Supplementary Figure 1. A synthetic route of dual stimuli-responsive hybrid anticancer drug QCA.
Supplementary Figure 2. $^1$H NMR spectrum of 1.
Supplementary Figure 3. $^1$H NMR spectrum of 2.
(A) 

(B)
Supplementary Figure 4. Characterization of QCA. (A) $^1$H NMR, (B) $^{13}$C NMR, (C) LC-MS spectroscopy.
Supplementary Figure 5. A synthetic route of $Q_1$ and its $^1$H NMR spectrum.
Supplementary Figure 6. Degradation of QCA in cancer cell specific environment associated with H$_2$O$_2$ and acidic pH.
Supplementary Figure 7. LC-MS/MS analysis of GSH and cinnamaldehyde in lysates of DU145 cells treated with QCA. Detection of GSH at \( m/z = 308 \rightarrow 162 \), Detection of cinnamaldehyde at \( m/z = 133 \rightarrow 114 \).
Supplementary Figure 8. Depletion of GSH in NIH3T3 cells treated with QCA. Cells (5×10⁵/well) were treated with Q₁ or QCA (50 or 100 μM) for 1.5 h and lysed with Triton-X lysis buffer. The content of GSH in the cell lysates was quantitatively measured using Elman’s reagent by measuring the absorbance at 405 nm. Percentage of GSH content from treated cells were compared to the basal GSH content measured in untreated cells.
Supplementary Figure 9. Comparison of the redox status in different cells. (A) The level of cellular GSH. (B) The level of H$_2$O$_2$. Cells were cultured in a 24 well-plate with the same density for 24 h. The content of GSH in cells cultured was quantitatively determined using Elman’s reagent. The level of H$_2$O$_2$ was determined by the Amplex red assay.
Supplementary Figure 10. ROS generation in DU145 cells treated with various formulations. (A) Inhibition of QCA-induced ROS generation by catalase (CAT). (B) Representative confocal fluorescent micrographs of DU145 cells treated with various formulations. a) untreated, b) 100 μM of cinnamaldehyde, c) 100 μM of Q1, d) 50 μM of QCA, e) 100μM of QCA, f) 100 μM of QCA+CAT. For the detection of ROS, cells were stained with DCFH-DA (dichlorofluorescein-diacetate) as a probe for intracellular ROS.
Supplementary Figure 11. Cytotoxicity of QCA against different cell lines determined by MTT assay. (A) DU145 cells, ***p<0.001 relative to the untreated group, †††p<0.001 relative to the QCA 100 (n=4, ±S.D). (B) SW620 cells, ***p<0.001 relative to the untreated group, (n=4, ±S.D). (C) NIH3T3 cells. Statistical comparisons between groups were made using one-way ANOVA (GraphPad Prism 6.0).
Supplementary Figure 12. Western blot assay of cells treated with various formulations.
Supplementary Figure 13. Induction of apoptosis of DU145 and SW620 cells. Cells were treated with various formulations for 12 h and stained with Annexin V-FITC and Propidium Iodide. A total of $1.0 \times 10^4$ cells stained were subjected to flow cytometric analysis to determine the distribution of cells.
Supplementary Figure 14. LC-MS/MS analysis of GSH and cinnamaldehyde in tumors and tissue lysates. Detection of GSH at \( m/z = 308 \rightarrow 162 \), Detection of cinnamaldehyde at \( m/z = 133 \rightarrow 114 \).
Supplementary Figure 15. Histological studies of tumor tissues. (A) H&E staining (×400), (B) TUNEL staining of tumor tissues after treatment (×200).
Supplementary Figure 16. Histology of liver and heart tissues of tumor-bearing mice. (A) H&E staining (×200), (B) TUNEL staining (×630). A therapeutically relevant dose of doxorubicin (10 mg/kg, i.p.) was used as a positive control because it is known to cause hepatic and cardiac toxicity by inducing apoptosis. Livers were removed five days after doxorubicin treatment.
Supplementary Figure 17. *In vivo* toxicity studies of QCA using normal mice. (A) The level of ALT, (B) H&E staining of heart and liver tissues from QCA-treated mice (×200), (C) TUNEL staining of heart and liver tissues from QCA-treated mice (×630). A therapeutically relevant dose of doxorubicin (10 mg/kg, *i.p.*) was used as a positive control.