Supporting Information

1. Experimental

Synthesis of europium complexes (Eu-L_1-P_n and Eu-L_2-P_n, n = 1 -3)

The general reaction scheme of six europium complexes is shown in **Scheme S1**. All analytical–grade solvents were dried by standard procedures, distilled and deaerated before use. NMR spectra were recorded on a Bruker Ultrashield 400 plus NMR spectrometer. The ^{1}H NMR chemical shifts were referenced to tetramethylsilane, TMS (d = 0.00). The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. High-resolution mass spectra were obtained on a Bruker Autoflex MALDI–TOF mass spectrometer.

Synthesis of 2-(chloromethyl)-4-((4-propoxyphenyl)ethynyl)pyridine (4)

To a stirred solution of (4-((4-propoxyphenyl)ethynyl)pyridin-2-yl)methanol (**3**) (0.95 g, 3.6 mmol) in DCM (20ml) at 0 ºC was added thionyl chloride (0.52 mL, 7.1 mmol) slowly. The resulting mixture was stirred at room temperature for 2 hour and then treated with a saturated aqueous solution of $NaHCO_3$. The aqueous layer was extracted with DCM (20 mL ×3), and then the combined organic extracts were dried over sodium sulfate, filtered and concentrated. Silica gel flash column chromatography (hexane : ethyl acetates = 10:1) of the residue gave a white solid (0.99 mg, 3.48 mmol, 98%**)** as the product. ^{1}H NMR($CDCl_3$, 400MHz): δ 8.55 (dd, J_1 = 0.2 Hz, J_2 = 3.3 Hz,1H), 7.56 (s, 1H), 7.49 (d, J = 4.4 Hz, 2H), 7.30 dd, J_1 = 0.8 Hz, J_2 = 2.6 Hz,1H), 6.90 (d, J = 4.4 Hz, 2H), 4.67 (s, 2H), 3.96 (t, J = 6.8 Hz, 2H), 1.88-1.79 (m, 2H), 1.06 (t, J = 7.2 Hz, 3H) ; ^{13}C NMR ($CDCl_3$, 50MHz): δ 160.0, 156.5, 149.3, 133.5, 133.0, 124.5, 124.4, 114.6, 113.6, 95.0, 85.3, 69.5, 46.4, 22.4,

10.4; HRMS m/z calcd. for $C_{17}H_{17}ClNO^+$ $(M + H)^+$ 286.0999, found 286.0990.

Synthesis of tert-butyl 2,2'-(4-((4-(4-propoxy-phenyl)ethynyl)pyridin-2-yl) methyl) -1,4,7,10-tetraazacyclododecane-1,7-diyl)diacetate (6)

To a stirred solution of tert-butyl 2,2'-(1,4,7,10-tetraazacyclododecane-1,7-diyl) diacetate (**5)** (140 mg, 0.35 mmol) in anhydrous MeCN was added $NaHCO_3$ (74 mg, 0.88 mmol) and 2-(chloromethyl)-4-((4-propoxyphenyl)ethynyl)pyridine (**4**) (50 mg, 0.18 mmol). The resulting mixture was stirred at room-temperature for 4 hours. The mixture was then filtered and the filtrate was concentrated. Silica gel flesh column chromatography (CH_2Cl_2: MeOH = 20:1) of the residue gave a pale yollowed solid (99 mg, 0.15 mmol, 87%) as the product. ^{1}H NMR ($CDCl_3$, 400MHz): δ 10.27 (br, 1H) 8.85 (d, *J* = 2.4 Hz, 1H), 7.49 (d, *J* = 4.4 Hz, 2H), 7.31 (s, 1H), 7.29 (d, *J* = 2.6 Hz, 1H), 6.90 (d, *J* = 4.6 Hz, 2H), 3.96 (t, *J* = 6.4 Hz, 2H), 3.73 (s, 1H), 3.14 (br, 12H), 2.86(br, 2H), 2.65 (br, 4H), 1.86-1.81 (m, 2H), 1.67 (br, 2H), 1.44 (s, 18H), 1.05 (t, *J* = 7.2, 3H) ; ^{13}C NMR ($CDCl_3$, 75MHz): δ 170.5, 159.6, 157.5, 150.1, 133.4, 132.1, 125.1, 124.1, 114.6, 113.6, 94.6, 85.5, 81.4, 69.6, 56.7, 56.0, 54.2, 50.7, 50.5, 46.8, 28.2, 22.4, 10.5; HRMS m/z calcd. for $C_{37}H_{56}N_5O_5^+$ $(M + H)^+$ 650.4281, found 650.4271.

Synthesis of tert-butyl 2,2'-(4-(2-ethoxy- 2-oxoethyl)-10-((4-((4-propoxyphenyl)ethynyl)pyridin-2-yl)methyl)-1,4,7,10-tetraazacyclododecane-1,7-diyl)diacetate (7)

To a stirred solution of Synthesis of tert-butyl 2,2'-(4-((4-((4-propoxyphenyl)ethynyl) pyridin-2-yl)methyl)-1,4,7,10-tetraazacyclododecane-1,7-diyl)diacetate (**6)** (334 mg, 0.51 mmol) in anhydrous MeCN (1.5mL) was added K_2CO_3 (355 mg, 2.57 mmol) followed by ethyl 2-chloroacetate (151 µL, 1.54 mmol). The resulting mixture was stirred at 50 ^{o}C for 5 hours The mixture was then filtered and the filtrate was

concentrated. Silica gel flesh column chromatography (CH_2Cl_2: MeOH = 30:1) of the residue gave a pale yollowed solid (302 mg, 0.42 mmol, 82%) as the product. ^{1}H NMR ($CDCl_3$, 400MHz): δ 8.24 (d, *J* = 2.6 Hz, 1H), 7.46 (d, *J* = 4.4 Hz, 2H), 7.27 (s, 1H), 7.20 (dd, J_1 = 0.6 Hz, J_2 = 2.4 Hz, 1H), 6.90 (d, *J* = 4.4 Hz, 2H), 4.21 (br, 2H), 3.94 (t, *J* = 6.8 Hz, 2H), 3.20-2.20 (m, 24 H), 1.85-1.79 (m, 2H), 1.40 (s, 18H), 1.30 (t, *J* = 7.2 Hz, 3H), 1.04 (t, *J* = 7.6 Hz, 3H); HRMS m/z calcd. for $C_{40}H_{60}N_5O_7^+$ $(M + H)^+$ 722.4493, found 722.4486.

Synthesis of 2-(4,10-bis(2-tert-butoxy-2-oxoethyl)-7-((4-((4-propoxy -pheny)ethynyl)pyridin-2-yl)methyl)-1,4,7,10-tetraazacyclododecan-1-yl)acetic acid (2)

tert-butyl 2,2'-(4-(2-ethoxy-2-oxoethyl)-10-((4-((4-propoxyphenyl)ethynyl)pyridin-2-yl)methyl)-1,4,7,10-tetraazacyclododecane-1,7-diyl)diacetate (**7**) (300 mg, 0.41mmol) was dissolved in 2mL of dioxane : 0.4M NaOH at 1:1 (v:v). This solution was stirred 5h hours under N_2 at rt.. Dioxane was evaporated under reduced pressure, and water (5 mL) was added. After extracting with DCM (15mL × 4), the organic phases were combined and washed with water (15 mL) and brine (15 mL), dried with anhydrous Na_2SO_4, and concentrated to give an off-white solid (180 mg, 0.25 mmol, yield = 62%) as the product. ^{1}H NMR ($CDCl_3$, 300MHz): δ 8.43 (d, *J* = 8.5 Hz, 1H), 8.38 (br, 1H), 7.46 (d, *J* = 9 Hz, 2H), 7.38 (s, 1H), 7.20 (d, *J* = 5.1 Hz, 1H), 6.88 (d, *J* = 8.7 Hz, 2H), 4.53 (d, *J* = 5.1 Hz, 2H), 3.94 (t, *J* = 6.6 Hz, 2H), 3.46-2.10 (m, 24H), 1.85-1.78 (m, 2H), 1.34 (s, 18H), 1.031 (t, *J* = 7.2, 3H); ^{13}C NMR ($CDCl_3$, 125MHz): δ 174.8, 171.8, 171.6, 160.1, 157.7, 148.5, 133.5, 133.0, 123.8, 123.1, 114.8, 113.8, 94.9, 85.7, 81.9, 69.7, 56.7, 56.4, 56.0, 50.6 (br), 44.1, 28.1, 22.5, 14.0, 10.4; HRMS m/z calcd. for $C_{39}H_{58}N_5O_7^+$ $(M + H)^+$ 708.4336, found 708.4325.

Synthesis of proposed Cyclin A specific peptides

Desired peptides were prepared by means of SPPS microwave synthesis. (Scheme 1) Resin was swollen in DMF for 15 minutes prior to use in subsequent synthesis. Microwave conditions were used as follows. Microwave coupling: 10 min, 20 w, 75˚C. Microwave Fmoc deprotection: 3 min, 20 w, 75 ˚C. Microwave peptide cleavage: 18 min, 20 w, 38 ˚C. Rink amide resin (200-400 mesh, 0.62 mmol g -1 loading) was purchased from Nova Biochem. Fmoc-protected amino acids were purchased from Nova Biochem. PyBOP™ was purchased from CEM. NMM, DMSO and TFA were purchased from Aldrich. N,N-dimethylformamide and HPLC grade water and MeOH were obtained from Fischer Scientific. Side chain protecting groups for Fmoc-amino acids were Boc for Lys and Pbf for Arg. MALDI-TOF mass spectra were recorded on an Applied BiosystemsTM Voyager-DE STR instrument in positive ion mode using an α-cyano-4-hydroxycinnamic acid matrix. HPLC data was obtained on a Waters Mass Directed Prep System instrument, using a 3100 Mass Detector and Diode Array Detector. For analytical HPLC, a 4.6 x 100 mm xbridge column was used, with a flow rate of 1 ml/min (run time 16.5 min). For Preparatory scale HPLC, 1 19 x 100 mm xbridge column was used, with a flow rate of 17 ml/min (run time 16.5 min). A gradient elution with 0.1 % formic acid was used, as shown in Table S1.

Peptide 1: GAKRRLIF-NH_2

This peptide was obtained by a stepwise elongation of the peptide chain by the method outlined above. 0.5 g of the rink amide resin (0.62 mmol/g loading) was suspended in a 20% solution of piperidine in DMF, stirred for 20 min at room temperature, and washed with DMF prior to use in subsequent steps. The first amino acid to be coupled, Fmoc-Phe-OH (480 mg, 4 equiv) was dissolved in DMF and

coupled to the resin in the presence of PyBOP (645 mg, 4 equiv) and NMM (135 µl, 4 equiv) with the use of microwave chemistry as described previously. Other Fmoc amino acid derivatives: Fmoc-Ile-OH (438 mg, 4 equiv), Fmoc-Leu-OH (438 mg, 4 equiv), Fmoc Arg (Pbf)-OH (804 mg, 4 equiv), Fmoc Lys (Boc)-OH (581 mg, 4 equiv), Fmoc-Ala-OH (386 mg, 4 equiv), and Fmoc-Gly-OH (369 mg, 4 equiv) were connected to the resin using an analogous synthetic strategy. Following the final removal of the Nα-Fmoc group, the peptide-resin was washed with DMF. The free peptide was obtained by cleavage through use of 9 ml of TFA in the presence of 750 µl of water and 750 µl of TIPS according to the standard procedure. Following cleavage, the peptide was purified by use of preparative HPLC. The main peptide-containing fractions were collected and lyophilized. The purity of all final products was confirmed by HPLC. Peptides two and three were obtained and purified by the same methodology as used for peptide one. Following the synthesis of peptide 1, the resin was split into three equal portions of 170 mg for a divergent synthetic strategy adopted.

Peptide 2: GGAKRRLIF-NH_2

Fmoc-GAKRRLIF-NH2 (0.10 mmol) prepared previously was Fmoc-deprotected using the microwave procedure described above. Peptide coupling with Fmoc-Gly-OH (123 mg, 4 equiv), PyBOP (215 mg, 4 equiv) and NMM (45 µl, 4 equiv) and the microwave peptide coupling program was then performed. Finally, removal of the N-terminal Fmoc group gave peptide fragment B with a free amino group on the N-terminus. Cleavage of a small amount of the peptide from the resin using TFA: TIPS: H2O (0.9 ml: 0.05 ml: 0.05 ml) gave a sample of the free peptide and its identity was confirmed by MALDI-TOF mass spectra.

Peptide 3: Hex-GAKRRLIF-NH_2

An additional coupling of Fmoc-ε-Ahx-OH 145 mg, 3 eq, was performed utilizing the methodology outlined above.

General procedures for peptide coupling

A stirred solution of acid **1** or **2** (0.032 mmol) in anhydrous DMF (2 mL) was mixed with benzotriazol-1-yl-oxytri pyrrolidinophosphonium hexafluorophosphate (PyBop) (17mg, 0.032mmol), N,N-diisopropylethylamine (DIPEA) (9 ìL,0.048 mmol). After 5-minute stirring at room temperature for activation of carboxylate, this solution was added over the resin-bounded peptides (**P1**, **P2** and **P3**) (0.016 mmol). Nitrogen gas was passed through the resin suspension for 8 hours. The resin was then filtered and washed with DMF (3mL × 3 × 3min). General procedures for global deprotection and cleavage from the resin are listed: A 3 mL of cleavage cocktail (150 µL of DCM, 75 µL of TIS, and TFA to 3mL) was added to the resin-bounded coupling products. The resulting mixture was passed with N_2 and mixed for 8 hours. The resin was then filtered, and the TFA filtrate was concentrated under reduced pressure. The residue was washed with diethyl ether and dried under reduced pressure to give ligands as pale yellow solids.

Synthesis of complexes Eu-L_1-P_n and Eu-L_2-P_n (n = 1, 2 and 3)

Ligands (**L_1-P_n** and **L_2-Pn (n = 1, 2 and 3)**, 0.01mmol each) were dissolved in MeOH/H_2O (2ml, 1:1) in six different round bottom flasks, $EuCl_3.6H_2O$ (0.013 mmol) were added and keep the PH value of the solution at 6-7 by adding NaOH aqueous solution (0.4M). The resulting solution were stirred at 25 ^oC for 24 hours. Any excess solid was filtered off and the solvent was removed under vacuum. **Eu-L_1-P_1**, Pale yellow solid. MALDI-MS m/z calcd. for $C_{77}H_{118}EuN_{22}O_{15}^+$ $(M + H)^+$ 1743.8359,

found 1743.6483; **Eu-L_1-P_2**, Pale yellow solid. MALDI-MS m/z calcd. for $C_{79}H_{121}EuN_{23}O_{16}^{+}$ $(M + H)^{+}$ 1800.8574, found 1800.9763; **Eu-L_1-P_3**, Pale yellow solid. MALDI-MS m/z calcd. For $C_{83}H_{129}EuN_{23}O_{16}^{+}$ $(M + H)^{+}$ 1856.9200, found 1856.8767; **Eu-L_2-P_1** Pale yellow solid. MALDI-MS m/z calcd. for $C_{75}H_{118}EuN_{21}O_{14}^{+}$ $(M + H)^{+}$ 1686.8119, found 1686.7962; **Eu-L_2-P_2**, Pale yellow solid. MALDI-MS m/z calcd. for $C_{77}H_{118}EuN_{22}O_{15}^{+}$ $(M + H)^{+}$ 1743.8632, found 1743.9058; **Eu-L_2-P_3**, Pale yellow solid. MALDI-MS m/z calcd. for $C_{81}H_{126}EuN_{22}O_{15}^{+}$ $(M + H)^{+}$ 1799.9695, found 1799.8910

Molecular docking

Theoretical calculation of Peptides and its Ln-Pn complexes (Eu-Ln-Pn complexes that without Eu metal) were carried out by AutoDock Vina which was explored by Dr. Oleg Trott in the Molecular Graphics Lab at The Scripps Research Institute (O. Trott, A. J. Olson, AutoDock Vina: improving the speed and accuracy of docking with a new scoring function, efficient optimization and multithreading, Journal of Computational Chemistry 31 (2010) 455-461). Briefly, Cyclin A protein (PDB code: 1OKV) were operated in AutoDocTools-1.5.4 to select the docking area (center_x = 42.7; center_y = 26.323; center_z = 6.811 and size_x = 50; size_y = 40; size_z = 46). Peptides as well as its Ln-Pn complexes were molecular graphed by GaussView and saved as pdb file. Then they were also operated in AutoDocTools-1.5.4 to choose torsions and saved as pdbqt file. Finally, the molecular docking were processed in DOS (window xp) and the results were presented with the best binding type and affinity values.

Photo-physical measurement

Linear induced photophysical propertis

UV-Visible absorption spectra in the spectral range 200 to 1100 nm were recorded by an HP Agilent UV-8453 Spectrophotometer. Single-photon luminescence spectra were recorded using an Edinburgh instrument FLS920 combined fluorescence lifetime and steady state spectrophotometer that was equipped with a visible to near-infrared-sensitive photomultiplier in nitrogen flow cooled housing. The spectra were corrected for detector response and stray background light phosphorescence. The quantum yields of the complexes were measured by comparative method and integrated sphere.

Stability test via titration

Titration experiments were conducted to investigate the effect of several common biological anions and HSA on the six europium complexes. Liquid concentrated stock solutions of each anion, as well as HSA, were added individually and gradually to a solution of the complex concerned. Addition was ceased either when the volume of added anion totaled 5% of the complex solution or the influence on complex luminescence was saturated. Single-photon luminescence spectra were determined via the aforementioned procedures.

Two/three photon induced emission measurement

For multi-photon experiments, the 750 nm pump source arose from the fundamental of a femtosecond mode-locked Ti:Sapphire laser system (output beam ~ 150 fs duration and 1 kHz repetition rate). The lasers were focused to spot size ~ 50 m via an f = 10 cm lens onto the sample. The emitting light was collected with a backscattering configuration into a 0.5 m spectrograph and detected by a liquid nitrogen-cooled CCD detector. A power meter was used to monitor the uniform excitation.

In-vitro studies

Tissue culture

Human HeLa (cervical carcinoma) cells were grown in DMEM medium; HK-1 (nasopharyngeal carcinoma) were grown in RMPI-1640 medium; All the mediums were supplemented with 10% (v/v) fetal bovine serum (FBS), 100 units/ml penicillin and 100 μg/ml streptomycin.

Preparation of Plasmids, Proteins and Antibodies

Human Cyclin A2 (173-432 a.a.) and CyclinD1 (full length) cDNA were amplified by PCR and subcloned into pGEX-KG vector for expression of GST (Glutathione S transferase) fusion proteins. All sequences were confirmed by DNA sequencing. Recombinant GST-tagged Cyclin A2 or Cyclin D1 was IPTG-induced (1 mM) expressed in bacteria E.coli BL21 and purified with High-Affinity Glutathione Sapharose 4B resin (GE Healthcare Life Sciences). Protein concentration was measured by NanoDrop 2000 spectrophotometer (Thermo Scientific). Anti-Rb phosphor-Ser807 (#sc-293117), anti-Rb phosphor-Ser795 (#sc-21875), anti-P53 phospho-Ser315 (#sc-101763) as well as anti-E2F1 phospho-Ser337 (#sc-130188) antibodies were purchased from Santa Cruz. Goat anti-rabbit IgG-HRPs were purchased from Jackson Laboratories Inc (West Grove, PA, USA).

The cellular uptake of europium complexes by ICP-MS

To measure the intracellular concentration of complex, 1 x 105 cells were plated in each well and incubated with the complex for different concentrations (0.01, 0.025, 0.05, 0.1 and 0.2 mM). After co-incubation, the cell culture medium containing complex was removed and exposed cells were further washed with 1 x PBS for 3 times to remove complex adhering to the outer cell membrane. Then the cells were

harvested from the well plates using trypsin-EDTA and dispersed into 1.5 ml of culture medium. The exposed cells were collected by centrifuge and the cell pellet was digested in 500 • l of concentrated HNO_3 at 70 ^oC for 4 hours. The intracellular concentration of Eu was determined using an Agilent 7500 series of inductively coupled plasma mass spectroscopy (ICP-MS). All ICP experiments were performed in triplicate and values obtained were averaged. The concentration of Eu per cell was calculated by determining the concentration of Eu in the cell lysate by ICP-MS and then dividing it by the number of cells which counted by haematocytometer.

Two-Photon In-vitro imaging

Cells were seeded on coverslip in 35-mm culture dishes overnight. The cells were initially incubated with compounds (1 μM and 3 hours incubation). Then the unabsorbed chemicals were washed out with PBS and the cells were subject to two-photon induced confocal microscopic imaging. In short, images were captured using the Leica SP5 (upright configuration) confocal microscope equipped with a femtosecond-pulsed Ti:Sapphire laser (Libra II, Coherent) inside the tissue culture chamber (5% CO_2, 37 ^oC). The excitation beam produced by the femto-second laser, which was tunable from 680-1050 nm, was focused on the adherent cells through a 40x oil immersion objective.

Western blotting

Exponentially grown HeLa cells seeded in 6 well plates were treated with chemicals (20 μM each) for 24 hours, and then the cells were resined in PBS twice after removal of the culture medium, directly lysis in 50 mM Tris-HCl, pH=6.8, 1% SDS, 5% glycerol and totally denatured in hot water boiling. After centrifugations, the

supernatant concentrations were measured with NanoDrop 2000 spectrophotometer. Equally mount of total cell proteins were loaded onto the 10% SDS-PAGE gel to allow electrophoresis separation. Then proteins were transferred into nitrocellular membranes. Efficiency of protein transfer was monitored by fast green staining. Then NC membranes were blocked in 2% skim milk solved in 0.3% Tween-20 TBS (TTBS), with shaking for 1hour. The proteins were examined by primary antibodies, respectively. Afterwards, free primary antibodies were removed by TTBS washing for 30 minutes. The membranes were then incubated with the respective HRP-conjugated secondary antibody for 1 h under. Finally, exposure detection was performed by using the chemiluminescence procedure (ECL, Pierce).

Small RNA interferences

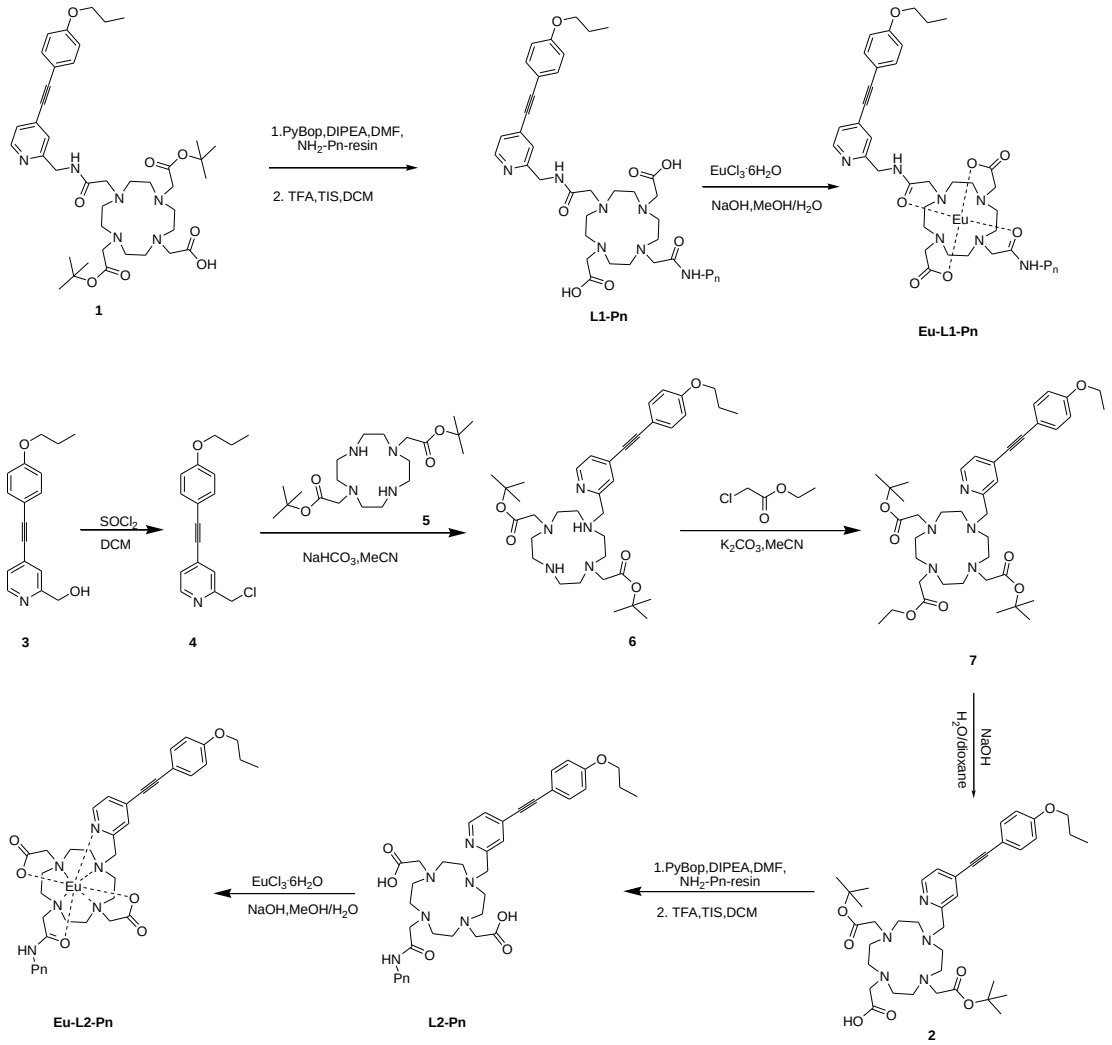
[1] Small RNA (5-CCAUUGGUCCCUCUUGAUUTT-3) targeting Cyclin A on 5-CCATTGGTCCCTCTTGATT-3 (420-438), and CyclinD1 (5-GUAGGACUCUCAUUCGGGATT-3) on 5-GTAGGACTCTCATTCGGGA-3 (3642-3641) have been described previously. HeLa cells seeding with 20% confluency were transfected with 50 ng/mL small RNA mdiated by Thermo Scientific DharmaconFECT transfection reagents. After 48 hours post-transfection, HeLa cells were either dosed with Eu-$\mathbf{L_2}$-$\mathbf{P_3}$ complexes for imaging or harvested for western blotting to examine RNA interferences efficiency. (X H Wang, Y J Song, J S Ren and X G Qu. Knocking-down Cyclin A2 by siRNA Suppresses Apoptosis and Switches Differentiation Pathways in K562 Cells upon Administration with Doxorubicin. PLoS one. 2009, 4: e6665-6674; S Weinstein, R Emmanuel, A M Jacobi, A Abraham, M A Behlke, A G Sprague, T Novobrantseva, A Nagler, D Peer. RNA Inhibition Highlights Cyclin D1 as a Potential Therapeutic Target for Mantle Cell Lymphoma. PLoS one. 2012, 7: e43343-43347)

Competitive binding assay

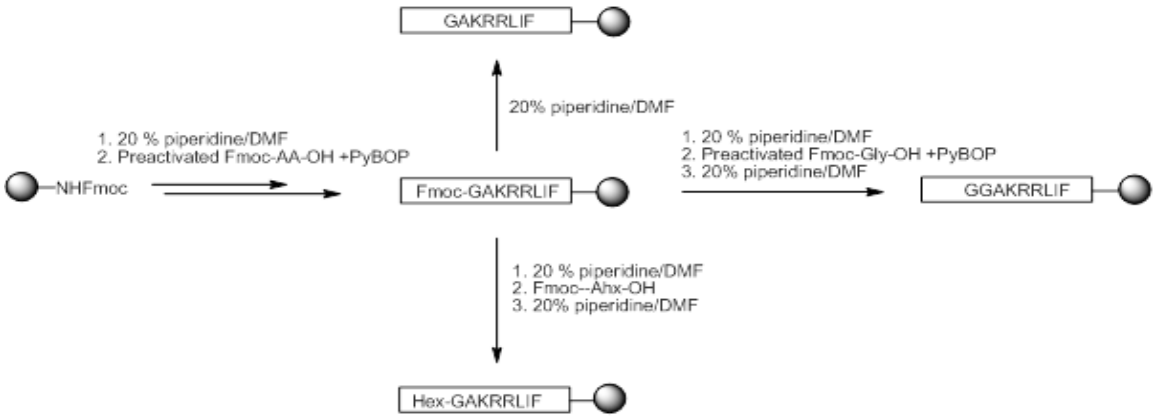
Cyclin A binding to p27/Kip1-peptide Sulfolink beads can be used to detect the ability of Eu-$\mathbf{L_n}$-$\mathbf{P_n}$ complexes of inhibiting Cyclin A. Briefly, p27/Kip1-peptide Sulfolink beads were incubated with 1 μM Cyclin A protein, before adding Eu-$\mathbf{L_n}$-$\mathbf{P_n}$ complexes. After 2 hours incubation at 4 ^{o}C, free proteins and chemicals were washed out, and peptide-bound proteins were harvested for western blotting using anti-Cyclin A antibodies. The density of protein bands in X-film was measured with Gel-pro analyzer software and underwent data normalization.

MTT cell viability assay

Exponentially growth HeLa cells ($1x10^3$) were distributed into 96-well plates and were dosed with a set of concentrations of peptides as well as Eu-Ln-Pn complexes for 36 h, respectively. Then equal amounts (20 μL) of MTT, 3-(4, 5-dimethylthiazol-2-yl)-2 and 5-diphenyltetrazolium bromide (0.5 mg/ml) were added to the cells, and further incubated at 37 ºC, 5% CO_2 for 4 hours to produce formazan during cell metabolism. Finally, produced formazan were dissolved by dimethyl sulfoxide post-removing the medium, and the absorbances of solutions were measured in Bio-Rad iMark microplate reader. Triplicates were performed for each concentration of the peptides and the complexes. Data collection and plotting were conducted with the GraphPad Prism 5 software.



Scheme S1. The general reaction scheme of our target europium complexes.



Scheme S2. Synthesis of peptide fragments.

Table S1. The calculated binding affinities between Cyclin A and peptides or L_n-P_n ligands. The binding affinities were theoretically calculated to evaluate the relative affinity of the molecules to the protein, while the real binding might be slightly different.

	kcal/mol		kcal/mol		kcal/mol
P_1	-8.6	**L_1-P_1**	-10.9	**L_2-P_1**	-10.3
P_2	-8.5	**L_1-P_2**	-11.2	**L_2-P_2**	-10.6
P_3	-9.0	**L_1-P_3**	-11.3	**L_2-P_3**	-11.6

Table S2. Solvent gradients used throughout analytical-scale HPLC.

Time (min)	**% H_2O**	**% MeOH**
0.0	**90.0**	**10.0**
10.0	**5.0**	**95.0**
13.0	**5.0**	**95.0**
13.5	**90.0**	**10.0**
16.5	**90.0**	**10.0**

Table S3. Mass spectra data of three Cyclin A specific peptides.

Peptide	**M_r (Calc)**	**M_r(obs)**
GAKRRLIF-NH_2	959	959
GGAKRRLIF-NH_2	1016	1016
Hex-GAKRRLIF-NH_2	1072	1072

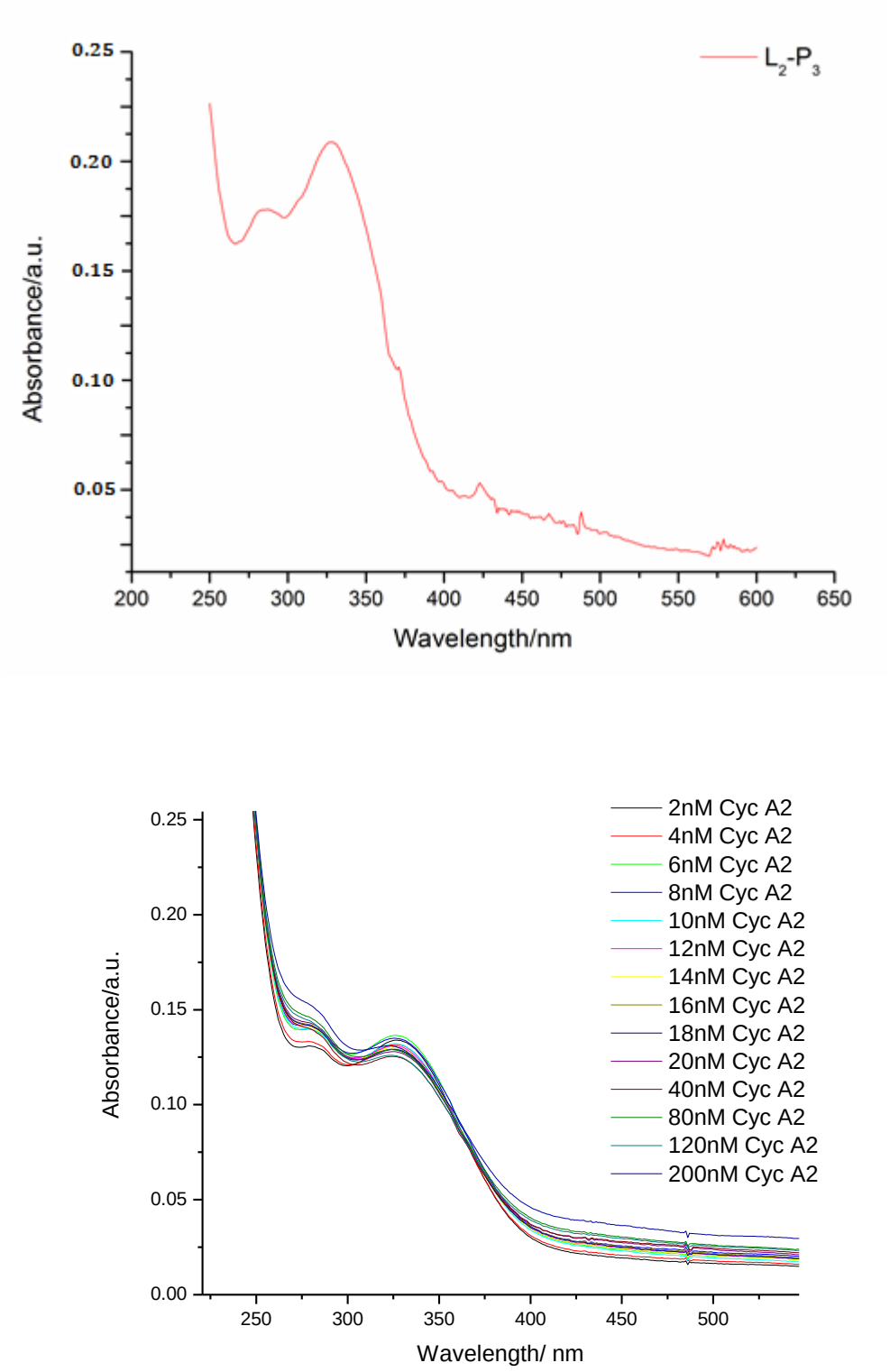
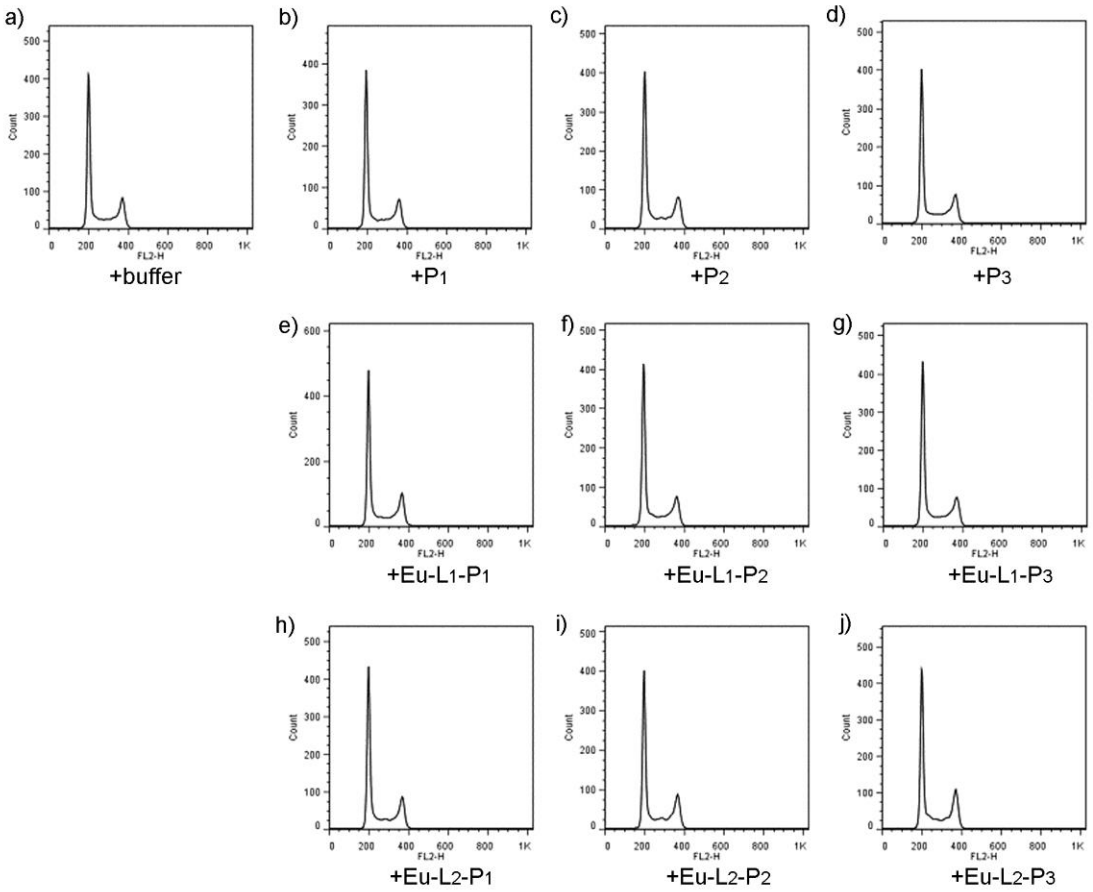


Figure S1. The UV absorption spectra of Eu-$\mathbf{L_2}$-$\mathbf{P_3}$ in aqueous solution (upper) with addition of Cyclin A (lower).



k)

	sub-G1 (%)	G1 (%)	S (%)	G2 (%)	super-G2 (%)
buffer	2.19	53.53	33.01	15.00	2.72
P1	3.90	53.28	31.27	14.62	1.98
P2	1.54	51.83	34.05	13.31	2.76
P3	1.94	55.07	30.11	14.05	2.06
Eu-L1-P1	6.08	53.95	32.37	12.83	2.51
Eu-L1-P2	4.34	51.34	32.70	13.03	2.00
Eu-L1-P3	3.50	53.84	34.04	11.60	2.17
Eu-L2-P1	3.38	51.95	31.57	16.00	2.79
Eu-L2-P2	2.22	50.66	33.40	16.46	1.77
Eu-L2-P3	3.13	53.21	32.32	13.29	2.90

Figure S2. Flow cytometry analysis of HeLa cell cycle treated with peptides or Eu-$\mathbf{L_n}$-$\mathbf{P_n}$ complexes (20 μM each). 70% ethanol fixed cells were suspended in PBS and DNA-stained by prodium iodide (20 μg/mL), then subject to cell cycle analysis under BD Biasciences FACSCalibur Analyzer. Phase distribution of cells was calculated using Flowjo 7.6.5 software and tabled. The results showed the low cellular toxic peptides and the Eu-Ln-Pn complexes show no obvious effect on the cell cycle.

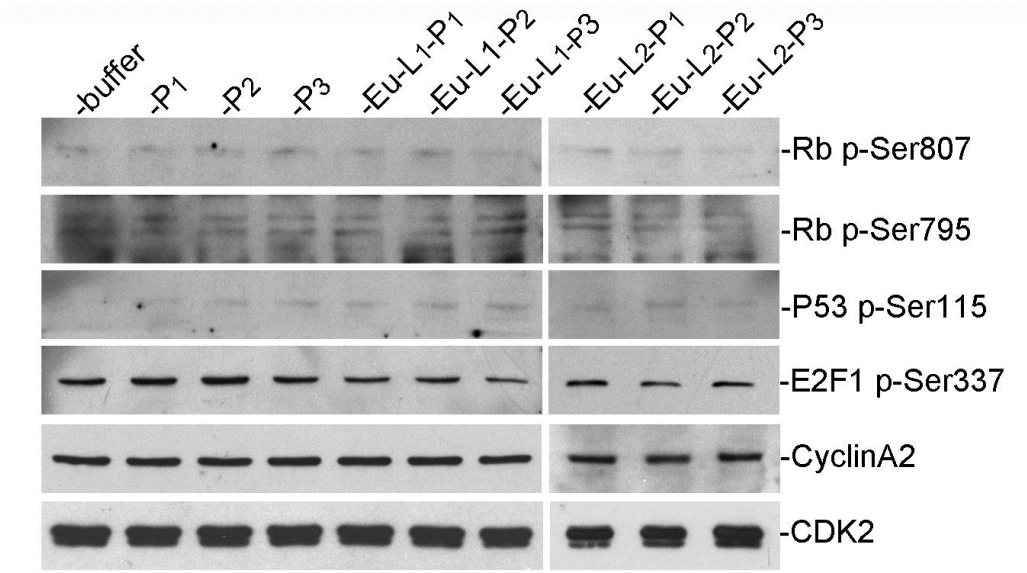


Figure S3. Western blotting analysis of CDK2/CyclinA regulated cell cycle factors in HeLa cells treated with peptides or Eu-$\mathbf{L_n}$-$\mathbf{P_n}$ complexes (20 μM each). Phosphorylation of Rb, P53 and E2F1 can well elucidate functions of CDK2/CyclinA during cell cycle. Consistent with flow cytometry analysis (**Figure S1**), the peptides and the Eu-$\mathbf{L_n}$-$\mathbf{P_n}$ complexes show no obvious effect on CDK2/CyclinA regulated substrates.

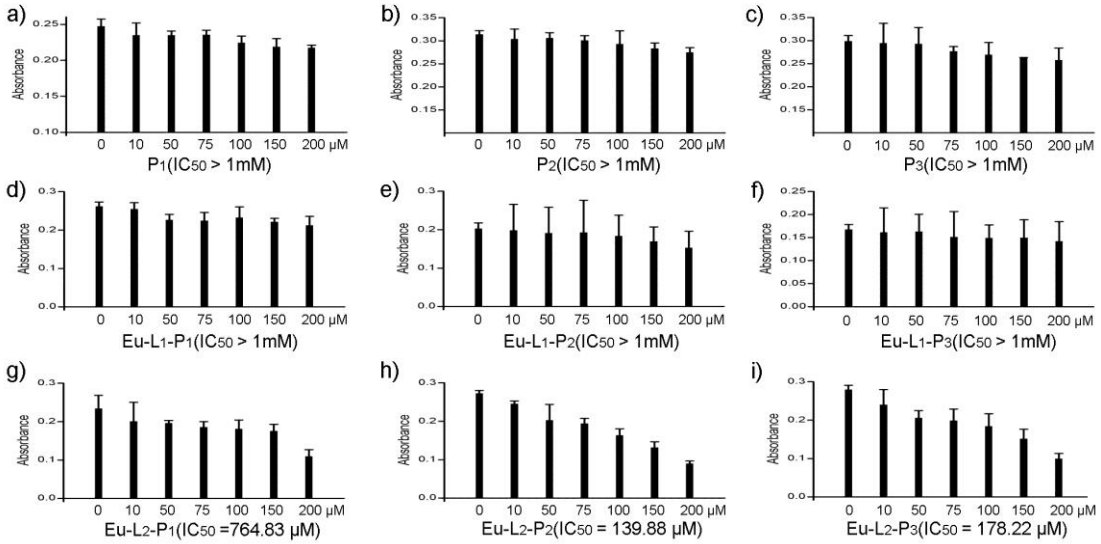


Figure S4. MTT assays show the low cellular toxicity of the peptides and the Eu-$\mathbf{L_1}$-$\mathbf{P_n}$ and Eu-$\mathbf{L_2}$-$\mathbf{P_n}$ (n = 1, 2 or 3) complexes to human cervical carcinoma HeLa cells.

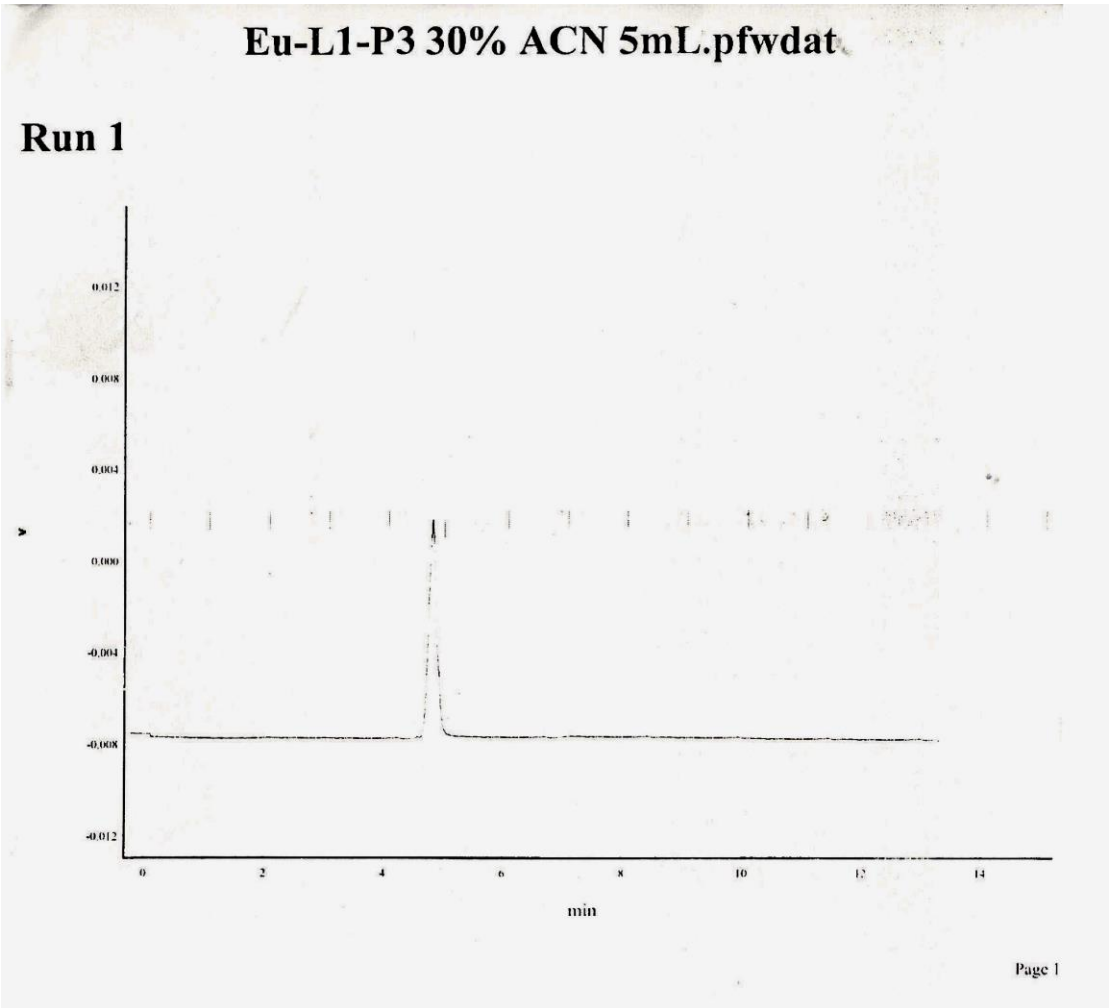


Figure S5 HPLC (CH_3CN/H_2O) of Eu-L_1-P_3