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Pharmaceutically active compounds (PhACs) have been recognized as a group of emerging contaminates found in surface water worldwide. The occurrence, transportation, fate and its adverse effects on the ecological systems have raised concern among the public, scientists and engineers, and regulatory groups. Photochemical degradation would be one of important natural elimination processes for this group contaminates. This review thus presents an overview of the importance of photodegradation under solar or solar simulated irradiation. The kinetic studies, degradation mechanisms and toxicity assessments of photoproducts are three major topics included in this review.

Photo-transformation of pharmaceutically active compounds in the aqueous environment: A review

*Shuwen Yan and Weihua Song**

Shanghai Key Laboratory of Atmospheric Particle Pollution and Prevention, Department of Environmental Science & Engineering, Fudan University, Shanghai, 200433, P. R. China

Corresponding Author: email: wsong@fudan.edu.cn

Phone: (+86)-21-6564-2040

Abstract

In the past few years, the fate and transportation of pharmaceutically active compounds (PhACs) in the aqueous environments have raised significant concerns among the public, scientists and regulatory groups. Photodegradation is one of the important removal processes in surface waters. This review summarizes the recent 10 years (2003-2013) of studies of the solar or solar-simulated photodegradation of PhACs in the aqueous environments. PhACs catalogues covered include: beta-blockers, antibiotics, non-steroidal anti-inflammatory drugs (NSAIDs), histamine H_2–receptor antagonists, lipid regulators, carbamazepine, steroid hormones, and x-ray contrast media compounds. Kinetic studies, degradation mechanism and toxicities removal are three major topics involved in this review. The quantum yield for direct photolysis of PhACs, bimolecular reaction rate constants of PhACs with reactive oxygen species (ROS), such as •OH radical and singlet oxygen, are also summarized. This information is not only important to predict the PhACs photodegradation fate, but also very useful for advanced treatments technologies, such as ozone or advanced oxidation processes.

Introduction

The presence of pharmaceutically activate compounds (PhACs) in aqueous environment, from various sources, is an emerging environmental issue.[1, 2] The main concern regarding PhACs as pollutants is that their biological activity will lead to adverse effects on human health and aquatic ecosystems.[3]

Most pharmaceuticals administered to patients are excreted either as metabolites or as the unchanged parent compounds,[4] and it is not uncommon to dispose of outdated medicines "down the drain." In either way, they end up in wastewater treatment plants. Recent studies, although there is considerable variability among individual compounds, have shown that conventional wastewater treatment processes are relatively inefficient in removing those drugs,[5-13] and, some pharmaceuticals escape degradation in wastewater treatment plants, and enter environment. Pharmaceuticals used in veterinary practices are quite different than for human use, i.e. they are more likely to directly contaminate soil and/or groundwater without any or minimal treatments.[14, 15] Once released into the environment the fate of pharmaceuticals is largely unknown.

The presence of pharmaceuticals in the aquatic environment was reported as early as the beginning of the 1980s.[16] In an USGS study[17], they were found in 80 % of 139 streams across 30 states. Trace amounts have also been found in tap water at concentrations ranging between 20 μg L^{-1} to 1 ng L^{-1}.[18-23] However, it has been estimated that less than 15% of the pharmaceuticals thought to be in the environment are actually analyzed due to the lack of adequate analytical methods.[9, 24]

In general, it's an emerging research area regarding the environmental occurrence, transport, and ultimate fate of pharmaceuticals designed for a physiological response in humans and animals.[25-31] In surface waters, the main removal processes are biodegradation, sorption, and photodegradation. Some pharmaceuticals have been designed to be resistance to biodegradation, thereby inhibiting one of the

major elimination mechanisms.[26, 32] Sediment type has been shown to significantly affect the sorption of pharmaceuticals, thus implying that is site specific and cannot be relied on a global basis.[33] Therefore photodegradation driven by sunlight would be the major concern in the present review.

Photodegradation includes direct photodegradation and indirect photodegradation. Direct photolysis requires an over-lap of the pharmaceuticals electronic absorption spectra and irradiation wavelength(s). Stated another way, a compound must absorb light in order for direct photolysis to occur; however, just because a chemical absorbs light does not mean that it will undergo photolysis (e.g. most dyes). Therefore, photochemical processes will be considerably different from one compound to the next and will depend upon 1) overlap of their electronic absorption spectra and solar irradiation (environmental fate), and 2) molecular structure. Therefore, the quantum yield for direct photolysis of PhACs would be the key parameter for the photochemical fate prediction. The quantum yields could be calculated from the data obtained during the irradiation experiments of both PhACs and actinometer, using the following equation:[34, 35]

$$\Phi_{PhACs} = \Phi_{act} \frac{k_{phot} \sum_{\lambda} (\varepsilon_{\lambda} L_{\lambda})_{act}}{k_{act} \sum_{\lambda} (\varepsilon_{\lambda} L_{\lambda})_{PhACs}} \quad (1)$$

Where k_{phot} is the calculated direct photolysis rate constant for PhACs and k_{act} is the rate constant for the direct photolysis of the standard solution of the actinometer, calculated from the actinometer solar experiment data. Φ_{act} is the actinometer quantum yield of direct photolysis. ε_{λ} ($M^{-1}cm^{-1}$) is the molar absorption coefficient at the wavelength λ; and L_{λ} (milli-Einstein*cm^{-2}*d^{-1}) is the average daily value for irradiance at the wavelength λ.

If there is no overlap then the only photochemical process is indirect photolysis (e.g. Figure 1). In most natural waters and for many treated waters, dissolved organic matter (DOM) mediates indirect photolysis. In effluents, we refer to this fraction as effluent organic matter (EfOM), and usually we think

of that fraction as the organic matter that gives effluent its 'colored' appearance. In natural waters, the fraction of the DOM that absorbs sunlight is referred to as CDOM (chromophoric DOM, with absorption of > 295 nm).

Photosensitizer (DOM or EfOM) absorb light in the ground state and excite to the singlet-excited state (Figure 1, Pathway 1). The excited state may return to the ground state or undergo reactions that result in chemical changes (photo-ionization or destruction) of the parent molecule. Alternatively, it may undergo intersystem crossing (ISC) to the excited triplet state and return to the ground state or further react with, for example O_2 or PhACs in solution. If it reacts with O_2, the two main reactants are the $^1\Delta_g$ excited state of bimolecular O_2, ($^1\Delta O_2$),[36] or superoxide anion radical ($O_2^{\bullet-}/HO_2^{\bullet}$) which usually disproportionates to H_2O_2, and further forming hydroxyl radicals (•OH) through Fenton-like reaction, or direct split H_2O_2 to produce •OH.[37, 38] These are pathways 3 and 4 in Figure 1. These reactive oxygen species can react with PhACs and result in the photodegradation.[39] Finally, it is also possible that the photoexcited state of organic matter (either the singlet, path 1, or triplet excited state, path 2, could react via several pathways (Path 7–9) with pharmaceutical compounds and result in decomposition.[40]

(Insert Figure 1)

Within the last decade an increasing number of reviews covering pharmaceuticals input, occurrence,[41-44] fate,[45-50] advanced treatments[51-56] and the ecological effects[57-61] have been published, but there is still a lack of focused summary about the studies of photochemical transformation of pharmaceuticals in the aquatic environment.[62] This review covers direct and indirect photodegradation of PhACs in the natural water and wastewater effluents under solar or solar simulated conditions. PhACs includes β-blockers, antibiotics, non-steroidal anti-inflammatory drugs (NSAIDs), Histamine H_2–receptor antagonists, steroid hormones, lipid regulators, and x-ray contrast media compounds.

Beta-blockers

Beta (β)-blockers are a class of pharmaceutical compounds prescribed to treat a variety of cardiovascular diseases, such as hypertension (high blood pressure), angina and coronary artery disease by blocking the action of epinephrine and norepinephrine on the β-adrenargic receptors in the body, primarily in the heart.[63] Among β-blockers, atenolol, metoprolol, propranolol and nadolol have been widely used in Europe and North America. Liu *et al*. demonstrated that the direct photodegradation of propranolol, atenolol and metoprolol followed pseudo first order kinetics under the solar simulation conditions and half-lives were approximately 16, 350 and 630 hrs, respectively.[64] Propranolol was likely to be degraded through direct photolysis under solar irradiation.[64-66] the hydroxylation and ring-open processes have been proposed as major degradation mechanisms, as illustrated in Figure 2a.[67]

(Insert Figure 2)

Photodegradation rates of atenolol and metoprolol were two and ten times faster in river waters than in DI-water due to the indirect photodegradation.[68] Among the indirect photodegradation processes, reactions with ROS are of importance. The bimolecular reaction rates of •OH, $^1O_2$ with β-blockers were summarized in the Table 1. Hydroxyl radical additions have been identified as an important degradation pathway for especially pindolol and timolol, leading to several positional isomers, corresponding to mono-, di- or tri-hydroxylations.[69] $^3DOM^*$ appeared to be the major loss factor for atenolol and metoprolol and the degradation mechanism had been proposed. The electron transfer reaction between $^3DOM^*$ and atenolol (or timolol) lead to an N-centered radical, subsequent with α-hydrogen abstraction, finally forming cleavage products, as show in Figure 2b.[70-72] Chen *et al.*[71] investigated the effect of metal ions on the photodegradation rates of atenolol. Paramagnetic metal ions would significantly inhibit the photosensitized degradation of atenolol in the fulvic acid enriched solutions, in the order of $Cr^{3+} < Fe^{3+} < Cu^{2+} < Mn^{2+}$.[71] The authors suggested that it was due to the complexation ability with fulvic acid.

To our best knowledge, there are few studies which focused on the toxicity testing of photodegradation products of β-blockers. Algal and rotifer screen tests have been employed to measure the toxicity of propranolol degraded mixtures. Their results suggested a reduction of toxicity in photodegraded mixtures compared to the parent propranolol.[73]

Antibiotics

Antibiotics are a group of pharmaceuticals used for the treatment of both human and animals with bacterial and fungal infections.[74, 75] Many of the antibiotics are derived from wholly or partially from certain microorganisms, but some are synthetic (e.g., sulfonamides). A wide range of antibiotics with diverse structures have been frequently found in the environment.[76-78] In this review, they will be divided into five sub-classes, including β-lactams, sulfonamides, fluoroquinolones, tetracyclines, as well as several other types of antibiotics that do not belong to these subclasses. The chemical structure, photo quantum yield and radical reaction rate constants of these antibiotics are shown in Table 1.

Beta-lactams

The β-lactam ring is part of the core structure of several antibiotic families, the principal ones being the penicillins, cephalosporins, carbapenems and monobactams, which are called β-lactam antibiotics. Nearly all of these antibiotics work by inhibiting bacterial cell wall biosynthesis. This has a lethal effect on bacteria. The consumption of β-lactams accounts for 50–70% of the total amount of antibiotics applied in human medicine in most countries.[79] They are also one of the most widely used groups of antibiotics used in veterinary medicine.[80] Several studies have indicated that these antibiotics are practically nonbiodegradable and have the potential to survive in the wastewater treatments.[81] The concentrations at which these compounds are generally found in surface waters are quite low and range from ng L^{-1} to μg L^{-1}. However, the possibility of inducing resistance in bacterial strains, which could pass to humans via environmental exposure, cannot be excluded.[82-85]

Based on the recent 10 years references, photodegradation of amoxicillin was one of the most research focuses.[54, 86-88] Andreozzi *et al*. reported that under abiotic conditions both hydrolysis and direct photolysis could be responsible for the transformation and removal of amoxicillin in aqueous environments. Quantum yield calculated under solar irradiation are 5.97×10^{-3} at pH 7.5 and 4.47×10^{-3} at pH 5.5. Their results showed that nitrate ion has no noteworthy influence on photodegradation rate of amoxicillin, however humic acids are able to enhance its degradation rate.[89] In addition, Xu *et al.* studied on the indirect photodegradation mechanism of amoxicillin in the DOM enriched solutions. While $^1O_2$ only accounted for 0.03-0.08% of the total loss rate, the hydroxyl radical contributed 10-22% under varied Suwannee River DOMs. The •OH reaction rate of amoxicillin was summarized in Table 1, not only implied for the indirect photodegradation prediction, but also for advanced oxidation processes. It appears that the direct reaction of $^1DOM^*$ and $^3DOM^*$ with amoxicillin accounts for 48-74% of the loss of amoxicillin.[90] Reynoso *et al*. reported that the bacteriostatic activity of amoxicillin decreases in parallel to its sensitized photodegradation initialed by Rose Bengal.[91]

The cephalosporins, a class of β-lactam antibiotics, have large family members of five "generations" now, such as cephalexin (CFX), cephradine (CFD), cefotaxime (CTX), cefazolin (CFZ), cephapirin (CFP) and so on.

Jiang *et al.* studied the photodegradation of cephalosporins of four generations in aquatic environmental system under various conditions, their data indicate that abiotic hydrolysis (for CFD, cefuroxime, and cefepime) and direct photolysis (for ceftriaxone) were the primary processes for elimination of the cephalosporins in surface water, whereas biodegradation was responsible for the elimination of the cephalosporins in the sediment.[92] Wang *et al.*[93] investigated the photodegradation of five cephalosporins in surface water, and found that some cephalosporins underwent the mainly direct photolysis (such as CFZ, CFP), while some were mainly transformed by indirect photolysis (such as

CFX, CFD), their quantum yields were showed in Table 1, the authors also suggested that the carbonate radical enhanced the photo-transformation of CFD and CFX, which generated from the reaction of •OH with bicarbonate. The pathway of the direct and indirect photolysis of CFD and CFP were summarized in Figure 3, the •OH and $^1O_2$ reaction rates of cephalosporins were showed in Table 1.[94]

One concern is that the photodegradation byproducts of cephalosporins were found to be even more photostable and more toxic,[93] the Microtox acute toxicity test showed that all target cephalosporins had increased toxicity while underwent direct photolysis especially CFZ, this potential risk of increased ecotoxicity from cephalosporins after exposure to sunlight should attracted attention.

(Insert Figure 3)

Sulfonamides

Sulfonamide drugs were the first developed antimicrobial drugs initiated by the laboratory of Bayer AG in 1932, then paved the way for the antibiotic revolution in medicine. They share a common core chemical structure (*p*-aminobenzene sulfonamide), which inhibits multiplication of bacteria by acting as competitive inhibitors of *p*-aminobenzoic acid in the folic acid synthesis cycle.[63] Until now, a variety of sulfonamides have been produced, consumed and subsequently detected in the environment.

Boreen *et al.*[95, 96] reported that the rate of direct photolysis of five-membered heterocyclic sulfonamides (sulfamethoxazole, sulfisoxazole, sulfamethizole, sulfathiazole and sulfamoxole) dependent upon the identity of the five-membered heterocyclic R group as well as the pH of the solution. The quantum yields calculated range from < 0.005 for the neutral state of sulfamethizole to 0.7 ± 0.3 for the protonated state of sulfisoxazole, therefore the protonation state of five-membered heterocyclic sulfonamides is the most photoreactive varies among the sulfa drugs. The sulfanilic acid was identified as the main direct photodegradation product for five-membered heterocyclic sulfonamides through σ cleavage (Figure 4a). The six-membered heterocyclic sulfonamides were significantly less direct

photoreactive than five-membered one. Thus as indirect photodegradation would be the major degradation process in the DOM solutions or wastewater effluents.[97] The primary product formed in both direct and indirect photodegradation of six-membered heterocyclic sulfonamides was identified as a sulfur dioxide extrusion product, as illustrated in Figure 4b.[98] Guerard *et al*. investigated the compositional role of DOM in the photosensitized degradation of sulfadimethoxine.[99, 100] The DOM originating from highly autochthonous water bodies was more reactive than the allochthonous resource. They hypothesized that aromatic ketones and phenols present in dissolved organic matter could be responsible for their observations. Wenk *et al*. supported this hypothesis, and concluded that substituted phenolic compounds exhibiting antioxidant character were able to slow down the photosensitized degradation of several typical sulfonamides in aerated solution. A simultaneous accelerated degradation of the phenols in the presence of sulfonamides was also observed.[101] Photolysis products of these sulfa drugs did not retain any measurable ability to inhibit growth of *Escherichia coli* DH5α..[102]

(Insert Figure 4)

Tetracyclines

The tetracyclines, a large family of antibiotics, were discovered as natural products by Benjamin Minge Duggar in 1945 and first prescribed in 1948. They were ranked as the second antibiotics in production and usage worldwide,[103] which are commonly used as therapeutics and growth promoters in husbandry, cattle, swine, poultry and fishery, with a widespread presence in surface waters.[104] The tetracycline resistance genes have been detected in aquatic system. The potential detrimental impact of tetracyclines on aquatic ecosystem therefore made it essential to study their photochemical fate before an ecological risk assessment.

The kinetic studies of photochemical transformation of tetracycline were investigated by several research groups.[105-110] The pH, Ca^{2+} and Mg^{2+} effects on the photo quantum yield of tetracycline were

studied, and shown in Table 1. It appeared that the photodegradation rate for tetracycline can vary by upto an order of magnitude with the varied Mg^{2+} and Ca^{2+} concentrations.[105] Chen *et al.*[111] reported that the quantum yield of chlortetracycline (CTC) increased from 3.3×10^{-4} to 8.5×10^{-3} within the pH range of 6.0 to 9.0 under solar simulated irradiation. The quantum yield of CTC on the clay surface was estimated to be $(1.3 \pm 0.7) \times 10^{-4}$, significant lower than the quantum yield of the aqueous CTC zwitterion.[112]

The direct photolysis of CTC yielded a serious of degradation products including tetracycline and H_2O_2 (Figure 5), which may cause the toxicity increase. Regarding the toxicity of photodegradation products of tetracycline, conflict results have been reported from two different bioactivities test. Jiao *et al.* observed that the acute toxicity increase with irradiation using luminescent bacterium (30 min).[113] Wammer *et al.* performed the long-term effect assay (4 hrs) using two bacterial strains: *Escherchia coli* DH5α and *Vibrio fischeri*. Their results suggested that photoproducts have no significant antibacterial activity.[110]

(Insert Figure 5)

Fluoroquinolones

Fluoroquinolones (FQs) are broad-spectrum antibiotics that play an important role in treatment of serious bacterial infections, especially hospital-acquired infections and others in which resistance to older antibacterial classes is suspected. Because the use of broad-spectrum antibiotics encourages the spread of multidrug resistant strains and the development of Clostridium difficile infections, treatment guidelines from the Infectious Disease Society of America recommend minimizing the use of FQs antibiotics in less severe infections.

Ge *et al.*[114] determined photolytic quantum yields of 8 FQs, as summarized in Table 1. Therefore solar photodegradation half-lives for the FQs in pure water and at 45°N latitude were calculated to range

238 from 1.25 mins for enrofloxacin to 58.0 mins for balofloxacin, suggesting that FQs would intrinsically
239 photodegrade fast in sunlit surface waters. They proposed that FQs underwent both direct photolysis and
240 self-sensitized photo-oxidation via •OH and $^1O_2$.[115] Studies of the photodegradation mechanism under
241 solar irradiation are available for a number of FQs, including: Difloxacin, Sarafloxacin[116], Ciprofloxacin
242 [117-119], Enrofloxacin, Marbofloxacin[120], Flumequine [121] and norfloxacin.[122]

243 Previous studies suggested that oxidative degradation of the piperazine side chain, reductive
244 defluorination and fluorine solvolysis were three major processes for direct photolysis of FQs, as
245 illustrated in Figure 6.[116, 117, 120, 122, 123] Distinct photolytic mechanisms for different dissociation species
246 of ciprofloxacin have been recently reported.[124] Regarding of photolysis of enrofloxacin, the formation
247 of ciprofloxacin were observed by Knapp *et al*.[119]. Since the FQ ring, required for the biological effect,
248 is not affected during the first steps of the photolytic process, a number of byproducts active against both
249 gram-negative and gram-positive bacteria are formed. [125-127]

250 (Insert Figure 6)

251 **Trimethoprim**

252 Trimethoprim (TMP) belongs to a family of synthetic 2, 4-diaminopyrimidines with potent
253 microbicidal activity for a wide variety of bacteria. TMP is a folic acid antagonist and dihydrofolate
254 reductase inhibitor, which catalyses the conversion of dihydrofolate to tetrahydrofolic acid, affecting the
255 biosynthesis of DNA. This drug is always combined with sulfamethoxazole to treat bacterial infections,
256 including gastro, respiratory and urinary infections.[128]

257 The quantum yield of trimethoprim has been reported as varied from 6.2×10^{-4} to 1.2×10^{-3} with
258 pH increase at air saturated solution, as shown in Table 1. Deoxygenation also dramatically increased
259 the quantum yield, indicating that triplet excited state of TMP is effectively quenched by oxygen.[97] The
260 half-life of TMP was 780 mins under solar simulated irradiation.[129] Demethylation and hydroxylation

were two major processes involved in the direct photolysis mechanism, as shown in Figure 7. Due to relatively slow direct photodegradation, the loss of TMP in sunlit natural water appears to be dependent on indirect photodegradation. Both •OH and $^1O_2$ are ROS involved in indirect photodegradation, and bimolecular reaction rate constants are reported as 8.66×10^9 M^{-1} s^{-1} and $(3.2 \pm 0.2) \times 10^6$ M^{-1} s^{-1}, respectively. However, reactions with ROS are minor pathways for the photochemical loss of TMP when compared to the apparent reaction with $^3DOM^*$.[130] Indirect photolysis of TMP in wastewater effluents also had been investigated by Ryan *et al*.[97] •OH and $^3EfOM^*$ have been proposed as the responsible species, as contributed 62% and 20% removal respectively. It's most likely due to the fact the high concentration of NO_3^- existed in the effluents.

Studies on the toxicity change of TMP in its environmental photochemical fate were limited. Michael *et al*. performed toxicity assays in simulated wastewater and real effluent indicating that toxicity is attributed to the compounds present in real effluent and their by-products formed during solar Fenton treatment and not to the intermediates formed by the oxidation of TMP.[131]

(Insert Figure 7)

NSAID drugs

NSAIDs comprise one of the major classes of pharmaceuticals commonly consumed in both prescription and non-prescription drugs. The NSAIDs covered in this review include diclofenac, ibuprofen and naproxen. These are the drugs with analgesic (reduce pain), antipyretic (reduce fever), and anti-inflammatory effects by inhibiting prostaglandin synthesis by inhibition of cyclooxygenase.[63]

Diclofenac

Diclofenac is taken to reduce inflammation and as an analgesic reducing pain in certain conditions. This acidic drug has been frequently detected in surface water, ground water and wastewater effluents. Even at very low concentrations there are adverse effects in different organisms. In the livers,

kidneys and gills of rainbow trout, the lowest observed effect concentration for cytopathology occurred at 1 μg L^{-1}.[132] An ecological effect resulted from diclofenac residues which caused the vulture population decline in Pakistan.[133]

The quantum yield of diclofenac has been reported as 0.094 and presents a half-life of 39 mins in DI-water under solar simulated irradiation.[134] The significant amount of absorbance in the solar region helps to explain that rapid direct photodegradation is the dominant degradation mechanism for diclofenac.[135-138] Addition of isopropanol (IPA) led to more rapid transformation, possibly due to formation of other radical species or photoreduction with IPA serving as the H-source. Pigment, nitrate and nitrite have been reported to have inhibiting effects on the photodegradation of diclofenac.[139, 140]

The direct photodegradation routes of diclofenac have been predicted by *Musa et al.* through computational quantum chemistry method.[141] As illustrated in Figure 8, the deprotonated species instinctively lose one chlorine from the excited triplet state leading to ring closure reaction to form an active photoproduct: chlorocarbazole acetic acid (CCA), The formed CCA is also photodegraded easily through dechlorination and decarboxylation.[141] Mefenamic acid is also a diphenylamine derivative; the solar quantum yield was measured as $(1.5 \pm 0.3) \times 10^{-4}$. Model photosensitizer experiments indicated that direct reaction with excited triplet-state DOM is the major photosensitization process.[142]

(Insert Figure 8)

Ibuprofen

Ibuprofen is one of important NSAIDs widely used for the relief of headache, rheumatoid arthritis, fever and general pain; also it is an active ingredient of a number of over-the-counter pain-relief drugs. Ibuprofen has been frequently detected in the aquatic environment.[143, 144] The polychromatic UVB photolysis quantum yield was determined as $\Phi_{IBP} = 0.33 \pm 0.05$.[145] Several groups[146-150] have investigated the indirect photolysis under solar or solar simulated conditions. The

presence of fulvic acid (FA) significantly increased photolysis rates of ibuprofen, but the rates are highly dependent upon DOM composition.[147] 1-(4-isobutylphenyl) ethanol, hydroxylation derivatives of ibuprofen and 4-isobutylacetophenone (IBAP) have been identified as three major products through LC-TOF and NMR, as illustrated in Figure 9. IBAP present adverse effects on tissue cells and nervous system.[151] It can be formed upon direct photolysis (yield 25 ±7 %), reaction with •OH (yield 2.3 ±0.1%) and reaction with $^{3}CDOM^{*}$ (yield 31 ±4%).

(Insert Figure 9)

Naproxen

Since the naproxen presents high quantum yield (0.036) for photodegradation and its UV-vis spectrum largely overlaps with solar irradiation, it is subject to direct photolysis with a half-life in river water of 42 mins under natural sunlight (summer, 45° latitude).[134, 152] Four major photoproducts of naproxen haven been identified using LC-ESI-MS.[153] Bioassays of the naproxen and its photo derivatives were performed on *Vibrio fischeri*, algae, rotifers and microcrustaceans to assess acute and chronic toxicity.[154, 155] Furthermore, possible genotoxic effects of photoderivatives were investigated using SOS chromotest and Ames fluctuation test. Their results indicated that photoproducts were more toxic than the parent compounds both for acute and chronic values, while genotoxic and mutagenic effects were not found.[156]

Histamine H_2–receptor antagonists: Ranitidine and cimitidine

The H_2 receptor antagonists (H_2RA) are a class of drugs used to block the action of histamine on parietal cells (specifically the histamine H_2 receptors) in the stomach, decreasing the production of acid by these cells. The H_2RA covered in this review includes ranitidine and cimetidine, they are used in the treatment of dyspepsia, although they have been surpassed in popularity by the more effective proton pump inhibitors.

Ranitidine (common brand name Zantac) was measured in the effluents of nine STPs in Italy with a median value of 288.2 ng L^{-1}, and in surface waters in the north Italy at a maximum concentration of 4 ng L^{-1}.[157] The low residence concentration was due to the rapid photodegradation. Latch et al. reported that the half-life of ranitidine was 35 mins under noon summertime sunlight at 45 ° latitude[158], and the direct photolysis quantum yields for the pharmaceutical kept constant over the pH range of 6–10. The bimolecular rate constants for ranitidine reacting with $^1O_2$ range from $(1.6 \pm 0.2) \times 10^7$ M^{-1} s^{-1} at pH 6, increasing to $(6.4 \pm 0.2) \times 10^7$ M^{-1} s^{-1} at pH 10. Reaction of ranitidine with •OH proceeds with a rate constant of $(1.5 \pm 0.2) \times 10^{10}$ M^{-1} s^{-1}. Results shows that photodegradation by direct photolysis is expected to be the major pathway for ranitidine, with some degradation caused by $^1O_2$. Ranitidine was transformed mainly into two photoproducts, as illustrated in Figure 10.

(Insert Figure 10)

Bioassays were performed by Isidori *et al.*[159] on rotifers and microcrustaceans to assess acute and chronic toxicity, their results found that ranitidine did not show any acute toxicity at the highest concentration tested (100 mg L^{-1}) for all the organisms utilized in the bioassays. Bergheim also found that neither ranitidine, nor its photoderivatives were found to be readily or inherently biodegradable[160].

Cimetidine was also one of the prototypical H_2 antagonists, which was shown to be resistant to direct photolysis[158] and the expected half-life is 7 days at 12 hrs sunlight per day. For cimetidine, the reaction rate constant for •OH is $(6.5 \pm 0.5) \times 10^9$ M^{-1} s^{-1}. Between the pH 4 to 10, cimetidine reacts with $^1O_2$ with bimolecular rate constants changing significantly from $(3.3 \pm 0.3) \times 10^6$ M^{-1} s^{-1} at low pH to $(2.5 \pm 0.2) \times 10^8$ M^{-1} s^{-1} in alkaline solutions. The major pathway of cimetidine was estimated to reaction with $^1O_2$ formed from the interaction of sunlight with DOM.

Lipid regulators

Lipid regulators are the fibrate pharmaceuticals used for a range of metabolic disorders, mainly

hypercholesterolemia. They are phenoxyalkanoic acid derivatives, either free acid or esters, and accelerate the clearance of very-low-density lipoproteins. Bezafibrate, clofibrate, fenofibrate and gemfibrozil and their hydrolyzed metabolites, including clofibric acid and fenofibric acid have been frequently found in the aquatic environment in a number of countries.

Gemfibrozil, bezafibrate and fenofibrate which was included in the 2002 list of the most used pharmaceuticals in the world, its concentration was found in different effluent waters range from 0.84 to 4.76 μg L^{-1} with gemfibrozil, 1.07–4.6 μg L^{-1} with bezafibrate and 0.14-0.16 μg L^{-1} with fenofibrate.[161] Irradiation with a solar simulator in distilled water caused about 10% degradation of gemfibrozil, bezafibrate and fenofibrate after 200 hrs.[162] The half-lives of gemfibrozil were reported from 15 hr to 288.8 days in different nature waters, [161, 163, 164] its direct photoproduct may be rationalized by the photooxidation promoted by ortho aryloxy function, showed in Figure 11 (I), and the photodegradation mechanism of bezafibrate and fenofibrate was illustrated in Figure 11 (II for both and III for bezafibrate), however, there is a dearth of information for the indirect photodegradation mechanism of fibrate drugs, Razavi *et al*. reported the bimolecular reaction rate constants for •OH with fibrate drugs were (6.98 ± 0.12) × 10^9, (8.00 ± 0.22) × 10^9 and (10.0 ± 0.6) × 10^9 M^{-1} s^{-1}, for clofibric acid, bezafibrate and gemfibrozil, respectively.[165]

(Insert Figure 11)

The toxic effect of gemfibrozil were reported by Zurita *et al*.[166] using three bioassays, found that one of the possible mechanism of gemfibrozil toxicity seems to be the binding to sulphydryl groups, however, comparing the concentrations in water and the toxicity quantified in the assayed systems, gemfibrozil is not expected to represent acute risk to the aquatic biota. The toxic and genotoxic impact of fibrate and their photoproducts also studies by Isidori *et al*.[167] and found that acute toxicity was in order of dozens of mg L^{-1} for all the trophic levels utilized in bioassays, also genotoxic and mutagenic

effects were especially found for the gemfibrozil photoproducts.

The mechanistic pathway for the formation of the photoproducts of fibrate drugs was summarized by Cermola *et al*. in Figure 11.[162, 168] The degradation pathway of those drugs all involve the aryloxy moiety as key reactive site and well-stabilized radicals (or radical ions) as intermediates. Pathway I: the formation of aldehyde rationalized by a photooxidation promoted by the ortho aryloxy function; Pathway II: homolytic cleavage of the aryloxy bond followed by hydrogen abstraction from the solvent in aerobic conditions; Pathway III: an ionic photodecarboxylation process; Pathway IV: witting rearrangement followed by photodecarboxylation; Pathway V: electron release results in photodecarboxylation accompanied with CO_2 losses.

Carbamazepine

Carbamazepine is an anticonvulsant and mood-stabilizing drug used primarily in the treatment of epilepsy and bipolar disorder, as well as trigeminal neuralgia. Approximately one thousand tons of carbamazepine is sold annually worldwide.[169] The low removal efficiency (7%) of this drug in sewage treatment plant has been reported.[170] As a result, the typical average concentrations of carbamazepine in sewage treatment plant effluent and surface water were 2.1 and 0.25 μg L^{-1} in Germany.[6, 171] The biodegradation was less important than photodegradation in limiting their persistence.[172] So the photodegradation of carbamazepine was extensive investigated.

Doll found that the initial concentration has an exponential relationship to the degradation rate constant of carbamazepine,[32, 173] Calisto also suggested that the direct photodegradation rate of carbamazepine is pH dependent and be influenced by the dissolved oxygen. The quantum yields calculated for carbamazepine range from $(0.2 – 6.4) \times 10^{-5}$ at different pH conditions,[174] the direct photolysis products of carbamazepine was identified and illustrated in Figure 12. Two main routes were proposed by Chiron.[175] The minor pathway was the hydration of the C_{10}-C_{11} double bond and generate

399 compound I; the major pathway involved a ring contraction process and followed by the formation of
400 carbamazepine-9-carboxaldehyde, and this intermediate might degrade in three different ways then
401 product the products II-VI, especially the compound VI (acridine), a stable azaarence drug with known
402 mutagenic and carcinogenic activity.[175, 176] The second order constant for carbamazepine with •OH was
403 measured as $(9.4 \pm 0.4) \times 10^9$ M^{-1} s^{-1},[96] $8.8 \pm 1.2 \times 10^9$ M^{-1} s^{-1} [177]and $(3.07 \pm 0.33) \times 10^9$ $M^{-1}s^{-1}$.[178]

404 (Insert Figure 12)

405 Kosjek have compared the efficiency of three common water treatment methods in
406 carbamazepine treatment and found that the most successful method for the removal of carbamazepine
407 was UV treatment, while the toxic photodegradation product acridine and acridone were more
408 susceptible to biological treatment.[179]

409 **Steroid hormones**

410 A number of natural and synthetic steroid hormones are used in treatment of various types of
411 medical conditions such as menopausal symptoms, growth hormone deficiency and hypothyroidism.[180]
412 Some natural and synthetic estrogen hormones are also used as oral contraceptives. Two types of steroid
413 hormones are covered in this review, including 17β-estradiol (E2), estrone (E1), 17α-ethinylestradiol
414 (EE2), rostenedione (AD) and testosterone (T) While the former theree are natural (endogenous)
415 estrogenic hormones, the last two are androgenic hormones.[181]

416 E2 is an endogenous estrogen responsible for the development of female secondary sex
417 characteristics and reproduction. In addition to its endogenous occurrence, this natural estrogen is
418 manufactured and used in oral contraceptives and hormone replacement therapy in large quantities. E2
419 has been frequently detected in the aquatic environment, and is considered as a major contributor of
420 estrogenic activity found in municipal sewage treatment plant effluent[182]. Under solar simulated
421 irradiation (>290 nm), the photo-transformation of E2 and EE2 in aqueous solution occurs with a quite

low quantum yield about 0.07 ± 0.01 and 0.08 ± 0.01 for E2 and EE2, respectively [183]. The exclusively $^1O_2$ mediated photooxidation mechanism was studied by Diaz *et al.*[184] through employing the artificial dye RB as a sensitizer. As illustrated in Figure 13, the primary oxidation occurred at the aromatic ring.

(Insert Figure 13)

Photodegradation of E1 was studied in aqueous solution under simulated sunlight by Chowdhury *etc.*[185, 186], who determined the effects of several parameters such as initial concentration, solar intensity, pH and effect of humic substances. E1 was found to be degraded rapidly, with a half-life of 48 to 123 min, depending on irradiation intensity and initial concentrations, the maximum E1 degradation occurring for a humic acid content of 8 mg L^{-1} and a neutral pH.[185] Scavenger experiments indicated that $^3DOM^*$ and •OH play a significant role in the photodegradation.[187]

Several research groups reported that the photodegradation rate of E2 increased significantly when the NO_3^-, Fe^{3+} and humic acid presented in the aqueous solution, which is attributed to photosensitization by the reactive species, while HCO_3^- slowed down the degradation rate because of •OH scavenging.[164, 188-193] Grebel *et al.*[194] studied the effects of halide ions on DOM-sensitized photolysis of β-estradiol in saline waters. The photodegradation rate significantly decreased with increasing halide concentrations up to seawater levels. Approximately 70% of this decrease was due to ionic strength effects, and the remainder was the results of halide-specific effects. Halide promotion of DOM chromophore photo bleaching was shown to play a major role in the halide-specific effect.

Whidbey *et al.*[195] focused on the photoinduced changes of *in vitro* estrogenic activity of steroid hormones, including E1, E2, EE2, equilin (EQ) and equilenin (EQN). Results of yeast estrogen screen (YES) assay experiments showed that only the direct photolysis of E1 gave estrogenic product (lumiestrone)[196], which exhibited moderate estrogenic activity. When photolysed in the presence of sensitizer, E1 degraded via an indirect photolysis pathway and did not produce lumiestrone or any other

active products. Under typical natural water conditions photochemical reactions of E2, EE2, EQ and EQN are expected to produce inactive products.

Compare to a large number of papers on estrogenic hormones, few studies focused on the androgenic hormones. [197-201] Androstenedione (AD) and testosterone (T) undergo fast photodegradation with half-lives ranging from 3.7 to 10.8 hrs.[198] The light screening effect is the primary role of DOM in the natural photodegradation of AD and T. Trenbolone acetate (TBA) is a high-value steroidal growth promoter often administered to veterinary practices. Manufacturer studies demonstrated that the limited ecosystem risks of TBA metabolites are presented due to rapid photodegradation.[202] However, recent studies reported that the photodegradation product of TBA is reversible to the parent compound under environmental conditions.[201]

X-ray contrast media compounds

A few studies have reported the photodegradation of X-ray contrast media compounds (ICM) in water.[203, 204] In two studies, Doll and Frimmel[173, 205] reported the photodegradation of iomeprol in water under simulated sunlight; they tested the effects on rates of photodegradation of the initial concentration of the compound and of other compounds. Iomeprol was degraded by photolysis by simulated UV solar radiation in Milli-Q water, with a high photochemical degradation rate constant (1.1×10^{-3} min^{-1}). The initial iomeprol concentration did not have much effect on the degradation constants. Formation of iodide was observed during irradiation of iomeprol. This was indicative of the production of other iodinated intermediates (they were not identified in this study) and the loss of iodine during irradiation. Perez *et al*.[206] investigated the photo transformation reactions of iopromide under simulated solar irradiation using UPLC-QTOF-MS, as shown in Figure 14. A series of products have been identified and their formation was the result of four principal photoreactions: (I) gradual, and eventually complete, deiodination of the aromatic ring; (II) substitution of the halogen by a hydroxyl group; (III) N-

dealkylation of the amide in the hydroxylated side chain; and (IV) oxidation of a methylene group in the hydroxylated side chain to the corresponding ketone.

(Insert Figure 14)

Concluding Remarks

PhACs contamination of surface water is an emerging issue in environmental science and engineering. After the administration to humans or animals, these medications are partially metabolized and excreted in the urine and/or the feces, and subsequently enter the aquatic environment through a number of routes. Some of the PhACs are fairly biodegradable, while others are more persistent and mobile in the aquatic environment. Although there is no clear evidence of immediate public health impacts of these trace PhACs in water, there are several groups of substances with unambiguous toxic and estrogenic properties such as antibiotics and natural and synthetic hormones, which can indeed affect populations of aquatic organisms.[207, 208] Therefore, the removal of these substances before entering the aquatic environment is probably desirable based on the precautionary principle. Photochemical enhanced removal of PhACs through solar irradiation would be economically feasible when open water treatments have been applied as advanced processes, such as constructed wetlands, equalization basin and so on. Some pharmaceuticals are extremely photoreactive, such as amoxicillin, cephalexin, FQs and cimetidine. There are also some pharmaceuticals relatively resistant to photodegradation, including but not limit to atenolol, gemfibrozil, and ibuprofen. The synergistic increase in toxicity caused by pharmaceutical photoproducts has raised attention to research community,[93, 209] and future investigation are indeed. Combination of series of treatment processes, such as bank filters,[210] coagulation, bio-treatments could be a feasible removal routine for trace amount pharmaceuticals presented in the aqueous environments.

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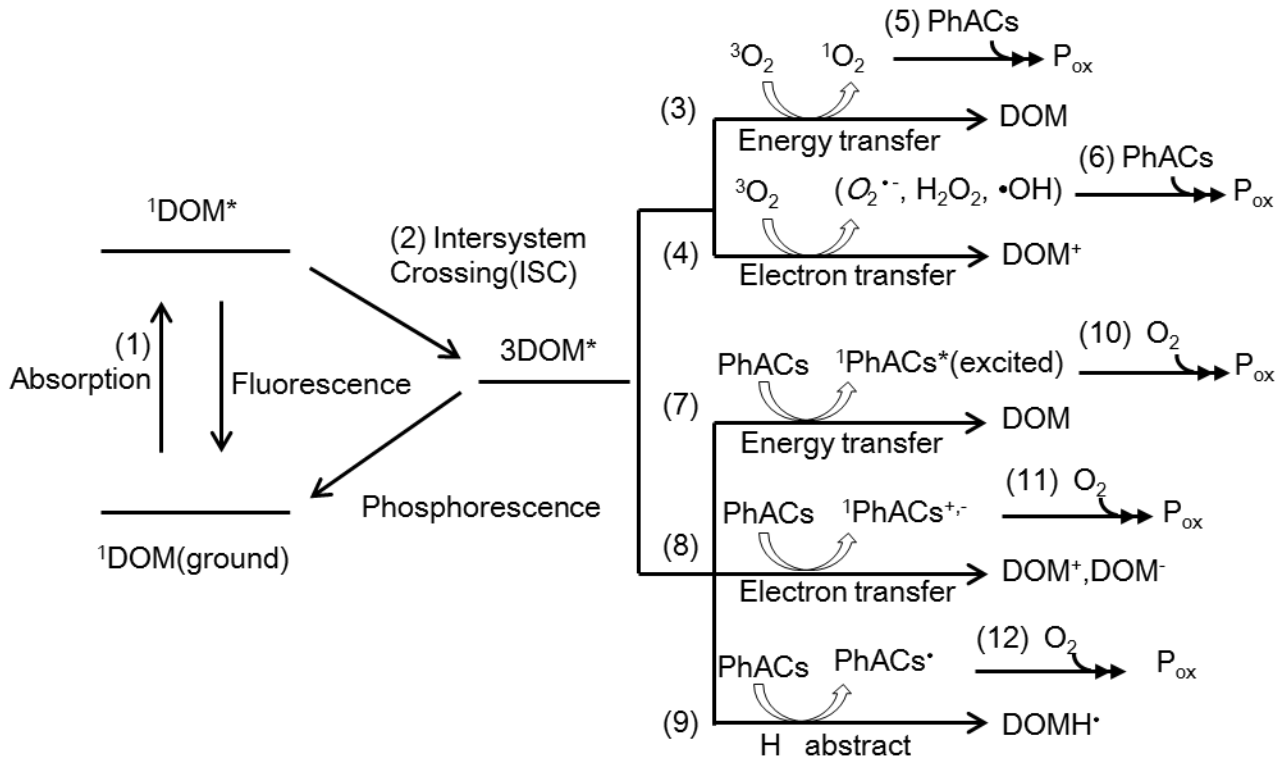

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1029 **Figure 1.** Indirect Photochemical degradation pathways of PhACs in the DOM enriched solutions.

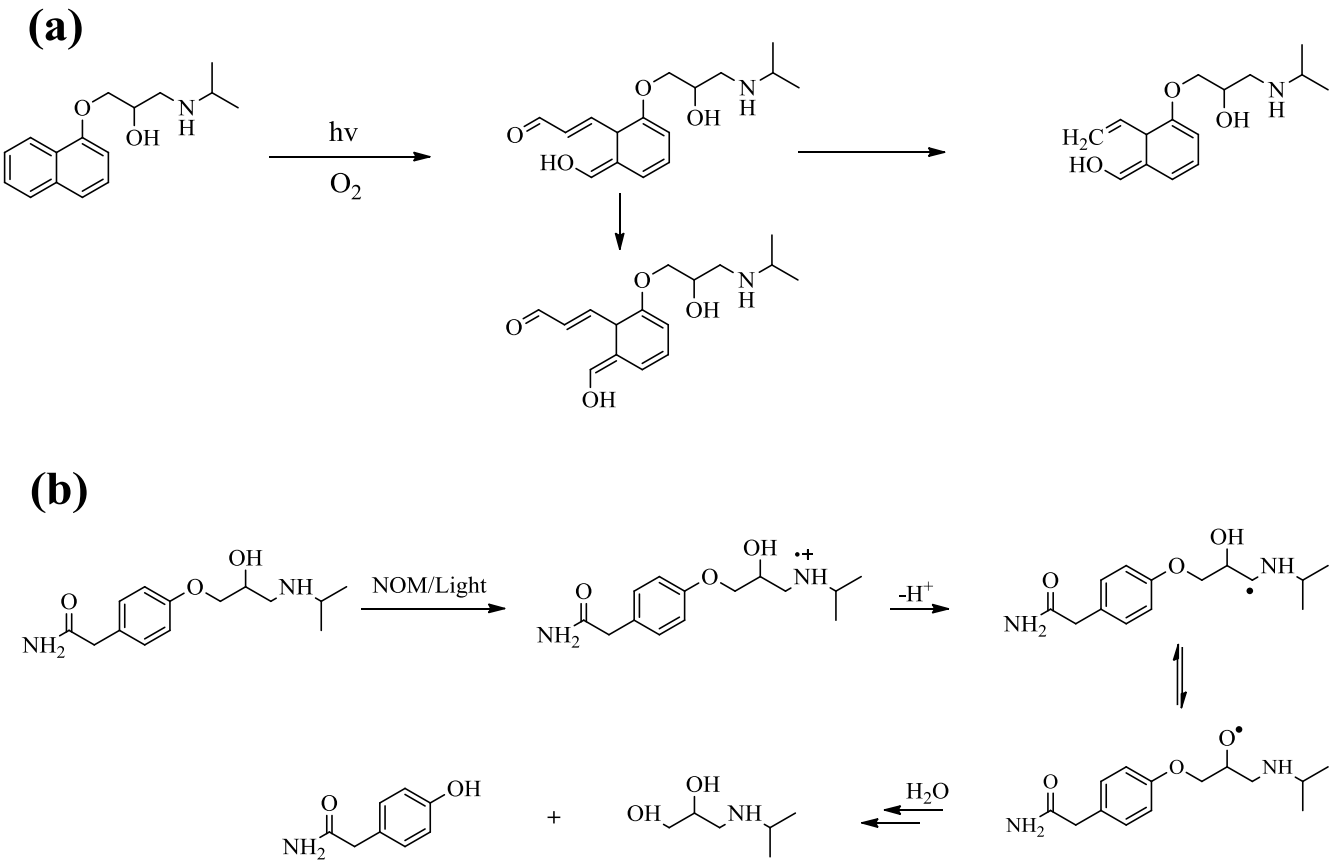


Figure 2. Proposed photodegradation pathways of β-blockers: (a) direct photolysis of propranolol, [64]redrawn with permission from Ref. 64. © 2007 American Chemical Society (b) indirect photolysis of atenolol in the NOM solution,[70] reproduced with permission from Ref. 70. © 2012 Elsevier B. V.

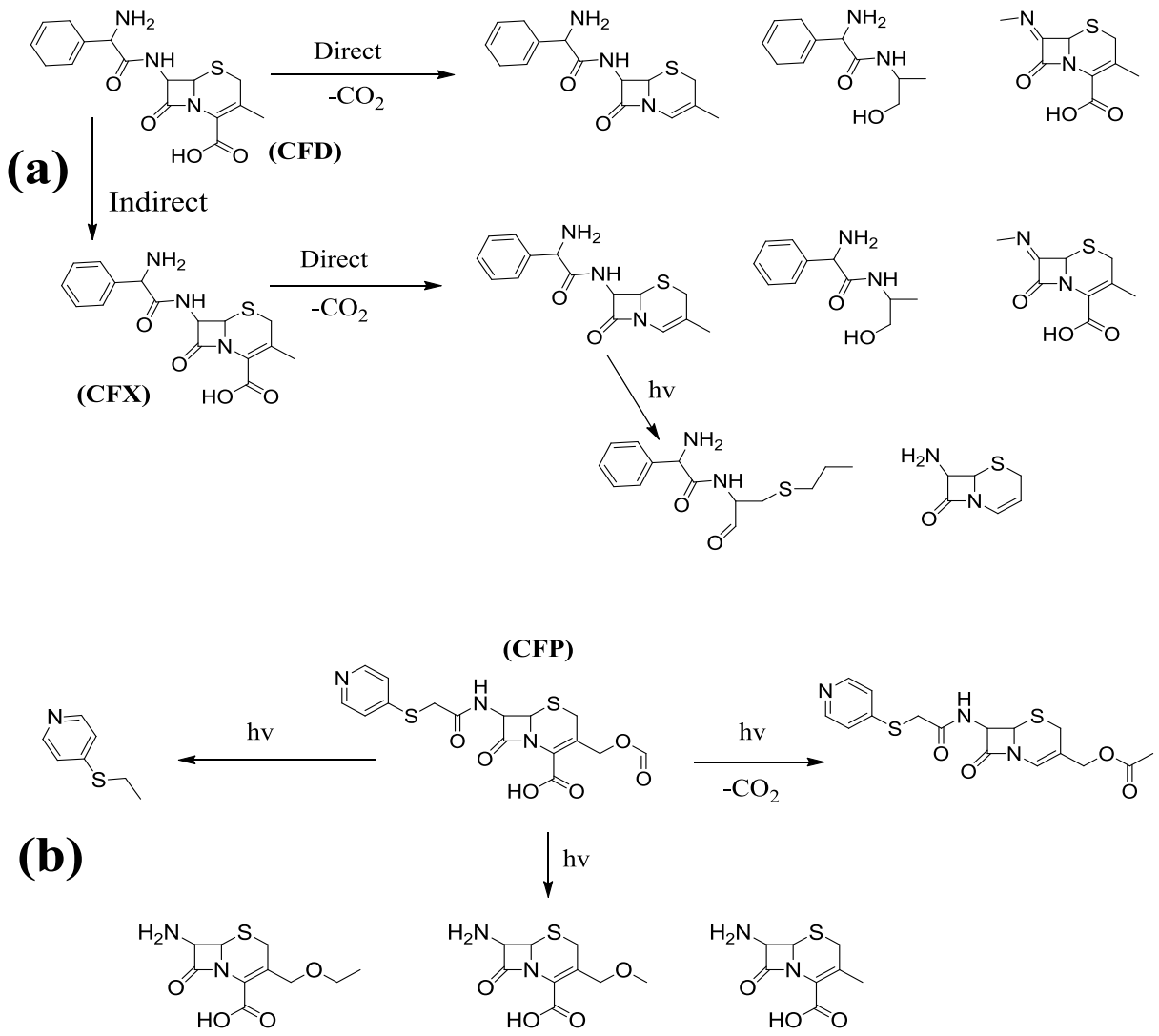


Figure 3. (a). Predicted direct and indirect photolysis products and degradation pathway of CFD. **(b)**. Predicted direct photolysis products and degradation pathway of CFP.[93] Reproduced with permission from Ref. 93.© 2012 American Chemical Society.

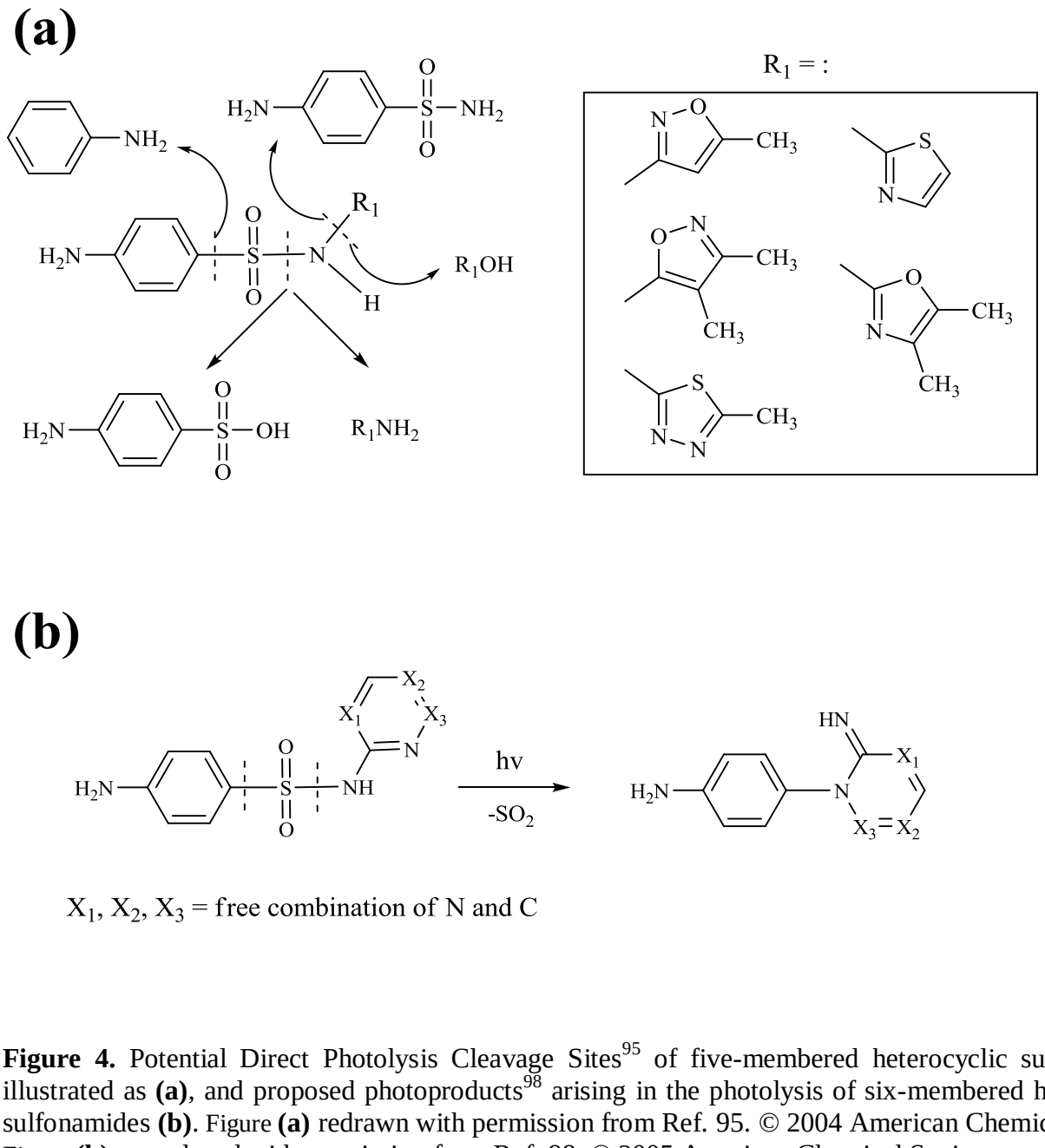


Figure 4. Potential Direct Photolysis Cleavage Sites[95] of five-membered heterocyclic sulfonamides illustrated as **(a)**, and proposed photoproducts[98] arising in the photolysis of six-membered heterocyclic sulfonamides **(b)**. Figure **(a)** redrawn with permission from Ref. 95. © 2004 American Chemical Society. Figure **(b)** reproduced with permission from Ref. 98. © 2005 American Chemical Society.

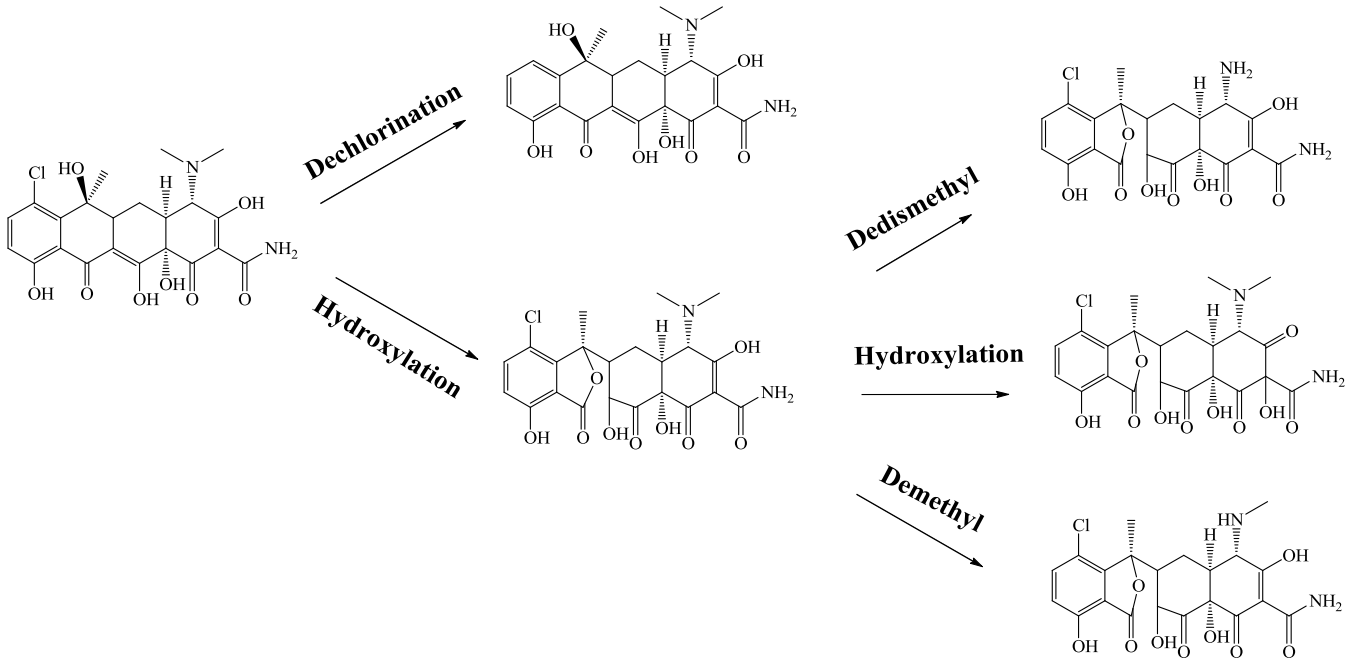


Figure 5. The hydroxylation, N-demethyl/dedismethyl, and dechlorination processes of CTC during direct photodegradation under simulated sunlight.[111] Reproduced with permission from Ref. 111. © 2012 Elsevier Ltd.

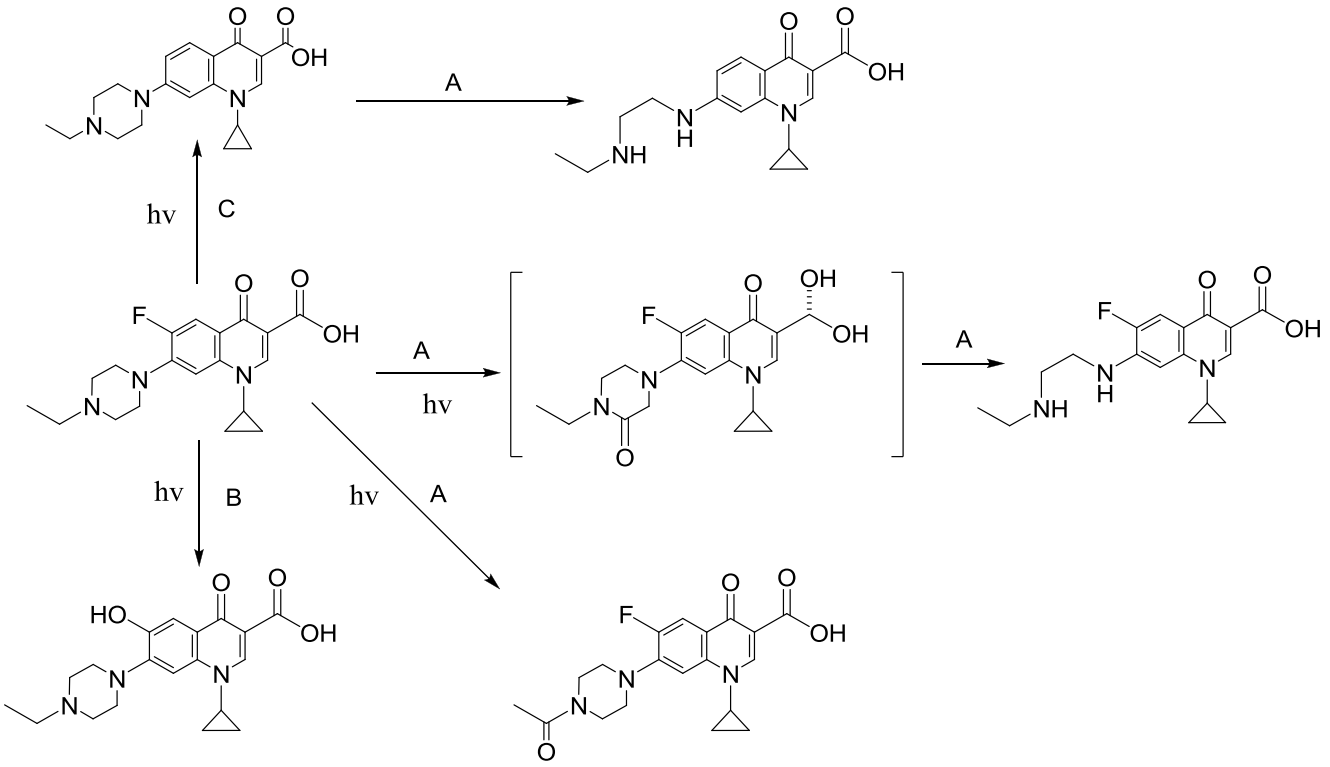


Figure 6. Three major processes for direct photolysis of Fluoroquinolones.[120] Which **A** stands for the oxidative degradation of the piperazine side chain, and **B** stands for the reductive defluorination process, fluorine solvolysis was **C**. Redrawn with permission from Ref. 120. © 2010 American Chemical Society.

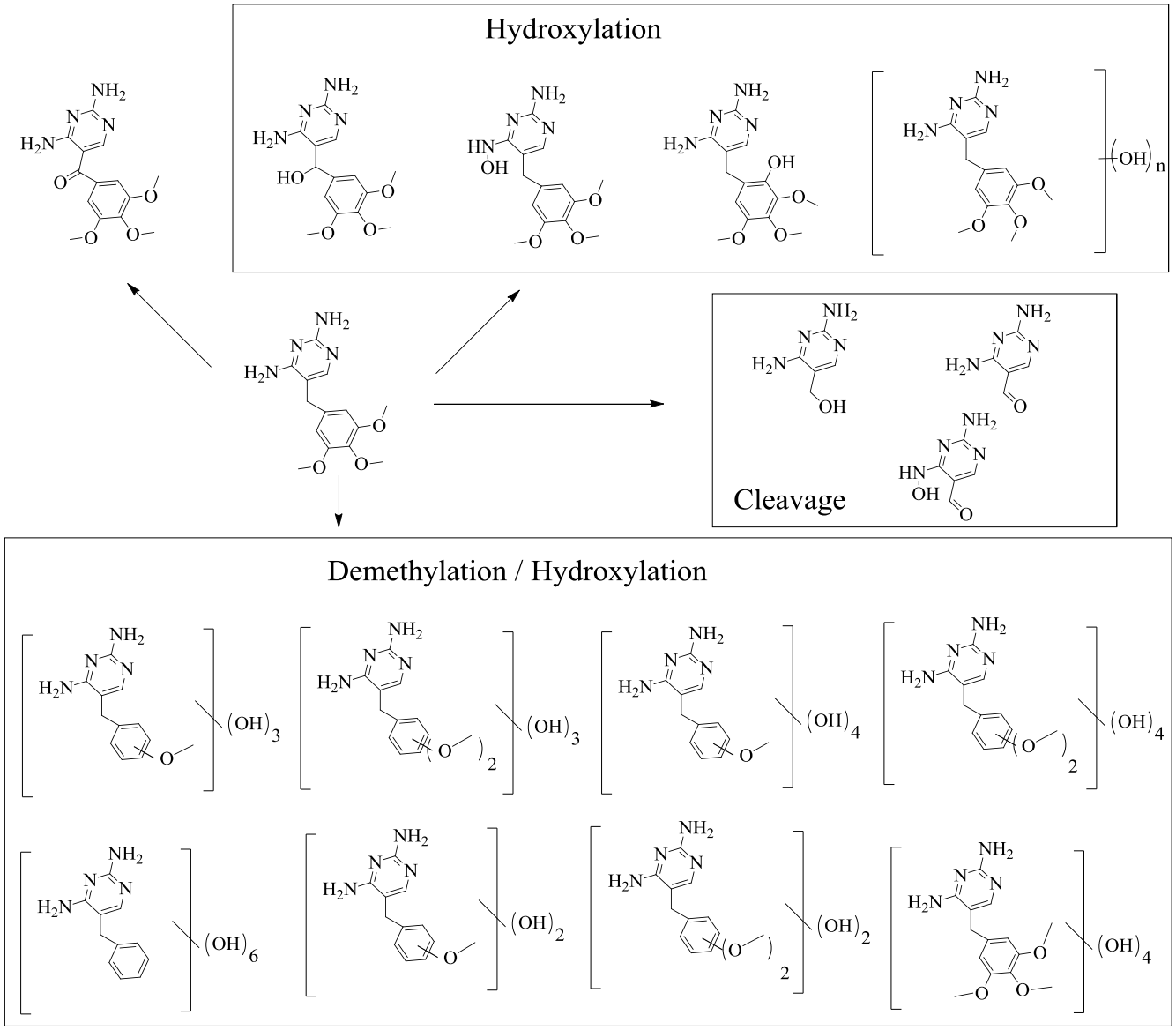


Figure 7. Two major processes (Demethylation and hydroxylation) involved in the direct photolysis mechanism of TMP.[129] Redrawn with permission from Ref. 129. © 2010 Elsevier Ltd.

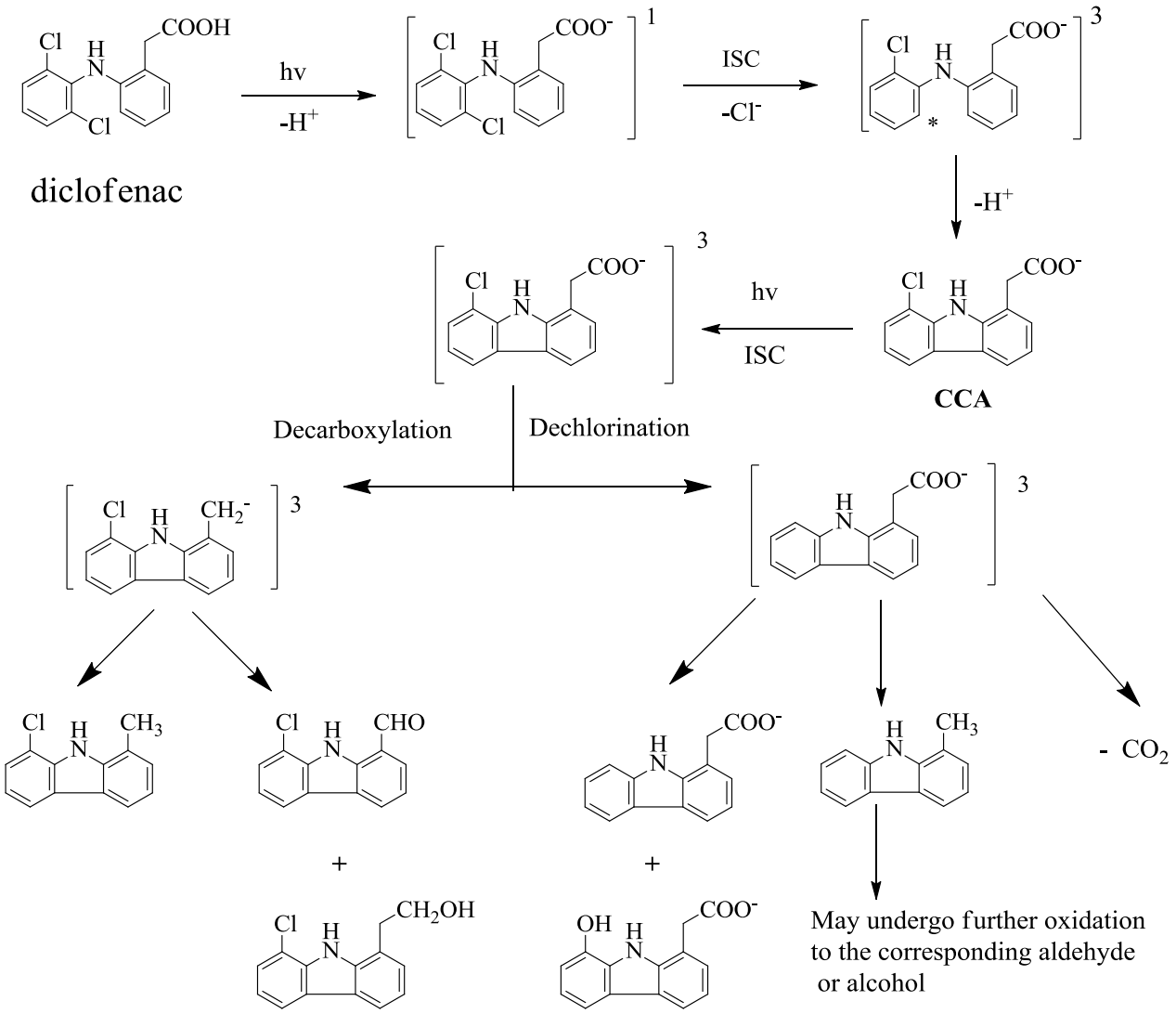


Figure 8. The direct photodegradation routes of diclofenac.[141] Reproduced from Ref. 141 © 2009 with permission from the PCCP Owner Societies.

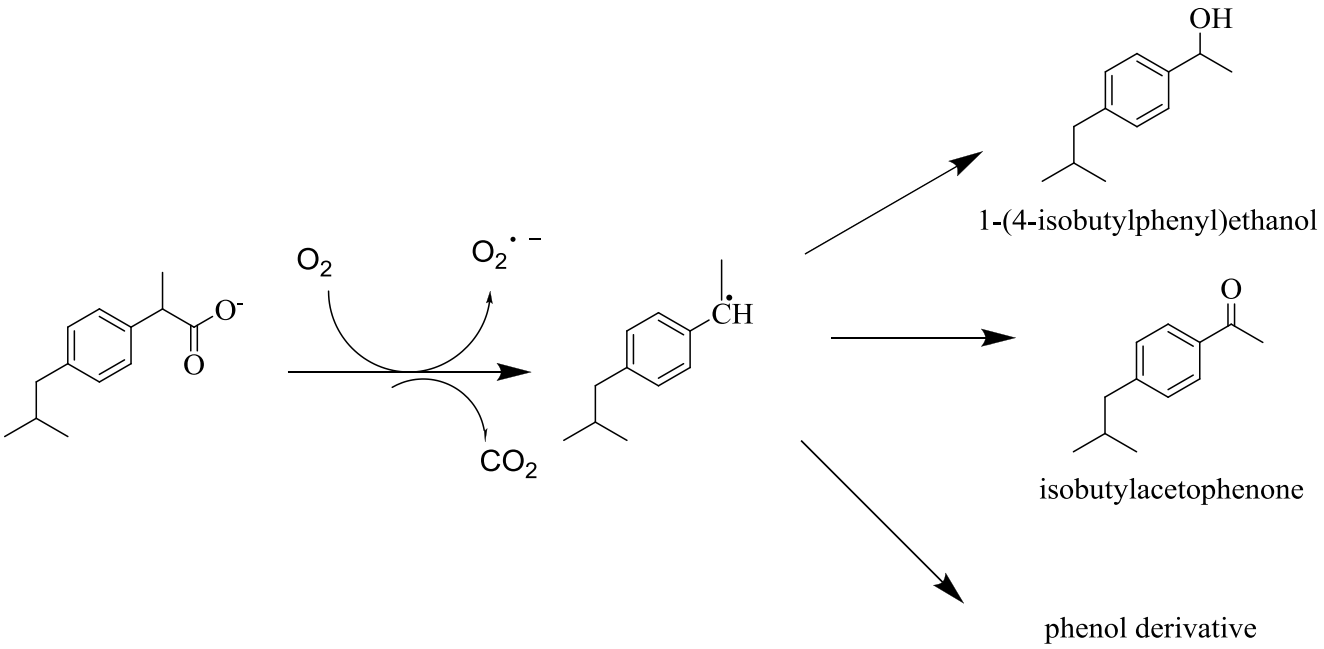


Figure 9. Proposed reactions: Ibuprofen photodecarboxylation : followed by oxygen addition to carbon centered radical and subsequent rearrangement resulting in the formation of isobutylacetophenone and the hydroxylation of carbon centered radical to form 1-(4-isobutylphenyl)ethanol.[147] Experiments have also shown that hydroxylation of the benzene ring takes place. Redrawn with permission from Ref. 147.

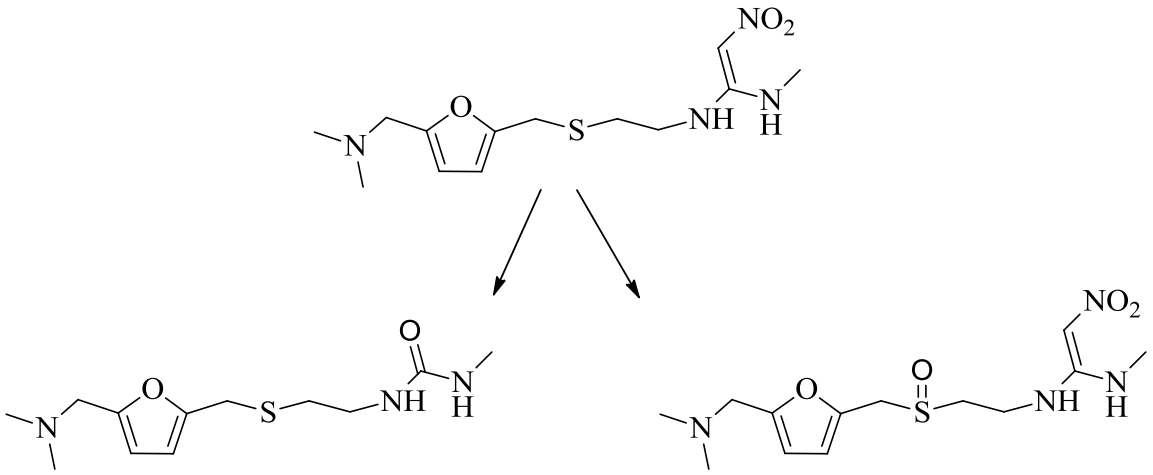


Figure 10. Ranitidine and its photoproducts structures.[159] Redrawn with permission from Ref. 159. © 2008 Elsevier Ltd.

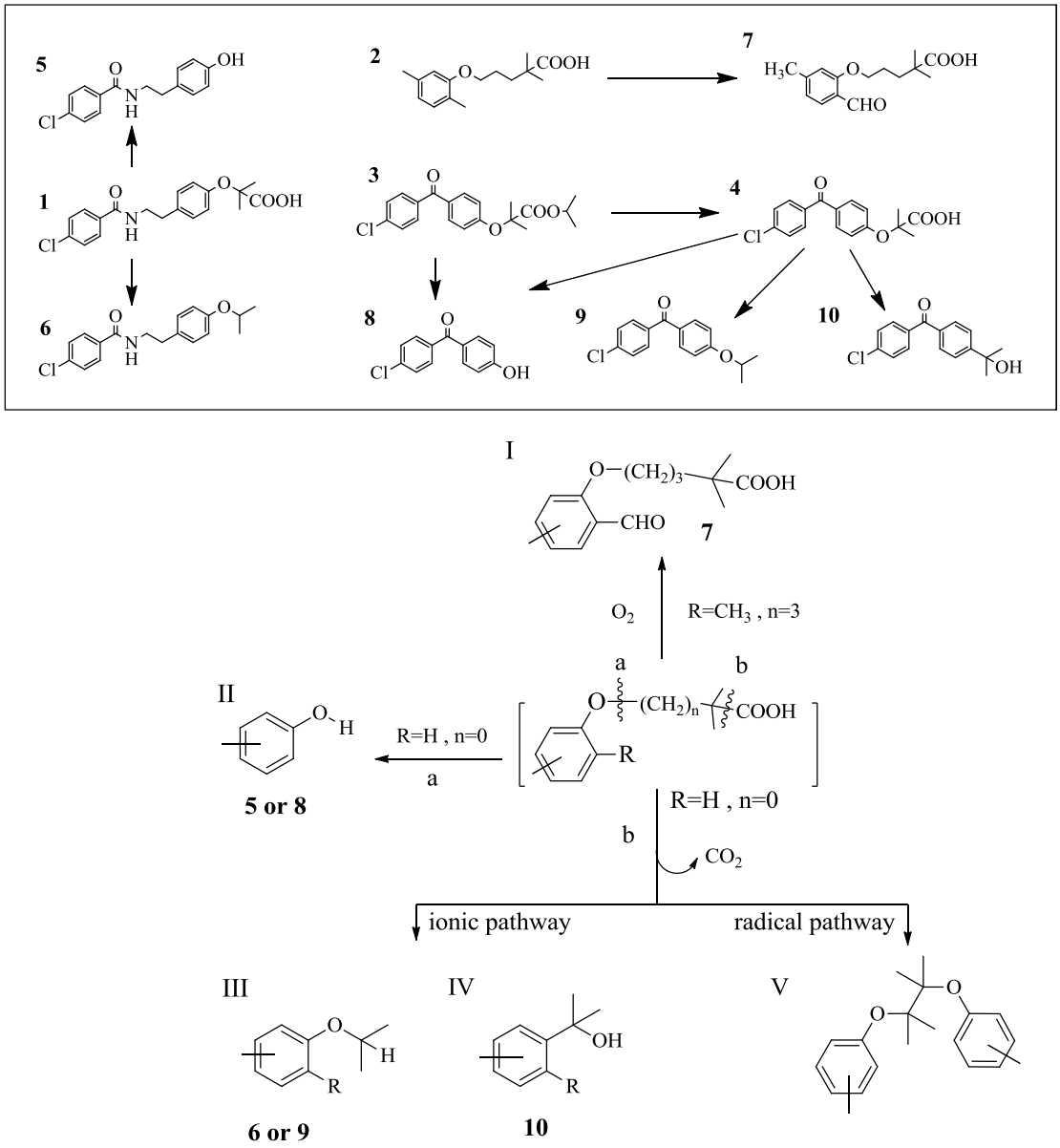


Figure 11. Suggested photodegradation mechanisms of fibrate drugs,[162] the structures in the figure 1: bezafibrate, 2: gemfibrozil, 3: fenofibrate, 4: fenofibric acid. Redrawn with permission from Ref. 162. © 2005 Springer-Verlag

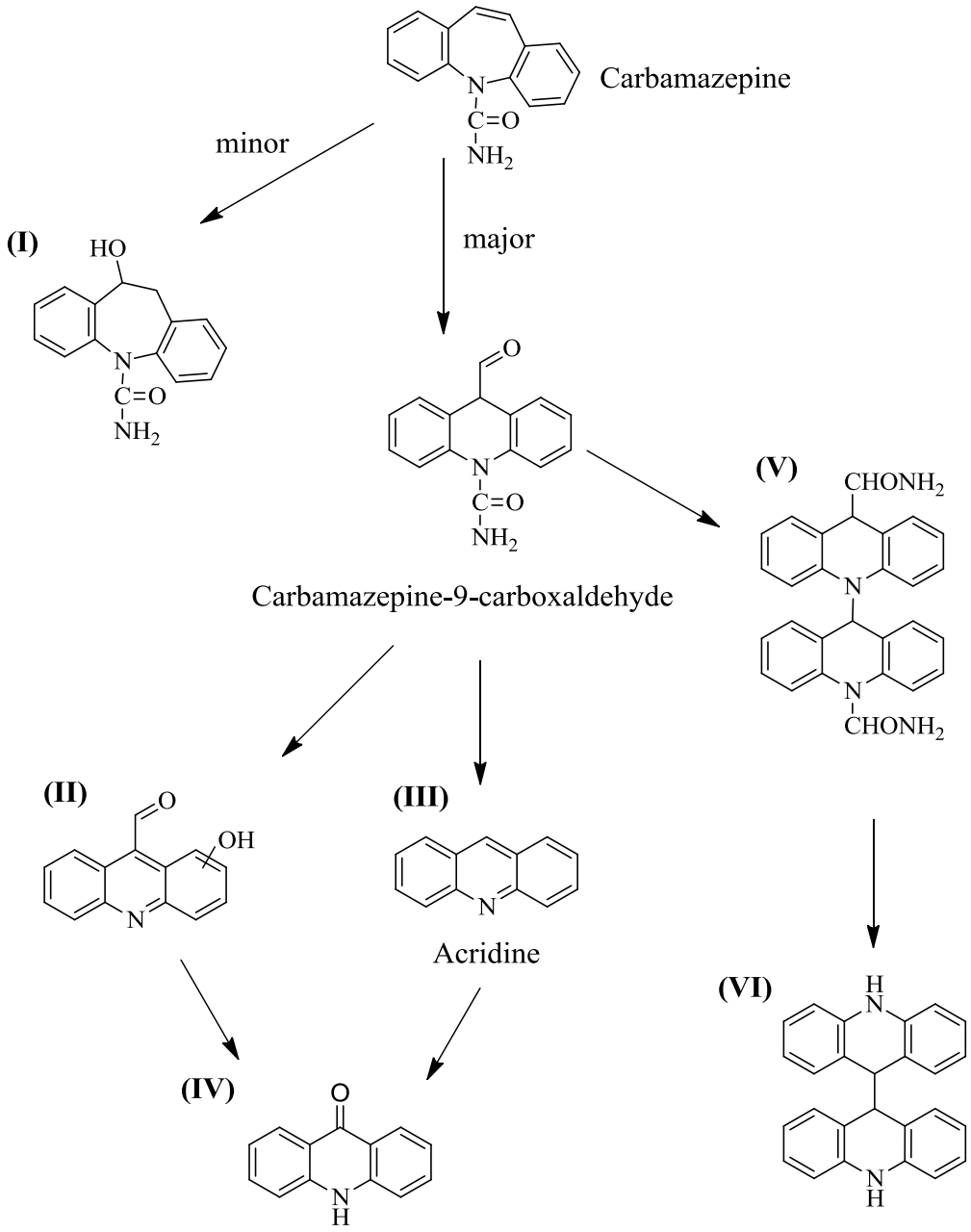


Figure 12. Direct photodegradation pathway of carbamazepine.[175] Redrawn with permission from Ref. 175. © 2006 American Chemical Society.

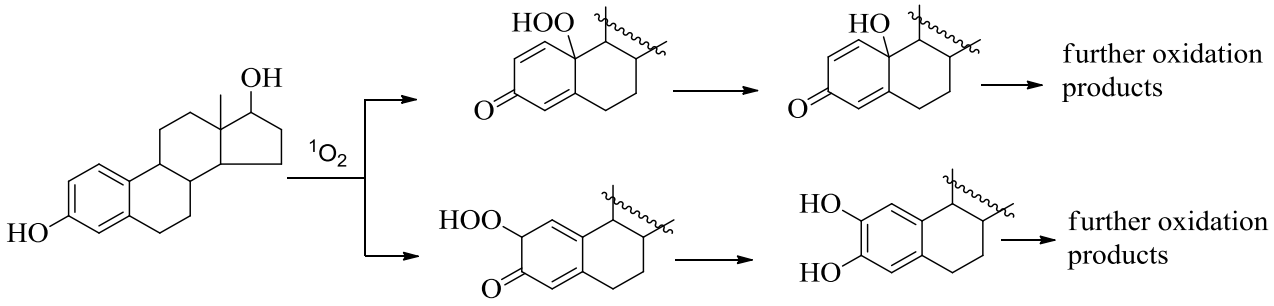


Figure 13. Proposed primary mechanism[184] in the Rose Bengal-sensitized photooxidation of 17β estradiol. Reproduced with permission from Ref. 184. © 2008 Elsevier B.V.

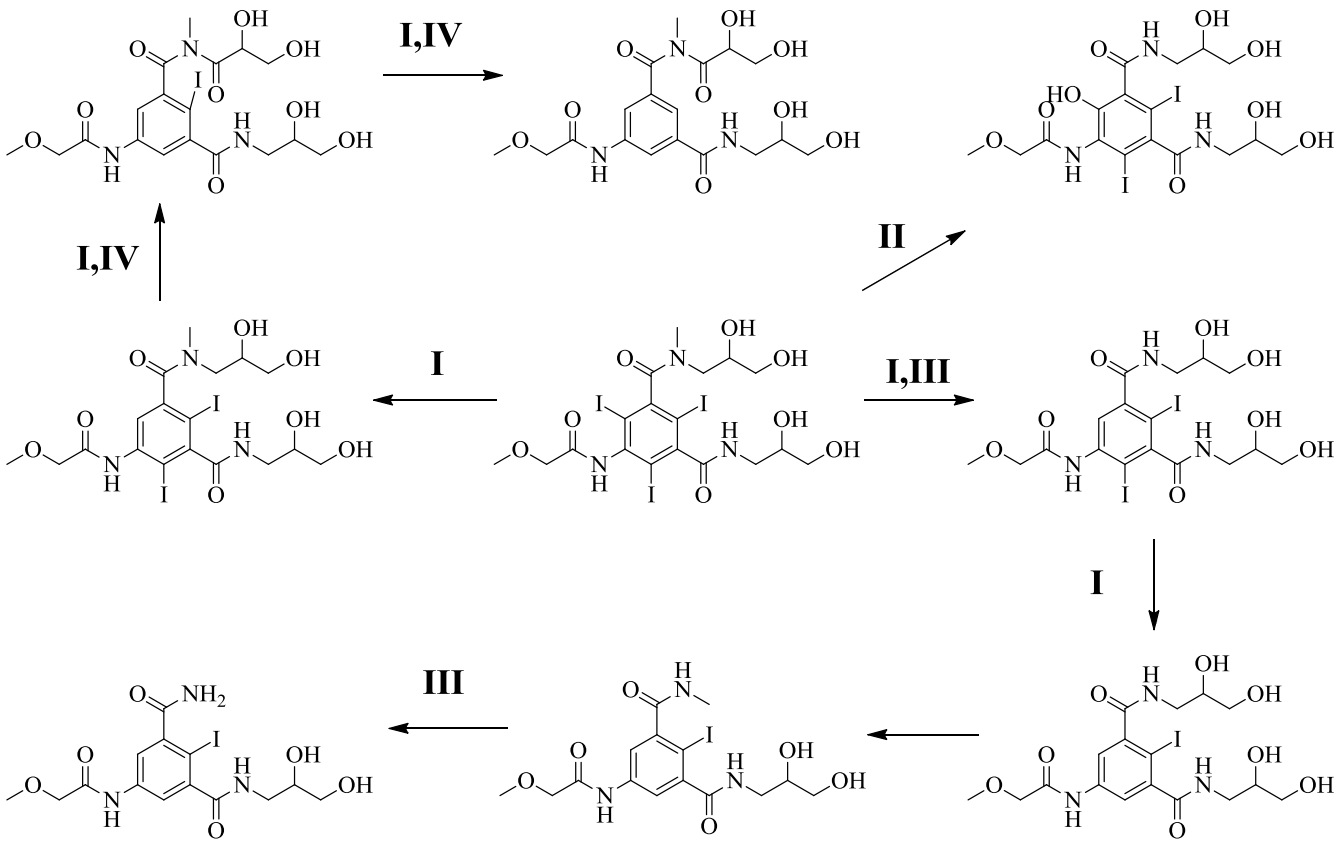
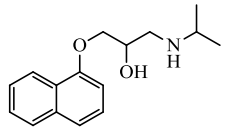
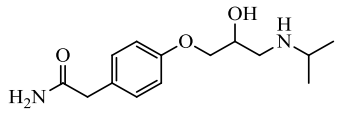
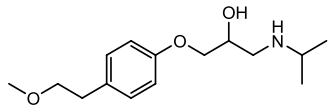
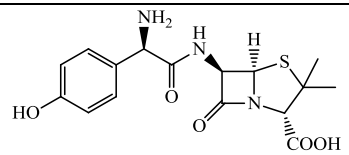
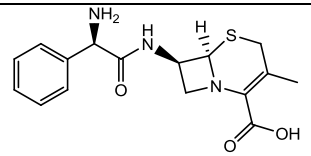
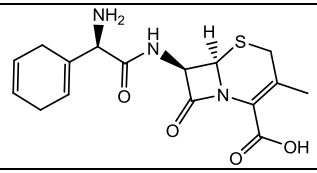
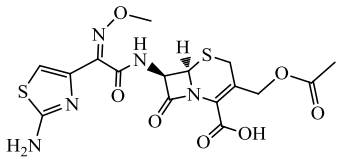
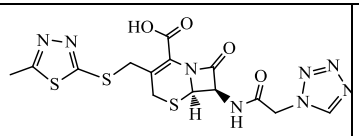
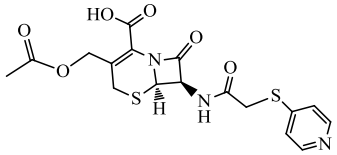
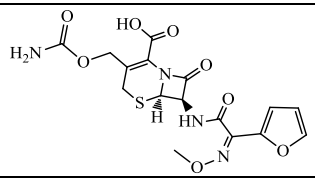
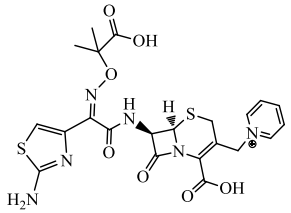
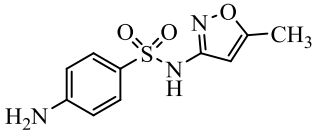
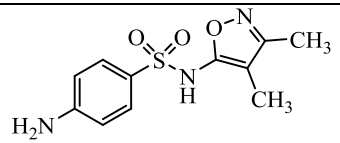
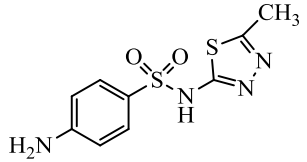
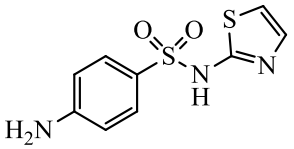
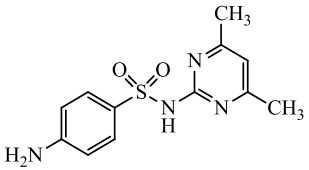
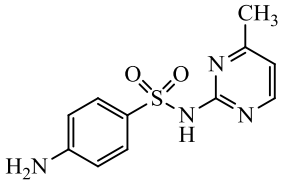
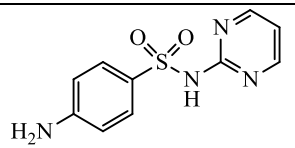
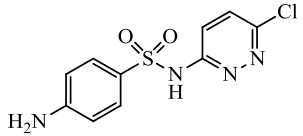
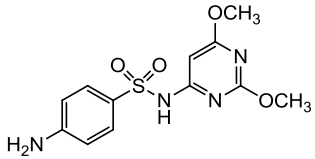
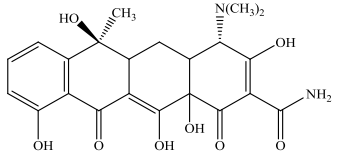
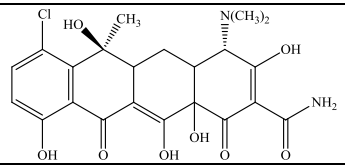


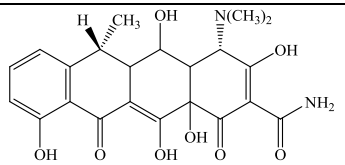
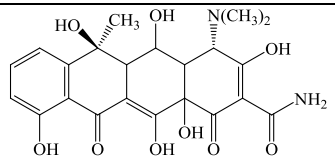
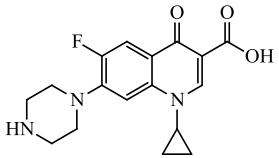
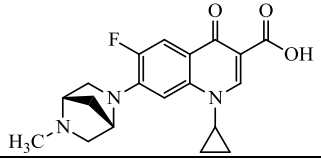
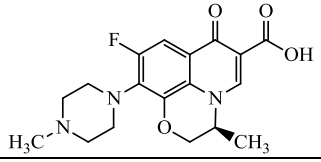
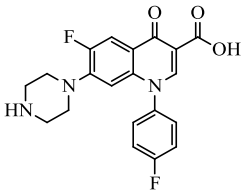
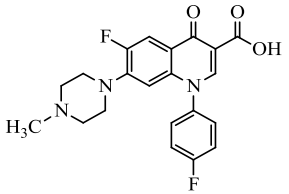
Figure 14. Proposed phototransformation products of iopromide,[206] the I-IV represent four photodegradation pathway described in the literature. In the depicted structure the position of the iodine atom on the aromatic ring is chosen arbitrarily. Reproduced with permission from Ref. 206. © 2009 John Wiley & Sons, Ltd.

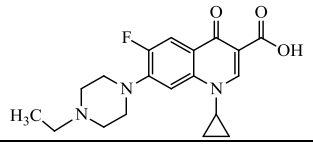
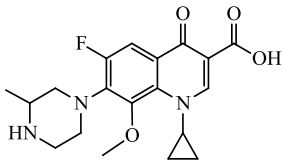
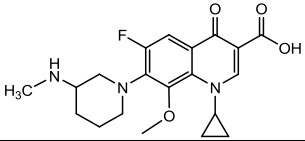
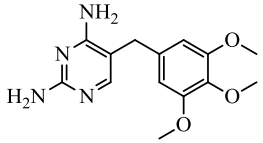
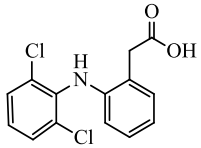
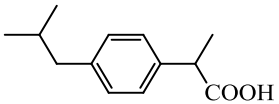
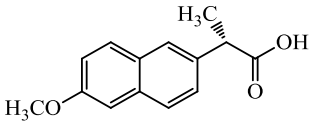
1122 **Table 1** Summary of photodegradation quantum yields of PhACs, and bimolecular reaction rates of •OH and $^1O_2$.

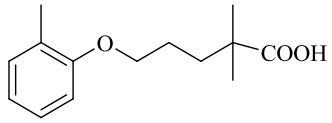
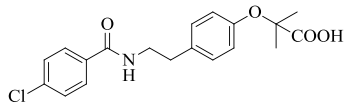
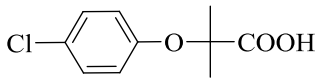
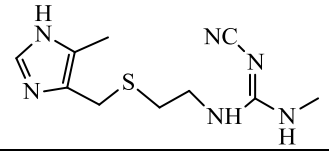
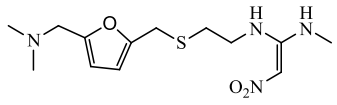
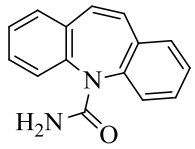
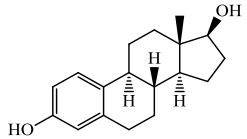
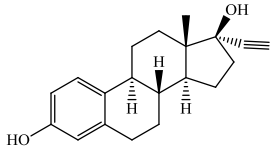
PhACs groups	Name	Structure	Φ	Ref.	•OH ($M^{-1}s^{-1}$)	Ref.	$^1O_2$ ($M^{-1}s^{-1}$)	Ref.
β-blockers	Propranolol		0.00222	211	$(1.07 \pm 0.02) \times 10^{10}$ $(8.7 \pm 0.3) \times 10^{9}$	212 211	$(9.3 \pm 0.4) \times 10^{6}$	211
	Atenolol		--		$(7.05 \pm 0.27) \times 10^{9}$	212	$(8.47 \pm 0.56) \times 10^{3}$	70
	Metoprolol		--		$(8.39 \pm 0.06) \times 10^{9}$	212	$(6.18 \pm 0.25) \times 10^{3}$	70
β-lactams	Amoxicillin		0.571	81	6.94×10^{9}	90	1.44×10^{3}	90
	Cephalexin		0.091	93	7.10×10^{9}	93	--	
	Cephradine		0.076		1.10×10^{10}		--	
	Cefotaxime		0.001		8.10×10^{9}		$(6 \pm 2) \times 10^{6}$	94

	Cefazolin		0.060		$(6.48\pm0.48)\times10^{9}$	213	--	
	Cephapirin		0.007		--		--	
	Cefuroxim		--		$(9.9\pm0.5)\times10^{9}$	94	$(5\pm2)\times10^{6}$	94
	Ceftazidime		--		$(1.0\pm0.05)\times10^{10}$		$(8\pm2)\times10^{6}$ $(1\pm2)\times10^{6}$	
5-membered heterocyclic sulfonamides	Sulfamethoxazole		SH_2^+ 0 SH 0.50 ±0.09 SH^- 0.09 ±0.01	95	$(8.5\pm0.3)\times10^{9}$	214	--	95
					$(5.8\pm0.3)\times10^{9}$	95		
	Sulfisoxazole		SH_2^+ 0.7 ±0.3 SH 0.17 ±0.03 SH^- 0.07 ±0.02		$(6.6\pm0.2)\times10^{9}$	95	$(5.5\pm0.4)\times10^{7}$	
	Sulfamethizole		SH_2^+ ≤0.01 SH ≤0.005 SH^- 0.05 ±0.01		$(7.9\pm0.4)\times10^{9}$	214	--	
					$(4.9\pm0.1)\times10^{9}$	95		

	Sulfathiazole		SH_2^+ 0.02 ± 0.02 SH 0.07 ± 0.03 SH^- 0.40 ± 0.04		$(7.1 \pm 0.2) \times 10^9$	95	$(6.9 \pm 0.3) \times 10^7$	
6-membered heterocyclic sulfonamides	Sulfamethazine		SH $(3 \pm 1) \times 10^{-4}$ S^- $(5 \pm 2) \times 10^{-3}$	98	$(5.0 \pm 0.3) \times 10^9$	98	6.0×10^7	98
					$(8.3 \pm 0.8) \times 10^9$	214		
	Suflamerazine		SH $(2.3 \pm 0.2) \times 10^{-4}$ S^- $(3.0 \pm 0.1) \times 10^{-3}$		$(3.8 \pm 0.4) \times 10^9$	98	9.1×10^7	
					$(7.8 \pm 0.3) \times 10^9$	214		
	Sulfadiazine		SH $(4 \pm 2) \times 10^{-4}$ S^- $(1.2 \pm 0.2) \times 10^{-3}$		$(3.7 \pm 0.5) \times 10^9$	98	8.9×10^7	
	Sulfachloropyridazine		SH $(3 \pm 3) \times 10^{-4}$ S^- $(2.3 \pm 0.3) \times 10^{-3}$		$(4.4 \pm 0.2) \times 10^9$		6.8×10^7	
	Sulfadimethoxine		SH $(1.0 \pm 0.3) \times 10^{-5}$ S^- $(4 \pm 1) \times 10^{-5}$		$(6.1 \pm 0.6) \times 10^9$		--	
Tetracyclines	Tetracycline		pH 6.0 3.4×10^{-4} pH 9.0 1.1×10^{-2}	106	$(6.3 \pm 0.1) \times 10^9$	215	$< 10^4$	216
	Chlortetracycline		pH 6.0 3.3×10^{-4} pH 9.0 8.5×10^{-3}	111	$(5.2 \pm 0.2) \times 10^9$		1.5×10^6	

	Doxycycline		--		$(7.6 \pm 0.1) \times 10^{9}$		1.4×10^{6}	
	Oxytetracycline		--		$(5.6 \pm 0.1) \times 10^{9}$		1.1×10^{6}	
Fluoroquinolones	Ciprofloxacin		$(5.48 \pm 1.92) \times 10^{-2}$	114	$(2.15 \pm 0.10) \times 10^{10}$	217	--	
	Danofloxacin		$(3.03 \pm 0.54) \times 10^{-2}$		$(6.15 \pm 0.11) \times 10^{9}$	218	--	
	Levofloxacin,		$(8.26 \pm 1.08) \times 10^{-3}$		$(7.59 \pm 0.16) \times 10^{9}$		--	
	Sarafloxacin		$(3.97 \pm 1.10) \times 10^{-2}$		--		--	
	Difloxacin		$(3.13 \pm 0.41) \times 10^{-2}$		--		--	

	Enrofloxacin		$(6.97 \pm 1.41) \times 10^{-2}$		$(7.95 \pm 0.23) \times 10^{9}$	218	--	
	Gatifloxacin		$(5.94 \pm 0.95) \times 10^{-3}$		--		--	
	Balofloxacin		$(4.72 \pm 0.56) \times 10^{-3}$		--		--	
	Trimethoprim		air saturated pH 5 6.2×10^{-4} pH 8 1.2×10^{-3} Deoxygenated pH 5 7.9×10^{-3} pH 8 7.0×10^{-2}	97	8.66×10^{9}	130	$(3.2 \pm 0.2) \times 10^{6}$	130
NSAIDs	Diclofenac		9.4×10^{-2} 0.0375	134	$(9.29 \pm 0.11) \times 10^{9}$	219	--	
	Ibuprofen		0.33 ± 0.05	145	$(7.4 \pm 1.2) \times 10^{9}$	177	--	
	Naproxen		0.036 0.026	134	7.99×10^{9}	220	$(1.1 \pm 0.1) \times 10^{5}$	134

Lipid regulators	Gemfibrozil		--		10.00×10^9	165	--	
	Bezafibrate		--		8.00×10^9		--	
	Clofibric acid		5.53×10^{-3}	161	6.98×10^9	165	--	
histamine H_2-receptor antagonists	Cimetidine		--		SH^+ $(6.5 \pm 0.5) \times 10^9$	158	S 2.5×10^8 SH^+ 3.3×10^6	158
	Ranitidine		SH^+ $(5.3 \pm 0.1) \times 10^{-3}$ S $(5.5 \pm 0.1) \times 10^{-3}$	158	SH^+ $(1.46 \pm 0.24) \times 10^{10}$	158	S $(6.4 \pm 0.4) \times 10^7$ SH^+ $(1.6 \pm 0.2) \times 10^7$	158
	Carbamazepine		pH 2.9 6.4×10^{-5} pH 4.0 2.9×10^{-6} pH 5.8 1.1×10^{-5} pH 9.0 2.0×10^{-6}	174	$(9.4 \pm 0.4) \times 10^9$ $(8.8 \pm 1.2) \times 10^9$ $(3.07 \pm 0.33) \times 10^9$	96 177 178	--	
Steroid hormones	17β-estradiol		0.067 ± 0.007	183	$(1.15 \pm 0.28) \times 10^{10}$	221	--	
	17α-ethinylestradiol		0.062 ± 0.007		$(1.52 \pm 0.23) \times 10^{10}$		--	

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Graphic Abstract