Supporting Information

Targeting Heterogeneous Tumors Using a Multifunctional Molecular Prodrug

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Table of Contents

Supplemental Methods
Synthetic Scheme
Synthetic Procedures
Figures S1-S24
References
Supplemental Methods

Synthesis and characterization

All compounds used in this investigation were synthesized according to the procedures summarized in the synthetic scheme (Supplementary Scheme 1). All chemicals and solvents used for synthesis were purchased from Sigma-Aldrich, Alfa, or TCI-Korea and used as such without further purification. Moisture sensitive reactions were generally carried out under argon gas. NMR spectral analyses were performed on Bruker NMR (500 MHz for \(^1\)H, 125 MHz for \(^{13}\)C) or Varian (400 MHz for \(^1\)H, 100 MHz for \(^{13}\)C) instruments at room temperature using CDCl\(_3\), MeOD, or DMSO-\(d_6\) as the solvents and TMS as the internal standard. Chemical shifts (\(\delta\)) are recorded in ppm and coupling constants are given in Hz. High-resolution mass spectra were recorded on an Ion Spec Hi Res ESI mass spectrometer. HPLC analyses were performed on a YL9101S (YL-Clarity) instrument equipped with a reverse-phase column (C18, 5 mm, Waters). The eluent used for analysis (K1) was a water-acetonitrile gradient (0-35 min; acetonitrile from 5% to 85%) with a 0.5 mL/min flow rate. For K2 analysis, water-acetonitrile gradient (0-35 min; acetonitrile from 10% to 80%; flow rate 1 mL/min) was used. A UV-vis detector (365 nm) was used.

Stability of K1 in human serum

Human serum (H3667) were purchased from Sigma Aldrich. For serum stability of K1 and K2, we monitored the change in absorbance of 20 \(\mu\)M solutions of K1, K2, and SN-38, respectively, as a function of serum dose (1, 10 and 30%) in phosphate buffer (pH 7.4, 2% DMSO) for 0 h to 24 h at 37 °C. Absorbance changes were monitored by UV/Vis spectroscopy at 365 nm (JASCO, Inc., Japan).

Human normal and cancer cell lines

Human cancer cell lines, NHDF (normal human dermal fibroblast) and MCF10A (non-cancerous) cells were purchased from American Type Culture Collection (Rockville, MD, USA) or Korea Cell Line Bank (Seoul, South Korea). The cells were maintained in Dulbecco's modified Eagle's medium supplemented with 10% FBS (GIBCO BRL) at 37°C in a humidified atmosphere with 5% CO\(_2\).

Reagents and siRNA transfection

NAC (N-acetyl-L-cysteine), SN-38 (7-Ethyl-10-hydroxycamptothecin), H\(_2\)O\(_2\), and LPS (Lipopolysaccharide) were purchased from Sigma-Aldrich. Transfection of si-RNA control or siRNA for GSH knockdown was performed using a siRNA-Oligofectamine mixture or electroporation (Neon transfection system; Invitrogen).

Semi-quantitative RT-PCR analysis

Our strategy for the semi-quantitative RT-PCR analysis was previously described.\(^{1,2}\) Briefly, 1 \(\mu\)g of total cellular RNA was converted to cDNA by reverse transcription using MoMuLV reverse
transcriptase and random hexamer primers (Invitrogen). PCR was initially performed over a range of cycles (30–45 cycles) by using diluted cDNA, and 1:4 diluted cDNA (12.5 ng per 50 µl of PCR) undergoing 24–38 cycles was found within the logarithmic phase of amplification with primers. Nucleotide sequences of primers, including an endogenous expression standard gene GAPDH, are available upon request. PCR was performed in 1.5 mM MgCl2-containing reaction buffer. Ten 10 µl of the resulting PCR products were resolved on 2% (wt/vol) agarose gels.

**Immunoblotting assay**

Immunoblot analyses were performed using antibodies specific for COX-2 (4842), cleaved PARP (5625), cleaved caspase-3 (9664), phospho-AKT (4060), AKT (4685), phosphor-p38 (4511), p38 (8690), phosphor-p65 (3031), p65 (8242), phosphor-IκBα (2859) purchased from Cell Signaling Technology or Santa Cruz Biotechnology. Anti-tubulin antibodies were obtained from Sigma-Aldrich. Briefly, cells were washed twice in cold PBS and lysed in RIPA (radioimmunoprecipitation assay buffer) containing 25 mM Tris·HCl (pH 7.5), 200 mM NaCl, 0.1% SDS, 1% Triton X-100, 1% sodium deoxycholate, and protease inhibitor mixture. After sonication, the lysate was centrifuged, and the supernatant was recovered and loaded on a 12% SDS–polyacrylamide gel for electrophoresis.

**Cell viability and growth assay**

Cells were seeded in 24 well plates at 2 × 10^5 cells per well and were allowed to adhere for at least 24 h. Growth medium was replaced with medium containing K1 and/or K2 at the indicated concentrations and times, and cell viability was assessed via the WST-1 assay (Roche Diagnostics, Laval, QC, Canada). For the colony formation assay, cells were seeded in 6-well plates. After 24 h, cells were maintained in the presence of each compound or vehicle dimethyl sulfoxide (DMSO) for 8 days. Colonies were fixed with methanol for 10 min and stained with 0.05% crystal violet in 20% ethanol.

**Cell viability in 3D culture**

3D cell spheroids were formed in the Cellrix 3D culture system (MediFab Co., Ltd, Seoul, South Korea). Casting gel plates were generated with the manufacturer's casting gel solution with 5 × 10^4 LoVo cells per well being embedded into the casting gel. After gelation, each LoVo tumor cell spheroid was transferred to a well within a 96 well plate using DMEM medium. Growth medium was replaced with medium containing K1 and/or K2 at the indicated concentrations and times, and cell viability was assessed via the Cellrix Viability Assay kit (MediFab Co., Ltd). All experiments were performed following 24 h of cell growth and repeated at least 3 times.

**ELISA assay**

The cells were seeded in 12-well plates (1 × 10^5 cells/well) in 1% FBS culture medium. After 24 h, cells were treated with each compound for the indicated dose or time course. The supernatant
from the cells were collected at the indicated time points after treatment of compounds and diluted 50-fold. IL-6, IL-10, TNF-α, and PGE2 were measured in the supernatant following a protocol from an ELISA kit purchased from R&D system (R&D Systems, Minneapolis, MN, USA). In order to normalize, cells were counted using trypan blue exclusion using the BioRad cell counter.

*In vivo and ex vivo fluorescent imaging*

For animal fluorescent imaging, six-week-old immunodeficient nude mice (nu/nu) (Orient Bio, Inc.) were used. To analyze tumor target specificity and the organ distribution of K1 *in vivo* and *ex vivo*, SW620 cells (1×10⁷) were injected subcutaneously into the mouse hind flank. The mice were treated with vehicle (DMSO) or K1 (5 mg/kg/d) by I.P. injection. After 12 hours of treatment, the animals were euthanized via CO₂ asphyxiation. The xenograft tumors were excised and photographed. Ex vivo fluorescence images of the tumors and organs of the control and injected mice were recorded and quantified using a Maestro2 instrument (excitation and emission wavelengths: 500 and 650 nm, respectively). The fluorescence images and auto-fluorescence were then deconvoluted using the software provided with the instrument (Maestro software ver.2.4, CRi, Woburn, MA, USA) using the multiexcitation spectral analysis function.

*Animal studies*

Six-week-old immunodeficient nude mice (nu/nu) mice (Orient Bio, Inc., Korea) were maintained in pressurized ventilated cages under conditions of repeated controlled illumination (12 h dark; 12 h light) with ad libitum access to sterilized water and food (Cat no:1314Fort, ALTROMIN company, Germany). SW620 cells (1 × 10⁷) in 200 µl PBS were injected subcutaneously into the hind flank of each mouse. When the tumor volumes reached 80-100 mm³, the mice were randomized into 3 treatment groups; K1, SN-38 and vehicle control (DMSO) (n = 5 per group). The mice were injected intraperitoneally with K1 (5 mg/kg/d), SN-38 (5 mg/kg/d), or vehicle (DMSO) once every five days for three weeks. Tumor growth was monitored periodically, and the tumor volume (V) was calculated by using the modified ellipsoidal formula: \( V = \frac{1}{2} \times \text{length} \times \text{width}^2 \). After 15 days of treatment, animals were euthanized by CO₂ asphyxiation. The xenograft tumors were excised and photographed. Each animal was subject to a complete post-mortem examination and an effort was made to minimize the number of animals used and their suffering. All animal studies were performed with the approval of the Korea University Institutional Animal Care and Use Committee and in accord with the Korean Animal Protection Act.

*Statistical analyses*

Statistical significance was determined using a one-way ANOVA test with post-hoc Bonferroni analysis. In the figures, different letters are used to denote data points and sets that are statistically differentiated (p < 0.05).
Synthetic Scheme

Scheme S1. Reagent and conditions. a) EDC.HCl, HOBr, DMF, N-Boc-1,4-Butanediamine, DMAP, 12 h; b) TFA, CH₂Cl₂, 12 h; c) TEA, 60 °C, 12 h; d) EDC.HCl, HOBr, DMAP, SN-38, DMF, 12 h; e) TFA, CH₂Cl₂, 24 h; f) EDC.HCl, HOBr, DMAP, 2, DMF, 12 h.

Synthetic Procedures

Compound 1

Compound 1 was synthesized in accordance with a previously reported procedure.³ To a stirred solution of indomethacin (0.21 g, 0.588 mmol) in anhydrous DMF (10 mL), EDC•HCl (0.135 g, 0.705 mmol), and HOBr (0.095 g, 0.705 mmol) was added and mixture was stirred at RT for 30 min. tert-Butyl (4-aminobutyl)carbamate (320 mg, 1.7 mmol) and DMAP (catalytic) were added and resulting mixture was stirred overnight. Water (20 mL) was added to the reaction mixture and aqueous solution was extracted with ethyl acetate (3 X 30 mL). The combined organic layer was separated, dried over anhydrous sodium sulfate, filtered and evaporated under reduced pressure. The crude mixture was purified by column chromatography using silica gel with a eluant gradient of 2-5% MeOH in CH₂Cl₂ to obtain compound 1 as yellow solid (145 mg, yield 46 %).¹H NMR (500 MHz, CDCl₃): δ 1.41 (s, 9H), 1.43 (br s, 4H), 2.38 (s, 3H), 3.03-3.07 (m, 2H), 3.19-3.23 (m, 2H), 3.63 (s, 2H), 3.82 (s, 3H), 4.55 (br s, 1H), 5.73 (br s, 1H), 6.68-6.71 (m, 1H), 6.85-6.89 (m, 1H), 7.47-7.50 (m, 2H), 7.66-7.68 (m, 2H). ¹³C NMR (125 MHz, CDCl₃): δ 13.31, 26.66, 27.45, 28.40, 32.23, 39.27, 40.01, 40.02, 55.77, 79.13, 101.06, 112.09, 112.96, 115.11, 129.21, 130.38, 130.91, 131.18, 136.53, 156.03, 156.20, 168.33, 169.93. MS (ESI): m/z calcd. for C₂₈H₃₄ClN₃O₅: 527.22 Found: 550.20 [M + 23]+.
To a stirred solution of compound 1 (0.130 g, 0.264 mmol) in CH₂Cl₂ (10 mL), TFA (0.5 mL) was added and mixture was stirred under an inert atmosphere overnight. After completion, the mixture was evaporated under reduced pressure to obtain compound 2. The TFA salt of 2 appeared as a brown solid and was used directly in next step. MS (ESI): m/z calcd. for C₂₃H₂₆ClN₃O₃: 427.17 Found: 428.17 [M + 1]+.

**Compound 3**

2-Mercapto propionic acid (0.5 g, 4.71 mmol) and tert-Butyl acrylate (0.602 g, 4.71 mmol) was taken in round bottom flask. To this mixture, triethylamine (TEA, 0.5 mL) was added and mixture was stirred at 45 °C for 48 h. The mixture was cooled, diluted with methylene chloride (100 mL), washed with water (100 mL). The organic layer was separated, dried over anhydrous sodium sulfate, filtered and evaporated under reduced pressure to obtain compound 3 as colorless oil used as such for further steps. ¹H NMR (500 MHz, CDCl₃): δ 1.45 (s, 9H), 1.47 (s, 3H), 2.54-2.57 (m, 2H), 2.85-2.97 (m, 2H), 3.43-3.48 (m, 1H). ¹³C NMR (125 MHz, CDCl₃): δ 16.86, 26.79, 28.09, 29.71, 35.56, 40.90, 81.12, 171.08.

**Compound K2**

To a solution of compound 3 (0.10 g, 0.426 mmol) in anhydrous DMF (5 mL), EDC•HCl (0.098 g, 0.51 mmol) and HOBt (0.068 g, 0.51 mmol) were added and mixture was stirred at room temperature (RT) for 30 min. SN-38 (0.166 g, 0.426 mmol) and DMAP (catalytic) was added and mixture was stirred at RT for additional 24 h. After completion, the mixture was diluted with CH₂Cl₂ (100 mL), washed with aqueous sodium bicarbonate (100 mL X 3). The combined organic extract was separated, dried over anhydrous sodium sulfate and concentrated and reduced pressure. The crude mixture was purified by flash chromatography using silica gel with an eluant of 5 % MeOH/ CH₂Cl₂ to obtain compound K2 as off-white solid (0.200 g, yield 77%). ¹H NMR (500 MHz, CDCl₃): δ 1.04 (t, 3H, J = 7.35 Hz), 1.43 (m, 2H), 1.48 (s, 9H), 1.64 (d, 3H, J = 7.15 Hz), 1.87-1.93 (m, 3H), 2.61-2.64 (m, 2H), 3.00-3.06 (m, 2H), 3.17-3.19 (m, 2H), 3.72-3.73 (m, 2H), 5.27 (s, 2H), 5.31 (d, 1H, J = 16.3 Hz), 5.75 (d, 1H, J = 16.2 Hz), 7.59-7.64 (m, 1H), 7.65 (m, 1H), 7.90 (m, 1H), 8.26 (d, 1H, J = 9.2 Hz). ¹³C NMR (125 MHz, CDCl₃): δ 8.07, 14.24, 17.24, 23.34, 26.97, 26.98, 28.26, 28.30, 31.82, 35.83, 41.47, 49.59, 66.41, 73.07, 81.39, 98.42, 114.66, 118.91, 125.29, 127.56, 127.61, 132.31, 145.67, 146.84, 147.52, 149.78, 150.43, 152.05, 157.77, 171.06, 171.58, 173.93. MS (ESI): m/z calcd. for C₃₂H₃₆N₂O₈S: 608.22 Found: 607.20 [M - 1]⁺.

**Compound 4**

Compound K2 (0.150 g, 0.246 mmol) was taken in anhydrous CH₂Cl₂ (50 mL). TFA (1 mL in 10 mL CH₂Cl₂) was added to the solution dropwise and resulting mixture was stirred at RT overnight. After completion (TLC), the solvent was evaporated under reduced pressure to obtain pale yellow solid used as such for next step.

**Compound K1**
To a solution of compound 4 (0.12 g, 0.217 mmol) in anhydrous DMF (10 mL), EDC•HCl (0.05 g, 0.238 mmol) and HOBt (0.035 g, 0.238 mmol) were added and mixture was stirred at RT for 30 min. Compound 2 (0.093 g, 0.217 mmol) and DMAP (catalytic amount) were added and mixture was stirred overnight at RT. After completion, the mixture was diluted with CH₂Cl₂ (100 mL), washed with aqueous sodium bicarbonate solution (100 mL X 3) and extracted with CH₂Cl₂ (3 X 100 mL). The organic layer was separated, dried over anhydrous sodium sulfate, concentrated under reduced pressure and purified by flash chromatography using and eluent gradient of 2-5% MeOH in CH₂Cl₂ to obtain compound K1. The final product was precipitated from CH₂Cl₂ solution with diethyl ether and dried as off-white solid. (0.06 g, yield 30 %). ¹H NMR (500 MHz, CDCl₃): δ 1.03 (t, 3H, J = 7.3 Hz), 1.39 (t, 3H, J = 7.5 Hz), 1.42-1.50 (m, 5H), 1.64 (d, 3H, J = 7.2 Hz), 1.85-1.94 (m, 2H), 2.33 (s, 3H), 2.58 (t, 2H, J = 7.1 Hz), 3.05-3.18 (m, 4H), 3.20-3.27 (m, 4H), 3.64 (m, s, 2H), 3.71-3.76 (m, 1H), 3.79 (s, 3H), 5.27 (s, 2H), 5.32 (d, 1H, J = 16.3 Hz), 5.73 (d, 1H, J 16.3 Hz), 6.13 (m, 1H, NH), 6.41 (m, 1H, NH), 6.66-6.68 (m, 1H), 6.82-6.87 (m, 2H), 7.46-7.50 (m, 2H), 7.58-7.60 (m, 1H), 7.62-7.65 (m, 2H), 7.73 (s, 1H), 7.88 (m, 1H), 8.26 (m, 1H). ¹³C NMR (125 MHz, CDCl₃): δ 0.20, 7.97, 13.40, 14.18, 17.26, 23.43, 26.27, 26.80, 27.56, 31.78, 31.83, 36.34, 39.45, 39.49, 41.81, 49.90, 56.08, 66.34, 73.02, 76.65, 76.91, 99.57, 99.59, 101.25, 111.95, 111.97, 112.36, 114.89, 115.29, 119.03, 125.71, 127.63, 127.79, 129.49, 130.19, 131.14, 131.44, 131.77, 133.46, 136.94, 140.04, 146.55, 149.96, 156.39, 157.93, 168.61, 171.71, 172.34, 173.93. MS (ESI): m/z calcd. for C₅₁H₇₂ClN₅O₁₀S: 962.31 Found: 962.15 [M + 1]⁺.
**Figure S1.** High performance liquid chromatogram of K1 (10 µM) recorded at 0 h and 24 h after incubation in phosphate saline buffer (PBS, pH = 7.4) at 37 °C.

**Figure S2.** UV-vis absorbance spectra of K1 (10 µM) recorded upon treatment with 5 mM GSH (A) and 0.125 mM H₂O₂ (B) in PBS (2% DMSO v/v) at 37 °C.
Figure S3. Time dependent fluorescence intensity changes (at 540 nm) of K1 (10 µM) incubated with various concentrations of (A) GSH and (B) H₂O₂ in phosphate buffered saline (PBS, pH = 7.4) at 37 °C.

Figure S4. Mass spectrum of the intermediate formed upon reaction of K1 (10 µM) with GSH (5 mM) at 37 °C after 10 h.
Figure S5. Mass spectrum of the intermediate formed upon reaction of K1 (10 µM) with H2O2 (10 µM) at 37 °C for 4 h.
Figure S6. UV-vis absorbance spectra of K2 (10 µM) recorded before and after incubation with (A) GSH (5 mM) and (D) H₂O₂ (0.25 mM) for 4 h (PBS, 2% DMSO v/v) at 37 °C. Time dependent fluorescence intensity change corresponding to SN-38 release seen upon incubation of K2 (10 µM) with (B) GSH (5 mM, 30 min) and (E) H₂O₂ (0.25 mM, 10 min) in PBS (37 °C, λex = 365 nm, Slit width 1.5/3). Time dependent fluorescence intensity changes (at 540 nm) of K2 (10 µM) incubated with various concentrations of (C) GSH and (D) H₂O₂ in phosphate saline buffer (PBS, pH = 7.4) at 37 °C. High-performance liquid chromatogram of K2 (10 µM) recorded at different time intervals (G); stability tests following treatment with (H) GSH (5 mM), (I) H₂O₂ (0.25 mM), and SN-38 in PBS (37 °C).
Figure S7. Stability data for prodrugs K1 and K2. Absorbance changes at 365 nm for K1 (20 µM) (A-C) and K2 (20 µM) (D-F) after incubating with human serum (1%, 10% and 30%) in PBS (2% DMSO v/v) at 37 °C. The red line corresponds to free SN-38 (20 µM, as positive control) in human serum (1%, 10% and 30%) in PBS (2% DMSO v/v) at 37 °C.

Figure S8. Western blot analysis of COX-2 protein expression levels in the non-cancer cell (MCF10A), normal fibroblast cell (NHDF) and colon cancer cells (Caco2, DLD-1, SW620, HT-29, LoVo, and SW480).
Figure S9. Effect of K1 on tumor cell viability and its association with expression status of COX-2 levels in SW620 cancer cells. Figures showed the role of Cox-2 in K1-mediated cytotoxicity (upper) and siRNA-mediated knockdown of COX-2 expression (lower).
Figure S10. Growth-inhibiting effect of K1 under conditions of intracellular oxidative or reductive stress. (A) Colony-forming assay showing K1 and SN-38 effect on cancer cell growth. LoVo cells transfected with either GSH siRNA (siGSH) or control siRNA (siControl) were treated with NAC (50 µM) and indicated doses of K1 or SN-38 for 48 h. Cancer cell colonies were stained with crystal violet solution. (B) RT-PCR analysis of GSH mRNA levels in LoVo cells transfected with siGSH and siControl.
**Figure S11.** Growth-inhibiting effect of K1 in microenvironments characterized by oxidative stress or reductive stress. Cell viability determined by means of a Cellrix viability assay after treatment with K1 on LoVo tumor cell spheroid in response to siGSH transfection or NAC treatment. Statistical significance was determined using a one-way ANOVA test with a post-hoc Bonferroni analysis. Different letters signify data that are statistically differentiated (p < 0.05).

**Figure S12.** Comparative analysis of the cytotoxicity of K1, SN-38, indomethacin, and SN-38 plus indomethacin in SW620 cells. SW620 cells were treated with DMSO, indomethacin, SN-38, SN-38 plus Indomethacin, or K1 for 48 h at the indicated concentrations. Cell viability was assessed by means of a WST assay (mean ± SD, n = 3, * p < 0.05).
Table S1. Drug concentrations resulting in 50% inhibition of cell population (IC$_{50}$) were determined from the drug dose-response curves. SW620 cells were treated with DMSO, Indomethacin, SN-38, SN-38 plus Indomethacin, or K1 for 48 h at the indicated concentrations. Experiments were carried out in triplicate.

<table>
<thead>
<tr>
<th></th>
<th>K1</th>
<th>Indomethacin</th>
<th>SN-38</th>
<th>SN-38 + Indomethacin</th>
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<td>IC$_{50}$ (nM) in SW620</td>
<td>4.25±0.036</td>
<td>125.33±0.970</td>
<td>19.82±0.147</td>
<td>12.7±0.154</td>
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Figure S13. Excised xenograft tumor weight. Differences in tumor weight between DMSO, SN-38, and K1-injected mice were statistically significant, *, p < 0.05; **, p < 0.01; n = 5/group.
Figure S14. Body weight change in nude mice bearing SW620 xenograft tumors upon treatment with DMSO (control), SN-38, and K1. Blue (DMSO), green (K1), and red (SN-38).

Figure S15. AST and ALT activity levels in the blood serum of DMSO (control), SN-38, and K1-treated mice groups. (mean ± SD; * p < 0.05).
Figure S16. Serum creatinine activity levels of DMSO (control), SN-38, and K1-treated mice groups. (mean ± SD; ** p < 0.01).
Figure S17. $^1$H NMR spectrum of compound 1 (CDCl$_3$)
Figure S18. $^{13}$C NMR spectrum of compound 1 (CDCl$_3$)
Figure S19. ESI mass spectrum of compound 1 (CDCl₃)
Figure S20. ESI mass spectrum of compound 2
Figure S21. $^1$H NMR spectrum of compound 3 (CDCl$_3$)
Figure S22. $^{13}$C NMR spectrum of compound 3 (CDCl$_3$)
Figure S23. $^1$H NMR spectrum of compound K2 (CDCl$_3$).
Figure S2. $^{13}$C NMR spectrum of compound K2 (CDCl$_3$)
Figure S25. ESI mass spectrum of compound K2
Figure S26. $^1$H NMR spectrum of compound K1 (CDCl$_3$). The broad peak at 5.03 ppm corresponds to CDCl$_3$ (water) interacting with the acidic protons of K1.
Figure S27. $^{13}$C NMR spectrum of compound K1 (CDCl$_3$)
Figure S28. ESI mass spectrum of compound K1
References

