[Supplemental Materials and Methods]

Hierarchical clustering and Heatmap visualization

For calculation of Enrichment Scores (*ES*), the association of DEGs and a gene set (Signature) was assessed with a contingency table and the *P* value was calculated using Fisher's exact test. Then all the *P* values are transformed by a formula (-Log10(*P* value)) into ES calculated as follows:

$$ES = (-\log10(P1)) + (-\log10(P2)) - (-\log10(N1)) - (-\log10(N2))$$

P1 and *P2* mean positive correlation between DEGs and Signature, both log FC of DEGs and Signature, log FC > 0 or < 0. *N1* and *N2* means negative correlation between DEGs and Signature, DEGs log FC > 0 and Signature logFC < 0, or DEGs log FC > 0 and Signature logFC < 0.

Preparation of enteric Compound A microparticles (MPs)

0.25 g of Compound A and 1.5 g of polymer mixture of Eudragit S100 and Eudragit RS (1:2 (w/w)) were suspended in 15 mL of ethanol and acetone mixture (1:1). The solution was emulsified into 83 g of liquid paraffin containing sorbitan sesquioleate (Span 83) (1%, w/w) as a dispersing agent. The stirring speed was set at 1,000 rpm using a magnetic stirrer. After an over-night stirring, solidified enteric Compound A MPs were collected by centrifugation (1,000 rpm, 3 min) and washed three times with 50 ml of n-hexane and dried at room temperature. The drug concentration was determined by HPLC at a wavelength of 285 nm.

Microarray analysis

Total RNAs were extracted using the RNeasy Miniprep kit (Qiagen, Valencia, CA, USA) according to the manufacturer's protocol. Preparation of cDNAs and cRNAs, hybridization, and microarray scanning were performed according to the manufacturer's protocols (Affymetrix Inc., Santa Clara, CA, USA). Biotinylated cRNAs were hybridized to Affymetrix Human Genome U133A Array or U133 Plus 2.0 Array. The data were analyzed with Microarray Suite version 5.0 (MAS5) using Affymetrix default analysis settings and global scaling as normalization method.

Pharmacokinetic studies

Quantification of drug concentration by LC-MS/MS: Aliquots 5 μL of the plasma or 30 μL of the colon homogenate were mixed with acetonitrile containing the internal standards. The mixtures were centrifuged at 4,283 × g and 4°C for 5 min. The supernatants were diluted with solvents for LC-MS/MS. The diluted solutions (5 or 7 μL) were injected into an LC-MS/MS instrument (API5000 or QTRAP5500, AB Sciex, Framingham, MA, USA) equipped with Shimadzu Shim-pack XR-ODS (2.2 μm, 2.0 × 30 mm) maintained at 50°C. Mobile phase condition consisted of 10 mM ammonium formate/formic acid (100/0.2, v/v) (mobile phase A) and acetonitrile/formic acid (100/0.2, v/v) (mobile phase B). The chromatographic separation was performed with a gradient elution at a flow rate of 0.7 mL/min. Mobile phase B was held at

5% for 0.2 min, and increased linearly to 99% for 1.1 min. After mobile phase B was held at 99% for another 0.7 min, it was brought back to 5% for mobile phase B followed by re-equilibration for 0.6 min. The total cycle time for one injection was 2.6 min. Compounds were detected using a multiple reaction monitoring mode. Analyst software TM (version 1.6.2, AB Sciex) was used for data acquisition and processing.