Toxicological and environmental risks of enalapril and their possible transformation products generated under phototransformation reactions

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ABSTRACT

Pharmaceutical active compounds (PACs) in the concentration range of hundreds of ng/L to μg/L have been identified in urban surface water, groundwater, and agricultural land where they cause various health risks. These pollutants are classified as emerging and cannot be efficiently removed by conventional wastewater treatment processes. The use of nano-enabled photocatalysts in the removal of pharmaceuticals in aquatic systems has recently received research attention owing to their enhanced properties and effectiveness. In the current study, toxicological and environmental risks of enalapril (ENL) and their possible transformation products (TPs) generated under phototransformation processes (e.g., photolysis and photocatalysis reactions) were assessed. In photolysis reaction, removal of ENL was incomplete (< 16 %), while mineralization degree was negligible. In contrast, total removal of ENL was achieved through the photocatalytic process and its maximum mineralization ratio was 66 % by using natural radiation. Proposed transformation pathways during the phototransformation of ENL include hydroxylation and fragmentation reactions generating transformation products (TPs) such as hydroxylated TPs (m/z 393) and enalaprilat (m/z 349). Potential environmental risks for aquatic organisms were not observed in the concentrations of both ENL and enalaprilat contained in surface water. However, the acute and chronic toxicities prediction of TPs such as m/z 409, 363, and 345 showed toxic effects on aquatic organisms. Thus, more studies regarding TPs monitoring for both ENL and PhACs with the highest occurrence worldwide are necessary for the creation of a database of the concentrations contained in surface water and groundwater for the assessment of the potential environmental risk for aquatic organisms.

1. Introduction

Pharmaceutical active compounds (PhACs) have been cataloged as "ubiquitous" pollutants detected in wastewater and aquatic environments worldwide. Their presence in water bodies from concentration levels from ng L^{-1} to μg L^{-1} may cause long term adverse effects in the aquatic environment. Industrialization, agricultural growth, and urban development have contributed to the highest occurrence of PhACs in water bodies [1]. The urban (e.g., scholar, home, office), hospital, and industries wastewater discharges on sewage municipal promotes high concentrations and great variability of PhACs as well as metabolites and their transformation products (TPs). Subsequently, these effluents are collected in the municipal wastewater treatment plants (WWTPs), where it is not entirely eliminated, and as consequence, PhACs, metabolites, and TPs arrival to water bodies [2–4]. PhACs transformation depends on factors such as drugs physicochemical properties, wastewater treatments, and its operation conditions, resulting in three possible outcomes: PhACs complete degradation, partial degradation to TPs or even being unaffected at all [5]. Thus, these compounds are discharged into aquatic environments, here, parent compound of PhACs, metabolites, their TPs can be naturally attenuated by environmental processes (e.g., biodegradation, sorption, dilution, photolysis, hydrolysis) resulting in an enhanced "mobility" due to polarity increase of the TPs [6]. Particularly, photolysis process is one of the most important natural

attenuation processes involving PhACs removal. Photolysis process are chemical reactions in which a compound is transformed by light. In photolysis direct reaction the PhACs absorb light, while in photolysis indirect reaction reactive oxygen species (ROS) are generated via photosensitization [7]. These reactions are heavily influenced dependent of PhACs molecular structures [8], for example in drugs that contained C=C conjugated double bonds, a C-heteroatom double bond, amine, sulfur groups, aromatic and heteroaromatic compounds [9].

In municipal WWTPs, treatments such as sludge adsorption and biodegradation are the most used for the PhACs removal [10]. However, PhACs removal using these treatments is incomplete in conventional WWTPs worldwide [10]. Recently, in the European Union (EU) through the Urban Wastewater treatment Directive (UWWT, 91/271/EEC) has stablished schemes for the removal de organic contaminants contained in WWTPs effluents, for example, the implementation of a quaternary treatment for the total removal of many emerging contaminants (ECs) from urban wastewater, considering removal efficiencies from 80 % for contaminants that represent significant part of the pollution, for example, PhACs [11]. Therefore, control emissions of PhACs from municipal WWTPs using advances technologies for the total removal of PhACs is necessary. Advanced Oxidation Processes (AOPs) are technologies able to of the total degradation of a wide range of PhACs through hydroxyl radical (HO$^\bullet$) [11–13]. For example, heterogeneous photocatalysis belongs to the class of AOPs. The generation of HO$^\bullet$ radicals and other ROS is performed through activation of a semiconductor material under a light source. The materials such as TiO_2 and ZnO are the most used catalysts to remove organic pollutants in water. Mainly, TiO_2 is used as photocatalysts due to low cost, null toxicity, and good chemical and physical stability [14].

Photocatalysis degradation of several PhACs has demonstrated the total degradation of many PhACs as well as mineralization ratios ranging from 15 % to 100 % [15–17]. Unfortunately, reaction time needed to degrade the parent compounds completely is insufficient for the total mineralization. Mineralization efficiency is a kay parameter of the photocatalytic reaction that showed the oxidation of the major TPs generated into simple molecules (e.g., carboxylic acids, H_2O, CO_2, inorganic ions) as well as compounds less toxic that the parent compound. Therefore, mineralization monitoring of PhACs as well as toxicity studies of the major TPs for each PhACs is essential for study of the compounds contained in WWTPs effluents that are discharged into aquatic environments. Unfortunately, TPs monitoring of PhACs is scarcely studied. Especially, for PhACs such as sulfamethoxazole, carbamazepine, diclofenac, tramadol, venlafaxine, citalopram, has been reported that their metabolites and TPs are quantified in WWTPs effluents worldwide, demonstrating that PhACs, metabolites and their TPs can be discharged into aquatic environments [18].

Especially, enalapril (ENL) is a drug with antihypertensive activity that can experiment phototransformation reactions in municipal WWTPs and aquatic environments because has been detected in hospital wastewater, municipal WWTPs, and surface water in concentrations ranging from 0.002 to 0.43 µg L^{-1}, while their major metabolite, enalaprilat has been quantified at WWTPs effluent and surface water from 0.01 to 0.38 µg L^{-1} (see supplementary material Table **A1**). ENL has been studied under different processes for their degradation in aqueous solution (e.g., biotransformation, photoelectro-Fenton, photolysis, photocatalysis, non-thermal plasma, stress stability, forced degradation) demonstrating their total removal [19–26]. During the reaction monitoring, two major TPs has been identified, for example the major impurity, enalaprilat as well as their hydroxylated TPs. Unfortunately, toxicity tests of the major TPs of ENL are scarcely studied. Recent studies have demonstrated that TPs of several PhACs generated during the AOPs can be more or less toxic to aquatic biota (e.g., fish, daphnia, green algae) compared to parent compound of the PhACs. In addition, mixtures of several TPs may cause potential toxic effects in aquatic organisms consequence synergistic, additive, or antagonistic effect, demonstrating that toxicity of a single TP might be lower than the effects

of a mixture of the TPs [27–30]. Therefore, more studies on the generation of the major TPs of PhACs and toxicity assessment for these compounds are necessary because WWTPs effluents, hospital wastewater, and drugs manufacturing wastewater contained several PhACs as well as their TPs. In addition, toxicity tests for the major TPs of organic compounds with the highest occurrence in water bodies could help to implementation of environmental programs in aquatic environments and knowledge generation on toxicological risks in aquatic biota.

For this reason, in this study, toxicological and environmental risks of ENL and their possible TPs generated under photransformation reactions (photocatalysis and photolysis reactions) were studied. Unfortunately, ENL has been studied scarcely under photolysis and photocatalysis reactions generating uncertainty about their major TPs generated under phototransformation processes as well as its toxicological and environmental risks. In addition, the degradation of ENL during the photolysis and heterogeneous photocatalysis processes using chitosan microbeads with C,N-codoped TiO_2 as catalyst [31] and under natural sunlight radiation and simulated in both processes was compared. The main goals of this research were: 1) obtain degradation efficiency of ENL both photolysis and photocatalytic processes; 2) a proposal of the major transformation pathways of ENL under phototransformation processes; 3) toxicities prediction of ENL and their major TPs as well as its environmental risk assessment.

2. Material and methods

2.1. Reagents

ENL was of high purity grade (>90 %) and purchased from USP reference standards. All solutions were prepared with ultrapure water (18 MΩ) from a Milli-Q-system. Acetonitrile and acetic acid of chromatography quality were purchased from Sigma Aldrich.

2.2. Catalyst synthesis and preparation of the chitosan microbeads with TiO_2

The chitosan microbeads with C,N-codoped TiO_2 catalyst were synthesized using the same sol-gel method described by Aba-Guevara et al. (see more details in supplementary material **Text. A1**). Subsequently, characterization tests were conducted for the catalyst (see supplementary material **Text A2**, **Fig. A1 and A2**).

2.3. Photolysis and photocatalysis experiments

Photolysis and photocatalysis tests were carried out in a cylindrical quartz batch reactor containing 100 mL at an initial concentration of 5 mg L^{-1} of ENL adjusted at pH 7 (concentration and pH value were used as reference according to PhACs and physicochemical parameters detected in drugs manufacturing wastewater [32–35]. In the photocatalytic experiments, reaction suspension was prepared by adding 1 g L^{-1} of chitosan microbeads catalyst in the ENL aqueous solution which was stirred for 30 min in the dark. For the photolysis tests, ENL dissolution was only irradiated by the natural and simulated light. In both reactions, the solutions were continuously stirred during the phototransformation reactions. The simulated sunlight radiation was provided by a Sciencetech Solar Simulator SS150 (G-Lab, Saarbrücken, Germany) equipped with a Xenon arc lamp (150 W) simulating natural sunlight (includes ultraviolet, visible, and near-infrared light). The irradiation control system for monitoring and controlling the emission of the lamp operated a 340 nm. The natural sunlight radiation was obtained in totally sunny and clear days during spring 2022. The UV radiation was measured with a Kipp & Zonen CUV 5 global UV radiometer, and the average UV irradiation intensity was 35 W m^{-2}. In both processes, aliquots were taken from the initial solution after 5, 10, 20, 30, 60, 90, 120, and 150 min of reaction. In the photocatalysts tests, the sample aliquots were filtered before analysis with a syringe filter of

0.2 μm pore size (Minisart RC 4, Satorius, GB). The amount of ENL in the solution was analyzed after the powder was added to consider possible ENL adsorption by the catalyst. This quantity was set as the initial concentration.

2.4. HPLC analysis

During the photolysis and photocatalysis reactions, degradation efficiency was evaluated through ENL concentration monitoring using a Waters Alliance e2695 high-performance liquid chromatography (HPLC) system coupled to a photodiode array (PDA) detector with the detection wavelength set to 206 and 210 nm. The chromatographic separation was performed in reversed-phase using a C-18 Kinetex (50 mm×4.6 mm, i.d. 2.6 μm) column (Phenomenex), and injection volume of 20 μL. The mobile phase components were (A) pure acetonitrile and (B) dissolution of 0.1 % acetic acid with elution on linear gradient mode at 1.0 mL min^{-1} flow rate and run time of 10 min. The elution gradient mode was: initial (10 % A), 10 min (11 % A). Additionally, the mineralization grade was monitored by measuring Total Organic Carbon (TOC) using a Shimadzu TOC-VCSH system.

2.5. Environmental risk assessment of ENL and its TPs

Environmental risk assessment of ENL and its TPs were assessed as the potential risks of the residues contained in surface water against aquatic organisms. Initially, environmental risk assessment was obtained following the recommendations of the European Regulatory Guidance, The European Technical Guidance Document on Risk Assessment [36] (see more details supplementary material **Text. A3** and **Table A2**). The Risk Quotient (RQ) was calculated using the Eq. 1:

$$RQ = MEC/PNEC \qquad (1)$$

where MEC is measured environmental concentration and PNEC is to the predicted no effect concentration values of ENL and their TPs. Predetermined criteria were adopted to assist in the ranking of risks: RQ < 0.1, low risk; 0.1 ≤ RQ < 1, medium risk; and RQ ≥ 1, high risk [37–39].

2.6. Toxicity prediction of ENL and their TPs

Ecological Structure Activity Relationships (ECOSAR) class program is a computerized predictive system that estimates aquatic toxicity of organic compounds (https://www.epa.gov/tsca-screening-tools/ecological-structure-activity-relationships-ecosar-predictive-model). In the current work, ECOSAR tests was development using SMILES notation, obtained from the National Cancer Institute (https://cactus.nci.nih.gov/translate/). ECOSAR was used as a tool for prediction of the potential toxicological effects such as acute and chronic toxicities of ENL and their TPs against aquatic organisms such as fish, algae and Daphnid. Acute and chronic toxicities were classified as: > 100 mg L^{-1} are considered non-toxic, from 10 to 100 mg L^{-1} are contemplated to have harmful effects, from 1 to 10 mg L^{-1} are considered toxic, and < 1 mg L^{-1} are contemplated to very toxic [27–30].

3. Results and discussion

3.1. Photolysis process

ENL absorbs light from UV spectrum region e.g., at λ_{max}= 206 nm (UV-C), showing that could directly absorb sunlight that is the basis for the photolysis process (absorption spectrum of ENL see supplementary material, **Fig. A3**). Photolysis reactions of ENL were conducted to initial concentration of 5 mg L^{-1}, pH 7, under natural sunlight radiation and simulated. During the photolysis process, ENL was not completely removed (Fig. 1).

Specifically, under natural sunlight radiation ENL was removed 4 %,
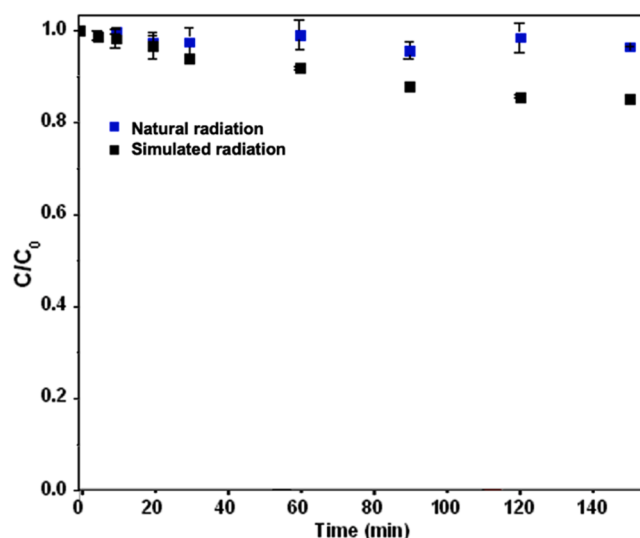

Fig. 1. Photolysis processes of ENL (initial concentration of 5 mg L^{-1}, pH 7, under natural sunlight radiation and simulated).

while using simulated sunlight was degraded 16 %. Unfortunately, this drug has been little studied during their photolysis reaction in aqueous solutions. Particularly, a study reported by Pérez et al. (2007) conducted the phototransformation of ENL at initial concentration of 40 mg L^{-1} under simulated sunlight radiation. The results showed than 90 % of ENL was removed after of 40 h of irradiation [21]. These results suggest that for the total transformation of ENL during the photolysis process are necessary largest time of reaction using simulated sunlight radiation, while under radiation natural could be a recalcitrant compound in aquatic environments.

3.2. Photocatalysis process

In the photocatalytic process, chitosan microbeads C,N-TiO$_2$ was used as catalyst. In this reaction, ENL was entirely removed (Fig. 2).

Initially, the amount of ENL adsorbed on the catalyst was negligible (6 %) at the used concentration. During the photocatalytic reaction under natural sunlight ENL was totally removed in the first 120 min of reaction, while using simulated sunlight radiation was entirely degraded at 150 min of reaction. Particularly, Hernández-Tenorio, R. (2020),
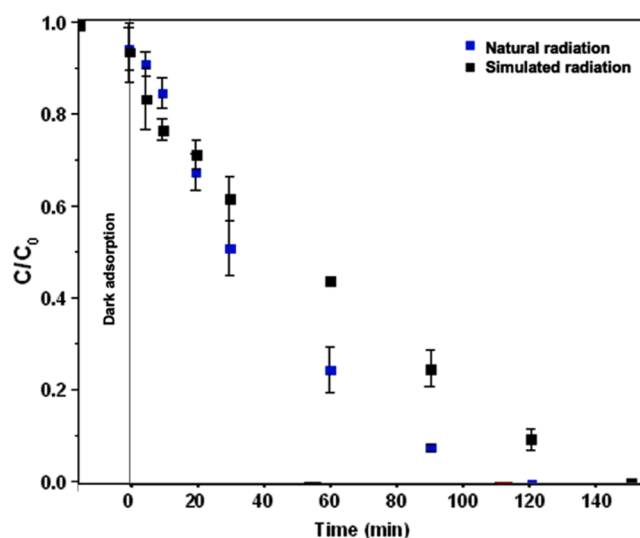

Fig. 2. Photocatalytic processes of ENL (1 g L^{-1} catalyst, initial concentration of 5 mg L^{-1}, pH 7, and under natural sunlight radiation and simulated).

performed the photocatalytic reaction of ENL using bare ZnO and ZnO modified by incorporating 10 wt% fluorine, initial concentration of 10 mg L^{-1}, pH 8, 1 g L^{-1} catalyst, and simulated sunlight radiation. The total removal of ENL with both catalysts was achieved in the first 250 kJ m^{-2} of accumulated energy, while at the end of reaction the mineralization ratio was < 30 % with both catalysts [26]. In contrast to photolysis process, in the photocatalytic reaction, the generation of the ROS such as hydroxyl radicals (HO$^{\bullet}$), superoxide, (O$_2^{\bullet}$), singlet oxygen (^{1}O$_2$) as well as photoactivated holes (h^+) allows that could be accomplished the total oxidation of organic pollutants [14], thus, the removal efficiency was the highest in this process during the photo-transformation of ENL. Additionally, the mineralization of ENL was assessed by using total organic carbon (TOC) monitoring in both processes. In photolysis reaction, the TOC abatement was negligible using both radiations. This behavior suggests that the parent compound of ENL is not experiencing chemical oxidation. Despite < 16 % of ENL was degraded in photolysis process, this drug only is being transformed structurally, for example, the breakdown of bonds, intramolecular reactions, the loss of a heteroatom, functional group, or the molecule fragmentation by the action of the light [40]. Previous reports have determined that the TPs generated during the photolysis reaction of PhACs could be recalcitrants in aqueous solution [41–43]. In contrast, in photocatalytic reaction, the mineralization of ENL was 41 % under simulated sunlight radiation, while using natural radiation was 66 %. These results confirm that many TPs are oxidize during the reaction. As with ENL, TPs could be removed during the photocatalysis reaction because ROS (e.g., HO$^{\bullet}$, O$_2^{\bullet}$) can accomplish the oxidation of all the generated subproducts. Therefore, is necessary a proposal of the major TPs of ENL generated under phototransformation processes for understander the major transformation pathways of ENL.

Table 1
Major TPs of ENL generated under several transformation processes.

3.3. Proposed phototransformation pathways of ENL

The phototransformation of ENL is a topic scarcely studied worldwide. Some studies have been reported the TPs monitoring of ENL under transformation processes such as photolysis, photoelectro-Fenton, stress stability, forced degradation, hydrolytic degradation, non-thermal plasma and photocatalysis (see more details supplementary material **Text A4 and Table A3**). A summary of the major TPs detected for ENL under several transformation processes is showed in Table 1.

Particularly, hydroxylated TPs (TP 393) and several impurities (TP 359, 349) are the major TPs detected under several transformation processes of ENL. For example, hydroxylated TPs has been identified in processes such as photolysis, forced degradation, photocatalysis, and non-thermal plasma. Currently, hydroxylated TPs of PhACs has been considered as primary compounds generated under several processes used in municipal WWTPs such as ozonation, chlorination, photolysis, and biological processes [44]. On the other hand, impurities of ENL are detected under stress stability, forced degradation, hydrolytic degradation, and phototransformation processes. Especially, for several PhACs their major metabolites are detected, for example, for sulfamethoxazole, the major metabolite is N-acetyl-sulfamethoxazole, for fluoxetine is the norfluoxetine [44]. Thus, for ENL, their major metabolite is the enalaprilat (TP 349), the generation of this compound can be considered as a primary transformation under several conditions (e.g., temperature, oxidation, photolysis).

In this study, especial attention will be paid to treatments such as photolysis and heterogeneous photocatalysis. In photolysis reaction, the impurity TPs *m/z* 359 and the major metabolite, *m/z* 349 seem to be associated with the parent compound of ENL that undergoes processes as cyclization and ester hydrolysis to give diketopiperazine derivative and the metabolite enalaprilat, respectively [24]. In photocatalysis reaction the major TPs detected are hydroxylated compounds (*m/z* 393), these TPs are generated consequence of HO• radical attack in the parent compound of ENL [26]. Thus, in the first step of each reaction let us assume that the ENL can be transformed following two main degradation pathways during the photolysis and photocatalysis reactions (Fig. 3).

Especially, under AOPs such as photolysis, photocatalysis, and non-thermal plasma have been identified several hydroxylated TPs, these compounds is isomers TPs probably by hydroxylation at different

position of the parent compound of ENL. Generally, using reverse-phase chromatography column hydroxylated TPs can be visible as two or more chromatographic peaks with the same molecular mass but lower retention time that parent compound of ENL [25,26]. In addition, during the photolysis reaction, hydroxylated TPs of ENL can be generated through of the singlet excited state ([1]ENL) and subsequent triple excited state ([3]ENL), which can react with dissolved oxygen to form ROS; particularly, HO• radical could generate the hydroxylated TPs during the photolysis reaction [26,42]. Therefore, the contained concentrations in aquatic environments of ENL could favor the formation of their hydroxylated TPs due to the dissolved organic matter (DOM) in the water bodies is known as a source of light-absorbing components and provides ROS as HO• radicals [45]. According to TPs identified during the photolysis and photocatalysis two major phototransformation pathways of ENL were proposed (Fig. 4).

The degradation pathway I, involve the photolysis reaction; the major metabolite of ENL, the TP *m/z* 349 is generated by hydrolysis reaction of ester group of the parent compound [21,24], while TP *m/z* 359 (diketopiperazine impurity) is formed by dehydration and subsequently cyclization intramolecular of the parent compound of ENL [22]. On the other hand, the degradation pathway II involve the photocatalytic reaction; hydroxylated TPs *m/z* 393 are generated by HO• radical attacking on the ring aromatic of the parent compound [25,26], Subsequently, a fragmentation process by decarboxylation reaction was proposed for the hydroxylated TPs generating the TP *m/z* 345 [26]. In the degradation pathway II, a second HO• radical attack was proposed for the hydroxylated TPs *m/z* 393, generating the dihydroxylated TPs *m/z* 409. During the photocatalytic processes the electrophilic addition reaction between organic pollutants and HO• radical allows the generation of mono and dihydroxylated TPs [46,47]. In addition, dihydroxylated TPs *m/z* 409 can be the initial point for the generation of other TPs. For example, the photooxidation reaction of TP *m/z* 409 allows the generation of TP *m/z* 411, while a fragmentation process can be undergone as decarboxilation reaction or by simultaneously occurring photolysis generating TP *m/z* 363 [26]. Additionally, the TP *m/z* 280 has been detected in several AOPs processes, their formation is consequence of a hydrolysis reaction of the proline group of the parent compound of ENL [24–26]. This compound has been considered as other impurity of ENL [25]. Generally, ENL shows instability on exposure to high temperature and humidity, generating to two major TPs such as enalaprilat
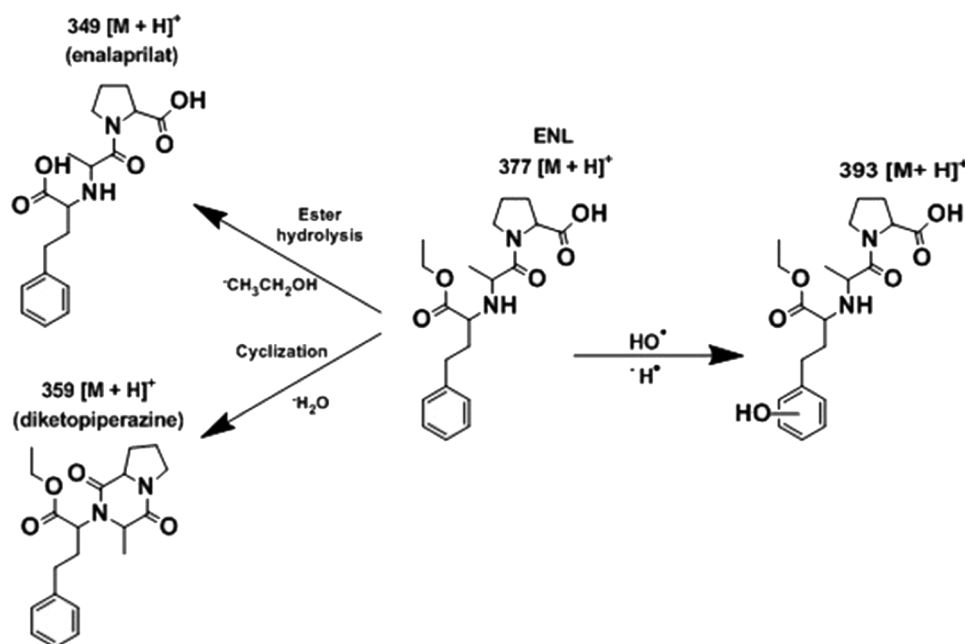

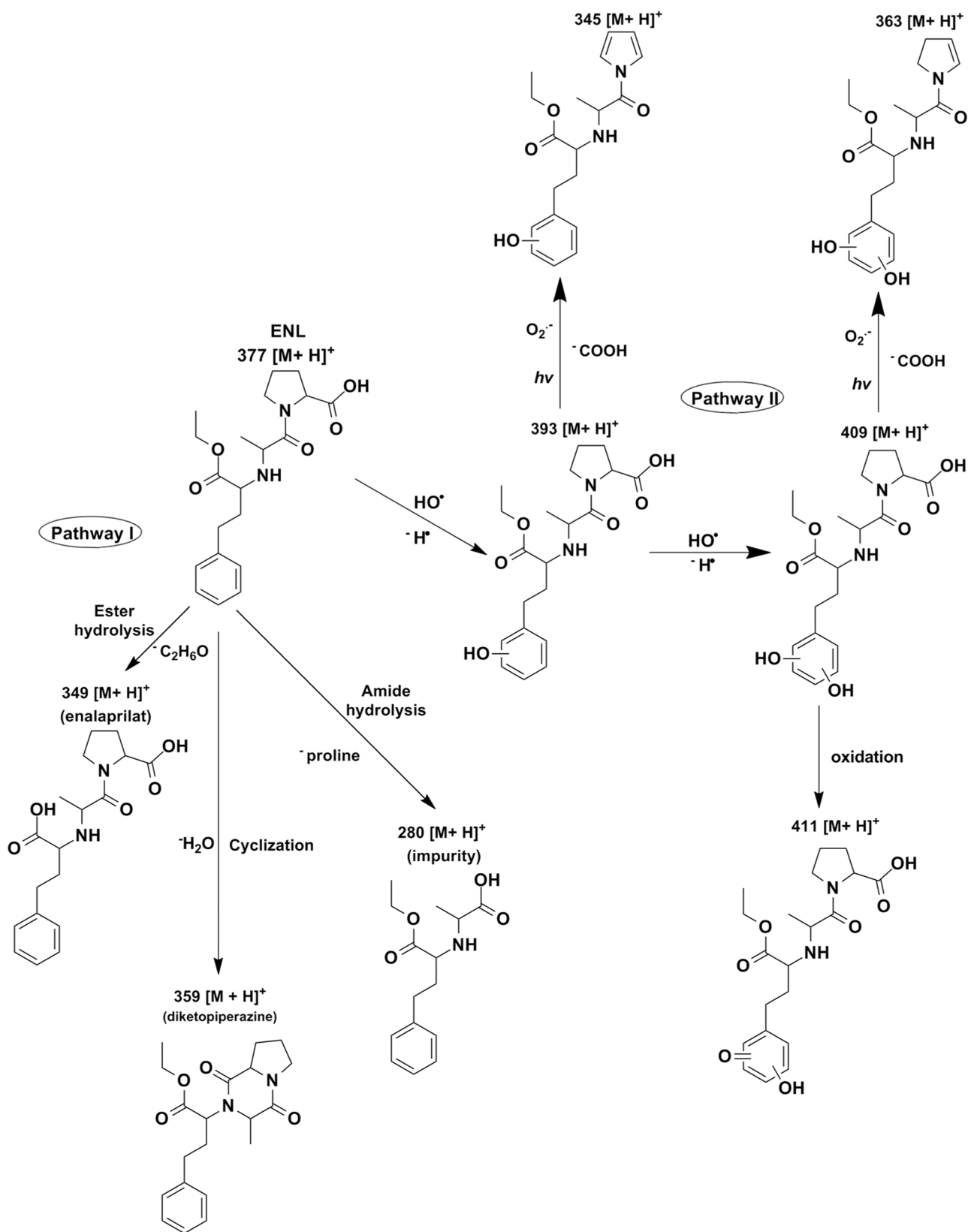**Fig. 3.** Initial phototransformation pathways of ENL during the photolysis and photocatalysis processes.

Fig. 4. Proposed phototransformation pathways of ENL under phototransformation processes.

(m/z 349) and diketopiperazine derivate (m/z 280) [24].

3.4. Environmental risk assessment of ENL and their TPs

During the PhACs monitoring worldwide, concentrations of ENL and their TPs has been scarcely identified in aquatic environments. In some

studies, ENL and their main metabolite, *m/z* 349 enalaprilat has been detected in WWTPs effluent and surface water [48–56] (see supplementary material Table **A1**). For example, from a WWTP effluent of Catalonia, Spain, ENL was detected in concentration from 0.25 µg L^{-1}, while enalaprilat was quantified around 0.38 µg L^{-1} [51]. On the other hand, in surface water of Spain, ENL was quantified in concentration around 0.002 µg L^{-1}, while enalaprilat was detected in concentrations ranging from 0.011 to 0.012 µg L^{-1} [49,50]. In surface water of Romania, ENL was identified around 0.064 µg L^{-1}, while enalaprilat was quantified from 0.14 µg L^{-1} [51]. The above PhACs monitoring suggest that TPs of ENL can be identified with the highest concentrations compared to parent compound of ENL. Therefore, is essential the environmental risks assessment both ENL and their TPs. Currently, this topic has been reported using concentrations data of several PhACs quantified in aquatic environments of different geographical regions worldwide [37–39]. Thus, following these methodologies (Section 2.5) were assessed the environmental risks of ENL and enalaprilat against aquatic organisms using the quantified concentrations in surface water worldwide (Table 2).

Potential environmental risks both ENL and enalaprilat are negligible against aquatic organisms. Currently, in countries of Asia (India, Pakistan, Sri Lanka, Bangladesh) and Latin America (Mexico) has been reported several environmental risks of PhACs quantified in surface water against different species such as fish, algae, and crustaceans [38, 57]. For example, in Mexico, for naproxen, ibuprofen, diclofenac, acetaminophen, carbamazepine, ketoprofen, and caffeine quantified in surface water of different regions of Mexico were observed several

environmental risks (RQ > 1) against fish, algae, and crustaceans [57]. In Asian region, for example, in surface waters of Pakistan, for diclofenac were observed the potential environmental risks (RQ = 13320) against aquatic biota, while in surface waters of Sri Lanka, ibuprofen, diclofenac, clarithromycin, carbamazepine, and atorvastatin showed environmental risks against aquatic biota [38]. Unfortunately, in the above studies, ENL was not included, confirming the few data available on residues both ENL and its TPs in aquatic environments. Therefore, is very important that during the PhACs monitoring in aquatic environments is necessary to select other PhACs and organic compounds as well as metabolites and TPs for the generation of more studies on potential environmental risks worldwide. Thus, this study can be considered as a primary reference for ENL and its major TPs generated under phototransformation reactions.

3.5. Toxicity prediction

The lack of data on concentrations in aquatic environments as well as toxicological data of ENL and its TPs against aquatic organisms suggest the implementation of tools to obtain acute and chronic toxicity predictions against aquatic organisms. Thus, for ENL and its TPs were obtained acute toxicity values (half lethal concentration (LC50) values for fish and Daphnid, median effective concentration (EC50) value for Green Algae), while chronic toxicity (ChV) were obtained for fish, Daphnid, and Green Algae. A summary on the acute and chronic toxicity predictions of ENL and their TPs is show in Table 3.

The results obtained from ECOSAR software showed less or similarly acute and chronic toxicity values for ENL and their TPs. Especially, for ENL, enalaprilat, TPs 411, 393, and 280 acute and chronic toxicities values were non-toxic against aquatic organisms. Only, for ENL, chronic toxicity value was harmulf (< 100 mg L^{-1}) against Daphnid. However, for TPs 409, 363, 359, and 345 potential toxicities were observed against aquatic organisms. For example, for TP *m/z* 409 acute toxicity value was harmful against green algae, while chronic toxicity values were harmful against fish, Daphnid, and green algae. For TP *m/z* 363 acute toxicity values as harmulf were observed for fish, Daphnid, and green algae, while chronic toxicity values as toxic (< 10 mg L^{-1}) were observed for fish, Daphnid, and green algae. For TP *m/z* 345 acute toxicity values as harmful were obtained for Daphnid, and green algae, while chronic toxicity values were harmful and toxic against fish, green algae and Daphnid, respectively.

Recently, results similar were observed during the phototransformation process for other PhACs and organic compounds (Table 4).
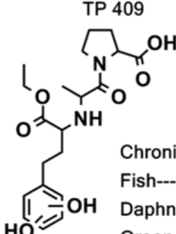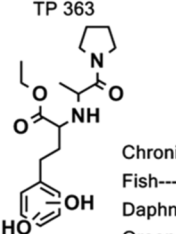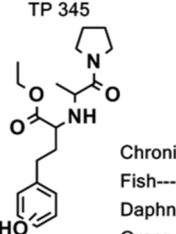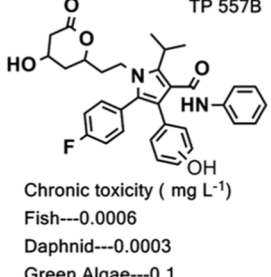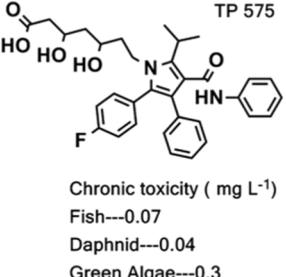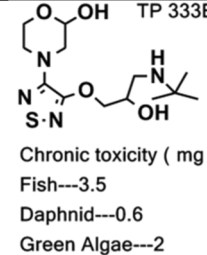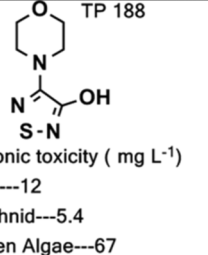
Chronic toxicity values were similar for TPs of ENL and TPs of the PhACs as timolol and atorvastatin as well as for a fungicide

Table 2
Environmental risk assessment of ENL and enalaprilat detected in surface water (RQ values were classified as RQ < 0.1, low risk, 0.1 ≤ RQ < 1, medium risk, and RQ ≥ 1, high risk).

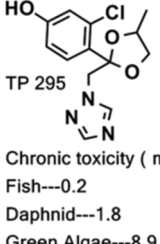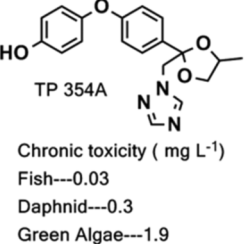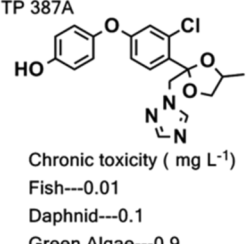| PhACs	Sampling site	PNEC (µg L^{-1})	Species	MEC (µg L^{-1})	RQ
[a]ENL	Surface water/ Ebro river basin, Spain.	1230	Fish	0.002	0.000001
		643	Algae		0.000003
		728	Crustacean		0.000002
[a] Enalaprilat		126000	Fish	0.012	9.5E−8
		13200	Algae		9.1E−7
		54400	Crustacean		2.2E−7
[b] ENL	Surface water/ Transylvania, Romania.	1230	Fish	0.064	0.00005
		643	Algae		0.00009
		728	Crustacean		0.00008
[b] Enalaprilat		126000	Fish	0.14	0.000001
		13200	Algae		0.00001
		54400	Crustacean		0.000002
[c] ENL	Surface water/ Negeri Sembilan, Malaysia.	1230	Fish	0.014	0.00001
		643	Algae		0.00002
		728	Crustacean		0.00001
[d] ENL	Surface water/ River Lambro, Italy.	1230	Fish	0.0036	0.00002
		643	Algae		0.00005
		728	Crustacean		0.00004
[e] ENL	Surface water/ Southwestern Finland.	1230	Fish	0.013	0.00001
		643	Algae		0.00002
		728	Crustacean		0.00001
[f] ENL	Surface water/ City of Milan, Italy.	1230	Fish	0.007	0.000005
		643	Algae		0.00001
		728	Crustacean		0.000009
[g] ENL	Surface water/ Rivers Torococha and Coata, Peru	1230	Fish	0.04	0.00003
		643	Algae		0.00006
		728	Crustacean		0.00005

[a] [49,50]
[b] [51]
[c] [52]
[d] [53]
[e] [54]
[f] [55]
[g] [56].

Table 3
Acute and chronic toxicity predictions of ENL and its TPs by ECOSAR software (non-toxic > 100 mg L^{-1}, harmful 10–100 mg L^{-1}, toxic 1–10 mg L^{-1}, and very toxic < 1 mg L^{-1}).

Compound	Acute toxicity (mg L^{-1})			Chronic toxicity (mg L^{-1})		
	Fish (LC50, 96 h)	Daphnid (LC50, 96 h)	Green Algae (EC50, 96 h)	Fish	Daphnid	Green Algae
ENL	1230	728	643	126	79	185
Enalaprilat	1260000	544000	132000	89000	24900	18800
TP 411	259000	121000	404000	20100	6880	6870
TP 409	217	123	92	21	12	24
TP 393	3460	1960	1440	337	189	375
TP 363	62	37	35	6	4	10
TP 359	1480	784	434	133	62	96
TP 345	134	79	67	13	8	19
TP 280	111000	53100	19300	8850	3200	3440

Table 4
Chronic toxicity prediction of several organic compounds by ECOSAR.

(difenoconazole), demonstrating that the TPs generated under photo-transformation reaction could be potentially toxic under longer exposure times into aquatic environments [28,58,59]. These results can be used as reference for the more studies on the major and toxic TPs of ENL generated under phototransformation reactions. However, is very important consider that the combination of the TPs may cause the highest toxic effect, for example, synergistic or additive effect, thus, more studies on chronic bioassays are needed for each single compound [28]. Therefore, further efforts are necessary to improve planning, and management of environmental monitoring programs for the quantification and identification of the major TPs of ENL as well as PhACs with highest occurrence in aquatic environments, for the creation of a databases on the concentration ranges of these compounds in surface water, allowing the environmental risk assessment on aquatic biota.

4. Conclusions

In the present study, incomplete removal of ENL under photolysis process using natural sunlight radiation and simulated was observed. In contrast, total removal of ENL under photocatalytic reaction was achieved. The highest mineralization ratio of ENL using natural sunlight radiation was reached. This research is an important reference on the proposal of the major transformation pathways of ENL under photo-transformation processes, demonstrating that hydroxylation and fragmentation reactions can be used as reference during the generation of the major TPs of ENL. Especially, hydroxylated compounds (TPs 393) and impurities such as enalaprilat (TP 349) and diketopiperazine (TP 359) can be major TPs generated in photolysis and photocatalysis processes, respectively. ECOSAR software showed chronic toxicity potential of TPs of ENL, especially, TPs m/z 409, 363, and 345. In the future, these compounds can be used for toxicity tests both in mixture as single

Overall, this study illustrates that, ENL is a PhAC monitored scarcely in aquatic environment worldwide, thus, their presence in wastewater generates uncertainly on the TPs that can be discharged into water bodies. AOPs can be effective treatment for the total removal of ENL in aqueous solutions. For first time, a proposal of the major TPs of ENL is described under phototransformation reactions, allowing the generation of more knowledge on major TPs of PhACs detected in aquatic environments. In addition, ECOSAR tool showed to three TPs of ENL (e.g., TPs m/z 409, 363, and 345) as candidates for future toxicity tests, demonstrating that it's important not only to treat as priority the presence of PhACs in aquatic environments, but also the quantification and toxicity tests of the major TPs of PhACs contained in water bodies. Unfortunately, the quantification of these compounds is a topic poorly

studied worldwide. In the next years, PhACs monitoring could include the major TPs of each PhACs, for example, the TPs generated under phototransformation processes, for the collection of a database of the quantified concentrations in water bodies, for to carry out more researchers in order to identify the potential environmental and toxicological risks on freshwater fish and aquatic biota.

CRediT authorship contribution statement

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper

Acknowledgments

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.toxrep.2024.101796.

Data availability

No data was used for the research described in the article.

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