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Significant cell uptake of Gd(III)-diphenylphosphoryl-diphenylphosphonium complexes: Evidence for a new type of conformationally-dependent tumour cell targeting vector

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Experimental section

All precursor chemicals were commercially available; cyclen was obtained from Nowapharm China, while all other chemicals were purchased from Merck or Sigma-Aldrich. For experiments requiring H_2O, ultrapure H_2O was collected from a Milli-Q® water purification system. Anhydrous MeCN, DMF, and toluene were obtained using a Puresolv® system. Et_2O was dried over sodium wire, distilled and stored under N_2 over microsieves. MeOH was stored under N_2 over 4Å sieves. All other solvents were used without further purification. Reactions requiring an inert atmosphere were performed under anhydrous N_2 and employed conventional Schlenk techniques.[1]

Characterisation

All ^{1}H, $^{13}C\{^{1}H\}$, and $^{31}P\{^{1}H\}$ NMR spectra were recorded at 300 K on a Bruker Avance 300 (5 mm QNP probe, ^{1}H at 300 MHz, ^{13}C at 75 MHz, and ^{31}P at 121 MHz), a Bruker Avance III 400 (5 mm BBFO probe, ^{1}H at 400 MHz, ^{13}C at 100 MHz, and ^{31}P at 162 MHz), or a Bruker Avance III 500 (5 mm BBFO probe, ^{1}H at 500 MHz, ^{13}C at 125 MHz, and ^{31}P at 202 MHz). All NMR signals (δ) are reported in ppm. ^{1}H and ^{13}C NMR spectra were referenced according to their solvent residual peaks. $^{13}C\{^{1}H\}$ NMR spectra in D_2O were referenced according to an internal standard of DMSO-d_6 (39.39 ppm). $^{31}P\{^{1}H\}$ NMR spectra were referenced to external 1% TMS in $CDCl_3$ using the unified reference scale.[2] Coupling constants are reported in Hz. Peak multiplicities have been abbreviated as s (singlet), d (doublet), t (triplet), q (quartet), dd (doublet of doublets), dt (doublet of triplets), br (broad), and m (multiplet – unassignable multiplicity). Proton and carbon positions within aryl rings have been abbreviated *i*- (1, 1), *o*- (1, 2), *m*- (1, 3), and *p*- (1, 4). The xylyl linker has been abbreviated to 'xy' for clarity when assigning proton and carbon nuclei belonging to this linker group.

Low resolution ESI-MS were recorded on a Bruker amaZon SL mass spectrometer. MALDI-MS were recorded on a Bruker autoflex speed LRF MALDI-TOF mass spectrometer. High resolution ESI-FT-ICR-MS data were recorded on a Bruker Apex Qe 7T FTICR mass spectrometer. Quantitative MS was recorded on a Perkin Elmer NexION 350X ICP-MS with a quadrupole analyser.

Stock solutions of TA30 solvent (30:70 *v/v* MeCN : 0.1% TFA in water) saturated with *α*-cyano-4-hydroxycinnamic acid (4CCA) matrix were prepared. The samples were prepared at a concentration of 2 mg mL^{-1} in TA30. MALDI-TOF MS samples were prepared by combining 20 µL of matrix solution with 4 µL of sample solution. 0.5 µL of this sample was deposited on a Ground Steel MALDI target plate and allowed to air dry. Stock solutions of *trans*-2-[3-(4-*tert*-butylphenyl)-2-methyl-2-propenylidene]malononitrile (DCTB) (10 mg mL^{-1}) in 50:50 CH_2Cl_2:MeCN were prepared. The samples were prepared at a concentration of 2 mg mL^{-1} in CH_2Cl_2. MALDI-TOF MS samples were prepared by combining 20 µL of matrix solution with 4 µL of sample solution. 0.3 µL of this sample was deposited on a Ground Steel MALDI target plate and allowed to air dry.

HPLC methods

All HPLC methods were performed using a variety of Waters HPLC systems equipped with Waters 2695 separation modules and tuneable absorbance UV/vis detectors (λ = 400-230 nm). Preparative separations utilised a Waters SunfireTM C18 preparative column (100 Å, 5 µm, 19 × 150 mm) and a flow rate of 7 mL min^{-1}. Semi-preparative separations were selected when experiments yielded side products that eluted without considerable baseline separation in preparative methods, and utilised a Waters SunfireTM C18 semi-preparative column (100 Å, 5 µm, 10 × 250 mm) and a flow rate of 2 mL min^{-1}. Analytical HPLC utilised a Waters SunfireTM C18 analytical column (100 Å, 5 µm, 4.6 × 250 mm) and a flow rate of 0.2 mL min^{-1}. Mobile phases consisted of two solvent mixtures: H_2O with 0.1% TFA and MeCN with 0.1% TFA, run in a gradient from 95% H_2O/5% MeCN to 100% MeCN over 45 min.

Lipophilicity studies

Lipophilicity is a critical parameter for all new drugs as it determines their cell and mitochondrial membrane permeability, and strongly influences their *in vivo* absorption, distribution, metabolism and excretion.[3-6]

The log*P* values of the Gd(III) complexes were measured by means of a standard reverse-phase HPLC method on a Waters 2695 separations module equipped with the Waters Alliance column heater (set at 30°C) and Waters 2996 Photodiode Array (PDA) detector using a Waters SunfireTM C18 column (100 Å, 5 µm, 2.1 × 150 mm). The mobile phase consisted of 65% (*v/v*) MeOH in a 50 mM sodium phosphate buffer adjusted to pH 7.4 by mixing 50 mM solutions of Na_2HPO_4 and NaH_2PO_4. The samples, along with a set of standards with known log*P* values, were determined using the solvent with an isocratic flow-rate of 0.2 mL min^{-1}. The retention times of acetone (log$D_{7.4}$ −0.24), aniline (log$D_{7.4}$ 0.90), phenol (log$D_{7.4}$ 1.50), toluene (log$D_{7.4}$ 2.730), cumene (log$D_{7.4}$ 3.66), triphenylamine (log$D_{7.4}$ 5.74), and hexachlorobenzene (log$D_{7.4}$ 6.35) were plotted against their literature log$D_{7.4}$ values, adjusting for the T_0, to establish a calibration curve.[7] Fitting an exponential curve to the dataset generated the equation (y = 0.8822ln(x) + 1.8164; r^2 = 0.984) from which the sample log*P* values could be derived using their retention times. The HPLC experiments were performed in triplicate.

Synthetic methods

1,4,7,10-Tetraazacyclododecane-1,4,7-tris(*tert*-butyl acetate) (DO3A-^{t}Bu$_3$·HBr) was prepared using a method adapted from Moore *et al.*[8-10] 1,4,7,10-Tetraazacyclododecane-1,4,7-tris(*tert*-butyl acetate)-10-acetic acid (DOTA-^{t}Bu$_3$) was prepared using a modified method adapted from Strauch.[11] 2,2',2''-(10-(4-((Triphenylphosphonio)methyl)benzyl)-1,4,7,10-tetraazacyclododecane-1,4,7-triyl)triacetatogadolinium(III) trifluoroacetate (13) was prepared as previously described by Morrison *et al*.[12] 2,2',2''-(10-(2-Oxo-2-((4-((triphenylphosphonio)methyl)benzyl)amino)ethyl)-1,4,7,10-tetraazacyclododecane-1,4,7-triyl)triacetatogadolinium(III) trifluoroacetate (14) was prepared as previously described.[13]

General mono-oxidation procedure[14] (*GP1*) (7–9)

Commercially-available bis(diphenylphosphino)alkane (dppm, dppe, or dppp), 1,2-dibromoethane, and a catalytic quantity of palladium(II) acetate were dissolved in 1,2-dichloroethane under N_2 and stirred at RT. A concentrated NaOH solution was added and the mixture was stirred vigorously under reflux until the reaction had reached completion by TLC. The organic phase was separated from the aqueous phase, dried over sodium sulfate, solvent removed under a stream of N_2, and the product isolated by means of silica gel chromatography, eluting with a mixture of CH_2Cl_2 and ethyl acetate (EtOAc). The fractions containing product were combined, concentrated to dryness *in vacuo*, dissolved in a minimum amount of boiling CH_2Cl_2, treated with Et_2O or *n*-pentane, and left at −4°C overnight to afford the desired bis(diphenylphosphino)alkane monooxides as colourless needles.

General phosphonium salt formation procedure (*GP2*) (10–12)

Phosphonium salts **10**–**12** were prepared by means of dropwise addition of the precursor bis(diphenylphosphino)alkane monooxides (7-9 prepared in ***GP1***) in toluene to a stirred solution of *α*,*α*'-dibromo-*p*-xylene in toluene, followed by heating at reflux for 24 h. The crystallised product was collected by filtration and washed with warm toluene and diethyl ether to yield the phosphonium salt in high purity.

General DO3A linking procedure (*GP3*) (Linker = CH_2)

The phosphonium salts (**10**–**12** prepared in ***GP2***) were dissolved in MeCN, added to a stirred solution of DO3A-^{t}Bu$_3$·HBr and K_2CO_3 in MeCN, and the mixture was refluxed for 24 h. The K_2CO_3 was removed by filtration and the filtrate reduced *in vacuo* to yield the crude *tert*-butyl pro-ligand as a residue. The crude material was deprotected through the addition of cold, neat TFA and stirring the mixture for a further 12 h at RT. The volatiles were removed *in vacuo*, and the crude residue dissolved in H_2O and washed with $CHCl_3$. The aqueous fraction was reduced *in vacuo* to give a hygroscopic solid which was purified by means of reverse-phase HPLC, and the product lyophilised to afford the pure ligand.

General DOTA linking procedure (*GP4*) (Linker = $CH_2NHC(O)CH_2$)

The alkylbromide groups of the phosphonium salts (**10**–**12** prepared in ***GP2***) were converted to azide groups by stirring with NaN_3 in DMF at RT for 72 h. The DMF was removed under a flow of N_2, and the residue was then dissolved in $CHCl_3$ and any excess NaN_3 removed by filtration. The filtrate was reduced *in vacuo* to yield the phosphonium-azido intermediate in high purity (> 95%). The azide group was reduced to an amine using 10 mol% Pd/C stirred in MeOH under a H_2 atmosphere at RT for 6 h. The catalyst was removed by filtration through a Celite pad, and the solvent volume reduced to afford the phosphonium-amine in high purity. The phosphonium targeting vectors were coupled to the DOTA chelating component by means of a peptide coupling reaction performed in peptide-grade DMF with the HATU coupling reagent in the presence of excess NMM and stirred at RT for 24 h. The DMF and NMM were removed under N_2, and the residue was deprotected by the addition of neat TFA upon stirring the mixture for a further 12 h at RT. The volatiles were removed *in vacuo*, and the crude residue dissolved in H_2O and washed with $CHCl_3$. The aqueous fraction was reduced *in vacuo* to give a hygroscopic solid which was purified by means of reverse-phase HPLC, and the product lyophilised to afford the pure ligand.

General metal complexation procedure (*GP5*)

The purified ligands were complexed with Gd^{3+} ions by stirring a suspension of excess Gd_2O_3 in a minimum amount of H_2O for 72 h at RT. Any remaining Gd_2O_3 was removed by means of centrifugation and subsequent filtration through a 0.22 µm filter. The filtrate was lyophilised to afford the purified Gd(III) complex as a colourless powder.

*(4-(Bromomethyl)benzyl)((diphenylphosphoryl)methyl)diphenylphosphonium bromide (**10**)*

Following ***GP1**,* bis(diphenylphosphino)methane (dppm) (3.00 g, 7.80 mmol), 1,2-DBE (1.35 mL, 15.61 mmol), and $Pd(OAc)_2$ (21.3 mg, 94.87 µmol) in 1,2-DCE (14 mL), and NaI (62.4 mg, 0.42 mmol) in aqueous NaOH (20% *w/v*, 10 mL) heated at reflux for 4 h. Silica gel chromatography was performed using a CH_2Cl_2/EtOAc (3:1) elution mixture, fractions reduced, redissolved in CH_2Cl_2, and treated with Et_2O to yield 2.50 g (81%) bis(diphenylphosphino)methane monooxide (**7**). ***GP2*** followed, accordingly dppm-O (1.01 g, 2.51 mmol) in toluene (30 mL) was added to *α*,*α*'-dibromo-*p*-xylene (1.04 g, 3.96 mmol) in toluene (30 mL), additional toluene (60 mL) was added before heating to reflux. Yield: 1.30 g (79%). ESI-MS for [M^+(^{79}Br)]: calculated *m/z* 583.10, observed *m/z* 583.07. ^{1}H NMR ($CDCl_3$) *δ* 7.98-7.89 (m, 4H, Ar, *o*-PhP(O), $^3J_{HH}$ = 8.0 Hz, $^3J_{HP(O)}$ = 12.0 Hz), 7.89-7.50 [m, 6H: 7.79-7.73 (dd, 2H, Ar, *p*-PhP(O), $^3J_{HH}$ = 8.0 Hz, $^5J_{HP(O)}$ = 2.0 Hz), 7.65-7.50 (m, 4H, Ar, *m*- PhP(O), $^3J_{HH}$ = 8.0 Hz, $^4J_{HP(O)}$ = 2.0 Hz)], 7.33-7.27 (m, 10H, Ar, *o*-PhP$^+$, *p*-PhP$^+$, *m*-PhP$^+$), 7.21-7.15 (m, 2H, Ar, *o*-xy, $^3J_{HH}$ = 9.0 Hz, $^4J_{HP}$ = 6.0 Hz), 7.11-7.00 (m, 2H, Ar, *m*-xy, $^3J_{HH}$ = 9.0 Hz), 4.86 (dt, 2H, P(O)CH2P$^+$, $^2J_{HP}$ = 48.0 Hz, $^2J_{HP(O)}$ = 13.5 Hz), 4.69 (t, 2H, $^+$PCH$_2$, $^2J_{HP}$ = 13.5 Hz), 4.27 (s, 2H, BrCH$_2$). ^{13}C NMR ($CDCCl_3$) *δ* 137.9 (s, Ar, *p*-xy), 134.5 (m, Ar, *p*-PhP$^+$), 133.5 (dd, Ar, *m*-PhP$^+$, $^3J_{PC}$ = 7.6 Hz, $^5J_{P(O)C}$ = 2.6 Hz), 132.4 (m, Ar, *p*-PhP(O)), 131.2- 130.7 (m, Ar, *o*-xy), 130.6 (dd, Ar, *m*-PhP(O), $^3J_{P(O)C}$ = 9.8 Hz, $^5J_{PC}$ = 3.4 Hz), 129.9 (dd, Ar, *o*-PhP$^+$, $^2J_{PC}$ = 12.8 Hz, $^4J_{P(O)C}$ = 4.2 Hz), 129.3-129.0 (m, Ar, *m*-xy), 128.8 (dd, Ar, *o*-PhP(O), $^2J_{P(O)C}$ =

12.1 Hz, $^{4}J_{PC}$ = 4.0 Hz), 127.2 (d, Ar, *i*-xy, $^{2}J_{PC}$ = 7.9 Hz), 116.5 (dd, Ar, *i*-PhP^{+}, $^{1}J_{PC}$ = 83.0 Hz, $^{3}J_{P(O)C}$ = 3.3 Hz), 116.3 (dd, Ar, *i*-PhP(O), $^{1}J_{P(O)C}$ = 82.3 Hz, $^{3}J_{PC}$ = 4.1 Hz), 33.6 (s, $BrCH_2$), 32.1 (m, $^{+}PCH_2xy$), 31.2 (m, $P(O)CH_2P^{+}$). $^{31}P\{^{1}H\}$ NMR ($CDCl_3$) δ 24.4 (d, 1P, P=O, $^{2}J_{PP}$ = 82.6 Hz), 24.3 (d, 1P, P^{+}, $^{2}J_{PP}$ = 80.4 Hz).

*(4-(Bromomethyl)benzyl)((2–diphenylphosphoryl)ethyl)diphenylphosphonium bromide (**11**)*
Following ***GP1**,* 1,2-bis(diphenylphosphino)ethane (dppe) (3.99 g, 10.02 mmol), 1,2-DBE (1.31 mL, 15.13 mmol), and $Pd(OAc)_2$ (11.7 mg, 52.11 µmol) in 1,2-DCE (30 mL), and aqueous NaOH (10% *w/v*, 20 mL) heated at reflux for 8 h. Silica gel chromatography was performed using a CH_2Cl_2/EtOAc (5:3) elution mixture, fractions reduced, re-dissolved in CH_2Cl_2, and treated with Et_2O to yield 3.49 g (84%) 1,2-bis(diphenylphosphino)ethane monooxide (**8**). ***GP2*** followed, accordingly dppe-O (0.94 g, 2.27 mmol) in toluene (30 mL) was added to *α*,*α*'-dibromo-*p*-xylene (0.66 g, 2.50 mmol) in toluene (30 mL), additional toluene (60 mL) was added before heating to reflux. Yield: 1.30 g (84%). ESI-MS for [M^{+}(^{79}Br)]: calculated *m/z* 597.11, observed *m/z* 597.08. ^{1}H NMR ($CDCl_3$) δ 7.79-7.66 (m, 4H, Ar, *o*-PhP(O), $^{3}J_{HH}$ = 7.6 Hz, $^{3}J_{HP(O)}$ = 11.7 Hz), 7.65-7.58 (m, 2H, Ar, *p*-PhP(O), $^{3}J_{HH}$ = 8.0 Hz, $^{5}J_{HP(O)}$ = 2.0 Hz), 7.55-7.29 (m, 14H, Ar, *m*-PhP(O), *o*-PhP^{+}, *p*-PhP^{+}, *m*-PhP^{+}, $^{3}J_{HH}$ = 8.0 Hz), 7.20-7.12 (br d, 2H, Ar, *o*-xy, $^{3}J_{HH}$ = 7.6 Hz, $^{4}J_{HP}$ = 2.0 Hz), 7.09-7.02 (d, 2H, Ar, *m*-xy, $^{3}J_{HH}$ = 7.6 Hz), 4.57 (d, 2H, $^{+}PCH_2xy$, $^{2}J_{HP}$ = 14.1 Hz), 4.23 (m, 2H, $BrCH_2$), 3.13-2.98 (br m, 2H, $P(O)CH_2$), 2.90-2.73 (m, 2H, $^{+}PCH_2CH_2$, $^{2}J_{HP}$ = 20.4 Hz). ^{13}C NMR ($CDCCl_3$) δ 137.0 (s, Ar, *p*-xy), 134.2 (m, Ar, *p*-PhP^{+}), 133.2 (dd, Ar, *m*-PhP^{+}, $^{3}J_{PC}$ = 8.7 Hz, $^{6}J_{P(O)C}$ = 2.1 Hz), 132.2 (m, Ar, *p*-PhP(O)), 131.4-131.1 (m, Ar, *o*-xy), 130.7 (dd, Ar, *m*-PhP(O), $^{3}J_{P(O)C}$ = 9.8 Hz, $^{6}J_{PC}$ = 2.6 Hz), 129.8 (dd, Ar, *o*-PhP^{+}, $^{2}J_{PC}$ = 13.6 Hz, $^{5}J_{P(O)C}$ = 2.5 Hz), 129.4-128.9 (m, Ar, *m*-xy), 128.6 (dd, Ar, *o*-PhP(O), $^{2}J_{P(O)C}$ = 12.4 Hz, $^{5}J_{PC}$ = 2.8 Hz), 127.4 (d, Ar, *i*-xy, $^{2}J_{PC}$ = 7.9 Hz), 116.2 (m, Ar, *i*-PhP^{+}, $^{1}J_{PC}$ = 86.6 Hz), 115.3 (dd, Ar, *i*-PhP(O), $^{1}J_{P(O)C}$ = 81.0 Hz, $^{4}J_{PC}$ = 2.5 Hz), 34.1 (s, $BrCH_2$), 31.2 (m, $^{+}PCH_2xy$), 27.2 (m, $P(O)CH_2$). $^{31}P\{^{1}H\}$ NMR ($CDCl_3$) δ 32.7 (d, 1P, P=O, $^{3}J_{PP}$ = 48.6 Hz), 26.1 (d, 1P, P^{+}, $^{3}J_{PP}$ = 47.4 Hz).

*(4-(Bromomethyl)benzyl)((3–diphenylphosphoryl)propyl)diphenylphosphonium bromide (**12**)*
Following ***GP1**,* 1,3-bis(diphenylphosphino)propane (dppp) (3.14 g, 7.60 mmol), 1,2-DBE (0.99 mL, 11.49 mmol), and $Pd(OAc)_2$ (7.84 mg, 34.91 µmol) in 1,2-DCE (12 mL), and aqueous NaOH (25% *w/v*, 8 mL) heated at reflux for 7 h. Silica gel chromatography was performed using a CH_2Cl_2/EtOAc (5:3) elution mixture, fractions reduced, re-dissolved in CH_2Cl_2, and treated with Et_2O (10 mL) followed by *n*-pentane (60 mL) to yield 2.30 g (72%) of 1,3-bis(diphenylphosphino)propane monooxide (dppp-O, **9**). ***GP2*** followed, accordingly dppp-O (1.67 g, 3.89 mmol) in toluene (50 mL) was added to *α*,*α*'-dibromo-*p*-xylene (1.64 g, 6.21 mmol) in toluene (50 mL), additional toluene (100 mL) was added before heating to reflux. Yield: 2.20 g (81%). ESI-MS for [M^{+}(^{79}Br)]: calculated *m/z* 611.13, observed *m/z* 611.11. ^{1}H NMR ($CDCl_3$) δ 7.62-7.58 (m, 4H, Ar, *o*-PhP(O), $^{3}J_{HH}$ = 8.0 Hz, $^{3}J_{HP(O)}$ = 12.0 Hz), 7.56-7.51 (m, 6H, Ar, *p*-PhP(O), *m*-PhP(O), $^{3}J_{HH}$ = 8.0 Hz, $^{4}J_{HP(O)}$ < 2.0 Hz), 7.41-7.36 (m, 4H, Ar, *om*-PhP^{+}, $^{3}J_{HH}$ = 7.8 Hz), 7.32-7.22 [m, 6H: 7.32-7.29 (m, 2H, Ar, *p*-PhP^{+}, $^{5}J_{HH}$ = 7.5 Hz), 7.28-7.22 (m, 4H, Ar, *m*-PhP^{+}, $^{4}J_{HH}$ = 7.6 Hz)], 7.05 (dd, 2H, Ar, *o*-xy, $^{3}J_{HH}$ = 8.0 Hz $^{4}J_{HP}$ = 2.0 Hz), 6.98 (d, 2H, Ar, *m*-xy, $^{3}J_{HH}$ = 7.6 Hz), 4.44 (d, 2H, $^{+}PC\underline{H_2}xy$, $^{2}J_{HP}$ = 16.0 Hz), 4.21 (m, 2H, $BrC\underline{H_2}$), 2.62 (br m, 2H, $P(O)C\underline{H_2}$), 2.40 (m, 2H, $^{+}PC\underline{H_2}CH_2$, $^{2}J_{HP}$ = 12.0 Hz), 1.58 (m, 2H, $C\underline{H_2}$). ^{13}C NMR ($CDCl_3$) δ 138.2 (s, Ar, *p*-xy), 134.9 (m, Ar, *p*-PhP^{+}), 133.8 (dd, Ar, *m*-PhP^{+}, $^{3}J_{PC}$ = 9.1 Hz, $^{7}J_{P(O)C}$ = 2.0 Hz), 132.6 (m, Ar, *p*-PhP(O)), 131.4-130.4 (m, Ar, *o*-xy), 131.0 (dd, Ar, *m*-PhP(O), $^{3}J_{P(O)C}$ = 9.8 Hz, $^{7}J_{PC}$ = 3.0 Hz), 130.2 (dd, Ar, *o*-PhP^{+}, $^{2}J_{PC}$ = 12.8 Hz, $^{6}J_{P(O)C}$ = 2.5 Hz), 129.6-129.3 (m, Ar, *m*-xy), 129.2 (dd, Ar, *o*-PhP(O), $^{2}J_{P(O)C}$ = 12.1 Hz, $^{6}J_{PC}$ = 2.3 Hz), 127.8 (d, Ar, *i*-xy, $^{2}J_{PC}$ = 7.6 Hz), 116.9 (dd, Ar, *i*-PhP^{+}, $^{1}J_{PC}$ = 83.0 Hz, $^{5}J_{P(O)C}$ < 1.0 Hz), 116.7 (dd, Ar, *i*-PhP(O), $^{1}J_{P(O)C}$ = 82.3 Hz, $^{5}J_{PC}$ = 1.0 Hz), 32.2 (s, $Br\underline{C}H_2$), 29.7 (m, $^{+}P\underline{C}H_2xy$), 29.2 (m, $CH_2\underline{C}H_2P^{+}$), 21.1 (m, $P(O)\underline{C}H_2$), 15.1 (m, $CH_2\underline{C}H_2CH_2$). $^{31}P\{^{1}H\}$ NMR ($CDCl_3$) δ 32.0 (d, 1P, P(O), $^{4}J_{PP}$ = 27.5 Hz), 26.1 (d, 1P, P^{+}, $^{4}J_{PP}$ = 21.1 Hz).

*2,2',2''-(10-(4-((((Diphenylphosphoryl)methyl)diphenylphosphonio)methyl)benzyl)-1,4,7,10-tetraazacyclododecane-1,4,7-triyl)triacetatogadolinium(III) trifluoroacetate (**1**)*

(a) Synthesis of deprotected ligand: Following ***GP3***, compound **10** (250 mg, 376 µmol) in MeCN (15 mL) was added to a solution of DO3A-^{t}Bu$_3$·HBr (224 mg, 376 µmol) and K_2CO_3 (74 mg, 547 µmol) in MeCN (25 mL), and heated to reflux for 24 h. The crude material was deprotected using TFA (10 mL) over 12 h, dissolved in H_2O (100 mL), washed with $CHCl_3$ (3 × 50 mL), purified by means of reverse-phase HPLC, and the product lyophilised to afford the pure ligand as a colourless powder (258 mg, 71%). MALDI-MS for [M$^+$·tBu$_3$]: calculated *m/z* 1017.54, observed *m/z* 1017.53. MALDI-MS for [M$^+$]: calculated *m/z* 849.35, observed *m/z* 849.33. ^{1}H NMR (D_2O) δ 7.83-7.79 (m, 4H, Ar, *o*-PhP(O), $^3J_{HH}$ = 7.2 Hz, $^3J_{HP(O)}$ = 11.7 Hz), 7.76-7.51 [m, 6H: 7.72-7.68 (dd, 2H, Ar, *p*-PhP(O), $^3J_{HH}$ = 7.6 Hz, $^5J_{HP(O)}$ = 1.8 Hz), 7.59-7.53 (m, 4H, Ar, *m*-PhP(O), $^3J_{HH}$ = 8.1 Hz, $^4J_{HP(O)}$ = 2.1 Hz)], 7.36-7.23 (m, 10H, Ar, *o*-PhP$^+$, *p*-PhP$^+$, *m*-PhP$^+$), 7.11-7.05 (m, 2H, Ar, *o*-xy, $^3J_{HH}$ = 8.8 Hz, $^4J_{HP}$ = 5.7 Hz), 7.01-6.90 (m, 2H, Ar, *m*-xy, $^3J_{HH}$ = 8.4 Hz), 4.88 (dt, 2H, P(O)CH_2P$^+$, $^2J_{HP}$ = 46.3 Hz, $^2J_{HP(O)}$ = 13.7 Hz), 4.62 (t, 2H, $^+$PCH_2, $^2J_{HP}$ = 14.2 Hz), 4.20-3.0 [m, 24H: 4.02 (br s, 2H, xyCH_2N), 3.43 (br s, 6H, CH_2C(O)O), 3.16 (br s, 16H, NCH_2CH_2N). ^{13}C NMR (D_2O) δ 163.7 (q, C(O)O, $^1J_{CO}$ = 35.4 Hz), 138.4 (s, Ar, *p*-xy), 134.8 (m, Ar, *p*-PhP$^+$), 133.6 (dd, Ar, *m*-PhP$^+$, $^3J_{PC}$ = 7.5 Hz, $^5J_{P(O)C}$ = 2.6 Hz), 132.7 (m, Ar, *p*-PhP(O)), 131.5-130.7 (m, Ar, *o*-xy), 130.6 (dd, Ar, *m*-PhP(O), $^3J_{P(O)C}$ = 9.5 Hz, $^5J_{PC}$ = 3.3 Hz), 130.3 (dd, Ar, *o*-PhP$^+$, $^2J_{PC}$ = 13.1 Hz, $^4J_{P(O)C}$ = 4.0 Hz), 128.5 (dd, Ar, *o*-PhP(O), $^2J_{P(O)C}$ = 11.8 Hz, $^4J_{PC}$ = 3.9 Hz), 128.0-127.3 (m, Ar, *m*-xy), 126.7 (d, Ar, *i*-xy, $^2J_{PC}$ = 7.7 Hz), 117.2 (dd, Ar, *i*-PhP$^+$, $^1J_{PC}$ = 83.1 Hz, $^3J_{P(O)C}$ = 3.3 Hz), 116.1 (dd, Ar, *i*-PhP(O), $^1J_{P(O)C}$ = 83.2 Hz, $^3J_{PC}$ = 3.9 Hz), 57.2 (s, CH_2C(O)O), 50.7 (s, xyCH_2N), 49.0 (br s, NCH_2CH_2N), 32.2 (m, $^+$PCH_2xy), 31.0 (m, P(O)CH_2P$^+$). ^{31}P{^{1}H} NMR (D_2O) δ 24.5 (d, 1P, P(O), $^2J_{PP}$ = 81.9 Hz), 23.9 (d, 1P, P$^+$, $^2J_{PP}$ = 80.5 Hz).

*(b) Synthesis of complex **1***: According to ***GP5*** the purified deprotected ligand prepared above (236 mg, 245 µmol) was stirred with Gd_2O_3 (70 mg, 193 µmol) in H_2O, excess Gd_2O_3 removed, the solution lyophilised, and complex **1** was collected as a colourless powder (268 mg, 95%). Purity > 90% by HPLC. MALDI-TOF-MS for [M$^+$]: calculated *m/z* 1004.255, observed *m/z* 1004.248.

*2,2',2''-(10-(4-((((Diphenylphosphoryl)ethyl)diphenylphosphonio)methyl)benzyl)-1,4,7,10-tetraazacyclododecane-1,4,7-triyl)triacetatogadolinium(III) trifluoroacetate (**2**)*

(a) Synthesis of deprotected ligand: Following ***GP3***, compound **11** (752 mg, 1.11 mmol) in MeCN (20 mL) was added to a solution of DO3A-^{t}Bu$_3$·HBr (694 mg, 1.16 mmol) and K_2CO_3 (240 mg, 1.74 mmol) in MeCN (30 mL), and heated to reflux for 24 h. The crude material was deprotected using TFA (10 mL) over 12 h, dissolved in H_2O (100 mL), washed with $CHCl_3$ (3 × 50 mL), purified by means of reverse-phase HPLC, and the product lyophilised to afford the pure ligand as a colourless powder (715 mg, 66%). MALDI-MS for [M·^{t}Bu$_3$]$^+$: calculated *m/z* 1031.56, observed *m/z* 1031.54. MALDI-MS for [M$^+$]: calculated *m/z* 863.37, observed *m/z* 863.34.^{1}H NMR (D_2O) δ 7.87-7.76 (m, 4H, Ar, *o*-PhP(O), $^3J_{HH}$ = 7.7 Hz, $^3J_{HP(O)}$ = 12.2 Hz), 7.70-7.61 (m, 2H, Ar, *p*-PhP(O), $^3J_{HH}$ = 8.4 Hz), 7.52-7.28 (m, 14H, Ar, *m*-PhP(O), *o*-PhP$^+$, *p*-PhP$^+$, *m*-PhP$^+$, $^3J_{HH}$ = 8.0 Hz), 7.19-7.13 (br d, 2H, Ar, *o*-xy, $^3J_{HH}$ = 7.7 Hz), 7.08 (d, 2H, Ar, *m*-xy, $^3J_{HH}$ = 7.7 Hz), 4.49 (d, 2H, $^+$PCH_2xy, $^2J_{HP}$ = 15.0 Hz), 4.30-3.0 [m, 26H: 4.11 (br s, 2H, CH_2NH_2), 3.41 (br s, 6H, CH_2C(O)O), 3.16 (br s, 16H, NCH_2CH_2N), 3.08 (br s, 2H, P(O)CH_2)], 2.87-2.71 (m, 2H, $^+$PCH_2CH_2, $^2J_{HP}$ = 22.3 Hz). ^{13}C NMR (D_2O) δ 164.1 (q, C(O)O, $^1J_{CO}$ = 35.9 Hz), 138.2 (s, Ar, *p*-xy), 135.1 (m, Ar, *p*-PhP$^+$), 134.1 (d, Ar, *m*-PhP$^+$, $^3J_{PC}$ = 8.5 Hz), 132.6 (m, Ar, *p*-PhP(O)), 131.9-131.3 (m, Ar, *o*-xy), 130.8 (br d, Ar, *m*-PhP(O), $^3J_{P(O)C}$ = 8.7 Hz), 130.0 (br d, Ar, *o*-PhP$^+$, $^2J_{PC}$ = 14.1 Hz), 128.7 (dd, Ar, *o*-PhP(O), $^2J_{P(O)C}$ = 12.4 Hz, $^5J_{PC}$ = 2.1 Hz), 126.0-125.3 (m, Ar, *i*-xy, *m*-xy), 115.7 (m, Ar, *i*-PhP$^+$, $^1J_{PC}$ = 81.6 Hz), 114.8 (dd, Ar, *i*-PhP(O), $^1J_{P(O)C}$ = 80.8 Hz, $^4J_{PC}$ = 2.1 Hz), 57.2 (s, CH_2C(O)O), 49.1 (br s, NCH_2CH_2N), 46.1 (s, xyCH_2N), 31.2 (m, $^+$PCH_2xy), 27.0 (m, P(O)CH_2). ^{31}P{^{1}H} NMR (D_2O) δ 31.9 (d, 1P, P(O), $^3J_{PP}$ = 44.7 Hz), 25.4 (d, 1P, P$^+$, $^3J_{PP}$ = 43.1Hz).

*(b) Synthesis of complex **2***: According to ***GP5*** the purified deprotected ligand prepared above (629 mg, 644 µmol) was stirred with Gd_2O_3 (175 mg, 483 µmol) in H_2O, excess Gd_2O_3 removed, the solution lyophilised, and complex **2** was collected as a colourless powder (689 mg, 92%). Purity > 95% by HPLC. MALDI-TOF-MS for [M^+]: calculated *m/z* 1018.270, observed *m/z* 1018.234.

*2,2',2''-(10-(4-((((Diphenylphosphoryl)propyl)diphenylphosphonio)methyl)benzyl)-1,4,7,10-tetraazacyclododecane-1,4,7-triyl)triacetatogadolinium(III) trifluoroacetate (**3**)*
(a) Synthesis of deprotected ligand: Following ***GP3***, compound **12** (221 mg, 318 µmol) in MeCN (10 mL) was added to a solution of DO3A-^{t}Bu$_3$·HBr (189 mg, 318 µmol) and K_2CO_3 (65 mg, 472 µmol) in MeCN (20 mL), and heated to reflux for 24 h. The crude material was deprotected using TFA (6 mL) over 12 h, dissolved in H_2O (100 mL), washed with $CHCl_3$ (3 × 50 mL), purified by means of reverse-phase HPLC, and the product lyophilised to afford the pure ligand as a colourless powder (243 mg, 77%). MALDI-MS for [M^+·tBu$_3$]: calculated *m/z* 1045.57, observed *m/z* 1045.64. MALDI-MS for [M^+]: calculated *m/z* 877.39, observed *m/z* 877.40. ^{1}H NMR (D_2O) δ 7.76-7.67 (m, 4H, Ar, *o*-PhP(O), $^3J_{HH}$ = 7.9 Hz, $^3J_{HP(O)}$ = 12.2 Hz), 7.64-7.59 (m, 6H, Ar, *p*-PhP(O), *m*-PhP(O), $^3J_{HH}$ = 8.0 Hz, $^4J_{HP(O)}$ = 1.4 Hz), 7.51-7.43 (m, 4H, Ar, *o*-PhP$^+$, $^3J_{HH}$ = 7.6 Hz), 7.39-7.22 [m, 6H: 7.37-7.34 (m, 2H, Ar, *p*-PhP$^+$, $^3J_{HH}$ = 7.8 Hz), 7.31-7.25 (m, 4H, Ar, *m*-PhP$^+$, $^3J_{HH}$ = 7.9 Hz)], 7.16 (d, 2H, Ar, *o*-xy, $^3J_{HH}$ = 8.3 Hz), 7.07 (d, 2H, Ar, *m*-xy, $^3J_{HH}$ = 7.9 Hz), 4.37 (d, 2H, $^+$PCH$_2$xy, $^2J_{HP}$ = 15.0 Hz), 4.20-3.00 [m, 24H: 4.06 (br s, 2H, xyCH$_2$N), 3.40 (br s, 6H, CH$_2$C(O)O), 3.12 (br s, 16H, NCH$_2$CH$_2$N), 2.62 (br m, 2H, P(O)CH$_2$), 2.45 (m, 2H, $^+$PCH$_2$CH$_2$, $^2J_{HP}$ = 12.6 Hz), 1.58 (m, 2H, CH$_2$). ^{13}C NMR (D_2O) δ 162.8 (q, C(O), $^1J_{CO}$ = 36.2 Hz), 139.3 (s, Ar, *p*-xy), 134.8 (m, Ar, *p*-PhP$^+$), 133.4 (br d, Ar, *m*-PhP$^+$, $^3J_{PC}$ = 8.4 Hz), 132.1 (m, Ar, *p*-PhP(O)), 131.2-130.3 (m, Ar, *o*-xy), 130.2 (br d, Ar, *m*-PhP(O), $^3J_{P(O)C}$ = 9.3 Hz), 129.7 (br d, Ar, *o*-PhP$^+$, $^2J_{PC}$ = 13.4 Hz), 128.8 (br d, Ar, *o*-PhP(O), $^2J_{P(O)C}$ = 12.7 Hz), 128.1-126.0 (m, Ar, *m*-xy, *i*-xy), 116.5 (br d, Ar, *i*-PhP$^+$, $^1J_{PC}$ = 87.1 Hz), 116.0 (br d, Ar, *i*-PhP(O), $^1J_{P(O)C}$ = 85.4 Hz), 57.7 (s, CH$_2$C(O)O), 49.5 (br s, NCH$_2$CH$_2$N), 48.6 (s, xyCH$_2$N), 29.8 (m, $^+$PCH$_2$xy), 29.1 (m, CH$_2$CH$_2$P$^+$), 21.2 (m, P(O)CH$_2$), 15.2 (m, CH$_2$CH$_2$CH$_2$). ^{31}P{^{1}H} NMR (D_2O) δ 31.5 (d, 1P, P(O), $^4J_{PP}$ = 24.6 Hz), 25.6 (d, 1P, P$^+$, $^4J_{PP}$ = 23.7 Hz).

*(b) Synthesis of complex **3***: According to ***GP5*** the purified deprotected ligand prepared above (223 mg, 225 µmol) was stirred with Gd_2O_3 (61 mg, 169 µmol) in H_2O, excess Gd_2O_3 removed, the solution lyophilised, and complex **3** was collected as a colourless powder (242 mg, 91%). Purity > 95% by HPLC. MALDI-TOF-MS for [M^+]: calculated *m/z* 1032.286, observed *m/z* 1032.313.

*2,2',2''-(10-(2-((4-((((Diphenylphosphoryl)methyl)diphenylphosphonio)methyl)benzyl)amino)-2-oxoethyl)-1,4,7,10-tetraazacyclododecane-1,4,7-triyl)triacetatogadolinium(III) trifluoroacetate (**4**)*
(a) Synthesis of deprotected ligand: Following ***GP4***, compound **10** (418 mg, 0.63 mmol) and NaN_3 (207 mg, 3.18 mmol) were stirred in DMF (15 mL) for 72 h. The DMF was removed under reduced pressure and the product extracted using $CHCl_3$, affording 338 mg (86%) of the azido-intermediate. This intermediate (254 mg, 0.41 mmol) was reduced under H_2 in the presence of 10 mol% Pd/C (20 mg) in MeOH (20 mL) for 6 h. The catalyst was removed by filtration through a Celite pad and the solvent removed under reduced pressure, affording 193 mg (79%) of the amine intermediate. The amine (140 mg, 232 µmol) in DMF (5 mL) was added to DOTA-^{t}Bu$_3$ (141 mg, 247 µmol), HATU (114 mg, 299 µmol), and NMM (110 µL, 998 µmol) in DMF (10 mL) and stirred for 24 h. The DMF was removed under nitrogen, and the residue deprotected over 12 h using neat TFA (7 mL). Reversed-phase HPLC purification of the crude ligand, and subsequent lyophilisation, afforded the pure ligand (137 mg, 58%). MALDI-MS for [MH^+·tBu$_3$]: calculated *m/z* 1074.56, observed *m/z* 1075.54. MALDI-MS for [M^+]: calculated *m/z* 906.38, observed *m/z* 906.37. ^{1}H NMR (D_2O) δ 7.80-7.75 (m, 4H, Ar, *o*-PhP(O), $^3J_{HH}$ = 7.2 Hz, $^3J_{HP(O)}$ = 11.5 Hz), 7.69-7.47 [m, 6H: 7.68-7.63 (dd, 2H, Ar, *p*-PhP(O), $^3J_{HH}$ = 7.7 Hz, $^5J_{HP(O)}$ = 1.9 Hz), 7.59-7.50 (m, 4H, Ar, *m*-PhP(O), $^3J_{HH}$ = 8.2 Hz, $^4J_{HP(O)}$ = 1.9 Hz)], 7.32-7.21 (m, 10H, Ar, *o*-PhP$^+$, *p*-PhP$^+$, *m*-PhP$^+$), 7.10-7.7.04 (m, 2H, Ar, *o*-xy, $^3J_{HH}$ = 8.9 Hz, $^4J_{HP}$ = 6.1 Hz), 7.00-6.87 (m,

2H, Ar, *m*-xy, $^{3}J_{HH}$ = 8.2 Hz), 4.89 (dt, 2H, P(O)CH_2P^+, $^{2}J_{HP}$ = 47.2 Hz, $^{2}J_{HP(O)}$ = 13.9 Hz), 4.57 (t, 2H, $^{+}PCH_2$, $^{2}J_{HP}$ = 14.0 Hz), 4.20-3.0 [m, 26H: 3.99 (br s, 2H, xyCH_2N), 3.66 (br s, 2H, NCH_2C(O)), 3.37 (br s, 6H, NCH_2C(O)O), 3.22 (br s, 16H, NCH_2CH_2N)]. ^{13}C NMR (D_2O) *δ* 162.8 (q, C(O), $^{1}J_{CO}$ = 35.9 Hz), 138.7 (s, Ar, *p*-xy), 134.6 (m, Ar, *p*-PhP$^+$), 133.4 (dd, Ar, *m*-PhP$^+$, $^{3}J_{PC}$ = 7.6 Hz, $^{5}J_{P(O)C}$ = 2.5 Hz), 132.4 (m, Ar, *p*-PhP(O)), 131.3-130.9 (m, Ar, *o*-xy), 130.6 (dd, Ar, *m*-PhP(O), $^{3}J_{P(O)C}$ = 9.6 Hz, $^{5}J_{PC}$ = 3.2 Hz), 130.1 (dd, Ar, *o*-PhP$^+$, $^{2}J_{PC}$ = 12.9 Hz, $^{4}J_{P(O)C}$ = 4.2 Hz), 128.5 (dd, Ar, *o*-PhP(O), $^{2}J_{P(O)C}$ = 11.7 Hz, $^{4}J_{PC}$ = 3.8 Hz), 128.3-127.9 (m, Ar, *m*-xy), 126.5 (d, Ar, *i*-xy, $^{2}J_{PC}$ = 7.8 Hz), 116.8 (dd, Ar, *i*-PhP$^+$, $^{1}J_{PC}$ = 82.5 Hz, $^{3}J_{P(O)C}$ = 3.2 Hz), 115.8 (dd, Ar, *i*-PhP(O), $^{1}J_{P(O)C}$ = 82.8 Hz, $^{3}J_{PC}$ = 4.0 Hz), 54.9 (s, CH_2C(O)N), 53.3 (s, CH_2C(O)O), 50.8-48.9 (br m, NCH_2CH_2N), 42.2 (s, xyCH_2NH), 32.1 (m, $^{+}PCH_2$xy), 31.2 (m, P(O)CH_2P^+). $^{31}P\{^{1}H\}$ NMR (D_2O) *δ* 24.3 (d, 1P, P(O), $^{2}J_{PP}$ = 82.7 Hz), 23.9 (d, 1P, P$^+$, $^{2}J_{PP}$ = 80.3 Hz).

*(b) Synthesis of complex **4***: According to ***GP5*** the purified deprotected ligand prepared above (125 mg, 123 µmol) was stirred with Gd_2O_3 (36 mg, 99 µmol) in H_2O, excess Gd_2O_3 removed, the solution lyophilised, and complex **4** collected as a colourless powder (138 mg, 93%). Purity > 90% by HPLC. MALDI-MS for [M$^+$]: calculated *m/z* 1061.276, observed *m/z* 1061.264. MALDI-MS for [M+Na]$^{2+}$: calculated *m/z* 542.133, observed *m/z* 542.150.

*2,2',2''-(10-(2-((4-(((2-(Diphenylphosphoryl)ethyl)diphenylphosphonio)methyl)benzyl)amino)-2-oxoethyl)-1,4,7,10-tetraazacyclododecane-1,4,7-triyl)triacetatogadolinium(III) trifluoroacetate (**5**)*
(a) Synthesis of deprotected ligand: Following ***GP4***, compound **11** (1.01 g, 1.49 mmol) and NaN_3 (293 mg, 4.51 mmol) were stirred in DMF (30 mL) for 72 h. The DMF was removed under reduced pressure and the product extracted using $CHCl_3$, affording 832 mg (87%) of the azide intermediate. This intermediate (345 mg, 0.54 mmol) was reduced under H_2 in the presence of 10 mol% Pd/C (30 mg) in MeOH (15 mL) for 6 h. The catalyst was removed by filtration through a Celite pad and the solvent removed under reduced pressure, affording 311 mg (94%) of the amine intermediate. The amine (221 mg, 359 µmol) in DMF (5 mL) was added to DOTA-$^{t}Bu_3$ (210 mg, 366 µmol), HATU (172 mg, 452 µmol), and NMM (170 µL, 1.55 mmol) in DMF (15 mL) and stirred for 24 h. The DMF was removed under nitrogen, and the residue deprotected over 12 h using neat TFA (8 mL). Reversed-phase HPLC purification of the crude ligand, and subsequent lyophilisation, afforded the pure ligand (279 mg, 75%). MALDI-MS for [M·tBu_3+Na]$^{2+}$: calculated *m/z* 555.78, observed *m/z* 555.83. MALDI-MS for [M$^+$]: calculated *m/z* 920.39, observed *m/z* 920.42. ^{1}H NMR (D_2O) *δ* 7.86-7.72 (m, 4H, Ar, *o*-PhP(O), $^{3}J_{HH}$ = 7.8 Hz, $^{3}J_{HP(O)}$ = 11.6 Hz), 7.69-7.60 (m, 2H, Ar, *p*-PhP(O), $^{3}J_{HH}$ = 7.9 Hz), 7.51-7.28 (m, 14H, Ar, *m*-PhP(O), *o*-PhP$^+$, *p*-PhP$^+$, *m*-PhP$^+$, $^{3}J_{HH}$ = 7.8 Hz), 7.16-7.10 (br d, 2H, Ar, *o*-xy, $^{3}J_{HH}$ = 8.1 Hz), 7.06-7.00 (d, 2H, Ar, *m*-xy, $^{3}J_{HH}$ = 7.6 Hz), 4.52 (d, 2H, $^{+}PCH_2$xy, $^{2}J_{HP}$ = 14.5 Hz), 4.20-3.15 [m, 26H: 4.06 (m, 2H, CH_2NH_2), 3.69 (br s, 2H, NCH_2C(O)), 3.40 (br s, 6H, NCH_2C(O)O), 3.22 (br s, 16H, NCH_2CH_2N)], 3.09-2.98 (br m, 2H, P(O)CH_2), 2.85-2.70 (m, 2H, $^{+}PCH_2CH_2$, $^{2}J_{HP}$ = 20.6 Hz). ^{13}C NMR (D_2O) *δ* 162.6 (q, C(O), $^{1}J_{CO}$ = 36.2 Hz), 138.7 (s, Ar, *p*-xy), 135.0 (m, Ar, *p*-PhP$^+$), 133.8 (d, Ar, *m*-PhP$^+$, $^{3}J_{PC}$ = 9.1 Hz), 131.8 (m, Ar, *p*-PhP(O)), 131.4-130.9 (m, Ar, *o*-xy), 130.5 (br d, Ar, *m*-PhP(O), $^{3}J_{P(O)C}$ = 9.7 Hz), 129.6 (br d, Ar, *o*-PhP$^+$, $^{2}J_{PC}$ = 14.8 Hz), 128.2 (dd, Ar, *o*-PhP(O), $^{2}J_{P(O)C}$ = 12.3 Hz, $^{5}J_{PC}$ = 1.9 Hz), 126.2-125.4 (m, Ar, *i*-xy, *m*-xy), 116.1 (m, Ar, *i*-PhP$^+$, $^{1}J_{PC}$ = 83.9 Hz), 115.2 (dd, Ar, *i*-PhP(O), $^{1}J_{P(O)C}$ = 81.7 Hz, $^{4}J_{PC}$ = 2.3 Hz), 54.9 (s, CH_2C(O)N), 53.3 (s, CH_2C(O)O), 50.8-48.9 (br m, NCH_2CH_2N), 42.1 (s, xyCH_2N), 31.4 (m, $^{+}PCH_2$xy), 27.1 (m, P(O)CH_2). $^{31}P\{^{1}H\}$ NMR (D_2O) *δ* 32.2 (d, 1P, P(O), $^{3}J_{PP}$ = 46.1 Hz), 25.6 (d, 1P, P$^+$, $^{3}J_{PP}$ = 45.4Hz).

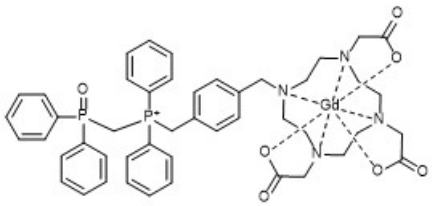
*(b) Synthesis of complex **5***: According to ***GP5*** the purified deprotected ligand prepared above (261 mg, 252 µmol) was stirred with Gd_2O_3 (72 mg, 199 µmol) in H_2O, excess Gd_2O_3 removed, the solution lyophilised, and complex **5** was collected as a colourless powder (297 mg, 96%). Purity > 95% by HPLC. MALDI-MS for [M$^+$]: calculated *m/z* 1075.292, observed *m/z* 1075.272. MALDI-MS for [M+Na]$^{2+}$: calculated *m/z* 549.141, observed *m/z* 549.140.

*2,2',2''-(10-(2-((4-(((3-(Diphenylphosphoryl)propyl)diphenylphosphonio)methyl)benzyl)amino)-2-oxoethyl)-1,4,7,10-tetraazacyclododecane-1,4,7-triyl)triacetatogadolinium(III) trifluoroacetate (**6**)*

(a) Synthesis of deprotected ligand: Following ***GP4***, compound **12** (282 mg, 0.41 mmol) and NaN_3 (96 mg, 1.48 mmol) were stirred in DMF (12 mL) for 72 h. The DMF was removed under reduced pressure and the product extracted using $CHCl_3$, affording 246 mg (92%) of the azide intermediate. This intermediate (166 mg, 0.25 mmol) was reduced under H_2 in the presence of 10 mol% Pd/C (20 mg) in MeOH (20 mL) for 6 h. The catalyst was removed by filtration through a Celite pad and the solvent removed under reduced pressure, affording 138 mg (86%) of the amine intermediate. The amine (131 mg, 209 µmol) in DMF (5 mL) was added to DOTA-^{t}Bu$_3$ (121 mg, 211 µmol), HATU (100 mg, 263 µmol), and NMM (95 µL, 864 µmol) in DMF (30 mL) and stirred for 24 h. The DMF was removed under nitrogen, and the residue deprotected over 12 h using neat TFA (10 mL). Reversed-phase HPLC purification of the crude ligand, and subsequent lyophilisation, afforded the pure ligand (111 mg, 51%). MALDI-MS for [M^+·tBu$_3$]: calculated *m/z* 1102.59, observed *m/z* 1102.58. MALDI-MS for [M^+]: calculated *m/z* 934.41, observed *m/z* 934.42. ^{1}H NMR (D_2O) δ 7.72-7.65 (m, 4H, Ar, *o*-PhP(O), $^3J_{HH}$ = 8.2 Hz, $^3J_{HP(O)}$ = 12.0 Hz), 7.62-7.56 (m, 6H, Ar, *p*-PhP(O), *m*-PhP(O), $^3J_{HH}$ = 8.3 Hz, $^4J_{HP(O)}$ = 1.8 Hz), 7.46-7.40 (m, 4H, Ar, *o*-PhP$^+$, $^3J_{HH}$ = 8.2 Hz), 7.36-7.17 [m, 6H: 7.32-7.28 (m, 2H, Ar, *p*-PhP$^+$, $^3J_{HH}$ = 8.1 Hz), 7.26-7.21 (m, 4H, Ar, *m*-PhP$^+$, $^3J_{HH}$ = 8.1 Hz)], 7.14 (d, 2H, Ar, *o*-xy, $^3J_{HH}$ = 8.0 Hz), 7.02 (d, 2H, Ar, *m*-xy, $^3J_{HH}$ = 7.6 Hz), 4.44 (d, 2H, $^+$PCH$_2$xy, $^2J_{HP}$ = 14.7 Hz), 4.20-3.00 [m, 26H: 4.11 (m, 2H, xyCH$_2$N), 3.72 (br s, 2H, NCH$_2$C(O)), 3.41 (br s, 6H, NCH$_2$C(O)O), 3.24 (br s, 16H, NCH$_2$CH$_2$N)], 2.64 (br m, 2H, P(O)CH$_2$), 2.49 (m, 2H, $^+$PCH$_2$CH$_2$, $^2J_{HP}$ = 12.9 Hz), 1.58 (m, 2H, CH$_2$). ^{13}C NMR (D_2O) δ 163.1 (q, C(O), $^1J_{CO}$ = 37.1 Hz), 138.9 (s, Ar, *p*-xy), 134.7 (m, Ar, *p*-PhP$^+$), 133.6 (dd, Ar, *m*-PhP$^+$, $^3J_{PC}$ = 8.4 Hz, $^7J_{P(O)C}$ = 2.2 Hz), 132.3 (m, Ar, *p*-PhP(O)), 131.5-130.6 (m, Ar, *o*-xy), 130.3 (br d, Ar, *m*-PhP(O), $^3J_{P(O)C}$ = 9.0 Hz), 129.7 (br d, Ar, *o*-PhP$^+$, $^2J_{PC}$ = 12.3 Hz), 128.8 (br d, Ar, *o*-PhP(O), $^2J_{P(O)C}$ = 12.3 Hz), 128.1-127.8 (m, Ar, *m*-xy), 126.3 (d, Ar, *i*-xy, $^2J_{PC}$ = 7.7 Hz), 116.2 (br d, Ar, *i*-PhP$^+$, $^1J_{PC}$ = 84.1 Hz), 115.8 (br d, Ar, *i*-PhP(O), $^1J_{P(O)C}$ = 80.3 Hz), 55.5 (s, CH$_2$C(O)N), 53.7 (s, CH$_2$C(O)O), 51.2-49.1 (br m, NCH$_2$CH$_2$N), 47.4 (s, CH$_2$NH$_2$), 29.6 (m, $^+$PCH$_2$xy), 29.3 (m, CH$_2$CH$_2$P$^+$), 21.0 (m, P(O)CH$_2$), 15.0 (m, CH$_2$CH$_2$CH$_2$). ^{31}P{^{1}H} NMR (D_2O) δ 31.6 (d, 1P, P(O), $^4J_{PP}$ = 25.8 Hz), 25.7 (d, 1P, P$^+$, $^4J_{PP}$ = 24.9 Hz).

*(b) Synthesis of complex **6***: According to ***GP5*** the purified deprotected ligand (102 mg, 97 µmol) was stirred with Gd_2O_3 (30 mg, 83 µmol) in H_2O, excess Gd_2O_3 removed, the solution lyophilised, and complex **6** was collected as a colourless powder (118 mg, 98%). Purity > 95% by HPLC. MALDI-MS for [M^+]: calculated *m/z* 1089.307, observed *m/z* 1089.264.

Mass spectra - experimental and calculated (for the monocation, $[M]^+$)



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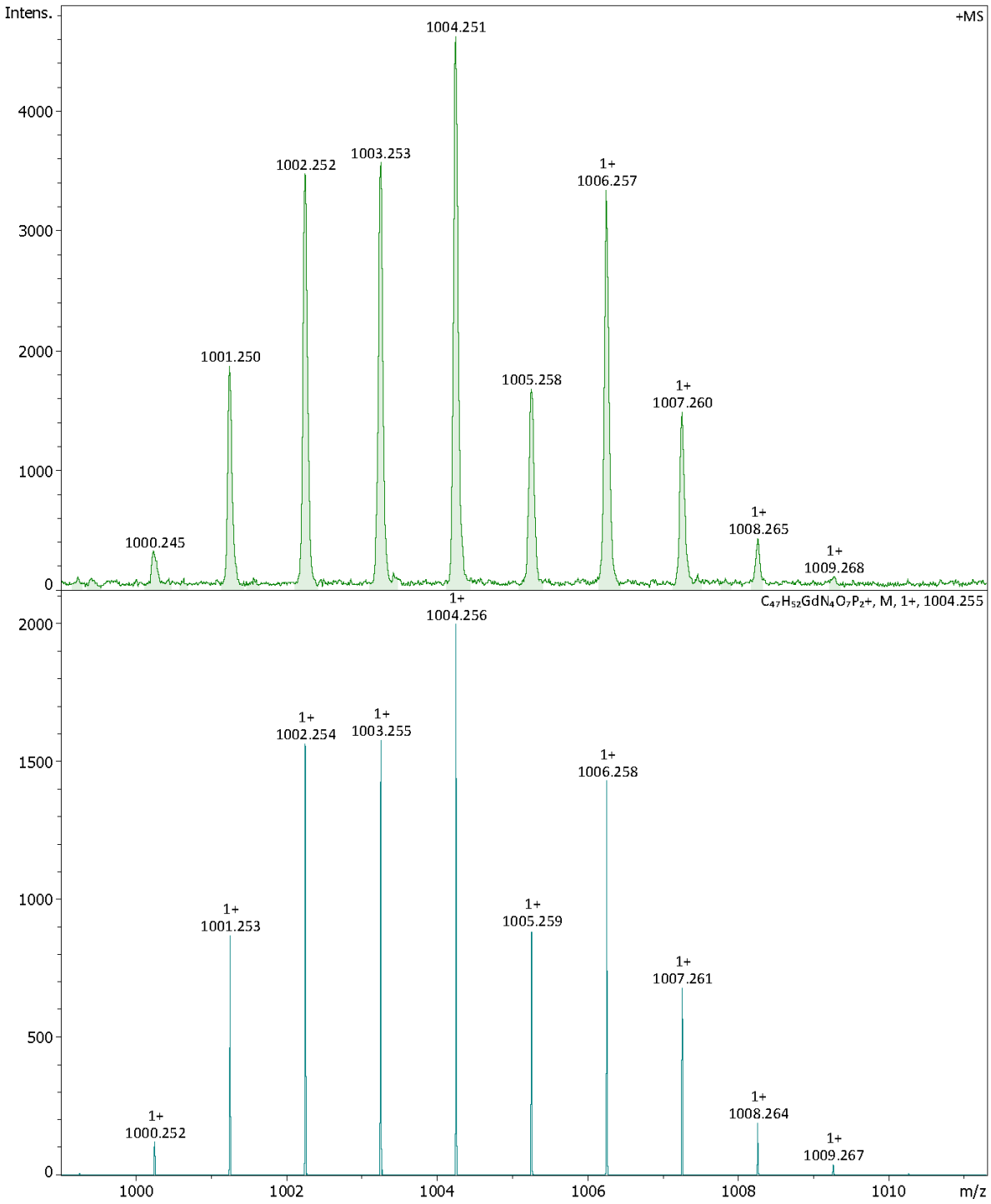

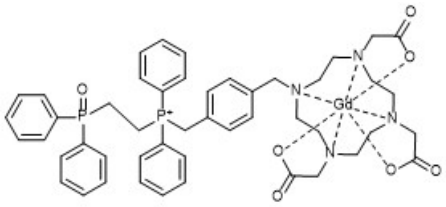

Chemical Formula: $C_{48}H_{54}GdN_4O_7P_2^+$
Exact Mass: 1018.27

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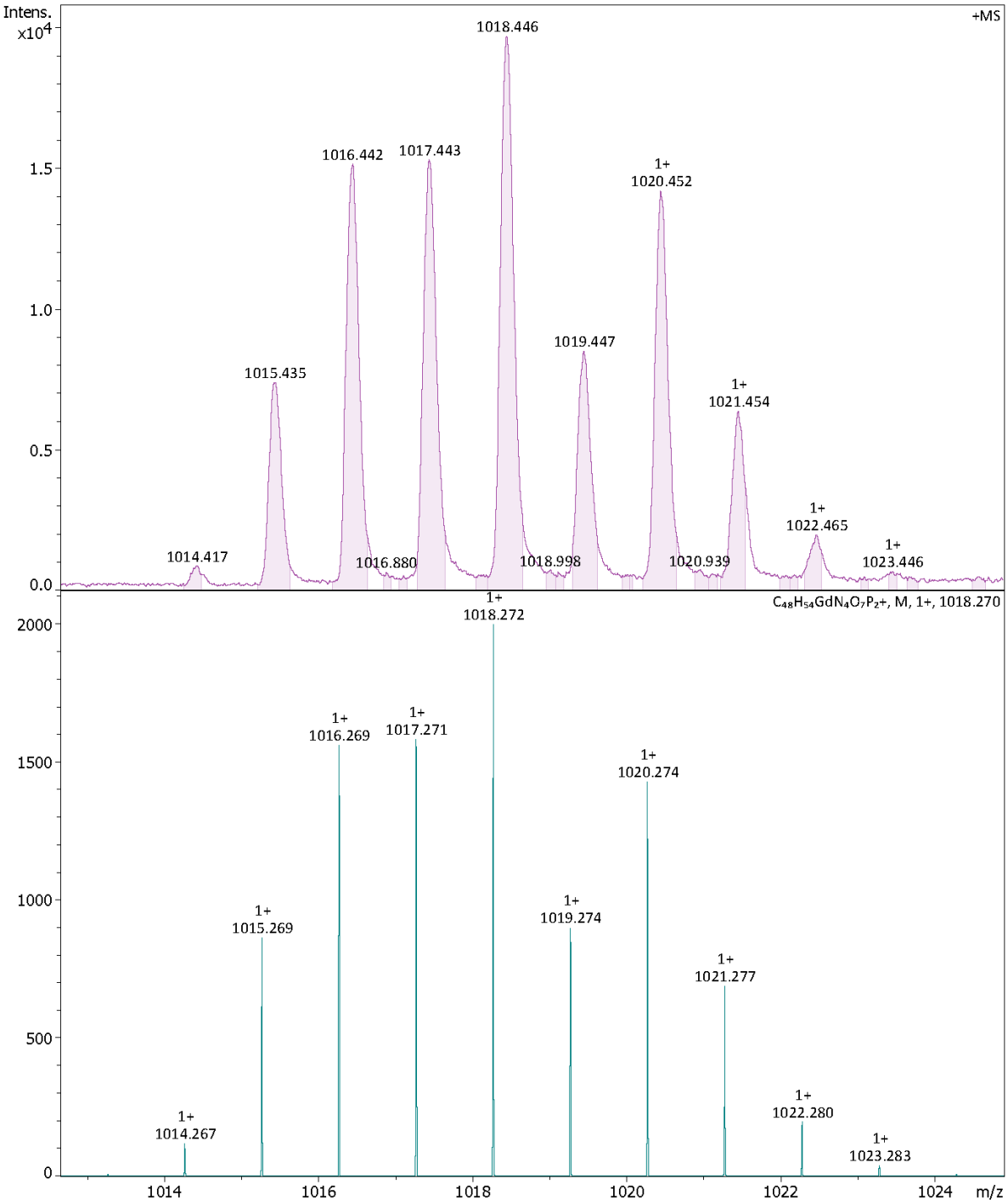

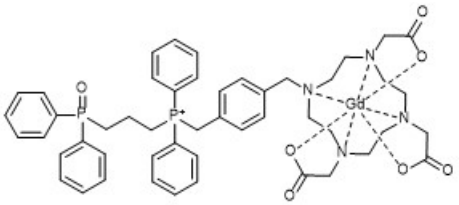

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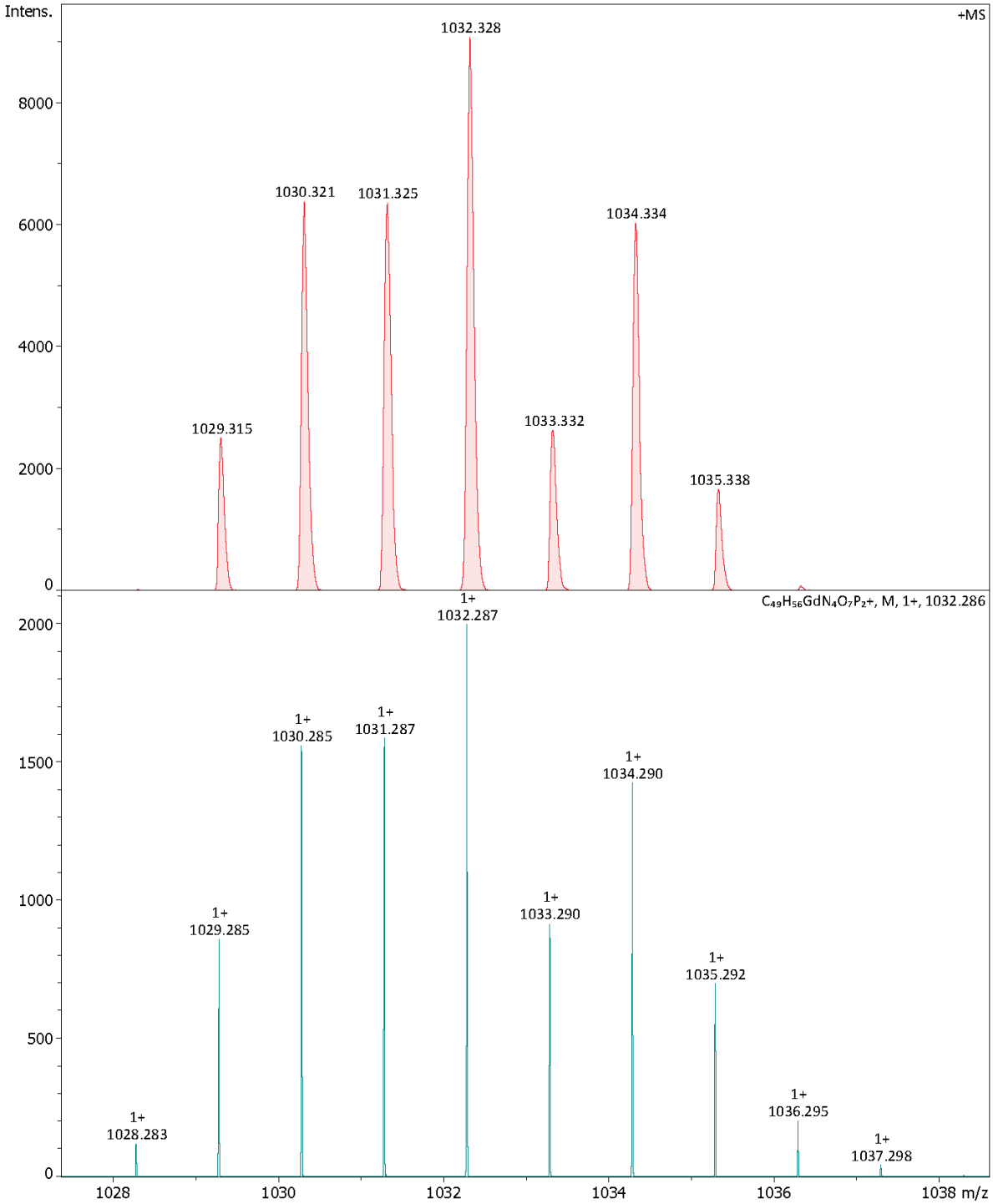

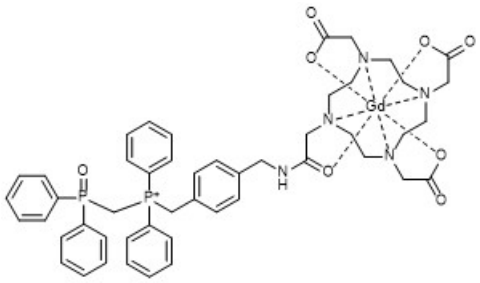

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Exact Mass: 1061.28

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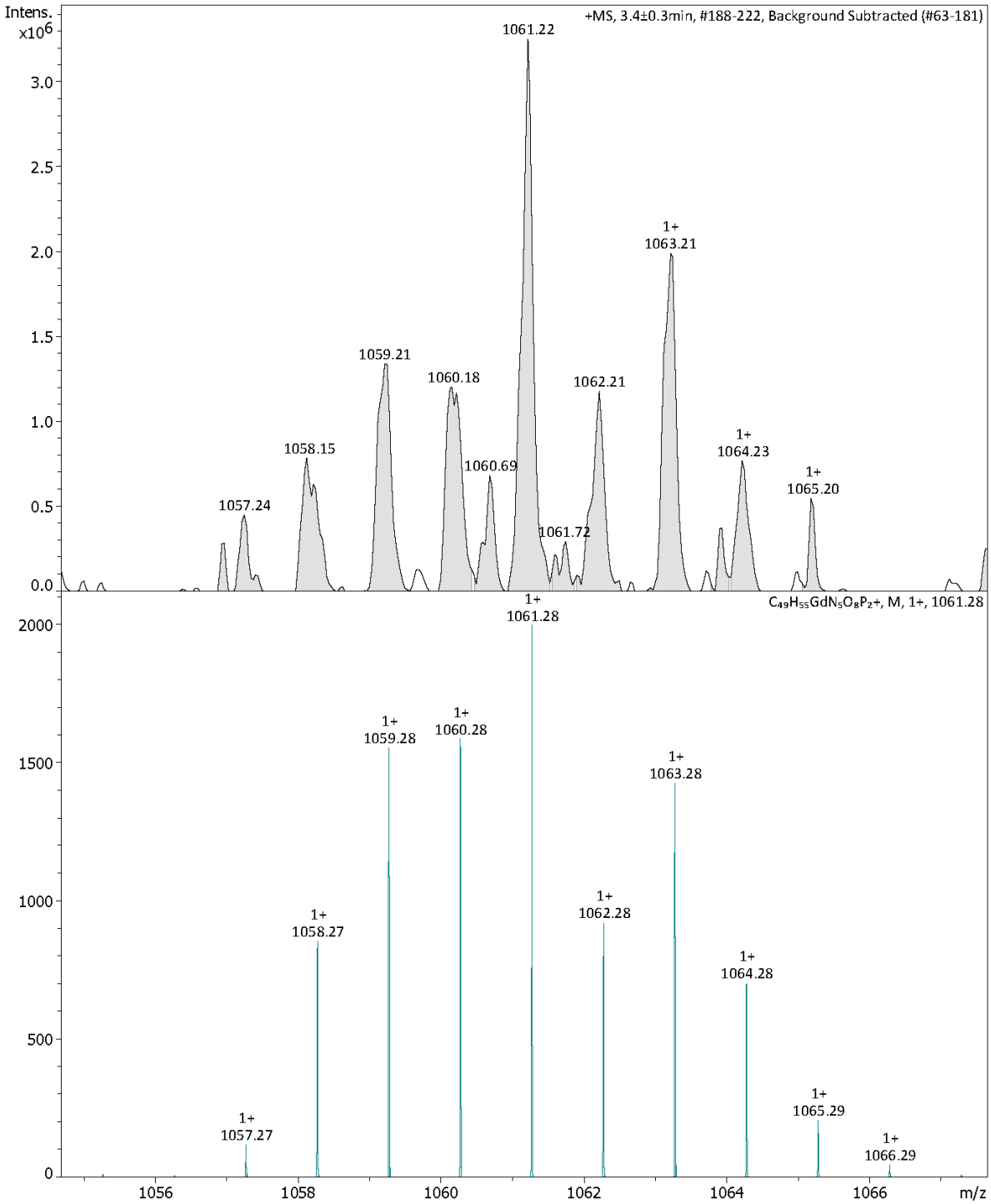

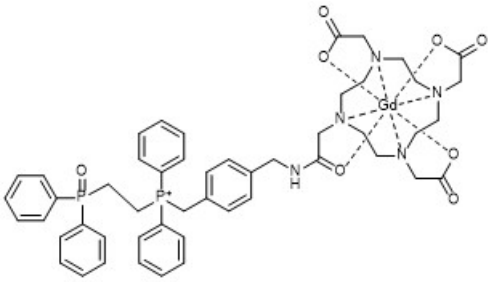
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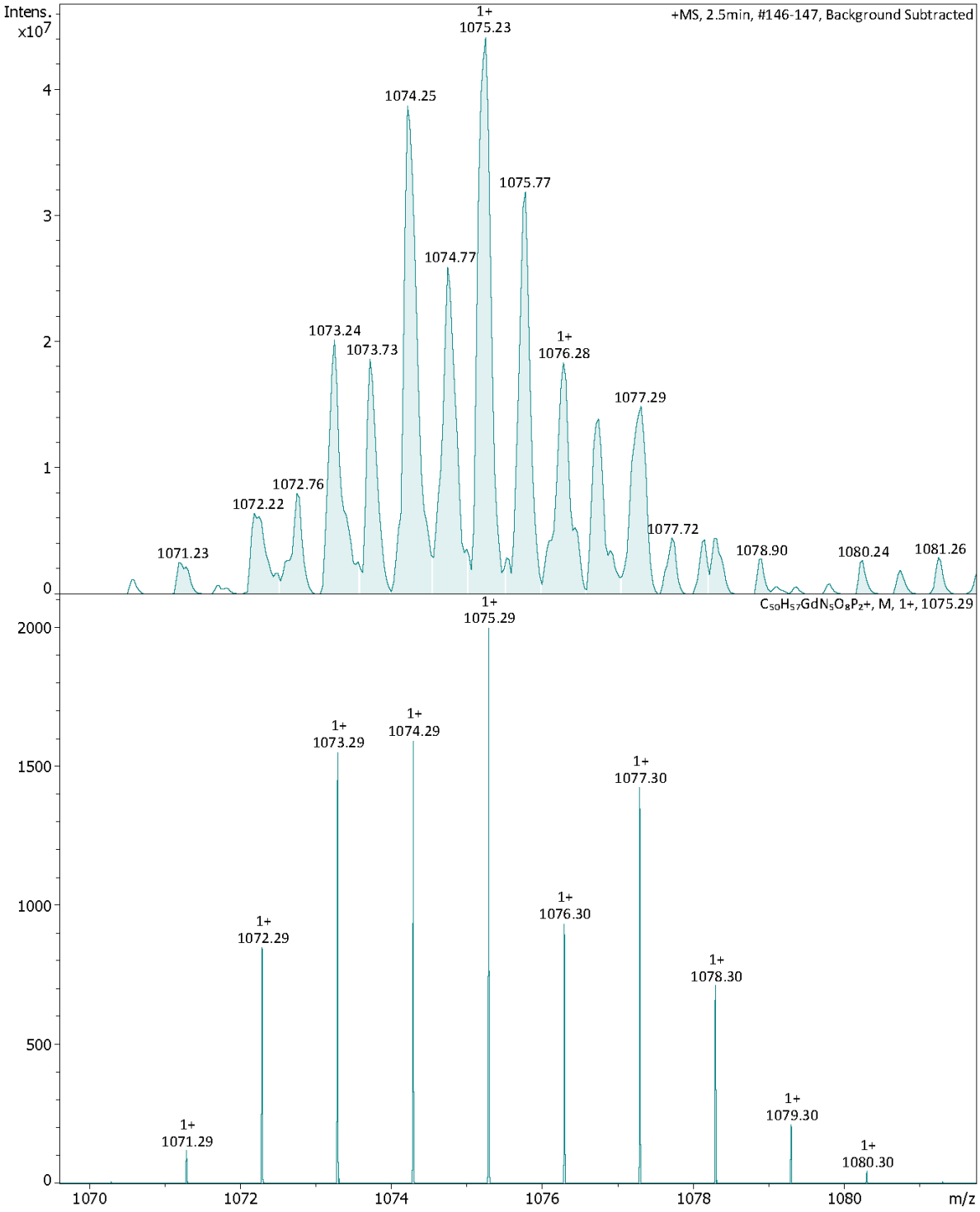
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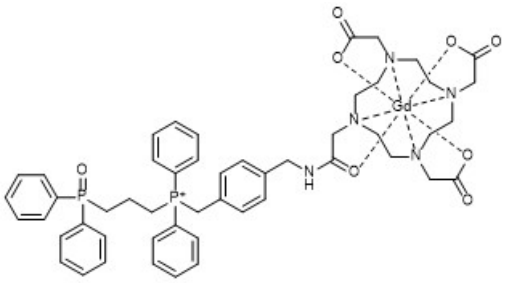
m/z



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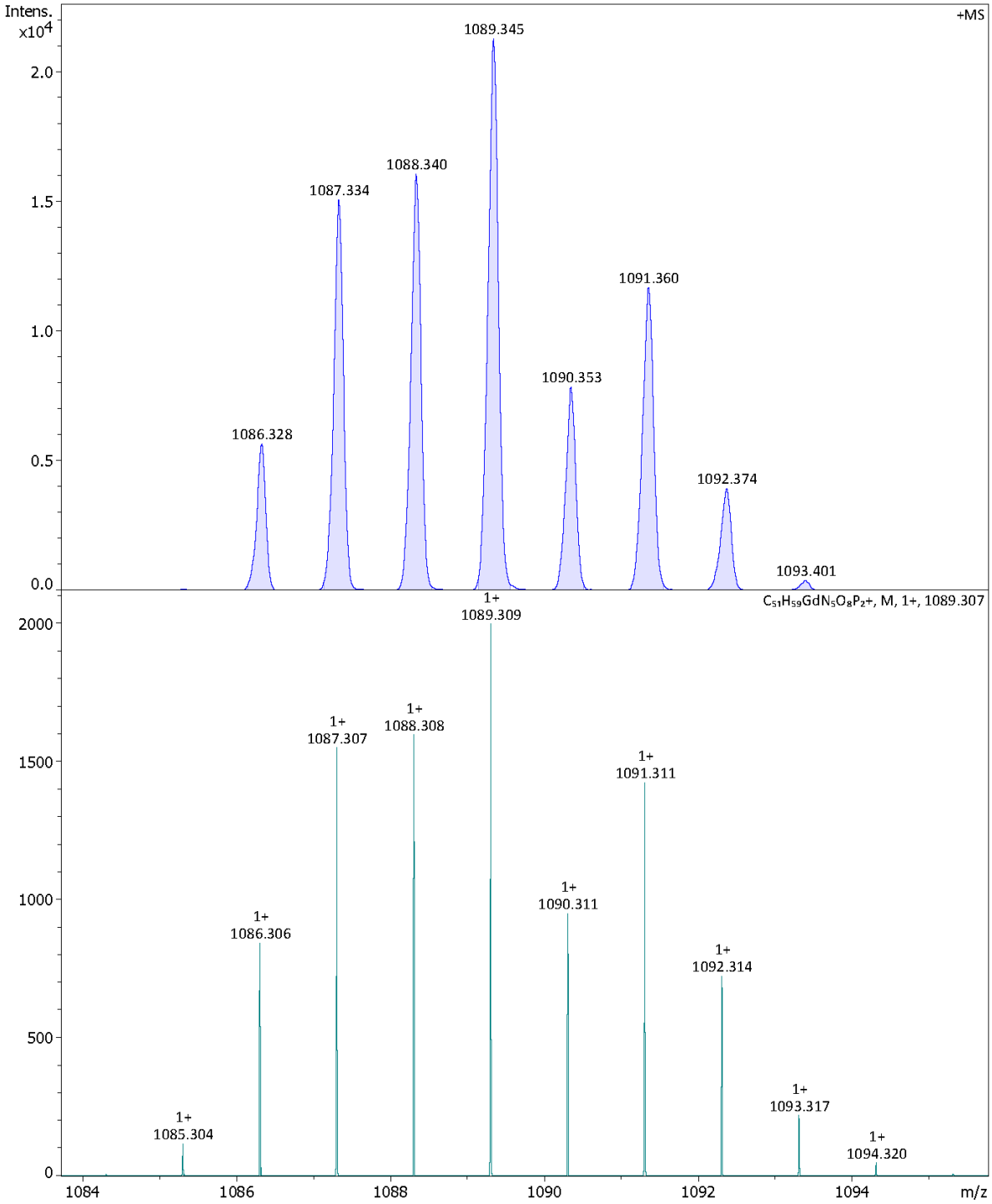

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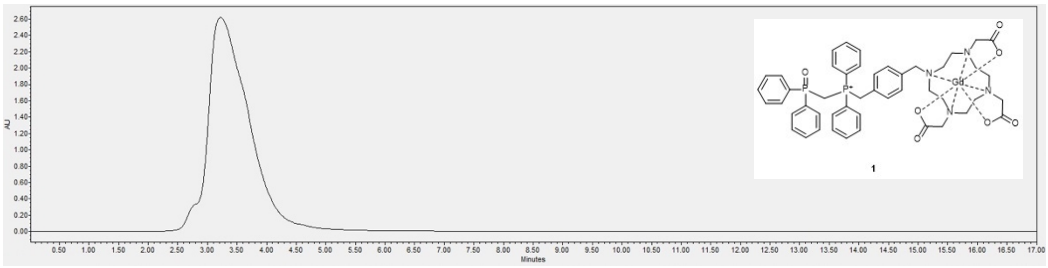

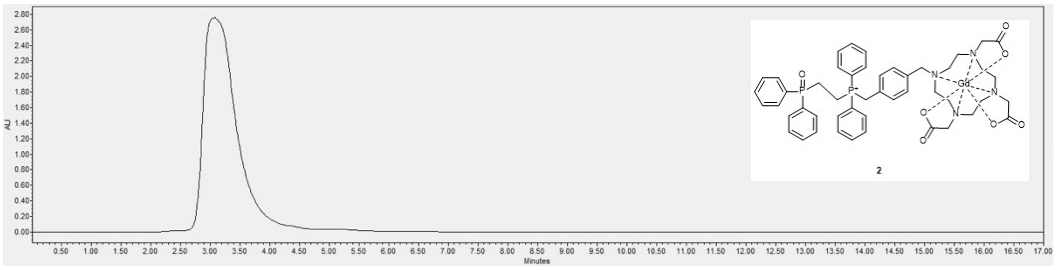
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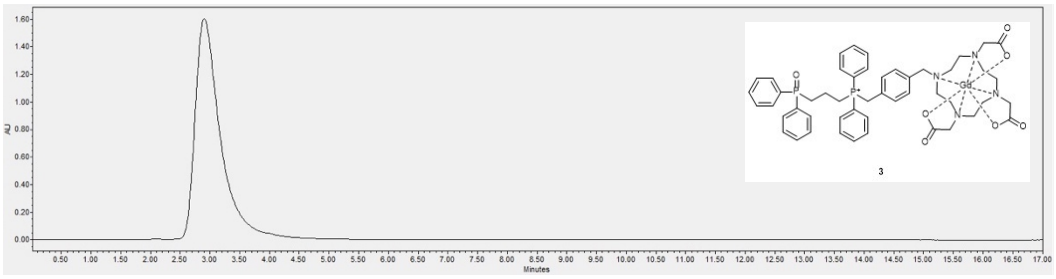
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Minutes
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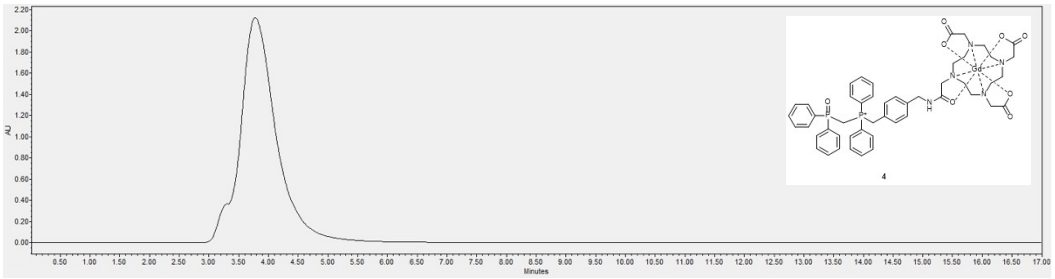
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Gd
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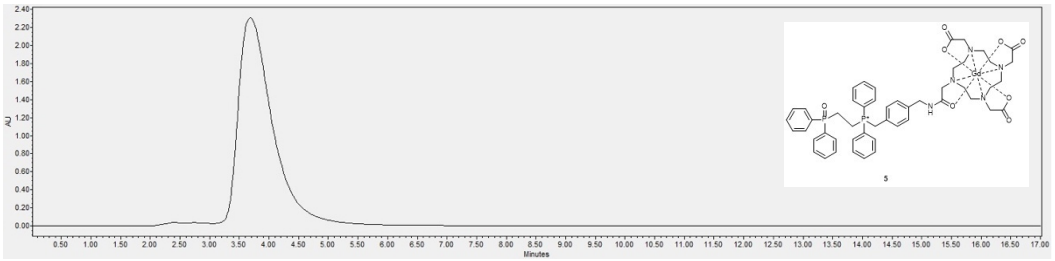
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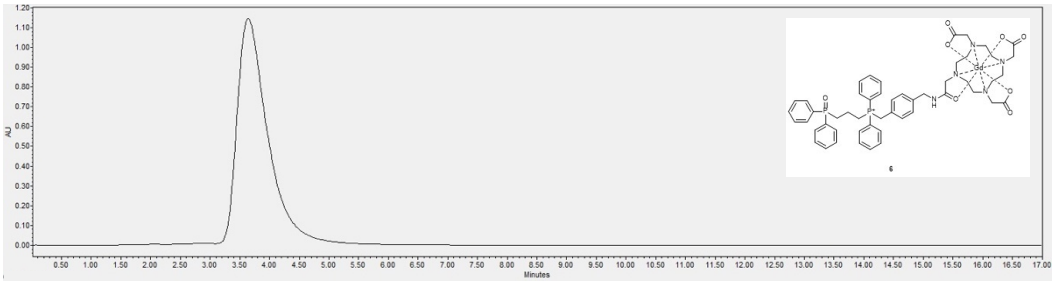
AU
Minutes
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Cell culture studies

The human glioblastoma (T98G) and human glial (SVG p12) cell lines were purchased from ATCC and were maintained as monolayers in a minimum essential medium (MEM) supplemented with foetal bovine serum (FBS) (10% *v*/*v*), penicillin (100 units mL^{-1}), streptomycin (100 µg mL^{-1}) and *L*-glutamine (2.5 mM), within incubators at 37°C in a humidified 5% CO_2 atmosphere. Centrifugation was performed at 3000 rpm for 5 min. MEM with Earle's salts, FBS, PBS, trypsin, *L*-glutamine, and the antibiotic solutions were purchased from ThermoFisher Scientific.

Cytotoxicity assays

The *in vitro* cytotoxicity of the Gd(III) complexes was assessed for both cell lines using the colourimetric 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay.[15] Briefly, cells were harvested with trypsin (0.1% *v/v*), the trypsin deactivated with medium, and cell pellets isolated *via* centrifugation. Any remaining traces of trypsin were removed from the pellet *via* a suspension/centrifugation step. The pellets were then re-suspended to a single cell suspension, the cells.mL^{-1} were determined using a hemocytometer (Weber), and the solution diluted such that 90 µL aliquots of cell suspension per well of a 96-well plate yielded 1×10^4 cells per well. The cells were incubated for 24 h to allow them to adhere.

The cells were subsequently dosed with 10 µL per well of a sterile 10× stock serial dilution of a Gd(III) complex or the relevant vehicle (control). Each dilution/vehicle pair was repeated in triplicate within a plate and each plate was repeated in triplicate, for both cell lines. The maximum concentrations for these experiments were 2 mM due to solubility limitations. After 72 h incubation, MTT solution in phosphate-buffered saline (PBS; 30 µL, 0.17% *w/v*) was added to all wells including dosed and control cells and background control wells containing only culture medium and the vehicle control. The addition was done without exposure to light and the incubation was continued for a further 4 h. The culture medium and excess MTT solution were carefully removed so as not to disrupt any MTT–formazan crystals formed during the incubation and were subsequently dissolved in 150 µL of DMSO.

Cell viability was determined by measuring the absorbance at 600 nm using a BMG LABTECH POLARstar Omega UV spectrometer. All readings were corrected for absorbance from the background control wells, and the level of MTT was expressed relative to the corresponding vehicle-treated controls as % viability. Corresponding IC_{50} values for each of the compounds tested were then determined at the dose required to induce a 50% decrease in cell viability. IC_{50} values (Table S1) are reported with standard errors.

Table S1 IC_{50} values (with standard errors) for complexes **1**–**6**, **13** and **14** in SVG p12 and T98G cell lines (*N*=9).

	IC_{50} (mM)	
Complex	**SVG p12**	**T98G**
1	1.28 ± 0.03	1.46 ± 0.05
2	1.67 ± 0.08	1.36 ± 0.04
3	> 2.00 [a]	> 2.00 [a]
4	1.81 ± 0.06	1.37 ± 0.05
5	1.37 ± 0.04	1.23 ± 0.04
6	> 2.00 [a]	> 2.00 [a]
13	2.13 ± 0.09 [b,c]	1.22 ± 0.04
14	2.09 ± 0.15 [b,c]	1.72 ± 0.08 [b]

[a] *Value was found to be too large to accurately predict using available data between 62.5 µM and 2 mM.* [b] *Value reported previously.*[5,6] [c] *IC_{50} values determined by means of the GraphPad Prism® 7 non-linear regression analysis tool.*

Cell uptake studies

25 cm^3 cell culture flasks were seeded with 3 mL of a cell suspension to yield 2×10^5 cells per flask as and were incubated until they were 80% confluent (usually 72 h). Sterile 20 mM stock solutions of the solid Gd(III) complexes were diluted with warm (37°C) culture medium to yield a series dilution of final concentrations including 500 µM, 250 µM, 125 µM and 62.5 µM. The non-dosed culture medium in each flask was removed and replaced with drug-dosed media or a relevant vehicle (control), each concentration was repeated in triplicate for both cell lines along with the relevant control. The cells were incubated for a further 48 h after which they were harvested.

The culture medium was removed, and the monolayers washed with warm (37°C) PBS (1 mL) before treatment with trypsin (0.1% *v/v*). The trypsin was deactivated with medium, and cell pellets isolated *via* centrifugation before the supernatant was removed and the pellets re-suspended in warm PBS. Centrifugation produced washed pellets, eliminating the possibility of residue Gd(III) complex remaining outside the cells, which were subsequently re-suspended in warm PBS (1 mL). From this suspension, 100 µL was set aside for protein analysis and the remaining 900 µL was centrifuged to isolate the cell pellets, the supernatant was removed, and the cell were digested in preparation for Gd content analysis.

Cell pellets were digested in HNO_3 (110 µL, 69%) at 40°C in a heating block for 24 h. 100 µL of the digest solution was diluted to 10 mL to result in a 1% HNO_3 solution which was measured for Gd content by means of ICP-MS. ICP-MS was run on a Perkin Elmer ELAN 6100 Inductively Coupled Plasma Emission Mass Spectrometer (ICP-MS) within the School of Geosciences at the University of Sydney. Gadolinium uptake is reported as µg Gd/mg protein.

Statistical analysis of the cell uptake data was performed by means of a two-way ANOVA, demonstrating significantly higher uptake (p = 0.05) for the T98G tumour cell line over the SVG p12 parent line for concentrations below 500 µM, with the exception of complex **6** whereby its 125 µM uptake data did not have a significant difference between the two lines, although this result might be accounted for by the considerable error of the corresponding SVG p12 data point. The tendency for lower concentration doses to result in higher tumour selectivity is consistent with the tumour cell's elevated $\Delta\Psi_m$ being responsible for the tumour-selective accumulation up to a point, beyond which high levels of Gd accumulation within mitochondria leads to depolarisation and passive Gd influx may then become the dominant mechanism of mitochondrial accumulation.[16-18] This hypothesis is further supported by the 500 µM dose data which demonstrated no significant difference in Gd uptake between the two different cell lines for complexes **1**, **2** and **5**. A similar trend was observed for tumour cell retention, which was typically at a maximum at the 125 µM concentration and trended downward as the Gd dose was increased. While complex **4** performed best of all complexes assessed at 125 µM, the related complexes **3** and **6** performed best at the highest concentrations.

Statistical analysis by means of a two-way and single factor ANOVA demonstrated no significant difference in tumour *selectivity* between the Gd(III) complexes containing the amide linker with an extra O-donor atom (i.e. complexes **4**–**6** and **14**) and their related alkyl-linker analogues (i.e. DO3A-derived complexes **1**–**3** and **13**), with the exception of complex **2** which demonstrated a higher tumour cell selectivity than complex **5** at the 125 µM dose. Based on our previously-reported work,[6] inclusion of the additional O-donor atom into the ligand structure improves metal complex stability without compromising tumour cell selectivity. Importantly, the tumour cell selectivities for the Gd(III) complexes reported here were found to be similar to those of previously-reported Gd(III)-

triphenylphosphonium complexes, despite the reduced number of phosphonium aryl rings in complexes **1**–**6** (*cf*. **13** and **14**). For example, in the case of complex **4** at 125 µM, which exhibited the highest T:N ratio of all the assessed doses (2.6), the parent triphenylphosphonium complex **14** at the same dose had a comparable T:N ratio of 2.4.

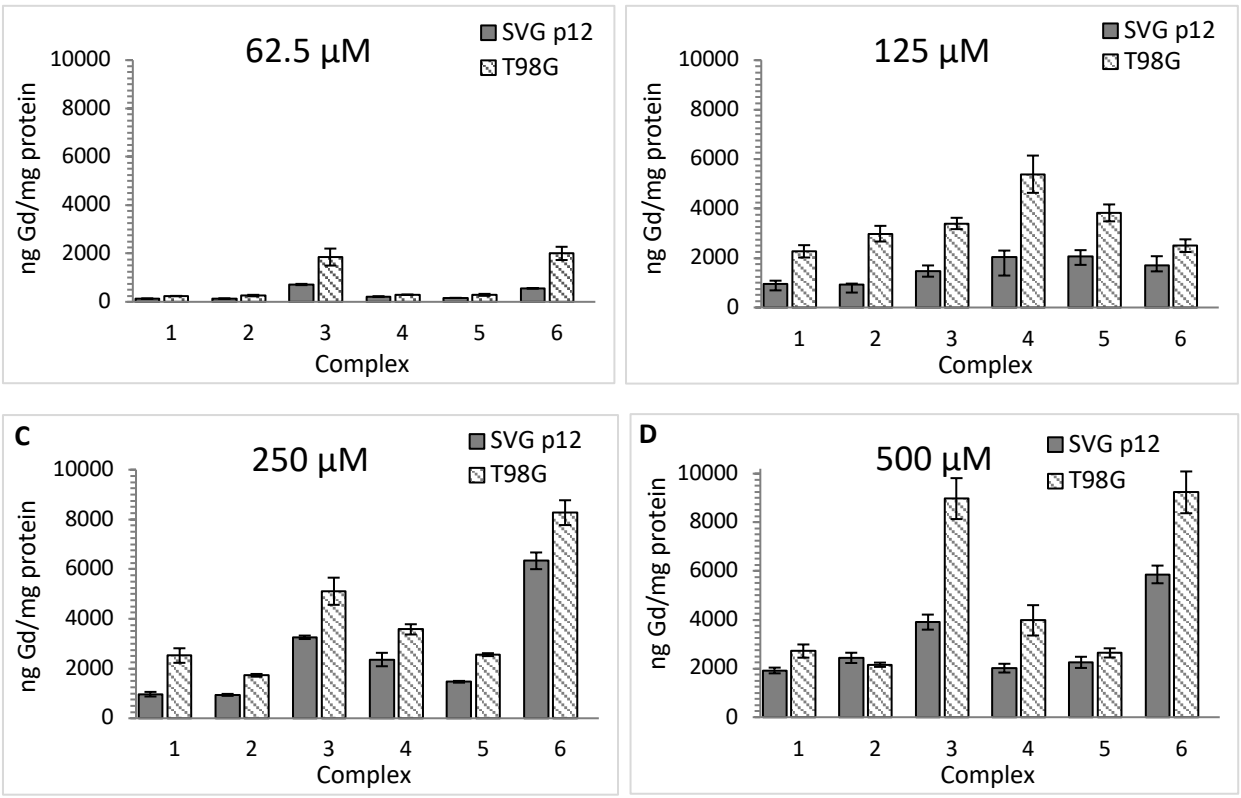

Figure S1 *Graphical representation of Gd uptake (ng Gd/ mg protein) for complexes **1** – **6** in SVG p12 and T98G cells.*

Protein analysis

The BIORAD DC^{MT} protein assay kit was used to determine protein concentrations.[19]

A bovine serum albumin (BSA) protein standard curve was prepared each time the assay was performed, ranging from 1.0-0.1 mg mL^{-1} in PBS. Lysis of the 100 µL cells suspension was achieved using three snap freeze–thaw cycles and pipette mixing. The protein content of each solution was then analysed by pipetting 5 µL samples of the blanks, vehicle (control), and treated cell solutions into a 96-well plate, adding 25 µL of the alkaline copper(II) tartrate solution and 200 µL of the Folin reagent solution included in the BIORAD kit avoiding exposure to light. The plates were incubated for 15 minutes and the absorbance measured at 750 nm using a BMG LABTECH POLARstar Omega UV spectrometer. The protein concentration was determined by correcting all measurements with the background controls and comparing the absorbance with that of the BSA standard curve.

Computational Section

Computational Methods

DFT calculations were carried out with the Q-Chem package[20] using Q-Chem 5.3.[21] Gas-phase optimised geometries were calculated using the B3LYP hybrid functional,[22,23] together with Grimme's DFT-D3 empirical dispersion corrections,[24] and the def2-SV(P) basis set.[25] All DFT calculations employed an unpruned EML (75,302) quadrature formula. Frequency calculations confirmed the

structures were local minima (absence of imaginary frequencies) and provided thermochemical data using the unscaled frequencies (Table S2). Wavefunctions for quantum chemical topology analyses were generated through single point calculations using B3LYP with the def2-TZVPD[25] basis set. QTAIM[26,27] and IQA[28] analyses were carried out using the AIMAll[29] package.

Conformational Analysis of $[Ph_2P(O)CH_2PBnPh_2]^+$ (15)

The QTAIM molecular graph of the global minimum energy conformation of **15**, **15a**, is illustrated in Figure S2. Notable is the *gauche* arangement of the P=O and C–P^+ bonds in **15a**, with the distance between the O and P^+ atoms being 3.18 Å. In conformation **15c** these bonds are *anti*, with the the distance between the O and P^+ atoms now 4.44 Å. The calculated IQA interaction energy (E_{IQA}) between the O and P^+ atoms for conformation **15c** is 455 kJ mol^{-1} higher in energy than **15a** (entries 4 and 8, Table S3), which is clearly a substantial contribution to the overall relative instability of this conformation (ΔG = 57.7 kJ mol^{-1}).

Another significant contribution to the overall relative stabilty of the various conformations of **15** (and of the model compounds **16** and **17** discussed below) appears to be the potential for energetically favorable close contacts between the O atom and electropositive H atoms associated with the phosphonium ion substituents. In many cases this leads to the appearance of a bond path between the O and H atoms. In the case of **15a** two bond paths are observed between an *ortho*-H of the benzyl-substituent (H1) and a benzylic-H (H2). The E_{IQA} values for these interactions are −64 and −126 kJ mol^{-1}, respectively (entries 1 and 2, Table S3).

Table S3 lists the E_{IQA} values and key QTAIM parameters for the bond critical points (bcp) observed for similar interactions for the selected conformations of all the model compounds. The values for the electron denities ($\rho(r)$) at the bcp are all small, ranging from 0.0083 to 0.0230 ea_0^{-3}; the values for the Laplacian of the electron density at the bcp ($\nabla^2\rho(r)$) are all small and positive, ranging from 0.029 to 0.082 ea_0^{-5}; and finally, the vaules for the electronic energy density at the bcp ($H(r)$) are also small and positive, ranging from 0.0014 to 0.0025 $E_h a_0^{-3}$. These parameters are all consistent with a closed-shell electrostatic interaction, similar to more familiar hydrogen bonding situations.[26,27]

In some instances, a bond path/bcp may not be present, but a favorable O,H-interaction is evident from the E_{IQA}; for example the interaction of the O atom of **15a** with an *ortho*-H of a phenyl-substituent of the phosphonium ion (H3) has a stabilising interaction of −48 kJ mol^{-1} (entry 3, Table S3). Maximising the number of these close contacts has an important role in the observed overall stability of the diferent conformations of **15**, in addition to the usual roles of steric and torsional strains; for example conformation **15b** has only two (as opposed to three) O,H-interactions (both with *ortho*-Hs of phenyl substituents) and is 17.6 kJ mol^{-1} higher in free energy than **15a**.

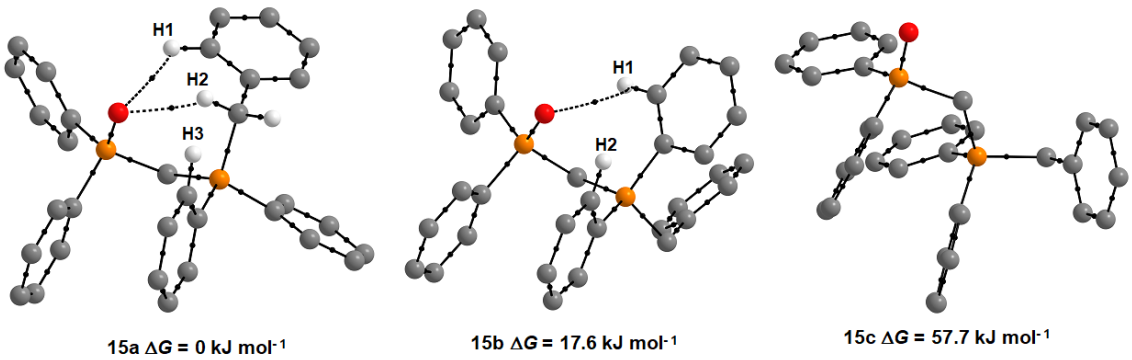

Figure S2 *Perspective views of the molecular graphs of selected minimum energy conformations of **15**. Black lines depict located bond paths and the black dots indicate located bond critical points.*

Dashed lines represent weak bond paths, where the electron density at the bond critical point is $\rho(r) < 0.025\ ea_0^{-3}$. Only selected H-atoms and their associated bond paths/critical points are shown, and some weak bond paths have been omitted, for clarity.

Conformational Analysis of $[Ph_2P(O)(CH_2)_2PBnPh_2]^+$ (16)

The observations made above for **15** also apply to the conformational analysis of **16**. The QTAIM molecular graph of the global minimum energy conformation of **16**, **16a**, is illustrated in Figure S3. Notable is the *gauche* arangement of the C–P(O) and C–P^+ bonds, with the oxygen also oriented towards the P^+, in **16a**, with the distance between the O and P^+ atoms being 3.11 Å. In conformation **16d** these bonds are *anti*, with the the distance between the O and P^+ atoms now 4.81 Å. The calculated E_{IQA} between the O and P^+ atoms for conformation **16d** is 430 kJ mol^{-1} higher in energy than **16a** (entries 12 and 19, Table S3), substantially contributing to the higher overall free energy of **16d** (ΔG = 45.7 kJ mol^{-1}).

Conformation **16a** is very similar to **15a**, being supported by three O,H-interactions involving an *ortho*-H of the benzyl-substituent (H1), a benzylic-H (H2) and an *ortho*-H of a phenyl substituent (H3). Higher free energy conformations **16b** and **16c** each feature only two O,H-interactions.

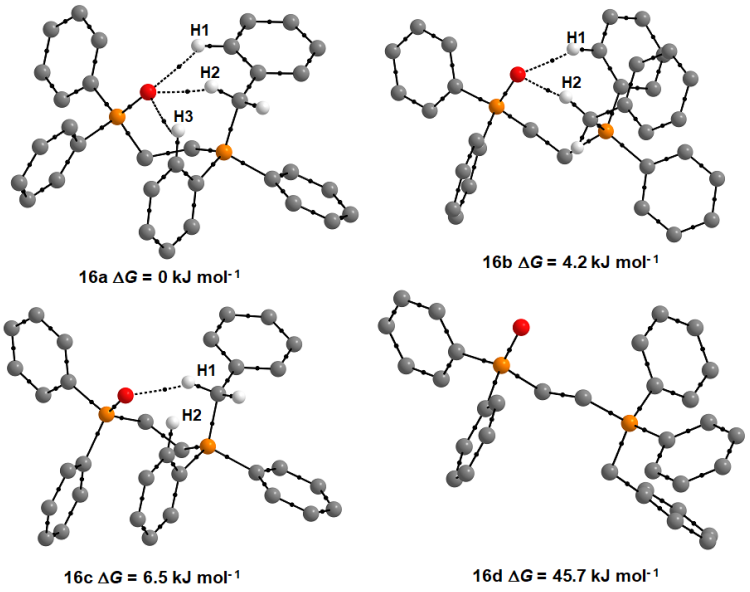

Figure S3 *Perspective views of the molecular graphs of selected minimum energy conformations of **16**. Black lines depict located bond paths and the black dots indicate located bond critical points. Dashed lines represent weak bond paths, where the electron density at the bond critical point is $\rho(r) < 0.025\ ea_0^{-3}$. Only selected H-atoms and their associated bond paths/critical points are shown, and some weak bond paths have been omitted, for clarity.*

Conformational Analysis of $[Ph_2P(O)(CH_2)_3PBnPh_2]^+$ (17)

Once again, we see with **17** that collapsed structures, minimising the O–P^+ distance, are favored over extended structures, with the global minimum conformation **17a** 37.3 kJ mol^{-1} lower in free energy than **17c** (Figure S4). As with conformations **15a** and **16a**, conformation **17a** is stabilised by three O,H-interactions, however, in this case one of these interations involve the tether methylene attached to the phosphonium ion. The next lowest free energy conformation **17b** also maintains this interaction. Also noteworthy is the unfavorable near-eclipsed conformation across the CH_2–CH_2P^+ bond of **17a**, which further highlights the importance of electrostatics in overall conformational preferences; as well as maintaing a third O,H-interation, this arrangement also brings the O and P^+

atoms closer together than for **17b** (distances of 3.54 and 4.29 Å, repectively, leading to the E_{IQA} for the O,P^{+}-interaction being 210 kJ mol^{-1} lower in energy for **17a** (entries 23 and 26, Table S3)). Thus, the conformational profile of **17** is seen to be distinct from **15** and **16**.

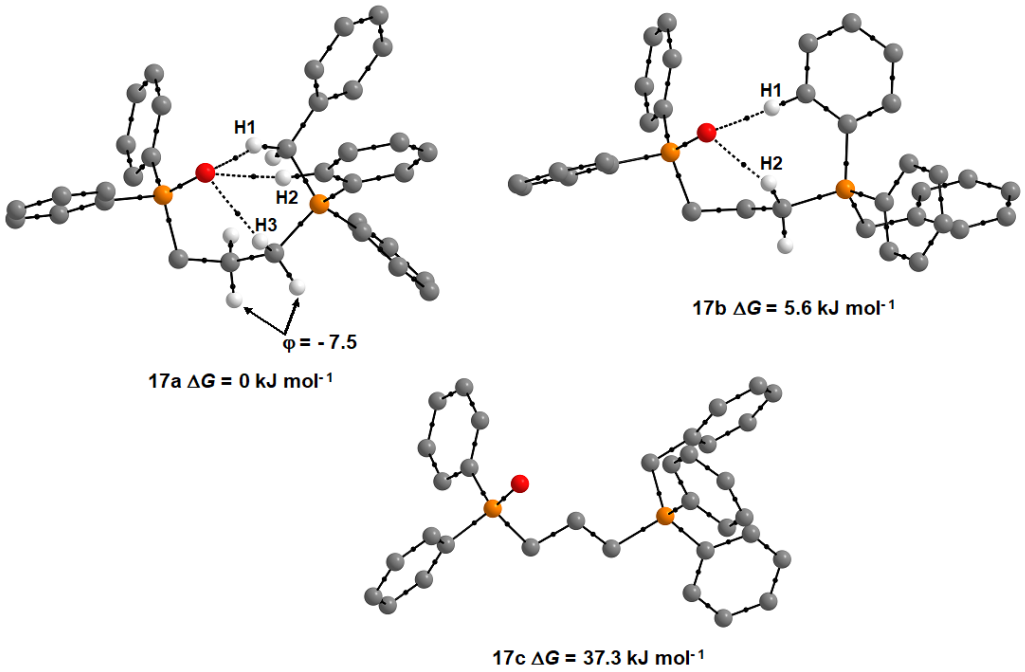

Figure S4 *Perspective views of the molecular graphs of selected minimum energy conformations of **17**. Black lines depict located bond paths and the black dots indicate located bond critical points. Dashed lines represent weak bond paths, where the electron density at the bond critical point is $\rho(r) < 0.025\ ea_0^{-3}$. Only selected H-atoms and their associated bond paths/critical points are shown, and some weak bond paths have been omitted, for clarity.*

Table S2 Calculated electronic and thermochemical data for selected conformations of compounds **15**, **16** and **17** using B3LYP-D3/def2-SV(P)/gas/T = 298 K.

Entry	Structure	E (E_h)	ZPE (kJ mol^{-1})	H (E_h)	S (J mol^{-1} K^{-1})	G (E_h)
1	**15a**	-1993.535355	1368.10	-1992.982592	852.44	-1993.079394
2	**15b**	-1993.527676	1367.02	-1992.975237	858.09	-1993.072681
3	**15c**	-1993.515766	1368.82	-1992.962961	831.93	-1993.057435
4	**16a**	-2032.821667	1444.63	-2032.238675	873.19	-2032.337834
5	**16b**	-2032.818926	1444.22	-2032.236035	882.43	-2032.336243
6	**16c**	-2032.819153	1444.16	-2032.236270	872.61	-2032.335363
7	**16d**	-2032.801679	1442.88	-2032.219904	871.33	-2032.318852
8	**17a**	-2072.103496	1519.67	-2071.490569	908.68	-2071.593758
9	**17b**	-2072.100664	1518.89	-2071.488003	912.37	-2071.591611
10	**17c**	-2072.086802	1518.00	-2071.474179	927.97	-2071.579558

Table S3 Calculated quantum chemical topology data for selected conformations of compounds **15**, **16** and **17** using single point B3LYP/def2-TZVPD wavefunctions.

Entry	Interaction	E_{IQA} (kJ mol^{-1})	$\rho(r)$ (ea_0^{-3})	$\nabla^2\rho(r)$ (ea_0^{-5})	$H(r)$ ($E_h a_0^{-3}$)
1	**15a**(O,H1)	−64	0.0085	0.029	0.0014
2	**15a**(O,H2)	−126	0.0145	0.054	0.0021
3	**15a**(O,H3)	−48	no bcp		
4	**15a**(O,P$^+$)	−1630	no bcp		
5	**15b**(O,H1)	−58	0.0088	0.033	0.0016
6	**15b**(O,H2)	−72	no bcp		
7	**15b**(O,P$^+$)	−1670	no bcp		
8	**15c**(O,P$^+$)	−1175	no bcp		
9	**16a**(O,H1)	−60	0.0083	0.029	0.0014
10	**16a**(O,H2)	−146	0.0191	0.076	0.0025
11	**16a**(O,H3)	−75	0.0098	0.036	0.0016
12	**16a**(O,P$^+$)	−1500	no bcp		
13	**16b**(O,H1)	−146	0.0179	0.066	0.0023
14	**16b**(O,H2)	−190	0.0230	0.082	0.0019
15	**16b**(O,P$^+$)	−1370	no bcp		
16	**16c**(O,H1)	−161	0.0197	0.074	0.0023
17	**16c**(O,H2)	−60	no bcp		
18	**16c**(O,P$^+$)	−1500	no bcp		

19	**16d**(O,P$^+$)	−1070	no bcp		
20	**17a**(O,H1)	−140	0.0167	0.058	0.0021
21	**17a**(O,H2)	−104	0.0117	0.045	0.0021
22	**17a**(O,H3)	−105	0.0146	0.054	0.0020
23	**17a**(O,P$^+$)	−1380	no bcp		
24	**17b**(O,H1)	−139	0.0158	0.056	0.0023
25	**17b**(O,H2)	−160	0.0186	0.067	0.0021
26	**17b**(O,P$^+$)	−1170	no bcp		
27	**17c**(O,P$^+$)	−1070	no bcp		

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