OXIDATION OF PHARMACEUTICALS AND PERSONAL CARE PRODUCTS BY PERMANGANATE

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OXIDATION OF PHARMACEUTICALS AND PERSONAL CARE PRODUCTS BY PERMANGANATE

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[To my husband]

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LIST OF ABBREVIATIONS

ACN	acetonitrile
DI	deionized
HCl	hydrochloric acid
HPLC	high performance liquid chromatography
mL	milliliter
mM	millimoles per liter
NaOH	sodium hydroxide
nm	nanometer
NSAIDs	non-steroidal anti-inflammatory drugs
PPCPs	pharmaceutical and personal care products
s^{-1}	per second
TCEP	tri(2-carboxyethyl)phosphine

SUMMARY

Pharmaceuticals and personal care products (PPCPs) are widely used, resulting in trace amounts being detected in the aquatic environment. This presence is of human health and ecological concern and it is necessary to determine the best methods to eliminate them from our waters. The oxidation of PPCPs by permanganate was evaluated using a spectrophotometer to monitor permanganate reduction. Thirty-nine compounds were chosen to represent numerous classifications, including beta blockers, cephalosporins, fluoroquinolones, macrolides, non-steroidal anti-inflammatory drugs, phenol structures, polypeptides, sulfonamides, tetracyclines, and triazines. The reactivity of each compound was determined by measuring the absorbance of permanganate over time as it reacted with an excess of the compound. The absorbance data was fit to a pseudo-first-order reaction model that accounted for the growth of manganese dioxide colloids. The most reactive groups that reduced permanganate within minutes at pH 7.0 were the cephalosporins, phenol structures, and tetracyclines. The majority of the remaining pharmaceuticals and personal care products were moderately or weakly reactive (reducing permanganate within hours). Caffeine, carbadox, monensin, simetone, and tri(2-carboxyethyl)phosphine were poorly reactive (reducing permanganate over days). Metoprolol was the only selected compound that was determined to be potentially non-reactive (no reaction after 1 day). Polarizability and refractive index of the organic compounds showed significant positive correlations ($R^2 > 0.50$) with the first-order reaction rates for non-steroidal anti-inflammatory drugs and the phenol structures group.

The half-life of each PPCP was determined based on a typical dosage of permanganate used for pre-oxidation. Eleven of the thirty-nine PPCPs had a half-life of less than thirty minutes (a typical contact time), indicating that oxidation by permanganate may be a viable option. There are many opportunities for further research in this area, including investigating more PPCPs, physicochemical property correlations, and the impact of water quality conditions

CHAPTER 1: INTRODUCTION

Pharmaceutical and personal care products (PPCPs) encompass a wide range of compounds that are utilized in the daily human life. They are designed to assist with personal health and beauty and are also used within agriculture and animal husbandry. With such an extensive list of uses, PPCPs are employed frequently and nearly everywhere. As a result, in recent years, the presence of numerous PPCPs in our waterways has been discovered, even extending to our drinking water. When consumed by humans and animals, pharmaceuticals are not completely ingested and up to 100% of it can be excreted, depending on the compound (Besse et al., 2008). This ends up in the wastewater system and the treatment plant frequently cannot entirely remove the pharmaceuticals. The PPCPs' presence can also be attributed to runoff (urban, agricultural, and animal manure) and the application of sewage sludge onto land.

The use of PPCPs has only increased in recent years, despite the growing concern of their potentially adverse ecological and human effects. Numerous studies have enumerated the pharmaceuticals (particularly antibiotics), hormones, and other PPCPs found in the aquatic environment, including drinking water, rivers and wastewater effluent (Benotti et al., 2008, Focazio et al., 2008, Hirsch et al., 1999, Kolpin et al., 2002, Kumar et al., 2010, Lindberg et al., 2005, and Richardson, 2007). One of the greater concerns as a result of pharmaceutical overuse is the development of antibiotic-resistant bacteria which are difficult to eliminate once present. Numerous antibiotic-resistant genes have already been discovered in all aspects of the aquatic environment (Zhang et

al., 2009). An area of research that is still emerging is the investigation of the long-term effects of chronic exposure to trace amounts of the PPCPs. While initial studies have determined that there is no known effect, it is difficult to conclude that there is no long-term effect from the consumption of any PPCP at a trace level (Jones et al., 2005 and Snyder et al., 2003). It is suggested that chronic exposure may cause minimal changes over time that go undetected until it is too late (Daughton and Ternes, 1999). Some PPCPs are classified as "endocrine disruptors." Research has shown that endocrine disruptors can have adverse effects on the reproductive system of animals, including humans (McLachlan, 2001). Thus, there is a valid concern of how the consumption of trace amounts of endocrine disruptors will have an impact on human and ecological health. A final concern is that PPCP contamination could potentially reduce our already dwindling water resources. Thus, it is necessary to determine the best methods to eliminate PPCPs from our waters.

Permanganate oxidation is potentially a viable option for the treatment of PPCPs. It is considered a desirable method due to permanganate's low cost, availability, and ease of handling (Abe et al., 2003). Permanganate is also commonly used as a pre-oxidant for taste and odor control in water and wastewater treatment plants. Studies on permanganate oxidation have been carried out for a wide range of individual substrates, including ethylenediaminetetraacetic acid (Chang et al., 2006), microcystins (Rodriguez et al., 2007), and methyl tert-butyl ether (Damm et al., 2002). Few studies have attempted to research the permanganate oxidation of many compounds (Waldemer and Tratnyek, 2005), but instead focus on the kinetics and mechanisms of the oxidation process of a specific compound, as well as the effects of water properties such as pH.

The majority of studies have concluded that, for their specific compounds, permanganate oxidation is an efficient and effective method of reduction.

Literature also discusses the kinetics and mechanisms of permanganate oxidation on specific functional groups of organic compounds. Phenols are considered to be highly reactive by permanganate oxidation (He et al., 2009 and Jiang et al., 2009). Research has also shown that amines are readily oxidized by permanganate as well. The reactivity lessens from primary to secondary to tertiary amines (Rawalay and Shechter, 1967 and Stewart, 1965). This same reactivity trend follows for alcohols as well, where primary alcohols are the most reactive with permanganate (Stewart, 1965). It is also suggested that alkenes are readily oxidized by permanganate (Stewart, 1965). Benzene rings and their derivatives (toluenes and xylenes) are considered to oxidize slowly by permanganate (Waldemer and Tratnyek, 2005). Other functional groups are suggested to be stable when permanganate is present in a neutral solution: amides, carboxylic acid, ketones, and aldehydes (Sharma et al., 2008 and Stewart, 1965). These typically are the final product for more reactive groups that do oxidize by permanganate. This information can help predict the behaviors of more complex compounds during oxidation by permanganate.

A significant amount of permanganate oxidation research has also been dedicated to the production of manganese dioxide. Manganese dioxide particles are a product of permanganate reduction and are of importance for monitoring permanganate consumption in research and also for their potential deposition during treatment. Studies have investigated how reaction conditions, such as pH, affect the production of manganese dioxide colloidal particles (Crimi and Siegrist, 2004).

The kinetics and mechanisms of permanganate oxidation of PPCPs have yet to be extensively researched, with the exception of only a few compounds including bisphenol-A (Xu, 2009), carbamazepine (Hu et al., 2008), ciprofloxacin (Thabaj et al., 2007), levofloxacin (Khan et al., 2010), norfloxacin (Naik et al., 2009), and triclosan (Jiang et al., 2009). Note that the previous studies on the fluoroquionlones were conducted with alkaline permanganate (pH > 11.0) (Thabaj et al., 2007; Naik et al., 2009; Khan et al., 2010), rendering applying the results to typical water treatment systems at circum-neutral pH conditions difficult. Thus, it is the main objective of this research to characterize the kinetics of the oxidation of a wide range of PPCPs by permanganate and to probe the reaction mechanisms. Thirty nine PPCPs (Table 1) were chosen to represent numerous medicinal and structural classifications, including beta blockers, cephalosporins, fluoroquinolones, macrolides, non-steroidal anti-inflammatory drugs, phenol structures, polypeptides, sulfonamides, tetracyclines, and triazines. Many of these PPCPs have been frequently detected in wastewater and surface waters across the U.S. Some basic physicochemical properties of the PPCPs and their structures are shown in Table 1 and Appendix Figures A1-11. Table 2 shows the uses for the PPCPs selected. For each PPCP, the reaction with permanganate was studied and the pseudo-first-order and second-order rate constants were determined. During the degradation of the permanganate with each PPCP, the growth of manganese dioxide particles was monitored. First-order rate constant correlations with selected physicochemical properties of the compounds were also explored.

Table 1: PPCPs investigated in this study and selected physicochemical properties

Classification	Compound	Molecular Formula	MW (g/mol)	Polariz-ability* (A^3/mol)	Electron Affinity* (eV)	Refractive Index*
Beta Blocker	Atenolol	$C_{14}H_{22}N_2O_3$	266.30	29.40	-0.15	1.56
	Metoprolol	$C_{15}H_{25}NO_3$	267.40	30.63	-0.68	1.52
Cephalosporin	Cefdinir	$C_{14}H_{13}N_5O_5S_2$	395.40	35.43	N/A	1.57
	Cephalexin	$C_{16}H_{17}N_3O_4S$	347.40	35.05	N/A	1.61
Fluoroquin-olone	Ciprofloxacin	$C_{17}H_{18}FN_3O_3$	331.30	34.85	-0.45	1.59
	Enrofloxacin	$C_{19}H_{22}FN_3O_3$	359.40	38.64	-0.43	1.56
	Flumequine	$C_{14}H_{12}FNO_3$	261.30	26.73	0.34	1.57
	Levofloxacin	$C_{18}H_{20}FN_3O_4$	361.40	37.51	-0.49	1.57
	Lomefloxacin	$C_{17}H_{19}F_2N_3O_3$	351.30	35.65	-0.46	1.56
	Norfloxacin	$C_{16}H_{18}FN_3O_3$	319.30	33.81	-0.44	1.58
	Ofloxacin	$C_{18}H_{20}FN_3O_4$	361.40	37.51	-0.49	1.57
	Pipemidic Acid	$C_{14}H_{17}N_5O_3$	303.30	32.34	-0.28	1.59
Macrolide	Erythromycin	$C_{37}H_{67}NO_{13}$	715.90	74.93	1.43	1.50
	Roxithromycin	$C_{41}H_{76}N_2O_{15}$	837.10	83.92	N/A	1.48
Non-steroidal anti-inflammatory	Diclofenac	$C_{14}H_{11}Cl_2NO_2$	318.10	30.19	0.32	1.64
	Ibuprofen	$C_{13}H_{18}O_2$	206.00	23.94	0.17	1.50
	Naproxen	$C_{14}H_{14}O_3$	230.30	26.24	0.40	1.59
Phenol Structure	Acetaminophen	$C_8H_9NO_2$	151.17	16.50	-0.11	1.57
	Bisphenol-A	$C_{15}H_{16}O_2$	228.30	27.02	-2.10	1.60
	Triclosan	$C_{12}H_7Cl_3O_2$	287.90	27.40	0.02	1.64
Polypeptide	Bacitracin	$C_{66}H_{103}N_{17}O_{16}S$	1422.70	144.00	N/A	1.55
	Colistin	$C_{52}H_{98}N_{16}O_{13}$	1155.50	119.20	-5.95	1.54
Sulfonamide	Sulfamethazine	$C_{12}H_{14}N_4O_2S$	278.40	28.77	N/A	1.75
	Sulfamethoxazole	$C_{10}H_{11}N_3O_3S$	253.00	23.55	N/A	1.71
Tetracycline	Chlortetracycline	$C_{22}H_{23}ClN_2O_8$	515.30	46.60	2.29	1.65
	Demeclocycline	$C_{21}H_{21}ClN_2O_8$	501.30	44.60	2.72	1.67
	Oxytetracycline	$C_{22}H_{24}N_2O_9$	496.90	45.14	2.82	1.67
	Tetracycline	$C_{22}H_{24}N_2O_8$	444.40	44.48	2.09	1.66
Triazine	Atrazine	$C_8H_{14}ClN_5$	215.68	22.90	-0.07	1.53
	Simetone	$C_8H_{15}N_5O$	197.20	21.68	-0.23	1.53
Others	Caffeine	$C_8H_{10}N_4O_2$	194.00	19.21	N/A	1.43
	Carbadox	$C_{11}H_{10}N_4O_4$	262.20	23.64	N/A	1.66
	Carbamazepine	$C_{15}H_{12}N_2O$	236.00	29.56	-0.59	1.84
	Cotinine	$C_{10}H_{12}N_2O$	176.20	19.60	0.17	1.54
	Dilantin	$C_{15}H_{12}N_2O_2$	252.30	27.55	-0.45	1.66
	Gemfibrozil	$C_{15}H_{22}O_3$	250.30	28.41	0.30	1.51
	Monensin	$C_{36}H_{62}O_{11}$	692.90	69.02	0.44	1.51
	TCEP**	$C_9H_{15}O_6P$	283.90	21.99	N/A	1.48
	Trimethoprim	$C_{14}H_{18}N_4O_3$	290.10	31.48	-1.11	1.63

*Value calculated by using EPA SPARC,
http://www.epa.gov/athens/research/projects/sparc/

** tris(2-carboxyethyl)phosphine

Table 2: PPCPs according to classification

PPCP Classification	Compound
Analgesic	acetaminophen, diclofenac, ibuprofen, and naproxen
Antibiotic	bacitracin, carbadox, cefdinir, cephalexin, chlortetracycline, ciprofloxacin, colistin, demeclocycline, enrofloxacin, erythromycin, flumequine, levofloxacin, lomefloxacin, monensin, norfloxacin, ofloxacin, oxytetracycline, pipemidic acid, roxithromycin, sulfamethazine, sulfamethoxazole, tetracycline, triclosan, and trimethoprim
Antiepileptic	carbamazepine and dilantin
Beta Blocker	atenolol and metoprolol
Flame Retardant	TCEP
Herbicide	atrazine and simetone
Lipid Regulator	gemfibrozil
Nicotine Metabolite	cotinine
Plasticizer	bisphenol-A
Stimulant	caffeine

CHAPTER 2: MATERIALS AND METHODS

2.1 Solution Preparation

All chemicals used were of analytical-reagent grade and were obtained from either Fisher Scientific (Pittsburgh, PA) or Sigma Aldrich (St. Louis, MO). Deionized (DI) water, prepared from a Millipore Milli-Q Nanopure water purification system, was used for all solutions (resistance of 18 ohms). Stock solutions were made for each selected PPCP compound and stored in the fridge or freezer to minimize degradation and evaporation. For the readily water-soluble compounds, the PPCP was dissolved in DI water for 1 millimole per liter (mM) stock solution (i.e. acetaminophen, atenolol, bacitracin, caffeine, cephalexin, colistin, lomefloxacin, metoprolol, simetone, and tris(2-carboxyethyl)phosphine). For the readily methanol-soluble compounds, the PPCP was dissolved in methanol for a 2.5 mM stock solution (i.e. atrazine, bisphenol-A, carbamazepine, chlortetracycline, cotinine, demeclocycline, diclofenac, dilantin, erythromycin, flumequine, gemfibrozil, ibuprofen, monensin, naproxen, oxytetracycline, sulfamethazine, sulfamethoxazole, tetracycline, triclosan, and trimethoprim). For several fluoroquinolones, a 1.0 mM stock solution was made with 100 mM hydrochloric acid (HCl) and DI water (i.e. ciprofloxacin, enrofloxacin, levofloxacin, norfloxacin, ofloxacin, and pipemidic acid). Three PPCPs could not dissolve by any of the above methods. Instead, carbadox was dissolved in 1:1 ratio of acetonitrile (ACN) and DI water by volume to make a 1.5 mM stock solution. Cefdinir was dissolved in DI water and 100

mM phosphate buffer for a 0.5 mM stock solution. Triclosan was dissolved in methanol for a final concentration of 1.25 mM.

For pH control, several stock solutions were made. Five hundred mM stock solutions were made for both monosodium phosphate and disodium phosphate by dissolving in DI water. One mole per liter HCl and 100 mM sodium hydroxide (NaOH) stock solutions were also made. Finally, a 1 normality potassium permanganate solution was dissolved in DI water to make a 10 mM potassium permanganate stock solution. The permanganate stock was stored in a dark, cool place and used for two to three days until a new solution was prepared.

2.2 Analytical Method

For the experiments, a concentration ratio of 5:1 PPCP to potassium permanganate was used so that the conditions were pseudo-first-order for the consumption of permanganate with an excess of PPCP for the length of the experiment. The reaction solution was set at pH 7.0 with the usage of phosphate buffer. The reaction was set up in triplicate in three 4.5-milliliter (mL) polystyrene cuvets with a 10-millimeter lightpath. For a total volume of four mL, each cuvete was filled with DI water, 50mM phosphate buffer (with the exception of cefdinir, which already had phosphate buffer in the stock), and 0.25mM PPCP. For the fluoroquinolones, the HCl in the stock was neutralized by the addition of NaOH. Each vial was then inverted to ensure equal distribution of the PPCP and buffer.

An UV/vis spectrophotometer (Genesys 20 Thermo Electron Spectrophotometer) was used to monitor the decrease in absorbance of permanganate, which has a maximum absorbance at 525 nanometers (nm). The growth of manganese dioxide particles was monitored at the wavelength of 418nm, where permanganate is not detected (Waldemer and Tratnyek, 2006). The spectrophotometer was turned on 30 minutes prior to the experiment, to ensure accurate readings, and then blanked. The first vial was spiked with 0.05mM of potassium permanganate, quickly inverted, and then placed in the spectrophotometer. The vial was scanned at 418nm and 525nm at specified times. This was continued until the absorbance at 525nm had decreased at least 100 times the standard deviation of the spectrophotometer, or 0.0316 (0.015mM). This was then repeated for the two remaining vials. It should be noted that a concentration-absorbance

calibration curve was developed for permanganate every time the spectrophotometer was utilized.

CHAPTER 3: RESULTS AND DISCUSSION

3.1 Calculation of Rate Constants

For each experiment, data was collected for the absorbance of permanganate over time. The method used to determine the pseudo-first-order reaction rate constant for each PPCP was adapted from Waldemer and Tratnyek (2006). While permanganate is the main source of the absorbance measurement at 525 nm, the growth of manganese dioxide particles contributes to the absorbance at this wavelength as well. This must be accounted for in the determination of the reaction rate for permanganate alone. Equation 1, used for curve fitting, is as follows

$$A_{525} = \left(C_i e^{-k_{obs}t}\right)\varepsilon^{525}_{MnO_4^-} + \left(C_i - C_i e^{-k_{obs}t}\right)\varepsilon^{525}_{MnO_2} \quad (1)$$

where A_{525} is the absorbance at time t at 525 nm, C_i is the initial concentration of potassium permanganate (in mM), k_{obs} is the pseudo-first-order reaction rate constant, $\varepsilon^{525}_{MnO_4^-}$ is the absorptivity of permanganate (2.46 $cm^{-1}mM^{-1}$), and $\varepsilon^{525}_{MnO_2}$ is the absorptivity of manganese dioxide particles. The absorbance versus time data for each PPCP was fit to this equation to determine the pseudo-first-order reaction rate. The calculated k_{obs} values for the PPCPs and R^2 values are listed in Table 3 by order of reactivity. An example of the curve fitting is illustrated in Figure 1 for lomefloxacin.

The methodology of using a 5:1 concentration ratio for PPCP to permanganate can be validated when looking at the R^2 values obtained in Table 3. The concern prior to running the experiments was that the amount of PPCP in excess might not be adequate to

allow for the full reduction of permanganate. However, good R^2 values were obtained for the PPCPs, which indicate a first-order degradation over the entirety of the experiment. A slowing or halting of the permanganate reduction would have been observed if the PPCP concentration were not in enough excess. Thus, it can be confirmed that for the PPCPs tested, it was acceptable to use a 5:1 ratio.

When spiking the cuvets with permanganate, the desired initial concentration was 0.05 mM. However, in using the developed calibration curve, a conversion of the initial absorbance to initial concentration revealed that it varied from the desired 0.05 mM. Over the 39 compounds, the initial concentration of the permanganate ranged from 0.018 mM to 0.059 mM. Most compounds, however, were within 0.005 mM of the desired initial concentration of 0.05 mM. The very low initial concentrations can be attributed to the extremely fast reactions that, in the time of inverting the cuvete and placing it in the spectrophotometer, the permanganate had already degraded. These calculated values of initial concentration were used for equation 1 instead of 0.05 mM to allow for a more accurate fit with the first-order model. Analysis of several PPCPs with varying initial permanganate concentrations among their three trials showed that there was no correlation between the initial concentration and the pseudo-first-order rate constant, confirming that the decay of permanganate is first-order in its concentration.

Using equation 1, the values for k_{obs} and $\varepsilon_{MnO_2}^{525}$ were solved simultaneously. The absorptivity of manganese dioxide is a measure of how strongly it absorbs light and this will be affected by the size distribution of the particles. The particle size will vary based on the rate of permanganate reduction, so it was necessary to account for this.

The k_{obs} values obtained from using equation 1 were then used to determine the second-order rate constant for each PPCP, based on the assumption that the reaction order is 1 for both permanganate and PPCP concentrations. The fact that the oxidation of tetracycline by permanganate is a second-order reaction has been verified in a separate study. In that study, reaction was conducted under excess permanganate conditions and the degradation of tetracycline was monitored by high performance liquid chromatography (HPLC). Loss of tetracycline over time followed pseudo-first-order decay (data not shown), and the first-order rate constant increased linearly with increasing permanganate concentration (Figure 2), confirming that the reaction is first order to both tetracycline and permanganate. The slope of the line in Figure 2 represents the second-order rate constant *k''*. Although experiments were not conducted to confirm the second-order reaction kinetics for all of the 39 PPCPs due to time limitation, it is assumed that most PPCPs will be oxidized by permanganate by a second-order reaction similar to tetracycline. The second-order rate constant *k*" was calculated using equation 2 below

$$k'' = \frac{k_{obs}}{[PPCP]} \qquad (2)$$

where [PPCP] is the initial concentration of the PPCP. This was 0.25 mM for all PPCPs. The values for the second-order rate constant, *k''*, are listed in Table 3.

An issue encountered prior to calculating the rate constants was with PPCPs that reacted very slowly by permanganate. The longest reactions were monitored for at most two days. It was determined through analysis that if the absorbance at 525 nm had not decreased by 0.0075 in two days, then the R^2 value gathered from the pseudo-first-order fit was typically zero. PPCPs that took longer than this to degrade the permanganate are

reported as slower than this minimum pseudo-first-order rate constant that could be determined reliably experimentally, which was calculated to be 4.5×10^{-7} per second (s^{-1}) or 1.8×10^{-3} per mole per second ($M^{-1}s^{-1}$).

Also reported in Table 3 are the estimated half-lives of each PPCP. The half-life was estimated by using a permanganate concentration of 1.5 milligrams per liter with the second-order reaction rate according to equation 3 below

$$t_{1/2} = \frac{\ln\left(\frac{C}{C_i}\right)}{-k''\left[KMnO_4\right]} \tag{3}$$

where the ratio of concentration to initial concentration is 0.5 when estimating the half-life. The permanganate concentration is a typical dosage used in water treatment plants for pre-oxidation (Liu et al., 2009).

Table 3: Reaction rate constants and half-life of PPCPs

Compound	k_{obs} (s^{-1})	k'' ($M^{-1}s^{-1}$)	$t_{1/2}$ (min)*	R^2
Acetaminophen	359.00±49.30 $x10^{-3}$	1436.00	0.86	0.88
Cefdinir	182.90±15.50 $x10^{-3}$	731.60	1.68	0.92
Triclosan	79.37±6.38 $x10^{-3}$	317.48	3.87	0.92
Carbamazepine	62.15±1.48 $x10^{-3}$	248.60	4.94	0.98
Bisphenol-A	32.23±0.15 $x10^{-3}$	128.92	9.53	0.98
Demeclocycline	26.30±1.67 $x10^{-3}$	105.20	11.68	0.98
Levofloxacin	17.43±4.29 $x10^{-3}$	69.72	17.63	0.96
Tetracycline	14.50±0.77 $x10^{-3}$	58.00	21.19	0.95
Oxytetracycline	13.40±4.47 $x10^{-3}$	53.60	22.93	0.98
Bacitracin	11.70±1.44 $x10^{-3}$	46.80	26.26	0.97
Chlortetracycline	11.10±4.62 $x10^{-3}$	44.40	27.68	0.97
Cephalexin	7.73±0.12 $x10^{-3}$	30.92	42.09	0.99
Roxithromycin	7.13±0.06 $x10^{-3}$	28.52	43.09	0.98
Ofloxacin**	1.10±0.09 $x10^{-3}$	4.40	279.31	0.97
	0.53±0.06 $x10^{-3}$	2.12	579.71	0.99
Trimethoprim	0.66±0.09 $x10^{-3}$	2.64	465.52	0.98
Diclofenac	0.65±0.03 $x10^{-3}$	2.60	472.69	0.97
Colistin	0.60±0.04 $x10^{-3}$	2.40	512.08	0.88
Enrofloxacin	0.51±0.03 $x10^{-3}$	2.04	602.44	0.96
Atenolol	0.47±0.15 $x10^{-3}$	1.88	653.72	0.52
Erythromycin	0.37±0.01 $x10^{-3}$	1.48	830.39	0.98
Ciprofloxacin	0.34±0.07 $x10^{-3}$	1.36	903.66	0.98
Sulfamethazine	0.30±0.05 $x10^{-3}$	1.20	1024.15	0.96
Atrazine	0.29±0.05 $x10^{-3}$	1.16	1059.47	0.91
Lomefloxacin	0.22±0.02 $x10^{-3}$	0.88	1396.57	0.99
Flumequine	0.21±0.05 $x10^{-3}$	0.84	1463.08	0.92
Norfloxacin	0.21±0.02 $x10^{-3}$	0.84	1463.08	0.98
Naproxen	0.21±0.01 $x10^{-3}$	0.84	1463.08	0.95
Ibuprofen	0.20±0.03 $x10^{-3}$	0.80	1536.23	0.93
Cotinine	0.20±0.15 $x10^{-3}$	0.80	1536.23	0.93
Gemfibrozil	0.20±0.02 $x10^{-3}$	0.80	1536.23	0.93
Dilantin	0.15±0.02 $x10^{-3}$	0.60	2048.31	0.95
Sulfamethoxazole	0.12±0.00 $x10^{-3}$	0.48	2560.38	0.98
Pipemidic Acid	0.10±0.02 $x10^{-3}$	0.40	3072.46	0.92
Caffeine	1.21±1.88 $x10^{-5}$	0.05	25392.24	0.66
Carbadox	9.18±4.34 $x10^{-6}$	0.04	33469.07	0.79
Monensin	8.90±1.20 $x10^{-6}$	0.04	34522.03	0.99
Simetone	6.86±1.76E $x10^{-6}$	0.03	44788.06	0.87
TCEP	$<4.50x10^{-7}$	$<1.80x10^{-3}$	>682769.09	N/A
Metoprolol	non-reactive ($<4.50x10^{-7}$)	$<1.80x10^{-3}$	>682769.09	N/A

*Based on $[KMnO_4]$=1.5mg/L

**Reported values for two different ofloxacin reagents

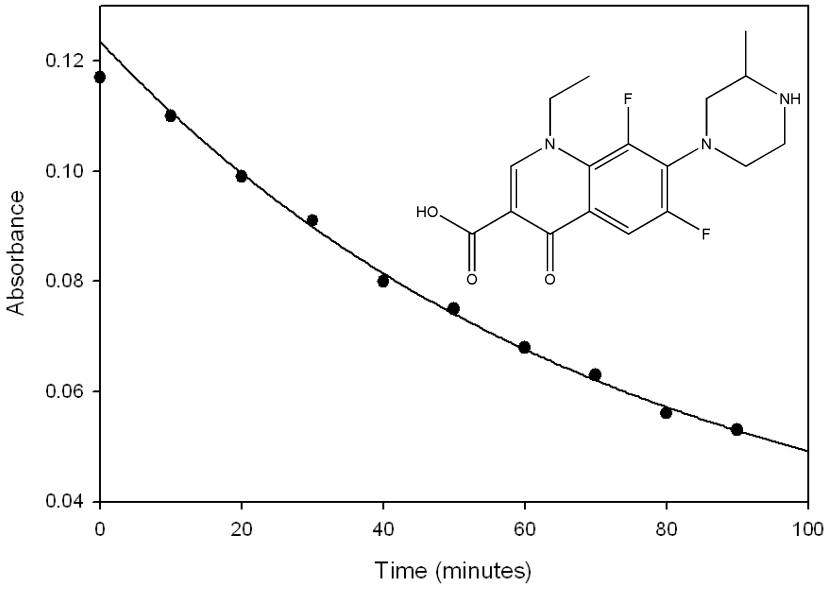


Figure 1: Curve fitting to equation 1 for permanganate reduction by lomefloxacin. C_i = 0.050 mM, k_{obs} = 0.23 x 10^3 s^{-1}, R^2 = 0.99

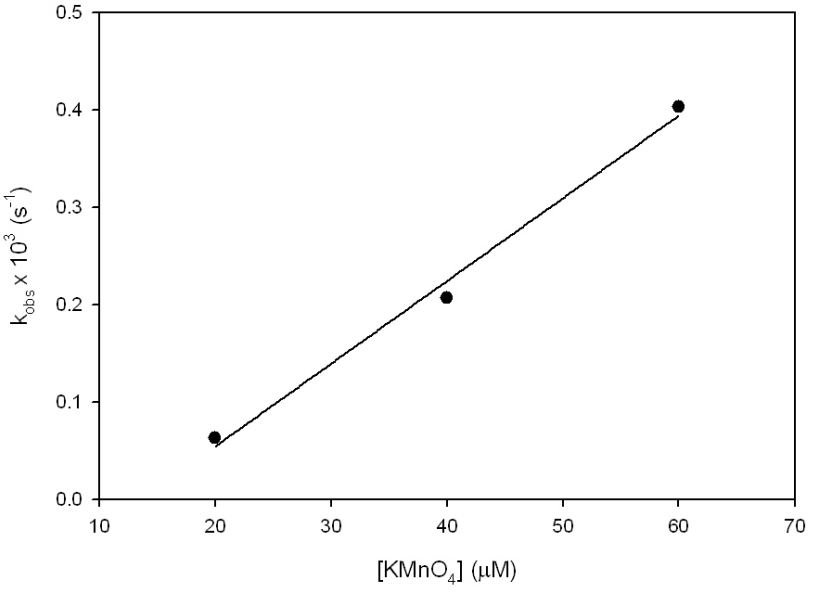


Figure 2: First-order reaction rate constant of tetracycline as a function of varying permanganate concentrations. $[TTC]_i$ = 0.020 mM, pH = 7.0, R^2 = 0.99

3.2 Critiques of Method

3.2.1 Product Formation

In order to determine if a pseudo-first-order degradation of permanganate occurred for each PPCP, the absorbance was converted to concentration by utilizing the developed calibration curve. Figure 3 illustrates the permanganate reduction by trimethoprim. The linearity supports the conclusion that permanganate oxidizes PPCP at a pseudo-first-order reaction rate. There were several PPCPs that had product formation during the experiment, which interfered with monitoring the decrease in absorbance of permanganate. The permanganate reaction with colistin was properly monitored for 45 minutes until a product formation caused the absorbance at 525 nm to increase significantly, instead of continuing to decrease (Figure 4). With PPCPs where such interference occurred, the data collected up to the point of product formation was used to calculate the rate constant. Those PPCPs included atenolol, atrazine, chlortetracycline, colistin, cotinine, demeclocycline, diclofenac, dilantin, flumequine, gemfibrozil, ibuprofen, naproxen, oxytetracycline, pipemidic acid, sulfamethazine, tetracycline, and triclosan. For the majority of these PPCPs, the deviation from linearity indicating interference did not occur until much later in the oxidation by permanganate (Figure 5). However, in some cases the decrease in absorbance before the product formation was not greater than 100 times the standard deviation (atenolol, colistin, and pipemidic acid). As a result, the R^2 values for those rate constants were not as high as desired.

The above interference problem could be handled by studying the reaction using HPLC technique, in which the degradation of PPCP (not permanganate) will likely be monitored. However, developing a suitable HPLC-based method for each of the 39

PPCPs will be highly laborious and time consuming. Thus, the spectrophotometer technique to monitor the degradation of permanganate was chosen in this study for its speed and convenience. Evidently, interfering products can be an issue for some PPCP compounds, and separation of the interfering products will be needed to improve the accuracy of the results.

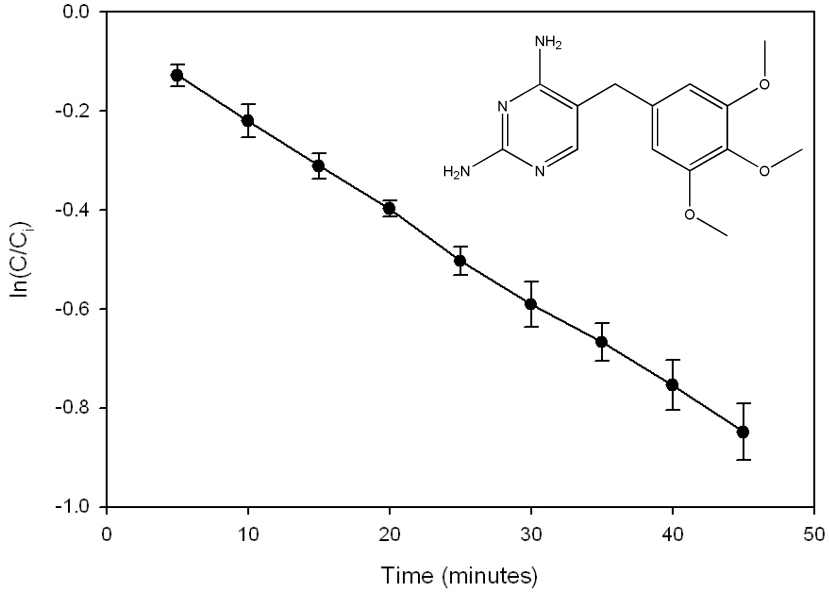


Figure 3: Permanganate reduction by trimethoprim. C_i = 0.046-0.050 mM

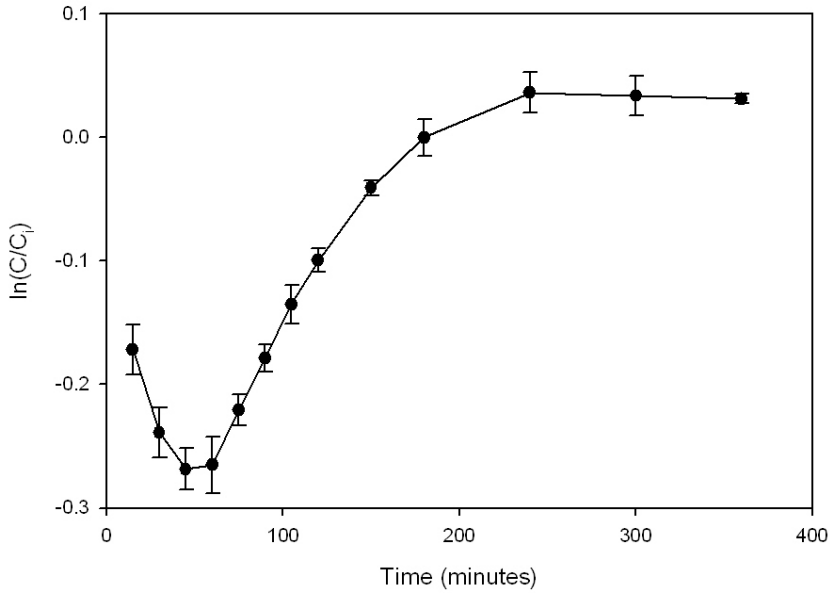


Figure 4: Product formation during permanganate reduction by colistin. C_i = 0.044-0.045 mM

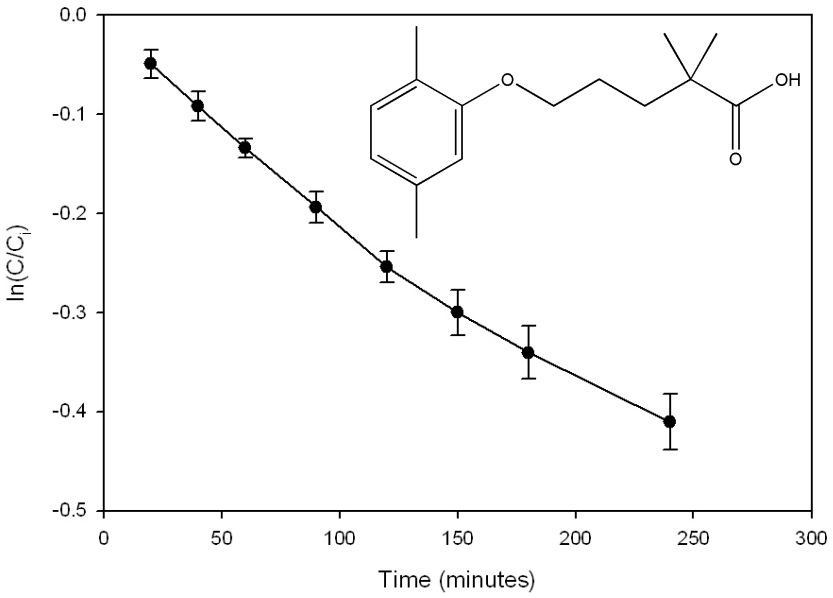


Figure 5: Minor interference by product formation during permanganate reduction by gemfibrozil. C_i = 0.051-0.052 mM

3.2.2 Absorbance Validation

Manganese dioxide particles that are formed during permanganate's reduction obey Beer's law until they flocculate. Once flocculation occurs, the flocs can scatter light within the spectrophotometer and alter the absorbance readings at 525 nm (Crimi et al., 2004). In order to determine when this flocculation occurs, Waldemer and Tratnyek suggest analyzing the absorbance measured at 418 nm against the absorbance measured at 525 nm (2006). With permanganate decreasing and forming manganese dioxide, there should be a linear correlation where A_{418} increases as A_{525} decreases. Once there is a deviation from this linearity, Waldemer and Tratnyek state that flocculation is occurring and the data used for curve fitting should stop at this point. Approximately half of the PPCPs tested adhered to this linearity prior to any product formation (acetaminophen, atenolol, atrazine, bacitracin, bisphenol-A, carbamazepine, cefdinir, cephalexin, ciprofloxacin, colistin, diclofenac, levofloxacin, ofloxacin, roxithromycin, triclosan, and trimethoprim). These PPCPs were typically the faster reacting compounds. It is possible that the manganese dioxide particles did not have enough time to flocculate before the permanganate had reduced the desired amount. Figure 6 illustrates the linearity between absorbances 525 nm and 418 nm for bacitracin.

There were two observed trends that challenge the validity of this method. Twelve of the PPCPs did not have a purely linear correlation, but a curved line that was concave up (cotinine, dilantin, erythromycin, flumequine, gemfibrozil, ibuprofen, lomefloxacin, naproxen, norfloxacin, pipemidic acid, sulfamethazine, and sulfamethoxazole). It should be noted that the PPCPs with the concave correlation were the compounds with the slower rate constants. Sulfamethoxazole had a curved

relationship for the absorbances at 525 nm and 418 nm (Figure 7). It appears that manganese dioxide growth is more than it should be with respect to the permanganate reduction. Literature suggests that the upward curvature may be a result of an increase in the manganese dioxide particle size due to an increase in the rate of flocculation (Perez-Benito, 2009). While this literature attributes the increase in particle size in their research to the presence of divalent cations (calcium), it cannot be the cause for this research. As this was observed in the slower reacting PPCPs, perhaps slower degradation of permanganate results in a steady increase in the rate of flocculation, thus resulting in the observed concave upward trend. When the compounds are plotted to show the permanganate reduction, the measured absorbances at 525 over time are linear and thus considered still valid to calculate pseudo-first-order reaction rate constants (Figure 8), leading to R^2 values greater than 0.90.

The second trend occurred for the four tetracycline antibiotics that were tested: chlortetracycline, demeclocycline, oxytetracycline, and tetracycline. For each tetracycline antibiotic, the manganese dioxide initially increased with respect to the reduction of permanganate but then began to decrease. This created a sideways parabola when plotting the absorbances at the two wavelengths (Figure 9). This trend can be explained by tetracycline's ability to react quickly with manganese oxides (Zhang et al., 2008). The initial absorbance trend, however, shows that manganese dioxide is initially created before it is consumed. The data that occurs before this point of decrease shows that permanganate reduction is occurring at the same rate as when manganese dioxide is consumed (Figure 10). The pharmaceutical is in excess of the permanganate; as a result, there is enough of it to reduce the permanganate and consume the manganese dioxide.

As a result, the absorbance data collected is still considered valid to fit to a pseudo-first-order model. Waldemer and Tratnyek's method of determining whether absorbance is inhibited by manganese dioxide particles does not account for reactions of manganese dioxide that could occur with the organic reductant but do not affect permanganate reduction.

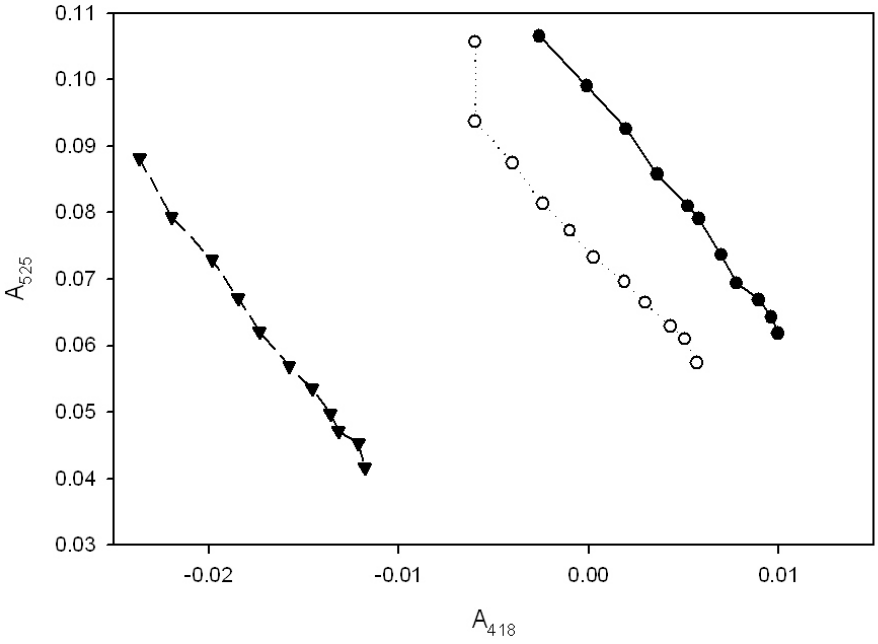


Figure 6: Relationship between absorbance at 525 nm and absorbance at 418 nm in three separate trials of permanganate reduction by bacitracin.

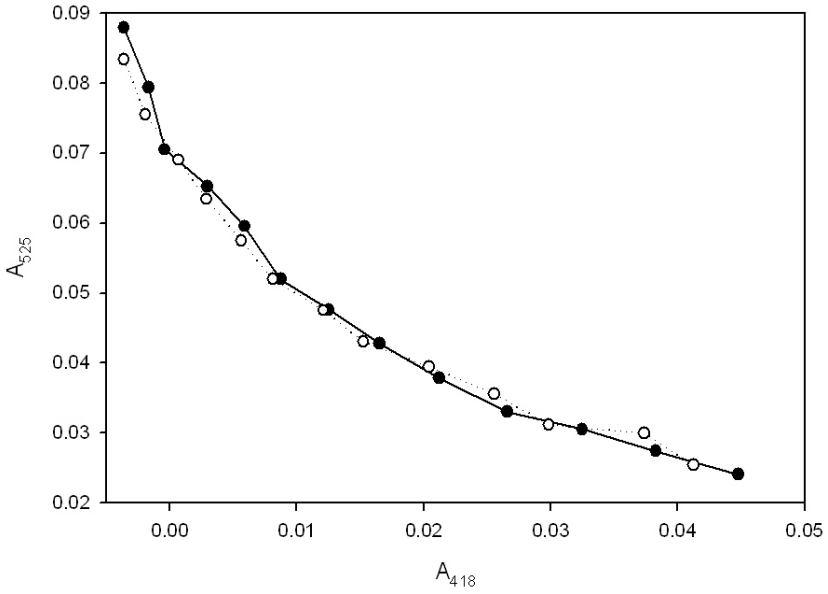


Figure 7: Relationship between absorbance at 525 nm and absorbance at 418 nm in two separate trials of permanganate reduction by sulfamethoxazole. The concave upward curve deviates from expected linearity.

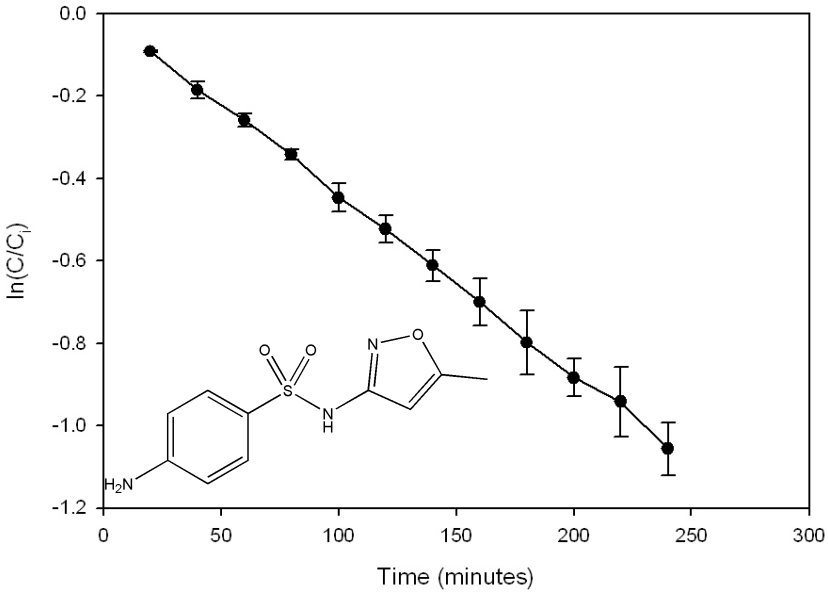


Figure 8: Permanganate reduction by sulfamethoxazole is linear in ln(C/C_i) plot. C_i = 0.037-0.039 mM

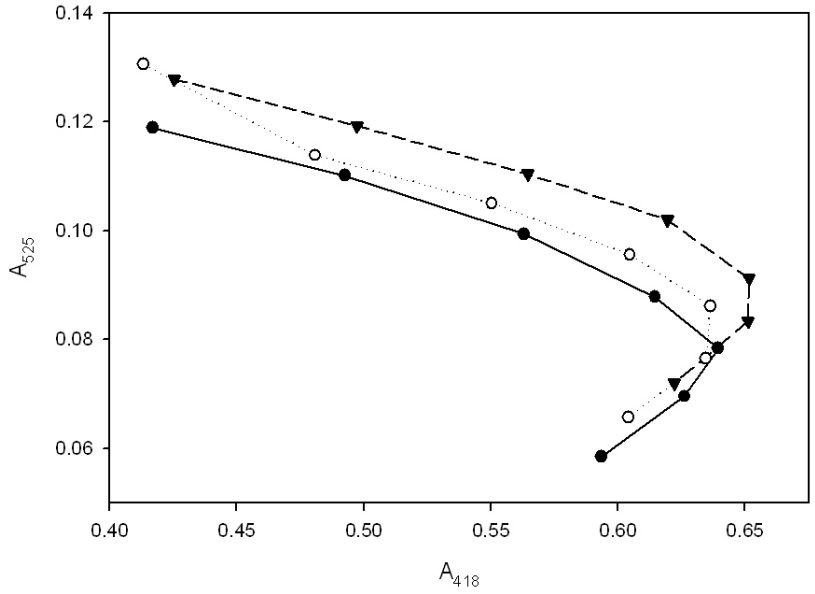


Figure 9: Relationship between absorbance at 525 nm and absorbance at 418 nm in three separate trials of permanganate reduction by oxytetracycline.

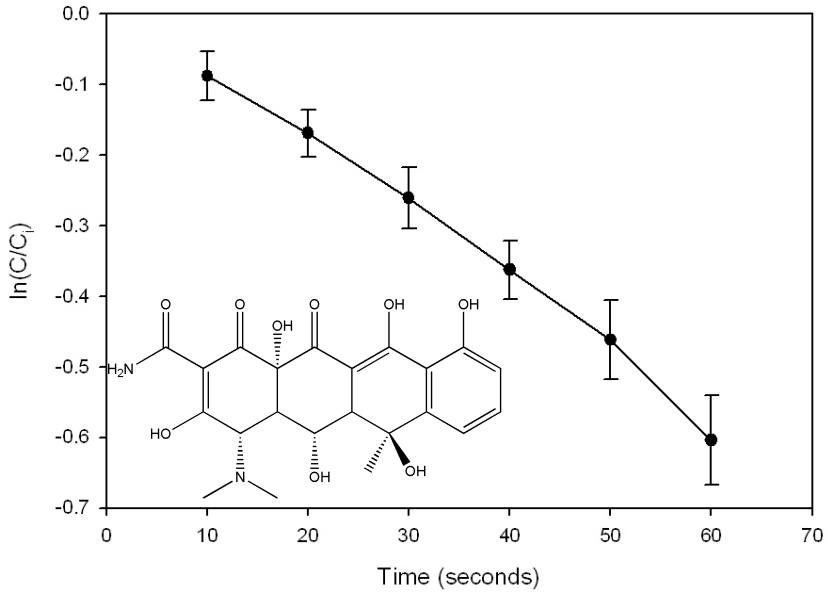


Figure 10: Permanganate reduction by oxytetracycline is linear in $\ln(C/C_i)$ plot. C_i = 0.049-0.059 mM

3.3 Comparison to Other Literature Values

The majority of the PPCPs tested have yet to be investigated with their oxidation by permanganate. There are a few from this research that have published first-order and second-order rate constants. However, some of the reaction conditions, such as pH and the ratio of PPCP to permanganate, are different. The literature on ciprofloxacin (Thabaj et al., 2007), levofloxacin (Khan et al., 2010), and norfloxacin (Naik et al., 2009) were only available in alkaline conditions with a pH of 11.0 to 14.0 and are thus not comparable. The other literature values, for pH 7.0, are compared by second-order rate constants to account for the differing ratios of the PPCP to permanganate concentration. The second-order rate constant for tetracycline from the previous HPLC research is also compared (as discussed in *3.1 Calculation of Rate Constants*). The second-order rate constant comparisons are listed in Table 4.

Table 4: Comparison of observed second-order rate constants to literature values.

Compound	k''_{obs} ($M^{-1}s^{-1}$)	$k''_{literature}$ ($M^{-1}s^{-1}$)	Reaction Conditions for literature value	Source
Bisphenol-A	128.92	99.5	1:10 [BPA]:[$KMnO_4$] pH 7	Xu, 2009
Carbamazepine	248.60	293.3	1:20 [CMP]:[$KMnO_4$] pH 7	Hu et al., 2009
Triclosan	317.48	129.5	1:10 [TCS]:[$KMnO_4$] pH 7	Jiang et al., 2009
Tetracycline	58.00	8.33	1:3 [TTC]:[$KMnO_4$] pH 7	Previous Research

The literature values for bisphenol-A, carbamazepine, triclosan, and tetracycline are all with permanganate in excess, which is unlike the experiments carried out for this research. The HPLC was also utilized instead of a spectrophotometer. However, the

literature values for bisphenol-A and carbamazepine are comparable to the values calculated from this research. Even though the triclosan values differ, they are within the same magnitude. The tetracycline values are not as comparable and may be a result of tetracycline readily consuming manganese dioxide (as discussed in *3.2.2 Absorbance Validation*). The other monitored tetracyclines (chlortetracycline, demeclocycline, and oxytetracycline) should also be measured on the HPLC to determine if the second-order rate constants exhibit a similar relationship with the spectrophotometer-measured constants. This comparison in values confirms that the spectrophotometer can produce results similar to those from HPLC analysis. It is also confirmed that having either the compound in excess or the permanganate in excess can produce similar second-order rate constants, which has previously been confirmed in other literature (Waldemer and Tratnyek, 2006).

3.4 Analysis of Reactivities of PPCPs

3.4.1 General Trends

To assist comparison, the reactivity of the thirty-nine PPCPs are classified into five different groups: highly reactive (k'' = 731.60 - 1436.00 $M^{-1}s^{-1}$), reactive (k'' = 105.20 - 317.48 $M^{-1}s^{-1}$), moderately reactive (k'' = 28.52 - 69.72 $M^{-1}s^{-1}$), weakly reactive (k'' = 0.40 to 4.40 $M^{-1}s^{-1}$), and poorly reactive (k'' < 0.1 $M^{-1}s^{-1}$). These classifications can be seen in Table 5 below. In analyzing the table, it can be seen that few PPCPs are reactive or highly reactive. The majority of PPCPs analyzed were weakly to moderately reactive when oxidized by permanganate. Only a few of the PPCPs were considered poorly reactive.

Table 5: Classification of PPCP reactivity

Classification	**k'' range ($M^{-1}s^{-1}$)**	**PPCP Reactivity**
Highly Reactive	731.60-1436.00	acetaminophen>cefdinir
Reactive	105.20-317.48	triclosan>carbamazepine>bisphenol-A >demeclocycline
Moderately Reactive	28.52-69.72	levofloxacin>tetracycline>oxytetracycline>bacitracin >chlortetracycline>cephalexin>roxithromycin
Weakly Reactive	0.40-4.40	ofloxacin~trimethoprim~diclofenac~colistin ~enrofloxacin>atenolol~erythromycin~ciprofloxacin ~sulfamethazine~atrazine>lomefloxacin~flumequine ~norfloxacin~naproxen~ibuprofen~cotinine ~gemfibrozil~dilantin~sulfamethoxazole ~pipemidic acid*
Poorly Reactive	<0.10	caffeine~carbadox~monensin~simetone>TCEP >metoprolol

*A sign of ~ indicates that the reactivity of those PPCPs was similar.

3.4.2 Phenol Structures

Acetaminophen was highly reactive (k'' = 1436.00 $M^{-1}s^{-1}$, Figure 11), while triclosan (k'' = 317.48 $M^{-1}s^{-1}$, Figure 12) and bisphenol-A (k'' = 128.92 $M^{-1}s^{-1}$, Figure 13) were slightly less reactive when oxidized by permanganate. Numerous papers have discussed the rapid oxidation of phenols, specifically by permanganate (He et al., 2009, and Jiang et al., 2009). One suggested mechanism for phenol oxidation by permanganate is a single electron transfer from the phenolate anion to permanganate, leading to a phenolic radical that can undergo further oxidative and coupling reactions to yield quinones or breakdown products (Waldemer and Tratnyek, 2006 and Lee and Sebastian, 1981). There has been little research done to detail the mechanisms of phenol oxidation by permanganate and it is recommended that this be further investigated.

Research has shown that the simple phenol compound will oxidize by permanganate at a second-order rate constant value of 35.40 $M^{-1}s^{-1}$ (Waldemer and Tratnyek, 2006). The three compounds studied here had faster second-order rate constants than a simple phenol most likely due to their additional properties. Acetaminophen was the fastest compound tested in this research, having reduced the permanganate within the first ten seconds of analysis (Figure 11). Its aromatic ring has both phenol and aniline characteristics (Figure A1-a), which are both very reactive with permanganate. It has been suggested that anilines, in a neutral solution, will oxidize very rapidly with permanganate (Stewart, 1965). The aniline characteristics, located at *para* position to the phenolic hydroxyl group, are suspected to have increased the acetaminophen reactivity in addition to the phenol's presence. Triclosan contains a 2,4-chloroalkoxylbenzene and a 2-alkoxyl-3-chlorophenol linked together by a joint oxygen

between the two moieties (Figure A1-c). The chlorinated phenol structures with activating substituent groups may contribute to the rapidity of the permanganate reduction as research shows that some chlorophenols react more quickly with permanganate than an unsubstituted phenol (Jin et al., 2003). As mentioned earlier in *Section 3.3* and Table 4, the second-order rate constant of triclosan measured in this study is comparable to the previously reported value (Jiang et al., 2009). The reported second-order reaction rate constant for oxidation of 2,4 chlorophenol by permanganate at pH 7.0 was 142.00 $M^{-1}s^{-1}$ (Waldemer and Tratnyek, 2006) or 19.1 $M^{-1}s^{-1}$ (Jiang et al., 2009). The reported second-order reaction rate constant for 3-chlorophenol was 13.4 $M^{-1}s^{-1}$ (Waldemer and Tratnyek, 2006). Triclosan is oxidized by permanganate faster than 2,4 chlorophenol and 3-chlorophenol, possibly due to interactions between its two aromatic moieties leading to higher reactivity (Figure 12). The previous work by Jiang et al. (2009) reported that phosphate may enhance oxidation of triclosan as well as other phenols by permanganate possibly through stabilizing manganese intermediates, but did not provide reasons for the unusually higher reactivity of triclosan toward permanganate than other substituted phenols. Bisphenol-A contains two alkylphenol moieties that are likely independent of each other electronically (Figure 13). Bisphenol-A's reactivity appears to fall between *p*-cresol (k'' = 237 $M^{-1}s^{-1}$) and simple phenol (k'' = 35.40 $M^{-1}s^{-1}$) (Waldemer and Tratnyek, 2005).

Attempts were made to obtain correlations between the pseudo-first-order rate constants and the organic compounds' polarizability, electron affinity, and refractive index. These physicochemical properties were selected based on a recent paper that found a correlation between chemical oxygen demand and molecular refractivity and

dipole moment of organic compounds (Kim et al., 2007). Chemical oxygen demand, which is typically measured by a sample's capability to consume a particular strong oxidant, is closely related to oxidation of organic compounds by permanganate, so similar physicochemical properties were selected. In addition to the three compounds (acetaminophen, triclosan and bisphenol-A) studied here, literature reported rate constants for various phenols are also included to establish the correlations (Waldemer and Tratnyek, 2006).

No correlation was found between the rate constants and electron affinity. Figures 14 and 15 appear to show that there is no correlation between polarizability and refractive index with the rate constants as well. However, further analysis of the figures reveals that the extreme reactivity of acetaminophen may be distorting the correlations. The amine attached to the phenol may promote such reactivity that is not seen in the other phenol structures. If this pharmaceutical is excluded, there is the potential for a correlation for both polarizability and refractive index. With the exclusion of acetaminophen, positive correlations are seen for both polarizability ($R^2 = 0.59$) and refractive index ($R^2 = 0.92$) for the phenol structures (Figures 16 and 17).

For the phenol structures, as the polarizability increases, the reaction rate with permanganate increases (Figure 16). Polarizability is the measure of a compound's tendency to have its charge distribution distorted by external sources. With a higher tendency to have its charge distribution distorted, this should allow for more opportunities for its oxidation by permanganate. As the refractive index increases, the phenol structures' reaction rates with permanganate decrease (Figure 17). The refractive index is a measure of how quickly light will travel through a medium and is based on

permittivity. Permittivity is related to a medium's ability to polarize in response to an electric field. Therefore, the higher the refractive index of a compound, the higher its ability to polarize in response to an electric field. The correlation explanation is similar to that of the polarizability; the higher the refractive index, the more likely a compound should be polarized and thus oxidized by the permanganate. This relationship between polarizability and refractive index is described in the Lorenz-Lorentz equation, where the two properties have a positive relationship (Schwarzenbach, 2003).

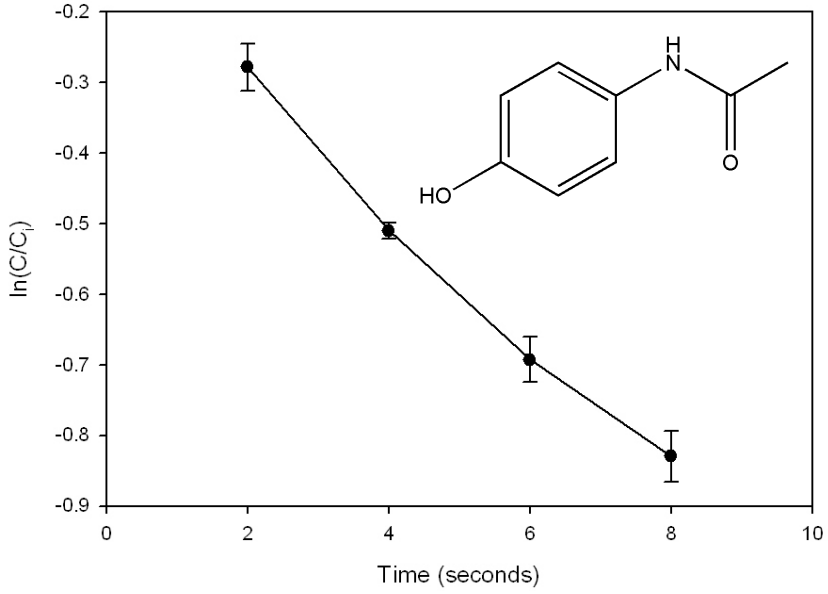


Figure 11: Permanganate reduction by acetaminophen. C_i = 0.018-0.019 mM

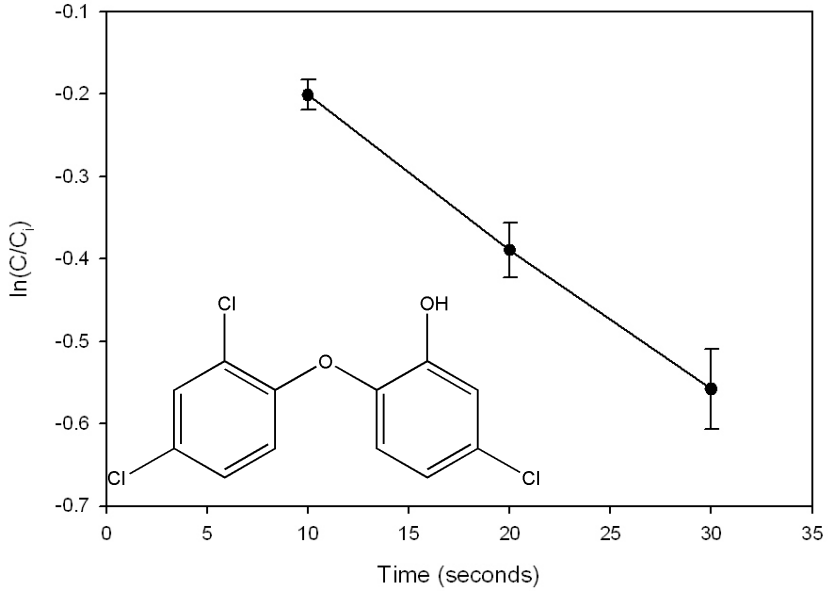


Figure 12: Permanganate reduction by triclosan. C_i = 0.031-0.033 mM

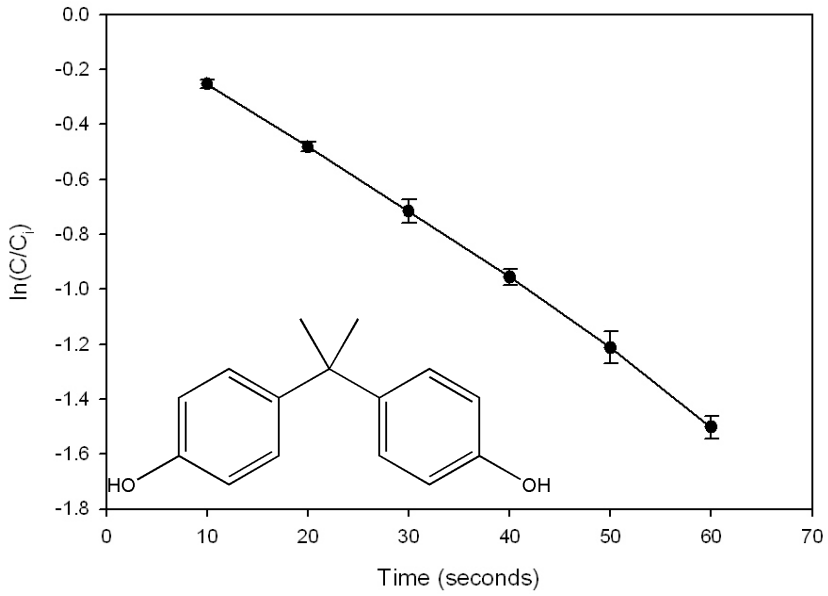


Figure 13: Permanganate reduction by bisphenol-A. C_i = 0.034-0.036 mM

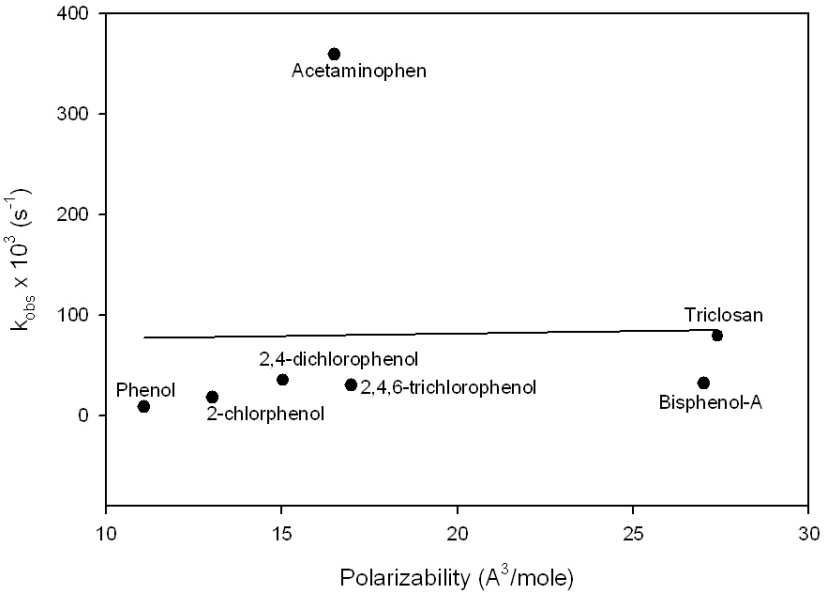


Figure 14: Attempted correlation between pseudo-first-order reaction rates for phenol structures and polarizability. R^2 = 0.00064

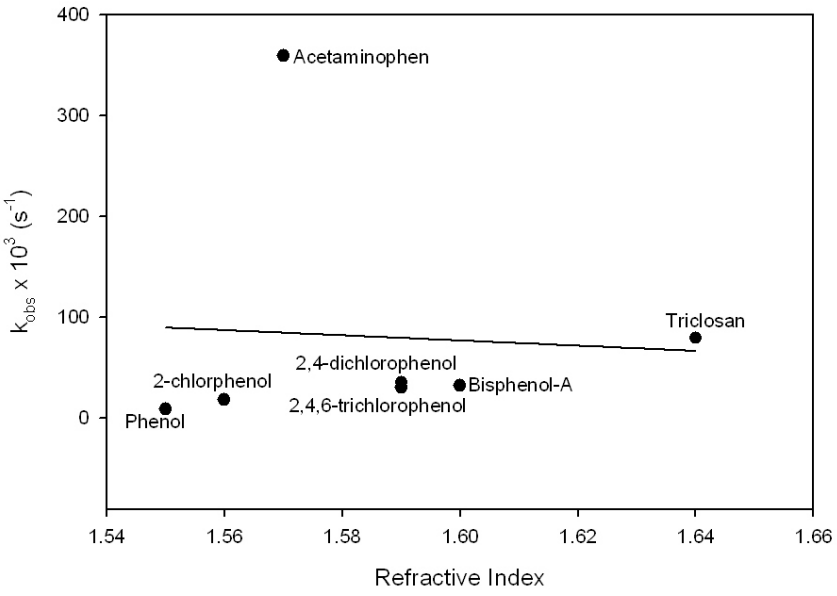


Figure 15: Attempted correlation between pseudo-first-order reaction rates for phenol structures and refractive index. R^2 = 0.0038

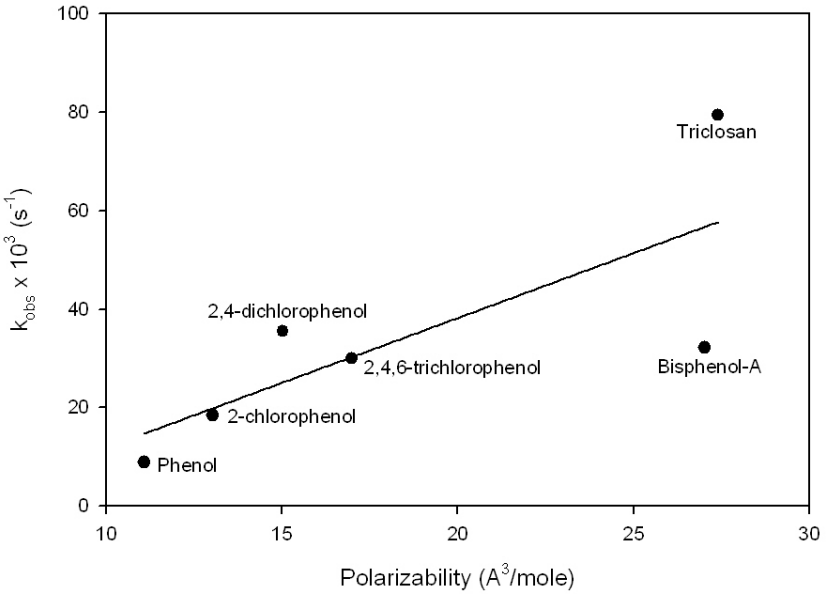


Figure 16: Adjusted positive correlation between pseudo-first-order reaction rates for phenol structures and polarizability. $R^2 = 0.59$

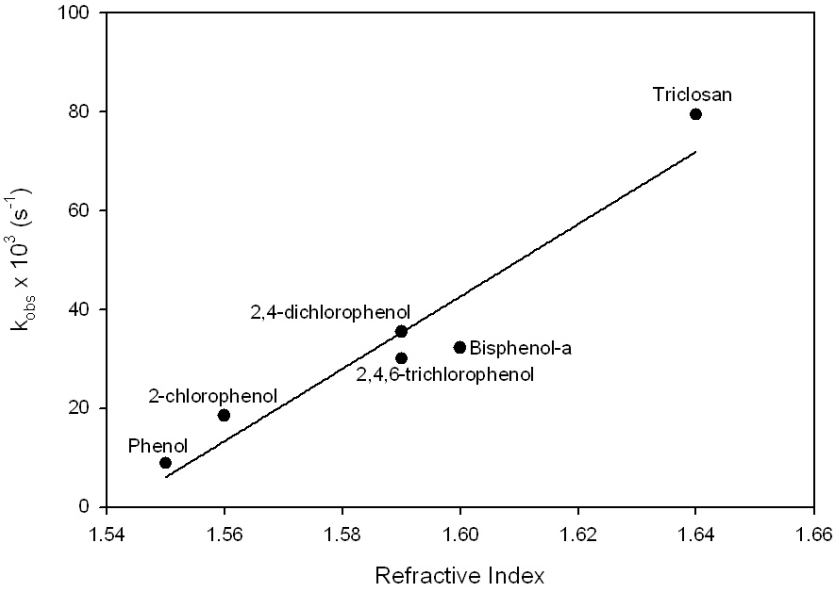


Figure 17: Adjusted positive correlation between pseudo-first-order reaction rates for phenol structures and refractive index. $R^2 = 0.92$

3.4.3 Cephalosporins

Cefdinir (k'' = 731.60 $M^{-1}s^{-1}$) was highly reactive and cephalexin (k'' = 30.92 $M^{-1}s^{-1}$) was moderately reactive with permanganate (Figure 18). Both cephalosporins have an amide, but this is not likely the reason for oxidation. Research has shown that an amide is typically not oxidized unless an acid is present (Sharma et al., 2008). The oxidation can be attributed to the presence of a primary amine for both pharmaceuticals. Research has shown that primary amines are oxidized rapidly by permanganate, even in neutral solutions (Rawalay and Shechter, 1967). The primary mechanism suggested for this rapid oxidation is that hydrogen abstraction occurs and the amine becomes an imine. While both rapid, cefdinir is significantly more rapidly oxidized by permanganate than cephalexin. This cannot be attributed to the presence of an oxime for cefdinir, which research shows is unreactive in water alone (Wali et al., 1993). The additional rapidity of cefdinir's oxidation may be due to the presence of an alkene side group (Figure 18). Alkenes are known to readily oxidize by permanganate where the double bond cleaves to produce aldehydes, ketones, and carboxylic acid groups (Stewart, 1965).

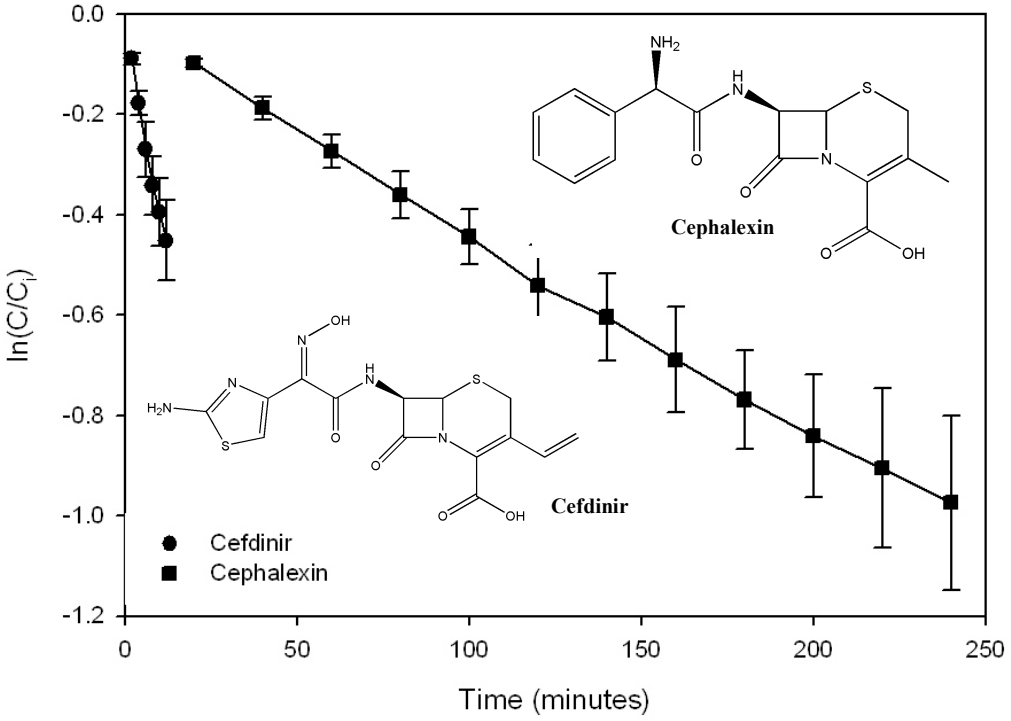


Figure 18: Permanganate reduction by cephalosporins. Cefdinir (C_i = 0.032-0.034 mM) reacted more rapidly than cephalexin (C_i = 0.043-0.052 mM).

3.4.4 Tetracyclines

Chlortetracycline (k'' = 44.40 $M^{-1}s^{-1}$), oxytetracycline (k'' = 52.60 $M^{-1}s^{-1}$), and tetracycline (k'' = 58.00 $M^{-1}s^{-1}$) were all moderately reactive toward permanganate, while demeclocycline (k'' = 105.20 $M^{-1}s^{-1}$) was more reactive. Tetracycline antibiotics have a very complicated ring structure with many potential sites for oxidation (Figures A3-a,b,c,d). Each antibiotic has several hydroxyl and hydrocarbon attachments around the ring structure, where hydrogen abstraction could potentially occur. The chlorine attachment to the outer ring for chlortetracycline and demeclocycline creates a chlorophenol, which can possibly be more reactive than the phenol rings for oxytetracycline and tetracycline (as discussed in *3.4.2 Phenol Structures*). The reactivities of these four tetracyclines were slightly faster than phenol (k'' = 35.40 $M^{-1}s^{-1}$) (Waldemer and Tratnyek, 2006). This may be attributed to the additional sites around the aromatic hydrocarbon structures. The four antibiotics also have a tertiary amine and an amide, but the potential for moderate oxidation at these sites is unlikely (as discussed in *3.4.3 Cephalosporins*).

Demeclocycline degrades twice as fast as the other three tetracycline antibiotics (Figure 19). This may be due to the combination of having a chlorophenol and more hydroxyl sites available for rapid oxidation. Demeclocycline also has a secondary alcohol at the bottom of a ring where the other tetracyclines have a tertiary alcohol. This secondary alcohol may be oxidized by permanganate by hydrogen abstraction with the benzylic C-H bond.

Correlations were attempted between the pseudo-first-order rate constant and tetracyclines' polarizability, electron affinity, and refractive index. No significant

correlations were found (polarizability: $R^2 = 0.35$, electron affinity: $R^2 = 0.19$, refractive index: $R^2 = 0.40$).

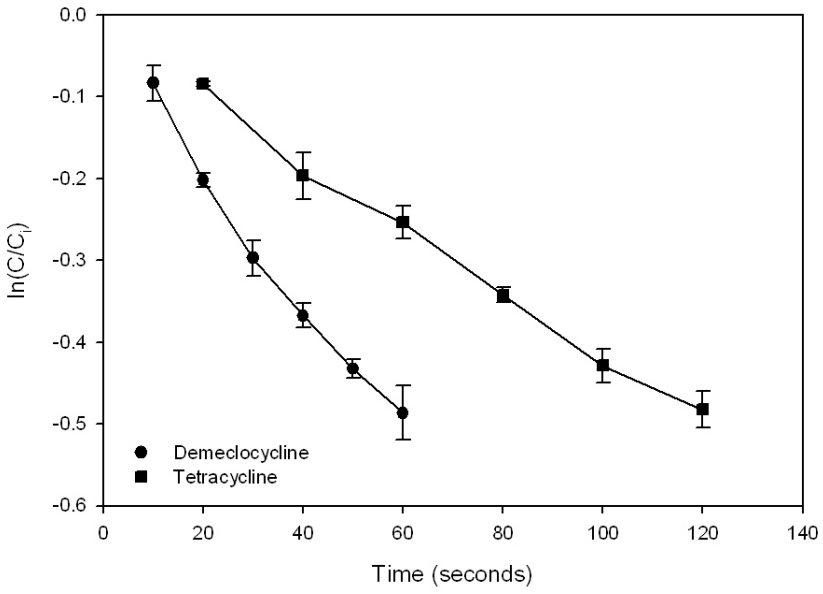


Figure 19: Permanganate reduction by tetracycline antibiotics. Demeclocycline (C_i = 0.052-0.055 mM) reacted more rapidly than tetracycline (C_i = 0.050-0.053 mM).

3.4.5 Polypeptides

Bacitracin (k'' = 46.80 $M^{-1}s^{-1}$) was oxidized moderately by permanganate (Figure 20) while colistin was weakly reactive (k'' = 2.40 $M^{-1}s^{-1}$) and had product formation interference (as discussed in *3.2.1 Product Formation*). When the polypeptides are analyzed structurally, they seem very similar (Figures A4-a,b). Both have numerous amides that are most likely not the site for permanganate oxidation. Bacitracin has two primary amine sites and colistin has five, suggesting a rapid oxidation could occur (as discussed in *3.4.3 Cephalosporins*).

The discrepancy between the two polypeptides should be further explored. The presence within bacitracin of a thiazole ring and an imidazole ring may react more strongly with permanganate than is expected, as this is the only significant difference between the two polypeptides (Soldatenkov et al., 2004). The interference of product formation with colistin may have resulted in a pseudo-first-order rate constant that is not wholly representative of the oxidation. The data used did not meet the requirements of "100 times the standard deviation" but an R^2 value of 0.88 was obtained. Since these polypeptides are made up of a mixture of related polypeptides, the exact structure of each is not known. The discussed structures are what the most common bacitracin and colistin structures are. It is possible that one of the chemicals obtained was not as comparable to the most common structure and is the reason for the differences in reactivity. To confirm this, more samples of bacitracin and colistin should be obtained to determine if the reaction rate constants are similar to those obtained in this research.

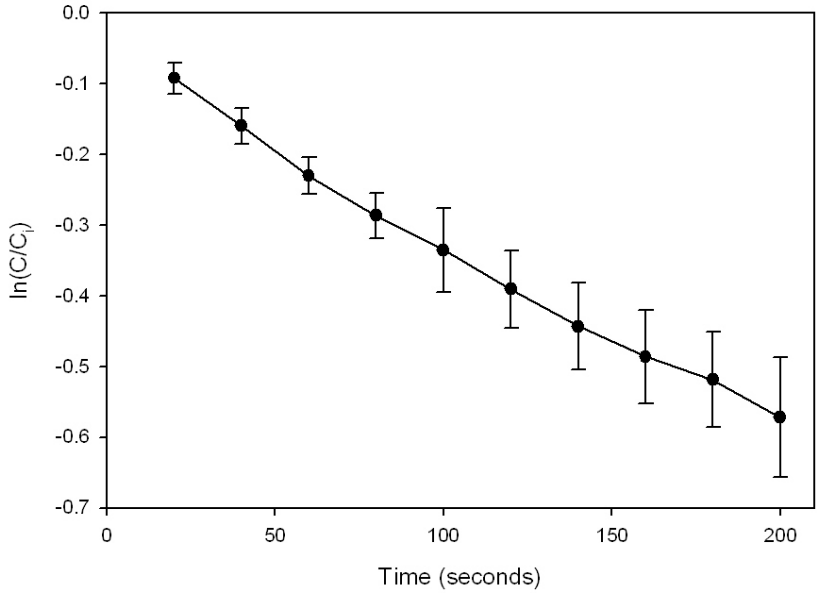


Figure 20: Permanganate reduction by bacitracin. C_i = 0.039-0.046 mM

3.4.6 Macrolides

Erythromycin was found to be weakly reactive (k'' = 1.48 $M^{-1}s^{-1}$) with permanganate while roxithromycin was moderately reactive (k'' = 28.52 $M^{-1}s^{-1}$) (Figure 21). These two antibiotics are nearly identical structurally, with the exception of the top-most site (Figures A5-a,b). Erythromycin has a ketone, while roxithromycin has an oxime/ether side chain. Differences in the reaction rates could be attributed to this difference in structures. Ketones are very stable and would not be expected to react with permanganate under these conditions. The reactivity of both pharmaceuticals can be attributed to the secondary alcohols. A secondary alcohol, while more stable than a primary alcohol, may still be oxidized by permanganate (Stewart, 1965). The suggested mechanism is that hydrogen atom abstraction occurs and then forms a more stable ketone. Each pharmaceutical has a tertiary amine, but these are considered much more stable than primary amines (Ralaway and Shechter, 1967).

The additional speed with which roxithromycin reacted with permanganate could be attributed to the oxime/ether side chain. However, research shows that oximes are not reactive with permanganate (as discussed in *3.4.3 Cephalosporins*) and ether side chains may be slowly reactive (Damm et al., 2002). There is the suggested mechanism of hydrogen/hydride extraction of ethers (Barter and Littler, 1967) that may have occurred to allow for a quicker oxidation of roxithromycin.

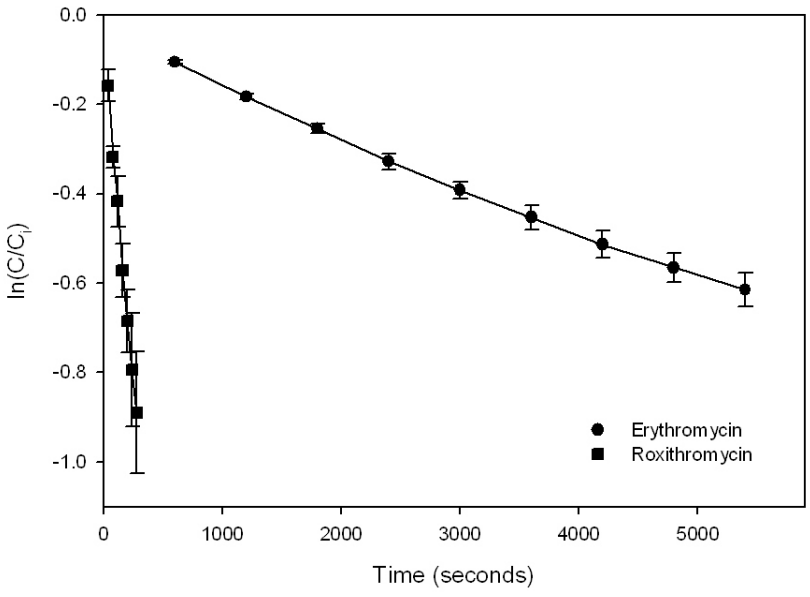


Figure 21: Permanganate reduction by macrolides. Roxithromycin (C_i = 0.040-0.046 mM) reacted more rapidly than erythromycin (C_i = 0.053-0.055 mM).

3.4.7 Fluoroquinolones

With the exception of levofloxacin, the fluoroquinolones were weakly reactive with permanganate: ciprofloxacin (k'' = 1.36 $M^{-1}s^{-1}$), enrofloxacin (k'' = 2.04 $M^{-1}s^{-1}$), flumequine (k'' = 0.84 $M^{-1}s^{-1}$), lomefloxacin (k'' = 0.88 $M^{-1}s^{-1}$), norfloxacin (k'' = 0.84 $M^{-1}s^{-1}$), ofloxacin (k'' = 4.40 $M^{-1}s^{-1}$, 2.12 $M^{-1}s^{-1}$), and pipemidic acid (k'' = 0.40 $M^{-1}s^{-1}$). Levofloxacin, in comparison, was moderately reactive (k'' = 69.72 $M^{-1}s^{-1}$) (Figure 22). Literature has found that the piperazine structure, common in all fluoroquinolones except flumequine, can be the site of oxidation by manganese dioxide (Zhang and Huang, 2005a) and free and combined chlorines (Dodd et al., 2005) and several mechanisms are suggested. However, since flumequine was just as reactive as the other fluoroquinolones, it is suggested that the site of oxidation is the quinolone group (Figure A6-c). This is supported by research that investigated the oxidation of levofloxacin and norfloxacin by permanganate in alkaline conditions (Khan et al., 2010 and Naik et al., 2009). The suggested mechanism in this literature is an electron transfer from the PPCP to permanganate, with the OH- stabilizing the resulting Mn(VI) product. The reactions monitored in this research at pH 7.0 may involve more complex intermediates and thus may not be the same as under the alkaline conditions.

An unexpected result is the discrepancy in rate constants between levofloxacin and the other fluoroquinolones, particularly ofloxacin. Ofloxacin is known as a "racemic mixture" that is 50% levofloxacin and 50% dextrofloxacin, which is levofloxacin's mirror image (Figures A6-d,g). It would be expected that ofloxacin's reactivity with permanganate would be very similar to levofloxacin's. However, initial experiments of ofloxacin resulted in a second-order rate constant of 2.12 $M^{-1}s^{-1}$, compared to a value of

69.72 $M^{-1}s^{-1}$ for levofloxacin. In knowing that the levofloxacin used to make the stock solution was new and the ofloxacin was relatively old, new ofloxacin was ordered. The result with the new product was slightly higher, 4.40 $M^{-1}s^{-1}$, but it was still not comparable to levofloxacin. The relationship between levofloxacin and ofloxacin should be further researched.

While not comparable with this research, the reactivity of ciprofloxacin, levofloxacin, and norfloxacin in alkaline conditions may be compared with each other. At pH 12.0 (pH 11.6 for levofloxacin) the three fluoroquinolones are weakly reactive by permanganate: ciprofloxacin (k'' = 1.63 $M^{-1}s^{-1}$), levofloxacin (k'' = 1.48 $M^{-1}s^{-1}$), and norfloxacin (k'' = 1.80 $M^{-1}s^{-1}$). The reactions were all monitored at a 10:1 ratio with permanganate in excess. The suggested site of oxidation for levofloxacin and norfloxacin is at the quinolone, as discussed previously. However, the oxidation of ciprofloxacin is suggested to be at the aromatic nitrogen atom of the piperazine ring (Thabaj et al., 2007). It should be noted though that the second-order rates were similar despite differing suggested mechanisms of oxidation.

Correlations were attempted between the pseudo-first-order rate constant and fluoroquinolones' polarizability, electron affinity, and refractive index. No significant correlations were found (polarizability: R^2 = 0.32, electron affinity: R^2 = 0.12, refractive index: R^2 = 0.09).

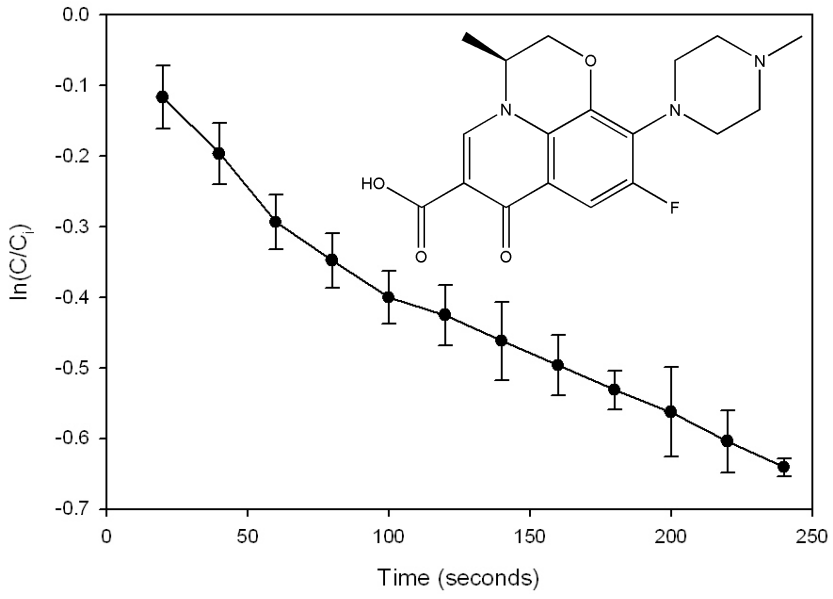


Figure 22: Permanganate reduction by levofloxacin. C_i = 0.037-0.041 mM

3.4.8 Non-steroidal Anti-inflammatory Drugs

Diclofenac (k'' = 2.60 $M^{-1}s^{-1}$), ibuprofen (k'' = 0.80 $M^{-1}s^{-1}$), and naproxen (k'' = 0.84 $M^{-1}s^{-1}$) were all weakly reactive with permanganate, with diclofenac oxidizing slightly more rapidly than the other two pharmaceuticals (Figure 23). The three pharmaceuticals all have a benzene ring that is connected to a carboxylic acid group (Figures A7-a,b,c). Additionally, diclofenac has a secondary amine that may have contributed to the faster oxidation (Stewart, 1967). Ibuprofen and naproxen had very similar pseudo-first-order rate constants (Figure 24). The carboxylic acid group is not expected to be reactive with permanganate either, as it is usually the product for other functional group oxidations. Thus, the site of reactivity is suggested to be the aromatic rings for both ibuprofen and naproxen. However, both ibuprofen and naproxen oxidized more quickly than the literature values for their aromatic ring structures. Ibuprofen has a p-xylene, which has a second-order rate constant of 1.15 x 10^{-3} $M^{-1}s^{-1}$ (Waldemer and Tratnyek, 2006). The additional alkane chain that extends from the xylene may be the explanation for ibuprofen's faster reactivity. Naproxen has a naphthalene, which has a second-order rate constant of 1.10 x 10^{-2} $M^{-1}s^{-1}$ (Waldemer and Tratnyek, 2006). It is possible that the ether connected to the naphthalene may contribute to naproxen's higher oxidation rate.

Correlations were attempted between the pseudo-first-order rate constant and compound polarizability, electron affinity, and refractive index. A preliminary correlation was found between the reaction rates for these three non-steroidal anti-inflammatory drugs (NSAIDs) and polarizability with an R^2 value of 0.88 (Figure 25). As the polarizability increases, the reaction rate with permanganate also increases. A

preliminary correlation was also found between the reaction rates for the drugs and the refractive index with an R^2 value of 0.62 (Figure 26). As the refractive index increases, the reaction rate with permanganate also increases. These correlations support the findings discussed earlier in *3.4.2 Phenol Structures* once acetaminophen was removed. However, more research is needed to include more compounds for study to verify the observed correlations.

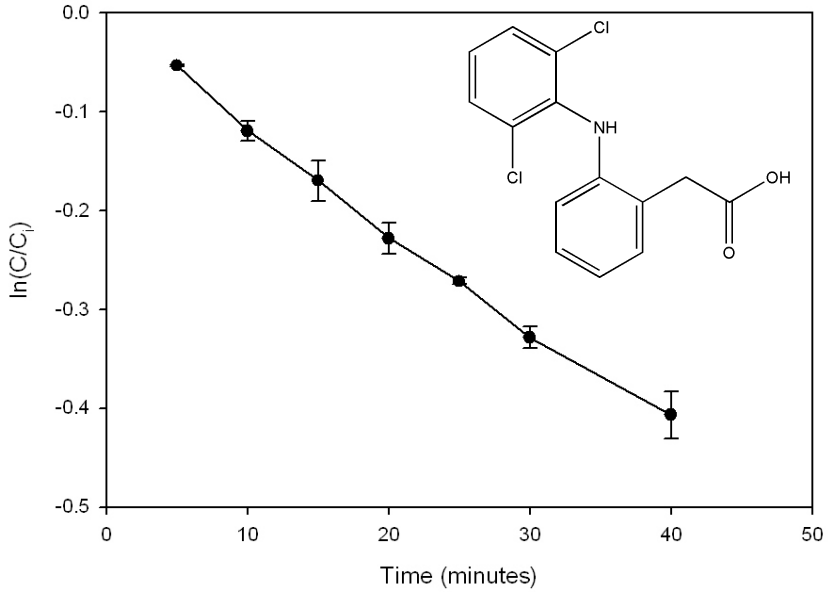


Figure 23: Permanganate reduction by diclofenac. C_i = 0.046-0.053 mM

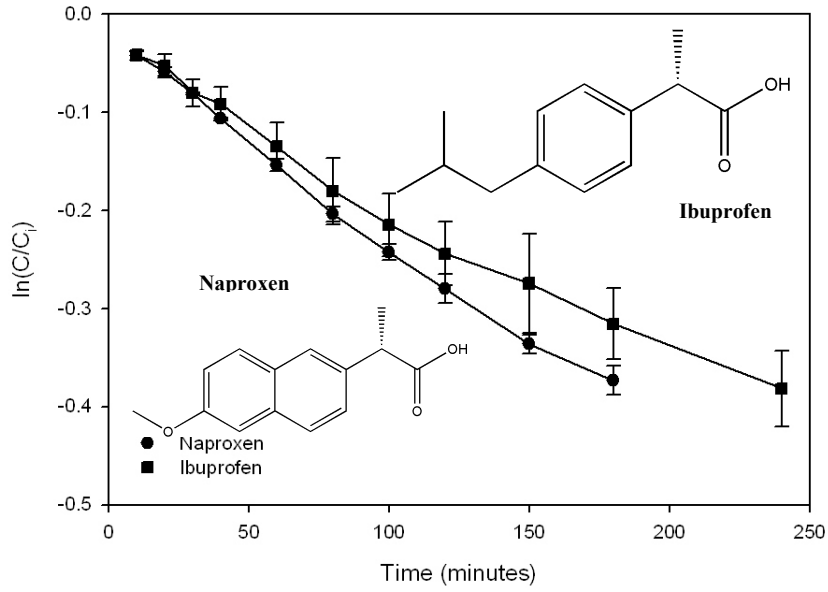


Figure 24: Permanganate reduction by NSAIDs. Naproxen (C_i = 0.051-0.052 mM) and ibuprofen (C_i = 0.050-0.052 mM) reacted at similar rates.

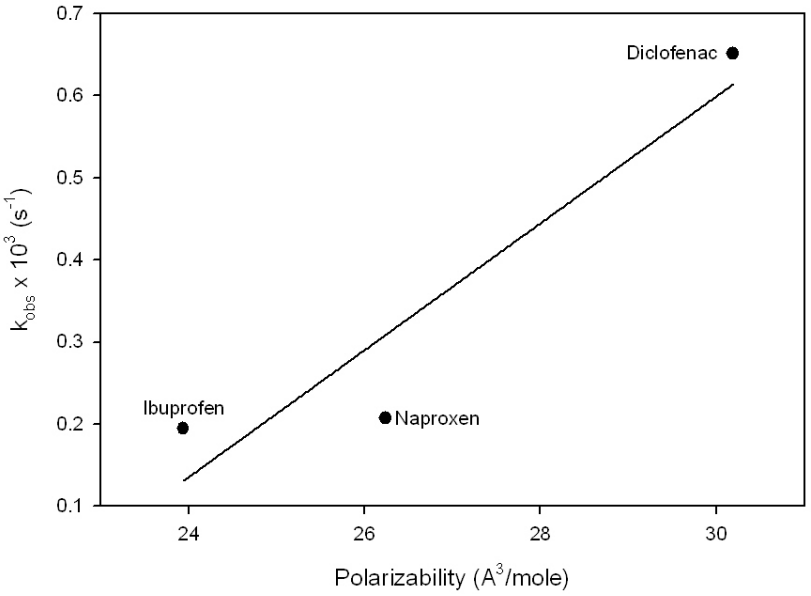


Figure 25: Positive correlation between pseudo-first-order reaction rates for NSAIDs and polarizability. $R^2 = 0.88$

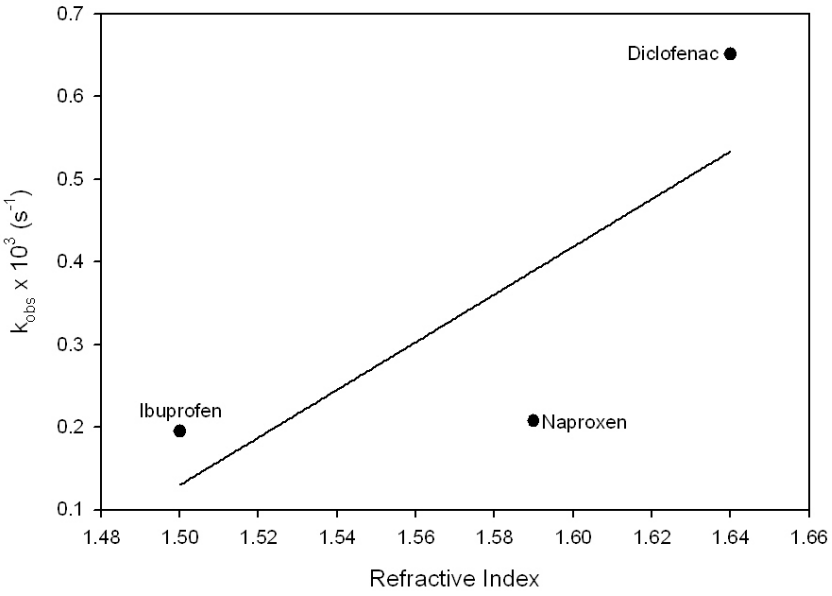


Figure 26: Positive correlation between pseudo-first-order reaction rates for NSAIDs and refractive index. $R^2 = 0.62$

3.4.9 Beta Blockers

It was determined that metoprolol was non-reactive ($k'' < 1.8 \times 10^{-3}$ $M^{-1}s^{-1}$) (Figure 27) with permanganate while atenolol was weakly reactive ($k'' = 1.88$ $M^{-1}s^{-1}$) (Figure 28). Atenolol and metoprolol have similar structures (Figures A8-a,b) but differ in what connects to their benzene ring. Metoprolol has a side chain of alkanes with an ether while atenolol has an amide. Differences in the reactivity of these two compounds with permanganate could be attributed to this.

Amides, however are not expected to be oxidized by permanganate (as discussed in *3.4.3 Cephalosporins*). Therefore, it is surprising that atenolol and metoprolol do not have similar reactivity. The shared structure of a secondary alcohol and a secondary amine should allow for oxidation by permanganate of both pharmaceuticals (as discussed in *3.4.6 Macrolides)*. The aromatic ring for atenolol and metoprolol is also expected to oxidize slowly by permanganate. The second-order rate constants for benzene derivatives (xylene, toluene, ethylbenzene) are less than 1.15×10^{-3} $M^{-1}s^{-1}$ (Waldemer and Tratnyek, 2006). However, the presence of an ether connected the aromatic ring during oxidation by permanganate has not been investigated and possibly contributes more to the oxidation than expected. It is not understood why atenolol was reactive while metoprolol was considerably non-reactive and it should be further investigated.

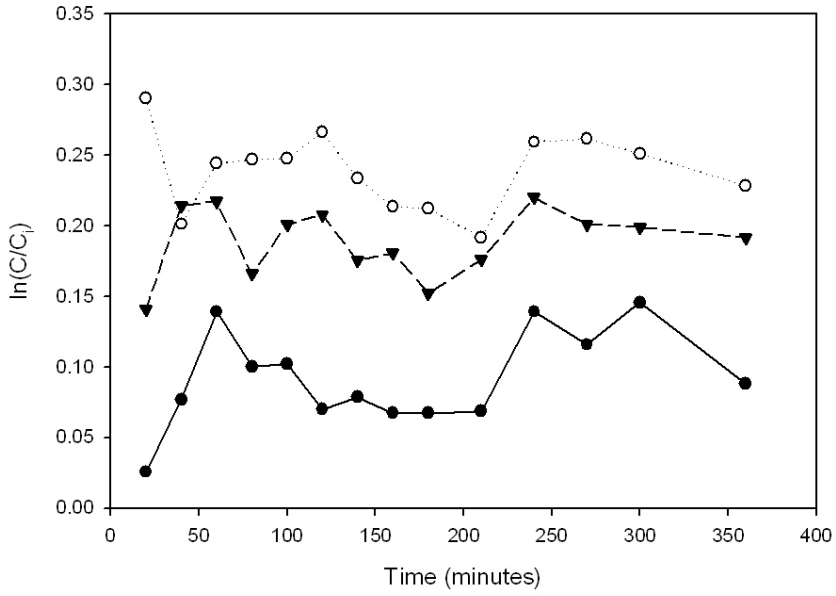


Figure 27: Non-reactivity of metoprolol by permanganate for three trials.

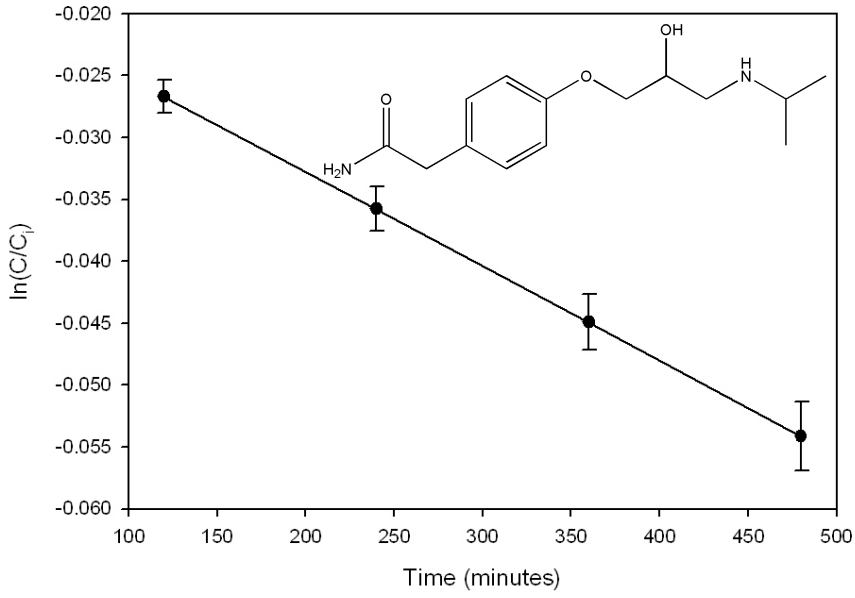


Figure 28: Permanganate reduction by atenolol. C_i = 0.047-0.050 mM

3.4.10 Sulfonamides

Sulfamethazine (k'' = 1.20 $M^{-1}s^{-1}$) and sulfamethoxazole (k'' = 48 $M^{-1}s^{-1}$) were both weakly reactive with the permanganate. This is potentially attributed to the presence of an aniline ring in both pharmaceuticals (as discussed in *3.4.2 Phenol Structures*). Another potential contribution to the reactivity is the secondary amine. However, the amine and aniline are both connected to a sulfonyl group (Figures A9-a,b). Sulfones are not reactive with permanganate and are typically the final product of sulfide oxidation (Stewart, 1967). The sulfonyl group is highly electron-withdrawing and is likely reducing the activity of its neighboring aniline and amine. Therefore, the reactivity of the secondary amine may be diminished by the stable sulfone.

While both moderately reactive, sulfamethazine's reaction was almost three times as fast as that of sulfamethoxazole (Figure 29). This may be attributed to their differences in structure, where sulfamethazine has a pyrimidine ring and sulfamethoxazole as an oxazole ring. Research has shown that pyrimidine will react with permanganate and become urea or N-substituted ureas (Chatamra and Jones, 1963). Literature has also determined that oxazole will be completely oxidized by permanganate as well (Terent'ev and Lomakina, 1976). This research suggests that pyrimidine oxidation may occur more quickly than oxazole oxidation; however, more study is needed to confirm this.

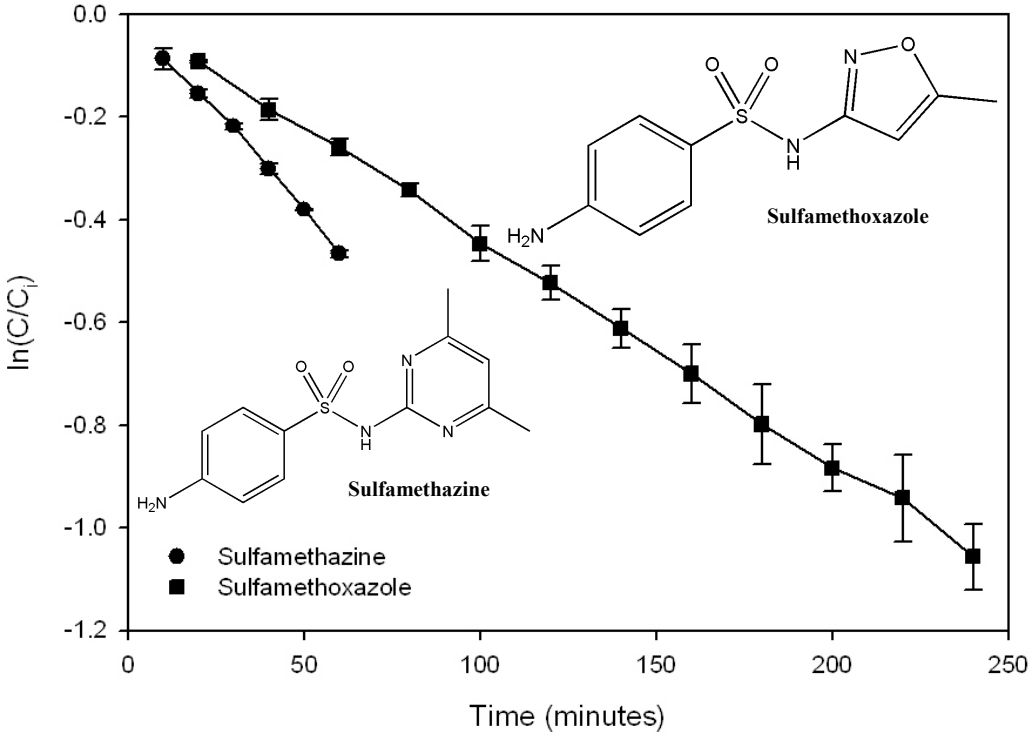


Figure 29: Permanganate reduction by sulfonamides. Sulfamethazine (C_i = 0.052-0.055 mM) reacted more rapidly than sulfamethoxazole (C_i = 0.037-0.039 mM).

3.4.11 Triazines

In their reaction with permanganate, atrazine was weakly reactive (k'' = 1.16 $M^{-1}s^{-1}$) (Figure 30) while simetone was poorly reactive (k'' = 0.03 $M^{-1}s^{-1}$). This difference is unexpected given the similarities in their structures (Figures A10-a, b). The main difference between the two compounds is that atrazine has a chlorine substituent whereas simetone has an ether substituent. Both have two secondary amines, which are the most likely site for permanganate oxidation to occur. The triazine ring that both compounds share is considered to be stable and does not readily contribute to the reaction.

It is unknown why simetone reacts so slowly with permanganate when it shares such a similar structure with atrazine and should be further investigated. The triazine ring connected to the ether may create a stability that makes it difficult for simetone to oxidize by permanganate.

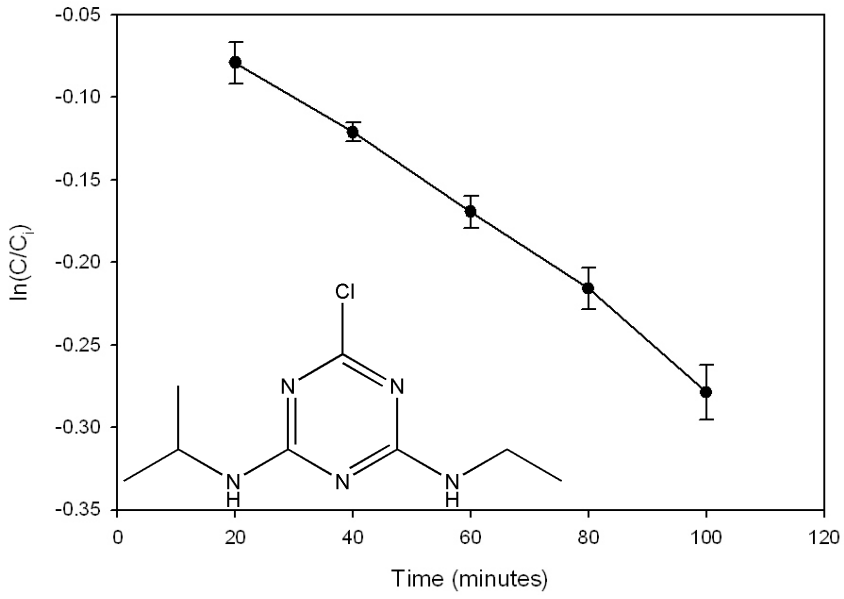


Figure 30: Permanganate reduction by atrazine. C_i = 0.051-0.055 mM

3.4.12 Others

Caffeine

Caffeine was oxidized poorly by permanganate (k'' = 0.05 $M^{-1}s^{-1}$). The two amides in the structure are considered stable and not the site of oxidation (Figure A11-a). The imidazole ring, which is also present in bacitracin, may be the site for reactivity.

Carbadox

Literature suggests that carbadox's (Figure A11-b) N-oxide groups could be sites for reaction with manganese dioxide (Zhang and Huang, 2005b), whereas carbadox's hydrazone side chain can be rapidly oxidized by chlorine and chloramine oxidants (Shah et al., 2006). Thus, the slow reactivity of carbadox (k'' = 0.04 $M^{-1}s^{-1}$) observed in this research was somewhat unexpected. The stock of this pharmaceutical has to be made with 50% ACN, resulting in the reacting cuvete containing less than 10% ACN. However, ACN has been shown not to inhibit oxidation of compounds in permanganate, but is frequently used as the solvent for such research (Shabaani et al., 2005).

Carbamazepine

Carbamazepine was quite reactive to oxidation by permanganate (k'' = 248.60 $M^{-1}s^{-1}$) (Figure 31). Our value is in agreement with previous literature (k'' = 293.30 $M^{-1}s^{-1}$) where the suggested mechanism is a reaction at the double bond within the seven-membered ring (Hu et al., 2009). The authors proposed twelve different products of oxidation of carbamazepine by permanganate, including the formation of alcohol, aldehyde, ketone, and carboxyl groups from the reaction at the double bond. It was also

determined through their research that pH change (pH 5.0-9.0) did not have a significant effect on the reaction kinetics.

Cotinine

Cotinine was weakly reactive with permanganate while it was expected to react more slowly, if at all ($k'' = 0.80\ M^{-1}s^{-1}$). The pyridine ring is considered to be stable with the reaction by permanganate (Stewart, 1965). Amides are also considered to be stable (as discussed in *3.4.3 Cephalosporins*). Thus, it is unclear why cotinine is relatively reactive and should be investigated further.

Dilantin

Dilantin was also oxidized weakly by permanganate ($k'' = 0.60\ M^{-1}s^{-1}$) (Figure 32). The two amides are not considered reactive. Thus, the oxidation is expected to occur at the two aromatic rings. The literature value for toluene, the closest resembling benzene derivative, is $1.7 \times 10^{-4}\ M^{-1}s^{-1}$ (Waldemer and Tratnyek, 2006). However, the two rings together connected to the amide structure may provide less stability and thus resulted in a faster oxidation by permanganate.

Gemfibrozil

Gemfibrozil was weakly reactive by permanganate as well ($k'' = 0.80\ M^{-1}s^{-1}$) (Figure 33). The 1,4 xylene ring has a second-order reaction rate constant of $1.15 \times 10^{-3}\ M^{-1}s^{-1}$, which is less than gemfibrozil's oxidation rate (Waldemer and Tratnyek, 2006).

However, the additional reactivity may be a result of the ether connected to the xylene ring.

Monensin

Monensin was oxidized poorly by permanganate while it was expected to be more reactive (k'' = 0.04 $M^{-1}s^{-1}$). It has a primary alcohol, which should oxidize readily by permanganate (as discussed in *3.4.6 Macrolides*). However, monensin's slow reactivity suggests that the overall structure is relatively stable with permanganate and this is most likely due to the use of monensin sodium salt in this study. Monensin is known to form stable sodium complex in water as shown in Figure 34 with hydrophilic nature inside the complex but hydrophobic nature on the outside of the complex (Westley, 1982). It's possible that monensin's alcohol groups are stabilized within the sodium complex and thus become less reactive to permanganate than expected.

Tri(2-carboxyethyl)phosphine

TCEP was the slowest PPCP of all the compounds tested (k'' < 1.80 x 10^{-3} $M^{-1}s^{-1}$). Its degradation was slower than the minimum calculated pseudo-first-order rate constant, 4.50 x 10^{-4} s^{-1}. Over a two-day period, TCEP degraded the permanganate from 0.050 mM to 0.048 mM. The extremely slow oxidation by permanganate may be attributed to the methylene groups of TCEP where hydrogen abstraction may occur (Figure A11-h).

Trimethoprim

Trimethoprim was oxidized weakly by permanganate (k'' = 2.64 $M^{-1}s^{-1}$). The 3,4,5-trimethoxybenzyl ring is expected to be relatively stable as it is composed of a benzene ring and relatively stable ethers. Thus, the expected site of oxidation may be the pyrimidine ring with a 2,4 diamine. The amines attached to the ring also have the potential to oxidize. Further study is needed to confirm the reactive sites.

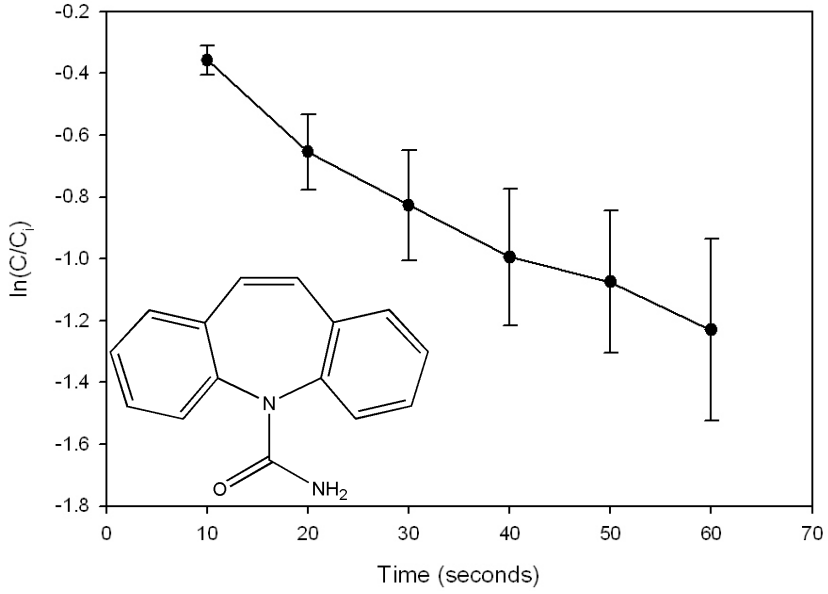


Figure 31: Permanganate reduction by carbamazepine. C_i = 0.029-0.043 mM

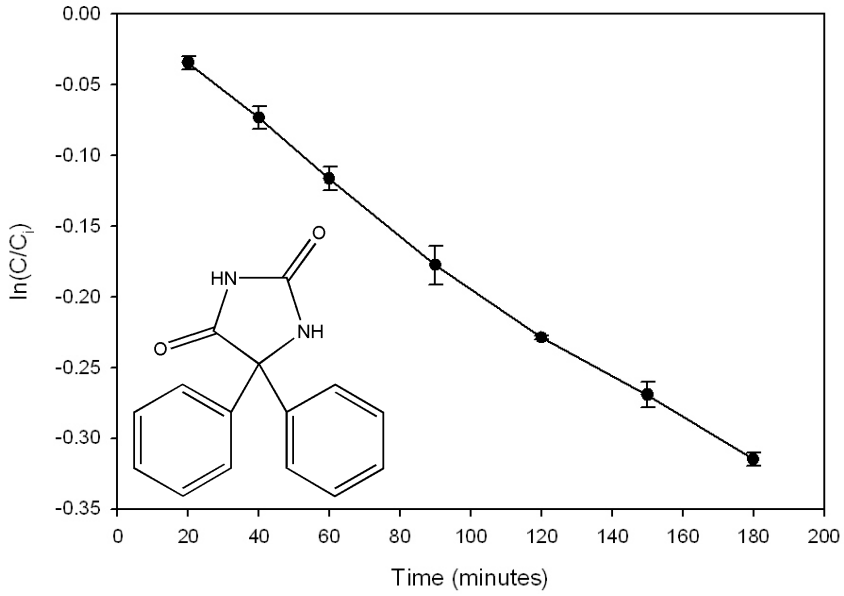


Figure 32: Permanganate reduction by dilantin. C_i = 0.051-0.052 mM

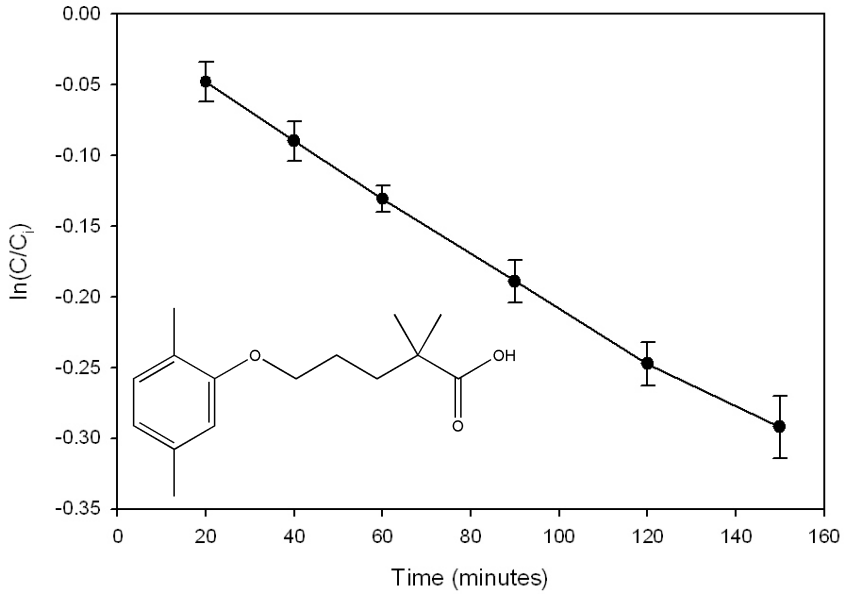


Figure 33: Permanganate reduction by gemfibrozil. C_i = 0.051-0.052 mM

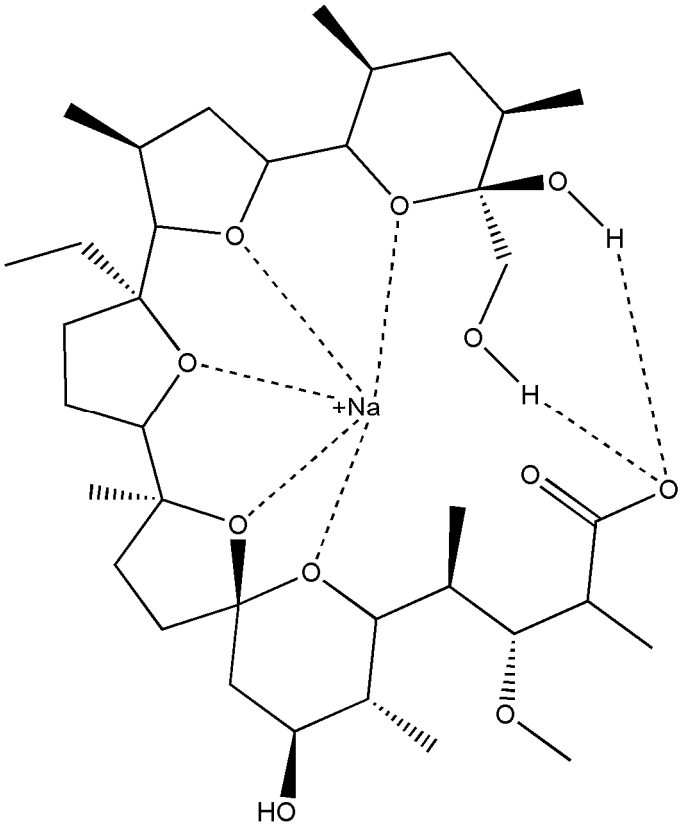


Figure 34: Structure of monensin sodium salt.

CHAPTER 4: CONCLUSIONS AND RECOMMENDATIONS

The oxidation by permanganate of the pharmaceuticals and personal care products (PPCPs) varied greatly across the different structural groups. The most reactive group was the phenol-structured and was a result of their phenol functional group. Tetracyclines also reduced the permanganate very quickly due to their phenols and hydroxyl groups. Other more reactive PPCPs included carbamazepine and cefdinir. Most of the remaining PPCPs were moderately reactive with permanganate as a result of various functional groups such as amines and alcohols. The slowest PPCPs were caffeine, carbadox, monensin, and simetone. Tris(2-carboxyethyl)phosphine reduced permanganate more slowly than could be monitored and metoprolol was determined to be non-reactive. For the non-steroidal anti-inflammatory drugs (NSAIDs) and the phenol-structured groups, positive correlations were found with the pseudo-first-order reaction rates and organic compound polarizability and refractive index. The exceptionally high reactivity of acetaminophen is likely due to its unique structural characteristics and cannot be compared with typical phenols.

The findings of this research indicate that oxidation by permanganate may be a viable option for some of the PPCPs selected. The determined second-order rate constants were used to calculate the half-life of each PPCP with a permanganate concentration of 1.5 milligrams per liter (a typical concentration in water treatment for pre-oxidation). If a contact time of thirty minutes is assumed, eleven of the PPCPs tested will be oxidized by half: acetaminophen, bacitracin, bisphenol-A, carbamazepine, cefdinir, chlortetracycline, demeclocycline, levofloxacin, oxytetracycline, tetracycline,

and triclosan. Thus, permanganate will most likely not be capable of oxidizing many of the PPCPs that may be in the water in the necessary time frame and other methods of oxidation may need to be explored. However, permanganate may also be used to control algae growth prior to water treatment, which requires a longer contact time. This treatment method would allow for more degradation of PPCPs that are not capable of rapid reactivity.

The spectrophotometer method utilized was critiqued for its inability to wholly monitor permanganate reduction by a compound that has absorbance interference from product formation. This resulted in lower R^2 values. The method also monitored the linearity of permanganate reduction at 525 nm with manganese dioxide growth at 418 nm in order to validate the first-order reaction. This was critiqued due to its exclusion of reactions that included an increase in manganese dioxide particle size in slower reacting compounds and the consumption of manganese dioxide by tetracycline antibiotics. These manganese dioxide reactions, however, have modest or little effect on the first-order reduction of permanganate and thus did not negate the overall results significantly.

The findings of this research are just the beginning of what can be done to explore the oxidation of PPCPs by permanganate. There are many opportunities to further research in this area. It is recommended that more PPCPs for each classification be investigated, particularly for the classifications where only two PPCPs were chosen (beta blockers, cephalosporins, macrolides, polypeptides, sulfonamides, and triazines). In doing this, it is expected that the more reactive structures within each PPCP may become more apparent. The suggested reactive sites for each PPCP can also be explored further

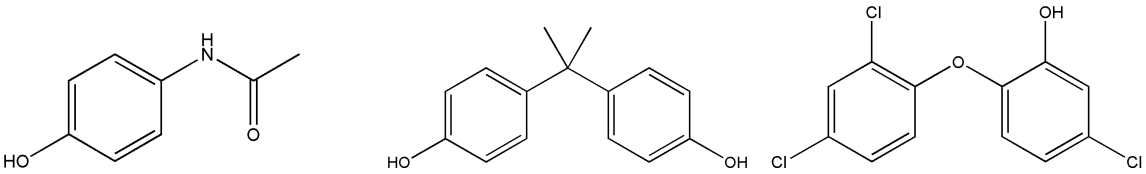
by using model compounds with similar structures. This would allow for further confirmation and expansion of the oxidation mechanisms suggested in this research.

It is recommended that the initial correlations found in this research between reaction rates and selected physicochemical properties be further investigated. In addition to polarizability and refractive index, the list of properties should be expanded to determine what other aspects of the compounds may indicate reactivity. The physicochemical properties used in this research were calculated using SPARC, an Environmental Protection Agency program. In the future, the properties should be calculated from several sophisticated computational chemistry programs in order to determine the most accurate values, as SPARC is still in the initial stages of use. With more PPCPs potentially being investigated and numerous chemical properties that could be gathered, it is recommended that more detailed statistical analysis be carried out.

The impact of water quality conditions was not studied within this research as all experiments were carried out at a set pH of 7.0 in deionized water. Investigating the effects of adjusting the pH, ionic strength, and temperature of the reaction is recommended. The presence of natural organic matter may also be an opportunity for further research. Finally, it is recommended that the oxidation products of each PPCP be investigated. The products of oxidation may be good indicators as to the mechanisms by which the PPCPs are oxidizing and will be the basis to evaluate the potential biological effect of oxidation products. This research on the oxidation of PPCPs by permanganate is the initial step towards many opportunities for further investigation.

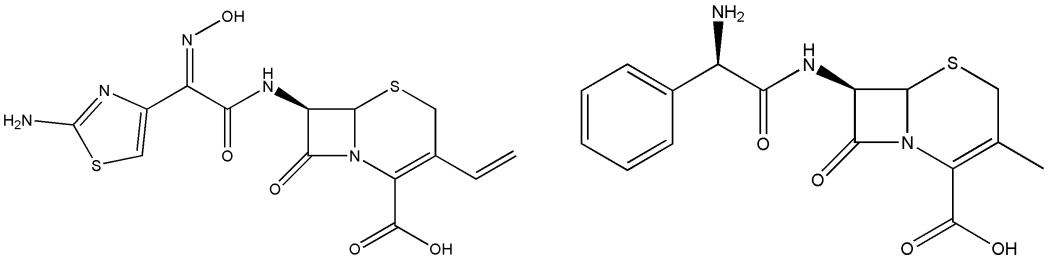
APPENDIX

PPCP STRUCTURES



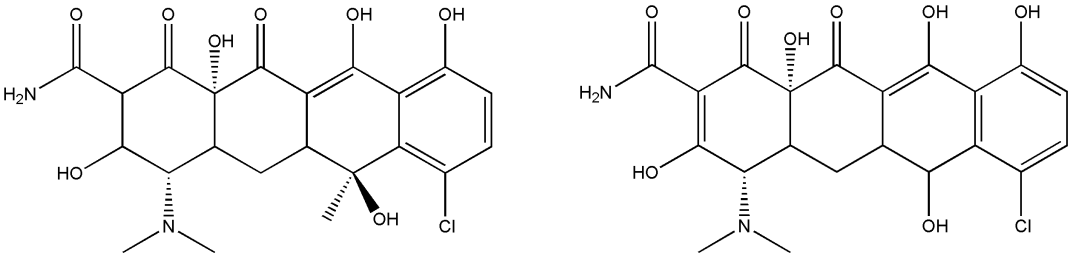
a. Acetaminophen b. Bisphenol-A c. Triclosan

Figure A1: Phenol Structures

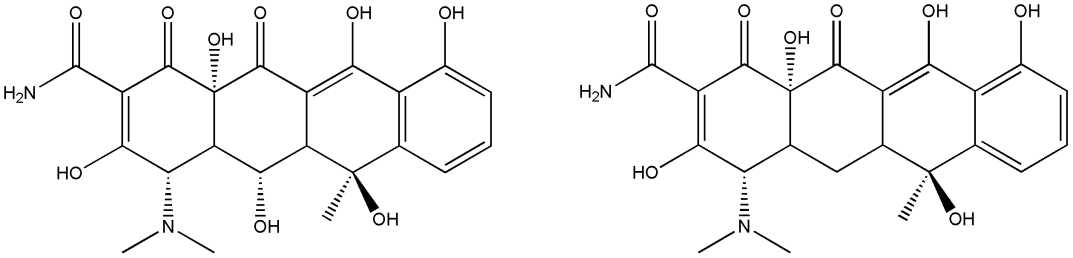


a. Cefdinir b. Cephalexin

Figure A2: Cephalosporin Structures

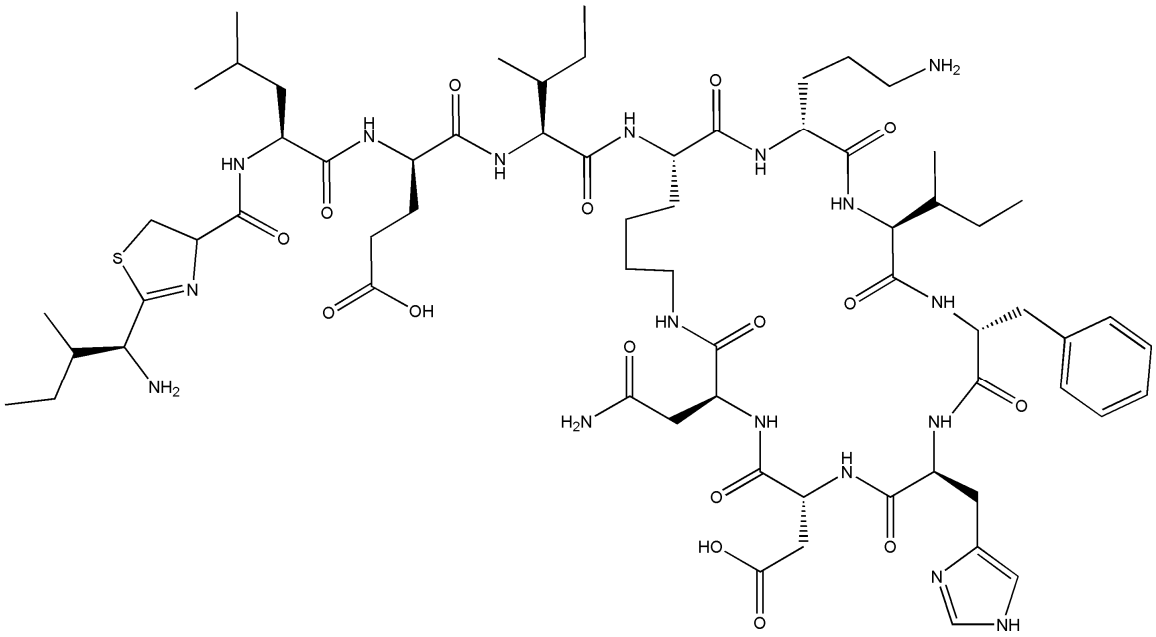


a. Chlortetracycline b. Demeclocycline

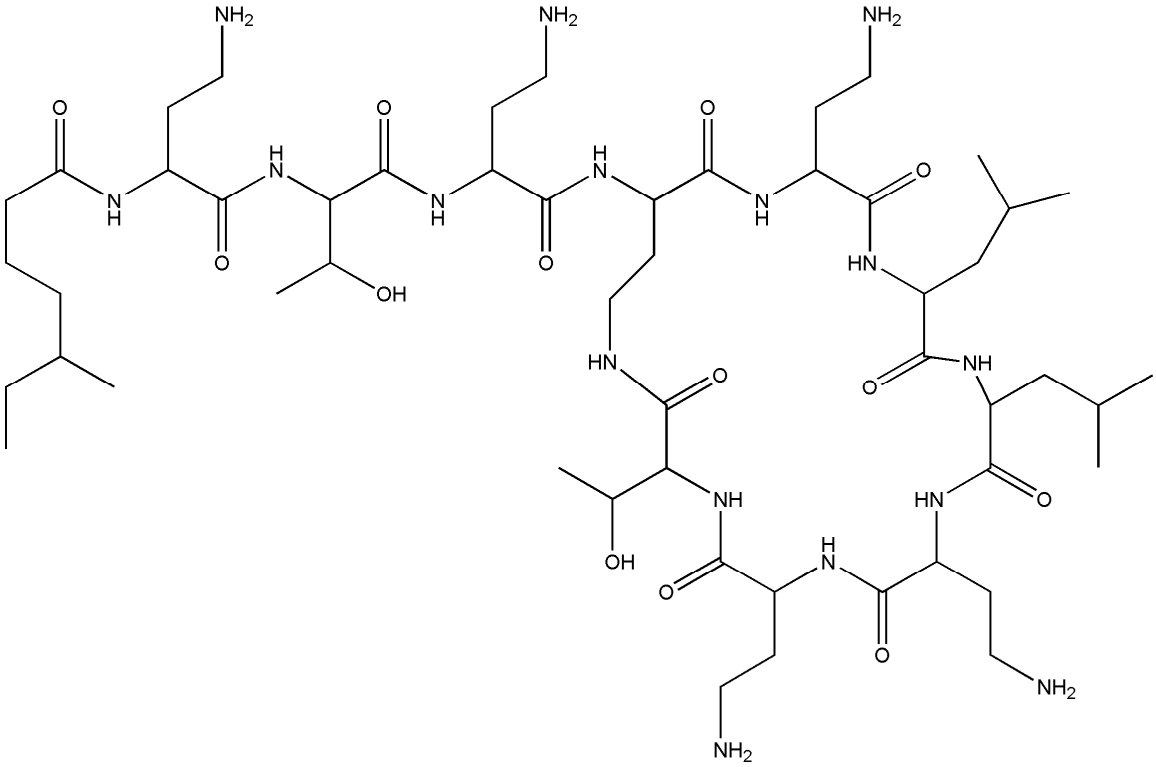


c. Oxytetracycline d. Tetracycline

Figure A3: Tetracycline Structures

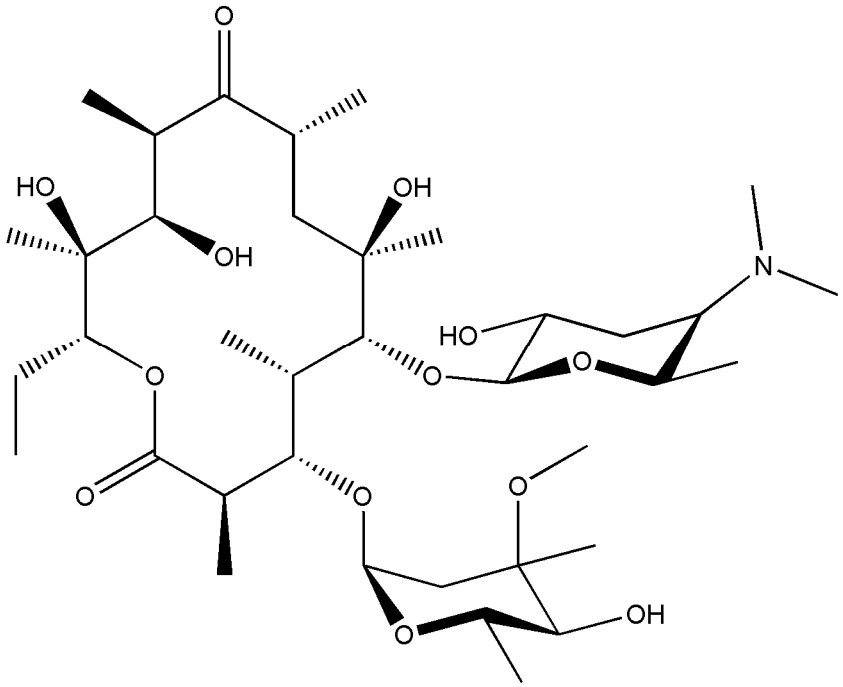


a. Bacitracin

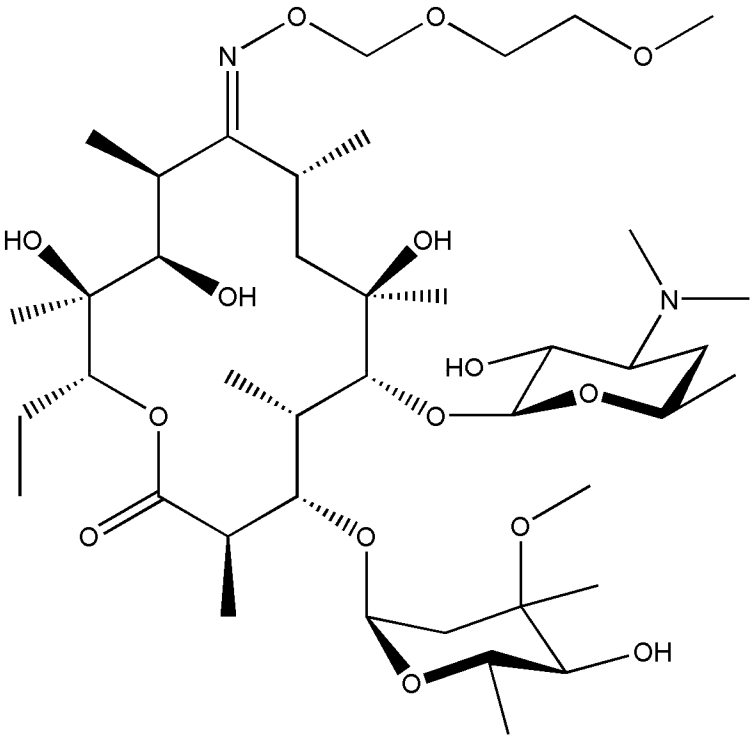


b. Colistin

Figure A4: Polypeptide Structures

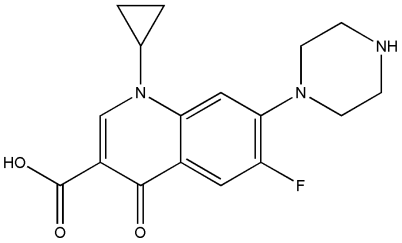


a. Erythromycin

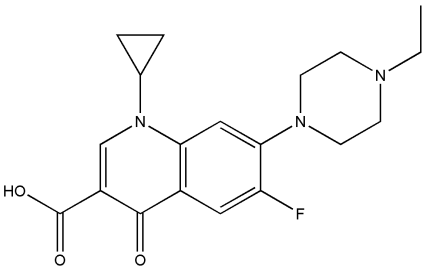


b. Roxithromycin

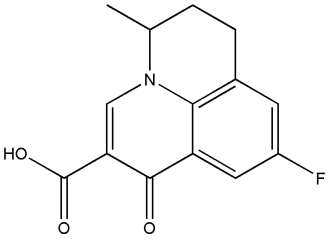
Figure A5: Macrolide Structures



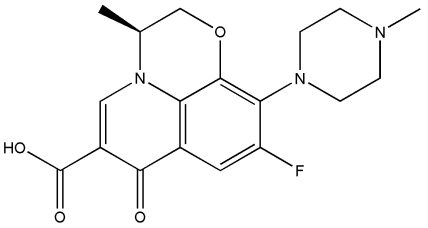
a. Ciprofloxacin



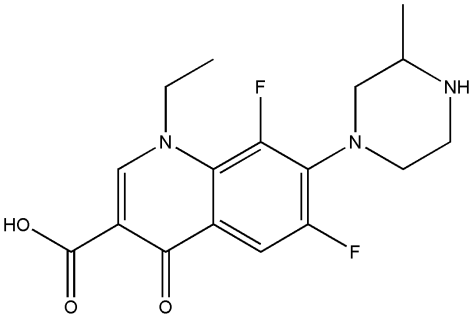
b. Enrofloxacin



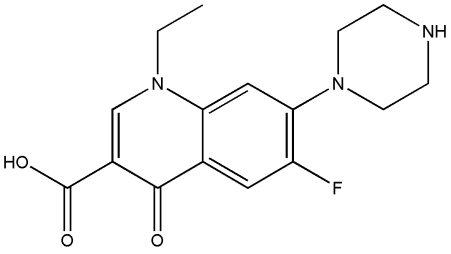
c. Flumequine



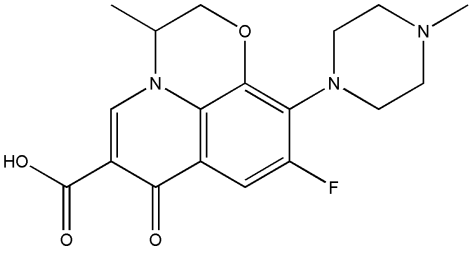
d. Levofloxacin



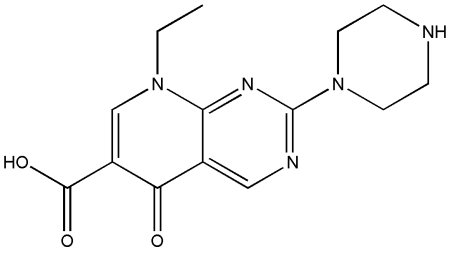
e. Lomefloxacin



f. Norfloxacin

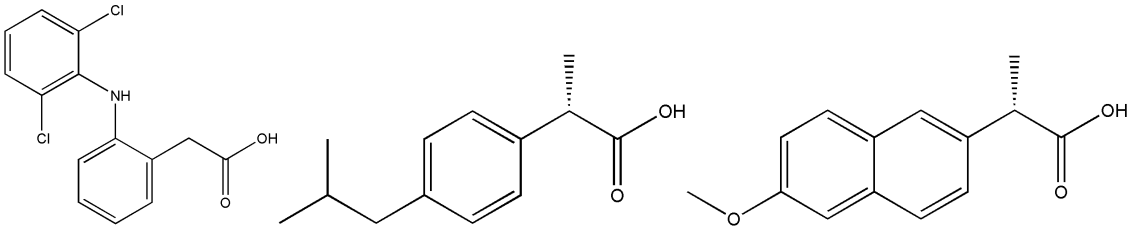


g. Ofloxacin



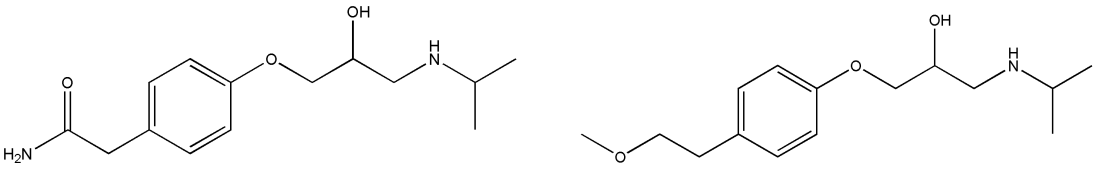
h. Pipemidic Acid

Figure A6: Fluoroquinolone Structures



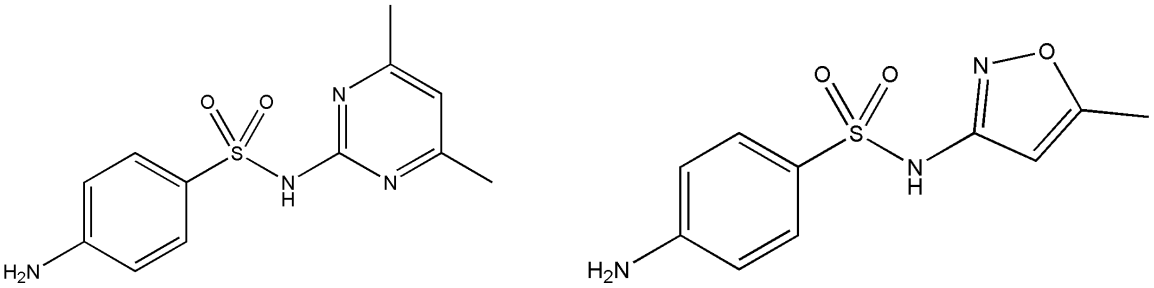
a. Diclofenac b. Ibuprofen c. Naproxen

Figure A7: Non-Steroidal Anti-Inflammatory Drugs



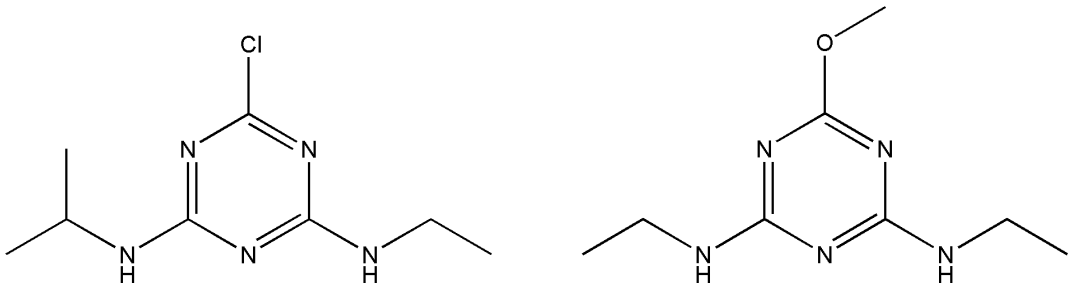
a. Atenolol b. Metoprolol

Figure A8: Beta Blocker Structures



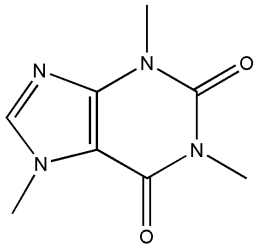
a. Sulfamethazine b. Sulfamethoxazole

Figure A9: Sulfonamide Structures

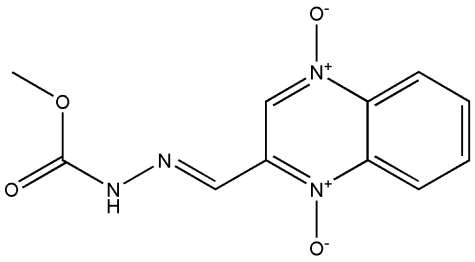


a. Atrazine b. Simetone

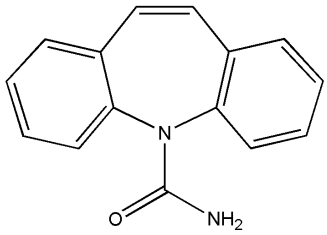
Figure A10: Triazine Structures



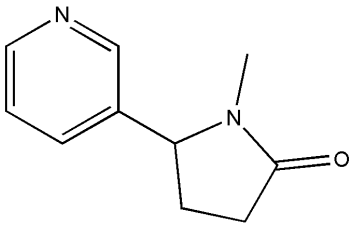
a. Caffeine



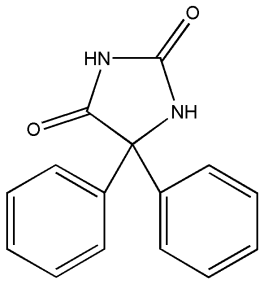
b. Carbadox



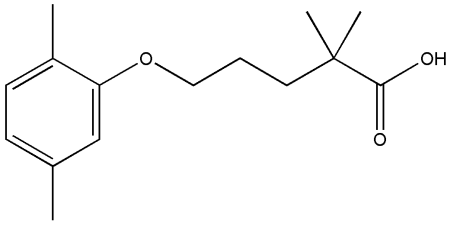
c. Carbamazepine



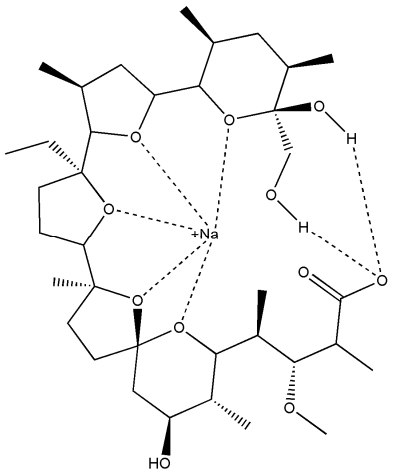
d. Cotinine



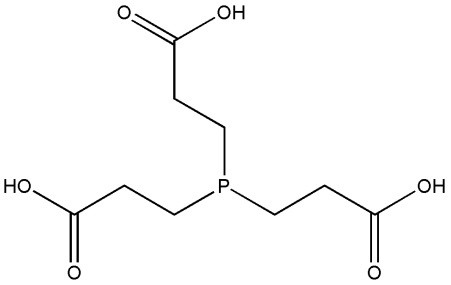
e. Dilantin



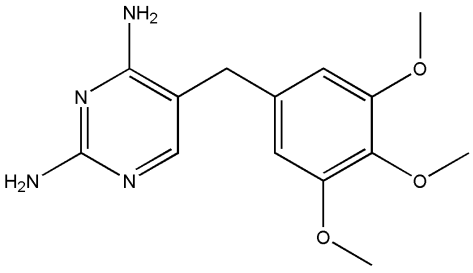
f. Gemfibrozil



g. Monensin



h. Tris(2-carboxyethyl)phosphine



i. Trimethoprim

Figure A11: Remaining Structures

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