Supporting Information

A highly efficient bifunctional ligand 3p-*C*-NETA for radioimmunotherapy applications

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1. Experimental Section

Instruments and Methods. ^{1}H, ^{13}C, and DEPT NMR spectra were obtained using a Bruker 300 instrument and chemical shifts are reported in parts per million on the δ scale relative to TMS. Elemental microanalyses were performed by Galbraith Laboratories, Knoxville, TN. Fast atom bombardment (FAB) high-resolution mass spectra (HRMS) were obtained on JEOL double sector JMS-AX505HA mass spectrometer (University of Notre Dame, South Bend, IN). The analytical HPLC was performed on an Agilent 1200 equipped with a diode array detector (λ = 254 and 280 nm), a themostat set at 35 °C, and a Zorbax Eclipse XDB-C18 column (4.6 × 150 mm, 80Å). The mobile phase of a binary gradient (0–100% B/40 min; solvent A, 0.05M AcOH/Et_3N, pH 6.0; solvent B, CH_3CN for method 1 or 0-50% B/30 min, 50-100% B/31min, 100%B/40min; solvent A, 0.05M AcOH/Et_3N, pH 6.0; solvent B, CH_3OH for method 2) at a flow rate of 1 mL/min was used. Size-exclusion HPLC (SE-HPLC) chromatograms were obtained on an Agilent 1200 equipped with an in-line IN/US γ-Ram Model 2 radiodetector (Tampa, FL), fitted with a TSKgel G3000PW column (Tosoh Biosep, Montgomeryville, PA). The isocratic mobile phase (0.05M $NaSO_4$, 0.02M NaH_2PO_4, 0.05% NaN_3, pH 6.8) at a flow rate of 1 mL/min was used for SE-HPLC. ^{90}Y and ^{177}Lu in the chloride form was obtained from NEN Perkin-Elmer.

Caution: ^{90}Y ($t_{1/2}$ = 72 h) is a β-emitting radionuclide. ^{177}Lu ($t_{1/2}$ = 6.7 days) is a β/γ-emitting radionuclide. Appropriate shielding and handling protocols should be in place when using the isotope.

4-nitrophenylpropyl bromide (2).[15] 1-bromo-3-phenylpropane **1** (10.0g, 50.3 mmol) was dissolved in the mixture of acetic anhydride (10.25 g, 100.6 mmol) and acetic acid (6.04 g, 100.6 mmol), and the resulting mixture was maintained at –40 °C while fuming nitric acid (6.33 g,

100.6 mmol) was added dropwise over 3.5 h. The resulting mixture was allowed to warm to room temperature and then neutralized in ice water with ammonium hydroxide. The reaction mixture was extracted with ethyl acetate (3 × 100 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo* to the dryness. The residue was purified via column chromatography on silica gel (220-440 mesh) eluting with 0.1% EtOAc in hexanes to provide the pure product as yellow oil **2** (5.29 g, 53%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.15-2.26 (m, 2H), 2.92 (t, J = 7.7 Hz, 2H), 3.39 (t, J = 6.4 Hz, 2H), 7.35 (d, J = 8.7 Hz, 2H), 8.15 (d, J = 9.1 Hz, 2H); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 32.5 (t), 33.5 (t), 33.6 (t), 123.8 (t), 129.4 (d), 146.6 (s), 148.4 (s).

2-Acetylamino-2-[3-(4-nitrophenyl)propyl]malonic acid diethyl ester (3). To a round bottom flask containing anhydrous EtOH (60 mL) was added portionwise Na (1.58 g, 68.66 mmol). To a clear solution of NaOEt was dropwise added a solution of diethyl acetamido malonate (14.92 g, 68.66 mmol) in ethanol (140 mL) over 30 min. The resulting mixture was then heated at 50 °C for 1.5 h and then reflux for 10 min. The solution became cloudy and light brownish indicating formation of deprotonated diethyl acetamido malonic ester. To the reaction mixture under reflux was dropwise added **2** (16.76 g, 68.66 mmol) in ethanol (120 mL) over 1 h. The reaction mixture was maintained at reflux for 4.5 days, while monitoring the reaction progress using TLC. The reaction mixture was allowed to cool to room temperature and then evaporated to dryness. To the residue, DI water (100 mL) was added and extracted with diethyl ether (3 × 150 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo* to the dryness. The residue was purified via column chromatography on silica gel eluting with 30% EtOAc/hexanes to afford a mixture of **3** and diethyl acetamido malonate (12.3 g), and the mixture was used for the next reaction without further purification.

Compound **3** was prepared for characterization in a small quantity. To a round bottom flask containing anhydrous EtOH (10 mL) was added portionwise Na (28.3 mg, 1.23 mmol). To a clear NaOEt solution was added a solution of diethyl acetamido malonate (267 mg, 1.23 mmol) in Ethanol (5 mL) dropwise over 30 min. The resulting mixture was then heated at 50 °C for 1.5 h and then reflux for 10 min. The solution became cloudy and light brownish indicating formation of deprotonated diethyl acetamido malonic ester. To the reaction mixture under reflux was dropwise added **2** (300 mg, 1.23 mmol) in ethanol (5 mL) over 1 h. The reaction mixture was maintained at reflux for 4.5 days while monitoring the reaction progress using TLC. The reaction mixture was allowed to cool to room temperature and then evaporated to dryness. The residue was purified via column chromatography on silica gel eluting with 30% EtOAc/hexanes to afford pure product **3**. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.23 (t, J = 7.7 Hz, 6H), 1.45-1.60 (m, 2H), 2.04 (s, 3H), 2.39 (t, J = 8.5 Hz, 2H), 2.73 (t, J = 7.7 Hz, 2H), 4.22 (q, J = 7.2 Hz, 4H), 7.29 (d, J = 7.7 Hz, 2H), 8.24 (d, J = 8.5 Hz, 2H); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 13.8 (q), 22.88 (t), 24.91 (t), 31.65 (t), 35.13 (t), 62.44 (t), 66.17 (s), 123.50 (d), 128.98 (d), 146.28 (s), 149.41 (s), 167.78 (s), 169.01 (s). HRMS (Positive ion FAB) Calcd for $C_{18}H_{24}N_2O_7$ $[M + H]^+$ m/z 381.1662. Found: $[M + H]^+$ m/z 381.1653.

2-Amino-5-(4-nitrophenyl)pentanoic acid (4). Compound **3** (12.3 g, 32.3 mmol) was dissolved in the mixture of acetic acid (30 mL) and conc. HCl (100 mL), and the resulting solution was maintained under reflux for 24 h. The reaction was allowed to room temperature, and the resulting precipitate was filtered, washed with isopropanol, and dried *in vacuo* to provide pure **3** (6.0 g). The volume of the filtrate was reduced to half and left in the freezer, and white solid formed was filtered. The repeated recrystallization afforded **4** (7.5 g, 46% from **2**). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.75-2.08 (m, 4 H), 2.84 (t, J = 6.9 Hz, 2 H), 4.02 (t, J = 5.7 Hz, 1 H), 7.47

(d, *J* = 8.5 Hz, 2 H), 8.15 (d, *J* = 8.7 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 25.97 (t), 29.61 (t), 34.48 (t), 52.44 (d), 123.22 (d), 129.29 (d), 146.45 (s), 149.50 (s), 170.32 (s). HRMS (Positive ion FAB) Calcd for $C_{11}H_{14}N_2O_4$ $[M + H]^+$ *m*/*z* 239.1032. Found: $[M + H]^+$ *m*/*z* 239.1029.

2-Amino-5-(4-nitrophenyl)pentanoic acid methyl ester (5). A Solution of **4** (7.1 g, 29.8 mmol) in MeOH (120 mL) at 0–5 °C was saturated with HCl (g) for 2 h, at which time the mixture was allowed to ambient temperature and then was stirred for 24 h. The resulting mixture was concentrated *in vacuo* to provide pure product **5** (7.4 g, 98%) as an acidic salt. ^{1}H NMR (D_2O, 300 MHz) δ 1.50-1.93 (m, 4H), 2.67 (t, *J* = 7.1 Hz, 2H), 3.68 (s, 3H), 4.03 (t, *J* = 5.9 Hz, 1H), 7.30 (d, *J* = 8.4 Hz, 2H), 8.03 (d, 2H, *J* = 8.2 Hz, 2H); ^{13}C NMR (D_2O, 300 MHz) δ 25.50, 29.26, 34.16, 52.66, 53.50, 123.30, 129.18, 145.50, 149.96, 170.37. A slurry of the ester salt **5** (10 mmol) in dry methanol (2.5 mL) was treated with Et_3N (10 mL). To the stirred slurry was then added anhydrous ether (100 mL), and the resulting mixture was cooled at −10 ^{o}C for 1 h. The resulted triethylamine hydrochloride salt was filtered off, and the filtrate was concentrated *in vacuo* to provide free amino ester **5** as a light yellow oil. ^{1}H NMR (CD_3OD, 300 MHz) δ 1.65-1.85 (m, 4 H), 2.78 (t, *J* = 6.8 Hz, 2 H), 3.60 (t, *J* = 5.7 Hz, 1 H), 3.73 (s, 3 H), 7.45 (d, *J* = 8.4 Hz, 2 H), 8.15 (d, *J* = 8.4 Hz, 2 H); ^{13}C NMR (MeOD, 300 MHz) δ 26.54 (t), 32.92 (t), 34.87 (t), 51.68 (d), 53.35 (t), 122.77 (d), 129.26 (d), 146.20 (s), 150.18 (s), 174.32 (s). HRMS (Positive ion FAB) Calcd for $C_{12}H_{16}N_2O_4$ $[M + H]^+$ *m*/*z* 253.1188. Found: $[M + H]^+$ *m*/*z* 253.1212.

2-Amino-5-(4-nitrophenyl)pentan-1-ol (6). A slurry of **5** (4.4 g, 17.4 mmol) in dry methanol (2 mL) was treated with Et_3N (2.68 mL, 19.1 mmol). The resulting mixture was stirred for 5 min. To the resulting slurry was added anhydrous ether (100 mL), and the solution was cooled at the freezer for 1 h. The resulting triethylamine hydrochloride salt was filtered off, and the filtrate

was concentrated *in vacuo* to provide free amino ester **5** as a light yellow oil. To a solution of **5** in methanol (80 mL) at 0 ^{o}C was added portionwise $NaBH_4$ (2.8 g, 69.6 mmol) over 20 min. The resulting mixture was allowed to warm to room temperature and stirred for 4-6 h, while the reaction progress was continuously monitored using TLC. The solvent was removed *in vacuo*, and the residue was treated with deionized water (50 mL) and extracted with ethyl acetate (3 × 100 mL). The combined organic layer was treated with $MgSO_4$, filtered, and concentrated *in vacuo* to provide amino alcohol **6** (3.9 g, 100%) that was used for the next step without further purification. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.19-1.88 (m, 4 H), 2.68-2.89 (m, 3 H), 3.20-3.35 (m, 1 H), 3.48-3.53 (m, 1 H), 7.33 (d, J = 8.7 Hz, 2 H), 8.15 (d, J = 8.7 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 27.2 (t), 32.6 (t), 35.4 (t), 52.4 (d), 66.0 (t), 123.2 (d), 129.2 (d), 146.2 (s), 150.6 (s); HRMS (Positive ion FAB) Calcd for $C_{11}H_{16}N_2O_3$ $[M + H]^+$ m/z 225.1239. Found: $[M + H]^+$ m/z 225.1243.

{*tert*-butoxycarbonylmethyl-[1-hydroxymethyl-4-(4-nitrophenyl)butyl]amino}acetic acid *tert*-butyl ester (7). To a solution of **6** (4.1 g, 18.2 mmol) and K_2CO_3 (5.5 g, 39.9 mmol) in CH_3CN (35 mL) at 0-5 °C was added dropwise a solution of *tert*-butyl bromoacetate (7.3 g, 37.2 mmol) in CH_3CN (15 mL) over 30 min while maintaining the temperature at 0 ^{o}C. The resulting mixture was allowed to room temperature and stirred for 24 h. The solvent was removed *in vacuo*, and the residue was treated with deionized water (50 mL) and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layer was dried ($MgSO_4$) and concentrated *in vacuo* to provide **7** (7.6 g, 93%) as a light yellow oil. Compound **7** was used for the next step without further column chromatographic purification. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.12-1.28 (m, 2H), 1.35-1.57 (m, 18 H), 1.60-1.83 (m, 2 H), 2.62-2.85 (m, 3 H), 3.18-3.30 (m, 1 H), 3.35-3.51 (m, 4 H), 3.72-3.78 (m, 1 H), 7.32 (d, J = 8.6 Hz, 2 H), 8.14 (d, J = 8.7, 2 H); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 27.7 (t),

27.8 (q), 28.3 (t), 35.9 (t), 53.0 (t), 62.6 (d), 65.1 (t), 81.2 (s), 123.5 (d), 129.1 (d), 146.2 (s), 150.1 (s), 172.2 (s). HRMS (Positive ion Calcd for $C_{21}H_{27}NO_3$ $[M + H]^+$ *m*/*z* 342.2064. Found: $[M + H]^+$ *m*/*z* 342.2065.

***tert*-Butyl 2,2'-(2-bromo-5-(4-nitrophenyl)pentylazanediyl)diacetate (10).** To a solution of **7** (7.6 g, 16.81 mmol) and PPh_3 (5.3 g, 20.17 mmol) in CH_2Cl_2 (70 mL) was portionwise added NBS (3.6 g, 20.17 mmol) at 0 °C over 30 min. The resulting mixture was stirred for 4 h while being maintained at 0 °C. The ice bath was removed, and the reaction mixture was warmed to RT and stirred for 1 h and concentrated to dryness *in vacuo*. The residue was purified via column chromatography on silica gel (70-230 mesh) eluting with 10% EtOAc in hexanes. The product **10** was thereby obtained as a yellowish oil (4.8 g, 66%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.42-1.48 (m, 18 H), 1.63-2.20 (m, 4 H), 2.65-2.82 (m, 2 H), 2.95 (dd, *J* = 14.3, 7.8 Hz, 1 H), 3.18 (dd, *J* =14.3, 6.1 Hz, 1 H), 3.31-3.52 (m, 4 H), 4.01-4.12 (m, 1 H), 7.35 (d, *J* = 8.6 Hz, 2 H), 8.12 (d, *J* = 8.6 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 28.0 (q), 28.6 (t), 34.9 (t), 35.2 (t), 55.0 (d), 57.0 (t), 62.3 (t), 80.4 (s), 123.4 (d), 129.1 (d), 146.2 (s), 149.9 (s), 170.3 (s); HRMS (Positive ion FAB) Calcd for $C_{23}H_{34}N_2O_6Br[M + H]^+$ *m*/*z* 515.1757. Found: $[M + H]^+$ *m*/*z* 515.1739. Anal. Calcd for $C_{23}H_{34}N_2O_6Br$: C, 53.59; H, 6.84, N, 5.43. Found: C, 53.32; H, 6.64; N, 5.31.

1,1-bis[2-(tert-butoxy)-2-oxoethyl]-2-[3-(4-nitrophenyl)propyl]aziridin-1-ium perchlorate (11). To a stirred solution of β-amino bromide **10** (30 mg, 0.06 mmol) in chloroform-D (0.5 mL) at −10 ^{o}C was added silver perchlorate (62.2 mg, 0.3 mmol). The resulting mixture was continuously stirred at −10 ^{o}C for 1 h, while the reaction progress was monitored using TLC. After completing of the reaction, silver bromide was filtered, and compound **11** present in the filtrate ($CDCl_3$) was directly characterized by ^{1}H and ^{13}C NMR. ^{1}H NMR ($CDCl_3$, 300 MHz) *δ* 1.48 (s, 9 H),1.49 (s, 9 H), 1.95-2.19 (m, 4 H), 2.72-2.90 (m, 2 H), 3.41-3.74 (m, 3 H), 3.94-4.29

(m, 4 H), 7.38(d, J = 8.6Hz, 2 H), 8.09(d, J = 8.6 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 36.1 (t), 27.1 (t), 27.9 (q), 27.9 (q), 28.1 (q), 34.5 (t), 47.9 (t), 53.3 (t), 56.0 (d), 60.4 (t), 85.9 (s), 86.0 (s), 123.6 (d), 123.7 (d), 129.4 (d), 129.5 (d), 146.5 (s), 149.2 (s), 163.8 (s), 164.0 (s).

{4-[2-(Bis-*tert*-butoxycarbonylmethylamino)-5-(4-nitro-phenyl)pentyl]-7-*tert*-butoxycarbonylmethyl-[1,4,7]triazonan-1-yl}acetic acid *tert*-butyl ester (13). To a solution of **12** (143 mg, 0.277 mmol) and DIPEA (121 mg, 0.937 mmol) in CH_3CN (5 mL) was added compound **10** (112 mg, 0.312 mmol). The resulting mixture was stirred for 5 days at room temperature. The reaction mixture was concentrated to the dryness *in vacuo*. DI water (5 mL) was added to the residue, and the resulting mixture was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated to the dryness *in vacuo*. The residue was purified via column chromatography on silica gel (220-440 mesh) eluting with 3 % CH_3OH in CH_2Cl_2. The product **13** was thereby obtained as a white solid (159 mg, 82 %). ^{1}H NMR ($CDCl_3$, 300MHz) δ 1.19-1.35 (m, 2 H), 1.41-1.49 (m, 36 H), 1.58-1.80 (m, 2 H), 1.81-2.10 (m, 1 H), 2.21-2.25 (m, 1 H), 2.64-2.95 (m, 15 H), 3.27 (s, 4 H), 3.39 (s, 4 H), 7.39 (d, J = 8.6 Hz, 2 H), 8.06 (d, J = 8.7 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 300 MHz) 27.77 (t), 28.09 (q), 30.82 (t), 35.87 (t), 53.13 (t), 55.21 (t), 55.78 (t), 56.50 (t), 59.74 (t), 60.05 (d), 60.72 (t), 80.50 (s), 123.45 (d), 129.30 (d), 146.12 (s), 151.05 (s), 171.39 (s). HRMS (Positive ion FAB) Calcd for $C_{41}H_{69}N_5O_{10}$ $[M + H]^+$ m/z 792.5123. Found: $[M + H]^+$ m/z 792.5121. Analytical HPLC (method 1, t_R = 42 min).

Synthesis of 13 under reflux. To a solution of **12** (400 mg, 0.78 mmol) and DIPEA (167 mg, 1.3 mmol) in CH_3CN (10 mL) was added compound **10** (231.3 mg, 0.65 mmol). The resulting mixture was refluxed for 48 h after which the reaction mixture was allowed to room temperature. The reaction mixture was concentrated to dryness, and CH_2Cl_2 (30 mL) was added to the residue.

The reaction mixture was filtered to remove the salt and concentrated *in vacuo*. The residue was purified via column chromatography on silica gel (220-440 mesh) eluting with 0-3 % CH_3OH in CH_2Cl_2 to afford **13** (185 mg, 30%). Most of the starting material was converted to **14** as evidenced by TLC.

{2-[3-(4-nitrophenyl)-propyl]-6-oxomorpholin-4-yl}acetic acid *tert*-butyl ester (14). To a solution of **10** (42 mg, 0.08 mmol) in CH_3CN (3 mL) was added DIPEA, and the reaction mixture was allowed to reflux for 3 days. After completion of the reaction as monitored using TLC, the reaction mixture was concentrated *in vacuo* and filtered to remove the salt while washing with CH_2Cl_2. The filtrate was concentrated *in vacuo*, and the crude product was purified by preparative TLC (silica gel, 60-230 mesh, 5 × 10 cm) gradually eluting with 25% ethyl acetate/hexanes starting from hexane to provide pure **14** (24 mg, 77%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.46 (s, 9 H), 1.56-2.10 (m, 4 H), 2.58 (dd, J = 12.2, 9.2 Hz, 1 H), 2.76 (t, J = 7.3 Hz, 2 H), 2.96 (ddd, J = 12.2, 3.2, 1.3 Hz, 1 H), 4.49-4.57 (m, 1 H), 7.33 (d, J = 8.7 Hz, 2 H), 8.15 (d, J = 8.7 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 26.2 (t), 28.1 (q), 32.7 (t), 35.4 (t), 53.2 (t), 54.0 (t), 57.5 (t), 79.2 (d), 82.1 (s), 123.7 (d), 129.2 (d), 146.5 (s), 149.5 (s), 167.4 (s), 168.7 (s). HRMS (positive ion FAB) Calcd for $C_{19}H_{26}N_2O_6$ $[M + H]^+$ *m/z* 379.1869. Found: $[M + H]^+$ *m/z* 379.1878.

{4-[2-(Bis-carboxymethylamino)-5-(4-nitrophenyl)pentyl]-7-carboxymethyl-[1,4,7]tri-azonan-1-yl}acetic acid (3p-*C*-NETA). HCl (g) in 1,4-dioxane (5 mL) was added dropwise to compound **13** (35 mg, 0.044 mmol) in a flask in an ice bath over 20 min. The resulting mixture was allowed to warm to room temperature and stirred for 18 h. Ether (~20 mL) was added to the reaction mixture which was continued to stir for 10 min. The resulting mixture was capped and placed in the freezer for 1 h. The solid formed was filtered, washed with ether, and quickly

dissolved in DI water. Concentration of the aqueous solution *in vacuo* gave **3p-*C*-NETA** (32 mg, 100%) as an offwhite solid. ^{1}H NMR (D_2O, 300MHz) δ 1.22–1.40 (m, 1 H), 1.48–1.70 (m, 3 H), 2.59-2.71 (m, 2 H), 2.05-3.18 (m, 2 H), 3.23-3.65 (m, 17 H), 3.89 (s, 4 H), 7.32 (d, J = 7.9 Hz, 2 H), 8.01 (d, J = 7.9 Hz, 2 H); ^{13}C NMR (D_2O, 300MHz) δ 26.08 (t), 26.85 (t), 34.73 (t), 50.43 (t), 50.66 (t), 50.87 (t), 52.63 (t), 56.63 (t), 58.69 (d), 60.07 (t), 123.6 (d), 129.41 (d), 145.93 (s), 150.41 (s), 171.49 (s), 174.99 (s). HRMS (Positive ion FAB) Calcd for $C_{25}H_{37}N_5O_{10}$ $[M + H]^+$ m/z 568.2619 Found: $[M + H]^+$ m/z 568.2614. Analytical HPLC (method 2, t_R = 17 min).

[1-Hydroxymethyl-4-(4-nitrophenyl)butyl]carbamic acid *tert*-butyl ester (16). To a solution of **6** (3.14 g, 14.0 mmol) in CH_3CN (50 mL) at room temperature was added dropwise BOC-ON (6.89 g, 28.0 mmol) in CH_3CN (50 mL) over 20 min. The resulting mixture was stirred for 4 h and concentrated. The residue was partitioned between ether (50 mL) and 10% NaOH solution (25 mL). The ether layer was separated and sequentially washed with deionized water (5 mL) and 10% NaOH solution (5 mL). The ether layer was dried, filtered, and concentrated *in vacuo*. The residue was washed with ether (20 mL) to provide **16** (3.70 g, 92%) as a white solid, which can be used for the next step without further purification. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.40-1.65 (m, 11 H), 1.66-1.82 (m, 2 H), 2.47 (bs, 1 H), 2.65-2.82 (m, 2 H), 3.50-3.60 (m, 1 H), 3.60-3.74 (m, 2 H), 4.70 (d, J = 8.0 Hz, 2 H), 7.32 (d, J = 8.5 Hz, 2 H), 8.13 (d, J = 8.6 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 27.4 (t), 28.4 (q), 31.1 (t), 35.5 (t), 52.3 (d), 65.6 (t), 79.7 (s), 123.7 (d), 129.2 (d), 146.4 (s), 150.0 (s), 156.4 (s). HRMS (Positive ion ESI) Calcd for $C_{16}H_{25}N_2O_5$ $[M + H]^+$ m/z 325.1758. Found: $[M + H]^+$ m/z 325.1730.

[1-Formyl-4-(4-nitrophenyl)butyl]carbamic acid *tert*-butyl ester (17). Oxalyl chloride (1.15 g, 9.08 mmol) was dissolved in dry dichloromethane (25 mL) and cooled to –60 °C. Dry DMSO (1.24 g, 15.9 mmol) was added dropwise to the reaction mixture over 15 min. After 5 min, *N*-

BOC protected amino alcohol **16** (1.47 g, 4.5 mmol) in CH_2Cl_2 (5 ml) was added dropwise over 10 min, and the mixture was stirred intensively for 1 h, while the temperature was maintained between –50 ~ –60 °C. Distilled triethylamine (2.3 g, 22.7 mmol) was added to the mixture, and the resulting mixture was stirred for additional 15 min. Saturated NH_4Cl solution (25 mL) and deionized water (25 mL) were sequentially added to the mixture, and the mixture was stirred for additional 5 min after which the mixture was gradually warmed to room temperature. The organic layer was washed with 5% citric acid solution (2 × 20 ml), deionized water (20 mL), and brine (20 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated *in vacuo* to provide **17** (1.4 g, 94%) as a yellowish solid, which was immediately used for the next step without further purification. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.20-1.30 (m, 1 H), 1.45 (s, 9 H), 1.51-1.20 (m, 6 H), 2.65-2.86 (m, 2 H), 7.33 (d, J = 8.6 Hz, 2 H), 8.15 (d, J = 8.6 Hz, 2 H), 9.57 (s, 1 H); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 26.2 (t), 28.2 (q), 28.5 (t), 35.2 (t), 59.4 (d), 80.1 (s), 123.6 (d), 129.2 (d), 146.3 (s), 149.6 (s), 155.7 (s), 199.9 (s). HRMS (Positive ion ESI) Calcd for $C_{16}H_{22}N_2NaO_5$ $[M + Na]^+$ *m/z* 345.1421. Found: $[M + Na]^+$ *m/z* 345.1426.

7-[2-*tert*-Butoxycarbonylamino-5-(4-nitrophenyl)pentyl]-[1,4,7] triazonane-1,4-dicarboxylic acid di-*tert*-butyl ester (19). To a mixture of **17** (1.4 g, 4.2 mmol) and **18** (1.4 g, 4.2 mmol) in 1,2-dichloroethane (35 mL) was added portionwise sodium triacetoxyborohydride (1.3 g, 5.9 mmol) over 20 min. The resulting mixture was stirred at room temperature for 24 h. The reaction mixture was quenched by adding saturated $NaHCO_3$ (40 mL) and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo* to provide pure **19** (2.7 g, 100%) as a yellowish solid. Compound **19** was used for the next step without further purification. An analytical sample of **19** was prepared by purification via silica gel (60-230 mesh) column chromatography eluted with 20% ethyl acetate in hexanes. ^{1}H NMR

($CDCl_3$, 300 MHz) δ 1.32-1.72 (m, 31 H), 2.44-3.70 (m, 19 H), 7.28 (d, J = 8.5 Hz, 2 H), 8.07 (d, J = 8.5, 2 H); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 27.2 (t), 27.3 (t), 28.4 (q), 28.5 (q), 28.6 (q), 33.1 (t), 33.3 (t), 35.6 (t), 48.4 (t), 49.0 (d), 49.6 (t), 50.2 (t), 50.4 (t), 50.9 (t), 52.1 (t), 53.7 (t), 54.1 (t), 55.0 (t), 60.8 (t), 61.1 (t), 79.5 (s), 79.6 (s), 79.7 (s), 79.7 (s), 123.5 (d), 129.2 (d), 146.2 (s), 150.4 (s), 155.5 (s), 155.5 (s), 156.1 (s), 156.2 (s). HRMS (Positive ion FAB) Calcd for $C_{32}H_{54}N_5O_8$ $[M + H]^+$ *m/z* 636.3972 Found: $[M + H]^+$ *m/z* 636.3974.

4-(4-Nitrophenyl)-1-[1,4,7]triazonan-1-ylmethyl-butylamine (20). 4M HCl (g) in 1,4-dioxane (40 mL) was added to compound **19** (2.7 g, 4.2 mmol) in a flask at 0-5 ^{o}C . The resulting mixture was stirred for 18 h. Ether (100 mL) was added to the reaction mixture, and the flask was placed in the freezer for 1 h. The solid formed was filtered, washed with ether, and quickly dissolved in deionized water. The aqueous solution was concentrated *in vacuo* to provide **20** (1.8 g, 90%) as an offwhite solid. ^{1}H NMR (D_2O, 300 MHz) δ 1.50-1.76 (m, 4 H), 2.71 (t, J = 6.9 Hz, 2 H), 2.77-2.90 (m, 4 H), 2.91-3.07 (m, 2 H), 3.20-3.31 (m, 4 H), 3.37-3.49 (m, 1 H), 3.57 (s, 4 H), 7.34 (d, J = 8.4 Hz, 2 H), 8.07 (d, J = 8.0 Hz, 2 H); ^{13}C NMR (D_2O, 300 MHz) δ 25.6 (t), 30.6 (t), 34.5 (t), 41.7 (d), 40.1 (t), 44.0 (t), 48.9 (t), 58.6 (t) 123.7 (d), 129.4 (d), 145.8 (s), 150.3 (s).

A solution of acidic salt **20** (814 mg, 1.7 mmol) in deionized water (5 mL) was neutralized using 0.5 M NaOH. The aqueous solution (pH 7) was then extracted with $CHCl_3$ (2 × 25 mL). The aqueous layer was further adjusted to pH 10 and then pH 13 and extracted with $CHCl_3$ (2 × 25 mL). The organic layers extracted from the two basic solutions (pH 10 and pH 13) were checked for the presence of less polar impurity by TLC analysis. The organic layers containing compound **20** were combined, dried over $MgSO_4$, filtered, and concentrated *in vacuo* to provide free amine **20** (570 mg, 100 %) as a yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.50-1.88 (m, 4 H), 2.15-2.32 (m, 2 H), 2.35-2.90 (m, 17 H), 7.33 (d, J = 8.5 Hz, 2 H), 8.13 (d, J = 8.4 Hz, 2 H); ^{13}C NMR

($CDCl_3$, 300 MHz) δ 27.5 (t), 35.0 (t), 35.8 (t), 46.3 (t), 46.6 (t), 49.2 (d), 53.3 (t), 65.4 (t), 123.4 (d), 129.0 (d), 146.2 (s), 150.3 (s). HRMS (Positive ion FAB) Calcd for $C_{17}H_{30}N_5O_2$ $[M + H]^+$ *m/z* 336.2400 Found: $[M + H]^+$ *m/z* 336.2383.

Synthesis of 13 from reaction of 20 with *tert*-butylbromoacetate. To a slurry of **20**·4HCl (1.09 g, 2.26 mmol) and KI (0.60 g, 3.62 mmol) in DMF (15 mL) at 0 ^oC was added dropwise DIPEA (3.91 g, 30.30 mmol) over 20 min. To the resulting solution was added dropwise *tert*-butyl bromoacetate (1.94 g, 9.96 mmol) over 20 min. The resulting mixture was stirred at 0 ^oC for 2 h and room temperature for 2 h. The reaction mixture was heated to 90 ^oC and stirred for 24 h after which time the reaction mixture was cooled to room temperature and then to 0 ^oC. 6M HCl (2 mL) and heptanes (20 mL) were sequentially added to the solution. The resulting solution was vigorously stirred for 15 min, and the heptane layer was separated. The aqueous layer was extracted with heptane (2 × 20 mL), and treated with 10% Na_2CO_3 (20 mL). Additional heptane (30 mL) was added into the aqueous solution, and the resulting mixture was stirred for 30 min, and the heptane layer was separated. The combined heptane layers were washed with DI water (10 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified via silica gel (220-400 mesh) column chromatography eluted with 3 % CH_3OH/CH_2Cl_2 to provide pure **13** (53 mg, 3%) as a light yellow oil. ^1H and ^{13}C NMR data of **13** were identical to those of **13** prepared by ring opening of aziridinium ion **9** (Scheme 1).

Radiolabeling of *C*-DOTA and 3p-*C*-NETA with ^{90}Y or ^{177}Lu. All HCl solutions were prepared from ultra pure HCl (JT baker, #6900-05). For metal-free radiolabeling, plasticware including pipette tips, tubes, and caps was soaked in 0.1N HCl overnight and washed thoroughly with Milli-Q (18.2MΩ) water, and air-dried overnight. Ultra pure ammonium acetate (Aldrich, #372331) was purchased from Aldrich and used to prepare buffer solutions (0.25 M) at different

pH. After adjusting pH using 0.1M/1M HCl or NaOH solution, 0.25M NH_4OAc buffer solutions were treated with Chelex-100 resin (Biorad, #142-2842, 1g/100ml buffer solution), shaken overnight at room temperature, and filtered through 0.22μM filter (Corning, #430320) prior to use. ^{90}Y and ^{177}Lu (25 μL in 0.05M HCl) were purchased from Perkin Elmer. The stock solution of the radioisotopes (25 μL) was diluted to 825 μL by adding 0.05N HCl solution (800 μL). TLC plates (6.6 × 2 cm, Silica gel 60 F_{254}, EMD Chemicals Inc., #5554-7) with the origin line drawn at 0.6 cm from the bottom were prepared.

To a buffer solution (100 μL, 0.25M NH_4OAc) in different pH in a capped microcentrifuge tube (1.5 mL, #05-408-129) was sequentially added a solution of *C*-DOTA (100 μg) or 3p-*C*-NETA (100 μg) in water (100 μL) and ^{90}Y in HCl (0.05M, 300 μCi) or ^{177}Lu in HCl (0.05M, 300 μCi). The total volume of the resulting solution was brought up to 200 μL by adding the buffer solution, and the reaction mixture was agitated on the thermomixer (Eppendorf, #022670549) set at 1,000 rpm at room temperature for 1 h. The labeling efficiency was determined by ITLC eluted with acetonitrile/water (3:2 v/v) as the mobile phase. A solution of radiolabeled complexes (1.5 μL) was withdrawn at the designated time points (1 min, 5 min, 10 min, 20 min, 30 min, and 60 min), spotted on a TLC plate, and then eluted with the mobile phase. After completion of elution, the TLC plate was warmed and dried on the surface of a heater maintained at 35 ^{o}C and scanned using TLC scanner (Bioscan, #FC-1000). Unbound and bound radioisotope appeared around 30mm and 50 mm from the bottom of the TLC plate, respectively.

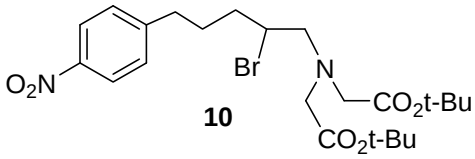
***In vitro* stability of radiolabeled complexes.** Human serum was purchased from Gemini Bioproducts (#100110). ^{90}Y-*C*-DOTA, ^{90}Y-3p-*C*-NETA, ^{177}Lu-*C*-DOTA, or ^{177}Lu-3p-*C*-NETA was prepared by reaction of *C*-DOTA (100 μg) or 3p-*C*-NETA (100 μg) with ^{90}Y (300 μCi) or ^{177}Lu (300 μCi) in 0.25M NH_4OAc buffer (pH 5.5). Radiolabeling of *C*-DOTA or 3p-*C*-NETA

with ^{177}Lu was complete in 1 h at room temperature. Radiolabeling of 3p-*C*-NETA with ^{90}Y was complete in 1 h at room temperature. The complexes ^{90}Y-3p-*C*-NETA, ^{177}Lu-*C*-DOTA, and ^{177}Lu-3p-*C*-NETA obtained from the reactions were pure as determined by ITLC and radio-HPLC and directly used for serum stability studies without further purification. Pure ^{177}Lu-*C*-DOTA (~230 μCi, 0.19 mL), ^{177}Lu-3p-*C*-NETA (~230 uCi, 0.19 mL), or ^{90}Y-3p-*C*-NETA was added to human serum (1 mL) in a microcentrifuge tube. *C*-DOTA (100 μg) was reacted with ^{90}Y (300 μCi) at 37 ^{o}C, and the radiolabeling reaction was not complete at 24 h. ^{90}Y-*C*-DOTA formed (~98% in purity) was purified by an ion-exchange chromatography using Chelex-100 column (5 mL volume bed, 200–400 mesh, Na^{+} form, Bio-Rad, Richmond, CA) eluted with PBS (pH 7.4, Fisher Scientific, #BP2438-4). Triplicate samples containing pure ^{90}Y-*C*-DOTA (78 μCi/0.75 mL PBS, 78 μCi/0.5 mL PBS, and 90 μCi/0.4 mL PBS) were prepared, and each of the samples was mixed with the respective volume of human serum (0.75 mL, 0.5 mL, and 0.4 mL). The stability of the pure radiolabeled complexes ^{90}Y-*C*-DOTA, ^{90}Y-3p-*C*-NETA, ^{177}Lu-*C*-DOTA and ^{177}Lu-3p-*C*-NETA in human serum was evaluated at 37 ^{o}C for 14 days. The serum stability of the radiolabeled complexes was assessed by measuring the transfer of the radionuclide from each complex to serum proteins using ITLC (acetonitrile/water = 3:2 v/v) and HPLC (0.05M $NaSO_4$ / 0.02M NaH_2PO_4 / 0.05% NaN_3, pH 6.8 as a mobile phase, flow rate = 1 mL/min). A solution of the radiolabeled complex in serum (2-18 μL for ITLC and 5-50 μl for HPLC) was withdrawn at the designated time point and evaluated by both ITLC and SE-HPLC. At each of the time points, the percentage of ^{90}Y or ^{177}Lu released from each of the radiolabeled complexes into serum was assessed by both ITLC and HPLC. ^{90}Y or ^{177}Lu released from each of the radiolabeled complexes into serum produced the peak at ~8.5 min on SE-HPLC. Unbound and bound radioisotope appeared ~30 mm and ~50 mm from the bottom of the TLC plate,

respectively. Any radioactivity peaks appeared at between 25 mm and 35 mm on ITLC were considered to be related to ^{90}Y or ^{177}Lu released from *C*-DOTA or 3p-*C*-NETA in serum.

2. ^{1}H and ^{13}C NMR spectra of compounds 10, 11, and 13

i) ^{1}H and ^{13}C NMR spectra of secondary β-amino bromide 10.



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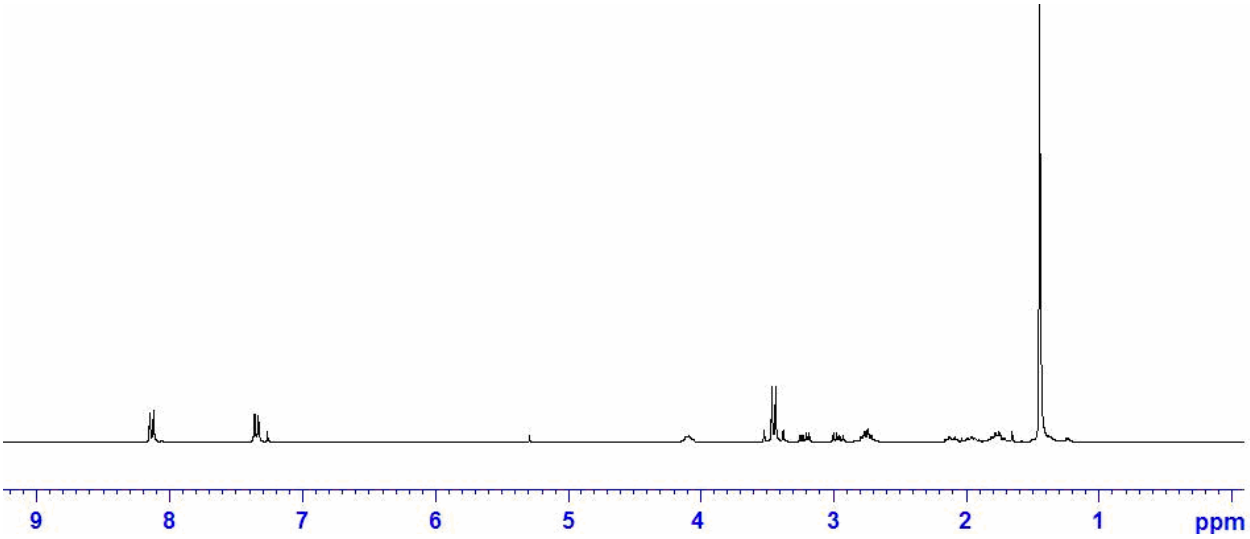
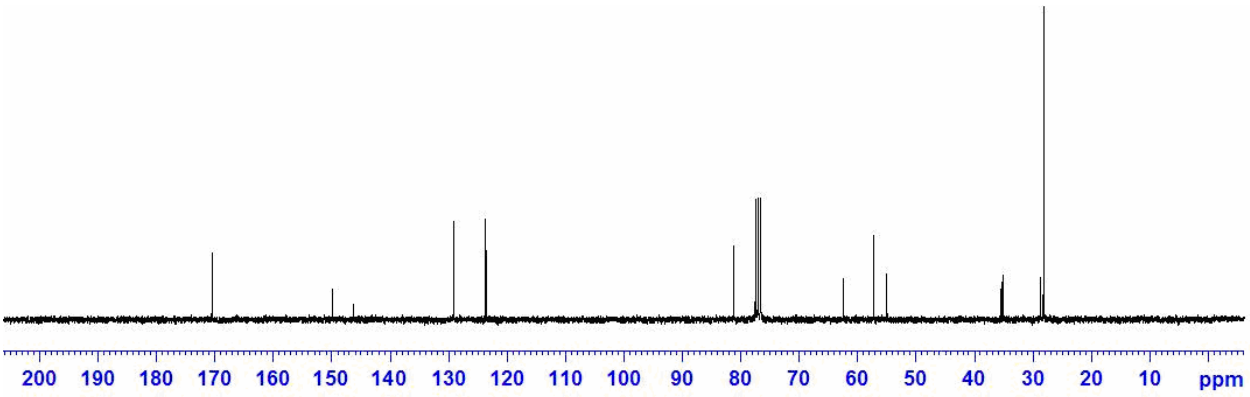
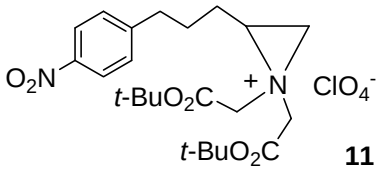




ii) ^{1}H and ^{13}C NMR spectra of aziridinium ion 11.



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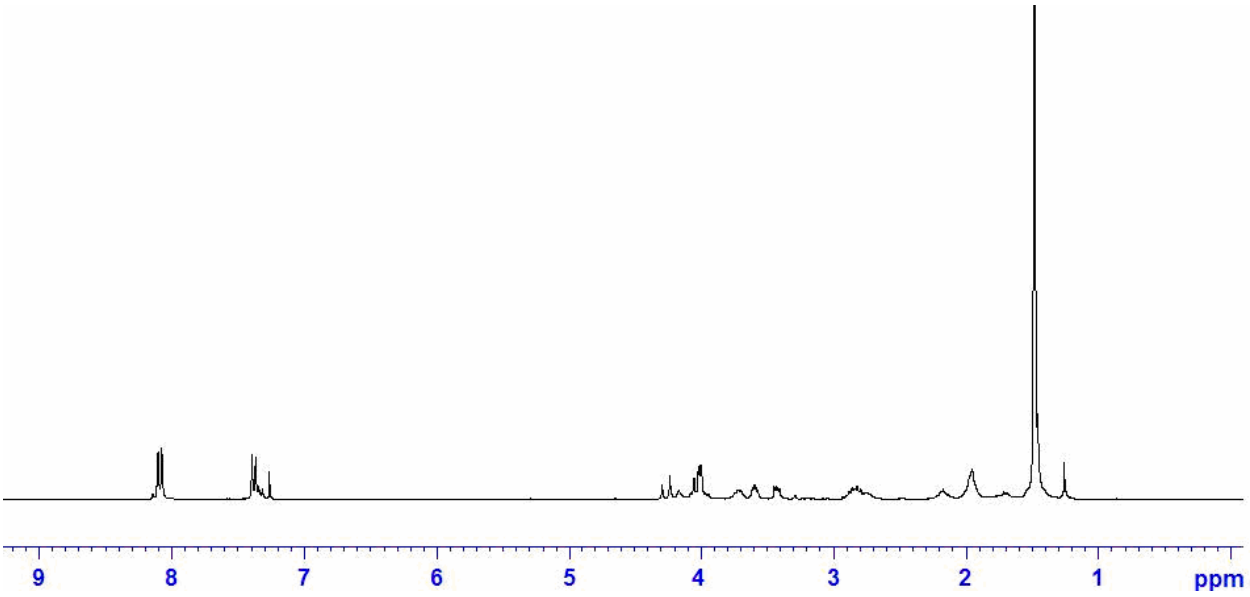
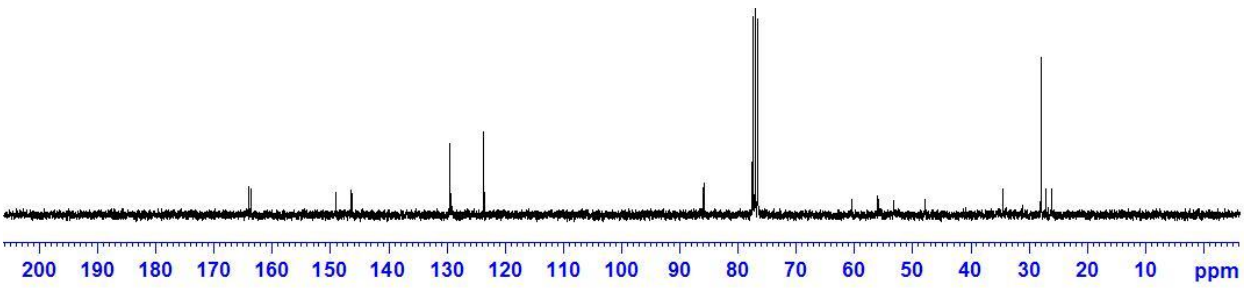
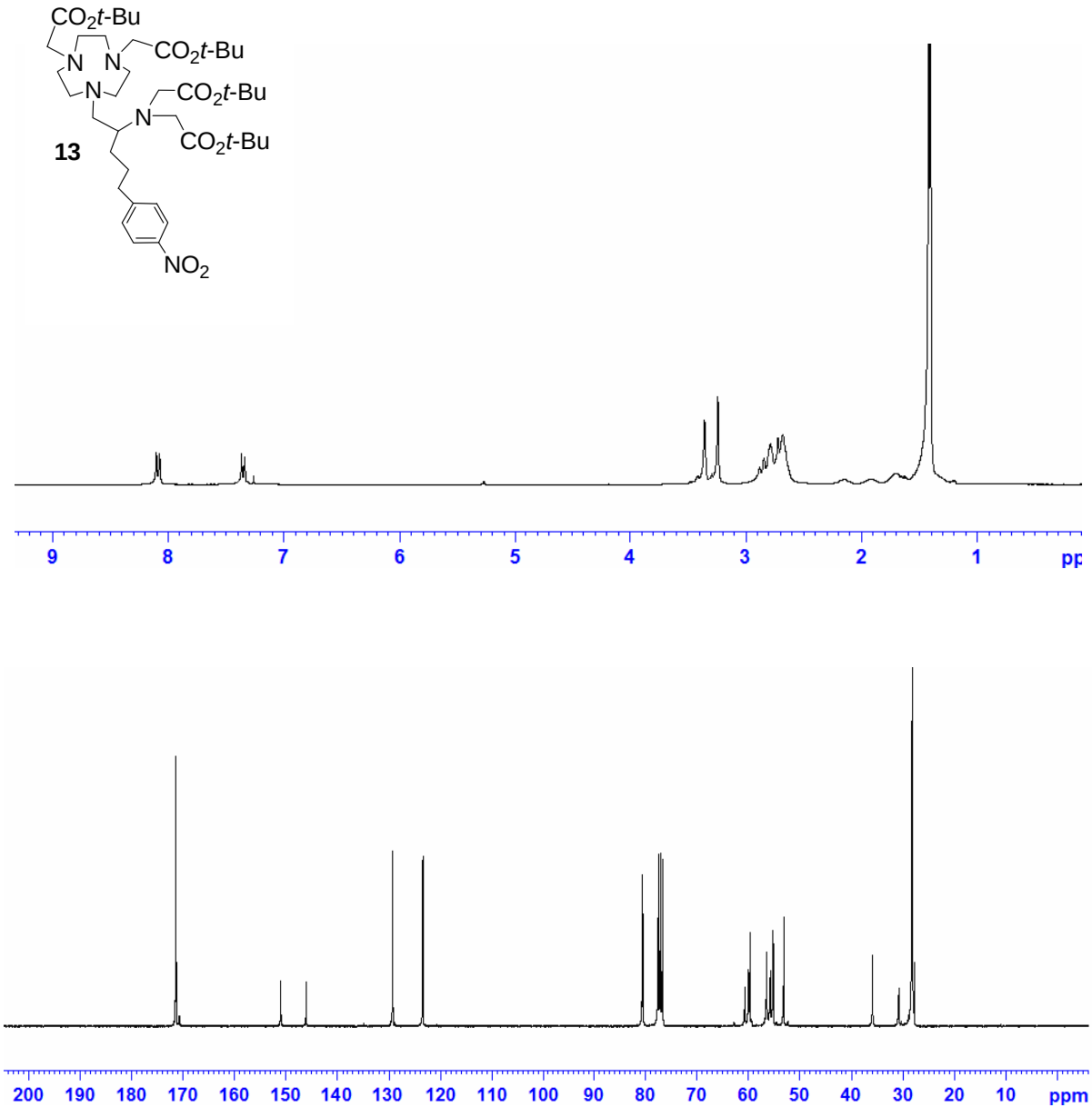




iii) ^{1}H and ^{13}C NMR spectra of compound 13.



3. Radiolabeling efficiency data of *C*-DOTA and 3p-*C*-NETA with ^{90}Y and ^{177}Lu at different pH.

i)*Radiolabling efficiency (%) of 3p-*C*-NETA with ^{90}Y (RT, 0.25M NH_4OAC)

Time (min)	pH 4.0	pH 4.5	pH 5.0	pH 5.5	pH 6.0	pH 6.5	pH 7.0
1	86.0 ± 12.4	86.9 ± 8.5	93.5 ± 4.6	97.4 ± 0.7	98.6 ± 0.6	98.5 ± 1.9	98.9 ± 1.6
5	89.9 ± 9.4	96.2 ± 0.8	94.8 ± 4.2	98.1 ± 1.1	99.1 ± 0.8	98.8 ± 1.6	98.9 ± 1.6
10	92.6 ± 7.2	92.7 ± 11.7	94.9 ± 5.2	98.7 ± 1.6	99.1 ± 0.9	98.9 ± 1.6	99.1 ± 1.2
20	94.9 ± 6.9	89.7 ± 17.4	95.3 ± 5.1	98.7 ± 2.2	100.0 ± 0.0	99.1 ± 1.4	99.3 ± 1.1
30	95.9 ± 5.1	95.7 ± 7.3	96.4 ± 5.1	99.4 ± 0.9	100.0 ± 0.0	99.0 ± 1.4	99.0 ± 1.4
60	98.8 ± 2.1	97.8 ± 3.9	98.6 ± 2.5	99.5 ± 0.9	100.0 ± 0.0	99.3 ± 1.2	99.3 ± 1.1

*Average of triplicate experiment

ii)*Radiolabling efficiency (%) of *C*-DOTA with ^{90}Y (RT, 0.25M NH_4OAC)

Time (min)	pH 4.0[#]	pH 4.5	pH5.0[#]	pH 5.5	pH6.0[#]	pH 6.5	pH 7.0[#]
1	56	56.8 ± 6.1	75.8	77.1 ± 3.7	80.5	71.4 ± 9.8	71
5	56.7	59.4 ± 7.5	77.8	78.8 ± 5.1	83.25	76.5 ± 11.2	70.8
10	42.2	47.0 ± 16.2	61.7	69.4 ± 10.6	70.6	71.0 ± 10.4	58.3
20	41.3	49.8 ± 13.8	57.2	71.2 ± 11.2	70.2	73.5 ± 10.1	59.1
30	57	59.2 ± 10.4	74.6	76.1 ± 9.5	85	76.5 ± 11.7	62.2
60	71.3	72.6 ± 8.6	84	83.5 ± 8.1	89.7	78.7 ± 11.9	73.4

*Average of triplicate experiment. [#]single run

iii) Radiolabling efficiency (%) of 3p-*C*-NETA with ^{177}Lu (RT, 0.25M NH_4OAC)

Time (min)	pH 4.0#	pH 4.5*	pH 5.0#	pH 5.5*	pH 6.0#	pH 6.5*	pH 7.0#
1	100.0	100.0 ± 0.0	100.0	100.0 ± 0.0	100.0	100.0 ± 0.0	100.0
5	100.0	100.0 ± 0.0	100.0	100.0 ± 0.0	100.0	100.0 ± 0.0	100.0
10	100.0	100.0 ± 0.0	100.0	100.0 ± 0.0	100.0	100.0 ± 0.0	100.0
20	100.0	100.0 ± 0.0	100.0	100.0 ± 0.0	100.0	100.0 ± 0.0	100.0
30	100.0	100.0 ± 0.0	100.0	100.0 ± 0.0	100.0	100.0 ± 0.0	100.0
60	100.0	100.0 ± 0.0	100.0	100.0 ± 0.0	100.0	100.0 ± 0.0	100.0

*Average of triplicate experiment. #single run

iv) *Radiolabling efficiency (%) of *C*-DOTA with ^{177}Lu (RT, 0.25M NH_4OAC)

Time (min)	pH4.0#	pH 4.5*	pH 5.0#	pH 5.5*	pH 6.0#	pH 6.5*	pH 7.0#
1	78.3	65.8 ± 3.5	98.1	94.5 ± 3.9	98.6	99.0 ± 0.8	98.7
5	92.7	95.0 ± 2.9	100.0	98.8 ± 1.1	100.0	99.6 ± 0.4	99.3
10	96.9	98.0 ± 0.8	100.0	99.5 ± 0.5	100.0	99.7 ± 0.4	99.3
20	98.8	99.5 ± 0.4	100.0	99.9 ± 0.1	100.0	100.0 ± 0.0	100.0
30	98.9	99.8 ± 0.3	100.0	99.9 ± 0.1	100.0	100.0 ± 0.0	100.0
60	100	100.0 ± 0.1	100.0	100.0 ± 00	100.0	100.0 ± 0.0	100.0

*Average of triplicate experiment. #single run

4. *In vitro* serum stability (radio SE-HPLC) of ^{90}Y- or ^{177}Lu-radiolabeled complexes (pH 7 and 37 ^{o}C)*

	Radiolabeled Complexes			
Time (d)	^{90}Y-*C*-DOTA	^{90}Y-3p-*C*-NETA	^{177}Lu-*C*-DOTA	^{177}Lu-3p-*C*-NETA
0	100.0 ± 0.0	100.0 ± 0.0	100.0 ± 0.0	100.0 ± 0.0
1	100.0 ± 0.0	100.0 ± 0.0	100.0 ± 0.0	100.0 ± 0.0
2	100.0 ± 0.0	100.0 ± 0.0	100.0 ± 0.0	100.0 ± 0.0
3	100.0 ± 0.0	100.0 ± 0.0	100.0 ± 0.0	100.0 ± 0.0
4	100.0 ± 0.0	100.0 ± 0.0	100.0 ± 0.0	100.0 ± 0.0
5	100.0 ± 0.0	100.0 ± 0.0	100.0 ± 0.0	100.0 ± 0.0
6	100.0 ± 0.0	100.0 ± 0.0	100.0 ± 0.0	100.0 ± 0.0
7	100.0 ± 0.0	100.0 ± 0.0	100.0 ± 0.0	100.0 ± 0.0
8	100.0 ± 0.0	100.0 ± 0.0	100.0 ± 0.0	100.0 ± 0.0
9	100.0 ± 0.0	100.0 ± 0.0	100.0 ± 0.0	100.0 ± 0.0
10	100.0 ± 0.0	100.0 ± 0.0	100.0 ± 0.0	100.0 ± 0.0
11	100.0 ± 0.0	100.0 ± 0.0	100.0 ± 0.0	100.0 ± 0.0
12	100.0 ± 0.0	100.0 ± 0.0	100.0 ± 0.0	100.0 ± 0.0
13	100.0 ± 0.0	100.0 ± 0.0	100.0 ± 0.0	100.0 ± 0.0
14	100.0 ± 0.0	100.0 ± 0.0	100.0 ± 0.0	100.0 ± 0.0

*Radio size exclusion-HPLC (isocratic, mobile phase: 0.05M $NaSO_4$, 0.02M NaH_2PO_4, 0.05% NaN_3, pH 6.8; flow rate 1 ml/ min). Serum stability (mean ± standard deviation %) was measured in triplicate.

5. *In vitro* serum stability (ITLC) of ^{90}Y- or ^{177}Lu-radiolabeled complexes (pH 7 and 37 ^{o}C)*

Time (d)	Radiolabeled Complexes			
	^{90}Y-*C*-DOTA	^{90}Y-3p-*C*-NETA	^{177}Lu-*C*-DOTA	^{177}Lu-3p-*C*-NETA
0	100.0 ± 0.1	99.9 ± 0.2	99.8 ± 0.2	99.9 ± 0.1
1	99.9 ± 0.2	99.8 ± 0.1	99.7 ± 0.2	100.0 ± 0.0
2	100.0 ± 0.0	99.8 ± 0.1	99.8 ± 0.2	100.0 ± 0.0
3	100.0 ± 0.0	99.9 ± 0.1	99.8 ± 0.1	99.9 ± 0.1
4	100.0 ± 0.0	99.7 ± 0.2	99.9 ± 0.1	100.0 ± 0.1
5	100.0 ± 0.0	99.9 ± 0.1	99.8 ± 0.1	100.0 ± 0.1
6	99.9 ± 0.2	99.9 ± 0.1	99.8 ± 0.1	99.9 ± 0.0
7	100.0 ± 0.0	100.0 ± 0.0	99.8 ± 0.2	100.0 ± 0.1
8	99.7 ± 0.5	100.0 ± 0.1	99.7 ± 0.1	100.0 ± 0.0
9	99.9 ± 0.2	100.0 ± 0.0	99.9 ± 0.1	100.0 ± 0.0
10	100.0 ± 0.0	100.0 ± 0.0	99.7 ± 0.2	99.9 ± 0.1
11	100.0 ± 0.0	99.8 ± 0.3	99.9 ± 0.1	99.9 ± 0.2
12	100.0 ± 0.0	99.9 ± 0.2	99.9 ± 0.1	99.9 ± 0.1
13	-	99.8 ± 0.3	99.9 ± 0.0	100.0 ± 0.1
14	-	100.0 ± 0.0	99.8 ± 0.3	100.0 ± 0.0

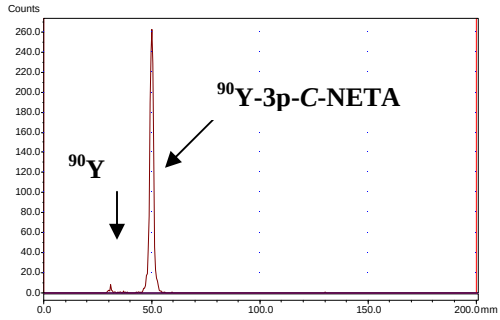
*ITLC (CH_3CN/H_2O = 3:2). Serum stability (mean ± standard deviation %) was measured in triplicate.

6. Representative ITLC spectra for evaluation of radiolabeling reaction kinetics.

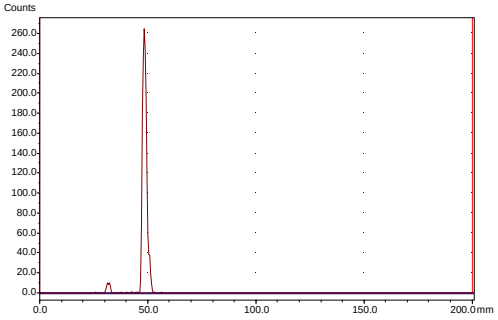
i) ITLC spectra of radiolabeling of 3p-*C*-NETA with ^{90}Y (taken from single run)

pH 4.0

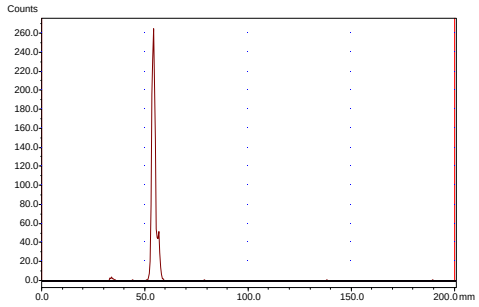
1 min



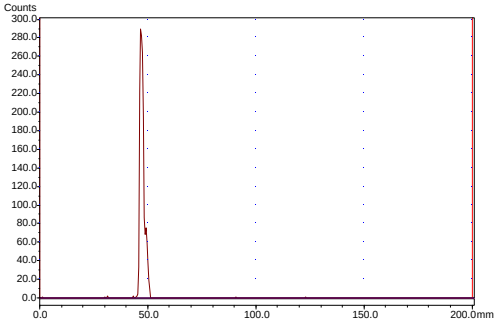
5 min



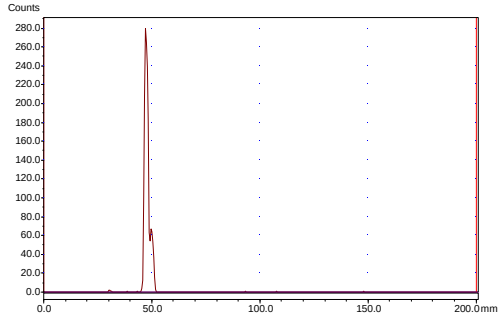
10 min



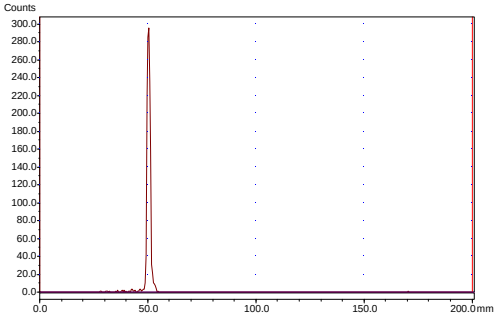
20min



30 min

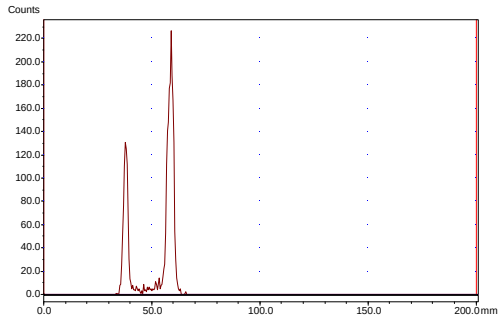


60 min

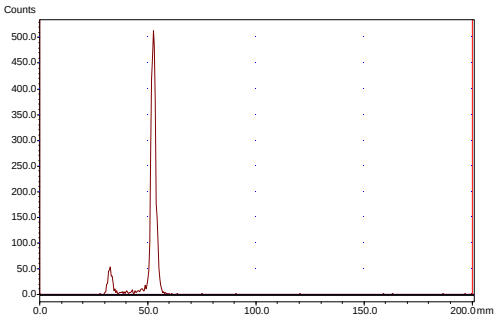


pH 4.5

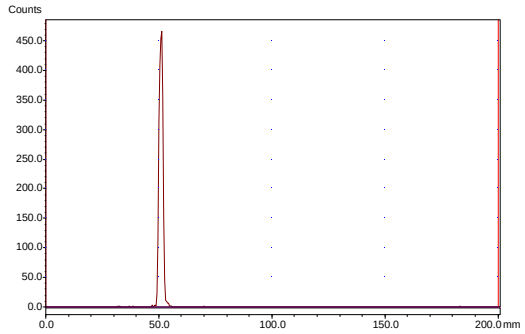
1 min



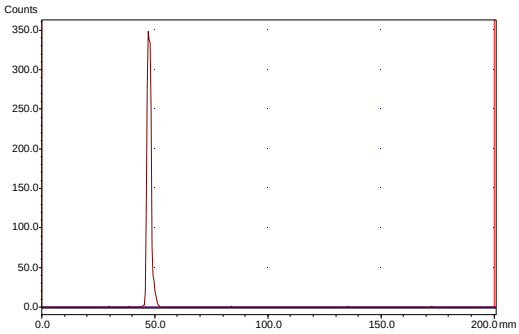
5 min



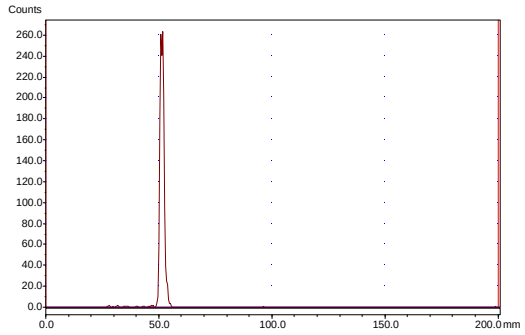
10 min



20 min



30 min



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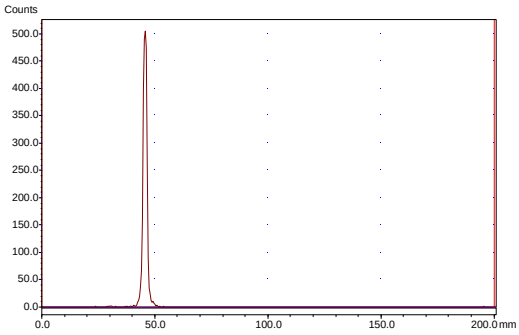
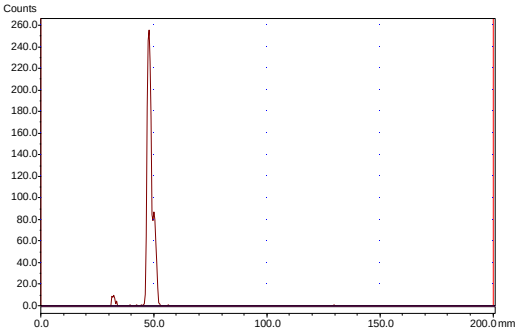
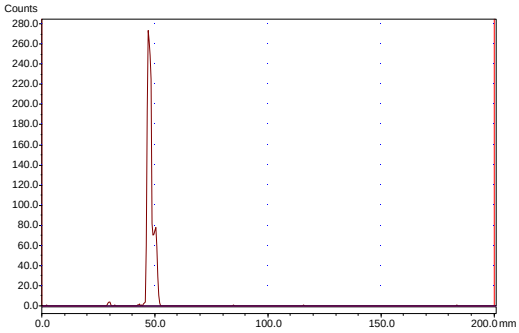


pH 5.0

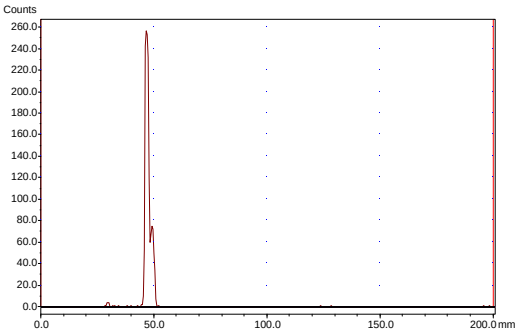
1 min



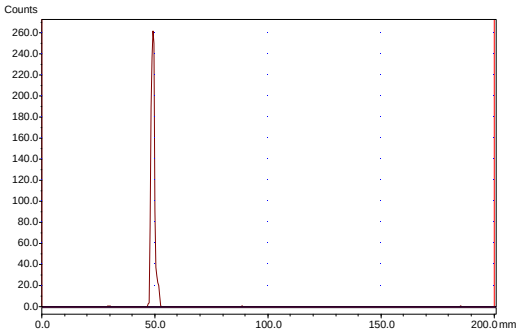
5 min



10 min



20 min



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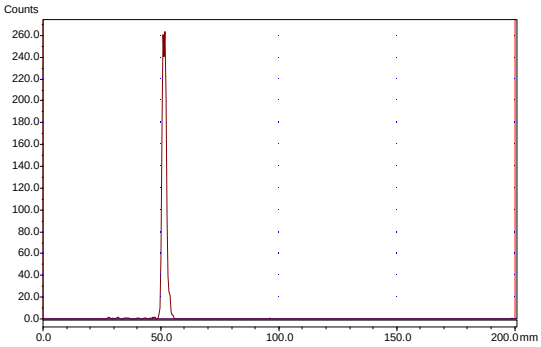

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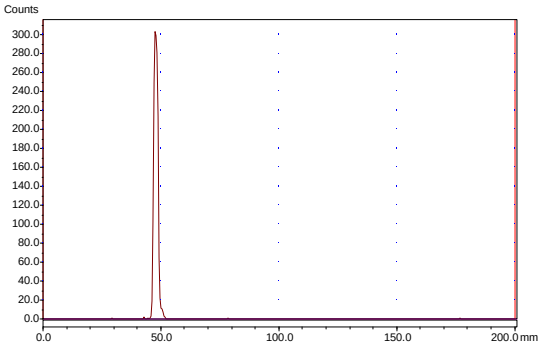
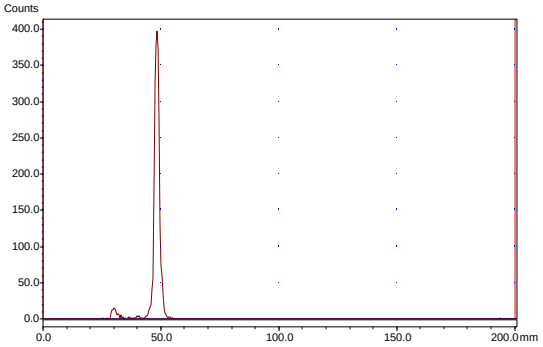
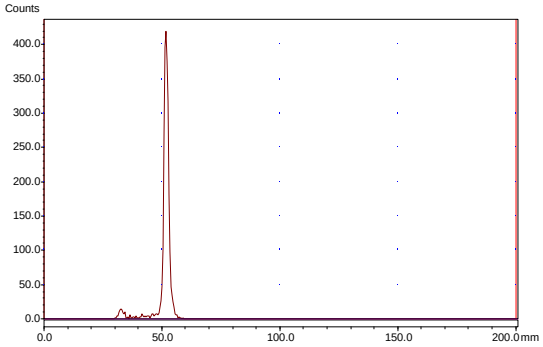


pH 5.5

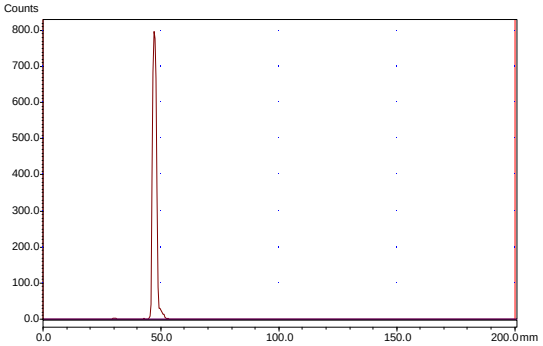
1 min



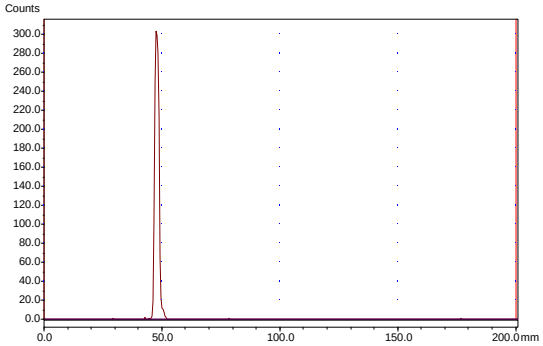
5 min



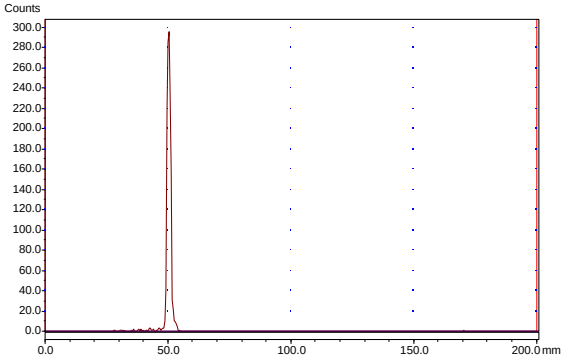
10 min



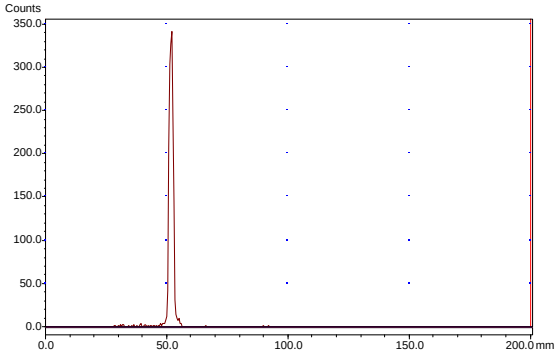
20min



30min

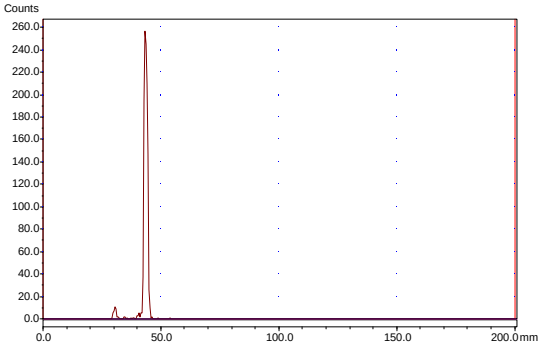


60min



pH 6.0

1min



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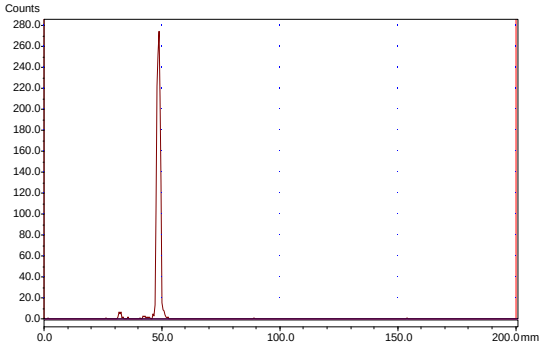

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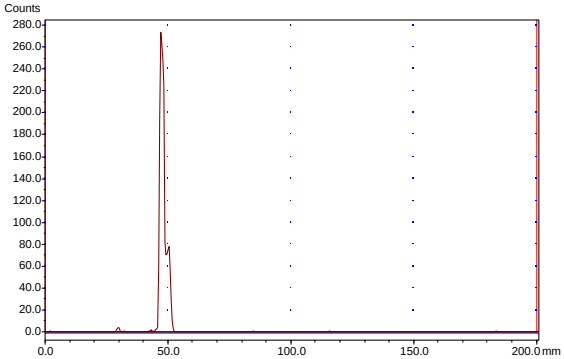

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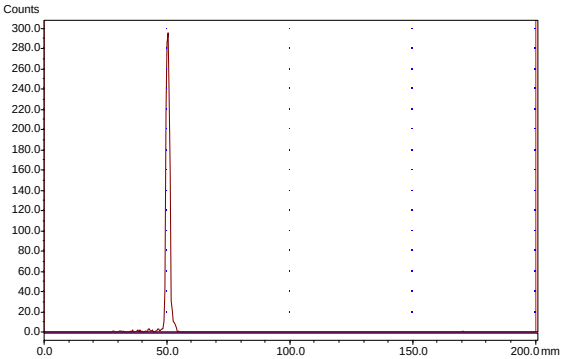

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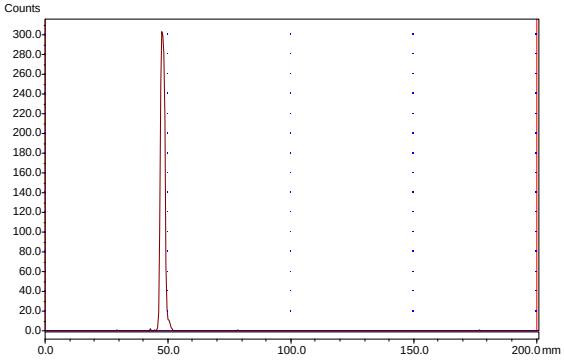

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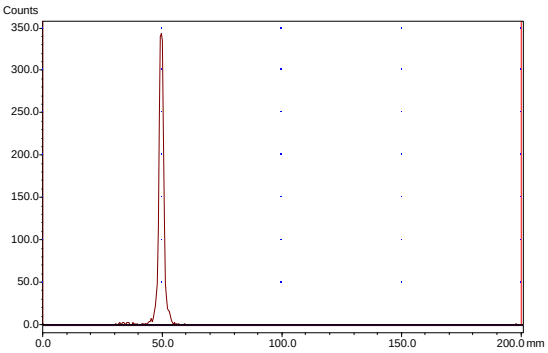
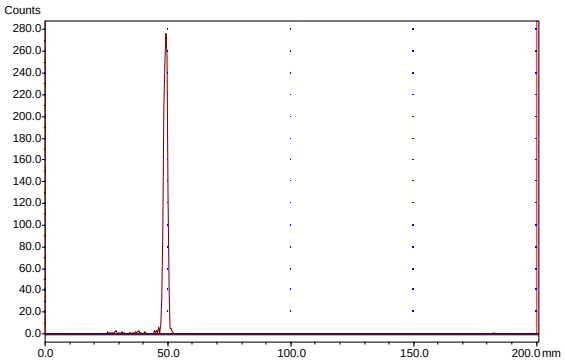


pH 6.5

1min



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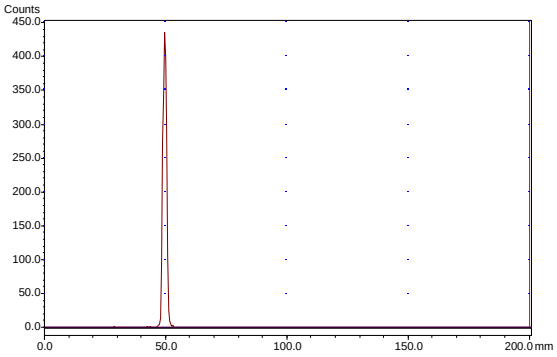

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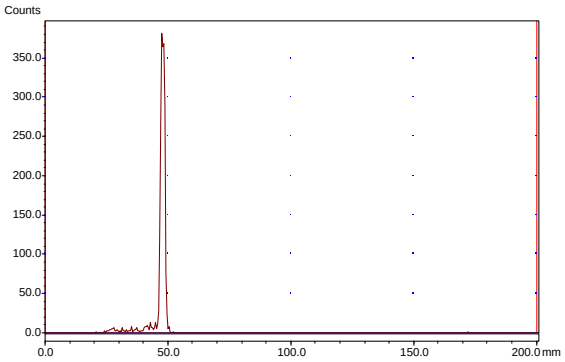

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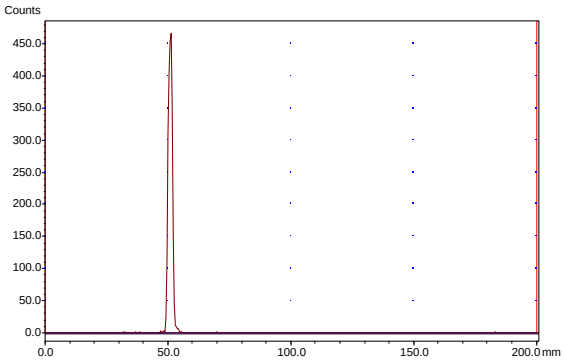

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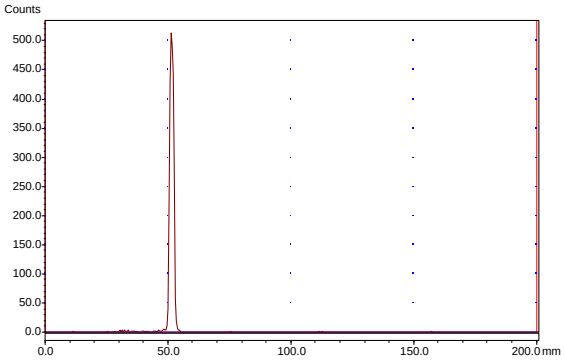

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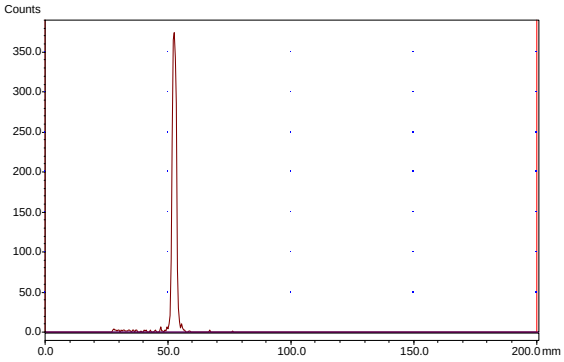
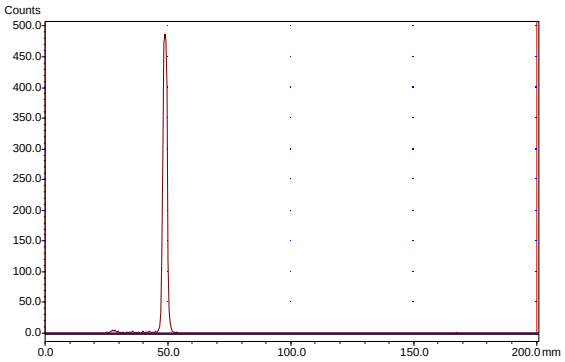


pH 7.0

1min



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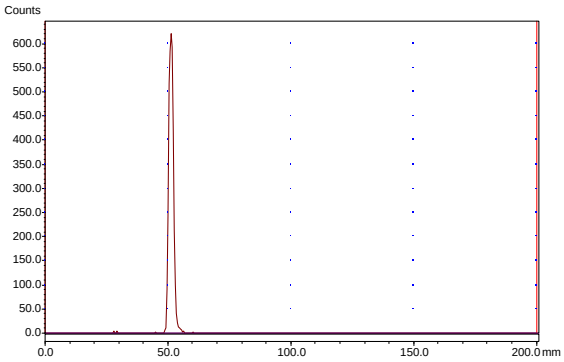

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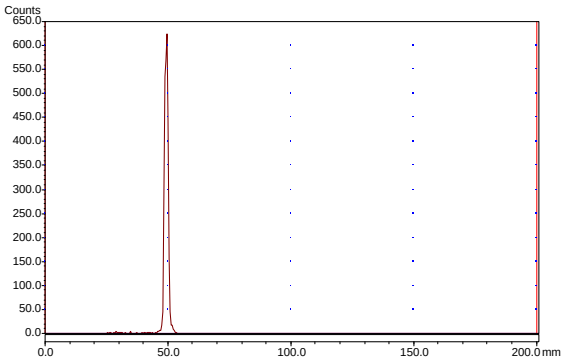

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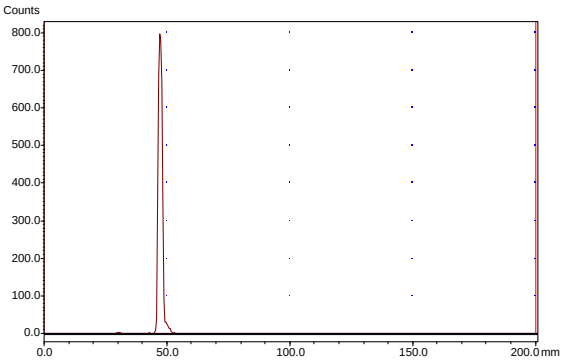

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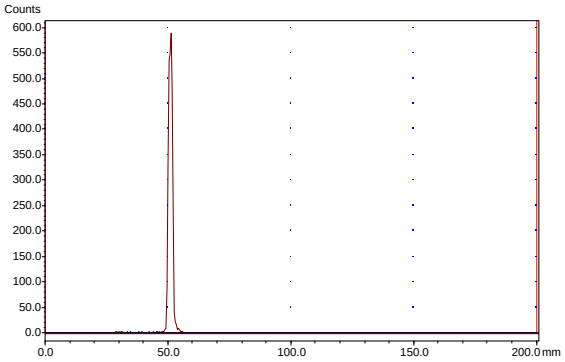

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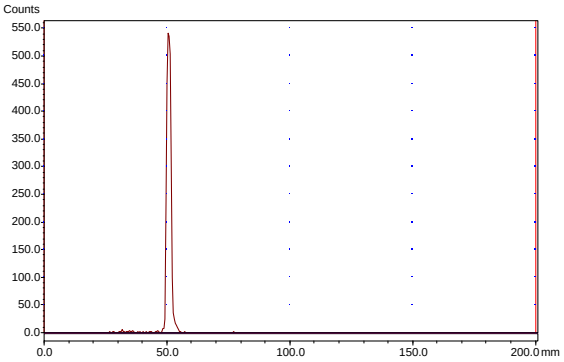
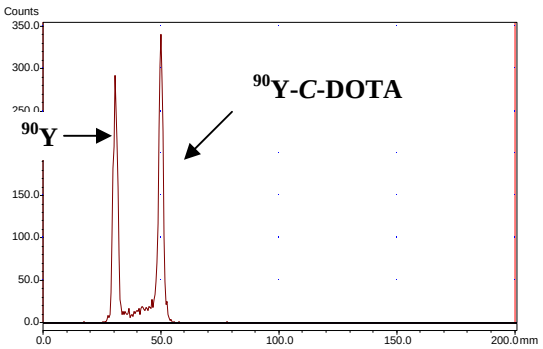


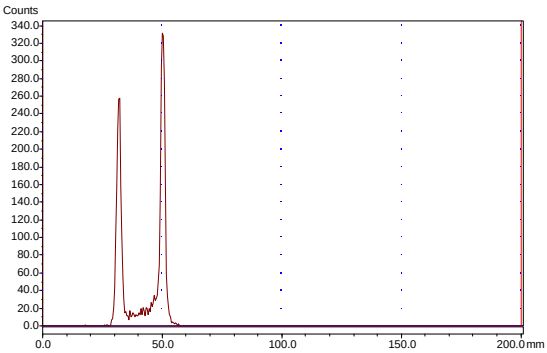
ii) ITLC spectra of radiolabeling of *C*-DOTA with ^{90}Y (taken from single run)

pH 4.0

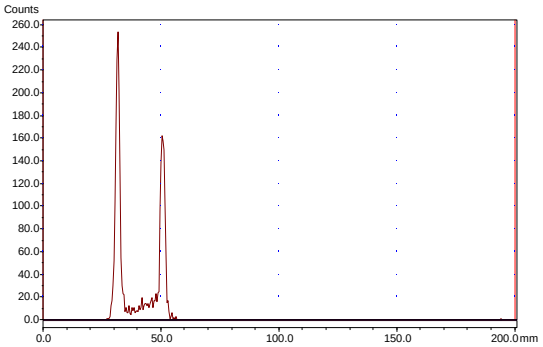
1min



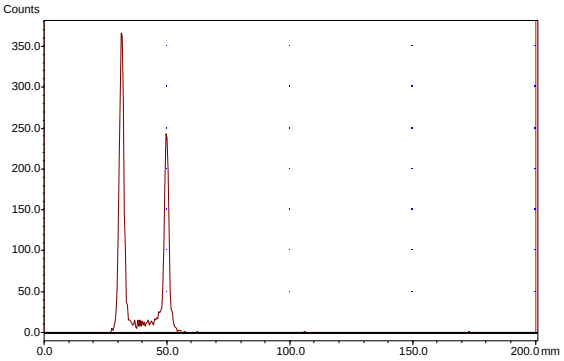
5min



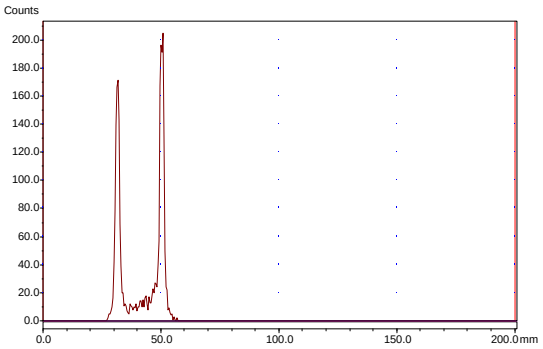
10min



20min



30min



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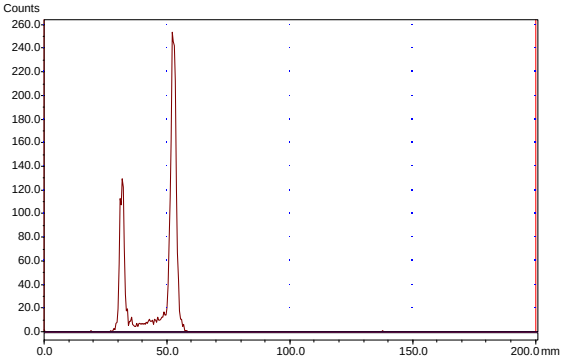
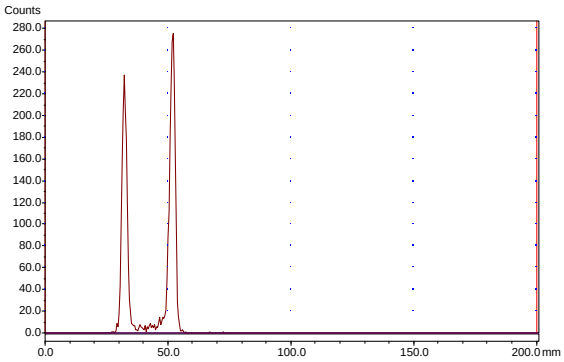
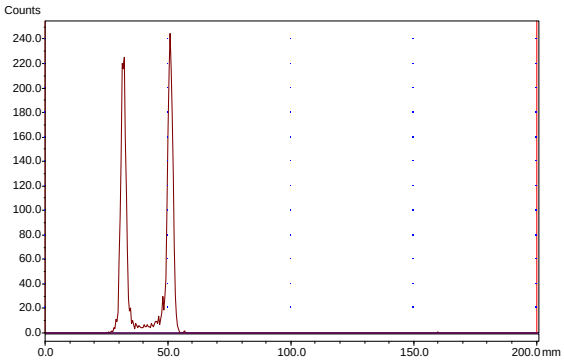


pH 4.5

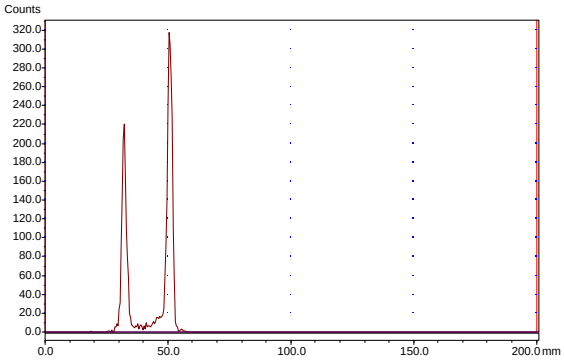
1min



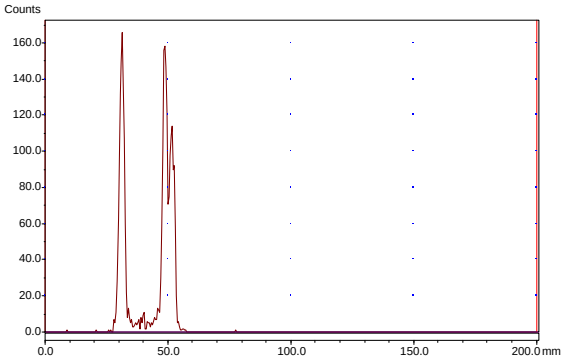
5min



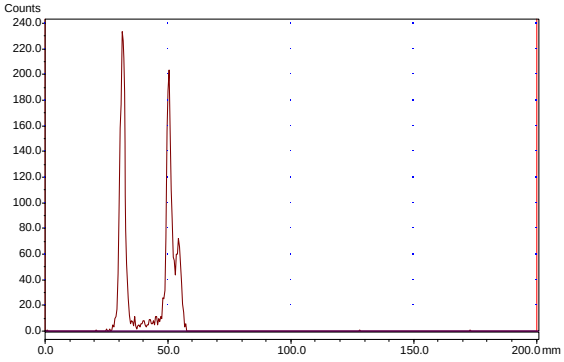
10min



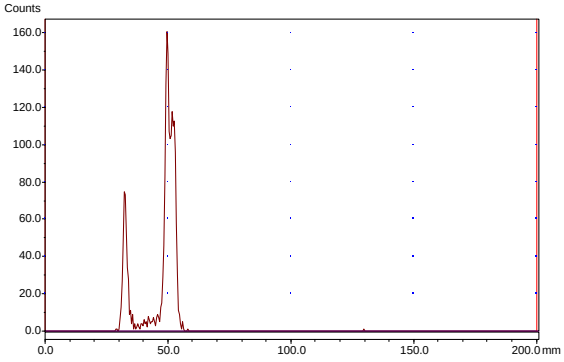
20min



30min

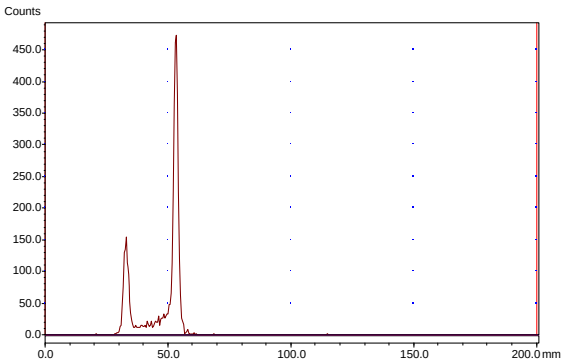


60min



pH 5.0

1min



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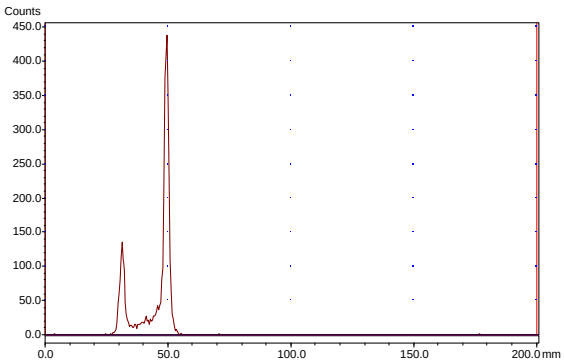

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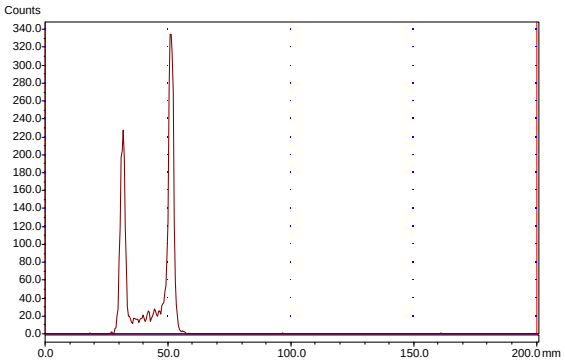
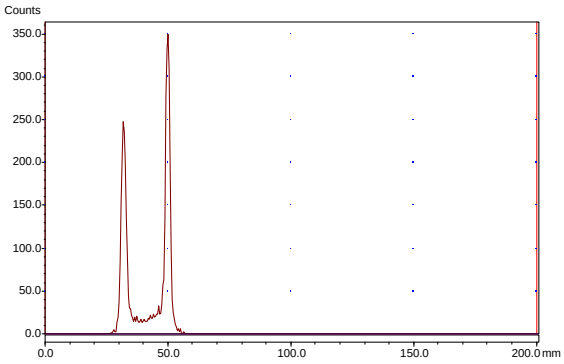


20min



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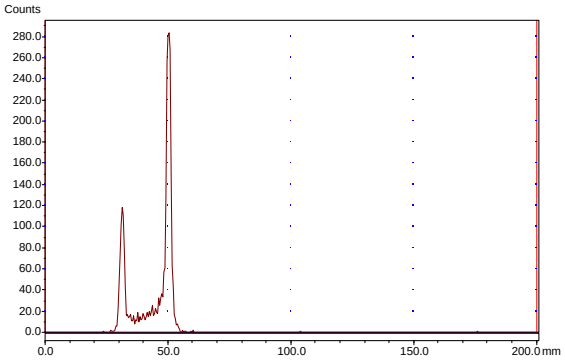

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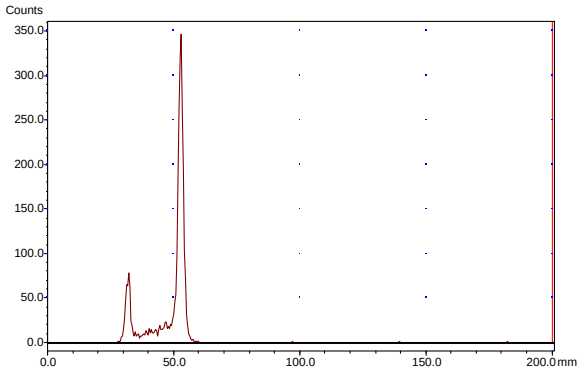
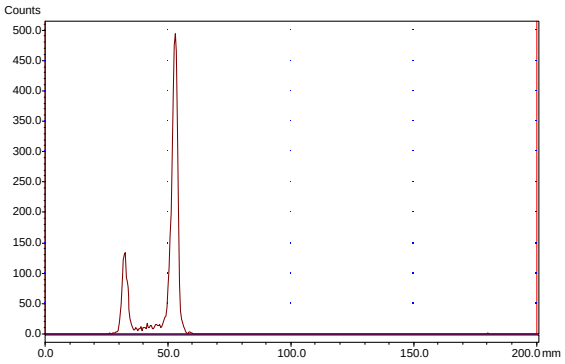
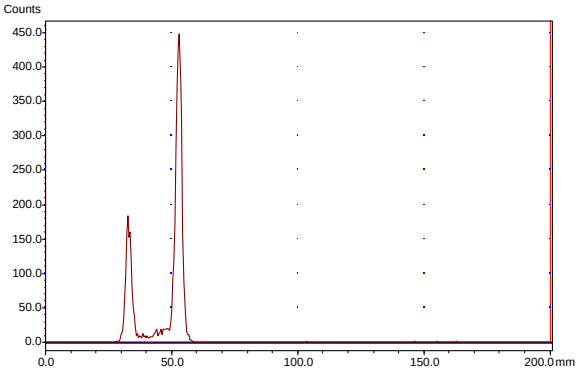


pH 5.5

1min



5min



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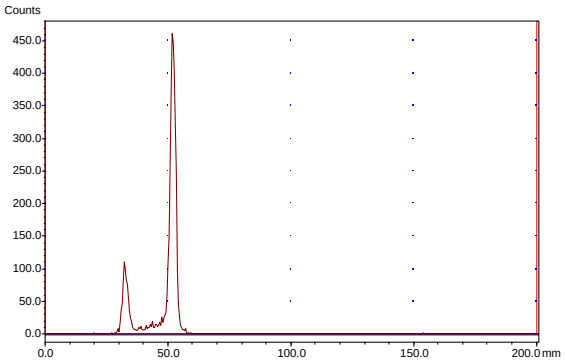

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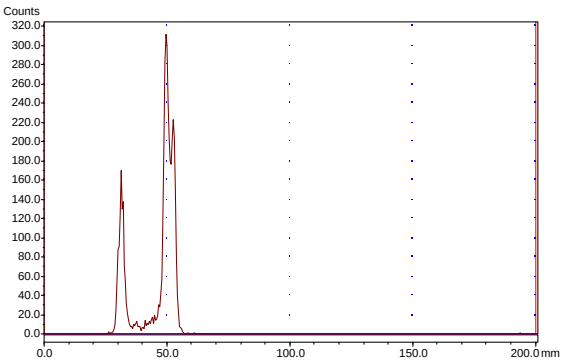

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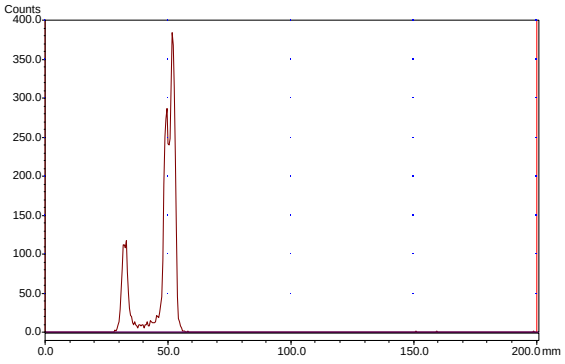

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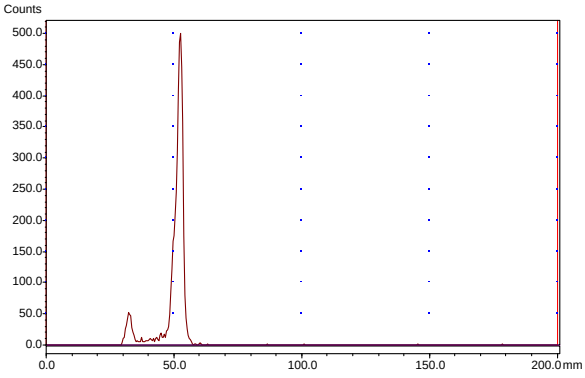
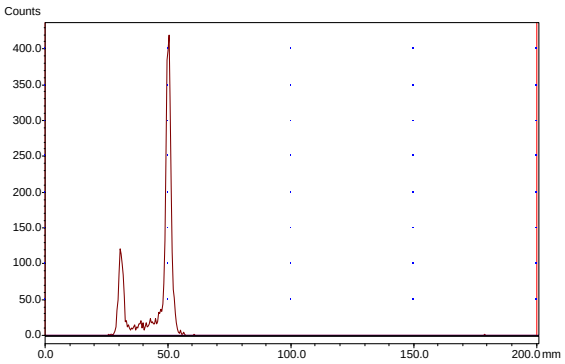


pH 6.0

1min



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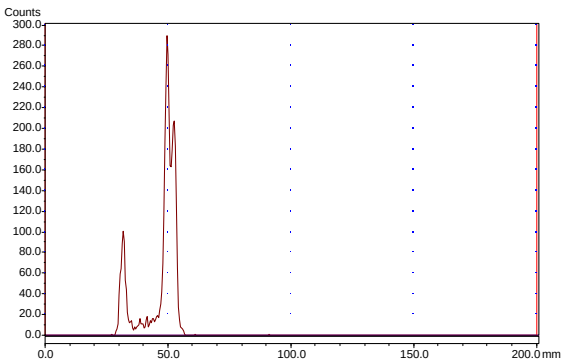

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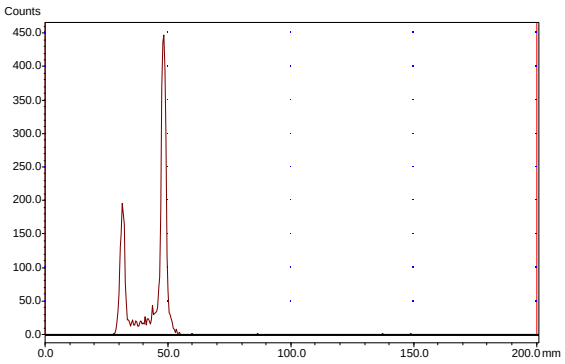

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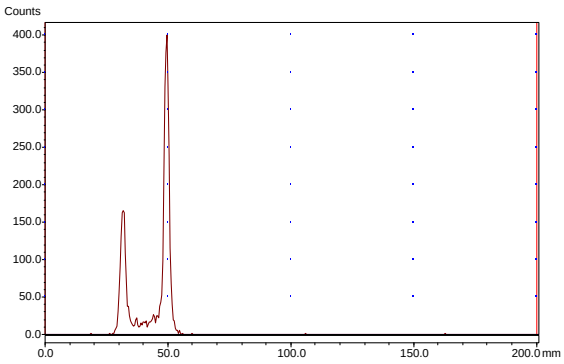

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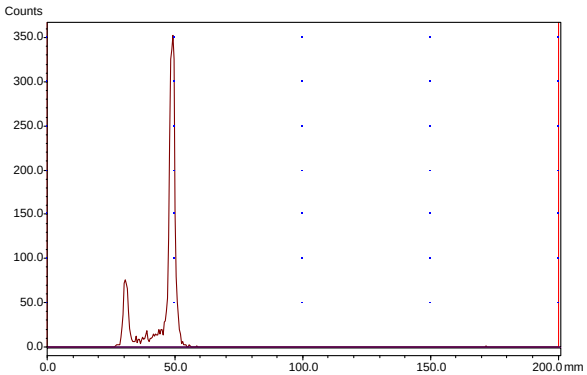

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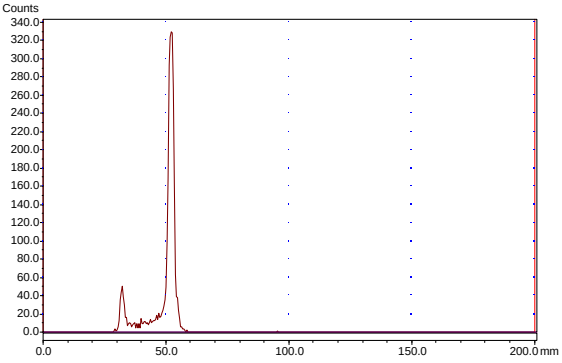
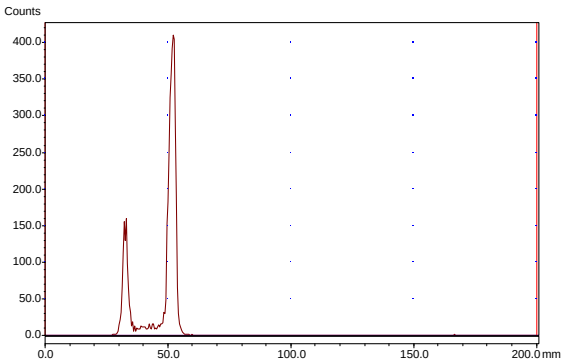


pH 6.5

1min



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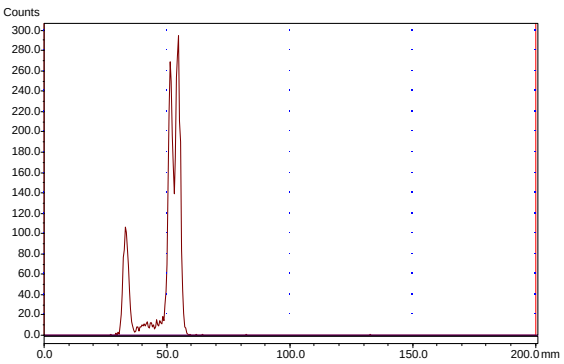

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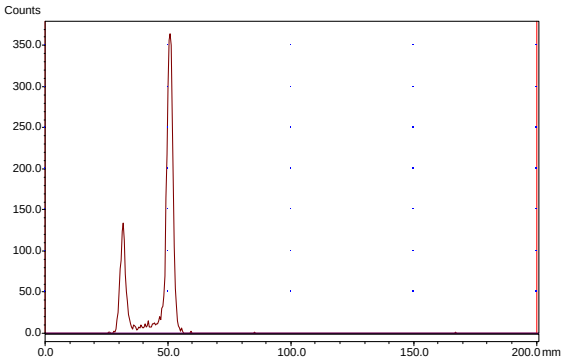

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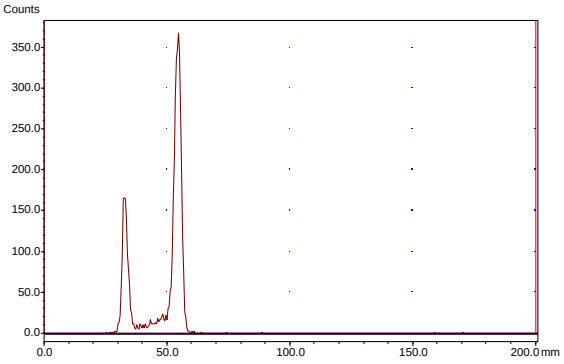

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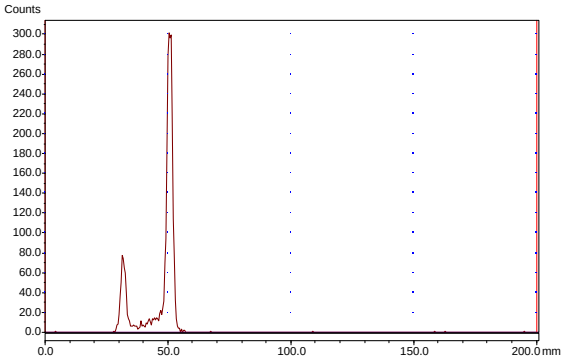

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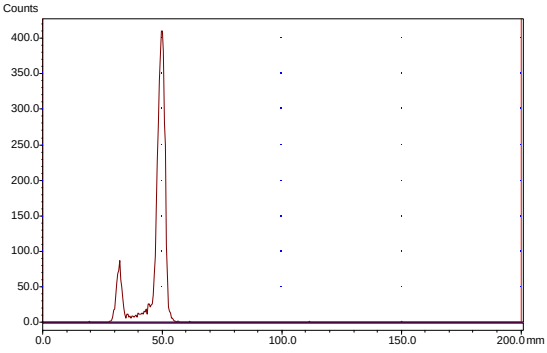
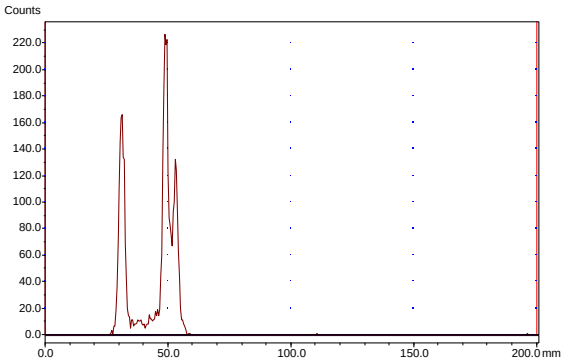


pH 7.0

1min



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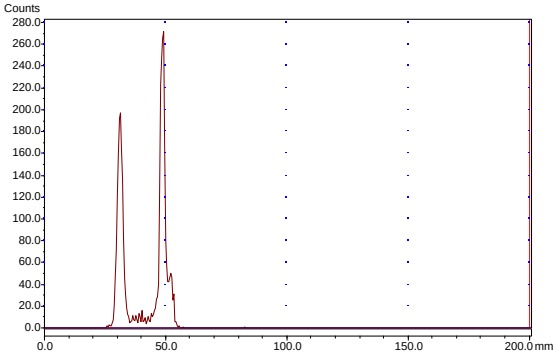

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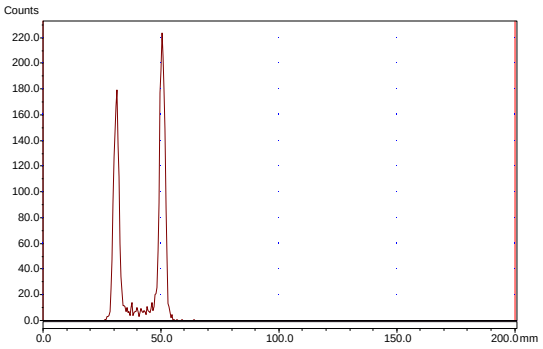

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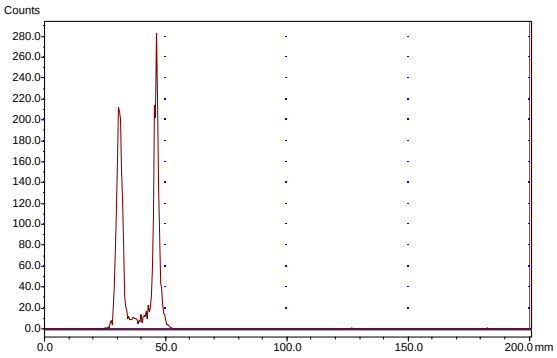

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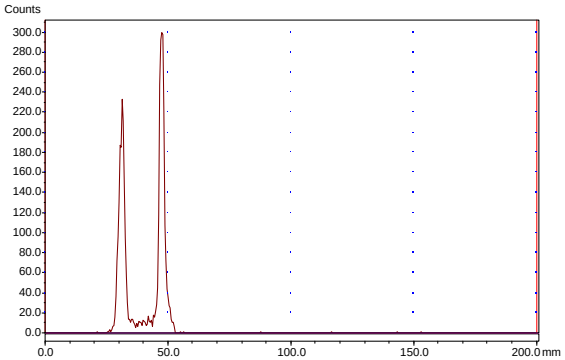

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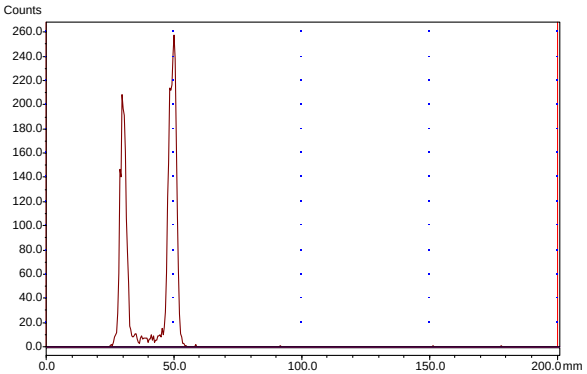
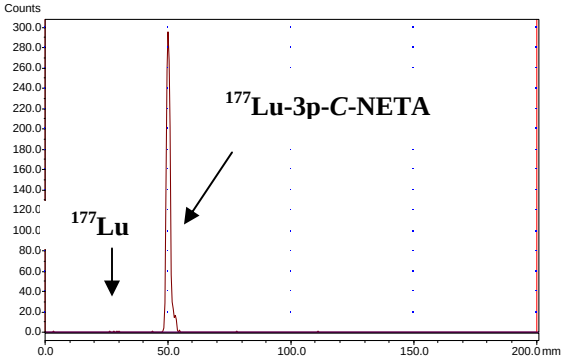


iii) ITLC spectra of radiolabeling of 3p-*C*-NETA with ^{177}Lu (taken from single run)

pH 4.0

1min



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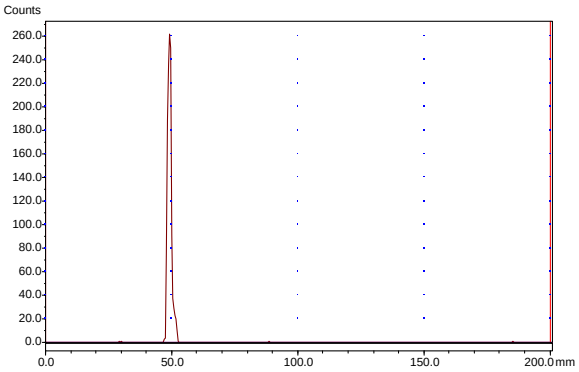

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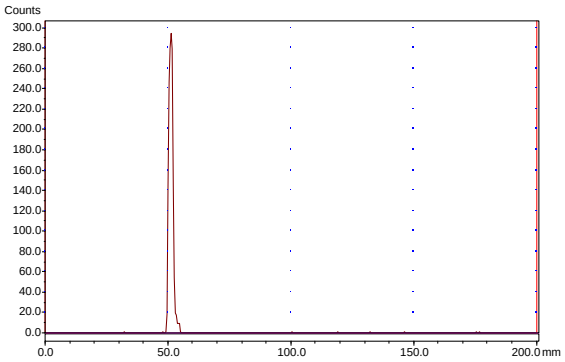

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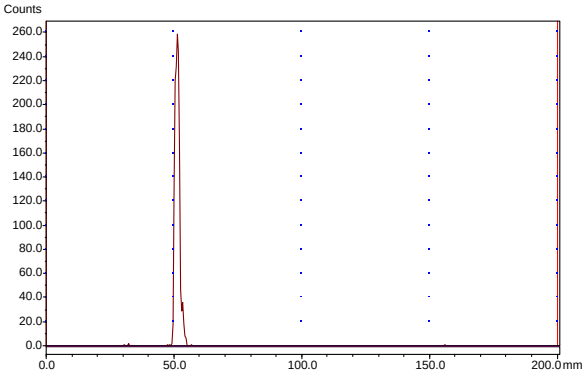

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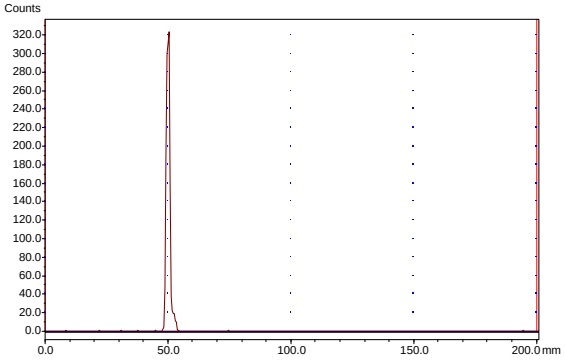

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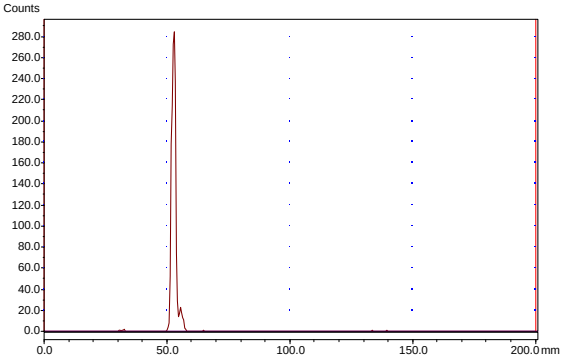
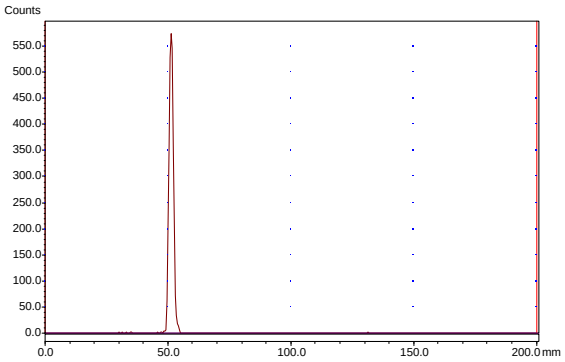
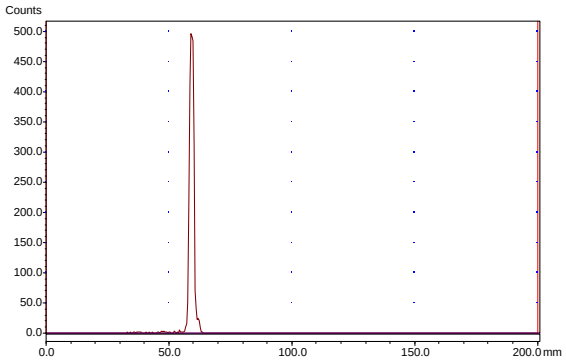


pH 4.5

1min



5min



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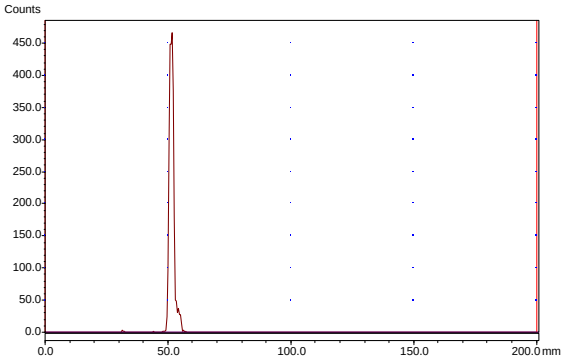

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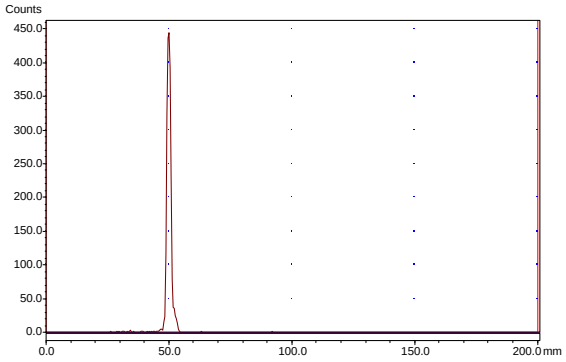

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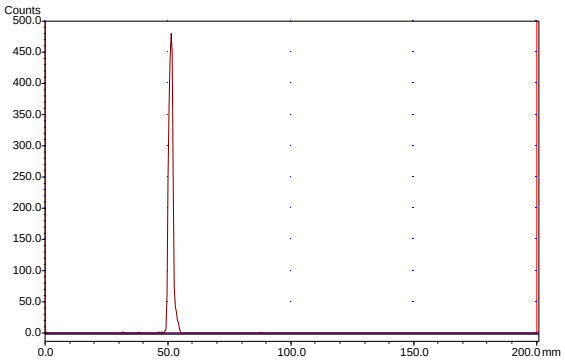

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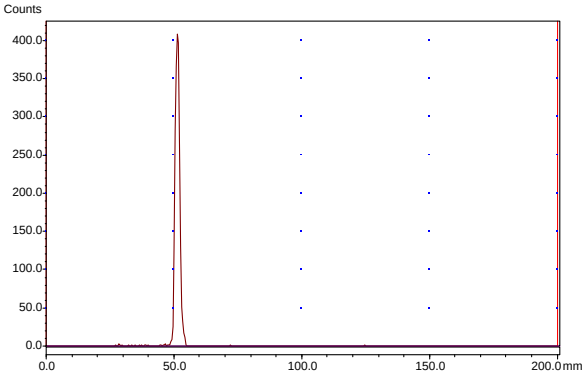
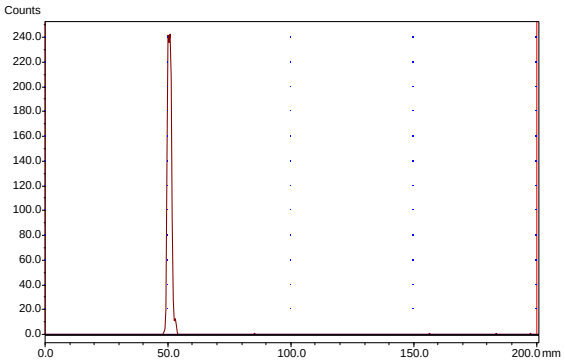


pH 5.0

1min



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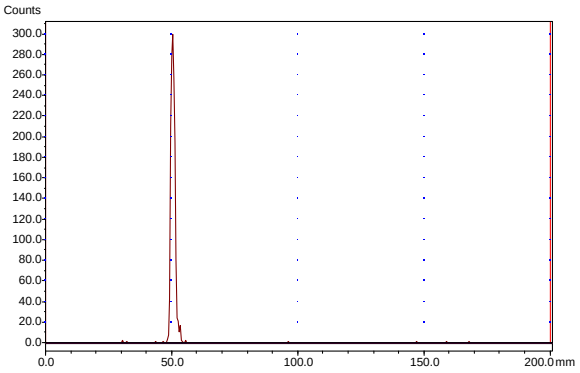

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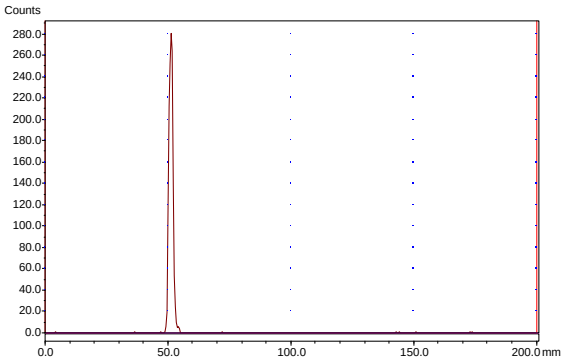

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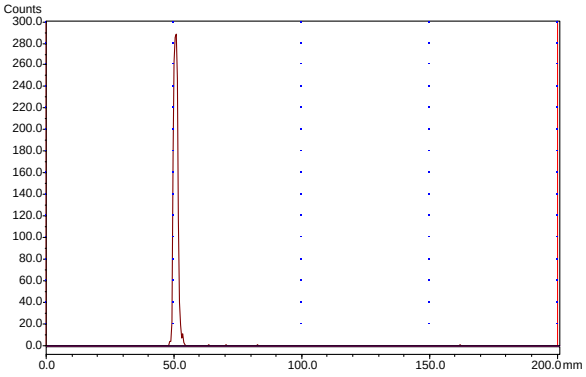

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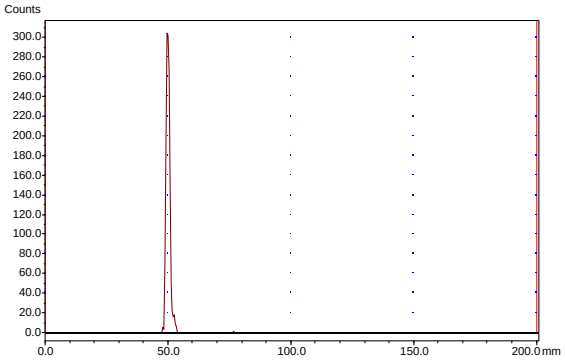

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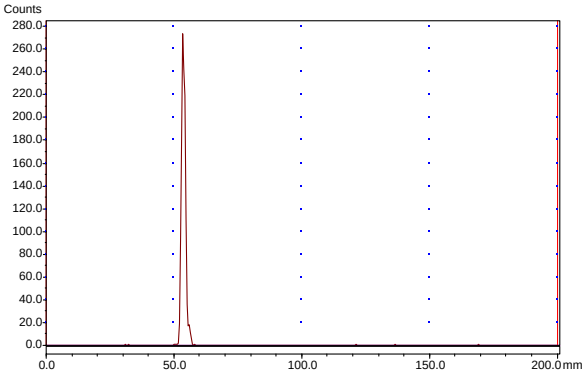
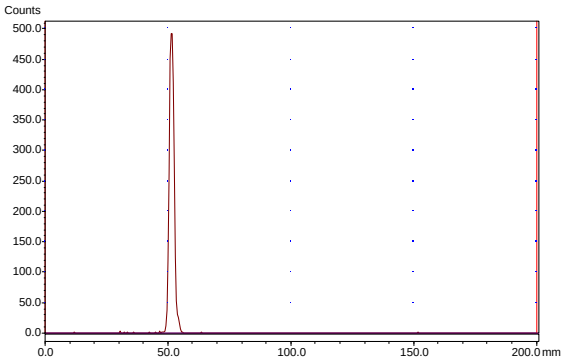


pH 5.5

1min



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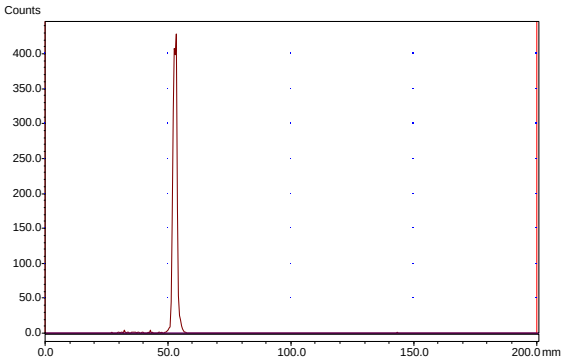

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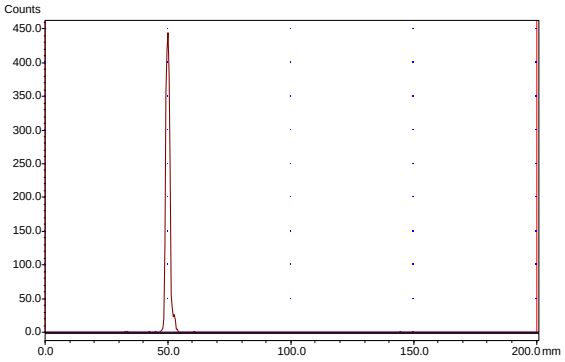

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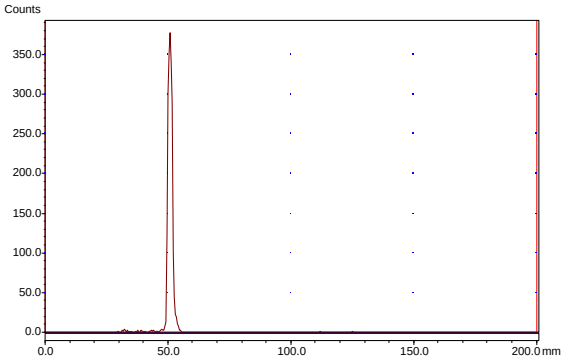

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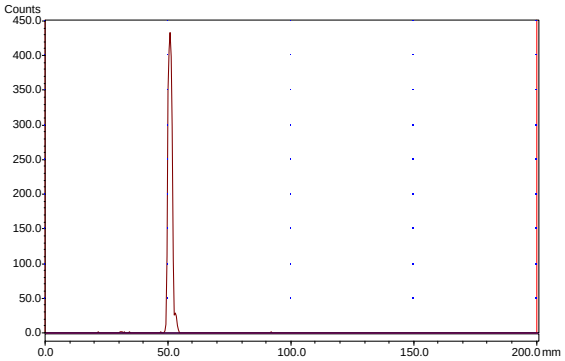

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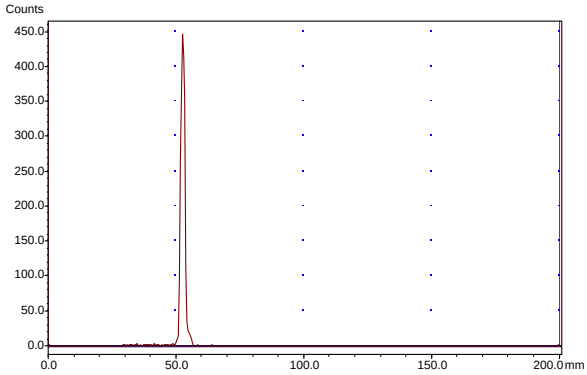
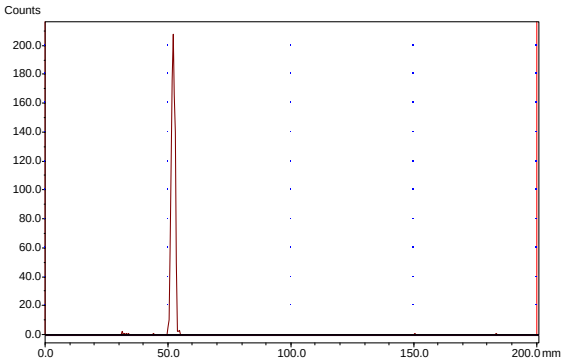


pH 6.0

1min



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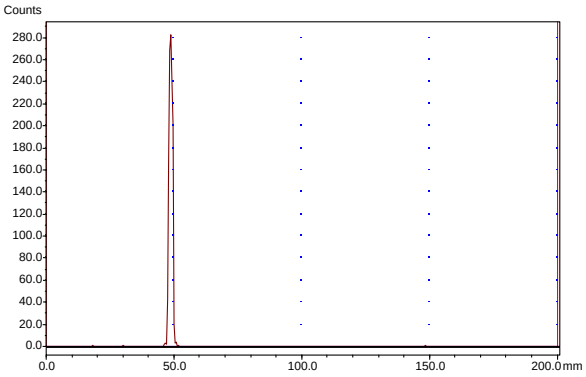

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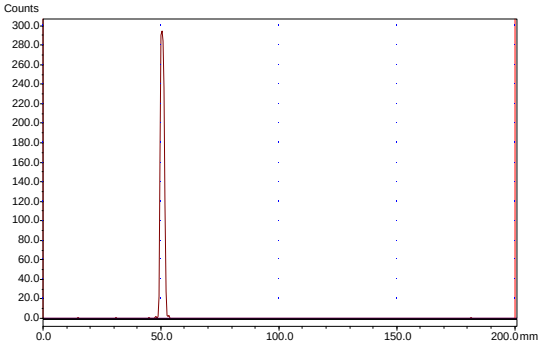

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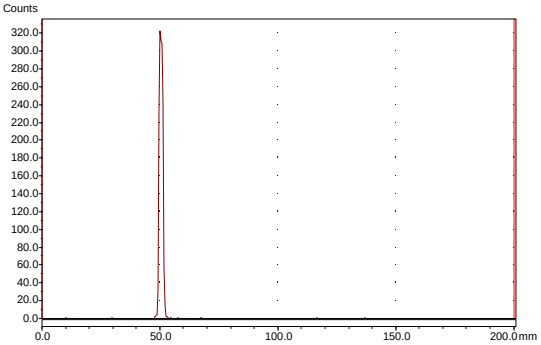

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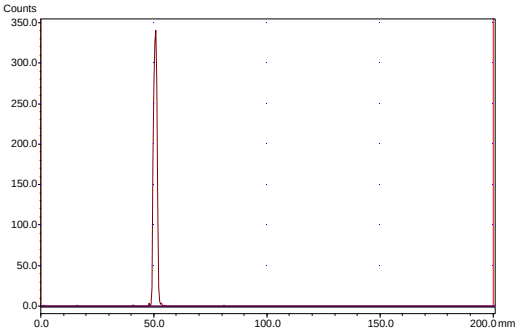

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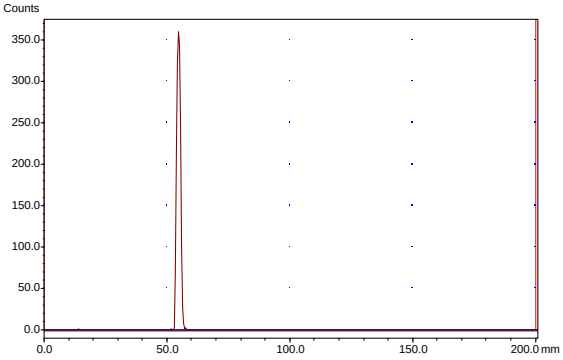
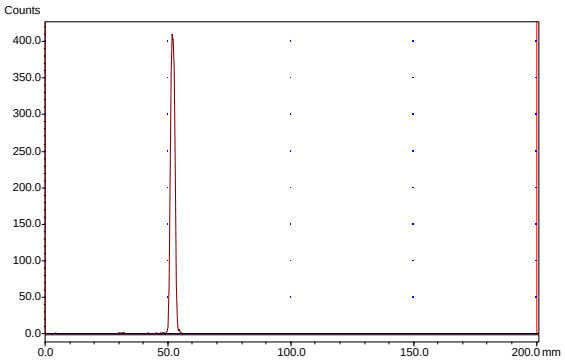


pH 6.5

1min



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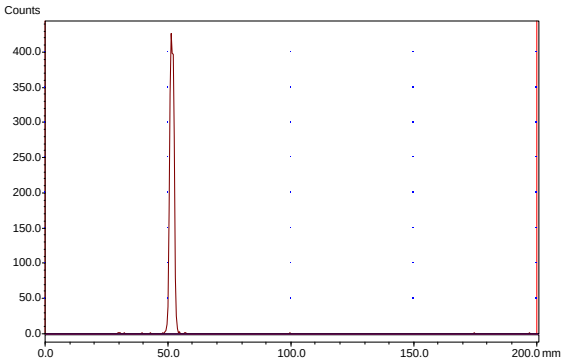

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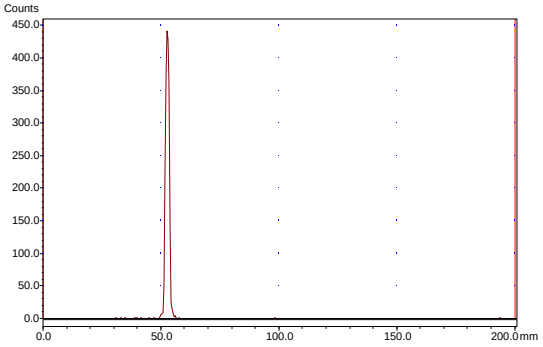

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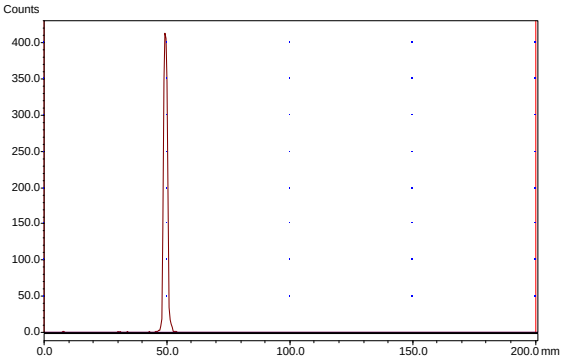

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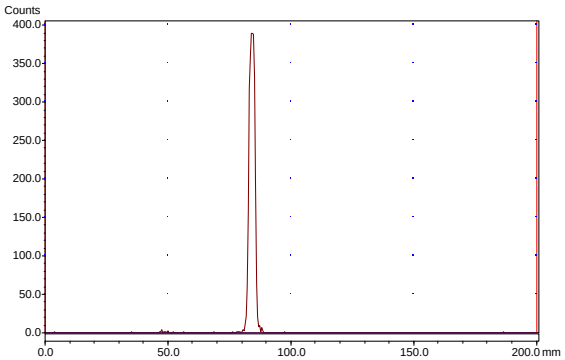

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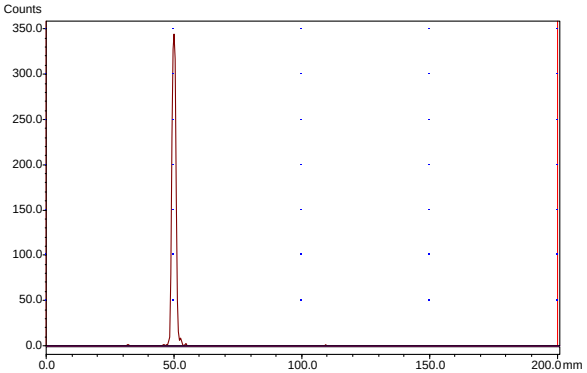
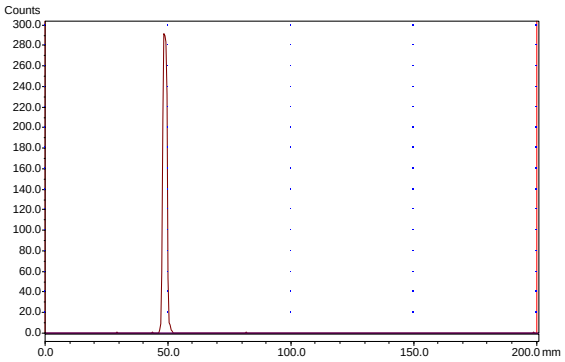


pH 7.0

1min



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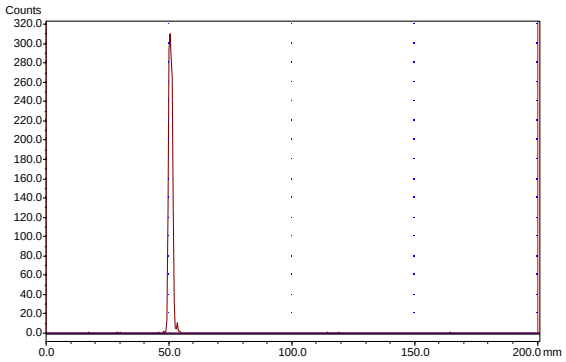
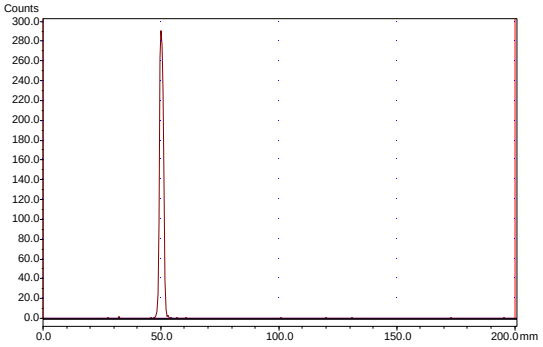


10min



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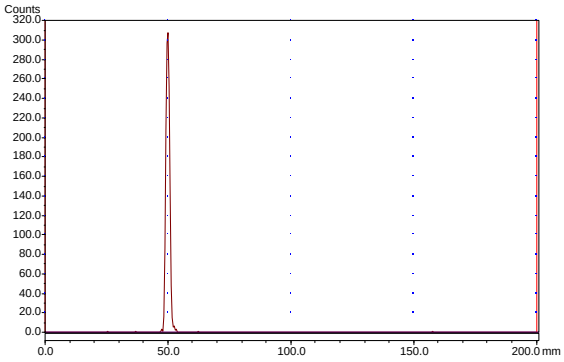

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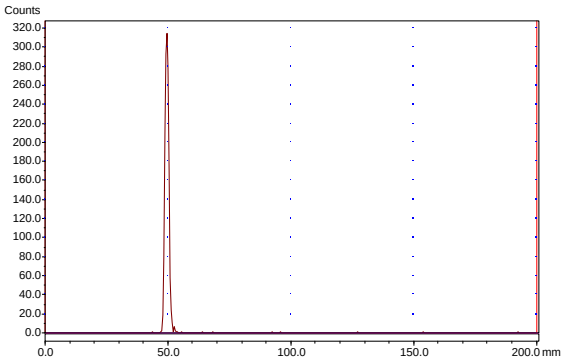

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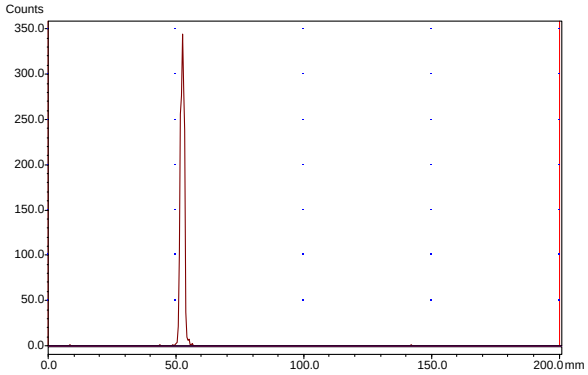
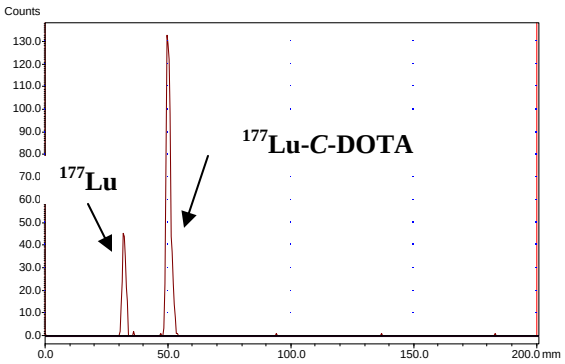


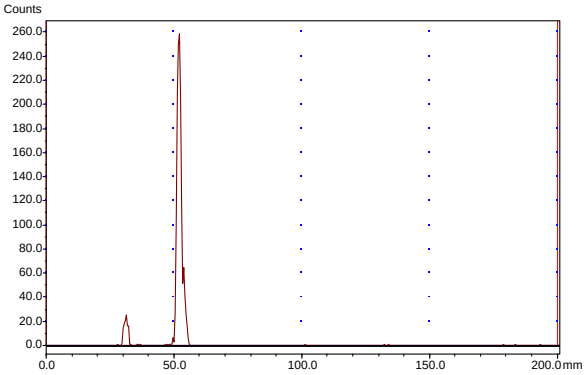
iv) ITLC spectra of radiolabeling of *C*-DOTA with ^{177}Lu (taken from single run)

pH 4.0

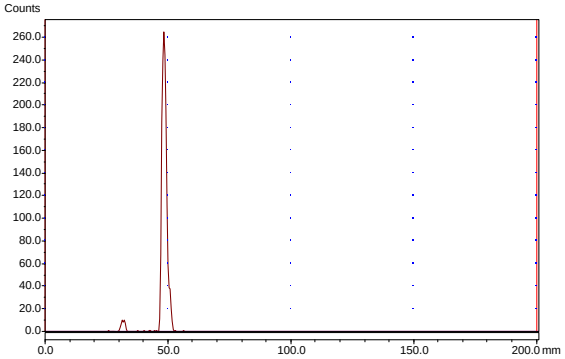
1min



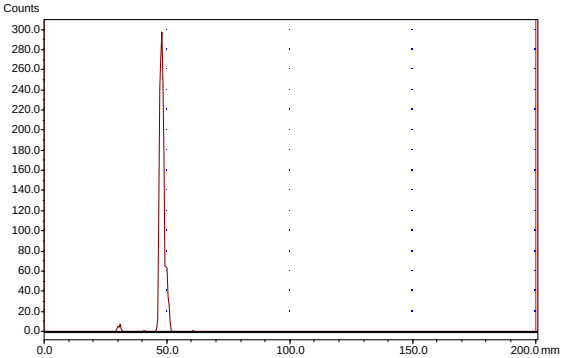
5min



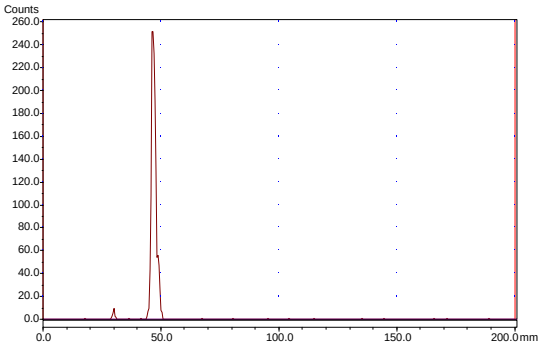
10min



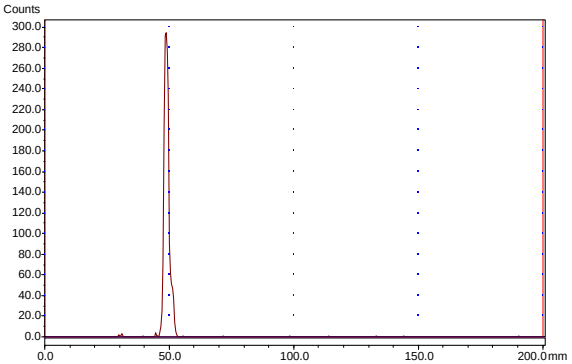
20min



30min

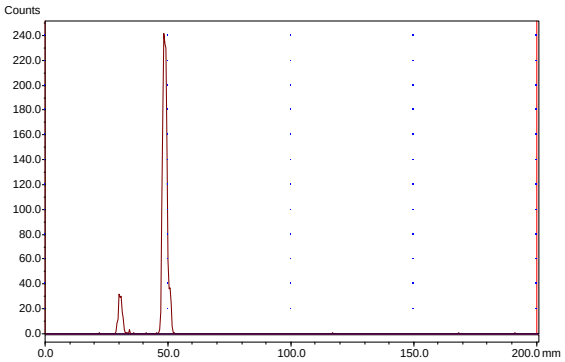


60min

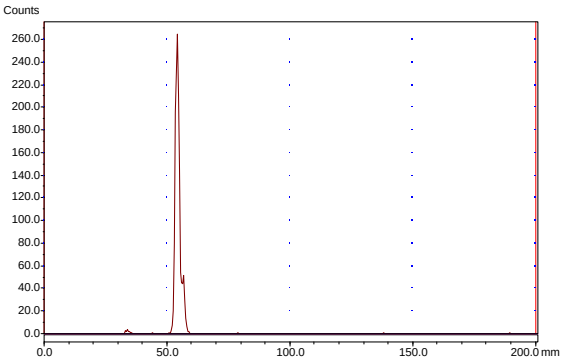


pH 4.5

1min



5min



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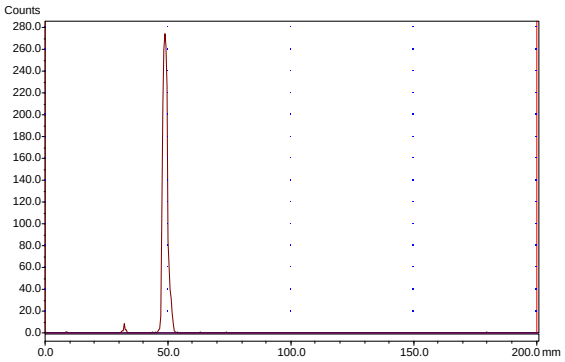

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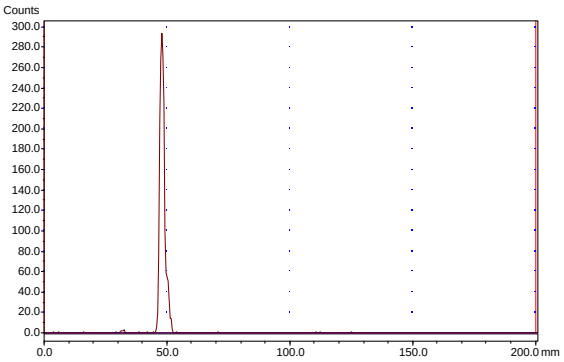

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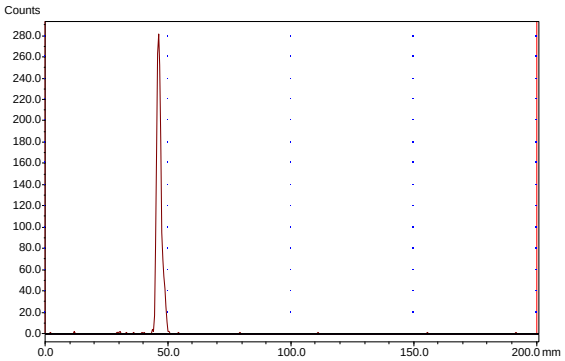

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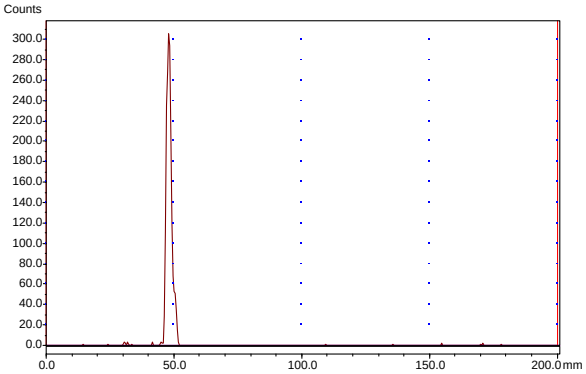
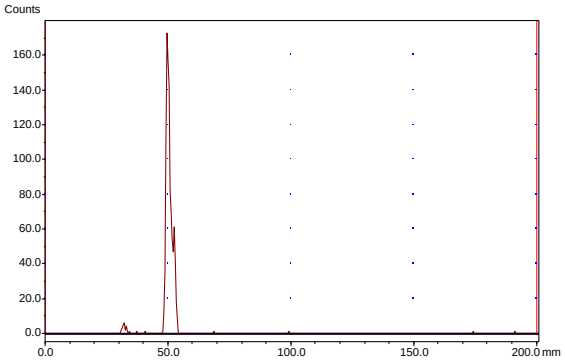


pH 5.0

1min



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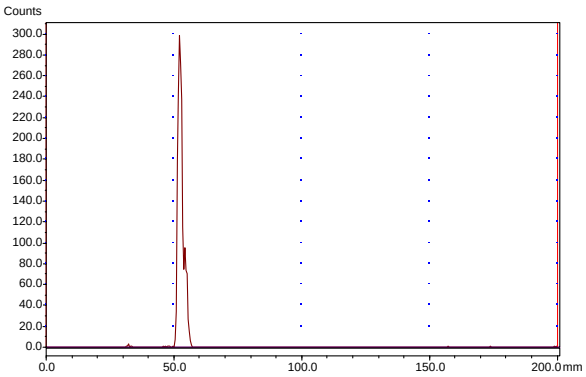

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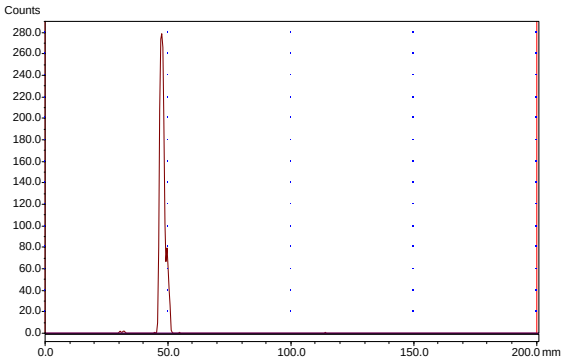

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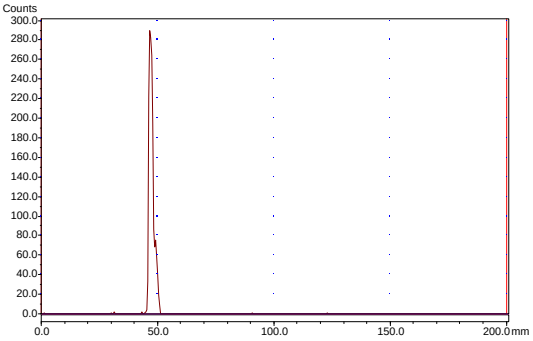

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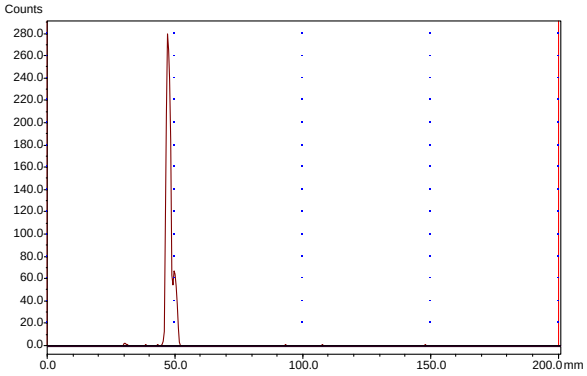

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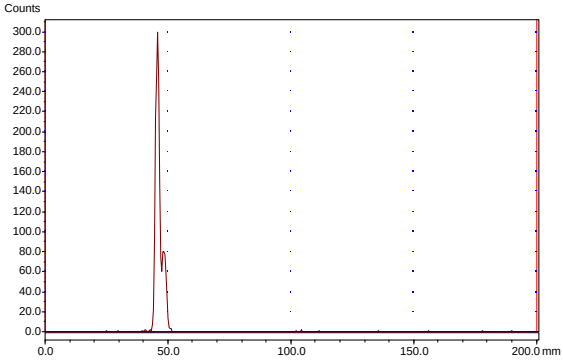
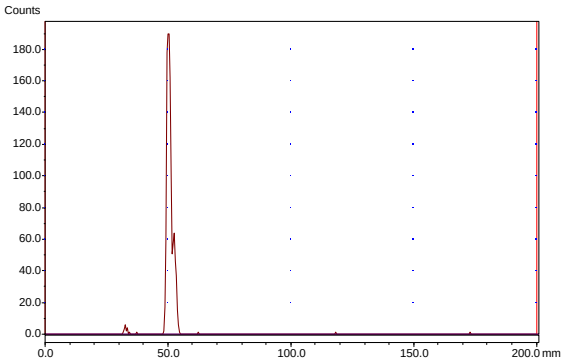


pH 5.5

1min



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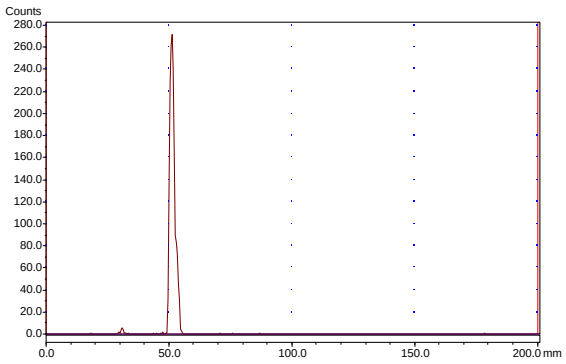

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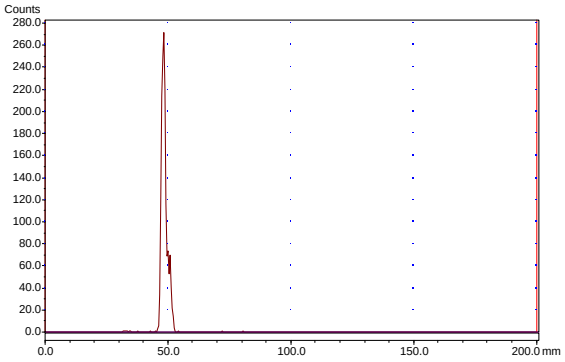

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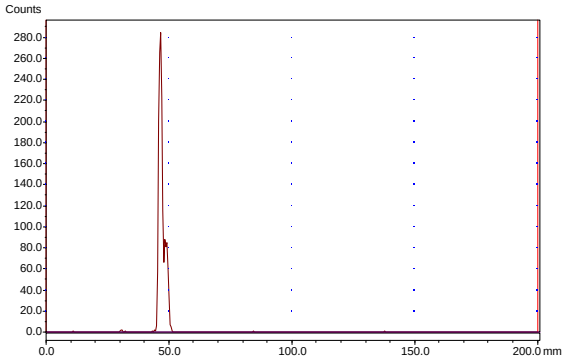

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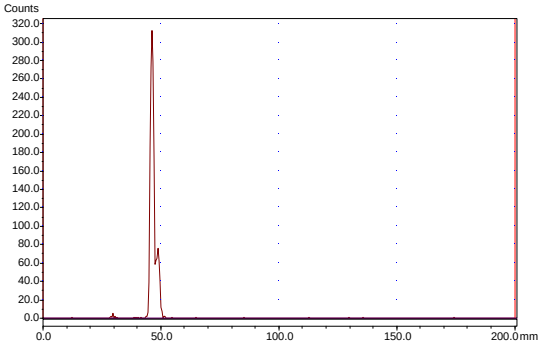

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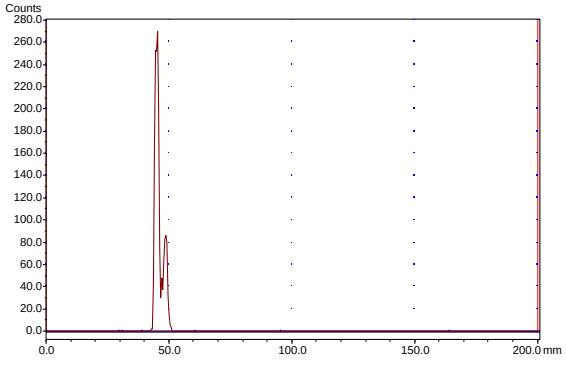
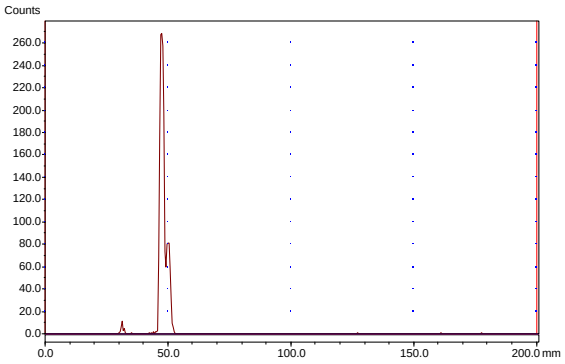


pH 6.0

1min



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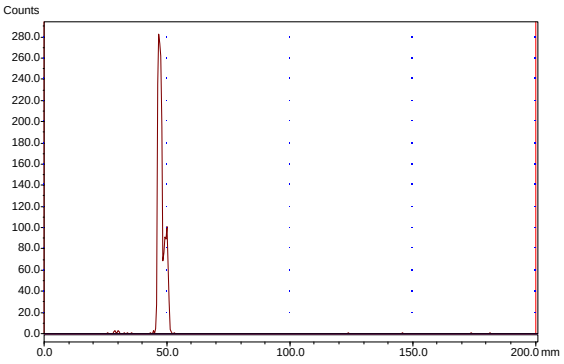

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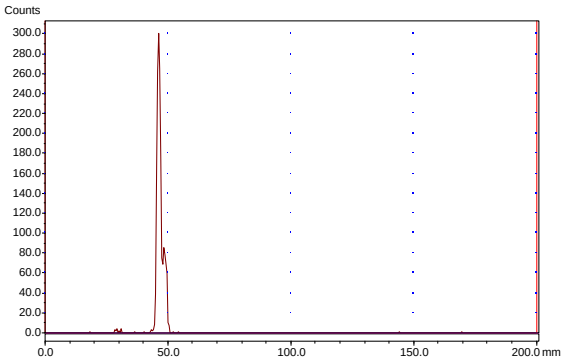

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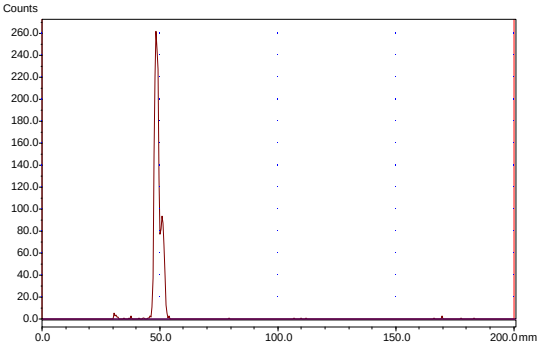

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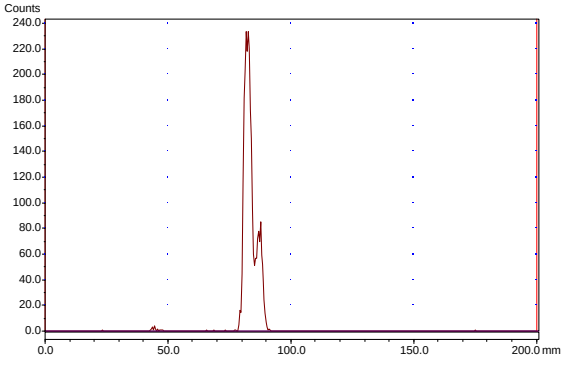

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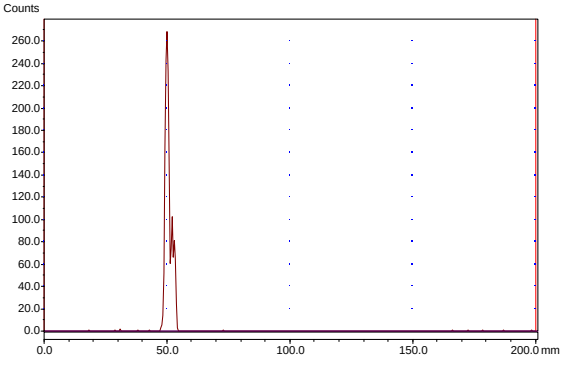
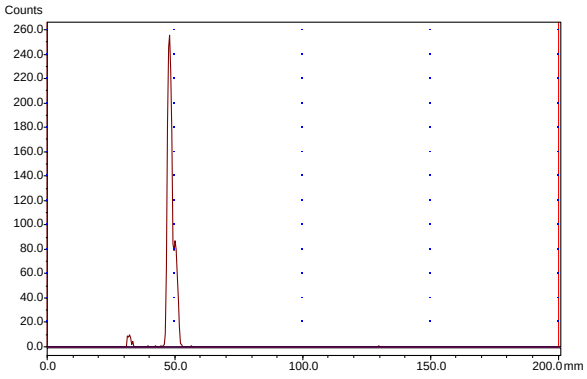


pH 6.5

1min



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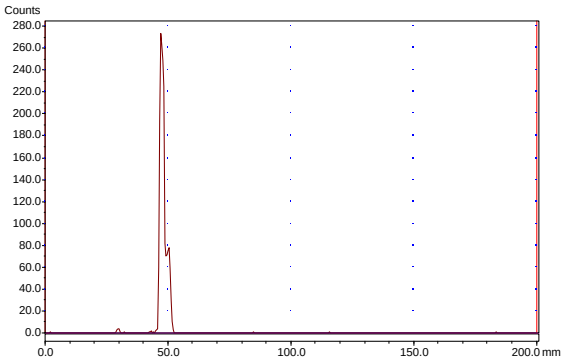

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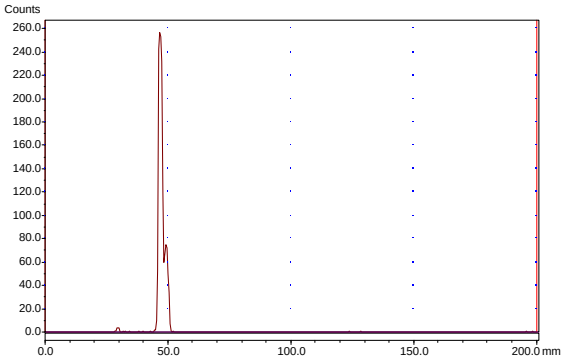

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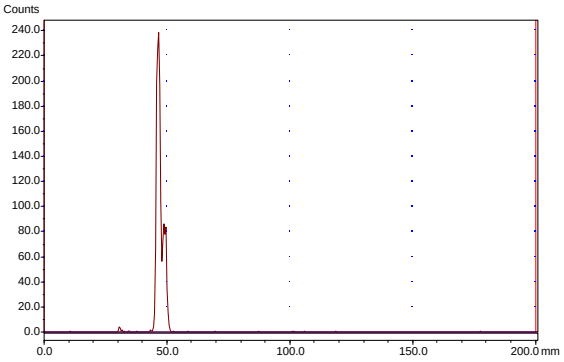

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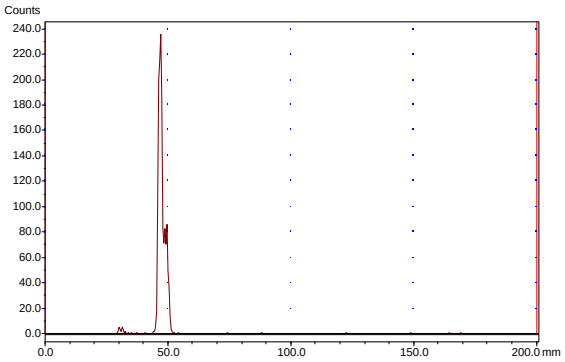

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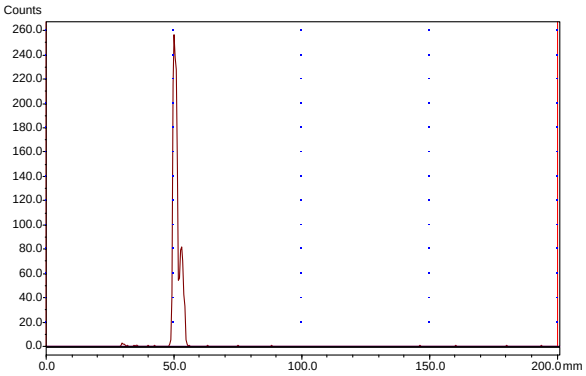
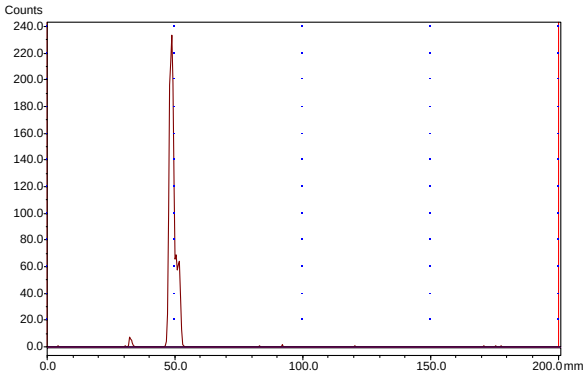
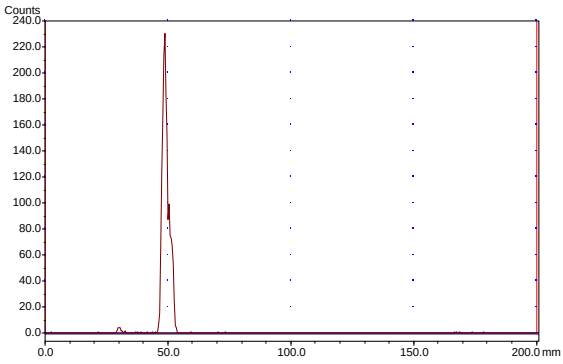


pH 7.0

1min



5min



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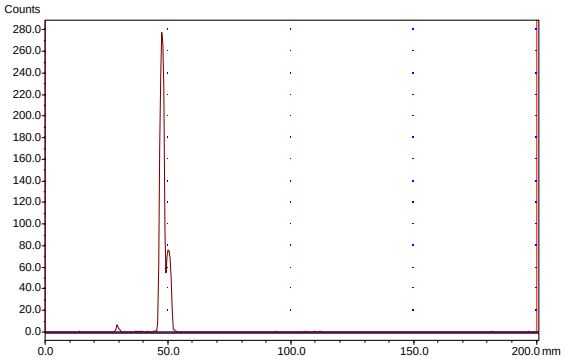

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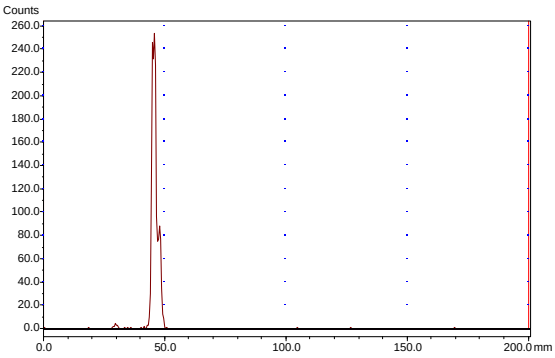

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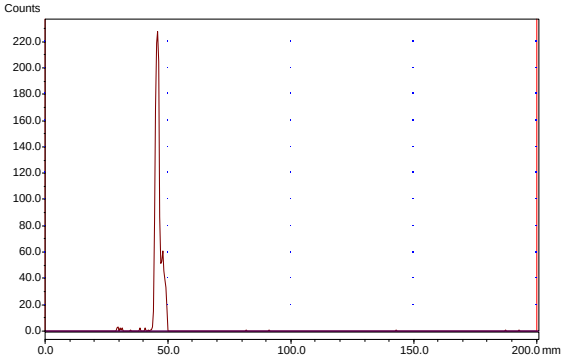

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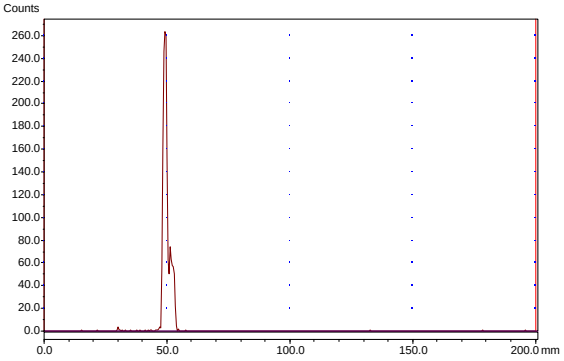
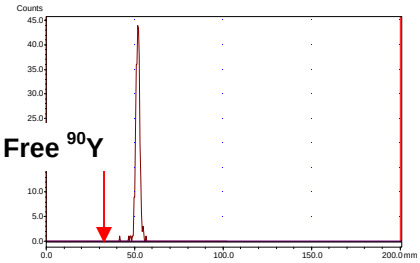


7. Serum stability data (ITLC and radio-HPLC spectra of triplicate samples)

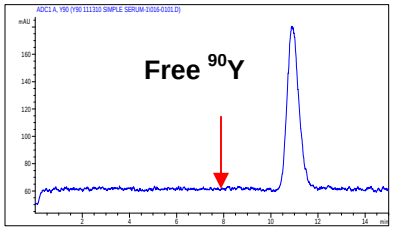
i) ^{90}Y-*C*-DOTA (n = 3)

Day 0

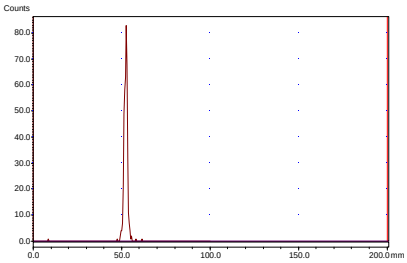
Sample 1
100%



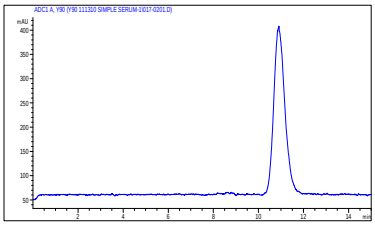
100%



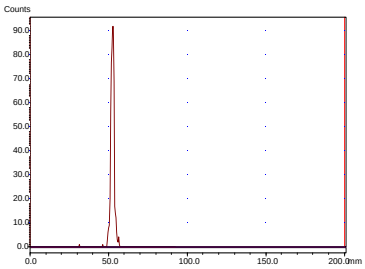
Sample 2
100%



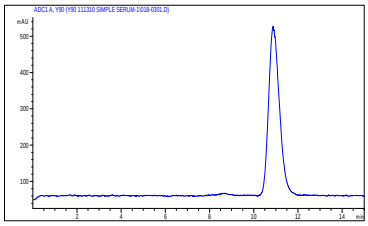
100%



Sample 3
99.9%

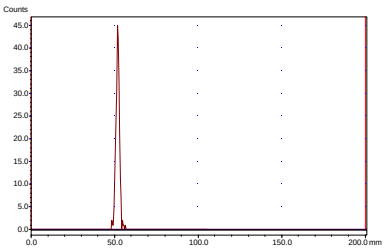


100%

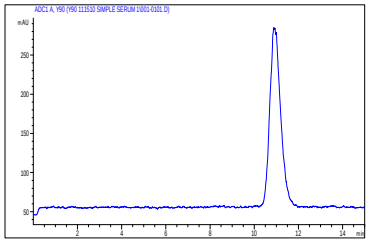


Day 1

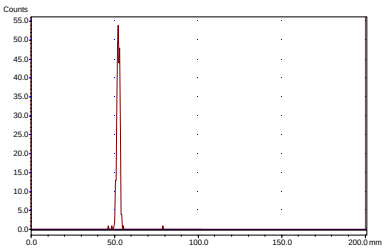
Sample 1
100%



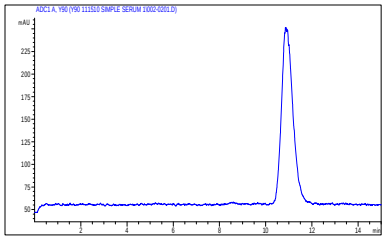
100%



Sample 2
100%



100%



Sample 3
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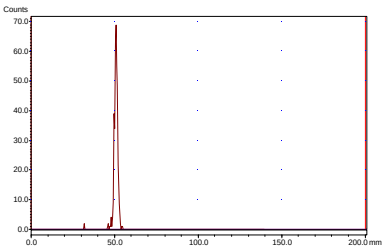

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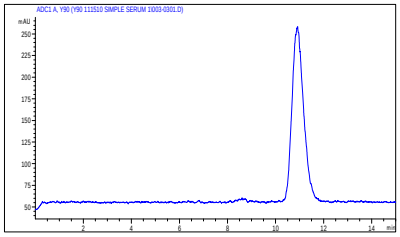

Day 2

Sample 1
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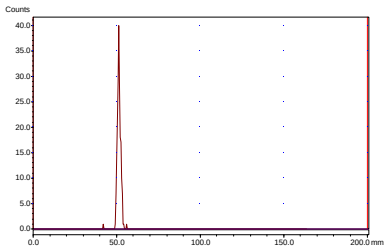

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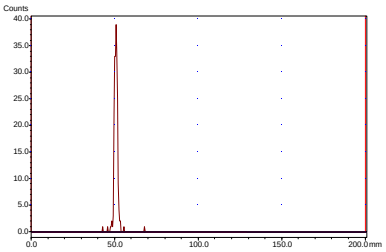

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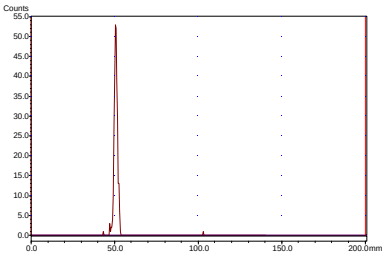

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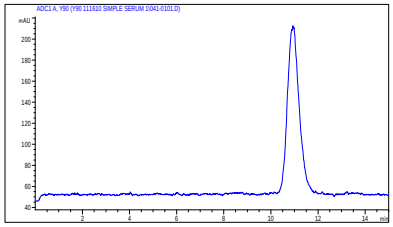

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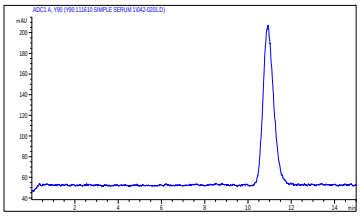

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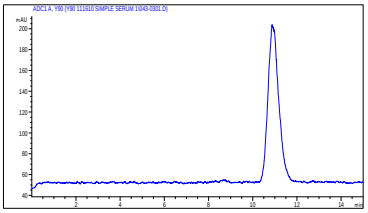

Day 3

Sample 1
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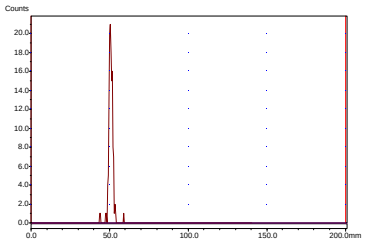

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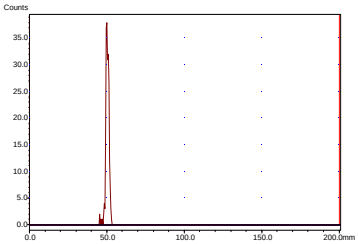

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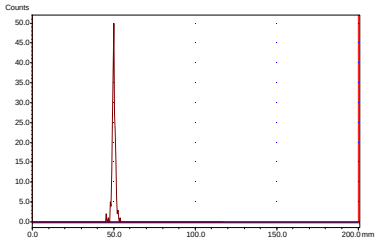

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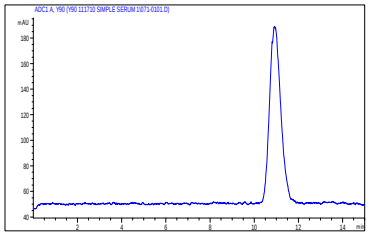

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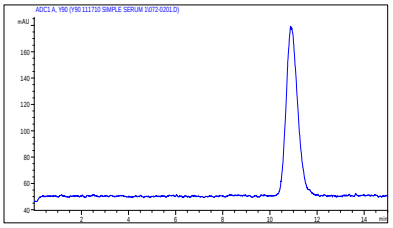

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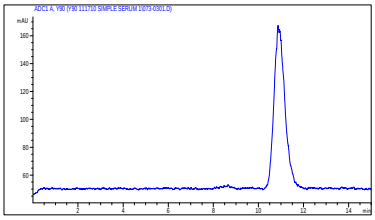

Day 4

Sample 1
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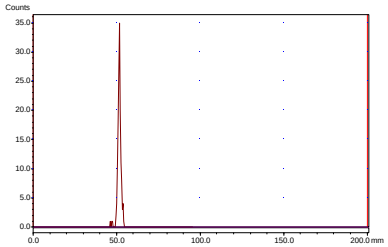

Sample 2
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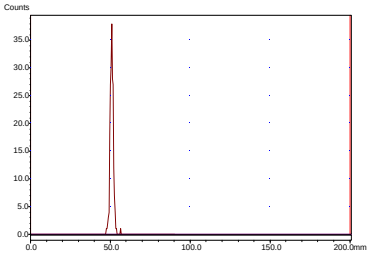

Sample 3
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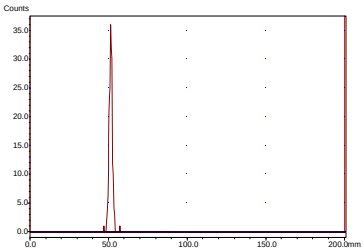

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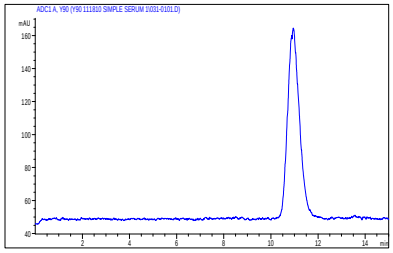

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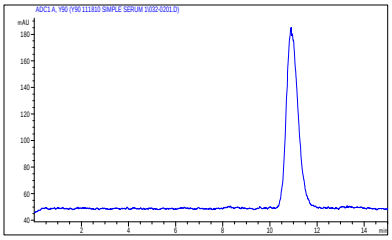

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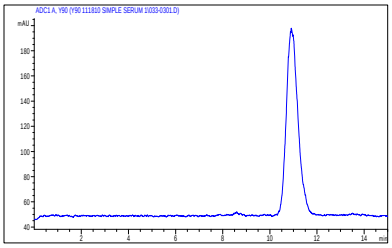

Day 5

Sample 1
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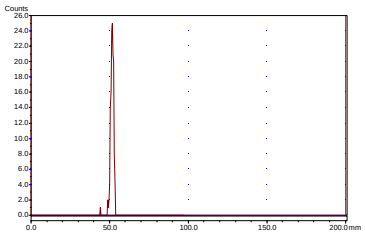

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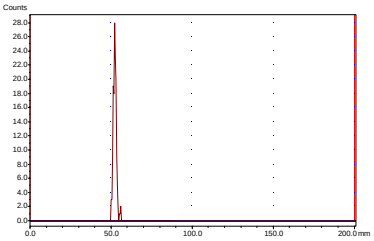

Sample 3
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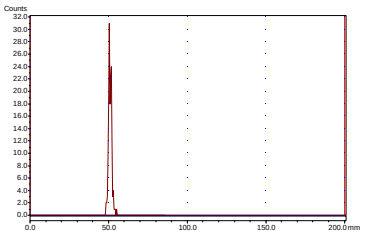

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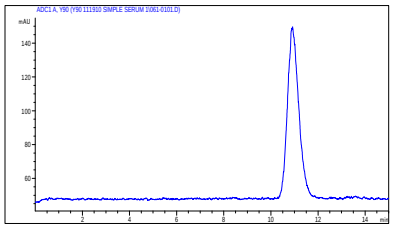

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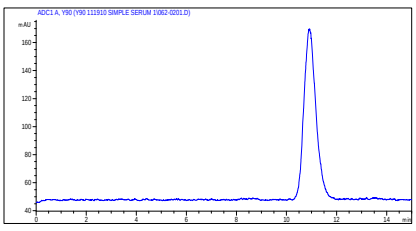

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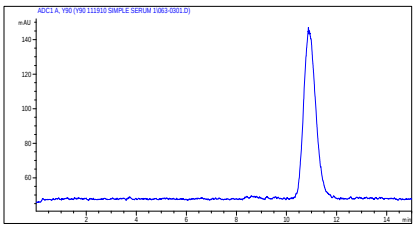

Day 6

Sample 1
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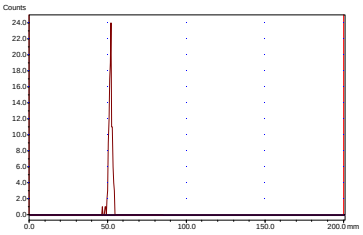

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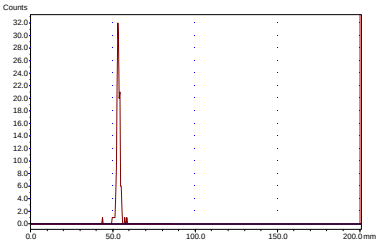

Sample 3
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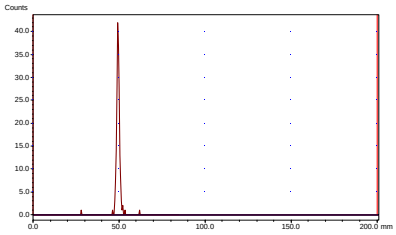

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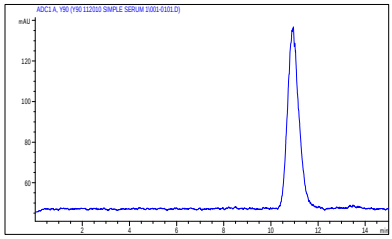

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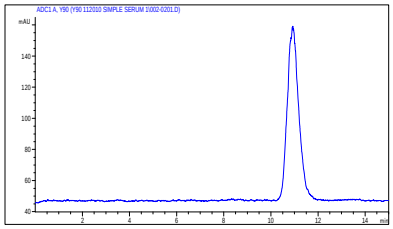

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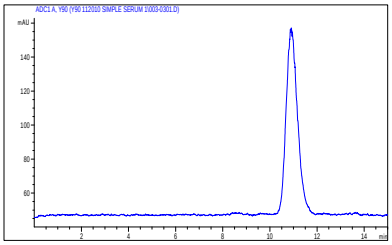

Day 7

Sample 1
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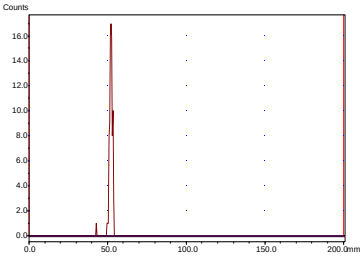

Sample 2
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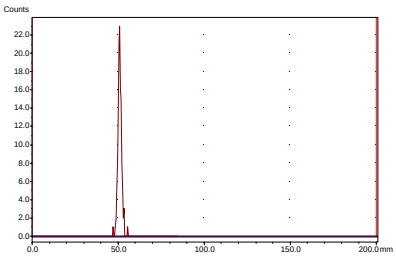
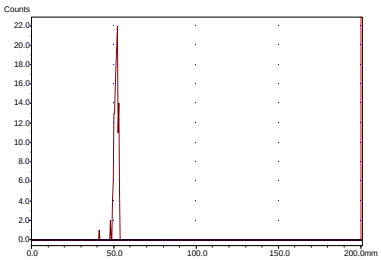


Sample 3
100%



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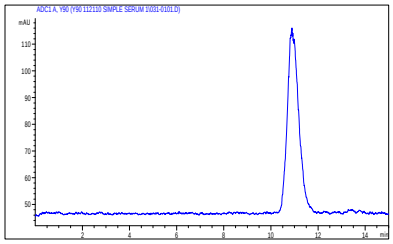

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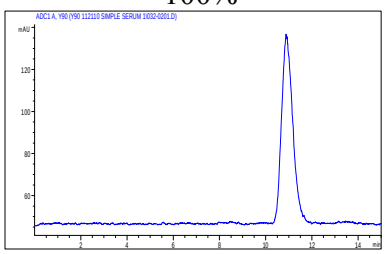

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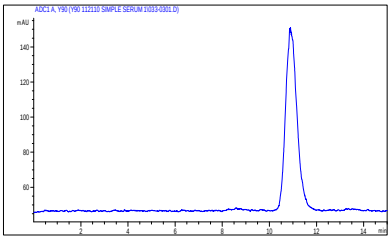

Day 8

Sample 1
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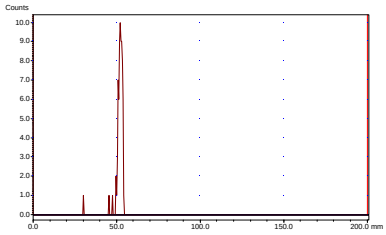

Sample 2
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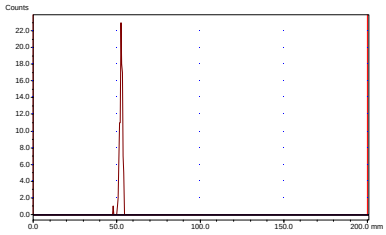
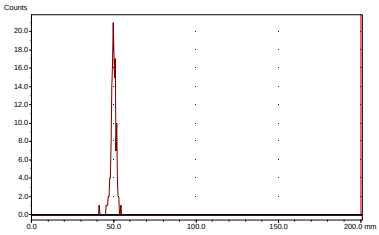


Sample 3
100%



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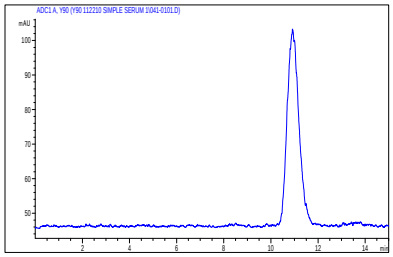

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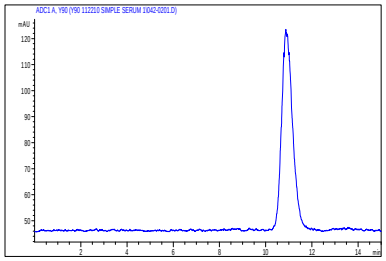

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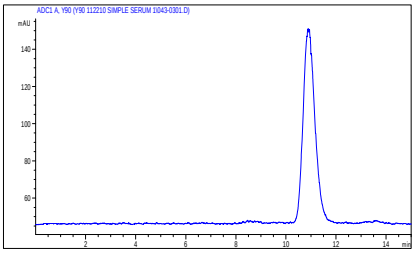

Day 9

Sample 1
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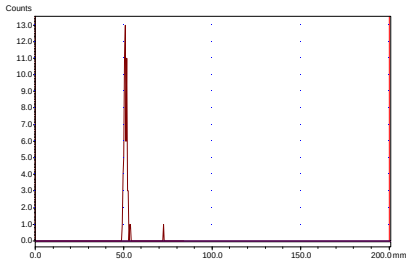

Sample 2
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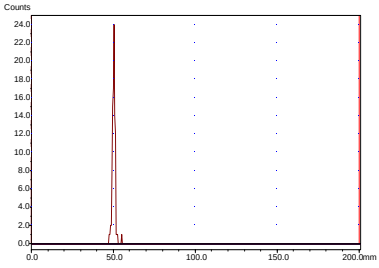

Sample 3
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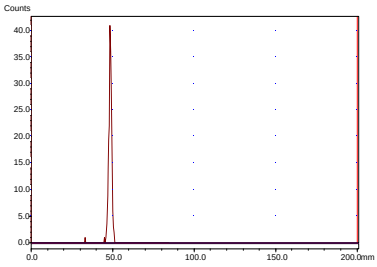

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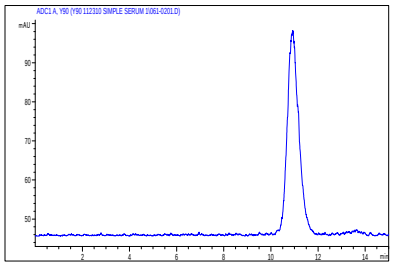

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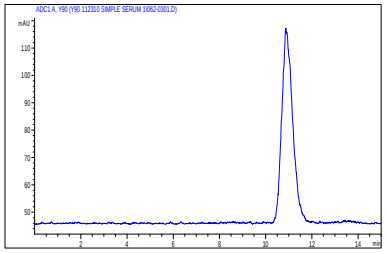

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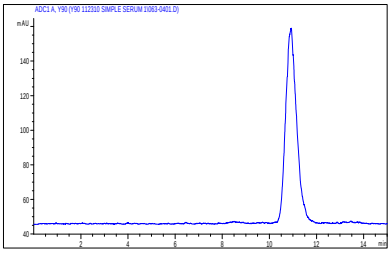

Day 10

Sample 1
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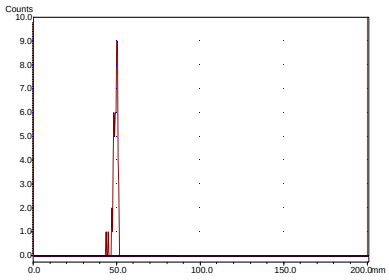
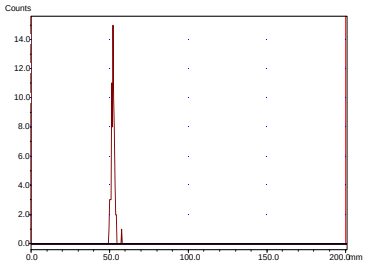


Sample 2
100%



Sample 3
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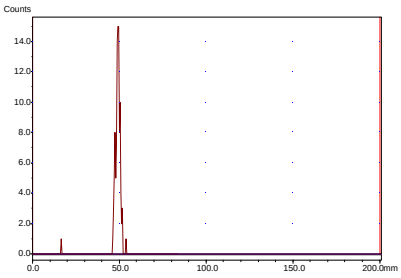

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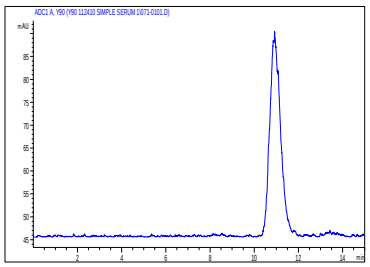

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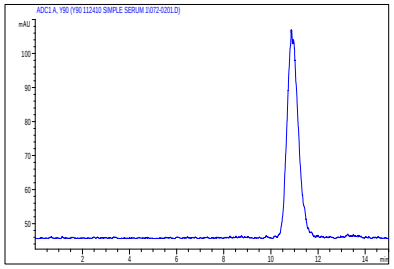

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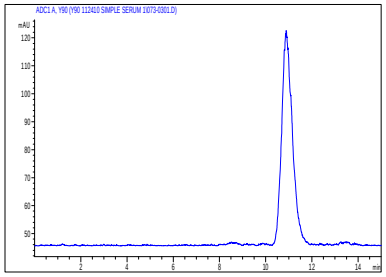
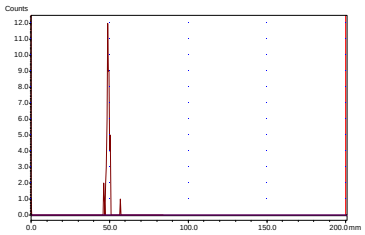
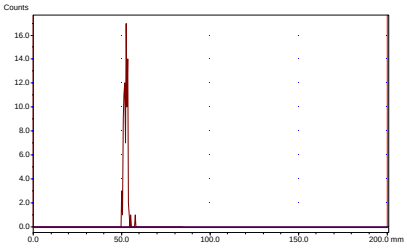


Day 11

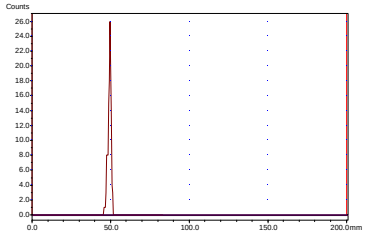
Sample 1
100%



Sample 2
100%



Sample 3
100%



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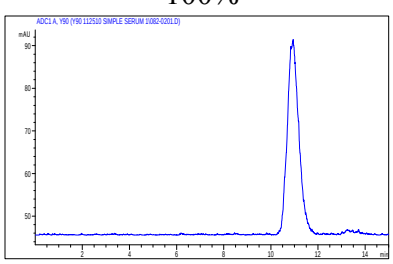

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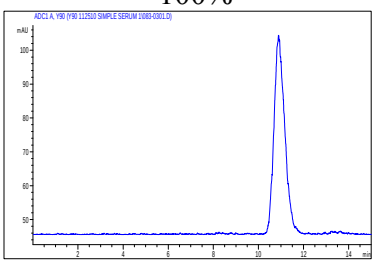

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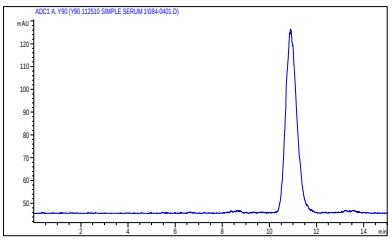

Day 12

Sample 1
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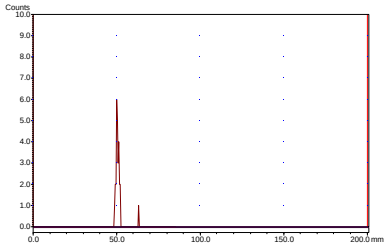

Sample 2
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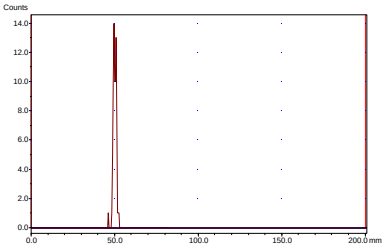
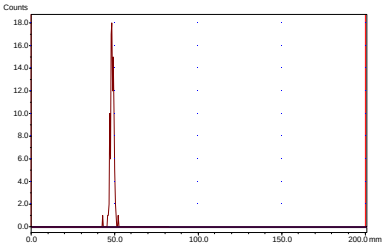


Sample 3
100%



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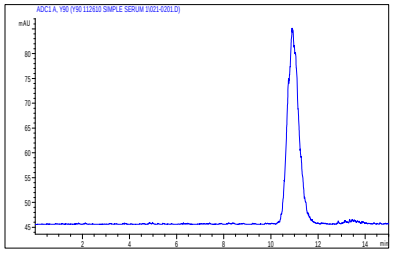

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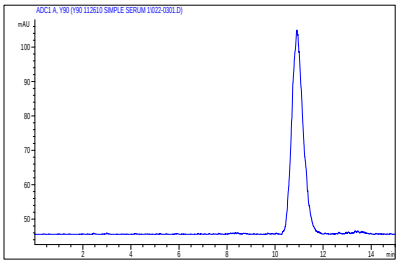

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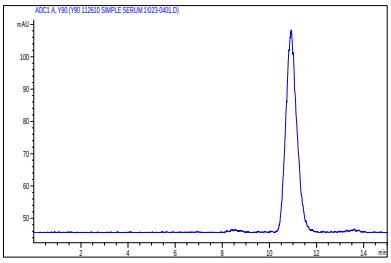
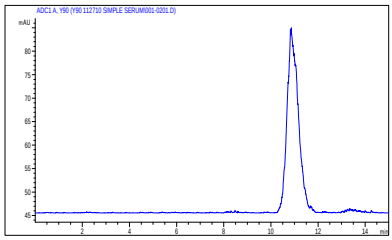
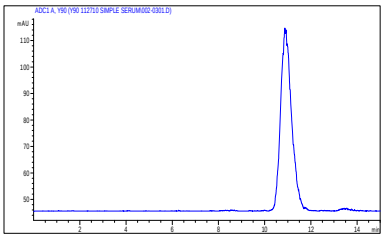


Day 13

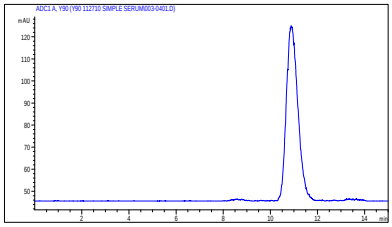
Sample 1
100%



Sample 2
100%

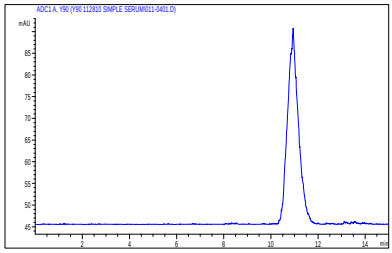


Sample 3
100%

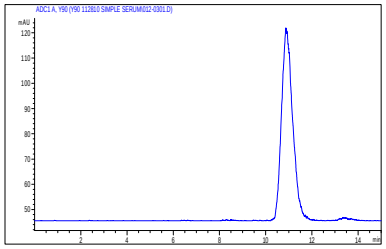


Day 14

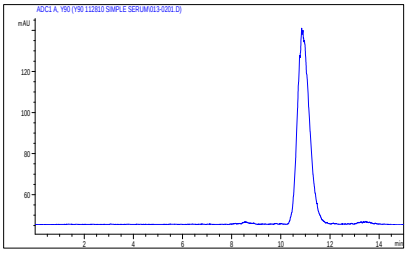
Sample 1
100%



Sample 2
100%



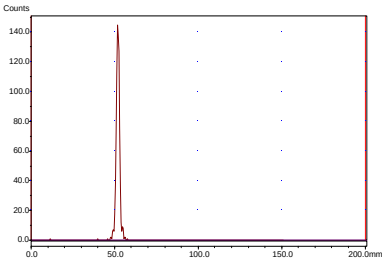
Sample 3
100%



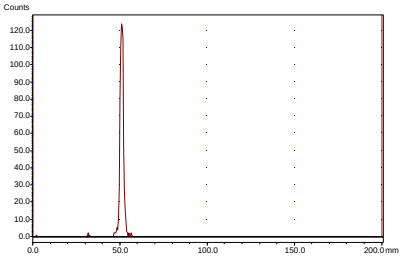
ii) ^{90}Y-3p-*C*-NETA (n = 3)

Day 0

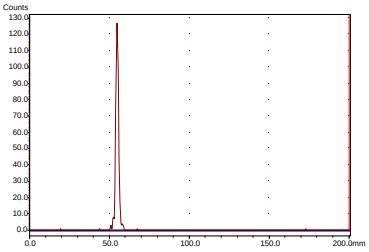
Sample 1
100%



Sample 2
99.7%



Sample 3
100%



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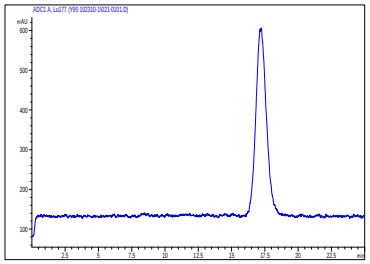

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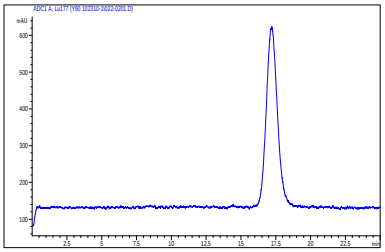

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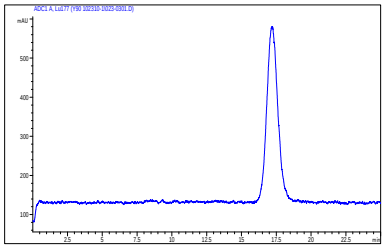
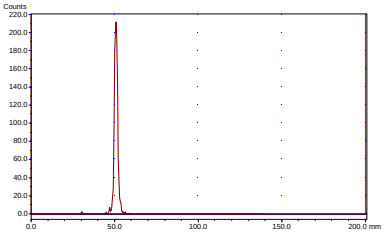
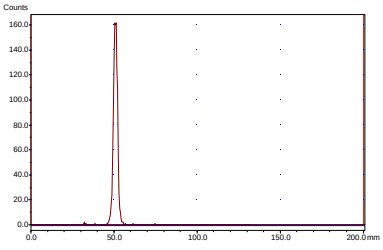


Day 1

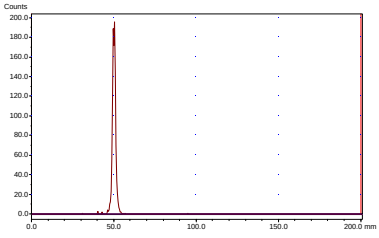
Sample 1
99.7%



Sample 2
99.8%



Sample 3
99.9%



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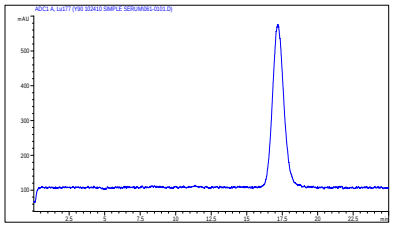

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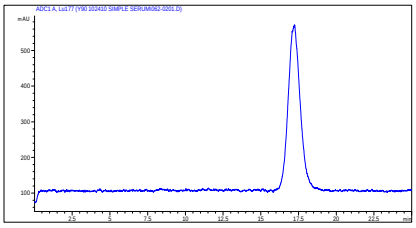

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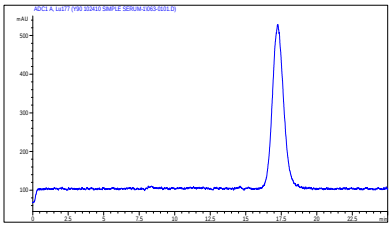
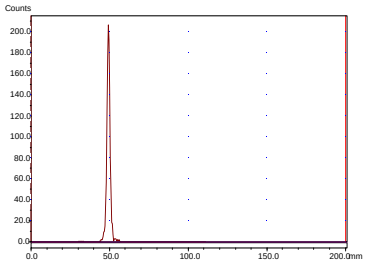
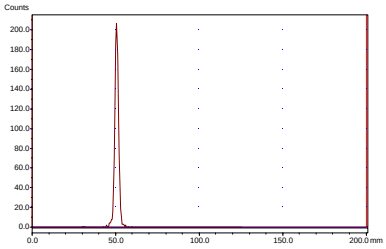


Day 2

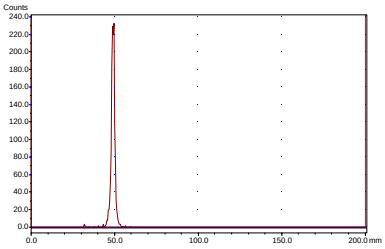
Sample 1
99.9%



Sample 2
99.9%



Sample 3
99.7%



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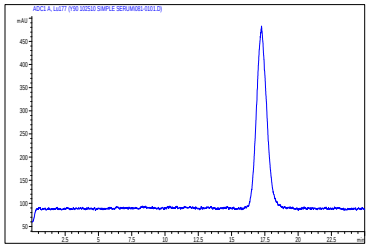

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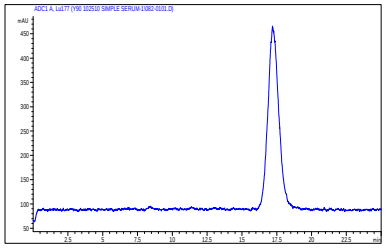

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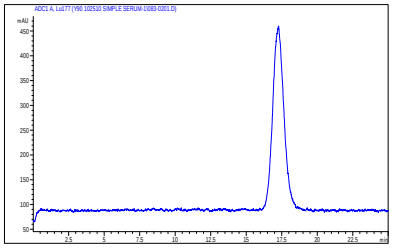
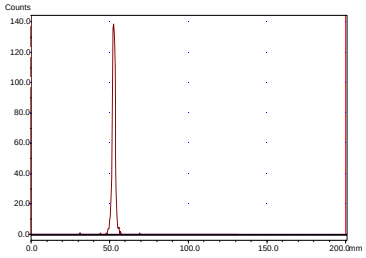
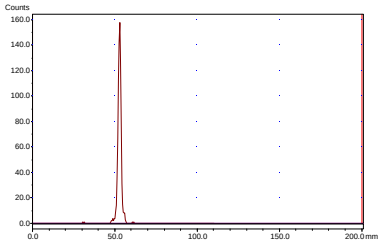


Day 3

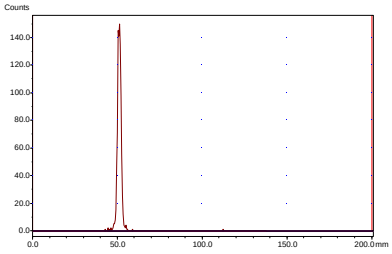
Sample 1
99.8%



Sample 2
99.9%



Sample 3
100%



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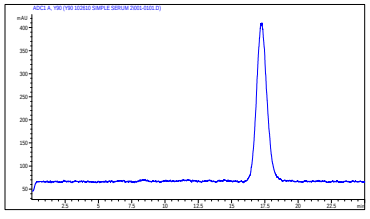

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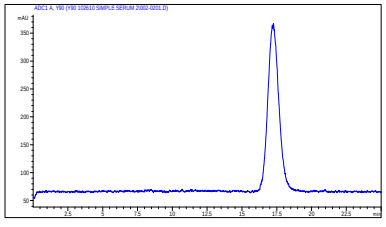

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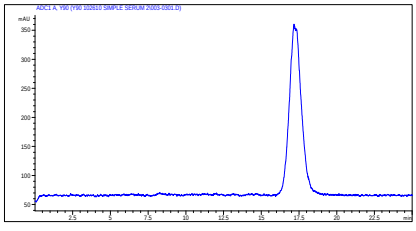
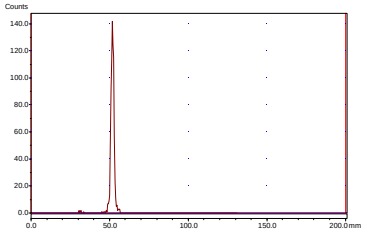


Day 4

Sample 1
99.5%



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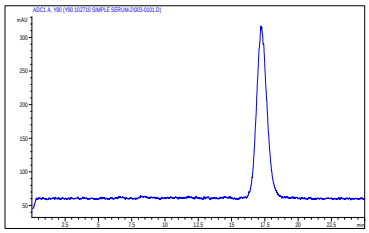
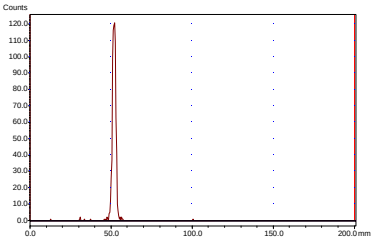
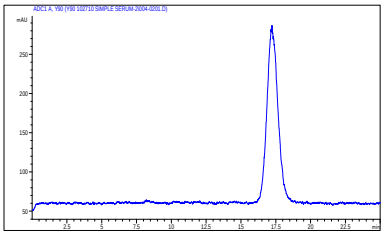


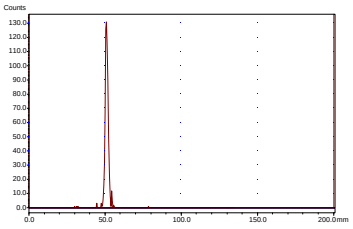
Sample 2
99.7%



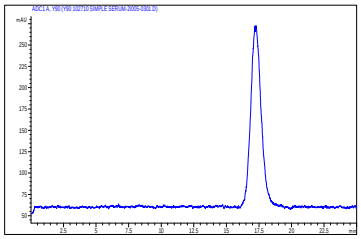
100%



Sample 3
99.8%

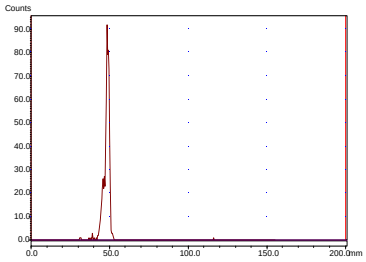


100%



Day 5

Sample 1
99.8%



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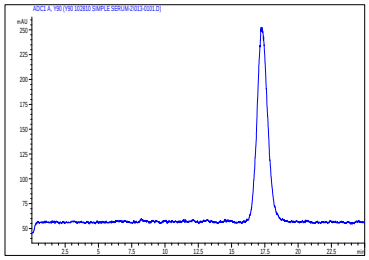
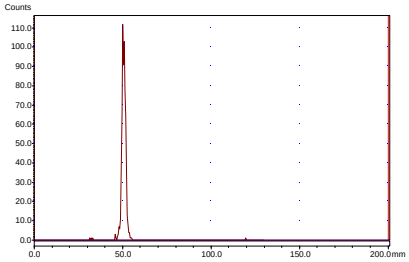


Sample 2
99.8%



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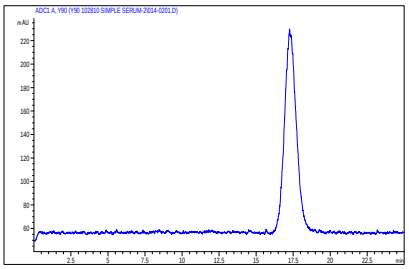
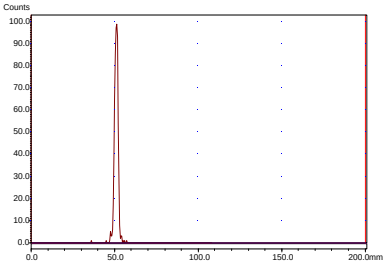


Sample 3
100%



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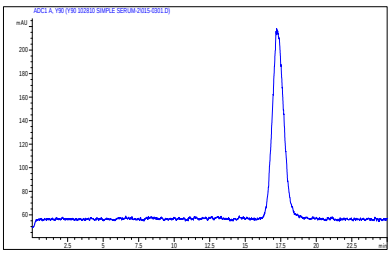
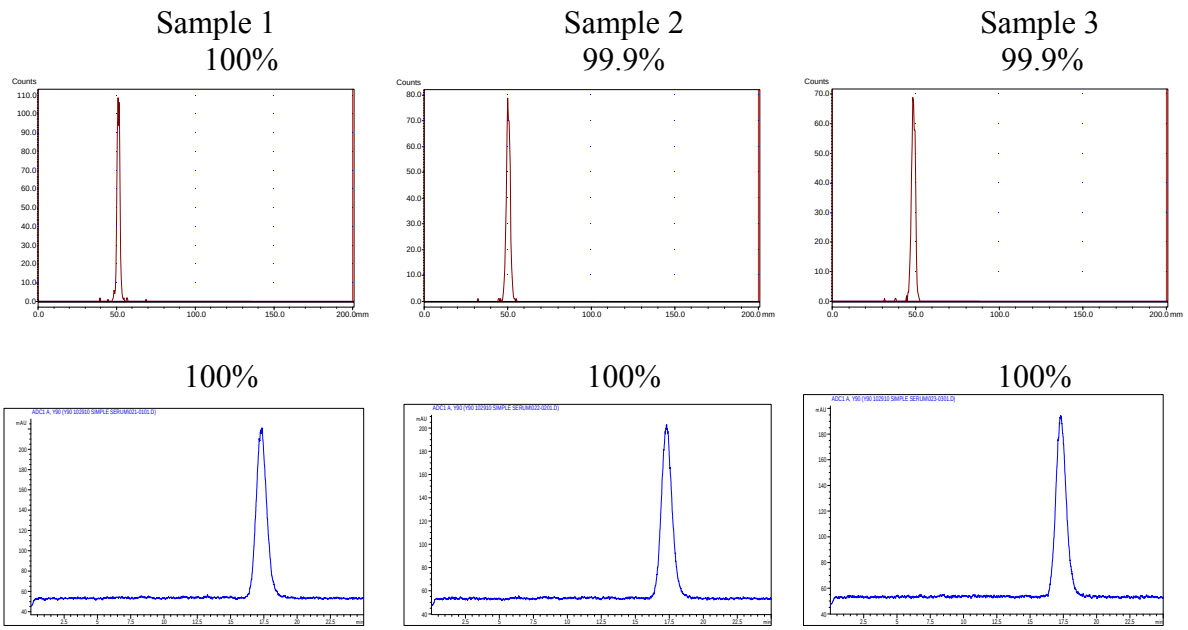
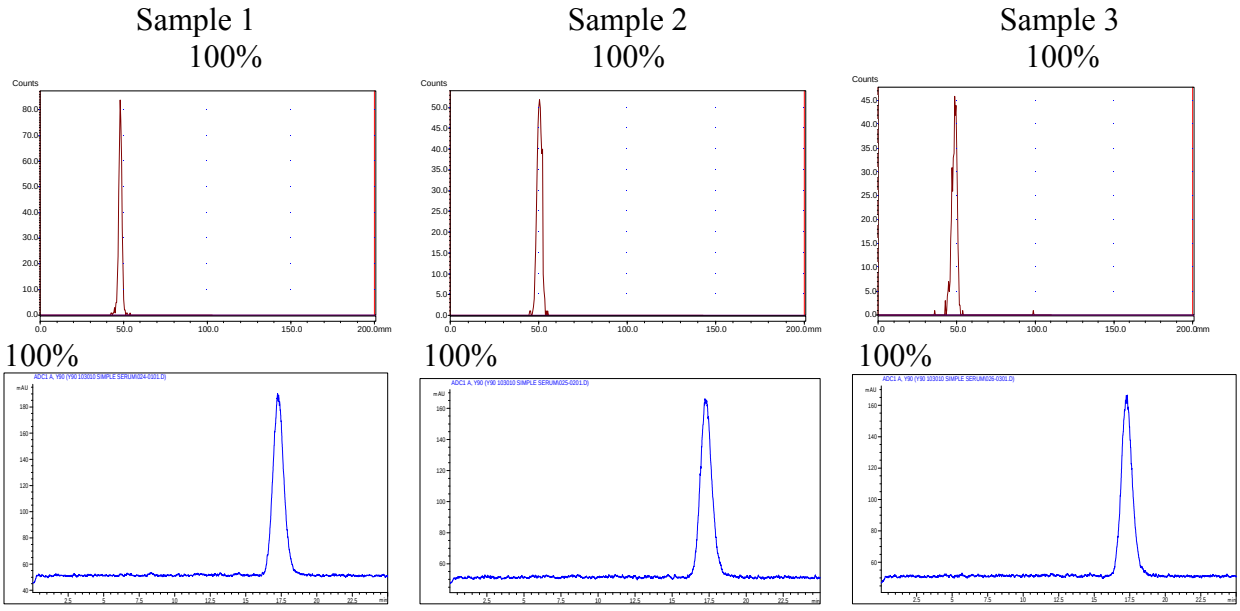


Day 6

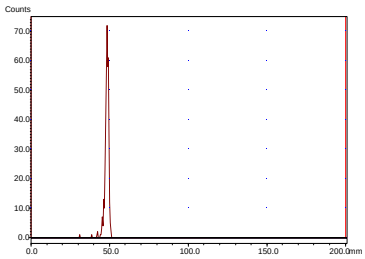

Sample 1
100%
Sample 2
99.9%
Sample 3
99.9%
100%
100%
100%

Day 7

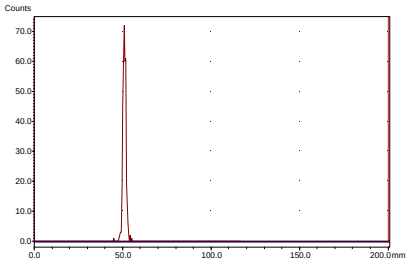

Sample 1
100%
Sample 2
100%
Sample 3
100%
100%
100%
100%

Day 8

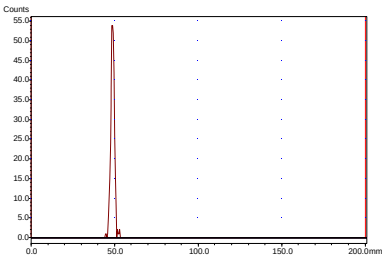
Sample 1
99.9%



Sample 2
100%



Sample 3
100%



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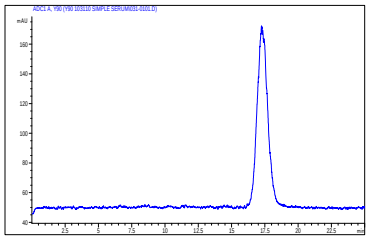

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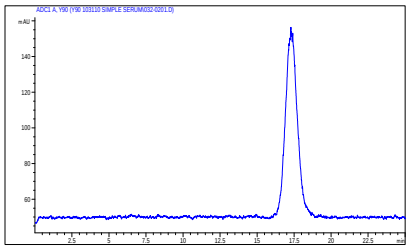

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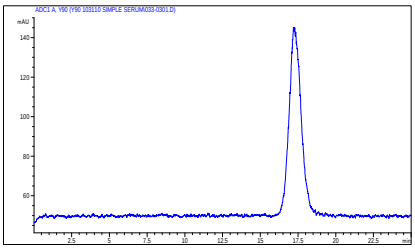

Day 9

Sample 1
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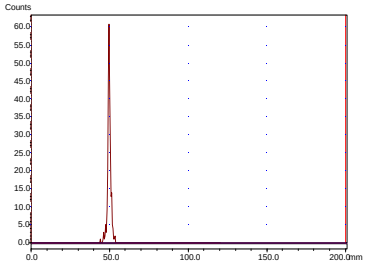
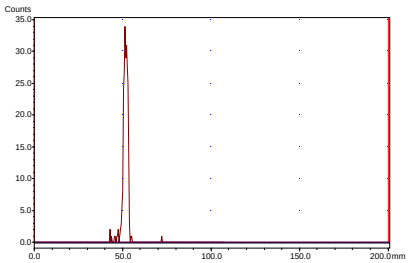
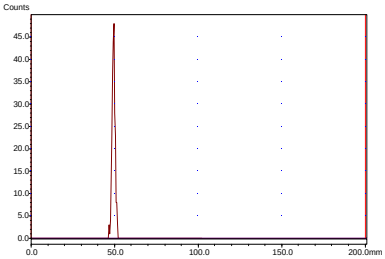


Sample 2
100%



Sample 3
100%



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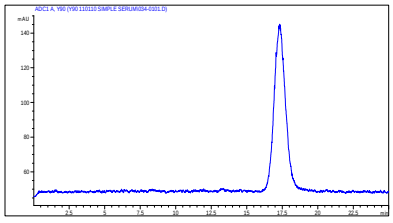

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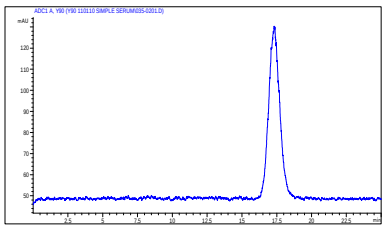

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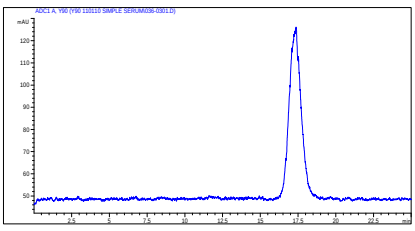

Day 10

Sample 1
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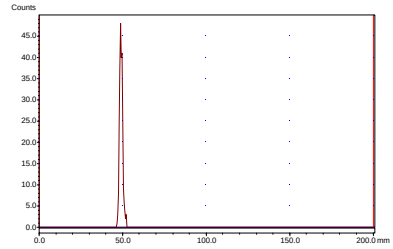

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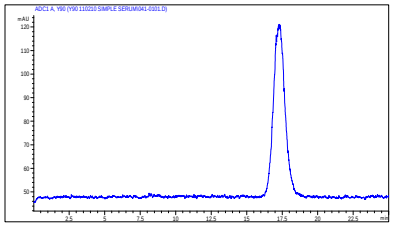

Sample 2
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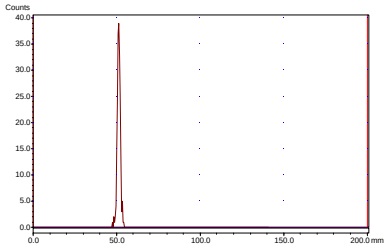

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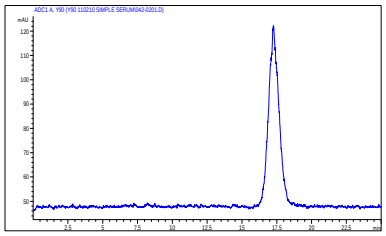

Sample 3
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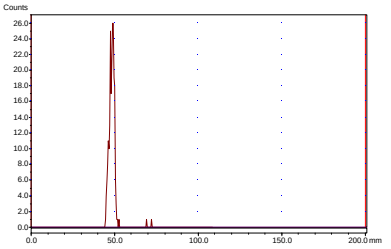

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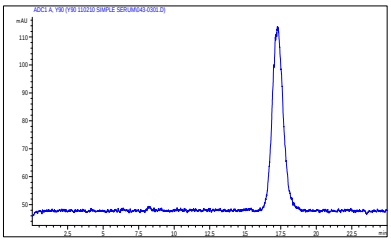

Day 11

Sample 1
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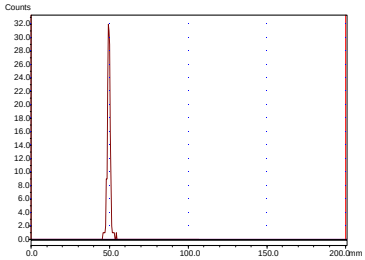

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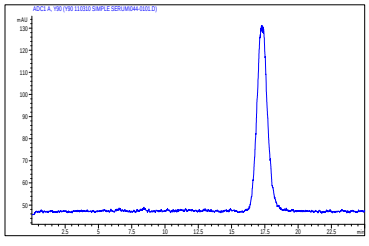

Sample 2
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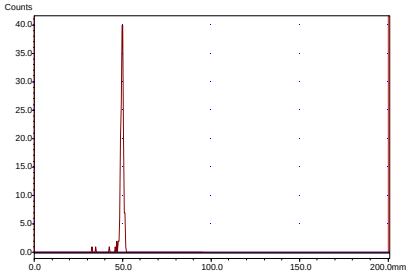

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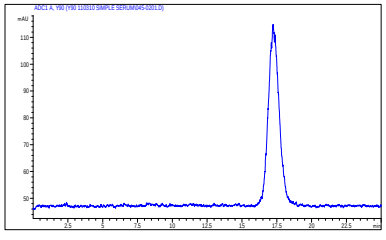

Sample 3
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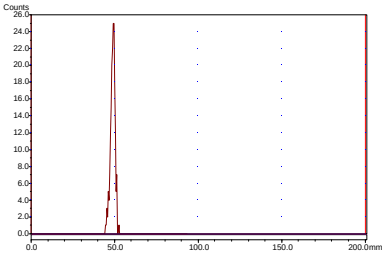

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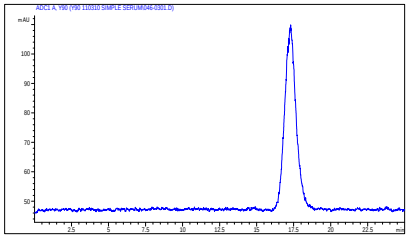
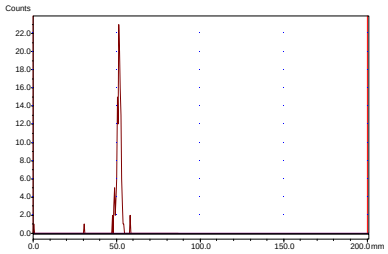
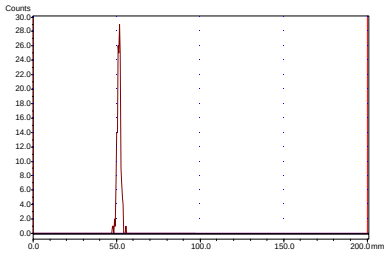


Day 12

Sample 1
99.6%



Sample 2
100%



Sample 3
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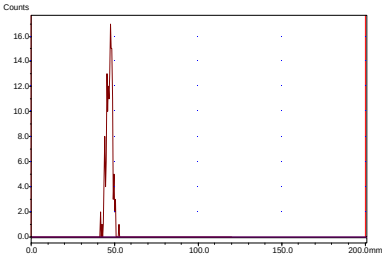

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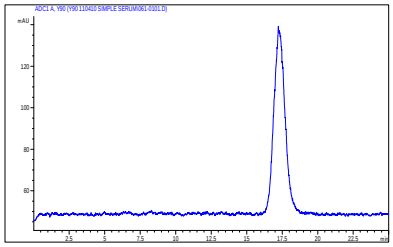

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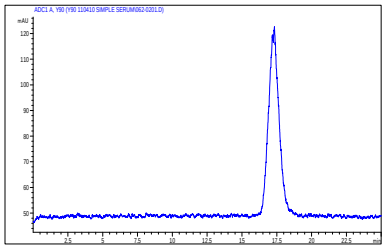

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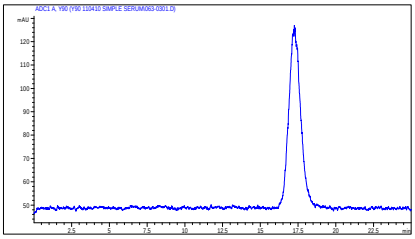

Day 13

Sample 1
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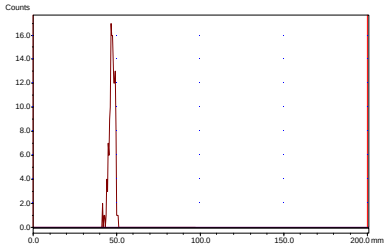

Sample 2
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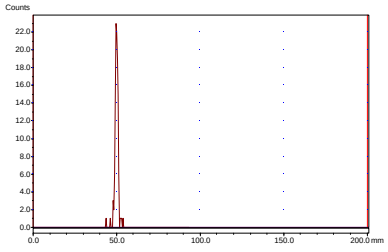
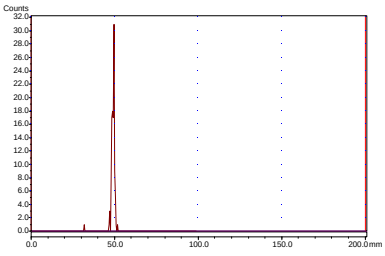


Sample 3
99.5%



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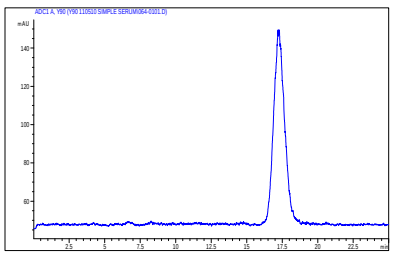

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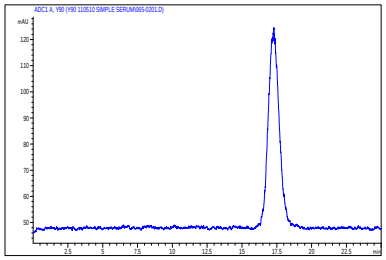

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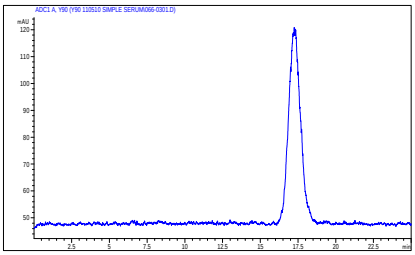
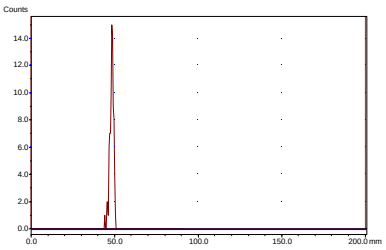
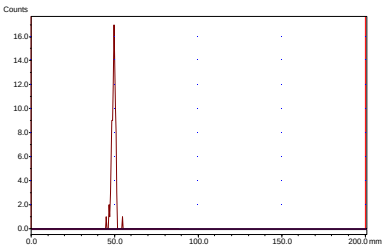


Day 14

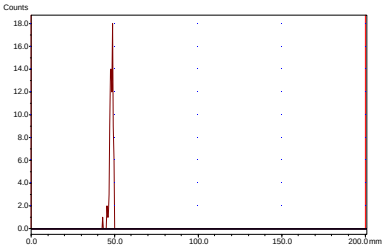
Sample 1
100%



Sample 2
100%



Sample 3
100%



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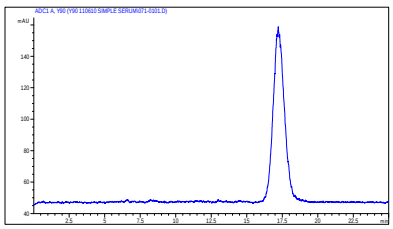

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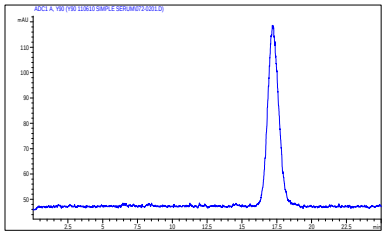

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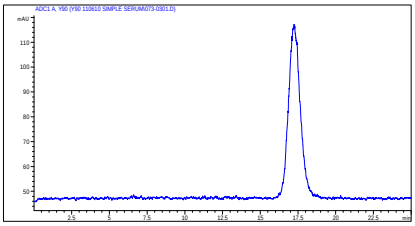
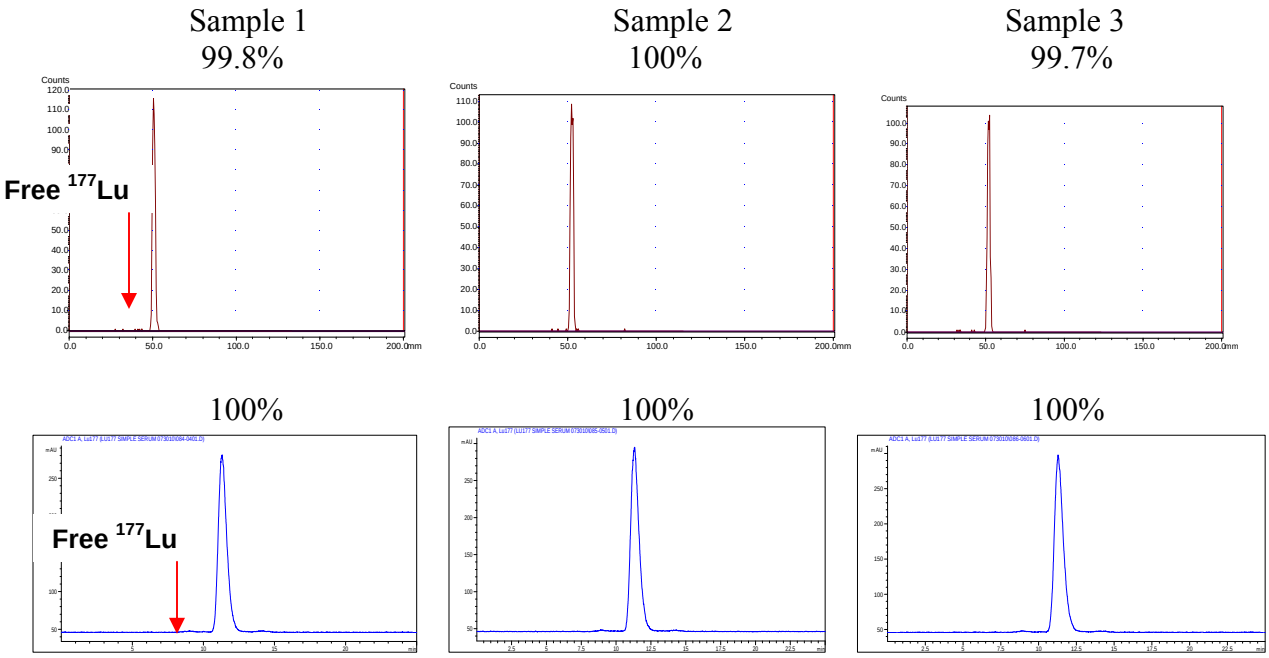
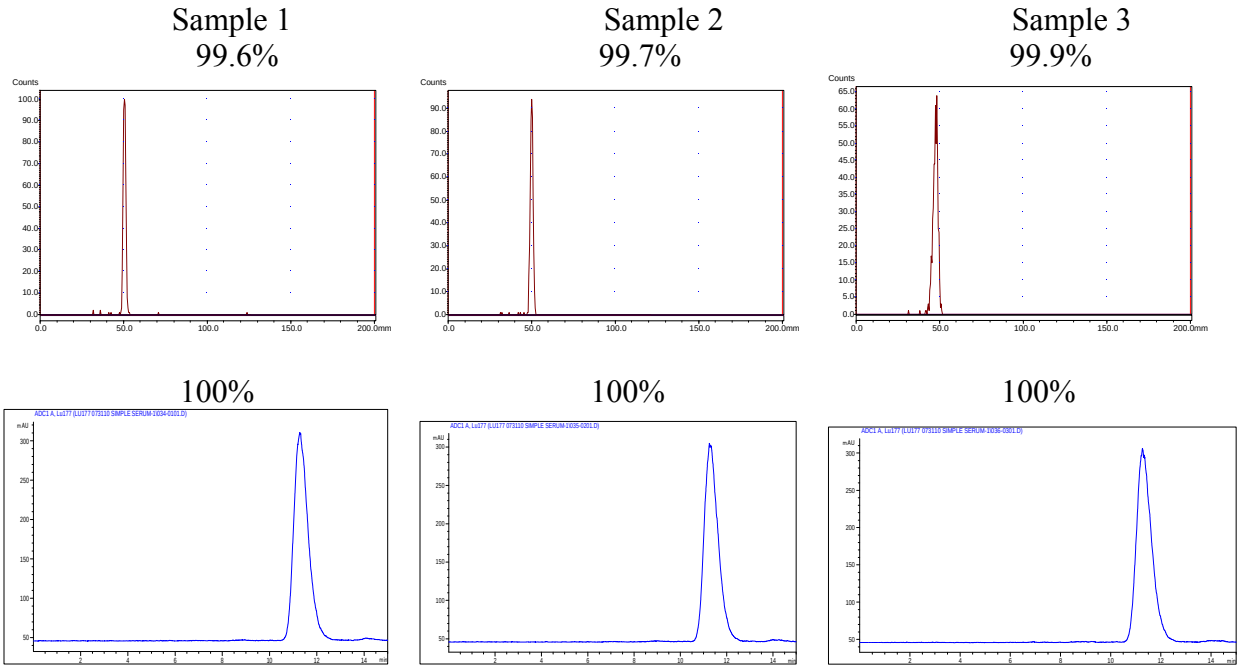


iii) ^{177}Lu-*C*-DOTA (n = 3)

Day 0

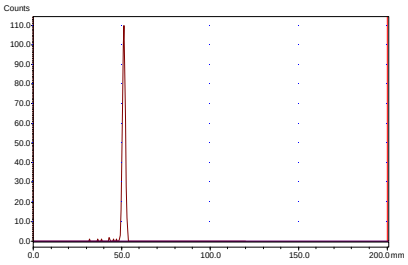


Day 1

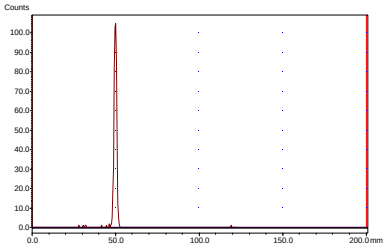


Day 2

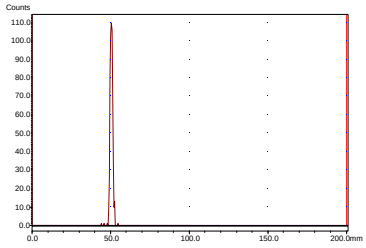
Sample 1
99.9%



Sample 2
99.6%



Sample 3
100%



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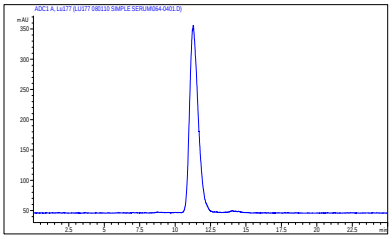

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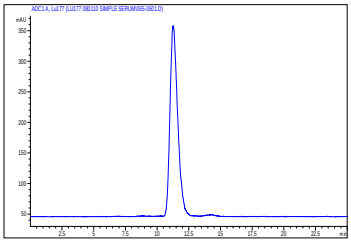
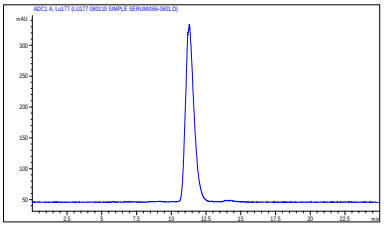
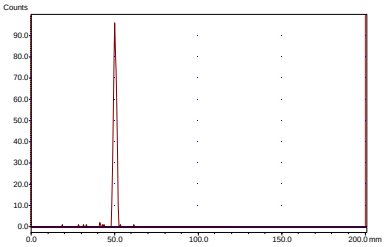


100%

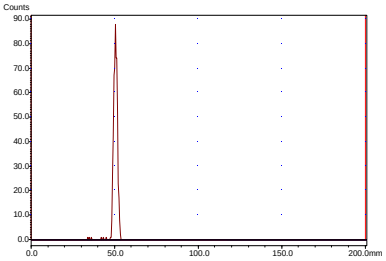


Day 3

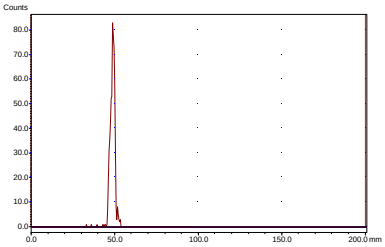
Sample 1
99.7%



Sample 2
99.8%



Sample 3
99.8%



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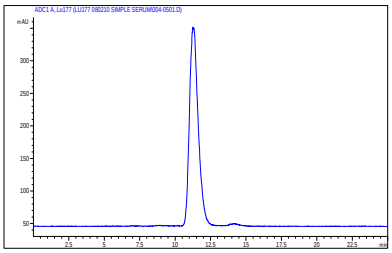

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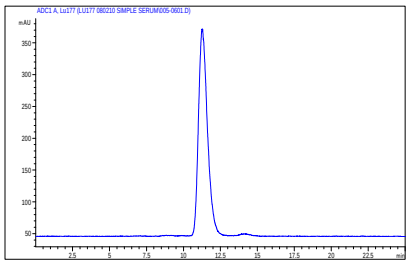

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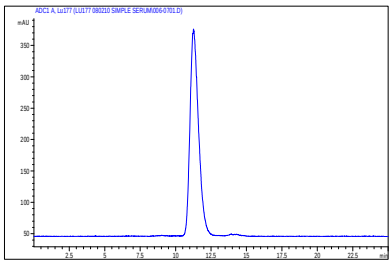
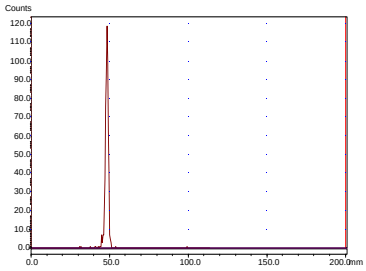


Day 4

Sample 1
99.8%



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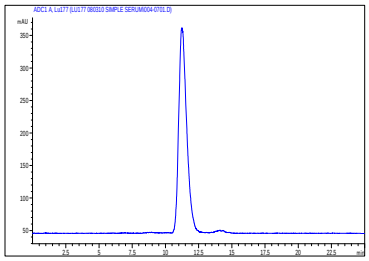
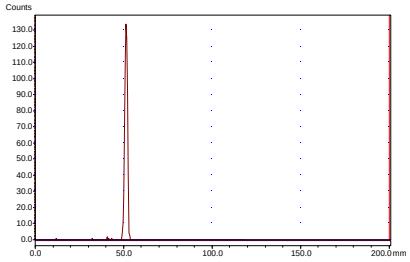


Sample 2
99.9%



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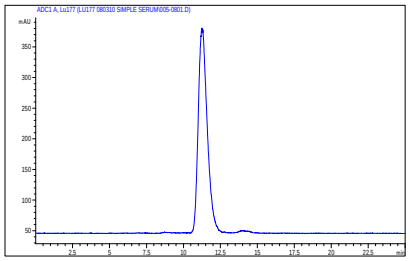
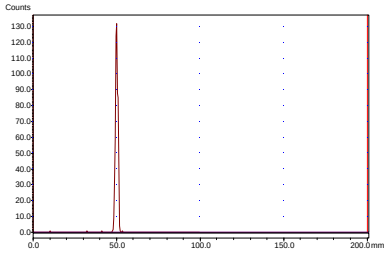


Sample 3
99.9%



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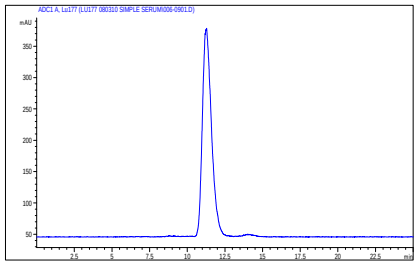
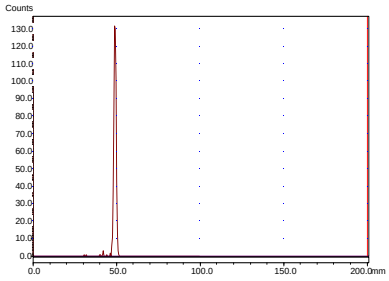


Day 5

Sample 1
99.8%



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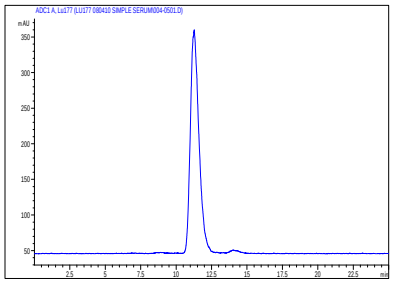
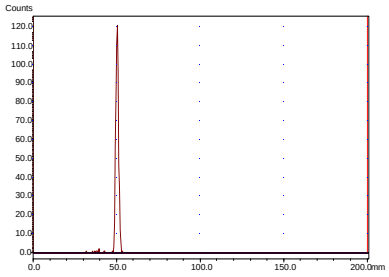


Sample 2
99.9%



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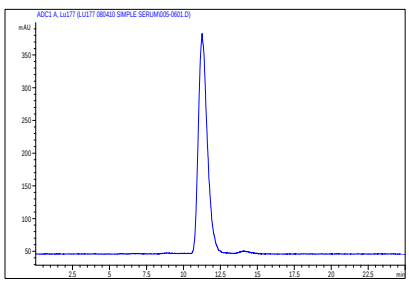
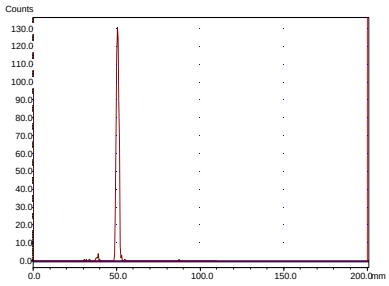


Sample 3
99.7%



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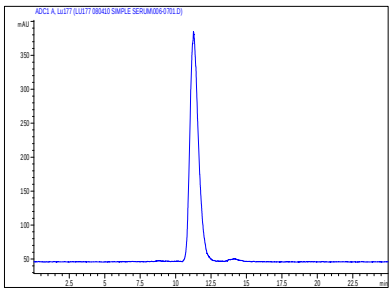
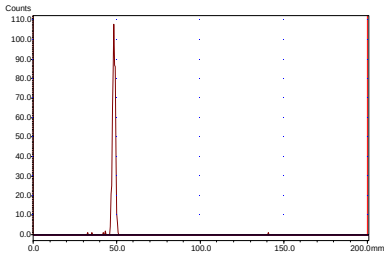


Day 6

Sample 1
99.7%



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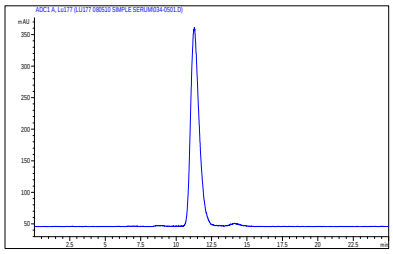
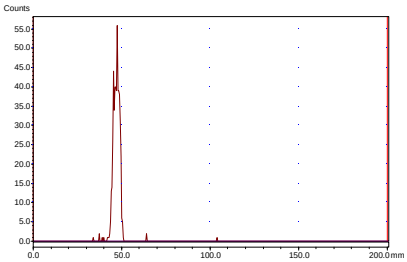


Sample 2
99.9%



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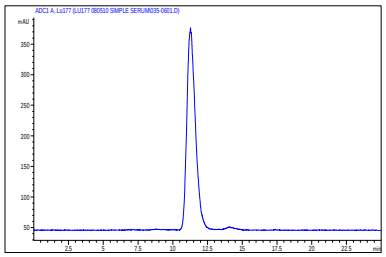
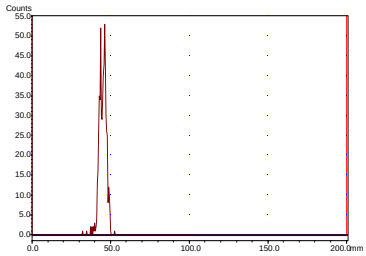


Sample 3
99.8%



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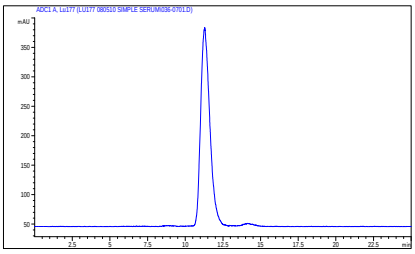
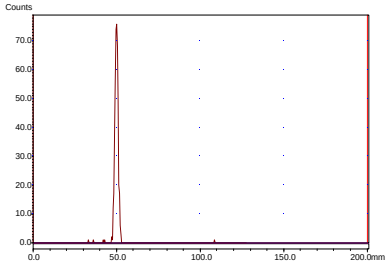


Day 7

Sample 1
99.9%



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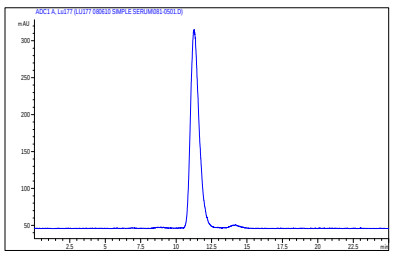
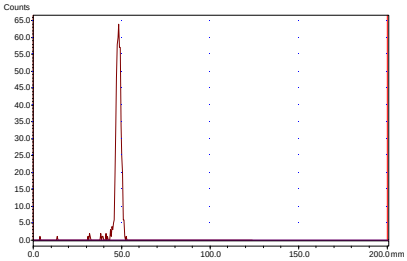


Sample 2
99.6%



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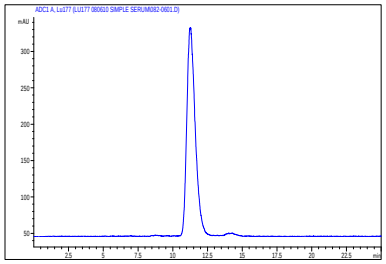
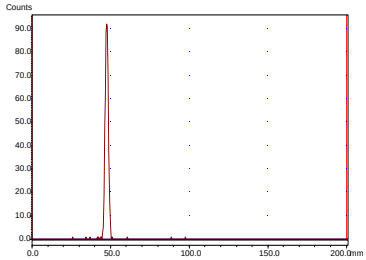


Sample 3
99.8%



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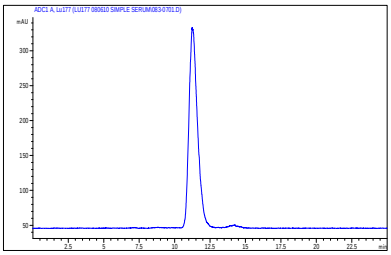
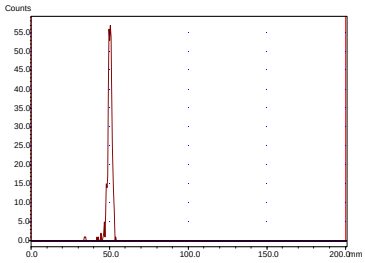
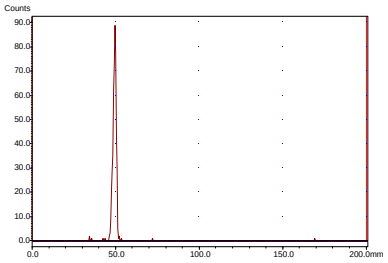


Day 8

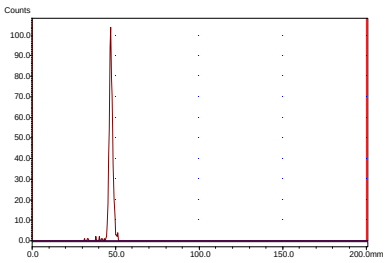
Sample 1
99.6%



Sample 2
99.7%



Sample 3
99.7%



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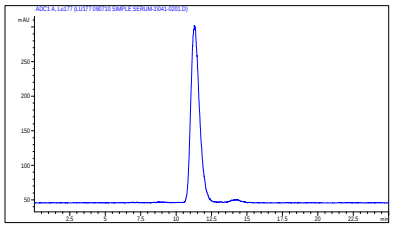

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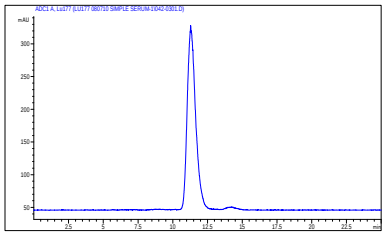

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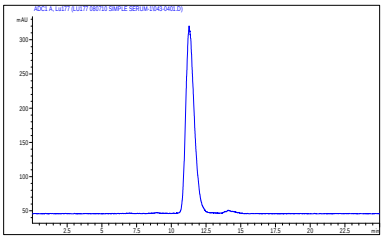
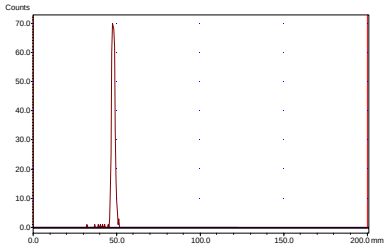
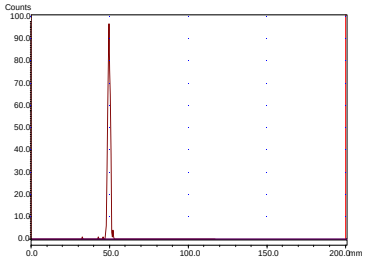


Day 9

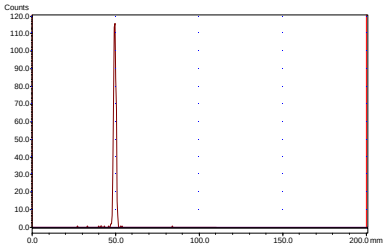
Sample 1
99.9%



Sample 2
99.9%



Sample 3
99.8%



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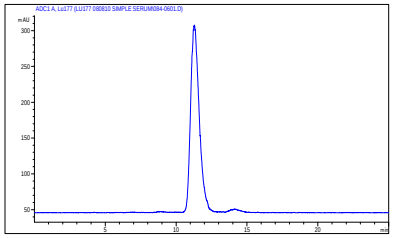

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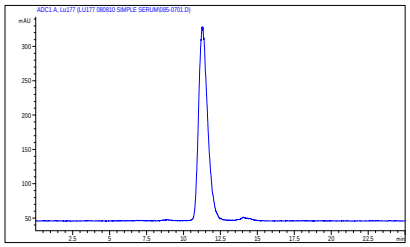

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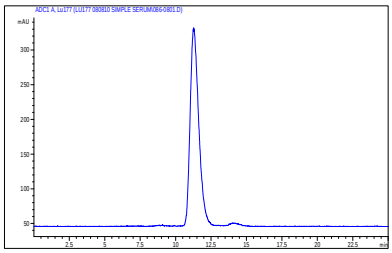
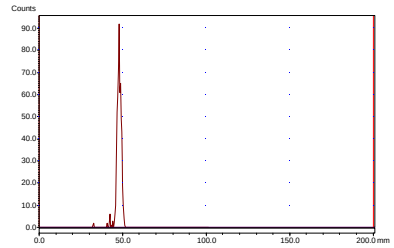
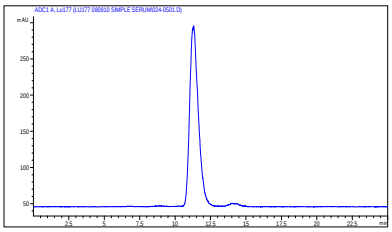


Day 10

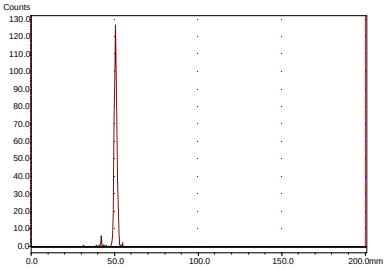
Sample 1
99.7%



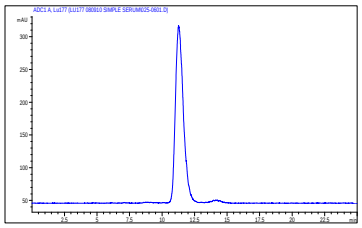
100%



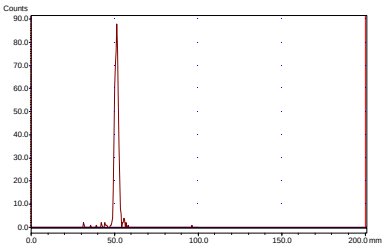
Sample 2
99.9%



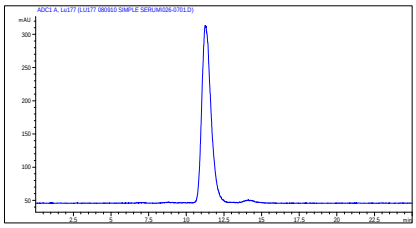
100%



Sample 3
99.5%

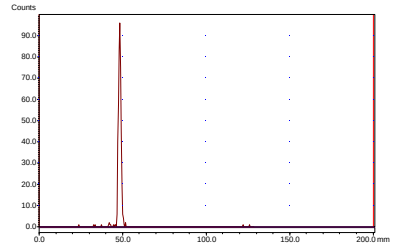


100%

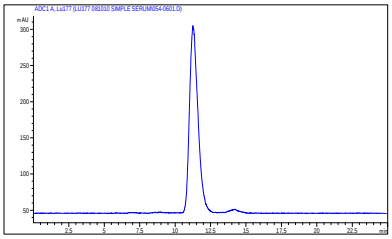


Day 11

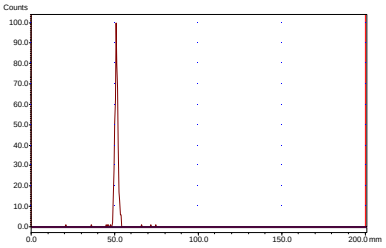
Sample 1
99.8%



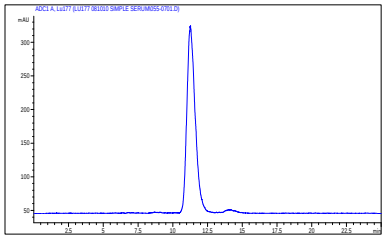
100%



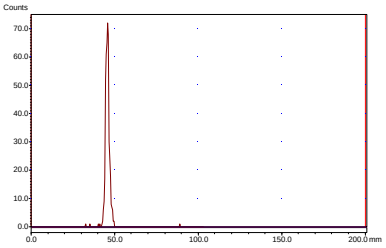
Sample 2
100%



100%



Sample 3
99.8%



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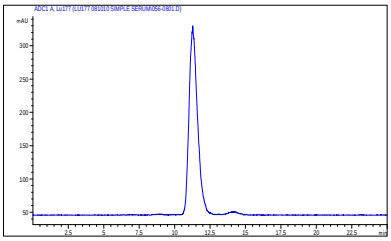
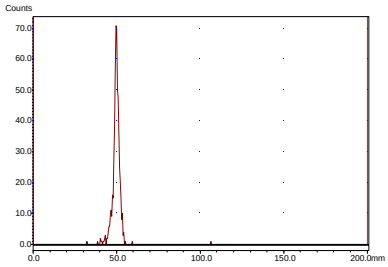
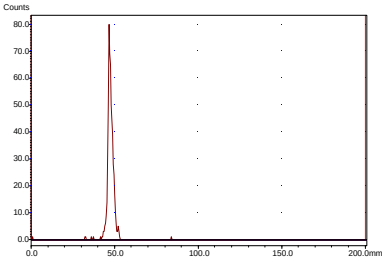


Day 12

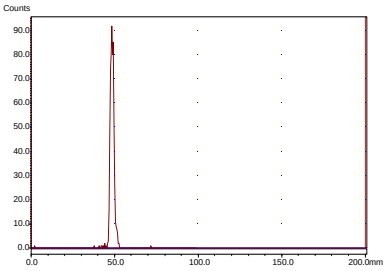
Sample 1
99.9%



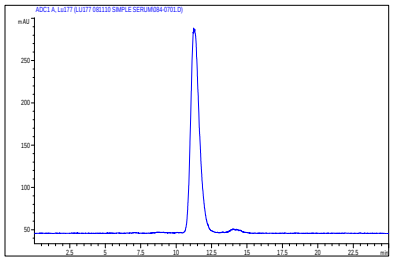
Sample 2
99.8%



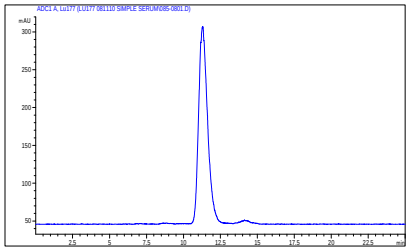
Sample 3
100%



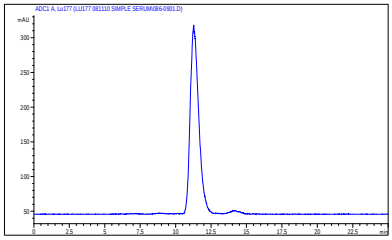
100%



100%

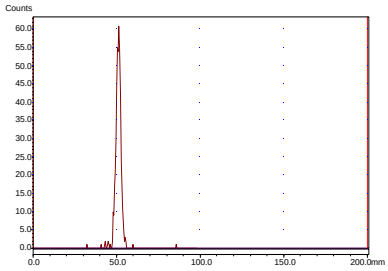


100%

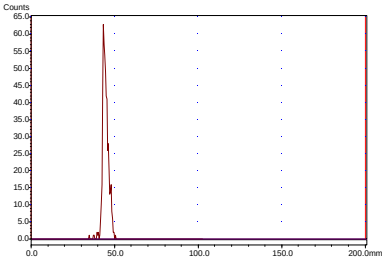


Day 13

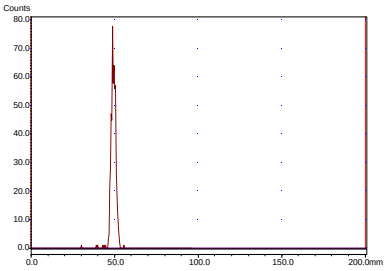
Sample 1
99.9%



Sample 2
99.9%



Sample 3
99.9%



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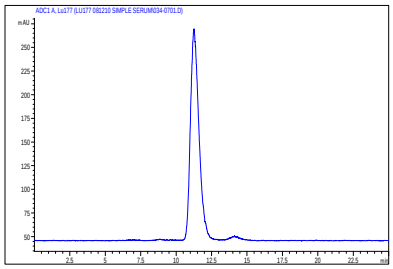

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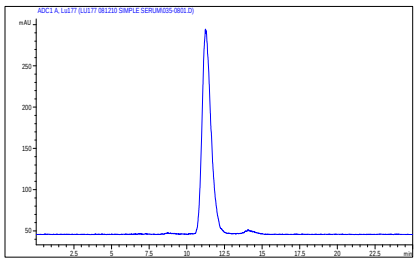
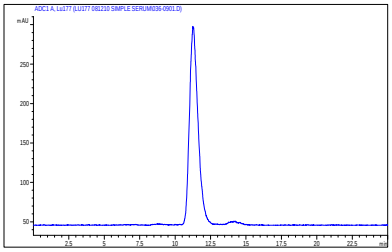
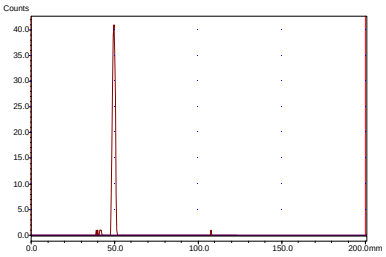


100%

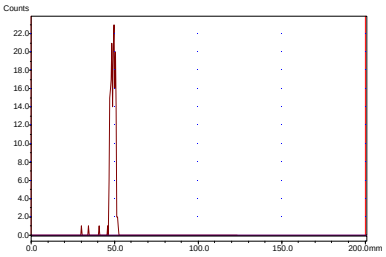


Day 14

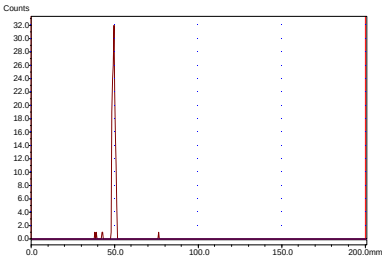
Sample 1
100%



Sample 2
99.4%



Sample 3
100%



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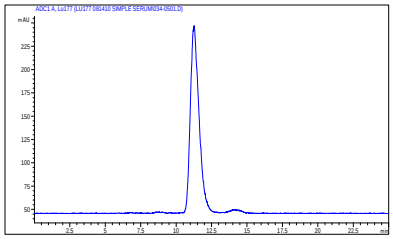

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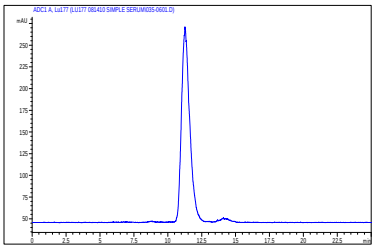

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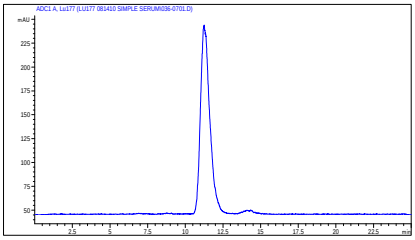
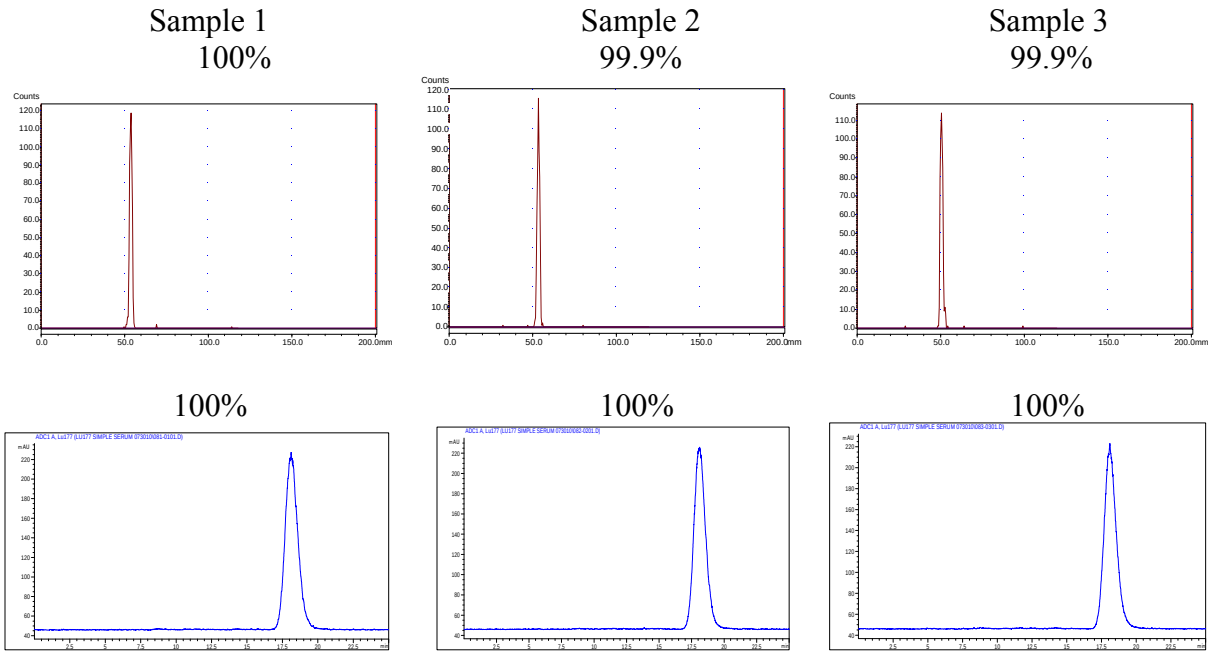
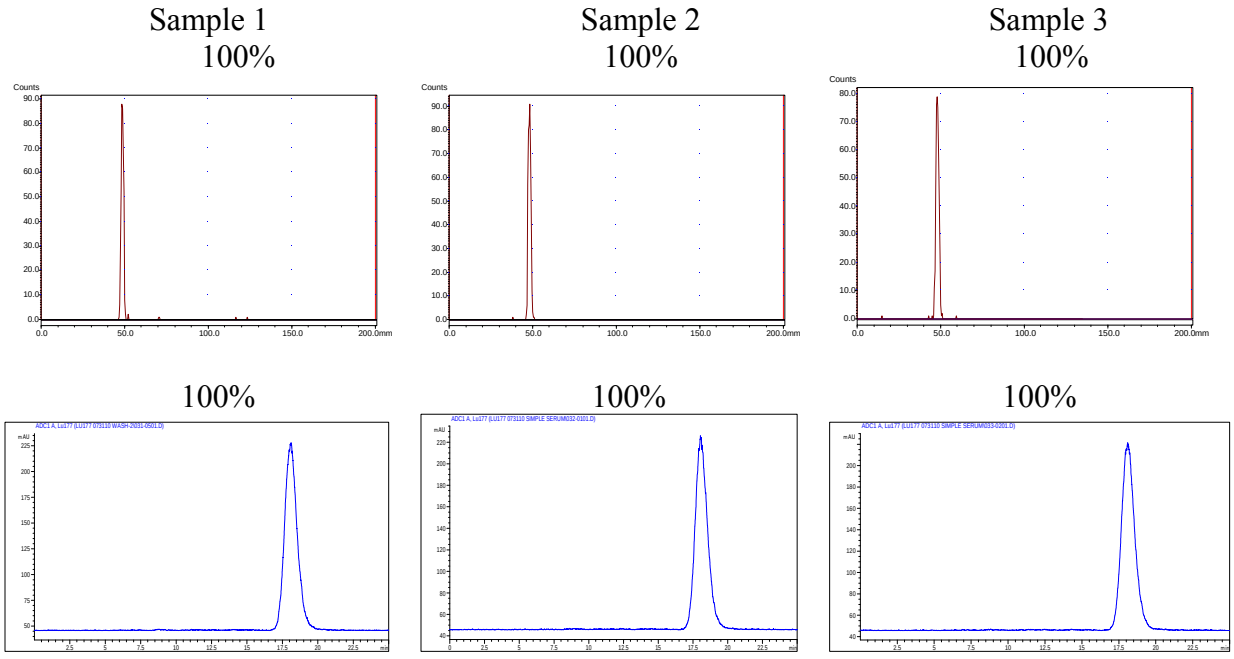


iv) ^{177}Lu-3p-*C*-NETA (n = 3)

Day 0



Day 1



Day 2

Sample 1
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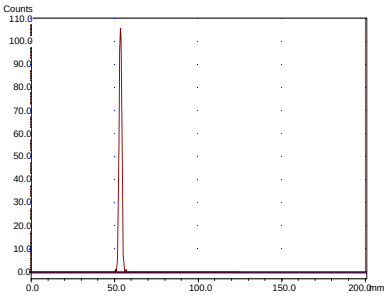

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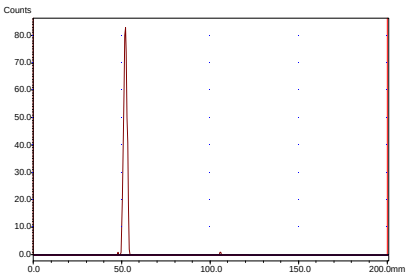

Sample 3
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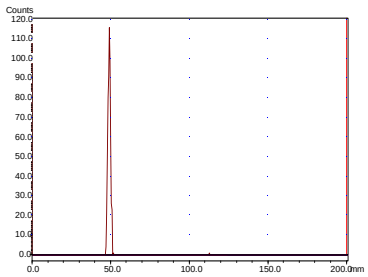

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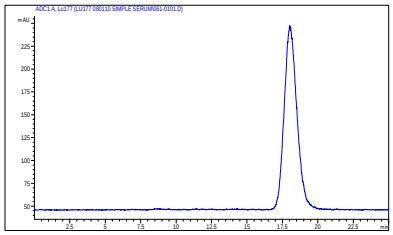

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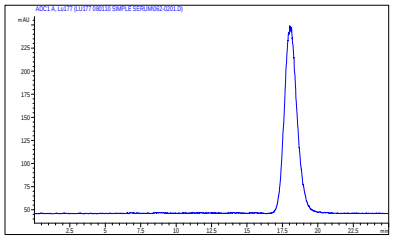

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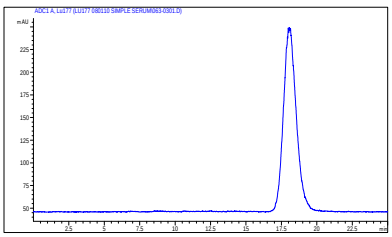

Day 3

Sample 1
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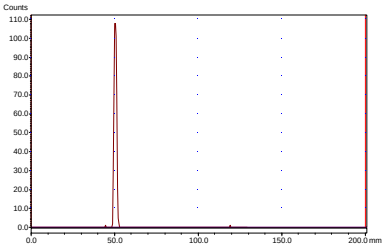

Sample 2
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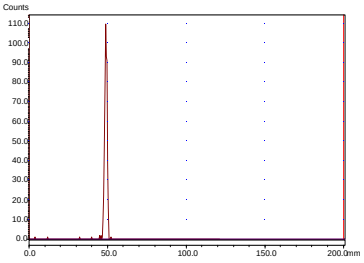
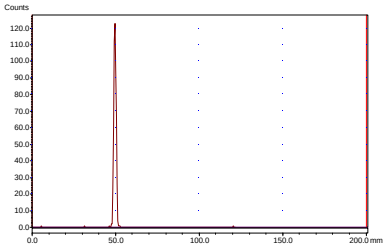


Sample 3
99.9%



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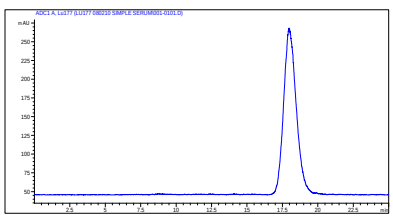

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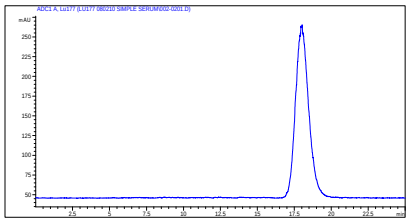

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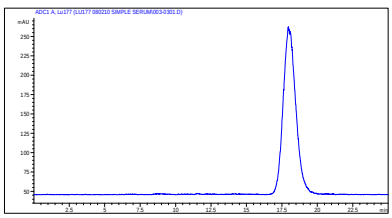

Day 4

Sample 1
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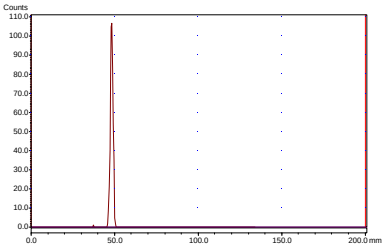

Sample 2
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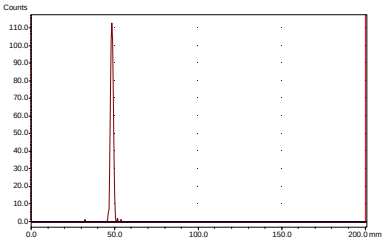

Sample 3
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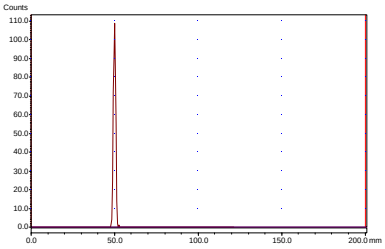

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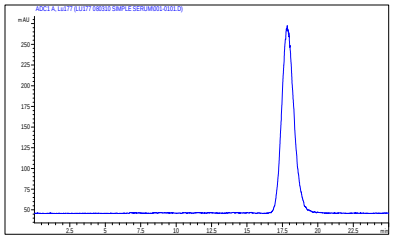

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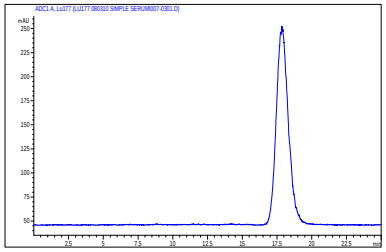

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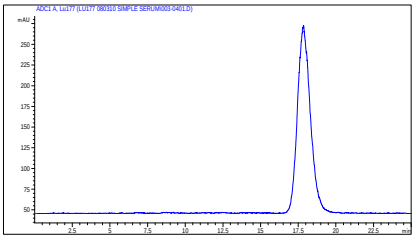

Day 5

Sample 1
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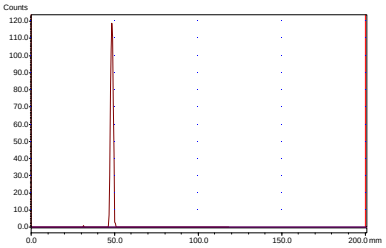

Sample 2
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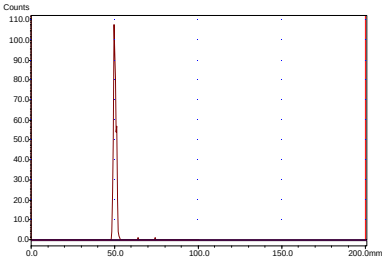

Sample 3
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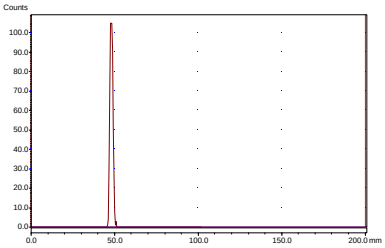

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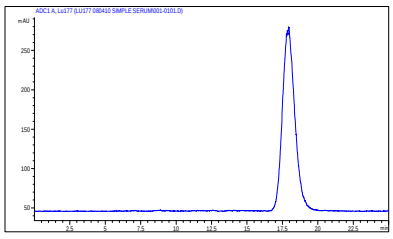

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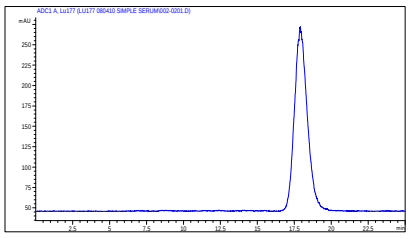

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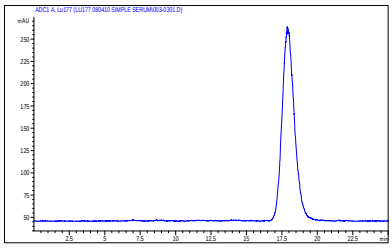

Day 6

Sample 1
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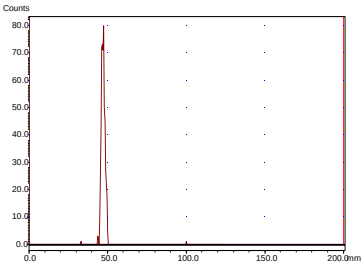

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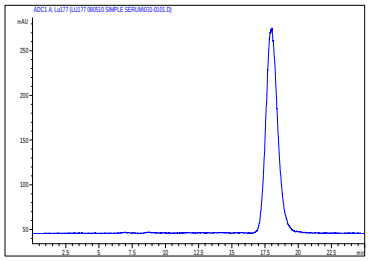

Sample 2
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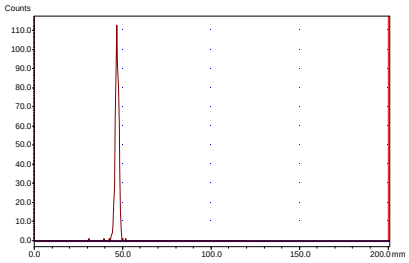

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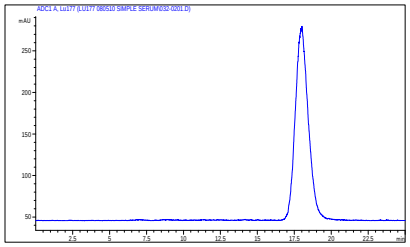

Sample 3
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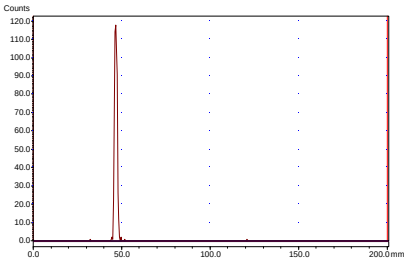

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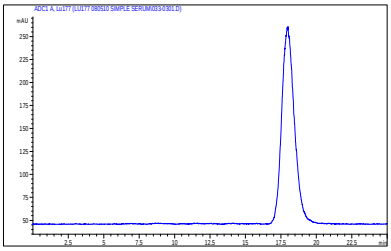
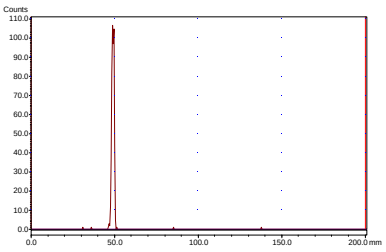


Day 7

Sample 1
99.9%



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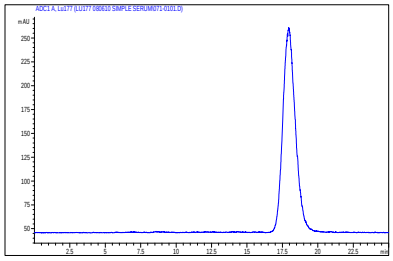
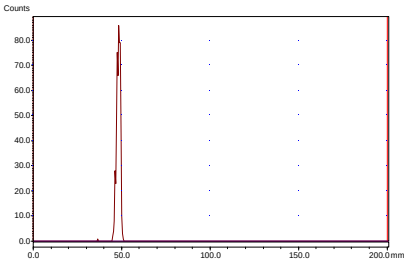


Sample 2
100%



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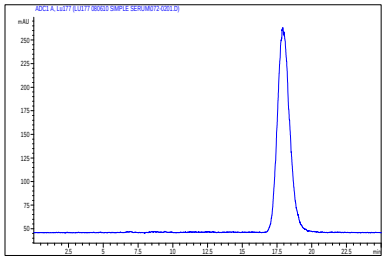

Sample 3
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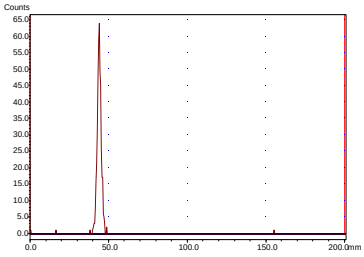

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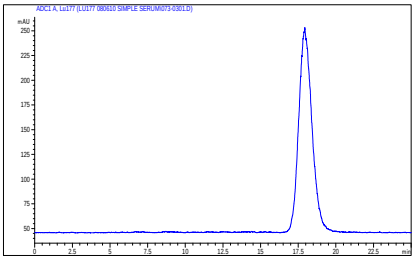

Day 8

Sample 1
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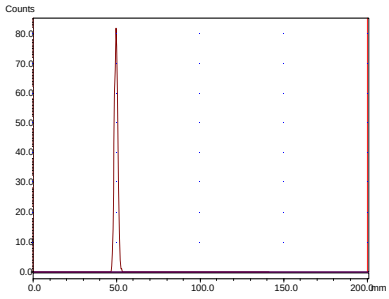

Sample 2
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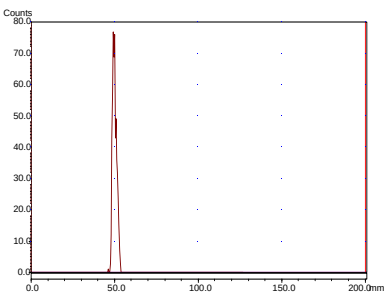

Sample 3
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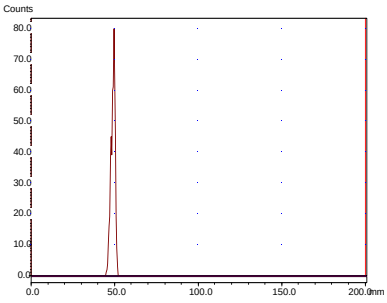

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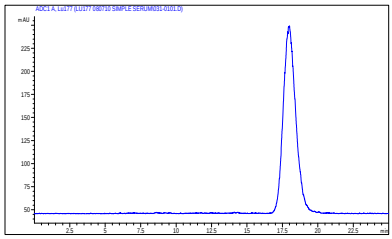

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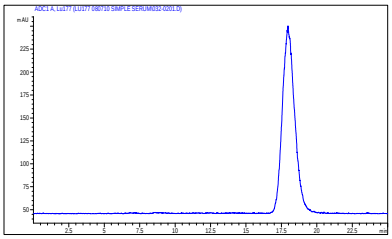

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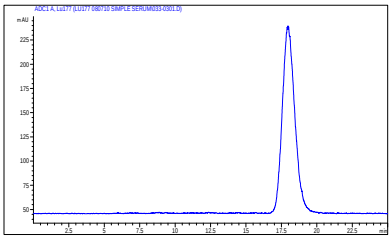

Day 9

Sample 1
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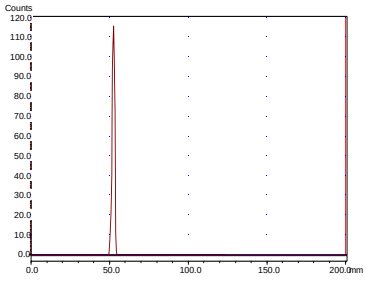
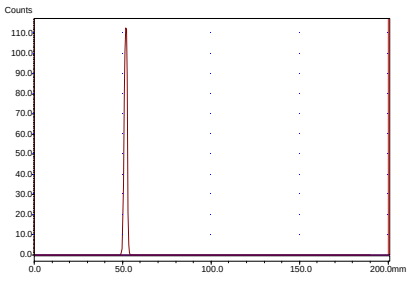
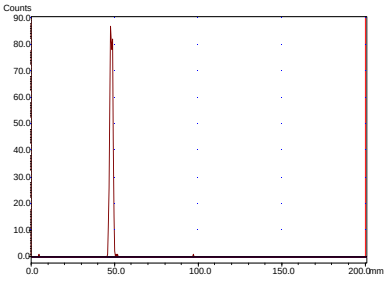


Sample 2
100%



Sample 3
100%



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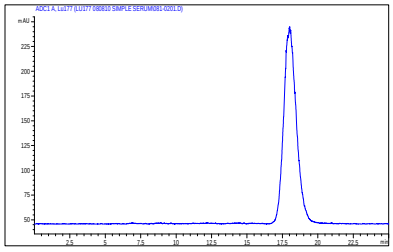

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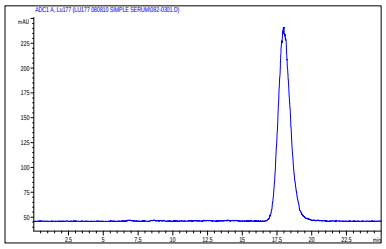

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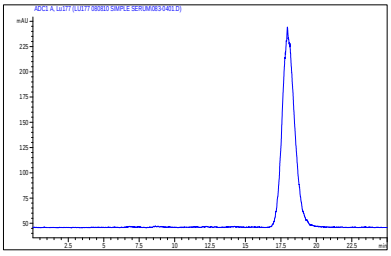

Day 10

Sample 1
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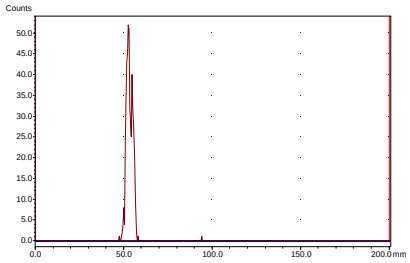
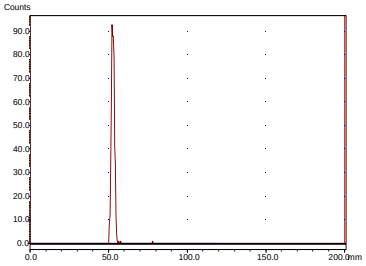
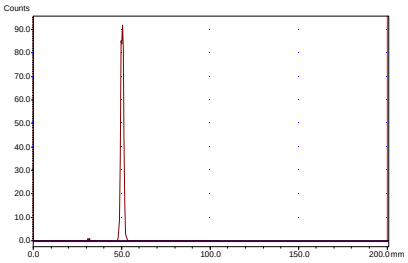


Sample 2
100%



Sample 3
99.8%



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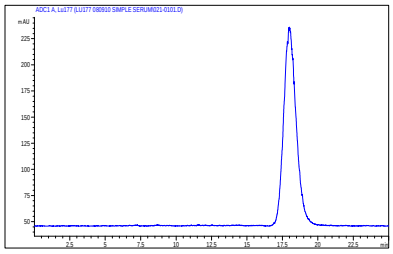

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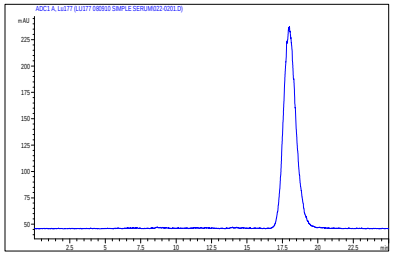

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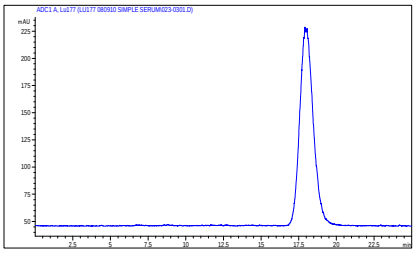
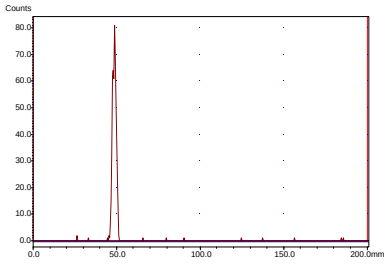
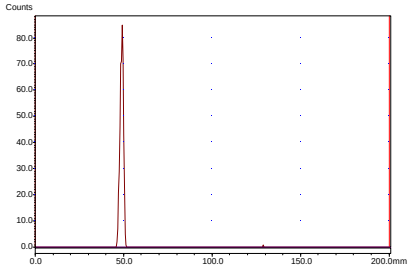


Day 11

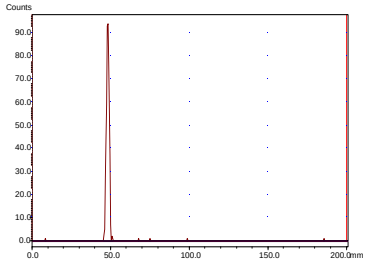
Sample 1
99.7%



Sample 2
100%



Sample 3
100%



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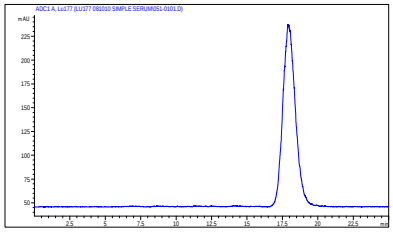

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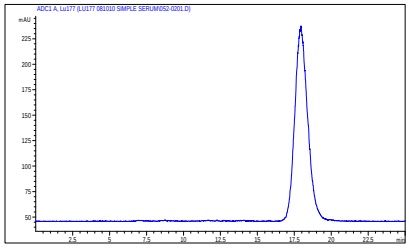

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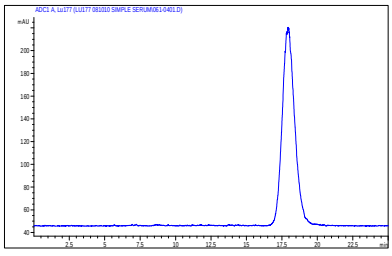
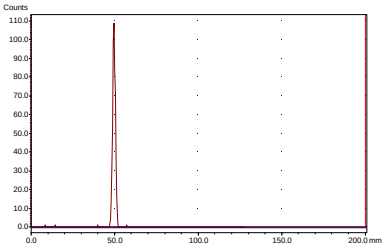
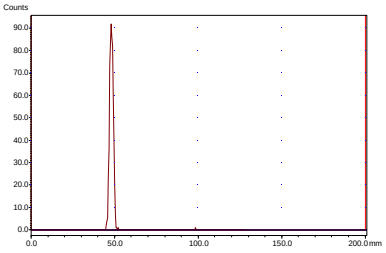


Day 12

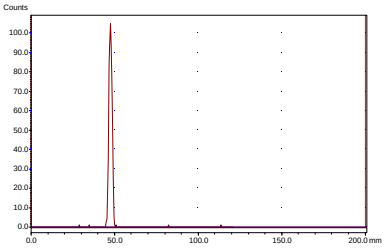
Sample 1
100%



Sample 2
100%



Sample 3
99.8%



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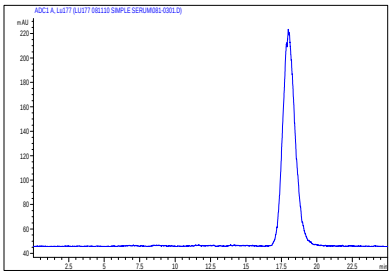

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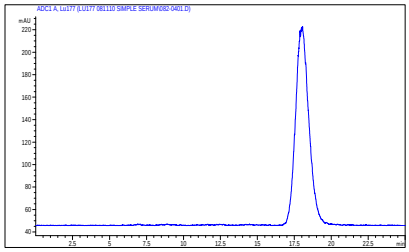

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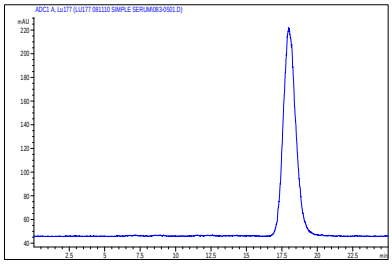
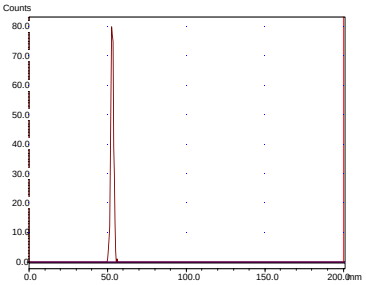
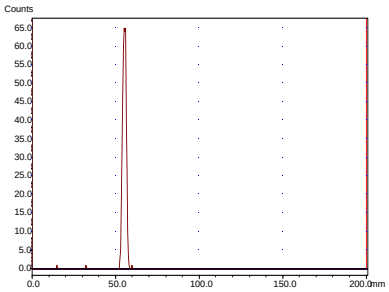


Day 13

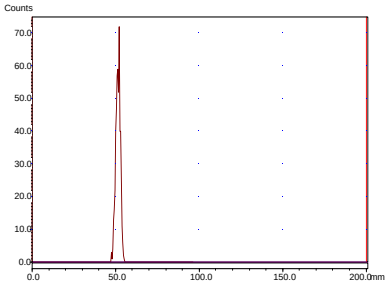
Sample 1
100%



Sample 2
99.9%



Sample 3
100%



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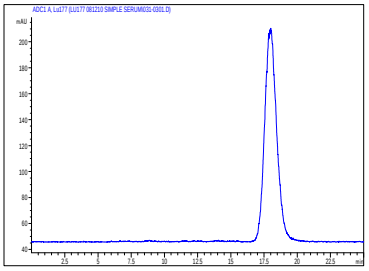

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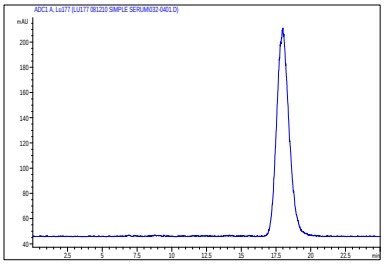

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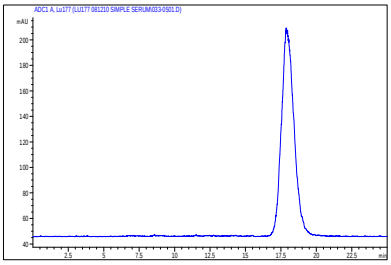
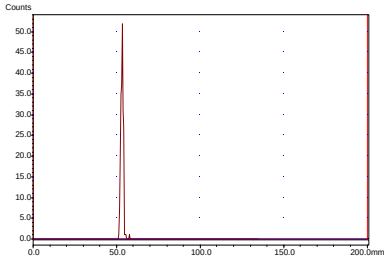
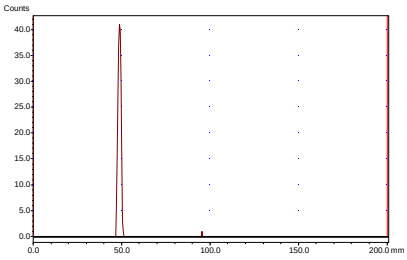


Day 14

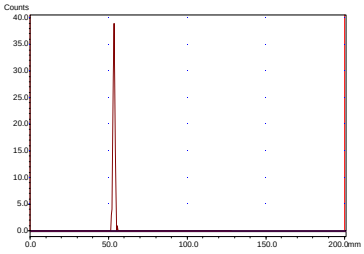
Sample 1
100%



Sample 2
100%



Sample 3
100%



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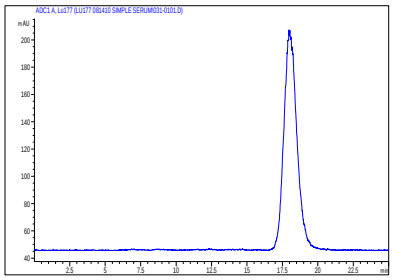

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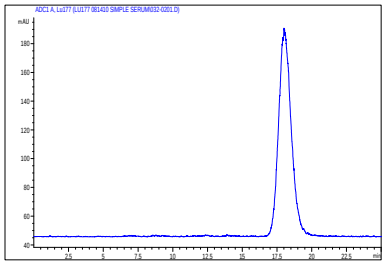

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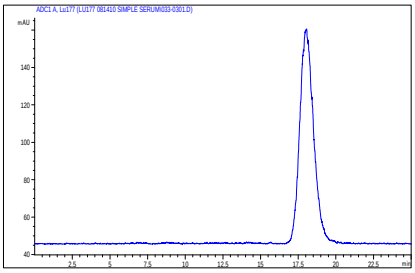
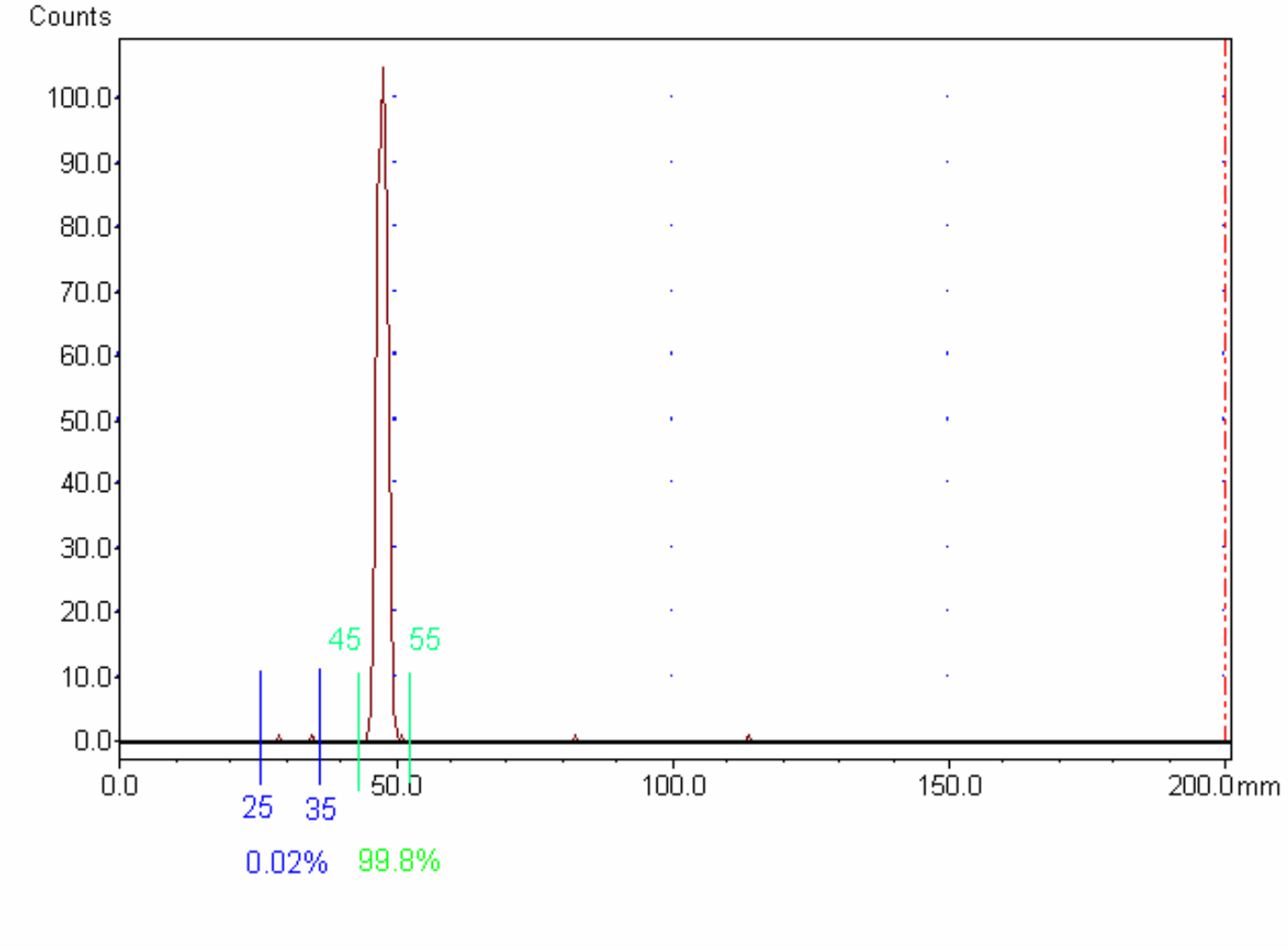
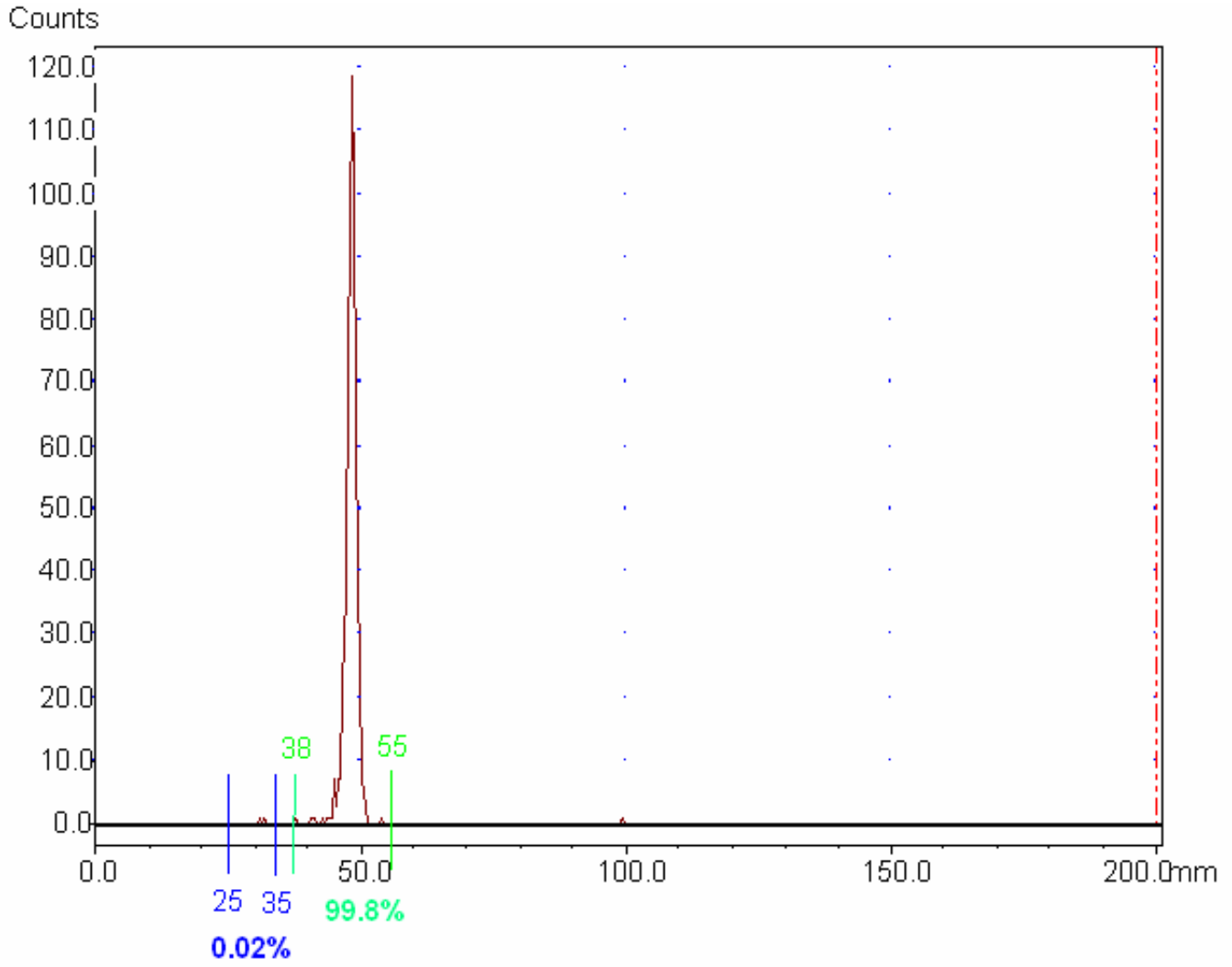


8. Examplary TLC chromatograms for assessment of ^{90}Y or ^{177}Lu released into serum.

^{90}Y-3p-*C*-NETA: Day 12 (Sample 3, 99.8%)



^{177}Lu-*C*-DOTA: Day 4 (Sample 1, 99.8%)



9. Radio-HPLC chromatogram of ^{177}Lu present in serum