Electronic Supplementary Material (ESI) for Dalton Transactions.

Supporting information

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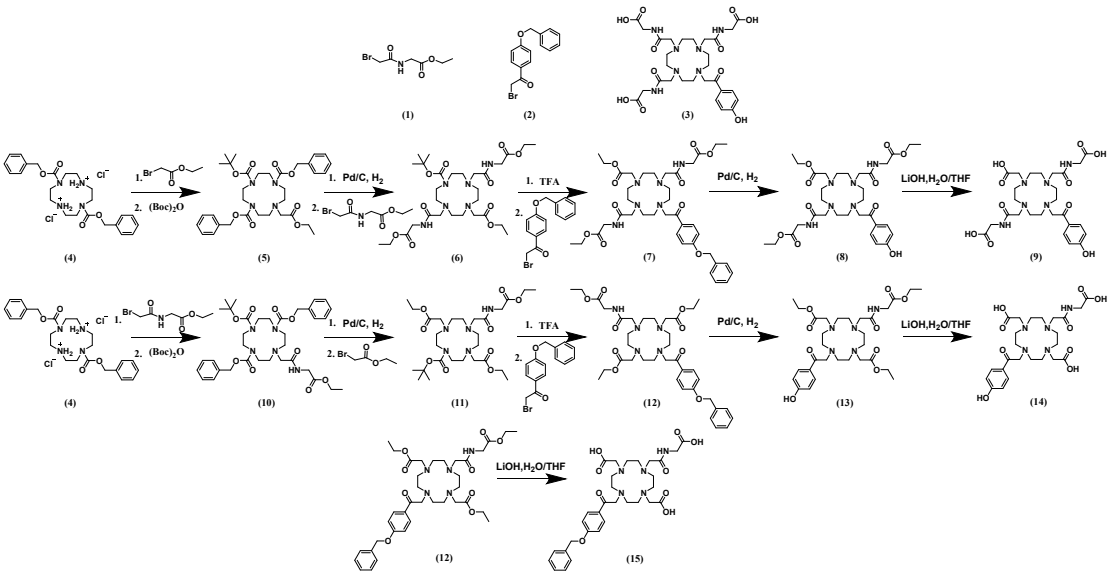
1 General

All reagents and solvents were purchased from commercial sources and used as received without other purification unless otherwise noted. ^{1}H, ^{13}C, T_1 and T_2 NMR spectra have been recorded on a Bruker AVANCE III 400 NMR spectrometer. LC-MS (Liquid Chromatography–mass Spectrometry) was performed on a Waters e2695 seperations module equipped with a QDa detector and a Phenomenex Kinetex® C18 column (5 um, 4.6 mm x 250 mm). HPLC methods: A: H_2O, B: ACN; gradient : 5% B to 100% B over 15 min; flow rate 1 mL/min.

2 Methods

2.1. Synthesis and characterization



Scheme S1. Synthetic routes of ligand 1-4.

N-(2-bromoacetyl)-L-glycine ethyl ester (1), 2-bromo-1-[4-(phenylmethoxy)phenyl]-ethanone (2), 10-[2-(4-hydroxyphenyl)-2-oxoethyl]-1,4,7,10-tetraazacyclododecane-1,4,7-tris(2-acetamido)-L-glycine (3)[1] and 1,4,7,10-tetraazacyclododecane-1,7-Bis(benzyloxy carbonyl) (4)[2] were synthesized using established procedures.

1,4,7,10-tetraazacyclododecane-1,7-Bis(benzyloxy carbonyl)-4-Acetate ester-10-(N-ethylene (tert-butoxycarbonyl) amino acetamide) (5): 1,4,7,10-tetraazacyclododecane-1,7-Bis(benzyloxy carbonyl) (4) (4.6 g, 9.1 mmol) and ethyl bromoacetate (1.02 mL ,9.1 mmol) were dissolved in anhydrous CH_3CN in the excess amount of K_2CO_3 (7 g, 50.5 mmol). The resulting solution was stirred at 65 ℃ overnight under N_2 condition and then the solution was filtered and solvents removed under vacuum. The residue was not purified and went to next step directly. The crude product and 6 mL triethylamine were dissolved in anhydrous CH_2Cl_2 (150 mL) and cooled by ice

water (0 ℃). Di-tert-butyl dicarbonate (1.99 g, 9.1 mmol) was dissolved CH_2Cl_2 (50 mL) and added dropwise to the mixed solution. The resulting solution was allowed to warm to room temperature and stirred for 8 hours. The solvent was removed under vacuum. The crude product was purified by flash column chromatography on silica, eluted with petroleum ether/ethyl acetate (50:50 v/v) to afford a colorless oil (1.20 g, 21%).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.25 (3H, dt, $CH_2C\underline{H}_3$), 1.28-1.50 (9H, m, $C(C\underline{H}_3)_3$), 2.65-3.60 (18H, $C\underline{H}_2$ on cyclen ring, $NC\underline{H}_2C{=}O$), 4.15 (2H, m, $C\underline{H}_2CH_3$), 5.10 (4H, d, $OC\underline{H}_2Ph$), 7.34 (10H, m, $CH_2\underline{Ph}$).

^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 14.3 ($CH_2\underline{C}H_3$), 28.3 ($C(\underline{C}H_3)_3$), 46-56 (cyclen ring $\underline{C}H_2$), 60.4 ($N\underline{C}H_2C{=}O$), 60.5 ($O\underline{C}H_2CH_3$), 67.0 ($\underline{C}H_2Ph$), 79.2 ($\underline{C}(CH_3)_3$), 128.0, 128.3, 128.4, 136.7 (Ph), 155.3 ($N\underline{C}{=}O$), 156.6 ($N\underline{C}{=}O$), 171.1 ($CH\underline{C}{=}OO$).

1,4,7,10-tetraazacyclododecane-1,7-di (2-acetamido)-L-glycine ethyl ester-4-acetate ester-10-(N-ethylene (tert-butoxycarbonyl) amino acetamide) (6): Compound 5 (1.20 g, 1.9 mmol) was dissolved in ethanol and transferred to a flask with 20% palladium on carbon (240 mg). The mixture was shaken on a Parr hydrogenator under a H_2 pressure of 60 psi at room temperature for 8 hours. The resulting solution was filtered and solvent was removed under vacuum to afford a colorless oil (511 mg, 93%). The deprotection oil and N-(2-bromoacetyl)-L-glycine ethyl ester (1) (784 mg, 3.5 mmol) were dissolved in anhydrous CH_3CN in the excess amount of K_2CO_3 (4 g, 29 mmol). The resulting solution was stirred at 65 ℃ overnight under N_2 condition for 12 hours and then the solution was filtered and solvents removed under vacuum. The crude product was purified by flash column chromatography on Al_2O_3, eluted with methanol/dichloromethane (2:98 v/v) to afford a pale yellow oil (993 mg, 88%).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.25 (3H, t, $CH_2C\underline{H}_3$), 1.27 (6H, t, $CH_2C\underline{H}_3$) 1.42 (9H, d, $C(C\underline{H}_3)_3$), 2.60-3.25 (16H, $C\underline{H}_2$ on cyclen ring), 3.32 (2H, s, $NC\underline{H}_2C{=}O$), 3.42 (4H, t, $NC\underline{H}_2C{=}O$), 4.02 (4H, d, $NHC\underline{H}_2C{=}O$), 4.09 (2H, q, $OC\underline{H}_2CH_3$), 4.17 (4H, q, $OC\underline{H}_2CH_3$), 8.10 (2H, t, $N\underline{H}$).

^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 14.2 ($CH_2\underline{C}H_3$), 28.4 ($C(\underline{C}H_3)_3$), 40.8 ($NH\underline{C}H_2C{=}O$), 47-54.5 (cyclen ring $\underline{C}H_2$), 55.9 ($N\underline{C}H_2C{=}O$), 58.8 ($N\underline{C}H_2$), 60.5 ($OC\underline{H}_2CH_3$), 61.1 ($OC\underline{H}_2CH_3$), 79.8 ($\underline{C}(CH_3)_3$), 155.9 ($N\underline{C}{=}O$), 170.1 ($CH_2\underline{C}{=}OO$),171.6 ($CH_2\underline{C}{=}OO$), 172.2 ($CH_2\underline{C}{=}ONH$).

10-[2-[4-(benzyloxy)phenyl]-2-oxoethyl-1,4,7,10-tetraazacyclododecane-1,7-di (2-acetamido)-L-glycine ethyl ester-4-Acetate ester (7): Compound 6 (993 mg, 1.5 mmol) was reacted directly with 5 mL TFA for 12 hours. The solvent was then removed under vacuum and poured saturated $NaHCO_3$ solution. The aqueous solution was extracted with CH_2Cl_2 for three times. The solvent was then removed under vacuum and obtained as a pale yellow oil. (805 mg, 96%). The pale yellow oil and 2-bromo-1-[4-(phenylmethoxy)phenyl]-ethanone (2) (438 mg, 1.45 mmol) were dissolved in anhydrous CH_3CN in the excess amount of K_2CO_3 (2 g, 14.5 mmol). The resulting solution was stirred at 65 ℃ overnight under N_2 condition for 12 hours and then the solution was filtered and solvents removed under vacuum. The crude product was purified by flash column chromatography on Al_2O_3, eluted with methanol/dichloromethane (3:97 v/v) to afford a yellow oil (903 mg, 81%).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.14 (6H, t, $CH_2C\underline{H}_3$), 1.24 (3H, t, $CH_2C\underline{H}_3$), 2.70 (16H, t, $C\underline{H}_2$ on cyclen ring), 3.16 (4H, s, $NHC\underline{H}_2C{=}O$), 3.30 (2H, s, $N\underline{C}H_2$), 3.87 (4H, q, $C\underline{H}_2CH_3$),3.95 (6H, t, $N\underline{C}H_2$), 4.08 (2H, q, $C\underline{H}_2CH_3$), 5.13 (2H, s, $C\underline{H}_2Ph$), 7.05, 7.30-7.46, 7.87 (9H, $\underline{Ph}$), 8.65

(2H, t, NH).
^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 14.0 (CH_2CH_3), 14.2 (CH_2CH_3), 41.2 ($NHCH_2C=O$), 52.7, 55.3, 54.6, 54.7 (cyclen ring CH_2), 56.6 ($NCH_2C=O$), 57.8 ($NCH_2C=O$), 60.4 ($NCH_2C=O$), 60.8 (CH_2CH_3), 61.6 (CH_2CH_3), 70.1 (OCH_2Ph), 114.6, 127.4, 128.3, 128.7, 129.2, 131.2, 136.0, 162.6 (Ph), 170.2 ($CH_2C=OO$), 171.2 ($CH_2C=ONH$), 172.7 ($CH_2C=OO$), 195.6 ($CH_2C=O$).

10-[2-(4-hydroxyphenyl)-2-oxoethyl]-1,4,7,10-tetraazacyclododecane-1,7-di (2-acetamido)-L-glycine ethyl ester-4-Acetate ester (8): Compound 7 (903 mg, 1.17 mmol) was dissolved in ethanol and transferred to a flask with 20% palladium on carbon (180 mg). The mixture was shaken on a Parr hydrogenator under a H_2 pressure of 80 psi at room temperature for 48 hours. The resulting solution was filtered and solvent was removed under vacuum to afford a yellow oil (706 mg, 89%).
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.12 (6H, t, CH_2CH_3), 1.23 (3H, t, CH_2CH_3), 2.40-2.80 (16H, m, br, CH_2 on cyclen ring), 3.26 (4H, s, $NCH_2C=O$), 3.32 (2H, s, $NCH_2C=O$), 3.80 (4H, d, $NHCH_2C=O$), 3.90 (4H, d, br, OCH_2CH_3), 3.95 (2H, s, $NCH_2C=O$), 4.05 (2H, q, OCH_2CH_3), 6.89, 7.76(4H, Ph), 8.78 (2H, s, NH).
^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 14.0 (CH_2CH_3), 14.1 (CH_2CH_3), 41.3($NHCH_2C=O$), 51.8, 52.4, 53.5 (cyclen ring CH_2), 56.7 ($NCH_2C=O$), 56.9 ($NCH_2C=O$), 60.5 ($NCH_2C=O$), 60.9 (OCH_2CH_3), 61.7 (OCH_2CH_3), 115.5, 127.5, 130.0, 162.8 (Ph), 170.1 ($CH_2C=OO$), 171.2 ($CH_2C=ONH$), 173.6 ($CH_2C=OO$), 195.5 ($CH_2C=O$).

10-[2-(4-hydroxyphenyl)-2-oxoethyl]-1,4,7,10-tetraazacyclododecane-1,7-di (2-acetamido)-L-glycine-4-Acetate acid (9): Compound 8 (706 mg, 1.04 mmol) was added into a mixture of aqueous LiOH solution (0.2 M, 10 mL) and THF (10 mL). The reaction mixture was stirred at room temperature for 8 hours. THF was then removed under vacuum and the solution was dialyzed by ultrapure water and lyophilized to get the off-white solid (531 mg, 86%).
^{1}H NMR (400 MHz, D_2O): δ (ppm) 2.6-3.46 (22H, m, br, CH_2 on cyclen ring and $NCH_2C=O$), 3.50 (4H, s, $NHCH_2C=O$), 3.73 (2H, s, $NCH_2C=O$), 6.75, 7.74 (4H, Ph).
^{13}C NMR (100 MHz, D_2O): δ (ppm) 43.0 ($NHCH_2C=O$), 48.2, 51.3, 52.0 (cyclen ring CH_2), 56.6 ($NCH_2C=O$), 57.2 ($NCH_2C=O$), 117.0, 123.7, 131.6, 166.7 (Ph), 170.1 ($CH_2C=ONH$), 172.0 ($CH_2C=O$), 176.5 ($CH_2C=OO$).

1,4,7,10-tetraazacyclododecane-1,7-Bis(benzyloxy carbonyl)-4-(2-acetamido)-L-glycine ethyl ester -10-(N-ethylene (tert-butoxycarbonyl) amino acetamide) (10): 1,4,7,10-tetraazacyclododecane-1,7-Bis(benzyloxy carbonyl) (4) (4.6 g, 9.1 mmol) and N-(2-bromoacetyl)-L-glycine ethyl ester (1) (2.04 g ,9.1 mmol) were dissolved in anhydrous CH_3CN in the excess amount of K_2CO_3 (7 g, 50.5 mmol). The resulting solution was stirred at 65 ℃ overnight under N_2 condition and then the solution was filtered and solvents removed under vacuum. The residue was not purified and went to next step directly. The crude product and 6 mL triethylamine were dissolved in anhydrous CH_2Cl_2 (150 mL) and cooled by ice water (0 ℃). Di-tert-butyl dicarbonate (1.99 g, 9.1 mmol) was dissolved CH_2Cl_2 (50 mL) and added dropwise to the mixed solution. The resulting solution was allowed to warm to room temperature and stirred for 8 hours. The solvent was removed under vacuum. The crude product was purified by flash column chromatography on silica, eluted with petroleum ether/ethyl acetate (65:35 v/v) to afford a pale yellow oil (1.17 g,

19%).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.25 (3H, t, $CH_2C\underline{H}_3$), 1.40 (9H, s, $C(C\underline{H}_3)_3$), 2.45-4.0 (20H, m, $C\underline{H}_2$ on cyclen ring, $NC\underline{H}_2C{=}O$, $NHC\underline{H}_2C{=}O$), 4.15 (2H, q, $C\underline{H}_2CH_3$), 5.10 (4H, s, $C\underline{H}_2Ph$), 7.28-7.39 (10H, m, Ph).

^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 14.2 ($CH_2\underline{C}H_3$), 28.4 ($C(\underline{C}H_3)_3$), 41.0 ($NH\underline{C}H_2C{=}O$), 44-58.5 (cyclen ring $\underline{C}H_2$), 60.4 ($N\underline{C}H_2C{=}O$), 61.2 ($O\underline{C}H_2CH_3$), 67.3 ($\underline{C}H_2Ph$), 79.8 ($\underline{C}(CH_3)_3$), 128.1, 128.5, 136.7 (Ph), 155.6 ($N\underline{C}{=}OO$), 157.0 ($N\underline{C}{=}OO$), 169.4 ($CH_2\underline{C}{=}OO$), 170.8 ($CH_2\underline{C}{=}ONH$).

1,4,7,10-tetraazacyclododecane-1,7-di acetate ester -4-(2-acetamido)-L-glycine ethyl ester -10-(N-ethylene (tert-butoxycarbonyl) amino acetamide) (11): Compound 10 (1.17 g, 1.7 mmol) was dissolved in ethanol and transferred to a flask with 20% palladium on carbon (235 mg). The mixture was shaken on a Parr hydrogenator under a H_2 pressure of 60 psi at room temperature for 8 hours. The resulting solution was filtered and solvent was removed under vacuum to afford a colorless oil (671 mg, 95%). The deprotection oil and ethyl bromoacetate (360 μL, 3.2 mmol) were dissolved in anhydrous CH_3CN in the excess amount of K_2CO_3 (5 g, 36 mmol). The resulting solution was stirred at 65 ℃ overnight under N_2 condition for 12 hours and then the solution was filtered and solvents removed under vacuum. The crude product was purified by flash column chromatography on Al_2O_3, eluted with methanol/dichloromethane (2:98 v/v) to afford a pale yellow oil (864 mg, 91%).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.26 (9H, q, $CH_2C\underline{H}_3$), 1.44 (9H, s, $C(C\underline{H}_3)_3$), 2.65-2.78 (8H, m, $C\underline{H}_2$ on cyclen ring), 2.99 (4H, t, $C\underline{H}_2$ on cyclen ring), 3.15 (2H, s, $NC\underline{H}_2C{=}O$), 3.36 (4H, s, $NC\underline{H}_2C{=}O$), 3.48 (4H, t, $C\underline{H}_2$ on cyclen ring), 4.03 (2H, d, $NHC\underline{H}_2C{=}O$), 4.09-4.18 (6H, dq, $C\underline{H}_2CH_3$), 8.08 (1H, t, $N\underline{H}$).

^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 14.2 ($CH_2\underline{C}H_3$), 14.3 ($CH_2\underline{C}H_3$), 28.4 ($C(\underline{C}H_3)_3$), 41.2 ($NH\underline{C}H_2C{=}O$), 45-54 (cyclen ring $\underline{C}H_2$), 54.5 ($N\underline{C}H_2C{=}O$), 55-56 (cyclen ring $\underline{C}H_2$), 58.5 ($N\underline{C}H_2C{=}O$), 60.3 ($\underline{C}H_2CH_3$), 61.0 ($\underline{C}H_2CH_3$), 79.3 ($\underline{C}(CH_3)_3$), 155.6 ($N\underline{C}{=}OO$), 170.2 ($CH_2\underline{C}{=}OO$), 171.2 ($CH_2\underline{C}{=}ONH$), 172.7 ($CH_2\underline{C}{=}ONH$).

10-[2-[4-(benzyloxy)phenyl]-2-oxoethyl-1,4,7,10-tetraazacyclododecane-1,7-di acetate ester-4-(2-acetamido)-L-glycine ethyl ester (12): Compound 11 (864 mg, 1.47 mmol) was reacted directly with 5 mL TFA for 12 hours. The solvent was then removed under vacuum and poured saturated $NaHCO_3$ solution. The aqueous solution was extracted with CH_2Cl_2 for three times. The solvent was then removed under vacuum and obtained as a pale yellow oil. (701 mg, 98%). The pale yellow oil and 2-bromo-1-[4-(phenylmethoxy)phenyl]-ethanone (2) (438 mg, 1.45 mmol) were dissolved in anhydrous CH_3CN in the excess amount of K_2CO_3 (2 g, 14.5 mmol). The resulting solution was stirred at 65 ℃ overnight under N_2 condition for 12 hours and then the solution was filtered and solvents removed under vacuum. The crude product was purified by flash column chromatography on Al_2O_3, eluted with methanol/dichloromethane (3.5:96.5 v/v) to afford a yellow oil (875 mg, 85%).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.22 (9H, t, br, $CH_2C\underline{H}_3$), 1.70-4.55 (32H, m, br, $C\underline{H}_2$ on cyclen ring, $NC\underline{H}_2C{=}O$, $NHC\underline{H}_2C{=}O$, $C\underline{H}_2CH_3$), 5.15 (2H, s, $C\underline{H}_2Ph$), 7.01, 7.32-7.45, 7.88 (9H, Ph), 9.12 (1H, t, $N\underline{H}$).

^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 14.1 ($CH_2\underline{C}H_3$), 41.1 ($NHC\underline{H}_2{=}CO$), 47-56 (cyclen ring $\underline{C}H_2$), 56.6 ($NC\underline{H}_2{=}CO$), 59.9 ($NC\underline{H}_2{=}CO$), 60.8 ($NC\underline{H}_2{=}CO$), 61.2 ($\underline{C}H_2CH_3$), 70.2 ($\underline{C}H_2Ph$),

114.7, 127.5, 128.3, 128.7, 128.8, 130.1, 136.0, 163.1 (Ph), 169.7 (NC$\underline{H}_2$=COO), 172.8 (NC$\underline{H}_2$=CONH), 197.2 (NC$\underline{H}_2$=CO).

10-[2-(4-hydroxyphenyl)-2-oxoethyl]-1,4,7,10-tetraazacyclododecane-1,7-di acetate ester-4-(2-acetamido)-L-glycine ethyl ester (13): Compound 12 (600 mg, 0.85 mmol) was dissolved in ethanol and transferred to a flask with 20% palladium on carbon (120 mg). The mixture was shaken on a Parr hydrogenator under a H_2 pressure of 80 psi at room temperature for 48 hours. The resulting solution was filtered and solvent was removed under vacuum to afford a yellow oil (480 mg, 91%).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.23 (9H, t, $CH_2\underline{C}H_3$), 2.58-3.08 (16H, m, C$\underline{H}_2$ on cyclen ring), 3.2-3.38 (6H, d, N$\underline{C}H_2$C=O), 4.0-4.16 (10H, N$\underline{C}H_2$C=O, NH$\underline{C}H_2$C=O, $\underline{C}H_2CH_3$), 6.85 (2H, d, Ph), 7.79 (2H, d, Ph), 9.11 (1H, s, N$\underline{H}$).

^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 14.1 ($CH_2\underline{C}H_3$), 14.2 ($CH_2\underline{C}H_3$), 41.5 (NHC$\underline{H}_2$=CO), 51-56 (cyclen ring $\underline{C}H_2$), 57.5 (NC$\underline{H}_2$=CO), 59.4 (NC$\underline{H}_2$=CO), 60.5 (NC$\underline{H}_2$=CO), 61.0 ($\underline{C}H_2CH_3$), 116.5, 125.3, 130.5, 164.7 (Ph), 170.3 (CH2$\underline{C}$=OO), 171.3 (CH2$\underline{C}$=OO), 172.7 ($CH_2\underline{C}$=ONH), 196.5 ($CH_2\underline{C}$=O).

10-[2-(4-hydroxyphenyl)-2-oxoethyl]-1,4,7,10-tetraazacyclododecane-1,7-di acetate acid-4-(2-acetamido)-L-glycine (14): Compound 13 (480 mg, 0.77 mmol) was added into a mixture of aqueous LiOH solution (0.2 M, 10 mL) and THF (10 mL). The reaction mixture was stirred at room temperature for 8 hours. THF was then removed under vacuum and the solution was dialyzed by ultrapure water and lyophilized to get the off-white solid (335 mg, 81%).

^{1}H NMR (400 MHz, D_2O): δ (ppm) 2.8-3.55 (20H, m, C$\underline{H}_2$ on cyclen ring, N$\underline{C}H_2$C=O), 3.68 (4H, s, N$\underline{C}H_2$C=O), 4.13 (2H, s, NH$\underline{C}H_2$C=O), 6.79 (2H, d, Ph), 7.74 (2H, d, Ph).

^{13}C NMR (100 MHz, D_2O): δ (ppm) 43.3 (NHC$\underline{H}_2$=CO), 48.2, 48.4, 51.0, 51.9 (cyclen ring $\underline{C}H_2$), 55.4 (NC$\underline{H}_2$=CO), 56.5 (NC$\underline{H}_2$=CO), 57.8 (NC$\underline{H}_2$=CO), 115.6, 127.5, 130.8, 161.5 (Ph), 170.1 ($CH_2\underline{C}$=OO), 172.2 ($CH_2\underline{C}$=OO), 176.9 ($CH_2\underline{C}$=ONH), 198.1 ($CH_2\underline{C}$=O).

10-[2-[4-(benzyloxy)phenyl]-2-oxoethyl-1,4,7,10-tetraazacyclododecane-1,7-di acetate acid-4-(2-acetamido)-L-glycine (15): Compound 12 (265 mg, 0.37 mmol) was added into a mixture of aqueous LiOH solution (0.2 M, 10 mL) and THF (10 mL). The reaction mixture was stirred at room temperature for 8 hours. THF was then removed under vacuum and the solution was dialyzed by ultrapure water and lyophilized to get the off-white solid (200 mg, 86%).

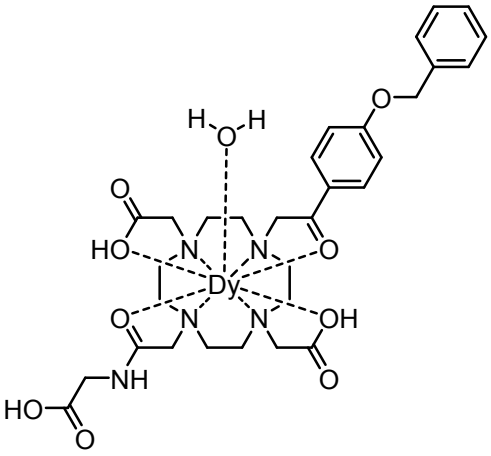
^{1}H NMR (400 MHz, D_2O): δ (ppm) 2.8-3.49 (16H, m, C$\underline{H}_2$ on cyclen ring), 3.5-3.65 (6H, d, NHC$\underline{H}_2$C=O, NC$\underline{H}_2$C=O), 3.75 (4H, s, NC$\underline{H}_2$C=O), 5.18 (2H, s, C$\underline{H}_2$Ph), 7.06 7.31-7.47, 7.88 (9H, Ph).

^{13}C NMR (100 MHz, D_2O): δ (ppm) 43.3 (NHC$\underline{H}_2$=CO), 47.8-48.5, 51.0, 51.8 (cyclen ring $\underline{C}H_2$), 55.3 (NC$\underline{H}_2$=CO), 56.6 (NC$\underline{H}_2$=CO), 57.8 (NC$\underline{H}_2$=CO), 70.3 (C$\underline{H}_2$Ph), 115.1, 128.1, 128.4, 128.6, 128.9, 130.5, 136.1, 162.7 (Ph), 170.0 ($CH_2\underline{C}$=OO), 172.2 ($CH_2\underline{C}$=OO), 176.9 ($CH_2\underline{C}$=ONH), 198.2 ($CH_2\underline{C}$=O).

2.2 Preparation of Dy^{3+} complexes

The ligand was dissolved in H_2O and 0.95 equivalent of $DyCl_3 \cdot 6H_2O$ was added. Concentrated solutions of 1 M NaOH and 1 M HCl were used to adjust the pH to 5.5-6.0, keeping for 6 h. The xylenol Orange test was performed until no free metal was detected. The sample was adjusted to pH 7.0 and then filtered using 0.45 μm membrane filter.The concentration of Dy^{3+} was measured by inductively coupled plasma mass spectrometry (ICP-MS).

2.3 Dy(III)-10-[2-[4-(benzyloxy)phenyl]-2-oxoethyl-1,4,7,10-tetraazacyclododecane-1,7-di acetate acid-4-(2-acetamido)-L-glycine (Dy-4).



Scheme S2. Chemical structure of Dy-4.

2.4 Preparation of test complexes

The samples were diluted to 500 μL with target Dy^{3+} concentration (1, 2, 3 and 4 mM), while Dy-3 were diluted to 1.2, 2.4, 3.6 and 4.8 mM, and then lyophilized under vacuum. The lyophilized powders were dissolved into 450 μL different pH values PB buffers (5.5, 6.0, 6.5, 7.0, 7.5, 8.0) and 50 μL D_2O.

2.5 Relaxivity study of four complexes.

The T_1 and T_2 of samples were measured at 298 K using a Bruker AVANCE III 400 MHz vertical bore spectrometer. T_1 of the solvent water was measured using a standard inversion recovery sequence. T_2 of the solvent water was measured by the Carr-Purcell Meiboom-Gill (CPMG). Transverse relaxivities and longitudinal relaxivities were determined by linear fitting of the relaxation rates versus four different concentrations as shown in Fig. S1-S4.

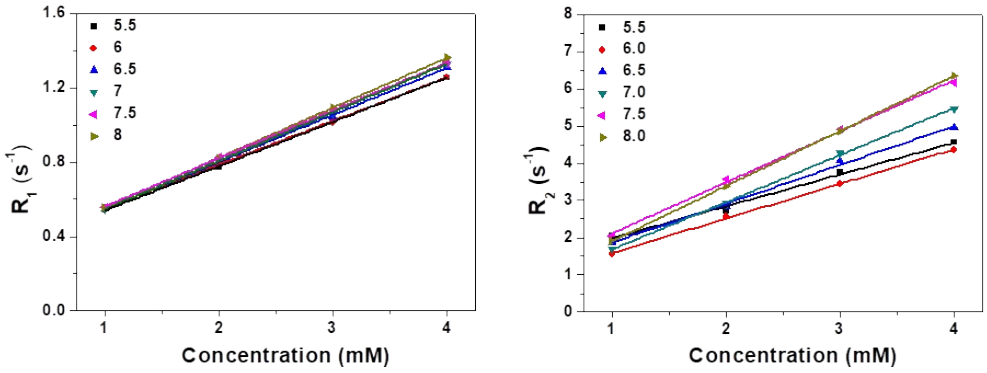


Figure S1. Determination of the r_1 and r_2 values for Dy-1 at different pH (5.5, 6.0, 6.5, 7.0, 7.5, 8.0), B_0= 9.4 T, T= 298 K.

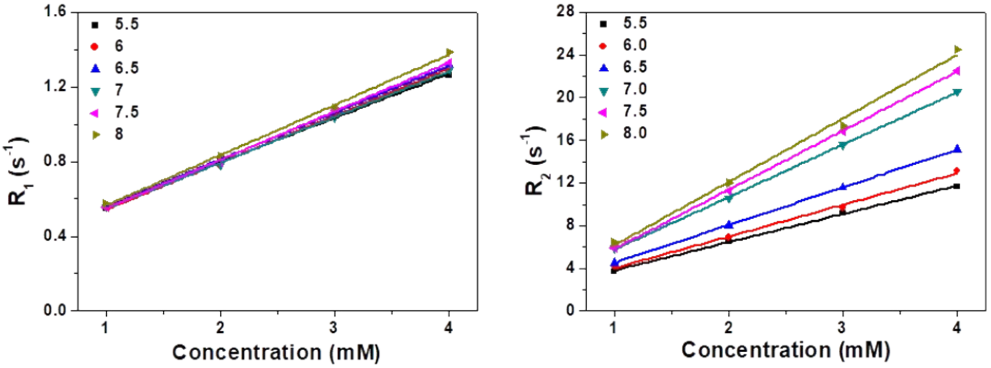


Figure S2. Determination of the r_1 and r_2 values for Dy-2 at different pH (5.5, 6.0, 6.5, 7.0, 7.5, 8.0), B_0= 9.4 T, T= 298 K.

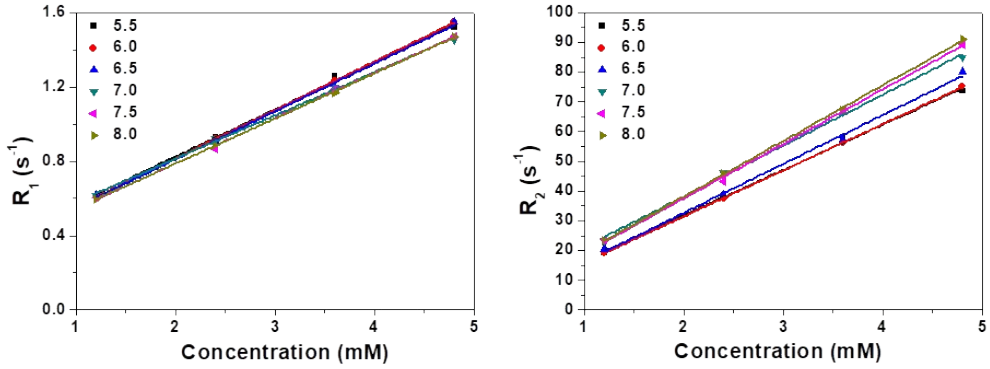


Figure S3. Determination of the r_1 and r_2 values for Dy-3 at different pH (5.5, 6.0, 6.5, 7.0, 7.5, 8.0), B_0= 9.4 T, T= 298 K.

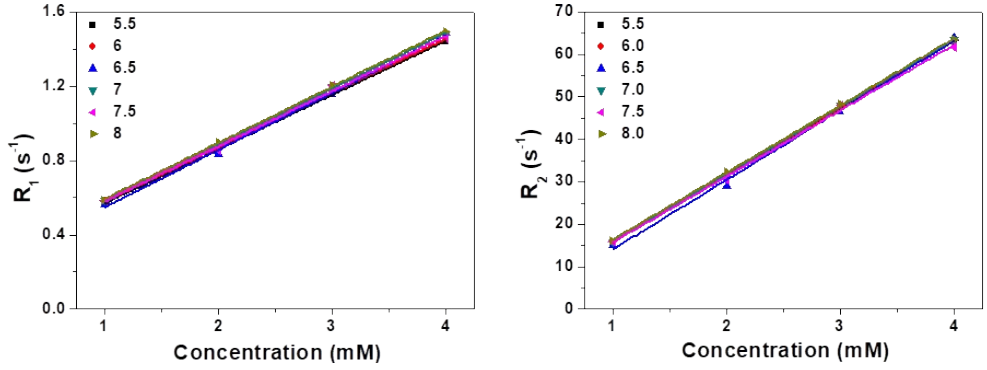


Figure S4: Determination of the r_1 and r_2 values for Dy-4 at different pH (5.5, 6.0, 6.5, 7.0, 7.5,

8.0), B_0= 9.4 T, T= 298 K.

2.6 Temperature dependent study

The T_2 of samples, including Dy-1, Dy-2 and Dy-3 at pH 5.5 and 8.0, were measured at 325 K on a Bruker AVANCE III 400 MHz vertical bore spectrometer, and the r_{2ex} values were given by linear fitting of the relaxation rates versus concentrations.

The Swift-Connick curve is a normal distribution curve, each r_{2ex} values mapping to two water residence times. The r_{2ex} values of Dy-1, Dy-2, Dy-3 at pH 5.5 and 8.0 at 298 K and 325 K were compared respectively, confirming the exact water residence time (Fig. S5).

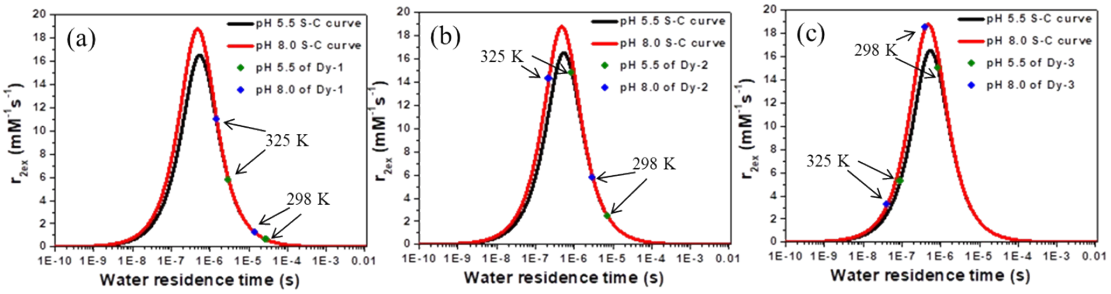


Figure S5. The Swift-Connick curves of (a) Dy-1, (b) Dy-2, (c) Dy-3 at two pH values (5.5 and 8.0) under 298 and 325 K. In here, we assume the chemical shifts of the bound water proton are the same that start from 730 ppm at pH 5.5 and it increase to 830 ppm at pH 8.0

2.7 Phantom study

The T_1 and T_2 phantom studies of Dy-2 (3 mM) at different pH values were performed on a 7.0 T Bruker BioSpec70/20USR. (T1: Repetition Time (TR)= 300 ms, Echo Time (TE)= 4.94 ms, Flip angle (FA)= 90. T2: TR= 3000 ms, TE= 40 ms, FA= 90.) The T_1 and T_2 values of 3 mM Dy-2 at six pH values were shown in Table S1.

pH	T_1 (s)	T_2 (ms)
5.5	1.22	112
6.0	1.20	106
6.5	1.15	92
7.0	1.13	76
7.5	1.23	72
8.0	1.10	62

Table S1. The T_1 and T_2 values of Dy-2 (3 mM).

3 NMR spectra of compound 5 to 15.

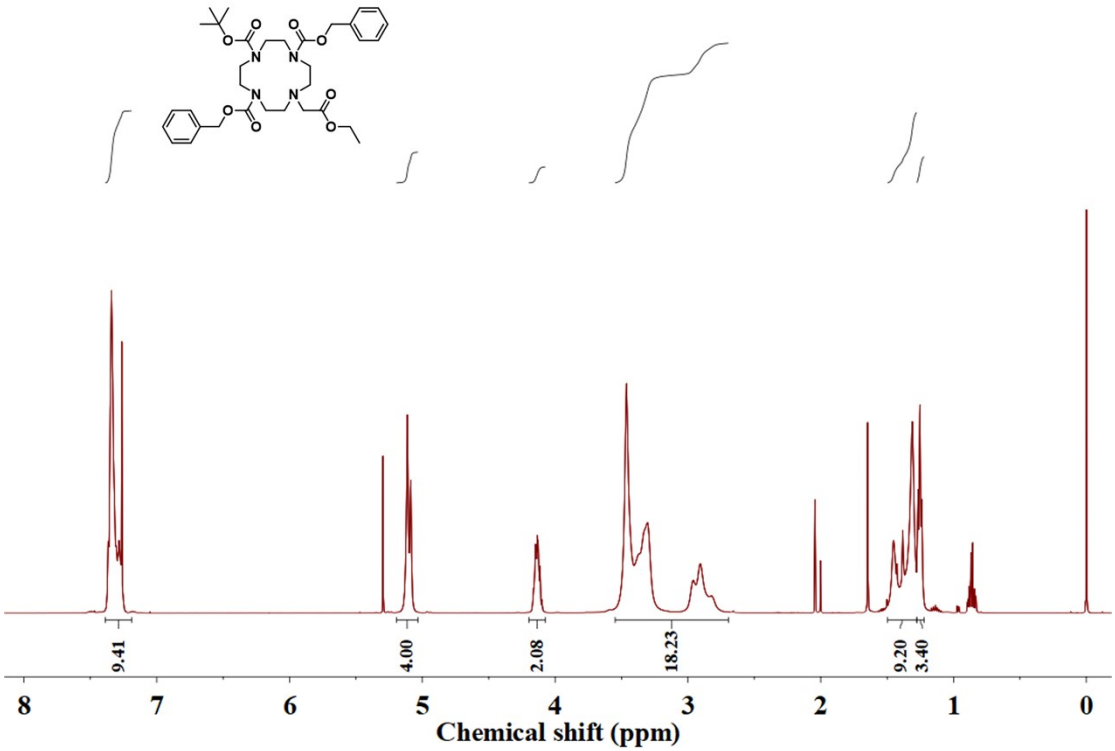


Figure S6. ^{1}H-NMR spectrum of 5 in $CDCl_3$.

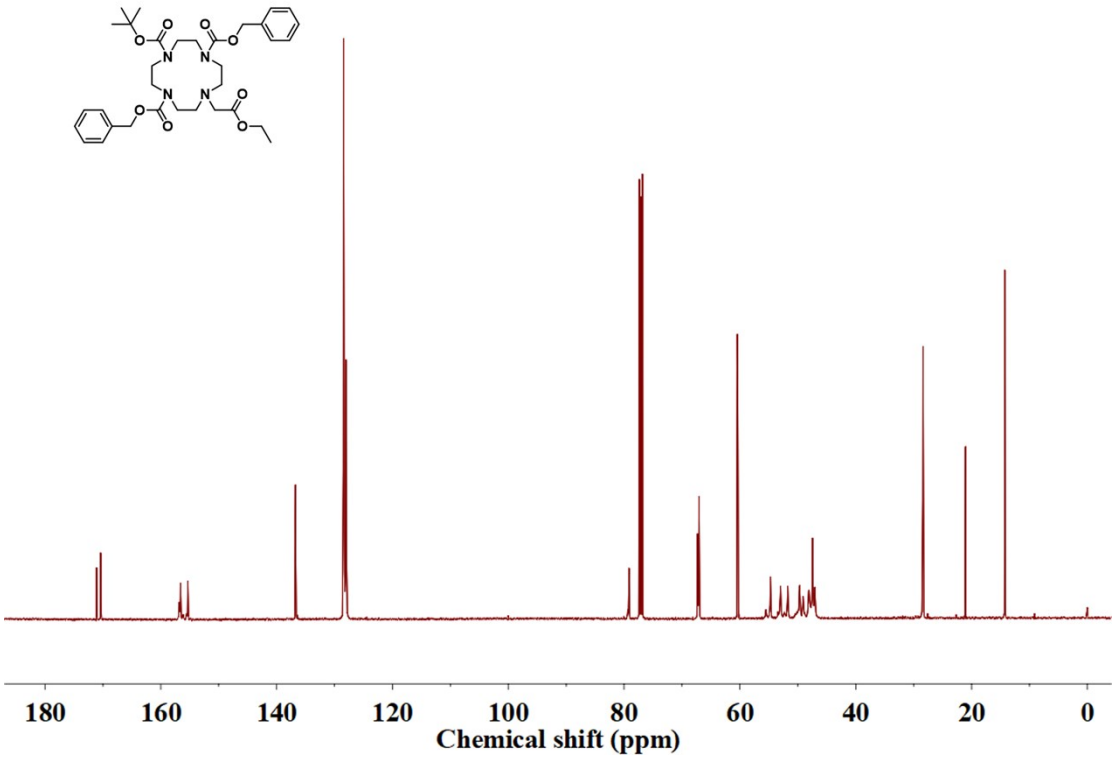


Figure S7. ^{13}C-NMR spectrum of 5 in $CDCl_3$.

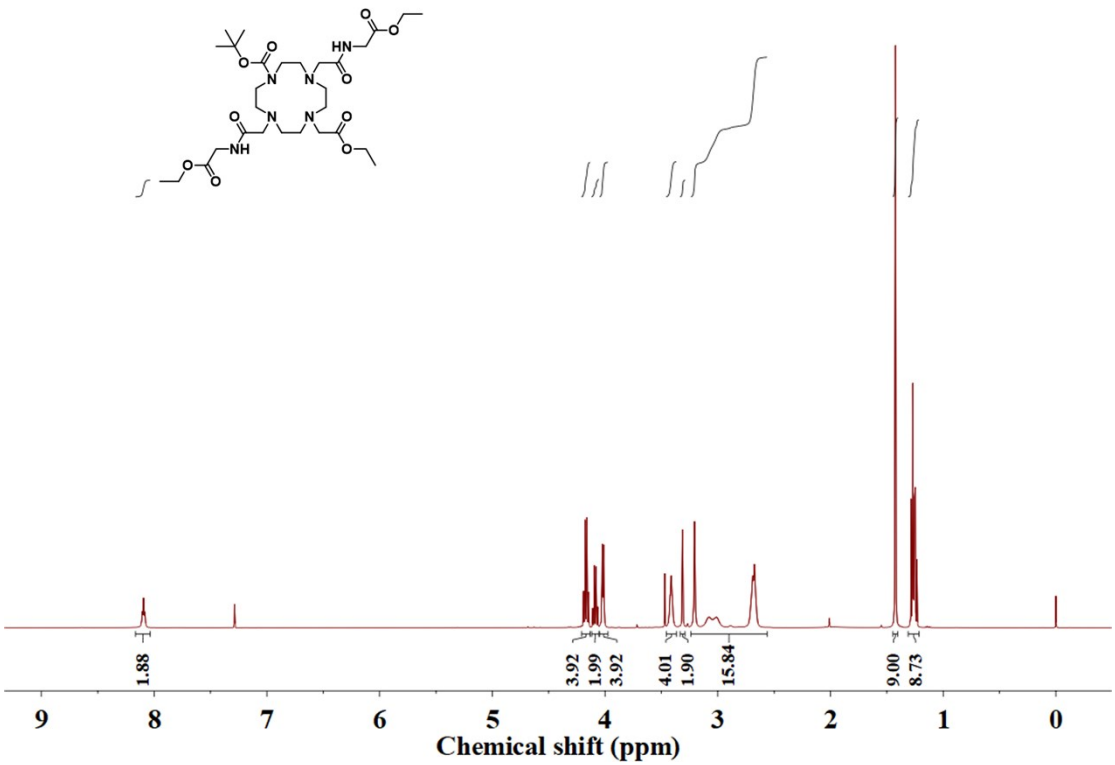


Figure S8. ^{1}H-NMR spectrum of 6 in $CDCl_3$.

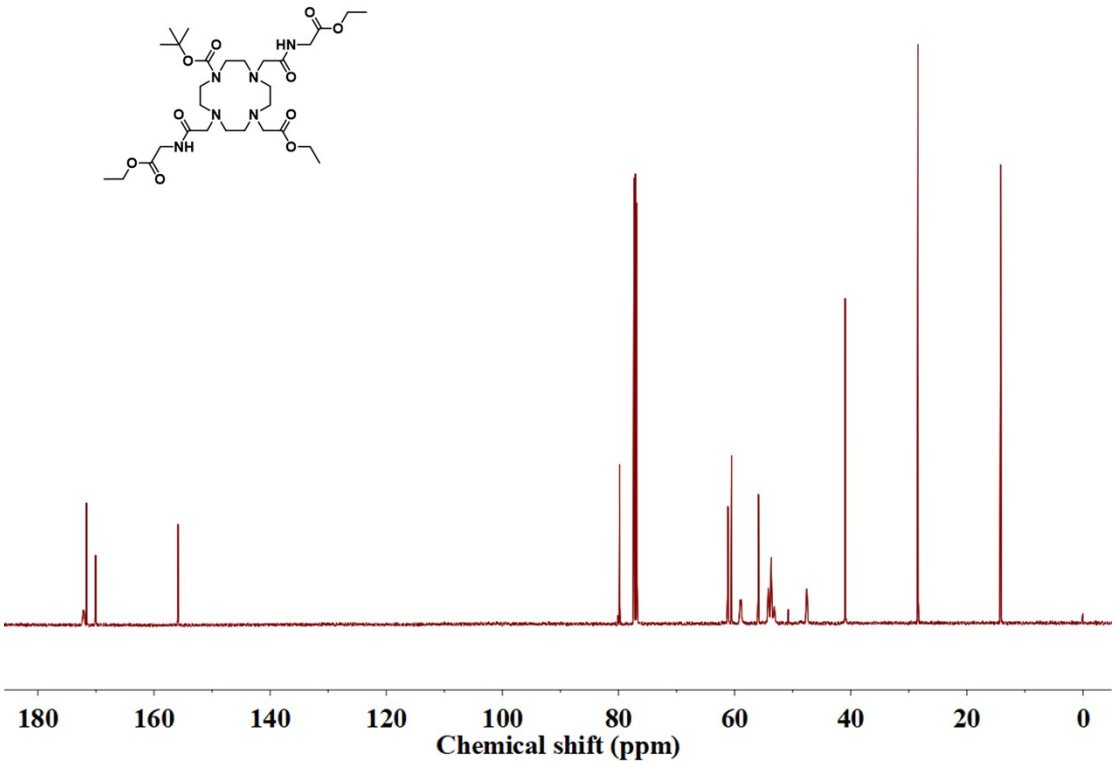


Figure S9. ^{13}C-NMR spectrum of 6 in $CDCl_3$.

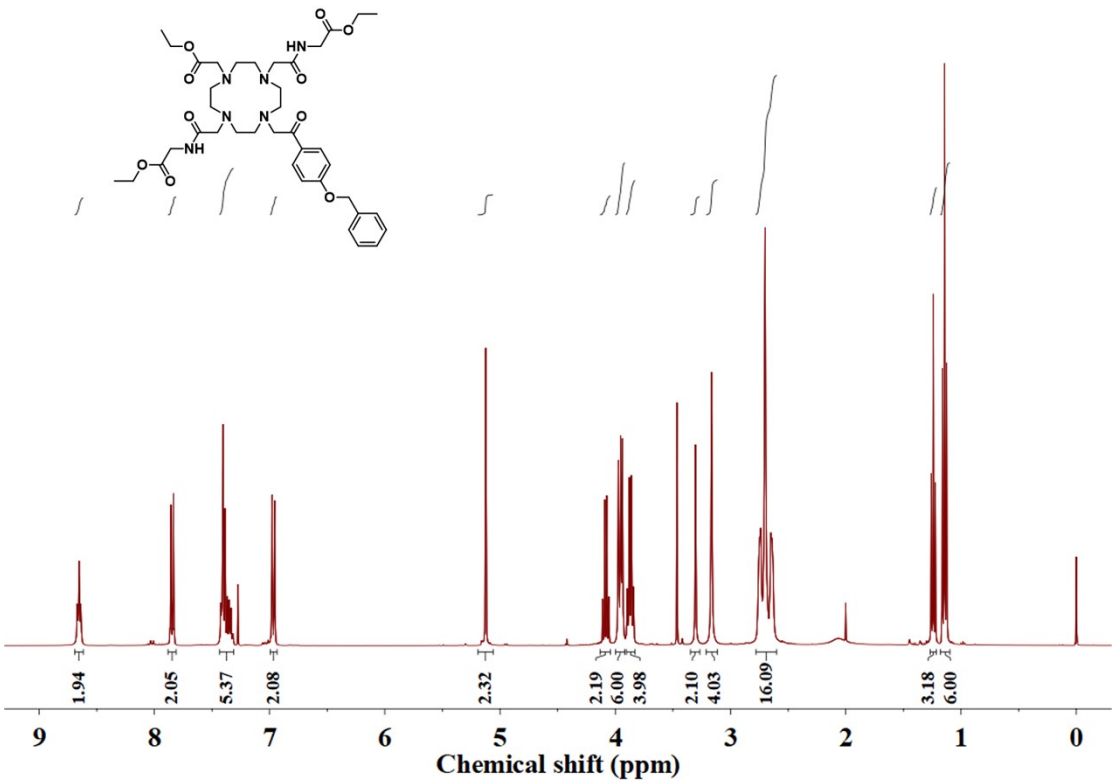


Figure S10. ^{1}H-NMR spectrum of 7 in $CDCl_3$.

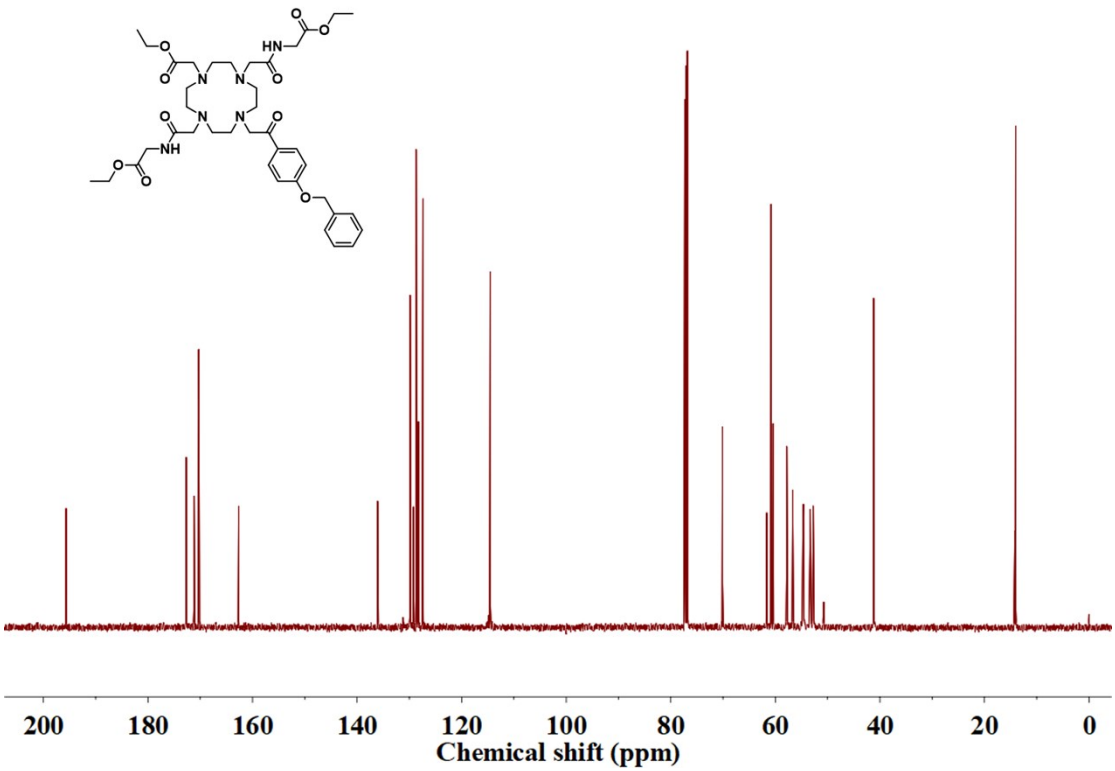


Figure S11. ^{13}C-NMR spectrum of 7 in $CDCl_3$.

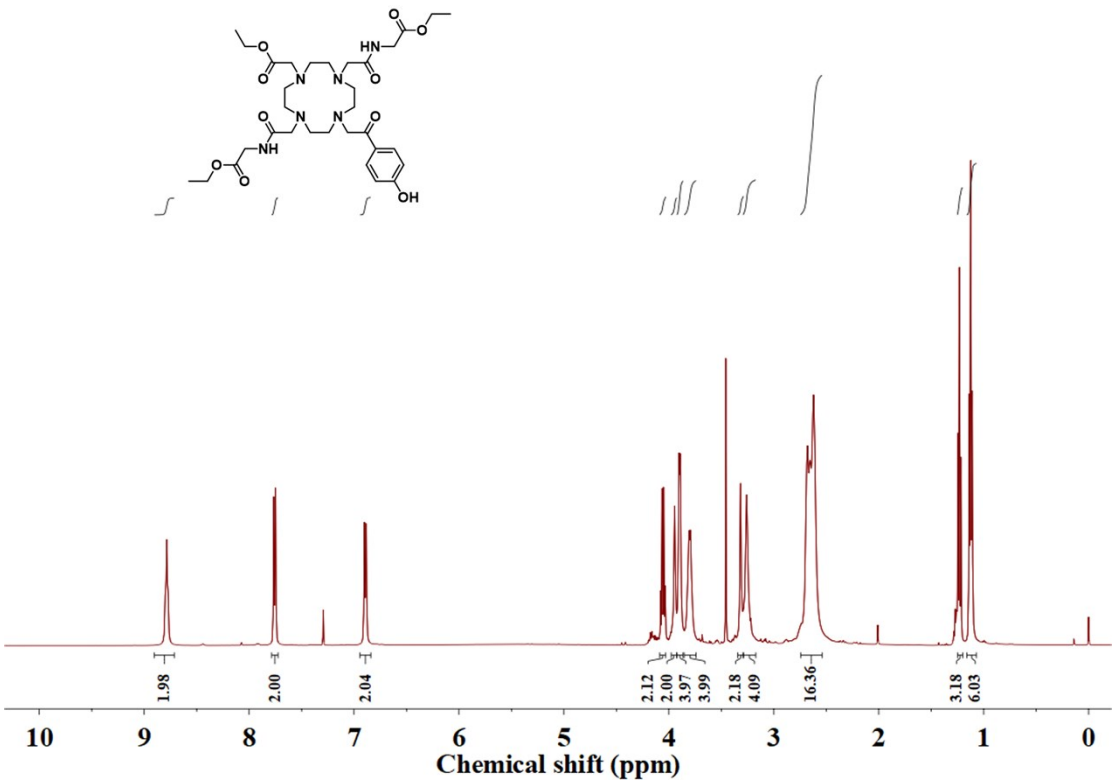


Figure S12. ^{1}H-NMR spectrum of 8 in $CDCl_3$.

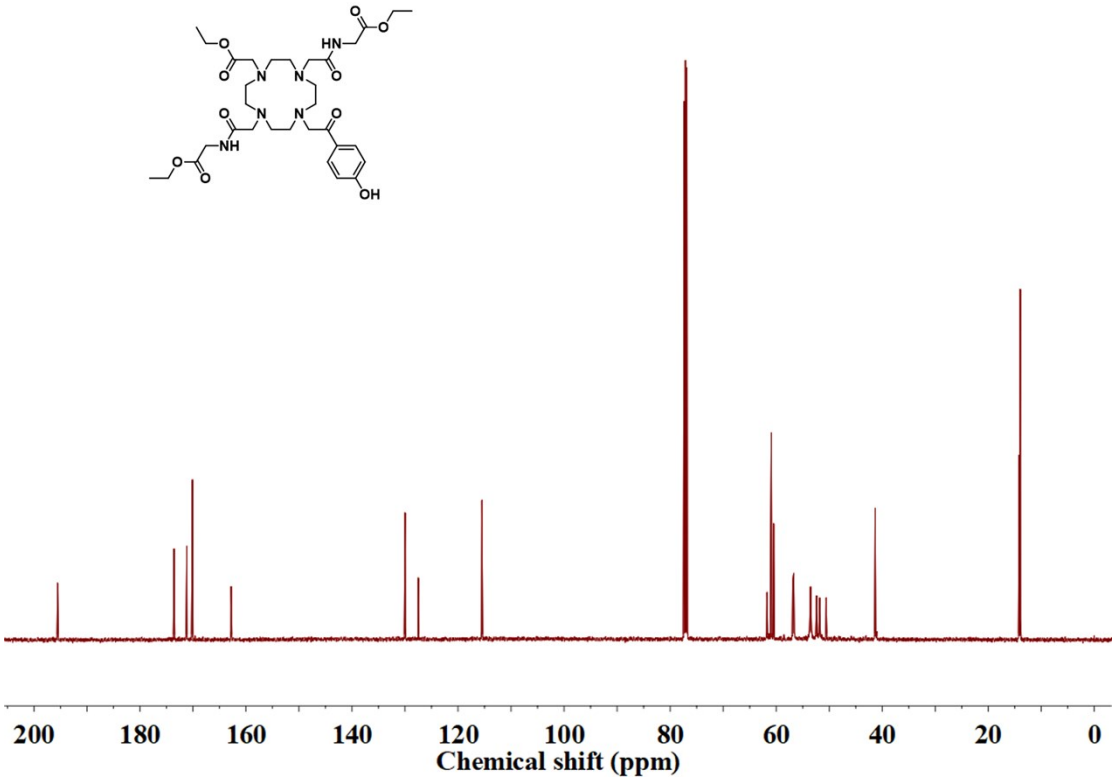


Figure S13. ^{13}C-NMR spectrum of 8 in $CDCl_3$.

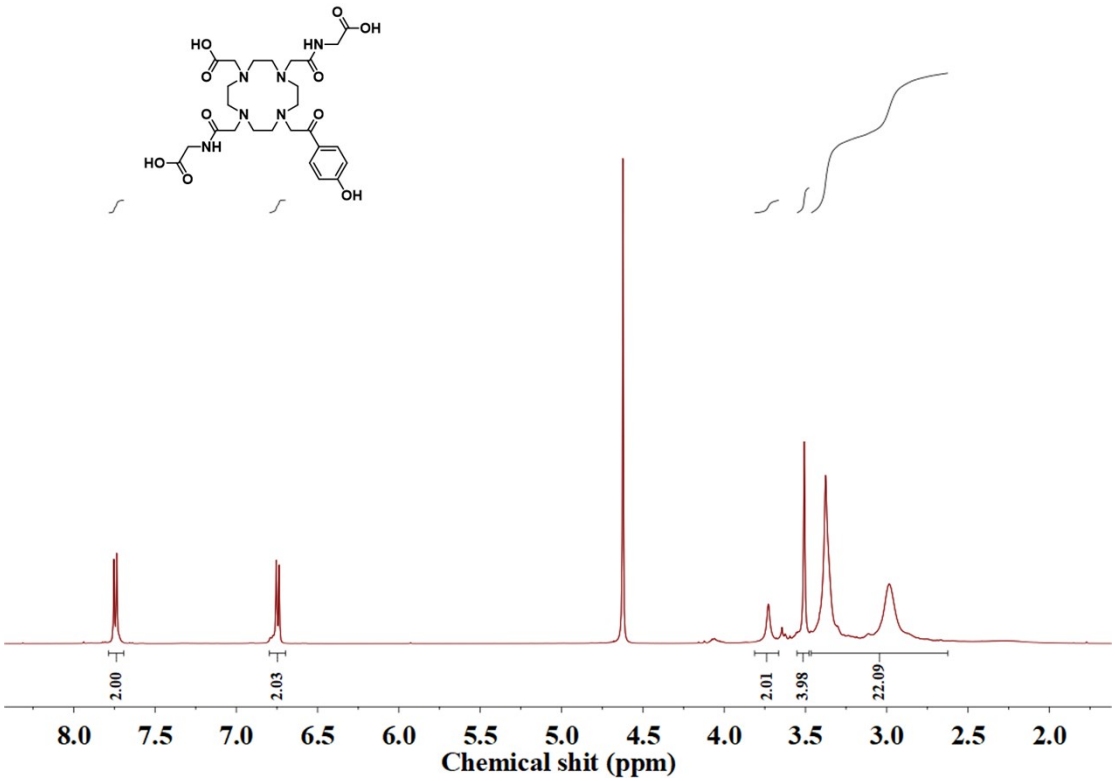


Figure S14. ^{1}H-NMR spectrum of 9 in D_2O.

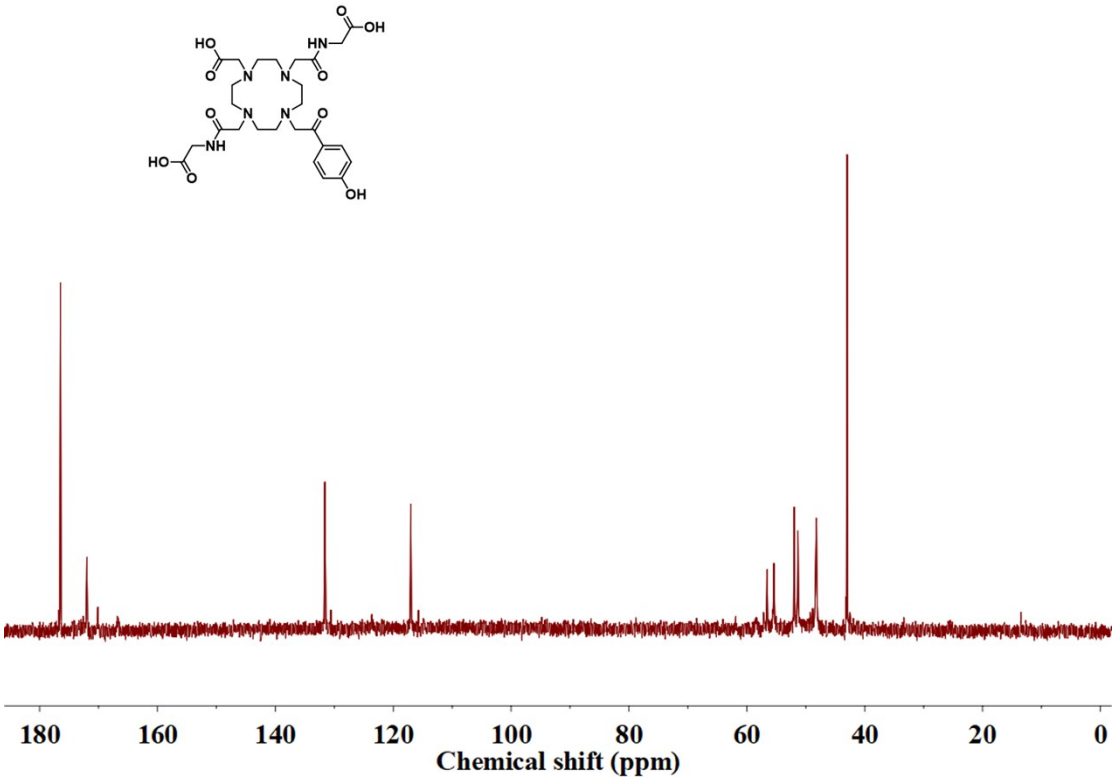


Figure S15. ^{13}C-NMR spectrum of 9 in D_2O.

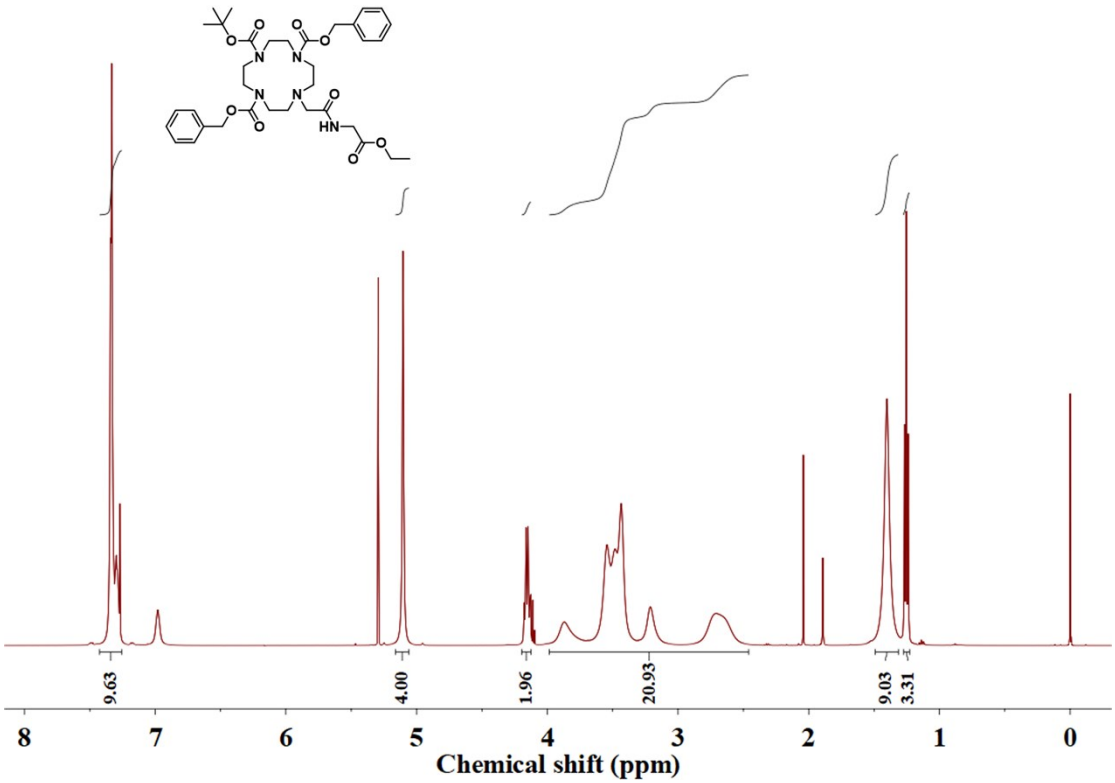


Figure S16. ^{1}H-NMR spectrum of 10 in $CDCl_3$.

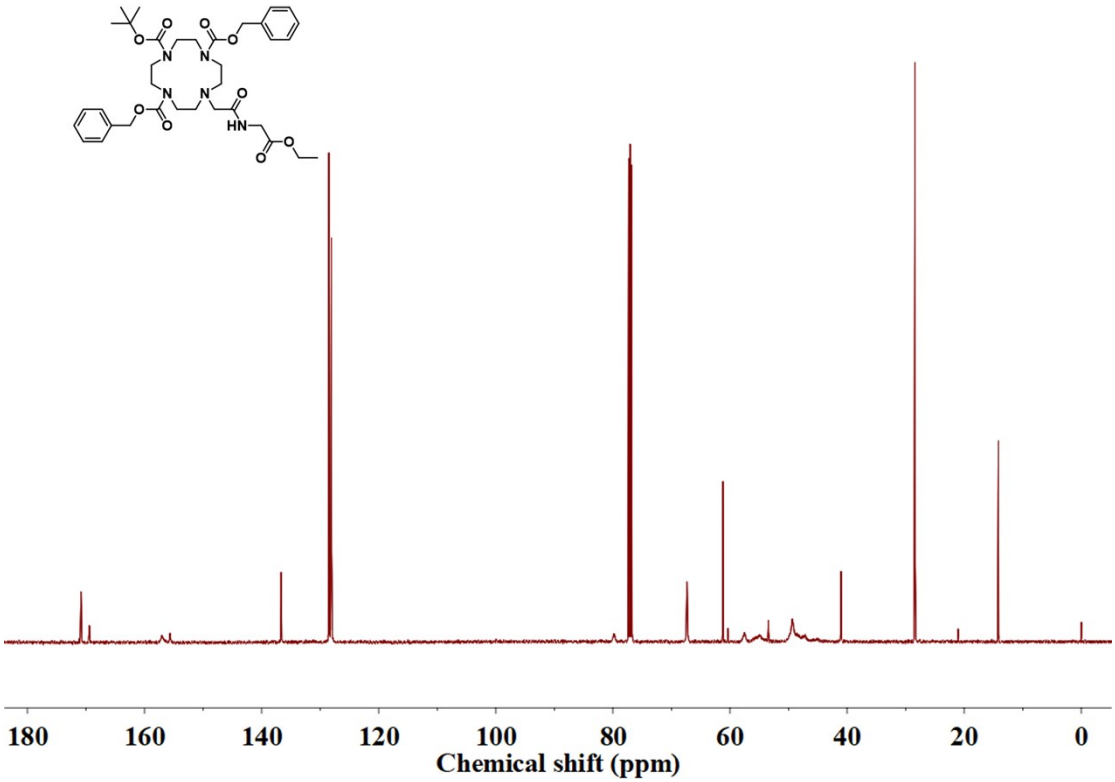


Figure S17. ^{13}C-NMR spectrum of 10 in $CDCl_3$.

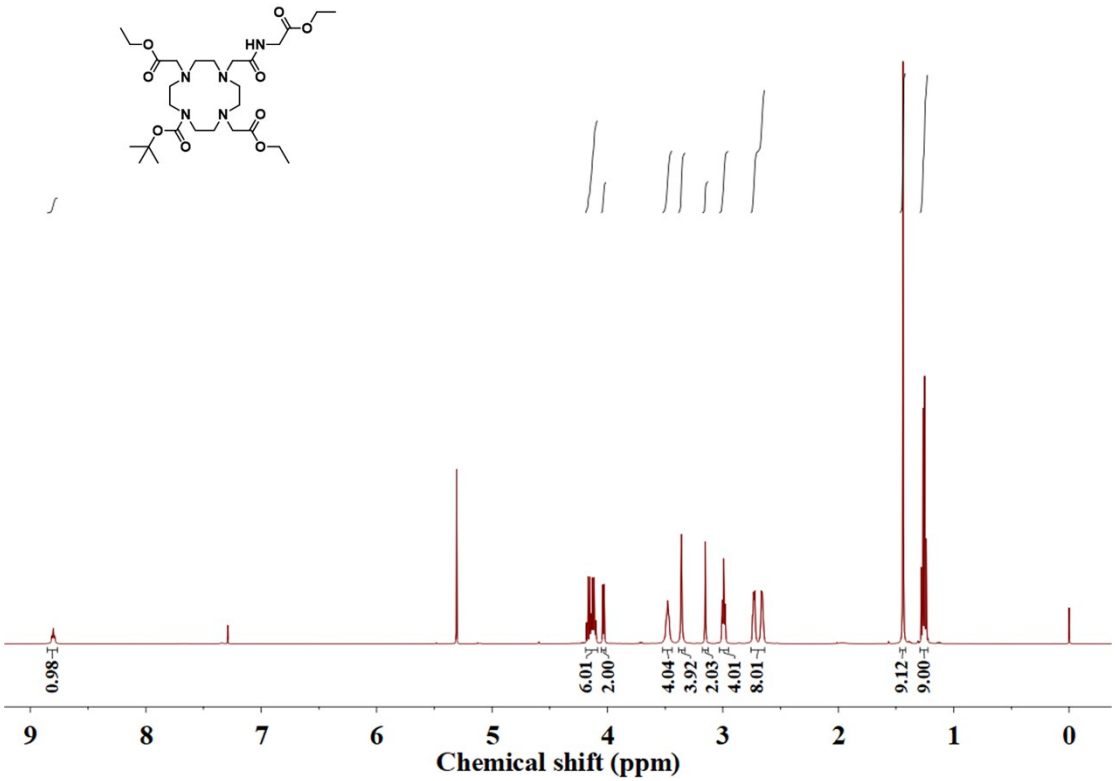


Figure S18. ^{1}H-NMR spectrum of 11 in $CDCl_3$.

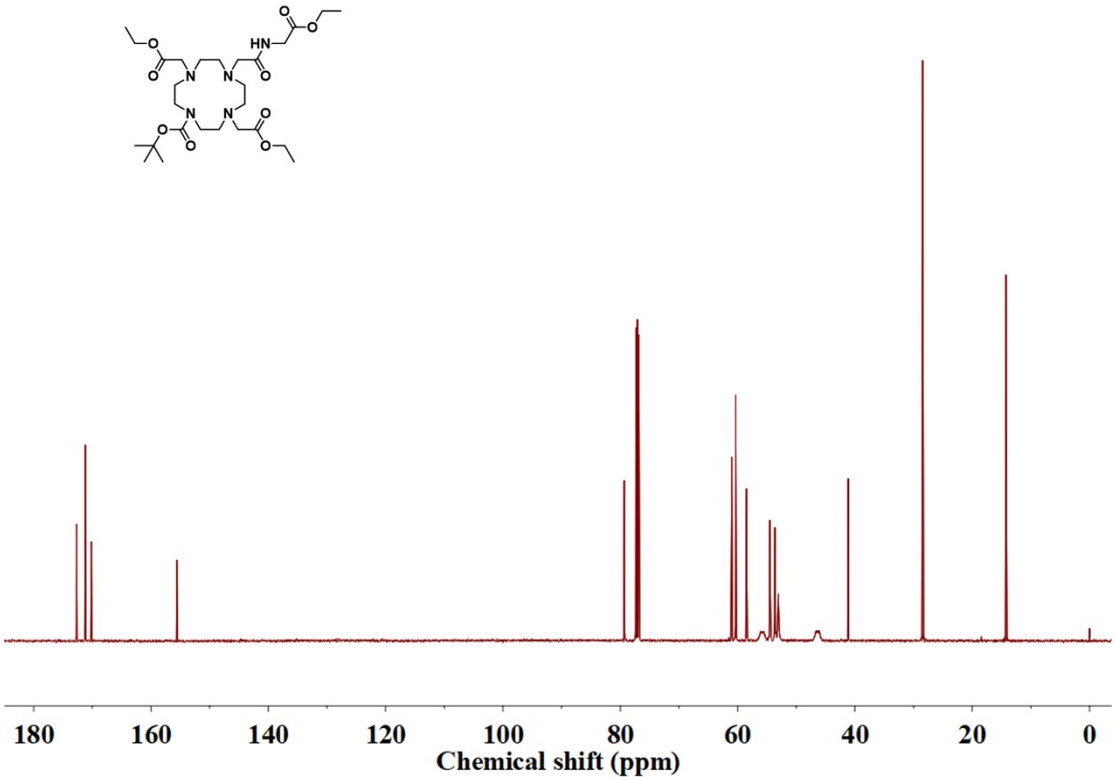


Figure S19. ^{13}C-NMR spectrum of 11 in $CDCl_3$.

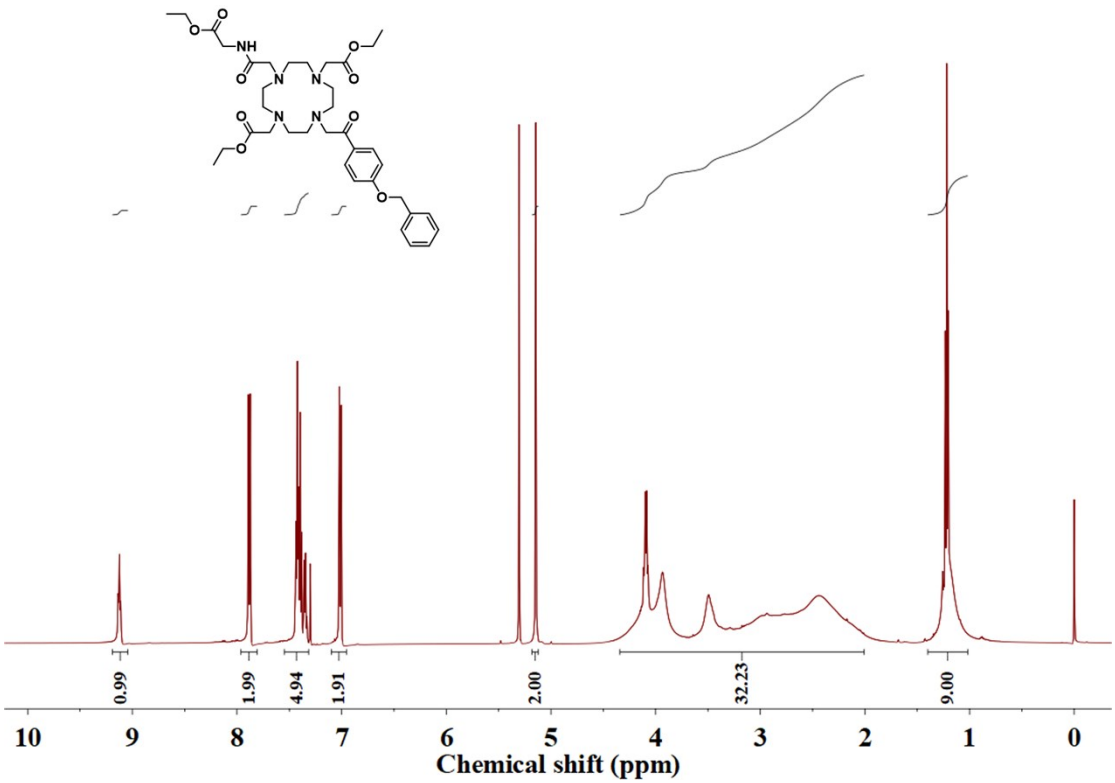


Figure S20. ^{1}H-NMR spectrum of 12 in $CDCl_3$.

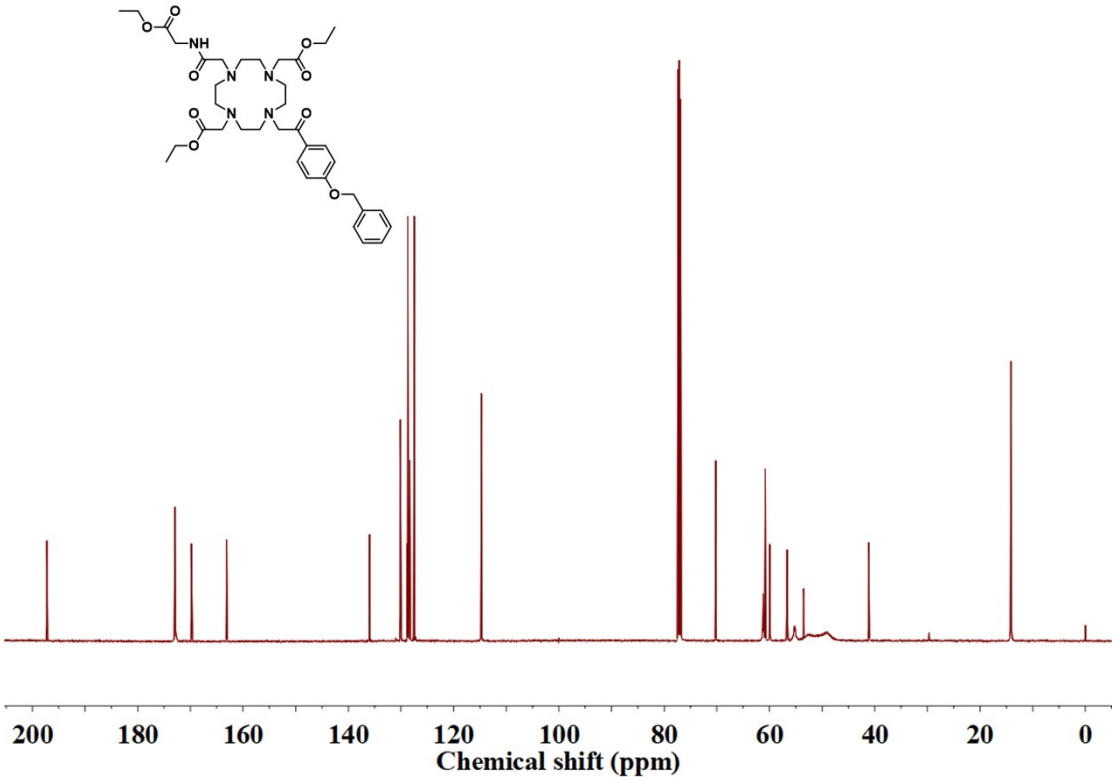


Figure S21. ^{13}C-NMR spectrum of 12 in $CDCl_3$.

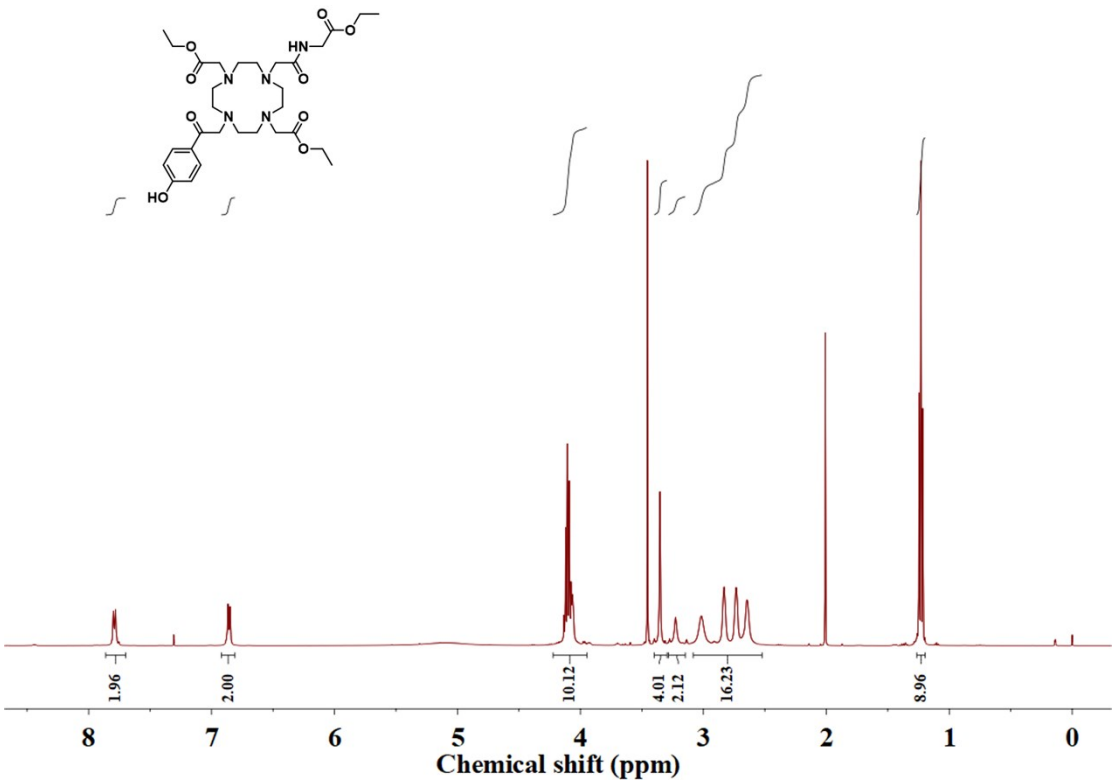


Figure S22. ^{1}H-NMR spectrum of 13 in $CDCl_3$.

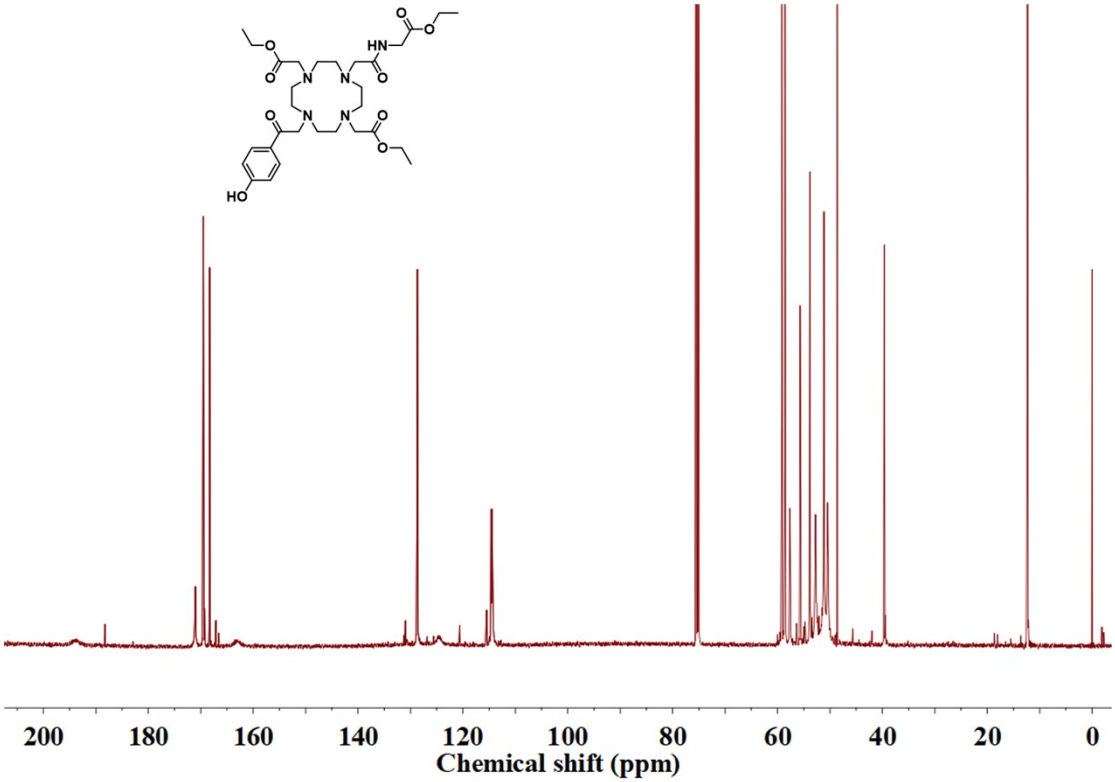


Figure S23. ^{13}C-NMR spectrum of 13 in $CDCl_3$.

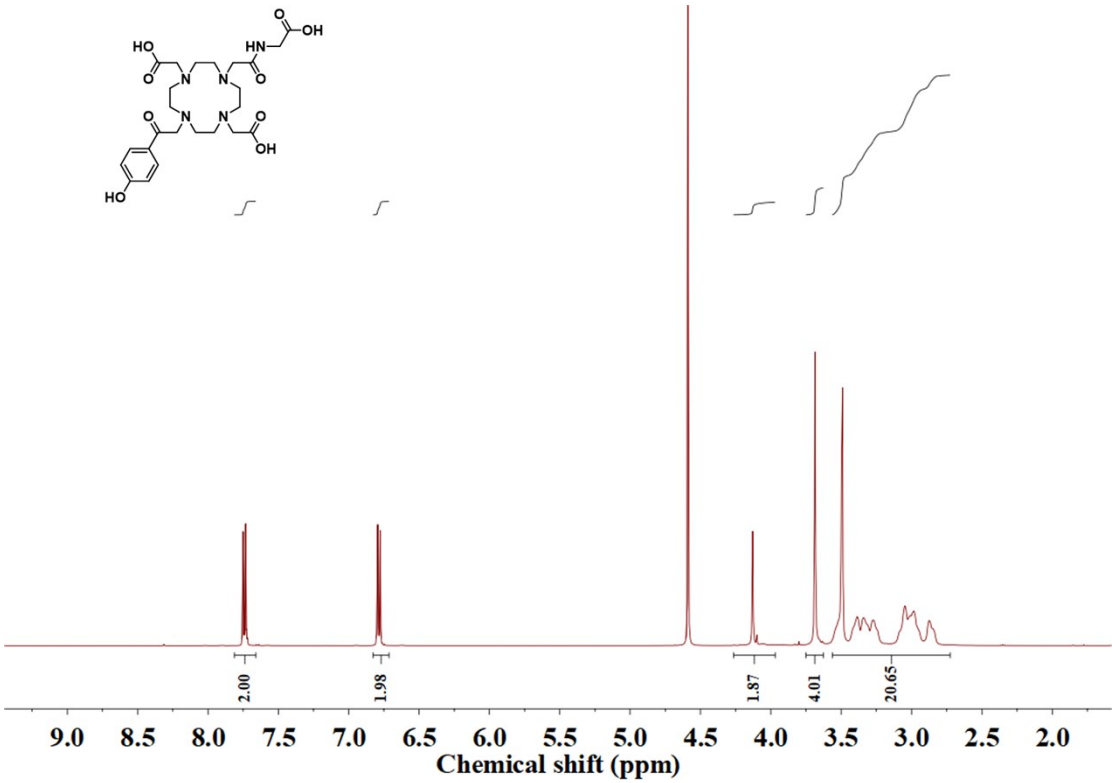


Figure S24. ^{1}H-NMR spectrum of 14 in D_2O.

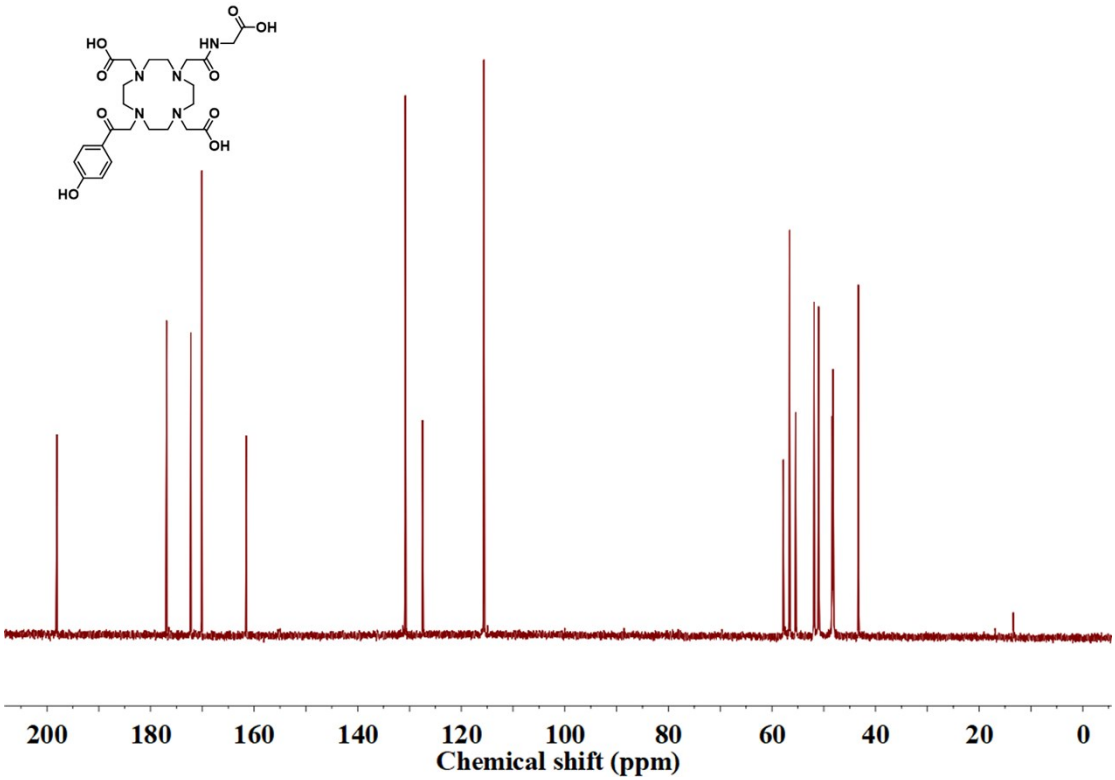


Figure S25. ^{13}C-NMR spectrum of 14 in D_2O.

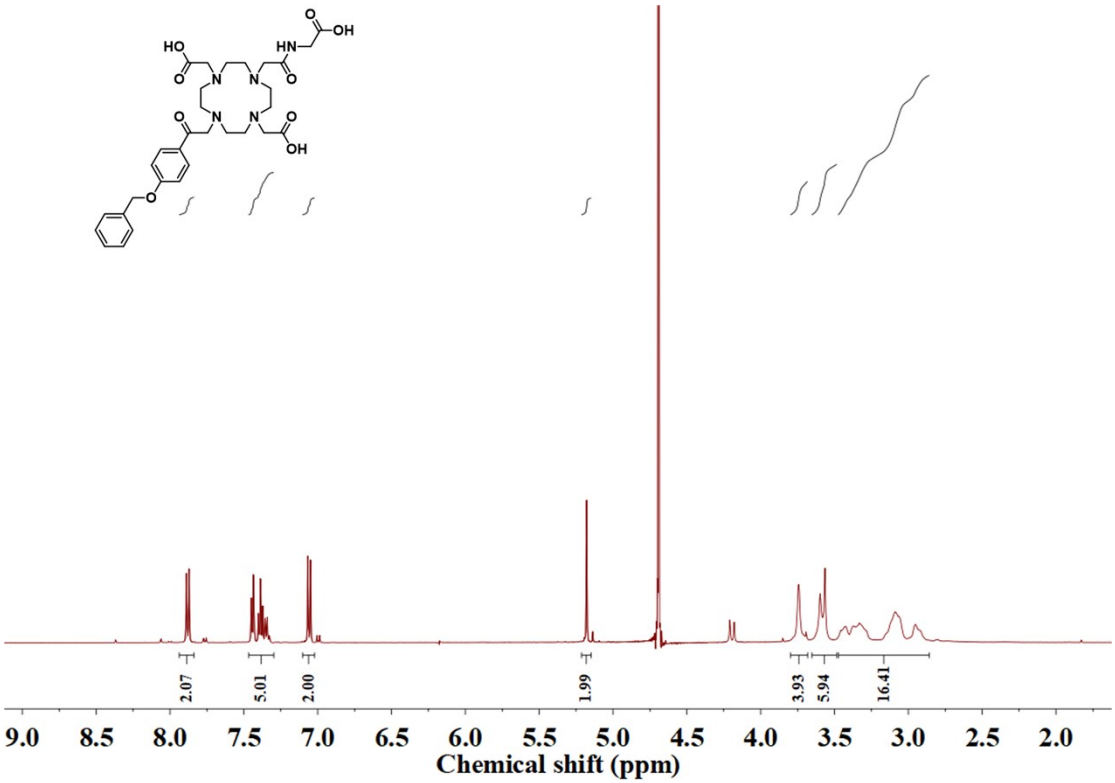


Figure S26. ^{1}H-NMR spectrum of 15 in D_2O.

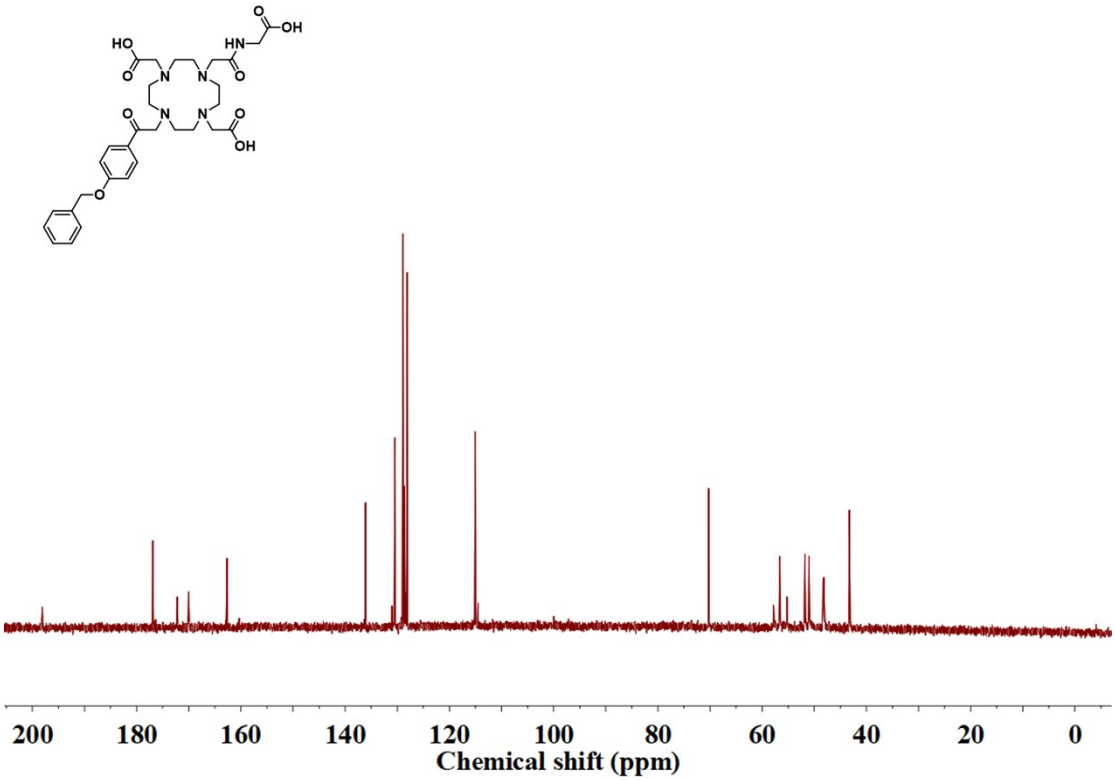


Figure S27. ^{13}C-NMR spectrum of 15 in D_2O.

4 LC-MS spectra of Dy1-4

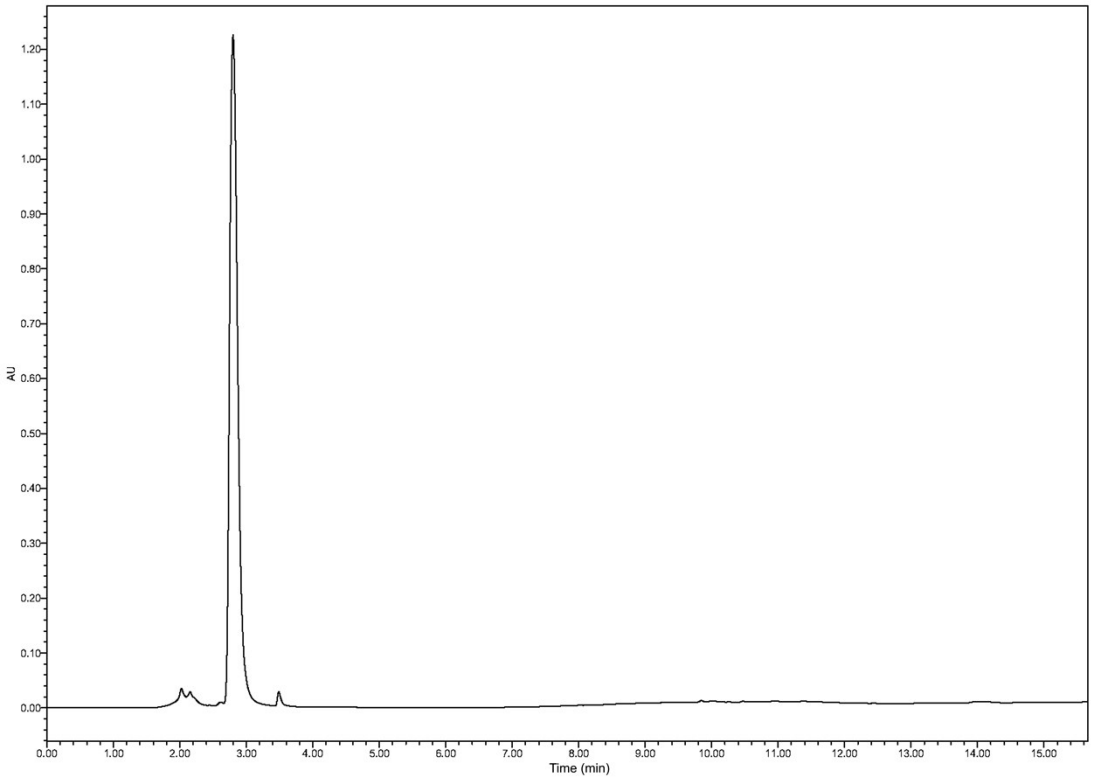


Figure S28. HPLC spectrum of Dy-1

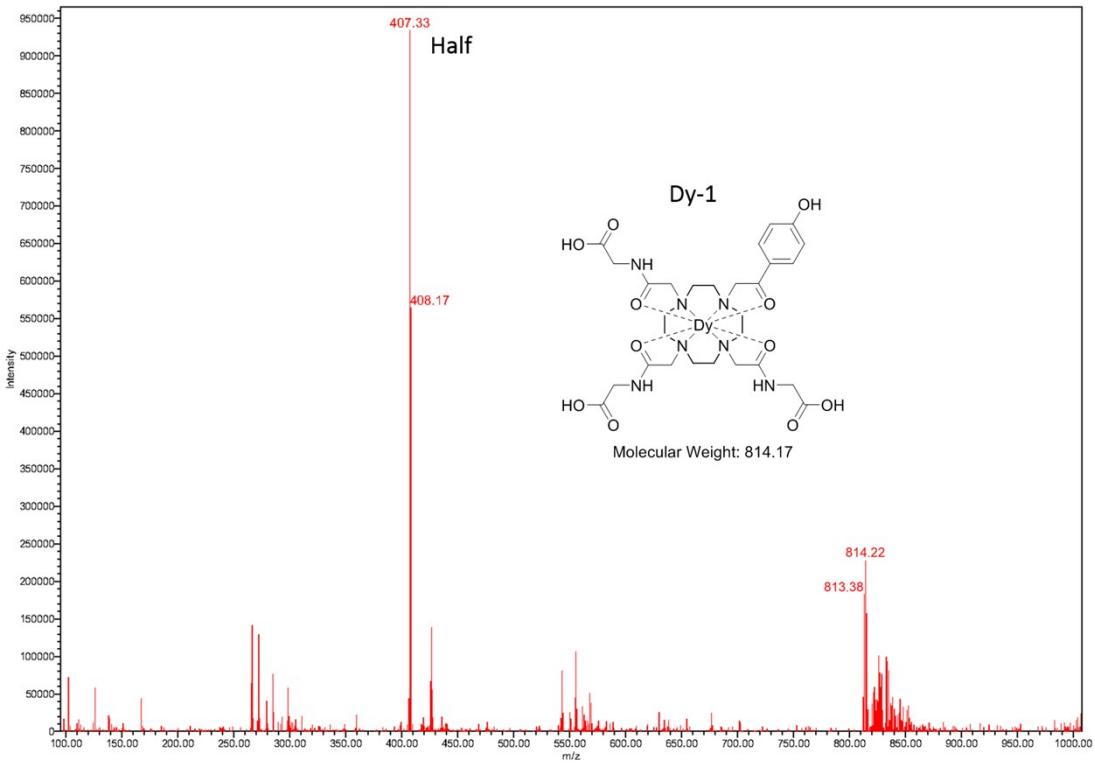


Figure S29. Mass spectrum of Dy-1

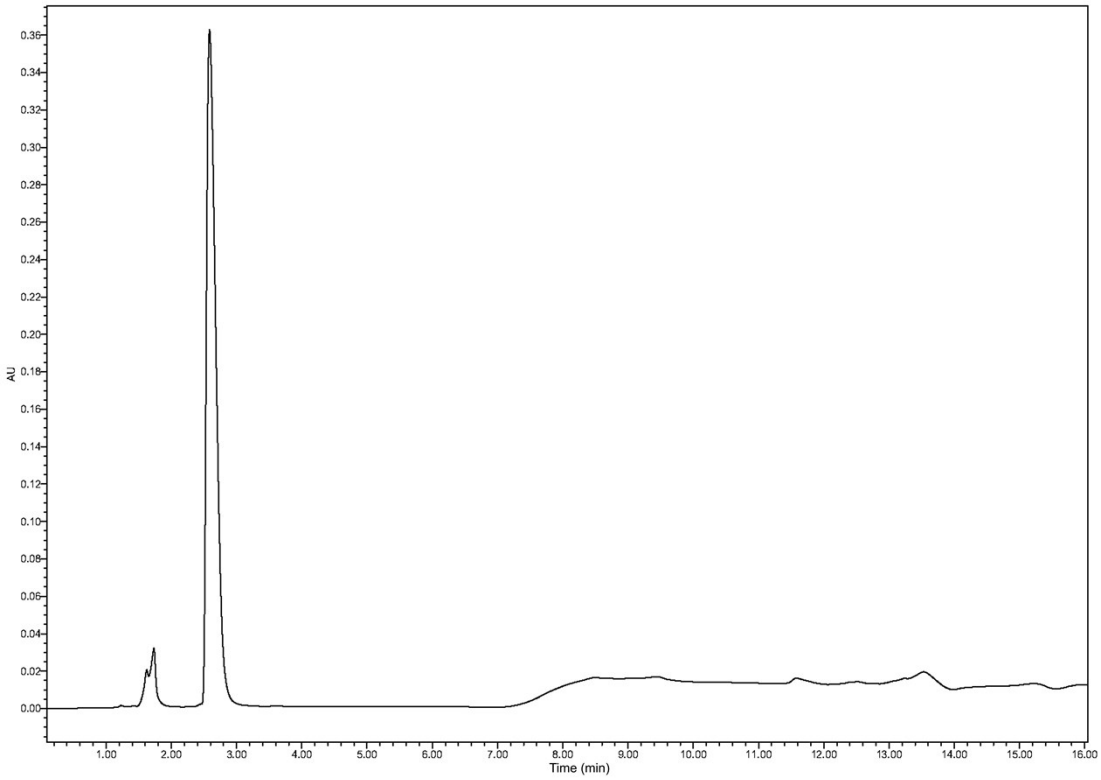


Figure S30. HPLC spectrum of Dy-2

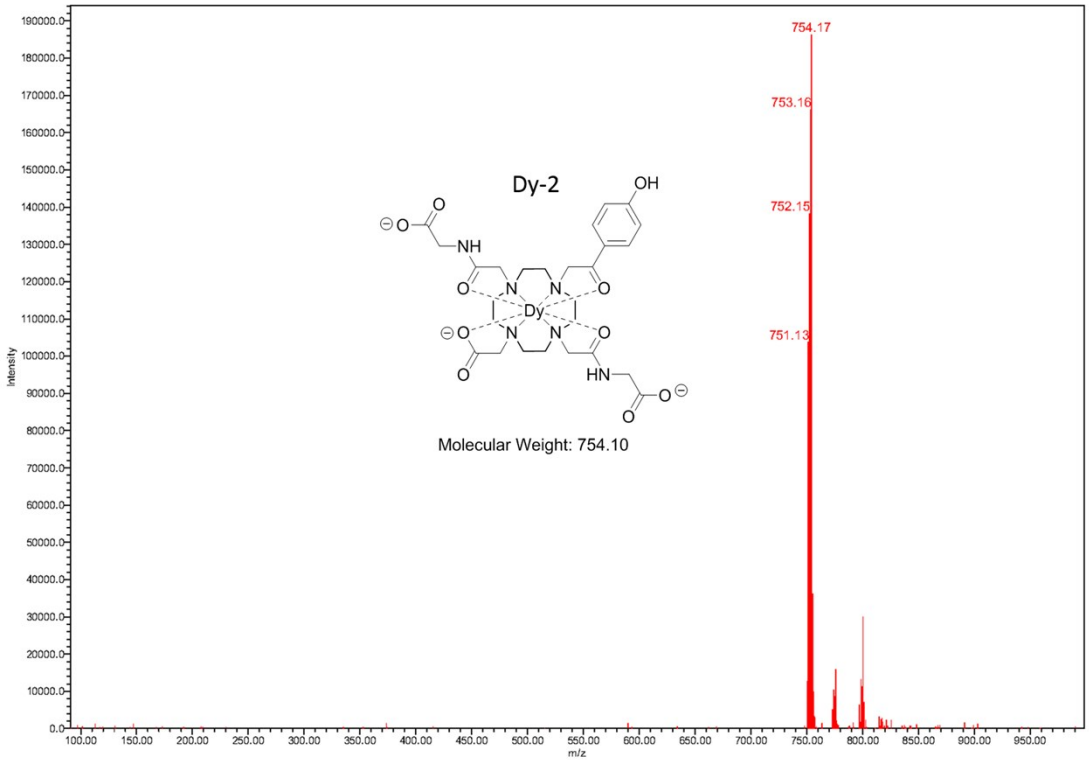


Figure S31. Mass spectrum of Dy-2

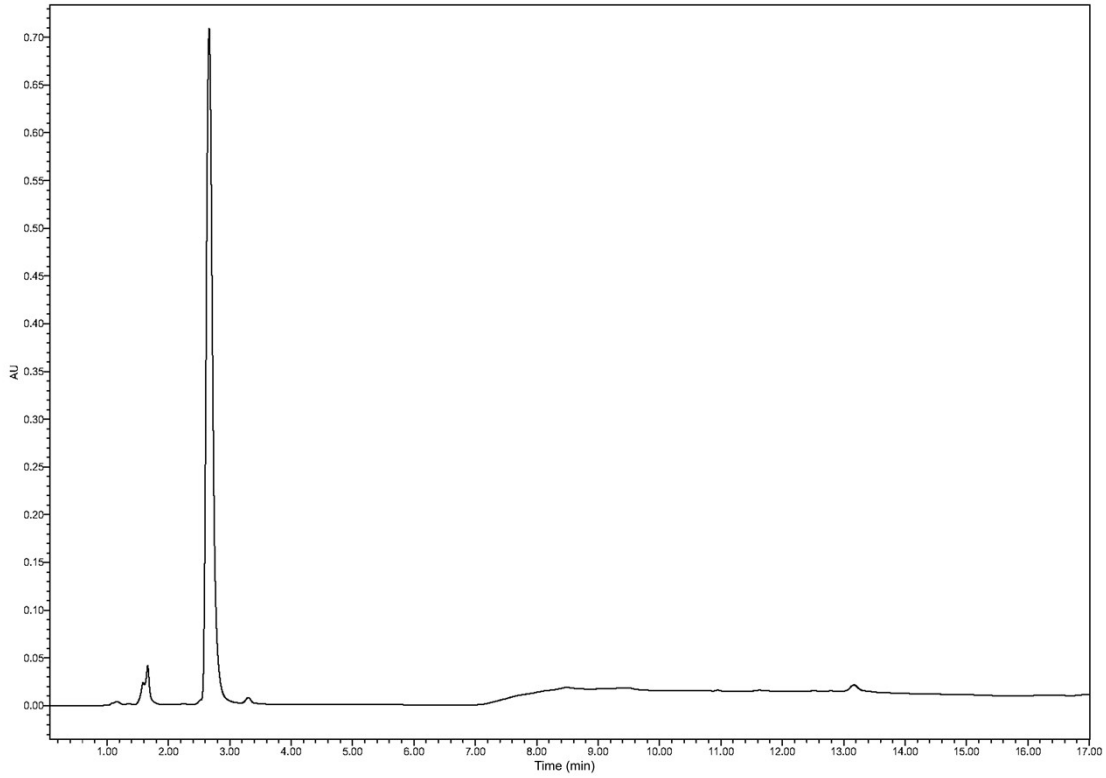


Figure S32. HPLC spectrum of Dy-3

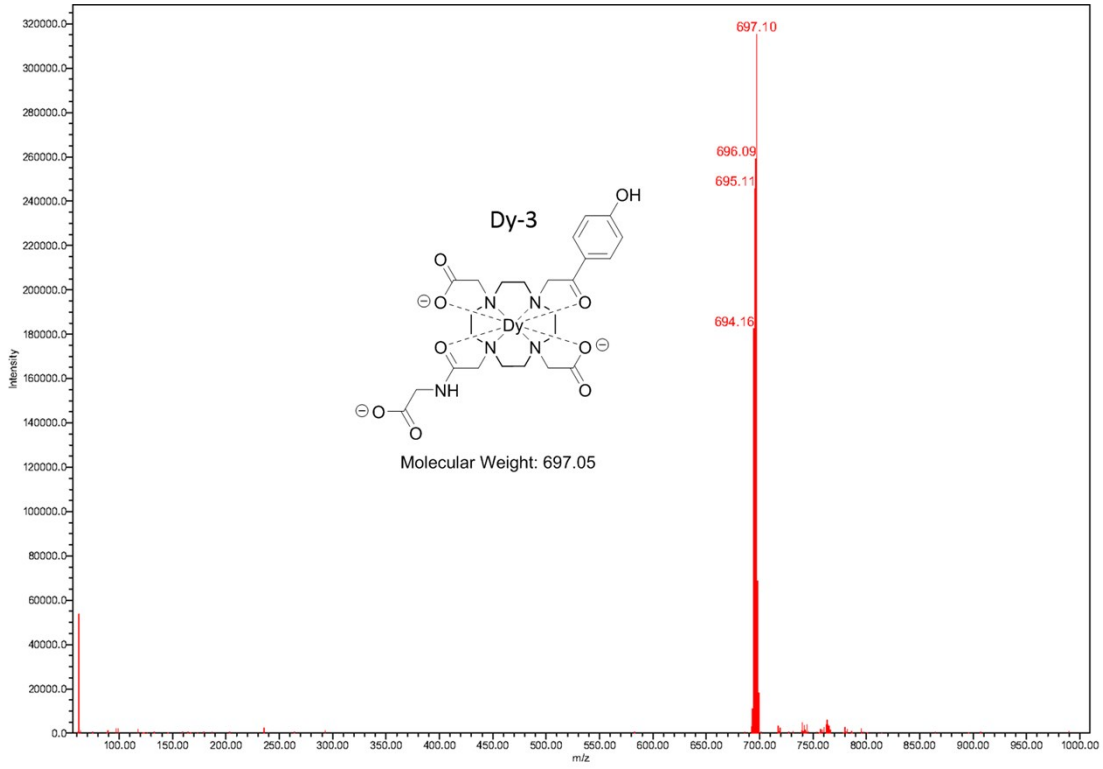


Figure S33. Mass spectrum of Dy-3

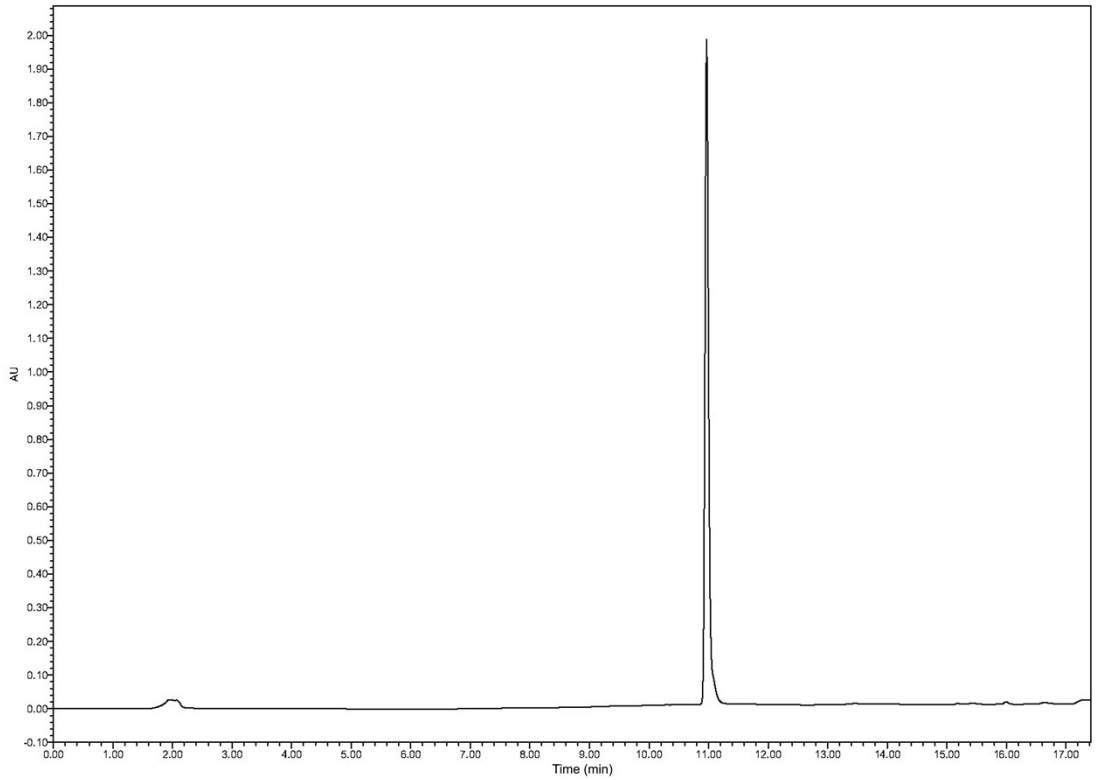


Figure S34. HPLC spectrum of Dy-4

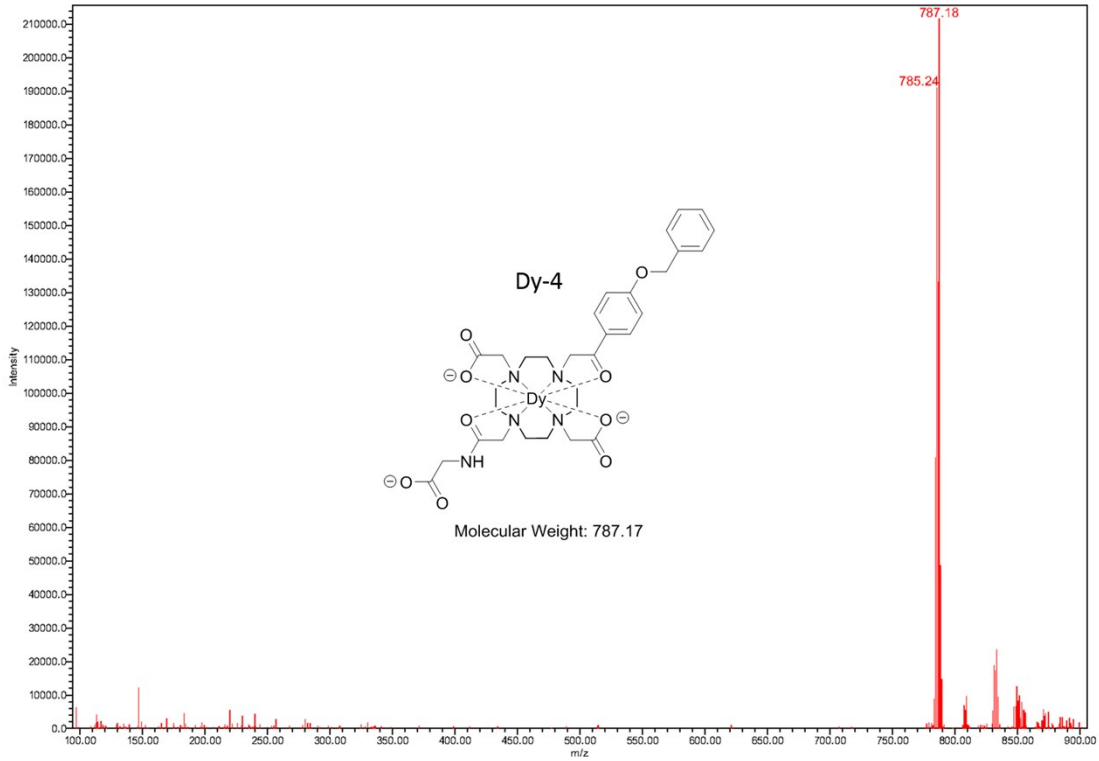


Figure S35. Mass spectrum of Dy-4

Reference

[1] Y. Wu, T. C. Soesbe, G. E. Kiefer, P. Zhao, A. D. Sherry, *Journal of the American*

Chemical Society **2010**, *132*, 14002-14003.

[2] K. N. Green, S. Viswanathan, F. A. Rojas-Quijano, Z. Kovacs, A. D. Sherry, *Inorganic Chemistry* **2011**, *50*, 1648-1655.