Supporting information

Text S1 Chemicals and reagents

Formic acid (98% purity), maleic acid (99% purity), *para*-chlorobenzoic acid (*p*CBA; 98% purity), 5-FU (99% purity), phenol (99.5% purity), and pyruvic acid (98% purity) were procured from Sigma-Aldrich (Shanghai, China). CAP (99% purity) and sulfamethoxazole (SMX; 98% purity) were supplied by Aladdin Reagent Co. Ltd. (Shanghai, China). A DNPH derivative test mixture, glyoxylic acid monohydrate (98% purity), 2,4-dinitrophenylhydrazine (DNPH; 98% purity), and oxalic acid (99% purity) were purchased from J&K Scientific Ltd. (Beijing, China). Other reagents (e.g., citric acid, hydrochloric acid, sodium chloride, sodium citrate, sodium hydroxide, sodium phosphate, sodium thiosulfate, sulfuric acid, and *tert*-butanol) were ordered through Modern Eastern Fine Chemical Co. Ltd. (Beijing, China). HPLC-grade reagents (e.g., acetonitrile, methanol, and methylene dichloride) were procured from Fisher Scientific (USA). Ultrapure water was generated from a Milli-Q system (Millipore; USA) and used for preparation of all aqueous solutions.

Text S2 Analysis of 5-FU, CAP, SMX, phenol, *p*CBA, organic acids, and transformation products

For the ozonation tests and experimental determination of second-order rate constants, 5-FU, CAP, SMX, phenol, and *p*CBA were measured by HPLC-UV with a SIL-20A autosampler, two LC-20AT pumps, a SPD-20A UV/VIS detector, a CTO-20A column oven, and a CBM-20A communications bus module. An Agilent Zorbax SB-C18 (4.6 mm×150 mm, 5 μm) column was employed to separate the analytes. Details of the mobile phase composition and detector wavelengths are provided in Table S2.

For experiments focused on calculating the contributions of aqueous ozone and $^{\bullet}OH$ to 5-FU and CAP degradation, analytes were measured by the HPLC-UV method described above; however, the *p*CBA probe was measured by LC-MS/MS with an Agilent Zorbax SB-Aq (3.0 mm×150 mm, 3.5 μm) column and a mobile phase composed of (A) methanol and (B) water with 10 mM ammonium acetate. The 5.6-min elution gradient was as follows: 0 min, 20% A; 0–1 min, linear increase to 50% A; 1–3 min, linear increase to 100% A; 3–5.5 min, constant at 100% A; and, 5.5–5.6 min, linear decrease to 20% A. Electrospray ionization was operated in negative mode, and the following MS/MS parameters were employed: parent ion m/z, 154.9; fragment ion m/z, 111.0; declustering potential, –35.0 V; and, collision energy, –18.0 V.

Transformation products were separated on a Waters Acquity UPLC BEH C18 (2.1 mm×100 mm, 1.7 μm) column using a mobile phase composed of (A) acetonitrile with 0.1% formic acid and (B) water with 0.1% formic acid. The 55-min elution gradient was as follows: 5% A for 5 min; linear increase to 100% A over 40 min; constant for 5 min; linear decrease to 5% A in 1 min; and, constant for 4 min to re-equilibrate the column chemistry. Mass spectra were obtained in both negative and positive mode, and data were collected in the 50 to 1200 Da range.

Organic acids were measured using the HPLC-UV method described above, and additional details are available in Table S2. Analytical separation was achieved with a Bio-Rad Aminex HPX-87H (7.8 mm×300 mm, 9 μm) column.

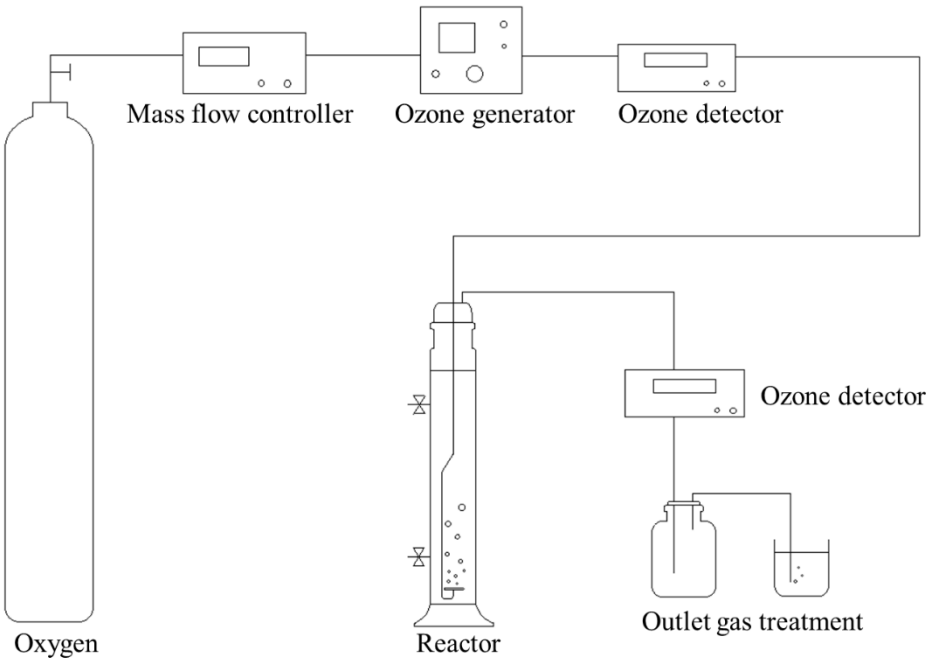
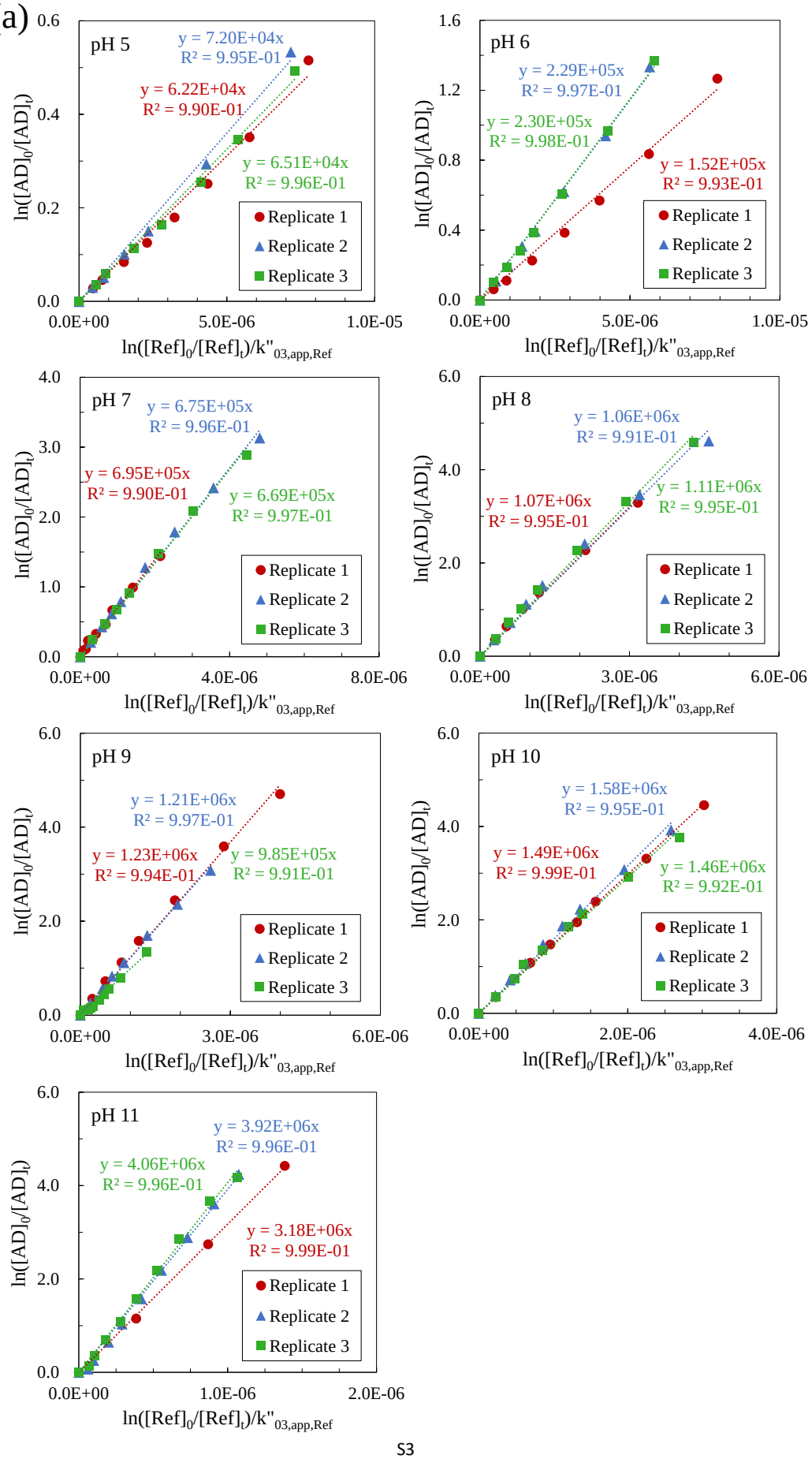


Fig. S1 Experimental setup of ozone reactor

(a)


pH 5
y = 7.20E+04x
R² = 9.95E-01
y = 6.22E+04x
R² = 9.90E-01
y = 6.51E+04x
R² = 9.96E-01
pH 6
y = 2.29E+05x
R² = 9.97E-01
y = 2.30E+05x
R² = 9.98E-01
y = 1.52E+05x
R² = 9.93E-01
pH 7
y = 6.75E+05x
R² = 9.96E-01
y = 6.95E+05x
R² = 9.90E-01
y = 6.69E+05x
R² = 9.97E-01
pH 8
y = 1.06E+06x
R² = 9.91E-01
y = 1.07E+06x
R² = 9.95E-01
y = 1.11E+06x
R² = 9.95E-01
pH 9
y = 1.21E+06x
R² = 9.97E-01
y = 1.23E+06x
R² = 9.94E-01
y = 9.85E+05x
R² = 9.91E-01
pH 10
y = 1.58E+06x
R² = 9.95E-01
y = 1.49E+06x
R² = 9.99E-01
y = 1.46E+06x
R² = 9.92E-01
pH 11
y = 3.92E+06x
R² = 9.96E-01
y = 4.06E+06x
R² = 9.96E-01
y = 3.18E+06x
R² = 9.99E-01
Replicate 1
Replicate 2
Replicate 3
ln([AD]0/[AD]t)
ln([Ref]0/[Ref]t)/k''03,app,Ref

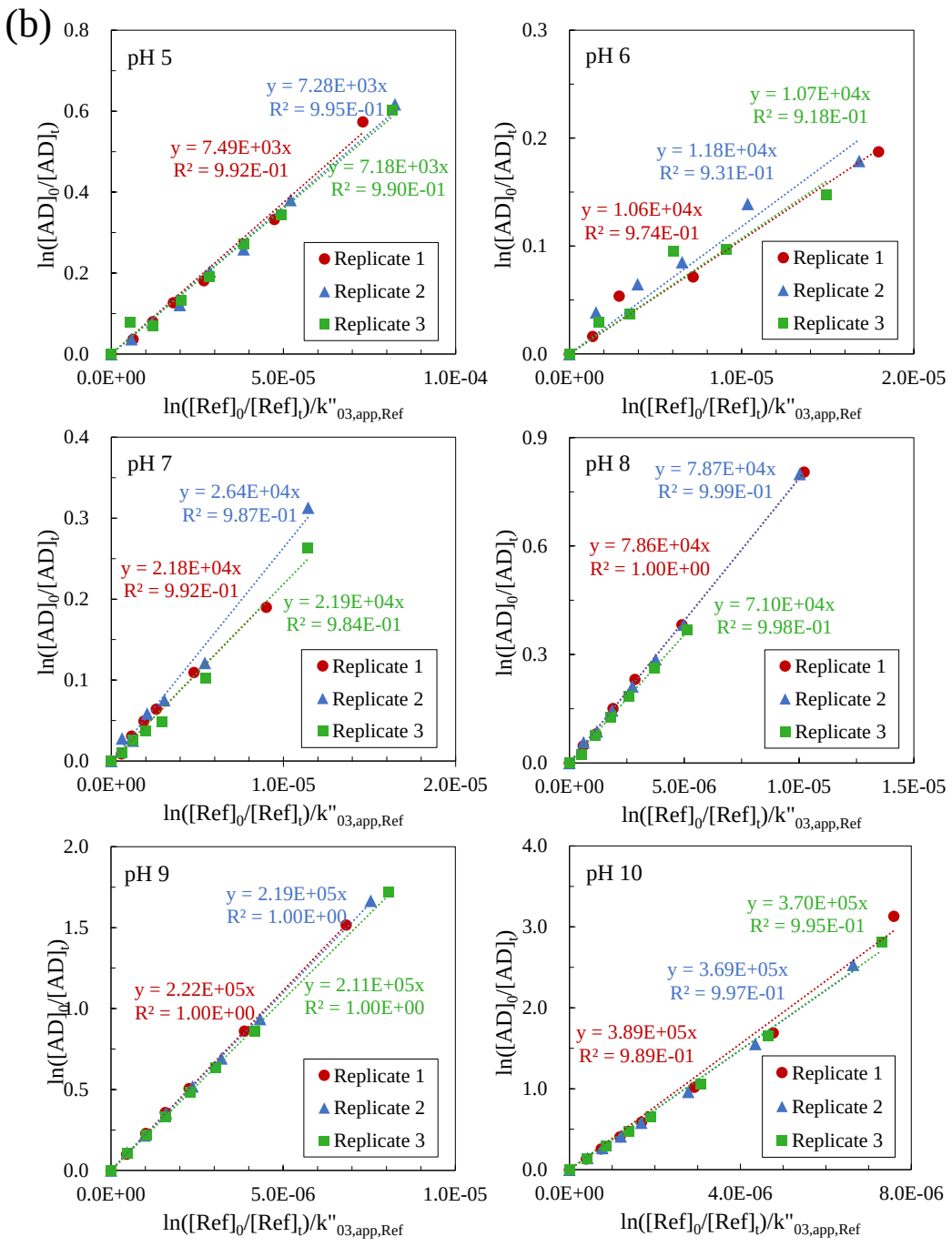


Fig. S2 Degradation of (a) 5-FU and (b) CAP by aqueous ozone at 27℃±1℃ in competition kinetics experiments using SMX and phenol as reference compounds (Ref). The solution pH was adjusted using 10 mM phosphate buffer

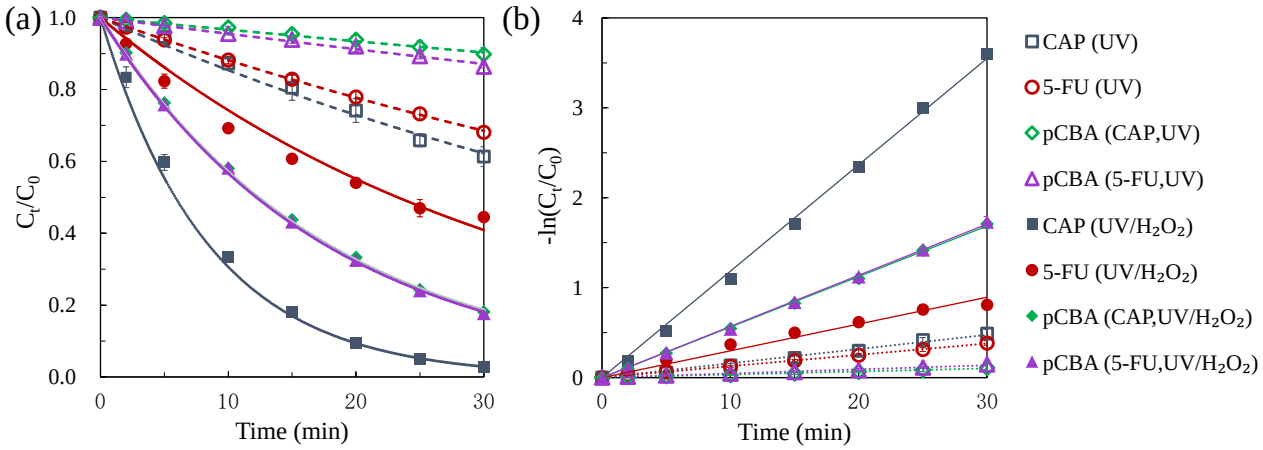


Fig. S3 Degradation of 5-FU, CAP, and *p*CBA in the UV and UV/H_2O_2 systems at 27℃±1℃ and pH 7 (10 mM phosphate buffer) plotted as (a) the fraction remaining vs. time and (b) the negative natural logarithm of the fraction remaining vs. time

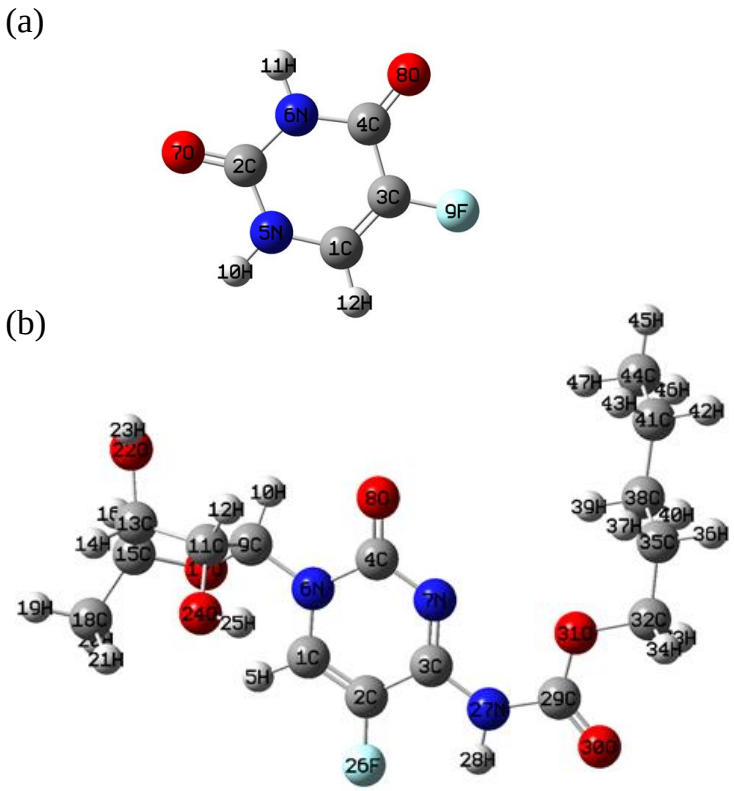


Fig. S4 Chemical structure and atomic numbering for (a) 5-FU and (b) CAP

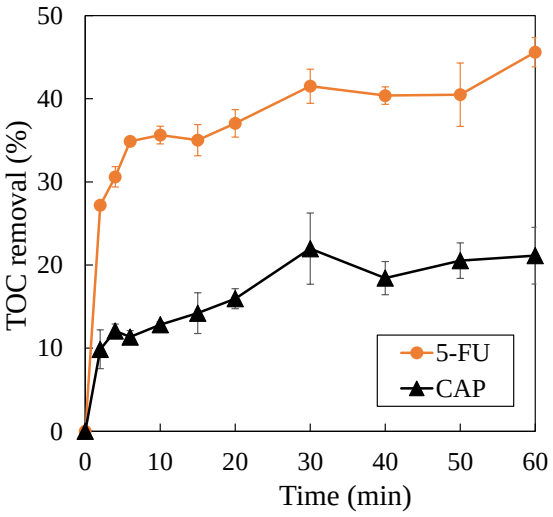
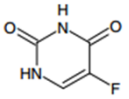
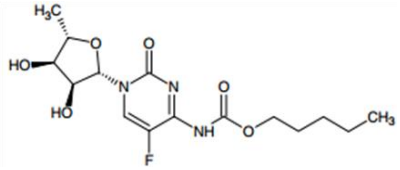


Fig. S5 TOC removal plotted as a function of ozonation time for solutions containing 5-FU and CAP. The experimental conditions were as follows: inlet ozone gas concentration, 8 g O_3/m^3; temperature, 27℃±1℃; pH, 7 (10 mM phosphate buffer); and, initial concentration of parent compound, 50 μM

Table S1 The physicochemical properties of 5-FU and CAP

Property	5-Fluorouracil (5-FU)	Capecitabine (CAP)
Chemical name	5-Fluoro-1h-pyrimidine-2,4-dione	Pentyl[1-(3,4-dihydroxy-5-methyl-tetrahydrofuran-2-yl)-5-fluoro-2-oxo-1h-pyrimidin-4-yl]aminomethanoate
CAS number	51-21-8	154361-50-9
Chemical formula	$C_4H_3FN_2O_2$	$C_{15}H_{22}FN_3O_6$
Chemical structure		
Class	Antimetabolic agent: pyrimidine analogue	Antimetabolic agent: pyrimidine analogue
Melting point (℃)	282	88–89
Molecular weight (Da)	130.08	359.35
pK_a [a)]	7.2; 12.0	8.8
Bioconcentration factor [b)]	3.6	1.3
log K_{ow} [b)]	–0.89	1.04
Solubility (mg/L) [c)]	1.11×10^4	2.60×10^4

Notes: a) (Kosjek and Heath, 2011; MarvinSketch, 2018); b) (Straub, 2009); c) (Kosjek and Heath, 2011; Zhang et al., 2013)

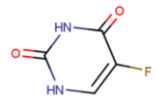
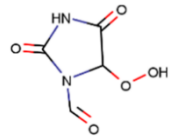
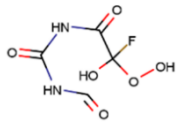
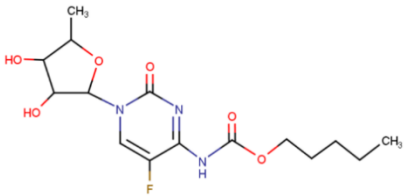
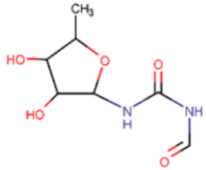
Table S2 Mobile phase composition and detector wavelength for 5-FU, CAP, SMX, phenol, *p*CBA, and aldehyde-based byproducts and organic acids

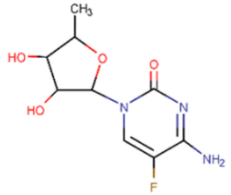
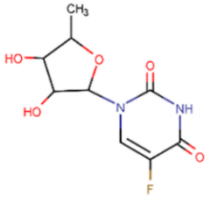
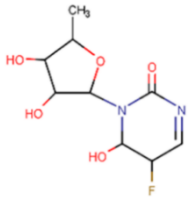
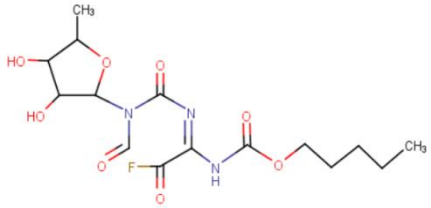
Analyte	Composition of mobile phase	Wavelength (nm)
5-FU	5% methanol : 95% water (0.1% phosphoric acid)	266
CAP	30% acetonitrile : 70% water (0.1% formic acid)	310
SMX	30% acetonitrile : 70% water (0.1% formic acid)	257
Phenol	50% methanol : 50% water	270
*p*CBA	50% acetonitrile : 50% water (0.05% formic acid)	236
Aldehyde byproducts	20% acetonitrile: 50% methanol : 30% water	360
Organic acids	4 mM H_2SO_4	210

Table S3 Summary of pseudo-first-order rate constants (with 95% confidence intervals) and average irradiance ratios at 27℃±1℃ and pH 7 (10 mM phosphate buffer). The initial concentrations of the ADs and *p*CBA were set to 25 μM

System	k'_{AD} (min^{-1})	k'_{pCBA} (min^{-1})	$k'_{d,AD}$ (min^{-1})	$k'_{d,pCBA}$ (min^{-1})	$\frac{E'_{with\ H_2O_2}}{E'_{no\ H_2O_2}}$
5-FU + *p*CBA	$2.76(\pm0.22)\times10^{-2}$	$5.75(\pm0.12)\times10^{-2}$	$1.26(\pm0.06)\times10^{-2}$	$4.64(\pm0.41)\times10^{-3}$	5.8×10^{-1}
CAP + *p*CBA	$1.21(\pm0.02)\times10^{-1}$	$5.69(\pm0.08)\times10^{-2}$	$1.67(\pm0.14)\times10^{-2}$	$3.53(\pm0.53)\times10^{-3}$	7.8×10^{-1}

Table S4 Transformation products identified by QTOF-MS during ozonation of 5-FU and CAP

Analyte	Label	Retention time (min)	Elemental composition	Parent ion $[M-H]^-$ m/z	Fragment ion $[M-H]^-$ m/z	Proposed structure
5-FU & transformation products	5-FU	1.20	$C_4H_3N_2O_2F$	129.0	59.0	
	TP-159	0.87	$C_4H_4N_2O_5$	159.0	131.0	
	TP-195	0.90	$C_4H_5N_2O_6F$	195.0	115.0	
CAP & transformation products	CAP	15.70	$C_{15}H_{22}N_3O_6F$	358.1	154.0 242.1	
	TP-203	17.17	$C_7H_{12}N_2O_5$	203.1	160.1	

TP-229	2.28	$C_9H_{11}N_2O_4F$	229.0	113.0	
TP-244	16.36	$C_9H_{12}N_3O_4F$	244.1	84.0	
TP-245	3.82	$C_9H_{11}N_2O_5F$	245.1	129.0	
TP-247	0.97	$C_9H_{13}N_2O_5F$	247.1	175.1 101.0	
TP-390	13.19	$C_{15}H_{22}N_3O_8F$	390.1	372.1	

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