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MINERALIZATION PATHWAYS AND KINETICS OF DEGRADATION OF EMERGING CONTAMINANTS AS MIXTURES USING UV/H₂O₂

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Abstract: The removal of pharmaceuticals and other substances of emerging concern is a major issue in water and wastewater treatment that is garnering increased attention internationally. As commonly employed modules in water treatment do not sufficiently remove these compounds, a need exists for new technologies that can effectively treat them. In this work, an evaluation of the advanced oxidation process UV/H₂O₂ is presented for the degradation of four pharmaceuticals from water: venlafaxine (VEN), carbamazepine (CBZ), fluoxetine (FLU) and sulfamethoxazole (SFX). Experimental results showed that all compounds could be successfully degraded to below detection limits following pseudo first order kinetics. SFX degraded significantly faster than the other compounds, with the other three degrading at very similar rates. Diminishing returns on increases in degradation rate were seen as H₂O₂ dosage was increased above 100 mg/L, indicating that higher levels of H₂O₂ dosing are unlikely to be cost effective. Comparison between compounds treated in a mixture compared to individually demonstrated only a minor decrease in reaction rate of 81-83%. Detailed study on the degradation pathway for each compound elucidated details on potential intermediate breakdown products. While the expected hydroxylation of aromatic structures was seen for all compounds, several other mechanisms were displayed that were compound specific. No notable breakdown products were detected after treatment period of 10 min for all the pharmaceuticals tested.

1. BACKGROUND

The removal of pharmaceuticals from water and wastewater is an emerging concern due to a myriad of potential negative impacts posed on ecosystem and human health. Significant evidence has shown that these contaminants can lead to negative consequences to the eco-system and human health (Hernando et al. 2006, Daughton and Thomas 1999, Boxall 2004). Concerns over the discharge of pharmaceuticals has led to governments in North America and Europe to set guidelines for their release (Ribeiro et al. 2015, Canada 2018, British Columbia 2009). However, as currently employed technologies in water and wastewater do not sufficiently remove pharmaceuticals from water, a need exists to advance current wastewater/water treatment technologies (Metcalf et al. 2003, Zhou et al. 2009, Verlicchi et al. 2012). Amongst existing technologies, advanced oxidation processes (AOPs) have very high potential as they can degrade pharmaceuticals without creating additional waste streams (Yang et al. 2009, Alharbi et al. 2017, Kim et al. 2009). Amongst AOPs, UV/H₂O₂ is a highly appealing process as it has the potential to be implemented into existing water and wastewater treatment facilities with minimal modification.

One major concern with the implementation of UV/H₂O₂ for the degradation of pharmaceuticals in wastewater treatment is the lack of understanding of the breakdown pathway of individual compounds. As pharmaceuticals are specifically designed compounds with highly unique structures, formation of

recalcitrant intermediate products due to incomplete mineralization by hydroxyl radical attack is a potential concern. This concern can be managed by detailing the breakdown pathway of target compounds to better understand what compounds remain in the water if mineralisation is incomplete.

Four pharmaceuticals were selected as candidates for this work due to their high prevalence in wastewater discharge as well as concerns over their possible environmental impacts: venlafaxine (VEN), fluoxetine (FLU), sulfamethoxazole (SFX) and carbamazepine (CBZ). VEN is a commonly prescribed antidepressant (trade name Effexor) that has been measured at concentrations as high as 2.6 µg/L in Canada, along with concentrations of desmethyl venlafaxine (a common metabolite of VEN) measured as high as 4.0 µg/L. VEN has been shown to have endocrine disrupting properties in fish at concentrations as low as 1 µg/L (Lajeunesse et al 2012, Melnyk-Lamont et al. 2014). FLU is another common antidepressant (trade name Prozac) that has been measured at concentrations of up to 8.6 ng/L in Canadian wastewater, with effects to fathead minnow at as low as 1 µg/L (Verlicchi et al. 2012, Weinberger II and Klaper 2014). SFX is a wide spectrum antibiotic that has been measured at concentrations as high as 2.9 µg/L in Canadian wastewaters (Chang et al. 2010). While the acute effects of the release of antibiotics into the ecosystem are limited, consistent loading of antibiotics into an environment has been shown to play a significant role in the selection of bacteria that are antibiotic resistant, which presents a significant long-term risk (Kümmerer 2003, Kim and Aga 2007).

This research focuses on the application of UV/H₂O₂ process for degradation of four prevalent pharmaceuticals including VEN, CBZ, FLU and SFX with emphasis on evaluating pathways of degradation. The experimental investigations included parametric study on the effect of increasing H₂O₂ dosage, determination of reaction kinetics as well as a detailed analysis of degradation intermediates to elucidate the breakdown pathway.

2. Materials and methods

2.1 Chemicals

HPLC grade methanol (99% purity) was obtained from Sigma-Aldrich. Hydrogen peroxide (30% purity) was obtained from Fluka Analytical. Phosphoric acid used in eluents was obtained from ACROS Organics (85% purity).

Fluoxetine hydrochloride (98% purity) and sulfamethoxazole (98% purity) were both obtained from Cayman Chemicals. Carbamazepine (98% purity) and venlafaxine hydrochloride (98% purity) were obtained from Sigma Aldrich, BOC Sciences respectively. A stock of the four pharmaceuticals was prepared in water to a concentration of 5 mg/L of each compound.

2.2 Analytical methods

Quantitative analysis of pharmaceuticals was performed on a Varian Prostar 210 high performance liquid chromatograph equipped with a UV-visible detector. Separation of the pharmaceuticals were achieved using a reverse phase C18 column with dimensions of 150x4.6 mm and a particle size of 5 µm, supplied by Restek. The injection loop of the instrument had a volume of 25 µL and manual injection was performed using a 50 µL for introducing the sample for analysis. A gradient elution was performed with a flow rate of 0.5 mL/min. Gradient method initialized at 4:6 methanol to water, ramping up to 7:3 methanol to water then back down to baseline. All eluents were acidified to 10 mM of phosphoric acid. Calibration was performed using 7 concentrations between 0.1-5 mg/L with multiple injections at each concentration. Calibrations were linear with a fit of $R^2 > 0.99$ for all tested pharmaceuticals.

Electrospray ionization mass spectrometry (ESI-MS) was used for the identification of intermediate breakdown products for all target pharmaceutical compounds. The analysis was performed on an Agilent 1200 series Mass spectrometer with triple Quadrupole Time of Flight detector. Methanol was used as mobile phase at a flowrate of 0.2 mL/min and the samples were directly injected manually. Source was set

to 200°C with a capillary voltage of 4000V, a fragmentor voltage of 80V, nebulizer pressure of 12 psi and drying gas flowrate of 7 L/min.

2.3 Photoreactor

All experiments were conducted in an LZC-ORG Luzchem batch reactor with internal dimensions of 30x30x22 cm. Internal housing fits up to 10 low pressure UV lamps emitting light at $\lambda = 254$ nm. Irradiation intensity was determined using ferrioxalate actinometry, which showed a linear relationship between number of lamps and light intensity per volume in a range between 647 W/m³ and 3502 W/m³, with methods used similar to Hollman et al. (2018).

2.4 Experimental procedure

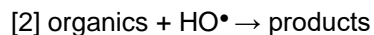
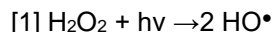
Batch experiments were conducted using a 200 mL quartz reaction vessel. The degradation of target contaminants were studied in mixtures by maintaining an initial concentration of 5mg/L for all target contaminants. It should be noted that the initial concentrations used in this study were significantly higher than those seen in municipal wastewaters, which are typically in the ng/L to µg/L range. Higher initial concentrations of the target compounds were chosen to obtain noticeable response for breakdown products so they could be identified and pathways of degradation could be established. High concentration of stock solution with mixture of all four target contaminants were spiked in deionised water prior to initiation of the experiments. H₂O₂ was spiked immediately after spiking the pharmaceuticals and the mixture was placed in the center of the UV reactor without delay. 2 mL samples were withdrawn at predetermined intervals for analysis in change of concentration of the target contaminants. Prolonged reactions in collected samples were quenched using methanol immediately upon withdrawal of the sample.

3. Results and discussion

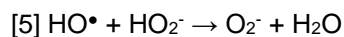
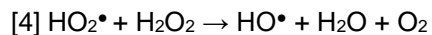
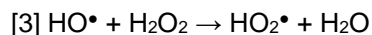
3.1 Degradation kinetics

Degradation of all pharmaceuticals were performed at H₂O₂ dosages of 0 (UV irradiation only), 50, 100 and 200 mg/L. All target contaminants were degraded to below detection limits, with prolonged times of reaction needed in case of pure UV photolysis for CBZ and VEN. Degradation kinetics for all compounds followed zero- and pseudo first-order kinetics in the absence and presence of H₂O₂.

The expected reaction mechanism of UV/H₂O₂ is through the cleavage of the double bond of H₂O₂, resulting in the production of two hydroxyl radicals that can subsequently react with organics in solution.



Additionally, it should be noted that hydroxyl radicals in solution also have the potential to react with H₂O₂ in solution, resulting in a cyclical reaction that limits potential maximum rate of contaminant degradation.



The practical implication of this reaction is that some optimum should exist beyond which additional dosage of H_2O_2 results in decreased effectiveness of reaction. In typical settings under reasonable dosages, this reaction limiting mechanism is displayed through diminished or non-existent returns in terms of increased rate of degradation per dosage of H_2O_2 applied.

Results of pseudo first order degradation rate constant of each compound under different H_2O_2 loadings is presented in Figure 1. As can be seen in the figure, SFX showed significantly faster degradation compared to the other 3 compounds. Amongst the remaining compounds, FLU degraded the fastest, followed by CBZ, followed by VEN; though there was very little distinction between these compounds, with 35% or less differentiating their rate constants at each dosage. Degradation rate of VEN, CBZ and FLU each showed diminished returns on the effectiveness of increased H_2O_2 as a result of the limiting reactions listed above. Though no optimum dosage was reached from a physical perspective, the significant decrease in value per additional chemical dosage that has been seen in this study likely indicates that a practical optimum will have been reached if cost is taken as a factor.

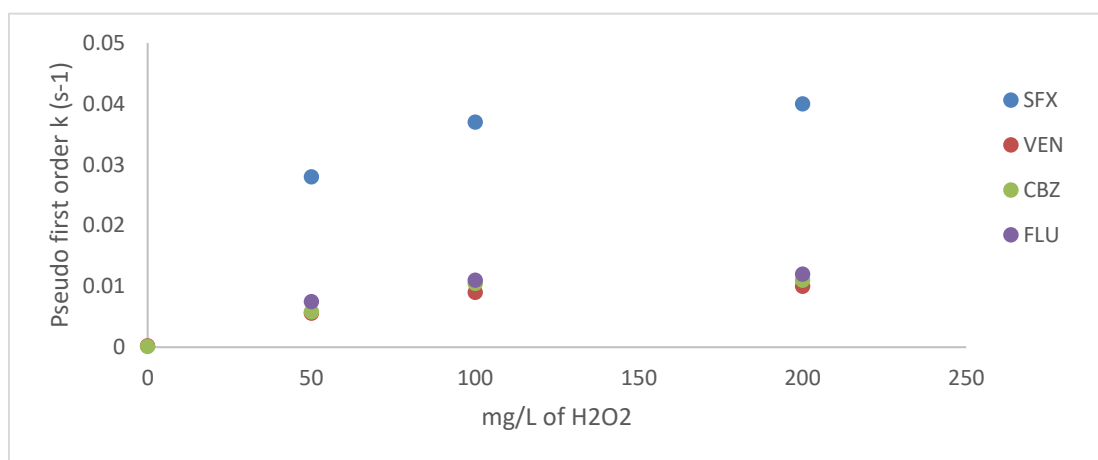


Figure 1: Effect of H_2O_2 dosage in pseudo first order rate constant

Comparison was also made between treating a single compound alone in solution compared to all four compounds as a mixture. Results of a comparison at 100 mg/L of H_2O_2 for VEN and CBZ are shown in Figure 2, with single compound data adapted from previous studies performed in the same laboratory and under the same conditions (Hollman 2018, Somathilake 2018). CBZ and VEN were chosen as they are the most recalcitrant compounds used in this study. Degradation in a mixture was slower than the compounds individually by 81 and 83% for VEN and CBZ respectively. Although some reduction in rate occurred, the similarity between the rates indicate that total number of hydroxyl radicals available for reaction in solution is not the primary factor controlling rate of reaction. Though a small decrease in reaction rate occurred it was relatively consistent between the two compounds, indicating that competition for molecular collision between hydroxyl radicals and target compounds was likely the primary factor leading to the decrease in reaction rate as opposed to a limit on total radicals available for reaction.

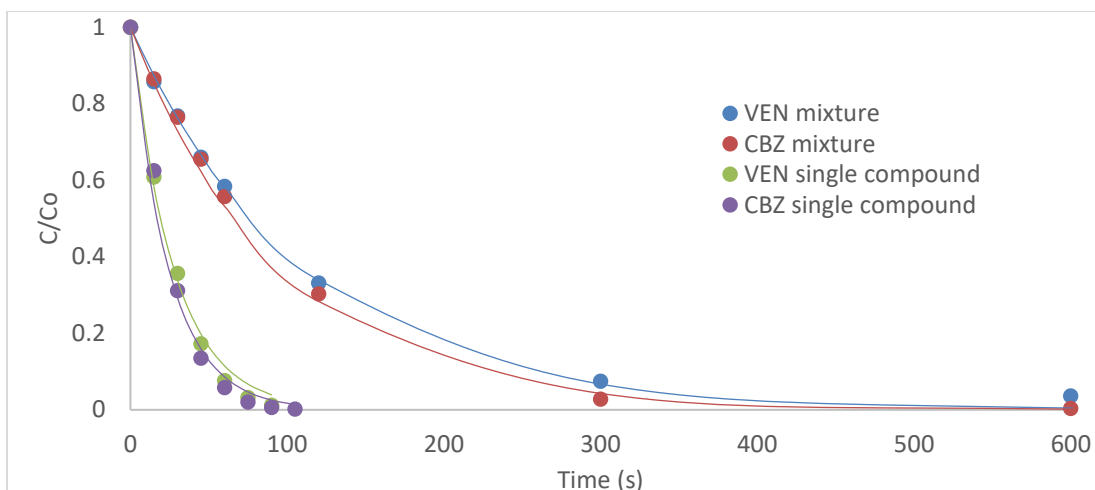


Figure 2: Degradation kinetics of VEN and CBZ as a single compound vs mixture

3.2 Breakdown pathway

Breakdown pathway of each pharmaceutical was investigated to better understand the potential by-products that may be present if incomplete treatment of these pharmaceuticals is performed. Degradation pathways for VEN is detailed in Figure 3. Based on compounds detected by ESI-MS, it has been determined that the primary mechanisms for breakdown consist of either: sequential hydroxylation, demethylation or the formation of hydroxylated-keto derivatives, which agreed with existing literature on the breakdown of VEN by photocatalysis, photo-Fenton and UV/H₂O₂ treatment (García-Galán et al. 2016, Giannakis et al. 2017, Lambropoulou et al. 2017). Pathway 1 in Figure 3 shows VEN being sequentially hydroxylated, resulting in non-hydroxylated (product 1A) and di-hydroxylated (product 1B) isomers of VEN. The sites of hydroxylation vary due to availability of multiple sites on the structure of the compound that are amenable for hydroxylation. Pathway 2 in Figure 3 shows the demethylation of VEN leading to the formation of O-desmethyl VEN (product 2A), a common VEN derivative. O-desmethyl VEN has been further shown to be subject to hydroxylation (product 2B), which is likely the first step in several leading to the mineralization of VEN. Further degradation of the intermediate products are hypothesised to occur by sequentially hydroxylation, however, these reactions occur at very high rates that they don't accumulate beyond the level of detection.

Degradation pathway for FLU is shown in Figure 4. Mechanisms for the degradation of FLU in the presence of hydroxyl radicals have been identified to follow substitution of the trifluoromethyl group, O-dealkylation and sequential hydroxylation, all of which agree with other established literature using various AOPs for the treatment of FLU (Lam et al 2005, Szabó et al. 2018, Méndez-Arriaga et al. 2011, Drzewicz et al. 2018). Pathway 1 in Figure 4 demonstrates the initiation of breakdown pathway by hydroxylation of the benzene ring (FLU product 1A) followed by substitution of the trifluoromethyl group (FLU product 1B). Pathway 2 demonstrates an additional route of mineralisation which follows O-dealkylation causing breaking of the ether bond resulting in p-trifluoromethylphenol (FLU product 2A) or 2-(methylamino) ethyl benzyl alcohol (FLU product 3). The by-product p-trifluoromethylphenol was detected corresponding substitution of the trifluoromethyl group (FLU product 2C) as well as secondary hydroxylation of the benzene ring (FLU product 2B). Additionally, ethyl benzyl alcohol (FLU product 3) may also undergo hydroxylation of the remaining benzene structure, which may have been one of the causes of FLU product 1B found in solution. Traces of N-methyl-3-propen-1-amine (FLU product 4) was detected in solution by the end of reaction beyond which degradation of intermediates were quicker as they degraded undetected.

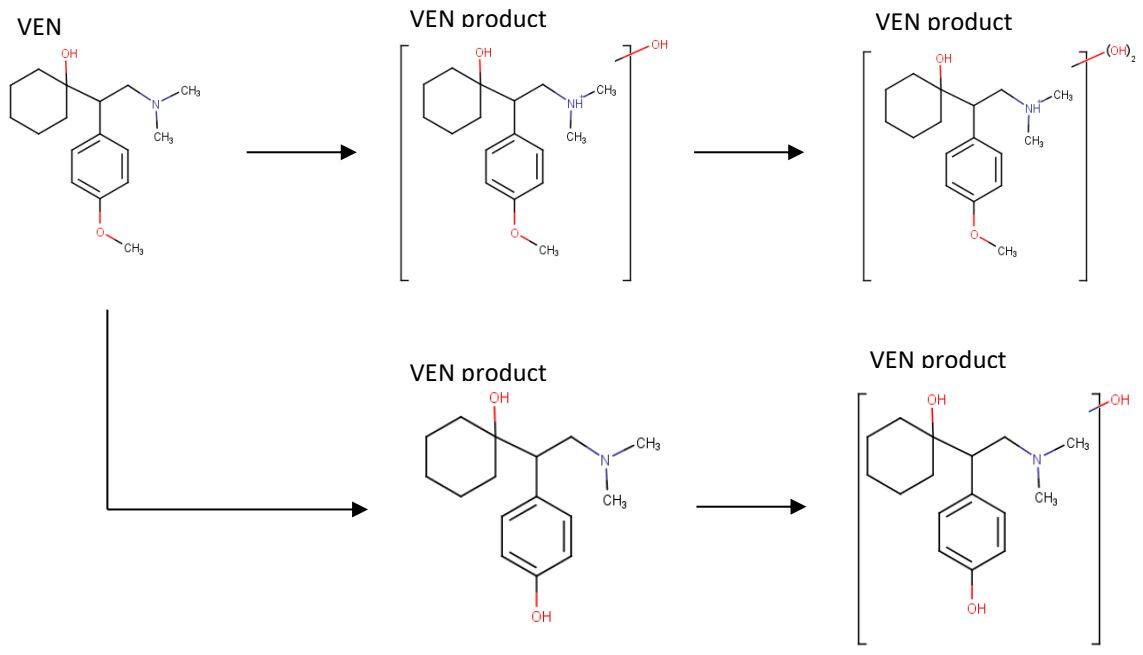


Figure 3: Breakdown pathway of venlafaxine

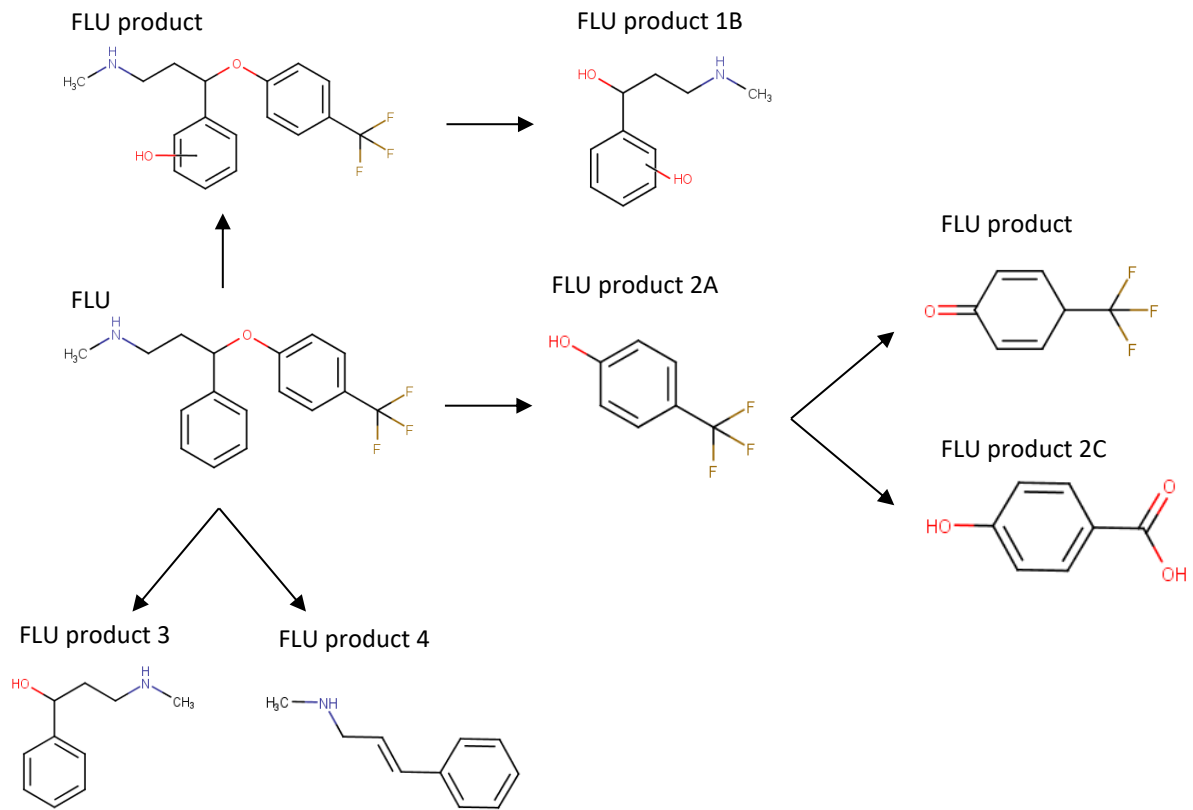


Figure 4: Breakdown pathway of fluoxetine

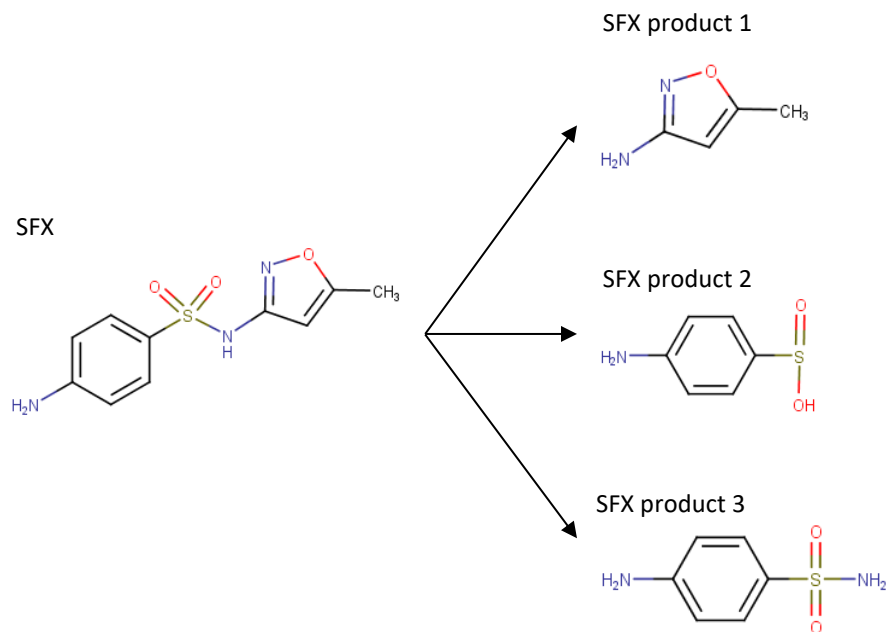


Figure 5: Breakdown pathway of sulfamethoxazole

The degradation pathway for SFX can be seen in Figure 5. No sequential reactions were detected in the degradation of SFX, likely owing to its comparatively fast degradation compared to other compounds tested, rendering the isolation of short-lived intermediate products unfeasible. Breakdown products detected were 3-amino-5-methylisoxazole (SFX product 1), 4-aminobenzenesulfonic acid (SFX product 2) and 4-aminobenzenesulfonamide (SFX product 3). The mechanism for the formation is expected to be cleavage of the sulfonamide bond, in agreement with other literature sources on the degradation of SFX by hydroxyl radicals (Qi et al. 2014, Kim et al. 2017).

Degradation pathway for CBZ can be seen in Figure 6. Three major mechanisms for the degradation of CBZ have been determined, corresponding primarily hydroxyl derivatives of CBZ as well hydration of a carbon bond in the aromatic structure, both of which agree with existing literature on degradation of CBZ by hydroxyl radical (Lekkerkerker-Teunissen et al. 2012, Vogna et al. 2004, Xu et al. 2013). CBZ product 1A is identified as 10,11-epoxycarbamazepine which likely formed through hydration of the $\text{C}_{10}\text{-C}_{11}$ double bond which may be followed by facile ring contraction of the epoxide ring followed by loss of CONH_2 and hydroxylation to form acridine-9-carboxaldehyde (CBZ product 1B). An additional product with a mass/charge ratio of 269 ($\text{M}+\text{H}^+$) was detected, which may potentially belong to one of two structures: a dehydroxylated derivative of CBZ (CBZ product 2) or acridine-9-carboxaldehyde (CBZ product 3).

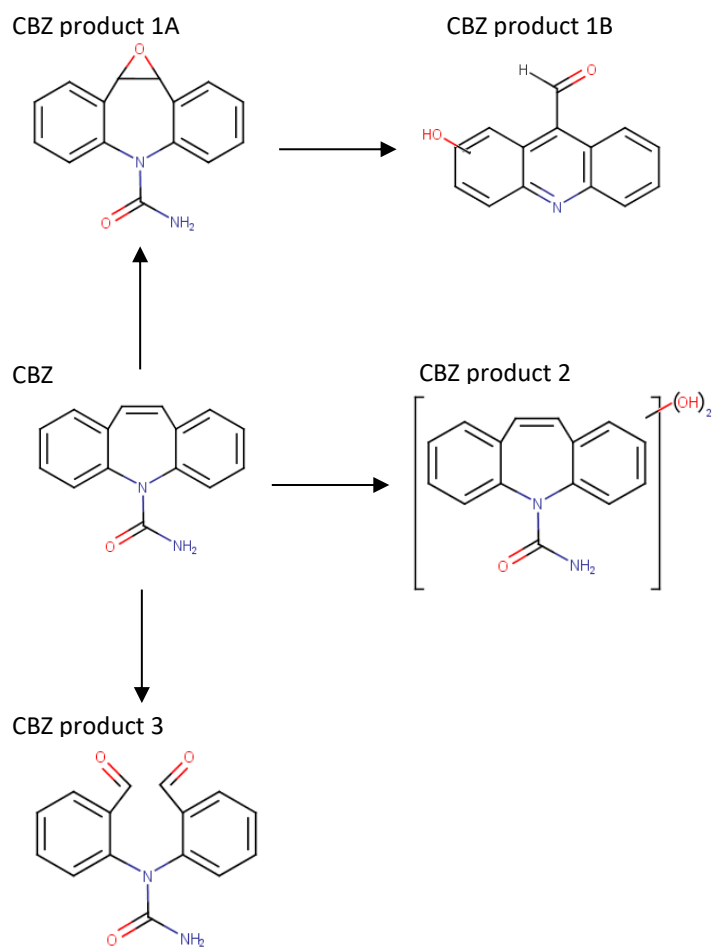


Figure 6: Breakdown pathway of carbamazepine

4. CONCLUSIONS

This present work demonstrates the effectiveness of UV/H₂O₂ process to degrade a mixture of recalcitrant pharmaceuticals including VEN, FLU, SFX and CBZ. All the target pharmaceuticals were successfully degraded to below detection limits with degradation kinetics for all compounds following pseudo first order kinetics. Among the compounds tested, SFX degraded almost 4 times faster than other compounds, with VEN, FLU and CBZ showing very similar degradation rates. Diminished returns on rate of degradation per chemical dosage were seen equally in all compounds for H₂O₂ doses above 100 mg/L due to recombination mechanisms that are inherent to UV/H₂O₂ reactions. Comparative study of compounds individually in solution compared to in a mixture indicated that only a minimal decrease in reaction rate of 0.17-0.19 times under laboratory conditions. Degradation pathway for each compound was determined from breakdown products detected by ESI-MS. Various reaction mechanisms initiated by attack of hydroxyl radical formed the basis of reaction pathway of all target compounds with no effects noted from degradation due to direct UV photolysis. These findings substantiate the possibility of using UV/H₂O₂ for treatment of emerging contaminants in water and wastewater applications.

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