**Supporting Information**

# Synthesis and biological evaluation of rhein-based MRI contrast agents for *in vivo* visualization of necrosis

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**Materials**

Rhein with purity greater than 97% was purchased from Chendu SinoStandards Biological Technology Co., Ltd. (Chendu, China). *N*-hydroxysuccinimide (NHS), 1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC), *O*-Benzotriazole-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate (HBTU), *N*-boc-ethylenediamine, *N*-boc-1,4-butanediamine, *N*-boc-1,6-hexanediamine were purchased from Bide Pharmatech Co., Ltd. (Shanghai, China). Tri-tert-butyl 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetate [DOTA-tris (tBu) ester] was purchased from Macrocyclics, Inc (Portland, OR, USA). Gadolinium chloride ($GdCl_3 \cdot 6H_2O$) and all solvents used were commercially available from Sinopharm Chemical Reagent Co., Ltd. (Shanghai, China).

All reaction mixtures were monitored using silica gel 60 TLC plates $F_{254}$ (Merck, Germany) and visualized by using UV or Iodine. $^1H$ NMR and $^{13}C$ NMR spectra were carried out on a Bruker 500 or 300 MHz NMR (Switzerland) at 303 K. Chemical shifts were given with reference to TMS as an internal standard. Electrospray-ionization mass spectrometry (ESI-MS) was carried out on an HP1100 mass spectrometer (Agilent, Santa Clara, CA, USA).

## Synthesis and Characterization of $GdL_n$

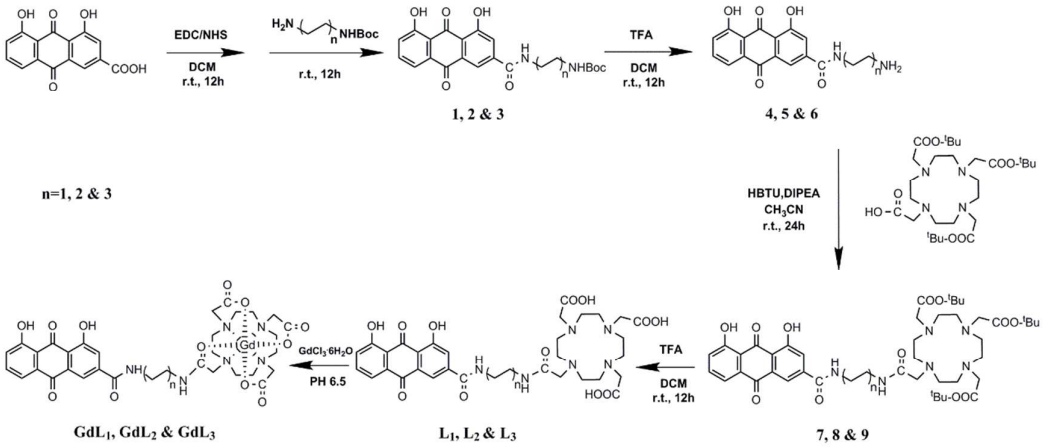


**Figure S1.** Synthetic route of $GdL_n$ (n = 1, 2, 3)

*Tert-butyl (2-(4,5-dihydroxy-9,10-dioxo-9,10-dihydroanthracene-2-carboxamido)ethyl)carbamate (**1**):*

Rhein (200 mg, 0.70 mmol), EDC (147 mg, 0.77 mmol), NHS (88 mg, 0.76 mmol) were dissolved in 100 mL of dichloromethane (DCM). The mixture was stirred at room temperature for 12 h. *N*-Boc-ethylenediamine (100 μL) was added dropwise to a stirred solution of the mixture. The reaction was stirred at room temperature for 12 h. The resultant yellow mixture was filtered and dried under vacuum to give a yellowish solid. The solid was purified by column chromatography on silica using $CH_2Cl_2$/MeOH (100:1). Compound **1** was abtained as a yellowish solid (213 mg, 71% yield). $^1$H NMR (300 MHz, DMSO-$d_6$) δ: 11.91 (s, 2H); 8.88 (s, 1H); 8.13 (s, 1H); 7.84 (dd, 1H, $J$ = 7.9, 8.0 Hz); 7.77-7.75 (m, 2H); 7.42 (d, 1H, $J$ = 8.1 Hz); 6.95 (s, 1H); 3.15 (t, 2H, $J$ = 6.5 Hz); 1.38 (s, 9H) ppm. ESI-MS *m/z* for $[M+Na]^+$ calcd 449.1, found 449.1. for $[M-H]^-$ calcd 425.2, found 425.2.

*Tert-butyl*

*(4-(4,5-dihydroxy-9,10-dioxo-9,10-dihydroanthracene-2-carboxamido)butyl)carbamat*

*e (**2**):*

The synthetic procedures of the title compound were similar to those of compound **1** except that *N*-boc-ethylenediamine was replaced with *N*-boc-1,4-butanediamine (200 μL). Obtained compound **2** (220 mg, 69% yield). $^{1}$H NMR (300 MHz, DMSO-$d_6$) δ: 11.91 (s, 2H); 8.88 (t, 1H, $J$ = 5.5 Hz); 8.14 (d, 1H, $J$ = 1.6 Hz); 7.84 (dd, 1H, $J$ = 7.8, 8.0 Hz); 7.78-7.75 (m, 2H); 7.42 (d, 1H, $J$ = 8.2 Hz); 6.78 (s, 1H); 3.26 (t, 2H, $J$ = 6.5 Hz); 2.95 (t, 2H, $J$ = 6.5 Hz); 1.53 (m, 2H); 1.45 (m, 2H); 1.37 (s, 9H) ppm. ESI-MS *m/z* for $[M+Na]^+$ calcd 477.2, found 477.2. for $[M-H]^-$ calcd 453.2, found 453.2.

*Tert-butyl*

*(6-(4,5-dihydroxy-9,10-dioxo-9,10-dihydroanthracene-2-carboxamido)hexyl)carbama*

*te (**3**):*

The synthetic procedures of the title compound were similar to those of compound **1** except that *N*-boc-ethylenediamine was replaced with *N*-boc-1,6-hexanediamine. Obtained compound **3** (203 mg, 60% yield). $^{1}$H NMR (300 MHz, DMSO-$d_6$) δ: 11.90 (s, 2H); 8.85 (s, 1H); 8.14 (s, 1H); 7.84 (dd, 1H, $J$ = 7.8, 8.0 Hz); 7.77-7.75 (m, 2H); 7.42 (d, 1H, $J$ = 8.1 Hz); 6.72 (s, 1H); 2.90 (t, 2H, $J$ = 6.5 Hz); 1.55 (m, 2H); 1.52 (m, 2H); 1.37 (s, 9H); 1.30 (m, 4H) ppm. ESI-MS *m/z* for $[M+Na]^+$ calcd 505.2, found 505.2. for $[M-H]^-$ calcd 481.2, found 481.2.

*N-(2-aminoethyl)-4,5-dihydroxy-9,10-dioxo-9,10-dihydroanthracene-2-carboxamide*

***(4)**:*

Compound **1** (200 mg, 0.47 mmol) was dissolved in a 15 mL solution of DCM /trifluoroacetic acid (TFA) (1:1, v:v) and was stirred at room temperature for 12 h. The solvent was then removed under reduced pressure to yield a reddish residue which was used in the next step without further purification. $^1$H NMR (300 MHz, DMSO-$d_6$) δ: 9.04 (s, 1H); 8.18 (s, 1H); 7.84 (dd, 1H, $J$ = 5.3, 7.9 Hz); 7.74-7.71 (m, 2H); 7.45 ( d, 1H, $J$ = 5.3 Hz); 3.58 (t, 2H, $J$ = 3.6 Hz); 3.07 (t, 2H, $J$ = 3.8 Hz) ppm. ESI-MS *m/z* for $[M+H]^+$ calcd 327.1, found 327.1. for $[M-H]^-$ calcd 325.1, found 325.1.

*N-(4-aminobutyl)-4,5-dihydroxy-9,10-dioxo-9,10-dihydroanthracene-2-carboxamide(*

***5**):*

The synthetic procedures of the title compound were similar to those of compound **4** except that compound **1** was replaced with compound **2**. The product was used for next step without further purification. $^1$H NMR (300 MHz, DMSO-$d_6$) δ: 12.04 (s, 2H); 8.96 (t, 1H, $J$ = 4.1 Hz); 8.16 (d, 1H, $J$ = 1.2 Hz); 7.86 (dd, 1H, $J$ = 4.9, 5.0 Hz); 7.80-7.77 (m, 2H); 7.42 (d, 1H, $J$ = 5.5 Hz); 3.35 (t, 2H, $J$ = 3.4 Hz); 2.86 (t, 2H, $J$ = 4.1 Hz); 1.64 (m, 4H) ppm. ESI-MS *m/z* for $[M+H]^+$ calcd 355.1, found 355.1. for $[M-H]^-$ calcd 353.1, found 353.1.

*N-(6-aminohexyl)-4,5-dihydroxy-9,10-dioxo-9,10-dihydroanthracene-2-carboxamide*

***(6)**:*

The synthetic procedures of the title compound were similar to those of **4** except that compound **1** was replaced with compound **3**. The product was used for next step

without further purification. $^1$H NMR(300 MHz, DMSO-$d_6$) δ: 8.92 (s, 1H); 8.17 (s, 1H); 7.88 (dd, 1H, *J* = 6.1, 7.5 Hz); 7.79-7.77 (m, 2H); 7.42 (d, 1H, *J* = 7.4 Hz); 3.59 (m, 2H); 2.83 (m, 2H); 1.60 (m, 4H); 1.37 (m, 4H) ppm. ESI-MS *m/z* for $[M-H]^-$ calcd 381.1, found 381.1.

*Tri-tert-butyl 2,2',2''-(10-(2-((2-(4,5-dihydroxy-9,10-dioxo-9,10-dihydroanthracene-2-carboxamido)ethyl)amino)-2-oxoethyl)-1,4,7,10-tetraazacyclododecane-1,4,7-triyl)triacetate (**7**):*

DOTA-tris (tBu) ester (421 mg, 0.74 mmol), HBTU (280 mg, 0.74 mmol) and *N*-ethyldiisopropylamine (DIPEA, 100 μL) were dissolved in 15 mL acetonitrile. The mixture was stirred at room temperature for 0.5 h. Compound **4** (241 mg, 0.74 mmol) was added and the mixture were stirred at room temperature for 24 h. The resultant mixture was dried under vacuum to give a yellow oil, which was purified by flash column chromatography on silica using $CH_2Cl_2$/MeOH (50:1) as the eluate to obtain compound **7** (385 mg, 59% yield). $^1$H NMR (300 MHz, $CD_3OD$) δ: 8.23 (d, 1H, *J* = 1.3 Hz); 7.86 (dd, 1H, *J* = 4.6, 4.9 Hz); 7.80-7.77 (m, 2H); 7.41 (d, 1H, *J* = 5.7 Hz); 3.68-2.32 (m, 28H); 1.54 (s, 9H); 1.53 (s, 18H) ppm. ESI-MS *m/z* for $[M-H]^-$ calcd 879.5, found 879.5.

*Tri-tert-butyl 2,2',2''-(10-(2-((4-(4,5-dihydroxy-9,10-dioxo-9,10-dihydroanthracene-2-carboxamido)butyl)amino)-2-oxoethyl)-1,4,7,10-tetraazacyclododecane-1,4,7-triyl)triacetate (**8**):*

The synthetic procedures of the title compound were similar to those of **7** except that compound **4** was replaced with compound **5** (200 mg). Obtained compound **8**

(216 mg, 42% yield). $^{1}$H NMR (300 MHz, DMSO-$d_6$) δ: 11.92 (s, 2H); 8.88 (s, 1H); 8.14 (s, 1H); 8.12 (s, 1H); 7.85-7.77 (m, 3H); 7.43 (d, 1H, $J$ = 8.1 Hz); 3.18-2.02 (m, 28H); 1.53-1.49 (m, 4H); 1.44 (s, 9H); 1.42 (s, 18H) ppm. ESI-MS *m/z* for $[M+H]^+$ calcd 909.5, found 909.5. for $[M-H]^-$ calcd 907.5, found 907.5.

*tri-tert-butyl 2,2',2''-(10-(2-((6-(4,5-dihydroxy-9,10-dioxo-9,10-dihydroanthracene-2-carboxamido)hexyl)amino)-2-oxoethyl)-1,4,7,10-tetraazacyclododecane-1,4,7-triyl)tri acetate (**9**):*

The synthetic procedures of the title compound were similar to those of **7** except that the compound **4** was replaced with the compound **6** (200 mg). Obtained compound **8** (150 mg, 30% yield). $^{1}$H NMR (500 MHz, DMSO-$d_6$) δ: 12.03 (s, 2H); 8.87 (m, 1H); 8.17 (t, 1H, $J$ = 6.6, 6.6); 8.12-8.10 (m, 1H); 7.89-7.80 (m, 2H); 7.45-7.27 (m, 2H); 3.43-1.94 (m, 28H);1.59-1.51 (m, 8H); 1.44 (s, 27H) ppm. ESI-MS *m/z* for $[M+H]^+$ calcd 937.5, found 937.6. for $[M+Na]^+$ calcd 959.5, found 959.6.

*2,2',2''-(10-(2-((2-(4,5-dihydroxy-9,10-dioxo-9,10-dihydroanthracene-2-carboxamido) ethyl)amino)-2-oxoethyl)-1,4,7,10-tetraazacyclododecane-1,4,7-triyl)triacetic acid (**$L_1$**):*

Compound **7** (200 mg, 0.23 mmol) was dissolved in a 15 mL solution of DCM /TFA (1:1, v:v) and stirred at room temperature for 12 h. The resultant mixture was dried under vacuum to yield $\mathbf{L_1}$ (150 mg, 93% yield). $^{1}$H NMR (300 MHz, DMSO-$d_6$) δ: 11.91 (s, 2H); 8.98 (s, 1H); 8.57 (s,1H); 8.13 (s, 1H); 7.87-7.82 (m, 1H); 7.80-7.75 (m, 2H); 7.43 (d, 1H, $J$ = 8.2 Hz); 3.93-2.59 (m, 28H) ppm. $^{13}$C NMR (75 MHz,

DMSO-$d_6$) δ: 190.91, 181.32, 170.29, 170.19, 164.10, 161.41, 161.36, 141.39, 137.19, 133.57, 133.25, 124.33, 122.99, 119.15, 117.96, 117.50, 116.18, 58.40, 55.52, 54.80, 50.49, 50.14, 49.85, 39.05 ppm. ESI-MS *m/z* for $[M+K-2H]^-$ calcd 749.2, found 749.2.

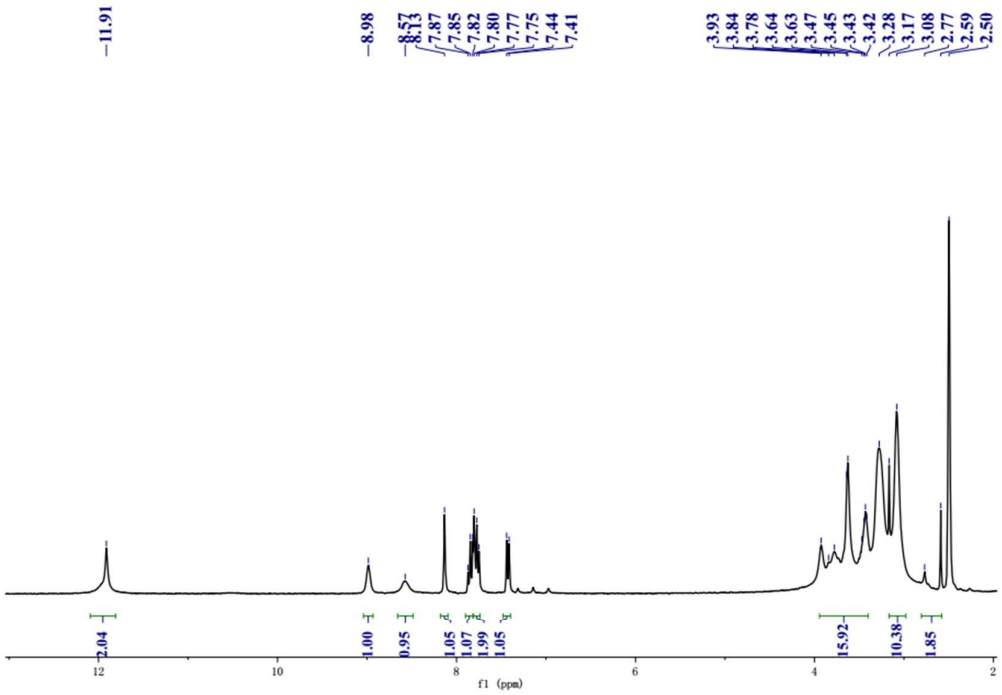


**Figure S2** $^1$H NMR spectrum of $L_1$ (DMSO-$d_6$, 300 MHz)

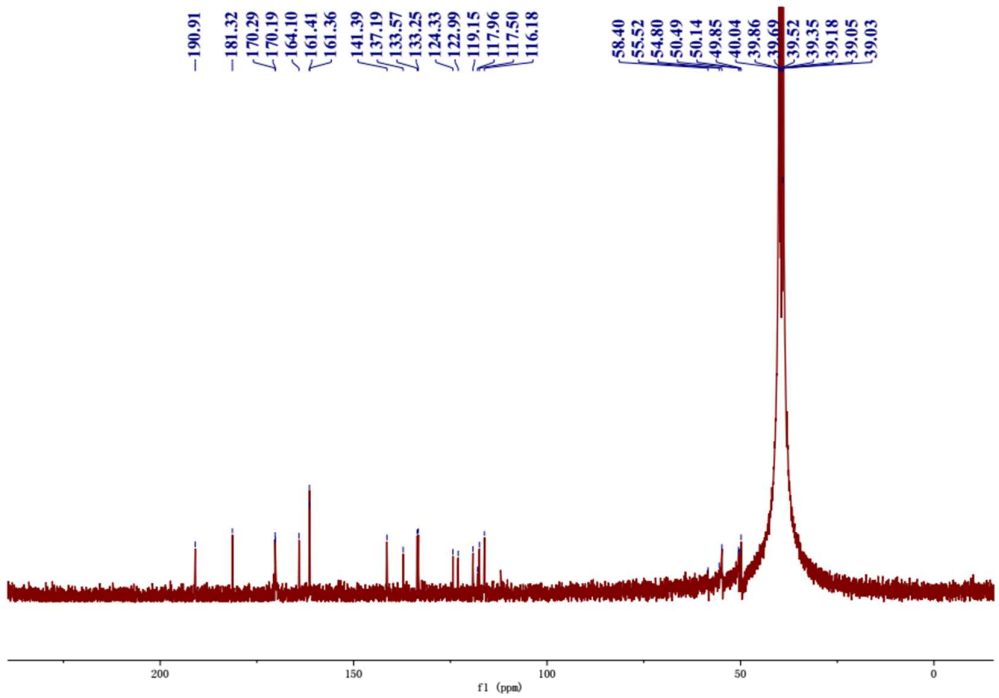


**Figure S3** $^{13}$C NMR spectrum of $L_1$ (DMSO-$d_6$, 75 MHz)

*2,2',2''-(10-(2-((4-(4,5-Dihydroxy-9,10-dioxo-9,10-dihydroanthracene-2-carboxamido )butyl)amino)-2-oxoethyl)-1,4,7,10-tetraazacyclododecane-1,4,7-triyl)triacetic acid (**L$_2$**):*

The synthetic procedures of the title compound were similar to those of **L$_1$** except that the compound **7** was replaced with the compound **8**. Obtained compound **L$_2$** (147 mg, 90% yield). $^1$H NMR (300 MHz, DMSO-$d_6$) δ: 9.66 (s, 1H); 8.18 (s, 1H); 8.15 (s, 1H); 7.90 (s, 1H); 7.82-7.71 (m, 2H); 7.40 (d, 1H, $J$ = 8.3 Hz); 3.52-2.61 (m, 28H); 1.57-1.55 (m, 4H) ppm. $^{13}$C NMR (75 MHz, DMSO-$d_6$) δ: 191.39, 181.20, 170.22, 170.15, 169.84, 163.78, 161.37, 161.24, 142.03, 137.39, 133.44, 133.33, 124.40, 122.70, 119.31, 117.87, 117.30, 116.11, 58.77, 55.37, 54.65, 50.92, 50.05, 49.94, 49.88, 37.93, 25.98, 25.65 ppm. ESI-MS *m/z* for $[M+K+Na-H]^+$ calcd 801.3,

found 801.3.

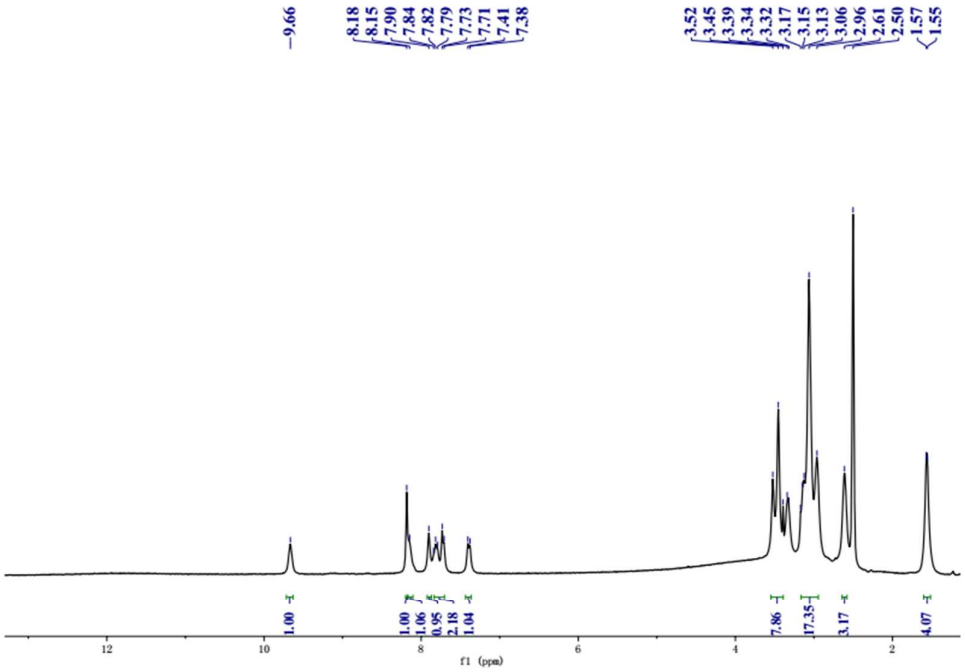


**Figure S4** $^{1}$H NMR spectrum of $L_2$ (DMSO-$d_6$, 300 MHz)

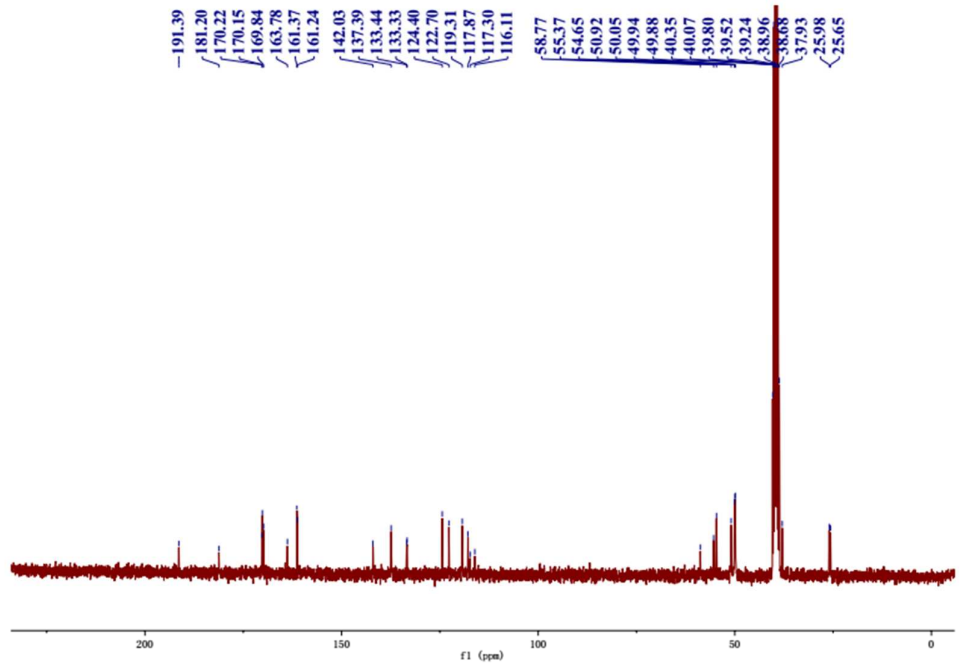


**Figure S5** $^{13}$C NMR spectrum of $L_2$ (DMSO-$d_6$, 75 MHz)

*)hexyl)amino)-2-oxoethyl)-1,4,7,10-tetraazacyclododecane-1,4,7-triyl)triacetic acid (**L**$_3$):*

The synthetic procedures of the title compound were similar to those of **L**$_1$ except that the compound **7** was replaced with the compound **9**. Obtained compound **L**$_3$ (154 mg, 94% yield). $^1$H NMR (300 MHz, DMSO-$d_6$) δ: 9.14 (s, 1H); 8.12 (s, 2H); 7.83-7.70 (m, 3H); 7.38 (d, 1H, $J$ = 8.5 Hz); 3.48-2.64 (m, 28H); 1.56-1.32 (m, 8H) ppm. $^{13}$C NMR (75 MHz, DMSO-$d_6$) δ: 191.26, 181.16, 170.19, 169.73, 163.76, 161.37, 161.23, 141.91, 137.37, 133.43, 133.28, 124.42, 122.54, 119.30, 117.62, 58.28, 55.60, 54.77, 51.13, 50.16, 50.00, 39.38, 38.33, 28.74, 28.47, 25.95 ppm. ESI-MS *m/z* for [M+K-2H]$^-$ calcd 805.3, found 805.3. for [M+Na-2H]$^-$ calcd 789.3, found 789.3

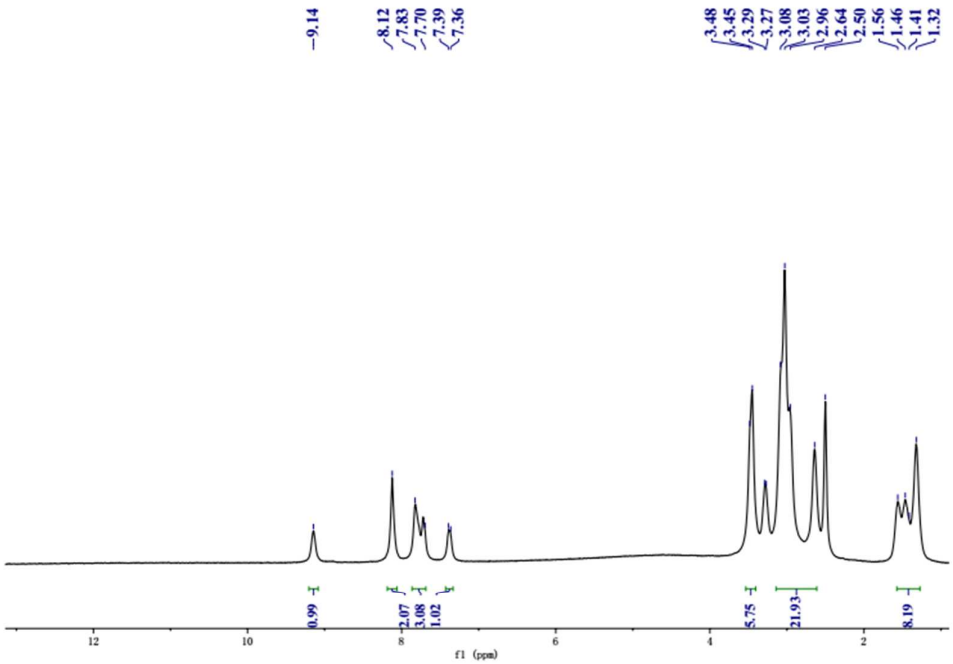


**Figure S6** $^1$H NMR spectrum of $L_3$ (DMSO-$d_6$, 300 MHz)

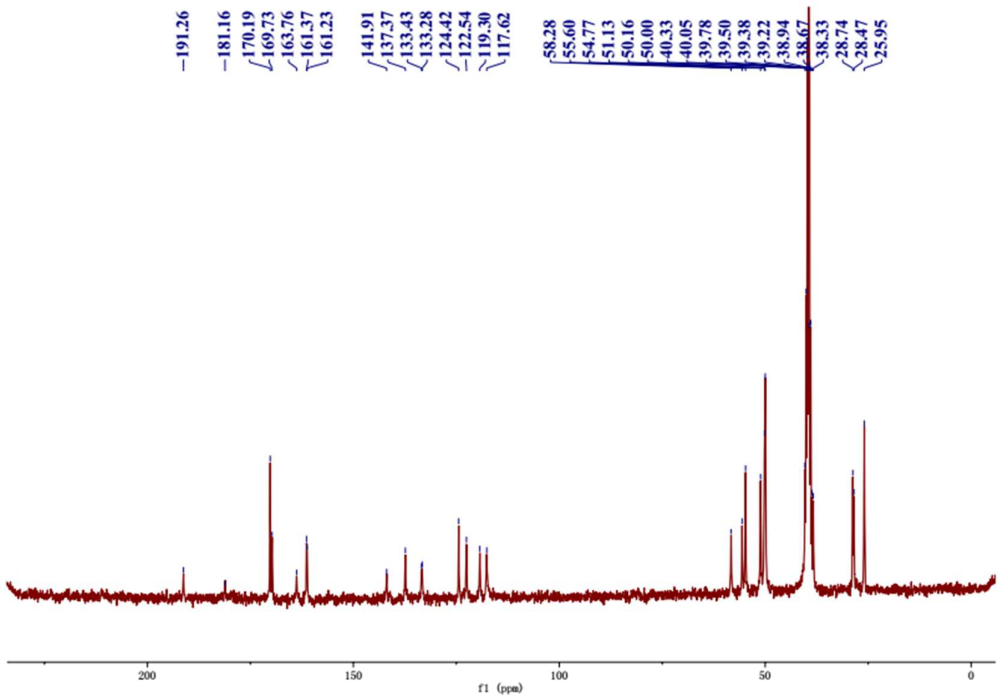


**Figure S7** $^{13}C$ NMR spectrum of $L_3$ (DMSO-$d_6$, 75 MHz)

*$GdL_1$*

**$L_1$** (200 mg, 0.28 mmol) and $GdCl_3 \cdot 6H_2O$ (104 mg, 0.28 mmol) was dissolved in 5 mL $H_2O$. The pH was maintained at 6.0-7.0 by adding 1 M NaOH. The mixture was stirred at room temperature for 24 h. The resultant mixture was dried under vacuum and purified by chromatography on silica (eluent gradient from MeOH/$H_2O$, 20%:80% to MeOH/$H_2O$, 40%:60%) to obtain **$GdL_1$** (198 mg, 81% yield). ESI-MS *m/z* for $[M+Na]^+$ calcd 893.2, found 893.2.

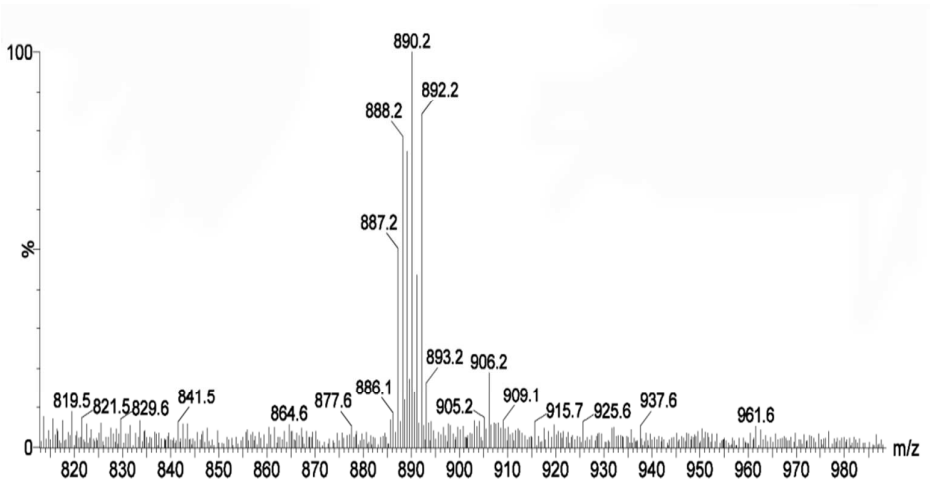


**Figure S8** ESI-MS spectrum of $GdL_1$ (MeOH)

*$GdL_2$*

The synthetic procedures of the title compound were similar to those of **$GdL_1$** except that the **$L_1$** was replaced with the **$L_2$**. Obtained **$GdL_2$** (180 mg, 74% yield). ESI-MS *m/z* for $[M+Na]^+$ calcd 921.2, found 921.2.

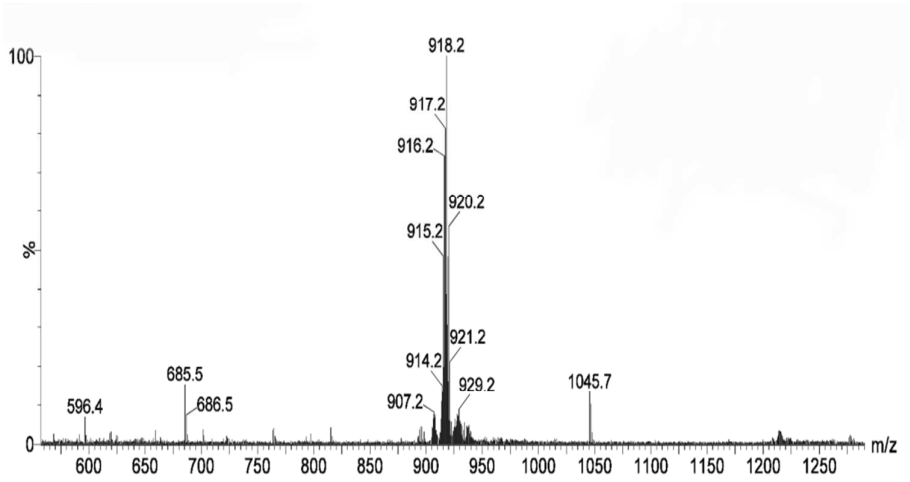


**Figure S9** ESI-MS spectrum of $GdL_2$ (MeOH)

*$GdL_3$*

The synthetic procedures of the title compound were similar to those of **$GdL_1$**

except that the $\mathbf{L_1}$ was replaced with the $\mathbf{L_3}$. Obtained $\mathbf{GdL_3}$ (176 mg, 73% yield). ESI-MS *m/z* for $[M+Na]^+$ calcd 949.2, found 949.2. for $[M-H]^-$ calcd 925.2, found 925.2.

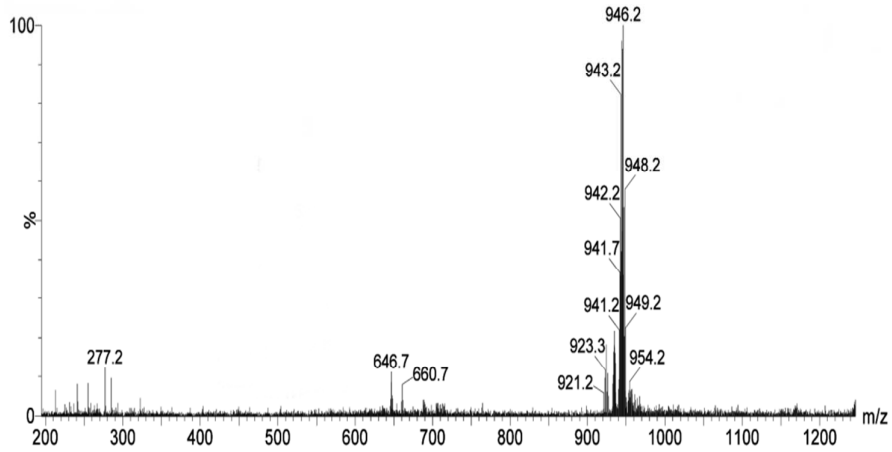


**Figure S10** ESI-MS spectrum of $GdL_3$ (MeOH)

**Transmetallation**. Possible transmetallation by zinc(II) ions was used as a stability test for the three complexes. The relative value of $R_1^P$ at any time t, $R_1^P(t)/R_1^P(0)$, is therefore a good estimate of the extent of transmetalation. Its evolution over time gives relevant information about the kinetics of the reaction, whereas the plateau value theoretically reached at $t = \infty$ will reflect the thermodynamic aspects of the system. This experiment was prepared according to the literature method. It is based on measurement of the evolution of the water proton longitudinal relaxation rate ($R_1^P$) of a buffered solution (phosphate buffer, pH 7.4) containing 2.5 mmol/L gadolinium complex and 2.5 mmol/L $ZnCl_2$. Then 10 μL of a 250 mmol/L solution of $ZnCl_2$ is added to 1 mL of a buffered solution of the paramagnetic complex. The mixture is vigorously stirred, and 300 μL is taken up for the relaxometric study. A control study, run on Gd-DOTA with zinc acetate, has given results identical to those obtained in the presence of $ZnCl_2$. The $R_1^P$ relaxation rate is obtained after subtraction of the diamagnetic contribution of the proton water relaxation from the observed relaxation rate $R_1 = (1/T_1)$. The measurements were performed on 0.5 T (21.25 MHz, Niumag Analytical Instrument Corporation, SHANGHAI). The temperature was controlled at 37 °C.

**Log *P* Determination**

Octanol-water partition coefficients (logP) were determined by the "shake-flask" method[1]. Octanol saturated with PBS (PH 7.4) and PBS saturated with octanol were used in this experiments. The PBS phase of $GdL_n$ absorbs strongly at approximately 435 nm, therefore, the partition was quantified using UV spectrophotometry with a Agilent Technologies Cary 60 UV-vis spectrophotometer[2]. A standard curve was made by plotting concentration of $GdL_n$ in PBS on the X axis, and the absorbance on the Y axis. A 1:1 volume ratio was used for the partitioning of the solution with $GdL_n$. Preparing 1 mL PBS solution of $GdL_n$ at a certain concentration and the concentration ($c_0$) was calculated using standard curves. Then 1 mL PBS solution of $GdL_n$ was added to 1 mL of the saturated phase of octanol. The resulting solution was vigorously vortexed for 10-15 min at room temperature and then centrifuged at 14000 rpm for 10 min. $GdL_n$ concentrations ($c_1$) in PBS phase were determined using standard curves. The partition coefficient was determined with the formula: $\log P = \log [(c_0 - c_1)/c_1]$. Each compound was measured three times.

***In vitro* stabilities of $GdL_n$**

$GdL_1$, $GdL_2$ or $GdL_3$ (10 mM, 50 μL)was added to rat serum (950 μL) and the mixtures were vortexed for 1 min and placed in an incubator at 37°C for different intervals (0, 6 and 24 h). Aliquots of serum (100 μL) were treated with EtOH (200 μL) for protein precipitation. Samples were centrifuged at 13,500 rpm for 10 min at 4°C. The supernatant solution was collected and determined by reversed-phase high performance liquid chromatography (RP-HPLC) that equipped with Waters 2998 PDA detector (Berthold Technologies, Germany), a Alltima $C_{18}$ column (250 × 4.6 mm, 5 μm, GRACE) and a pump (Waters 2695). The mobile phase was 0.1% TFA in acetonitrile/0.1% TFA in water, $GdL_1$ (27:73, v/v), $GdL_2$ (30:70, v/v), $GdL_3$ (33:67, v/v). A flow rate of 1 mL/min was used as elution condition.

***In Vitro* Cell Cytotoxicity.** The human lung cancer A549 cells were cultured in RPMI-1640 supplemented with 10% fetal bovine serum, penicillin (100 IU/mL), and streptomycin (100 mg/mL) maintained at 37 °C, 5% $CO_2$. The medium was replaced every 2 days, and cells were split into a 96-well plate ($1 \times 10^4$ cells/well). Various $GdL_n$ concentrations (0.025-1.0 mM) of the contrast agent were added into the culture serum free media followed by incubation for 24 h. Then 10 μL of stock MTT solution (5 mg/mL, Sigma) was added to each well, and cells were incubated for 4 h at 37 °C in a 5% $CO_2$ environment. The medium was aspirated from the well without disturbing the formazan crystals. DMSO (100 μL) was added to each well. The plates were shaken for 5 min on a plate shaker, and the absorbance at 570 nm was measured by ELISA reader.

**Interaction with DNA.** The interactions of compounds with DNA were examined by fluorescence and relaxometry.

Firstly, DNA-ethidium bromide (DNA-EB) fluorescence quenching experiments were performed to study the interaction mode between the compounds and DNA. The fluorescence emission spectra were carried out with Cary Elipse Fluorescence (Agilent Technologies Inc., USA) in the wavelength range of 530-750 nm. Different concentrations (0, 1.13, 2.21, 3.26, 4.26, $5.23 \times 10^{-5}$ M) of compounds (rhein, $L_n$ and $GdL_n$) were added directly into a quartz cell containing $0.60 \times 10^{-5}$ M ethidium bromide (EB) and $2.40 \times 10^{-5}$ M Ct-DNA (total volume 3 mL), and the reaction was performed at 25°C. The synchronous fluorescence spectra were recorded by scanning at excitation and emission wavelengths simultaneously. The emission spectrum of DNA-EB was taken in the region of 540-700 nm using an excitation wavelength at 530 nm. The relative binding of the compounds to Ct-DNA was determined by means of classical Stern-Volmer equation as follow:

$$F_0 / F = 1 + K_{SV}[Q]$$

Where $F$ and $F_0$ are the fluorescence intensity in presence and absence of the quencher, and [Q] is the concentration of the compound, $K_{SV}$ is the Stern-Volmer quenching constant.

To further describe the interaction between $GdL_1$ and DNA, we measured relaxation times of $GdL_1$ as the varied concentrations of DNA. $GdL_1$ (0.25 mM) was employed with increasing concentrations of DNA (0 to 0.31 mM). Relaxation times were measured as above. $1/T_1$ (R) values were fit to a non-linear dose-response

regression.

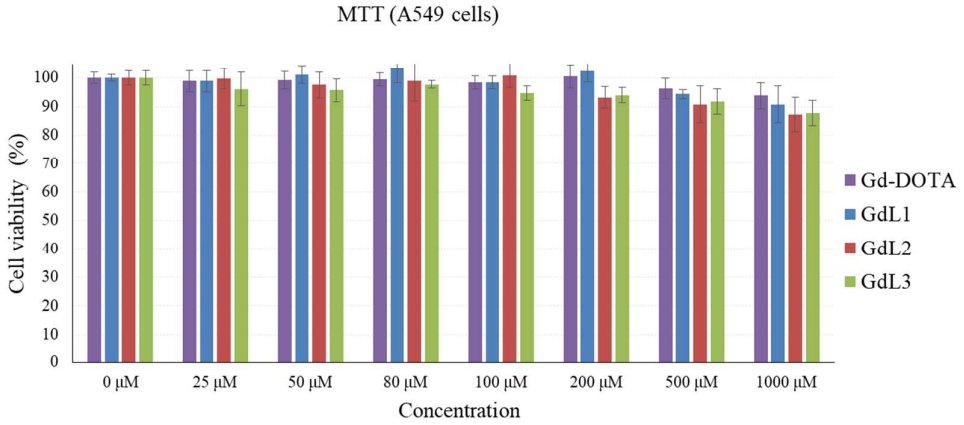


**Figure S11** Relative cell cytotoxicity (%) of human lung cancer A549 cells obtained by Gd-DOTA, $GdL_1$, $GdL_2$ and $GdL_3$. The standard deviations ((SD) were obtained on a triplicate analysis (n = 3).

## HPLC Retention Time of $L_1$ and $^{64}CuL_1$

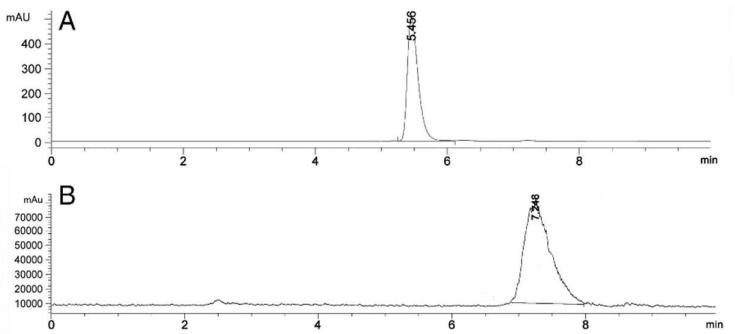


**Figure S12** HPLC chromatograms of $L_1$ and $^{64}CuL_1$

(A) ultraviolet-chromatogram of $L_1$; (B) radiochemical purity of $^{64}CuL_1$

**References**

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