Supporting information for

Tracking fluorine during aqueous photolysis and advanced UV treatment of fluorinated phenols and pharmaceuticals using a combined ^{19}F-NMR, chromatography, and mass spectrometry approach

by

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1. Chemicals

Fluoxetine HCl (pharmaceutical secondary standard), sitagliptin phosphate (pharmaceutical secondary standard), 2-fluorophenol (98%), 3-fluorophenol (98%), 4-fluorophenol (99%), 2,6-difluorophenol (99%), 3,5-difluorophenol (99%), 2-hydroxybenzotrifluoride (2-(trifluoromethyl)phenol; 97%), 3-(trifluoromethyl)phenol (99%), 4-(trifluoromethyl)phenol (97%), trifluoroacetic acid (99%),and methanol (>99.9%) were purchased from Sigma-Aldrich. Hexafluorobenzene (HFB; >99.0%) was purchased from Tokyo Chemical Industry. Sodium sulfite anhydrous (99.2%) and boric acid (analytical reagent grade) were purchased from Mallinckrodt. Hydrogen peroxide (30%), sodium phosphate monobasic monohydrate (certified ACS grade), ortho-phosphoric acid 85% (HPLC grade), sodium hydroxide (50% w/w), and 2-propanol (HPLC grade) were purchased from Fisher Chemical. Sodium phosphate dibasic anhydrous (ACS grade) and acetonitrile (HPLC grade) were purchased from J.T. Baker. Deuterium oxide (99.9%) was purchased from Cambridge Isotope Laboratories Inc. Hydrochloric acid was purchased from BDH Aristar. Ultrapure water (18.2 MΩ•cm) was produced by a Milli-Q Academic system (Millipore).

2. Sampling and High-Pressure Liquid Chromatography procedures

The quartz test tubes used in the study had an inner diameter (ID) of 11 mm, a height of 10 mm, a capacity of approximately 10 mL, and were filled with approximately 8 mL of the sample to be photolyzed. Before irradiation, an aliquot was taken from each of the quartz test tubes and placed into 2 mL amber HPLC vials for the initial unphotolyzed sample. Additional aliquots were subsequently taken at later time points and placed into amber HPLC vials for analysis. The

volume of each aliquot was 330 µL, enough for the injection needle to pull up 50 µL of sample. To quench the hydrolysis of the (trifluoromethyl)phenols and fluorophenols in the pH 10 boric acid buffer, 4.0 µL of 1 M HCl was added into the HPLC vial with the sample aliquot. To quench hydroxyl radicals, 10 µL isopropanol was added to the HPLC vial. The target exposure for degradation of each compound of interest was set at two half-lives.

An ultraviolet absorbance spectrum of each compound of interest was taken on a spectrophotometer to best choose a detection wavelength. Some compounds had products that were detectable at the same wavelength as that monitored for parent compound. Methods were optimized to separate any products from the parent peak. The conditions for each method are shown in Table S1.

Table S1. Agilent 1100 series HPLC conditions for each compound of interest. The pH 3 phosphate buffer has a ratio of 9:1 of 10 mM buffer to ACN. No gradients were used for any compound.

Compound	Mobile Phase (Total time)	Detection Wavelength (nm)	Column	Flow Rate (mL/min)
Trifluoromethyl-phenols	ACN: pH 3 phosphate buffer 35:65 (8 minutes)	220	Eclipse XDB-C18 3.5 µm 4.6 × 150 mm	1.5
Fluorophenols	ACN: pH 3 phosphate buffer 20:80 (11 minutes)	210	Eclipse XDB-C18 3.5 µm 4.6 × 150 mm	1.0

Difluorophenols	ACN: pH 3 phosphate buffer 45:55 (8 minutes)	220	Eclipse XDB-C18 3.5 µm 4.6 × 150 mm	1.0
Fluoxetine	ACN: pH 3 phosphate buffer 30:70 (15 minutes)	230	Eclipse XDB-C18 3.5 µm 4.6 × 150 mm	1.0
Sitagliptin	ACN: pH 3 phosphate buffer 15:85 (15 minutes)	210	Eclipse XDB-C18 3.5 µm 4.6 × 150 mm	1.0

To calculate rate constants and 95% confidence intervals, regression of $\ln(C/C_o)$ versus time was performed in Microsoft Excel. The upper 95% confidence interval was subtracted from the rate constant, yielding the total 95% confidence interval. A weighted average of the 95% confidence intervals from the replicates was taken for the final error, while the rate constants were averaged. Photolysis rate constants were found by subtracting the dark control hydrolysis rate constant from the total rate constant of the photolyzed sample.

3. ^{19}F-NMR procedure

The HFB internal standard was prepared at a concentration of 100 µM in 2-propanol and pipetted into melting-point tubes to serve as a coaxial insert.[1,2] Approximately 100µL of the HFB solution was added to the melting point tube such that the height in the tube, approximately 6 cm, was larger than the NMR acquisition window. The melting-point tubes were flame sealed to allow reuse. HFB was chosen due to the presence of 6 magnetically equivalent fluorine atoms, yielding a sharp singlet peak in the NMR spectrum. It was also assumed that HFB would not be a product

of any of the compounds of interest, meaning there would be a reduced chance of spectral overlap with photodegradation product resonances. The ^{19}F-NMR resonance corresponding to HFB is at -164.9 ppm.[1] All spectra are referenced to this value.

To account for the concentration of HFB in the smaller diameter melting point tube, a ratio between the fluorine atoms in the melting-point tube versus the fluorine atoms in the NMR tube was found, allowing for comparison between the standard and the sample.[3] For this, 500 µL of 100 µM trifluoroacetic acid (TFA) in solvent that was 9:1 MilliQ water to deuterium oxide was pipetted into the NMR tube and the melting-point tube containing the HFB standard was placed in the NMR tube. The relationship of the two measurements is

$$\frac{\mathrm{Area_{TFA}}}{[\mathrm{TFA}]*\mathrm{TFA_{\#F}}} = \frac{\mathrm{Area_{HFB}}*\mathrm{IS_{ratio}}}{[\mathrm{HFB}]*\mathrm{HFB_{\#F}}} \qquad \text{Equation S1}$$

with TFA and HFB having the same concentration of 100 µM, the [TFA] and [HFB] variables cancel out in Equation S1. The ratio between single fluorine atoms was found by solving for the IS_{ratio} in Equation S2. The TFA sample with the HFB standard was run three times, taking an average for the final ratio for each melting temp tube standard.

$$\mathrm{IS_{ratio}} = \frac{2*\mathrm{Area_{TFA}}}{\mathrm{Area_{HFB}}} \qquad \text{Equation S2}$$

Each standard was individually labeled and stored at room temperature. The NMR tube-melting point tube pair was kept the same and tubes were not exchanged amongst each other. After every use, both melting-point and NMR tubes were rinsed with methanol so that no residual fluorine remained on the tubes. IS_{ratio} values were recalculated using TFA in the same method described above before each run to take into account any loss or change in areas of the HFB peaks due to potential sample loss from evaporation.

Bruker Topspin 4.0.7 was used to analyze the NMR spectra. Detailed acquisition parameters are in **Table S2**. These were optimized to ensure complete relaxation of the molecules between magnetic pulses, which is a requirement for quantitative NMR. During data acquisition, a spectral window of 201 ppm with an offset of -100 (O1P) was used to capture the broad range of fluorine resonances. During data processing, the spectrum with the HFB standard resonance was phased first, baseline corrected, set to -164.9 ppm, and then integrated. Every additional experimental resonance in the spectrum was then individually brought into phase, baseline adjusted, and integrated. Each integration value was converted into moles of fluorine by the HFB internal standard with Equation S3 and solving for the unknown amount of fluorine using Equation S4. All other variables are known constants with [HFB] being 100 μM, $HFB_{\#F}$ being 6, and the areas of HFB and the peak being the integration values, the IS_{ratio} for a given melting point tube was previously found with Equation S2.

$$\left(\frac{\text{Area}_{\text{peak}}}{[\text{F}_{\text{unknown}}]}\right) = \frac{\text{Area}_{\text{HFB}} * \text{IS}_{\text{ratio}}}{[\text{HFB}] * \text{HFB}_{\#\text{F}}} \qquad \text{Equation S3}$$

$$[\text{F}_{\text{unknown}}] = \text{Area}_{\text{peak}} * \left(\frac{[\text{HFB}]}{\frac{\text{Area}_{\text{HFB}} * \text{IS}_{\text{ratio}}}{\text{HFB}_{\#\text{F}}}}\right) \qquad \text{Equation S4}$$

An additional calculation was made to correct for the dilution factor of the D_2O. A fluorine mass balance was conducted on the unphotolyzed and photolyzed samples after calculation of the fluorine resonances. Equations S5 and S6 show the calculation made, with M_1 being the concentration calculated from the total volume, V_1 being the total volume of 535 μL, V_2 being the 485 μL of sample added in the NMR tube, and M_2 being the unknown. For the case of (trifluoromethyl)phenols and fluorophenols in the pH 10 matrix, V_1 was 541 μL, accounting for the additional 6 μL of 1 M HCl added to the time-zero NMR tubes, V_2 remained the same.

$$M_1V_1 = M_2V_2 \qquad \text{Equation S5}$$

$$\frac{M_1V_1}{V_2} = M_2 \qquad \text{Equation S6}$$

Fluoride was sometimes present in the unphotolyzed sample (at -121.5 ppm). When this was the case, the amount of fluoride in the unphotolyzed sample was subtracted from both the photolyzed and unphotolyzed samples. Error in the mass balance was sometimes observed at roughly 5%, possibly because the photoproducts created were electromagnetically different from the parent compounds, such that different delay and acquisition times are required. Other factors include low signal to noise, especially on products that showed low concentrations and were multiplets. Low S/N ratios lead to inaccurate quantification, it was demonstrated that a S/N ratio must be 150:1 or greater to obtain < 1% error.[4] For spectra for **3a** and **3b**, some samples had a lower S/N ratio leading to error > 5%. It was also shown that S/N ratios are directly related to concentration.[5] Thus, if a parent molecule produces many fluorinated photoproducts, they may be at too low of concentration to obtain a large enough S/N ratio to perform accurate quantification.

A specific detection limit was not determined, but using a highly sensitive TCI cryoprobe with a rated sensitivity of 7000:1 S/N, good accuracy is obtained with integrations at S/N 3:1. The unphotolyzed sample of **1a** in Figure 3 was at 10 μM (30 μM fluorine) which had a S/N of 50, suggesting the concentration could be detected at 0.6 μM (1.8 μM fluorine). Detections limits for specific compounds will depend on the how broad the peak is. As shown in Table S2, the method uses 1024 scans, but 4 times as many scans would double the signal to noise due to the relationship of S/N to the square of the number of scans, and lower the detection limits accordingly.

Table S2. Parameters of NMR analysis, some values are rounded due to the relationship between the parameters.

Parameter	Value	Unit
Pulse Angle	90	degrees
Size of FID (TD)	68180	
Number of Dummy Scans (DS)	4	
Loop Count (TD0)	1	
Number of Scans (NS)	1024	
Sweep Width (SW)	201	ppm
Acquisition Time (AQ)	0.9	s
FID Resolution (FIDRES)	0.33	Hz
Filter Width (FW)	2.4×10^8	Hz
Delay (D1)	10.0	s
Receiver Gain (RG)	101	
Dwell Time	4.4	μs

4. LC-HRMS acquisition and analysis procedure

For analysis on the liquid chromatography-high resolution mass spectrometer (LC-HRMS), sample preparation was similar to the HPLC samples. Using the HPLC amber vials, an initial unphotolyzed sample, a final photolyzed sample were taken. Samples from intermediate time points were taken if products were formed and degraded by the time photolysis was completed. Each vial had a total volume of 330 µL, enough for the 4 µL injection of the instrument. A blank sample consisted of only the aqueous matrix of the photolysis experiments. The system was operated in the ESI positive mode. The optimized parameters were: spray voltage 5 kV, source temperature 275 °C; and data-dependent MS/MS scans at resolution 15,000, normalized collision energy 60, and isolation width of 3 m/z.

To be considered for analysis, a detected peak was required to have an area greater than 15,000, and the peak had to be 5 times greater in area than any corresponding peak in the blank and unphotolyzed sample. MS/MS fragmentation data was obtained for the most abundant ion masses of each peak that met these criteria. Peaks were either detected manually from the spectra or compound discoverer software by Thermo-Fischer Scientific was used to select peaks that met the area criterion mentioned above. MS/MS fragmentation data for these peaks was extracted and fragments were compared to the parent peak. An online chemical formula calculator was used to generate possible chemical formulas of fragments and products and isotopic patterns were calculated from enviPat.[6] Chemical structures matching these formulas were made in ChemDraw. Structures were made by using the parent compound as a starting point, then breaking bonds and adding atoms to obtain viable structures. Oxygen was the only atom allowed to be added to the structure. Levels of product identification are summarized in **Table S3**.[7]

Table S3. Levels of product identification with mass spectrometry.

Level	Description
1	Peak mass and retention are matched to a reference standard
2a	Matched peak mass to a spectrum in a library
2b	Matched largest mass and at least one fragment
3	Exact mass match and matches MassFrontier
4	Exact mass match
5	No mass match, but a clear peak

5. UV-Vis absorption spectra

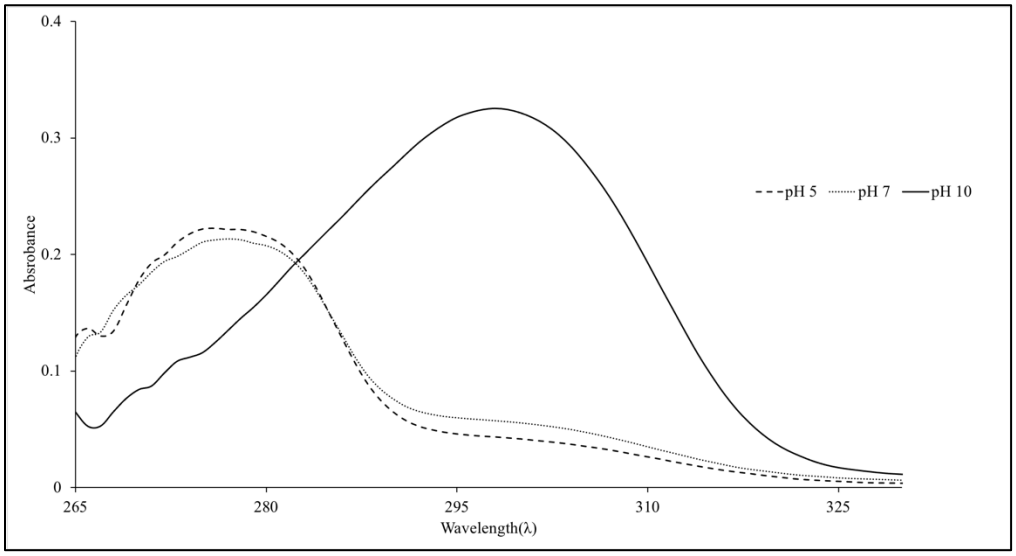


Figure S1. Ultraviolet absorbance spectra of 2-(trifluoromethylphenol) (**1a**) in pH 5 acetate buffer, pH 7 phosphate buffer, and pH 10 borate buffer.

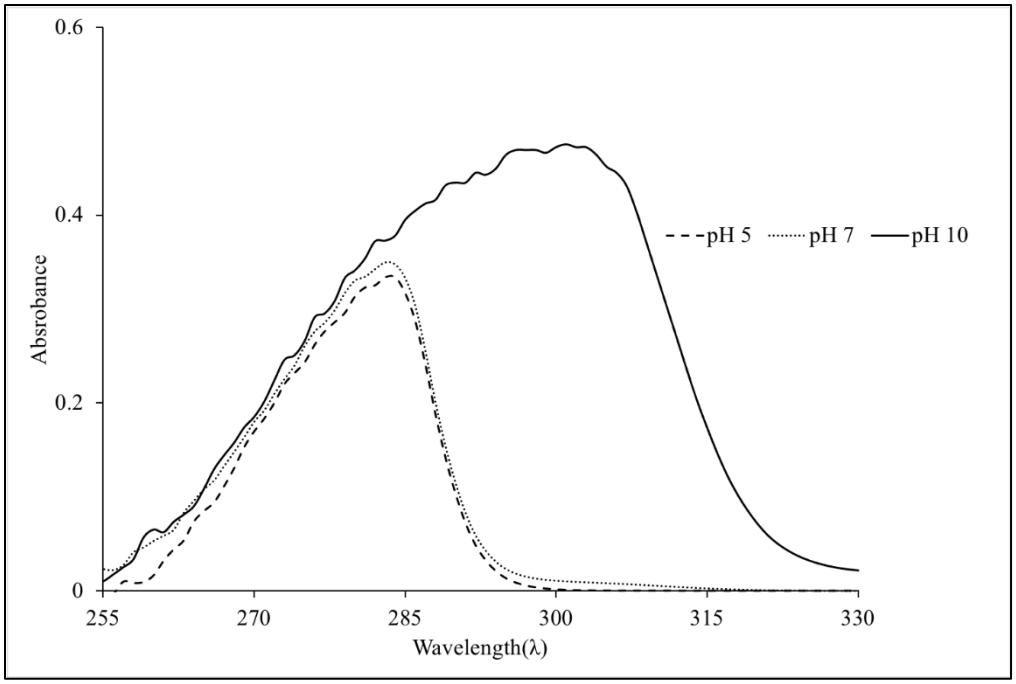


Figure S2. Ultraviolet absorbance spectra of 3-(trifluoromethyl)phenol (**1b**) in pH 5 acetate buffer, pH 7 phosphate buffer, and pH 10 borate buffer.

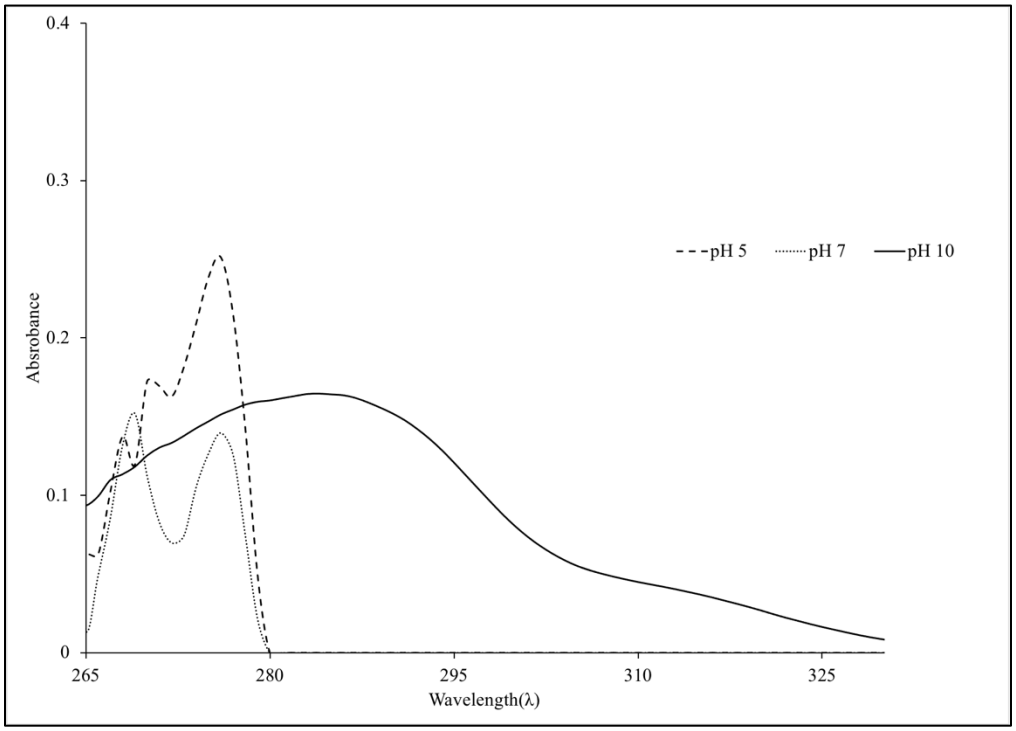


Figure S3. Ultraviolet absorbance spectra of 4-(trifluoromethyl)phenol (**1c**) in pH 5 acetate buffer, pH 7 phosphate buffer, and pH 10 borate buffer.

6. Kinetics and NMR data for all model compounds and pharmaceuticals

a. 2-(Trifluoromethyl)phenol

See main document for photolysis and dark control degradation plots, NMR spectra and NMR mass balance plots. The data for the NMR mass balance are given below

Table S4. 2-(Trifluoromethyl)phenol (**1a**) parent and photoproduct mass balance as μM of fluorine before and after photolysis.

	Sample	Parent/Product	[Fluorine] (μM)	Error ±
pH 5	Unphotolyzed	**1a**	30.85	0.22
		Total	30.85	0.22
	Photolyzed	**1a**	3.5	0.02
		Product A	20.5	0.06
		Fluoride	8	0.15
		Total	32	0.16
pH 7	Unphotolyzed	**1a**	31.02	0.3
		Total	31.02	0.3
	Photolyzed	**1a**	4.01	0.03
		Fluoride	25.1	0.22
		Total	29.11	0.22
pH 10	Unphotolyzed	**1a**	31.02	0.25
		Total	31.02	0.25
	Photolyzed	**1a**	1.52	3.30E-03
		Product B	1.01	2.20E-03
		Fluoride	28.49	0.11
		Total	31.02	0.11
H_2O_2	Unphotolyzed	**1a**	30.85	0.31
		Total	30.85	0.31
	Photolyzed	**1a**	5.1	0.06
		Fluoride	25.9	0.19
		Total	31	0.2
Sulfite	Unphotolyzed	**1a**	30.85	0.15
		Total	30.85	0.15
	Photolyzed	**1a**	1.3	3.60E-03
		Product B	1.99	4.40E-03
		Fluoride	26.2	0.16
		Total	29.5	0.16

b. 3-(Trifluoromethyl)phenol

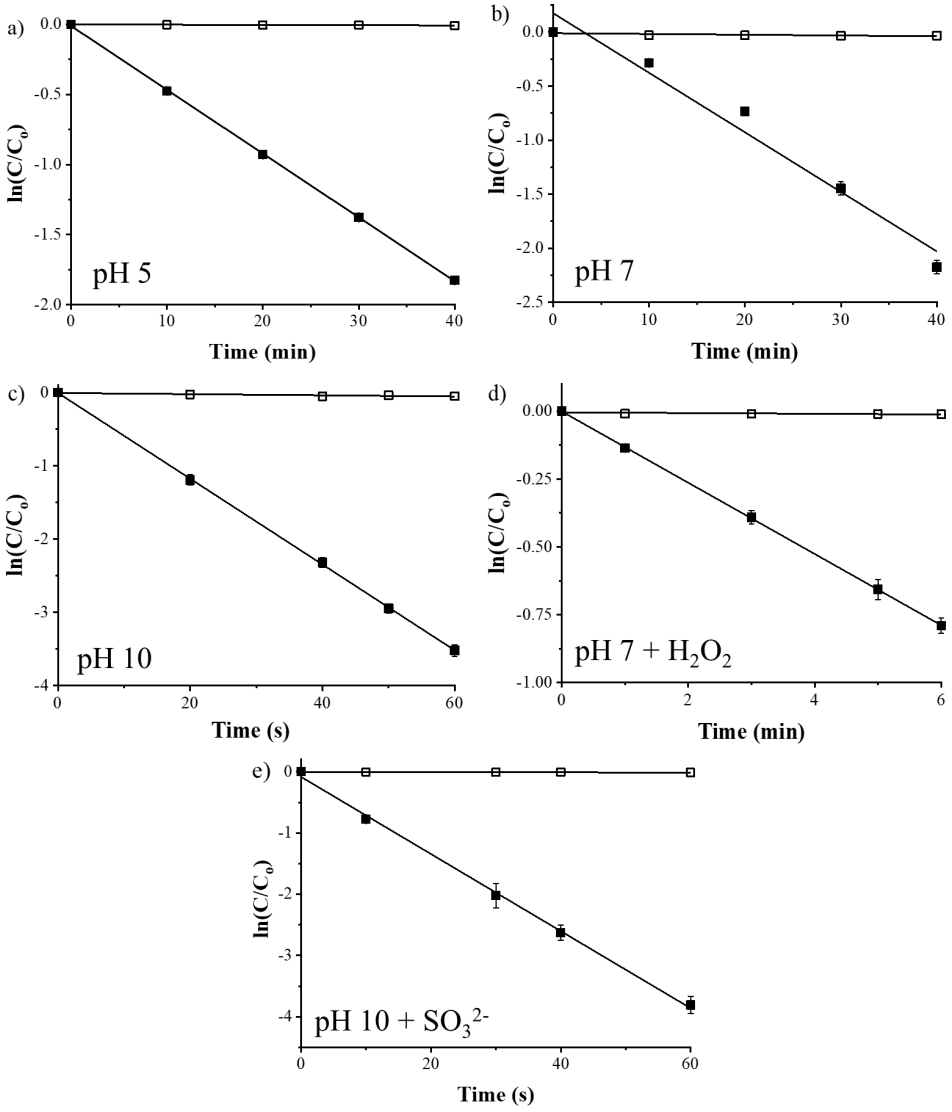


Figure S4. Photochemical degradation plots of 3-(trifluoromethyl)phenol (**1b**) with hydrolysis (□) and photolysis (■) rate constants of (a) 0.01 ± 0.01 h^{-1} and 2.72 ± 0.06 h^{-1} in a 10 mM pH 5 acetate buffer, (b) 0.04 ± 0.04 h^{-1} and 3.27 ± 0.63 h^{-1} in a 10 mM pH 7 phosphate buffer, (c) 2.84 ± 2.08 h^{-1} and 207.90 ± 7.51 h^{-1} in a 10 mM pH 10 borate buffer, (d) 0.08 ± 0.08 h^{-1} and 7.80 ± 0.20 h^{-1} in a 10 mM pH 7 phosphate buffer with 1 mM H_2O_2, and (e) 0.72 ± 0.41 h^{-1} and 225.83 ± 13.60 h^{-1} in a 10 mM pH 10 borate buffer with 0.5 mM SO_3^{2-}. Error bars represent the standard deviation between triplicate samples taken on HPLC. Reported rate constant errors represent the average 95% confidence interval determined by regression statistics, and photolysis rate constants are corrected for any loss in the dark controls. Note the change in units along the x-axis.

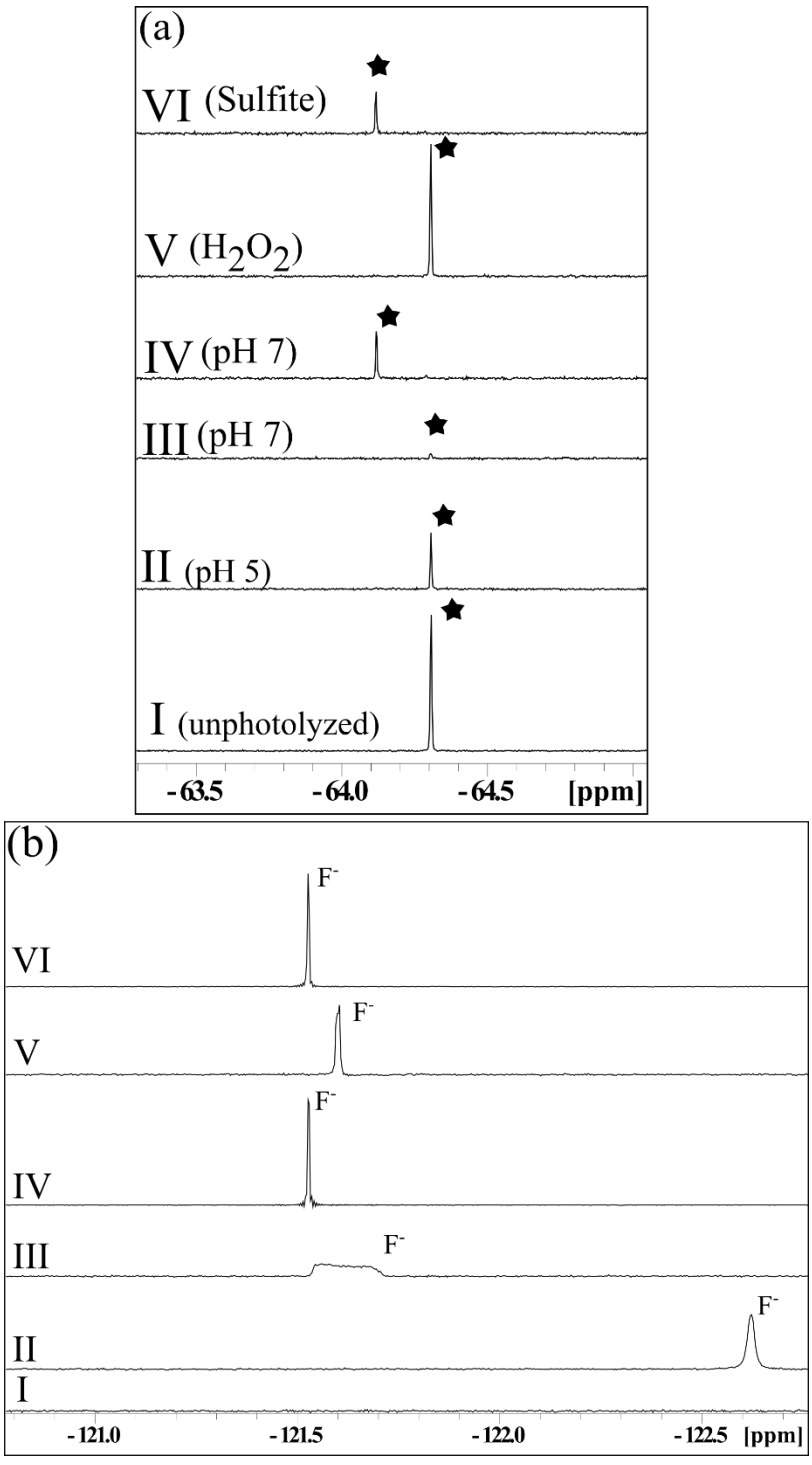


Figure S5. ^{19}F-NMR spectra of 3-(trifluoromethyl)phenol (**1b**) before photolysis (I) and after photolysis in pH 5 acetate buffer (II), pH 7 phosphate buffer (III), pH 10 borate buffer (IV), pH 7 buffer with 1 mM H_2O_2 (V), and pH 10 with 0.5 mM SO_3^{2-} (VI). The parent, **1b**, (black star) is shown in (a), the unphotolyzed sample was scaled by a factor of 4. Fluoride (F^-) production is shown in (b), the broad peak in sample IV could be due to the shimming of the NMR instrument. Samples III and I were scaled by a factor of 4. A slight shift in ppm is due to pH change.

Table S5. 3-(Trifluoromethyl)phenol (**1b**) parent and photoproduct mass balance as μM of fluorine before and after photolysis.

	Sample	Parent/Product	[Fluorine] (μM)	Error ±
pH 5	Unphotolyzed	**1b**	31.97	0.18
		Total	31.97	0.18
	Photolyzed	**1b**	10.92	0.07
		Fluoride	21.39	0.4
		Total	32.31	0.41
pH 7	Unphotolyzed	**1b**	29.1064	0.38
		Total	29.1064	0.38
	Photolyzed	**1b**	3.06	4.50E-03
		Fluoride	24.59	0.24
		Total	27.65	0.24
pH 10	Unphotolyzed	**1b**	29.1064	0.54
		Total	29.1064	0.54
	Photolyzed	**1b**	0.79	0.05
		Fluoride	27.2	0.54
		Total	27.99	0.54
H_2O_2	Unphotolyzed	**1b**	31.97	0.46
		Total	31.97	0.46
	Photolyzed	**1b**	13.95	0.18
		Fluoride	19.07	0.22
		Total	33.02	0.28
Sulfite	Unphotolyzed	**1b**	29.1064	0.37
		Total	29.1064	0.37
	Photolyzed	**1b**	0.93	0.03
		Fluoride	24.47	0.37
		Total	25.4	0.37

c. 4-(Trifluoromethyl)phenol

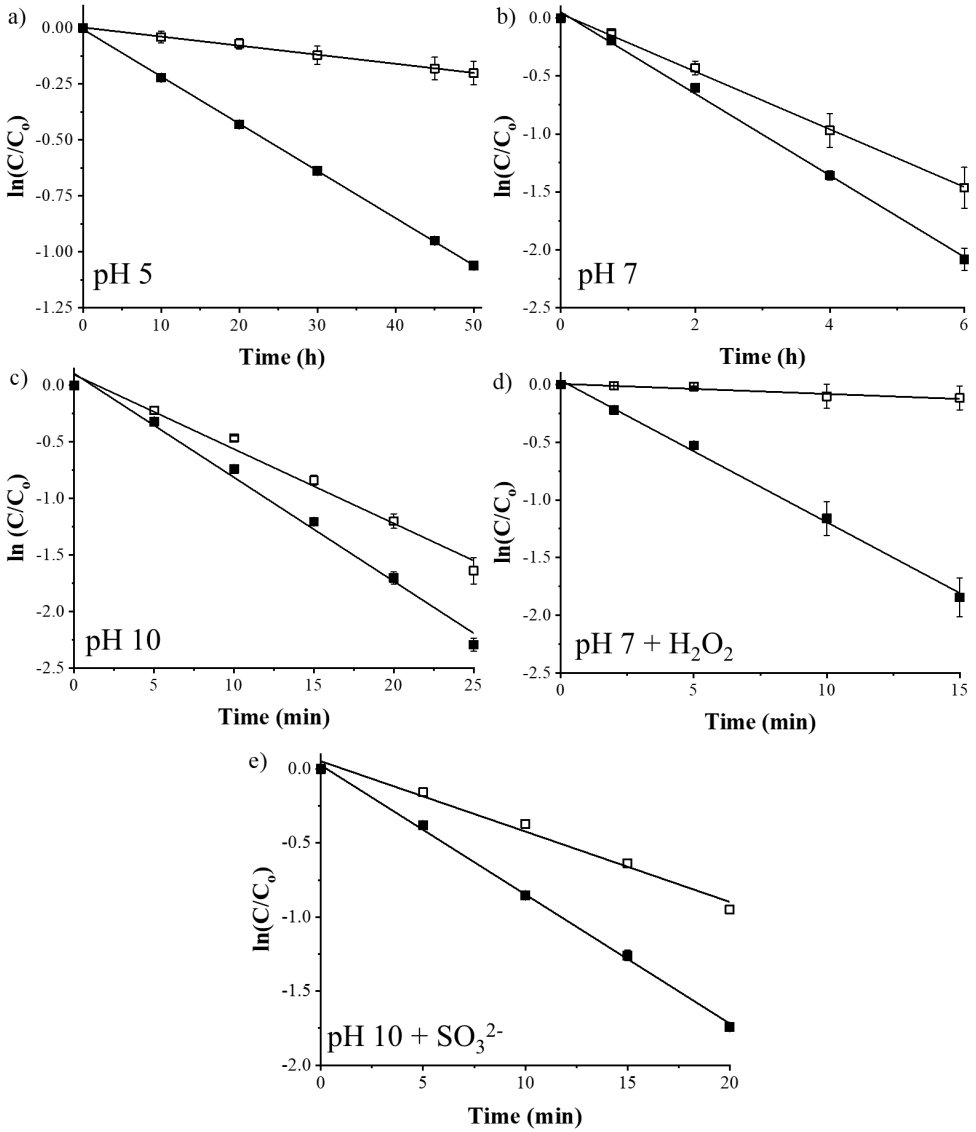


Figure S6. Photochemical degradation plots of 4-(trifluoromethyl)phenol (**1c**) with hydrolysis (□) and photolysis (■) rate constants of (a) 4.1×10^{-3} ± 3.6×10^{-4} h^{-1} and 0.02 ± 5.5×10^{-4} h^{-1} in a 10 mM pH 5 acetate buffer, (b) 0.25 ± 0.01 h^{-1} and 0.10 ± 0.02 h^{-1} in a 10 mM pH 7 phosphate buffer, (c) 3.93 ± 0.57 h^{-1} and 1.58 ± 0.71 h^{-1} in a 10 mM pH 10 borate buffer, (d) 0.52 ± 0.18 h^{-1} and 6.85 ± 0.93 h^{-1} in a 10 mM pH 7 phosphate buffer with 1 mM H_2O_2, and (e) 2.85 ± 0.39 h^{-1} and 2.38 ± 0.45 h^{-1} in a 10 mM pH 10 borate buffer with 0.5 mM SO_3^{-2}. Note the change in time units on the x-axis. Error bars represent the standard deviation between triplicate samples taken on HPLC. Reported rate constant errors represent the average 95% confidence interval determined by regression statistics, and photolysis rate constants are corrected for any loss in the dark controls.

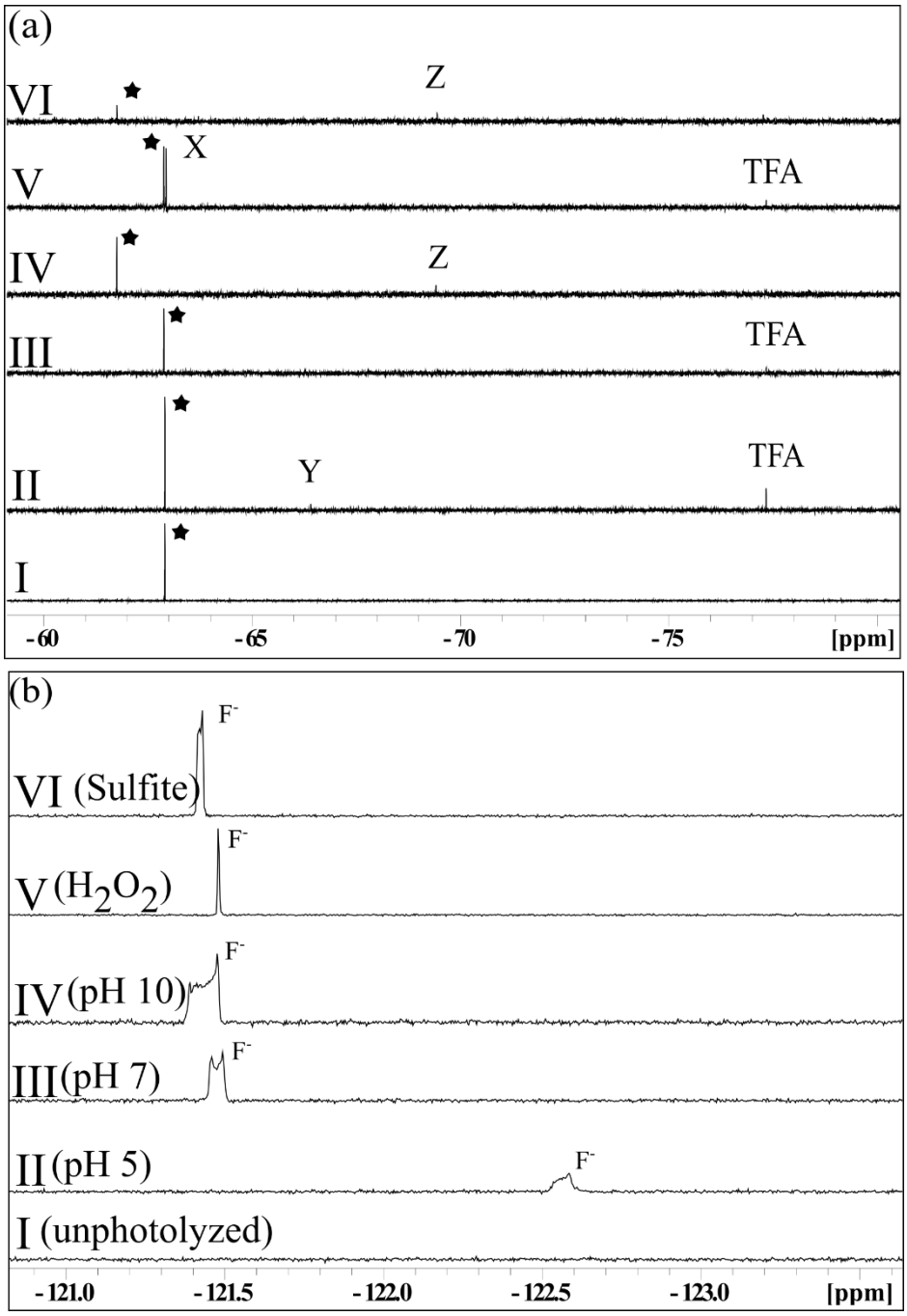


Figure S7. ^{19}F-NMR spectra of 4-(trifluoromethyl)phenol (**1c**) before photolysis (I) and after photolysis in pH 5 acetate buffer (II), pH 7 phosphate buffer (III), pH 10 borate buffer (IV), pH 7 buffer with 1 mM H_2O_2 (V), and pH 10 with 0.5 mM SO_3^{2-} (VI). The parent **1c**, (black star) and fluorinated photoproducts with similar NMR shifts (X, Y, and Z) including trifluoroacetic acid (TFA) are shown in (a), the unphotolyzed sample was scaled by a factor of 4. Fluoride (F^-) production is shown in (b) and samples I and II were scaled by a factor of 2.

Table S6. 4-(Trifluoromethyl)phenol (**1c**) parent and photoproduct mass balance as μM of fluorine before and after photolysis.

	Sample	Parent/Product	[Fluorine] (μM)	Error ±
pH 5	Unphotolyzed	**1c**	28.98	0.13
		Total	28.98	0.13
	Photolyzed	**1c**	8.02	0.05
		Product C	4.4	0.03
		TFA	2.64	7.30E-03
		Fluoride	15.05	0.06
		Total	30.11	0.08
pH 7	Unphotolyzed	**1c**	30.15	0.15
		Total	30.15	0.15
	Photolyzed	**1c**	3.1	0.02
		TFA	1.2	
		Fluoride	25.43	0.09
		Total	29.73	0.09
pH 10	Unphotolyzed	**1c**	28.98	0.11
		Total	28.98	0.11
	Photolyzed	**1c**	2.98	0.03
		Product D	1.02	7.60E-03
		Fluoride	25.66	0.32
		Total	29.66	0.32
H_2O_2	Unphotolyzed	**1c**	30.15	0.22
		Total	30.15	0.22
	Photolyzed	**1c**	4.99	0.03
		Product A	6.2	0.03
		TFA	2.3	3.70E-03
		Fluoride	16.7	0.06
		Total	30.19	0.07
Sulfite	Unphotolyzed	**1c**	30.15	0.26
		Total	30.15	0.26
	Photolyzed	**1c**	5.1	0.01
		Product D	2.1	0.01
		Fluoride	24.98	0.32
		Total	32.18	0.32

d. 2-Fluorophenol

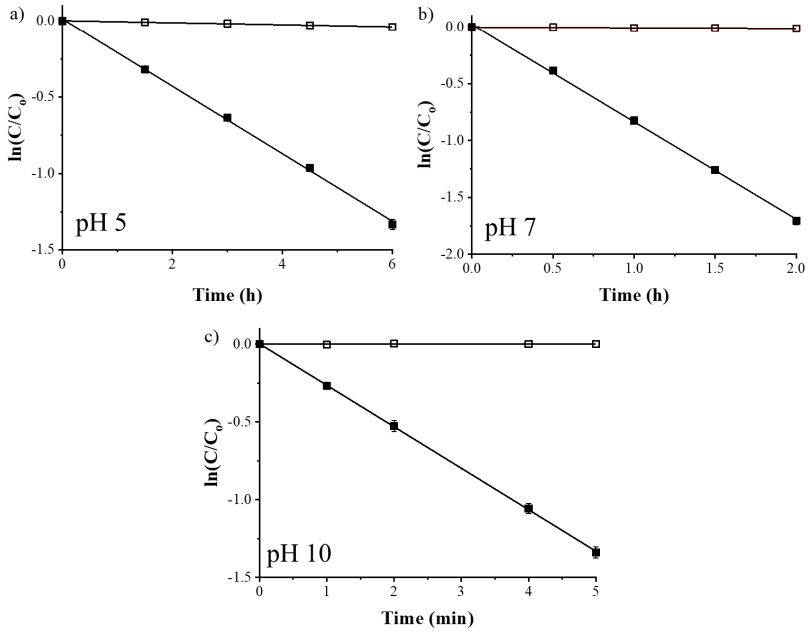


Figure S8. Photochemical degradation plots of 2-fluorophenol (**2a**) with hydrolysis (□) and photolysis (■) rate constants of (a) 0.01 ± 6.3×10^{-4} h^{-1} and 0.21 ± 0.01 h^{-1} in a 10 mM pH 5 acetate buffer, (b) 0.01 ± 2.9×10^{-3} h^{-1} and 0.85 ± 0.03 h^{-1} in a 10 mM pH 7 phosphate buffer, and (c) 0.01 ± 0.13 h^{-1} and 15.99 ± 0.37 h^{-1} in a 10 mM pH 10 borate buffer. Note the change in time units on the x-axis. Error bars represent the standard deviation between triplicate samples taken on HPLC. Reported rate constant errors represent the average 95% confidence interval determined by regression statistics, and photolysis rate constants are corrected for loss in dark controls.

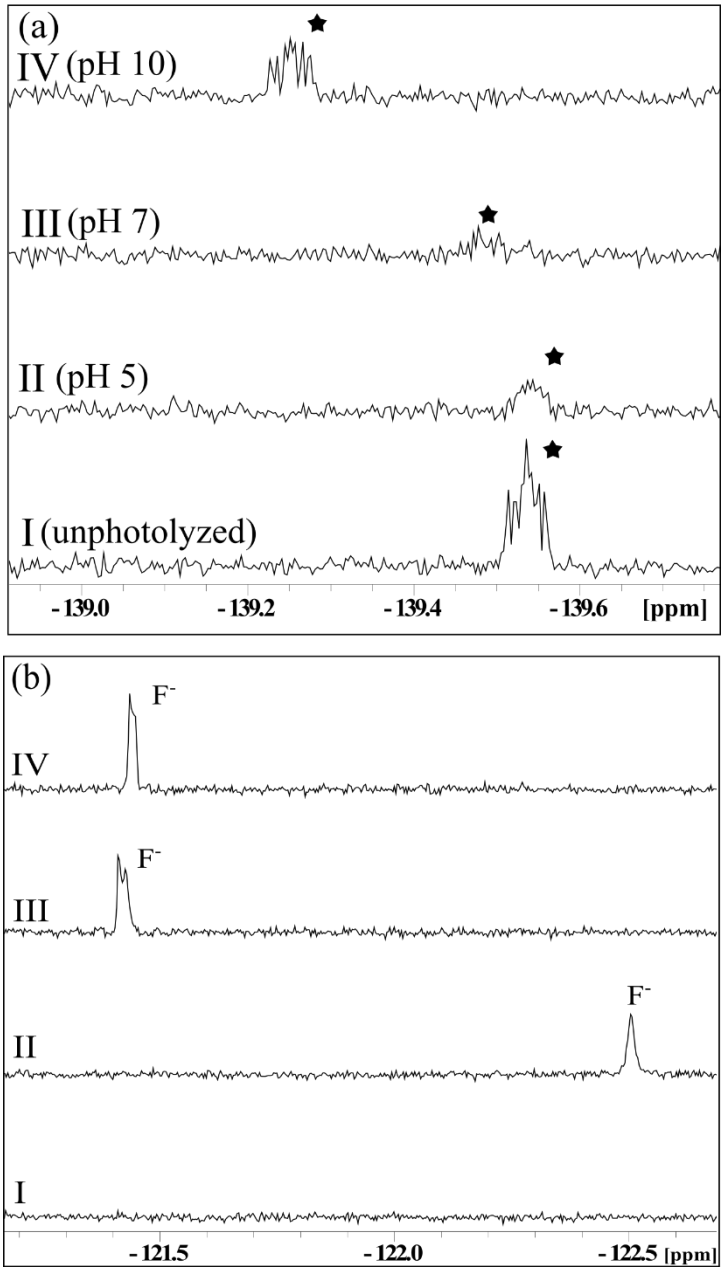


Figure S9. ^{19}F-NMR spectra of 2-fluorophenol (**2a**) before photolysis (I) and after photolysis in pH 5 acetate buffer (II), pH 7 phosphate buffer (III), and pH 10 borate buffer (IV). The parent **2a** (black star) is shown in (a), and the fluoride (F^-) production is shown in (b).

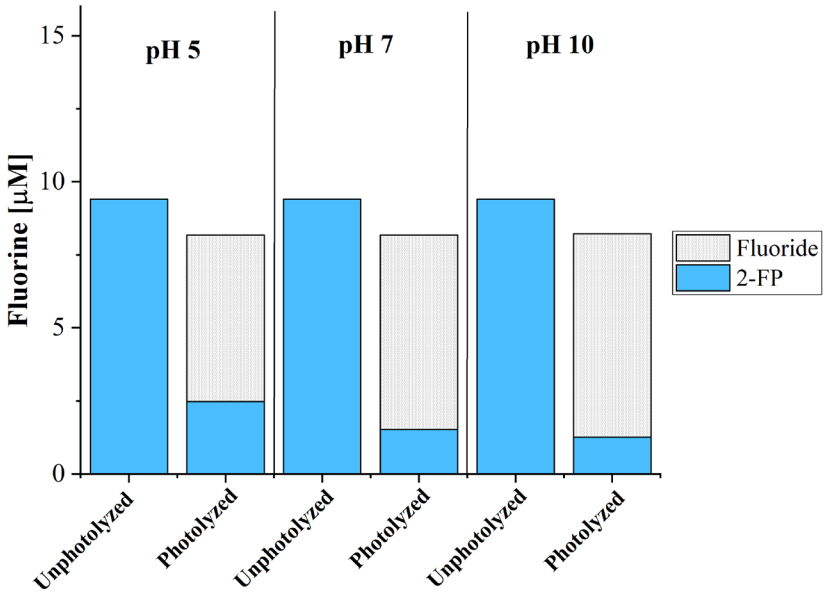


Figure S10. Fluorine mass balance as moles of total fluorine for the photolysis of 2-fluorophenol (**2a**) at 6 hours for pH 5, 2 hours for pH 7, and 5 minutes for pH 10.

Table S7. 2-Fluorophenol (**2a**) parent and photoproduct mass balance as µM of fluorine before and after photolysis.

	Sample	Parent/Product	[Fluorine] (µM)	Error ±
pH 5	Unphotolyzed	**2a**	9.4	0.03
		Total	9.4	0.03
	Photolyzed	**2a**	2.48	0.02
		Fluoride	5.69	0.05
		Total	8.17	0.06
pH 7	Unphotolyzed	**2a**	9.4	0.05
		Total	9.4	0.05
	Photolyzed	**2a**	1.52	0.02
		Fluoride	6.65	0.08
		Total	8.17	0.08
pH 10	Unphotolyzed	**2a**	9.4	0.1
		Total	9.4	0.1
	Photolyzed	**2a**	1.26	0.04
		Fluoride	6.96	0.1
		Total	8.22	0.11

e. 3-Fluorophenol

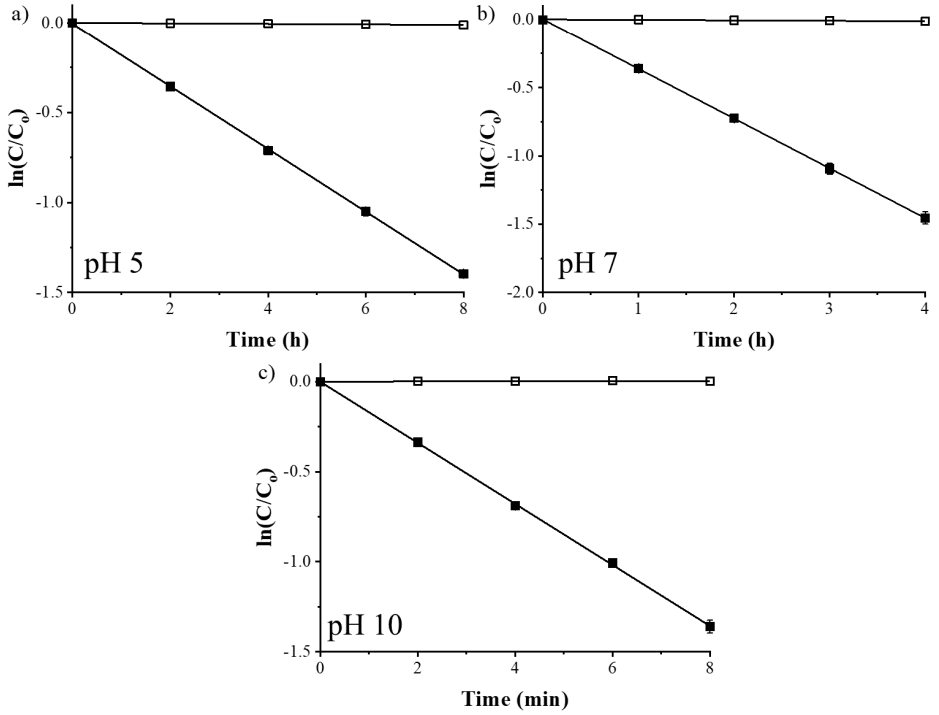


Figure S11. Photochemical degradation plots of 3-fluorophenol (**2b**) with hydrolysis (□) and photolysis (■) rate constants of (a) $1.4\times10^{-3} \pm 2.9\times10^{-4}$ h^{-1} and $0.17 \pm 2.5\times10^{-3}$ h^{-1} in a 10 mM pH 5 acetate buffer, (b) $3.1\times10^{-3} \pm 1.7\times10^{-3}$ h^{-1} and 0.36 ± 0.01 h^{-1} in a 10 mM pH 7 phosphate buffer, and (c) 0.02 ± 0.10 h^{-1} and 10.15 ± 0.29 h^{-1} in a 10 mM pH 10 borate buffer. Note the change in time units on the x-axis. Error bars represent the standard deviation between triplicate samples taken on HPLC. Reported rate constant errors represent the average 95% confidence interval determined by regression statistics, and photolysis rate constants were corrected for any losses in dark controls.

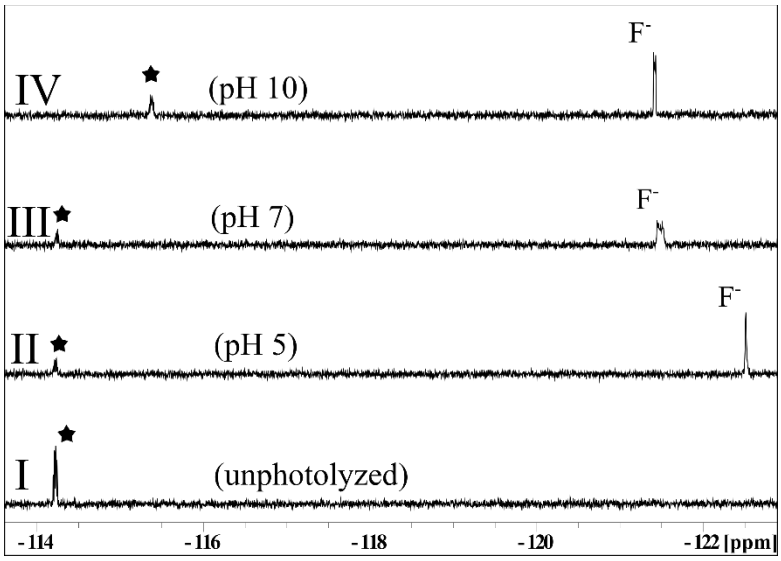


Figure S12. ^{19}F-NMR spectra of 3-fluorophenol (**2b**) before photolysis (I) and after photolysis in pH 5 acetate buffer (II), pH 7 phosphate buffer (III), and pH 10 borate buffer (IV). The parent **2b**, (black star) and fluoride (F^-) production are shown in the same panel.

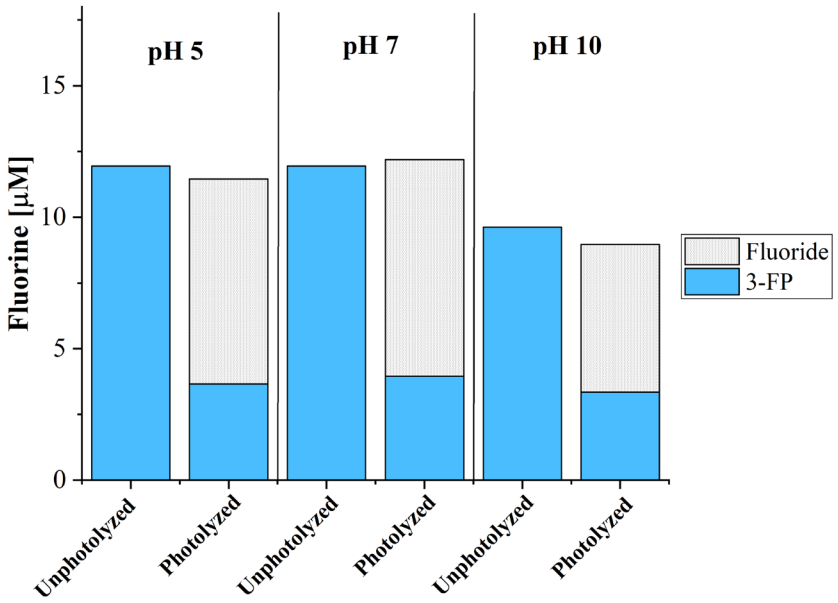


Figure S13. Fluorine mass balance as moles of total fluorine for the photolysis of 3-fluorophenol (**2b**) at 4 hours for pH 5, 4 hours for pH 7, and 8 minutes for pH 10.

Table S8. Mass balance data for **2b** as μM of fluorine.

	Sample	Parent/Product	[Fluorine] (μM)	Error ±
pH 5	Unphotolyzed	**2b**	11.94	0.1
		Total	11.94	0.1
	Photolyzed	**2b**	3.65	0.1
		Fluoride	7.81	0.03
		Total	11.46	0.04
pH 7	Unphotolyzed	**2b**	11.94	0.09
		Total	11.94	0.09
	Photolyzed	**2b**	3.95	0.01
		Fluoride	8.24	0.05
		Total	12.19	0.05
pH 10	Unphotolyzed	**2b**	11.94	0.13
		Total	11.94	0.13
	Photolyzed	**2b**	3.35	0.04
		Fluoride	5.61	0.08
		Total	8.96	0.09

f. 4-Fluorophenol

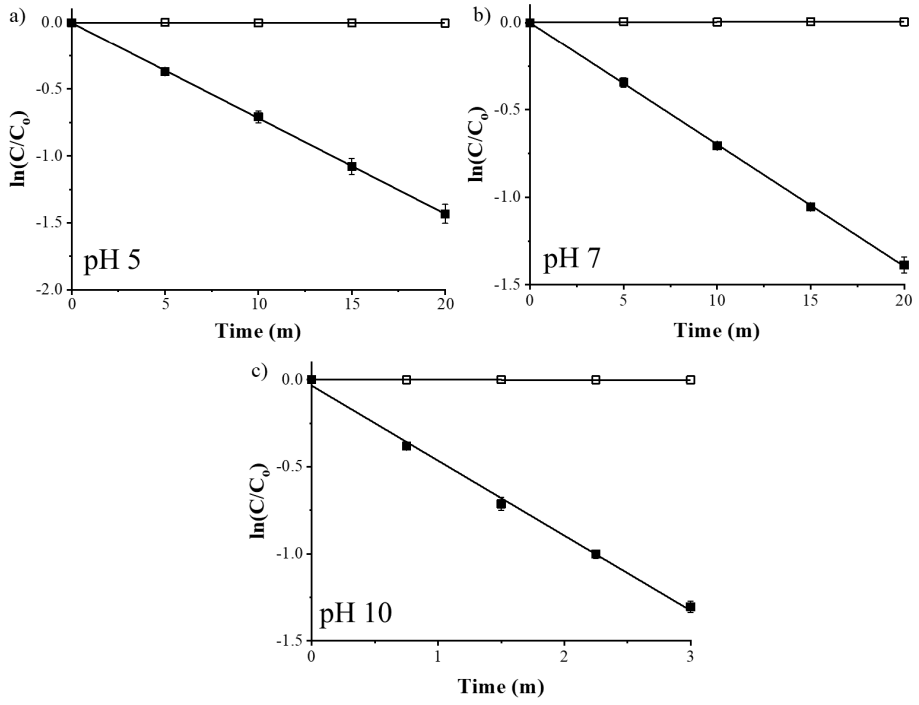


Figure S14. Photochemical degradation plots of 4-fluorophenol (**2c**) with hydrolysis (□) and photolysis (■) rate constants of (a) 0.01 ± 0.01 h^{-1} and 4.28 ± 0.10 h^{-1} in a 10 mM pH 5 acetate buffer, (b) 9.9×10^{-3} ± 0.02 h^{-1} and 4.17 ± 0.11 h^{-1} in a 10 mM pH 7 phosphate buffer, and (c) 0.01 ± 0.08 h^{-1} and 25.82 ± 1.66 h^{-1} in a 10 mM pH 10 borate buffer. Error bars represent the standard deviation between triplicate samples taken on HPLC. Reported rate constant errors represent the average 95% confidence interval determined by regression statistics, and photolysis rate constants are corrected for any losses in dark controls.

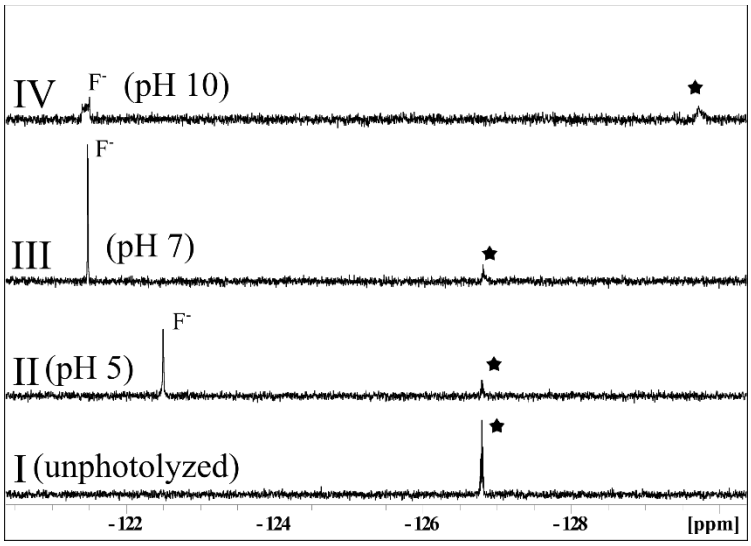


Figure S15. ^{19}F-NMR spectra of 4-fluorophenol (**2c**) before photolysis (I) and after photolysis in pH 5 acetate buffer (II), pH 7 phosphate buffer (III), and pH 10 borate buffer (IV). The parent **2c** and fluoride (F^-) production are shown in the same panel.

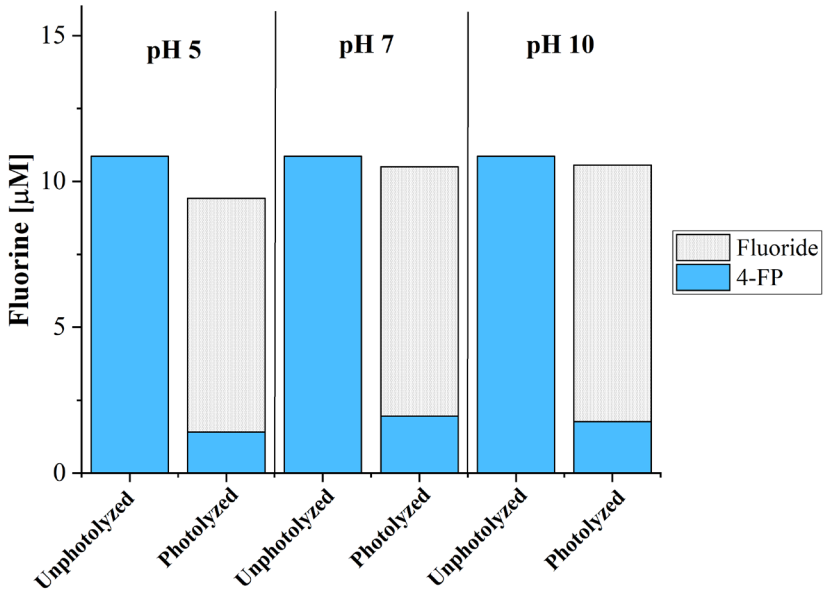
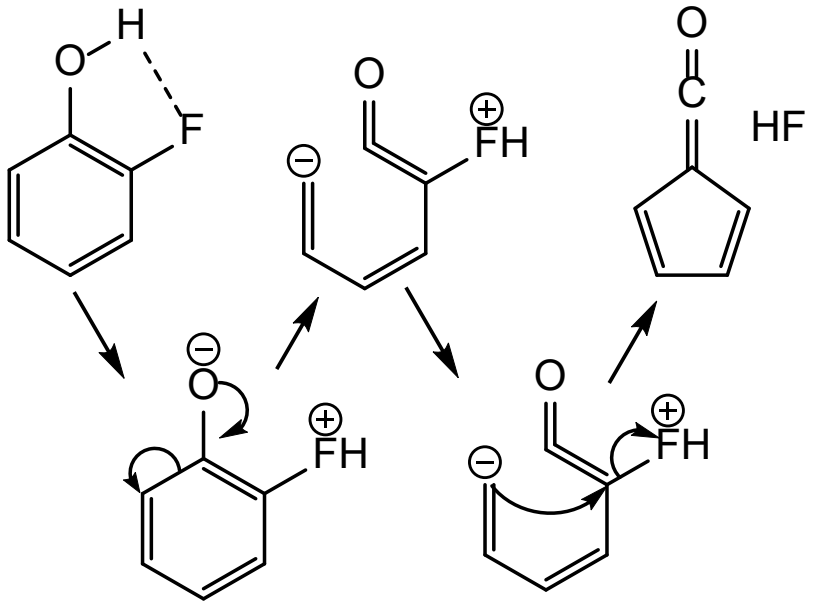


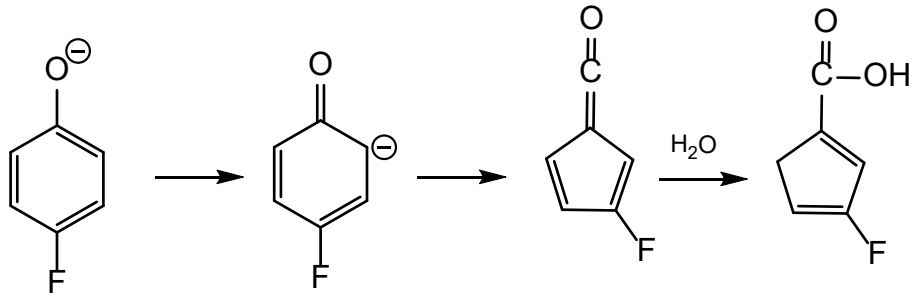
Figure S16. Fluorine mass balance as moles of total fluorine for the photolysis of 4-fluorophenol (**2c**) at 20 minutes for pH 5, 20 minutes for pH 7, and 3 minutes for pH 10.

Table S9. Mass balance data for **2c** as μM of fluorine.

	Sample	Parent/Product	[Fluorine] (μM)	Error ±
pH 5	Unphotolyzed	**2c**	10.86	0.03
		Total	10.86	0.03
	Photolyzed	**2c**	1.41	0.03
		Fluoride	8.01	0.04
		Total	9.42	0.08
pH 7	Unphotolyzed	**2c**	10.86	0.06
		Total	10.86	0.06
	Photolyzed	**2c**	1.95	0.01
		Fluoride	8.55	0.04
		Total	10.5	0.04
pH 10	Unphotolyzed	**2c**	10.86	0.04
		Total	10.86	0.04
	Photolyzed	**2c**	1.76	0.02
		Fluoride	8.8	0.03
		Total	10.56	0.04



Scheme S1. Mineralization pathway of 2-FP as proposed by Chatterjee et al.[8] Electron pushing is shown between the transition state.



Scheme S2. Possible photo-contraction of the 6-membered aromatic ring to a 5-memebered ring as proposed by Bole et al.[9]

g. 2,6-Difluorophenol

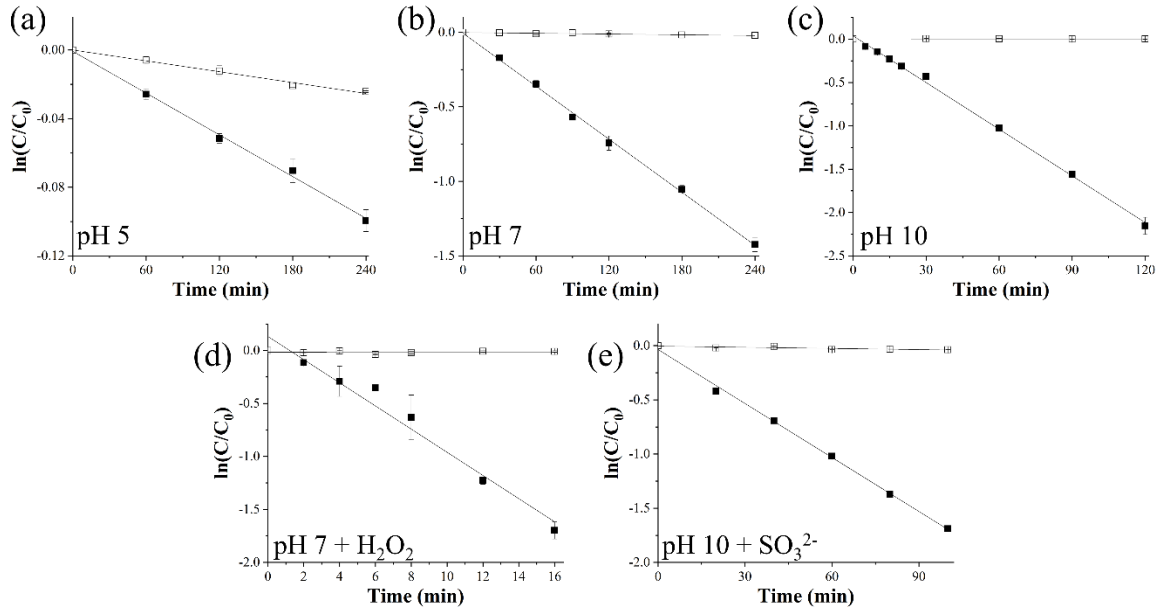


Figure S17. Photochemical degradation plots of 2,6-difluorophenol (**3a**) with hydrolysis (□) and photolysis (■) rate constants of (a) 0.024 ± 8.0 × 10^{-4} h^{-1} and 6.34 × 10^{-3} ± 3.9 × 10^{-4} h^{-1} in a 10 mM pH 5 acetate buffer, (b) 0.32 ± 6.2 × 10^{-3} h^{-1} and 5.4 × 10^{-3} ± 8.9 × 10^{-4} h^{-1} in a 10 mM pH 7 phosphate buffer, (c) 1.08 ± 0.02 h^{-1} and 8.4 × 10^{-4} ± 2.1 × 10^{-4} h^{-1} in a 10 mM pH 10 borate buffer, (d) 6.56 ± 0.51 h^{-1} and 9.32 × 10^{-4} ± 5.8 × 10^{-4} h^{-1} in a 10 mM pH 7 phosphate buffer with 1 mM H_2O_2, and (e) 1.0 ± 0.024 h^{-1} and 0.021 ± 7.23 × 10^{-3} h^{-1} in a 10 mM pH 10 borate buffer with 0.5 mM SO_3^{-2}. Note the change in time units on the x-axis. Error bars represent the standard deviation between triplicate samples taken on HPLC. Reported rate constant errors represent the average 95% confidence interval determined by regression statistics, and photolysis rate constants are corrected for any losses in dark samples.

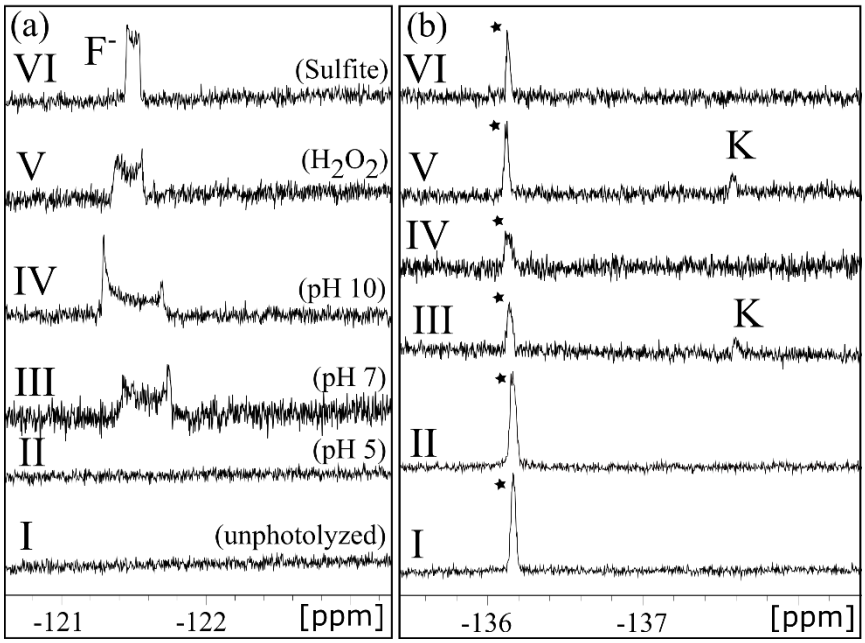


Figure S18. ^{19}F-NMR spectra of 2,6-difluorophenol (**3a**) before photolysis (I) and after photolysis in pH 5 acetate buffer (II), pH 7 phosphate buffer (III), pH 10 borate buffer (IV), pH 7 buffer with 1 mM H_2O_2 (V), and pH 10 with 0.5 mM SO_3^{2-} (VI). The parent and fluorinated photoproducts with similar NMR shifts (K) including trifluoroacetic acid (TFA) are shown in (b), the unphotolyzed sample was scaled by a factor of 4. Fluoride (F^-) production is shown in (a). Some samples had a lower S/N ratio leading to an error of <5% for **3a.**

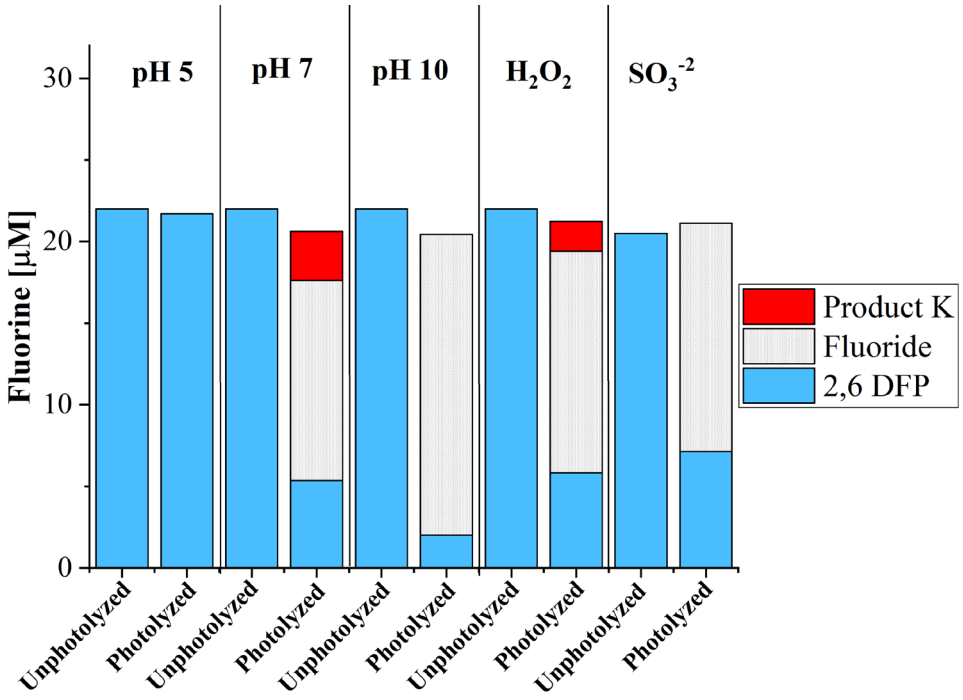


Figure S19. Fluorine mass balance as μM of total fluorine for the photolysis of **3a** at various conditions. The product K had a shift of -137.7 ppm.

Table S10. Fluorine mass balance as µM of total fluorine for the photolysis of **3a**

	Sample	Parent/Product	[Fluorine] (µM)	Error ±
pH 5	Unphotolyzed	**3a**	22	0.88
		Total	22	0.88
	Photolyzed	**3a**	21.7	0.63
		Fluoride	0	0
		Product K	0	0
		Total	21.7	0.63
pH 7	Unphotolyzed	**3a**	22	0.88
		Total	22	0.88
	Photolyzed	**3a**	5.35	0.2
		Fluoride	12.27	0.2
		Product K	3	0.08
		Total	20.62	0.48
pH 10	Unphotolyzed	**3a**	22	0.88
		Total	22	0.88
	Photolyzed	**3a**	2	0.08
		Fluoride	18.43	1.2
		Product K	0	0
		Total	20.43	2
H_2O_2	Unphotolyzed	**3a**	22	0.88
		Total	22	0.88
	Photolyzed	**3a**	5.83	0.16
		Fluoride	13.58	1.2
		Product K	1.83	0.03
		Total	21.24	1.39
Sulfite	Unphotolyzed	**3a**	20.5	0.4
		Total	20.5	0.4
	Photolyzed	**3a**	7.12	0.6
		Fluoride	14	1.1
		Product K	0	0
		Total	21.12	1.7

h. 3,5-Difluorophenol

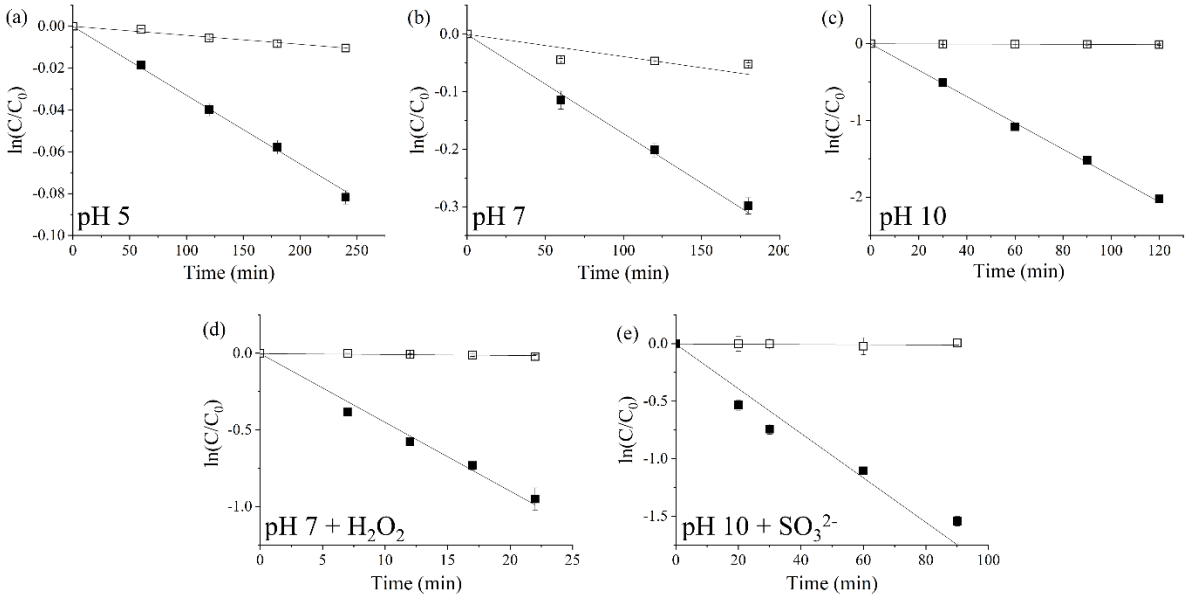


Figure S20. Photochemical degradation plots of 3,5-difluorophenol (**3b**) with hydrolysis (□) and photolysis (■) rate constants of (a) $2.9\times10^{-3} \pm 3\times10^{-4}$ h^{-1} and $2.1\times10^{-2} \pm 1\times10^{-4}$ h^{-1} in a 10 mM pH 5 acetate buffer, (b) 1.6 x $10^{-2} \pm 7.0\times10^{-3}$ h^{-1} and $9.8\times10^{-2} \pm 1\times10^{-3}$ h^{-1} in a 10 mM pH 7 phosphate buffer, (c) $7.9\times10^{-3} \pm 4.4\times10^{-3}$ h^{-1} and $1.0 \pm 3.7\times10^{-2}$ h^{-1} in a 10 mM pH 10 borate buffer, (d) $4.8\times10^{-2} \pm 2.6\times^{-2}$ h^{-1} and 2.68 ± 0.25 h^{-1} in a 10 mM pH 7 phosphate buffer with 1 mM H_2O_2, and (e) $4.0\times10^{-3} \pm 3.0\times10^{-2}$ h^{-1} and 1.07 ± 0.19 h^{-1} in a 10 mM pH 10 borate buffer with 0.5 mM SO_3^{-2}. Note the change in time units on the x-axis. Error bars represent the standard deviation between triplicate samples taken on HPLC. Reported rate constant errors represent the average 95% confidence interval determined by regression statistics, and photolysis rate constants are corrected for any losses in dark samples.

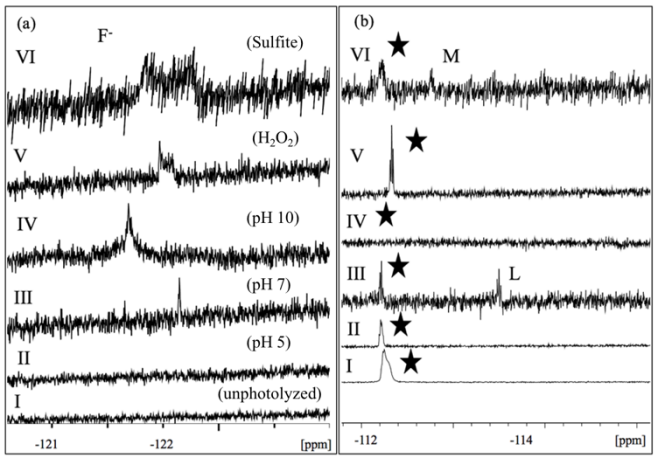


Figure S21. ^{19}F-NMR spectra of 3,5-difluorophenol (**3b**) before photolysis (I) and after photolysis in pH 5 acetate buffer (II), pH 7 phosphate buffer (III), pH 10 borate buffer (IV), pH buffer with 1 mM H_2O_2 (V), and pH 10 with 0.5 mM SO_3^{2-} (VI). The parent and fluorinated photoproducts

with similar NMR shifts (product L and M) are shown in (b) and Fluoride (F^-) production is shown in (a). Some samples had a S/N ratio of less than 150:1 leading to an error of <5%.

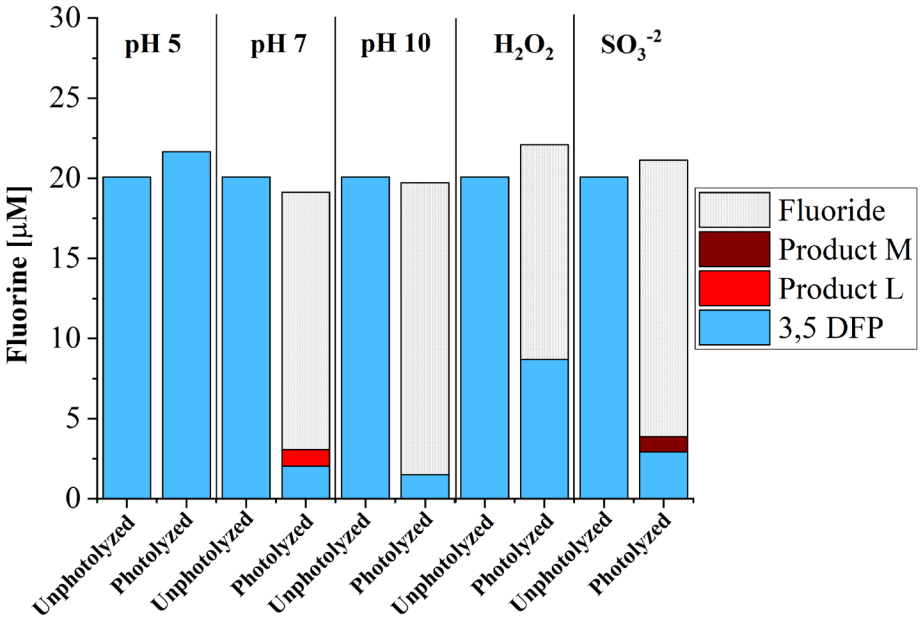


Figure S22. Fluorine mass balance as moles of total fluorine for the photolysis of **3b** at various conditions. Product L has a shift of -113.6 ppm and product M has a shift of -112.7 ppm.

Table S11. Fluorine mass balance as µM of total fluorine for the photolysis of **3b**

	Sample	Parent/Product	[Fluorine] (µM)	Error ±
pH 5	Unphotolyzed	**3b**	20	0.88
		Total	20	0.88
	Photolyzed	**3b**	21.7	0.63
		Fluoride	0	0
		Product M or L	0	0
		Total	21.7	0.63
pH 7	Unphotolyzed	**3b**	20	0.88
		Total	20	0.88
	Photolyzed	**3b**	2.03	0.2
		Fluoride	16.1	0.2
		Product L	1.04	0.08
		Total	19.17	0.48
pH 10	Unphotolyzed	**3b**	20	0.88

		Total	20	0.88
	Photolyzed	**3b**	1.51	0.08
		Fluoride	18.21	1.2
		Product M or L	0	0
		Total	19.72	2
H_2O_2	Unphotolyzed	**3b**	20	0.88
		Total	20	0.88
	Photolyzed	**3b**	8.68	0.16
		Fluoride	13.41	1.2
		Product M or L	0	0
		Total	22.09	1.39
Sulfite	Unphotolyzed	**3b**	20	0.4
		Total	20	0.4
	Photolyzed	**3b**	4.36	0.6
		Fluoride	17.25	1.1
		Product M	0	0
		Total	21.61	1.7

i. Fluoxetine

Kinetics

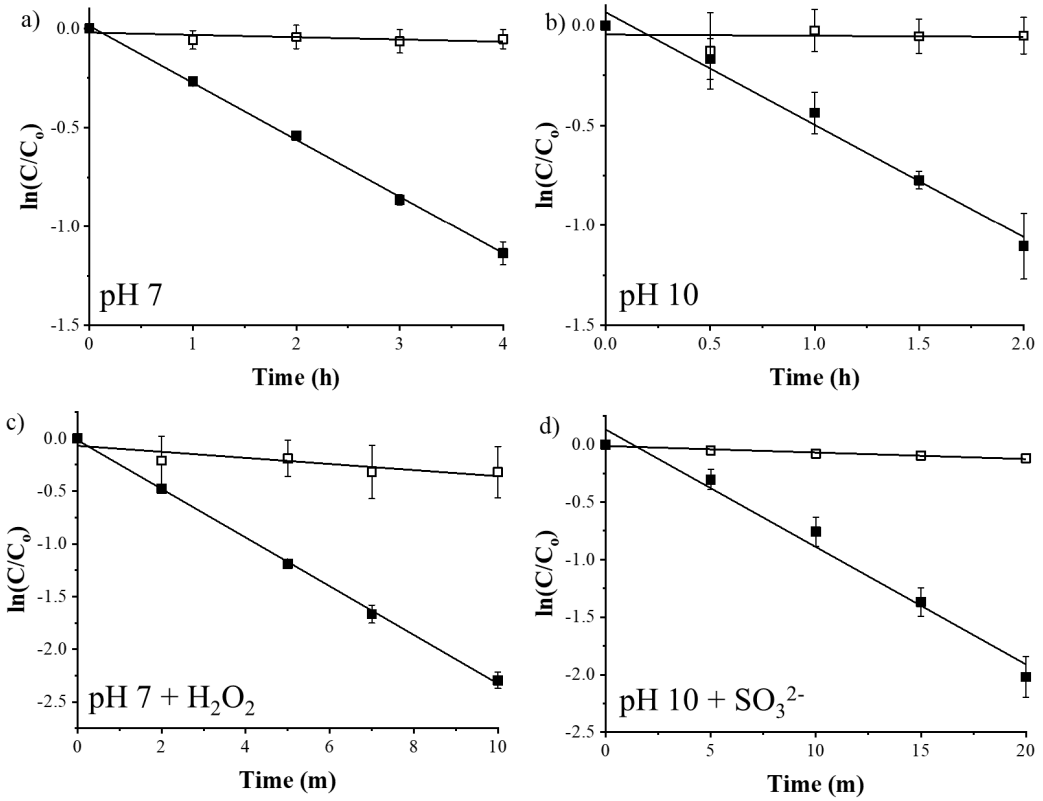


Figure S23. Photochemical degradation plots of fluoxetine (**4a**) with hydrolysis (□) and photolysis (■) rate constants of (a) 0.02 ± 0.01 h^{-1} and 0.27 ± 0.01 h^{-1} in a 10 mM pH 7 phosphate buffer, (b) 0.01 ± 0.10 h^{-1} and 0.56 ± 0.15 h^{-1} in a 10 mM pH 10 borate buffer, (c) 1.73 ± 1.46 h^{-1} and 12.13 ± 1.54 h^{-1} in a 10 mM pH 7 phosphate buffer with 1 mM H_2O_2, and (d) 0.34 ± 0.11 h^{-1} and 5.79 ± 0.95 h^{-1} in a 10 mM pH 10 borate buffer with 0.5 mM SO_3^{-2}. Note the change in time units on the x-axis. Error bars represent the standard deviation between triplicate samples taken on HPLC. Reported rate constant errors represent the average 95% confidence interval determined by regression statistics, and photolysis rate constants were corrected for any losses in the dark samples.

Table S12. Fluorine mass balance as moles of total µM fluorine for the photolysis of fluoxetine (**4a**).

	Sample	Parent/Product	[Fluorine] (µM)	Error ±
pH 7	Unphotolyzed	**4a**	30.78	0.12
		Total	30.78	0.12
	Photolyzed	**4a**	9	0.04
		Modified fluoxetine	5.1	0.05
		Product C	0.93	0.03
		Product D	1	4.00E-03
		TFA	1.2	3.60E-03
		Fluoride	16.9	0.07
pH 10	Unphotolyzed	**4a**	30.78	0.31
		Total	30.78	0.31
	Photolyzed	**4a**	9.01	0.1
		Modified fluoxetine	7.96	0.12
		Fluoride	13.81	0.13
H_2O_2	Unphotolyzed	**4a**	30.78	0.11
		Total	30.78	0.11
	Photolyzed	**4a**	2.3	0.04
		Modified Fluoxetine	0.4	0.04
		Product C	0.45	0.04
		Product D	1.26	0.02
		TFA	2.47	0.01
		Fluoride	23.13	0.08
Sulfite	Unphotolyzed	**4a**	30.78	0.19
		Total	30.78	0.19
	Photolyzed	**4a**	2.3	0.07
		Modified Fluoxetine	14.34	0.05
		Product E	1.92	0.02
		Fluoride	13.26	0.11

j. Sitagliptin

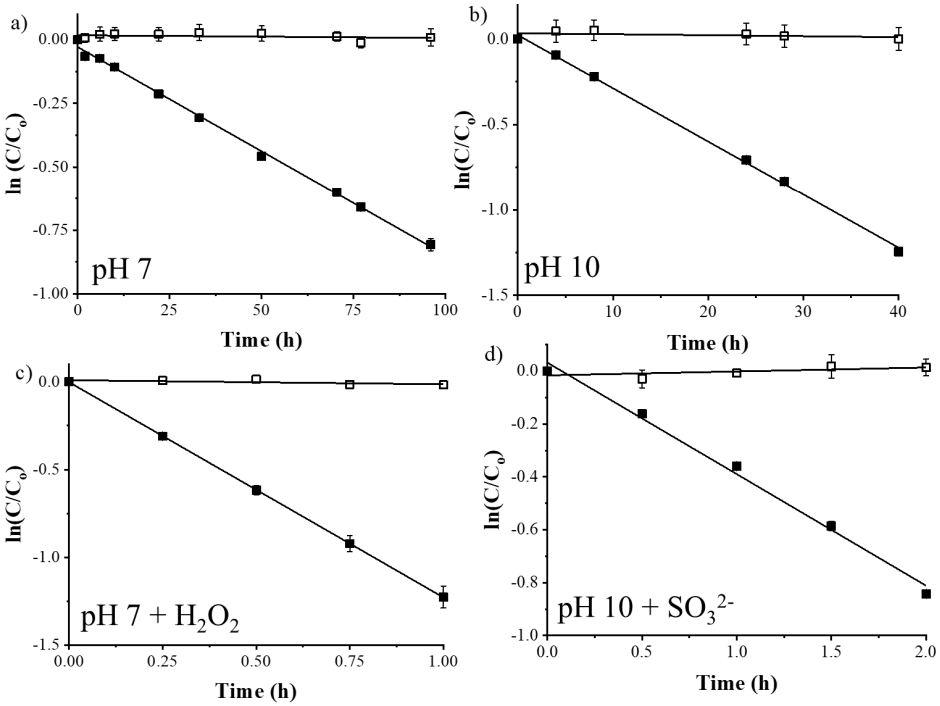


Figure S24. Photochemical degradation plot of sitagliptin (**4b**) with hydrolysis (□) and photolysis (■) rate constants of (a) $1.0\times10^{-4} \pm 2.1\times10^{-4}$ h^{-1} and $9.6\times10^{-3} \pm 3.8\times10^{-4}$ h^{-1} in a 10 mM pH 7 phosphate buffer, (b) $5.7\times10^{-4} \pm 1.1\times10^{-3}$ h^{-1} and $0.03 \pm 1.4\times10^{-3}$ h^{-1} in a 10 mM pH 10 borate buffer, (c) 0.02 ± 0.03 h^{-1} and 1.21 ± 0.04 h^{-1} in a 10 mM pH 7 phosphate buffer with 2 mM H_2O_2, and (d) -0.01 ± 0.04 h^{-1} and 0.43 ± 0.06 h^{-1} in a 10 mM pH 10 borate buffer with 0.5 mM SO_3^{-2}. Error bars represent the standard deviation between triplicate samples taken on HPLC. Reported rate constant errors represent the average 95% confidence interval determined by regression statistics, and photolysis rate constants were corrected for losses in dark samples.

Table S13. Fluorine mass balance as moles of total fluorine for the photolysis of sitagliptin (**4b**). Other products mentioned in figure 5 (main text) are products N, O, P, Q, R and S.

	Sample	Name	[Fluorine] (µM)	Error ±
pH 7	Unphotolyzed	Parent 1	30.2	2.61
		Parent 2	9.8	2.49
		Parent 3	10.1	1.14
		Parent 4	10.1	0.84
		Total	60.2	4.48
	Photolyzed	Parent 1	18.5	0.16
		Parent 2	7.51	0.15
		Parent 3	5.74	0.07
		Parent 4	6.19	0.05
		Fluoride	12.1	0.01
		Fluoride+2b	0	0
		Product N	0.44	0
		Product O	0	7.40×10^{-3}
		Product P	0	0
		Product Q	0.75	0.02
		Product R	1.27	0.02
		Product F	1.29	0.06
		Product G	3.66	0.04
		Product H	0	0
		Product I	2.12	7.90×10^{-3}
		Product S	0.9	0.2
		Product J	0.48	0.34
		Total	61	
pH 10	Unphotolyzed	Parent 1	30.2	0.18
		Parent 2	9.8	0.14
		Parent 3	10.1	0.07
		Parent 4	10.1	0.06
		Total	60.2	0.28
	Photolyzed	Parent 1	9.91	0.03
		Parent 2	7.28	0.02
		Parent 3	3.5	0.02
		Parent 4	4.82	0.02
		Fluoride	18.1	0.02
		Fluoride+2b	0	0
		Product N	0.58	0.01
		Product O	0.68	2.80×10^{-3}
		Product P	0	0

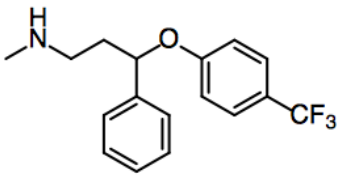
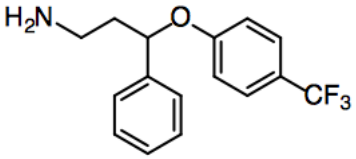
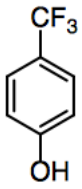
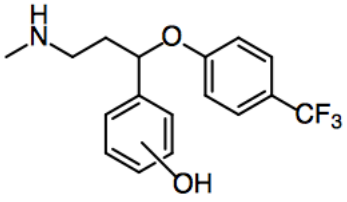
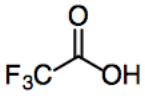
		Product Q	0	0
		Product R	0.79	3.90×10^{-3}
		Product F	0.80	0.02
		Product G	3.71	0.01
		Product H	2.12	3.00×10^{-3}
		Product I	0.61	2.90×10^{-3}
		Product S	0.59	0.03
		Product J	5.48	0.09
		Total	59	0.11
H_2O_2	Unphotolyzed	Parent 1	30.2	0.29
		Parent 2	9.8	0.24
		Parent 3	10.1	0.13
		Parent 4	10.1	0.1
		Total	60.2	0.48
	Photolyzed	Parent 1	14.7	0.08
		Parent 2	6.65	0.1
		Parent 3	3.74	0.05
		Parent 4	4.27	0.05
		Fluoride	19.3	0.05
		Fluoride+2b	0	0
		Product N	0	0
		Product O	0	0
		Product P	0	0
		Product Q	1.06	0.06
		Product R	1.1	0.03
		Product F	5.04	0.03
		Product G	2.27	2.40×10^{-3}
		Product H	2.60	6.10×10^{-3}
		Product I	0	0
		Product S	0.18	0.004
		Product J	0.49	0.003
		Total	61.5	
Sulfite	Unphotolyzed	Parent 1	30.2	2.98
		Parent 2	9.8	2.04
		Parent 3	10.1	1.28
		Parent 4	10.1	1.03
		Total	60.2	4.91
	Photolyzed	Parent 1	22.3	0.21
		Parent 2	3.43	0.03
		Parent 3	6.71	0.04
		Parent 4	6.52	0.1
		Fluoride	0	0

	Fluoride+2b	8.9	0.03
	Product N	0	0.04
	Product O	0	0
	Product P	0.74	0.02
	Product Q	2.33	0.03
	Product R	0	0
	Product F	0	0
	Product G	2.57	0.25
	Product H	0	0
	Product I	1.91	0.02
	Product S	0	0
	Product J	3.02	0.04
	Total	58.5	

7. LC-MS/MS

Fluoxetine

Table S14. Fluoxetine fluorinated photoproduct formation (and one major de-fluorinated identified product) from all reaction matrices. NMR data identifies 4 fluorinated products viz. modified fluoxetine, product C, D, and E along with TFA. Identification of products was done by LC-HRMS and confidence levels were given based on MS isotope ratios and MS/MS fragmentation data as given in **Table S3**.

Elution Time (min)	Name	Structure	Product Confidence
23.58	Parent m/z 310.1414		1
22.88	Modified Fluoxetine (Norfluoxetine) m/z 296.1257		1
26.267	Product C (**1c**) m/z 163.0389		1
21.635 21.678	Product E and D m/z 326.1362		2b
13.721	TFA m/z 115.0540		1

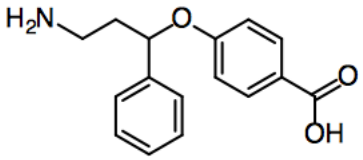
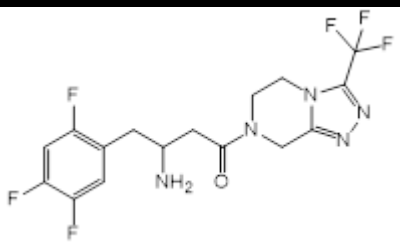
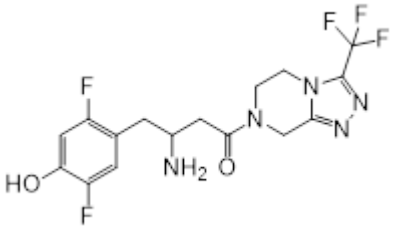
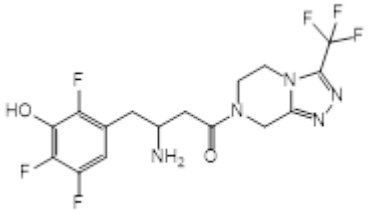
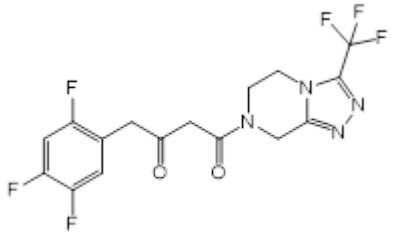
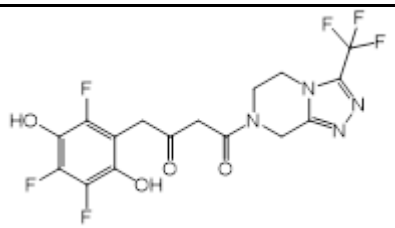
16.277	Product 3 (defluorinated major product) m/z 272.1281		2b

Table S15. Sitagliptin fluorinated photoproduct formation in a pH 7 phosphate buffer. Identification of products was done by LC-HRMS and confidence levels were given based on MS isotope ratios and MS/MS fragmentation data.

Elution Time (min)	Name	Structure	Product Confidence
19.7	Parent m/z 408.1248		1
19.4	Product 1 m/z 406.1296		2b
25.5	Product 2 m/z 424.1203		3
27.2	Product 3 m/z 407.0938		2b

28.5	Product 4 m/z 439.0833		3

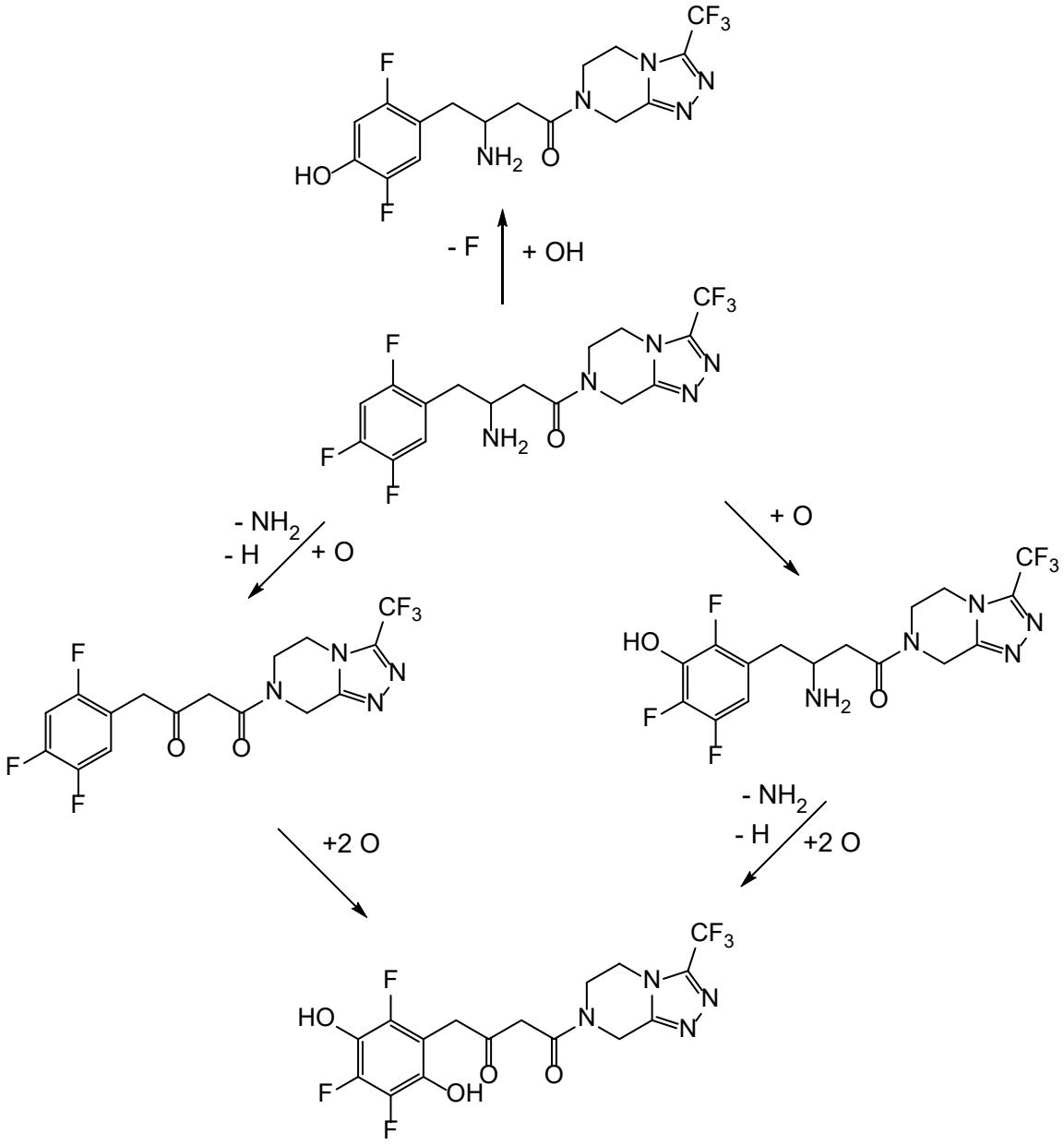


Figure S25. Possible scheme for photoproduct formation for sitagliptin at pH 7. The total atoms added and removed are shown next to the arrows.

Additional Mass Spectrometry Data

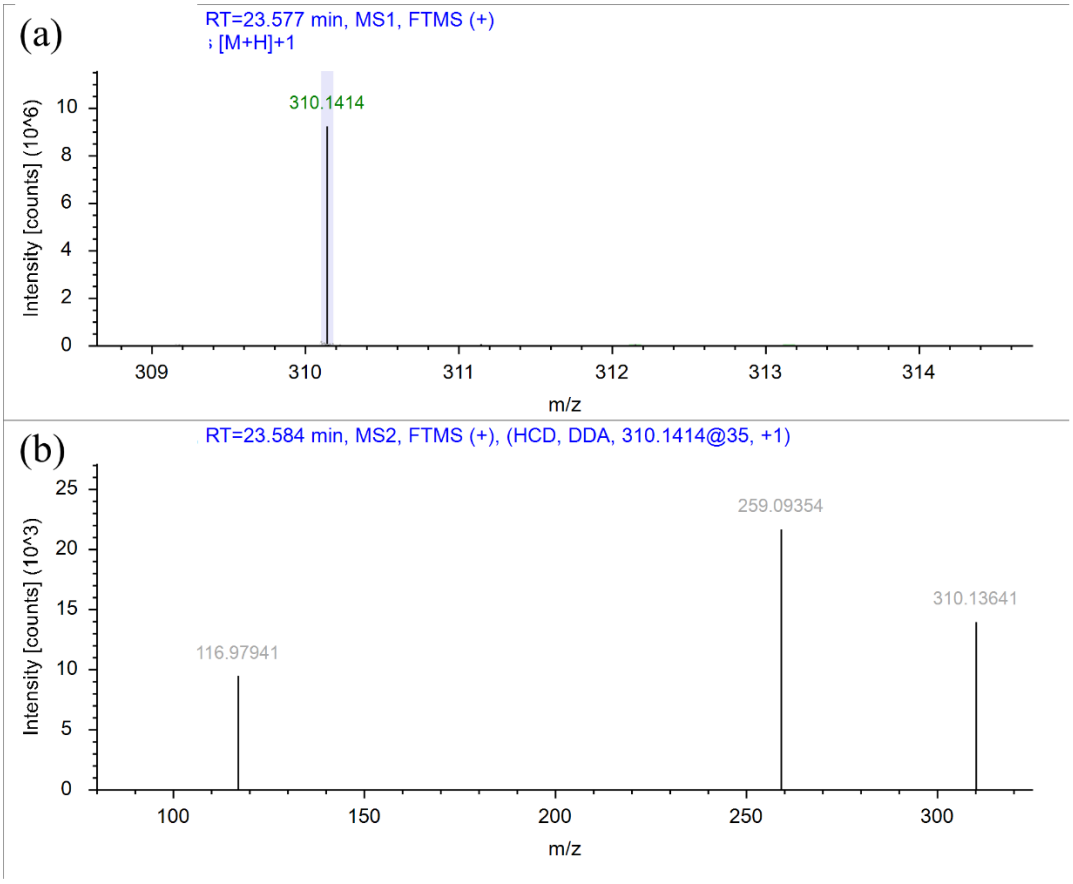


Figure S26. (a) Parent Fluoxetine MS spectra, and (b) MS/MS fragmentation spectra for (a). The compound was identified by the compound discoverer software from a reference standard.

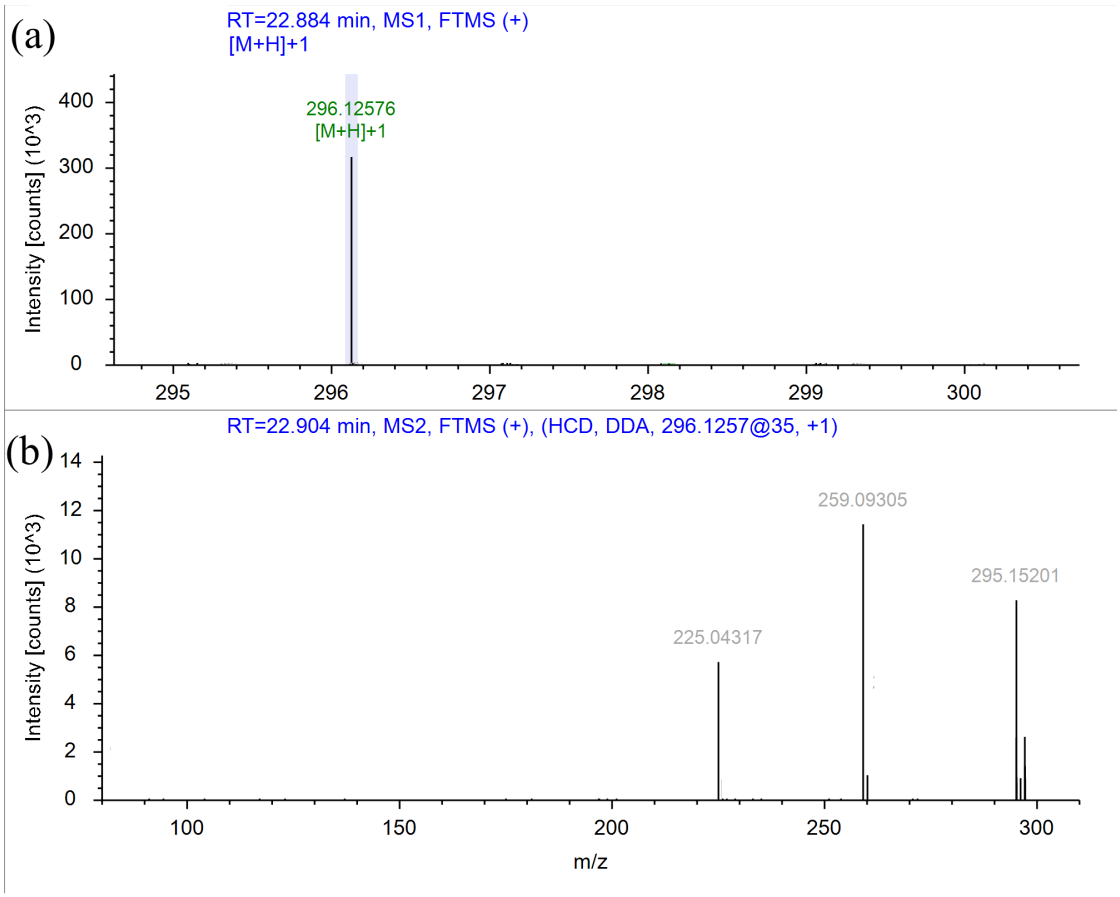


Figure S27. (a) Norfluoxetine (modified fluoxetine) MS spectra, and (b) MS/MS fragmentation data for (a)

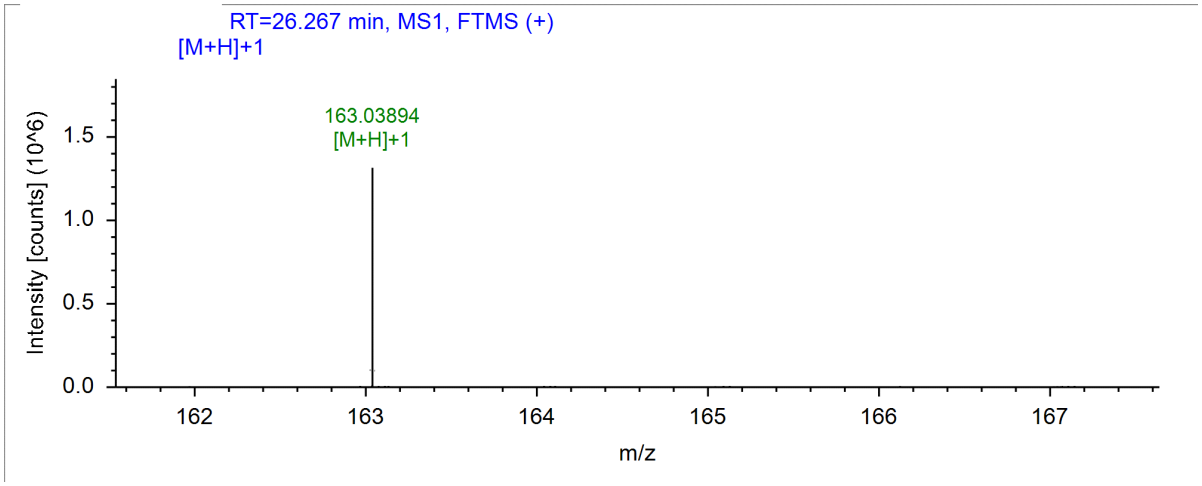


Figure S28. MS spectra for 4-(trifluoromethyl)phenol which was identified as a product of fluoxetine photolysis. The fragmentation data is not shown because the product was identified by the software directly from a reference standard with confidence level 1.

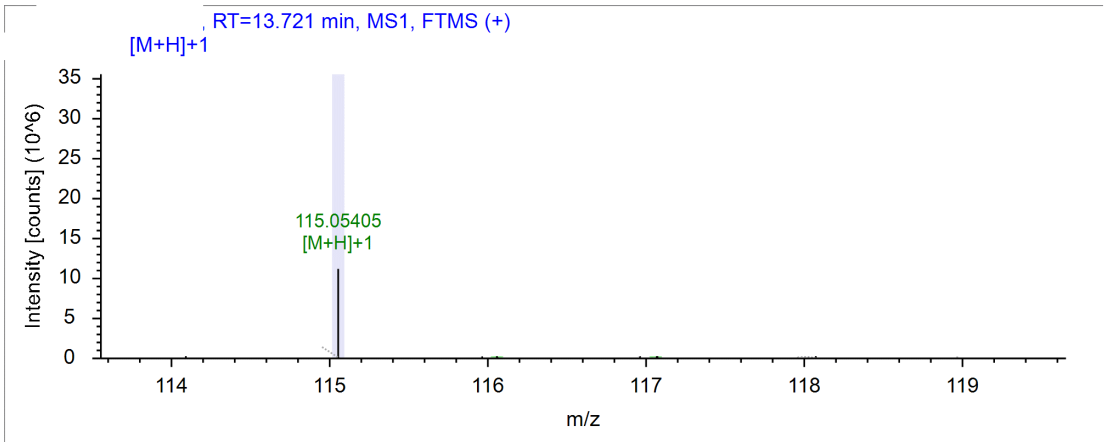


Figure S29. MS spectra for trifluoroaceic acid (TFA) which was identified as a product of fluoxetine photolysis. The fragmentation data is not shown because the product was identified by the software directly from a reference standard with confidence level 1.

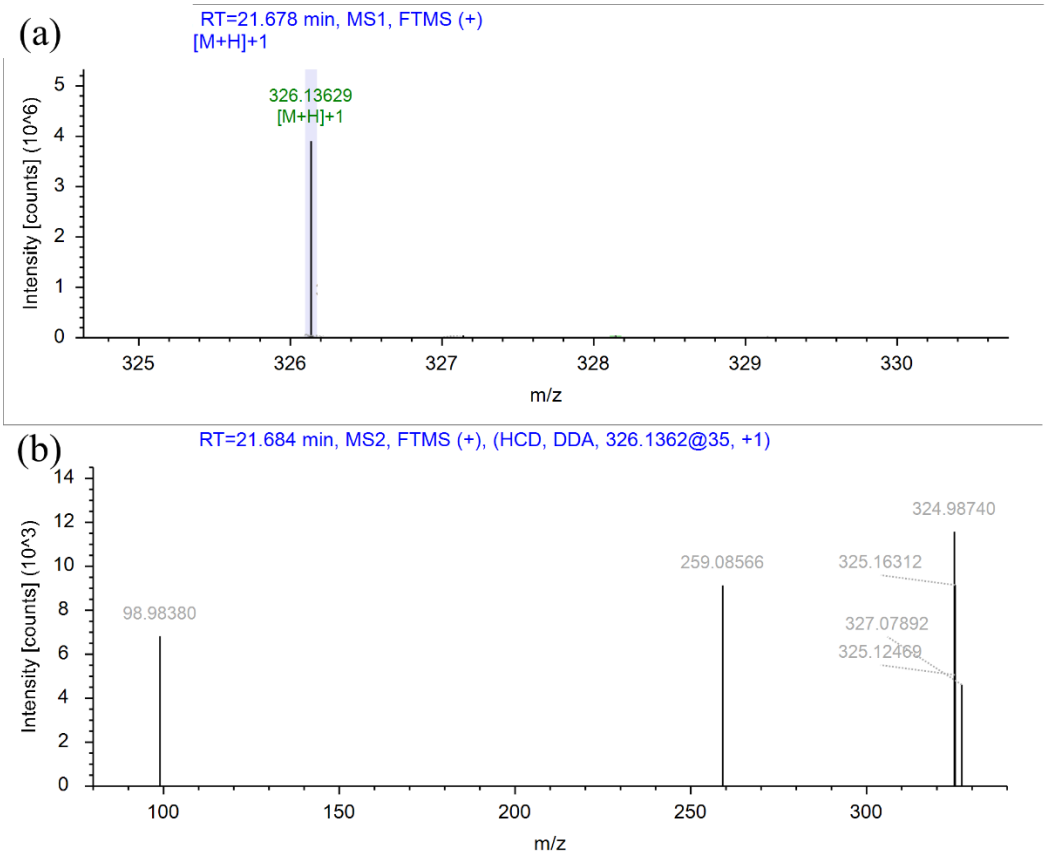


Figure S30. (a) MS spectra for both products E and D (E and D are the same products with possibly different positions of the OH group) and (b) MS/MS fragmentation data for the product where one fragment matches the fragment from the parent compound.

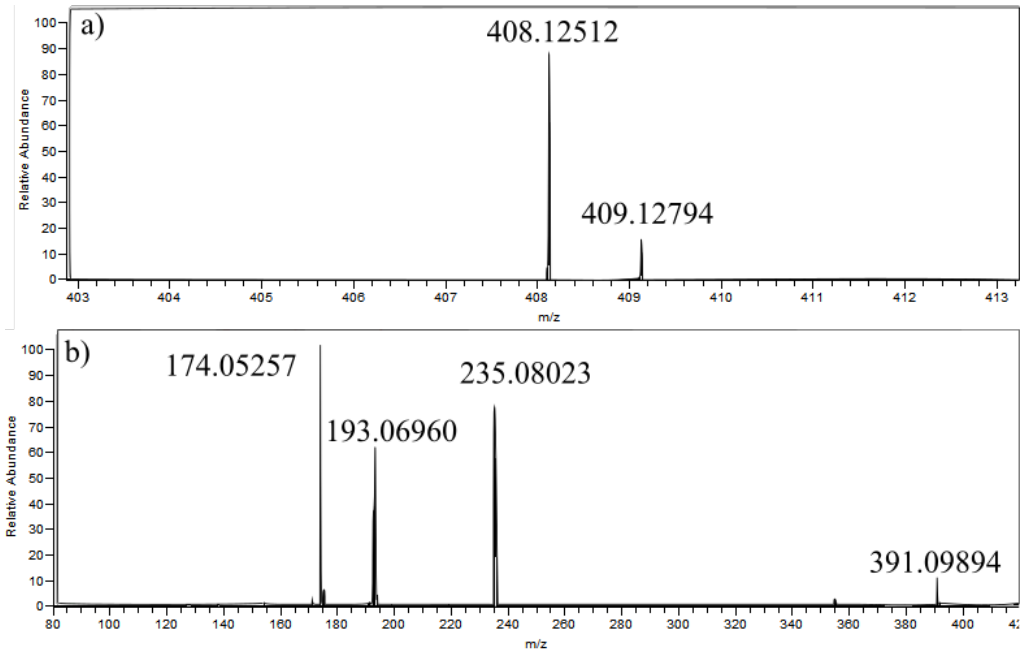


Figure S31. (a) Parent Sitagliptin MS and (b) MS/MS fragmentation spectra.

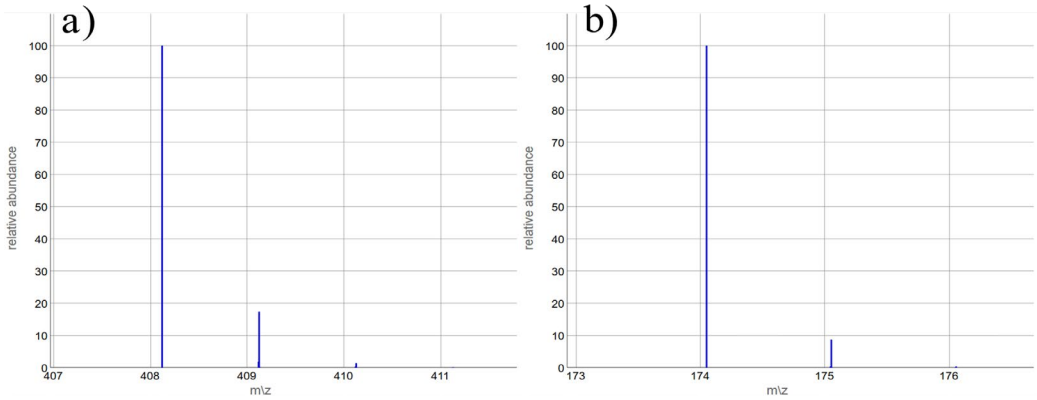


Figure S32. Predicted MS isotope ratio, based on chemical formula of $C_{16}H_{16}F_6N_5O^+$, which matches the spectra for the parent sitagliptin molecule (a) and MS/MS isotope ratio based on chemical formula of $C_8H_7F_3N^+$, which matches the actual spectra (b).

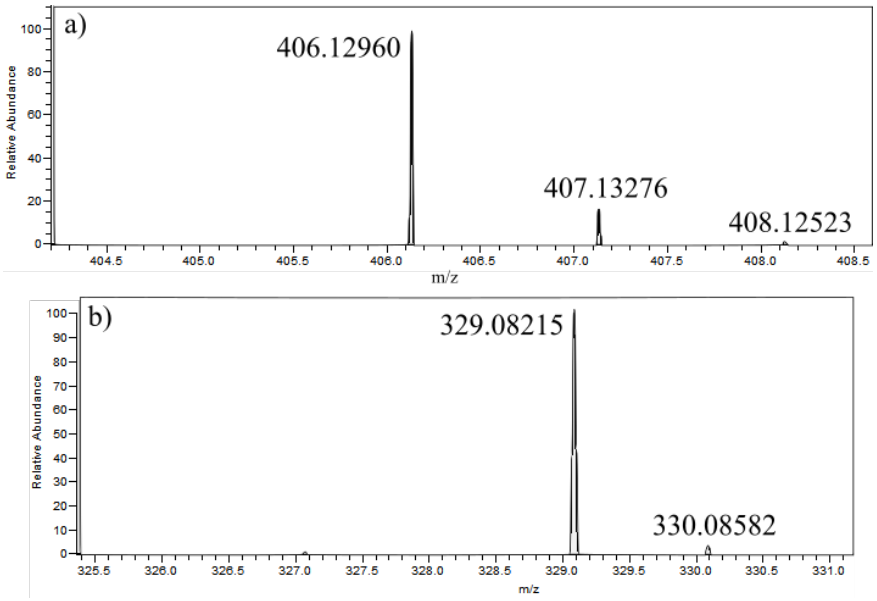


Figure S33. Possible photoproduct MS (a) and fragmentation (b) data. The possible photoproduct had a retention time of 19.4 minutes.

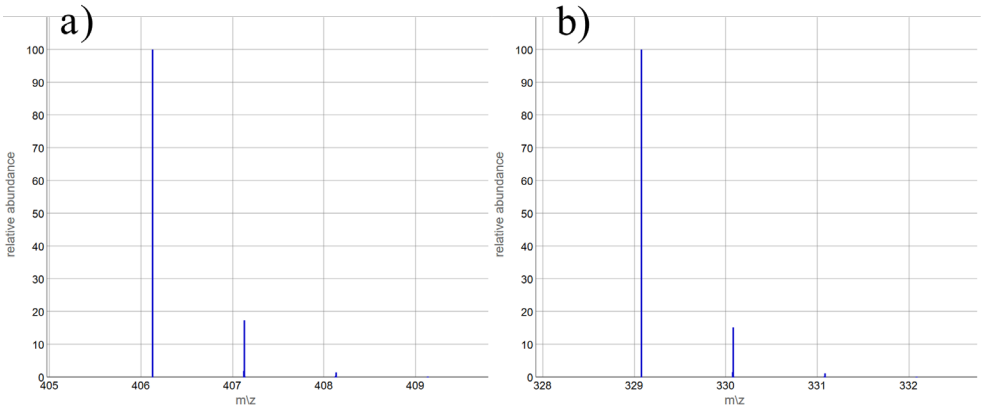


Figure S34. Predicted MS isotope ratio, based on chemical formula of $C_{16}H_{17}F_5N_5O_2^+$, which matches the spectra for the proposed chemical formula for the possible photoproduct (a) and MS/MS isotope ratio based on the chemical formula of $C_{14}H_{10}F_5N_4^+$, which matches the actual spectra (b).

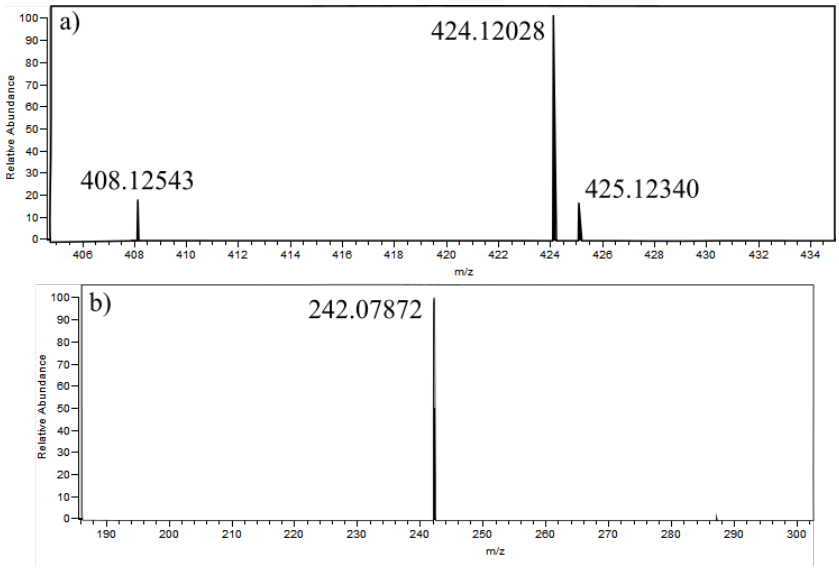


Figure S35. Possible photoproduct with a retention time of 25.5 minutes (a) MS and (b) MS/MS fragmentation data.

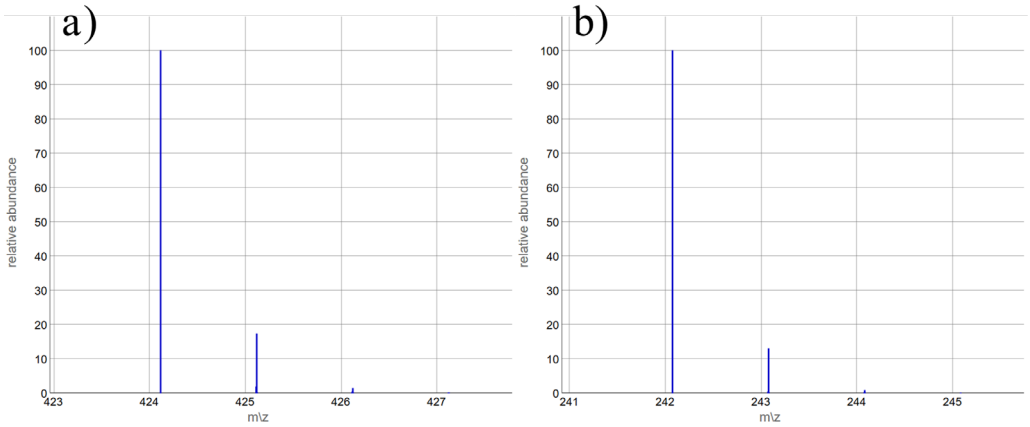


Figure S36. Predicted MS isotope ratio, based on chemical formula of $C_{16}H_{16}F_6N_5O_2^+$, which matches the spectra for the proposed chemical formula for the possible photoproduct (a) and MS/MS isotope ratio based on the chemical formula of $C_{12}H_{11}F_3NO^+$, this isotope ratio is not observed in the actual spectra (b).

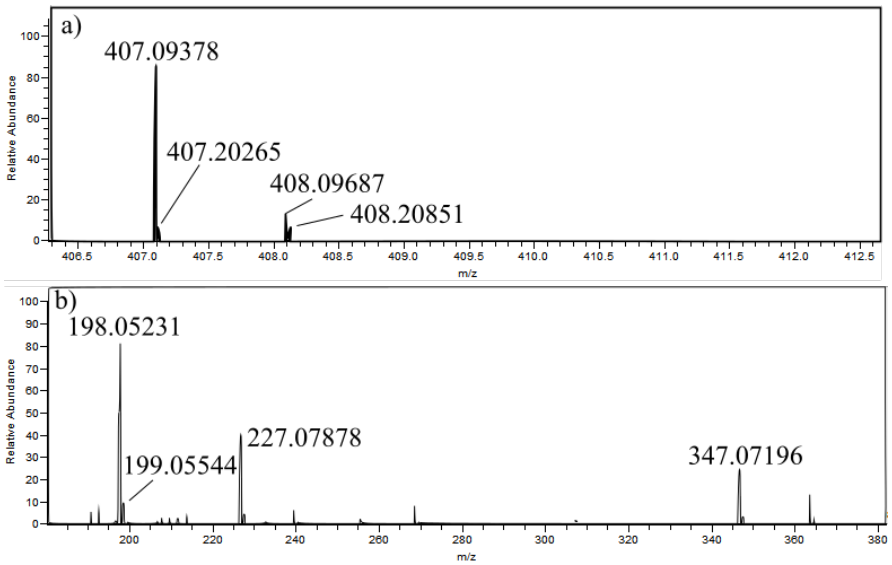


Figure S37. Possible photoproduct with a retention time of 27.3 minutes (a) MS and (b) MS/MS fragmentation data.

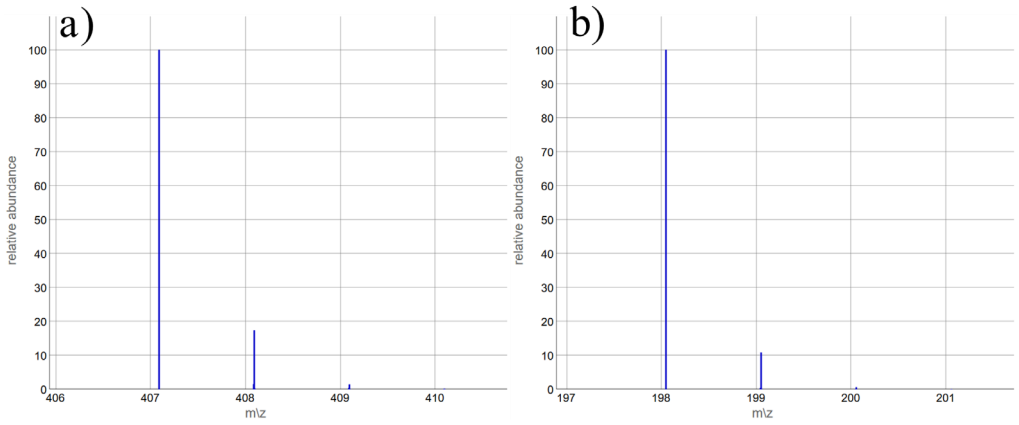


Figure S38. Predicted MS isotope ratio based on chemical formula of $C_{16}H_{13}F_6N_4O_2^+$, which matches the spectra for the proposed chemical formula for the possible photoproduct (a) and the MS/isotope ratio based on the chemical formula of $C_{10}H_7F_3N^+$, which matches the actual spectra.

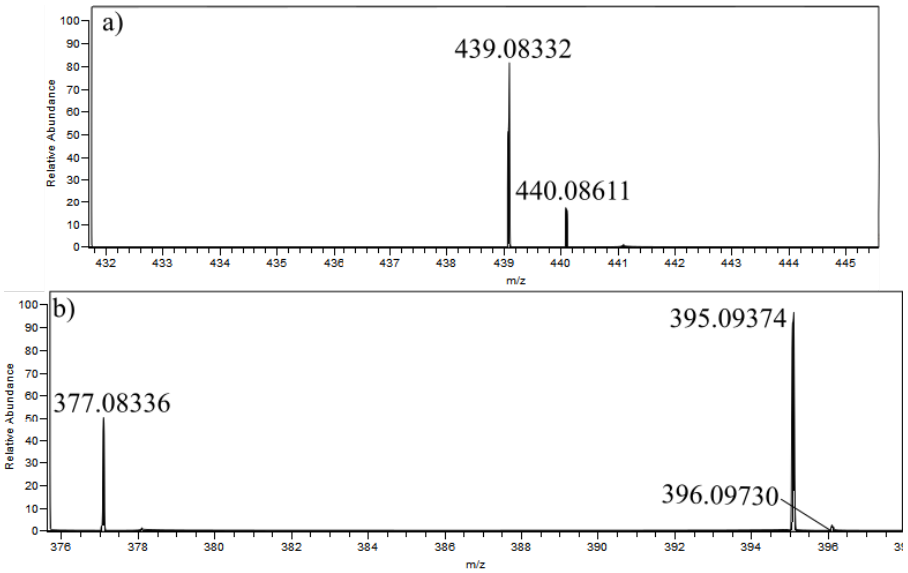


Figure S39. Possible photoproduct with a retention time of 28.5 minutes (a) MS and (b) MS/MS fragmentation data.

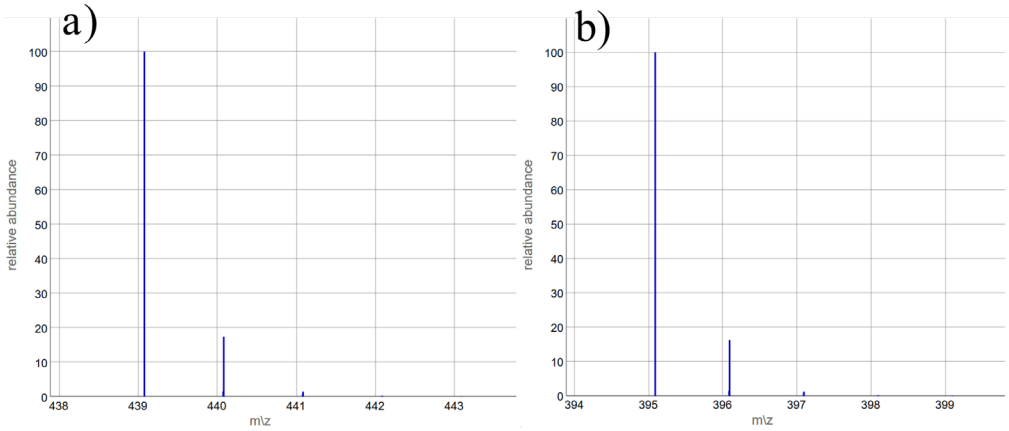


Figure S40. Predicted MS isotope ratio based on chemical formula of $C_{16}H_{13}F_6N_4O_4^+$, which matches the spectra for the proposed chemical formula for the possible photoproduct (a) and MS/MS isotope ratio based on the chemical formula of $C_{15}H_{15}F_3N_4O_4Na^+$, which have the same m/z values but differ in ratio (b).

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