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**Phosphonate derivatives of tetraazamacrocycles as new inhibitors of protein tyrosine phosphatases**

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**Supplementary information**

**General information**

THF was distilled under Ar from Na/benzophenone. CH₂Cl₂ was distilled under Ar from CaH₂. All other solvents and chemicals obtained from commercial sources were used as received. ¹H, ¹³C, ¹⁹F and ³¹P NMR spectra were recorded on a Varian AV-400 or Bruker Avance DRX500 instrument. ¹H and ¹³C NMR spectra were referenced with respect to solvent residual peaks. ¹⁹F NMR spectra were recorded with CFCl₃ (0.0 ppm) as internal standard. Splitting pattern abbreviations: s for singlet, d for doublet, t for triplet, q for quadruplet, bs for broad signal. Mass spectra were acquired on Agilent 1100 series LC/MSD instrument using atmospheric pressure ionization with electrospray (API-ES); positive ion spectra are denoted as pos, negative as neg. Progression of reactions was followed by NMR and/or TLC. Analytical TLCs were performed with Merck Silica gel 60 F₂₅₄ plates. Visualization was accomplished by UV-light or spraying with a solution of ceric ammonium molybdate in 10% sulfuric acid followed by brief heating. Flash chromatography was performed with Carl Roth Kieselgel 60, 40-63 μm.

**Synthesis of ammonium 1,1-difluoro-2-oxo-2-(m-tolyl)ethylphosphonate**

Preparation of diethyl 1,1-difluoro-2-oxo-2-(m-tolyl)ethylphosphonate

![Reaction Scheme](image)

An adopted literature procedure was used [1]. Cerium (III) chloride (5.06 g, 20.5 mmol), diisopropylamine (2.26 g, 22.3 mmol) and THF (35 mL) were placed in three-neck round-bottom flask equipped with rubber septum, nitrogen inlet and thermometer. To this mixture butyllithium (13.3 mL, 21.3 mmol, 1.6 M solution in hexane) was added at -70 °C and the resulting solution was allowed to warm to -30 °C. It was then cooled to -100 °C and diethyl (difluoromethyl)phosphonate (3.82 g, 20.3 mmol) in THF (5 mL) was added. Mixture was stirred at -100 to -90 °C for 1 hour while gradually turning light brown in color. Methyl 3-methylbenzoate (3.08 g, 20.5 mmol) was added. Mixture was stirred at -100 to -90 °C for 1 hour while gradually turning light brown in color. Methyl 3-methylbenzoate (3.08 g, 20.5 mmol) in THF (5 mL) was then added and the resulting mixture was stirred at -70 °C for 1 hour. Reaction was quenched with 30 mL of 1M HCl and was allowed to warm to rt. Organic layer was separated, aqueous layer was dried with Na₂SO₄ and the product was obtained as a pale yellow oil (5.26 g, 17.18 mmol, 85 % yield).

Hydrolysis of diethyl 1,1-difluoro-2-oxo-2-(m-tolyl)ethylphosphonate

![Reaction Scheme](image)

Schlenk flask was charged with diethyl (1,1-difluoro-2-oxo-2-(m-tolyl)ethyl)phosphonate (0.61 g, 2 mmol) and 10 mL of dry acetonitrile. Bromotrimethylsilane (1.55 g, 10 mmol) was added via a syringe and the resulting pale yellow solution was stirred at 35 °C overnight. Volatiles were evaporated in vacuum and the residue was dissolved in methanol (3 mL) and stirred for 20 min at r.t. Solvent was evaporated and the residue was treated with ammonia methanolic solution (3 mL). Product was
precipitated by adding 15 mL of acetone, filtered, washed with acetone and ether and dried in vacuum. Yield 0.36 g (64%); colorless crystalline solid; m.p. 142-143 °C; two groups of signals were usually observed in NMR spectra, they are attributed to keto (major) and gem-diol (minor) forms; δ<sub>n</sub> (500 MHz, D<sub>2</sub>O, Me<sub>4</sub>Si) 2.37 (0.6H, s, ArCH<sub>3</sub>, gem-diol), 2.37 (2.4H, s, ArCH<sub>3</sub>, keto), 7.29 (0.2H, d, δ<sub>H-H</sub> 7.3 Hz, Ar, gem-diol), 7.36 (0.2H, t, δ<sub>H-H</sub> 7.3 Hz, Ar, gem-diol), 7.43 (0.8H, t, δ<sub>H-H</sub> 7.3 Hz, Ar, keto), 7.48 (0.2H, d, δ<sub>H-H</sub> 7.3 Hz, Ar, gem-diol), 7.54 (1.0 H, d, δ<sub>H-H</sub> 7.3 Hz, Ar, gem-diol + keto), 8.01 (0.8H, d, δ<sub>H-H</sub> 7.3 Hz, Ar, keto), 8.06 (0.8H, s, Ar, keto) ppm; δ<sub>C</sub> (125 MHz, D<sub>2</sub>O, Me<sub>4</sub>Si) 20.4 (keto), 20.5 (gem-diol), 119.6 (td, δ<sub>C</sub> 270.3, δ<sub>C</sub> 157.6, COF<sub>2</sub>P, keto), 124.9 (gem-diol), 127.7 (keto), 127.9 (gem-diol), 128.3 (keto), 128.4 (gem-diol), 129.7 (gem-diol), 130.8 (keto), 133.0 (keto), 135.2 (keto), 137.3 (gem-diol), 138.0 (gem-diol), 138.6 (keto), 195.4 (td, δ<sub>C</sub> 21.4, δ<sub>C</sub> 11.0, COCF<sub>3</sub>P, keto) ppm; δ<sub>p</sub> (376 MHz, CDCl<sub>3</sub>, CFCl<sub>3</sub>) –122.0 (0.3F, d, δ<sub>F-P</sub> 80.4, gem-diol), –110.4 (1.7F, d, δ<sub>F-P</sub> 77.6, keto) ppm; δ<sub>p</sub> (202 MHz, CDCl<sub>3</sub>, H<sub>3</sub>PO<sub>4</sub>) 4.2 (t, δ<sub>P-F</sub> 96.0). MS(API-ES) m/z pos 501.0 (2M + H<sup>+</sup> – 4NH<sub>3</sub>, 40%), 251.0 (M + H<sup>+</sup> – 2NH<sub>3</sub>, 100%); neg 499.0 (2M – H<sup>+</sup> – 4NH<sub>3</sub>, 30%), 249.0 (M – H<sup>+</sup> – 2NH<sub>3</sub>, 100%). Found: C, 38.34; H, 5.19; P, 10.67. Calc. for C<sub>9</sub>H<sub>15</sub>F<sub>2</sub>N<sub>2</sub>O<sub>4</sub>P: C 38.04; H, 5.32; P, 10.90.

Preparation of diethyl 1,1-difluoro-2-oxo-2-(m-bromomethylphenyl)ethylphosphonate

![ChemicalStructureDiagram]

To a stirred and irradiated with 950 Wt UV lamp solution of diethyl (1,1-difluoro-2-oxo-2-(m-tolyl)ethyl)phosphonate (2.14 g, 7mmol) in CCl<sub>4</sub> (20 mL) solid NBS (1.31 g, 7.4 mmol) was added in 5 equal portions over 4 h. The reaction mixture was then cooled to rt and filtered. Solid was washed with CCl<sub>4</sub> (3x5 mL) and combined filtrate was concentrated in vacuum. Crude product consisted of 64:12:24 mixture of respectively monobrominated and dibrominated products, and starting material. Flash chromatography (gradient of EtOAc in hexane 20% -> 25%) afforded 1.14 g of pure BrCH<sub>2</sub>C<sub>6</sub>H<sub>4</sub>C(O)CF<sub>2</sub>P(O)(OEt)<sub>2</sub>. Yield 42.3%, pale yellow viscous oil. δ<sub>n</sub> (400 MHz, CDCl<sub>3</sub>, Me<sub>4</sub>Si) 1.37 (6H, t, δ<sub>H-H</sub> 7.2, 2xOCH<sub>2</sub>C<sub>2</sub>H), 4.24 - 4.41 (4H, m, 2xOCH<sub>2</sub>C<sub>2</sub>H), 4.52 (2H, s, ArCH<sub>2</sub>Br), 7.49 (1H, δ<sub>H-H</sub> 7.3, C<sub>6</sub>H<sub>4</sub>), 7.68 (1H, d, δ<sub>H-H</sub> 7.3, C<sub>6</sub>H<sub>4</sub>), 8.08 (1H, d, δ<sub>H-H</sub> 7.3, C<sub>6</sub>H<sub>4</sub>), 8.12 (1H, s, C<sub>6</sub>H<sub>4</sub>) ppm; δ<sub>n</sub> (16 MHz, CDCl<sub>3</sub>, Me<sub>4</sub>Si) 16.3 (d, δ<sub>C</sub> 5.5, OCH<sub>2</sub>C<sub>2</sub>H), 32.1, 65.4 (d, δ<sub>C</sub> 6.5), 114.9 (td, δ<sub>C</sub> 274.3, δ<sub>C</sub> 200.5, COCF<sub>3</sub>P), 129.2, 130.3, 130.6, 132.5, 135.2, 138.6, 187.5 (td, δ<sub>C</sub> 24.4, δ<sub>C</sub> 15.0 COCF<sub>3</sub>P) ppm; δ<sub>p</sub> (202 MHz, CDCl<sub>3</sub>, H<sub>3</sub>PO<sub>4</sub>) 4.2 (t, δ<sub>P-F</sub> 96.0) ppm; δ<sub>p</sub> (376 MHz, CDCl<sub>3</sub>, CFCl<sub>3</sub>) –110.8 (d, δ<sub>F-P</sub> 96.0).
Synthesis of difluoromethyl phosphonic acid derivatives of nitrogen-containing macrocycles

\[ N^1, N^4, N^8, N^{11}-\text{Tetrakis[3-(carboxymethyl)benzyl]-1,4,8,11-tetraazacyclotetradecane (1)} \]

Methyl 3-(bromomethyl)benzoate (0.93 g, 4.05 mmol) and 1,4,8,11-tetraazacyclotetradecane (0.20 g, 1 mmol) were dissolved in dry DMF (5 mL). To this solution finely powdered K$_2$CO$_3$ (1.38 g, 10 mmol) was added followed by catalytic amounts of KI (0.033 g, 0.20 mmol). The resulting mixture was stirred at 80 °C for 48 h. After cooling to r.t. the reaction mixture was poured into water (100 mL) and acidified with HCl to pH 5. The precipitate was washed with EtOH, filtered and dried in vacuum at 60 °C. Yield 56% (0.44 g, 0.56 mmol).

\[ ^{1}\text{H NMR} \ (\text{CDCl}_3, 500 \text{ MHz}) \delta \ 1.59-1.97 \ (m, 4H, cyclam), 2.25-2.85 \ (m, 16H, cyclam), 3.37 \ (s, 8H, NCH$_2$Ar), 3.84 \ (s, 12H, COCH$_3$), 7.19-8.05 \ (m, 8H, Ar), 7.73-7.95 \ (m, 8H, Ar); \ ^{13}\text{C NMR} \ (125 \text{ MHz, CDCl}_3) \delta \ 24.18 \ (\text{CH}_2\text{C}), 49.80, 50.95 \ (\text{cyclam, CH}), 51.57 \ (\text{CH}_2\text{Ar}), 57.98 \ (\text{OMe}), 127.61, 129.64, 133.15, 140.32 \ (Ar), 166.82 \ (CO). \] MS-ESI pos: 793 (20%, M + H$^+$), 397 (100%, M + 2H$^+$). Found: C, 69.51; H, 7.19; N, 7.22. Calc. for C$_{68}$H$_{84}$N$_8$O$_{26}$: C, 69.67; H, 7.12; N, 7.07.

\[ N^1, N^4, N^8, N^{11}-\text{Tetrakis[3-1′-oxo-2′,2′-difluoro-2′-(diethylphosphono)ethyl]benzyl]-1,4,8,11-tetraazacyclotetradecane (2)} \]

n-BuLi (1.56 mL of 1.6 M solution in hexane, 2.5 mmol) was added dropwise to a cold (-78 °C) solution of diisopropylamine (0.27 g, 2.6 mmol) in dry THF (8 mL). The solution was warmed to 0 °C for 10 min under argon then recolled to -78 °C. Freshly dried CeCl$_3$ (760 mg, 3.1 mmol) was added then in one portion. The resulting suspension was stirred vigorously at -78 °C for 20 min then it was cooled to -90 °C and a solution of diethyl difluoromethylphosphonate (427 mg, 2.27 mmol) in 2 mL of THF was added. Mixture was stirred at -90 °C for 1 h then a suspension of of tetramethyl 3,3′,3″,3‴-((1,4,8,11-tetraazacyclotetradecane-1,4,8,11-tetrayl)tetrakis(methylene))tetrabenzoate (400 mg, 0.5 mmol, 1 eq) in 10 mL of THF was added. Mixture became very thick and stirring was disabled. It was kept at -80 °C for 1 h and then allowed to warm to -30 °C during the second hour. Reaction was quenched by adding NH$_4$Cl aqueous solution. Product 2 was purified by flash chromatography (CH$_2$Cl$_2$:MeOH 100:4 => 100:7) in 54 % yield (382 mg, 0.27 mmol); $^{1}$H NMR (CDCl$_3$, 500 MHz) δ 1.34–1.41 (m, 24H, OCH$_2$), 1.77–1.83 (m, 4H, cyclam), 2.45–2.52 (m, 8H, cyclam), 2.65 (bs, 8H, cyclam), 3.43 (bs, 8H, NCH$_2$Ar), 4.32–4.39 (m, 16H, OCH$_2$CH$_3$), 7.32–7.38 (m, 4H, Ar), 7.59–7.63 (m, 4H, Ar), 7.99–8.05 (m, 8H, Ar). $^{31}$P NMR (CDCl$_3$, 376 MHz) δ −110.1 (d, $J_{P-F} = 95.0$ Hz). MS-ESI pos: 1418 (20%, M + H$^+$). Found: C, 52.68; H, 5.60; P, 8.55. Calc. for C$_{82}$H$_{86}$F$_8$N$_{8}$O$_{28}$P$_8$: C, 52.54; H, 5.97; P, 8.74.

\[ N^1, N^4, N^8, N^{11}-\text{Tetrakis[3-1′-oxo-2′,2′-difluoro-2′-(phosphono)ethyl]benzyl]-1,4,8,11-tetraazacyclotetradecane (3)} \]
To a solution of tetrakis(phosphate) 2 (300 mg, 0.2 mmol, 1 eq) in MeCN (5 mL) bromotrimethylsilane (1.19 g, 7.8 mmol, 36 eq) was added. The resulting solution was stirred at 35 °C overnight. Solvent was evaporated and the residue was treated with MeOH (3 mL). Mixture was stirred at 35 °C for 15 min and product was precipitated by adding acetone (30 mL). Solid was filtered, washed with EtOAc and dried on air overnight and then under vacuum at 70 °C for 2h to yield product 3 as colorless solid in 65% yield (165 mg, 0.14 mmol). 1H NMR (D2O, 500 MHz) δ 1.75–1.95 (m, 4H, cyclam), 2.50–2.85 (m, 16H, cyclam), 3.66 (s, 8H, NCH2Ar), 7.20–7.65 (m, 10H, Ar), 8.01–8.14 (m, 6H, Ar). 19F NMR (DMSO-d2, 376 MHz) δ –110.3 (d, JF-F = 96 Hz). 31P NMR (DMSO-d2, 202 MHz)  δ 3.8 (t, JF-P = 96 Hz), MS-ESI pos: 1418 (20%, M + H+). Found: C, 46.65; H, 4.51; N, 4.58. Calc. for C60H50F6P4O12: C, 46.32; H, 4.39; N, 4.70. Cyclam-tetrakis(phosphonic acid) was converted into its tetrasodium salt by dissolving the acid (1 eq) in NaHCO3 (4 eq) aqueous solution and evaporating the resulting solution to dryness. 1H NMR (D2O + K2CO3, 125 MHz) δ 1.80 (m, 4H, cyclam), 2.62–2.72 (m, 16H, cyclam), 3.59–3.65 (m, 8H, NCH2Ar), 7.23–7.60 (m, 10H, Ar), 8.01–8.14 (m, 6H, Ar) ppm; 13C NMR (D2O + K2CO3, 125 MHz) δ 20.2, 46.0, 50.7, 59.0, 119.9 (td, JF-C = 259.3, JF-C,P 156.2, CF3P), 128.8, 130.4, 131.8, 135.8, 136.9, 157.2 ppm. Compound 4 was synthesized similarly to 1 starting from homocyclam (0.32 g, 1.5 mmol) and m-bromomethylbenzoate (1.55 g, 6.23 mmol). After purification by FC (CH2Cl2/MeOH 10:0.6) product was obtained as viscous yellow oil. Yield 0.77 g (64%). 1H NMR (CDCl3, 500 MHz) δ 1.58–1.75 (m, 6H, cyclam), 2.39–2.53 (m, 12H, cyclam), 2.61 (s, 4H, cyclam), 3.44–3.64 (m, 8H, NCH2Ar), 3.80–3.95 (m, 12H, CO2CH3), 7.18–7.43 (m, 8H, Ar), 7.80–7.87 (m, 8H, Ar); 13C NMR (CDCl3, 125 MHz, TMS) δ 25.2, 51.4, 51.9, 52.0, 52.3, 59.5, 128.1, 128.2, 128.3, 129.8, 129.9, 130.0, 133.4, 133.5, 140.4, 140.6, 167.2 ppm; MS-ESI pos: 808 (5%, M + H+), 404 (70%, M + 2H+). Found: C, 70.16; H, 7.21; N, 6.74. Calc. for C77H84N2O20: C, 69.95; H, 7.24; N, 6.94. Compound 5 was synthesized similarly to 2 starting from ester 4 (0.70 g, 0.87 mmol) and diethyl difluoromethylphosphonate (0.82 g, 4.35 mmol). After purification by FC (CH2Cl2/MeOH 10:1) product was obtained as yellow oil. Yield 0.49 g (39%). 1H NMR (CDCl3, 400 MHz, TMS) δ 1.37 (m, 24H, OCH2CH2), 1.69 (m, 6H, cyclam), 2.48–2.62 (m, 16H, cyclam), 3.55 (m, 8H, NCH2Ar), 4.35 (m, 16H, OCH2CH2), 7.43–7.58 (m, 8H, Ar), 8.00 (m, 8H, Ar) ppm; 19F NMR (CDCl3, 376 MHz, CFCl3) δ –110.1 (d, JF-F = 94.8 Hz).
**N\textsuperscript{3},N\textsuperscript{4},N\textsuperscript{6},N\textsuperscript{12}-Tetakis\{3-\[1′-oxo-2′,2′-difluoro-2′-(phosphono)ethyl\]benzyl\}-1,4,8,12-tetraazacyclododecane (6)**

Compound 6 was obtained similarly to 3 starting from phosphonate 5 (0.36 g, 0.25 mmol). Beige solid, yield 0.29 g (95%). \textsuperscript{1}H NMR (D\textsubscript{2}O + K\textsubscript{2}CO\textsubscript{3}, 400 MHz, TMS) \(\delta\) 1.66 (m, 6H, cyclam), 2.50 (m, 16H, cyclam), 3.59–3.71 (m, 8H, NCH\textsubscript{2}Ar), 7.36–7.59 (m, 8H, Ar), 7.96–8.16 (m, 8H, Ar) ppm; \textsuperscript{13}C NMR (D\textsubscript{2}O + K\textsubscript{2}CO\textsubscript{3}, 100 MHz, TMS) \(\delta\) 25.1, 48.7, 50.0, 51.2, 58.2, 120.0 (td, \(\text{J}_{CF} = \text{J}_{CP} = 91\) Hz) ppm. \textsuperscript{19}F NMR (D\textsubscript{2}O + K\textsubscript{2}CO\textsubscript{3}, 376 MHz, CFCl\textsubscript{3}) \(\delta\) –110.1 (d, \(\text{J}_{CF} = 91\) Hz) ppm. \textsuperscript{31}P NMR (CDCl\textsubscript{3}, 202 MHz, 85% H\textsubscript{3}PO\textsubscript{4}) \(\delta\) 3.3 (t, \(\text{J}_{PF} = 91\) Hz) ppm. Found: C, 46.30; H, 4.70; N, 4.81. Calc. for C\textsubscript{63}H\textsubscript{72}F\textsubscript{8}N\textsubscript{3}O\textsubscript{16}P\textsubscript{4}: C, 69.40; H, 6.97; N 7.32.

**N\textsuperscript{3},N\textsuperscript{4},N\textsuperscript{7},N\textsuperscript{10}-Tetakis\{3-\[1′-oxo-2′,2′-difluoro-2′-(phosphono)ethyl\]benzyl\}-1,4,7,10-tetraazacyclododecane (9)**

This compound was synthesized starting from cyclen (0.70 g, 4.0 mmol) and methyl 3-bromomethylbenzoate (3.82 g, 16.7 mmol). Yield 1.14 g (37%). \textsuperscript{1}H NMR (CDCl\textsubscript{3}, 400 MHz) \(\delta\) 2.60–2.80 (br s, 16H, cyclam), 3.44 (s, 8H, NCH\textsubscript{2}Ar), 3.88 (s, 12H, OMe), 7.29 (t, \(J = 6\) Hz, 4H, Ar), 7.56 (d, \(J = 6\) Hz, 4H, Ar), 7.88 (d, \(J = 6\) Hz, 4H, Ar), 7.96 (s, 4H). \textsuperscript{13}C NMR (125 MHz, CDCl\textsubscript{3}) \(\delta\) 51.63 (cyclen, CH\textsubscript{2}N), 52.39 (NCH\textsubscript{2}Ar), 59.32 (OMe), 127.65, 129.80, 129.55, 133.25, 139.99 (Ar), 166.82 (CO). Found: C, 69.40; H, 6.97; N 7.55. Calc. for C\textsubscript{44}H\textsubscript{42}N\textsubscript{10}O\textsubscript{6}: C, 69.09; H, 6.85; N 7.32.

**N\textsuperscript{3},N\textsuperscript{4},N\textsuperscript{7},N\textsuperscript{10}-Tetakis\{3-\[1′-oxo-2′,2′-difluoro-2′-(diethylphosphono)ethyl\]benzyl\}-1,4,7,10-tetraazacyclododecane (8)**

This compound was synthesized similarly to 6 starting from carboxylate ester (0.52 g, 0.68 mmol) and diethyl difluoromethylphosphonate (0.57 g, 3.06 mmol). Yield 0.39 g (42%). \textsuperscript{1}H NMR (CDCl\textsubscript{3}, 400 MHz) \(\delta\) 1.31–1.45 (m, 24H, OCH\textsubscript{2}CH\textsubscript{2}),
2.63–2.72 (m, 16H, cyclen), 3.44 (br s, 8H, NC\textsubscript{H}\textsubscript{2}Ar), 4.25–4.38 (m, 16H, OC\textsubscript{H}\textsubscript{2}CH\textsubscript{3}), 7.35 (t, J = 6 Hz, 4H, Ar), 7.65–7.72 (m, 4H, Ar), 7.92–8.03 (m, 8H, Ar). \textsuperscript{19}F NMR (CDCl\textsubscript{3}, 376 MHz) \(\delta\) -110.2 (d, \(^2J_{F-P} = 93\) Hz). \textsuperscript{31}P NMR (CDCl\textsubscript{3}, 202 MHz) \(\delta\) 5.1 (t, \(^2J_{P-F} = 93\) Hz) ppm. Found: C, 52.10; H, 5.67; N, 3.80. Calc. for C\textsubscript{60}H\textsubscript{80}F\textsubscript{8}N\textsubscript{4}O\textsubscript{16}P\textsubscript{4}: C, 51.88; H, 5.80; N, 4.03.

\(N^1,N^4,N^7,N^{10}\)-Tetrakis\{3-[1′-oxo-2′,2′-difluoro-2′-(phosphono)ethyl]benzyl\}-1,4,7,10-tetraazacyclododecane (9)

This compound was obtained similarly to cyclam-tetrakis(phosphonic acid) starting from the phosphonate ester (0.34 g, 0.245 mmol). Beige solid, yield 0.12 g (40%). \textsuperscript{1}H NMR (DMSO-d\textsubscript{6}, 400 MHz) \(\delta\) 2.45–2.55 (m, 16H, cyclen), 3.05 (br s, 8H, NC\textsubscript{H}\textsubscript{2}Ar), 7.59–7.73 (m, 4H, Ar), 7.91–8.04 (m, 4H, Ar), 8.06–8.20 (m, 4H, Ar), 8.28–8.41 (m, 4H, Ar). \textsuperscript{19}F NMR (DMSO-d\textsubscript{6}, 376 MHz) \(\delta\) -110.4 (d, \(^2J_{F-P} = 87\) Hz). \textsuperscript{31}P NMR (DMSO-d\textsubscript{6}, 202 MHz) \(\delta\) -0.3 (t, \(^2J_{P-F} = 87\) Hz) ppm. Found: C, 45.12; H, 4.37; N, 4.64. Calc. for C\textsubscript{44}H\textsubscript{48}F\textsubscript{8}N\textsubscript{4}O\textsubscript{16}P\textsubscript{4}: C, 45.37; H, 4.15; N, 4.81. 1,4,7,10-tetraazacyclododecane-tetrakis(phosphonic acid) was converted into its tetrasodium salt by dissolving the acid (1 eq) in NaHCO\textsubscript{3} (4 eq) aqueous solution and evaporating the resulting solution to dryness.

References

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**1H NMR**

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Chemical Shift (ppm)

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7.89 7.98 7.46 7.27

12.40 7.77 3.90 3.81

3.37 2.45 3.69 3.98

8.06 7.89 2.46 2.43

1.82 1.90 1.79 1.79

Normalized Intensity

Chemical Shift (ppm)
$^{13}$C NMR
Acquisition Time (sec) 4.3673
Comment 1H
Date 15 Sep 2013 09:03:07
File Name \vsboxsrV\Documents\Spectral\NMR\FNPFNP-5-H-1.pdf
Nucleus 1H
Number of Transients 8
Origin ECX400
Receiver Gain 38.00
Spectrum Offset (Hz) 2029.1407
Sweep Width (Hz) 7503.00
Temperature (degree C) 22.400

Solvent residual peak (D₂O)
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**Diagram:**

![Diagram of a compound](image)

**Chemical Shift (ppm):**

- 194.43
- 184.47
- 93.21
- 123.38
- 117.25
- 116.43
- 66.61
- 56.80
- 50.73
- 50.90
- 46.05
- 23.49
- 20.22
- 20.06
- 16.98

**Chemical Structure:**

![Chemical Structure](image)
$^3$P NMR
$^{19}$F NMR
$^{31}$P NMR