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Electronic Supplementary Information

Synthesis of *meta* and *para*-substituted aromatic sulfonate derivatives of polydentate phenylazaphosphinate ligands: enhancement of the water solubility of emissive europium (III) EuroTracker dyes

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NMR Spectroscopy and Mass Spectrometry

^{1}H, ^{13}C, ^{19}F and ^{31}P NMR spectra were recorded in commercially-available deuteriated solvents on a Varian Mercury-200 (^{1}H at 199.975 MHz, ^{13}C at 50.289 MHz), Varian Mercury-400 or Bruker Avance-400 (^{1}H at 399.960 MHz, ^{13}C at 100.572 MHz, ^{31}P at 161.943 MHz), Varian Inova-500 (^{1}H at 499.772 MHz, ^{13}C at 125.671 MHz,) or Varian VNMRS-700 (^{1}H at 699.731 MHz, ^{31}P at 283.256 MHz) spectrometer. All chemical shifts are given in ppm and coupling constants are in Hz. Electrospray mass spectra were recorded on a Waters Micromass LCT or Thermo-Finnigan LTQ FT instrument operating in positive or negative ion mode as stated, with methanol as the carrier solvent. Accurate mass spectra were recorded using the Thermo-Finnigan LTQ FT mass spectrometer.

CPL Spectroscopy

CPL was measured with a home-built (modular) spectrometer. The excitation source was a broad band (200 – 1000 nm) laser- driven light source EQ 99 (Elliot Scientific). The excitation wavelength was selected by feeding the broadband light into an Acton SP-2155 monochromator (Princeton Instruments); the collimated light was focused into the sample cell (1 cm Quarts cuvette). Sample PL emission was collected perpendicular to the excitation direction with a lens (*f* = 150 mm). The emission was fed through a photoelastic modulator (PEM) (Hinds Series II/FS42AA) and through a linear sheet polariser (Comar). The light was then focused into a second scanning monochromator (Acton SP-2155) and subsequently on to a photomultiplier tube (PMT) (Hamamatsu H10723 series). The detection of the CPL signal was achieved using the field modulation lock-in technique. The electronic signal from the PMT was fed into a lock-in amplifier (Hinds Instruments Signaloc Model

2100). The reference signal for the lock-in detection was provided by the PEM control unit. The monchromators, PEM control unit and lock-in amplifier were interfaced to a desktop PC and controlled by a Labview code. The lock-in amplifier provided two signals, an *AC* signal corresponding to (I_L- I_R) and a *DC* signal corresponding to ($I_L + I_R$) after background subtraction. The emission dissymmetry factor was therefore readily obtained from the experimental data , as 2 AC/DC. Spectral calibration of the scanning monochromator was performed using a Hg-Ar calibration lamp (Ocean Optics). A correction factor for the wavelength dependence of the detection system was constructed using a calibrated lamp (Ocean Optics). The measured raw data was subsequently corrected using this correction factor. The validation of the CPL detection systems was achieved using light emitting diodes (LEDs) at various emission wavelengths. The LED was mounted in the sample holder and the light from the LED was fed through a broad band polarising filter and l/4 wave plate (Ocean Optics) to generate circularly polarised light. Prior to all measurements, the $\lambda/4$ plate and a LED were used to set the phase of the lock-in amplifier correctly. The emission spectra were recorded with 0.5 nm step size and the slits of the detection monochromator were set to a slit width corresponding to a spectral resolution of 0.25 nm. CPL spectra (as well as total emission spectra) were obtained through an averaging procedure of several scans. The CPL spectra have been smoothed using Savitzky-Golay smoothing (polynomial order 5, window size 9 with reflection at the boundaries) to enhance visual appearance; all calculations and error analyses were carried out using raw spectral data. The stated errors refer to the standard deviation from the mean of 5 consecutive CPL spectral acquisitions, for which the observed variation was found to occur in the AC rather than the DC signal, consistent with the high photostability of these systems. Smoothing was carried out simply to enhance the visual appearance of the spectrum.

Chromatography

Flash column chromatography was performed using flash silica gel 60 (230 - 400 mesh) from Merck. Thin layer chromatography (TLC) was performed on aluminum sheet silica gel plates with 0.2 mm thick silica gel 60 F_{254} (E. Merck) using different mobile phase. The compounds were visualized by UV irradiation (254 nm) or Dragendorff reagent staining.

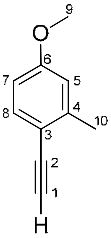
Reverse phase HPLC traces were recorded at 298 K using a Perkin Elmer system equipped with a Perkin Elmer Series 200 Pump, a Perkin Elmer Series 200 Autosampler and a Perkin Elmer Series 200 Diode array detector (operated at 254 nm). Separation was achieved using a semi-preparative Waters XBridge RP-C_{18} column (5 µm, 10 × 100 mm) at a flow rate maintained at 4.4 mL/min For purification of the anionic complexes a solvent system composed of 0.1 M NH_4HCO_3/methanol was used over the stated linear gradient. Analytical RP-HPLC was performed using a Waters XBridge RP-

C_{18} column (3.5 μm, 4.6 × 100 mm) at a flow rate maintained at 1.0 mL/ min over the stated linear gradient.

Measurement of logP (octanol/water) Three equimolar solutions of complex were prepared in the minimum volume of MeOH or water. The solvent was removed under reduced pressure and the resulting material was dissolved and stirred for 24 h in 0.9 mL of a mixture of water/octanol (2:1, 1:1, 1:2) giving a total concentration of approximately 2 μM. After equilibration, an emission spectrum for each layer was recorded in MeOH (50 μL of solution in 1 mL of MeOH), snd the relative amounts in each phase calculated as the ratio of the total emission intensity. For each different mixture, the logP value was calculated, as the mean of three separate experiments with the standard deviation from the mean quoted in parenthesis.

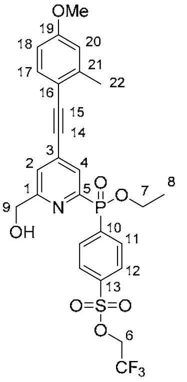
Ligand and complex syntheses

1-Ethynyl-4-methoxy-2-methylbenzene



3-Methyl-4-bromoanisole (700 mg, 3.48 mmol) was dissolved in anhydrous THF (12 mL) and the solution was degassed (freeze-thaw cycle) three times. Ethynyltrimethylsilane (0.74 mL, 5.24 mmol) and triethylamine (2.40 mL, 17.4 mmol) were added and the solution was degassed (freeze-thaw cycle) once more. [1,1-Bis(diphenylphosphino)ferrocene]dichloropalladium(II) (400 mg, 0.49 mmol) and CuI (66 mg, 0.35 mmol) were added and the resulting brown solution was stirred at 65 °C under argon for 16 h. The solvent was removed under reduced pressure and the resulting brown oil was purified by column chromatography (silica, *n*-hexane : DCM 10:0 to 10:1) to give (4-methoxy-2-methylphenylethynyl)trimethylsilane as a yellow oil (440 mg, 58%); R_f = 0.49 (silica, *n*-hexane : DCM 3:1). This compound (440 mg, 2.0 mmol) was immediately dissolved in anhydrous THF (5 mL) and triethylammonium dihydrofluoride (3.3 mL, 20 mmol) was added. The mixture was stirred at 35 °C under argon for 48 h. The solvent was removed under reduced pressure to give a yellow oil which was subjected to column chromatography (silica, *n*-hexane/CH_2Cl_2 3:1 v/v), to afford 1-ethynyl-4-methoxy-2-methylbenzene as a colourless oil (200 mg, 68%); δ_H ($CDCl_3$) 7.39 (1H, d, $^3J_{H\text{-}H}$ 8.6 Hz, H^8), 6.74 (1H, d, $^4J_{H-H}$ 2.6 Hz, H^5), 6.68 (1H, dd, $^3J_{H-H}$ 8.6 Hz, $^4J_{H-H}$ 2.6 Hz, H^7), 3.80 (3H, s, H^{10}), 3.19 (1H, s, H^1), 2.43 (3H, s, H^9); δ_C (151 MHz, CDCl$_3$) δ 160.0 (C^6), 142.7 (C^4), 134.0 (C^8), 115.2 (C^5), 114.3 (C^3), 111.3 (C^7), 82.7 (C^2), 79.6 (C^1), 55.4 (C^9), 21.0 (C^{10}); (HRMS$^-$) *m*/*z* 145.0667 [M - H]$^-$ ($C_{10}H_9O$ requires 145.0653); R_f = 0.46 (silica; *n*-hexane/ CH$_2$Cl$_2$, 2 : 1).

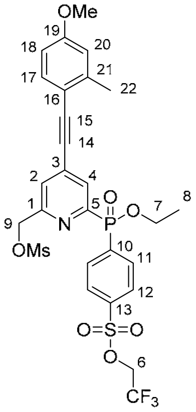
2,2,2-Trifluoroethyl-4-(ethoxy(6-(hydroxymethyl)-4-((4-methoxy-2-methylphenyl)ethynyl)pyridin-2-yl)phosphoryl)benzenesulfonate



2,2,2-Trifluoroethyl 4-((4-bromo-6-(hydroxymethyl)pyridin-2-yl)(ethoxy)phosphoryl)benzenesulfonate (230 mg, 0.44 mmol) was dissolved in dry THF (2 mL) and the solution was degassed (freeze-thaw cycle) three times. 1-Ethynyl-4-methoxy-2-methylbenzene (100 mg, 0.66 mmol) and NEt$_3$ (1.2 mL) were added and the solution degassed once more. [1,1'-Bis(diphenylphosphino)ferrocene]palladium(II) chloride (51 mg, 63 μmol) and CuI (8 mg, 42 μmol) were added and the solution was degassed a further three times. The solution was stirred at 65 °C under argon for 16 h, solvent was removed under reduced pressure and the crude material purified by column chromatography (silica, CH$_2$Cl$_2$: CH$_3$OH 0 – 2 %) to give a pale orange oil (185 mg, 72 %); δ_H (CDCl$_3$) 8.19 (2H, dd, $^3J_{H-P}$ 11 Hz, $^3J_{H-H}$ 8 Hz, H^{11}), 8.08 (1H, s, H^4), 7.98 (2H, d, $^3J_{H-H}$ 8 Hz, H^{12}), 7.48 (1H, s, H^2), 7.41 (1H, d, $^3J_{H-H}$ 8.5 Hz, H^{17}), 6.76 (1H, d, $^4J_{H-H}$ 2.5 Hz, H^{20}), 6.72 (1H, dd, $^3J_{H-H}$ 8.5 Hz, $^4J_{H-H}$ 2.5 Hz, H^{18}), 4.76 (2H, s, H^9), 4.39 (2H, q, $^3J_{F-H}$ 8 Hz, H^6), 4.16 (2H, m, H^7), 3.80 (3H, s, OMe), 3.57 (1H, br, OH), 2.46 (3H, s, H^{22}), 1.38 (3H, t, $^3J_{H-H}$ 7 Hz, H^8); δ_C (CDCl$_3$) 161.1 (s, C^1), 160.7 (s, C^{19}), 151.8 (d, $^1J_{C-P}$ 168 Hz, C^5), 142.9 (s, C^{21}), 138.6 (s, C^{13}), 137.3 (d, $^1J_{C-P}$ 137 Hz, C^{10}), 134.0 (s, C^{17}), 133.4 (s, C^{11}), 133.3 (s, C^3), 128.9 (s, C^4), 127.6 (d, $^4J_{C-P}$ 13 Hz, C^{12}), 124.3 (s, C^2), 121.7 (q, $^1J_{C-F}$ 279 Hz, CF$_3$), 115.3 (s, C^{20}), 113.4 (s, C^{16}),111.6 (s, C^{18}), 95.8 (s, C^{15}), 88.7 (s, C^{14}), 64.8 (q, $^2J_{C-F}$ 38.5 Hz, C^6), 64.1 (s, C^9), 62.6 (d, $^2J_{C-P}$ 6 Hz, C^7), 55.3 (s, OMe), 21.0 (s, C^{22}), 16.5 (s, C^8); δ_F (CDCl$_3$) -74.2 (t, $^3J_{F-H}$ 8 Hz); δ_P (CDCl$_3$) + 22.6;

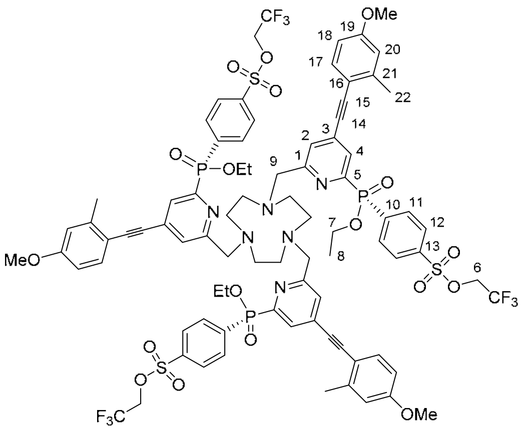
m/z (HRMS$^+$) 584.1111 [M + H]$^+$ ($C_{26}H_{26}F_3NO_7PS$ requires 584.1120); R_f = 0.52 (silica, DCM : MeOH 97 : 3).

2,2,2-Trifluoroethyl-4-(ethoxy(4-((4-methoxy-2-methylphenyl)ethynyl)-6-((methylsulfonyloxy)methyl)pyridin-2-yl)phosphoryl)benzenesulfonate, 13



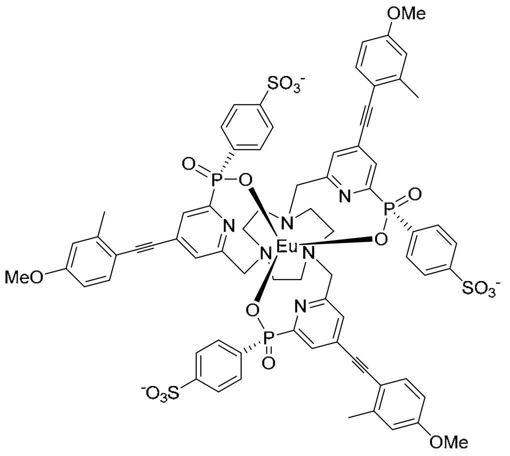
2,2,2-Trifluoroethyl-4-(ethoxy(6-(hydroxymethyl)-4-((4-methoxy-2-methylphenyl)ethynyl)pyridin-2-yl)phosphoryl)benzenesulfonate (185 mg, 0.32 mmol) was dissolved in anhydrous THF (5 mL) and NEt_3 (0.14 mL, 0.96 mmol) was added. The mixture was stirred at 5 °C and methanesulfonyl chloride (37 µL, 0.48 mmol) was added. The reaction was monitored by TLC (silica; CH_2Cl_2 : 5 % CH_3OH, R_f(product) = 0.75, R_f(reactant) = 0.61) and stopped after 30 min. The solvent was removed under reduced pressure and the residue dissolved in CH_2Cl_2 (15 mL) and washed with NaCl solution (saturated, 10 mL). The aqueous layer was re-extracted with CH_2Cl_2 (3 × 10 mL) and the organic layers combined, dried over $MgSO_4$ and the solvent removed under reduced pressure to leave a colourless oil (160 mg, 76 %); δ_H ($CDCl_3$) 8.23 (2H, dd, $^3J_{H\text{-}P}$ 11 Hz, $^3J_{H\text{-}H}$ 8 Hz, H^{11}), 8.08 (1H, d, $^4J_{H\text{-}H}$ 2.5 Hz, H^4), 8.03 (2H, d, dd, $^3J_{H\text{-}H}$ 8 Hz, $^4J_{H\text{-}P}$ 2 Hz, H^{12}), 7.59 (1H, s, H^2), 7.44 (1H, d, $^3J_{H\text{-}H}$ 8.5 Hz, H^{17}), 6.78 (1H, s, H^{20}), 6.74 (1H, dd, $^3J_{H\text{-}H}$ 8.5 Hz, $^4J_{H\text{-}H}$ 2.5 Hz, H^{18}), 5.29 (2H, m, H^9), 4.42 (2H, q, $^3J_{F\text{-}H}$ 8 Hz, H^6), 4.18 (2H, m, H^7), 3.82 (3H, s, OMe), 3.07 (3H, s, Ms), 2.48 (2H, s, H^{22}), 1.39 (3H, t, $^3J_{H\text{-}H}$ 7 Hz, H^8); δ_F ($CDCl_3$) -74.1 (t, $^3J_{F\text{-}H}$ 8 Hz); δ_P ($CDCl_3$) + 21.9; *m/z* (HRMS$^+$) 662.0900 [M + H]$^+$ ($C_{27}H_{28}NO_9F_3PS_2$ requires 662.0895); R_f = 0.75 (silica, DCM : MeOH 95 : 5).

2,2,2-Trifluoroethyl 6,6',6''-(1,4,7-triazacyclononane-1,4,7-triyl)tris(methylene)tris(4-((4-methoxy-2-methylphenyl)ethynyl)pyridine-6,2-diyl)tris(4-(ethoxy phosphoryl benzenesulfonate)



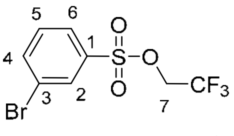
1,4,7-Triazacyclononane hydrochloride salt (3.0 mg, 12 μmol) and 2,2,2-trifluoroethyl 4-(ethoxy(4-((4-methoxy-2-methylphenyl)ethynyl)-6-((methylsulfonyloxy)methyl)pyridin-2-yl)phosphoryl)benzenesulfonate (24 mg, 36 μmol) were dissolved in anhydrous CH_3CN (1 mL) and K_2CO_3 (10 mg, 72 μmol) was added. The mixture was stirred under argon at 60 °C for 16 h. KI (catalytical) was added to the reaction and the mixture was heated for further 1 h. The reaction was cooled and the solution decanted from excess potassium salts. The solvent was removed under reduced pressure to give a yellow oil (15 mg, 69 %); δ_H ($CDCl_3$) 8.21 (6H, dd, $^3J_{H\text{-}P}$ 11 Hz, $^3J_{H\text{-}H}$ 8 Hz, H^{11}), 8.03 (3H, s, H^4), 7.98 (6H, d, $^3J_{H\text{-}H}$ 8 Hz, H^{12}), 7.53 (3H, s, H^2), 7.41 (3H, d, $^3J_{H\text{-}H}$ 8.5 Hz, H^{17}), 6.80 (3H, d, $^4J_{H\text{-}H}$ 2.5 Hz, H^{20}), 6.74 (3H, dd, $^3J_{H\text{-}H}$ 8.5 Hz, $^4J_{H\text{-}H}$ 2.5 Hz, H^{18}), 4.40 (6H, q, $^3J_{F\text{-}H}$ 8 Hz, H^6), 4.20 - 4.06 (6H, m, H^7), 3.85 (6H, s, H^9), 3.80 (9H, s, OMe), 2.46 (9H, s, H^{22}), 2.81 (12H, br, $9N_3$), 1.38 (9H, t, $^3J_{H\text{-}H}$ 7 Hz, H^8); δ_C ($CDCl_3$) 161.2 (s, C^1), 160.5 (s, C^{19}), 151.8 (d, $^1J_{C\text{-}P}$ 168 Hz, C^5), 142.7 (s, C^{21}), 138.6 (s, C^{13}), 137.4 (d, $^1J_{C\text{-}P}$ 137 Hz, C^{10}), 134.1 (s, C^{17}), 133.4 (s, C^{11}), 133.2 (s, C^3), 128.9 (s, C^4), 127.6 (d, $^4J_{C\text{-}P}$ 13 Hz, C^{12}), 124.2 (s, C^2), 121.7 (q, $^1J_{C\text{-}F}$ 279 Hz, CF_3), 115.1 (s, C^{20}), 113.4 (s, C^{16}),111.6 (s, C^{18}), 95.8 (s, C^{15}), 88.8 (s, C^{14}), 64.8 (q, $^2J_{C\text{-}F}$ 38.5 Hz, C^6), 62.9 (s, C^9), 62.7 (d, $^2J_{C\text{-}P}$ 14 Hz, C^7), 55.3 (s, OMe), 55.2-54.5 (br, $9N_3$), 21.0 (s, C^{22}), 16.5 (s, C^8); δ_F ($CDCl_3$) -74.2 (t, $^3J_{F\text{-}H}$ 8 Hz); δ_P ($CDCl_3$) + 22.6; *m/z* ($HRMS^+$) 1825.410 $[M + H]^+$ ($C_{84}H_{85}N_6O_{18}F_9P_3S_3$ requires 1825.415).

Eu(III) complex of 6,6',6''-(1,4,7-triazacyclononane-1,4,7-triyl)tris(methylene)tris(4-((4-methoxy-2-methylphenyl)ethynyl)pyridine-6,2-diyl)tris(4-(hydroxyphosphoryl benzenesulfonate), $[Eu.L^{1b}]^{3-}$



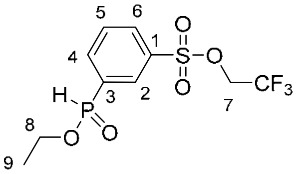
2,2,2-Trifluoroethyl 6,6',6''-(1,4,7-triazacyclononane-1,4,7-triyl)tris(methylene)tris(4-((4-methoxy-2-methylphenyl)ethynyl)pyridine-6,2-diyl)tris(4-(ethoxyphosphoryl benzenesulfonate) (5.0 mg, 2.7 μmol) was dissolved in CD_3OD (1.5 mL) and a solution of 0.1 M NaOH in D_2O (0.8 mL) was added. The mixture was heated to 60 °C under argon and monitored with ^{19}F-NMR [δ_F(reactant) = - 76.2, (δ_F(product, trifluoroethanol) = - 78.0] and ^{31}P-NMR [δ_P(reactant) = + 22.3, (δ_P(product) = + 13.1]. After 3 h the solution was cooled to RT and the pH was adjusted to 7 with HCl. $Eu(Cl)_3 6H_2O$ (1.0 mg, 2.9 μmol) was added and the mixture heated to 65 °C overnight under argon. The solvent was removed under reduced pressure and the product purified by HPLC ((XBridge C_{18} column, 19 x 100 mm, i.d. 5 μm) flow rate of 17 mL / min with H_2O (25 mM triethylammonium acetate buffer, pH = 7) – 2 % CH_3CN) as eluents (3 min) [linear gradient to 40 % MeOH (15 min), linear gradient to 100 % MeOH (3 min)], t_R = 19.8 min) giving the triethylammonium salt of the complex as a white solid (2.6 mg, 60 %); (HRMS$^-$) 1644.205 [$EuL^{1b}H_2$]$^-$ ($C_{72}H_{65}{}^{153}EuN_6O_{18}P_3S_3$ requires 1644.202); τ_{H_2O} = 1.09 ms; λ_{max} = 340 nm.

2,2,2-Trifluoroethyl 3-bromobenzenesulfonate, 2



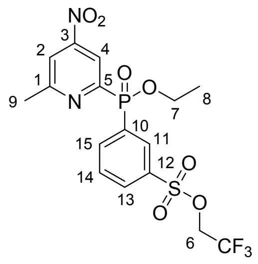
3-Bromobenzenesulfonyl chloride (5.00 g, 19.5 mmol) was dissolved in DCM (25 mL) and trifluoroethanol (1.40 mL, 19.5 mmol) was added. A solution of DABCO (2.60 g, 23.4 mmol) in DCM (15 mL) was added resulting in precipitate formation. The reaction was stirred for 1 h at RT, after which time a solution of 1 M NaOH (8 mL) was added. The reaction was diluted in EtOAc (100 mL) and washed with 0.5 M $NaHCO_3$, 0.1 M HCl, water and brine. The organic layer was dried over $MgSO_4$ and the solvent removed under reduced pressure to give a clear oil (5.50 g, 88 %); δ_H ($CDCl_3$) 8.06 (1H, d, $^4J_{H-H}$ 2 Hz, H^2), 7.86 (1H, dd, $^3J_{H-H}$ 8 Hz, $^4J_{H-H}$ 1.5 Hz, H^4), 7.84 (1H, d, $^3J_{H-H}$ 8 Hz, $^4J_{H-H}$ 1.5, H^6), 7.48 (1H, t, $^3J_{H-H}$ 8 Hz, H^5), 4.41 (2H, q, $^3J_{H-F}$ 8 Hz, H^7); δ_C ($CDCl_3$) 137.7 (C^6), 136.7 (C^3), 131.0 (C^5), 130.8 (C^2), 126.5 (C^4), 123.4 (C^1), 121.7 (q, J 278 Hz, C^5), 64.8 (q, J 38 Hz, CF_3); δ_F ($CDCl_3$) -73.8 (t, $^3J_{F-H}$ 7.0 Hz); *m/z* (HRMS+) 340.9077 $[M + Na]^+$ ($C_8H_6O_3S^{79}BrF_3Na$ requires 340.9071); R_f = 0.58 (silica, EtOAc : *n*-hexane 2 : 8).

2,2,2-Trifluoroethyl 4-(ethoxyhydrophosphoryl)benzenesulfonate, 4



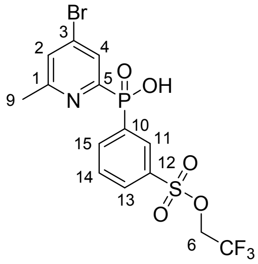
To a suspension of anilinium hypophosphite (1.20 g, 7.54 mmol) in dry toluene was added 2,2,2-trifluoroethyl 3-bromobenzenesulfonate (2.00 g, 6.27 mmol). Argon was bubbled through the solution for 30 min, then aminopropyltriethoxysilane (1.80 mL, 7.65 mmol) was added, and Argon was bubbled through the solution for additional 30 min. $PdCl_2(dppf)\cdot CH_2Cl_2$ (270 mg, 0.33 mmol) was added, and the mixture stirred at 100 °C for 30 min under argon. The reaction was monitored by ^{31}P-NMR [δ_P(reactant) = 7.4, δ_P(product) = 20.2, δ_P(diaryl phosphinate) = 24.9]. The solvent was removed under reduced pressure, 1 M HCl (12 mL) was added and the mixture extracted with EtOAc (3 x 30 mL). The organic fractions were combined, dried over $MgSO_4$ and concentrate to give a pale orange oil. The product was used for the next step without further purification; δ_H ($CDCl_3$) 8.32 (1H, m, H^2), 8.12 (2H, m, H^4 and H^6), 7.48 (1H, t, $^3J_{H-H}$ = 8 Hz, H^5), 7.67 (1H, d, $^1J_{P-H}$ 576 Hz, PH), 4.45 (2H, q, $^3J_{F-H}$ 9 Hz, H^7), 4.23 (2H, m, H^5), 1.42 (3H, t, $^3J_{H-H}$ 7.0 Hz, H^6); δ_F ($CDCl_3$) -74.2 (t, $^3J_{F-H}$ 8 Hz); δ_P ($CDCl_3$) +20.2; *m/z* (HRMS+) 333.0167 $[M + H]^+$ ($C_{10}H_{13}O_5SF_3P$ requires 333.0173).

2,2,2-Trifluoroethyl 3-(ethoxy(6-methyl-4-nitropyridin-2-yl)phosphoryl)benzenesulfonate, 6



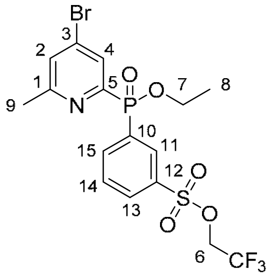
2,2,2-Trifluoroethyl-3-(ethoxyhydrophosphoryl)benzenesulfonate (1.60 g, 4.82 mmol) was added to degassed toluene (40 mL), followed by 2-bromo-6-methyl-4-nitropyridine (1.00 g, 4.61 mmol) and freshly distilled triethylamine (2.30 mL, 16.8 mmol). Argon was bubbled through the yellow solution for 30 min, then $PdCl_2(dppf)\cdot CH_2Cl_2$ (110 mg, 0.13 mmol) was added, and the mixture stirred at 120 °C overnight under argon, during which time the mixture turned brown. The solvent was removed under reduced pressure, with purification of the resulting black oil by column chromatography (silica, EtOAc : *n*-hexane 1:3 to 1:1) giving a clear oil (850 mg, 38 %); δ_H ($CDCl_3$) 8.61 (1H, dd, $^3J_{H\text{-}P}$ 6.5 $^4J_{H\text{-}H}$ 2 Hz, H^4), 8.57 (1H, d, $^3J_{H\text{-}P}$ 12 Hz, H^{11}), 8.33 (1H, dd, $^3J_{H\text{-}P}$ 12 Hz, $^3J_{H\text{-}H}$ 7.5 Hz, H^{15}), 8.09 (1H, d, $^3J_{H\text{-}H}$ 7 Hz, H^{13}), 7.94 (1H, s, H^2), 7.72 (1H, m, H^{14}), 4.41 (2H, q, $^3J_{F\text{-}H}$ 8 Hz, H^6), 4.24 – 4.11 (2H, m, H^7), 2.71 (3H, s, H^9), 1.38 (3H, t, $^3J_{H\text{-}H}$ 7.0 Hz, H^8); δ_C ($CDCl_3$) 163.5 (d, $^5J_{C\text{-}P}$ 21.5 Hz, C^1), 156.5 (d, $^1J_{C\text{-}P}$ 171.5 Hz, C^5), 154.2 (d, $^3J_{C\text{-}P}$ 14 Hz, C^3), 138.4 (d, $^2J_{C\text{-}P}$ 9.5 Hz, C^{15}), 135.7 (d, $^3J_{C\text{-}P}$ 14 Hz, C^{12}), 132.1 (d, $^2J_{C\text{-}P}$ 10.5 Hz, C^{11}), 132.0 (d, $^1J_{C\text{-}P}$ 142 Hz, C^{10}), 131.7 (d, $^4J_{C\text{-}P}$ 2.5 Hz, C^{13}), 129.8 (d, $^3J_{C\text{-}P}$ 13 Hz, C^{14}), 121.7 (q, $^1J_{C\text{-}F}$ 278 Hz, CF_3), 118.1 (d, $^4J_{C\text{-}P}$ 3 Hz, C^2), 118.0 (d, $^2J_{C\text{-}P}$ 24.5 Hz, C^4), 64.8 (q, $^2J_{C\text{-}F}$ 38.5 Hz, C^6), 62.8 (d, $^2J_{C\text{-}P}$ 6 Hz, C^7), 24.7 (s, C^9), 16.4 (d, $^3J_{C\text{-}P}$ 6 Hz, C^8); δ_F ($CDCl_3$) -74.2 (t, $^3J_{F\text{-}H}$ 7 Hz); δ_P ($CDCl_3$) + 20.4; *m/z* ($HRMS^+$) 469.0444 $[M + H]^+$ ($C_{16}H_{17}N_2O_7SF_3P$ requires 469.0446); R_f = 0.70 (silica, EtOAc : *n*-hexane 2 : 1).

4-Bromo-6-methylpyridin-2-yl(3-(2,2,2-trifluoroethoxysulfonyl)phenyl)phosphinic acid



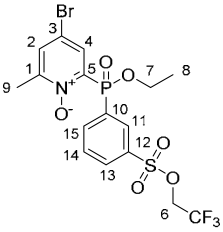
2,2,2-Trifluoroethyl-3-(ethoxy(6-methyl-4-nitropyridin-2-yl)phosphoryl)benzenesulfonate (300 mg, 0.64 mmol) was dissolved in CH_3COBr (2 mL) and the mixture stirred at 70 °C for 16 h under argon. The brown solution was dropped cautiously into CH_3OH (20 mL) stirred at 0 °C. The solvent was removed under reduced pressure to yield a pale brown solid. The resulting material, containing unidentified contaminants, was used without further purification, assuming quantitative conversion to the bromo-phosphinic acid; δ_H (CD_3OD) 8.53 (1H, d, $^3J_{H-P}$ 13, H^{11}), 8.46 (1H, d, $^3J_{H-P}$ 6.5 Hz, H^4), 8.40 (1H, m, H^{15}), 8.38 (1H, s, H^2), 8.18 (1H, d, $^3J_{H-H}$ 7.5 Hz, H^{13}), 7.91 (1H, td, $^3J_{H-H}$ 8 Hz, $^4J_{H-P}$ 3 Hz, H^{14}), 4.70 (2H, q, $^3J_{F-H}$ 8 Hz, H^6), 2.88 (3H, s, H^9); δ_C (CD_3OD) 158.1 (d, $^5J_{C-P}$ 7.5 Hz, C^1), 149.9 (d, $^1J_{C-P}$ 131 Hz, C^5), 144.2 (d, $^3J_{C-P}$ 11 Hz, C^3), 138.3 (d, $^2J_{C-P}$ 11 Hz, C^{15}), 135.8 (d, $^3J_{C-P}$ 15 Hz, C^{12}), 134.7 (C^2), 133.6 (d, $^1J_{C-P}$ 148 Hz, C^{10}), 132.1 (d, $^4J_{C-P}$ 2.5 Hz, C^{13}), 131.8 (d, $^2J_{C-P}$ 11.5 Hz, C^4), 131.3 (d, $^2J_{C-P}$ 12 Hz, C^{11}), 130.9 (d, $^3J_{C-P}$ 13.5 Hz, C^{14}), 122.3 (q, $^1J_{C-F}$ 277 Hz, CF_3), 65.4 (q, $^2J_{C-F}$ 37.5 Hz, C^6), 19.4 (s, C^9);δ_F (CD_3OD) -76.0 (t, $^3J_{F-H}$ 7 Hz); δ_P (CD_3OD) + 8.0; *m/z* ($HRMS^+$) 473.9389 $[M + H]^+$ ($C_{14}H_{13}NO_5F_3PS^{79}Br$ requires 473.9388).

2,2,2-Trifluoroethyl 3-((4-bromo-6-methylpyridin-2-yl)(ethoxy)phosphoryl)benzenesulfonate, 8



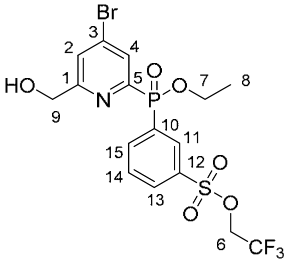
4-Bromo-6-methylpyridin-2-yl(3-(2,2,2-trifluoroethoxysulfonyl)phenyl)phosphinic acid (300 mg, 0.64 mmol) was added to $HC(OCH_2CH_3)_3$ (13 mL) and the mixture stirred at 140 °C for 16 h under argon. The solvent was removed under reduced pressure and the resulting residue was purified by column chromatography (silica, CH_2Cl_2 : 1 CH_3OH) to yield a yellow oil (256 mg, 77 % over two steps); δ_H ($CDCl_3$) 8.58 (1H, dt, $^3J_{H-P}$ 11.5, $^4J_{H-H}$ 1.5, H^{11}), 8.32 (1H, m, H^{15}), 8.11 (1H, d, $^3J_{H-P}$ 6.5 Hz, H^4), 8.07 (1H, dd, $^3J_{H-H}$ 8 Hz, $^4J_{H-H}$ 2 Hz, H^{13}), 7.69 (1H, td, $^3J_{H-H}$ 8 Hz, $^4J_{H-P}$ 3 Hz, H^{14}), 7.43 (1H, s, H^2), 4.40 (2H, qd, $^3J_{F-H}$ 8 Hz, $^2J_{H-H}$ 3.5 Hz, H^6), 4.12 (2H, m, H^7), 2.52 (3H, s, H^9), 1.36 (3H, t, $^3J_{H-H}$ 7 Hz, H^6); δ_C ($CDCl_3$) 161.3 (d, $^5J_{C-P}$ 22 Hz, C^1), 153.8 (d, $^1J_{C-P}$ 169.5 Hz, C^5), 138.3 (d, $^2J_{C-P}$ 9.5 Hz, C^{15}), 135.4 (d, $^3J_{C-P}$ 14 Hz, C^{12}), 133.6 (d, $^3J_{C-P}$ 15.5 Hz, C^3), 132.6 (d, $^1J_{C-P}$ 139 Hz, C^{10}), 132.1 (d, $^2J_{C-P}$ 10.5 Hz, C^{11}), 131.4 (d, $^4J_{C\text{-}P}$ 2.5 Hz, C^{13}), 129.6 (d, $^3J_{C\text{-}P}$ 12.5 Hz, C^{14}), 129.1 (d, $^4J_{C\text{-}P}$ 3 Hz, C^2), 128.9 (d, $^2J_{C\text{-}P}$ 24 Hz, C^4), 121.7 (q, $^1J_{C\text{-}F}$ 278 Hz, CF$_3$), 64.8 (q, $^2J_{C\text{-}F}$ 38 Hz, C^6), 62.5 (d, $^2J_{C\text{-}P}$ 6 Hz, C^7), 24.2 (C^9), 16.4 (d, $^3J_{C\text{-}P}$ 6 Hz, C^8);δ_F (CDCl$_3$) -74.2 (t, $^3J_{F\text{-}H}$ 7 Hz); δ_P (CDCl$_3$) + 21.1; *m/z* (HRMS$^+$) 501.9690 [M + H]$^+$ ($C_{16}H_{17}NO_5F_3PS^{79}Br$ requires 501.9701); R_f = 0.50 (silica, DCM : MeOH 96 : 4).

4-Bromo-2-(ethoxy(3-(2,2,2-trifluoroethoxysulfonyl)phenyl)phosphoryl)-6-methylpyridine 1-oxide



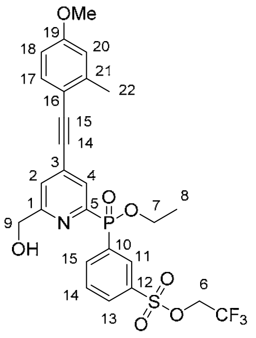
2,2,2-Trifluoroethyl 3-((4-bromo-6-methylpyridin-2-yl)(ethoxy)phosphoryl)benzenesulfonate (350 mg, 0.70 mmol) was dissolved in CHCl$_3$ (10 mL). 3-Chloroperbenzoic acid (240 mg, 1.39 mmol) was added and the solution stirred at 65 °C for 16 h. The solvent was then removed under reduced pressure, with the resulting material being re-dissolved in CH$_2$Cl$_2$ (15 mL), and washed with NaHCO$_{3(aq)}$ (0.5 M, 10 mL). The aqueous layer was re-extracted with CH$_2$Cl$_2$ (3 × 10 mL), the organic extracts combined, dried over MgSO$_4$, and the solvent removed under reduced pressure giving a yellow oil (320 mg, 85 %); δ_H (CDCl$_3$) 8.53 (1H, dt, $^3J_{H\text{-}P}$ 13.5, $^4J_{H\text{-}H}$ 1.5, H^{11}), 8.36 (1H, m, H^{15}), 8.09 (1H, dd, $^3J_{H\text{-}P}$ 8 Hz, $^4J_{H\text{-}H}$ 3 Hz, H^4), 8.05 (1H, d, $^3J_{H\text{-}H}$ 8 Hz, H^{13}), 7.68 (1H, td, $^3J_{H\text{-}H}$ 8 Hz, $^4J_{H\text{-}P}$ 3.5 Hz, H^{14}), 7.52 (1H, d, $^4J_{H\text{-}H}$ 3 Hz, H^2), 4.41 (2H, m, H^6), 4.18 (2H, m, H^7), 2.30 (3H, s, H^9), 1.38 (3H, t, $^3J_{H\text{-}H}$ 7 Hz, H^6); δ_C (CDCl$_3$) 150.8 (d, $^5J_{C\text{-}P}$ 4.5 Hz, C^1), 142.7 (d, $^1J_{C\text{-}P}$ 154 Hz, C^5), 139.2 (d, $^2J_{C\text{-}P}$ 10.5 Hz, C^{15}), 134.8 (d, $^3J_{C\text{-}P}$ 15.5 Hz, C^{12}), 133.1 (d, $^2J_{C\text{-}P}$ 11 Hz, C^4), 132.8 (d, $^2J_{C\text{-}P}$ 12.5 Hz, C^{11}), 132.7 (d, $^4J_{C\text{-}P}$ 2 Hz, C^2), 131.8 (d, $^4J_{C\text{-}P}$ 2.5 Hz, C^{13}), 131.4 (d, $^1J_{C\text{-}P}$ 129 Hz, C^{10}), 129.5 (d, $^3J_{C\text{-}P}$ 14 Hz, C^{14}), 121.8 (q, $^1J_{C\text{-}F}$ 278 Hz, CF$_3$), 117.9 (d, $^3J_{C\text{-}P}$ 13 Hz, C^3), 65.0 (q, $^2J_{C\text{-}F}$ 38 Hz, C^6), 62.9 (d, $^2J_{C\text{-}P}$ 6 Hz, C^7), 17.0 (C^9), 16.4 (d, $^3J_{C\text{-}P}$ 6 Hz, C^8); δ_F (CDCl$_3$) -74.2 (t, $^3J_{F\text{-}H}$ 7 Hz); δ_P (CDCl$_3$) + 17.0; *m/z* (HRMS$^+$) 517.9650 [M + H]$^+$ ($C_{16}H_{17}NO_6PS^{79}BrF_3$ requires 517.9650); R_f = 0.49 (silica, DCM : MeOH 96 : 4).

2,2,2-Trifluoroethyl-3-((4-bromo-6-(hydroxymethyl)pyridin-2 yl)(ethoxy)phosphoryl)benzenesulfonate, 12



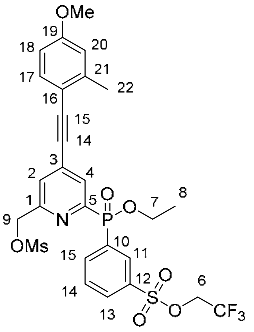
Trifluoroacetic anhydride (1.70 mL) was added to a solution of 4-bromo-2-(ethoxy(3-(2,2,2-trifluoroethoxysulfonyl)phenyl)phosphoryl)-6-methylpyridine 1-oxide (310 mg, 0.60 mmol) in dry $CHCl_3$ (15 mL). The reaction mixture was heated to 60 °C for 3 h under argon. The solvent was removed under reduced pressure and the resulting oil was dissolved in EtOH (12 mL) and H_2O (12 mL) and stirred for 1h. After this time the solution was concentrated (ca. 15 mL) and extracted with CH_2Cl_2 (3 × 30 mL). The organic extracts were combined, dried over $MgSO_4$, the solvent removed under reduced pressure and the resulting residue was purified by column chromatography (silica, CH_2Cl_2 : CH_3OH 100 : 0 to 97 : 3) to yield a clear oil (220 mg, 70 %); δ_H ($CDCl_3$) 8.55 (1H, dt, $^3J_{H-P}$ 12, $^4J_{H-H}$ 1.5, H^{11}), 8.29 (1H, m, H^{15}), 8.19 (1H, dd, $^3J_{H-P}$ 6.5 Hz, $^4J_{H-H}$ 2 Hz, H^4), 8.08 (1H, d, $^3J_{H-H}$ 8 Hz, H^{13}), 7.71 (1H, td, $^3J_{H-H}$ 8 Hz, $^4J_{H-P}$ 3 Hz, H^{14}), 7.66 (1H, s, H^2), 6.72 (1H, br, OH), 4.75 (2H, s, H^9), 4.43 (2H, m, H^6), 4.16 (2H, m, H^7), 1.37 (3H, t, $^3J_{H-H}$ 7 Hz, H^6); δ_C ($CDCl_3$) 162.7 (d, $^5J_{C-P}$ 20.5 Hz, C^1), 153.3 (d, $^1J_{C-P}$ 168.5 Hz, C^5), 138.2 (d, $^2J_{C-P}$ 10 Hz, C^{15}), 135.7 (d, $^3J_{C-P}$ 14 Hz, C^{12}), 134.5 (d, $^3J_{C-P}$ 14.5 Hz, C^3), 132.0 (d, $^1J_{C-P}$ 128.5 Hz, C^{10}), 131.9 (d, $^2J_{C-P}$ 11 Hz, C^{11}), 131.7 (d, $^4J_{C-P}$ 2.5 Hz, C^{13}), 130.3 (d, $^2J_{C-P}$ 23.5 Hz, C^4), 129.8 (d, $^3J_{C-P}$ 12.5 Hz, C^{14}), 126.5 (d, $^4J_{C-P}$ 3 Hz, C^2), 121.8 (q, $^1J_{C-F}$ 278 Hz, CF_3), 64.8 (q, $^2J_{C-F}$ 38 Hz, C^6), 64.0 (C^9), 62.8 (d, $^2J_{C-P}$ 6 Hz, C^7), 16.4 (d, $^3J_{C-P}$ 6 Hz, C^8); δ_F ($CDCl_3$) -74.3 (t, $^3J_{F-H}$ 7 Hz); δ_P ($CDCl_3$) + 21.9; *m/z* ($HRMS^+$) 517.9647 $[M + H]^+$ ($C_{16}H_{17}NO_6PS^{79}BrF_3$ requires 517.9650); R_f = 0.56 (silica, DCM : MeOH 96 : 4).

2,2,2-trifluoroethyl 3-(ethoxy(6-(hydroxymethyl)-4-((4-methoxy-2-methylphenyl)ethynyl)pyridin-2-yl)phosphoryl)benzenesulfonate



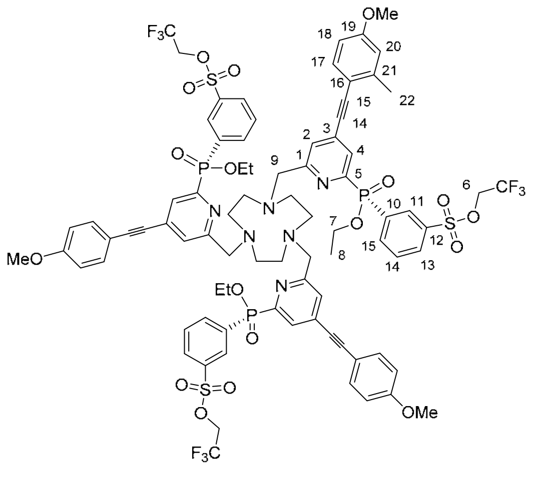
2,2,2-Trifluoroethyl 3-((4-bromo-6-(hydroxymethyl)pyridin-2-yl)(ethoxy)phosphoryl)benzenesulfonate (160 mg, 0.31 mmol) was dissolved in dry THF (1.5 mL) and the solution was degassed (freeze-thaw cycle) three times. 1-Ethynyl-4-methoxy-2-methylbenzene (68 mg, 0.47 mmol) and NEt_3 (0.90 mL) were added and the solution degassed once more. [1,1'-Bis(diphenylphosphino)ferrocene]palladium(II) chloride (36 mg, 58 μmol) and CuI (6 mg, 31 μmol) were added and the solution was degassed a further three times. The solution was stirred at 65 °C under argon for 16 h, solvent was removed under reduced pressure and the crude material purified by column chromatography (silica, CH_2Cl_2 : CH_3OH 0 – 2 %) to give an orange oil (90 mg, 50 %); δ_H ($CDCl_3$) 8.57 (1H, d, $^3J_{H\text{-}P}$ 11.5, H^{11}), 8.31 (1H, m, H^{15}), 8.10 (1H, d, $^3J_{H\text{-}P}$ 6 Hz, H^4), 8.07 (1H, d, $^3J_{H\text{-}H}$ 8 Hz, H^{13}), 7.70 (1H, td, $^3J_{H\text{-}H}$ 8 Hz, $^4J_{H\text{-}P}$ 3 Hz, H^{14}), 7.46 (1H, s, H^2) 7.42 (1H, d, $^3J_{H\text{-}H}$ 8.5 Hz, H^{17}), 6.77 (1H, d, $^4J_{H\text{-}H}$ 2.5 Hz, H^{20}), 6.72 (1H, dd, $^3J_{H\text{-}H}$ 8.5 Hz, $^4J_{H\text{-}H}$ 2.5 Hz, H^{18}), 4.75 (2H, s, H^9), 4.35 (2H, m, H^6), 4.16 (2H, m, H^7), 3.80 (3H, s, OMe), 3.44 (1H, br, OH), 2.47 (3H, s, H^{22}), 1.38 (3H, t, $^3J_{H\text{-}H}$ 7 Hz, H^8); δ_C ($CDCl_3$) 161.0 (d, $^4J_{C\text{-}P}$ 19 Hz, C^1), 160.7 (s, C^{19}), 151.9 (d, $^1J_{C\text{-}P}$ 169 Hz, C^5), 142.9 (s, C^{21}), 138.1 (d, $^2J_{C\text{-}P}$ 10 Hz, C^{15}), 135.6 (d, $^3J_{C\text{-}P}$ 14 Hz, C^{12}), 134.0 (s, C^{17}), 132.7 (d, $^1J_{C\text{-}P}$ 140 Hz, C^{10}), 131.9 (d, $^2J_{C\text{-}P}$ 11 Hz, C^{11}), 131.6 (s, C^3), 131.5 (s, C^{13}), 129.7 (d, $^3J_{C\text{-}P}$ 13 Hz, C^{14}), 128.8 (d, $^2J_{C\text{-}P}$ 23 Hz, C^4), 124.3 (s, C^2), 121.7 (q, $^1J_{C\text{-}F}$ 278 Hz, CF_3), 115.3 (s, C^{20}), 113.5 (s, C^{16}), 111.6 (s, C^{18}), 95.8 (s, C^{15}), 88.8 (s, C^{14}), 64.8 (q, $^2J_{C\text{-}F}$ 38.5 Hz, C^6), 64.0 (s, C^9), 62.6 (d, $^2J_{C\text{-}P}$ 6 Hz, C^7), 55.3 (s, OMe), 21.0 (s, C^{22}), 16.5 (s, $^3J_{C\text{-}P}$ 6 Hz, C^8); δ_F ($CDCl_3$) -74.2 (t, $^3J_{F\text{-}H}$ 8 Hz); δ_P ($CDCl_3$) + 22.2; *m/z* (HRMS$^+$) 584.1111 $[M + H]^+$ ($C_{26}H_{26}F_3NO_7PS$ requires 584.1120); $R_f = 0.52$ (silica, DCM : MeOH 97 : 3).

2,2,2-Trifluoroethyl 3-(ethoxy(4-((4-methoxy-2-methylphenyl)ethynyl)-6-((methylsulfonyloxy)methyl)pyridin-2-yl)phosphoryl)benzenesulfonate, 14



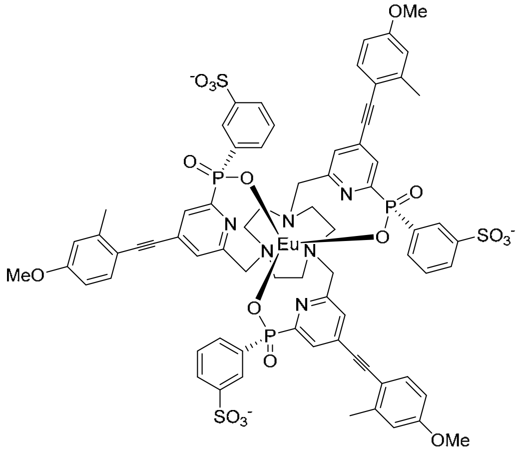
2,2,2-trifluoroethyl 3-(ethoxy(6-(hydroxymethyl)-4-((4-methoxy-2-methylphenyl)ethynyl)pyridin-2-yl)phosphoryl)benzenesulfonate (45 mg, 78 μmol) was dissolved in anhydrous THF (2.5 mL) and NEt_3 (32 mL, 0.23 mmol) was added. The mixture was stirred at 5 °C and methanesulfonyl chloride (9 μL, 0.12 mmol) was added. The reaction was monitored by TLC (silica; CH_2Cl_2 : 5 % CH_3OH, R_f(product) = 0.75, R_f(reactant) = 0.61) and stopped after 30 min. The solvent was removed under reduced pressure and the residue dissolved in CH_2Cl_2 (10 mL) and washed with NaCl solution (saturated, 10 mL). The aqueous layer was re-extracted with CH_2Cl_2 (3 × 10 mL) and the organic layers combined, dried over $MgSO_4$ and the solvent removed under reduced pressure to leave a colourless oil (40 mg, 76 %); δ_H ($CDCl_3$) 8.59 (1H, d, $^3J_{H\text{-}P}$ 11.5, H^{11}), 8.36 (1H, m, H^{15}), 8.18 (1H, d, $^3J_{H\text{-}P}$ 6.5 Hz, H^4), 8.10 (1H, d, $^3J_{H\text{-}H}$ 8 Hz, H^{13}), 7.73 (1H, td, $^3J_{H\text{-}H}$ 8 Hz, $^4J_{H\text{-}P}$ 3 Hz, H^{14}), 7.60 (1H, s, H^2), 7.45 (1H, d, $^3J_{H\text{-}H}$ 8.5 Hz, H^{17}), 6.83 (1H, s, H^{20}), 6.73 (1H, d, $^3J_{H\text{-}H}$ 8.5 Hz, H^{18}), 5.29 (2H, m, H^9), 4.44 (2H, q, $^3J_{F\text{-}H}$ 8 Hz, H^6), 4.16 (2H, m, H^7), 3.82 (3H, s, OMe), 3.09 (2H, s, Ms), 2.49 (3H, s, H^{22}), 1.42 (3H, t, $^3J_{H\text{-}H}$ 7 Hz, H^8); δ_F ($CDCl_3$) -74.1 (t, $^3J_{F\text{-}H}$ 8 Hz); δ_P ($CDCl_3$) + 21.5; *m/z* ($HRMS^+$) 662.0900 $[M + H]^+$ ($C_{27}H_{28}NO_9F_3PS_2$ requires 662.0895); R_f = 0.75 (silica, DCM : MeOH 95 : 5).

2,2,2-Trifluoroethyl-6,6',6''-(1,4,7-triazacyclononane-1,4,7-triyl)tris(methylene)tris(4-((4-methoxy-2-methylphenyl)ethynyl)pyridine-6,2-diyl)tris(3-(ethoxyphosphoryl benzenesulfonate)



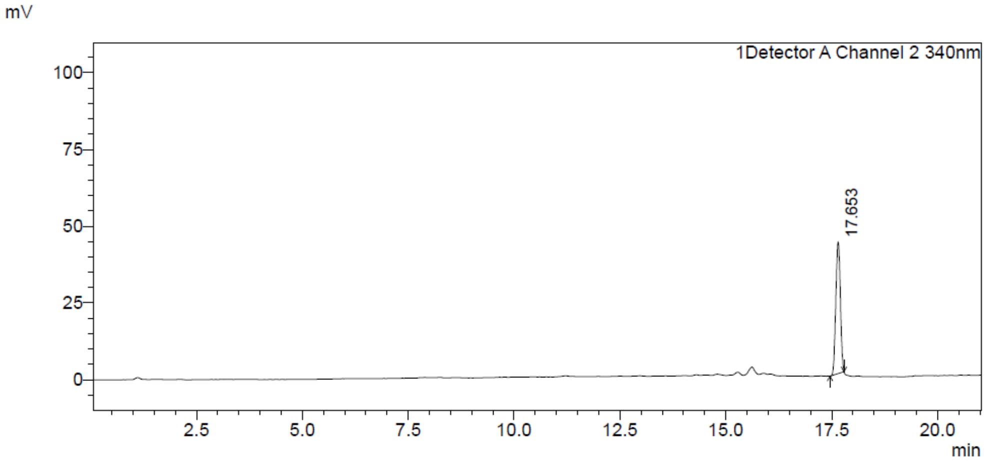
The hydrochloride salt of 1,4,7-triazacyclononane (5.0 mg, 20 μmol) and 2,2,2-trifluoroethyl 3-(ethoxy(4-((4-methoxy-2-methylphenyl)ethynyl)-6-((methylsulfonyloxy)methyl)pyridin-2-yl)phosphoryl)benzenesulfonate (40 mg, 60 μmol) were dissolved in anhydrous CH_3CN (1.5 mL) and K_2CO_3 (17 mg, 0.12 mmol) was added. KI (catalytical) was added to the reaction and the mixture was stirred under argon at 60 °C for 1 h. The reaction was cooled and the solution decanted from excess potassium salts. The solvent was removed under reduced pressure to give a yellow oil (18 mg, 51 %); δ_H ($CDCl_3$) 8.61 (3H, d, $^3J_{H\text{-}P}$ 11.5, H^{11}), 8.37 (3H, m, H^{15}), 8.12 (6H, m, $H^{4\text{-}13}$), 7.72 (6H, m, $H^{14\text{-}2}$), 7.41 (3H, d, $^3J_{H\text{-}H}$ 8.5 Hz, H^{17}), 6.83 (3H, s, H^{20}), 6.78 (3H, d, $^3J_{H\text{-}H}$ 8.5 Hz, H^{18}), 4.40 (6H, q, $^3J_{F\text{-}H}$ 8 Hz, H^6), 4.20 - 4.06 (6H, m, H^7), 3.83 (6H, s, H^9), 3.80 (9H, s, OMe), 2.48 (9H, s, H^{22}), 2.81 (12H, br, $9N_3$), 1.38 (9H, t, $^3J_{H\text{-}H}$ 7 Hz, H^8); δ_C ($CDCl_3$) 161.0 (d, $^4J_{C\text{-}P}$ 20 Hz, C^1), 160.3 (s, C^{19}), 151.4 (d, $^1J_{C\text{-}P}$ 169 Hz, C^5), 142.4 (s, C^{21}), 138.1 (d, $^2J_{C\text{-}P}$ 10 Hz, C^{15}), 135.7 (d, $^3J_{C\text{-}P}$ 12 Hz, C^{12}), 134.0 (s, C^{17}), 132.7 (d, $^1J_{C\text{-}P}$ 140 Hz, C^{10}), 131.9 (d, $^2J_{C\text{-}P}$ 11 Hz, C^{11}), 131.6 (s, C^3), 131.4 (s, C^{13}), 129.7 (d, $^3J_{C\text{-}P}$ 13 Hz, C^{14}), 128.6 (d, $^2J_{C\text{-}P}$ 23 Hz, C^4), 124.2 (s, C^2), 121.7 (q, $^1J_{C\text{-}F}$ 278 Hz, CF_3), 115.1 (s, C^{20}), 113.6 (s, C^{16}), 111.6 (s, C^{18}), 95.8 (s, C^{15}), 88.2 (s, C^{14}), 64.8 (q, $^2J_{C\text{-}F}$ 38.5 Hz, C^6), 62.9 (s, C^9), 62.7 (d, $^2J_{C\text{-}P}$ 7 Hz, C^7), 55.3 (s, OMe), 55.2-54.5 (br, $9N_3$), 21.0 (s, C^{22}), 16.5 (s, C^8); δ_F ($CDCl_3$) -74.1 (t, $^3J_{F\text{-}H}$ 8 Hz); δ_P ($CDCl_3$) + 22.3; *m/z* ($HRMS^+$) 1825.410 $[M + H]^+$ ($C_{84}H_{85}N_6O_{18}F_9P_3S_3$ requires 1825.415).

Eu(III) complex of 6,6',6''-(1,4,7-triazacyclononane-1,4,7-triyl)tris(methylene)tris(4-((4-methoxy-2-methylphenyl)ethynyl)pyridine-6,2-diyl)tris(3-(hydroxyphosphoryl benzenesulfonate), $[Eu.L^3]^{3-}$

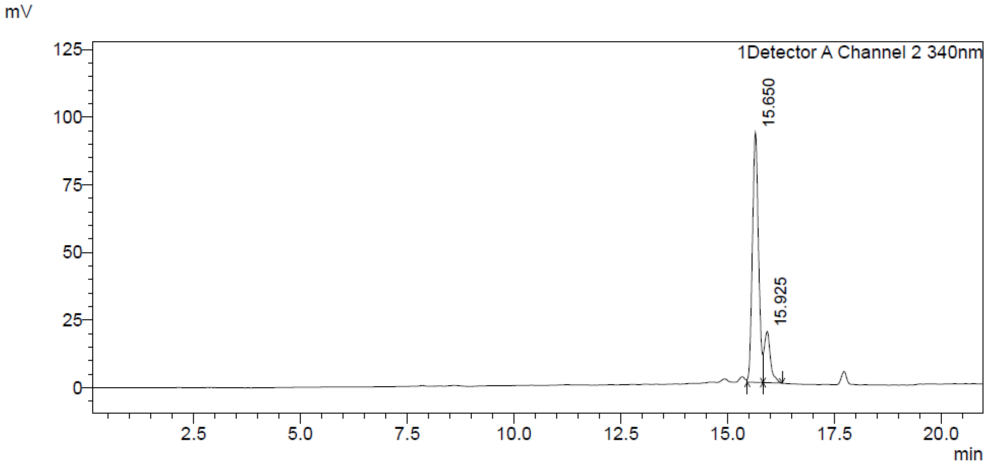


2,2,2-Trifluoroethyl-6,6',6''-(1,4,7-triazacyclononane-1,4,7-triyl)tris(methylene)tris(4-((4-methoxy-2-methylphenyl)ethynyl)pyridine-6,2-diyl)tris(3-(ethoxyphosphoryl benzenesulfonate) (5.0 mg, 2.7 µmol) was dissolved in CD_3OD (1.5 mL) and a solution of 0.1 M NaOH in D_2O (0.8 mL) was added. The mixture was heated to 60 °C under argon and monitored with ^{19}F-NMR [δ_F(reactant) = - 76.1, (δ_F(product, trifluoroethanol) = - 78.0] and ^{31}P-NMR [δ_P(reactant) = + 22.3, (δ_P(product) = + 12.9]. After 3 h the solution was cooled to RT and the pH was adjusted to 7 with HCl. $Eu(Cl)_3 6H_2O$ (1.0 mg, 2.9 µmol) was added and the mixture heated to 65 °C overnight under argon. The solvent was removed under reduced pressure and the product purified by HPLC ((XBridge C_{18} column, 19 x 100 mm, i.d. 5 µm) flow rate of 17 mL / min with H_2O (25 mM triethylammonium acetate buffer, pH = 7) – 2 % CH_3CN) as eluents (3 min) [linear gradient to 40 % MeOH (15 min), linear gradient to 100 % MeOH (3 min)], t_R = 19.2 min) giving the triethylammonium salt of the complex as a white solid (2.5 mg, 58 %); (HRMS$^-$) 1644.205 $[EuL^3H_2]^-$ ($C_{72}H_{65}{}^{153}EuN_6O_{18}P_3S_3$ requires 1644.202); τ_{H_2O} = 1.12 ms; λ_{max} = 340 nm.

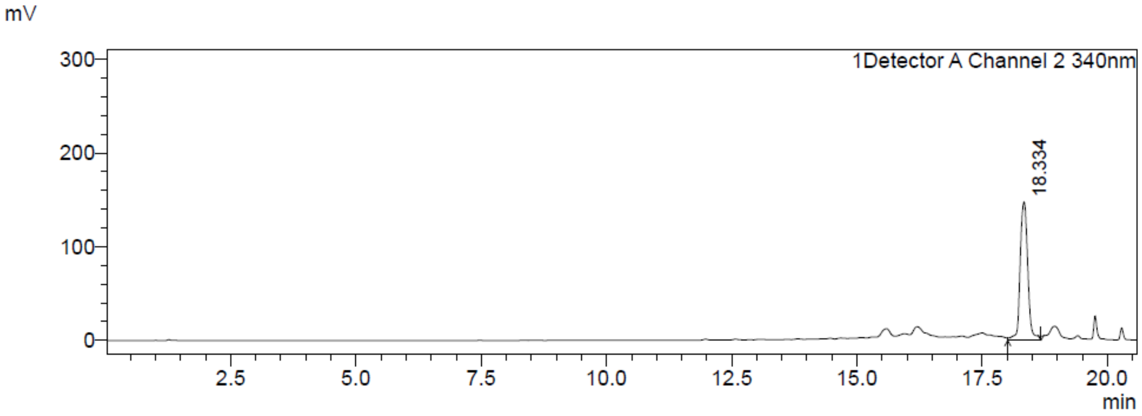
HPLC data for Europium(III) complexes



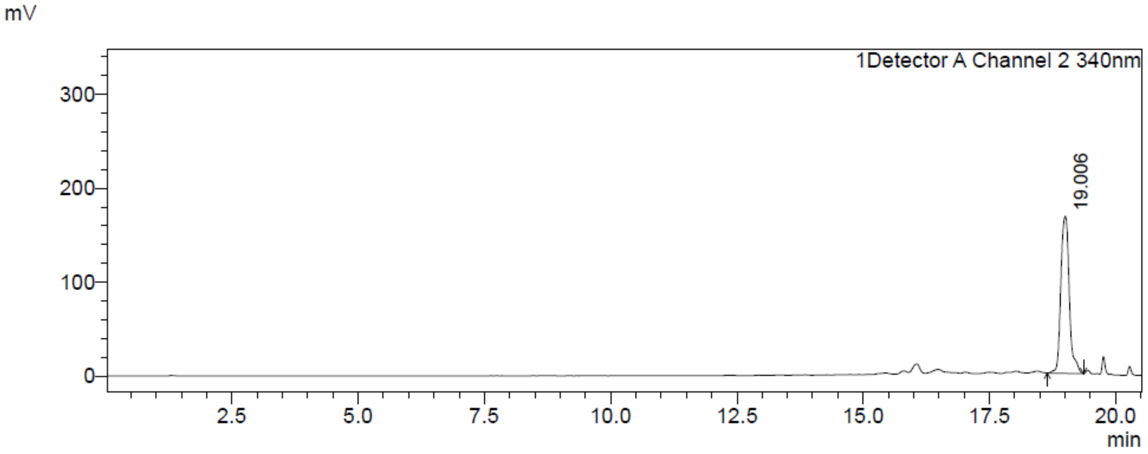
HPLC of [Eu.L^{1a}]$^{3-}$ ((XBridge C_{18} column, 4.6 x 100 mm, i.d. 5 µm) flow rate of 2 mL / min with H_2O (25 mM triethylammonium acetate buffer, pH = 7) – 2 % CH_3CN) as eluents (3 min) [linear gradient to 40 % MeOH (15 min), linear gradient to 100 % MeOH (3 min)], t_R = 17.7 min).



HPLC of[Eu.L^{2}]$^{2-}$ ((XBridge C_{18} column, 4.6 x 100 mm, i.d. 5 µm) flow rate of 2 mL / min with H_2O (25 mM triethylammonium acetate buffer, pH = 7) – 2 % CH_3CN) as eluents (3 min) [linear gradient to 40 % MeOH (15 min), linear gradient to 100 % MeOH (3 min)], t_R = 15.7 min).



HPLC of $[Eu.L^3]^{3-}$ ((XBridge C_{18} column, 4.6 x 100 mm, i.d. 5 µm) flow rate of 2 mL / min with H_2O (25 mM triethylammonium acetate buffer, pH = 7) – 2 % CH_3CN) as eluents (3 min) [linear gradient to 40 % MeOH (15 min), linear gradient to 100 % MeOH (3 min)], t_R = 18.3 min).

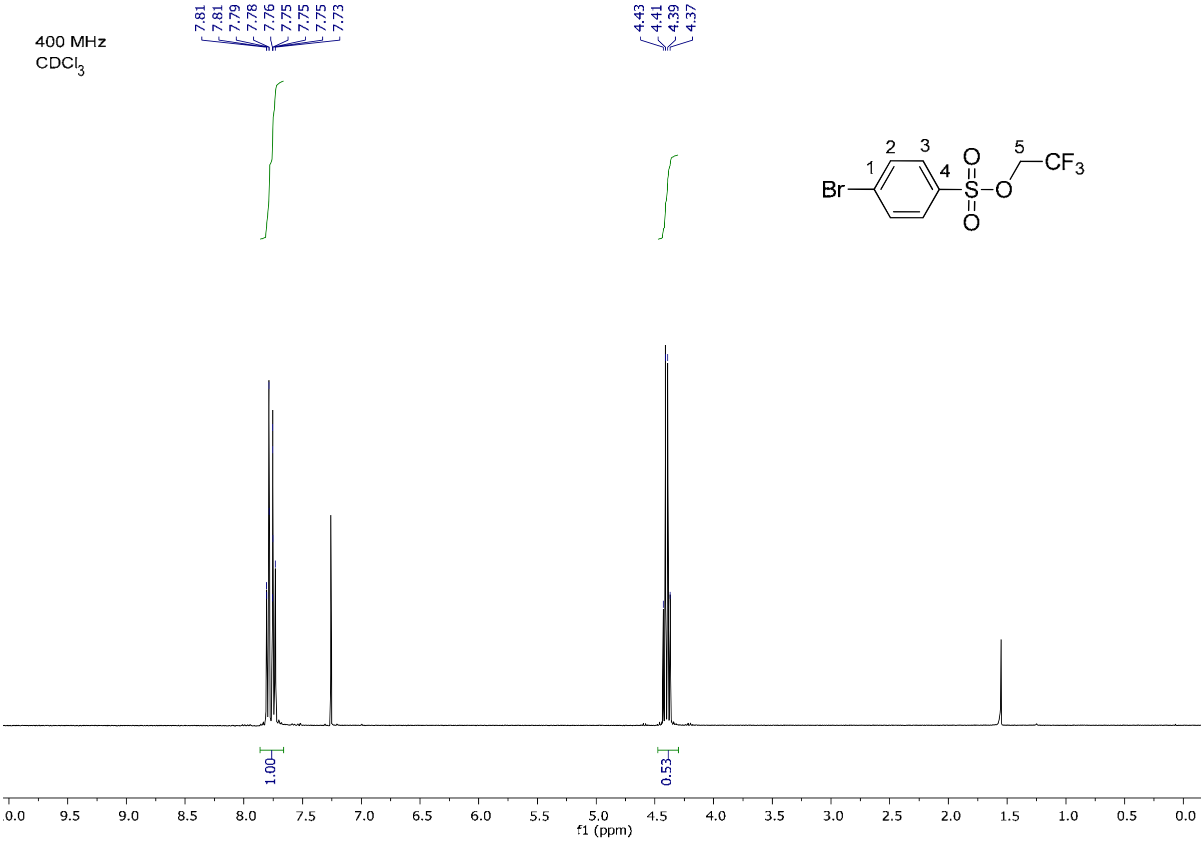


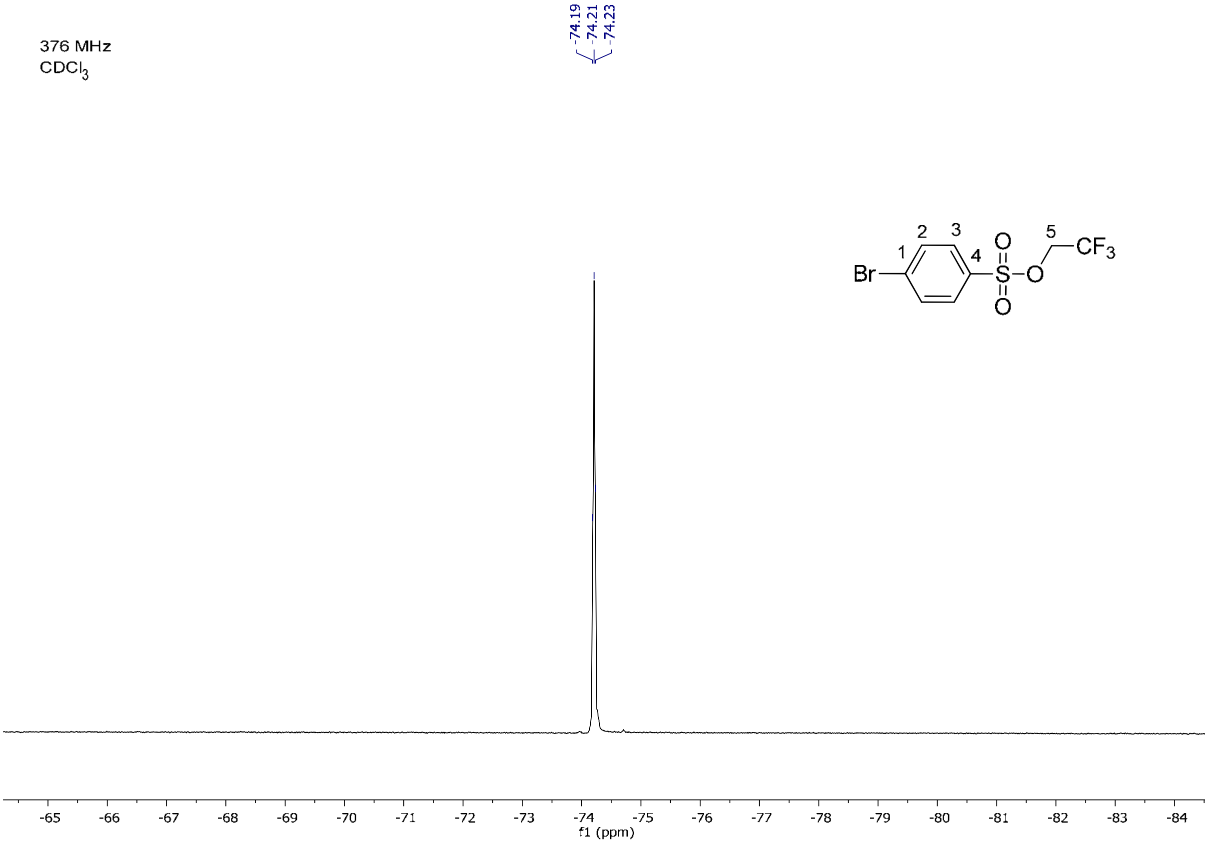
HPLC of $[Eu.L^{1b}]^{3-}$ ((XBridge C_{18} column, 4.6 x 100 mm, i.d. 5 µm) flow rate of 2 mL / min with H_2O (25 mM triethylammonium acetate buffer, pH = 7) – 2 % CH_3CN) as eluents (3 min) [linear gradient to 40 % MeOH (15 min), linear gradient to 100 % MeOH (3 min)], t_R = 19.0 min).

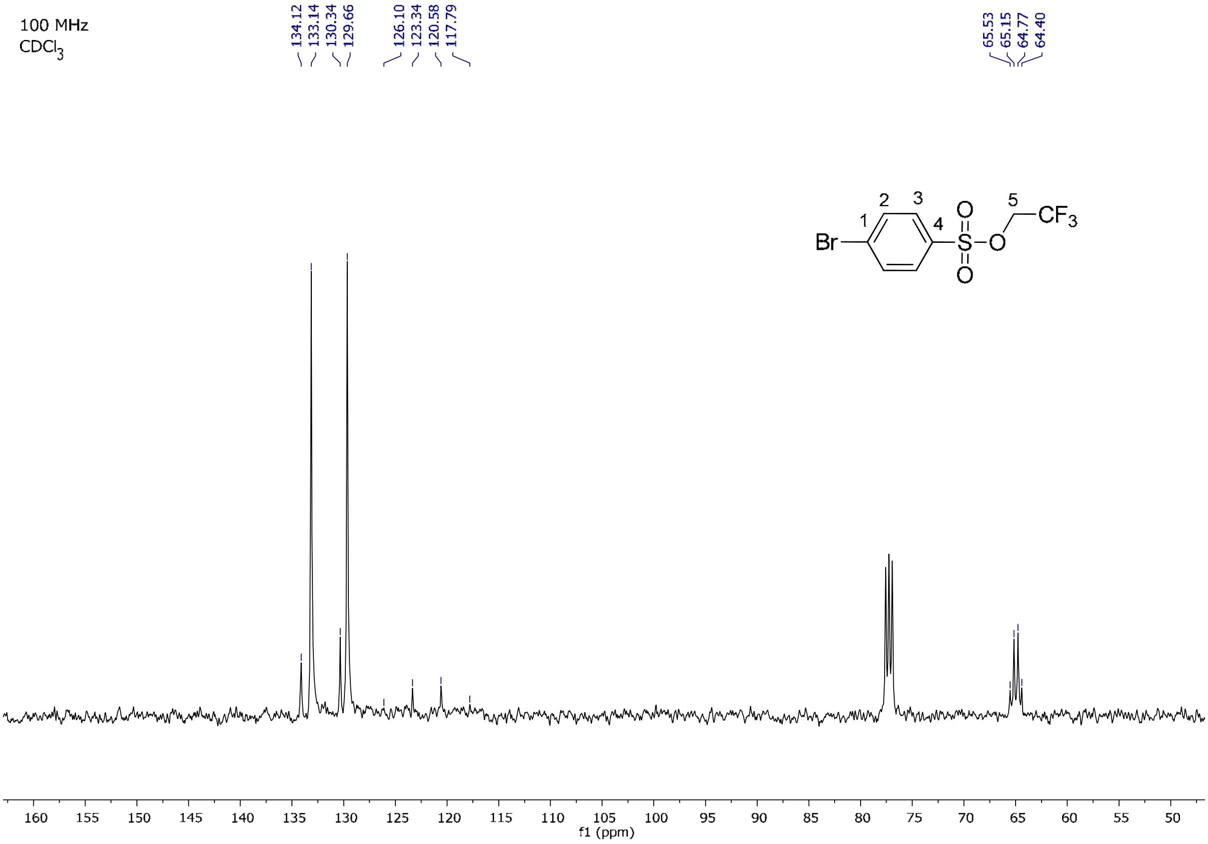
^{1}H, ^{19}F, ^{31}P and ^{13}C spectra

Each of the spectral assignments given here and in the main paper has been made with the aid of a variety of 2D NMR experiments (COSY, HMBC, HSQC). Two illustrative examples are reported for compounds **5** and **7,** e.g. pages 22-27.

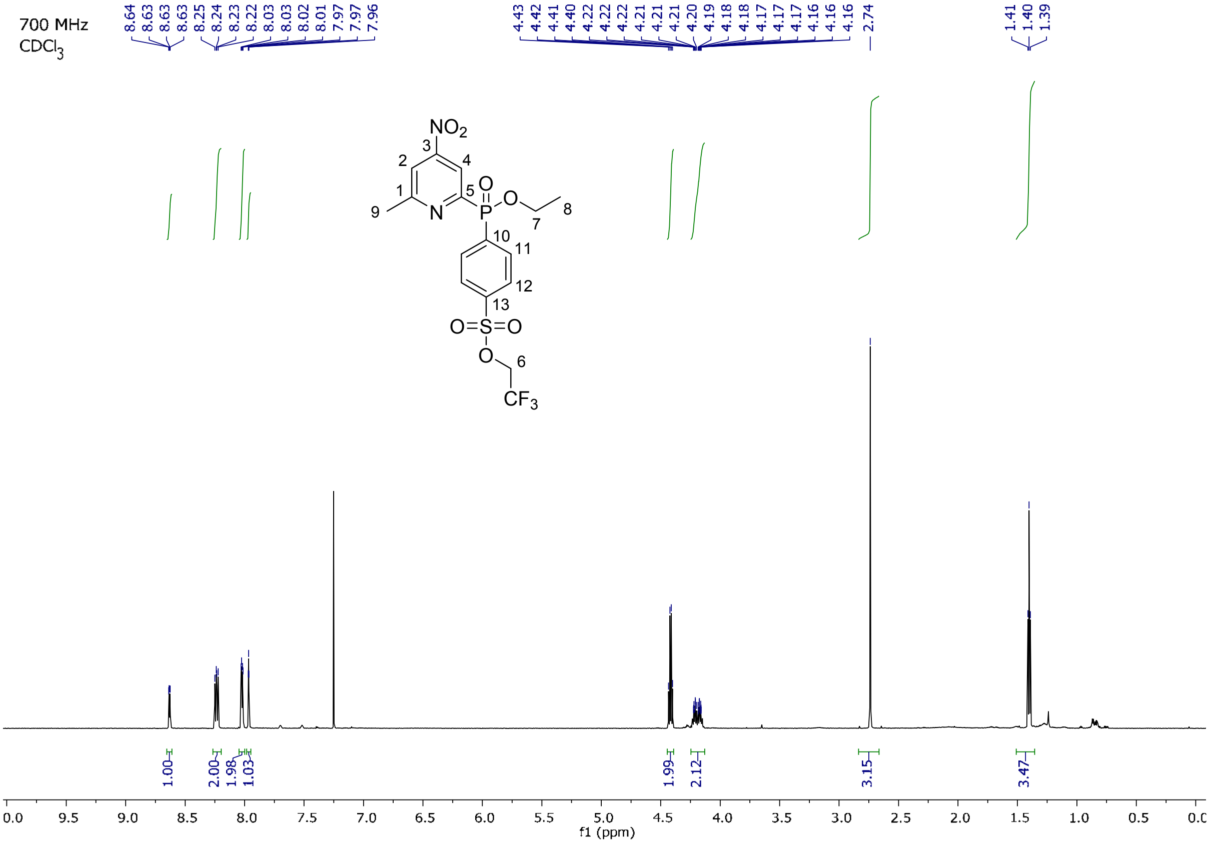
2,2,2-Trifluoroethyl 4-bromobenzenesulfonate, 1

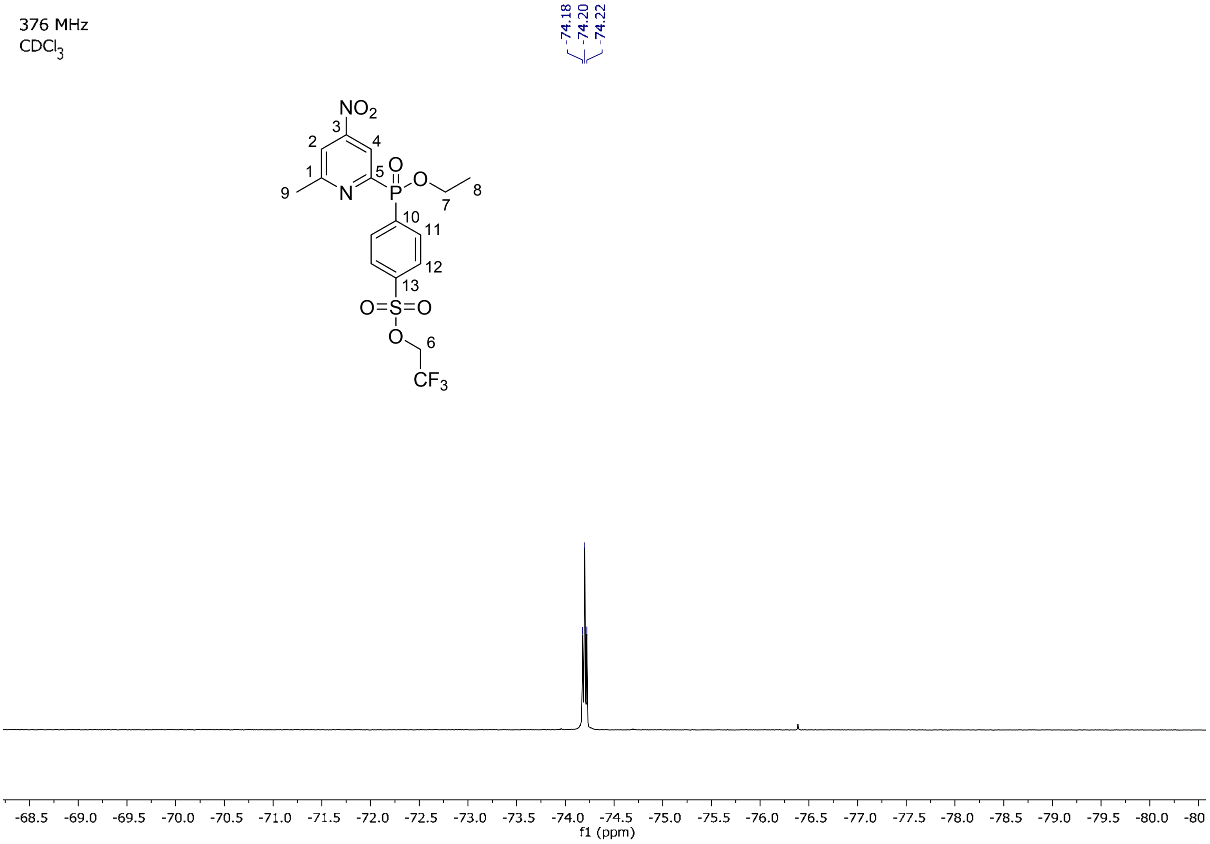


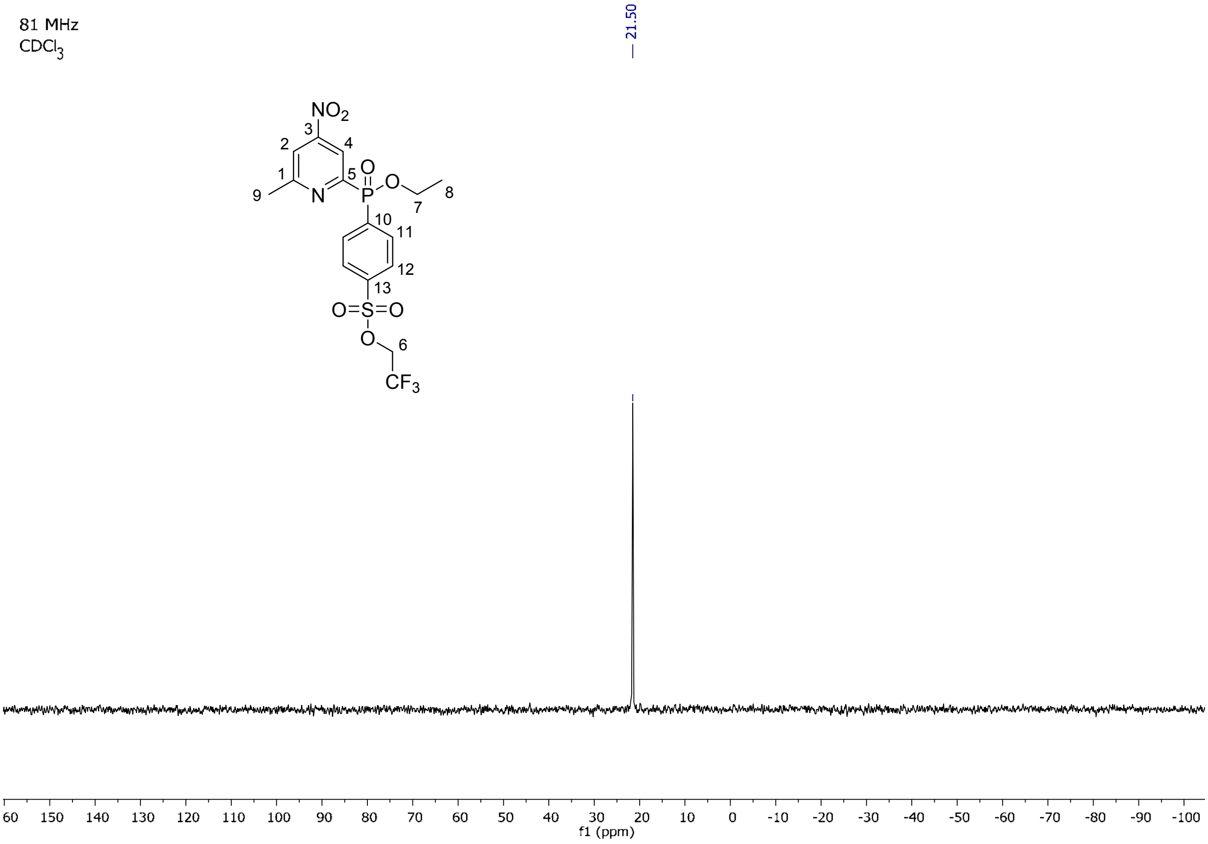


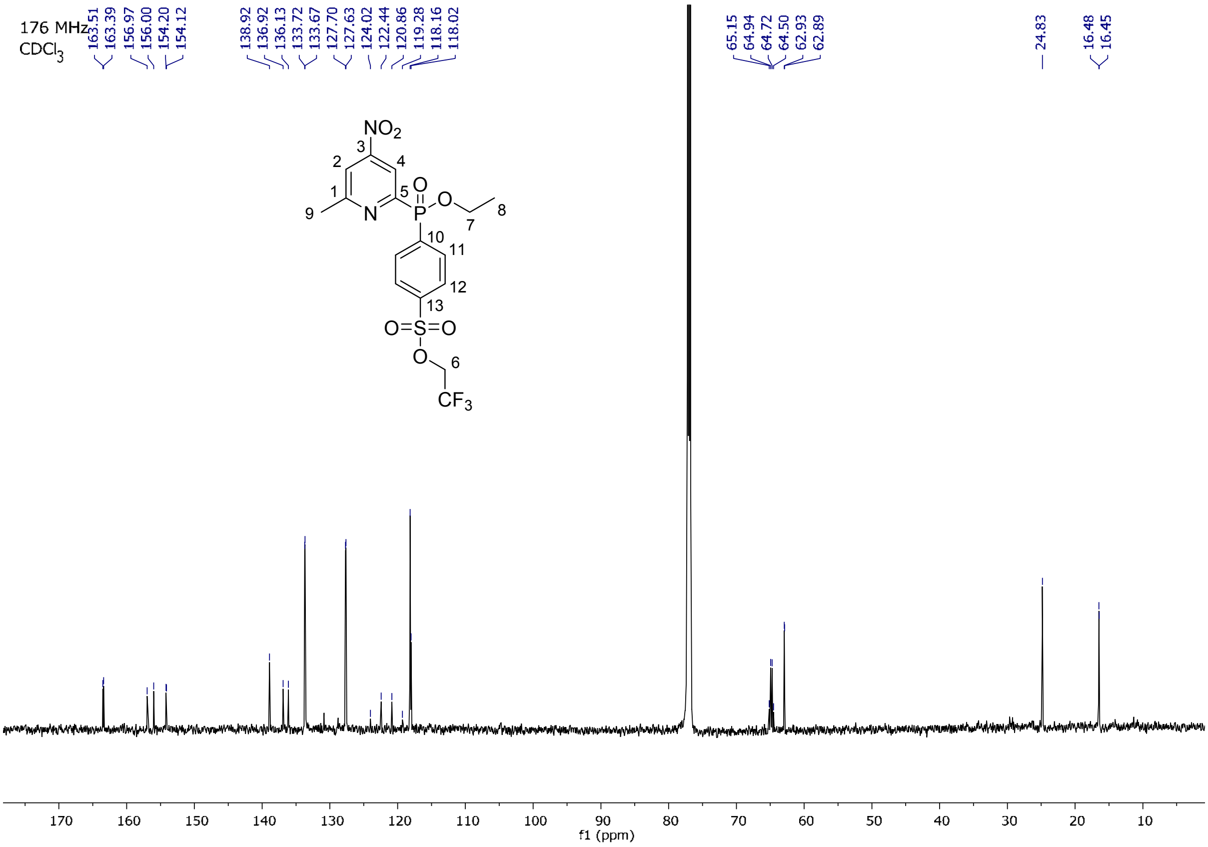


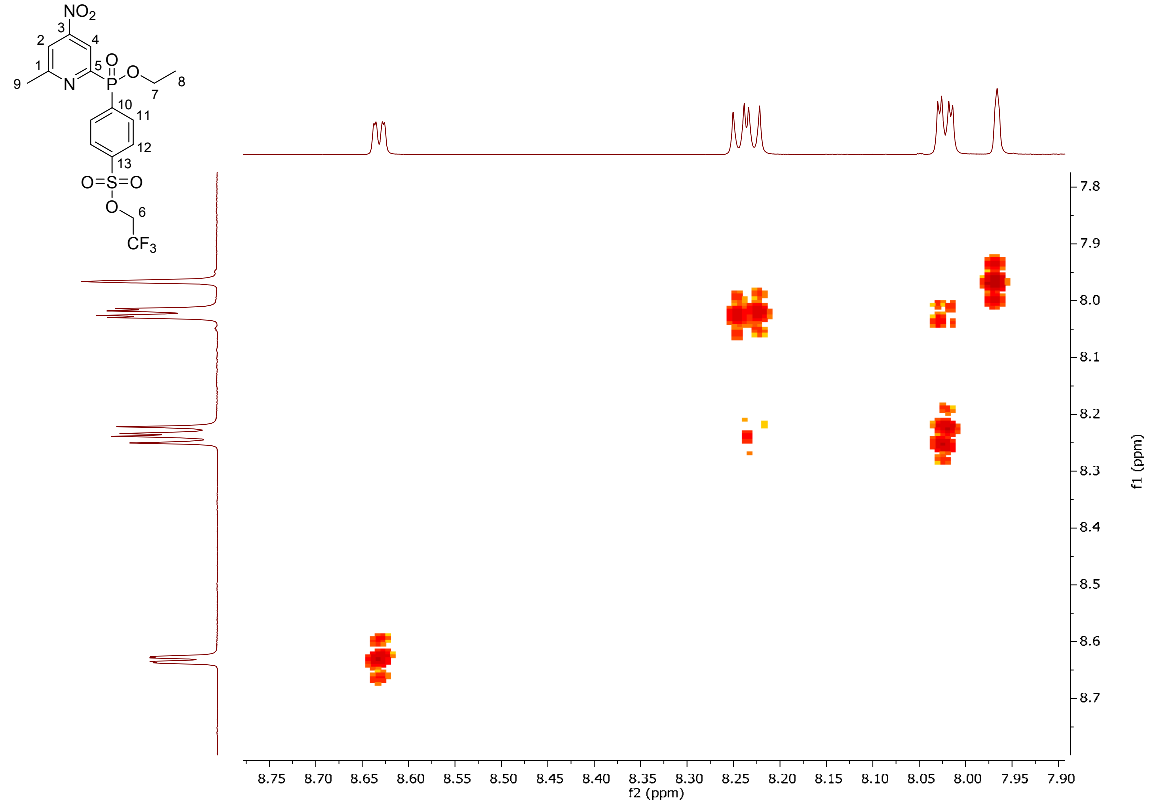
2,2,2-Trifluoroethyl 4-(ethoxy(6-methyl-4-nitropyridin-2-yl)phosphoryl)benzenesulfonate, 5

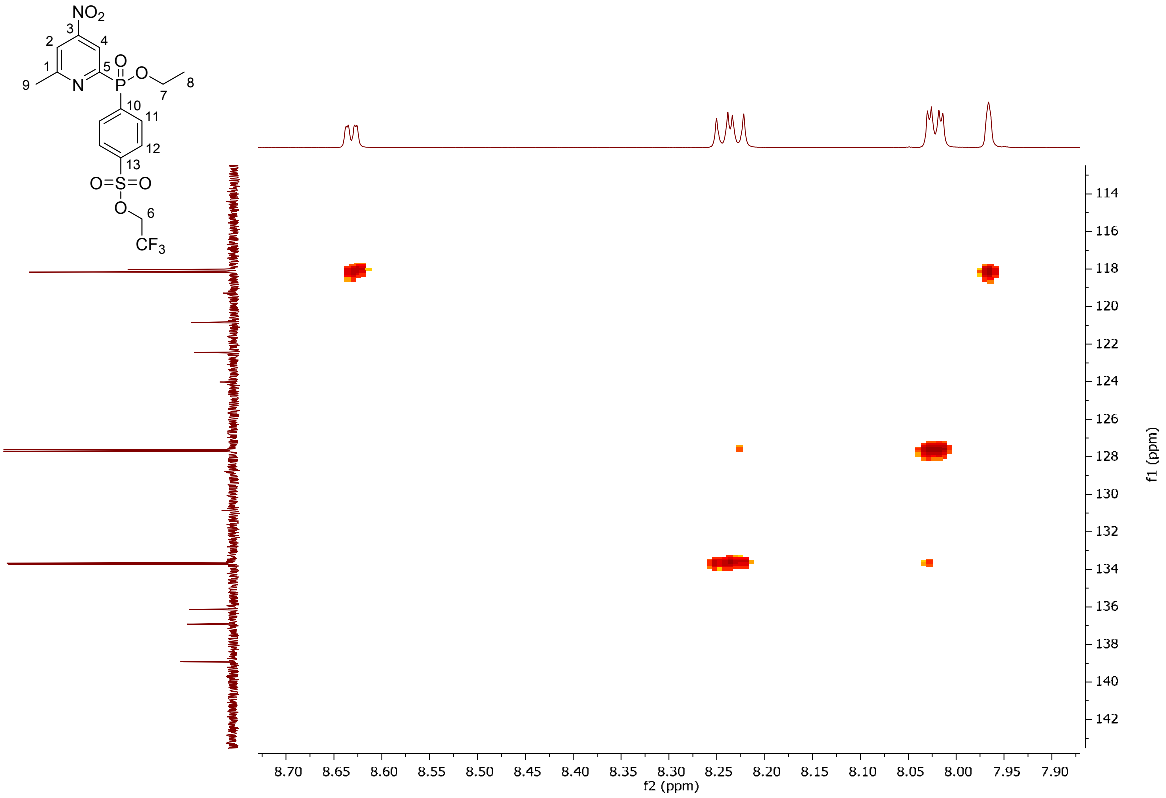

700 MHz
CDCl3
8.64 8.63 8.63 8.63 8.25 8.24 8.23 8.22 8.03 8.03 8.02 8.01 7.97 7.97 7.96
4.43 4.42 4.41 4.40 4.22 4.22 4.22 4.21 4.21 4.21 4.20 4.19 4.18 4.18 4.17 4.17 4.17 4.16 4.16
2.74
1.41 1.40 1.39
NO2
O
P
O
N
O=S=O
O
CF3
1 2 3 4 5 6 7 8 9 10 11 12 13
1.00
2.00
1.98
1.03
1.99
2.12
3.15
3.47
0.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

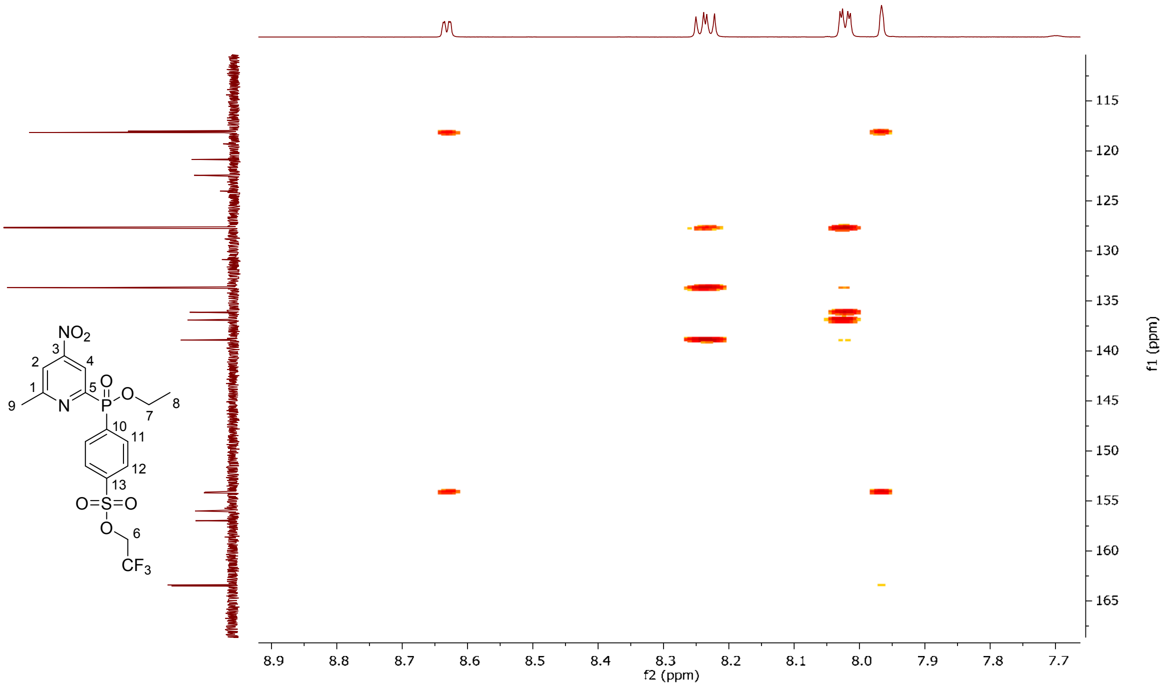

376 MHz
CDCl3
-74.18 -74.20 -74.22
NO2
O
P
O
N
O=S=O
O
CF3
1 2 3 4 5 6 7 8 9 10 11 12 13
-68.5 -69.0 -69.5 -70.0 -70.5 -71.0 -71.5 -72.0 -72.5 -73.0 -73.5 -74.0 -74.5 -75.0 -75.5 -76.0 -76.5 -77.0 -77.5 -78.0 -78.5 -79.0 -79.5 -80.0 -80
f1 (ppm)


81 MHz
CDCl$_3$
21.50
NO$_2$
1
2
3
4
5
6
7
8
9
10
11
12
13
N
P
O
O=S=O
CF$_3$
60
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
f1 (ppm)

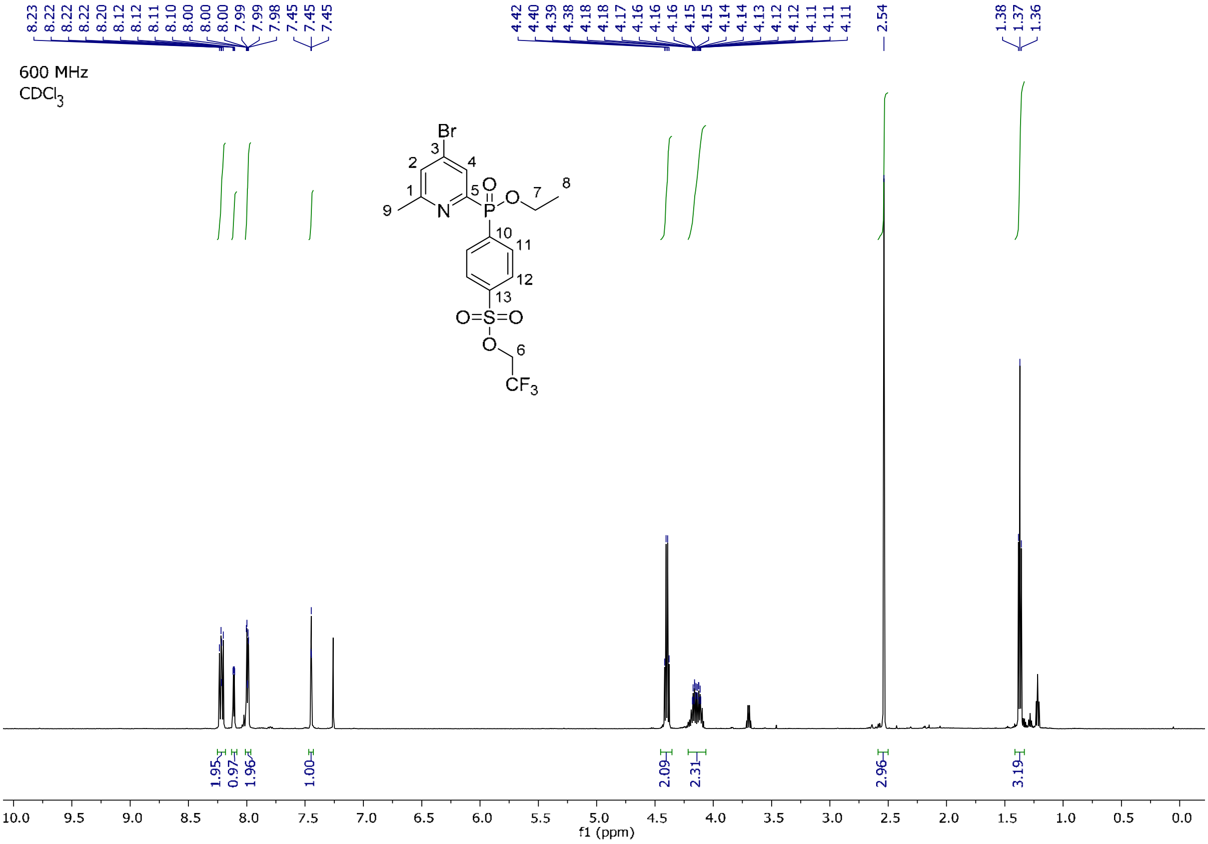

176 MHz
CDCl$_3$
163.51
163.39
156.97
156.00
154.20
154.12
138.92
136.92
136.13
133.72
133.67
127.70
127.63
124.02
122.44
120.86
119.28
118.16
118.02
65.15
64.94
64.72
64.50
62.93
62.89
24.83
16.48
16.45
NO$_2$
1
2
3
4
5
6
7
8
9
10
11
12
13
N
P
O
O=S=O
CF$_3$
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

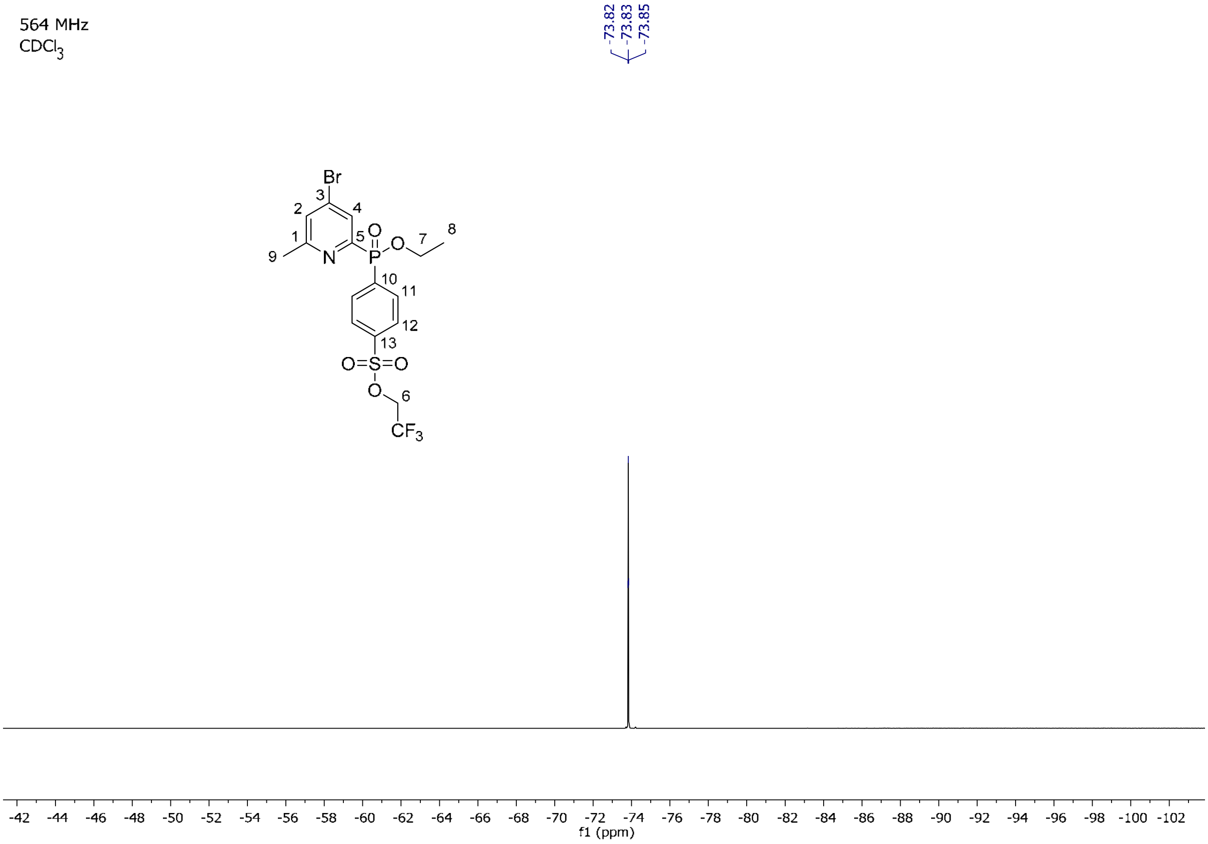

NO2
N
O
P
O
O=S=O
O
CF3
1
2
3
4
5
6
7
8
9
10
11
12
13
f1 (ppm)
7.8
7.9
8.0
8.1
8.2
8.3
8.4
8.5
8.6
8.7
f2 (ppm)
8.75
8.70
8.65
8.60
8.55
8.50
8.45
8.40
8.35
8.30
8.25
8.20
8.15
8.10
8.05
8.00
7.95
7.90


NO2
N
O
P
O
O=S=O
O
CF3
1
2
3
4
5
6
7
8
9
10
11
12
13
f1 (ppm)
114
116
118
120
122
124
126
128
130
132
134
136
138
140
142
f2 (ppm)
8.70
8.65
8.60
8.55
8.50
8.45
8.40
8.35
8.30
8.25
8.20
8.15
8.10
8.05
8.00
7.95
7.90



2,2,2-Trifluoroethyl 4-((4-bromo-6-methylpyridin-2-yl)(ethoxy)phosphoryl)benzenesulfonate, 7




564 MHz
$CDCl_3$
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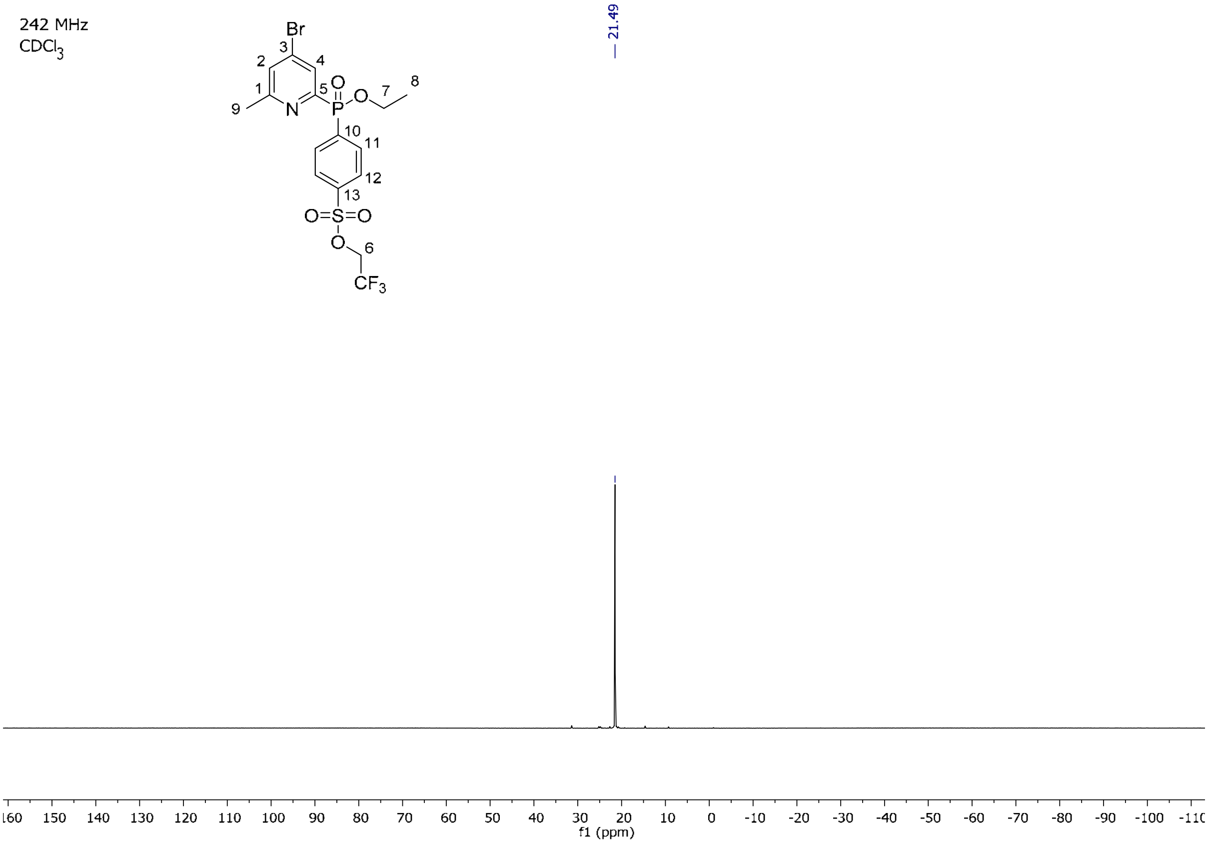
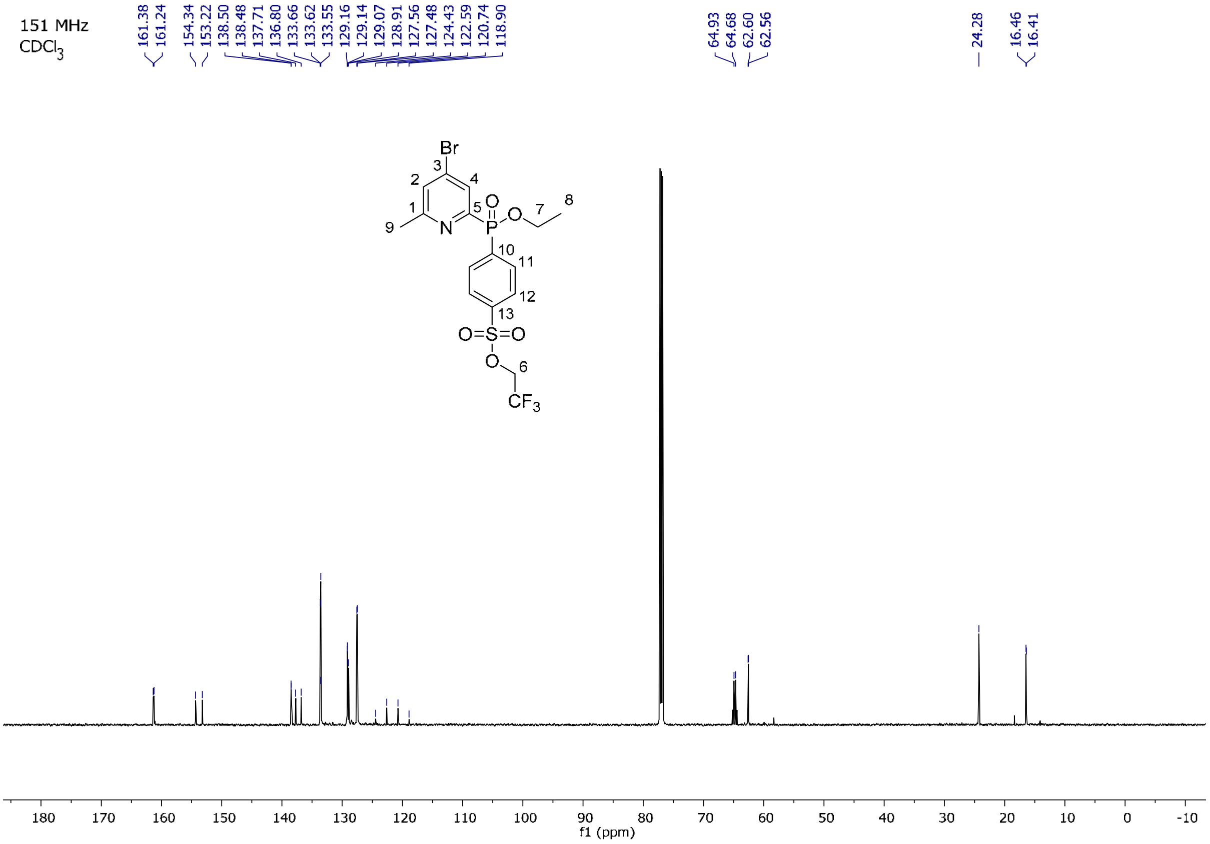
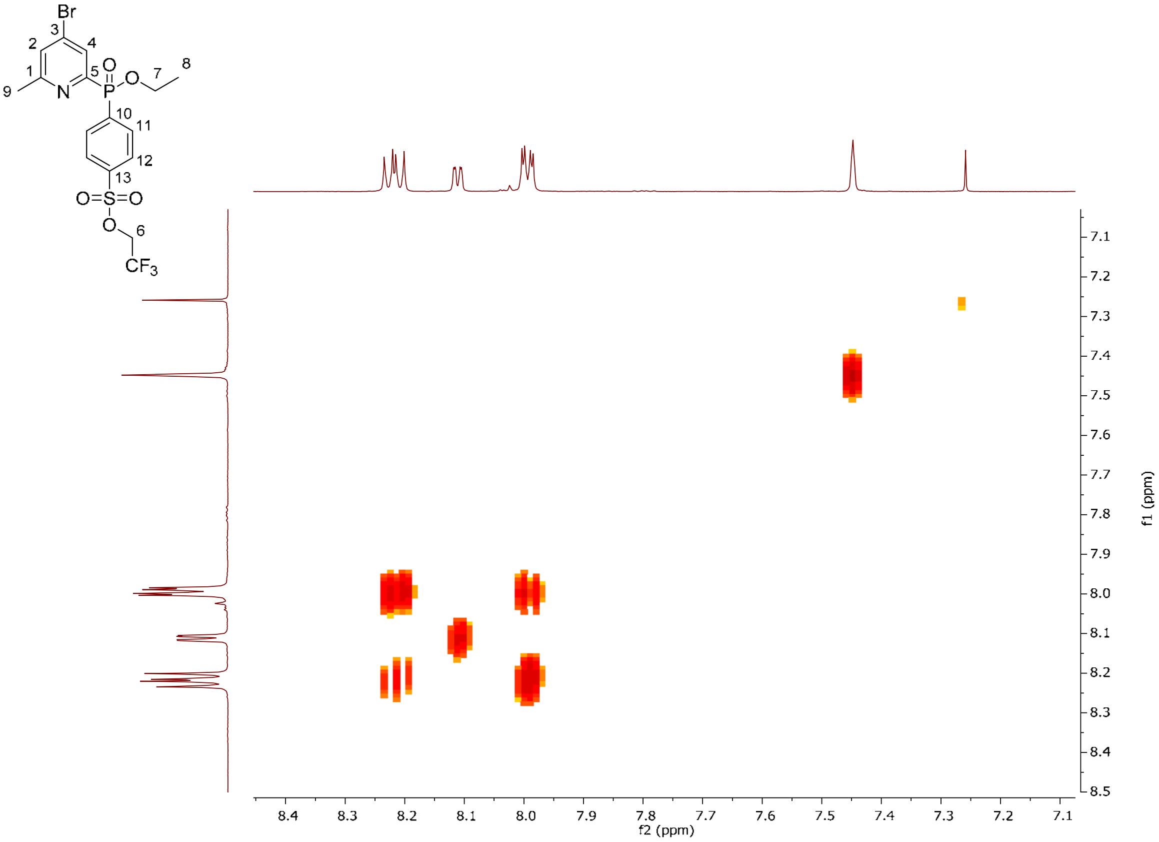
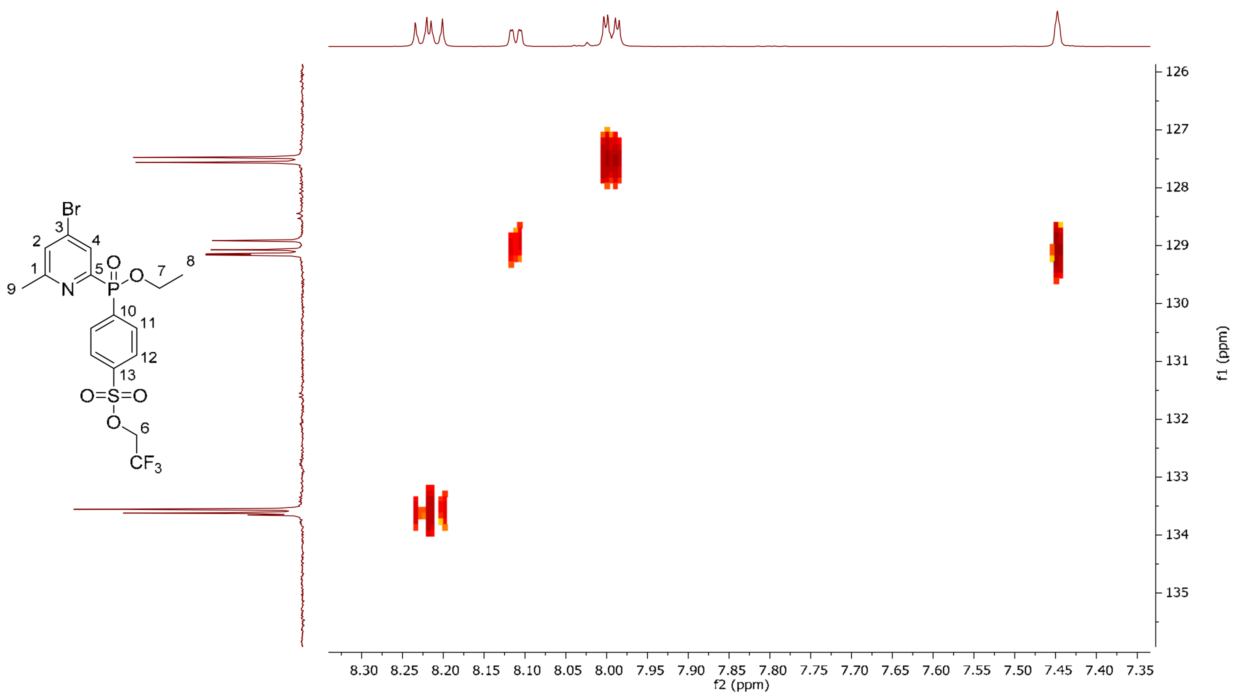
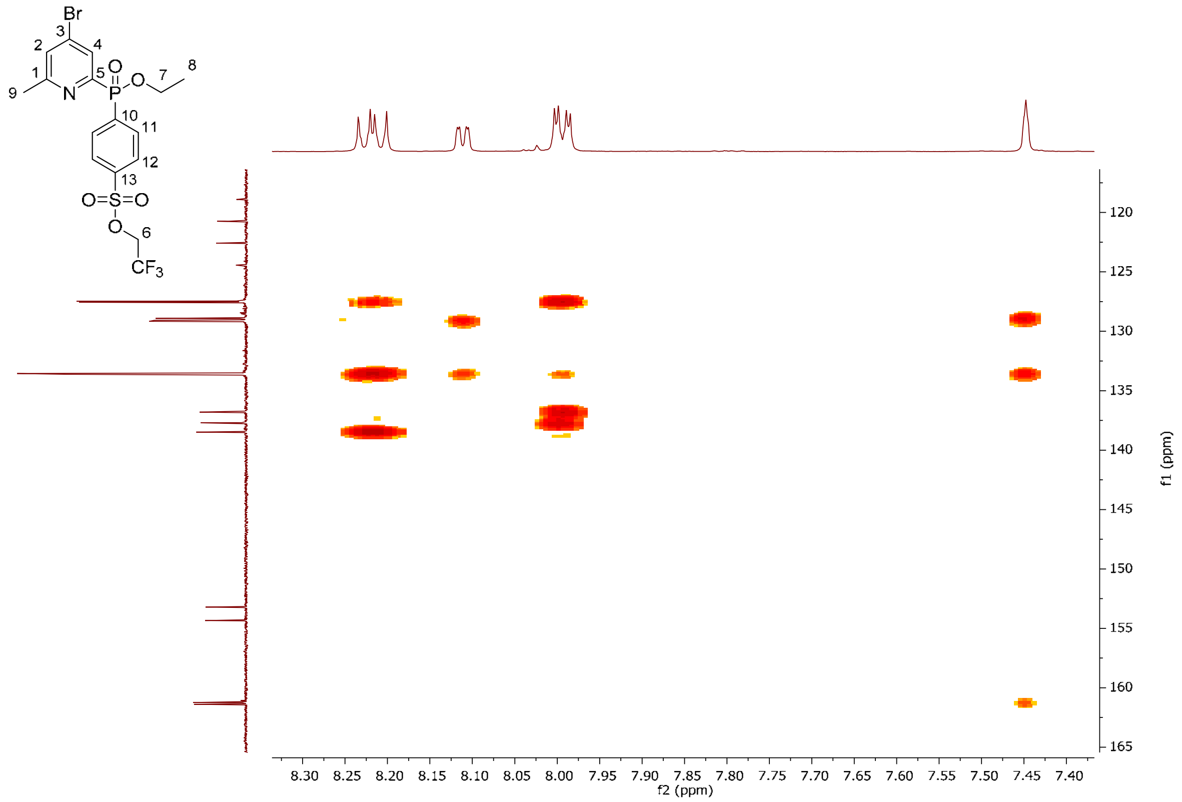
-73.83
-73.85
Br
1
2
3
4
5
6
7
8
9
10
11
12
13
N
P
O
O=S=O
CF_3
-42 -44 -46 -48 -50 -52 -54 -56 -58 -60 -62 -64 -66 -68 -70 -72 -74 -76 -78 -80 -82 -84 -86 -88 -90 -92 -94 -96 -98 -100 -102
f1 (ppm)


242 MHz
$CDCl_3$
21.49
Br
1
2
3
4
5
6
7
8
9
10
11
12
13
N
P
O
O=S=O
CF_3
160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110
f1 (ppm)

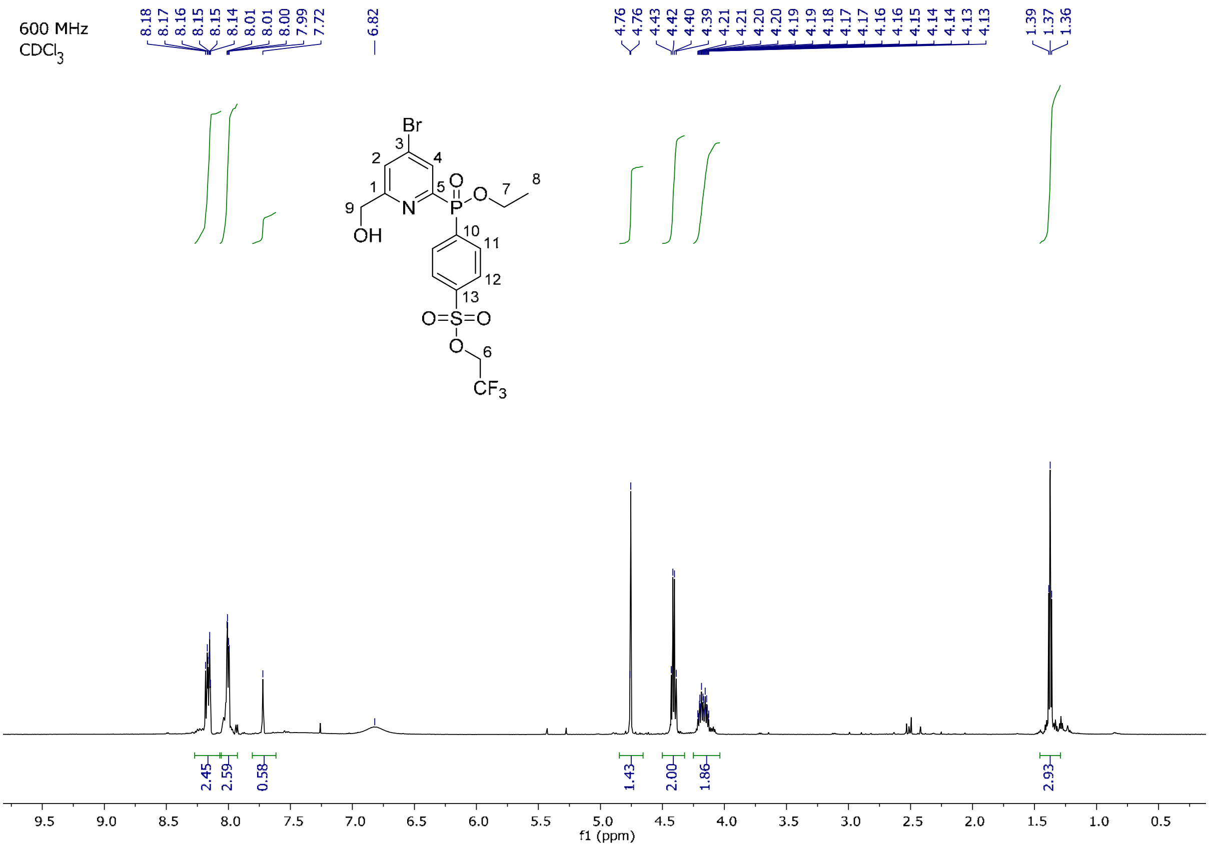

151 MHz
CDCl3
161.38
161.24
154.34
153.22
138.50
138.48
137.71
136.80
133.66
133.62
133.55
129.16
129.14
129.07
128.91
127.56
127.48
124.43
122.59
120.74
118.90
64.93
64.68
62.60
62.56
24.28
16.46
16.41
Br
N
P
O
O=S=O
CF3
1
2
3
4
5
6
7
8
9
10
11
12
13
f1 (ppm)
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

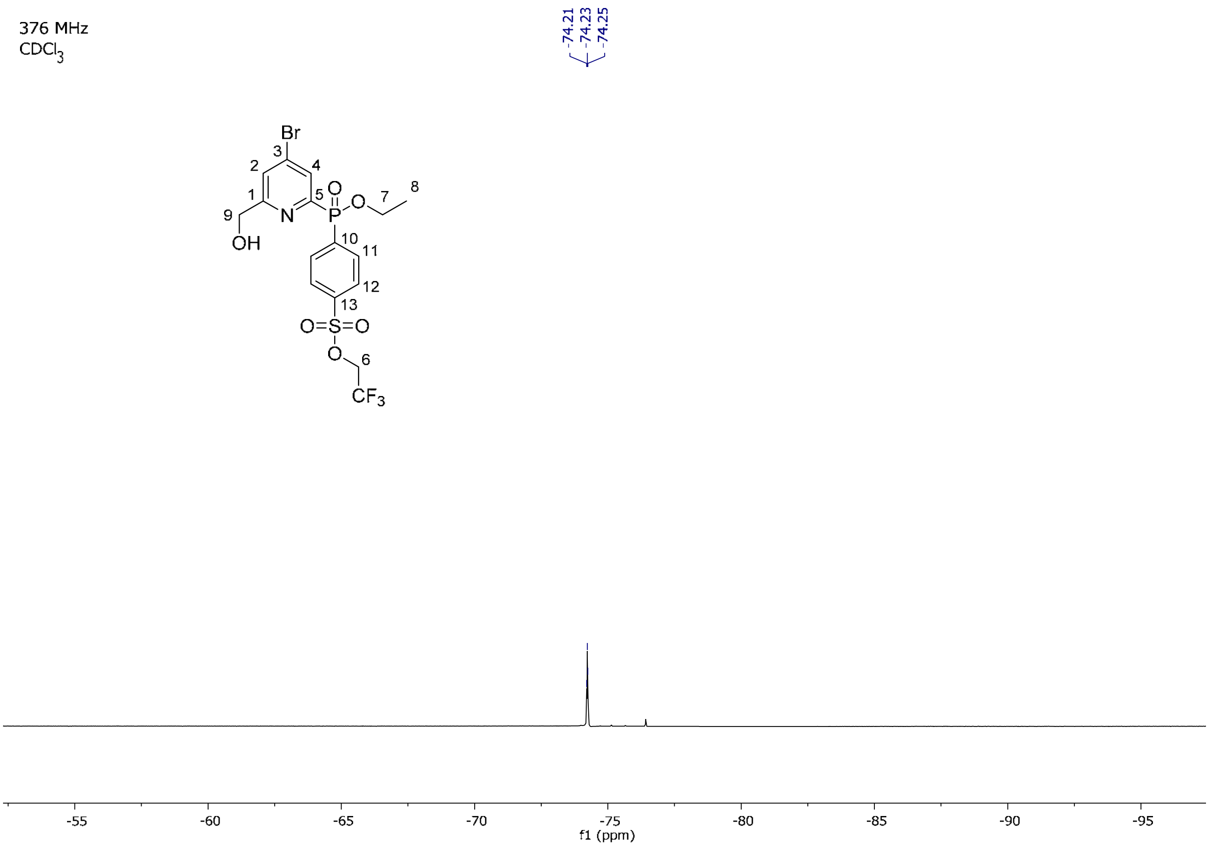

Br
N
P
O
O=S=O
CF3
1
2
3
4
5
6
7
8
9
10
11
12
13
f2 (ppm)
8.4
8.3
8.2
8.1
8.0
7.9
7.8
7.7
7.6
7.5
7.4
7.3
7.2
7.1
f1 (ppm)
7.1
7.2
7.3
7.4
7.5
7.6
7.7
7.8
7.9
8.0
8.1
8.2
8.3
8.4
8.5

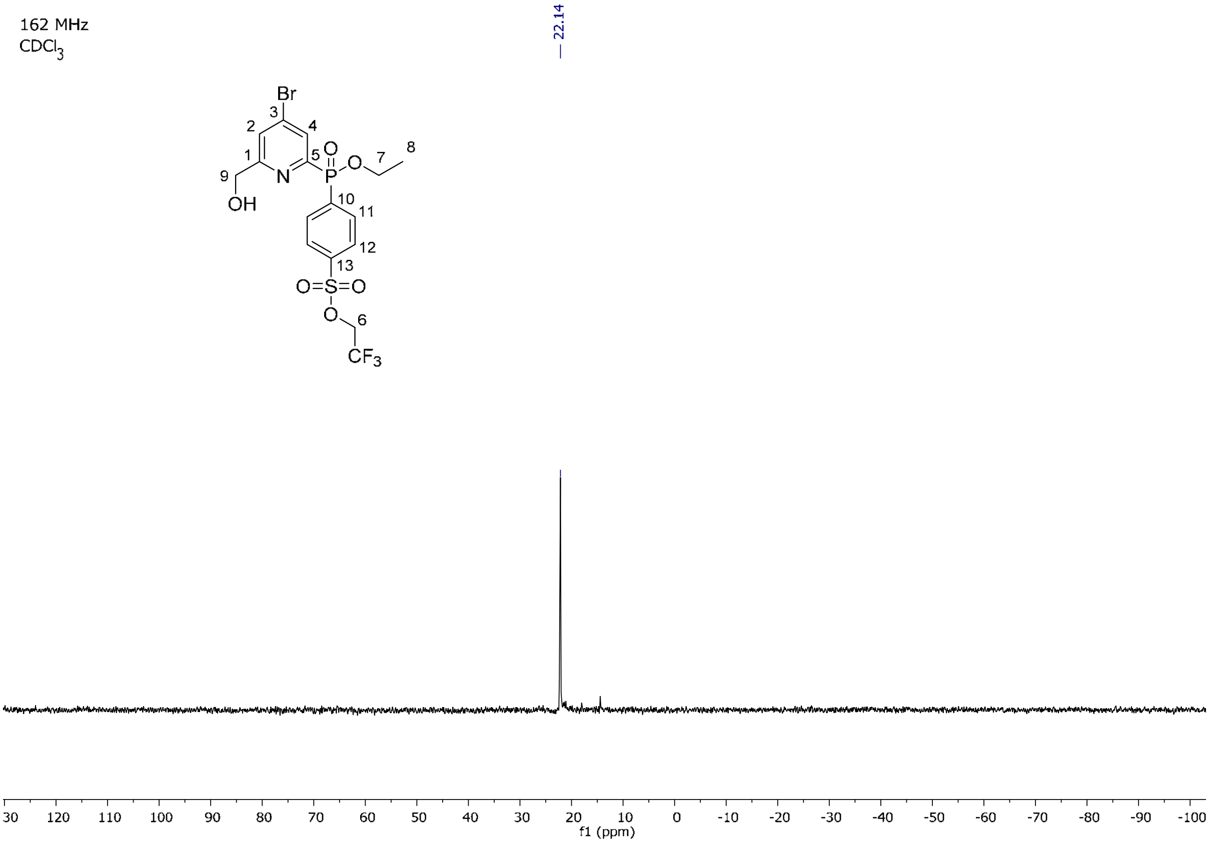




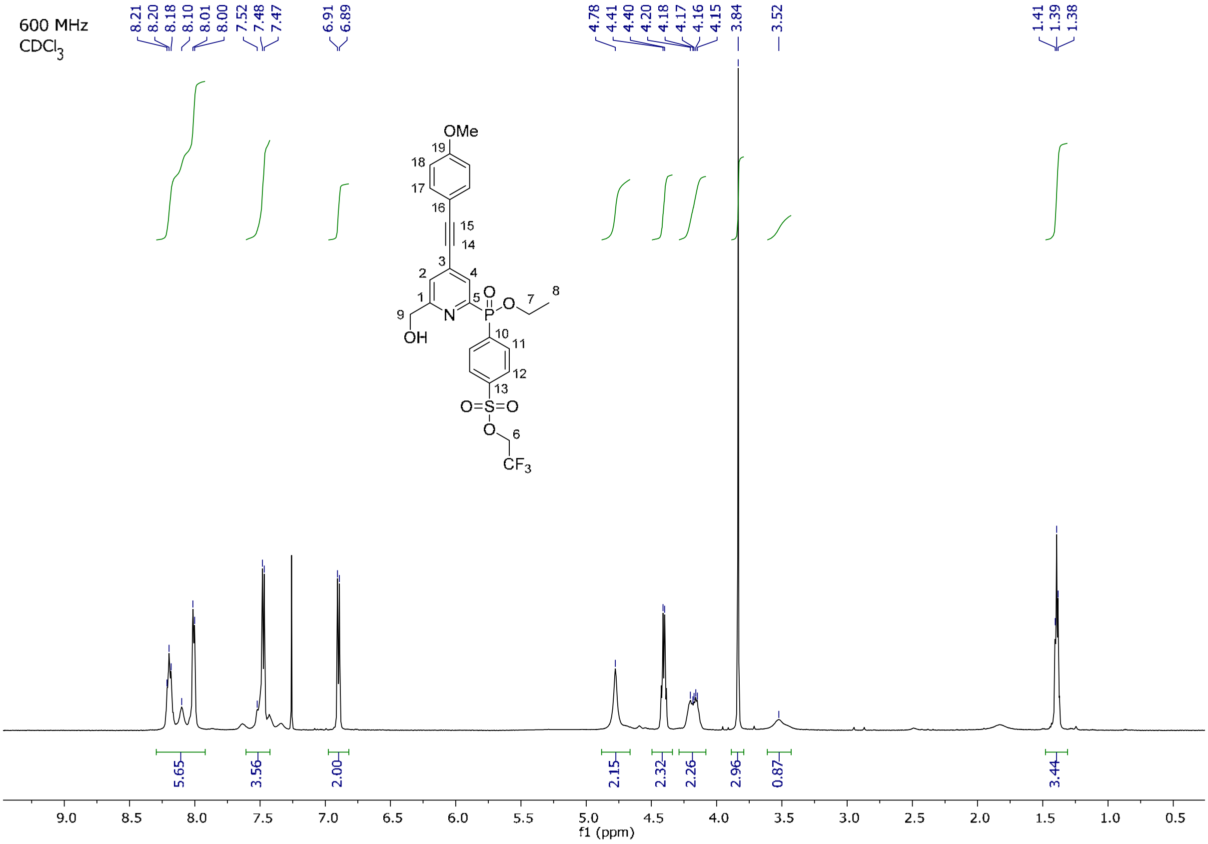
2,2,2-Trifluoroethyl-4-((4-bromo-6-(hydroxymethyl)pyridin-2-yl)(ethoxy)phosphoryl)benzenesulfonate, 11

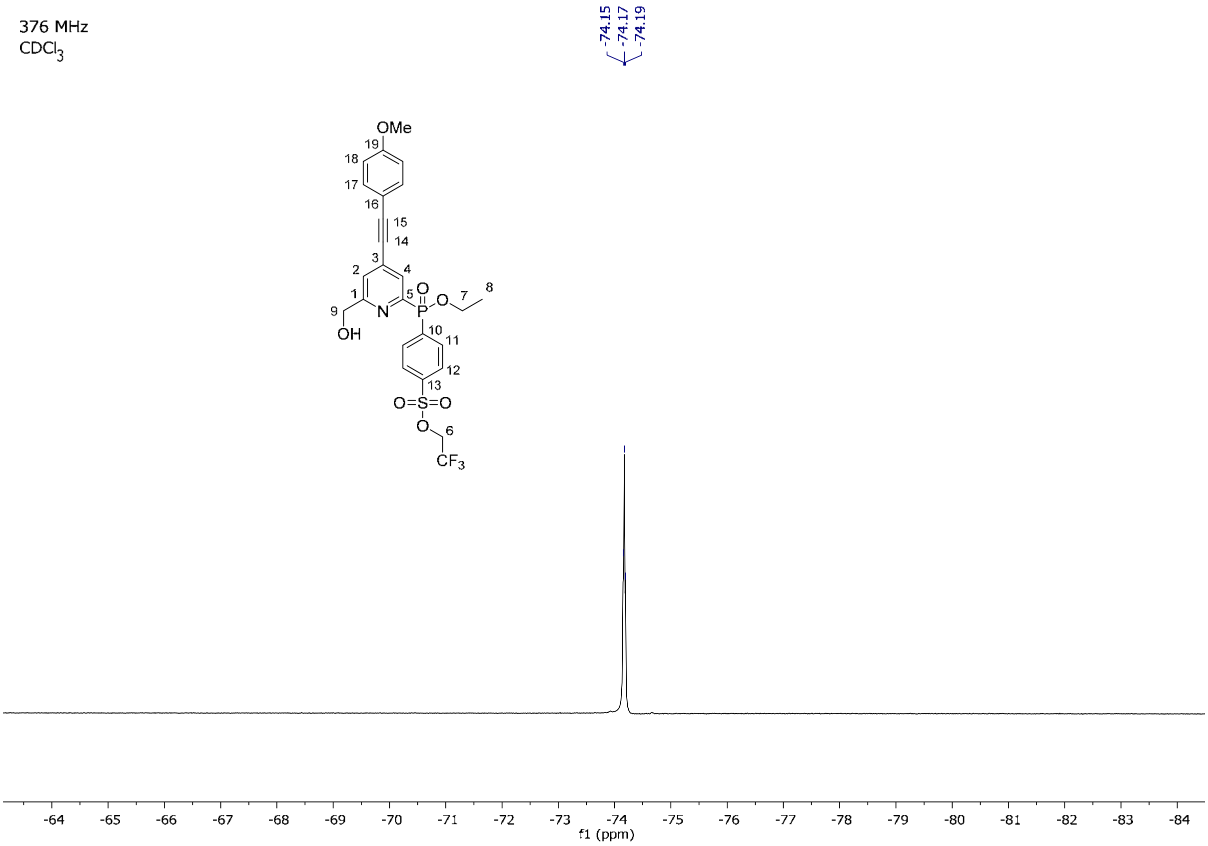

600 MHz
CDCl3
8.18 8.17 8.16 8.15 8.15 8.14 8.01 8.01 8.00 7.99 7.72
6.82
4.76 4.76 4.43 4.42 4.40 4.39 4.21 4.21 4.20 4.20 4.19 4.19 4.18 4.17 4.17 4.16 4.16 4.15 4.14 4.14 4.13 4.13
1.39 1.37 1.36
Br
OH
N
P
O
O=S=O
CF3
2.45
2.59
0.58
1.43
2.00
1.86
2.93
f1 (ppm)

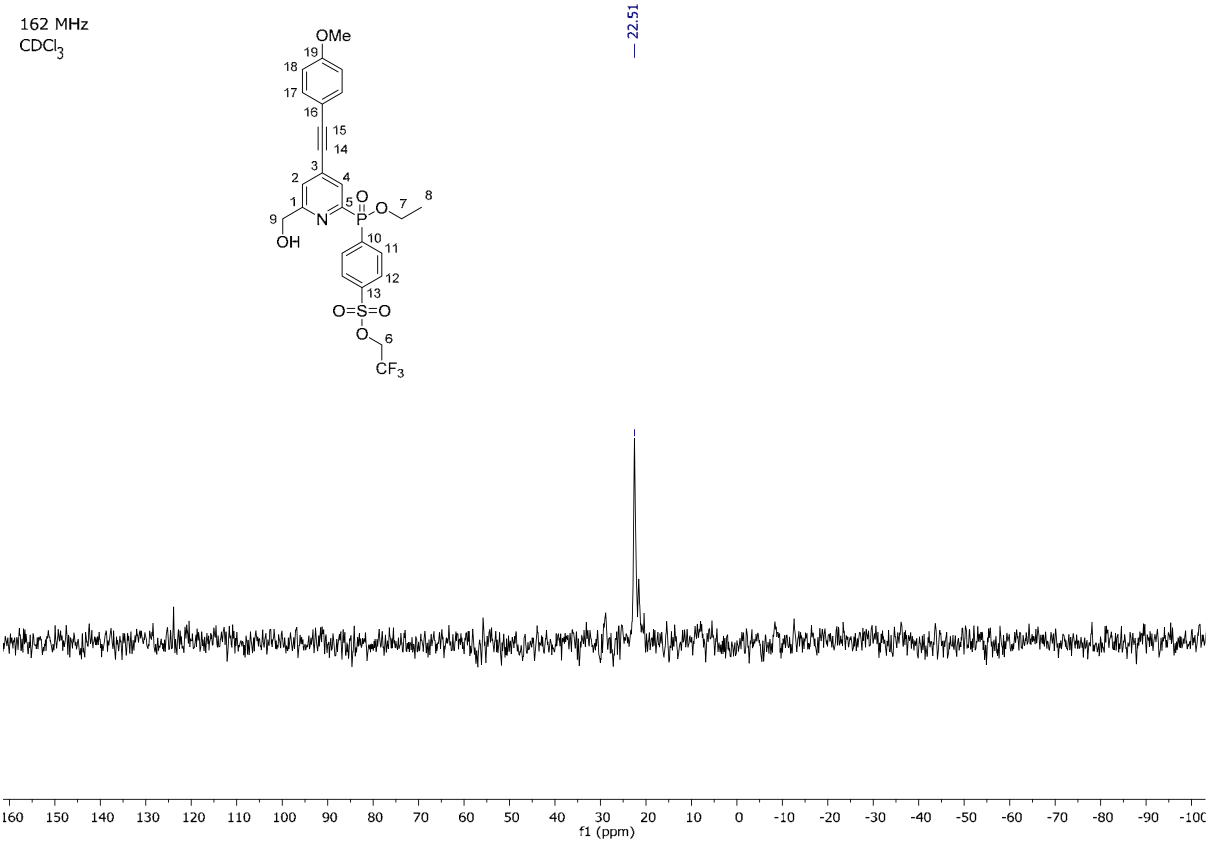

376 MHz
CDCl3
-74.21
-74.23
-74.25
Br
OH
N
P
O
O=S=O
CF3
f1 (ppm)



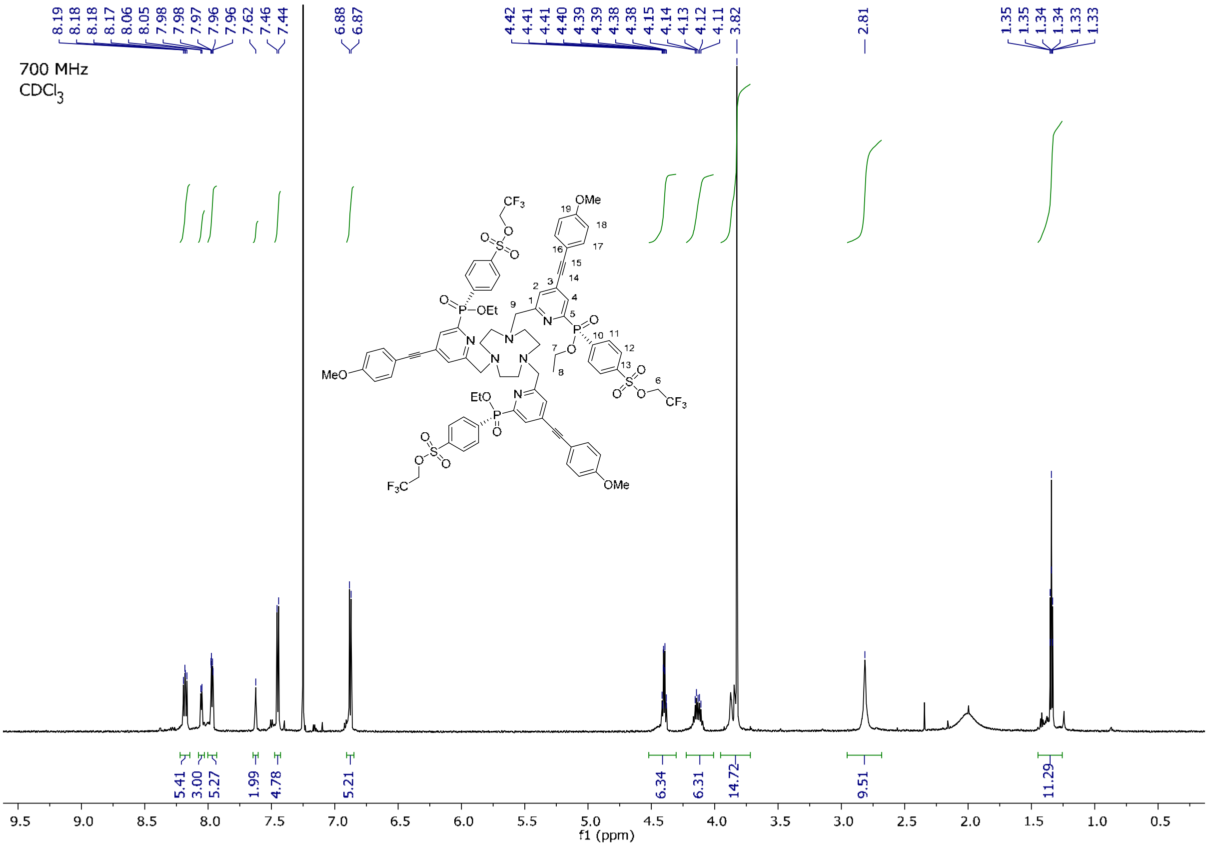
2,2,2-Trifluoroethyl-4-(ethoxy(6-(hydroxymethyl)-4-((4-methoxyphenyl)ethynyl)pyridin-2-yl)phosphoryl)benzenesulfonate

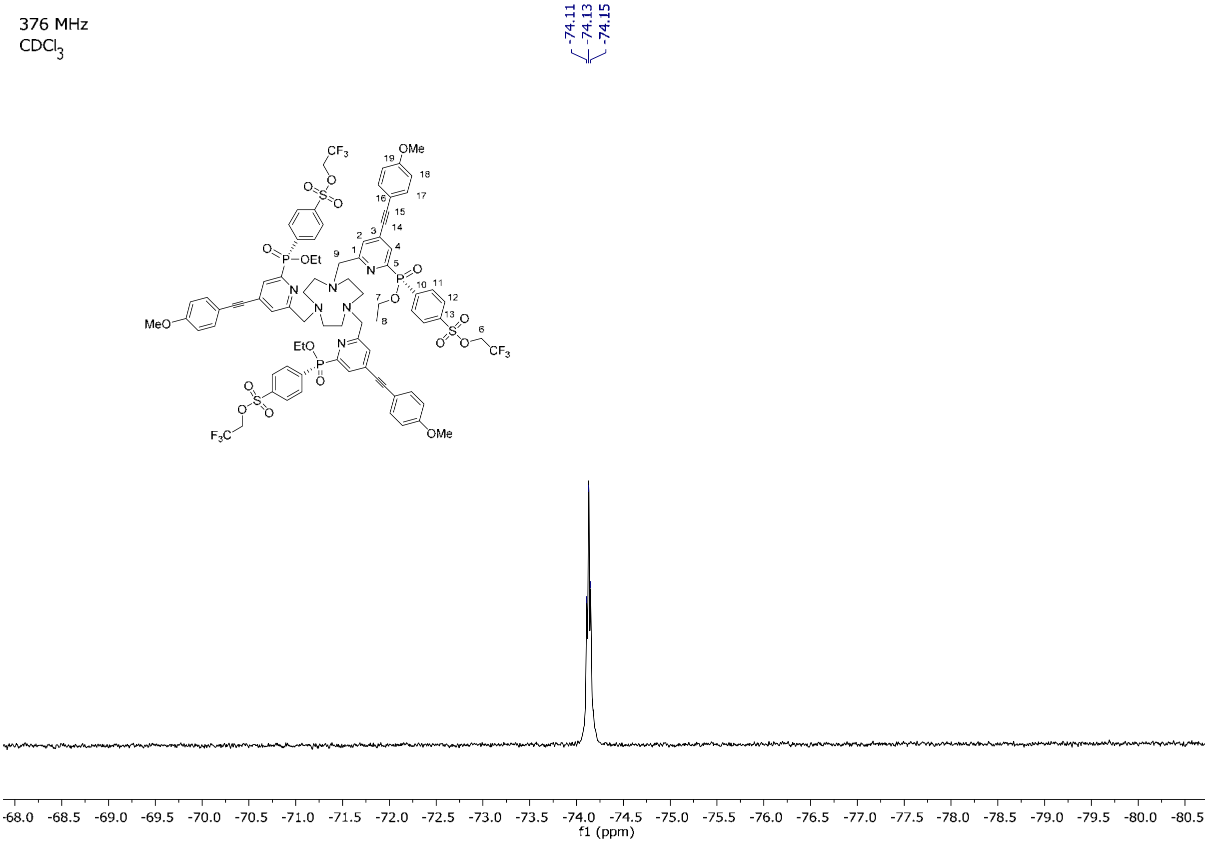

600 MHz
CDCl$_3$
8.21
8.20
8.18
8.10
8.01
8.00
7.52
7.48
7.47
6.91
6.89
4.78
4.41
4.40
4.20
4.18
4.17
4.16
4.15
3.84
3.52
1.41
1.39
1.38
OMe
19
18
17
16
15
14
3
2
4
1
5
O
P
O
7
8
9
N
OH
10
11
12
13
O=S=O
O
6
CF$_3$
5.65
3.56
2.00
2.15
2.32
2.26
2.96
0.87
3.44
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

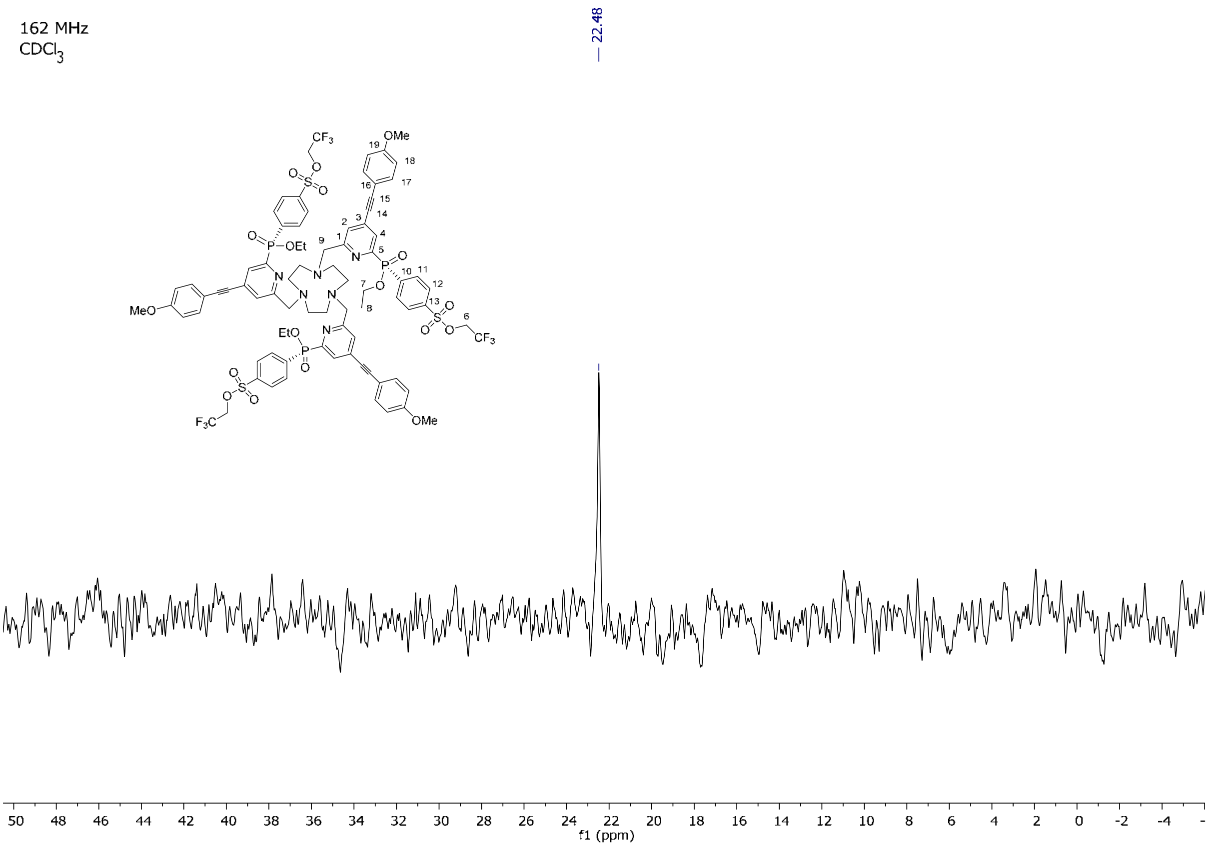

376 MHz
CDCl$_3$
-74.15
-74.17
-74.19
OMe
19
18
17
16
15
14
3
2
4
1
5
O
P
O
7
8
9
N
OH
10
11
12
13
O=S=O
O
6
CF$_3$
-64
-65
-66
-67
-68
-69
-70
-71
-72
-73
-74
-75
-76
-77
-78
-79
-80
-81
-82
-83
-84
f1 (ppm)



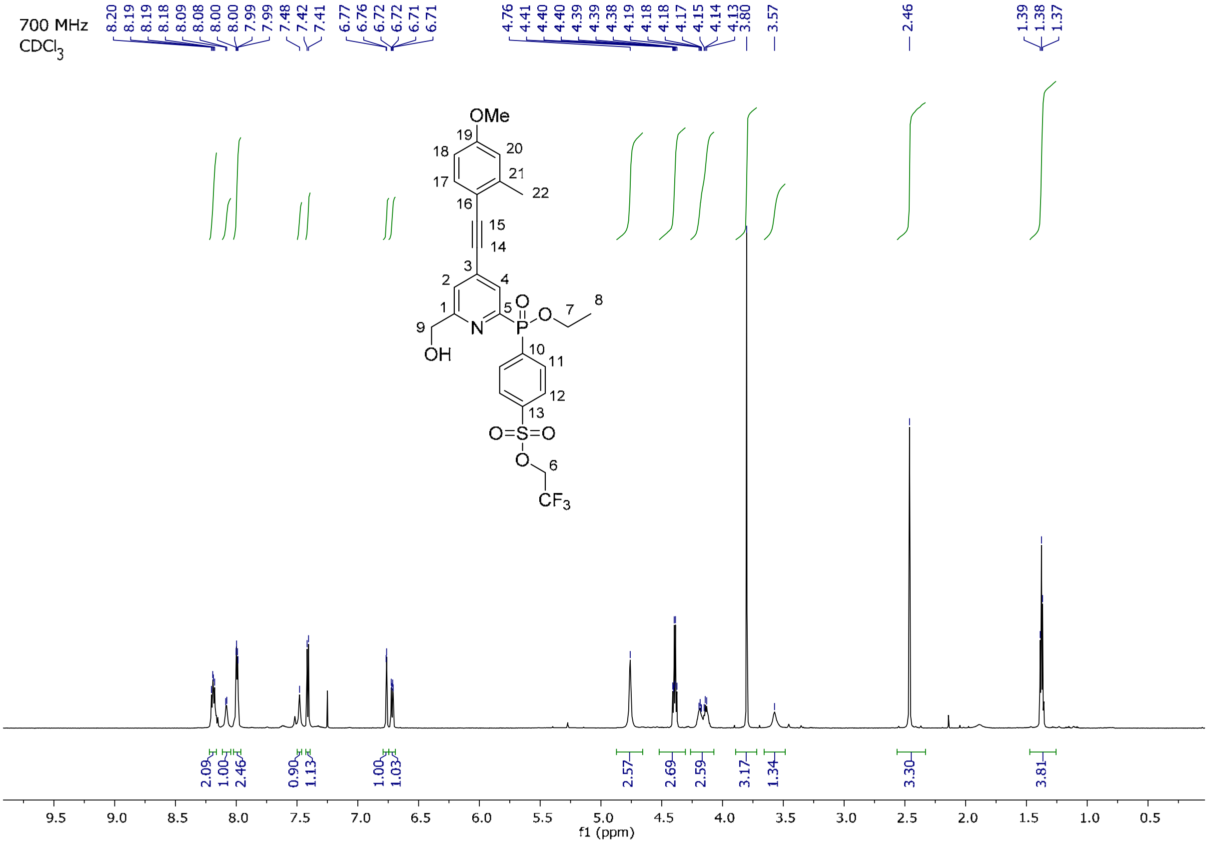
2,2,2-Trifluoroethyl 6,6',6''-(1,4,7-triazacyclononane-1,4,7-triyl)tris(methylene)tris(4-((4-methoxyphenyl)ethynyl)pyridine-6,2-diyl)tris(4-(ethoxyphosphoryl benzenesulfonate)

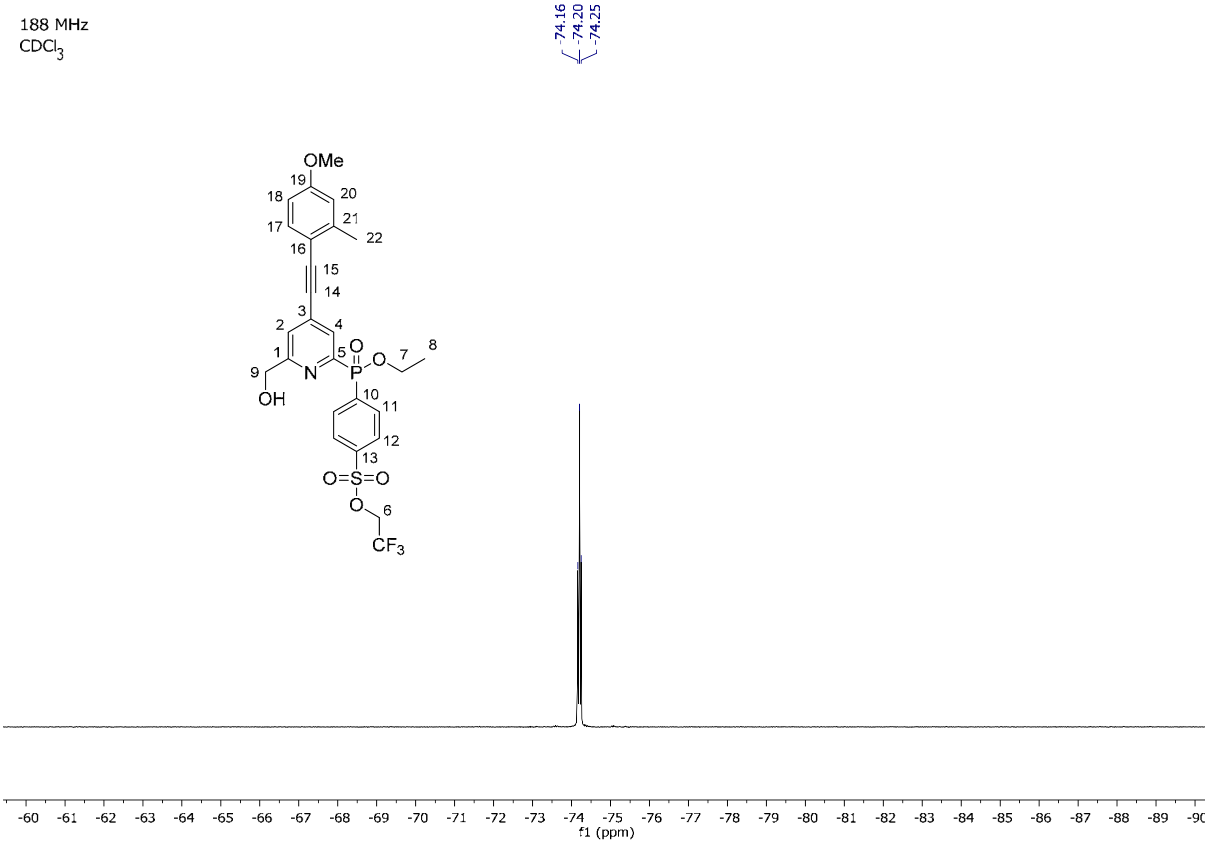


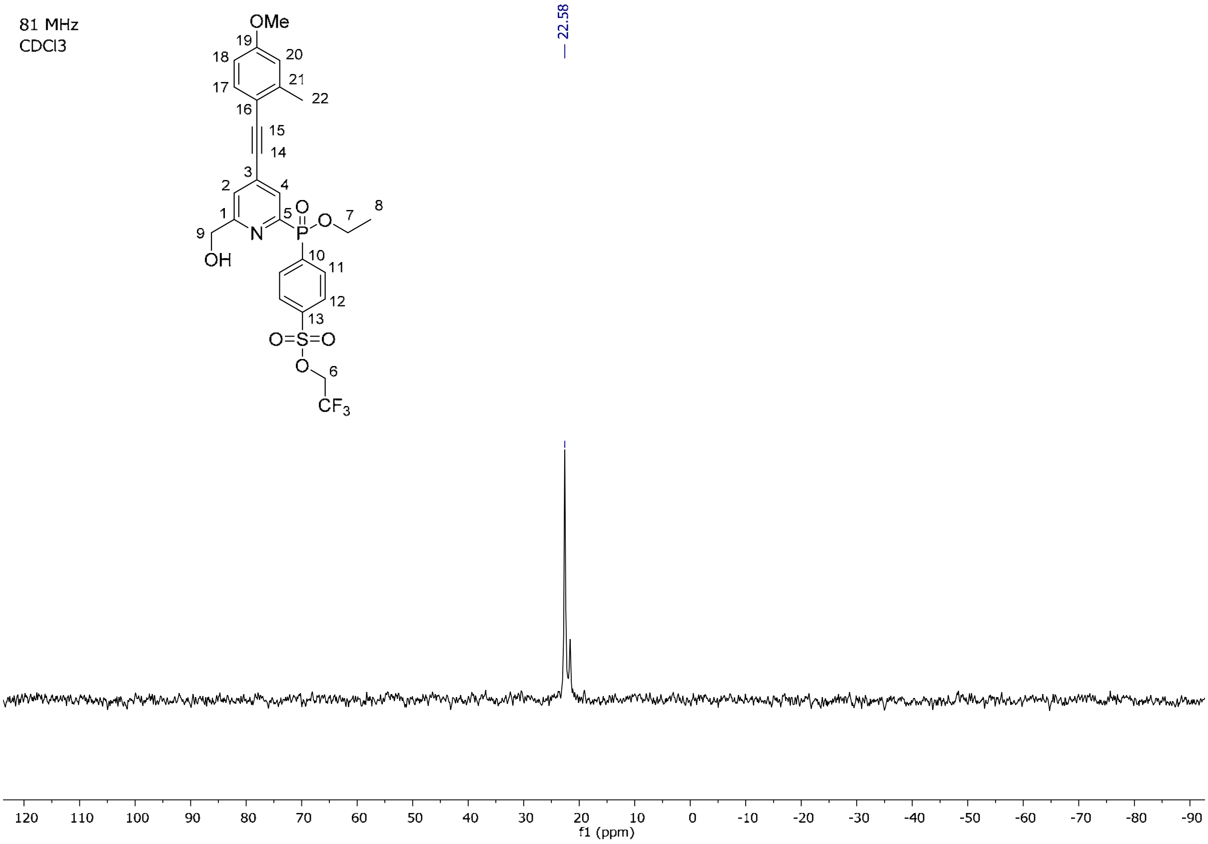

376 MHz
CDCl3
-74.11
-74.13
-74.15
CF3
OMe
19
18
17
16
15
14
2
3
4
1
9
5
O
P
OEt
N
10
11
12
13
6
7
8
MeO
EtO
F3C
f1 (ppm)
-68.0 -68.5 -69.0 -69.5 -70.0 -70.5 -71.0 -71.5 -72.0 -72.5 -73.0 -73.5 -74.0 -74.5 -75.0 -75.5 -76.0 -76.5 -77.0 -77.5 -78.0 -78.5 -79.0 -79.5 -80.0 -80.5


162 MHz
CDCl3
22.48
CF3
OMe
19
18
17
16
15
14
2
3
4
1
9
5
O
P
OEt
N
10
11
12
13
6
7
8
MeO
EtO
F3C
f1 (ppm)
50 48 46 44 42 40 38 36 34 32 30 28 26 24 22 20 18 16 14 12 10 8 6 4 2 0 -2 -4

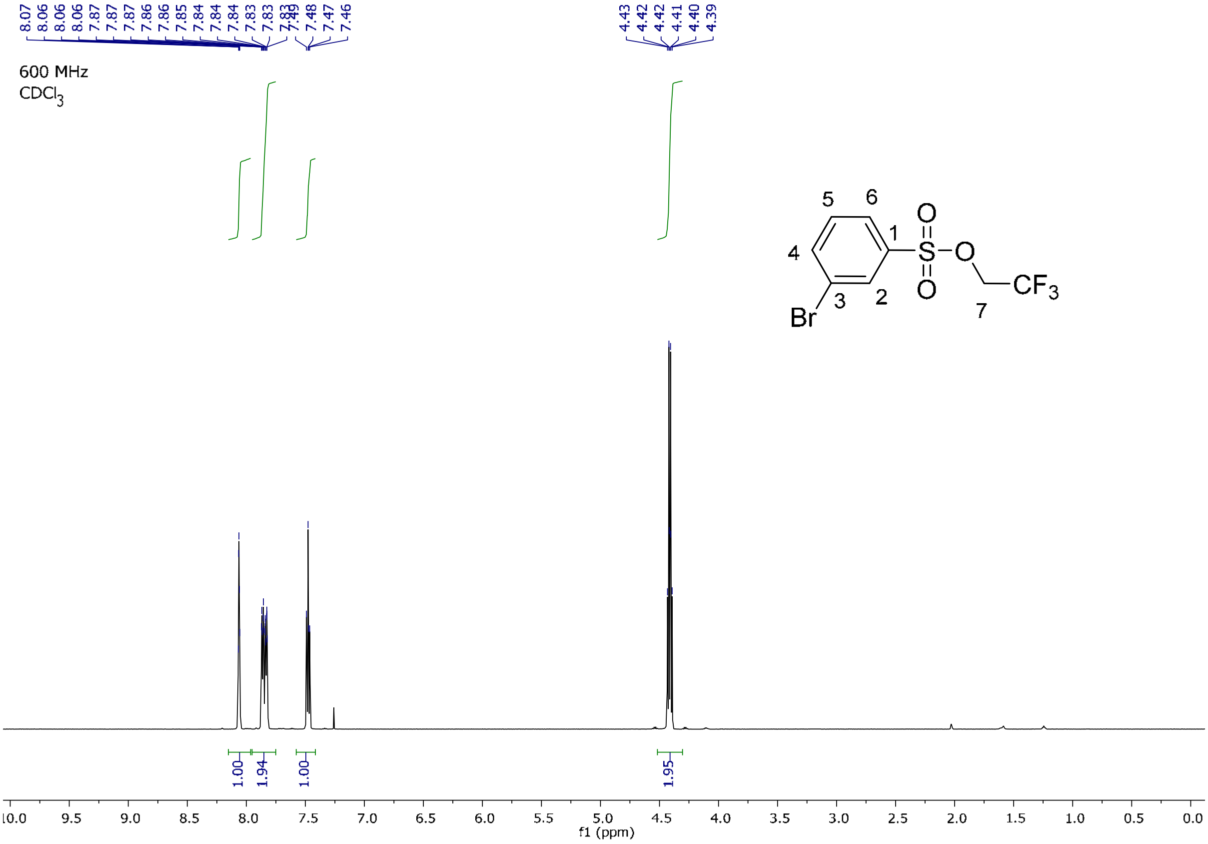
2,2,2-trifluoroethyl 4-(ethoxy(6-(hydroxymethyl)-4-((4-methoxy-2-methylphenyl)ethynyl)pyridin-2-yl)phosphoryl)benzenesulfonate

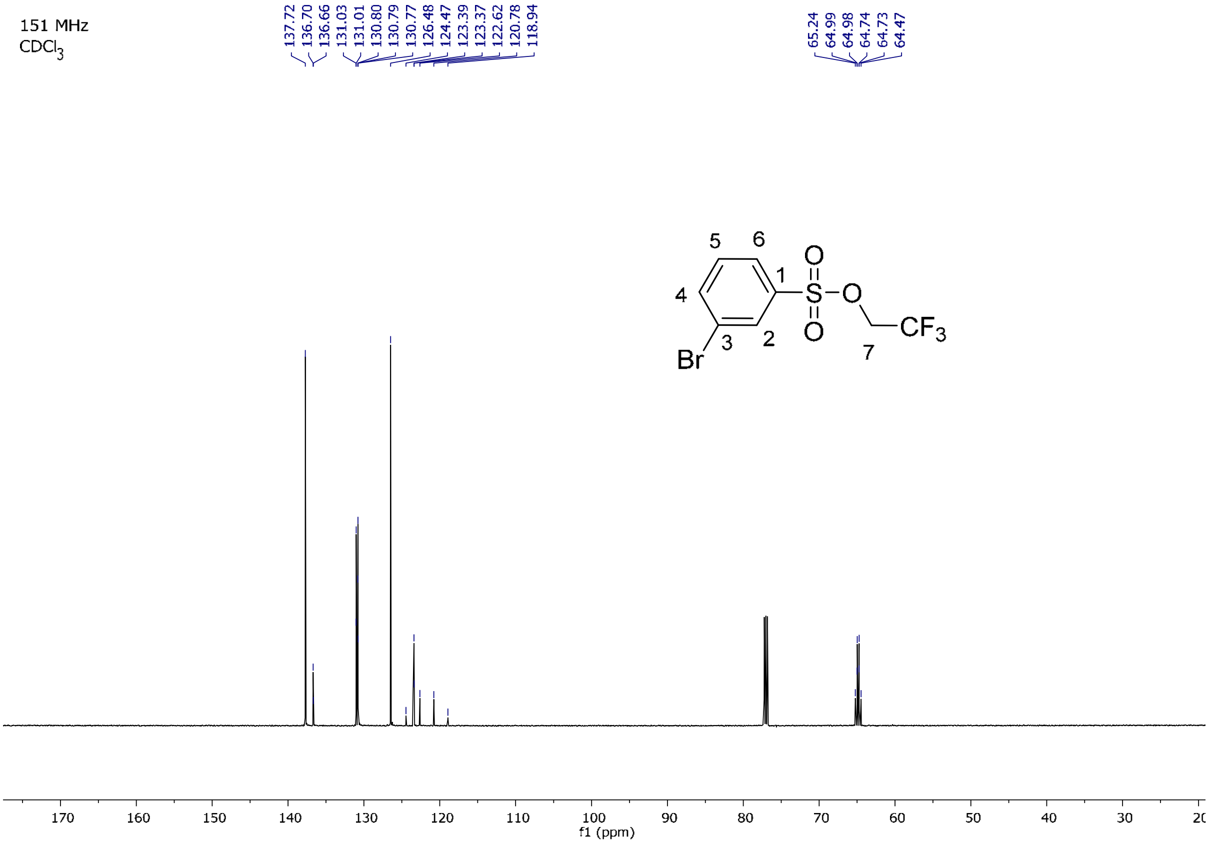


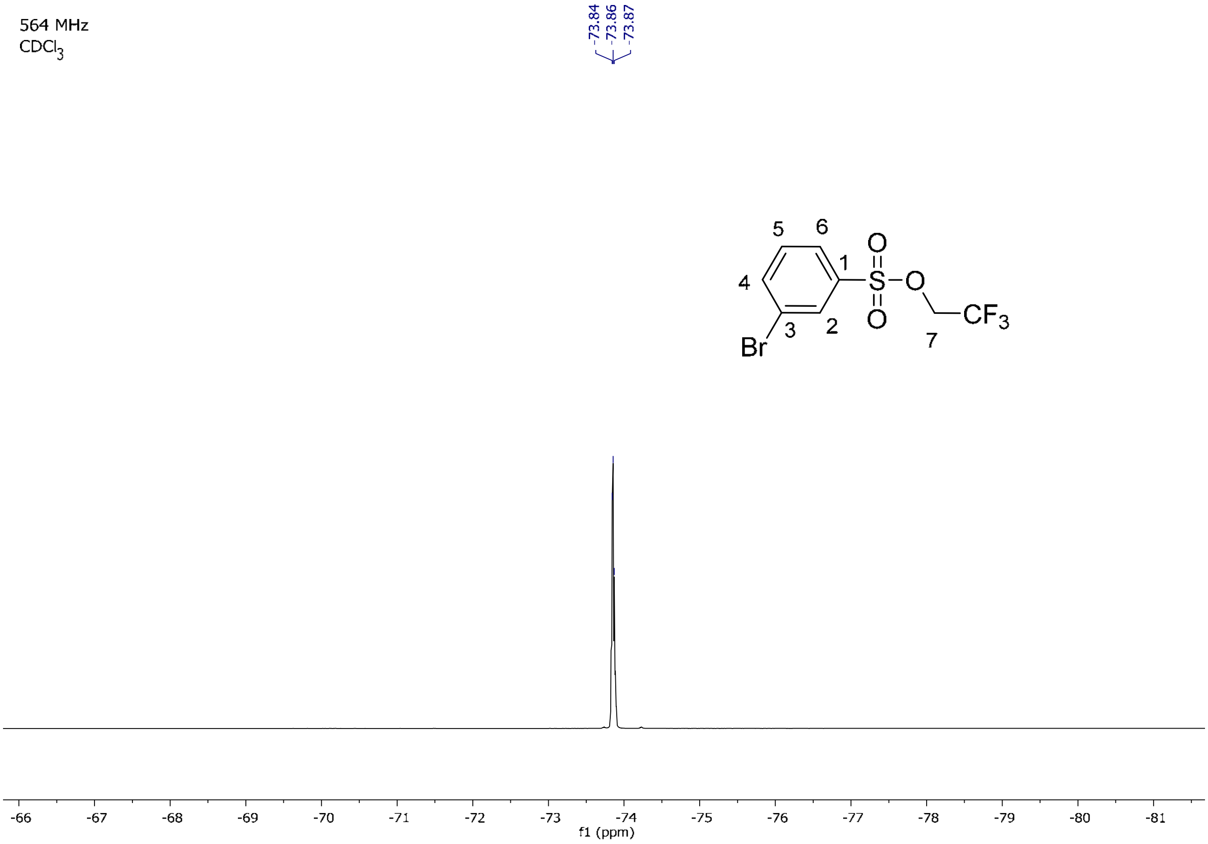




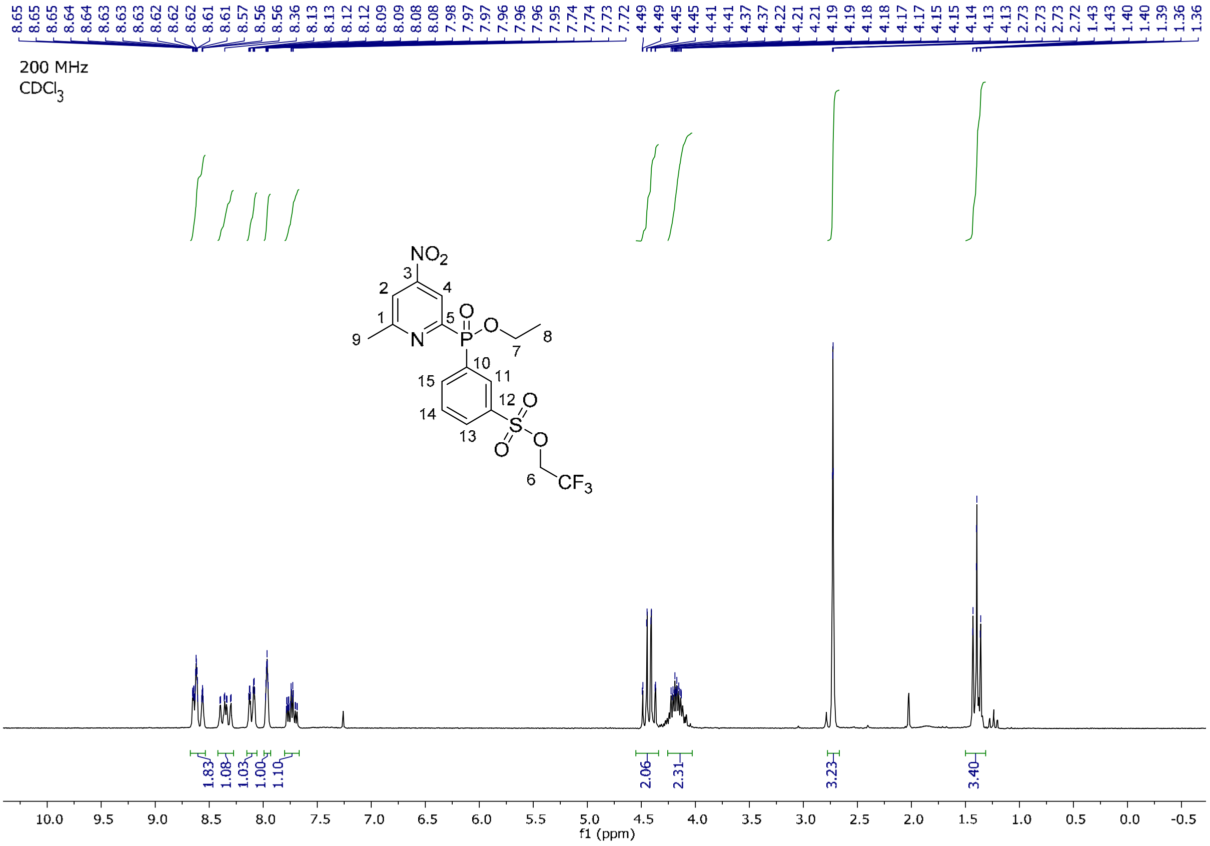
2,2,2-Trifluoroethyl 3-bromobenzenesulfonate, 2

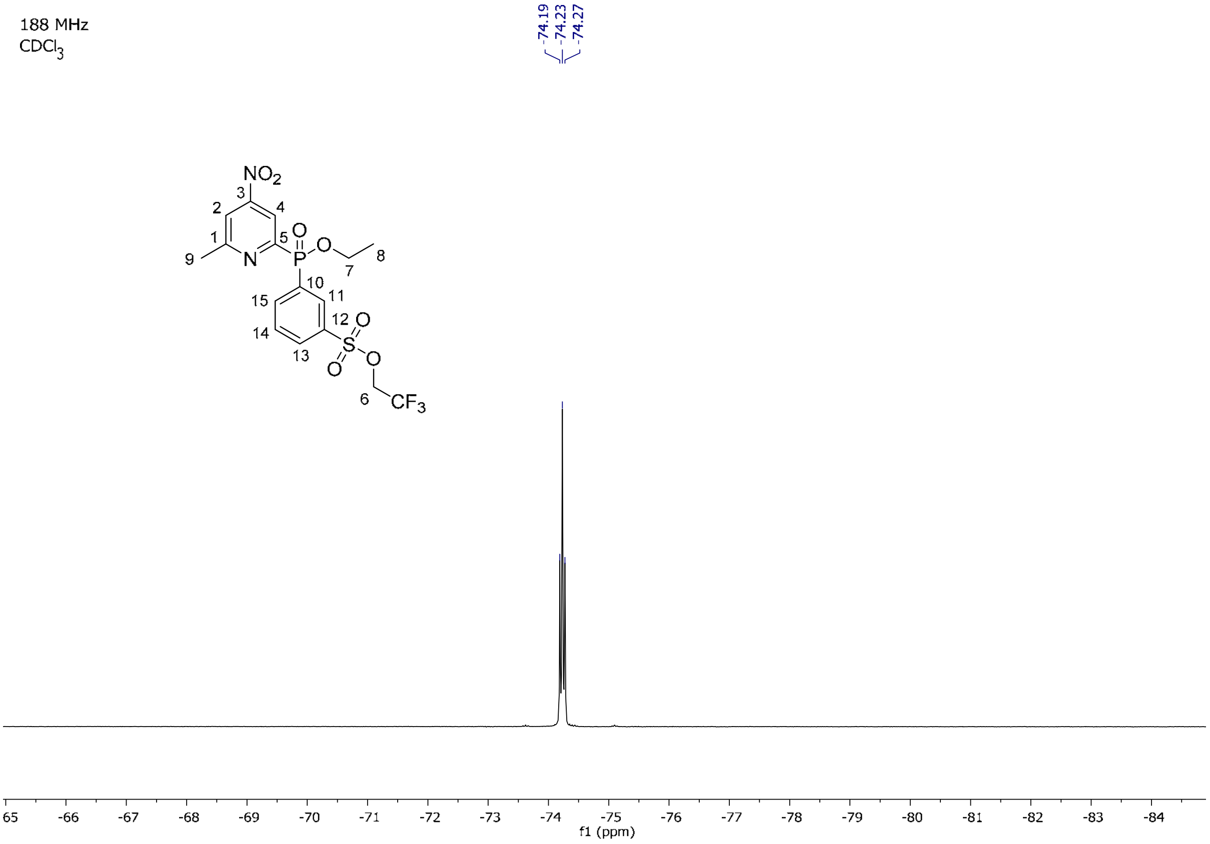


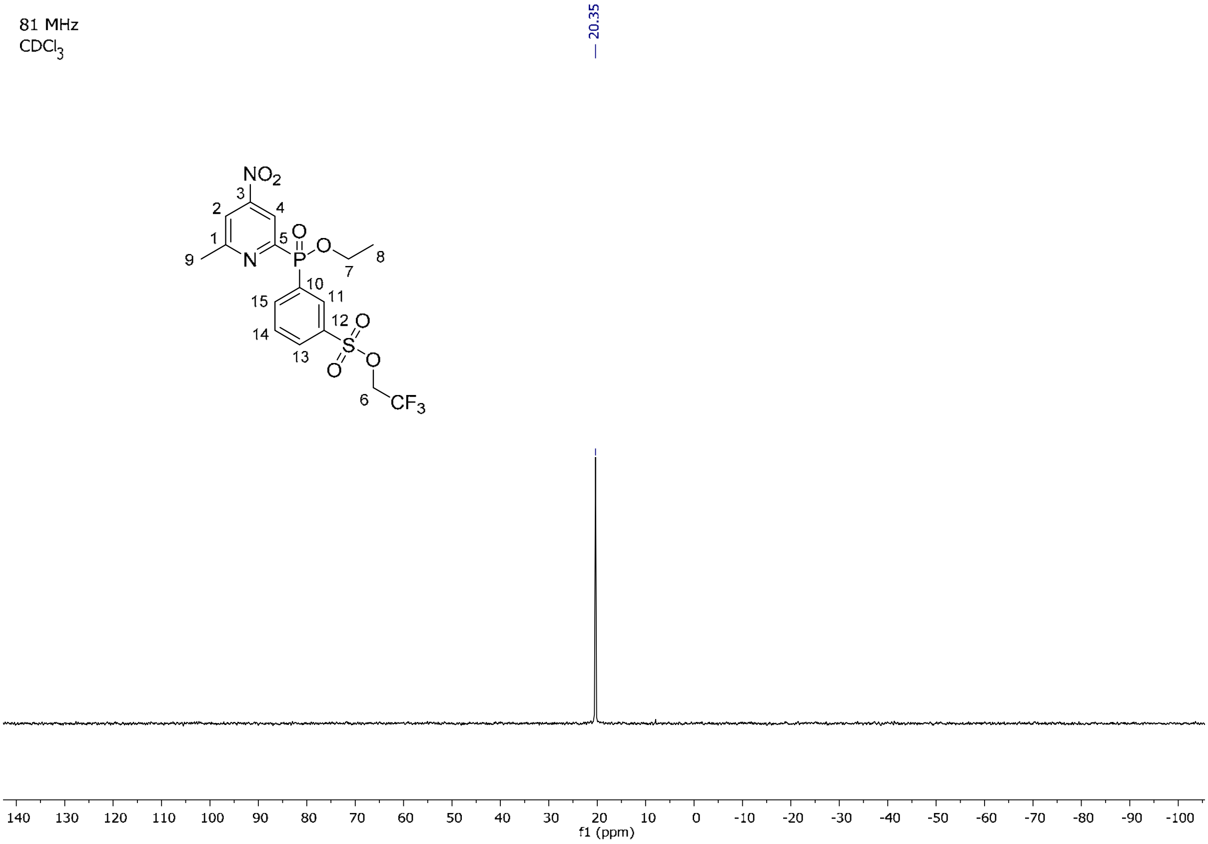


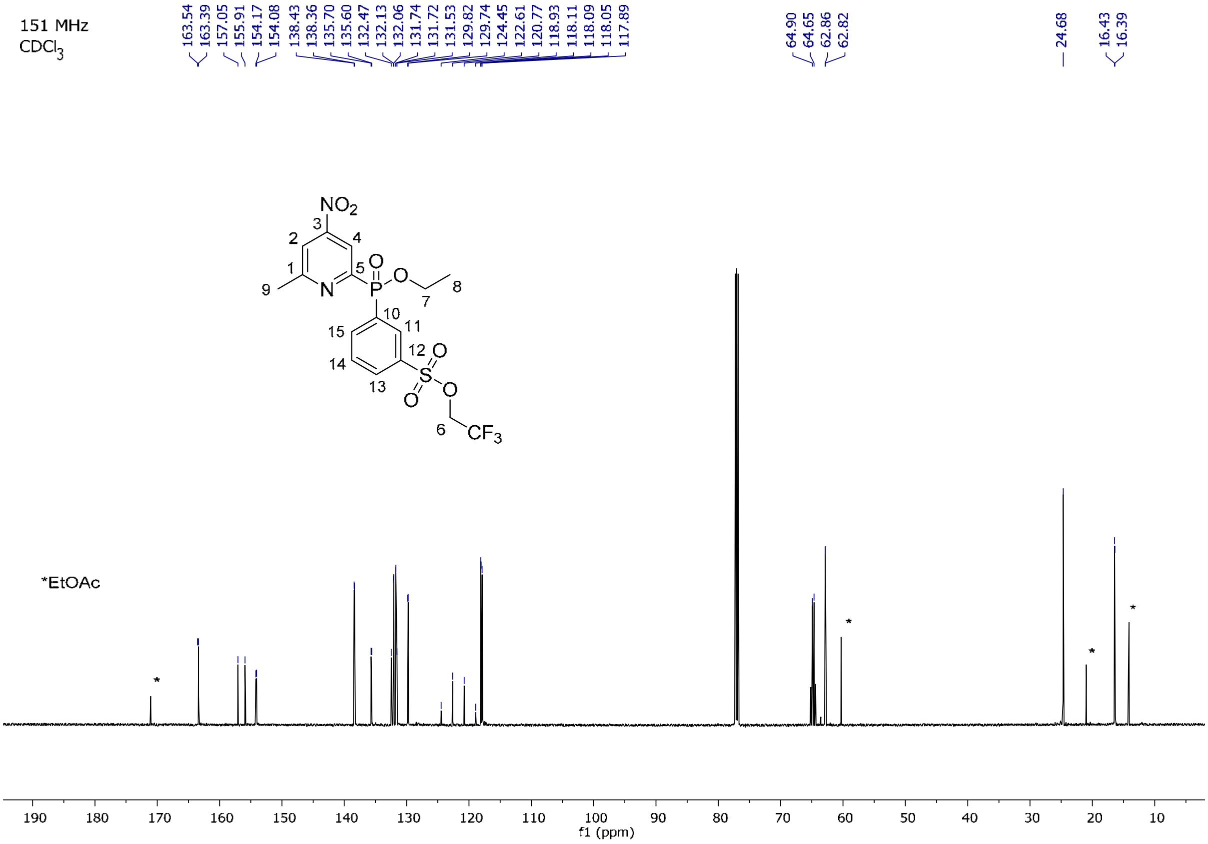


2,2,2-Trifluoroethyl 3-(ethoxy(6-methyl-4-nitropyridin-2-yl)phosphoryl)benzenesulfonate, 6

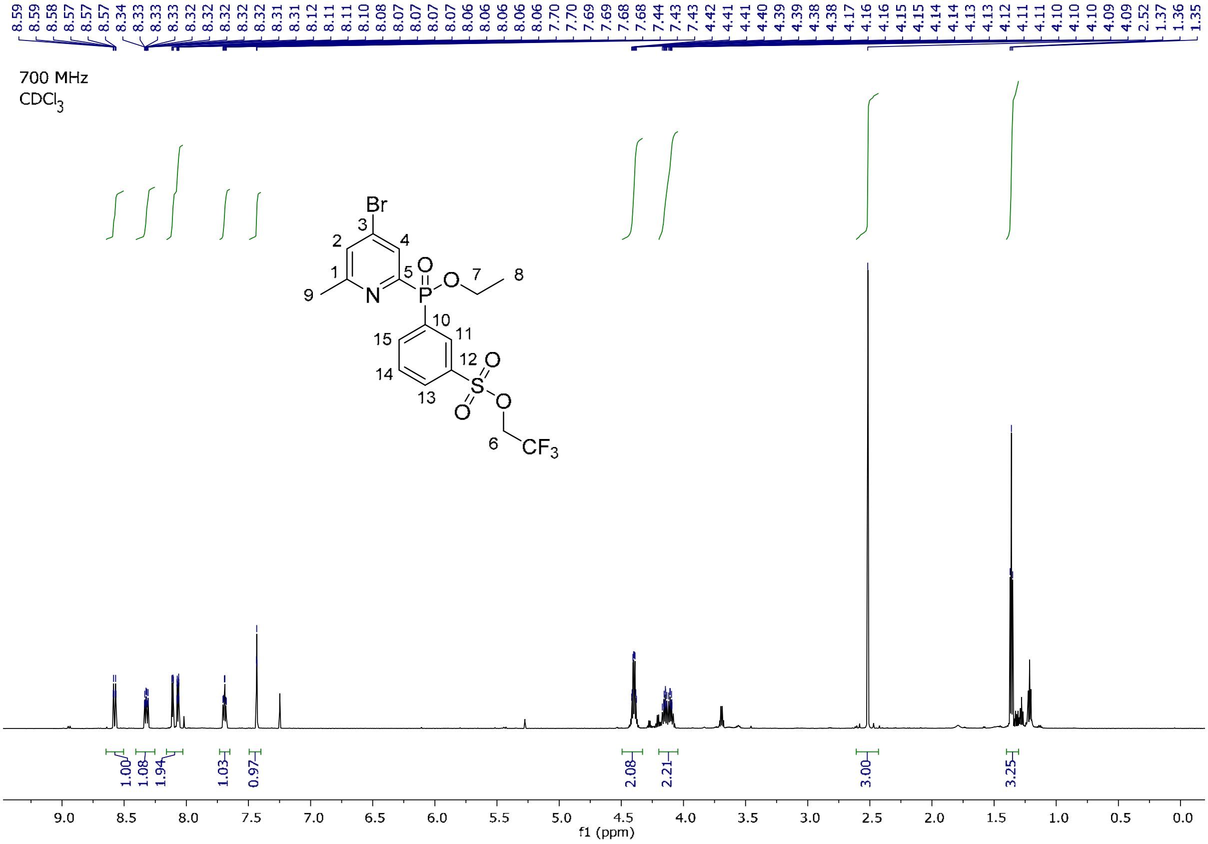

8.65 8.65 8.64 8.64 8.63 8.63 8.62 8.62 8.61 8.61 8.57 8.56 8.56 8.36 8.13 8.13 8.12 8.12 8.09 8.08 8.08 7.98 7.97 7.97 7.96 7.96 7.95 7.74 7.74 7.73 7.72 4.49 4.49 4.45 4.45 4.41 4.41 4.37 4.37 4.22 4.21 4.21 4.19 4.19 4.18 4.18 4.17 4.17 4.15 4.15 4.14 4.13 4.13 2.73 2.73 2.73 2.72 1.43 1.43 1.40 1.40 1.39 1.36 1.36
200 MHz
CDCl$_3$
NO$_2$
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
N
P
O
S
CF$_3$
1.83
1.08
1.03
1.00
1.10
2.06
2.31
3.23
3.40
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

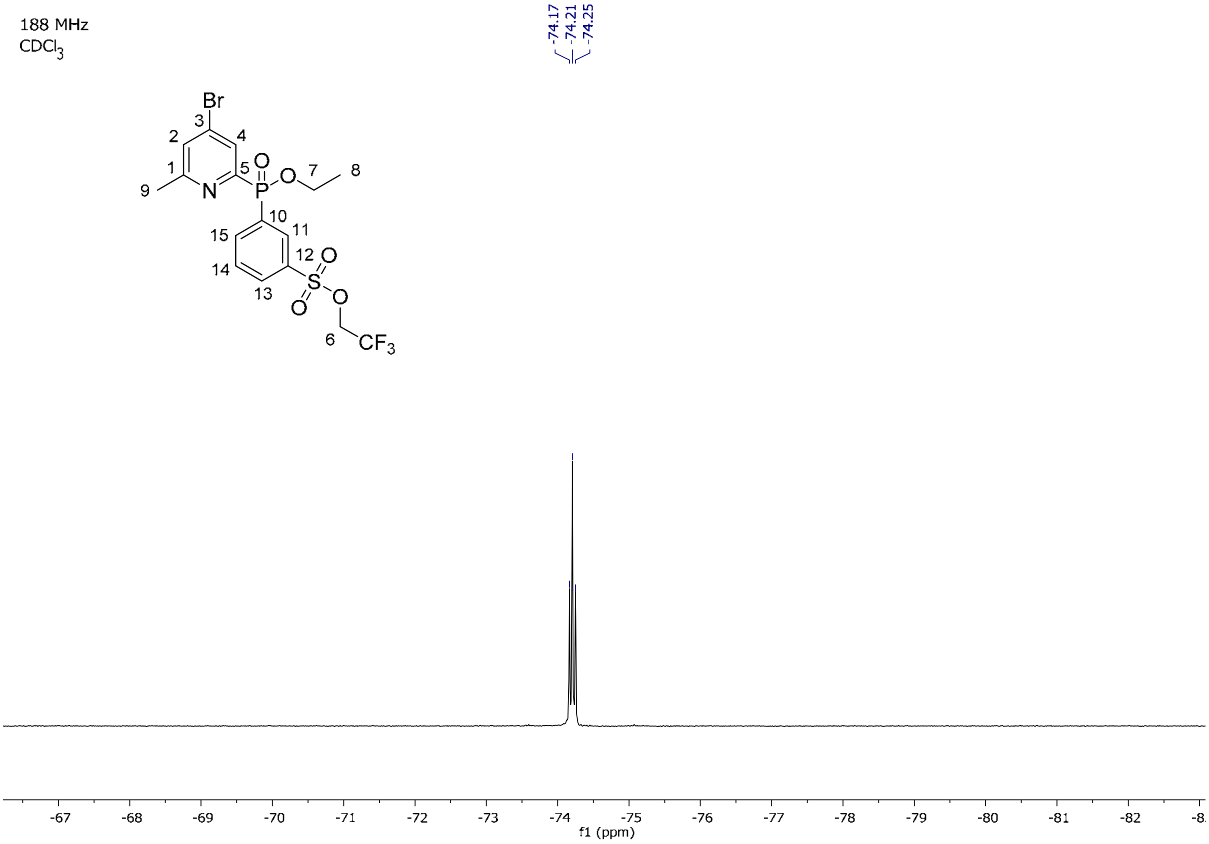

-74.19
-74.23
-74.27
188 MHz
CDCl$_3$
NO$_2$
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
N
P
O
S
CF$_3$
65 -66 -67 -68 -69 -70 -71 -72 -73 -74 -75 -76 -77 -78 -79 -80 -81 -82 -83 -84
f1 (ppm)





2,2,2-Trifluoroethyl 3-((4-bromo-6-methylpyridin-2-yl)(ethoxy)phosphoryl)benzenesulfonate, 8


8.59
8.59
8.58
8.57
8.57
8.57
8.34
8.33
8.33
8.33
8.32
8.32
8.32
8.32
8.31
8.12
8.11
8.11
8.10
8.08
8.07
8.07
8.07
8.06
8.06
8.06
8.06
7.70
7.69
7.69
7.68
7.68
7.44
7.43
7.43
4.42
4.41
4.41
4.40
4.39
4.39
4.38
4.38
4.17
4.16
4.16
4.15
4.15
4.14
4.14
4.13
4.13
4.12
4.11
4.11
4.10
4.10
4.09
4.09
2.52
1.37
1.36
1.35
700 MHz
CDCl3
Br
3
2
4
1
5
O
P
O
7
8
9
N
10
11
15
12
O
S
14
O
13
O
6
CF3
1.00
1.08
1.94
1.03
0.97
2.08
2.21
3.00
3.25
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


188 MHz
CDCl3
-74.17
-74.21
-74.25
Br
3
2
4
1
5
O
P
O
7
8
9
N
10
11
15
12
O
S
14
O
13
O
6
CF3
-67
-68
-69
-70
-71
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-74
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-78
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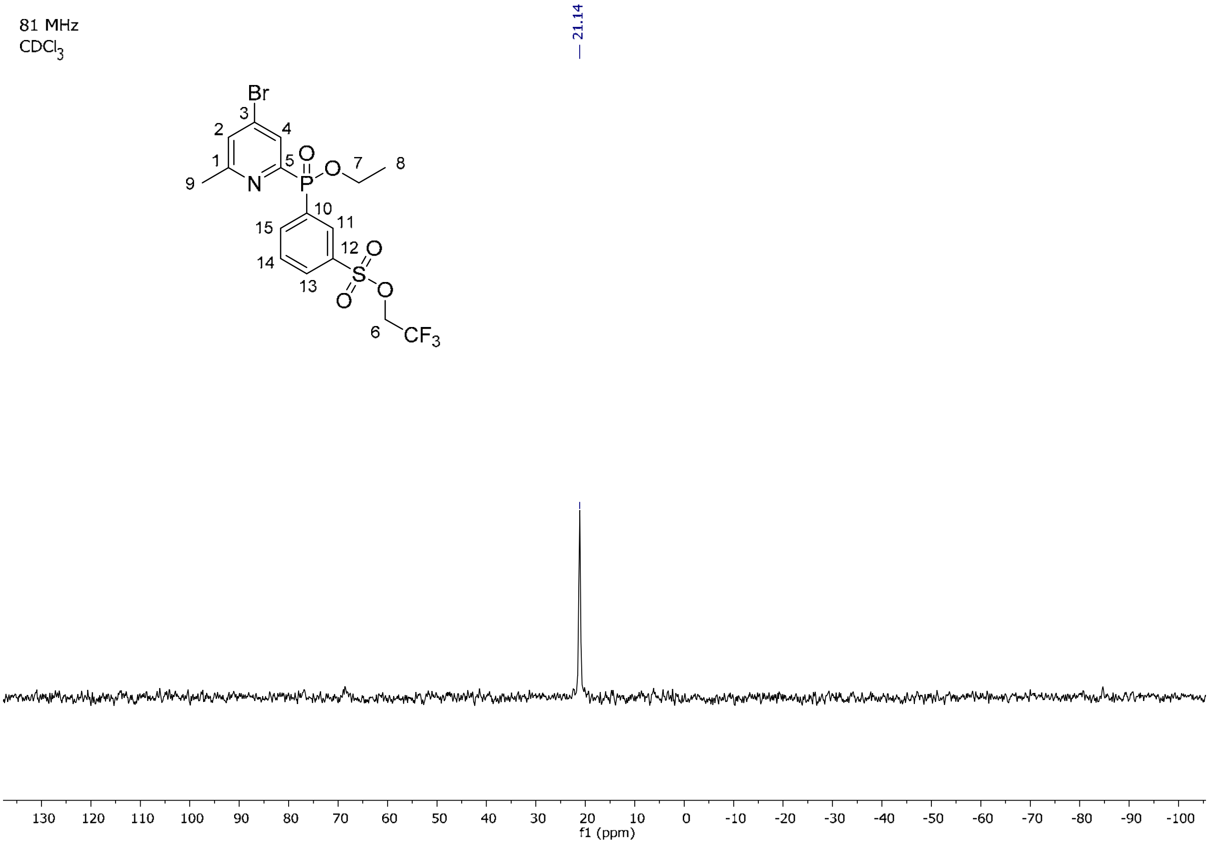
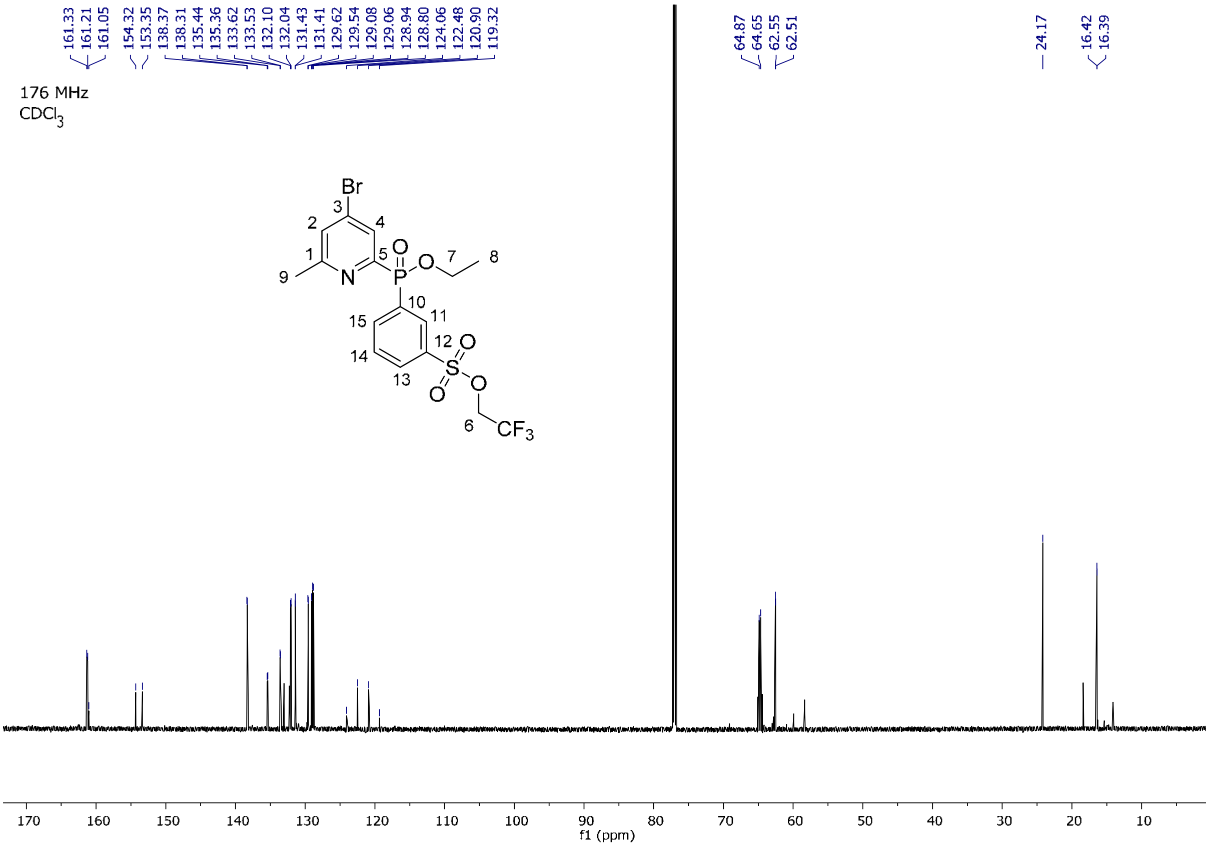
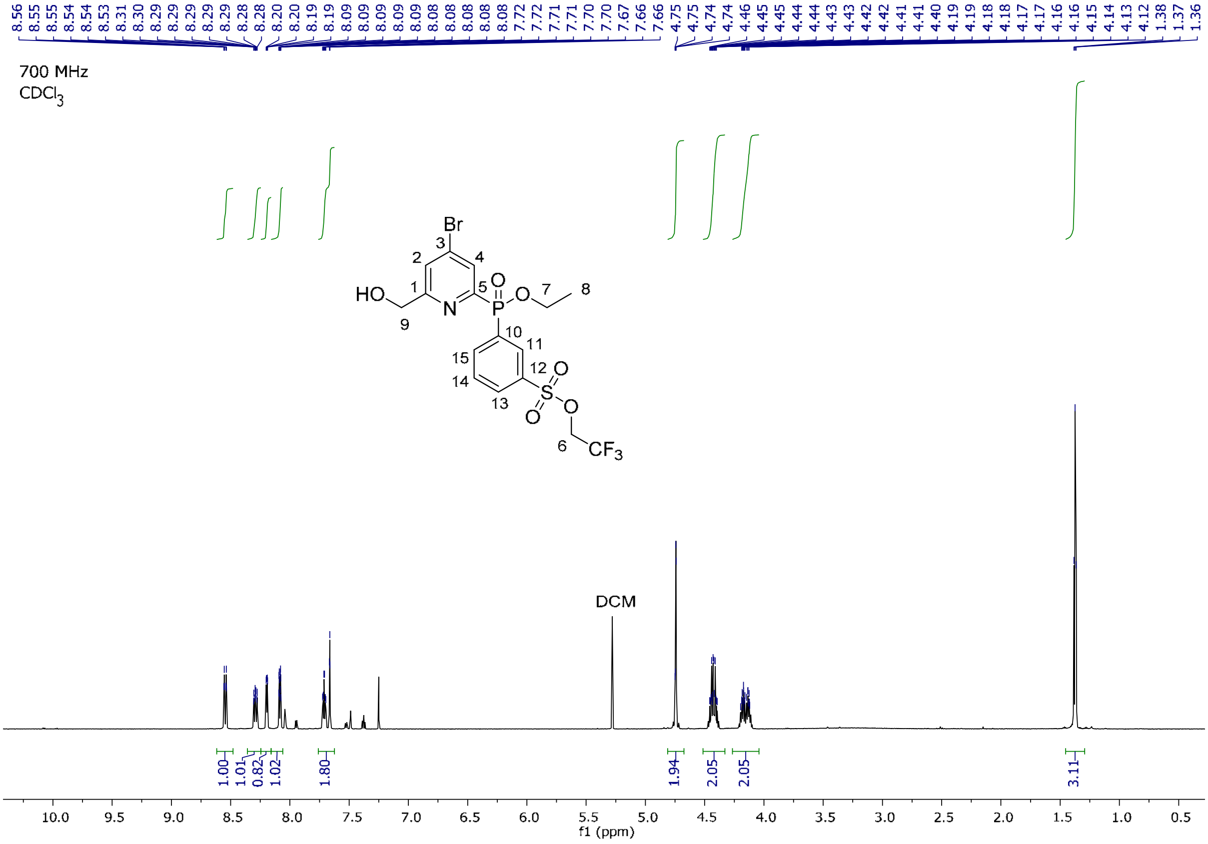
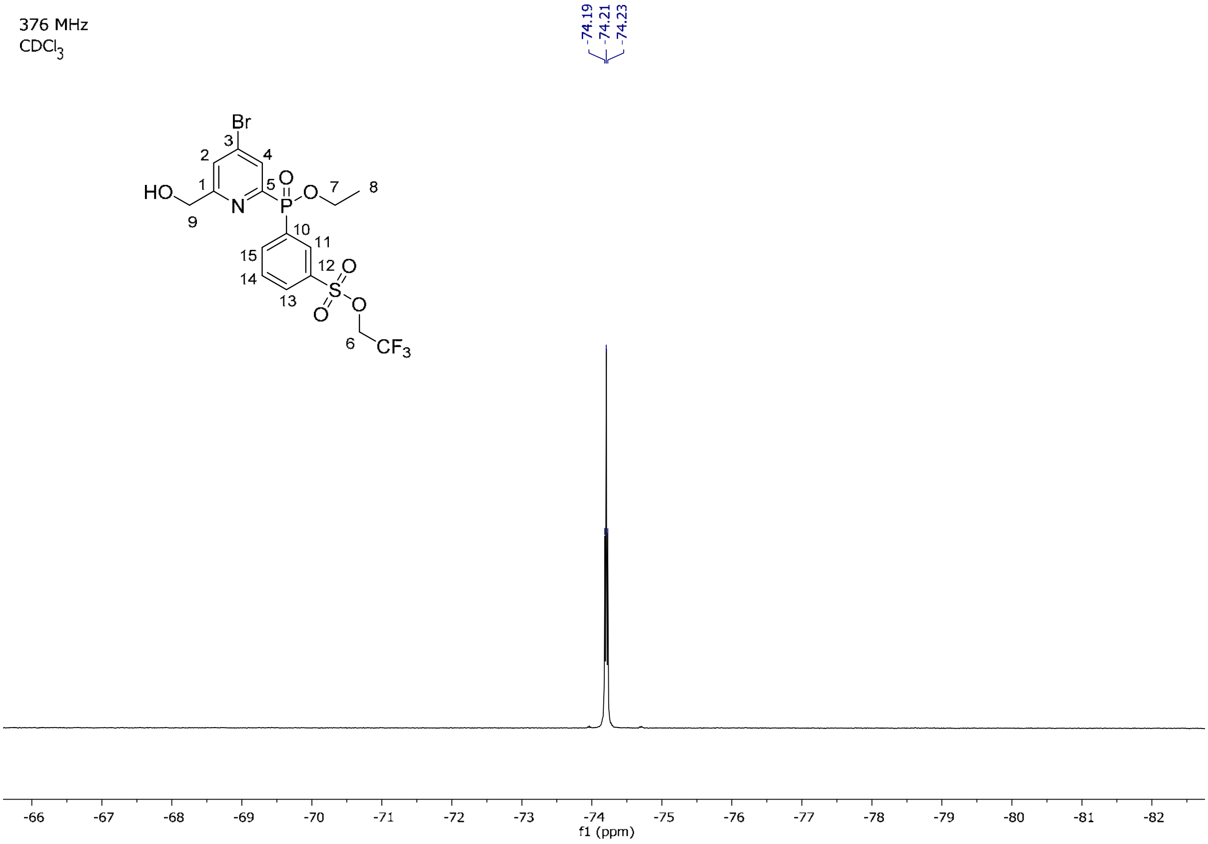
-80
-81
-82
-8
f1 (ppm)

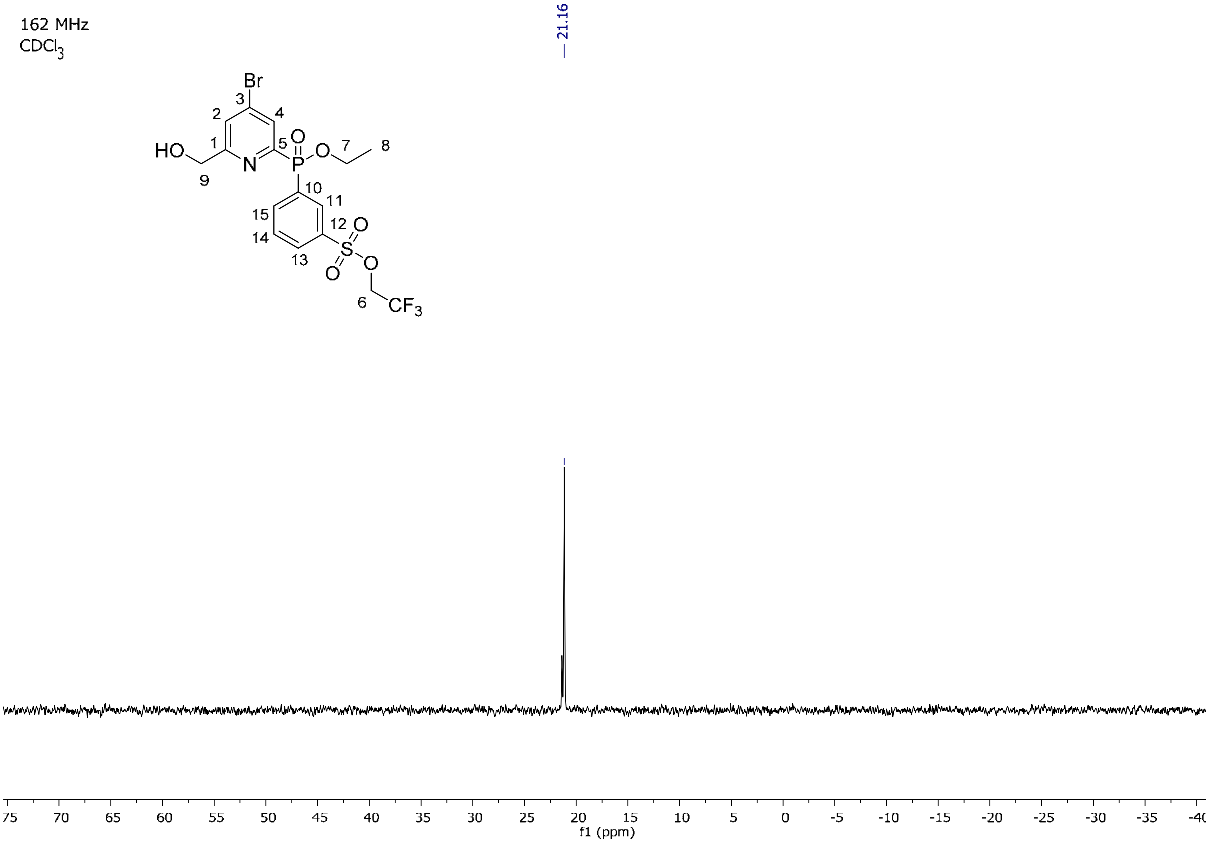




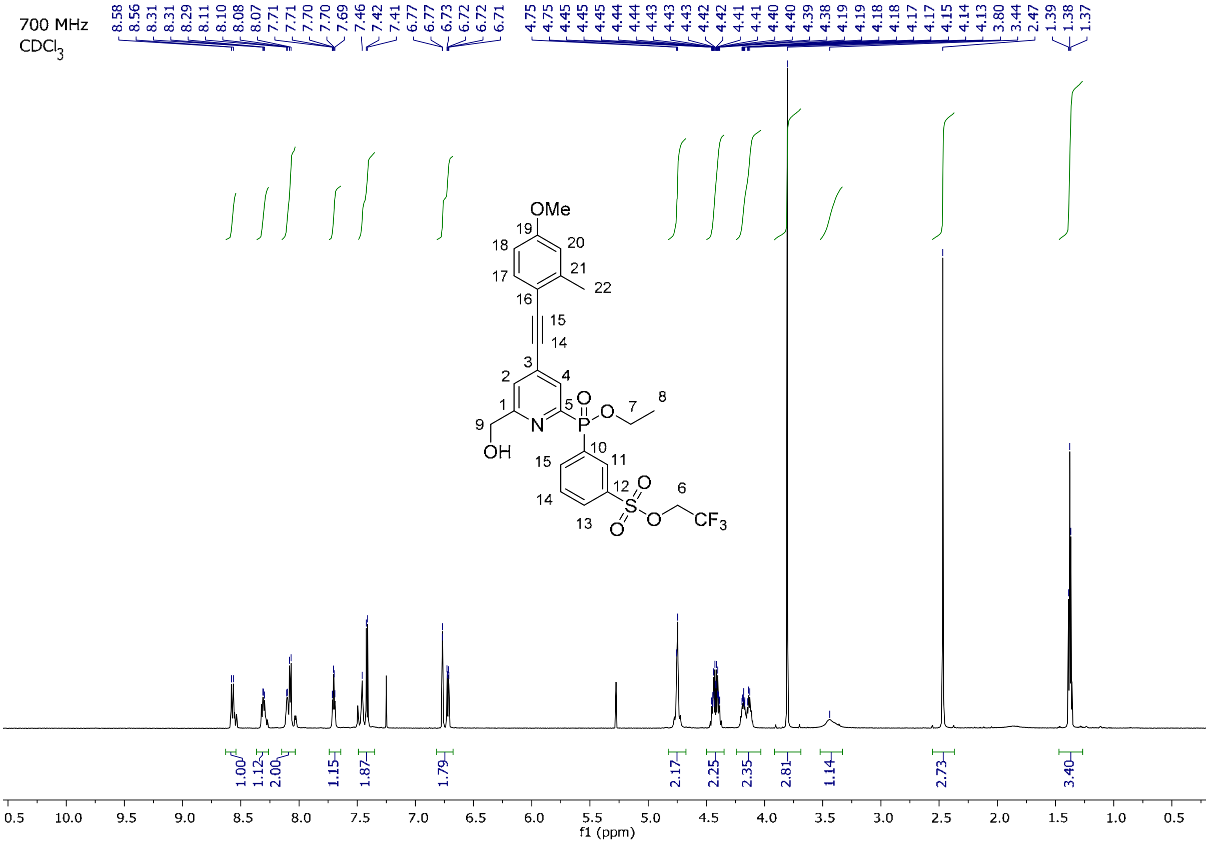
2,2,2-Trifluoroethyl 3-((4-bromo-6-(hydroxymethyl)pyridin-2-yl)(ethoxy)phosphoryl)benzenesulfonate, 12

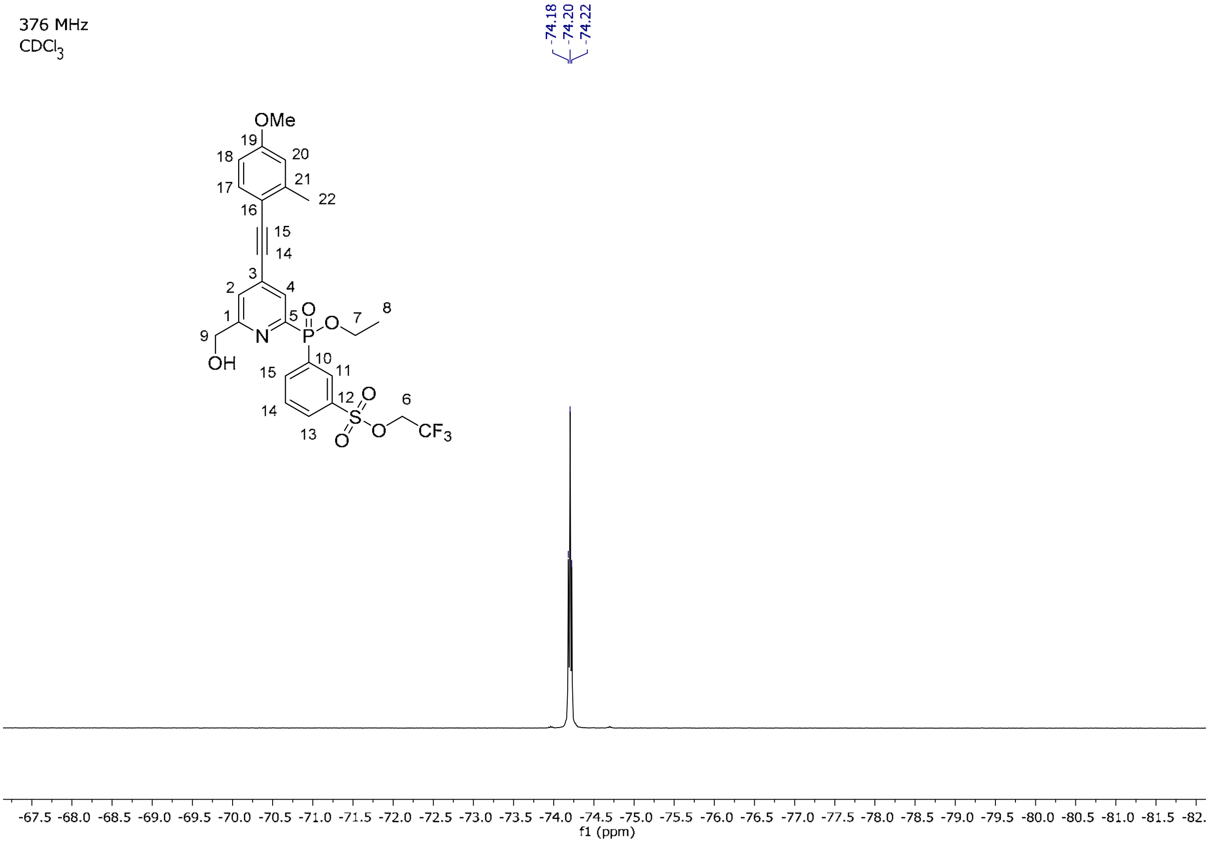

8.56
8.55
8.54
8.54
8.53
8.31
8.30
8.29
8.29
8.29
8.29
8.29
8.28
8.28
8.20
8.20
8.19
8.19
8.09
8.09
8.09
8.09
8.08
8.08
8.08
8.08
7.72
7.72
7.71
7.71
7.70
7.70
7.67
7.66
4.75
4.75
4.74
4.74
4.46
4.45
4.45
4.44
4.44
4.43
4.43
4.42
4.42
4.41
4.41
4.40
4.19
4.19
4.18
4.18
4.17
4.17
4.16
4.16
4.15
4.14
4.13
4.12
1.38
1.37
1.36
700 MHz
$CDCl_3$
Br
HO
N
P
O
S
CF_3
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
DCM
1.00
1.01
0.82
1.02
1.80
1.94
2.05
2.05
3.11
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

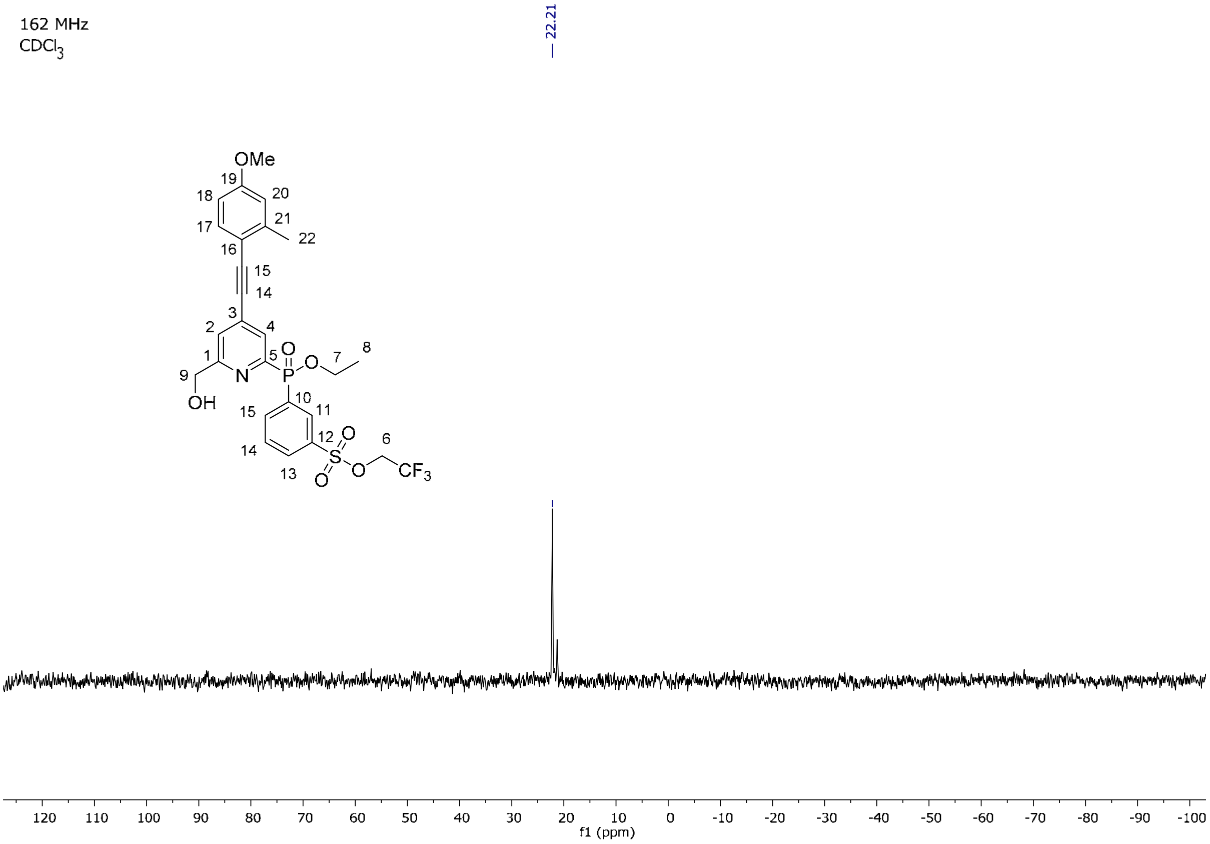

376 MHz
$CDCl_3$
-74.19
-74.21
-74.23
Br
HO
N
P
O
S
CF_3
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
-66
-67
-68
-69
-70
-71
-72
-73
-74
-75
-76
-77
-78
-79
-80
-81
-82
f1 (ppm)



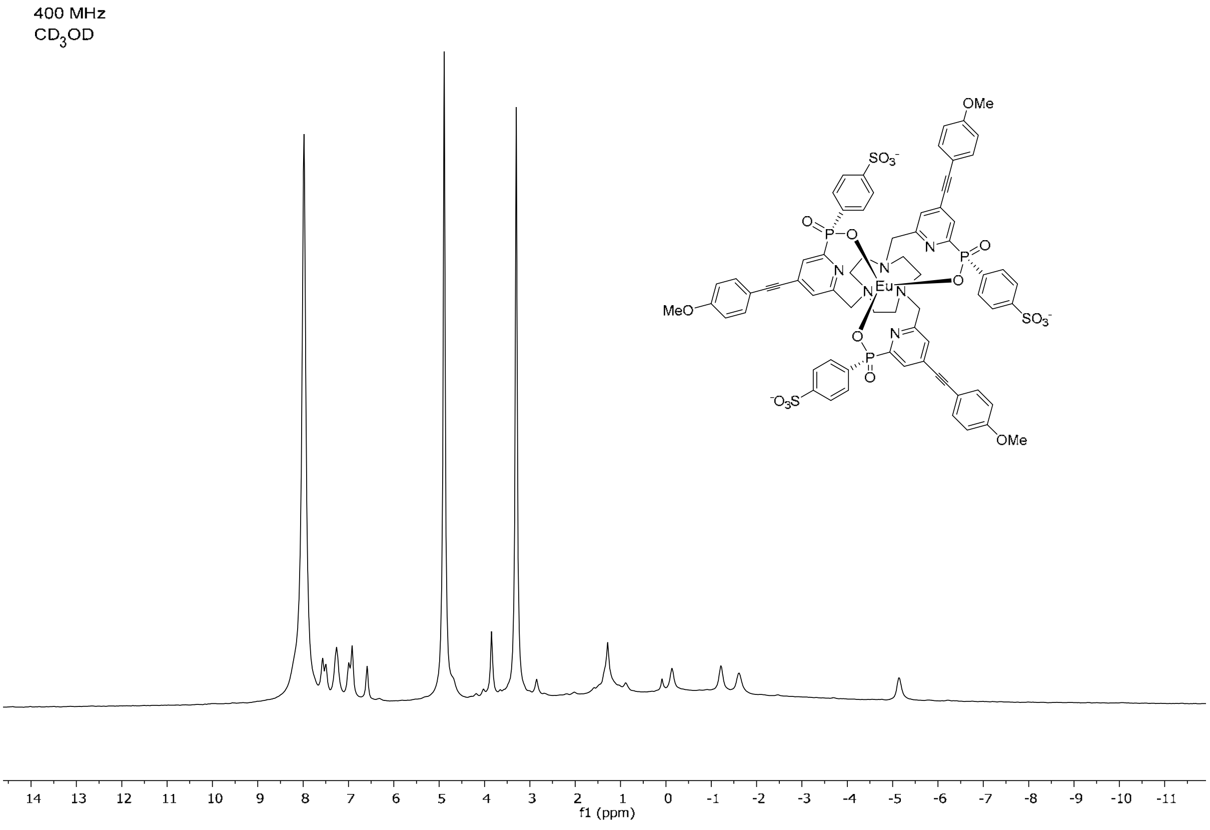
2,2,2-trifluoroethyl 3-(ethoxy(6-(hydroxymethyl)-4-((4-methoxy-2-methylphenyl)ethynyl)pyridin-2-yl)phosphoryl)benzenesulfonate

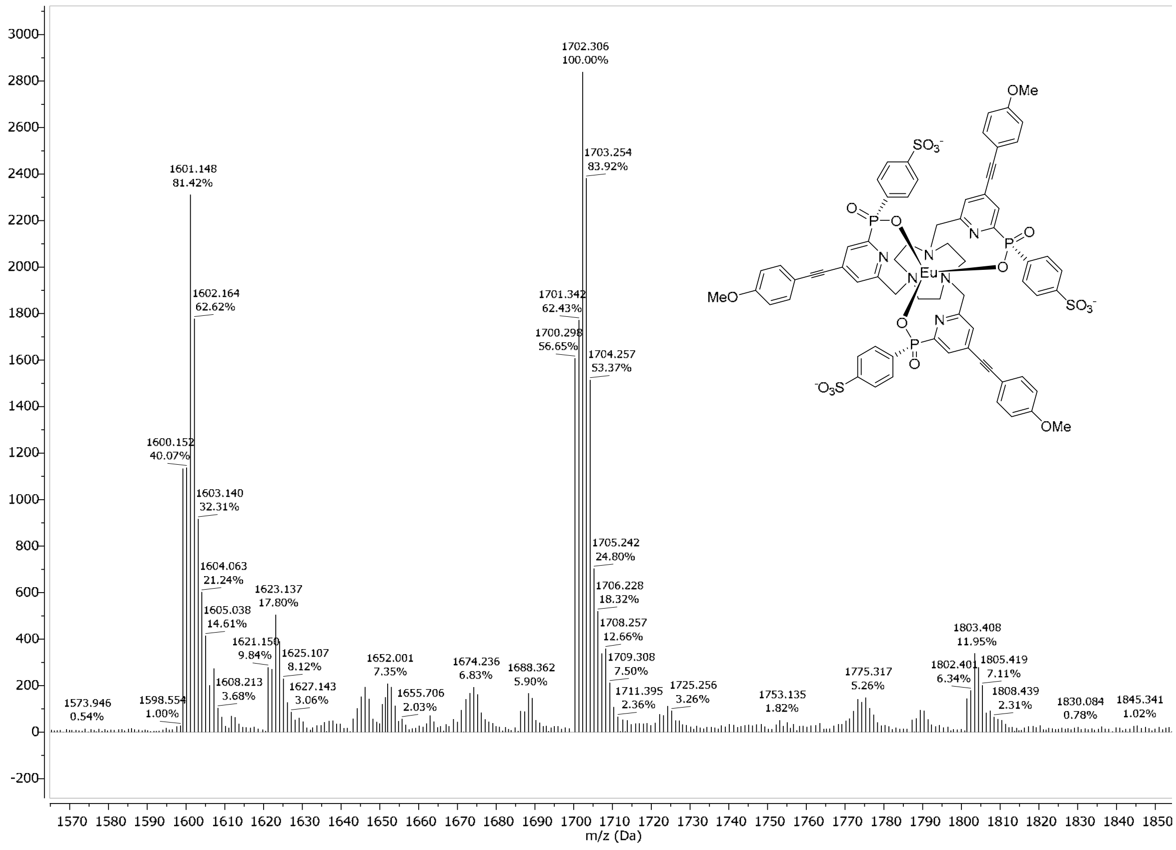



376 MHz
CDCl3
-74.18
-74.20
-74.22
OMe
19 18 20 17 21 22 16 15 14 3 2 4 1 5 O P O 7 8 9 N OH 10 15 11 12 O S 6 14 13 O O CF3
-67.5 -68.0 -68.5 -69.0 -69.5 -70.0 -70.5 -71.0 -71.5 -72.0 -72.5 -73.0 -73.5 -74.0 -74.5 -75.0 -75.5 -76.0 -76.5 -77.0 -77.5 -78.0 -78.5 -79.0 -79.5 -80.0 -80.5 -81.0 -81.5 -82.
f1 (ppm)


162 MHz
CDCl3
22.21
OMe
19 18 20 17 21 22 16 15 14 3 2 4 1 5 O P O 7 8 9 N OH 10 15 11 12 O S 6 14 13 O O CF3
120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100
f1 (ppm)

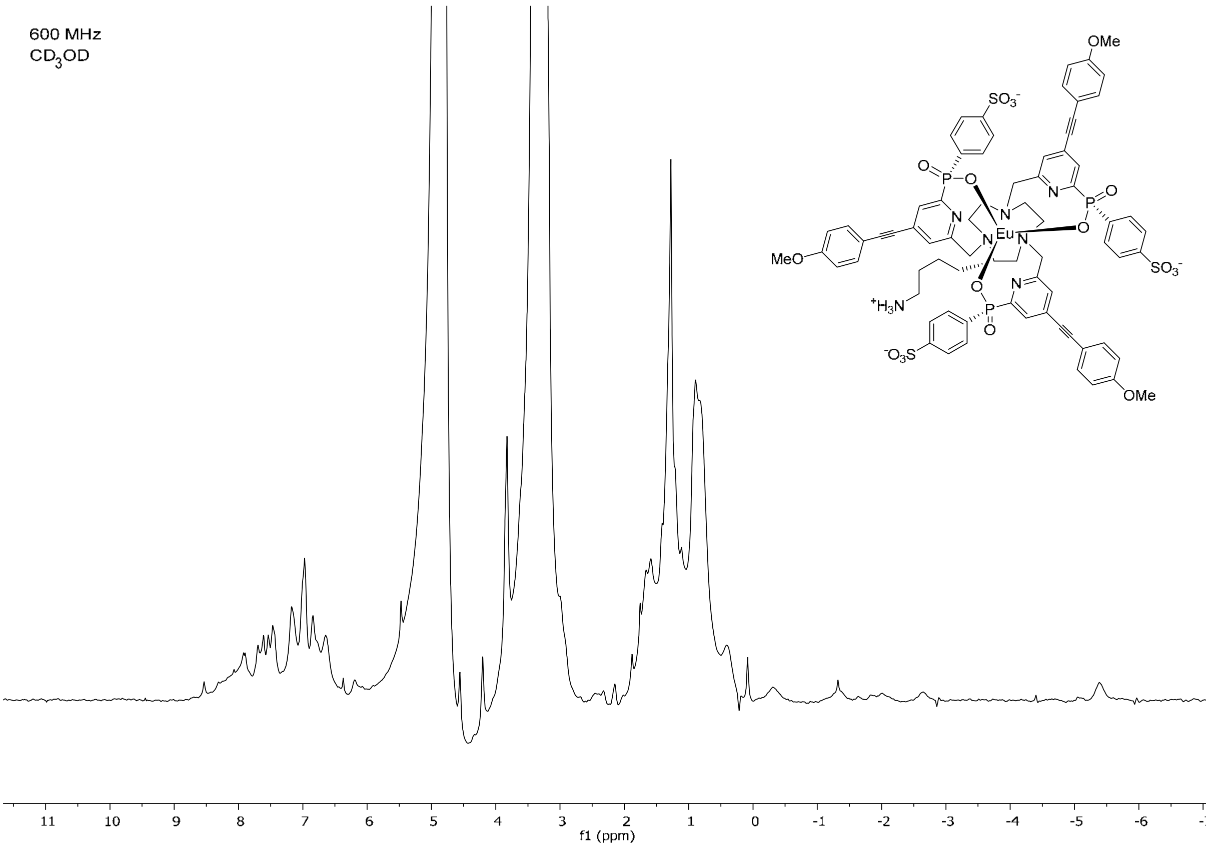
Eu(III) complex of 6,6',6''-(1,4,7-triazacyclononane-1,4,7-triyl)tris(methylene)tris(4-((4-methoxyphenyl)ethynyl)pyridine-6,2-diyl)tris(4-(hydroxyphosphoryl benzenesulfonate), [Eu.L^{1a}]$^{3-}$



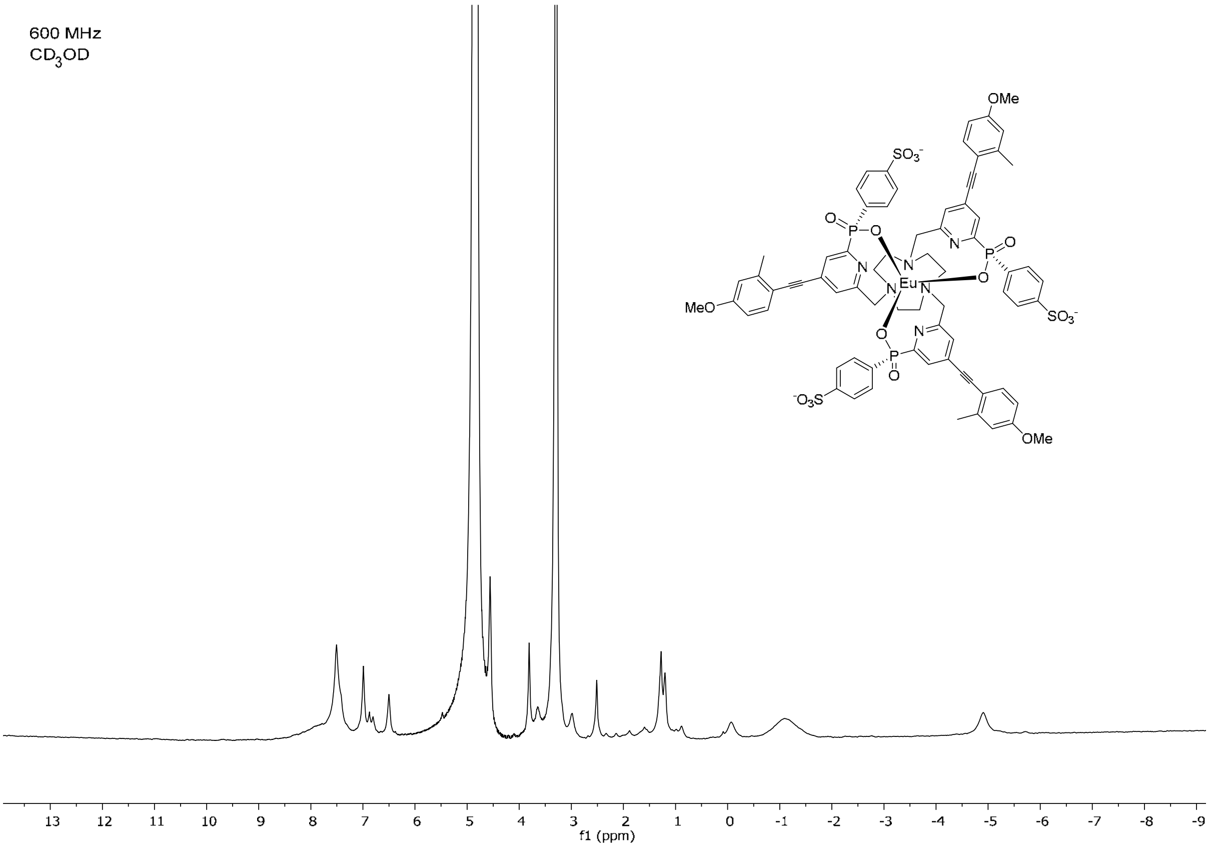


Q-TOF mass spectrometry showing the molecular ion and the Et_3NH^+ salt adducts.

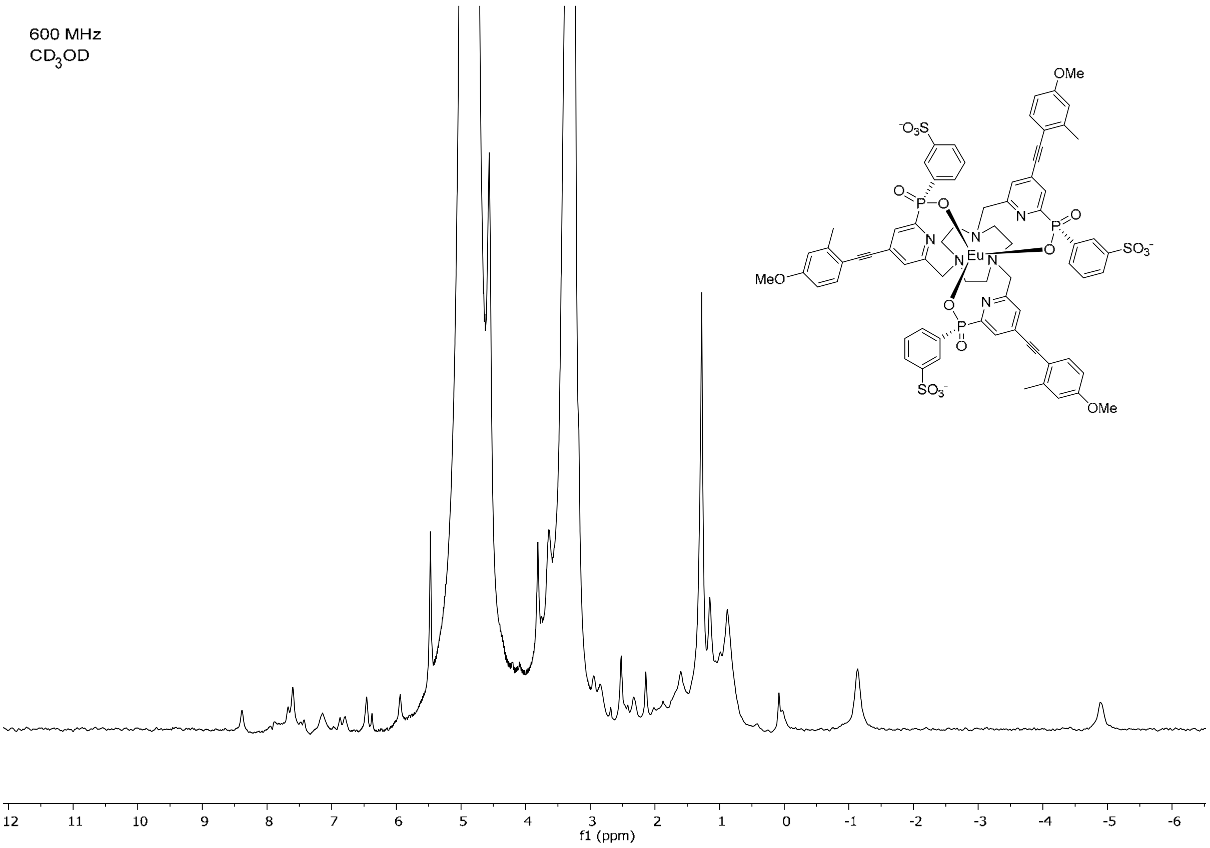
Eu(III) complex of 6,6',6''-((*S*)-2-(4-aminobutyl)-1,4,7-triazacyclononane-1,4,7-triyl)tris(methylene)tris(4-((4-methoxyphenyl)ethynyl)pyridine-6,2-diyl)tris(4-(hydroxyphosphoryl benzenesulfonate), $[Eu.L^2]^{2-}$



Eu(III) complex of 6,6',6''-(1,4,7-triazacyclononane-1,4,7-triyl)tris(methylene)tris(4-((4-methoxy-2-methylphenyl)ethynyl)pyridine-6,2-diyl)tris(4-(hydroxyphosphoryl benzenesulfonate), [Eu.L^{1b}]$^{3-}$



Eu(III) complex of 6,6',6''-(1,4,7-triazacyclononane-1,4,7-triyl)tris(methylene)tris(4-((4-methoxy-2-methylphenyl)ethynyl)pyridine-6,2-diyl)tris(3-(hydroxyphosphoryl benzenesulfonate), $[Eu.L^3]^{3-}$


600 MHz
CD_3OD
OMe
$^{-}O_3S$
O
P
O
N
N
Eu
N
N
O
P
O
SO_3^-
MeO
N
O
P
O
SO_3^-
OMe
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2
-3
-4
-5
-6
f1 (ppm)