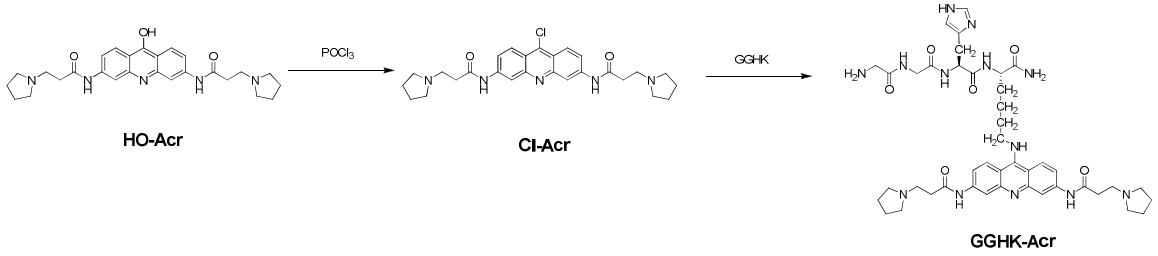
Supporting Information

Materials and Instruments.
All reagents were commercially available and of analytical grade. ^{1}H-NMR spectra were recorded at 298 K using a Bruker DPX-400 spectrometer and standard pulse sequences. Electrospray mass spectra (ESI-MS) were measured by Bruker MicroTOF, and the predicted isotope distribution patterns were calculated using the prediction program provided by the manufacturer. MALDI-TOF mass spectra were carried out by Bruker Microflex. Both HO-Acr and Cl-Acr were synthesized following the reported method,[1] and purified by HPLC before use. Peptides were synthesized by use of conventional solid state synthetic methods. All oligonucleotides were purchased from Integrated DNA Technologies.



Scheme S1. Synthesis of GGHK-Acr.

Synthesis of GGHK-Acr.
A 75.0 mg (0.152 mmol) mass of Cl-Acr was dissolved in 2 mL DMF and subsequently added to 60.1 mg (0.228 mmol) of GGHK-NH_2 in 2 mL DMF. After the addition of 100 mg DIPEA, the solution was stirred under an anaerobic atmosphere of argon for 24 h at 60°C. Semi-preparative HPLC was carried out by use of an HP 1100 Series HPLC apparatus (Isocratic: 13% acetonitrile, 0.1% TFA) with detection at 300 nm, and separation achieved with a C18 Vydac column (5 µM, 250 mm length, 10 mm I.D.). Yield: 13%. ^{1}H NMR (DMSO-d_6) δ 1.33 (m, 2H), 1.53 (m, 4H), 1.84 (m, 6H), 2.07 (m, .33 (t, 2H, J = 1.6 Hz), 2.67 (t, 2H, J = 1.7 Hz), 2.79 (m, 4H), 3.07 (m, 8H), 3.85 (d, 2H, J = 4.3 Hz), 4.14 (dd, 1H, J = 6.7, 12.1 Hz), 4.65 (dd, 1H, J = 7.5, 13.0 Hz), 4.74 (d, 2H, J = 4.3 Hz), 7.15 (s, 1H), 7.37 (s, 1H), 7.48-7.55 (m, 3H), 7.85 (m, 2H), 8.16 (d, 1H, J = 7.7 Hz), 8.34-8.47 (m, 5H), 8.84 (t, 1H, J = 5.7 Hz), 8.95 (s, 1H), 11.17 (s, 2H), 13.48 (s, 1H). HRMS (ESI) calcd for $[C_{43}H_{60}O_6N_6]^+$ $(M+H)^+$: m/z 854.4790, found 854.4772.

Synthesis of CuGGHK-Acr.
The concentration of metal-free ligand GGHK-Acr was quantified by independent UV titrations with both Cu(II) and Ni(II) at 240 nm, before further use in the synthesis of CuGGHK-Acr. A solution of CuGGHK-Acr was prepared in-situ by mixing equimolar amounts of GGHK-Acr and $CuCl_2$ in 10 mM Tris-HCl (pH = 7.4).

MALDI-TOF Mass spectrometry.
DNA samples were desalted by use of a C18 Ziptip (Millipore) before MS analysis. A matrix solution containing 0.3 M 4-hydroxypicolinic acid (HPA) and 30 mM ammonium citrate in 30% CH_3CN was prepared, and 1 µL of the matrix solution was spotted onto a Bruker ground steel 96-target microScout plate, and allowed to dry.[2] A 1 µL sample of a 1:1 DNA sample/matrix mixture was subsequently spotted onto the target plate. The A+G DNA ladder of 22G4 was prepared by the Maxam-Gilber method,[3] and were used as calibrants on a separate spot for

accurate measurement of mass spectra. A Bruker MicroFlex instrument, equipped with a gridless reflectron was used to obtain mass spectra for the DNA sample under the negative ion and reflectron mode. The pulsed ion extraction time was 1200 ns. At least 1000 shots were summed per spectrum.

MTT Assay.

Growth inhibition was measured in three human cancer cell lines (HuH-7, MCF7, Caco2) using the MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) assay. All cells were cultured in DMEM (Dulbecco's modified Eagle's medium) supplemented with 10% FBS (fetal bovine serum) in an atmosphere containing 5% CO_2 at 37°C. Approximately 3000 cells per well of the above cell lines were seeded into 96-well plates and allowed to attach for 24 h before adding the test articles. After incubation for a period of 72 h, 20 µL of MTT (5 mg/mL) in PBS was added to each well and subsequently incubated at 37 for 4 h. After the medium was carefully withdrawn, a 200 µL volume of DMSO was added to each well and the absorbance at 560 nm was measured by use of a SpectraMax M5 Multi-Mode Microplate Reader.

Senescence-Associated Beta-Galactosidase Assay.

The SA-beta galactosidase assay was performed according to a reported protocol.[4] Approximately 1×10^5 MCF7 cells were seeded onto a glass slip in a 6-well plate and allowed to attach for 24 h before the addition of test article. After a 7-day incubation period, the medium was withdrawn, and cells were rinsed twice with PBS. A solution of 3% formaldehyde in PBS was added to fix the cells at room temperature for 5 min. After the formaldehyde solution was removed, the cells were rinsed twice with PBS and stained by use of an X-gal solution (1 mg/mL, pH 6) for 16 h at 37°C as described in the reported method.[4] A light microscopy Zeiss Axioskop system with a 10× objective lens was used for phase-contrast imaging. More than 5 different fields of glass slip were randomly chosen, and over 1000 cells in the chosen fields were counted to calculate the percentage of senescent cells.

FITC-Annexin V/PI Assay.

Approximately 1×10^5 MCF7 cells were seeded into a 6-well plate and allowed to attach for 24 h, followed by a 7-day incubation period with test article. Subsequently, the cells were washed with PBS and harvested through trypsinization. Following resuspension, the cells were counted, and 1×10^5 cells were subsequently stained by FITC-Annexin V and PI from the Dead Cell Apoptosis Kit (Molecular Probes®) according to the manufacturer's protocol. Stained cells were analyzed by use of a BD LSR II Flow Cytometer System.

Real time-PCR.

1×10^5 MCF7 cells were seeded into a 6-well plate and allowed to attach for 24 h, before incubating with the indicated compounds. After 7 days, the medium was withdrawn, and the cells rinsed three times with PBS, followed by extraction of genomic DNA using a reported method[5]. The telomere length of each sample was subsequently measured by real time-PCR following a modified reported method[6]. Briefly, two PCR primers, teloF (TTGTTTGGGTTT GGGTTTGGGTTTGGGTTTGGGTT) and teloR (GGCTTGCCTTACCCTTACCCTTACCCT TACCCTTACCCT) were used to quantitate the amount of telomeric DNA nucleotide in the sample, while another two primers, 36B4F (GCAAGTGGGAAGGTGTAATCC) and 36B4R (CCCATTC TATCATCAACGGGTACAA) were used to measure the amount of a human single-copy gene (36B4) in the same sample, but in a separate well. A 10 µL solution containing 80 ng of genomic DNA extracted from MCF7 cells, and 2 µM of each primer (either for telomeric DNA or 36B4) in water was mixed with 10 µL Fast SYBR® Green Master Mix (purchased from Life technologies), yielding a final 20 µL reaction solution in each well of a 96-well PCR plate.

Standard wells containing known amounts of either teloSTD ($(TTAGG)_{14}$) or 36B4STD (AAGTGGGAAGGTGTAATCCGTCTCCACAGACAAGGCCAGGACTCGTTTGTACCCGT TGATGATAGAATGGG), 80 ng pUC19 plasmid DNA and the same amount of primers and SYBR® Green Master Mix. Real-time PCR was performed by use of an Applied Biosystems 7900HT Fast Real-Time PCR System using the below cycling conditions (optimized by manufracturer): 2 min at 95°C, then 20 sec at 95°C, followed by 40 cycles at 95°C for 15 sec and 60°C for 1 min, followed by a dissociation (or melt) curve. The amount of telomeric DNA or 36B4 in each sample was calculated from the standard plot of telomeric DNA or 36B4 respectively. To correct for difference between samples, 36B4 were used as an internal reference to normalize the amount of telomeric DNA in each sample. Relative telomere length was obtained by comparison to the telomere length of untreated MCF7 cells. All experiments were performed in triplicate.

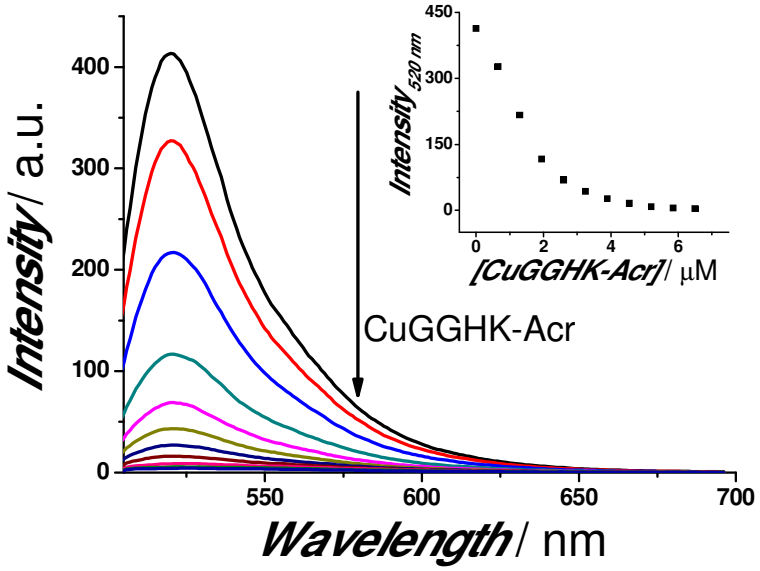


Figure S1. Fluorescence titration of CuGGHK-Acr to a solution of 22G4 in 10 mM Tris-HCl, 100 mM KCl, pH = 7.4. λ_{ex} = 494 nm. Insert: Change of emission intensity at 520 nm when CuGGHK-Acr was added.

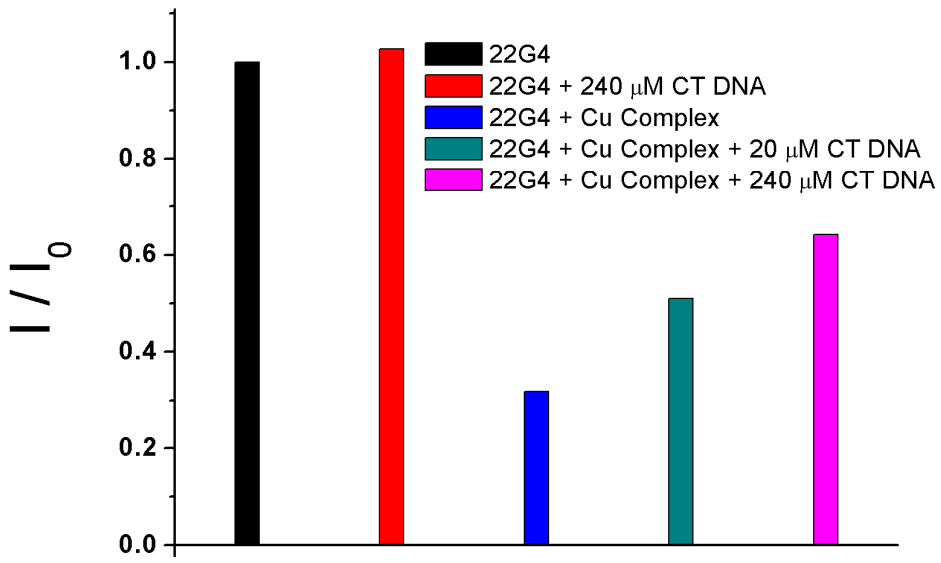


Figure S2. Relative emission intensity at 520 nm (ex 495 nm) in the presence or absence of CT-DNA. [22G4] = 2 μM; [CuGGHK-Acr] = 3 μM.

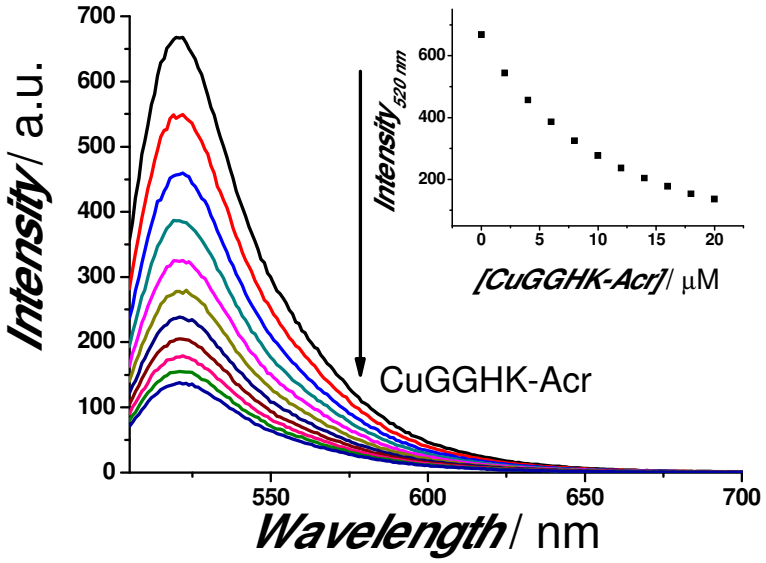


Figure S3. Fluorescence titration of CuGGHK-Acr to a solution of ds22telo in 10 mM Tris-HCl, 100 mM LiCl, pH = 7.4. λ_{ex} = 494 nm. Insert: Change of emission intensity at 520 nm when CuGGHK-Acr was added.

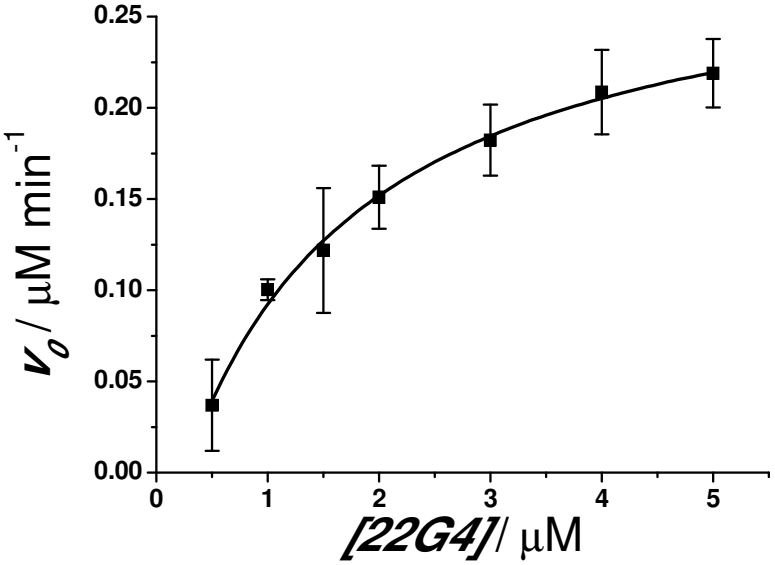


Figure S4. Michaelis–Menten kinetics. [CuGGHK-Acr] = 100 nM, [H_2O_2] = 0.2 mM, [ascorbate] = 0.2 mM, in 10 mM Tris-HCl, 100 mM KCl, pH = 7.4.

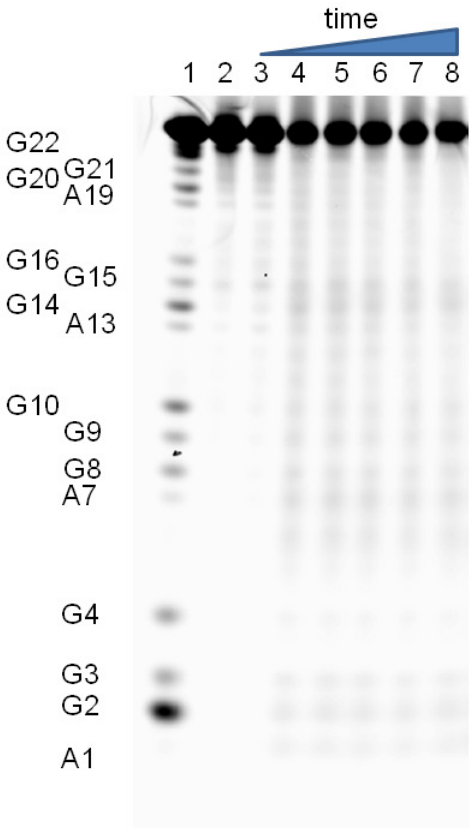


Figure S5. Denaturing polyacrylamide gel electrophoresis (15% PAGE) showing the cleavage of 22G4 by CuGGH in 10 mM tris-HCl and 100 mM KCl at 37℃. Lane 1: A+G DNA Ladder; Lane 2: control, DNA only; Lanes 3 to 8: CuGGH + DNA + ascorbate + H_2O_2 (0 min, 30 min, 60 min, 90 min, 120 min, 180 min). [22G4] = 10 μM (strand concentration), [CuGGH] = 2 μM, [ascorbate] = 1 mM, [H_2O_2] = 1 mM.

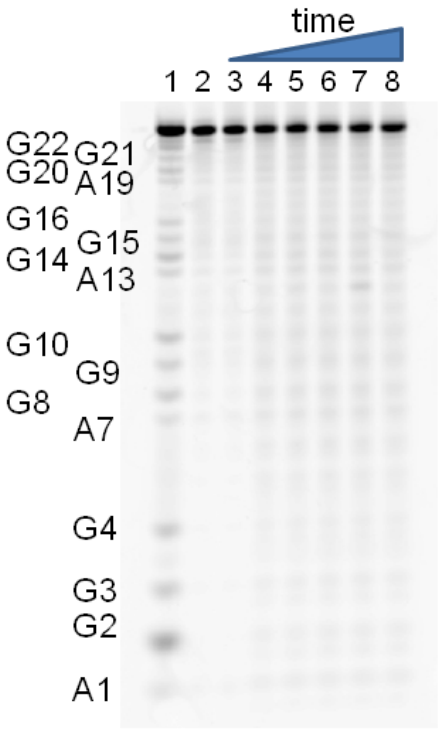


Figure S6. 15% Denaturing polyacrylamide gel electrophoresis showing the cleavage of 22G4 by CuGGHK-Acr in 10 mM tris-HCl without monovalent metal ion at 37℃. Lane 1: A+G DNA Ladder; Lane 2: control, DNA only; Lanes 3 to 8: CuGGHK-Acr + DNA + ascorbate + H_2O_2 (0 min, 30 min, 60 min, 90 min, 120 min, 180 min). [22G4] = 10 μM (strand concentration), [CuGGHK-Acr] = 2 μM, [ascorbate] = 1 mM, [H_2O_2] = 1 mM.

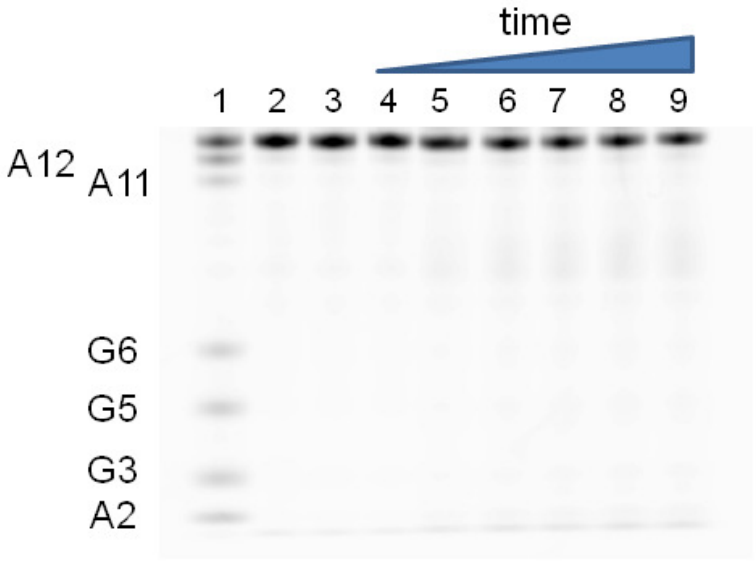


Figure S7. Denaturing polyacrylamide gel electrophoresis (25% PAGE containing 15% formamide) showing the cleavage of ds12Telo by CuGGHK-Acr in 10 mM tris-HCl and 100 mM LiCl at 37℃. Lane 1: A+G DNA Ladder; Lane 2: control, DNA only; Lane 3: DNA + ascorbate + H_2O_2; Lanes 4 to 9: CuGGHK-Acr + DNA + ascorbate + H_2O_2 (0 min, 30 min, 60 min, 90 min, 120 min, 180 min). [ds12Telo] = 10 μM (strand concentration), [CuGGHK-Acr] = 2 μM, [ascorbate] = 1 mM, [H_2O_2] = 1 mM.

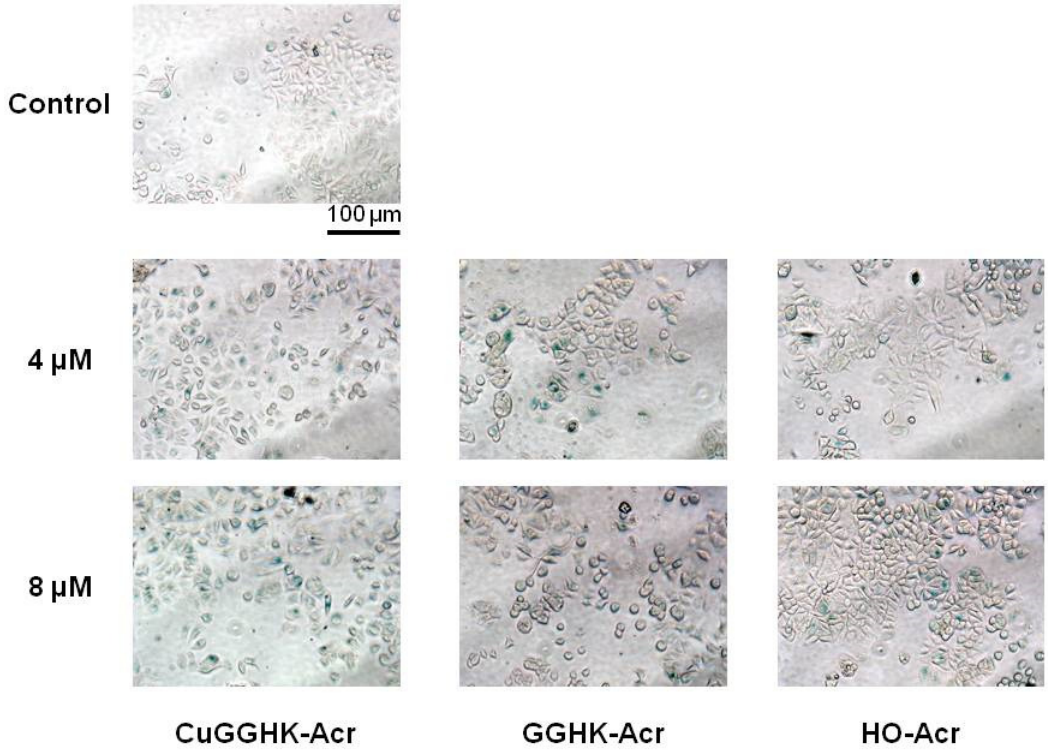


Figure S8. Phase-contrast imaging of MCF7 cells revealing cellular senescence by a senescence-associated beta-galactosidase assay after a 7-day treatment period with the indicated concentration of CuGGHK-Acr, GGHK-Acr or HO-Acr. Senescing cells are colored green by X-gal.

References.

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