Supplementary Figure S1. Chemical synthesis of SV119-Asp, the precursor for the generation of peptide conjugates.

Fmoc-Asp-O-tBu was purchased from EMD Biosciences, Inc. (California, USA). A solution of 1,3-dicyclohexylcarbodiimide (DCC, 390 mg, 1.89 mmol) in CH_2Cl_2 (2 mL) was added dropwise to a cold solution of Fmoc-Asp-O-tBu (630 mg, 1.53 mmol)) and N-hydroxysuccinimide (220 mg, 1.91 mmol) in CH_2Cl_2 (5 mL). After stirring at room temperature for 1 h, a solution of amine **SV119** (780 mg, 1.93 mmol) was slowly added. The mixture was stirred at room temperature for 4 h and the solid was filtered off. The organic layer was washed with water and then saturated K_2CO_3, dried over Na_2SO_4 and evaporated. The resulting residue was purified by column chromatography (5% CH_3OH in CH_2Cl_2) to give the t-butyl ester analog (840 mg, 68% yield). This ester was stirred with CF_3COOH (8 mL) in CH_2Cl_2 (8 mL) at room temperature for 1 h and evaporated. The resulting residue was purified by column chromatography (8% CH_3OH in CH_2Cl_2) to give **SV119-Asp** as white powder (700 mg, 87% yield). FAB/HRMS: 741.3881 ($M+H^+$). Purity: > 95% (HPLC).

Supplementary Figure S2. Chemical synthesis of the S2-Rapamycin conjugate.

Rapamycin was purchased from Molcan Corporation (Ontario, Canada). Other chemicals were obtained from standard commercial sources and used without further purification. In order to combine SV119 with rapamycin, a derivative was synthesized [42-*O*-(4-nitrophenyloxycarbonyl) rapamycin] according to published work (patent US 7160867 B2). A solution of SV-119 (79 mg, 0.20 mmol) in DMF (1 mL) was added to a solution of 42-*O*-(4-nitrophenyloxycarbonyl) rapamycin (212 mg, 0.20 mmol) in DMF (1 mL), followed by addition of DIPEA (400 µL). The mixture was stirred at room temperature overnight to complete the reaction. After DMF was

removed under high vacuum at room temperature, the residue was purified by silica gel chromatograph using dichloromethane/methanol/diethyl ether to afford 91 mg white power (34%). ESI/MS: 1343.98 ($M+H^+$). Purity: 99% (HPLC).

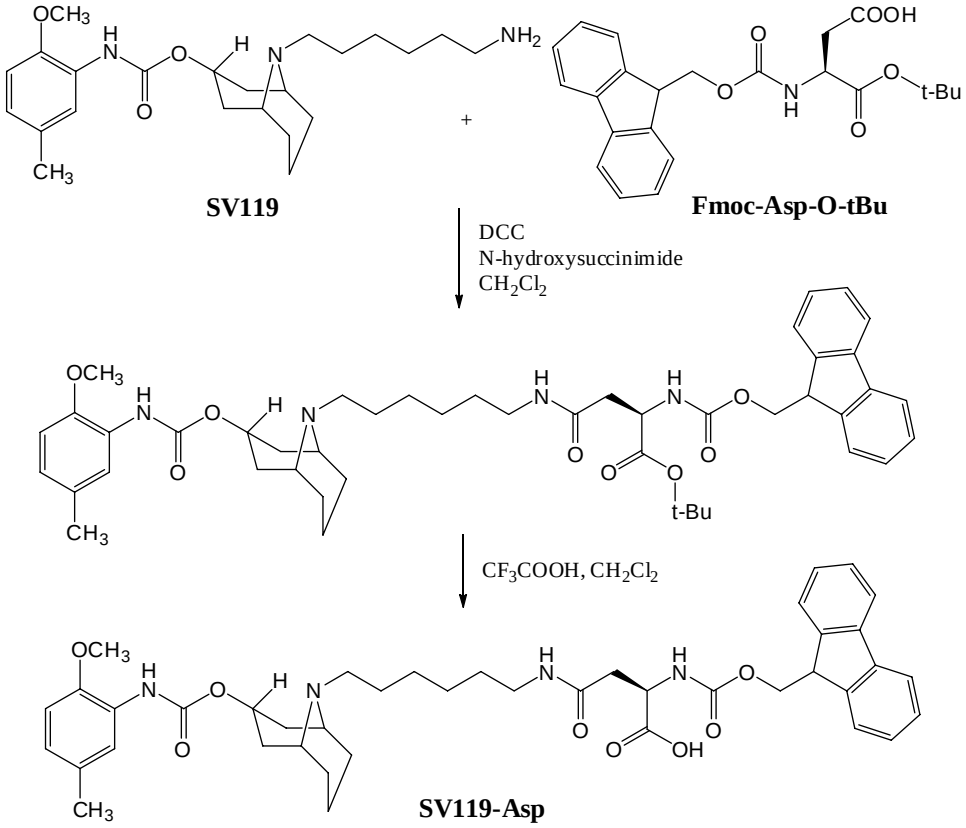
Supplementary Figure S3. Sigma-2-Bim causes apoptosis in a variety of human and mouse pancreatic adenocarcinoma cell lines *in vitro*.

Human (AsPC1 and Panc-1) and mouse (Panc02) pancreatic tumor cell lines were treated in vitro with increasing (μM) concentrations of the indicated reagents and analyzed for apoptosis induction by intracellular TUNEL staining using flow cytometry. The parental sigma-2 ligand SV119, S2-BimX and TAT-Bim were included as controls. Data are expressed as mean +/- 1.0 SE (n = 2).

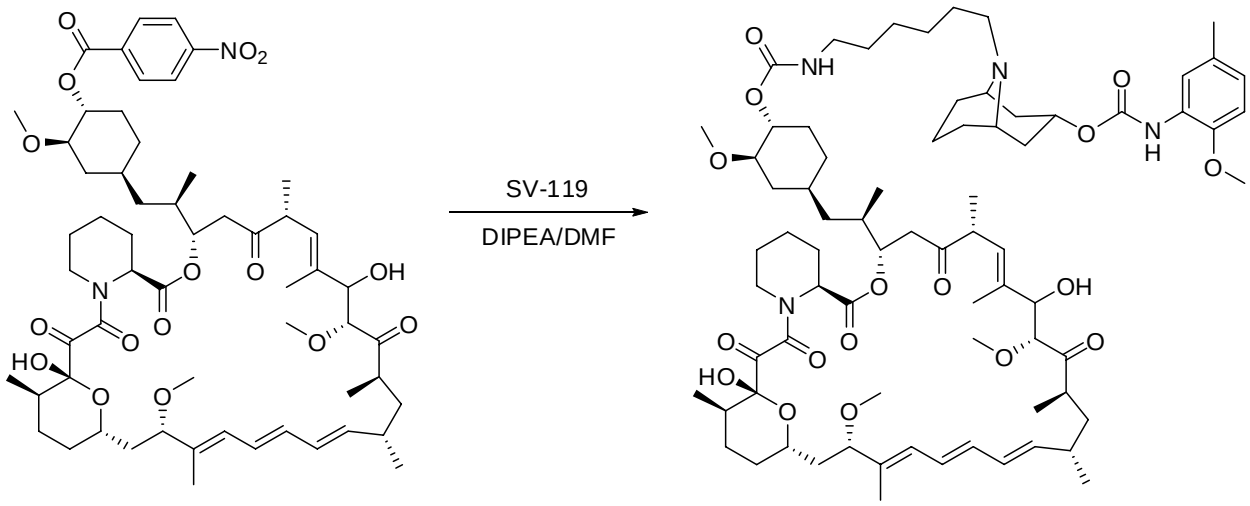
Supplementary Figure S4. Sigma-2-Bim prolongs the overall survival in a syngeneic tumor model of pancreatic adenocarcinoma.

C57BL/6 mice bearing established tumor grafts (Panc02) were treated every other day with the indicated therapeutics as described for Fig. 5 C. Tumor growth was determined by caliper measurement (n = 12 per group). Survival of mice treated with S2-Bim compared favorably to the mice treated with S2-BimX or vehicle control (*, $p = 0.002$). Survival endpoints were defined as tumor diameter >15 mm or tumor ulceration.

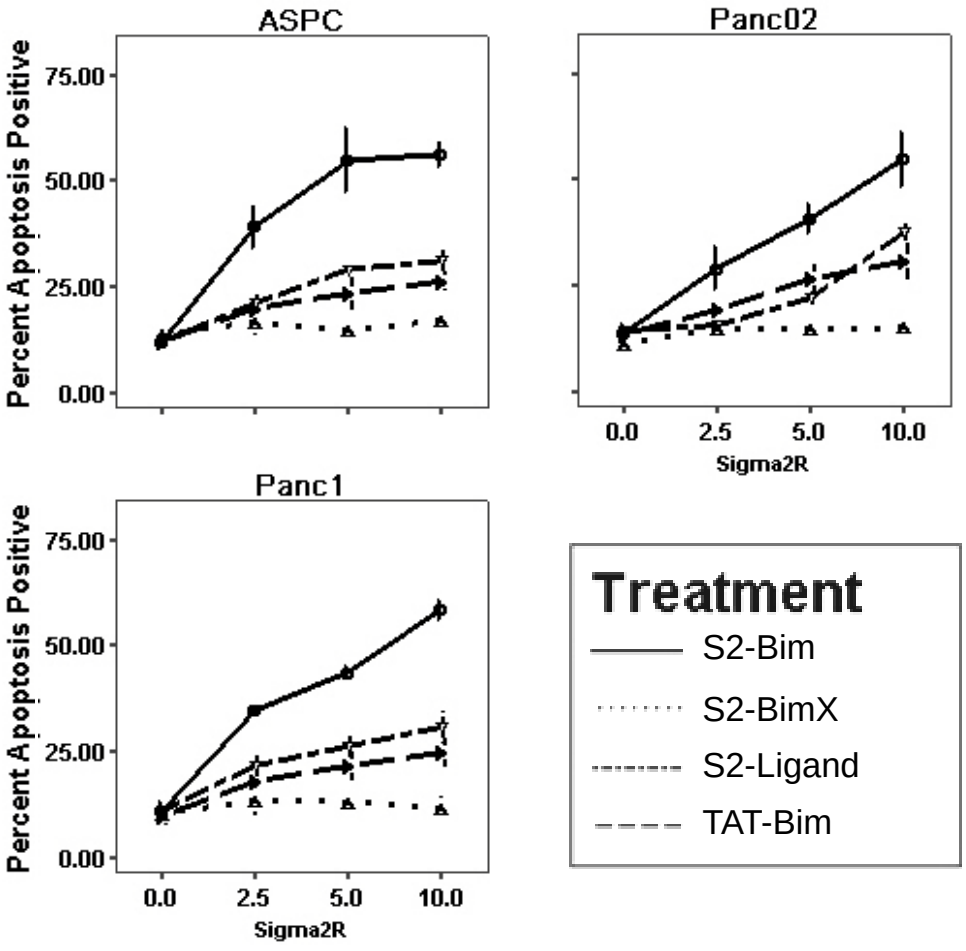
Supplementary FIGURE S1



Supplementary FIGURE S2



Supplementary FIGURE S3



Supplementary FIGURE S4