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Synthesis of 1-[1-(diphenoxyphosphoryl)alkyl]-3,4,6-trimethylglycolurils

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General

All reagents (Acros, Merck) were used as purchased, unless otherwise indicated. ^{1}H, ^{13}C and ^{31}P NMR spectra were recorded at 25 to 30 °C using Bruker AVANCE 400 III HD (^{1}H, 400.17 MHz; ^{13}C, 100.63 MHz, ^{31}P 162 MHz) and DMSO-d_6 as solvent. Chemical shifts are reported in the δ scale relative to tetramethylsilane for ^{1}H, ^{13}C, and H_3PO_4 for ^{31}P as internal standard. Preparative purification and separation of diastereomers **4a′-c′** and **4a″-c″** were performed on Shimadzu LC 20 Prominence chromatograph with the Kromasil C_{18} column 250 × 20 mm, 5 μm particle size and the column temperature was set at 25 °C (± 1 °C). The mobile phase consisted of the water–acetonitrile mixture (60:40). The flow rate was 5 ml min^{-1} in the isocratic mode, and the detection wavelength of UV detector was 250 nm. The samples were preliminary dissolved in acetonitrile (1:10, v/v).

Mass spectra (MS) were recorded with the chromatograph HPLC Prominence LC-20 (Shimadzu, Japan) with mass-spectrometric detector AB Sciex API2000 in electro spray ionization mode (ESI-MS). The LC-MS analysis was performed with column Zorbax Eclipse Plus C18, 4.6×100 mm, 3,5 μm in gradient elution mode at the flow rate 1,5 ml min^{-1} using 10 mM Ammonium solution with addition of 30 mM Formic acid as a mobile phase A and HPLC-grade acetonitrile as a mobile phase B. Gradient program: relative amount of eluent B increased from 50 to 90 % B for 13 min. Thermostat temperature was 25°C, and injection volume was 20 μl.

The mass-spectrometric detection was performed in scanning mode with *m/z* range from 105 to 900 Da at flow division of 1 to 3. Ion source temperature was 350 °C, ion source voltage was 4000 V, pressure of sheath gas, ion source 1 and ion source 2 was 40, 60, and 60 psi respectively. The declustering potential were equal to 20 V and focusing potential were equal to 200 V.

1-[1-(Diphenoxyphosphoryl)alkyl]-3,4,6-trimethylglycolurils **4a-d** (general procedure). Aldehyde **2** (2 mmol), triphenyl phosphite **3** (2 mmol) and methanesulfonic acid (10 mol%) were added to a suspension of 1,3,4-trimethylglycoluril **1** (2 mmol) in dry acetonitrile (4 ml) in an argon atmosphere. The mixture was stirred for 1 hour at room temperature, then distilled dry on a rotary evaporator. The residue was dissolved in toluene (10 ml) and washed with 5% aqueous Na_2CO_3 solution (3 × 10 ml), then the toluene solution was washed with water (3 × 10 ml). After that, the organic layer was dried over Na_2SO_4 and concentrated dry on a rotary evaporator. Concentrated viscous oil was purified by preparative HPLC on C18 stationary phase, and water-acetonitrile (60:40) mobile phase.

NMR spectra of compounds **4a′-d′** and **4a″-d″**

Diphenyl [1-(3,4,6-trimethyl-2,5-dioxohexahydroimidazo[4,5-d]imidazol-1(2H)-yl)ethyl]-phosphonate **4a**. Viscous yellow oil. Yield 56 %, **4a′**:**4a″** = 46:54.

4a′ viscous yellow oil: ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 1.68 (dd, J = 18.3, 7.4 Hz, 3H, CHMe), 2.82 (s, 3H, NMe), 2.83 (s, 3H, NMe), 2.86 (s, 3H, NMe), 4.46 – 4.65 (m, 1H, NCHMe), 5.11 (d, J = 8.7 Hz, 1H, CH-CH), 5.27 (dd, J = 8.6 Hz, 1.7 Hz, 1H, CH-CH), 7.08–7.25 (m, 6H, Ph), 7.31–7.44 (m, 4H, Ph). ^{13}C NMR (101 MHz, DMSO-d_6): δ (ppm) 12.96 (CHMe), 30.34 (NMe), 30.46 (NMe), 30.79 (NMe), 47.62 (d, $J_{(CP)}$ = 159.8 Hz, NCHP), 70.29 (CH-CH), 72.61 (CH-CH), 120.78 (d, $J_{(CP)}$ = 4.0 Hz, Ph), 121.05 (d, $J_{(CP)}$ = 4.1 Hz, Ph), 125.71 (d, $J_{(CP)}$ = 7.3 Hz, Ph), 130.30 (d, $J_{(CP)}$ = 4.2 Hz, Ph), 150.42 (dd, $J_{(CP)}$ = 13.6, 9.9 Hz, Ph), 158.33 (d, $J_{(CP)}$ = 2.5 Hz, C=O), 159.56 (C=O). ^{31}P NMR (162 MHz, DMSO-d_6): δ (ppm): 18.56. LC-MS m/z: 445.5 $[M + H]^+$ (calc. for $C_{21}H_{25}N_4O_5P$ + H, m/z: 445.2). Anal. Calcd for $C_{21}H_{25}N_4O_5P$. C, 56.75; H, 5.67; N, 12.61. Found: C, 56.61; H, 5.64; N, 12.75.

4a″ viscous yellow oil: ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 1,59 (dd, J = 17.5, 7.5 Hz, 3H, CHMe), 2.80 (s. 3H, NMe), 2.83 (s, 6H, NMe), 4.56 – 4.70 (m, 1H, NCHMe), 5.06 (d, J = 8.5 Hz, 1H, CH-CH), 5.40 (dd, J = 8.6 Hz, 1.0 Hz, 1H, CH-CH), 7.12 – 7.31 (m, 6H, Ph), 7.34 – 7.51 (m, 4H, Ph). ^{13}C NMR (101 MHz, DMSO-d_6): δ (ppm) 15.17 (d, $J_{(CP)}$ =4.4 Hz, CHMe), 29.84 (NMe), 30.41 (NMe), 30.95 (NMe), 46.31 (d, $J_{(CP)}$ = 153.6 Hz, CHP), 70.73 (CH-CH), 72.23 (CH-CH), 120.52 (d, $J_{(CP)}$ = 3.9 Hz, Ph), 120.65 (d, $J_{(CP)}$ = 4.1 Hz, Ph), 125.69 (d, $J_{(CP)}$ = 9.4 Hz, Ph), 130.16 (d, $J_{(CP)}$ = 7.7 Hz, Ph), 149.80 (t, $J_{(CP)}$ = 9.2 Hz, O-Ph), 157.71 (d, $J_{(CP)}$ = 2.1 Hz, C=O), 159.41 (C=O). ^{31}P NMR (162 MHz, DMSO-d_6): δ (ppm): 18.33. LC-MS m/z: 445.4 $[M + H]^+$ (calc. for $C_{21}H_{25}N_4O_5P$ + H, m/z: 445.2). Anal. Calcd for $C_{21}H_{25}N_4O_5P$. C, 56.75; H, 5.67; N, 12.61. Found: C, 56.42; H, 5.78; N, 12.66.

Diphenyl [1-(3,4,6-trimethyl-2,5-dioxohexahydroimidazo[4,5-d]imidazol-1(2H)-yl)propyl]-phosphonate **4b**. Viscous oil. Yield 51 %, **4b′**:**4b″** = 53:47.

4b′ viscous oil: ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 1.00 (t, 3H, J = 7.3 Hz, CH_2Me), 2.01 – 2.13 (m, 1H, C*H*H), 2.31 (s, 1H, CH*H*), 2.82 (s, 3H, NMe), 2.84 (s, 6H, NMe), 4.22 (s br., 1H, NCHP), 5.15 (d, 1H, J = 8.5 Hz, CH-CH), 5.21 (dd, 1H, J = 8.6, 1.8 Hz, CH-CH), 7.10 – 7.24 (m, 6H, Ph), 7.33 – 7.41 (m, 4H, Ph). ^{13}C NMR (101 MHz, DMSO-d_6): 11.53 (d, $J_{(CP)}$ = 14.6 Hz, CH_2Me), 20.10 (CH_2), 30.19 (NMe), 30.60 (NMe), 31.34 (NMe), 54.07 (d, $J_{(CP)}$ =159.3 Hz, CHP), 70.90 (CH), 72.59 (CH), 120.84 (d, $J_{(CP)}$ =4.1 Hz, Ph), 121.04 (d, $J_{(CP)}$ =4.0 Hz, Ph), 125.73 (d, $J_{(CP)}$ =2.3 Hz, Ph), 130.33 (Ph), 150.38 (t, $J_{(CP)}$ =9.7 Hz, Ph), 158.31 (C=O), 159.72 (C=O). ^{31}P NMR (162 MHz, DMSO-d_6): δ (ppm): 18.02. LC-MS **4b′** m/z: 459.5 $[M + H]^+$ (calc. for $C_{22}H_{27}N_4O_5P$ + H, m/z: 459.2 LC-MS m/z: 459.5 $[M + H]^+$ (calc. for $C_{22}H_{27}N_4O_5P$ + H, m/z: 459.2). Anal. Calcd for $C_{22}H_{27}N_4O_5P$. C, 57.64; H, 5.94; N, 12.22. Found: C, 58.78; H, 5.82; N, 12.38.

4b″ viscous oil: ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 0.95 (t, J = 7.2 Hz, 3H, CH_2Me), 1.97 (s br., 1H, C*H*H), 2.02 – 2.11 (m, 1H, CH*H*), 2.81 (s, 3H, NMe), 2.84 (s, 3H, NMe), 2.85 (s, 3H, NMe), 4.51 (s br., 1H, NCHP), 5.06 (d, 1H, J = 8.5 Hz, CH-CH), 5.39 (d, 1H, J = 8.6 Hz, CH-CH), 7.15 – 7.27 (m, 6H, Ph), 7.36 – 7.44 (m, 4H, Ph). ^{13}C NMR (101 MHz, DMSO-d_6): 10.49 (d, $J_{(CP)}$ = 14.4 Hz, CH_2Me), 21.76 (d, J=5.9 Hz, CH_2), 29.85 (NMe), 30.40 (NMe), 31.43 (NMe), 51.80 (d, $J_{(CP)}$ = 155.5 Hz, CHP), 71.31 (CH), 72.19 (CH), 120.45 (dd, $J_{(CP)}$ = 12.5, 4.1 Hz,), 125.60 (d, $J_{(CP)}$ = 6.2 Hz, Ph), 130.09 (d, $J_{(CP)}$ = 4.4 Hz, Ph), 149.61 (d, $J_{(CP)}$ = 4.9 Hz, Ph), 149.70 (d, $J_{(CP)}$ = 5.4 Hz, Ph), 157.96 (C=O), 159.63 (C=O). ^{31}P NMR (162 MHz, DMSO-d_6): δ (ppm): 17.52. LC-MS m/z: 459.4 $[M + H]^+$ (calc. for $C_{22}H_{27}N_4O_5P$ + H, m/z: 459.2). Anal. Calcd for $C_{22}H_{27}N_4O_5P$. C, 57.64; H, 5.94; N, 12.22. Found: C, 57.56; H, 6.05; N, 12.40.

Diphenyl [1-(3,4,6-trimethyl-2,5-dioxohexahydroimidazo[4,5-d]imidazol-1(2H)-yl)butyl]-phosphonate **4c**. Viscous oil. Yield 63 %, **4c′**:**4c″** = 57:43.

4c′ viscous oil: ^{1}H NMR (400 MHz, DMSO-*d*$_6$): δ (ppm) 0.92 (t, 3H, *J* = 7.5 Hz, CH_2Me), 1.35 (m, 1H, C*H*HMe), 1.45 (m, 1H, CH*H*Me), 1.96 (m, 1H, PCHC*H*H), 2.28 (s br. 1H, PCHCH*H*), 2.82 (s, 3H, NMe), 2.84 (s, 6H, NMe), 4.34 (s br., 1H, PCH), 5.14 (d, 1H, *J* = 8.3 Hz, CH-CH), 5.21 (d, 1H, J=8.7 Hz, CH-CH), 7.07 – 7.25 (m, 6H), 7.30 – 7.43 (m, 4H,). ^{13}C NMR (101 MHz, DMSO-*d*$_6$): 13.79 (CH_2Me), 19.58 (d, $J_{(CP)}$ =14.0 Hz, CH_2Me), 28.36 (CH_2CH_2Me), 30.21 (NMe), 30.59 (NMe), 31.48 (NMe), 51.68 (d, $J_{(CP)}$ = 150.8 Hz, CHP), 70.78 (CH-CH), 72.61 (CH-CH), 120.95 (d, $J_{(CP)}$ = 24.1 Hz, Ph), 125.72, 130.33, 150.39 (t, $J_{(CP)}$ = 9.9 Hz, Ph), 158.28 (C=O), 159.80 (C=O). ^{31}P NMR (162 MHz, DMSO-*d*$_6$): δ (ppm): 18.12. LC-MS m/z: 473.3 $[M + H]^+$ (calc. for $C_{23}H_{29}N_4O_5P$ + H, m/z: 473.2). Anal. Calcd for $C_{23}H_{29}N_4O_5P$. C, 58.47; H, 6.19; N, 11.86. Found: C, 58.71; H, 6.23; N, 12,11.

4c″ viscous oil: ^{1}H NMR (400 MHz, DMSO-*d*$_6$): δ (ppm) 0.90 (t, 3H, *J* = 7.3 Hz, CH_2Me), 1.27 – 1.46 (m, 2H, CH_2Me), 1.87 – 2.09 (m, 2H, $CHCH_2$), 2.81 (s, 3H, NMe), 2.83 (s, 3H, NMe), 2.85 (s, 3H, NMe), 4.63 (s br., 1H, CHP), 5.04 (d, 1H, *J* = 8.6 Hz, CH-CH), 5.39 (d, 1H, *J* = 8.5 Hz, CH-CH), 7.11 – 7.30 (m, 6H, Ph), 7.41 (m, 4H, Ph). ^{13}C NMR (101 MHz, DMSO-*d*$_6$): 13.59 (CH_2Me), 18.91 (d, $J_{(CP)}$ = 14.0 Hz, CH_2Me), 30.26 (NMe), 30.44 (d, $J_{(CP)}$ = 5.5 Hz, $CHCH_2$), 30.81 (NMe), 32.05 (NMe), 49.64 (d, $J_{(CP)}$ = 154.6 Hz, CHP), 71.66 (CH-CH), 72.64 (CH-CH), 120.75 (d, $J_{(CP)}$ = 4.0 Hz, Ph), 120.90 (d, $J_{(CP)}$ = 4.1 Hz, Ph), 126.04 (d, $J_{(CP)}$ = 4.2 Hz, Ph), 130.52 (d, $J_{(CP)}$ = 3.3 Hz, Ph), 149.99 (d, $J_{(CP)}$ = 2.9 Hz, Ph), 150.08 (d, $J_{(CP)}$ = 3.4 Hz, Ph), 158.32 (C=O), 160.13 (C=O). ^{31}P NMR (162 MHz, DMSO-*d*$_6$): δ (ppm): 17.71. LC-MS m/z: 473.4 $[M + H]^+$ (calc. for $C_{23}H_{29}N_4O_5P$ + H, m/z: 473.2). Anal. Calcd for $C_{23}H_{29}N_4O_5P$. C, 58.47; H, 6.19; N, 11.86. Found: C, 59.01; H, 6.30; N, 11.73.

Diphenyl [1-(3,4,6-trimethyl-2,5-dioxohexahydroimidazo[4,5-d]imidazol-1(2H)-yl)hexyl]-phosphonate ***4d′*** + ***4d″*** (60:40): viscous oil, yield 33 %. ^{1}H: (400 MHz, DMSO-*d*$_6$): δ (ppm) 0.85 (q, *J* = 6.9 Hz, 6H, CH_2Me **d′** + **d″**), 1.48 – 1.21 (m, 12H, $CH_2CH_2CH_2CH_3$ **d′** + **d″**), 2.06 – 1.90 (m, 3H, $CHCH_2$, **d′** + **d″**), 2.33 (s, br., 1H, $CHCH_2$, **d′**), 2.84 (s, 3H, NMe, **d″**), 2.85 (s, 6H, NMe, **d″**), 2.86 (s, 3H, NMe, **d′**), 2.87 (s, 3H, NMe, **d′**), 2.88 (s, 3H, NMe, **d′**), 4.35 (s, br., 1H, $CHCH_2$, **d′**), 4.66 (s, br., 1H, $CHCH_2$, **d″**), 5.04 (d, *J* = 8.6 Hz, 1H, CH-CH, **d″**), 5.15 (d, *J* = 8.5 Hz, 1H, CH-CH, **d′**), 5.23 (dd, *J* = 8.6, 1.9 Hz, 1H, CH-CH, **d′**), 5.42 (d, *J* = 8.5 Hz, 1H, CH-CH, **d″**), 7.27 – 7.13 (m, 12H, Ph **d′** + **d″**), 7.44 – 7.33 (m, 8H, Ph **d′** + **d″**). ^{13}C (101 MHz, DMSO-*d*$_6$): δ (ppm) 12.18, 12.21 (CH_2Me **d′** + **d″**), 20.25, 20.27 (CH_2CH_2Me **d′** + **d″**), 23.17, 23.31 ($CHCH_2CH_2$ **d′** + **d″**), 23.79, 23.92 ($CHCH_2CH_2$ **d′** + **d″**), 28.10, 28.19 (NMe **d′** + **d″**), 28.52 (CH_2CH_2Me **d′** + **d″**), 28.73, 28.80, 28.97, 29.33 (NMe **d′** + **d″**), 47.53, 48.99 (d, $J_{(CP)}$ = 147,6 Hz, CHP **d′** + **d″**), 68.78, 69.59, 70.55, 70.59 (CH-CH **d′** + **d″**), 118.65, 118.76, 118.83, 118.96 (Ph **d′** + **d″**), 123.59, 123.91, 128.20, 128.40 (Ph **d′** + **d″**), 147.98, 148.07, 148.40 (Ph **d′** + **d″**), 156.21, 157.64, 158.04 (C=O **d′** + **d″**). ^{31}P (162 MHz, DMSO-*d*$_6$): δ (ppm): 17.64 (**d″**), 18.12 (**d′**). LC-MS **4d′** m/z: 501.7 $[M + H]^+$ (calc. for $C_{25}H_{33}N_4O_5P$ + H, m/z: 501.2), **4d″** m/z: m/z: 501.6 $[M + H]^+$ (calc. for $C_{25}H_{33}N_4O_5P$ + H, m/z: 501.2). Anal. Calcd for $C_{23}H_{29}N_4O_5P$. C, 59.99; H, 6.65; N, 11.19. Found: C, 59.37; H, 6.52; N, 11.33.

Figure S1 ^{1}H NMR spectrum of compound **4a′**

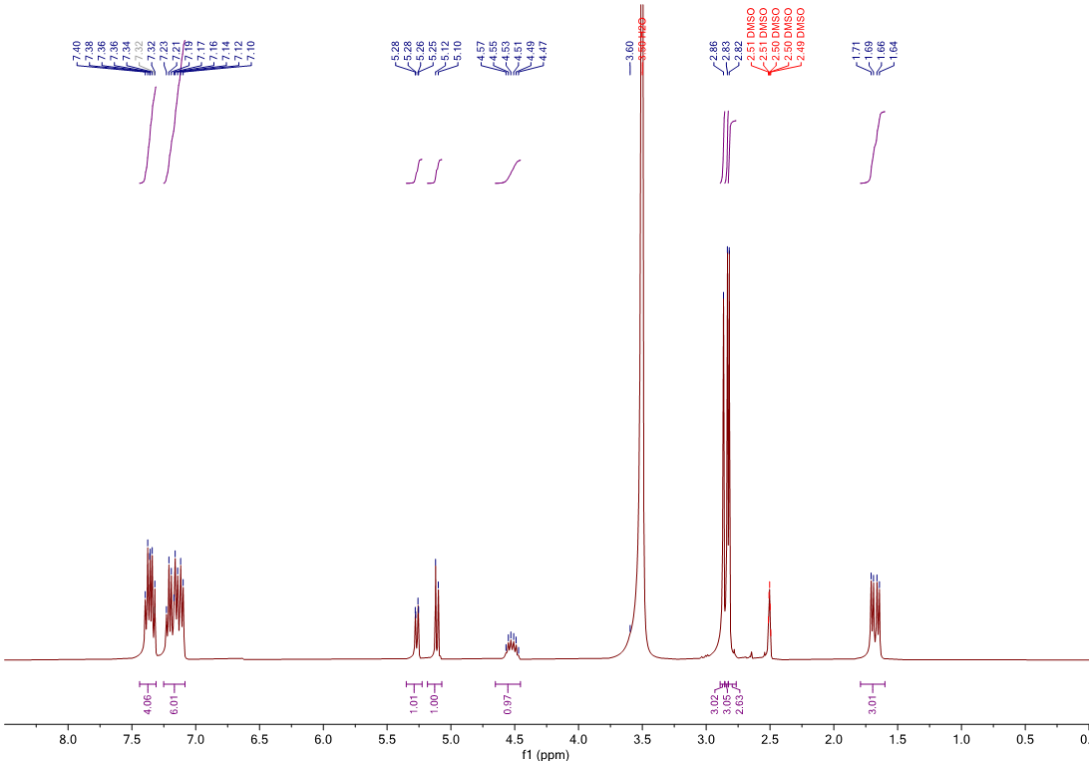


Figure S2 ^{13}C NMR spectrum of compound **4a′**

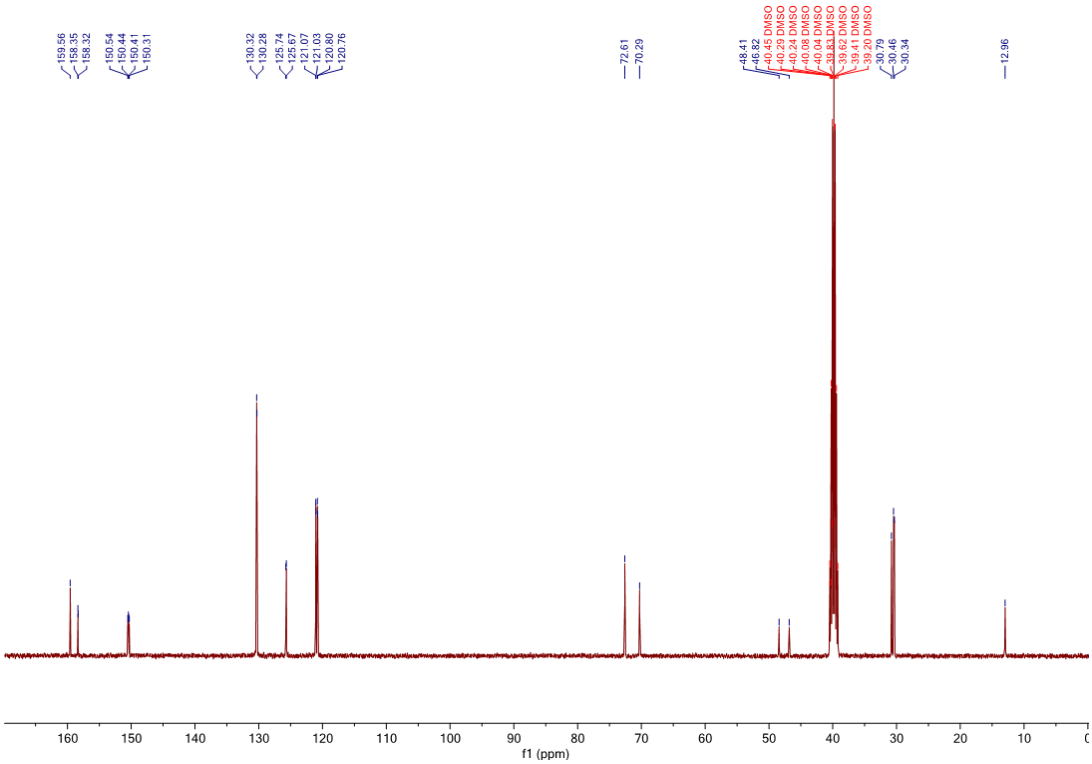


Figure S3 ^{31}P NMR spectrum of compound **4a′**

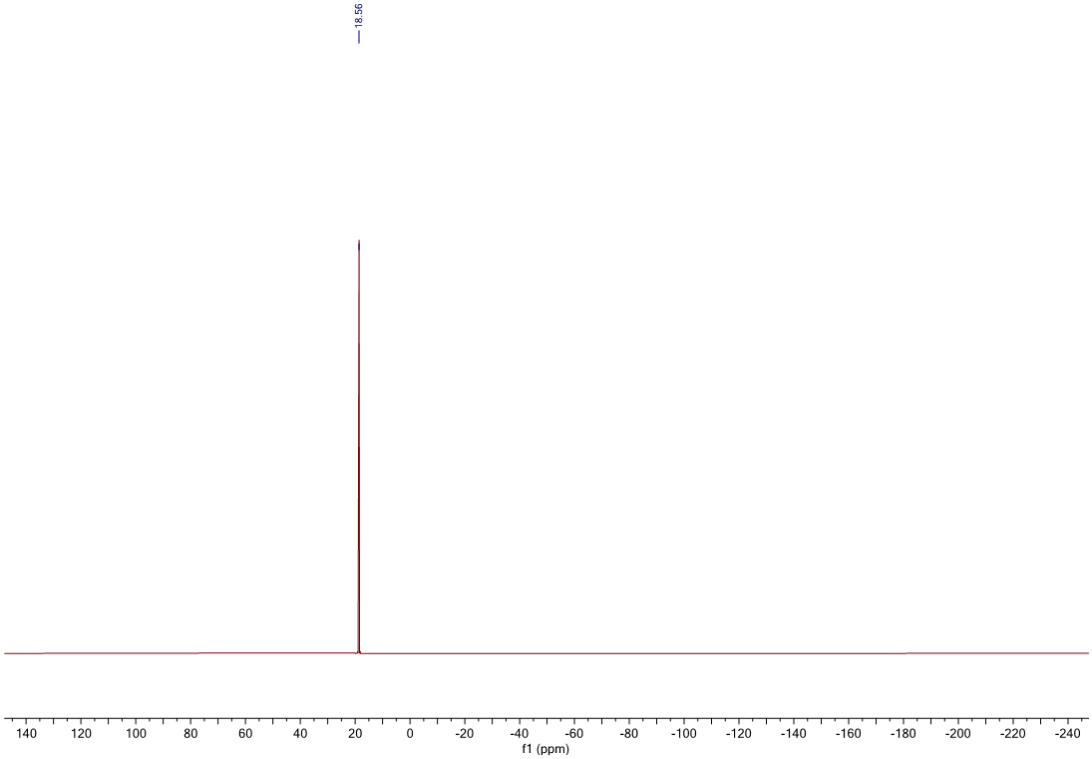


Figure S4 ^{1}H NMR spectrum of compound **4a″**

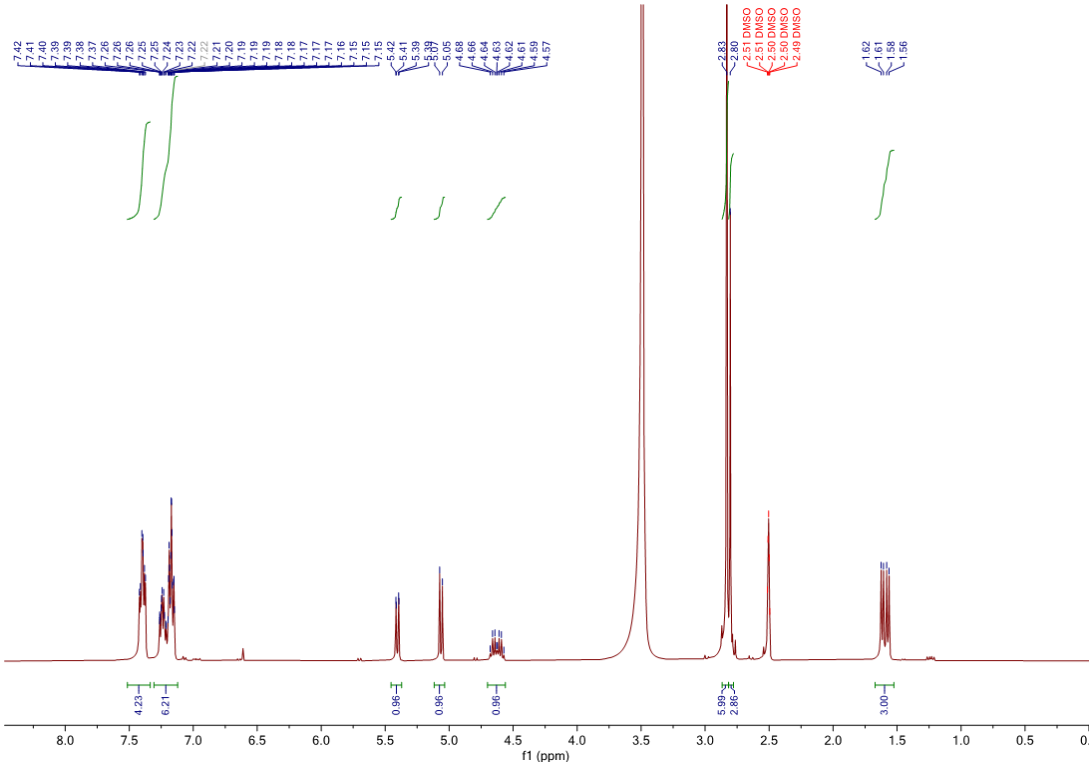


Figure S5 ^{13}C NMR spectrum of compound **4a″**

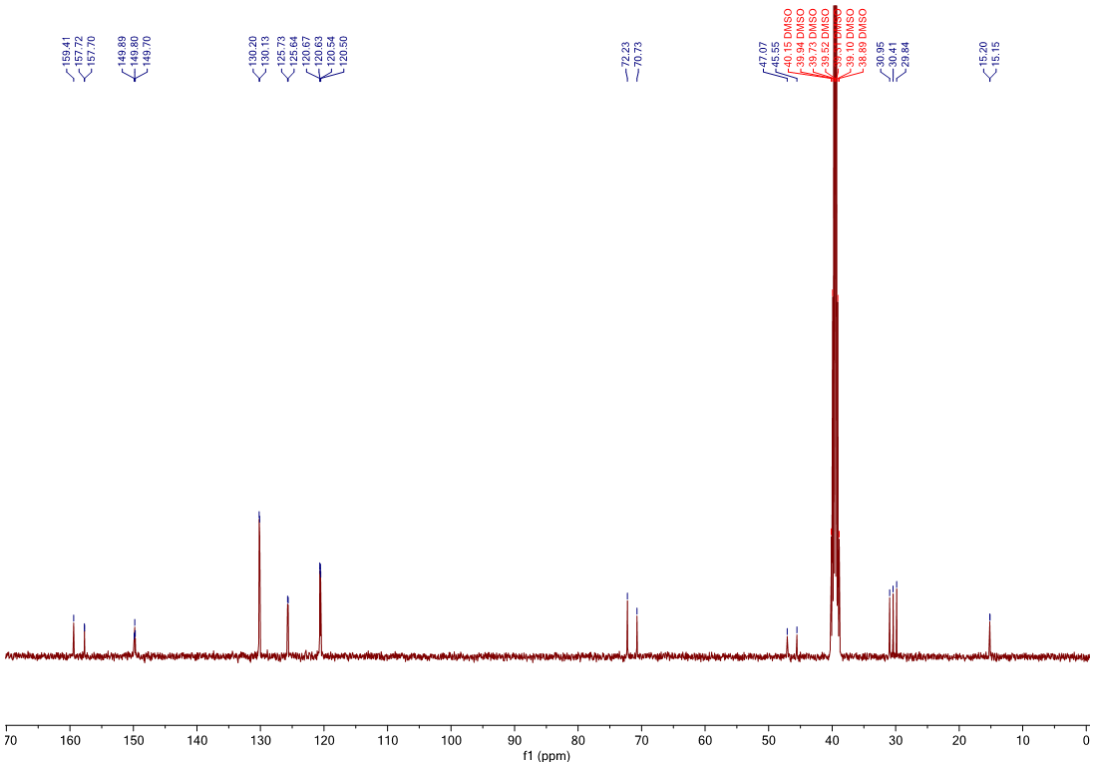


Figure S6 ^{31}P NMR spectrum of compound **4a″**

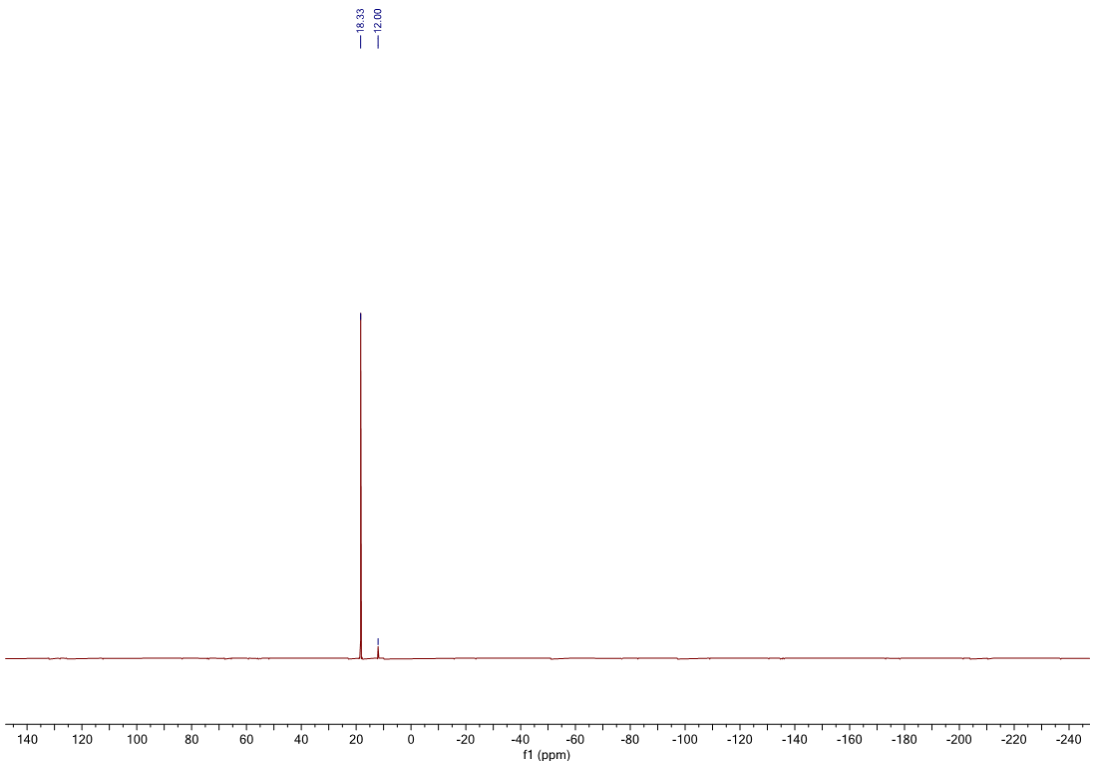


Figure S7 ^{1}H NMR spectrum of compound **4b′**

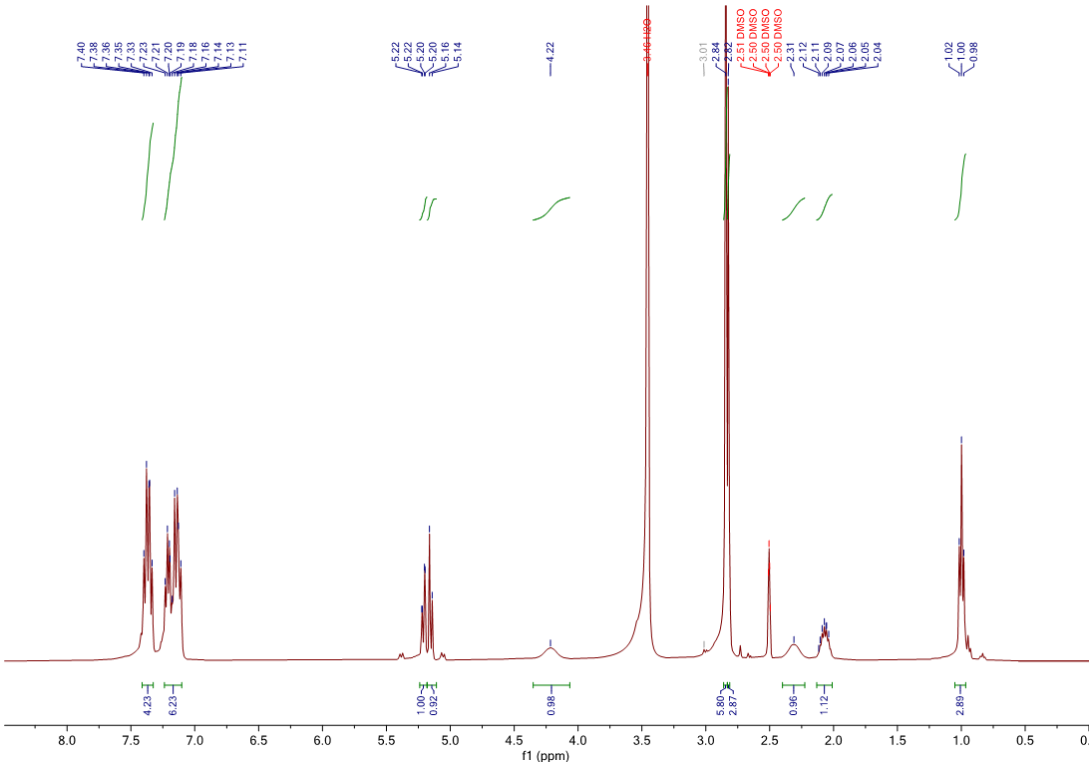


Figure S8 ^{13}C NMR spectrum of compound **4b′**

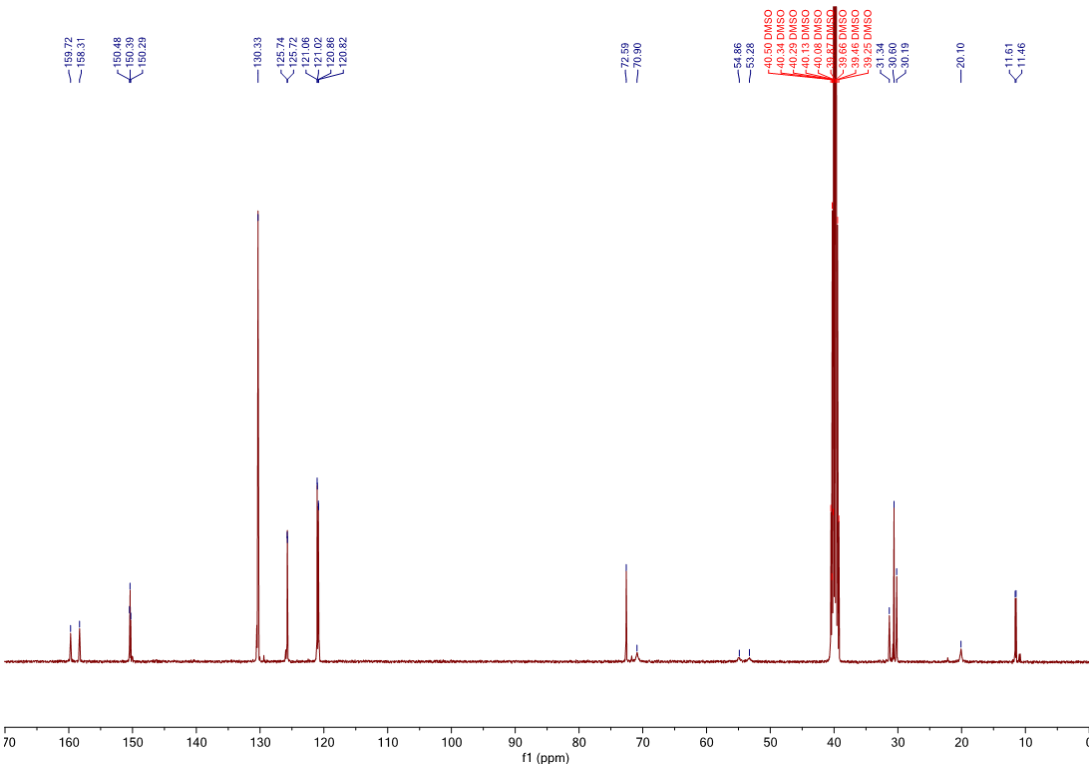


Figure S9 ^{31}P NMR spectrum of compound **4b′**

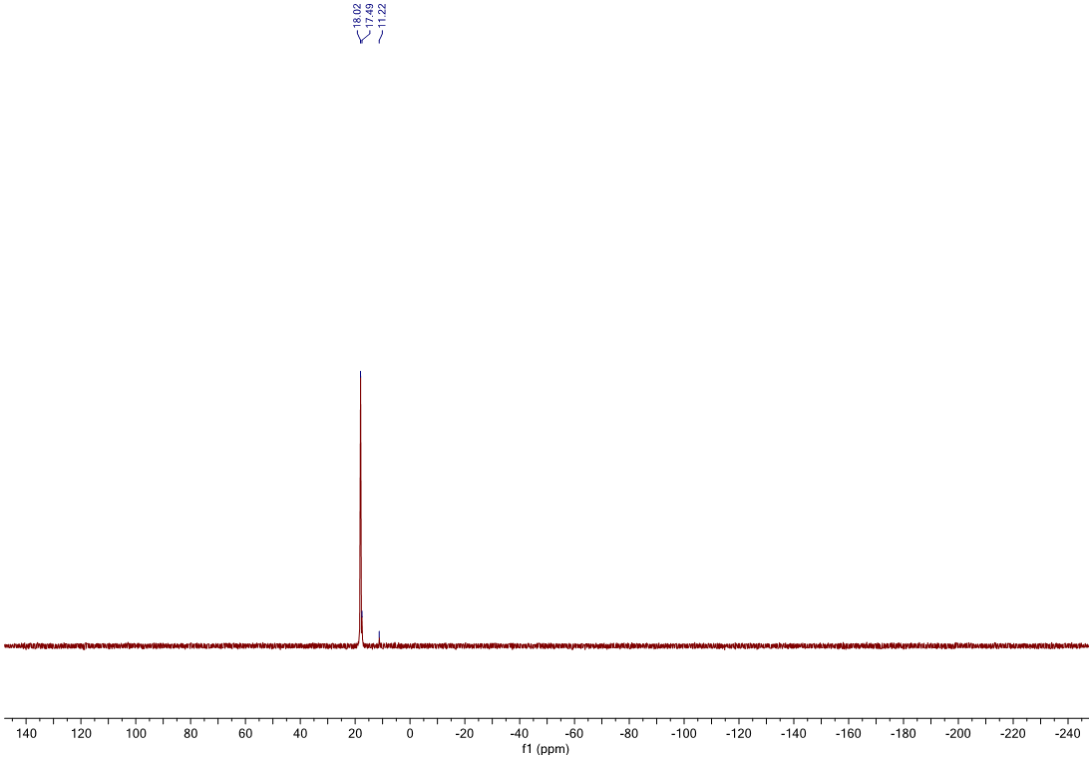


Figure S10 ^{1}H NMR spectrum of compound **4b″**

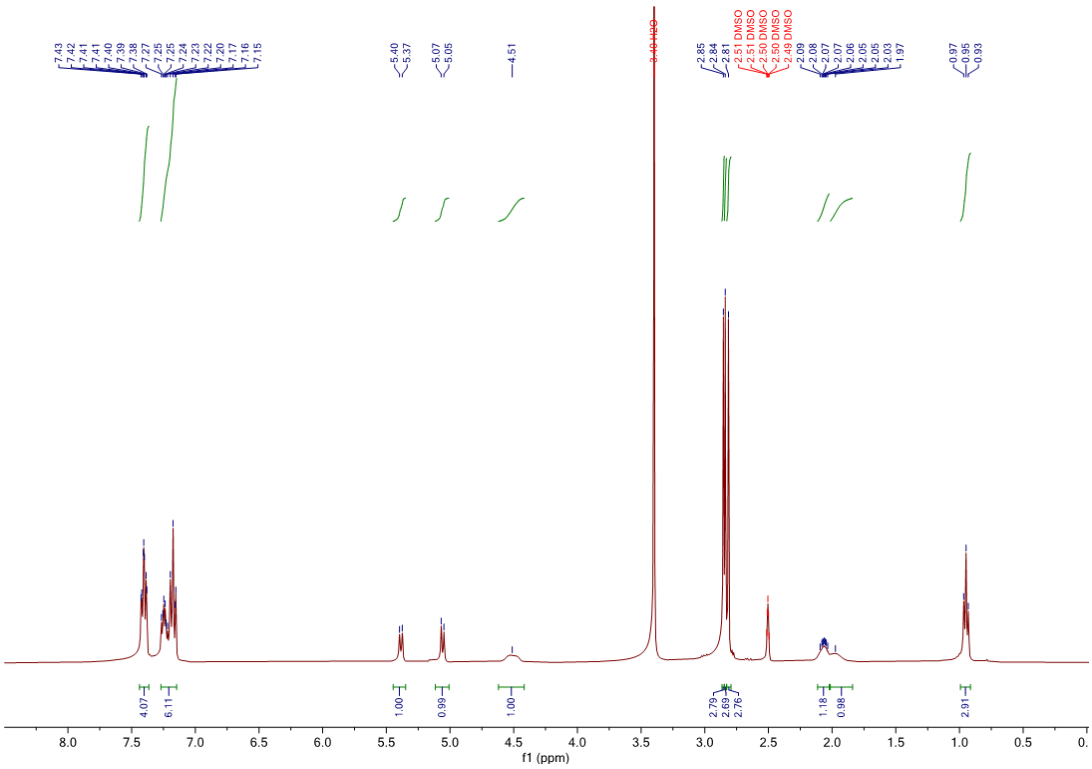


Figure S11 ^{13}C NMR spectrum of compound **4b″**

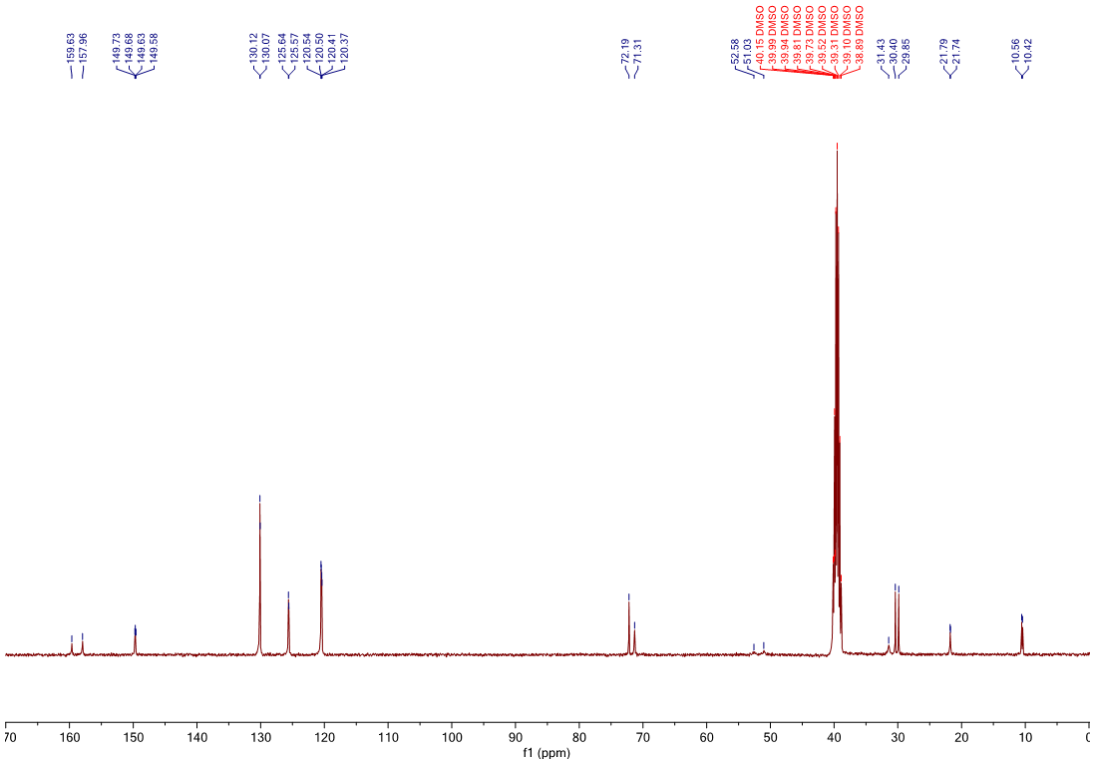


Figure S12 ^{31}P NMR spectrum of compound **4b″**

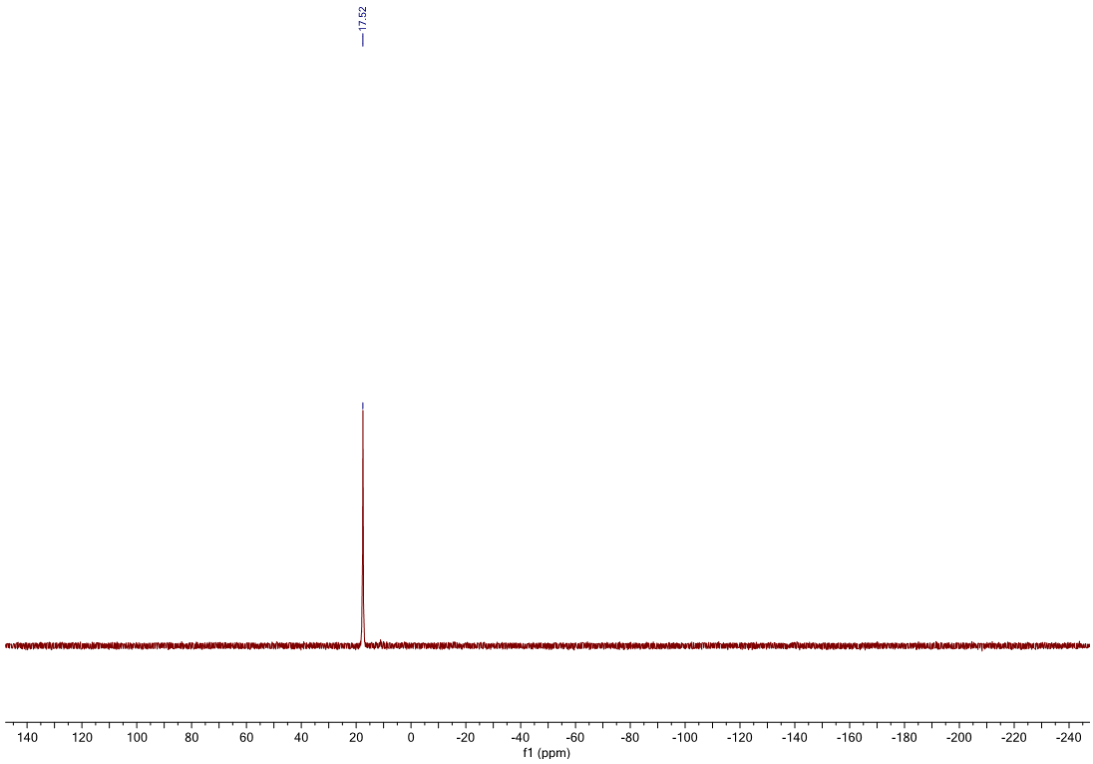


Figure S13 ^{1}H NMR spectrum of compound **4c′**

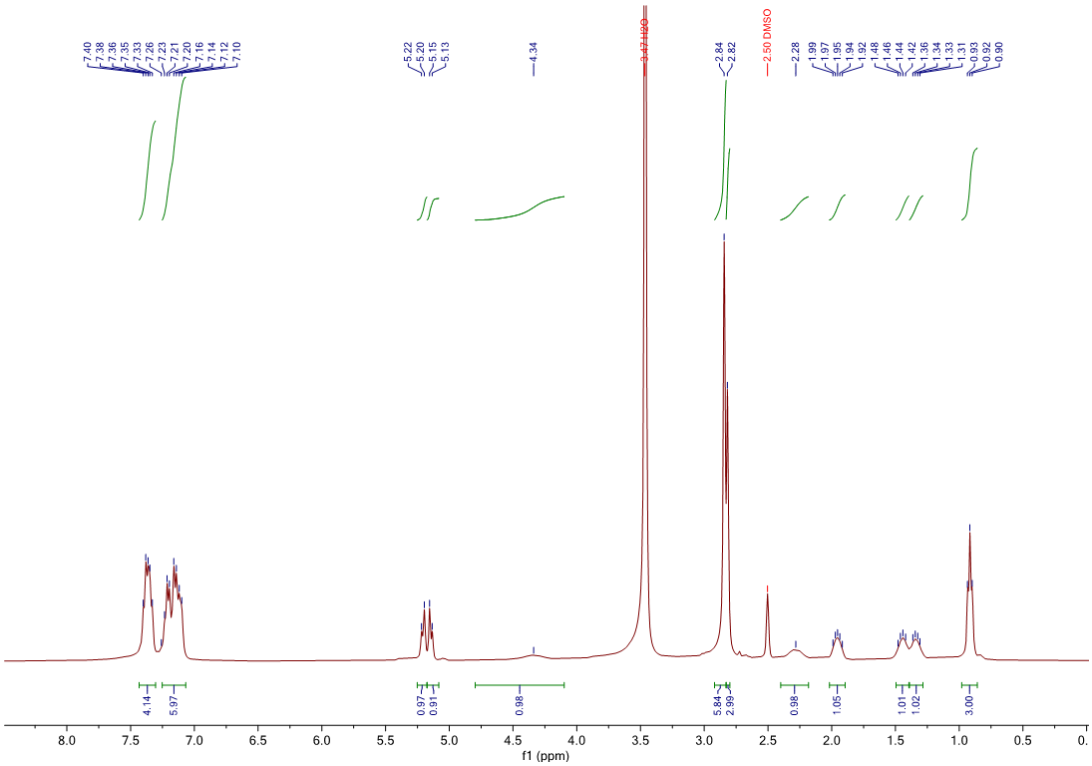


Figure S14 ^{13}C NMR spectrum of compound **4c′**

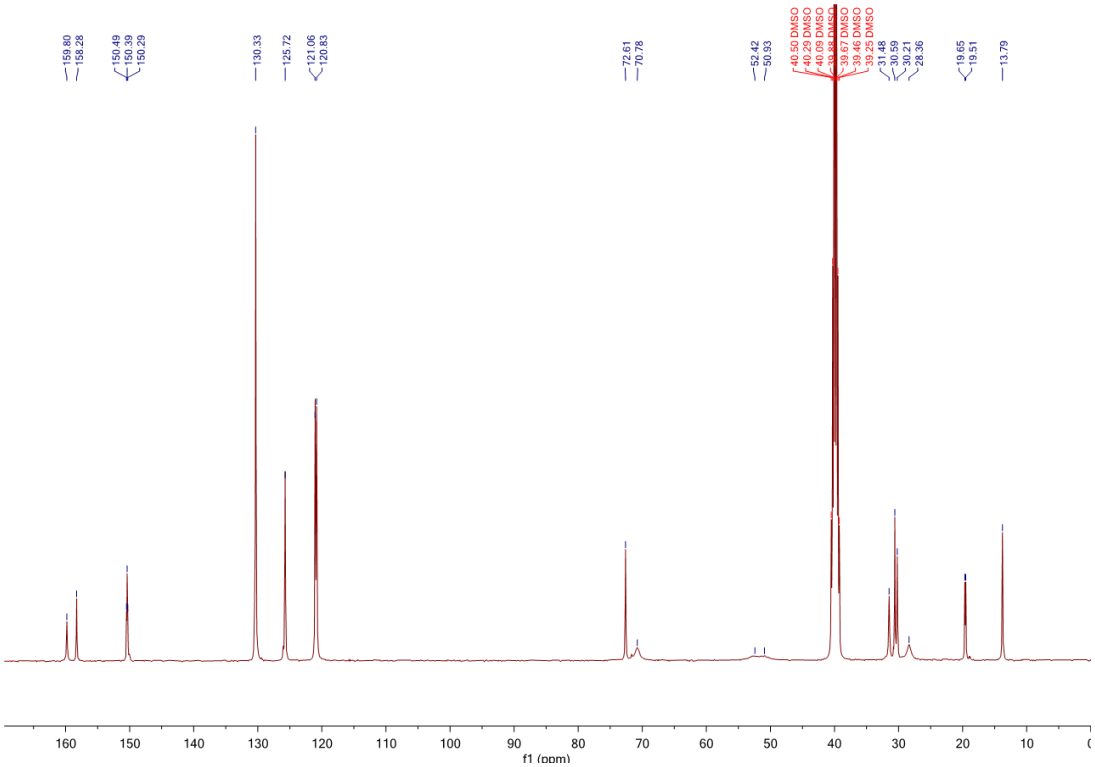


Figure S15 ^{31}P NMR spectrum of compound **4c′**

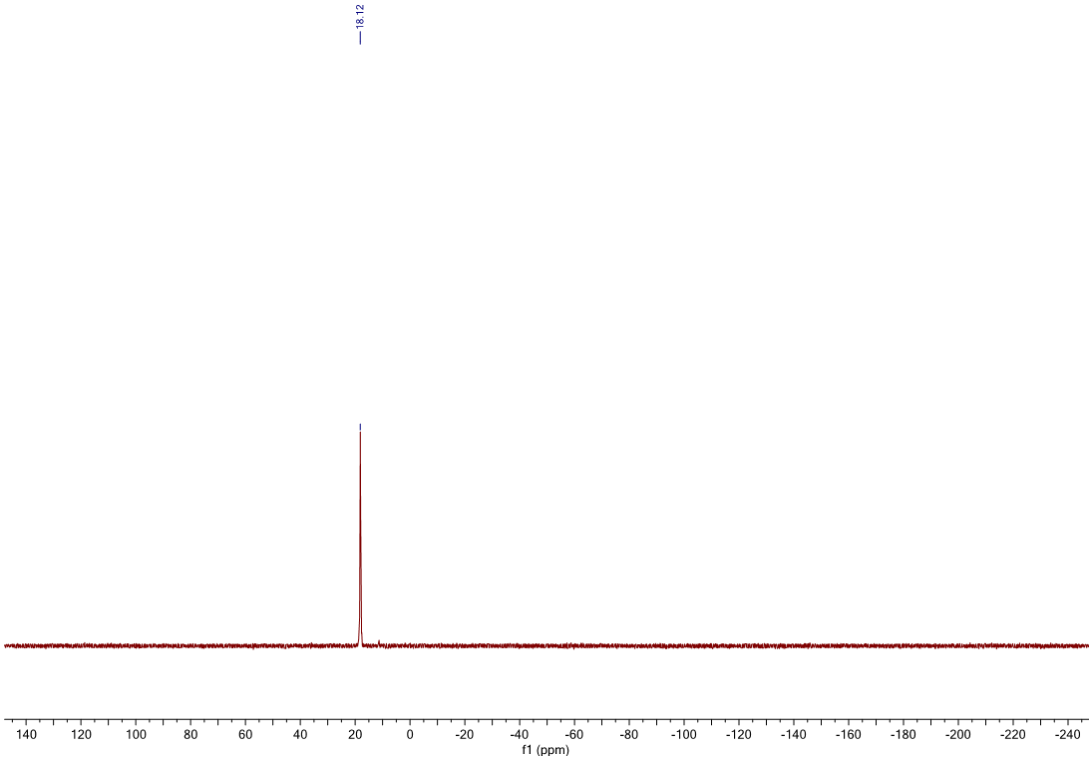


Figure S16 ^{1}H NMR spectrum of compound **4c″**

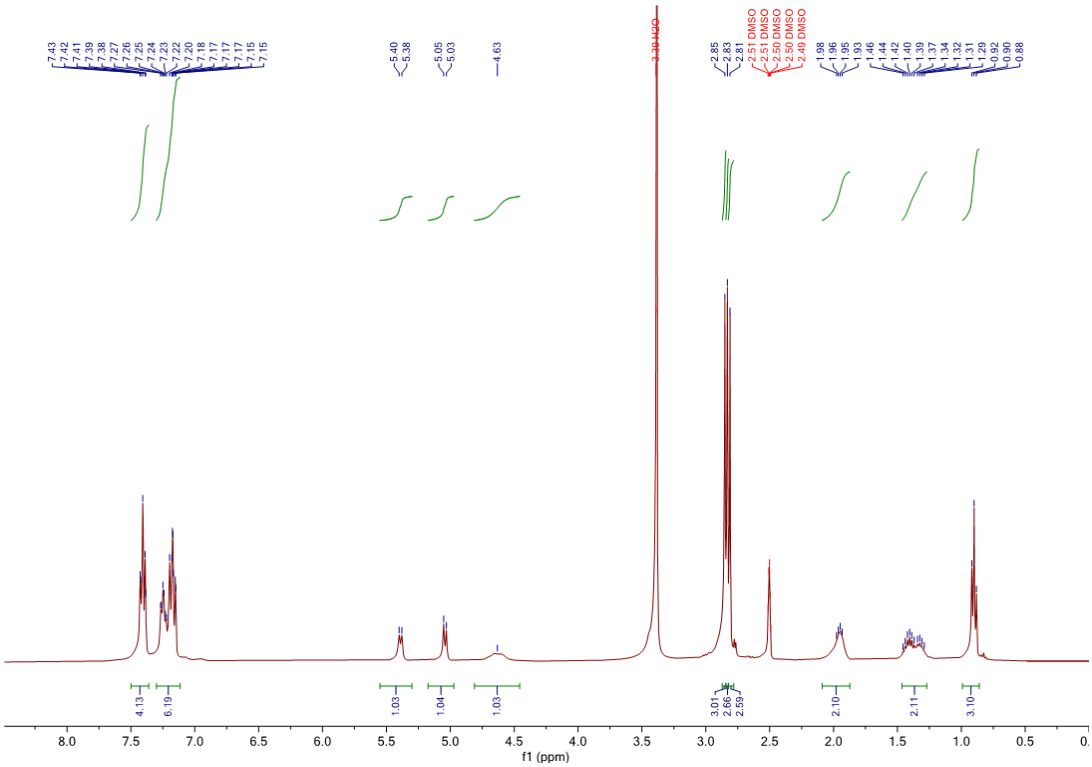


Figure S17 ^{13}C NMR spectrum of compound **4c″**

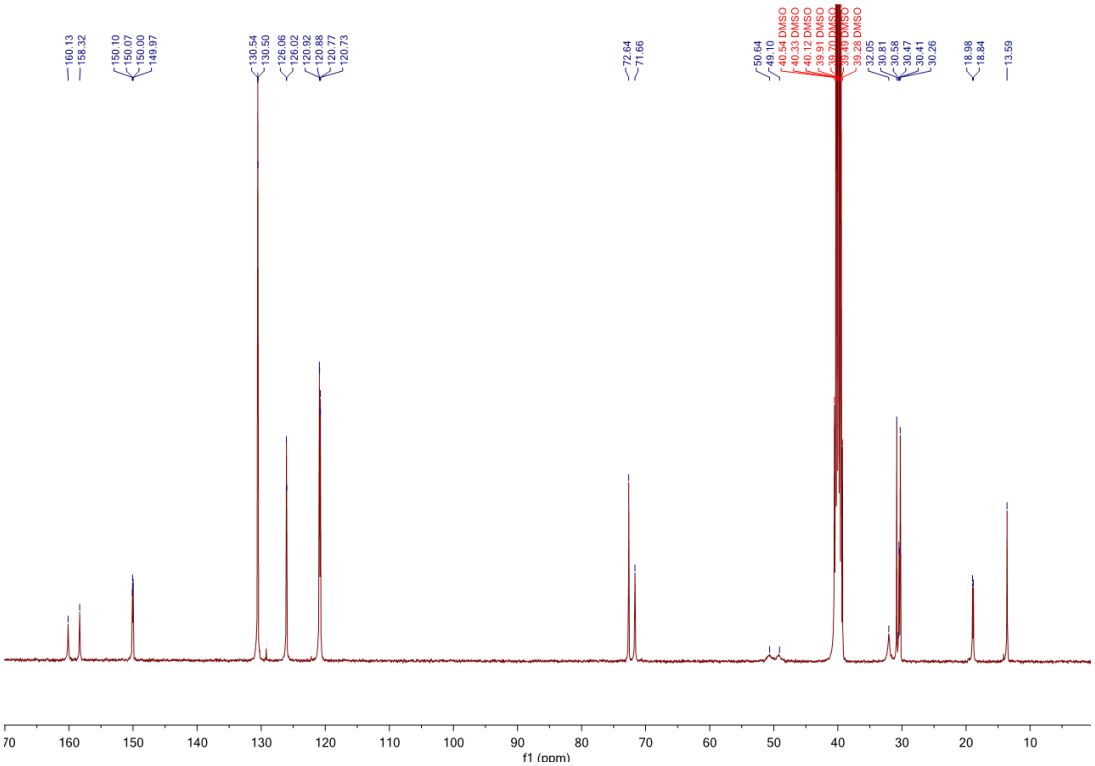


Figure S18 ^{31}P NMR spectrum of compound **4c″**

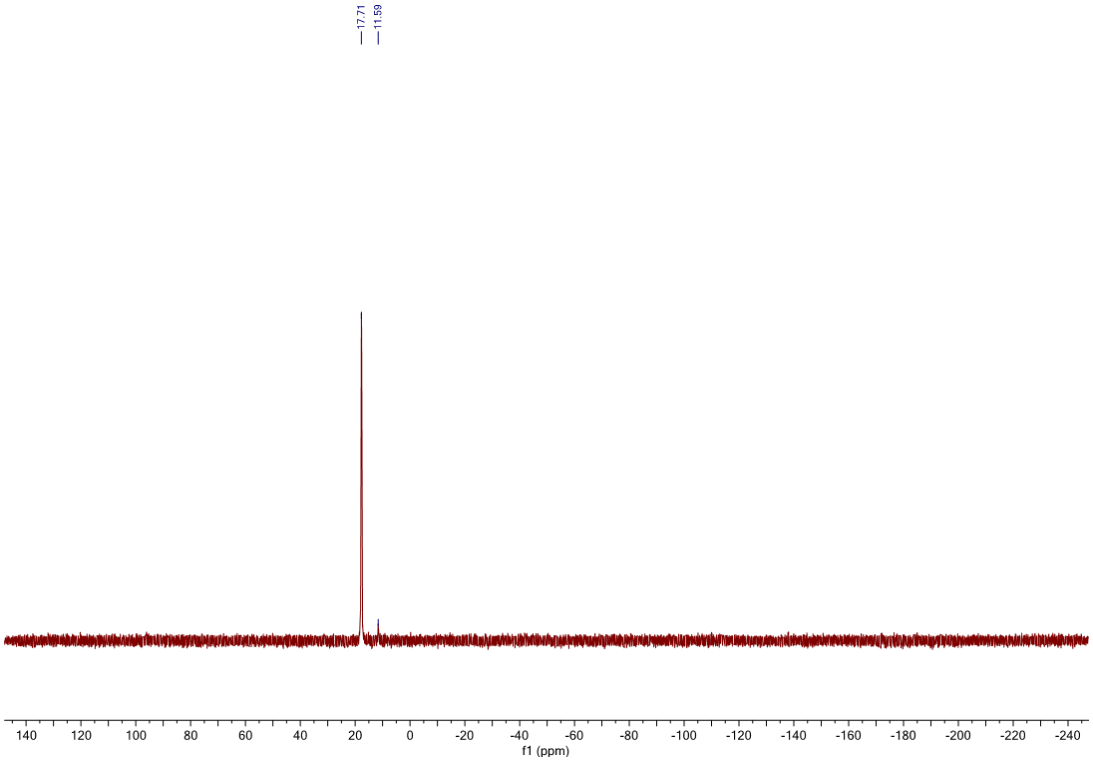


Figure S19 ^{1}H NMR spectrum of compounds **4d′** + **4d″**

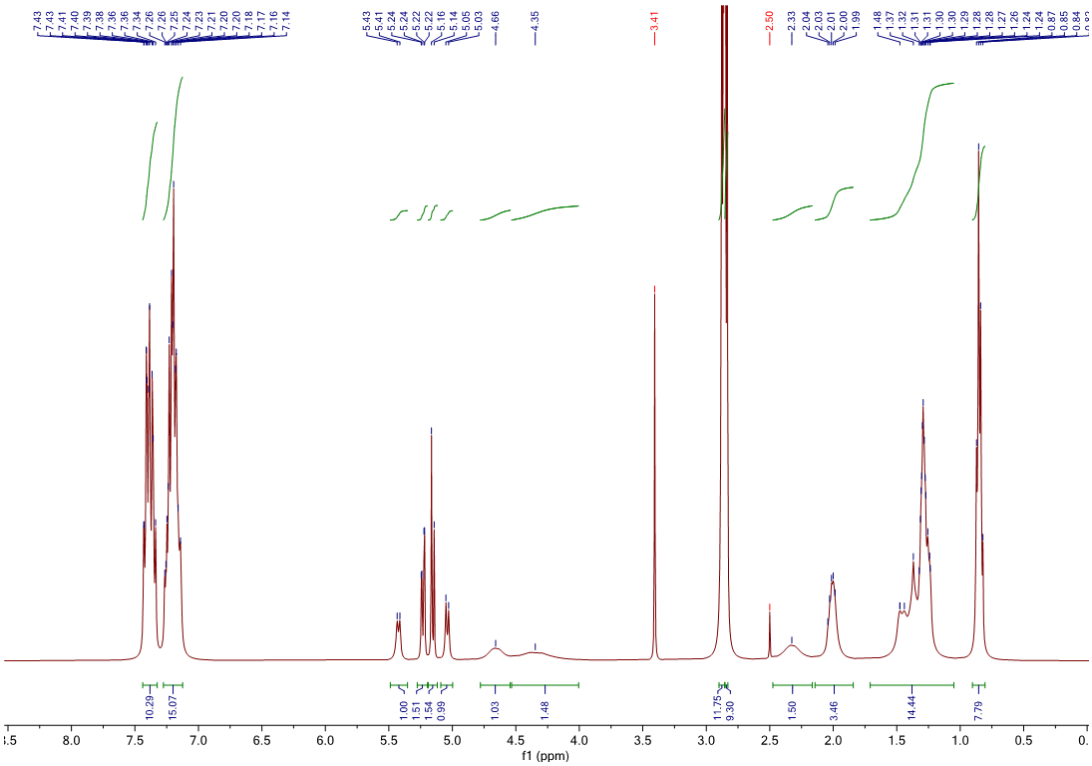


Figure S20 ^{13}C NMR spectrum of compounds **4d′** + **4d″**

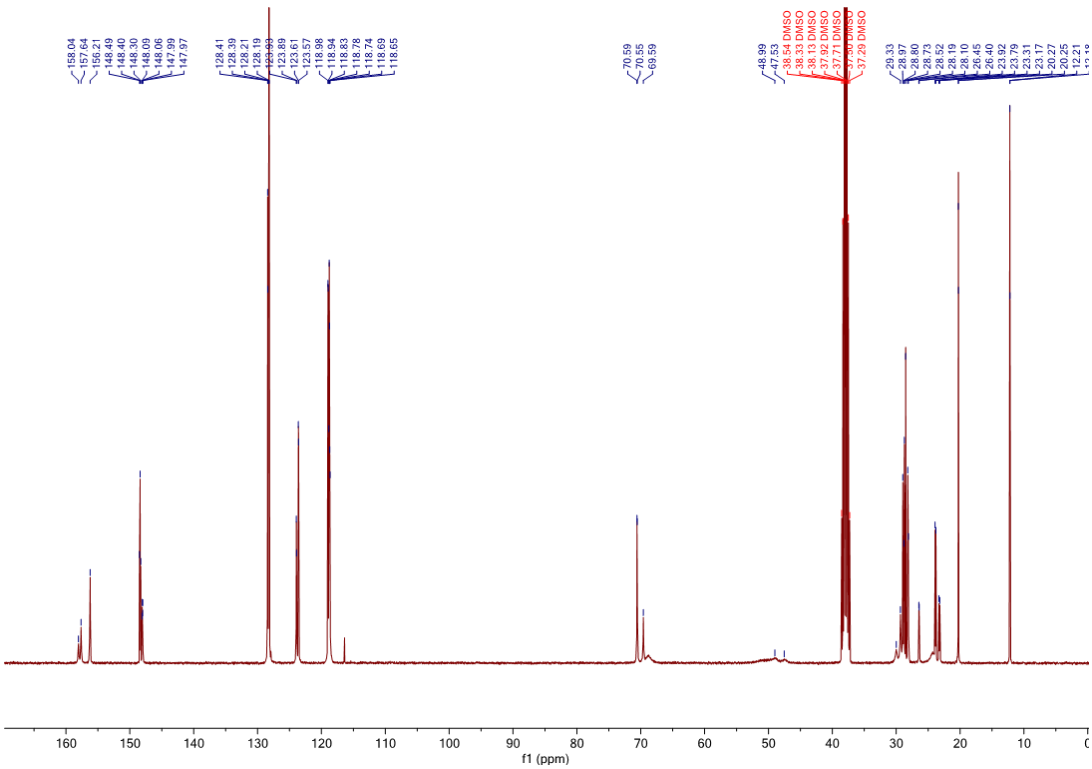
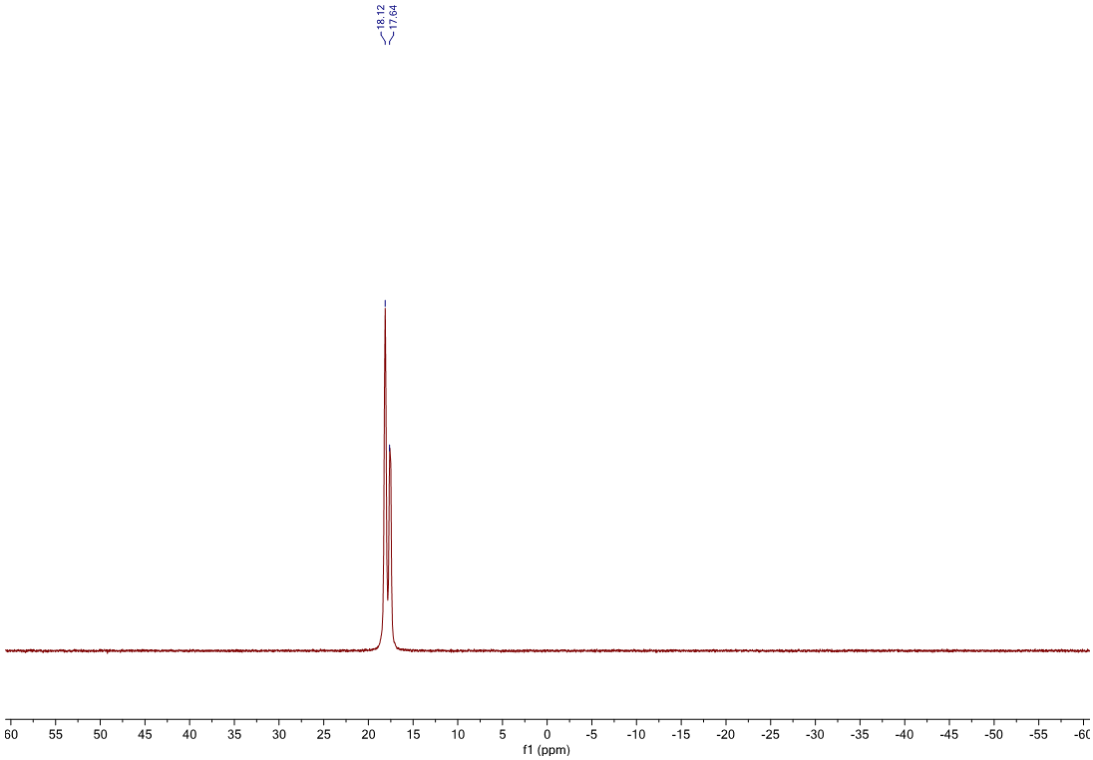


Figure S21 ^{31}P NMR spectrum of compounds **4d′** + **4d″**



MS spectra of compounds **4a-d**

Figure S22 MS spectrum of compound **4a′**

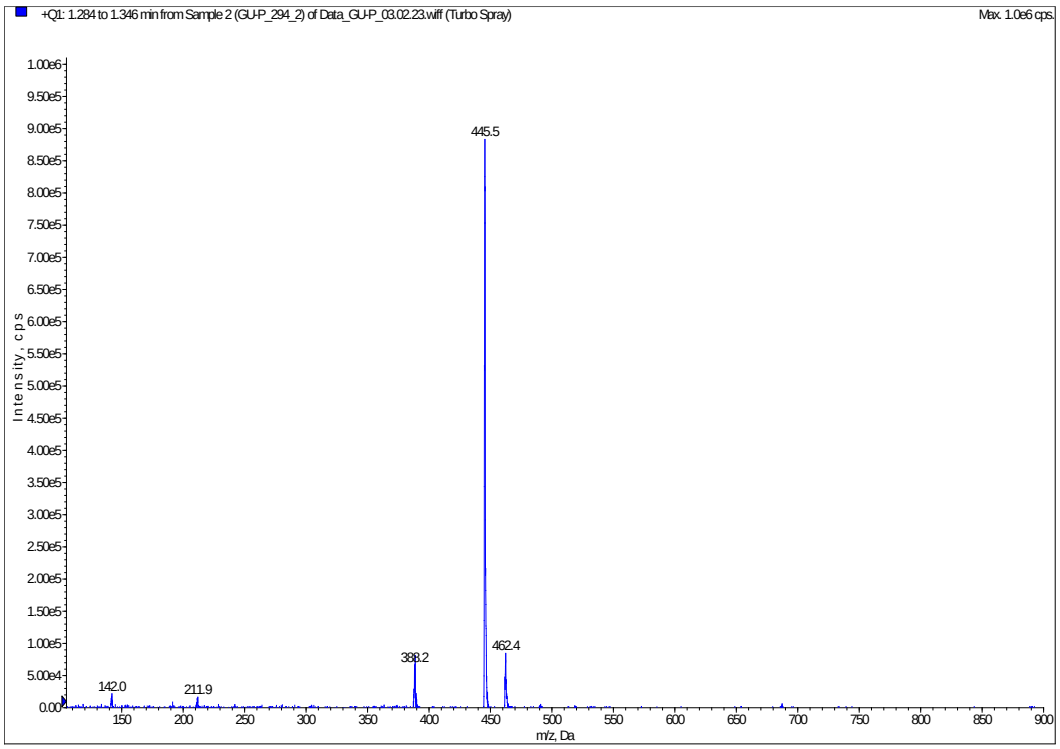


Figure S23 MS spectrum of compound **4a″**

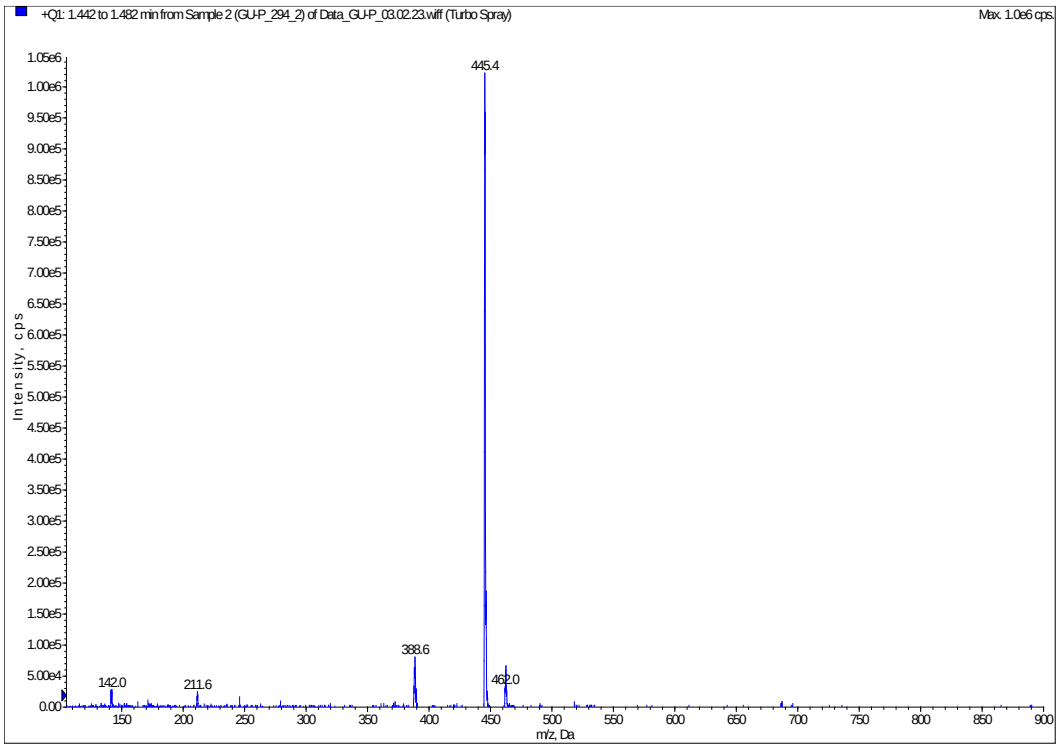


Figure S24 MS spectrum of compound **4b′**

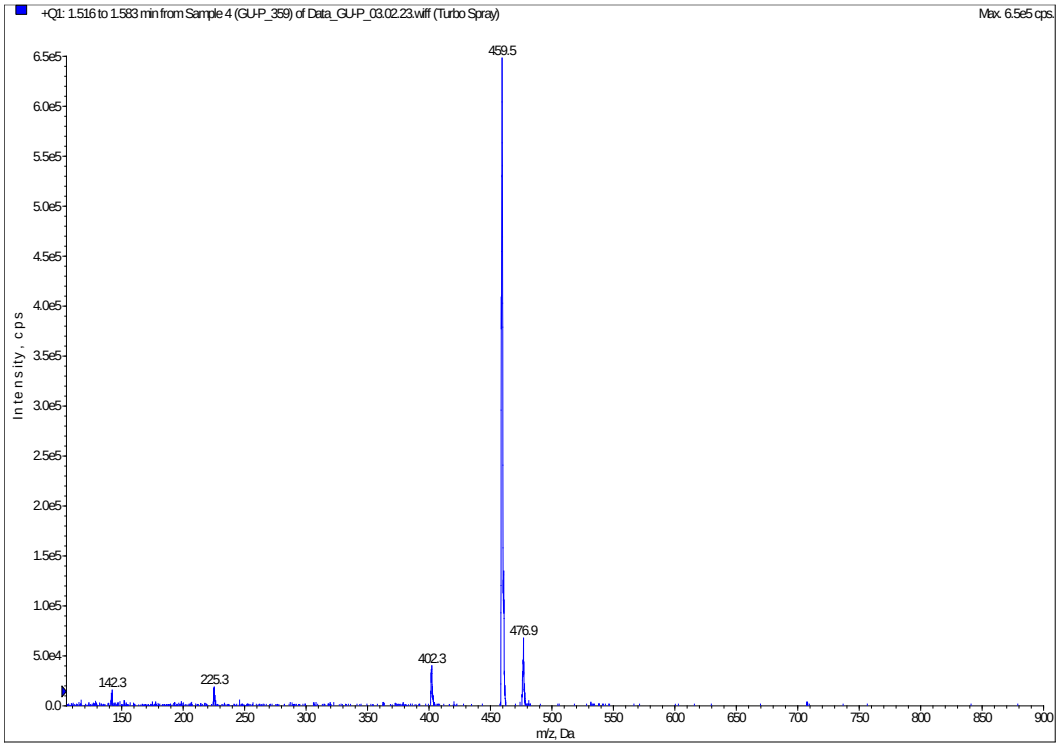


Figure S25 MS spectrum of compound **4b″**

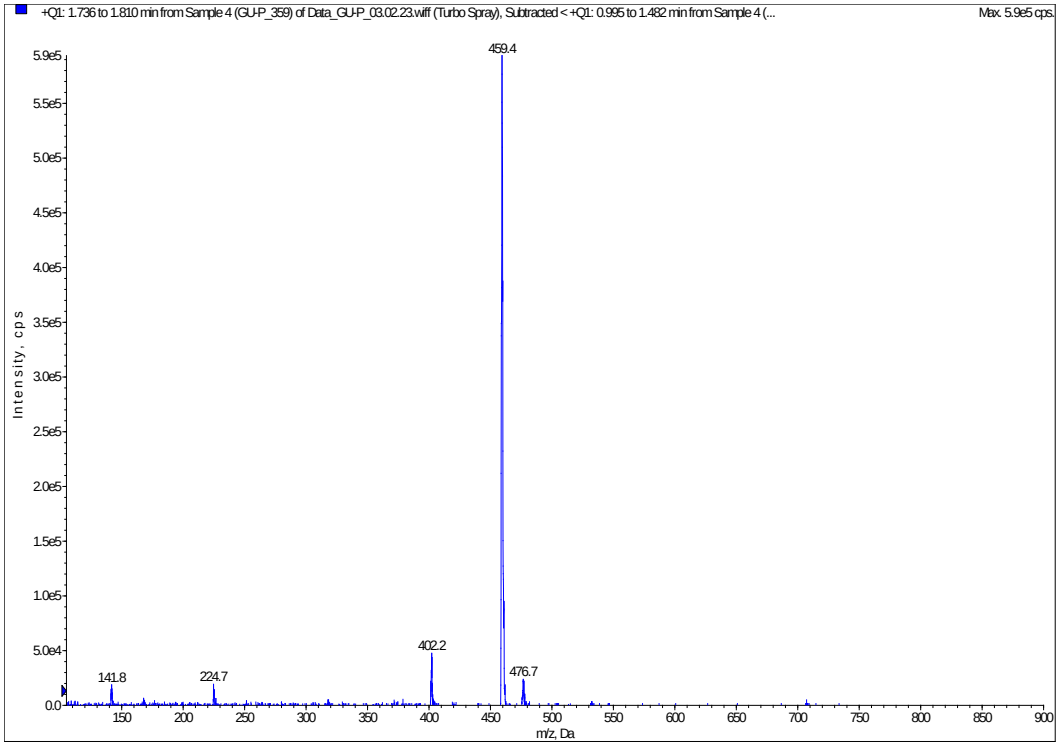


Figure S26 MS spectrum of compound **4c′**

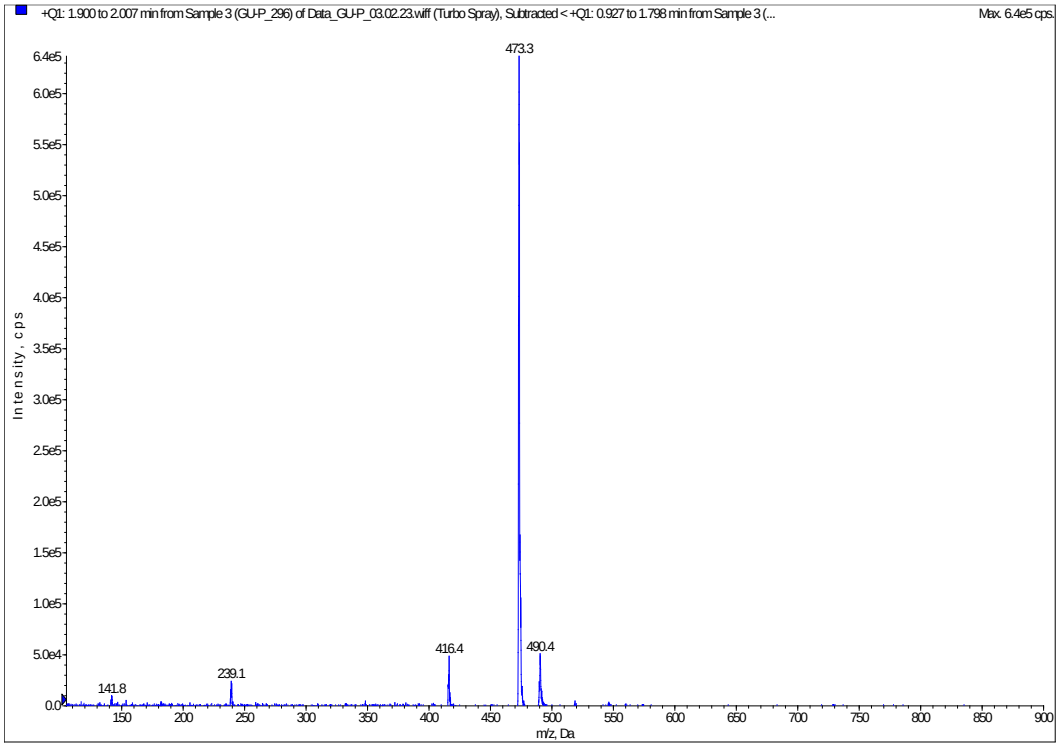


Figure S27 MS spectrum of compound **4c″**

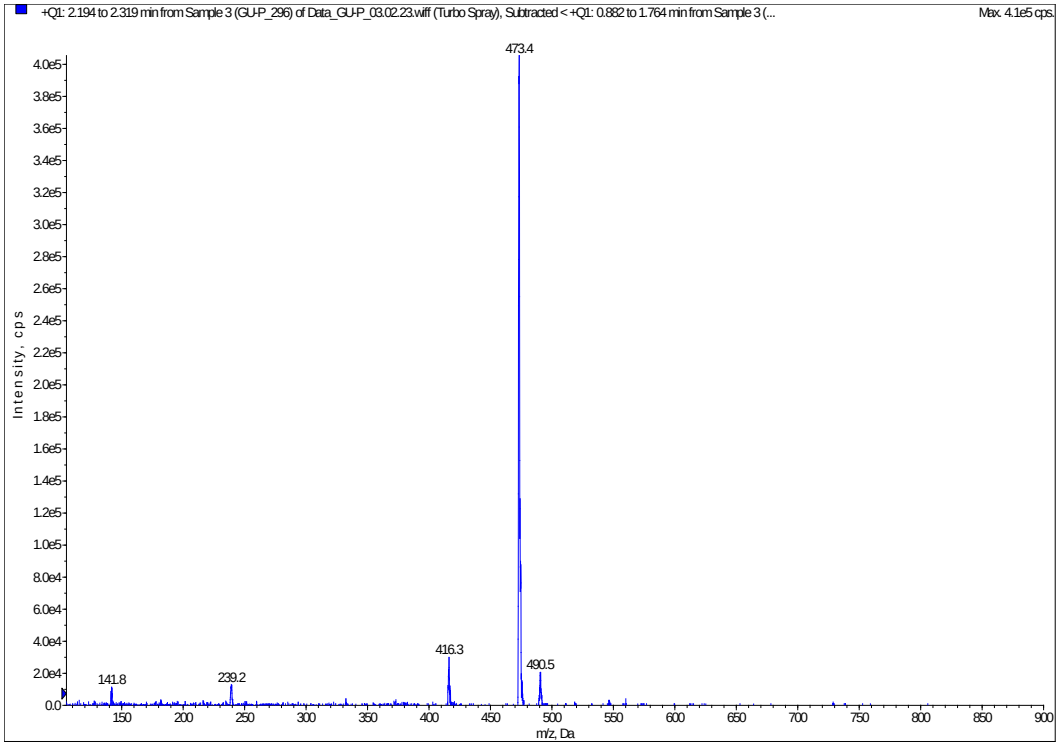


Figure S28 MS spectrum of compound **4d′**

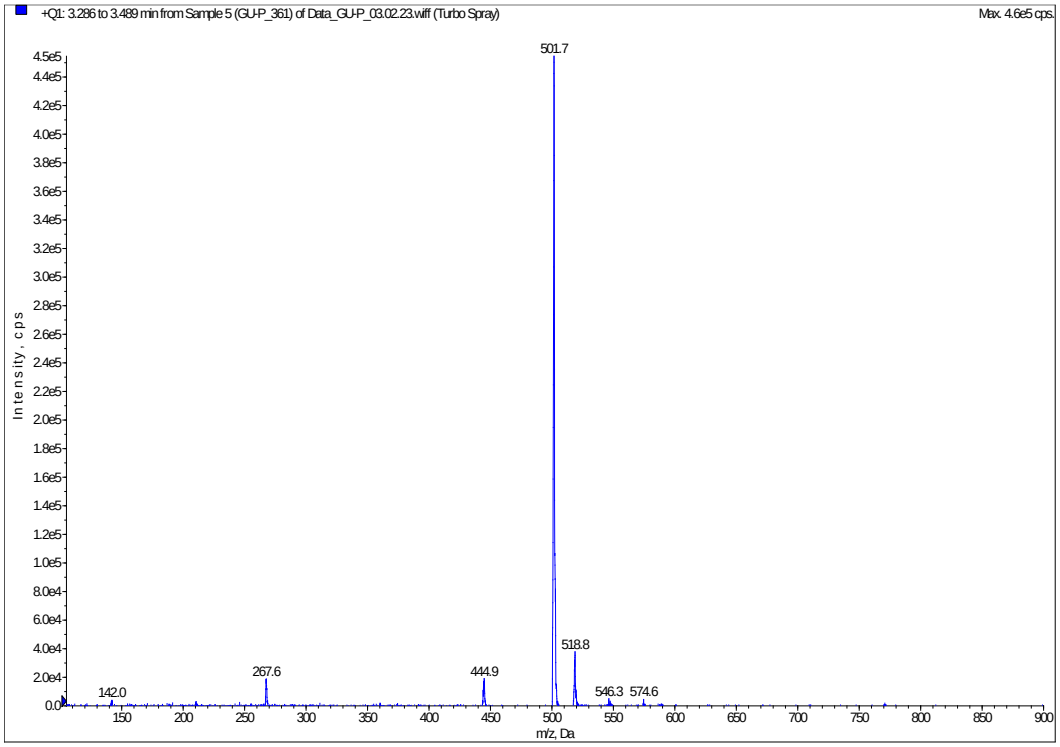


Figure S29 MS spectrum of compound **4d″**