**Supplemental Figure** **1. Effect of herbacetin or kaempferol on ODC activity.** (A)Herbacetin or (B) kaempferol was modeled as an allosteric inhibitor with the ODC crystal structure. (C) The effect of herbacetin or kaempferol (upper panels) on ODC activity (lower panel) was assessed using a human ODC recombinant protein. Each reaction was incubated at 37°C for 1 h and ODC activity was measured as the release of CO2 from L-[1-C14] ornithine. Data are represented as mean values ± S.D. of triplicate experiments. The asterisk (\*) indicates a significant decrease (*p* < 0.05) in ODC activity between herbacetin-treated samples compared to untreated or kaempferol-treated samples.

**Supplemental Figure** **2. Effect of herbacetin on activity of various kinases.** Herbacetin has no effect on (A) CHK1, (B) EGFR, (C) GSK3, (D) JNK1, (E) JNK2, (F) ERK1, (G) ERK2, (H) MEK1, (I) AKT1, (J) AKT2, (K) RSK2, (L) p38 or (M) PI3-K kinase activity or on (N) AdoMetDC activity. The effect of herbacetin on kinase or enzyme activity was determined by using an *in vitro* kinase or enzyme assay. All data are represented as mean values ± S.D. of values from duplicates experiments.

**Supplemental Figure** **3.** **The effect of polyamines on intracellular herbacetin concentration.** The effect of polyamines on the intracellular herbacetin level was determined using HCT116 colon cancer cells. Cells were treated with herbacetin and putrescine, spermidine or spermine for 5 h in medium supplemented with 10% FBS and intracellular herbacetin was extracted and analyzed by using HPLC. All data are represented as means ± S.D. of triplicate values from 3 independent experiments.

**Supplemental Figure** **4.** **The effect of herbacetin on cell cycle.** The effect of herbacetin or DFMO on cell cycle was determined using HCT116, DLD1 or HT29 colon cancer cells. Cells were treated with herbacetin or DFMO for 48 h in medium supplemented with 10% FBS and then cells were serum starved for 24 h in medium supplemented with 0.5% FBS. Cells were stained with propidium iodide(PI) and cell cycle was analyzed by Fluorescence Activated Cell Sorting (FACS). All data are represented as mean values ± S.D. of triplicate values from 3 independent experiments. The asterisk (\*) indicates a significant effect (*p* < 0.05) of herbacetin or DFMO compared to untreated control.

**Supplemental Figure** **5.** **The effect of herbacetin on AP-1 upstream proteins.** Colon cancer cells were treated with herbacetin for 48 h and expression of total and phosphorylated ERKs and RSK and total ODC was determined by Western blotting. -Actin was used as a loading control. Similar results were obtained from 3 independent experiments and representative blots are shown.

**Supplemental Figure 6. Effect of knocking down ODC expression in HCT116 colon cancer cells.** Colon cancer cells were stably transfected with *shMock* or *shODC*. Confirmation of (A, upper left panel) knockdown of ODC protein expression by Western blot; (A, upper right panel) knockdown of *ODC* transcription level by RT-PCR; and (A, lower panel) knockdown of ODC activity measured as release of L-[1-C14] ornithine. (B) The effect of knocking down ODC expression on anchorage-independent HCT116 colon cancer cell growth. Colonies were counted using a microscope and the Image-Pro PLUS (v6) computer software program. (C) The effect of knocking down ODC expression on HCT116 colon cancer cell growth was analyzed over 1, 2 or 3 days using the MTS assay. (D) The effect of knocking down ODC expression on *AP-1* reporter activity was measured using substrates in the reporter assay system. For A-D, data are represented as mean values ± S.D. of triplicate experiments and the asterisk (\*) indicates a significant difference (*p* < 0.05) versus *shMock* cells. (E) Effect of knocking down ODC expression on the phosphorylation of ERK1/2 and RSK was determined by Western blotting. Similar results were observed from two independent experiments and representative blots are shown.

**Supplemental Figure** **7.** **The effect of putrescine re-addition on intracellular polyamine levels in herbacetin- or DFMO-treated cells.** Colon cancer cells were treated with herbacetin or DFMO for 24 h and then putresine was or was not added for 30 min and intracellular polyamines were extracted and analyzed. All data are represented as means ± S.D. of triplicate values from 3 independent experiments. The asterisk (\*) indicates a significant effect (*p* < 0.05) of herbacetin or DFMO alone compared to cells with added putrescine treatment.

**Supplemental Figure** **8.** **The effect of polyamine depletion with herbacetin on cancer cell doubling time.** Colon cancer cells were stably transfected with *shControl,* *shODC, Mock* or *SAT1*. (A-B) The effect of herbacetin on HCT116 or HT29 colon cancer cell doubling time was assessed in *shControl* and *shODC*cells. (C-D) The effect of herbacetin on HCT116 or HT29 colon cancer cell doubling time was assessed in *Mock* and *SAT1* cells. All data are represented as mean values ± S.D. of triplicate values from 3 independent experiments. The asterisk (\*) indicates a significant effect (*p* < 0.05) of herbacetin compared to untreated controls.

**Supplemental Figure** **9.** **The effect of herbacetin on AP-1 upstream protein expression.** (A-B)Colon tumors were isolated from vehicle- and herbacetin-treated groups (A; treatment by I.P., B: treatment by oral administration) of mice for immunoblot analysis of AP-1 upstream proteins and (C) ODC expression by immunohistochemistry (IHC).

**Supplemental Figure** **10.** **The effect of herbacetin or DFMO on hearing in C57BL/6 mice as measured by PPI.** Vehicle, herbacetin (100 mg/kg B.W. p.o. or 2 mg/kg B.W. i.p.) or DFMO (1 g/kg B.W. p.o.) was administered by gavage or intraperitoneal injection 5 times per week for 5 weeks. (A) DFMO significantly decreased hearing (measured as prepulse inhibition or PPI) on day 35. Hearing as measured by PPI was not affected by oral administration (B) or intraperitoneal injection (C) of herbacetin. Data are shown as mean values ± S.E. The asterisk (\*) indicates a significant decrease (p < 0.05) in hearing in DFMO-treated mice compared to the vehicle-treated group.

**Supplemental Table 1.** List of potential ODC inhibitors generated by using computer screening.