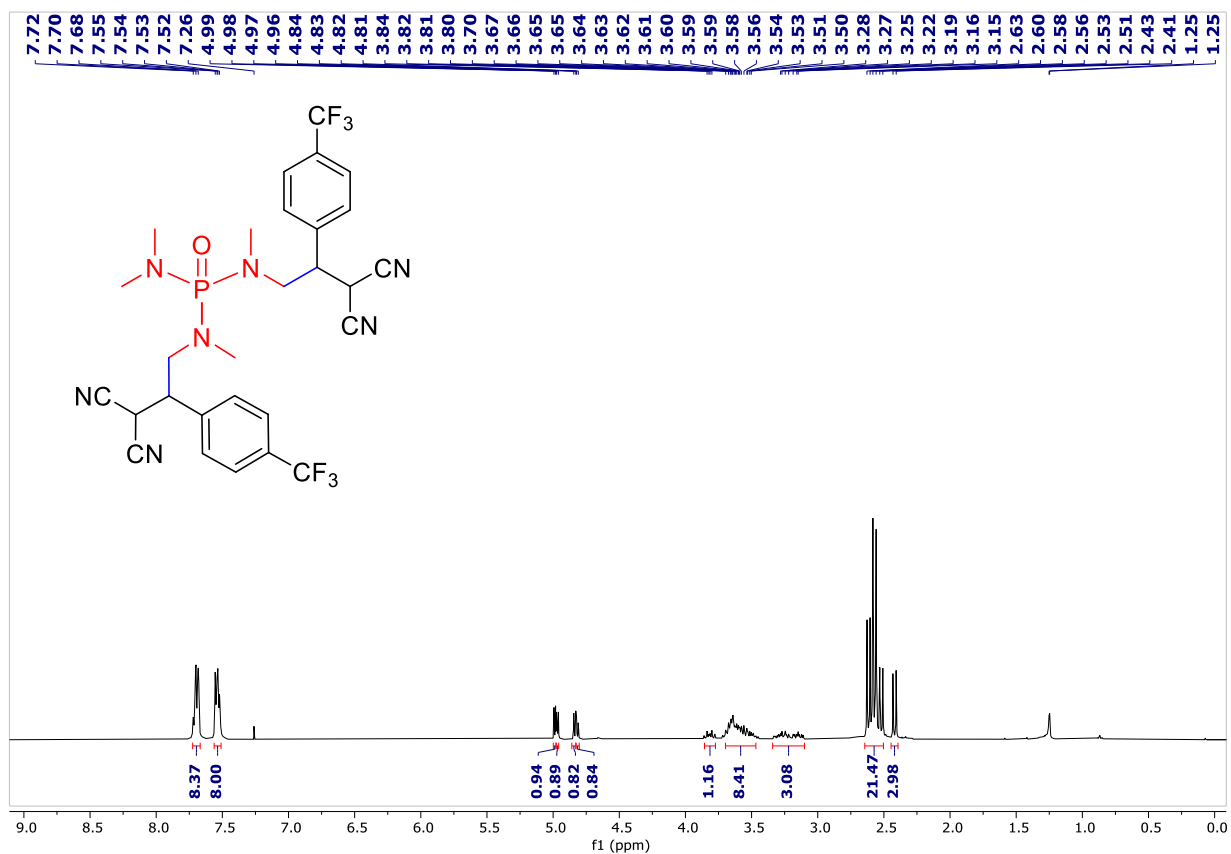
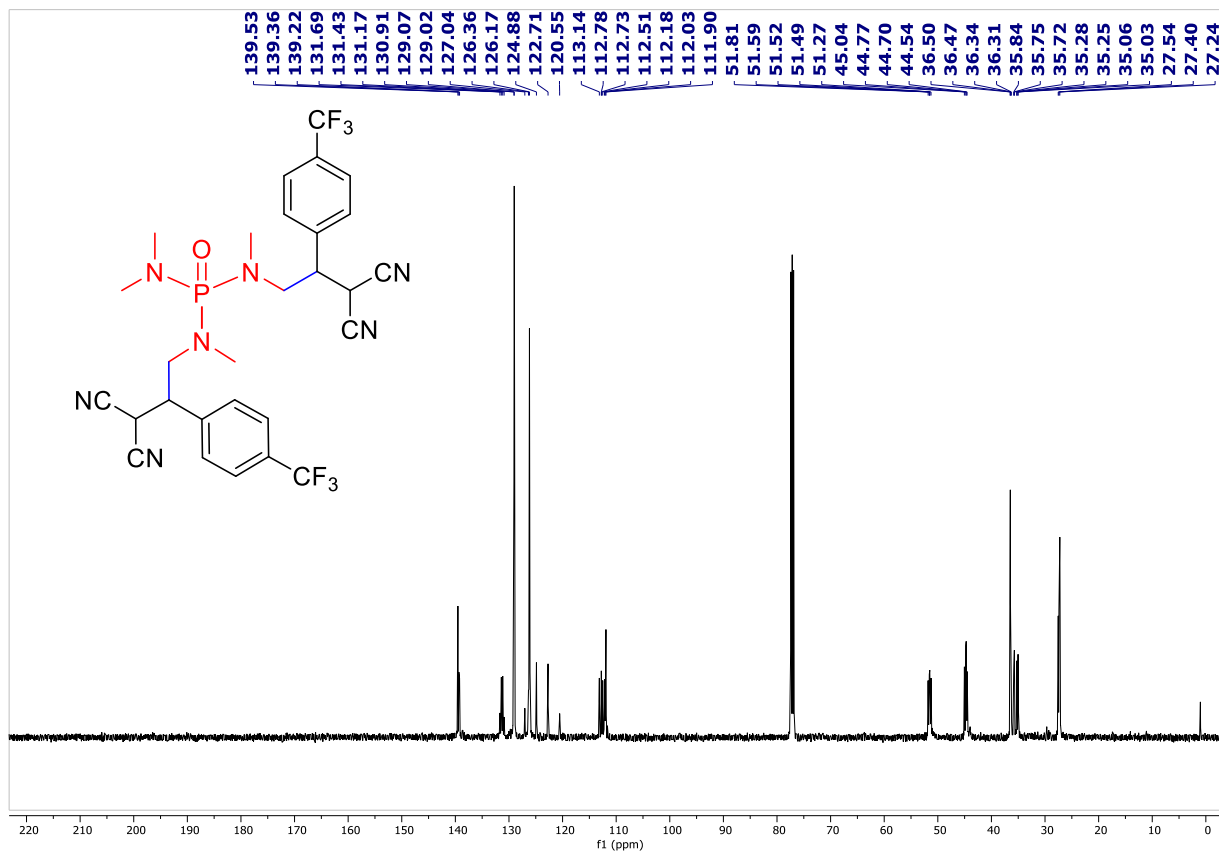
^{31}P NMR (203 MHz, $CDCl_3$) of compound **4j''** 1H NMR (400 MHz, $CDCl_3$) of compound **5a**

$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) of compound **5a** ^{31}P NMR (203 MHz, CDCl_3) of compound **5a**

^1H NMR (400 MHz, CDCl_3) of compound **5b** $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) of compound **5b**

^{31}P NMR (203 MHz, $CDCl_3$) of compound **5b** 1H NMR (400 MHz, $CDCl_3$) of compound **5c**

$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) of compound **5c** ^{31}P NMR (203 MHz, CDCl_3) of compound **5c**

1H NMR (400 MHz, $CDCl_3$) of compound **5d** $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) of compound **5d**

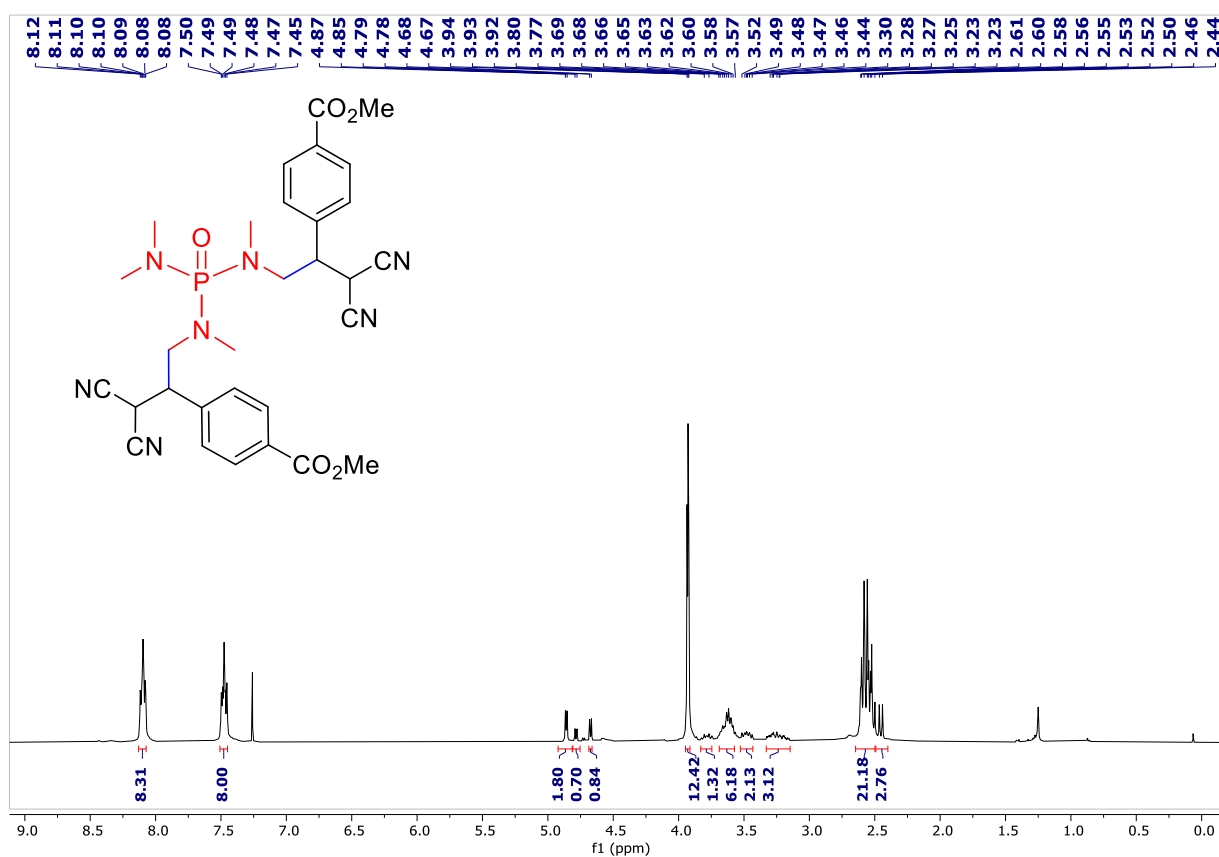
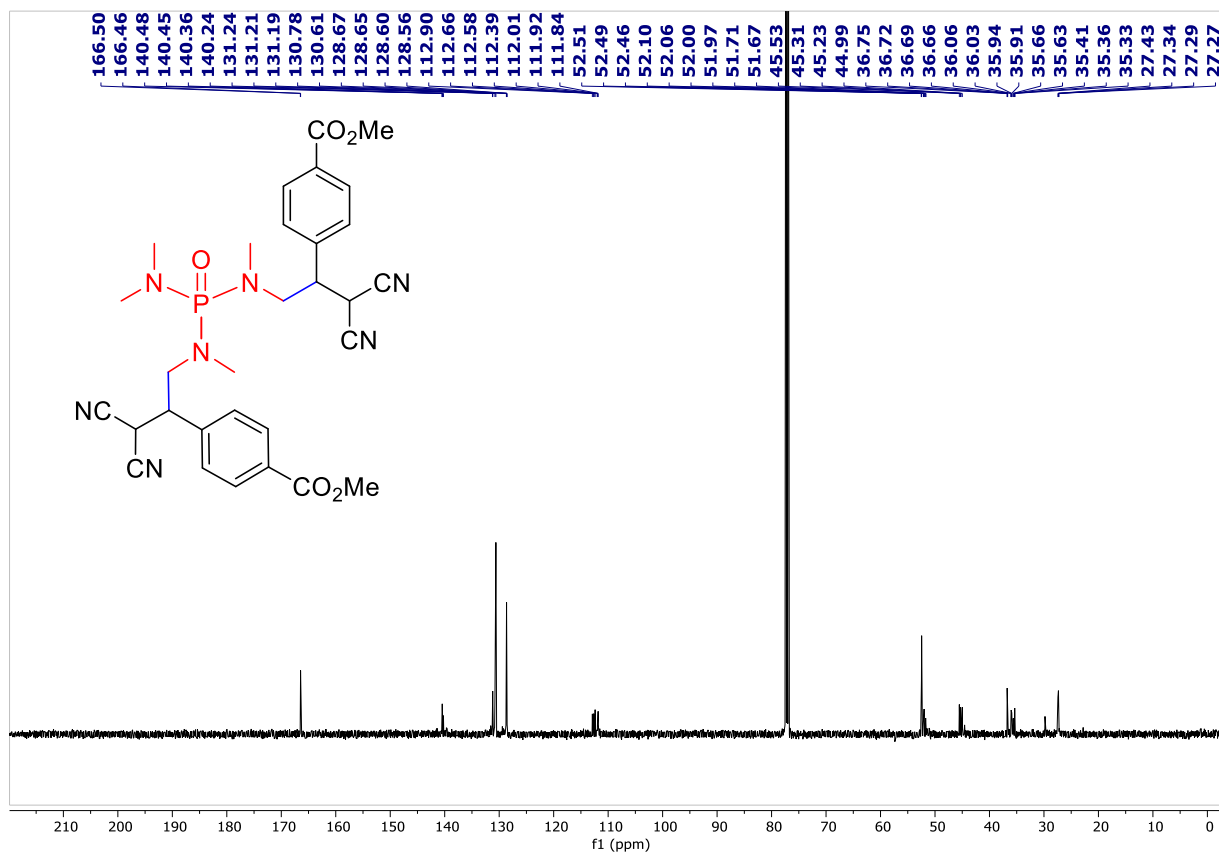
Chemical structure of the compound is shown above the spectrum. The structure is a bisphosphonate derivative, specifically a bisphosphonate salt of a bisphosphonate acid. The structure features a central phosphorus atom (P) bonded to two nitrogen atoms (N) and two oxygen atoms (O). The nitrogen atoms are further substituted with methyl groups (CH₃) and a 4-(trifluoromethyl)phenyl group (C₆H₄CF₃). The oxygen atoms are substituted with a 4-(trifluoromethyl)phenyl group (C₆H₄CF₃) and a 2,2,2-trifluoroethyl group (CF₃CH₂CH₂OH).

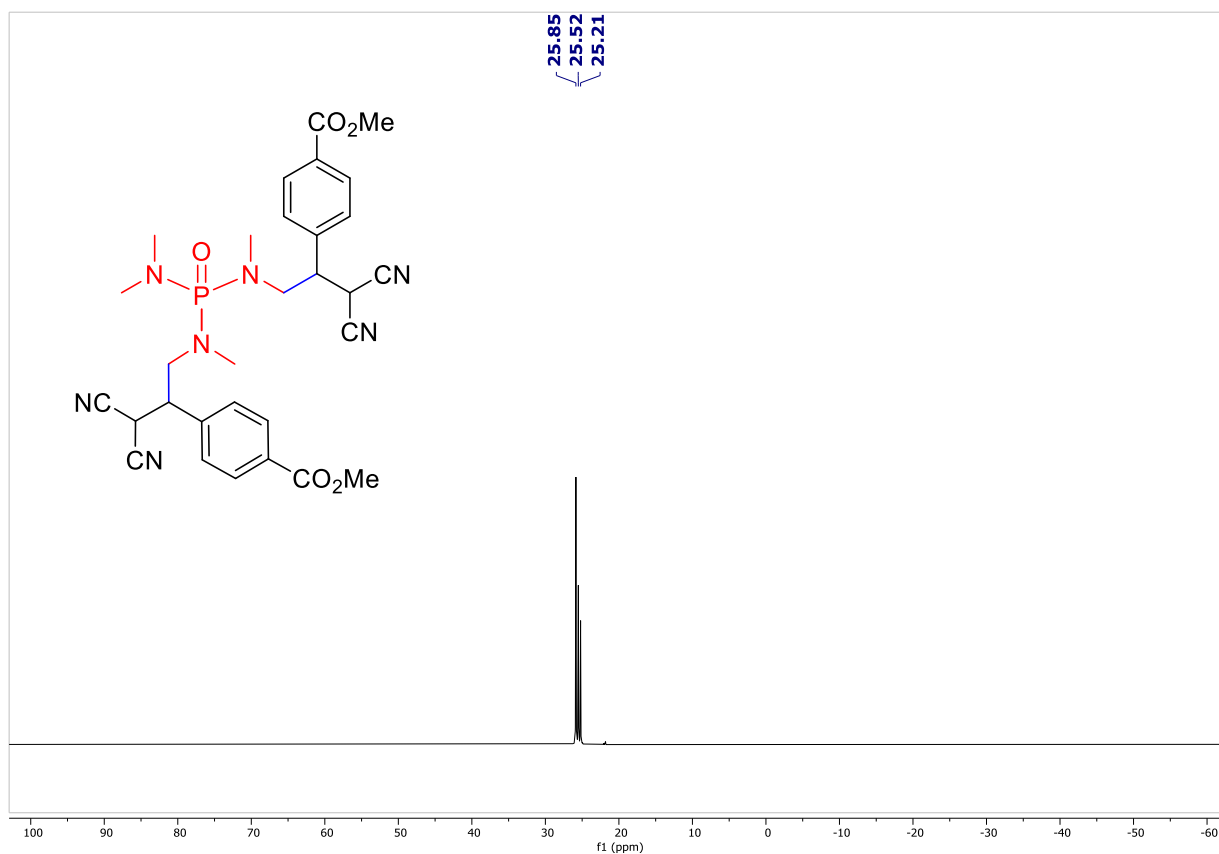
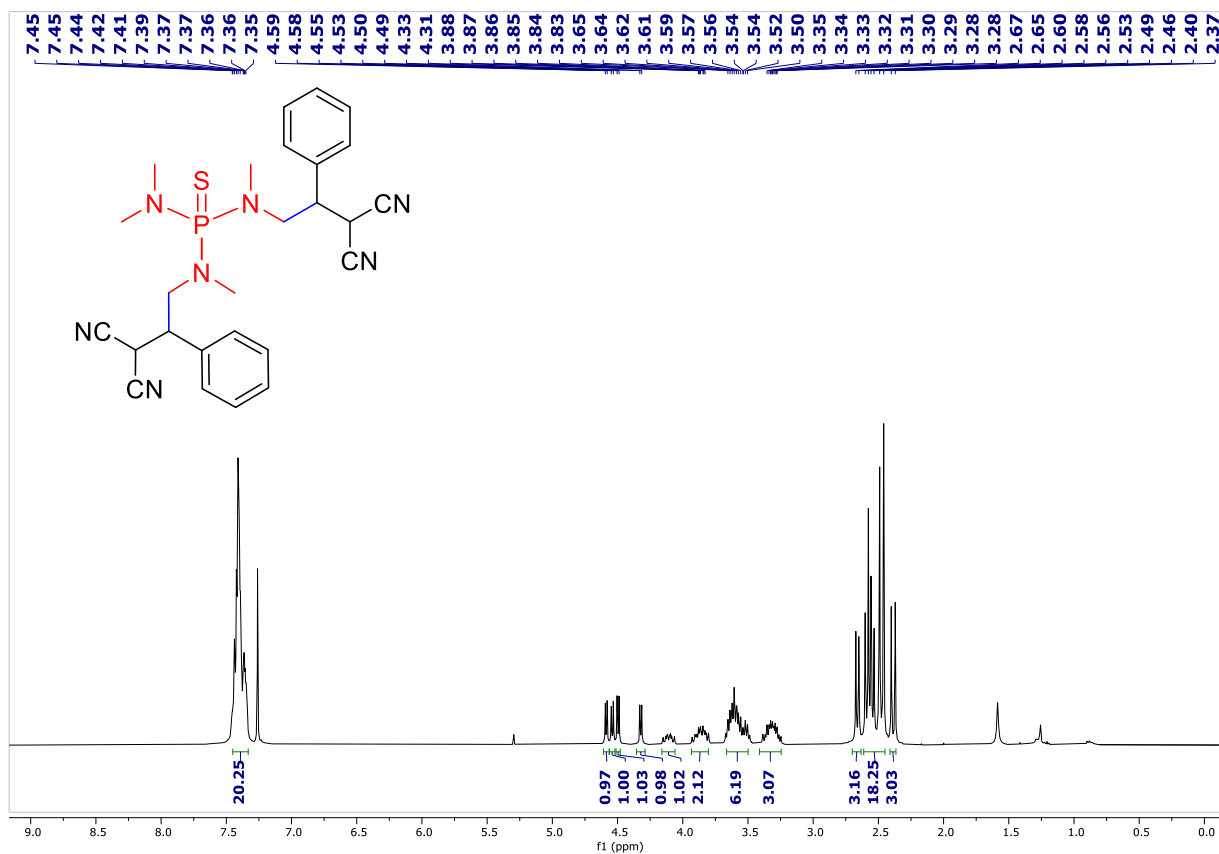
The spectrum shows a single sharp peak at 25.68 ppm, which is assigned to the methyl groups in the structure. The peak is labeled with its chemical shift value, 25.68, and the integration value, 2.00.

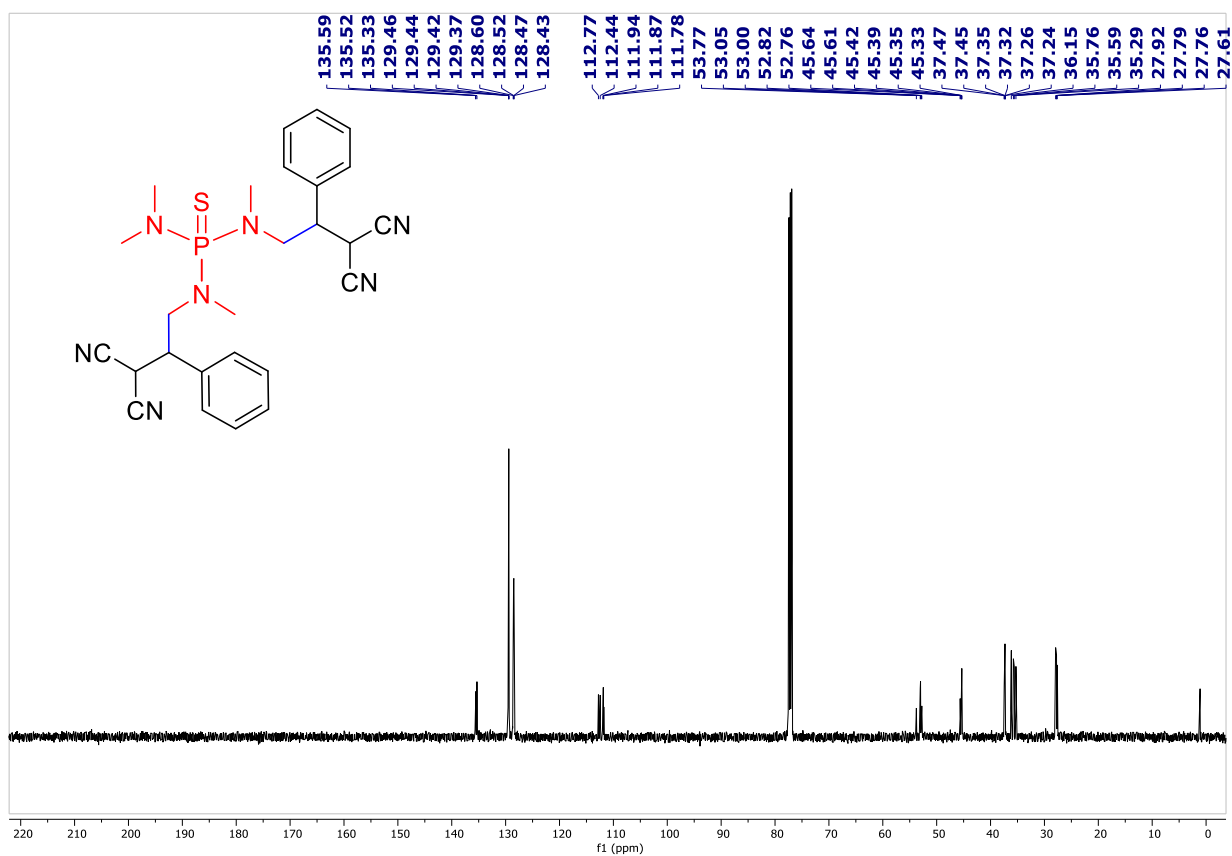
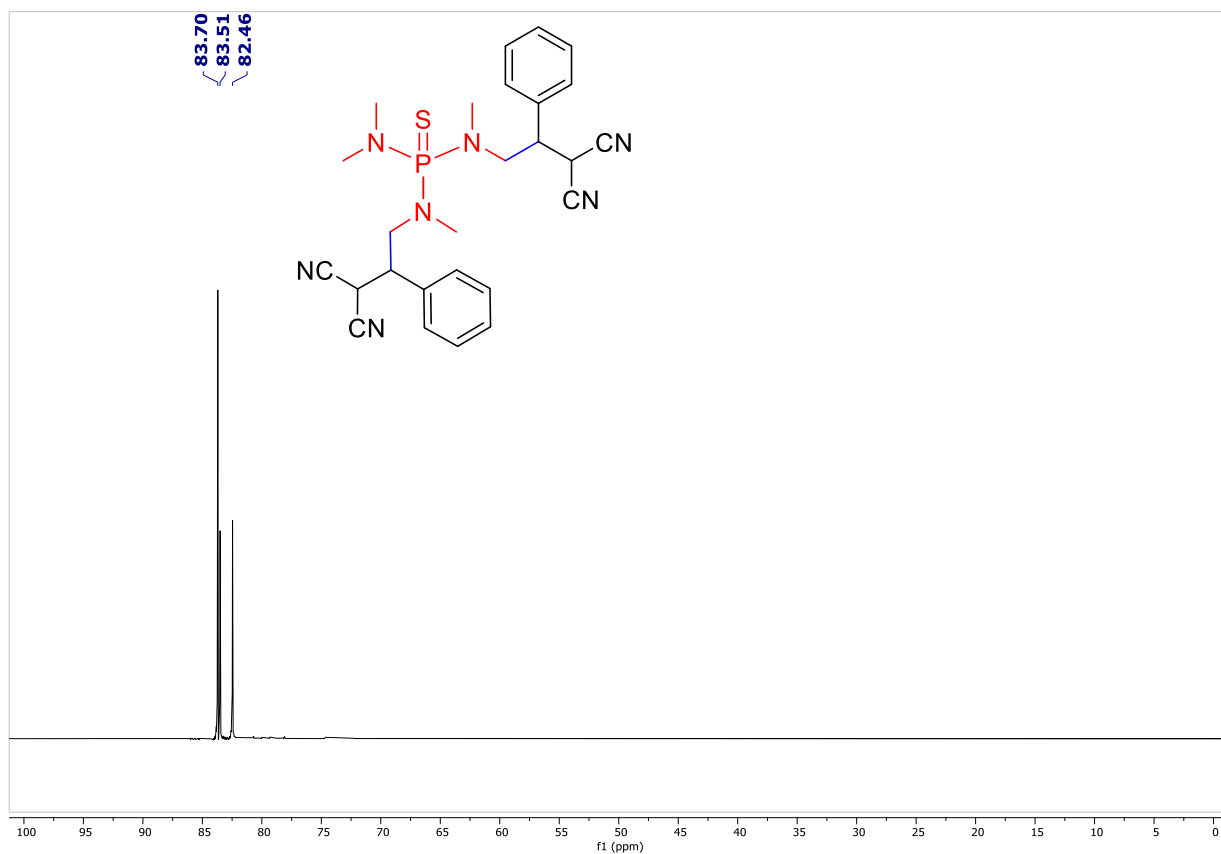
Chemical Shift (ppm)	Integration
25.68	2.00

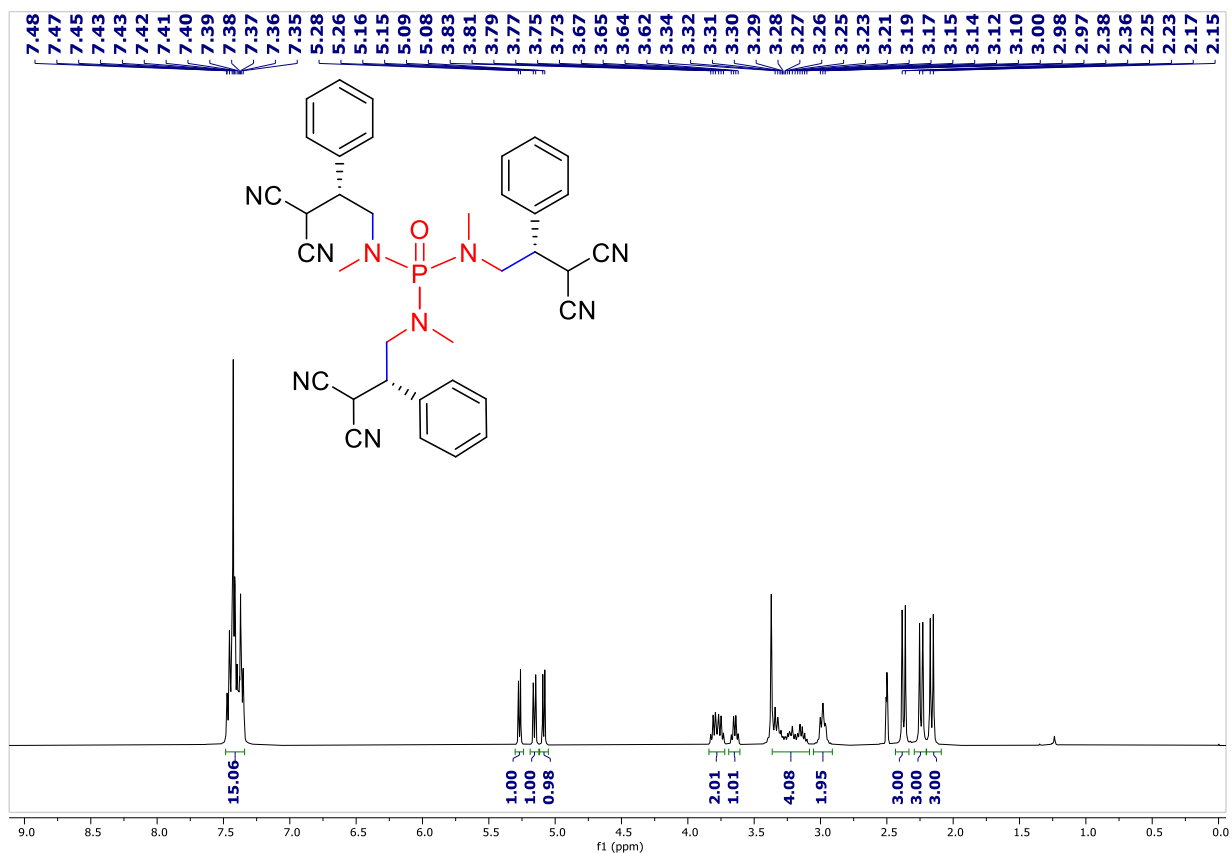
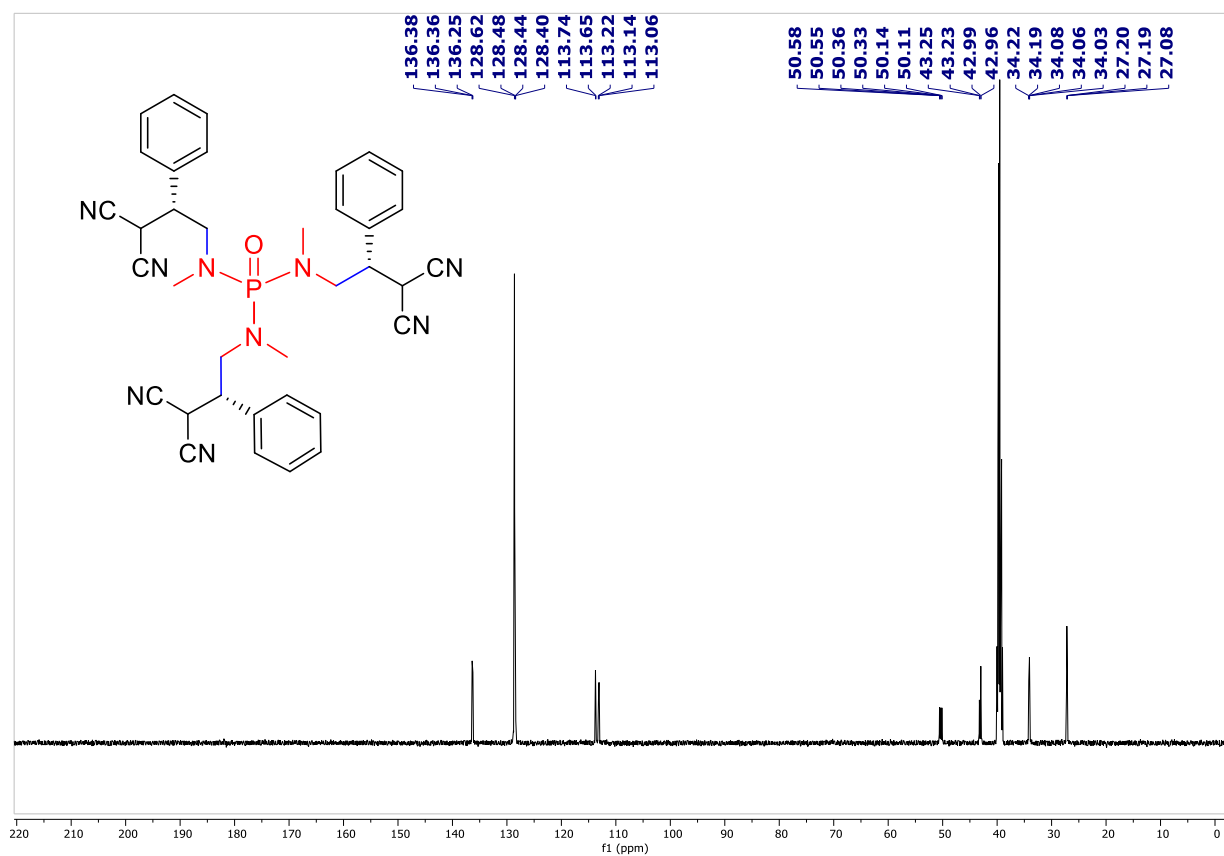
Chemical structure of the compound is shown above the spectrum. The structure is a bisphosphonate derivative, specifically a bisphosphonate salt of a bisphosphonate acid. The structure is a bisphosphonate salt of a bisphosphonate acid, specifically a bisphosphonate salt of a bisphosphonate acid. The structure is a bisphosphonate salt of a bisphosphonate acid, specifically a bisphosphonate salt of a bisphosphonate acid.

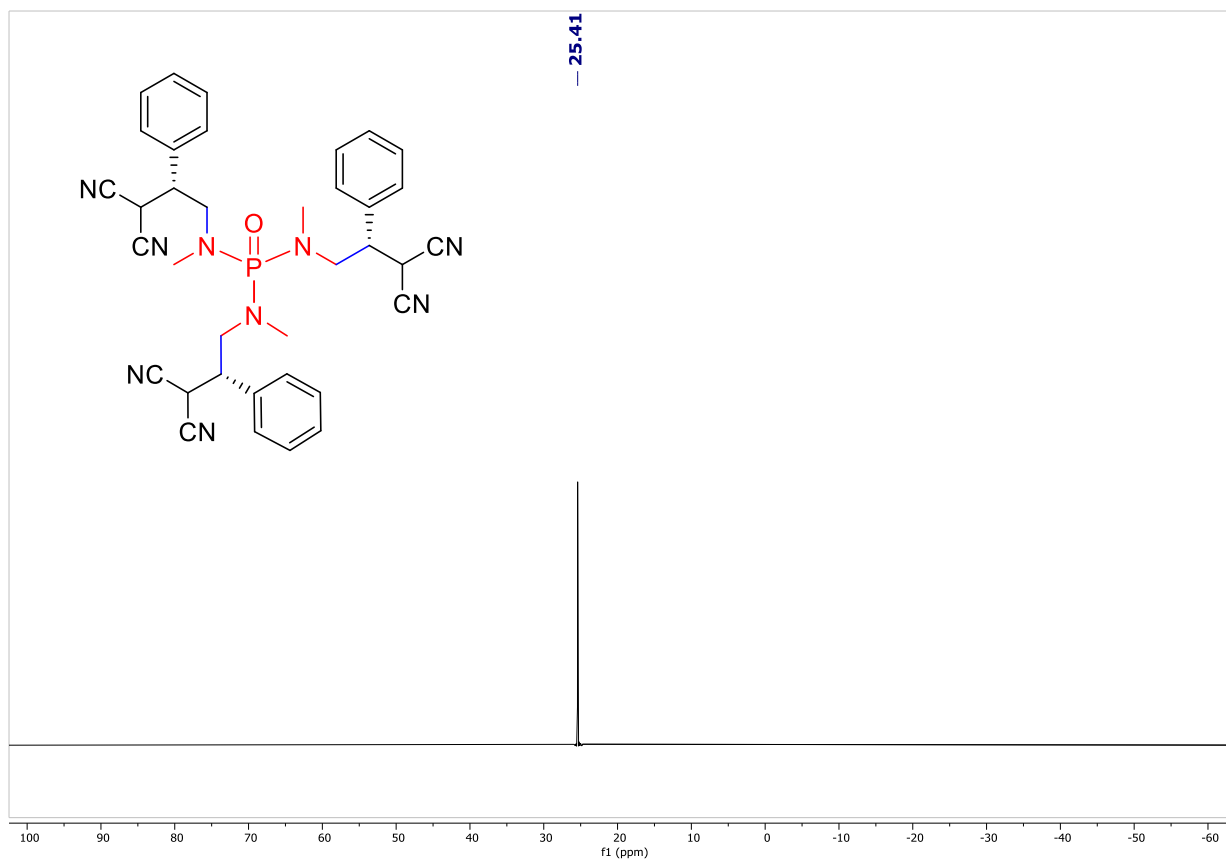
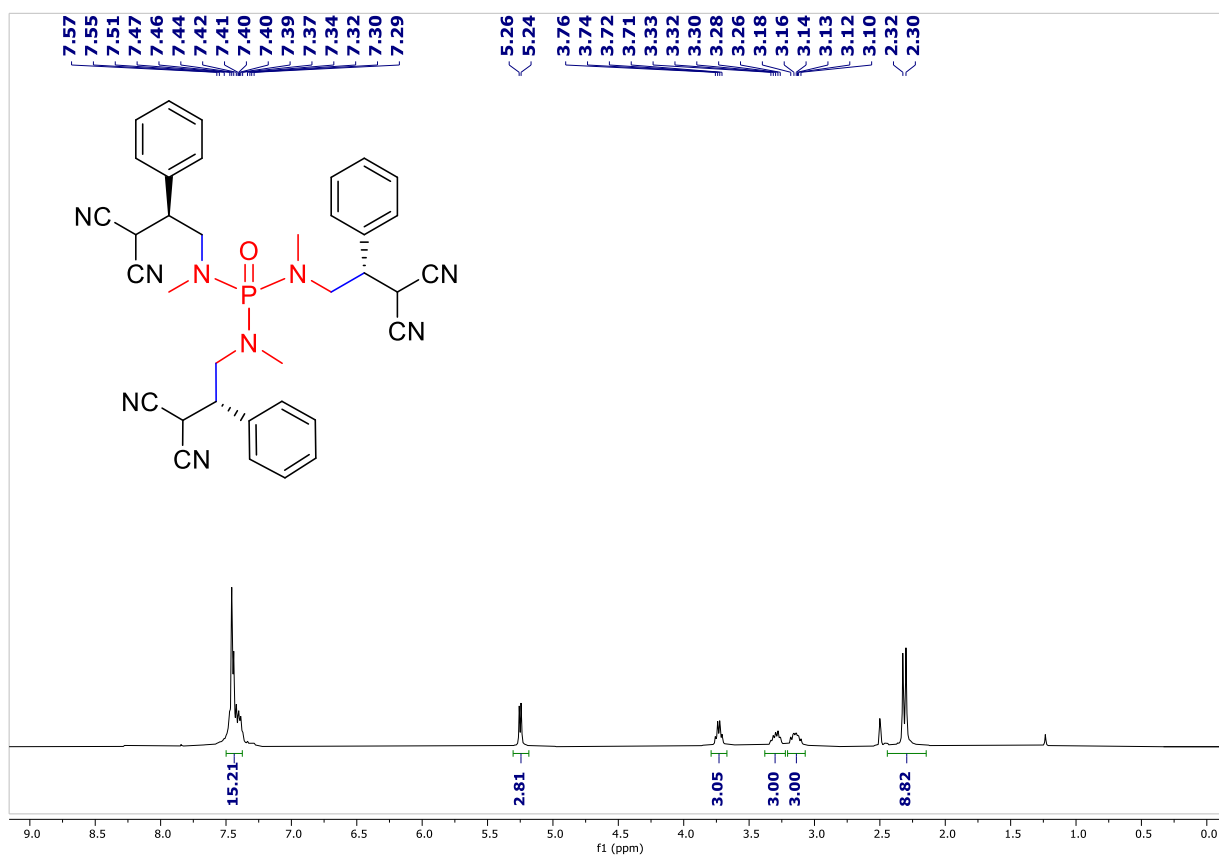
The spectrum shows a single sharp peak at approximately -61.1 ppm, which is characteristic of the phosphorus atoms in the compound. The peak is labeled with its chemical shift values: -61.10, -61.12, and -61.17 ppm.

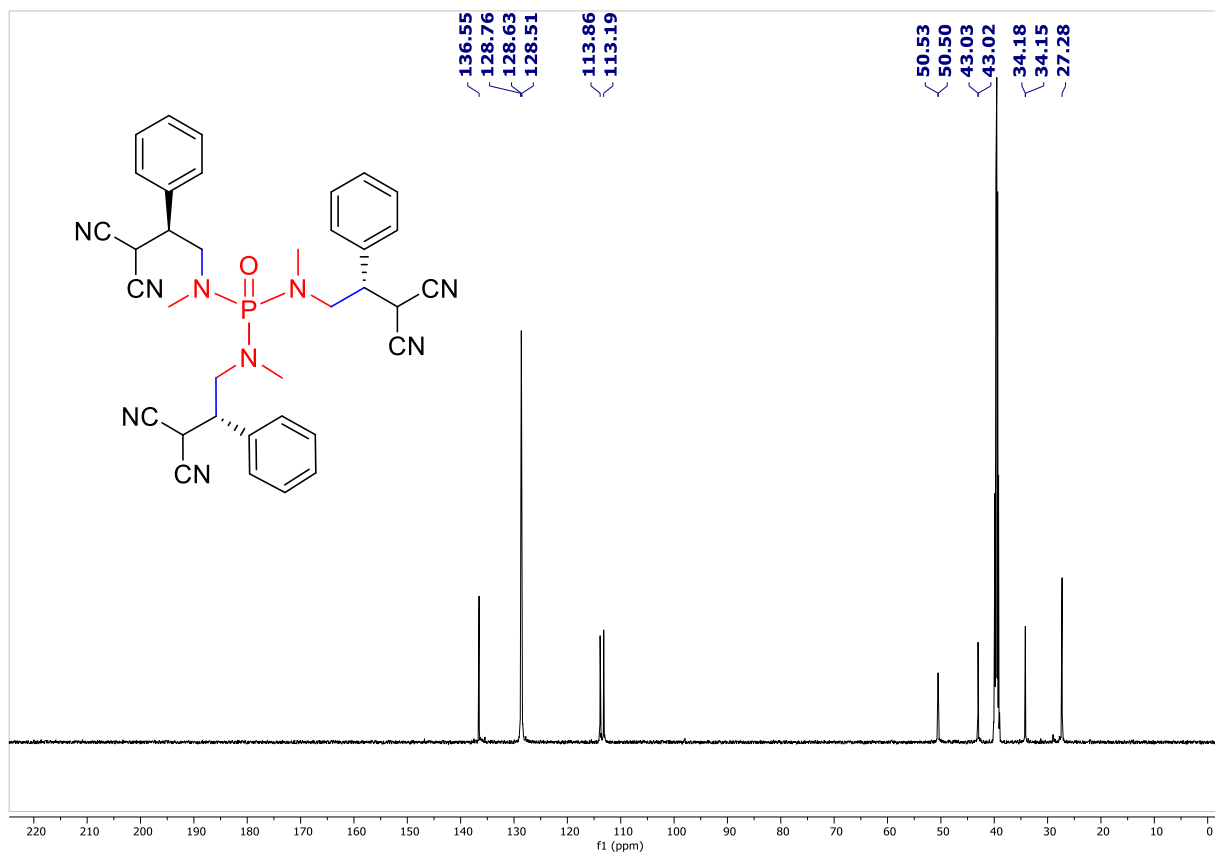
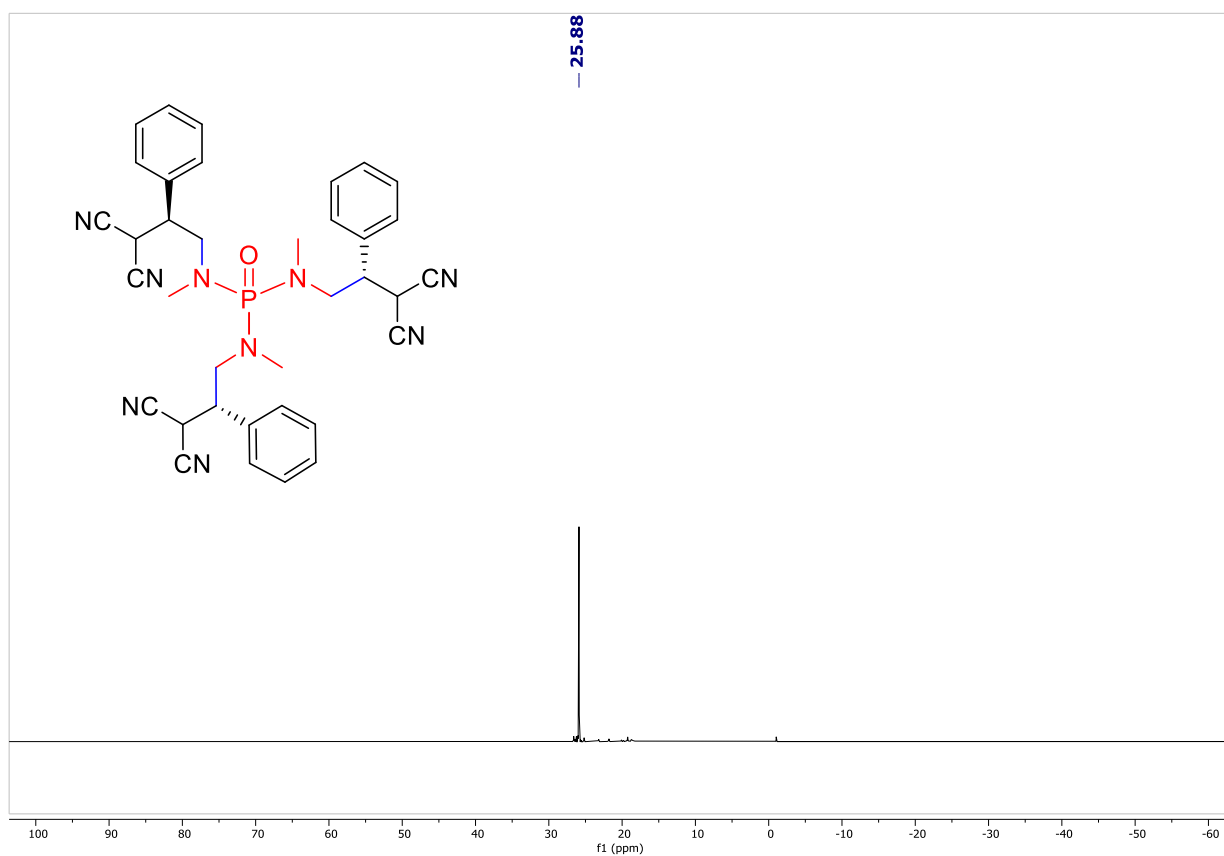
^1H NMR (400 MHz, CDCl_3) of compound **5e** $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) of compound **5e**

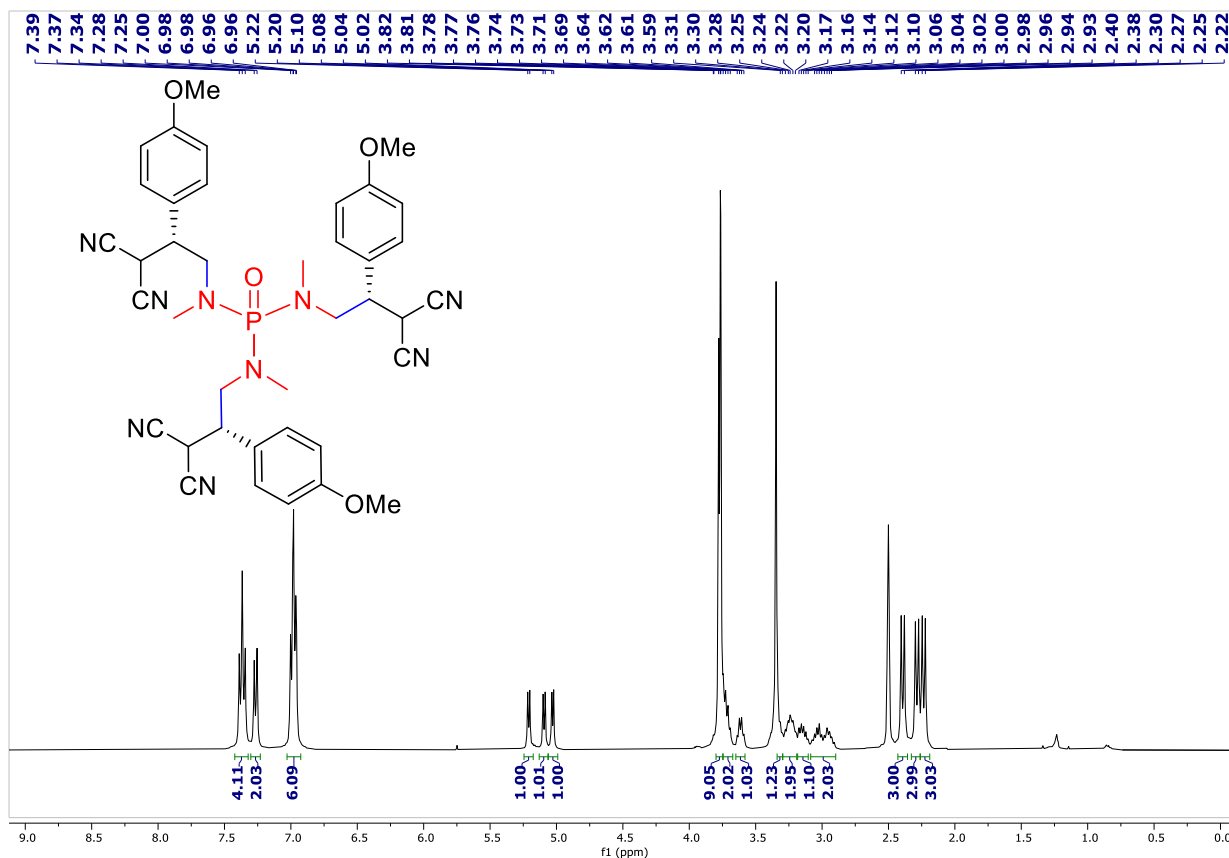
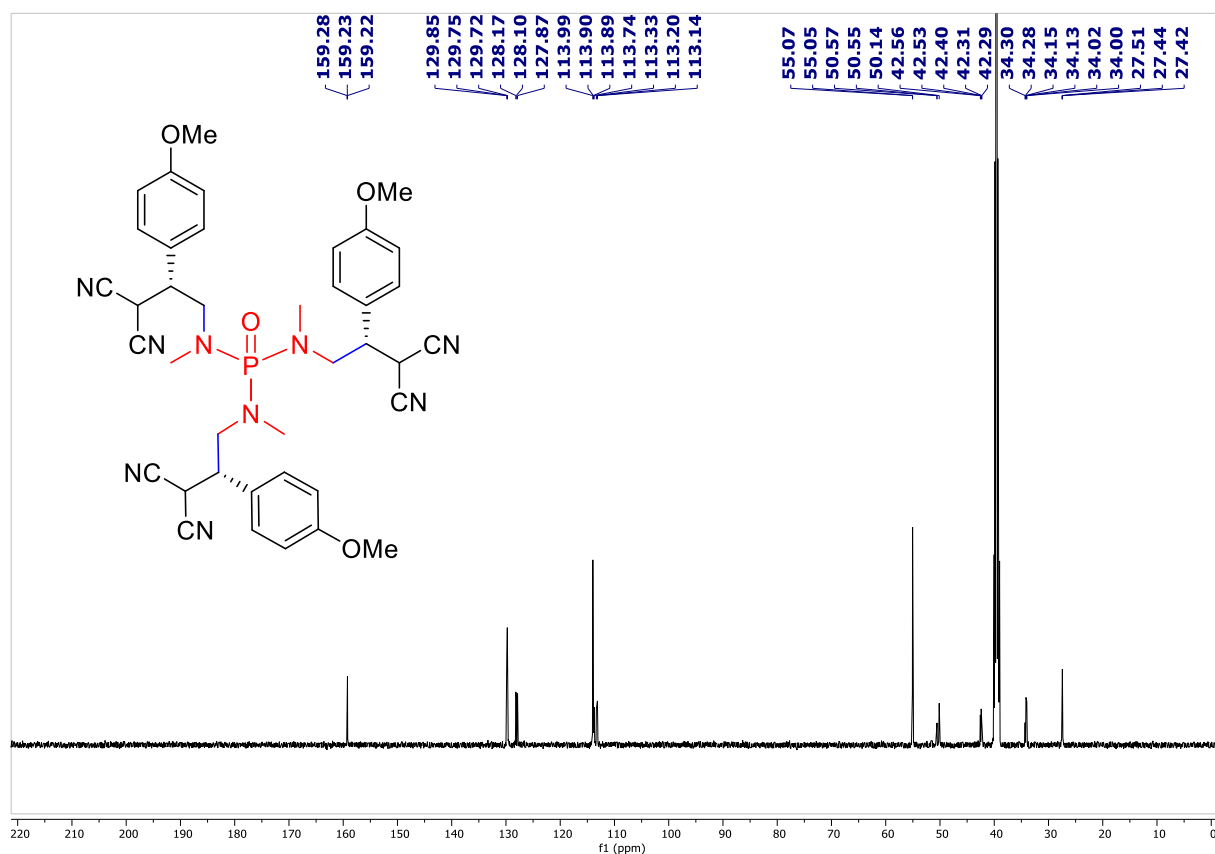
^{31}P NMR (203 MHz, $CDCl_3$) of compound **5e** 1H NMR (400 MHz, $CDCl_3$) of compound **5f**

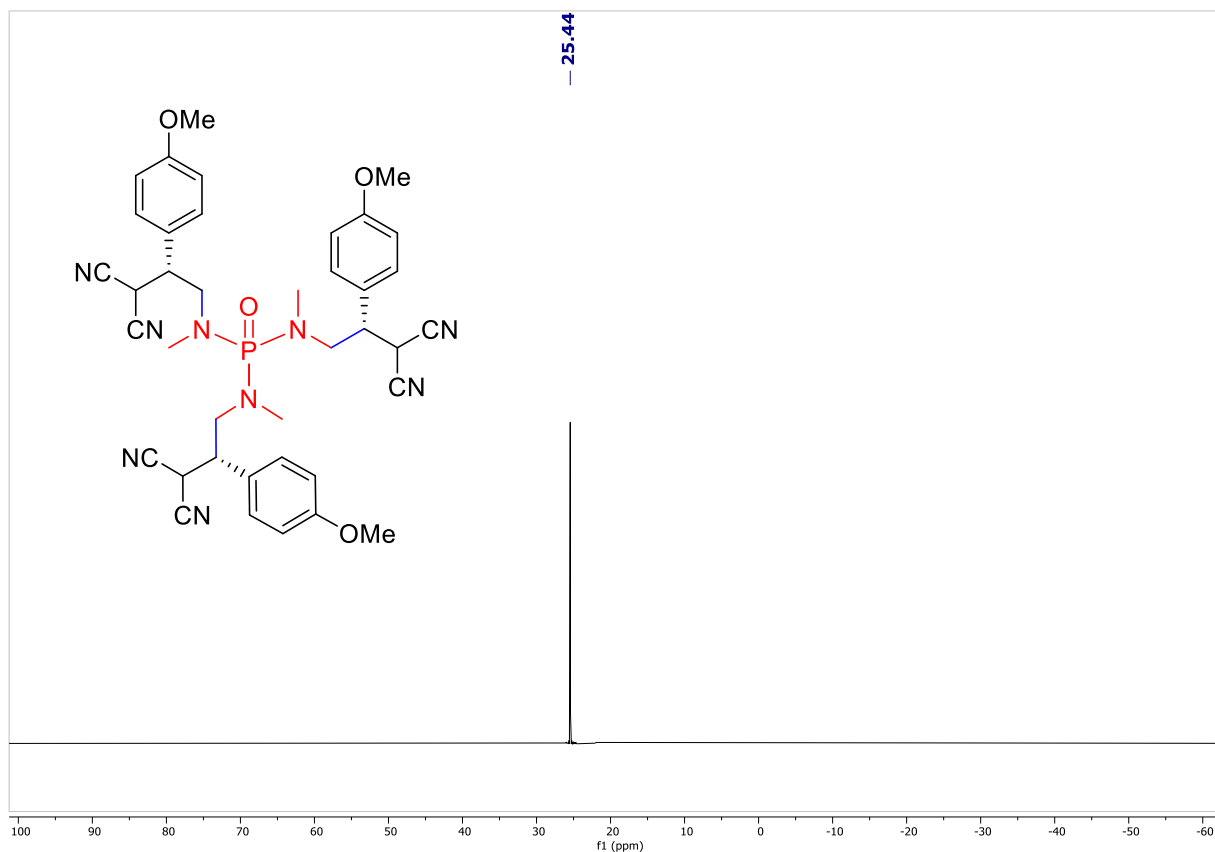
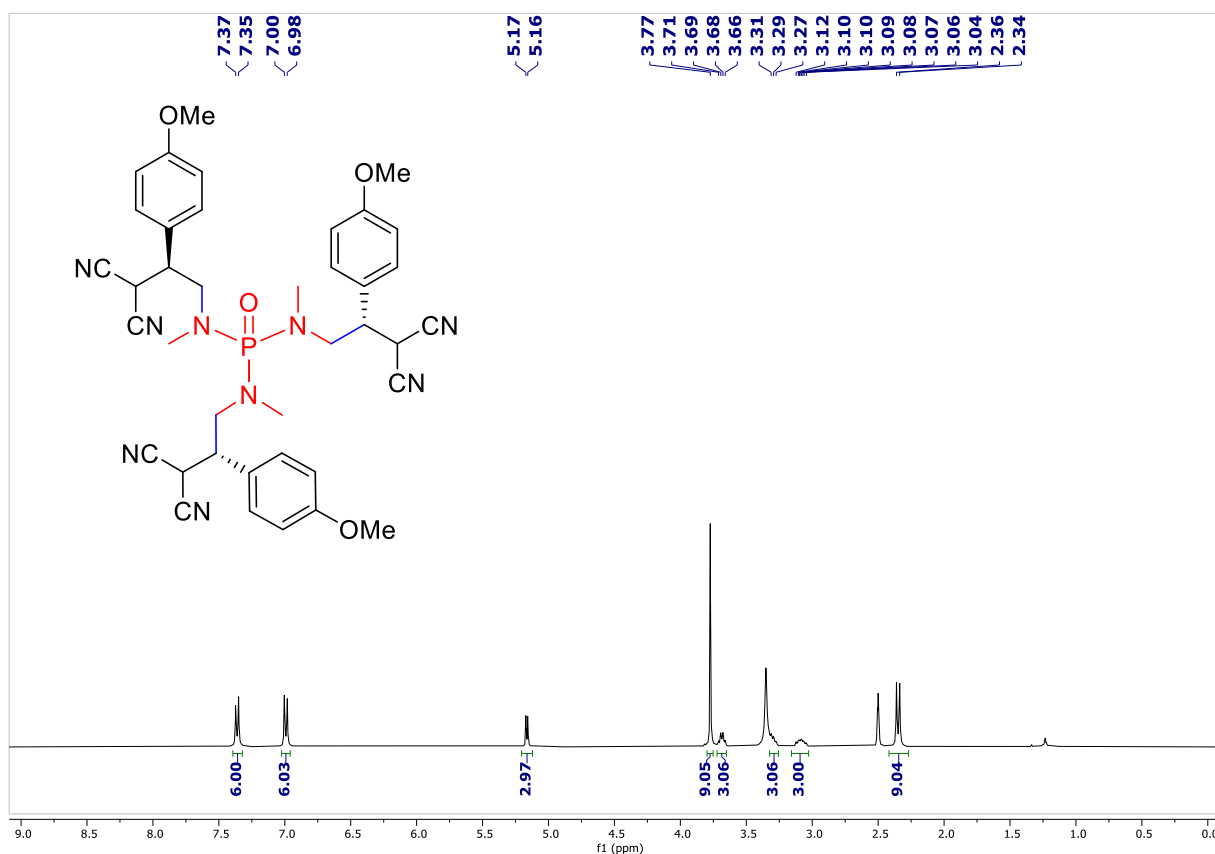
$^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) of compound **5f** ^{31}P NMR (203 MHz, $CDCl_3$) of compound **5f**

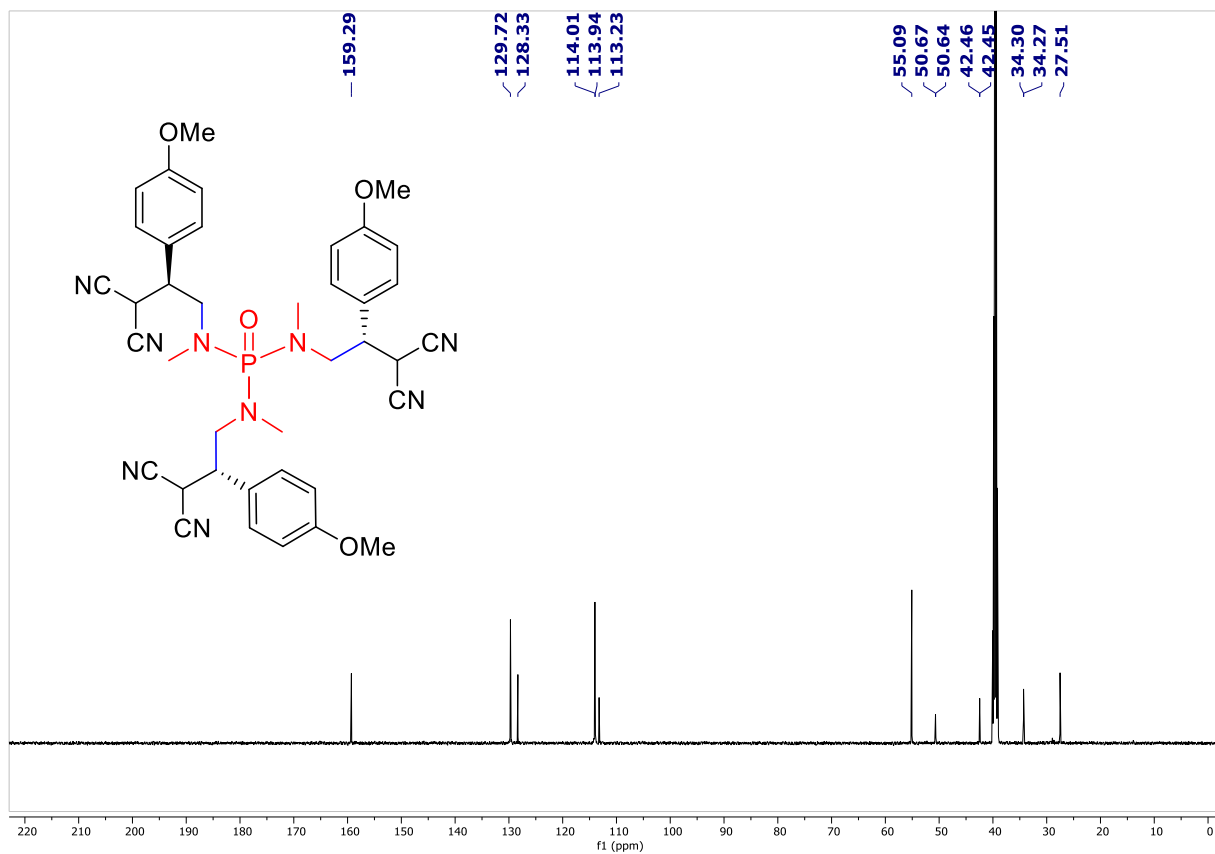
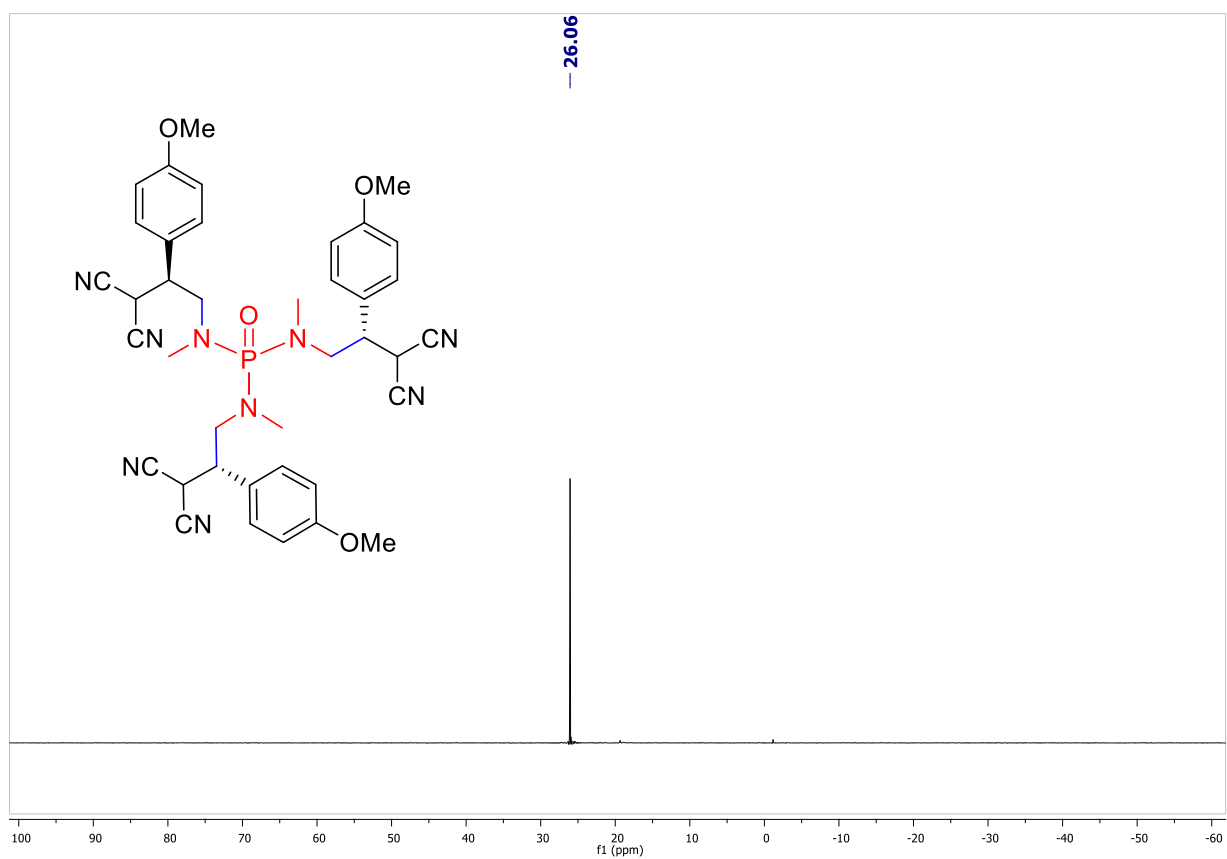
1H NMR (400 MHz, $DMSO-d_6$) of compound major (\pm)-6a' $^{13}C\{^1H\}$ NMR (126 MHz, $DMSO-d_6$) of compound major (\pm)-6a'

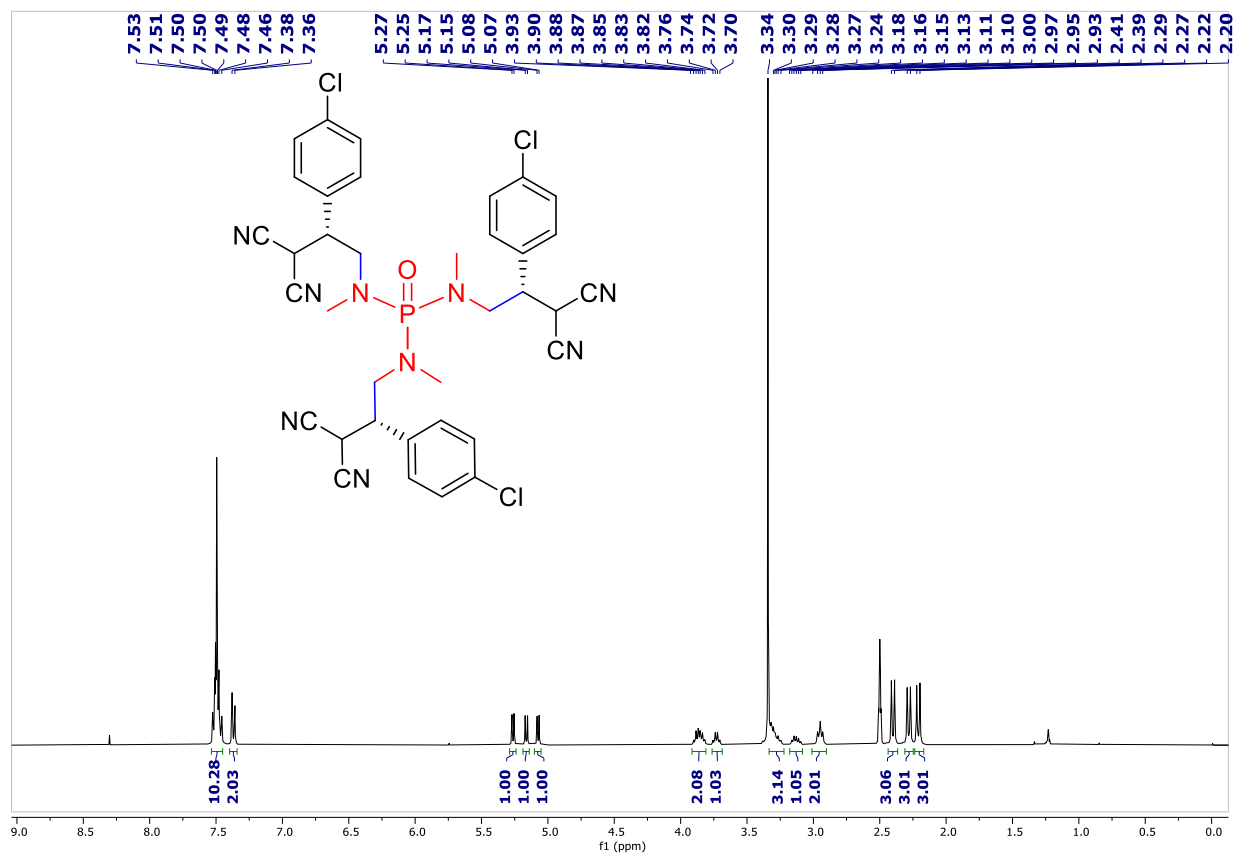
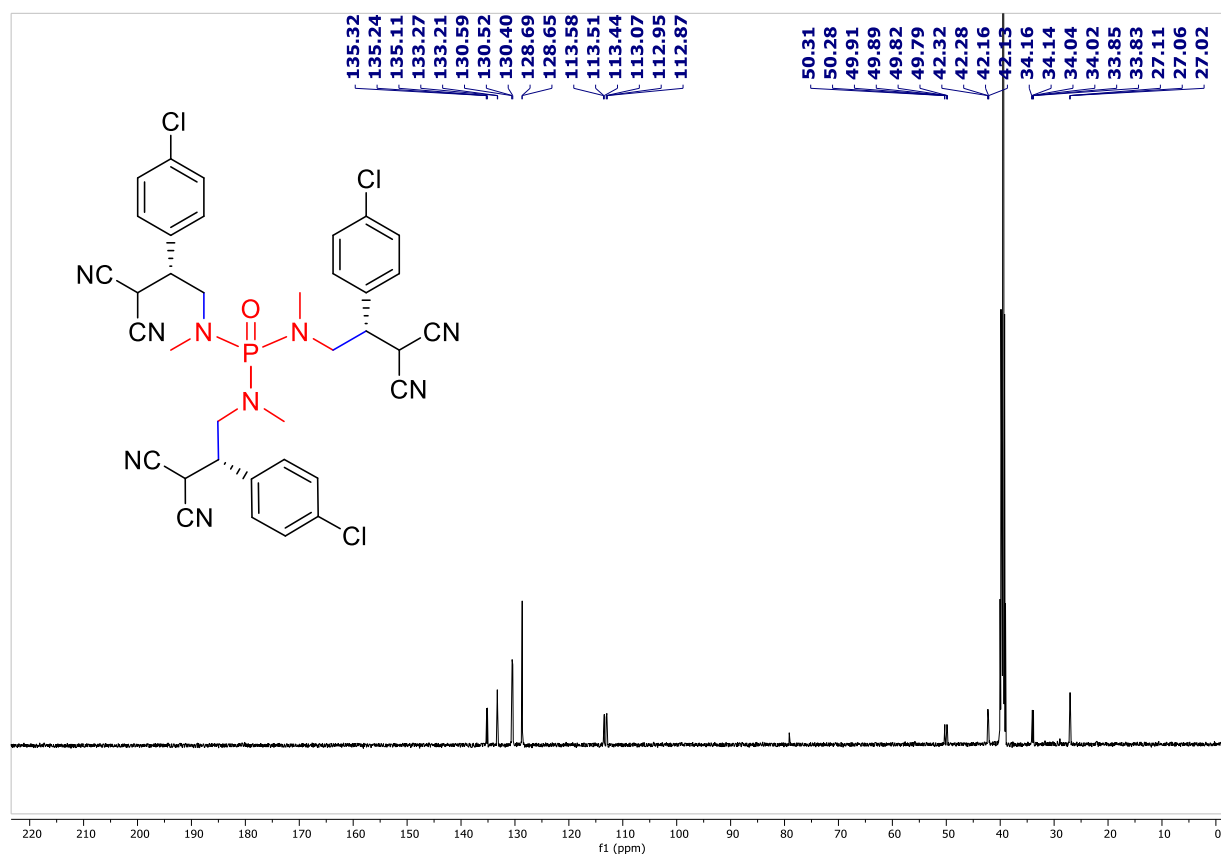
^{31}P NMR (203 MHz, $DMSO-d_6$) of compound major (\pm)-6a' 1H NMR (400 MHz, $DMSO-d_6$) of compound minor (\pm)-6a''

$^{13}C\{^1H\}$ NMR (126 MHz, $DMSO-d_6$) of compound minor (\pm)-**6a''** ^{31}P NMR (203 MHz, $DMSO-d_6$) of compound minor (\pm)-**6a''**

1H NMR (400 MHz, $DMSO-d_6$) of compound major (\pm)-**6b'** $^{13}C\{^1H\}$ NMR (126 MHz, $DMSO-d_6$) of compound major (\pm)-**6b'**

^{31}P NMR (203 MHz, $DMSO-d_6$) of compound major (\pm)-**6b'** 1H NMR (400 MHz, $DMSO-d_6$) of compound minor (\pm)-**6b''**

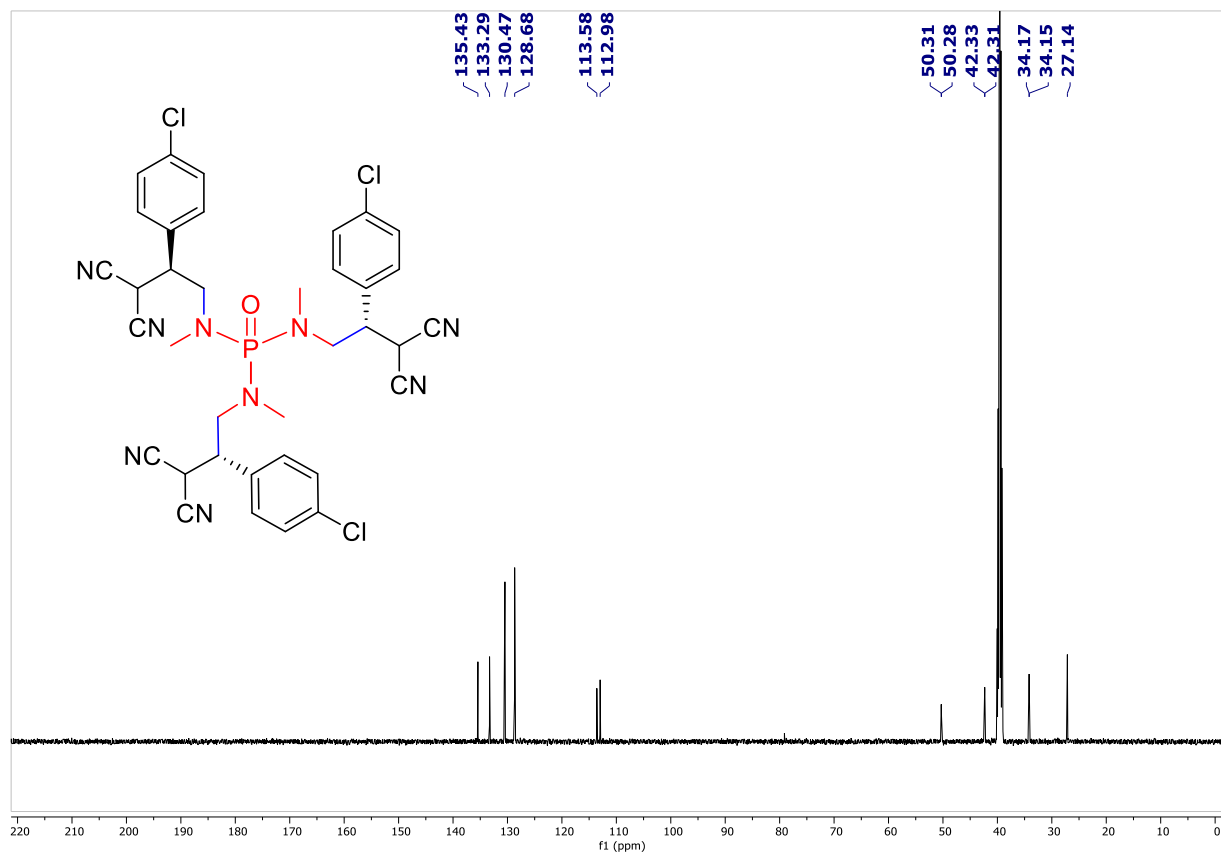
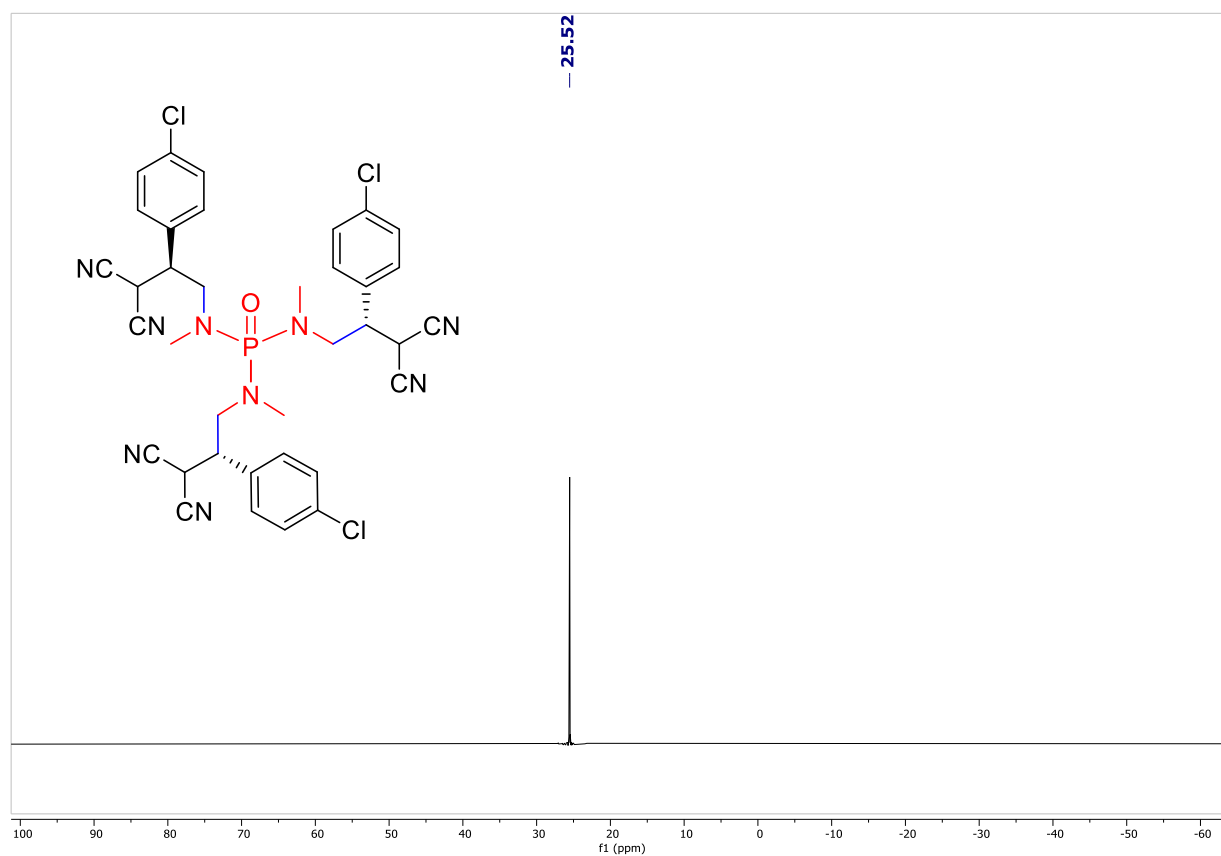
$^{13}C\{^1H\}$ NMR (126 MHz, $DMSO-d_6$) of compound minor (\pm)-**6b''** ^{31}P NMR (203 MHz, $DMSO-d_6$) of compound minor (\pm)-**6b''**

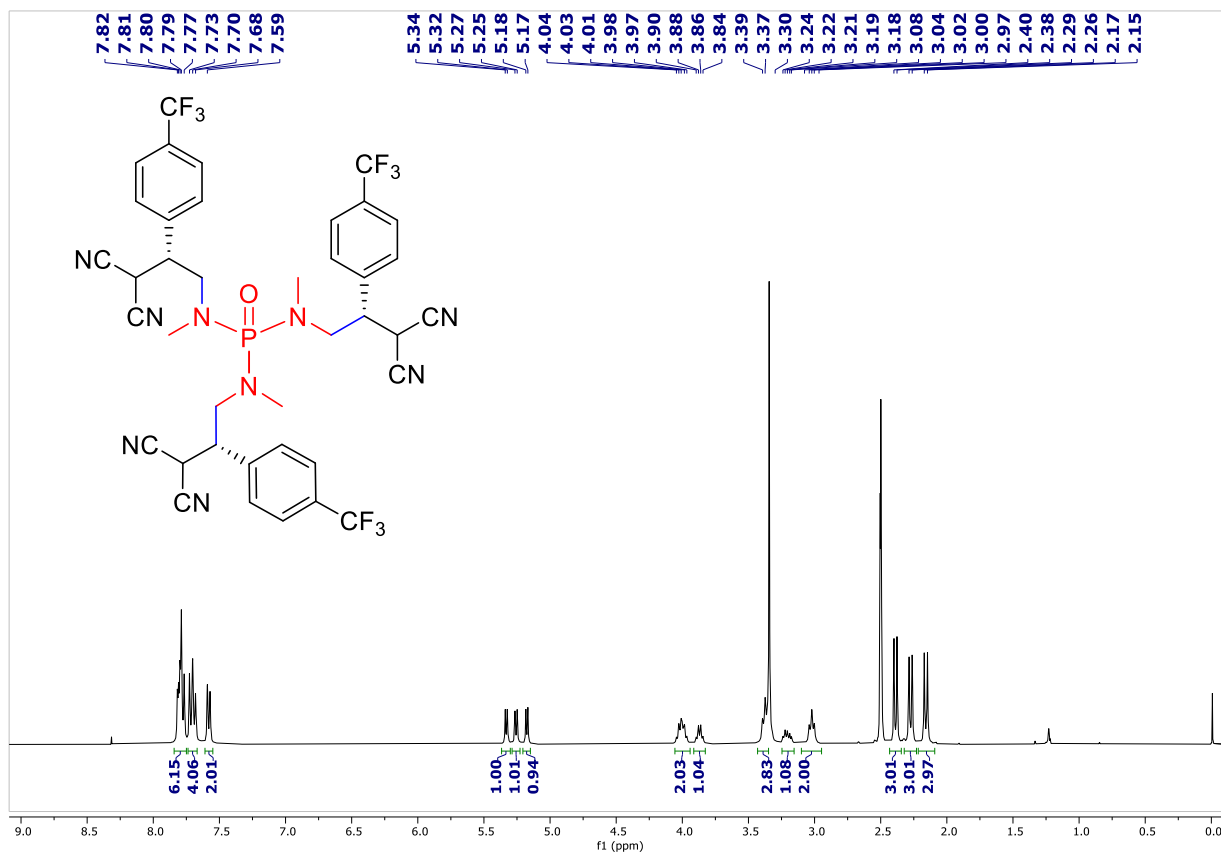
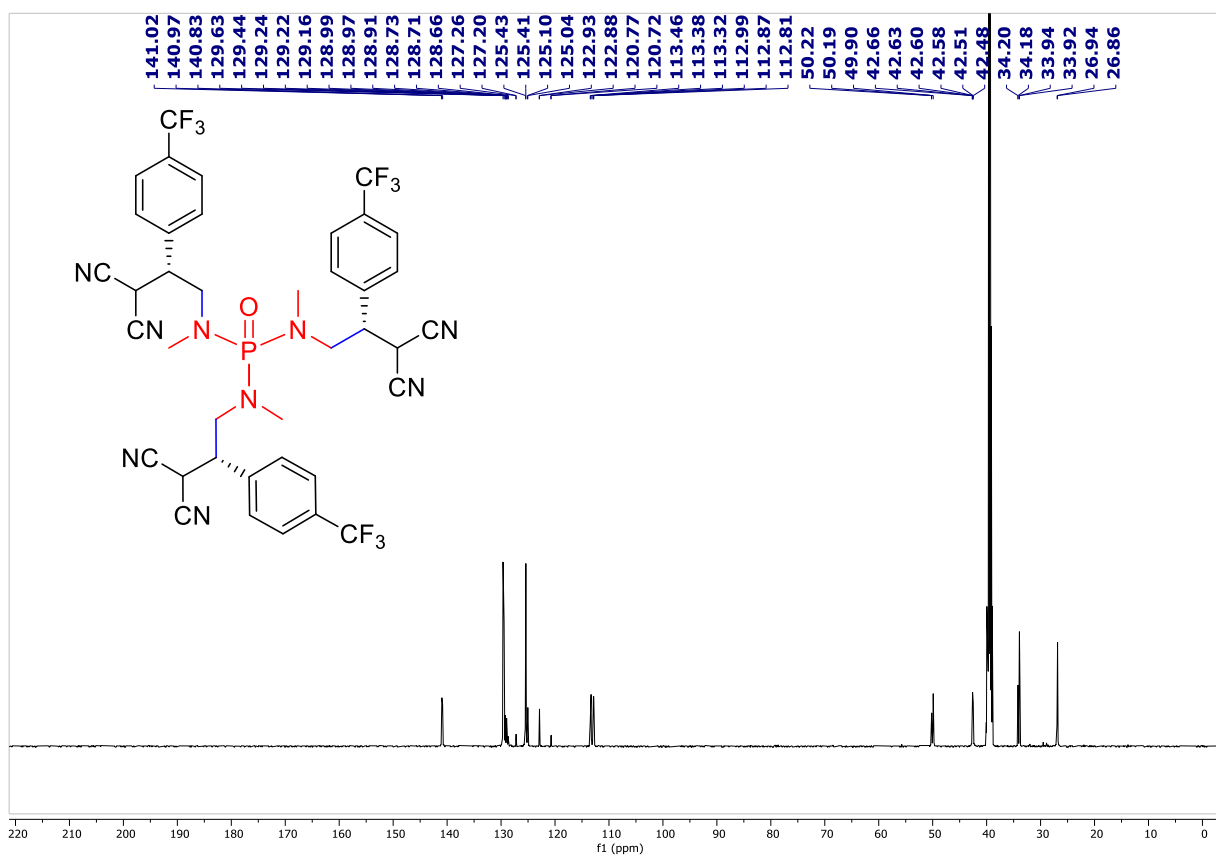
^1H NMR (400 MHz, $\text{DMSO}-d_6$) of compound major (\pm)-6c' $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, $\text{DMSO}-d_6$) of compound major (\pm)-6c'

Chemical structure of the compound is shown above the spectrum. The structure is a phosphazene derivative, specifically a bis-phosphazene compound. It features a central phosphorus atom (P) double-bonded to an oxygen atom (O) and single-bonded to three nitrogen atoms (N). The phosphorus atom is also bonded to a fourth nitrogen atom (N) which is part of a five-membered ring. The structure includes three 4-chlorophenyl groups and three 2,2-dicyanomethyl groups. The chemical structure is shown in a 3D representation with stereochemistry indicated by wedges and dashes.

The spectrum shows a single sharp peak at 25.26 ppm, which is labeled with its chemical shift value. The x-axis is labeled "f1 (ppm)" and ranges from 100 to -60 ppm. The y-axis represents intensity.

[illegible]

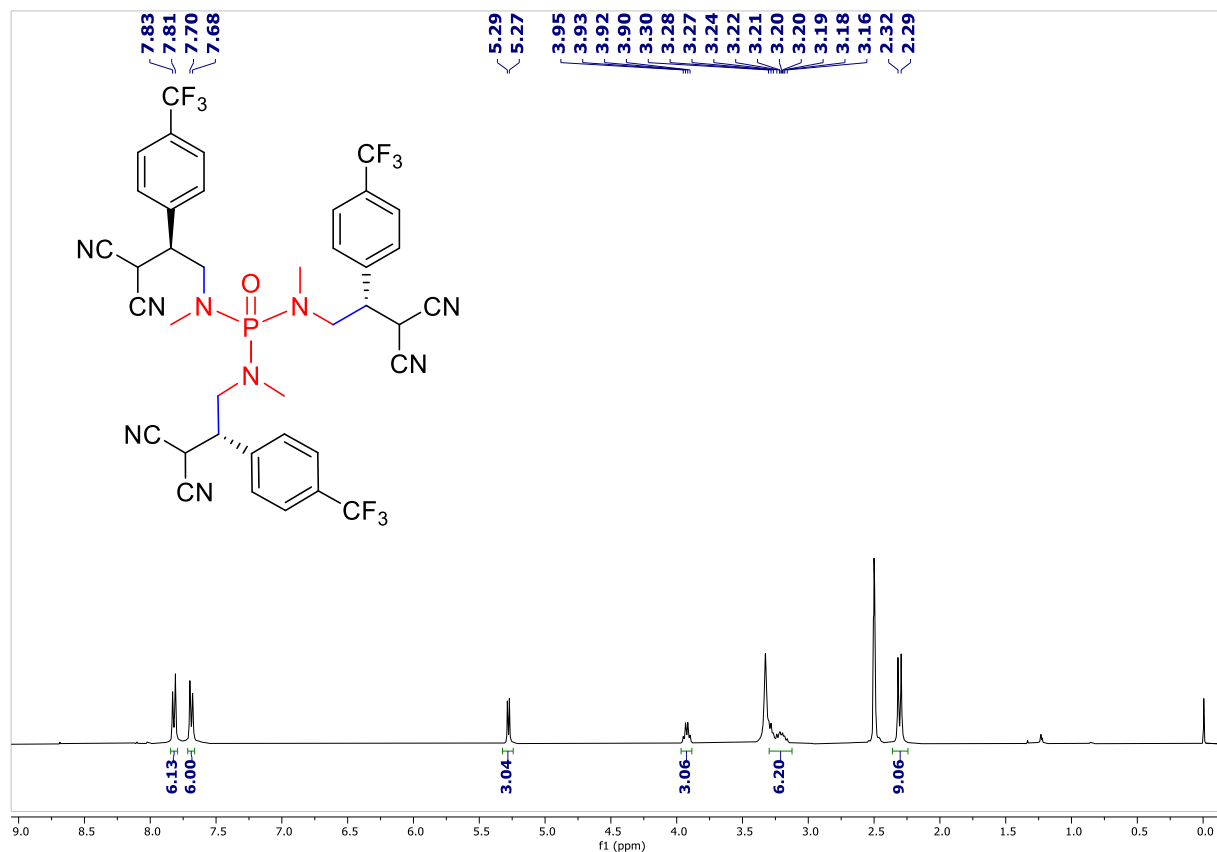
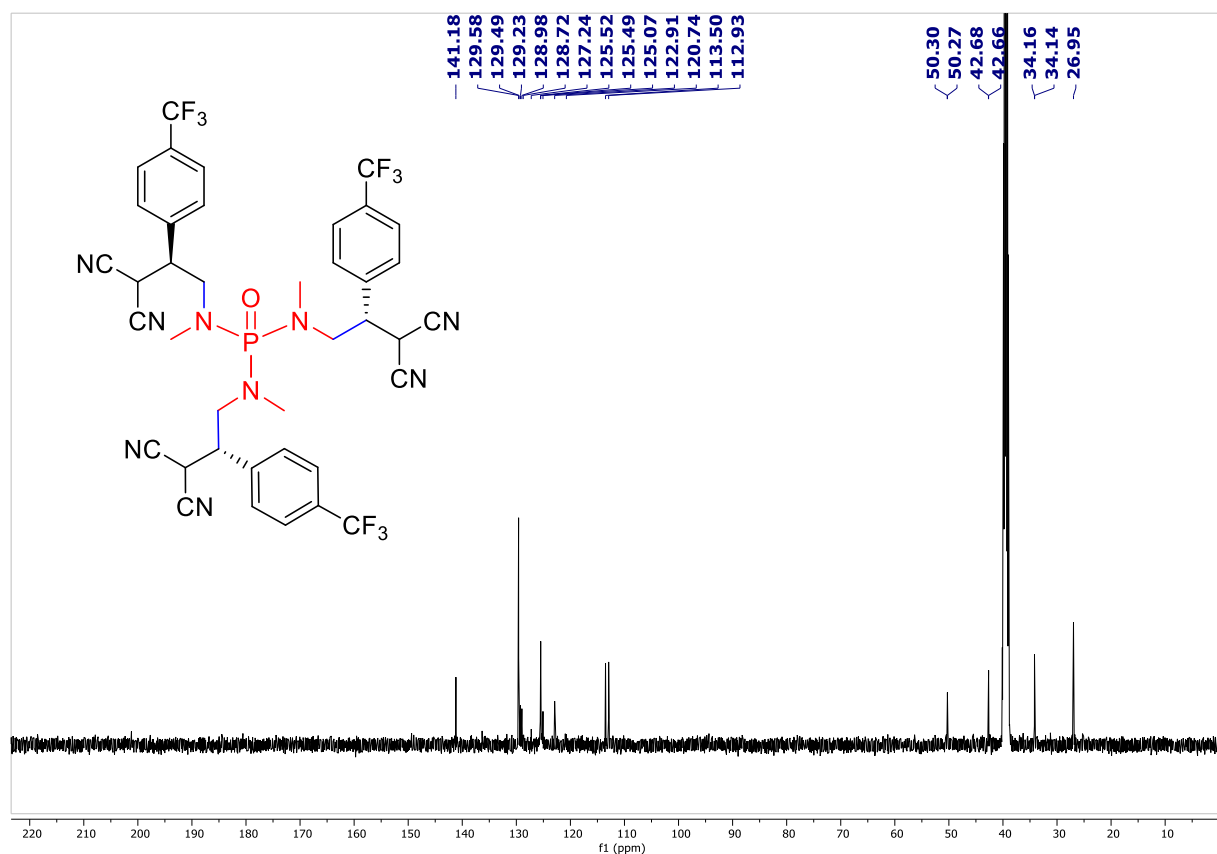
$^{13}C\{^1H\}$ NMR (126 MHz, $DMSO-d_6$) of compound minor (\pm)-6c'' ^{31}P NMR (203 MHz, $DMSO-d_6$) of compound minor (\pm)-6c''

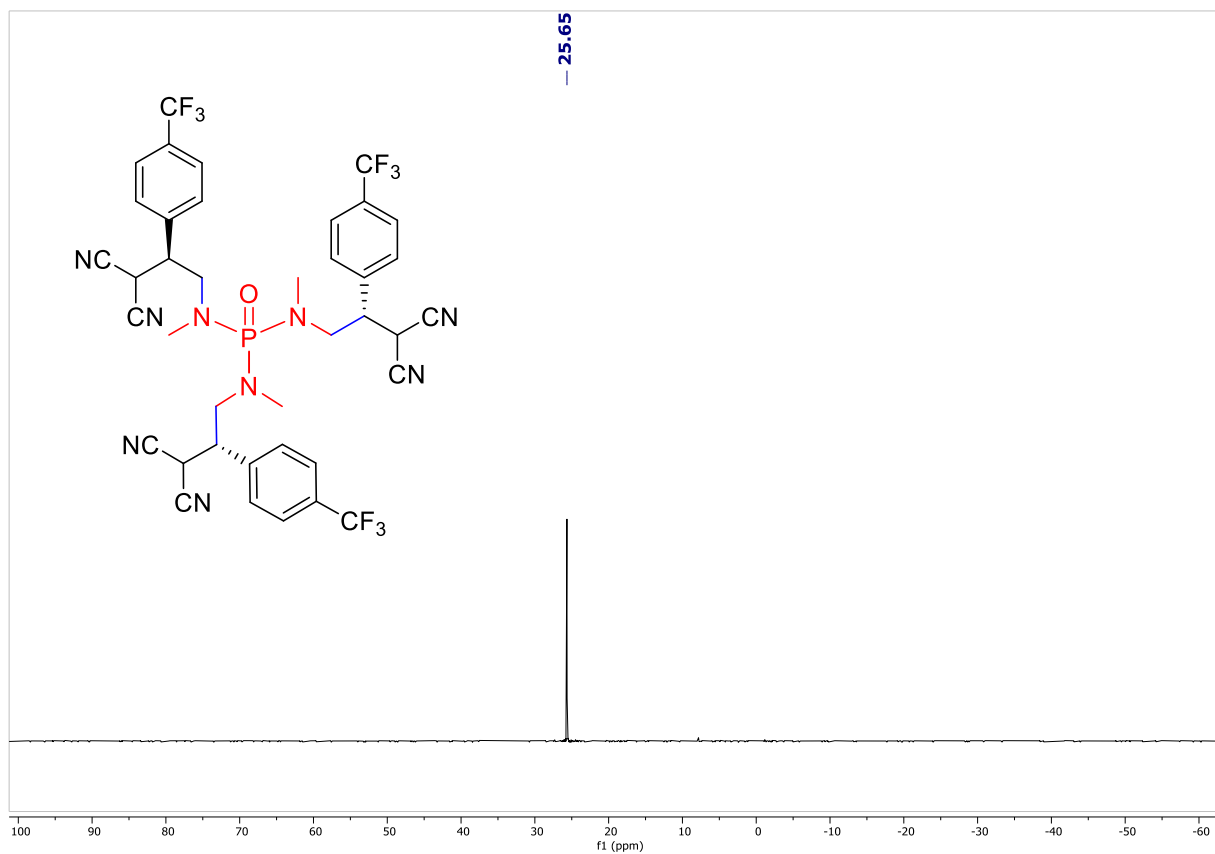
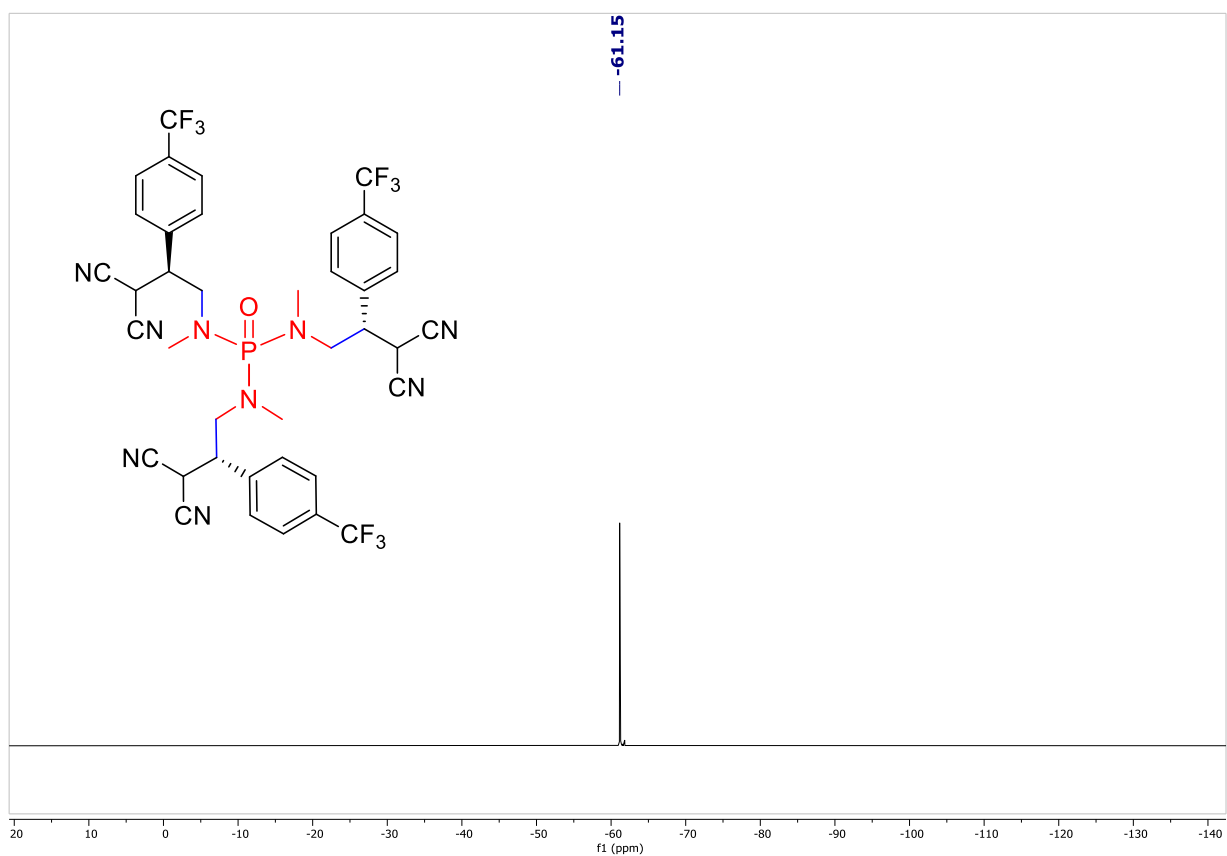
1H NMR (400 MHz, DMSO- d_6) of compound major (\pm)-**6d'** $^{13}C\{^1H\}$ NMR (126 MHz, DMSO- d_6) of compound major (\pm)-**6d'**

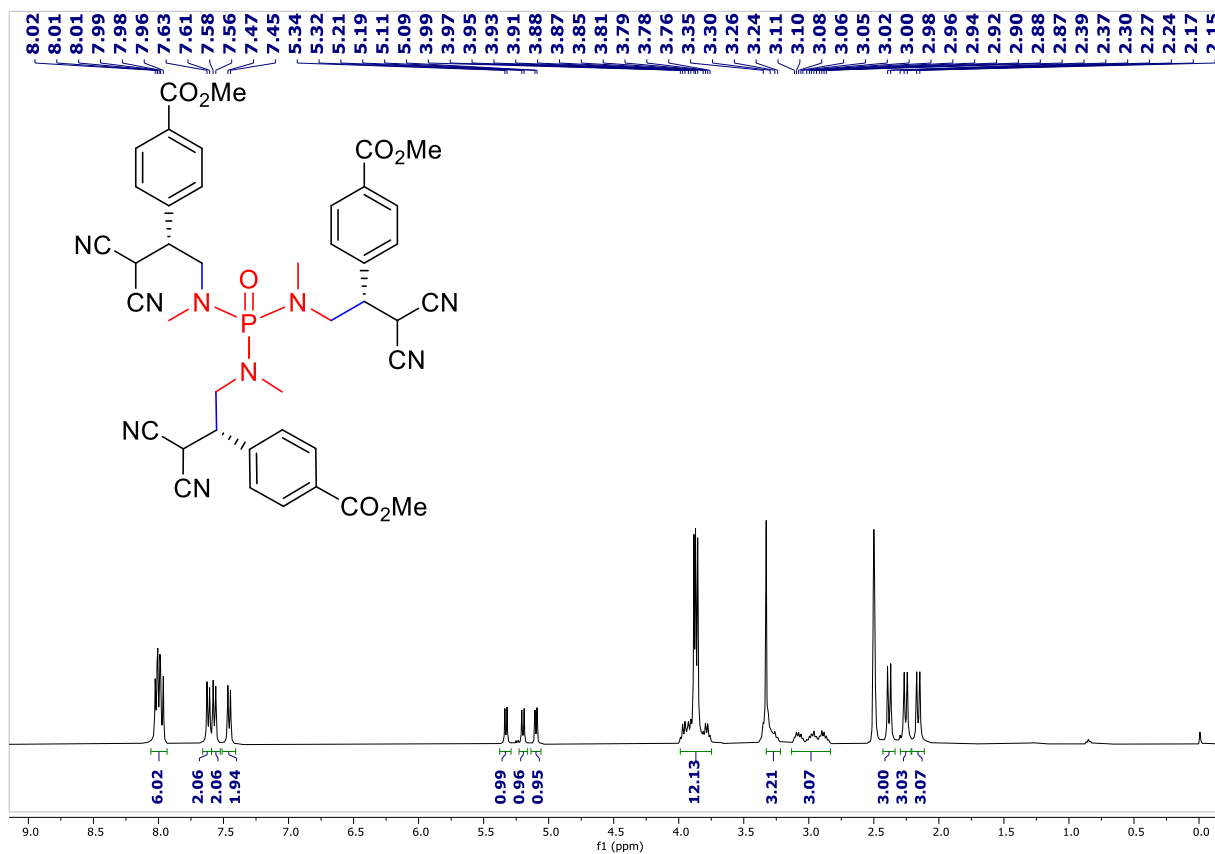
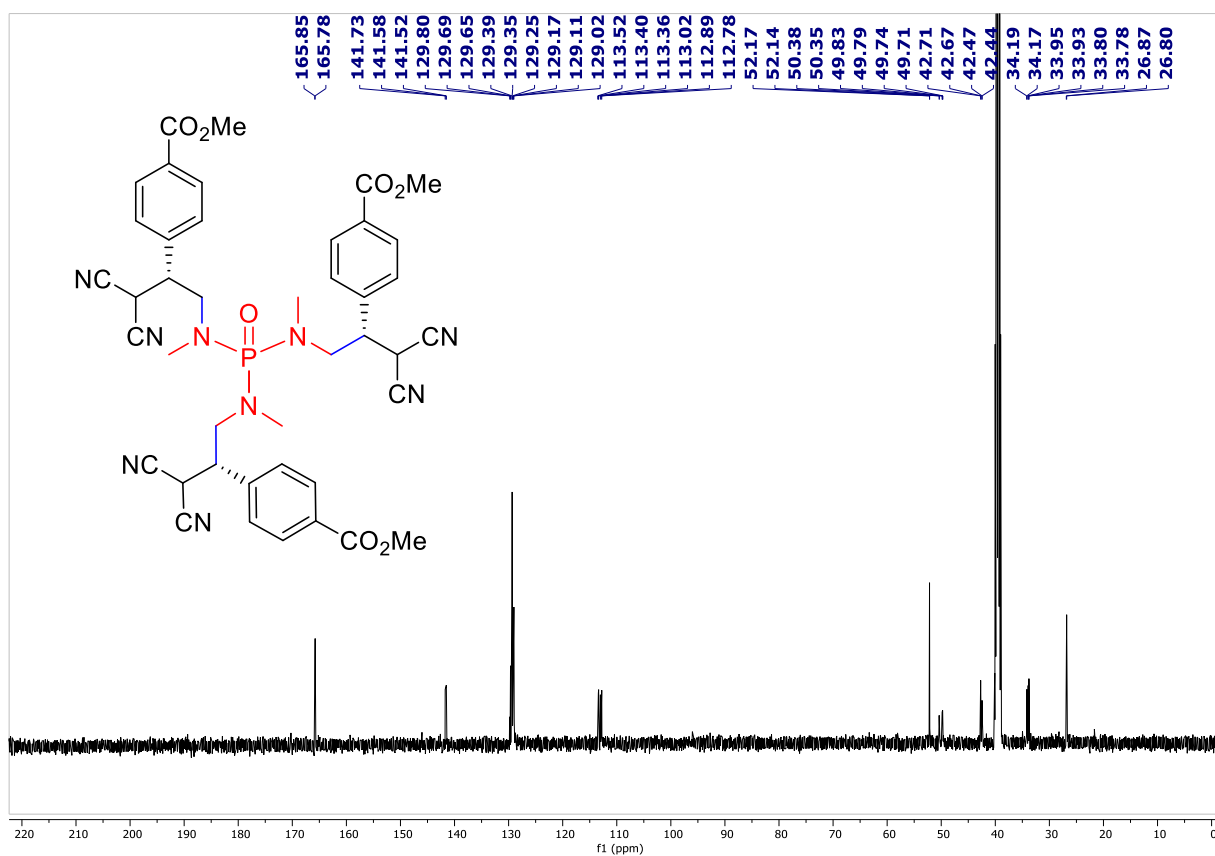
[illegible]

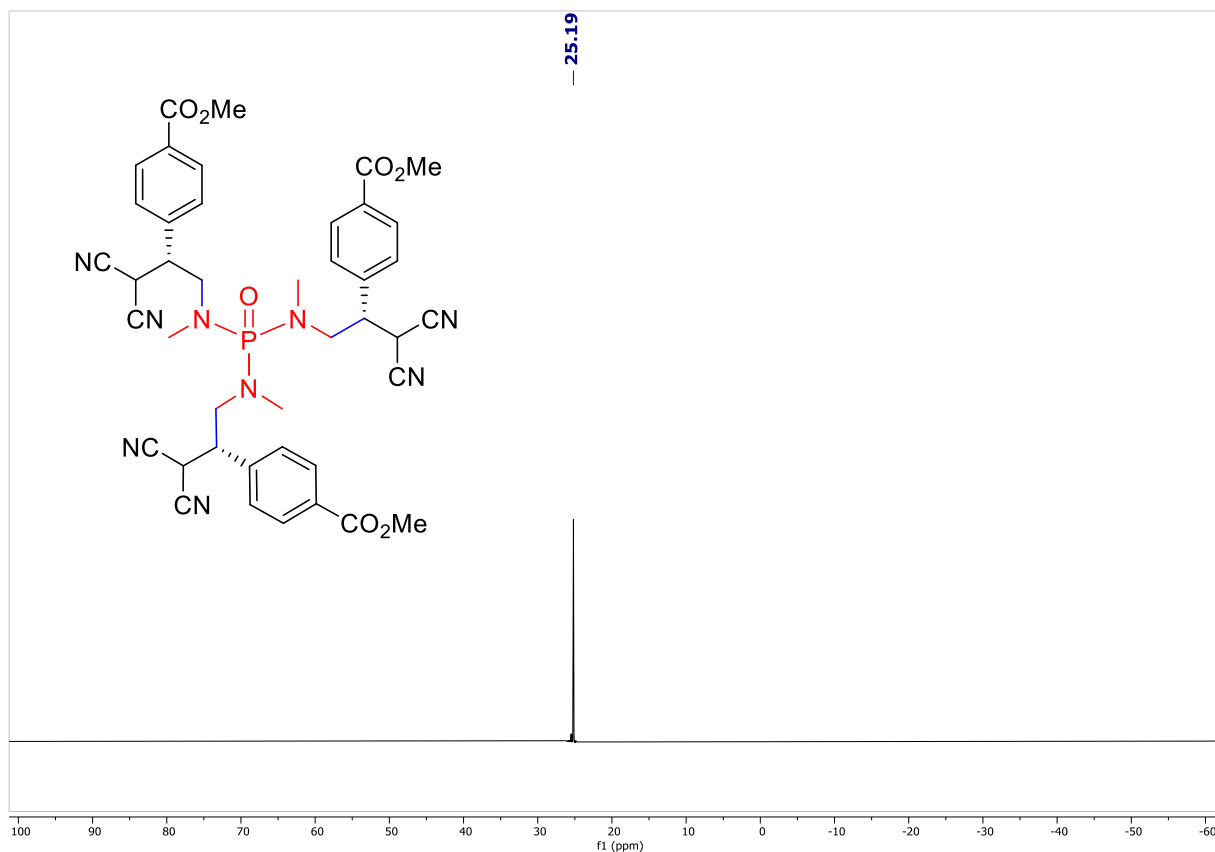
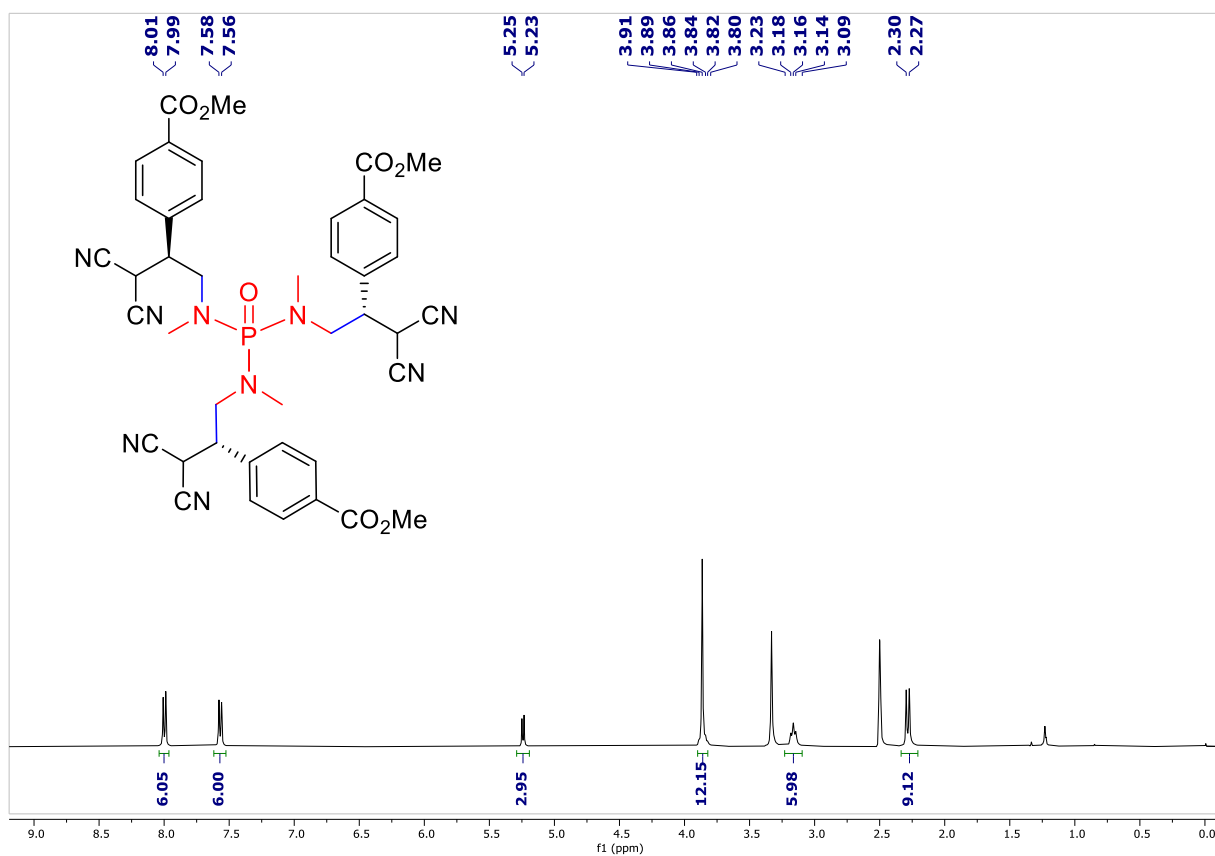
Chemical structure of the compound is shown above the spectrum. The structure is a bis-phosphonate derivative, specifically a bis-phosphonate salt of a bis-phosphonate derivative. The structure is a bis-phosphonate derivative, specifically a bis-phosphonate salt of a bis-phosphonate derivative. The structure is a bis-phosphonate derivative, specifically a bis-phosphonate salt of a bis-phosphonate derivative.

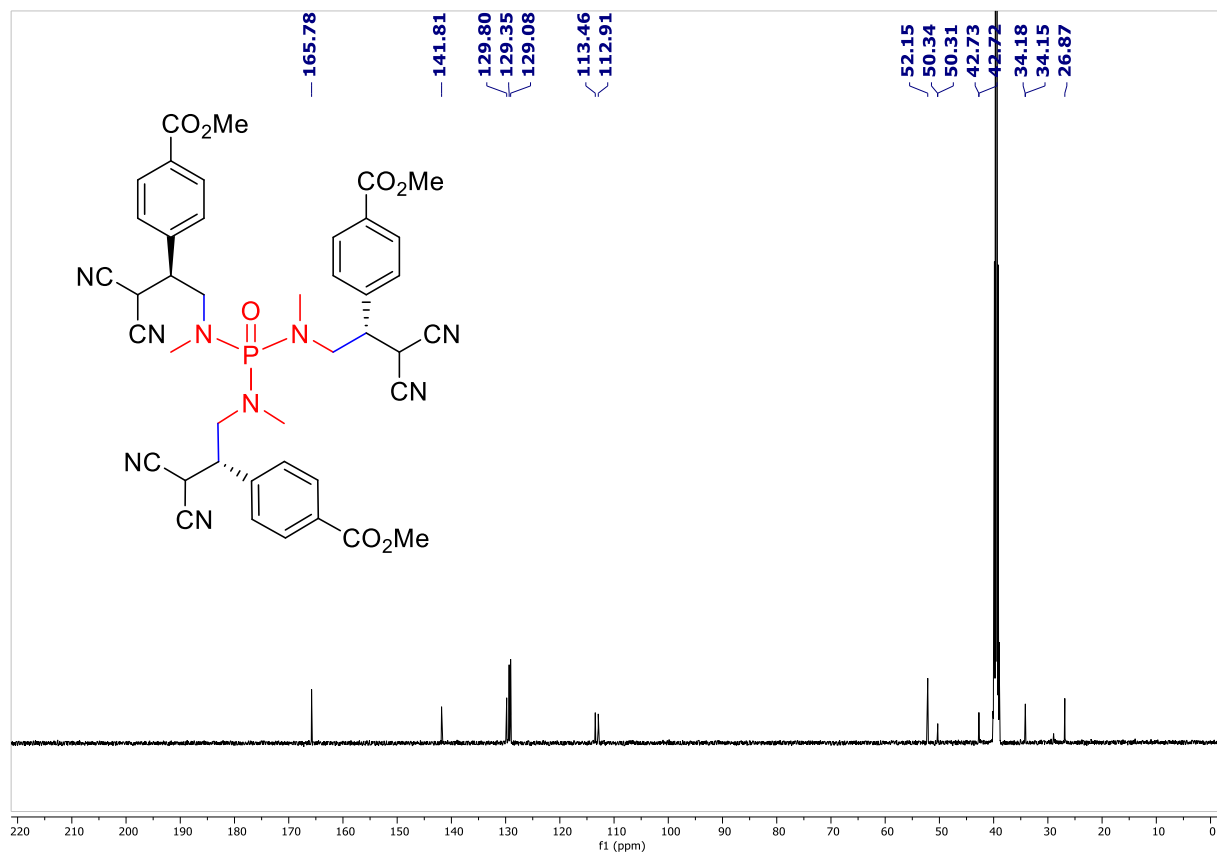
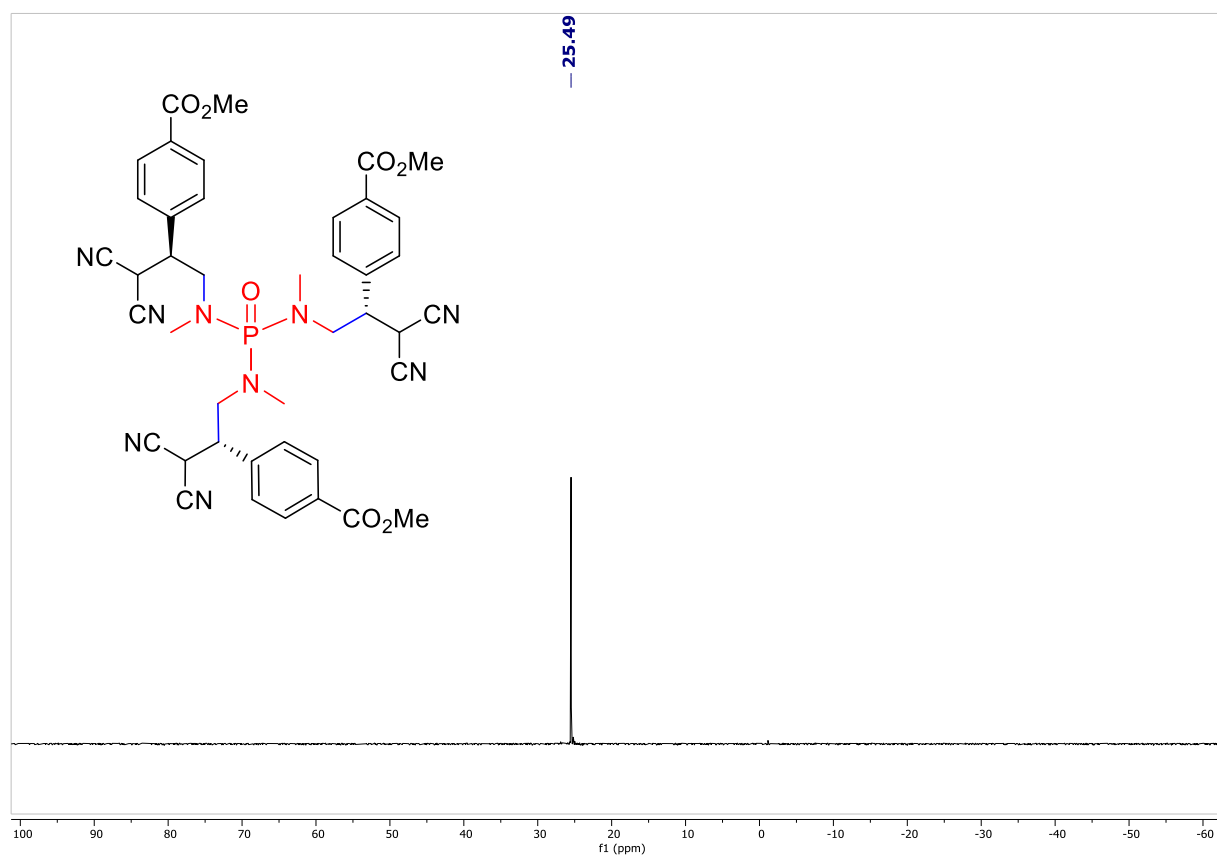
The spectrum shows a single sharp peak at approximately 61.1 ppm, which is labeled with the chemical shift values: -61.14, -61.17, and -61.24. The x-axis is labeled f1 (ppm) and ranges from 20 to -140.

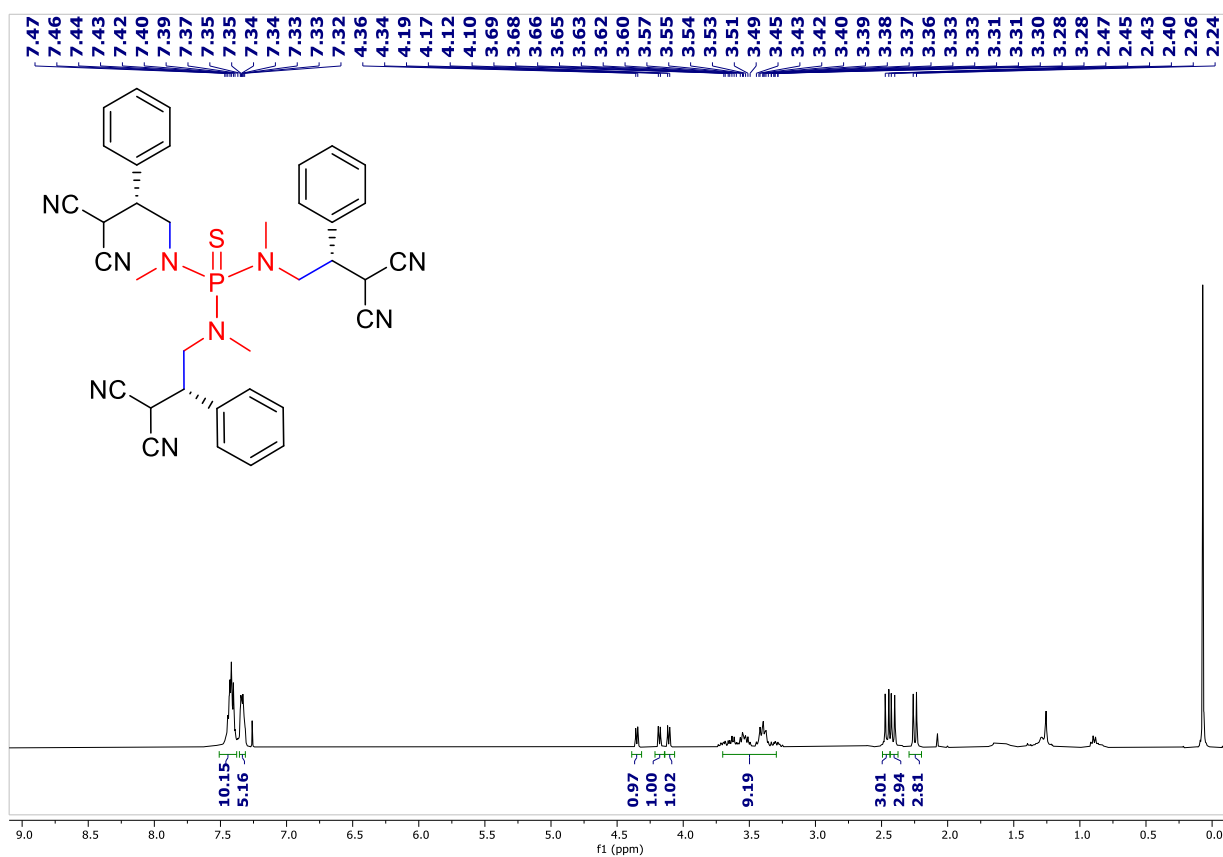
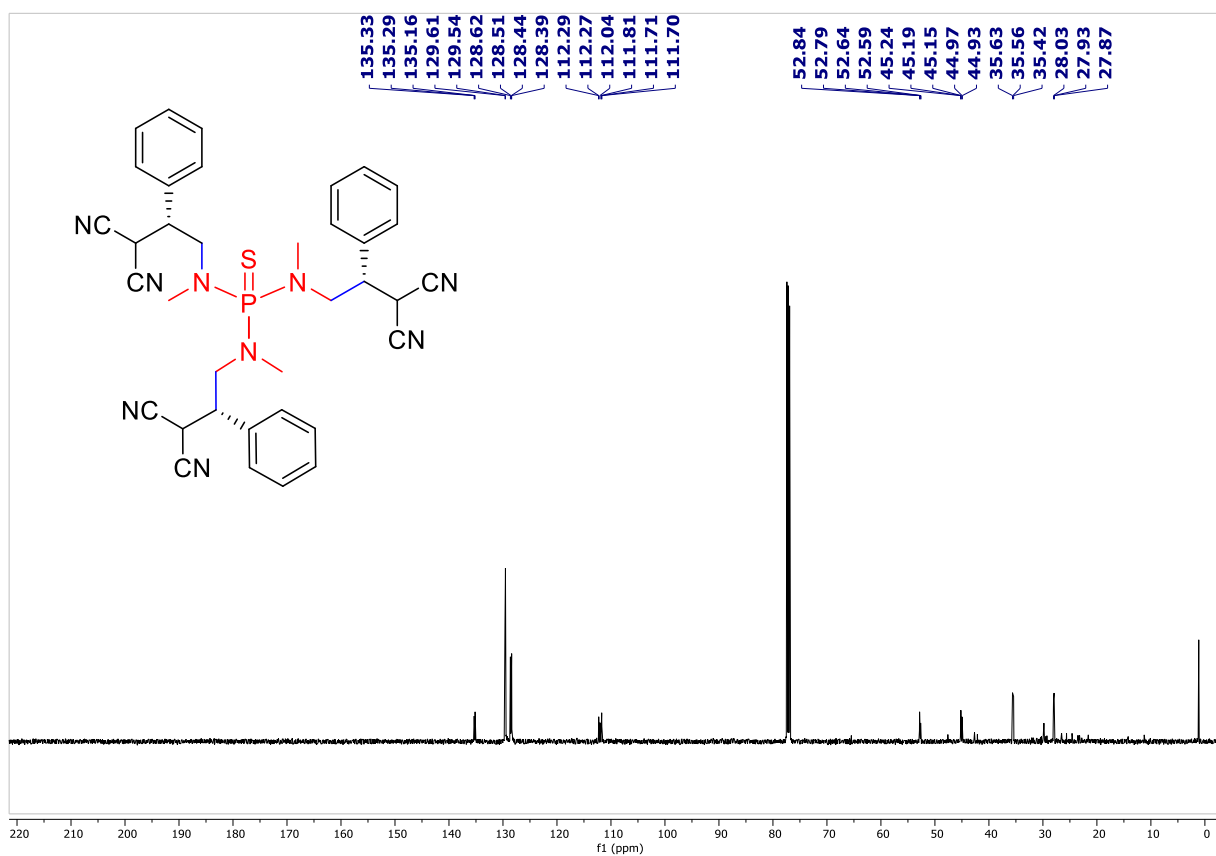
^1H NMR (400 MHz, $\text{DMSO}-d_6$) of compound minor (\pm)-**6d''** $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, $\text{DMSO}-d_6$) of compound minor (\pm)-**6d''**

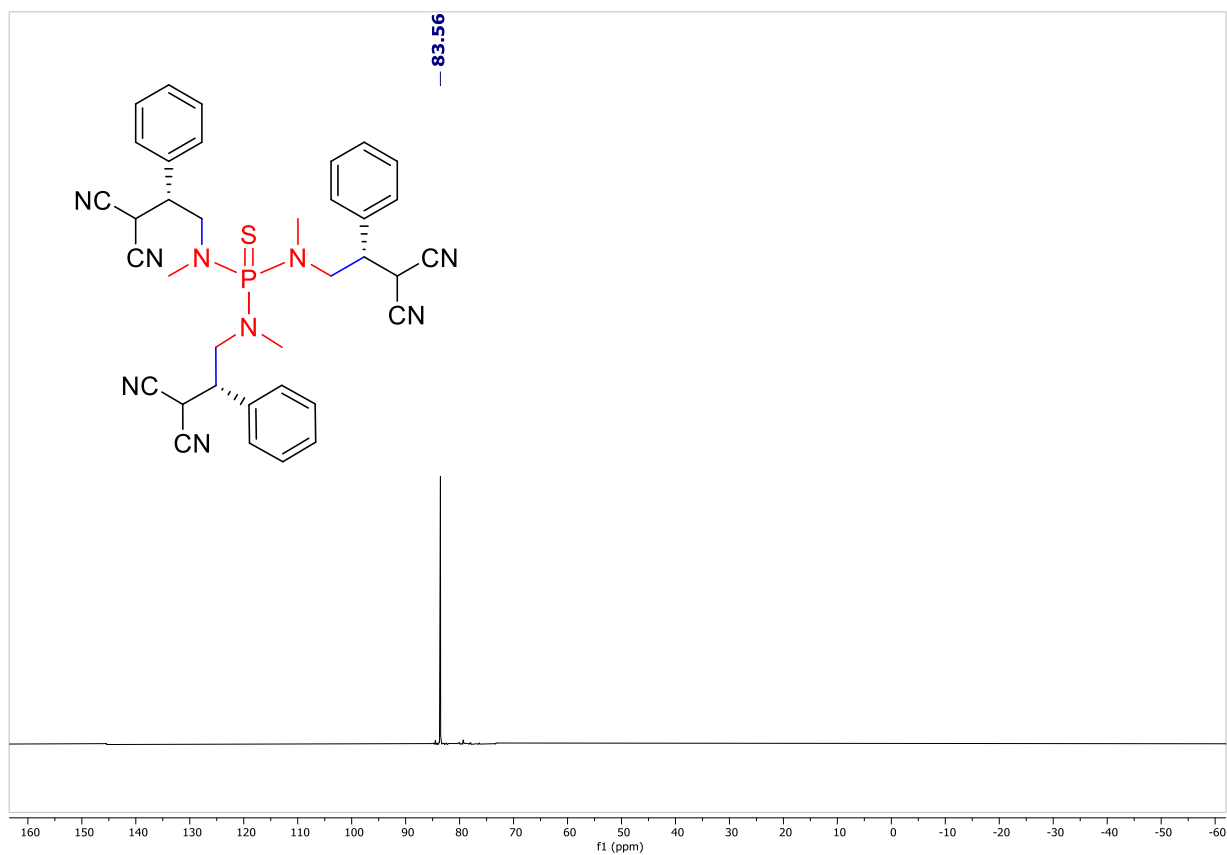
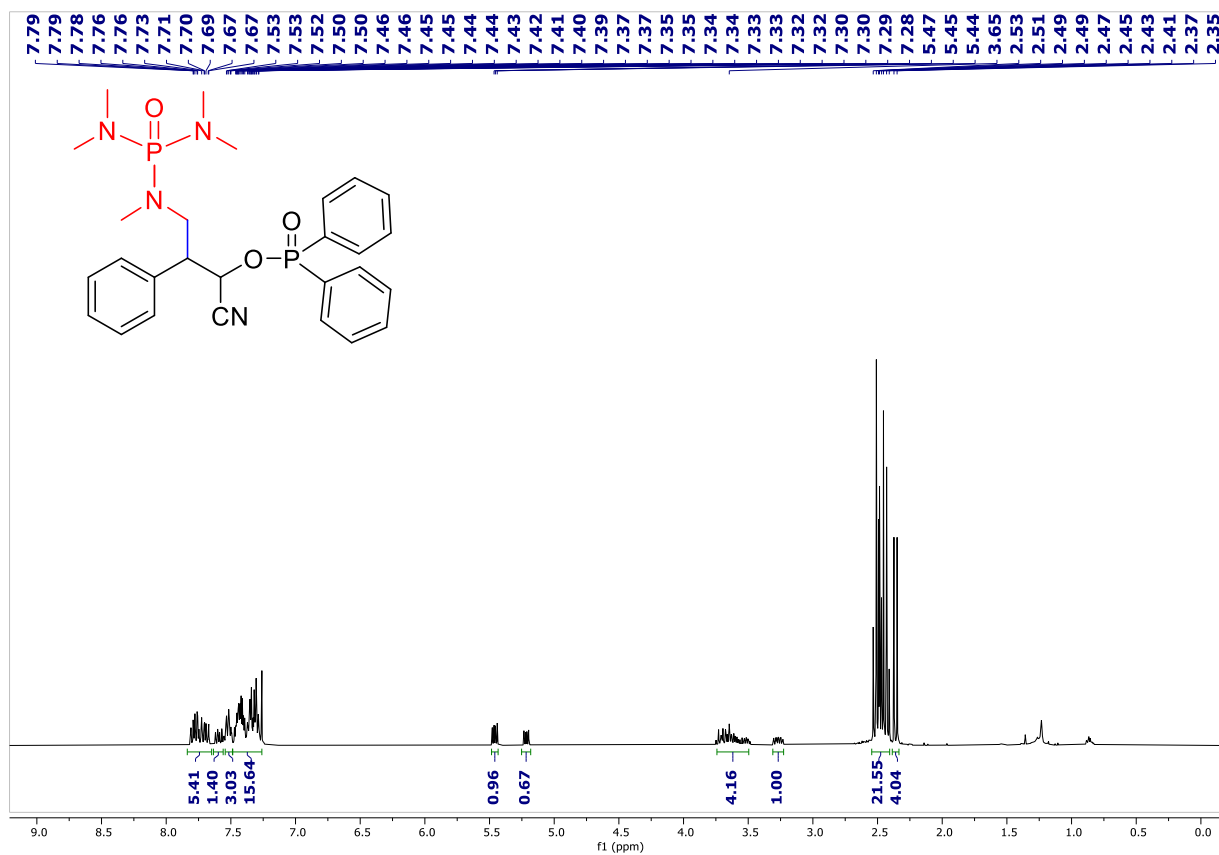
^{31}P NMR (203 MHz, $\text{DMSO}-d_6$) of compound minor (\pm)-**6d''** ^{19}F NMR (471 MHz, $\text{DMSO}-d_6$) of compound minor (\pm)-**6d''**

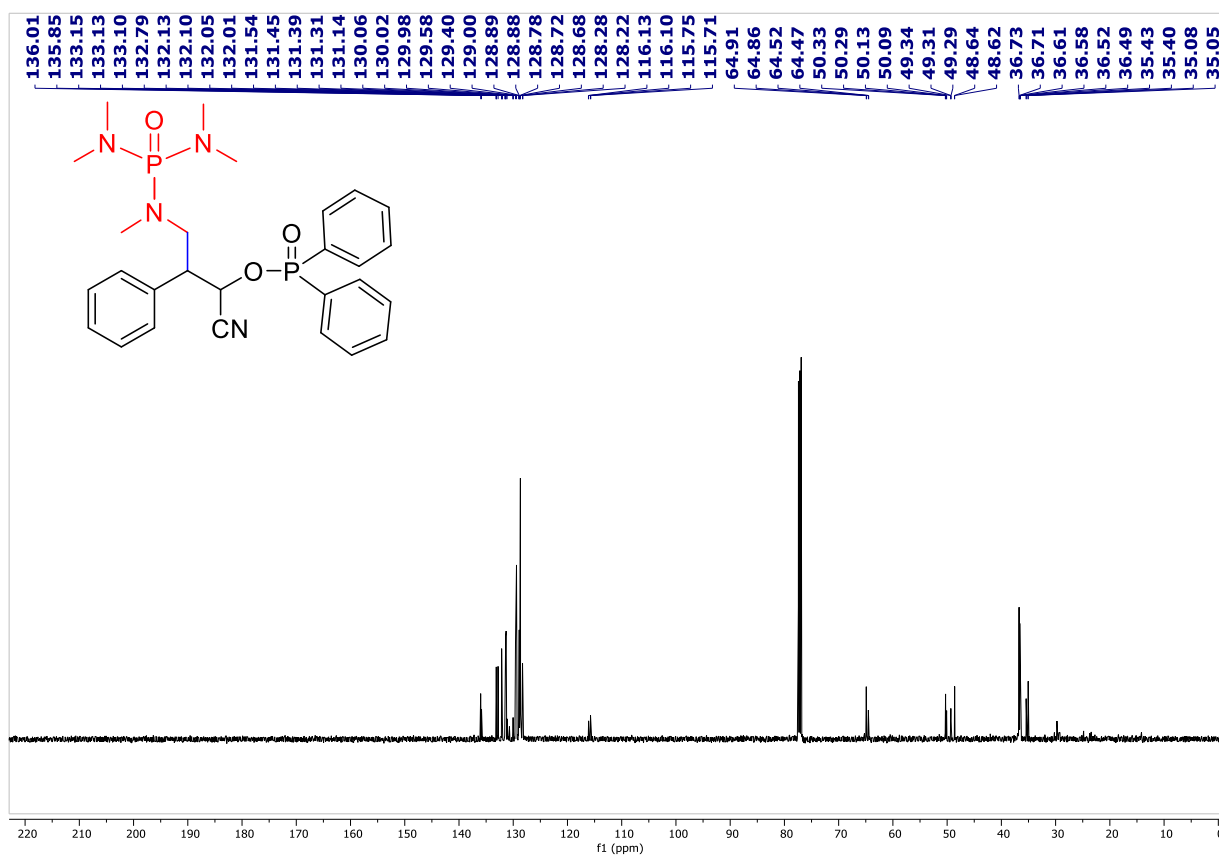
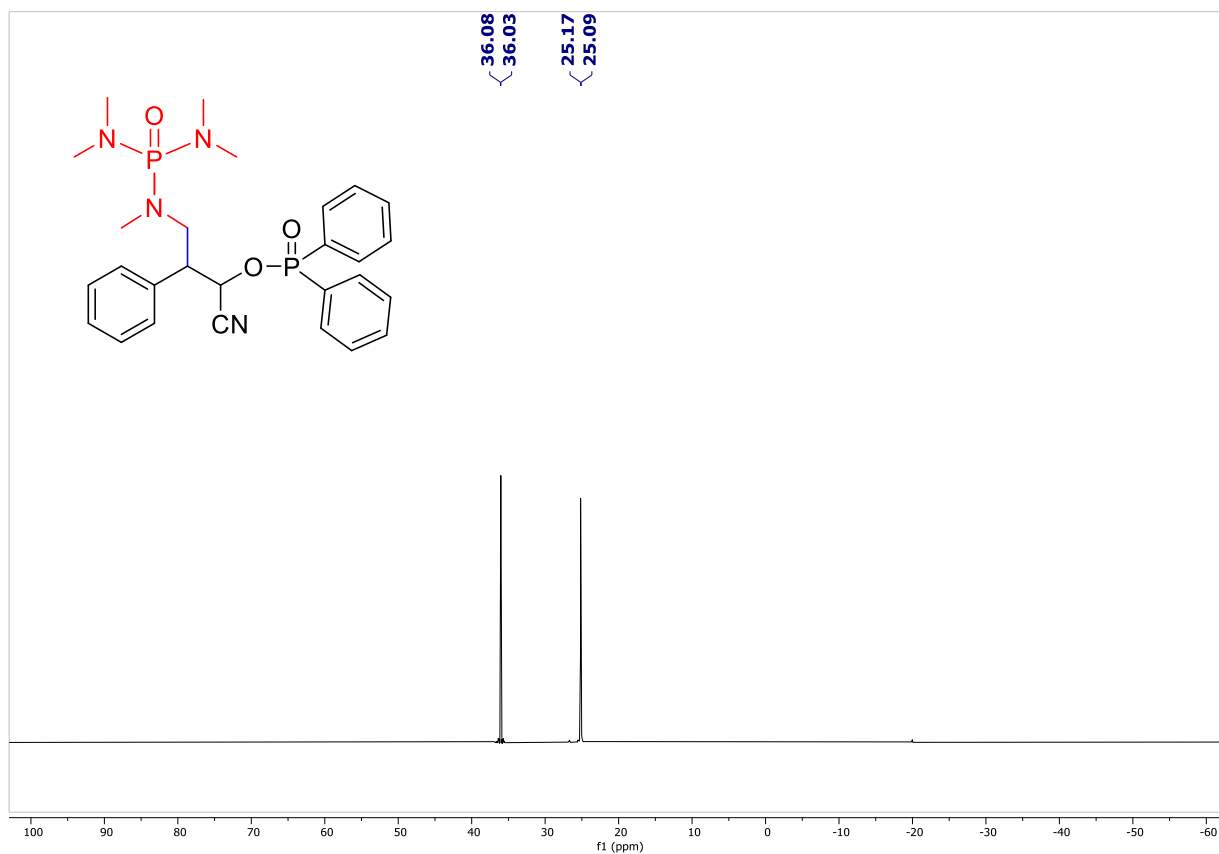
1H NMR (400 MHz, DMSO- d_6) of compound major (\pm)-6e' $^{13}C\{^1H\}$ NMR (126 MHz, DMSO- d_6) of compound major (\pm)-6e'

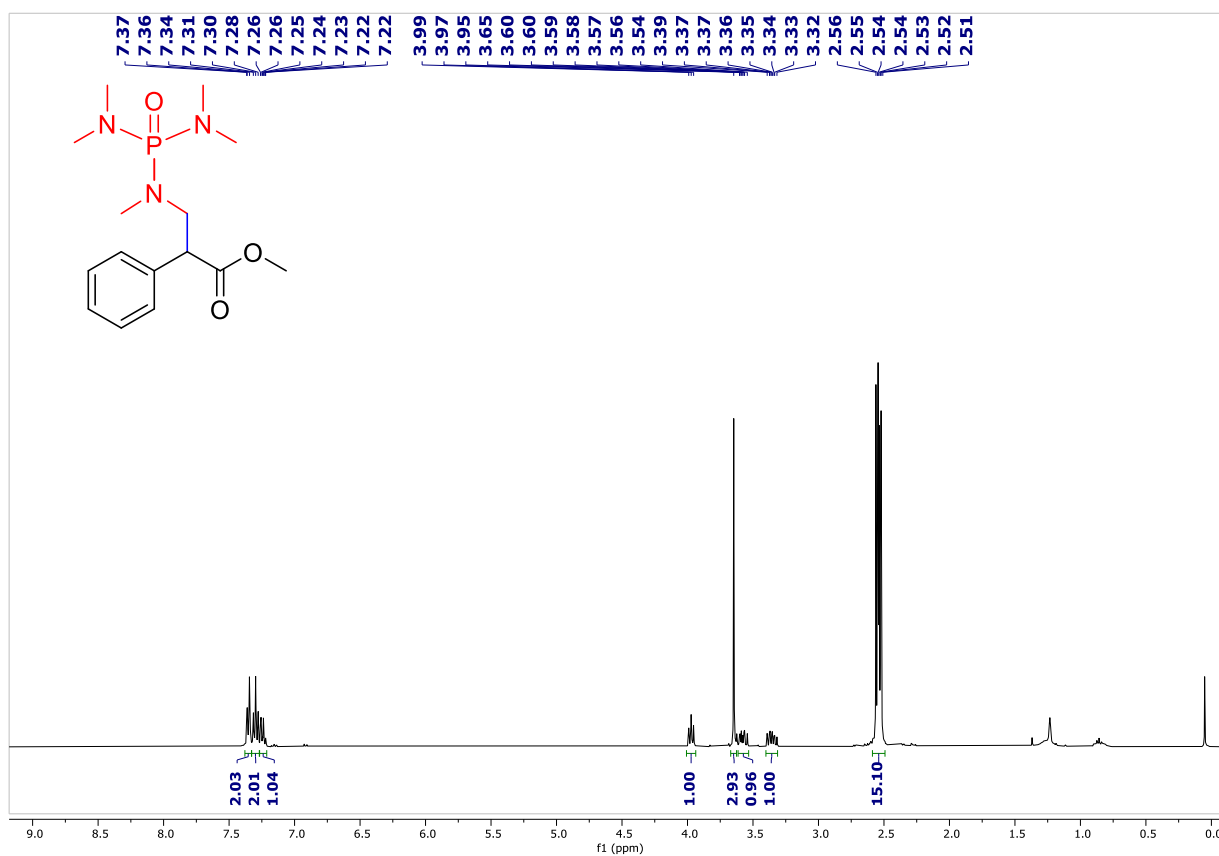
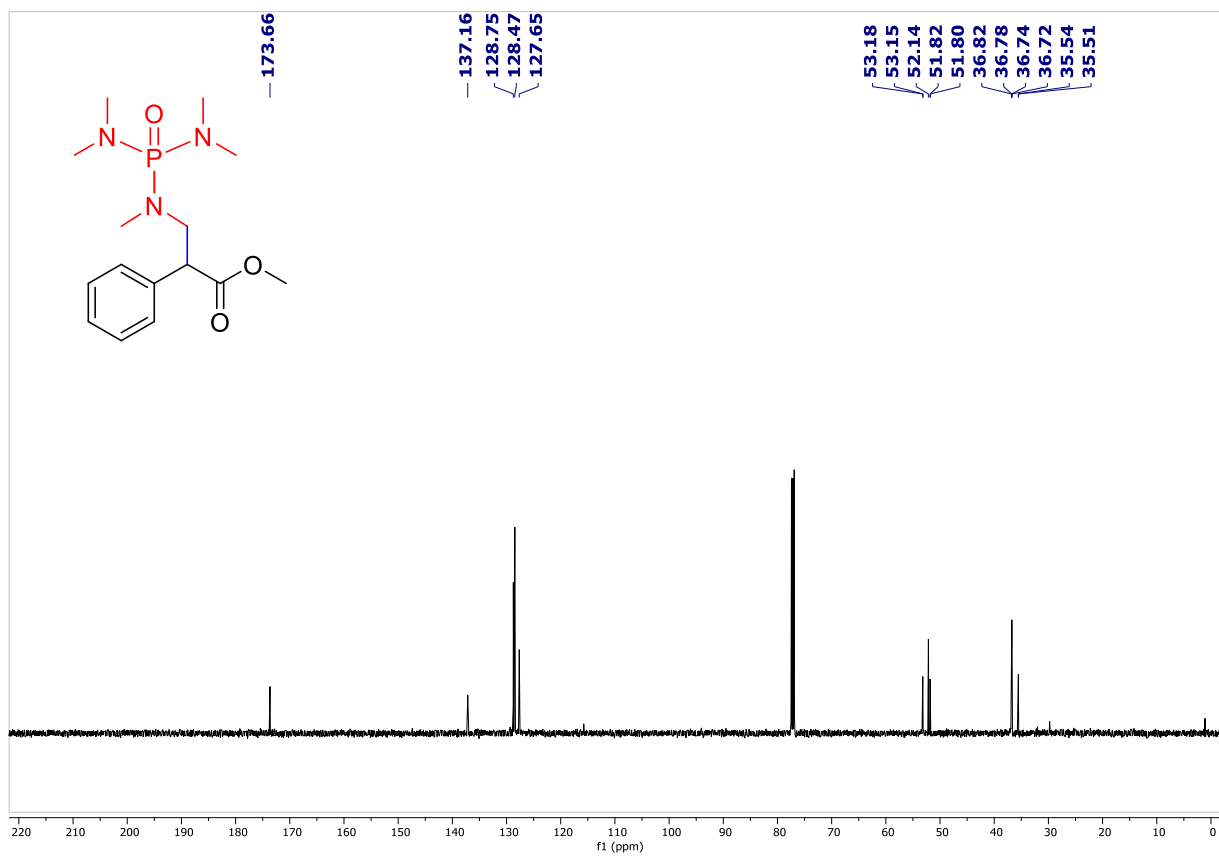
^{31}P NMR (203 MHz, DMSO- d_6) of compound major (\pm)-6e' 1H NMR (400 MHz, DMSO- d_6) of compound minor (\pm)-6e''

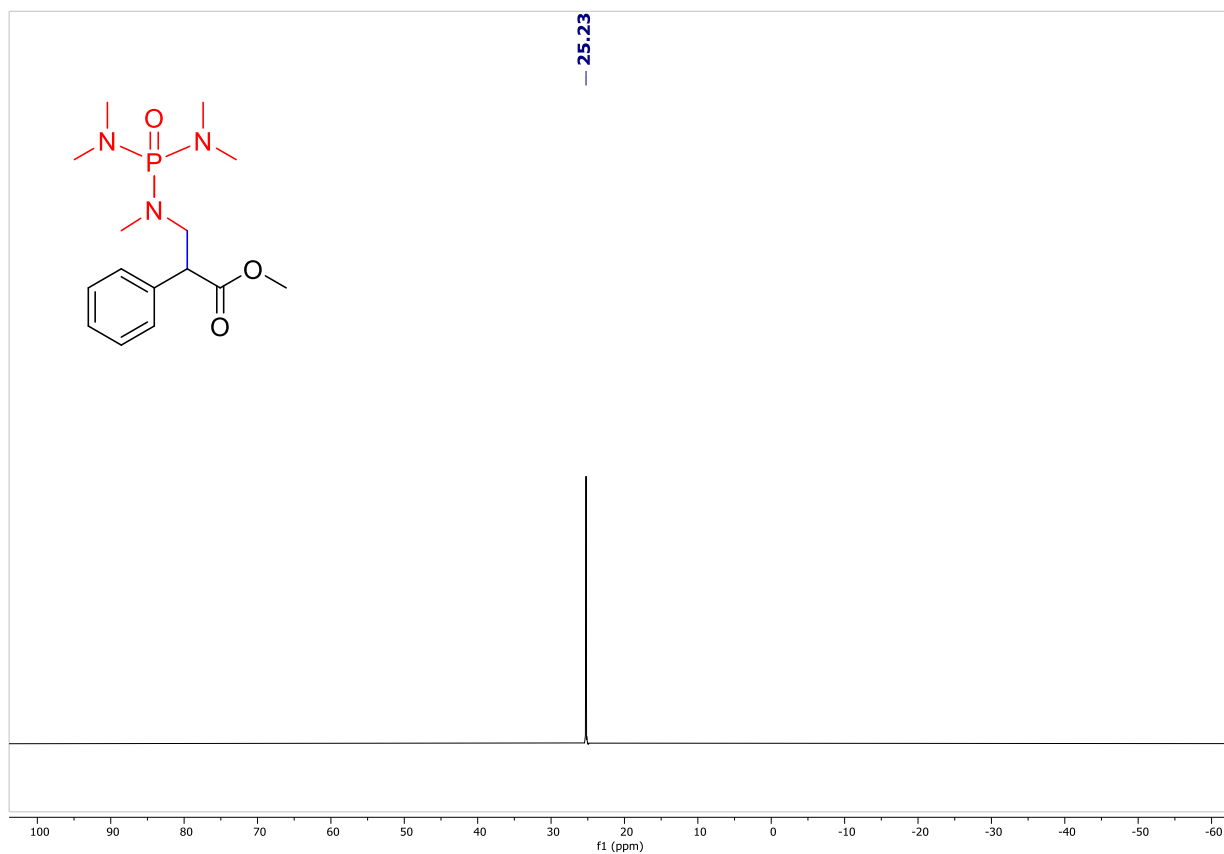
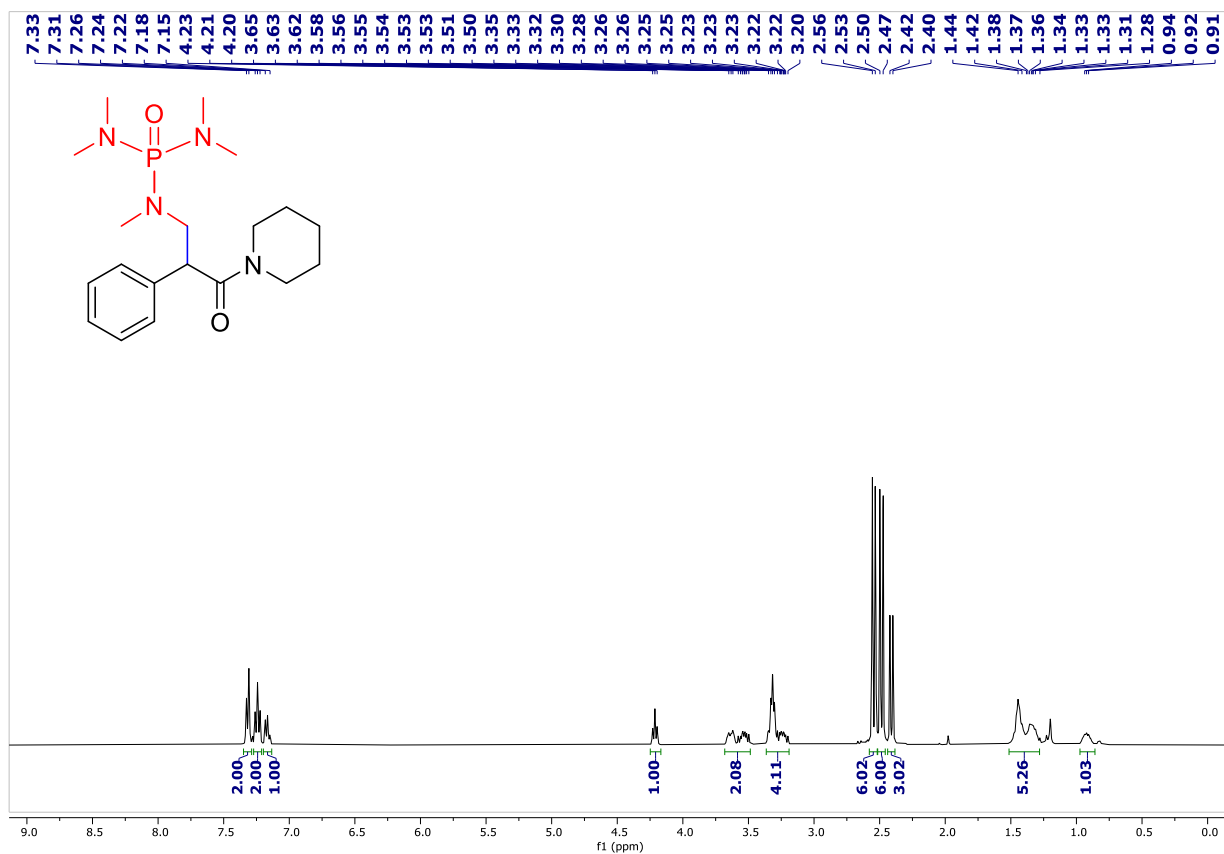
$^{13}C\{^1H\}$ NMR (126 MHz, $DMSO-d_6$) of compound minor (\pm)-**6e''** ^{31}P NMR (203 MHz, $DMSO-d_6$) of compound minor (\pm)-**6e''**

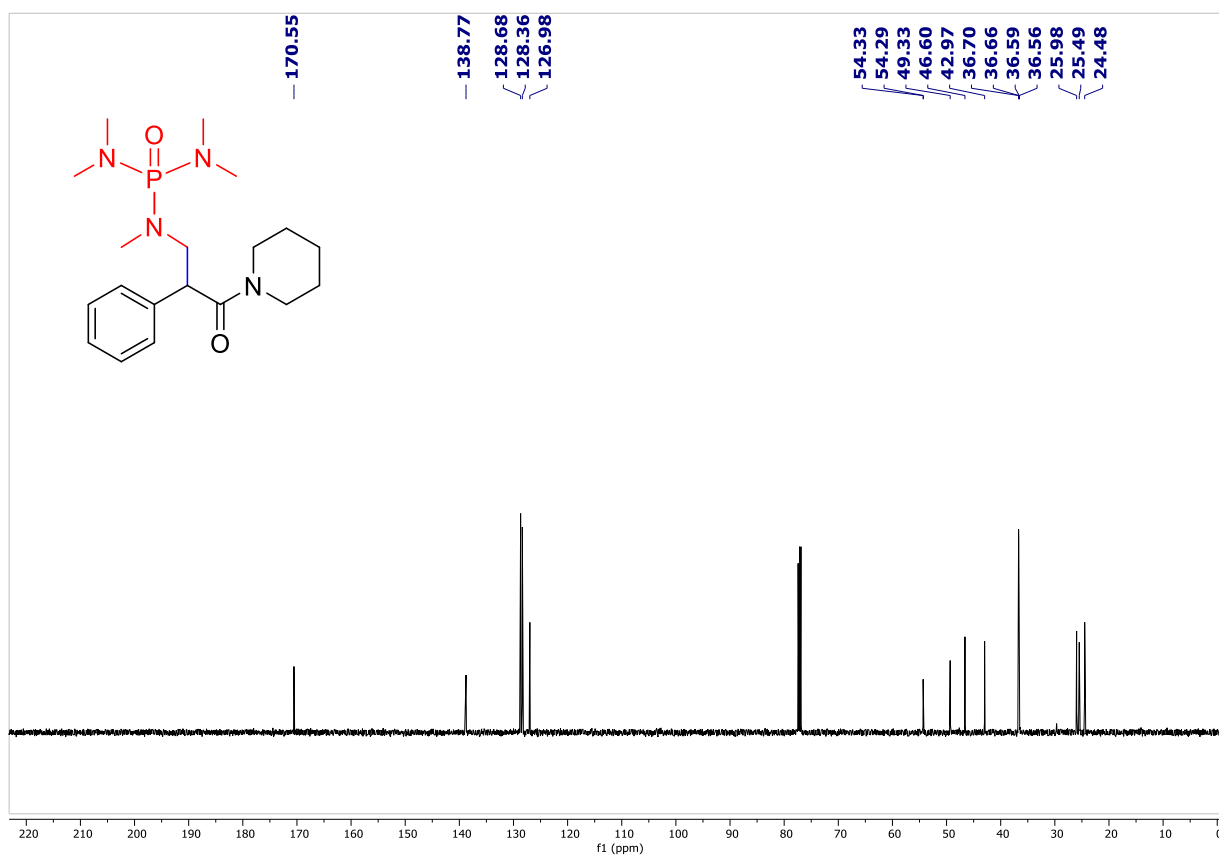
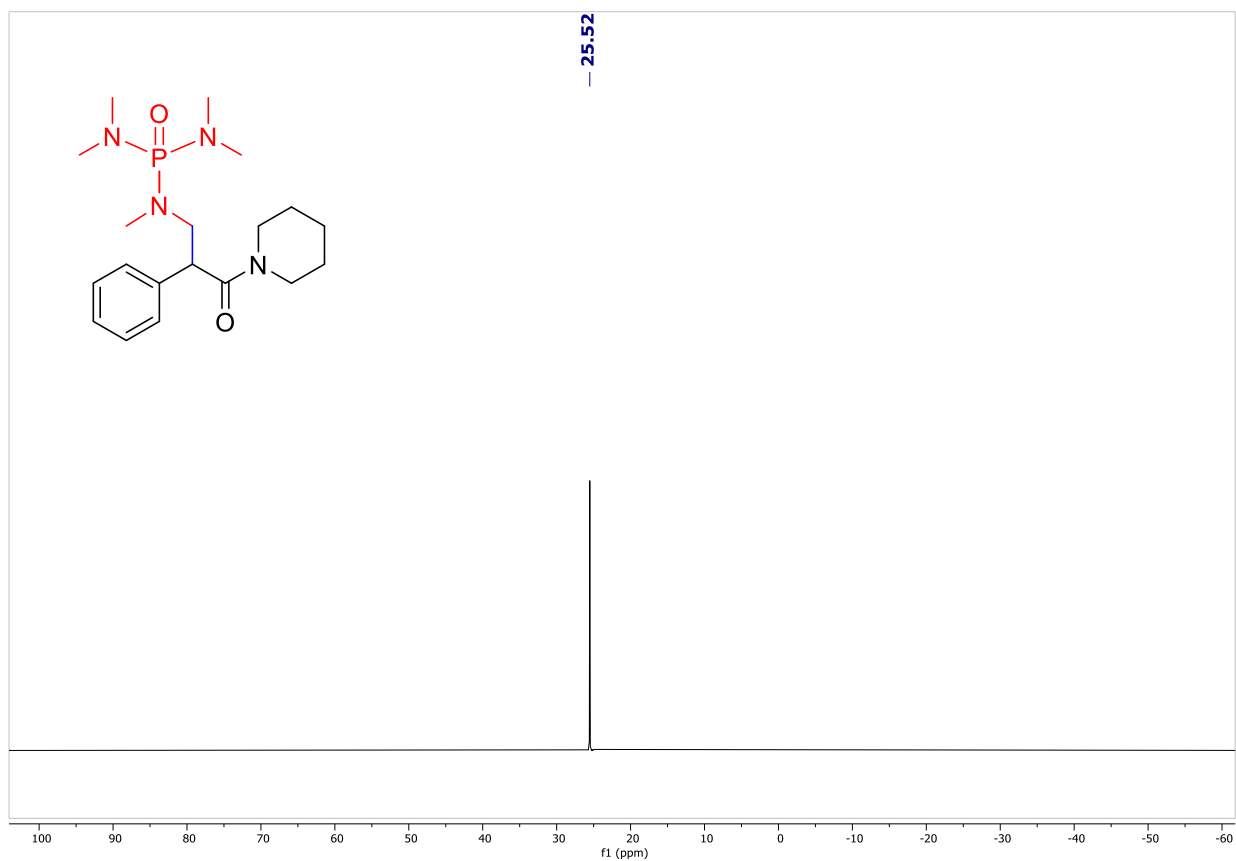
^1H NMR (400 MHz, CDCl_3) of compound (\pm)-**6f** $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) of compound (\pm)-**6f**

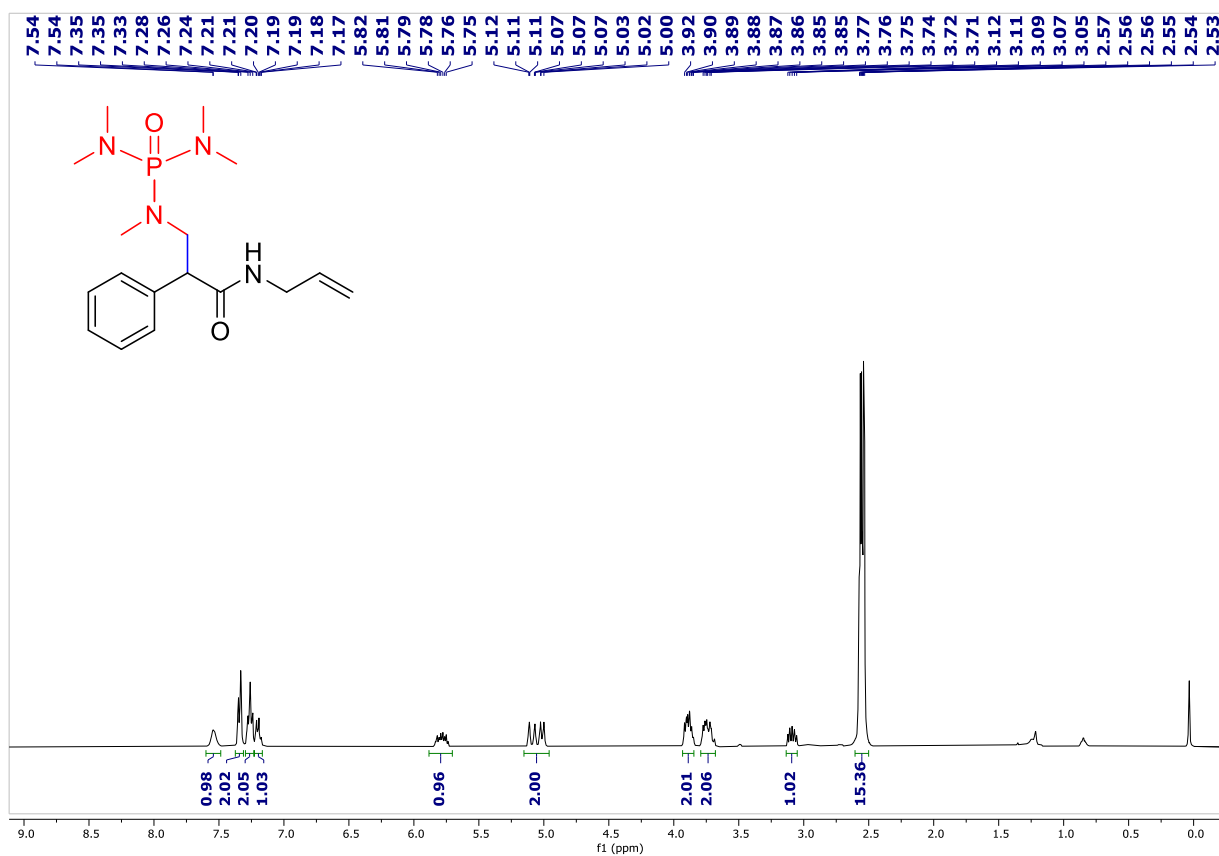
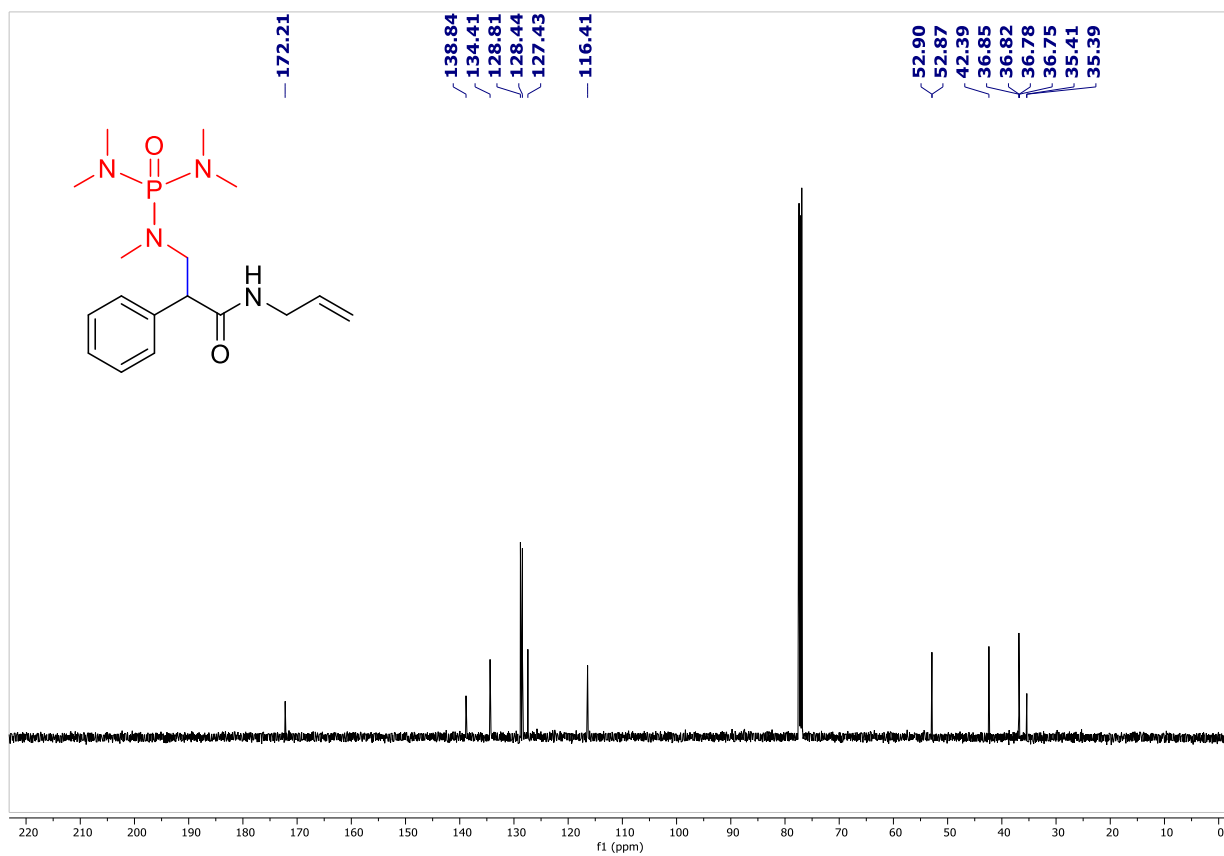
^{31}P NMR (203 MHz, CDCl_3) of compound (\pm)-**6f** ^1H NMR (400 MHz, CDCl_3) of compound **7**

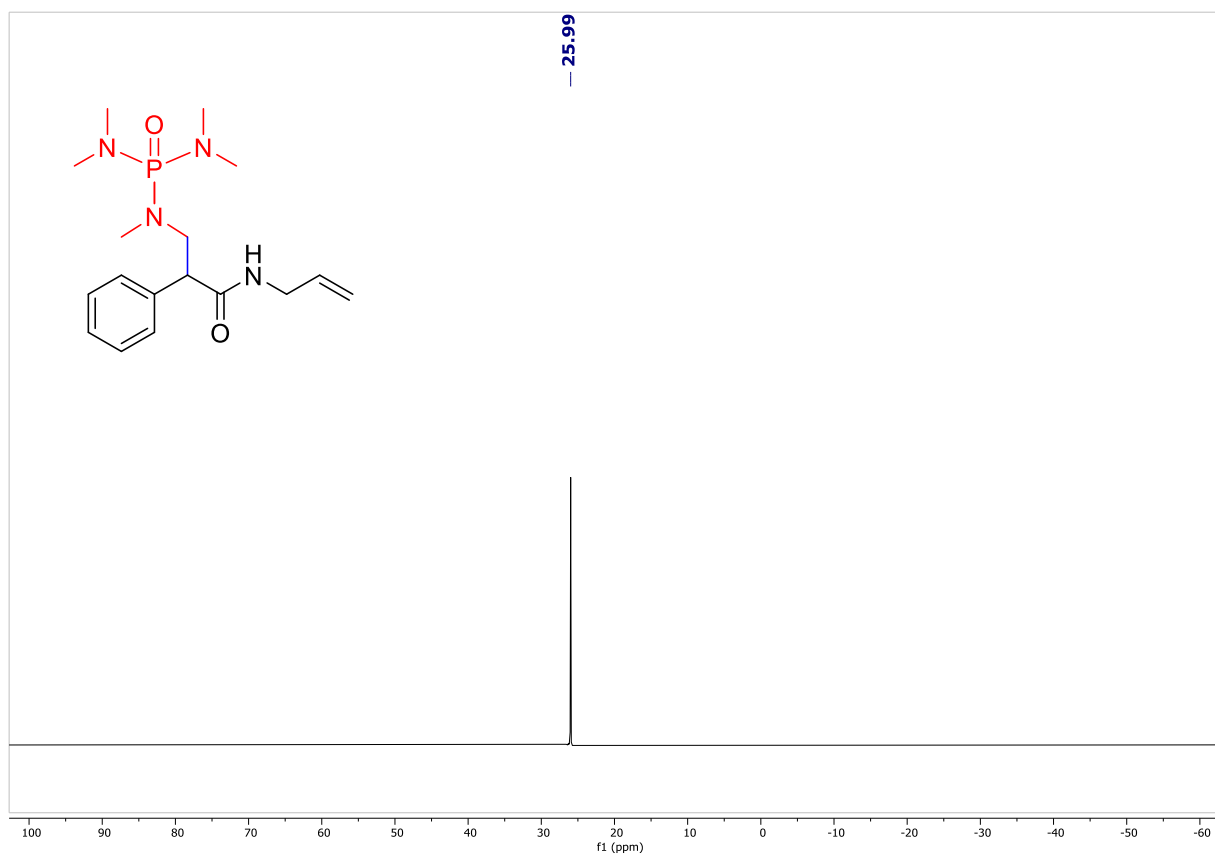
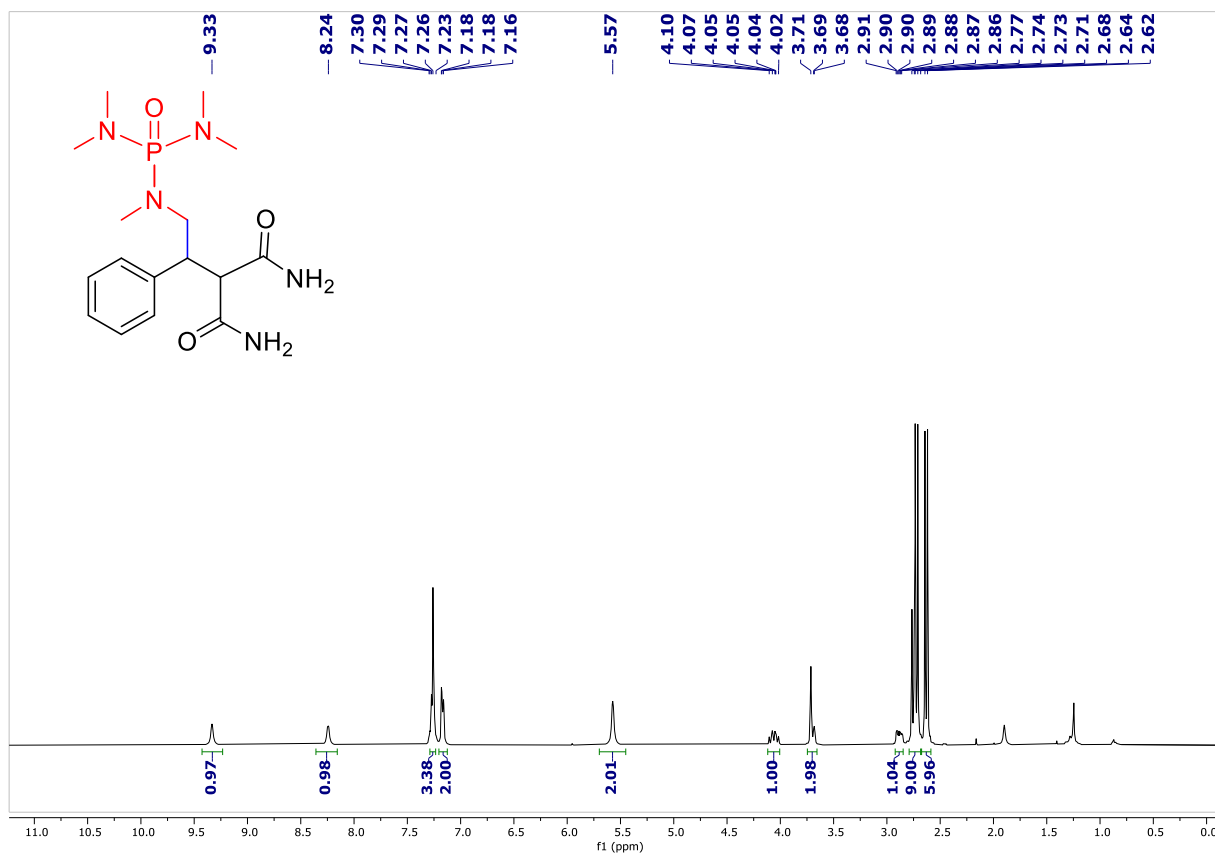
$^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) of compound 7 ^{31}P NMR (203 MHz, $CDCl_3$) of compound 7

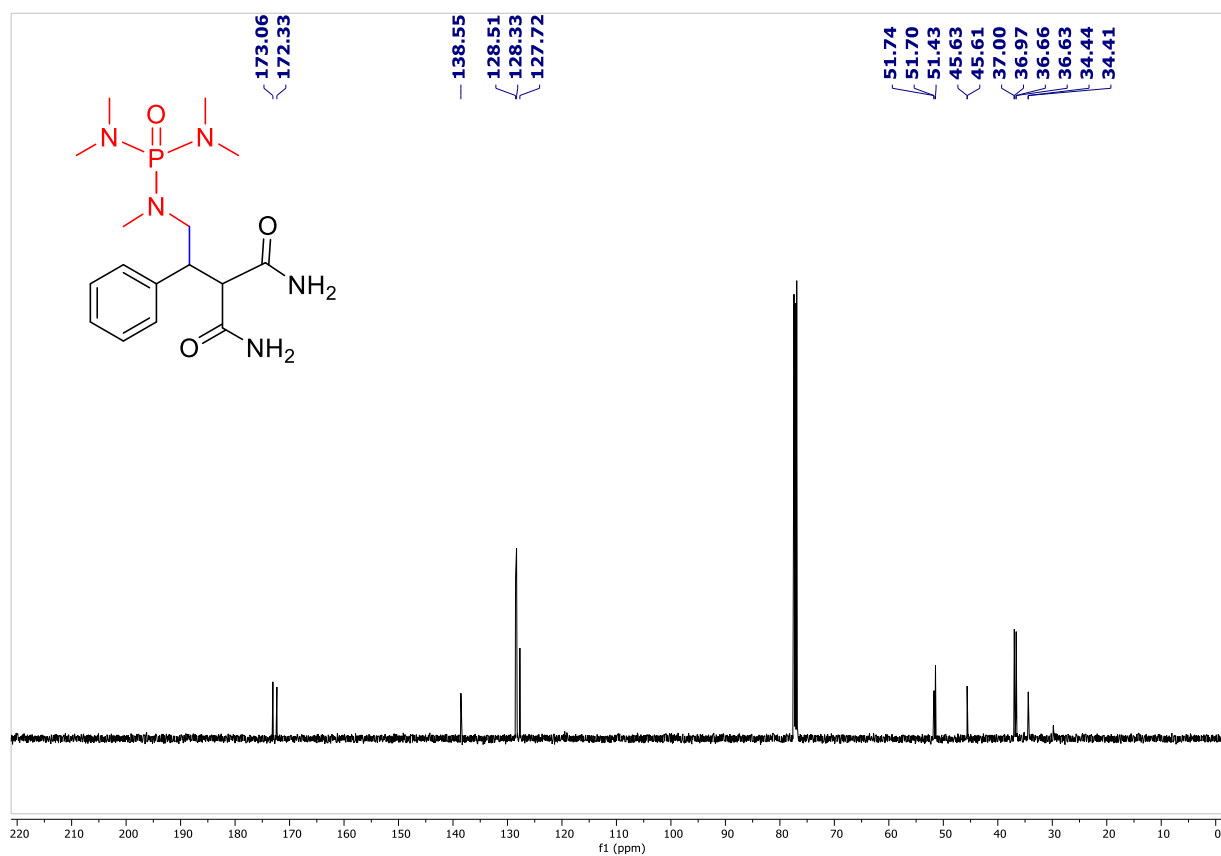
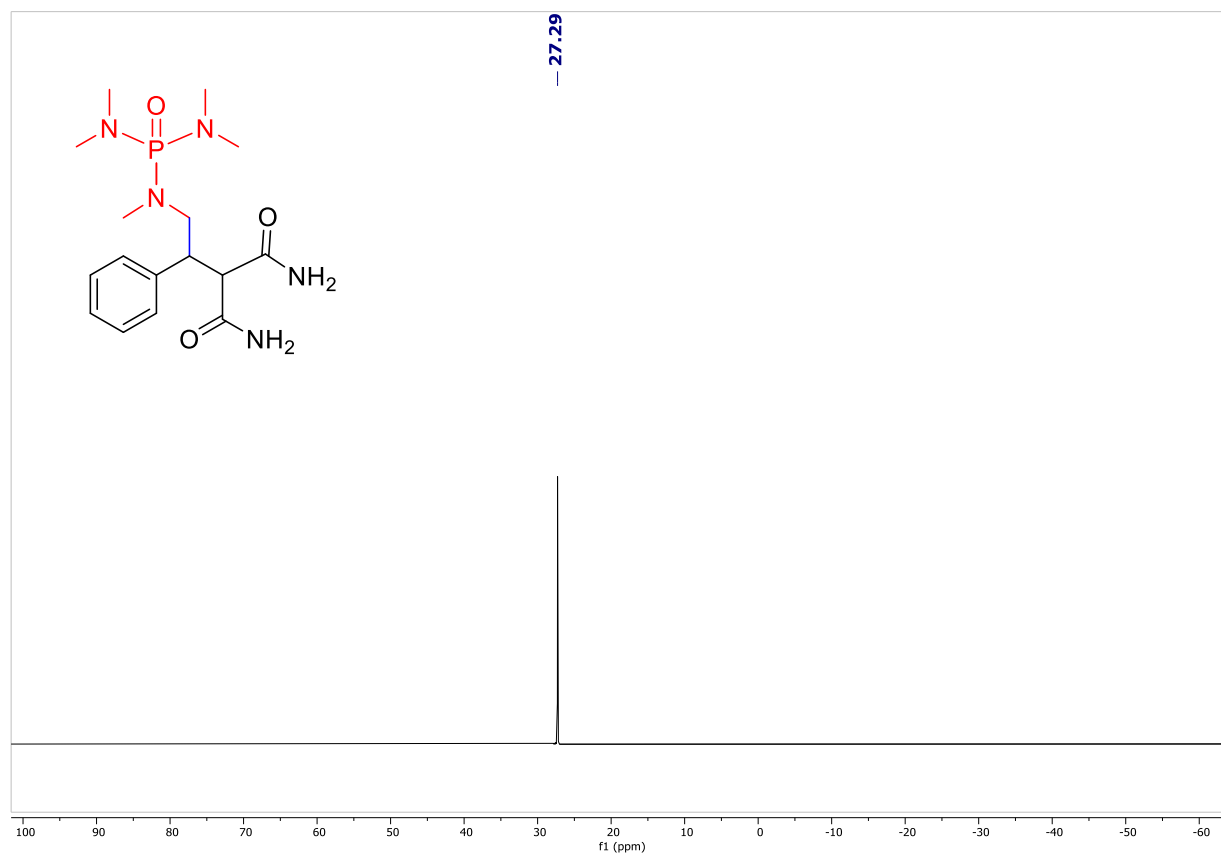
^1H NMR (400 MHz, CDCl_3) of compound 8 $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) of compound 8

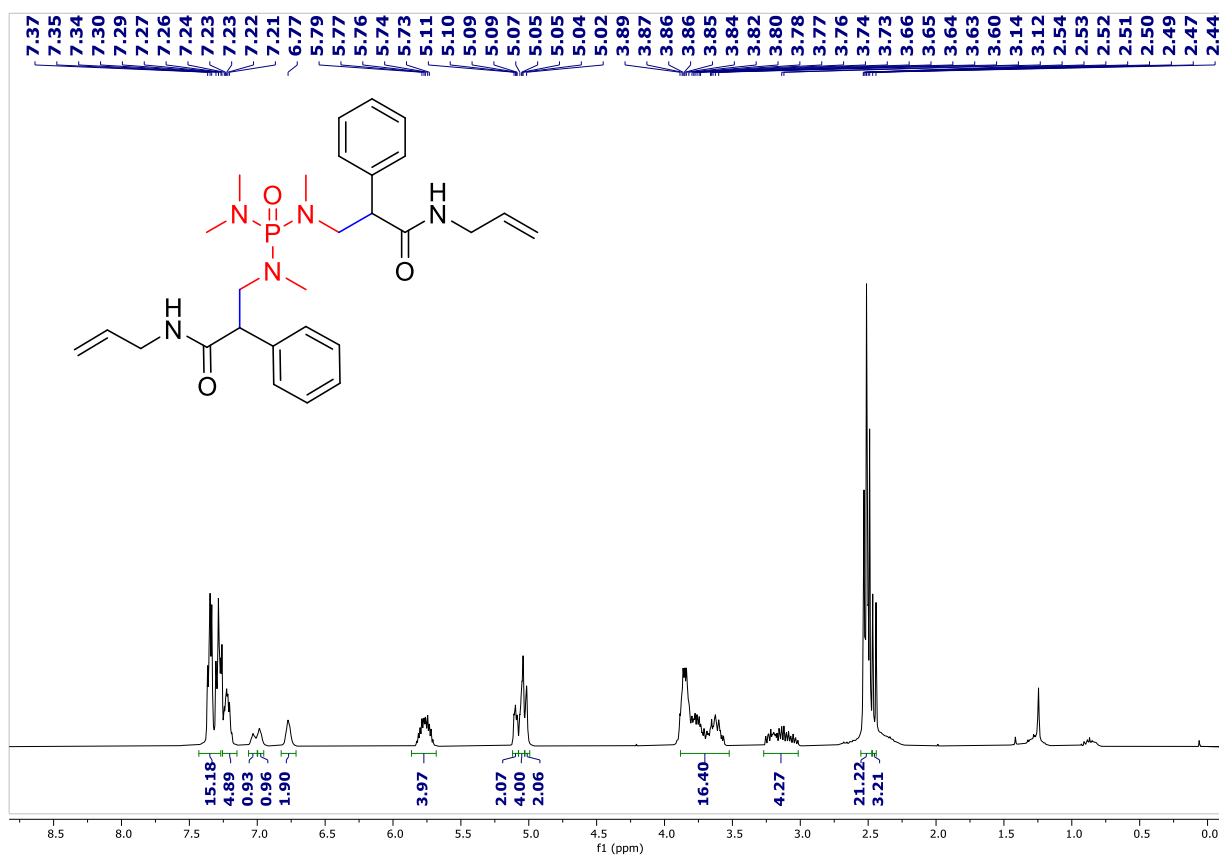
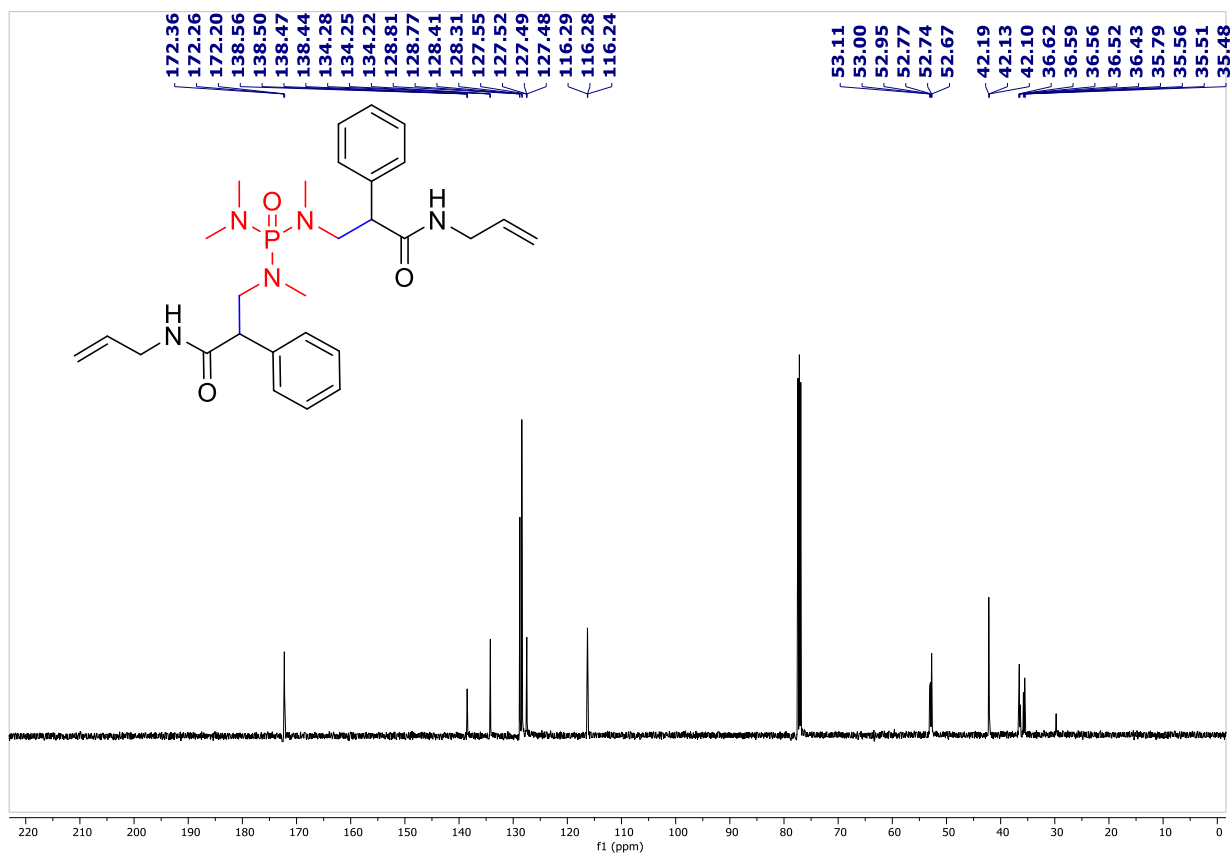
^{31}P NMR (203 MHz, $CDCl_3$) of compound 8 1H NMR (400 MHz, $CDCl_3$) of compound 9

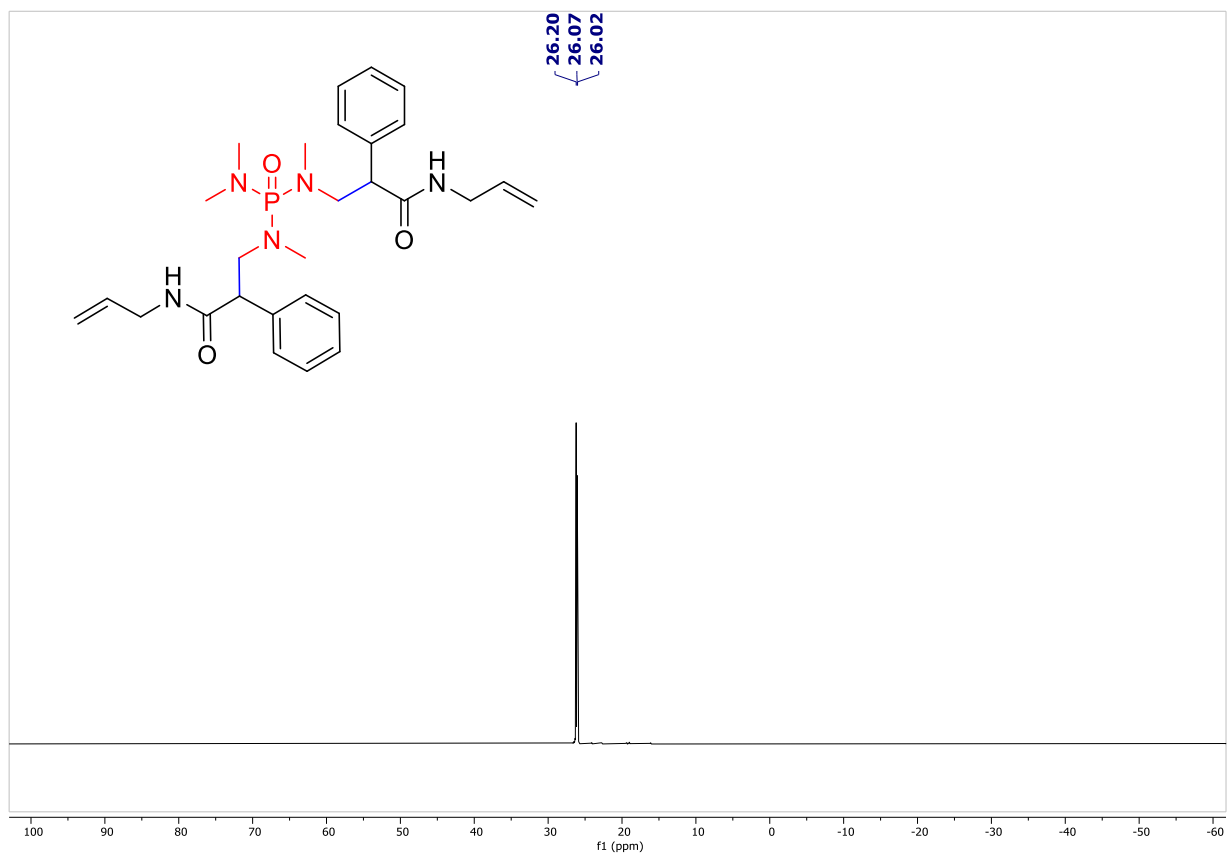
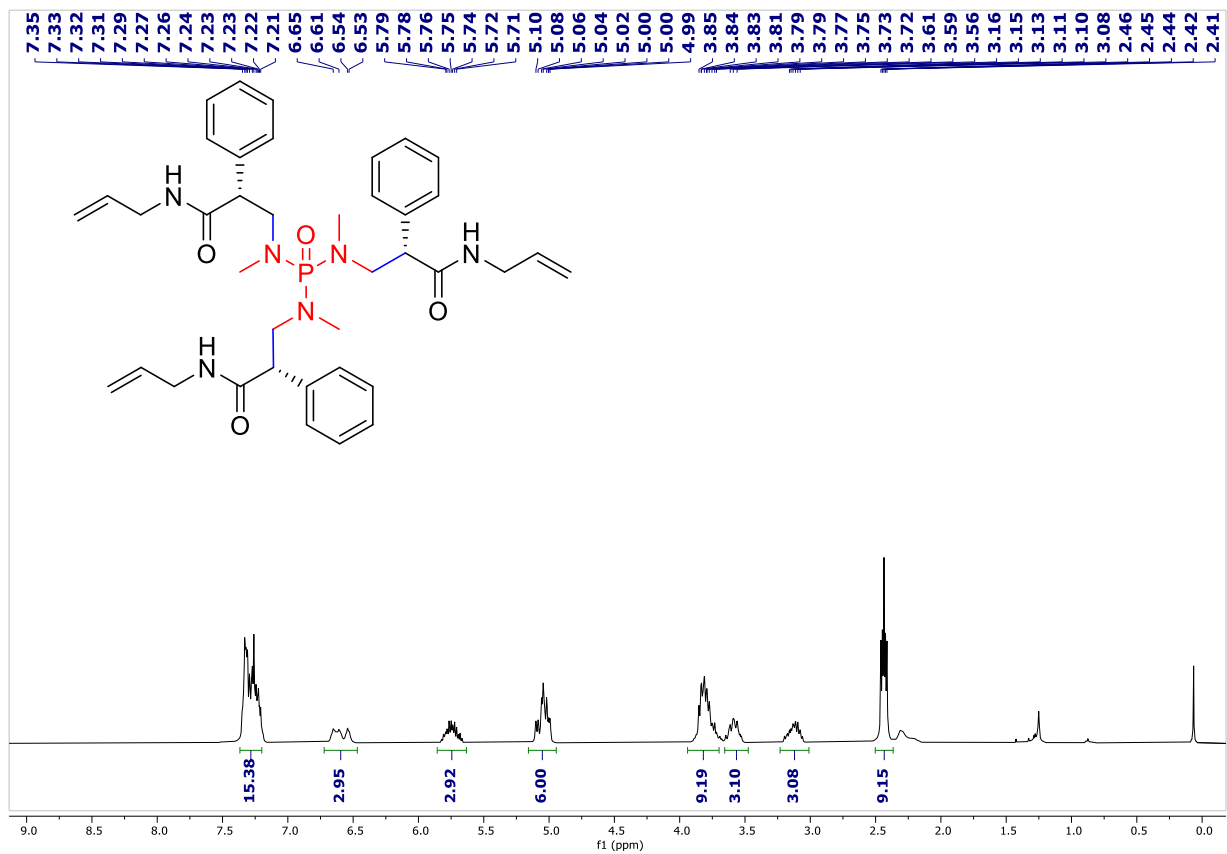
$^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) of compound **9** ^{31}P NMR (203 MHz, $CDCl_3$) of compound **9**

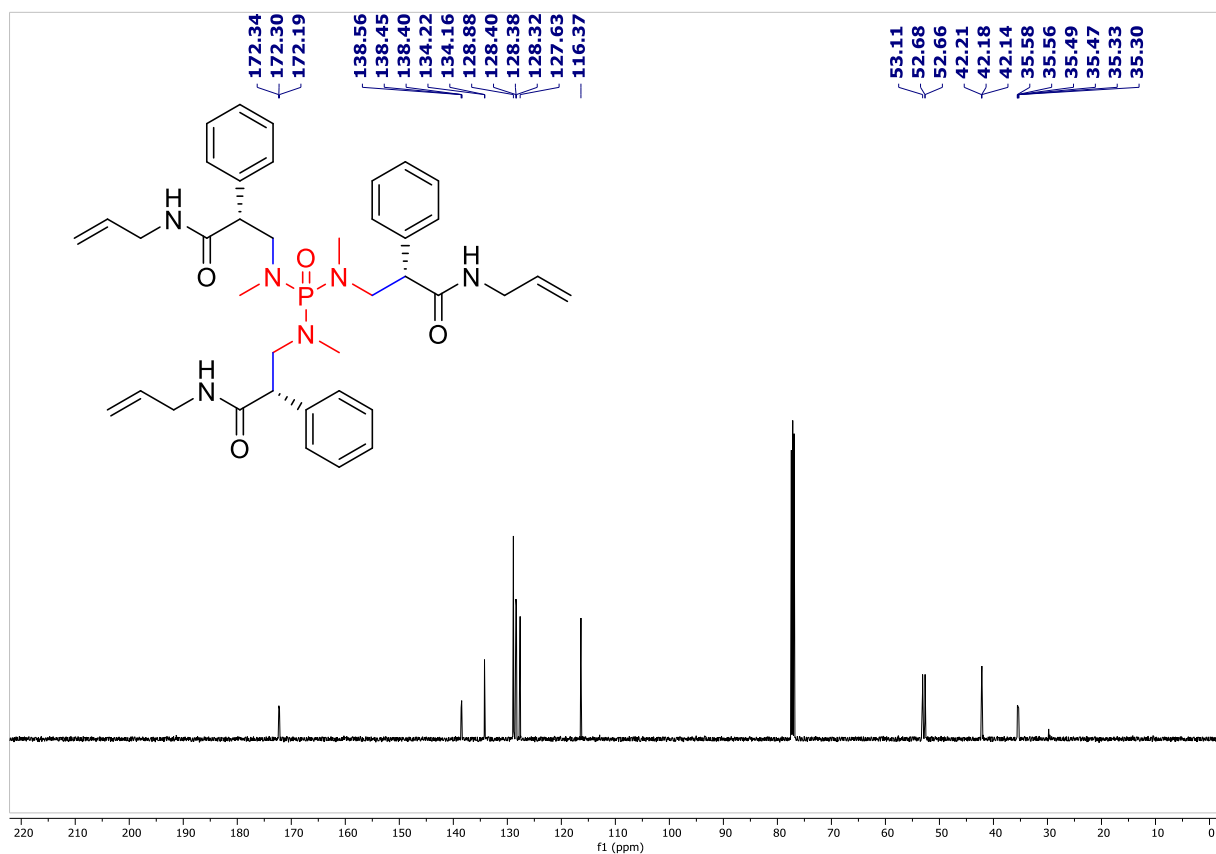
^1H NMR (400 MHz, CDCl_3) of compound **10** $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) of compound **10**

^{31}P NMR (203 MHz, $CDCl_3$) of compound **10** 1H NMR (400 MHz, $CDCl_3$) of compound **11**

$^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) of compound **11** ^{31}P NMR (203 MHz, $CDCl_3$) of compound **11**

1H NMR (400 MHz, $CDCl_3$) of compound **12** $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) of compound **12**

^{31}P NMR (203 MHz, CDCl_3) of compound **12** ^1H NMR (400 MHz, CDCl_3) of compound (\pm)-**13**

$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) of compound (\pm)-13 ^{31}P NMR (203 MHz, CDCl_3) of compound (\pm)-13