Solar photo-Fenton and UV/H₂O₂ processes against the antidepressant Venlafaxine in urban wastewaters and human urine. Intermediates formation and biodegradability assessment

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HIGHLIGHTS

- Venlafaxine (VFA) was treated by 5 Advanced Oxidation Processes (AOPs).
- The degradation kinetics were systematically assessed in water, wastewater and urine.
- UV light and HO•-induced attacks degraded VFA even in the chemically complex matrices.
- The degradation pathway was elucidated, indicating biodegradable intermediates.
- Increase of biodegradability was observed by applying AOPs prior to the Zahn-Wellens test.

GRAPHICAL ABSTRACT
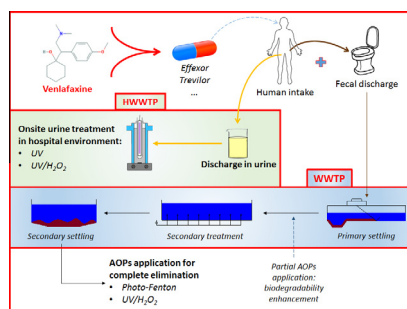
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ABSTRACT

In this work, the use of Advanced Oxidation Processes (AOPs) against the degradation of an emerging contaminant has been subjected under systematic investigation. The optimization of treatment of the antidepressant drug Venlafaxine (VFA) was performed, using UV light, the combined UV/H₂O₂ process, solar light, Fenton and finally the solar photo-Fenton process in laboratory scale. The degradation kinetics, the time necessary to remove 90% of the contaminant and the optimal reactants concentration were proposed. The treatment in pure water, (synthetic) wastewater and urine was assessed, in an effort to identify the opportunities and pitfalls the application of process would encounter in a field application. Treatment by the UV-based methods was found sufficiently efficient and the application of the solar photo-Fenton process showed feasibility in a potential field application with appropriate context. Real urban wastewater effluents after biological and physicochemical treatment were tested, as well as human urine, as a proposal for on-site collection and treatment was also treated. Biological treatment before applying the tested AOPs improved their efficiency, and the strategy of diluting urine prior to treatment greatly enhanced the efficacy of the process. Finally, the identification of the degradation pathway and the biodegradability tests of AOPs treated VFA solutions exhibit promising results concerning the strategy of treatment for similar pollutants of emerging concern.

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1. Introduction

During the last years, research has focused on the new challenges and problems that have emerged in Environmental Engineering and more specifically, wastewater (WW) treatment. Water scarcity and reuse [1], emerging pollutants [2] and the rise of antibiotic resistance [3] are only a few that are closely related to the absence of potent measures to limit or mitigate their effect. With that being said, wastewater treatment plants (WWTPs) hold their fair share of blame for inefficiently stopping some of the new threats.

One of the most crucial problems the WWTPs face, and is connected with the improvement of life standards globally, is the perception of illness and the ways drugs are administered nowadays. Apart from the physical illnesses, injuries etc. which require antibiotics, sanitizers and similar products, the taboos of psychological conditions have crumbled and as their recognition as "equally important" illnesses is established, and treatment is now considered as nothing out of the ordinary. The intense ways of living have been proven to increase the stress levels of people, leading to anxiety and chronic symptoms, as serious as sleep deprivation or depression [4]. The administration of proper medication has led to the second problem WWTPs have to face: emerging contaminants.

Venlafaxine (VFA, brand name: Effexor XR, Lanvexin or Trevilor), is an anti-depressant, which belongs in the general family of selective serotonin and norepinephrine reuptake inhibitors (SSNRIs) [5,6]. Practically, it treats depression, anxiety and panic disorders by increasing the concentrations these natural substances in the body and brain of the patient [7,8]. Chemically, it belongs to the class of benzene and substituted derivatives and is a tertiary amino compound that is *N,N*-dimethylethanamine substituted at position 1 by a 1-hydroxycyclohexyl and 4-methoxyphenyl group (Table 1). Its excretion from the body follows the renal route, ends up in WWTPs, and therefore it is found in natural waters as VFA, plus its metabolites are escaping in almost 50% rate the wastewater treatment process [9–12]. Measured concentrations range from 18 to 122 ng L^{-1} for VFA [13], or 102 and 690 ng L^{-1} [11,14] which could affect the natural biota.

Since this compound lacks functional groups that hydrolyze under environmental conditions (pH 5–9), hydrolysis is not expected to be an important environmental process, and therefore the risk of bioaccumulation is possible. With an estimated bioconcentration factor (BCF) of 60, the potential for bioconcentration in aquatic organisms is classified as moderate [15]. Furthermore, the exposure experiments of Bisesi et al. [16] have indicated that Venlafaxine exposures of bass increased the

required time to capture their prey (minnows), and the analysis of brain tissues revealed that VFA caused decrease in brain serotonin concentrations, thus explaining the behavior changes. Fong and Molnar [17] investigated the biological effects of antidepressants comprising VFA on the mollusks and crustaceans, i.e. foot detachment, a potentially sub-lethal effect that could result in transport to unfavorable habitats for the target organisms; VFA exposure caused this effect even by exposure to concentrations significantly lower than the ones found in WWTP effluents [18]. The question is due to the food chain and cycle of water, how this is going to demonstrate on human beings in long term.

As there risks similar to VFA in WW are increasing, WWTPs need to adapt to modern era threats more effectively. Under this spirit, the new Swiss regulations for wastewater treatment include a list of 12 priority contaminants for elimination from WWTPs, and VFA has become one of the recent additions to that list [19]. The said regulation involves the upgrade of WWTPs to employ activated carbon, ozone or another Advanced Oxidation Process (AOP) and ensure 80% removal of the chosen micropollutants. As it appears, AOPs can play an important role acting as a barrier for contaminants of emerging concern before reaching natural waters [20–22].
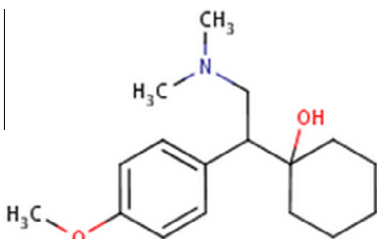
Recently, works have been initiated on the systematic degradation of VFA by UV/H_2O_2 and TiO_2 photocatalysis [23,24] dealing with the elucidation of the degradation pathway by these methods and also focusing on the toxicological safety of the degradation by-products. To contribute to this end, in our work we employ 5 Advanced Oxidation Processes (UV, UV/H_2O_2, solar light, Fenton, solar photo-Fenton) to degrade VFA in the matrices mostly expected to be encountered. After a systematic investigation of the opportunities and pitfalls of treatment in water, urban wastewater effluents and human urine containing VFA are employed and the degradation efficiency is assessed. Finally, we investigate the degradation pathway of VFA inflicted by the various AOPs and explore the use of AOPs as a pre-treatment step to increase the biodegradability of this contaminant with the Zahn-Wellens tests.

2. Materials and methods

2.1. Chemicals and reagents

The chemicals for the experiments were used as received. Venlafaxine HCl (see Table 1) was acquired from TCI (Germany), the HPLC solvents (acetonitrile, acetic acid and ammonium acetate) and the Fenton reagents (hydrogen peroxide 30% and iron sulfate heptahydrate) were acquired from Sigma-Aldrich (Switzerland).

Table 1
Venlafaxine characteristics and physicochemical properties [15].

Compound	Chemical structure	Molecular weight (g/mol)	Water solubility (mg/L)	log k_{ow}	pKa	Henry's coefficient (H) (atm m^3/mol)	HO$^{\cdot}$ reaction rate constant (M^{-1} s^{-1})[a,b,c,d,e]
Venlafaxine		$C_{17}H_{27}NO_2$ 277.402	267	3.20	10.01	2.0 x 10^{-11}	$(8.15 \pm 0.4) \times 10^9$ $(8.46 \pm 0.5) \times 10^9$ $(8.8 \pm 1.5) \times 10^9 10^{10}$

a: [23], b [24], c [21], d [25], e[26].

2.2. Water, wastewater and urine matrices

The preparation of the synthetic matrices involved dissolution of 100 mg/L VFA in either Mili-Q (MQ) water (18.2 MΩ cm^{-1}), synthetic wastewater (SWW) or synthetic urine (SUR), and all UV-related MQ experiments were conducted at near-neutral pH. The composition of the synthetic matrices is presented in Table 2. The pH of the simulated wastewater and urine is 7 and 6.5, respectively. The real WW effluents range from 6.5 to 7.5, so the pH was near-neutral unless otherwise indicated. Real wastewater samples were collected from the local wastewater treatment plant of Vidy, Lausanne (Switzerland), after an activated sludge process, a moving bed bio-reactor or a coagulation-flocculation unit. The corresponding (initial) concentrations before treatment were determined by HPLC/MS and were around 300 ng L^{-1}. For the real urine experiments, 10 μg/L VFA was added prior to experimentation.

2.3. Light sources and corresponding reactors-experimental apparatus

For the UV and UV/H_2O_2 experiments, two double-wall, water-jacketed glass batch reactors were used in parallel. The sample was placed within and the lamps, covered by a quartz sleeve were then submerged in it. The monochromatic, Hg discharge UV-C lamps (5×10^{-3} mW/cm^2 measured by iodide/iodate actinometry [25]) were 11-W Philips TUV mini (11W/G11 T5 UV) with $I_{11W} = 26$ μW/cm^2. For protection of the UV equipment and standardized conditions, water at 22 °C was recirculated with a Neslab RTE-111 thermostat. A similar set-up, but with a 35-W lamp was used for the real WW and urine experiments.

For solar and photo-Fenton experiments, a Hanau Suntest CPS solar simulator was used, employing a 1500-W Xenon lamp, equipped with UVC and IR cut-off filters. The intensity was set at 900 W/m^2 and temperature was kept below 38 °C at all times by air-cooling. The Pyrex-glass reactors were kept in constant agitation (350 rpm) by magnetic bars. The (dark) Fenton tests were performed in identical reactors and conditions without providing light to the system.

2.4. Analytical methods

2.4.1. Venlafaxine determination routine by HPLC

The determination of Venlafaxine concentration was performed through HPLC. An HP 1100 Agilent series HPLC was used. Briefly,

the mobile phase consisted of 0.14 M ammonium acetate buffer, (1.079 g/L acidified with glacial acetic acid (pH = 4). This was then mixed with 10% methanol/acetonitrile solution and sonicated for 15 min. Finally, filtration from 0.45 μL membrane was done. The HPLC conditions consisted of 40 °C temperature, 20 μL injection volume, RP-C18 column (4.6 mm $\times$ 250 mm) and detection of the peaks at 254.4 nm.

2.4.2. Venlafaxine quantification by UPLC/MS in real WW and RU

An online SPE-UPLC®/MS-MS (Acquity Xevo-TQ, Waters) was used. Samples were acidified to pH = 2.0 (32% chlorhydric acid), spiked with a standard mixture of surrogate, containing the MPs in deutered form and filtered with glass fiber filter (Simplepure PP + GF, 0.22 μm, 25 mm, BGB). Standard solutions have followed the same preparation. Five milliliters of each sample were loaded on an SPE column (Oasis HLB 25 μm, 2.1 $\times$ 20 mm, Waters) with ultrapure water, acidified at 1% of formic acid, as eluent. The online transfer of VFA to the analytical column (Acquity HSS T3, 1.8 μm, 2.1 $\times$ 100 mm, Waters) was made with a gradient of ultrapure water and acetonitrile acidified at 0.1% of formic acid. Multiple reaction monitoring mode with two transitions was used to detect MPs and quantification was performed with internal standard calibration.

2.4.3. Intermediates identification by TOF-MS analysis

HR-MS analyses were conducted on a Xevo G2-S QTOF mass spectrometer coupled to the Acquity UPLC Class Binary Solvent Manager and BTN Sample Manager (Waters, Corporation, Milford, MA). Mass spectrometer detection was operated in positive ionization using the ZSpray™ dual-orthogonal multimode ESI/APCI/ESCi® source. Samples were diluted in H_2O and directly infused into the mass spectrometer at a flow rate of 100 μL/min. The TOF mass spectra were acquired in the sensitive mode over the range of *m/z* 50–1200 at an acquisition rate of 1 s/spectra. A mass accuracy better than 5 ppm was achieved using a leucine-encephalin solution as lock-mass (200 pg/μL in ACN/H2O (50:50)) infused continuously using the LockSpray source (5 s reference Scan frequency). Source settings were as follows: cone, 25 V; capillary, 3 kV, source temperature, 120 °C; desolvation temperature, 500 °C, cone gas, 100 L/h, desolvation gas, 500 L/h. Data were processed using MassLynx™ 4.1 software.

2.4.4. Global chemical analyses (TOC, COD, H_2O_2 and UV/Vis absorbance)

The COD of the solution was monitored with HR/LR dichromate vials (HACH Lange, Switzerland) and TOC was followed by a Shimadzu TOC-VCSN analyzer, with an ASI-V automatic sampling module·H_2O_2 was determined spectrophotometrically, after the addition of 10 μL of titanium oxysulfate in 1 mL of sample and measurement at 410 nm (DIN 38402H15 method). Finally, the absorbance spectra was recorded at each sampling point (Shimadzu 1800 UV spectrophotometer) and the pH was followed by a Mettler-Toledo Seven Easy pH meter.

3. Results and discussion

3.1. UV-based AOPs degradation of Venlafaxine

3.1.1. Monochromatic UV-C photolysis

Fig. 1 presents the photolysis of Venlafaxine (VFA), under the exposure to monochromatic UV-C (peak at 253.7 nm) irradiation, at neutral pH. The photolysis rates, quantum yields and the proven, but limited efficiency to degrade VFA by UV light in a collimated beam apparatus have been recently documented [23,26]. The k_{phot}
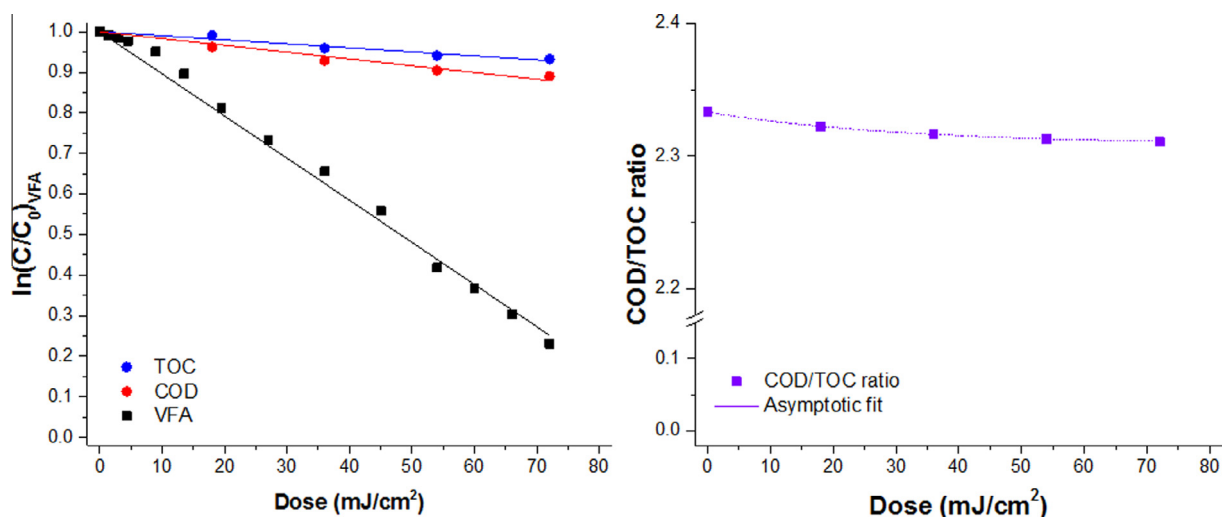
Table 2
Composition of the synthetic matrices used in this study.

Name	Chemical formula	SWW composition [mg/L]
Synthetic wastewater		
Peptone	–	160
Meat extract	–	110
Urea	CH_4N_2O	30
Dipotassium phosphate	HK_2PO_4	28
Sodium chloride	NaCl	7
Calcium chloride dihydrate	$CaCl_2 \cdot 2H_2O$	4
Magnesium sulfate heptahydrate	$MgSO_4 \cdot 7H_2O$	2

Name	Chemical formula	SUR composition [g/L]
Synthetic urine		
Urea	CH_4N_2O	25
Sodium chloride	NaCl	2.925
Sodium sulfate	Na_2SO_4	2.25
Potassium chloride	KCl	1.6
Potassium phosphate monobasic	KH_2PO_4	1.4
Calcium chloride dihydrate	$CaCl_2 \cdot 2H_2O$	1.103
Creatinine	$C_4H_7N_3O$	1.1
Ammonium chloride	NH_4Cl	1

Fig. 1. Summary of the UV-C photolysis experiments. (a) UV-induced degradation of Venlafaxine followed by HPLC, COD removal and TOC reduction during UV photolysis. (b) Evolution of the COD/TOC ratio.

has been in the order of 1.5×10^{-4} cm^2/J in the corresponding work.

In our work, a merry-go-round reactor with submerged lamp was employed and the corresponding kinetics are depicted in Fig. 1. In principle, the degradation follows a linear trend in (natural) logarithmic scale which allows the determination of first-order reaction kinetics, being 0.0104 cm^2/mJ, calculated as follows:

$$[I] = [I]_0 e^{-kt} \tag{1}$$

or as:

$$ln[I]_t = ln[I]_0 - kt \tag{2}$$

By re-arranging the equation 1, we get:

$$ln\left(\frac{I_t}{I_0}\right) = -kt \tag{3}$$

Due to the reactor design and configuration, the actual irradiance received by the system and determined by iodide/iodate actinometry [25] is 0.005 mW/cm^2, which is much higher than the collimated beam apparatus. Since the degradation follows first-order kinetics, the time necessary to degrade 90% of the initial concentration ($t_{90\%}$) has been determined and will be used for comparison among the various processes. From (3), by substitution we get:

$$ln\left(\frac{0.1I_0}{I_0}\right) = -kt \tag{4}$$

or:

$$t_{90\%} = -\frac{ln0.1}{k} \tag{5}$$

The required time for 90% was 163 min and until the $t_{90\%}$ was reached, the UV-C system removed 7% and 4% of COD and TOC. Even by extending the treatment for 4 h, UV-C alone is not sufficient to degrade more than 20% of COD or remove more than 15% of TOC. As it appears, the complex VFA structure is affected by UV in the double bonds present but light alone cannot efficiently mineralize the carbon content of the solution attributed to the degradation by-products and intermediates. Fig. 1b corroborates with the findings, and the depicted COD/TOC ratio presents asymptotic, plateau-like tendencies. This reveals the formation and accumulation of stable by-products, which after an initial fast oxidation, do not further undergo significant modification or min-

eralization. Furthermore, Fig. S1 of the supplementary material also confirms this tendency, where the absorbance spectra indicate that although VFA is removed (1st peak) a plateau is reached after 2 h of exposure, where a formation of intermediates is stable and fails to proceed further.

3.1.2. UV/H$_2$O$_2$ Advanced Oxidation Process

Following the UV photolysis, the same set-up was used to induce UV/H$_2$O$_2$ advanced oxidation of VFA. As indicated in many studies, the H$_2$O$_2$ addition must be assessed [27], therefore here in a H$_2$O$_2$ dosing optimization process 5 different H$_2$O$_2$ addition levels were tested, and the results are summarized in Fig. 2a and b.

The homolytic disruption of the HO–OH bond results in the release of hydroxyl radicals (HO·) [28]. The addition of H$_2$O$_2$ and the production of HO· has a direct effect on the degradation of Venlafaxine. Hydroxyl radicals can act on molecules via oxidation, –OH substitution, protonation, as well as water abstraction and decarboxylation, as seen in related works [23,24]. These attacks drastically modify the properties of VFA and proceed to more efficient degradation than UV alone.

The addition of even 5 mg/L H$_2$O$_2$ improved the VFA degradation 20% respectively, compared to the sole UV experiments. VFA has –OCH$_3$ and –OH groups that react fast when faced to hydroxyl radicals (order of $k_{HO} \approx 10^9$ M^{-1} s^{-1} and 10^8 M^{-1} s^{-1}, respectively), but also a –CN group that has a much slower rate constant ($k_{HO} \approx 10^7$ M^{-1} s^{-1}) [15], hence the overall degradation rate will be determined by these groups and the direct photolysis rate (k_{phot}) when treated by the UV/H$_2$O$_2$ process.

The stepwise increase in H$_2$O$_2$ concentration reveals the changes in degradation kinetics and the limitations of the employed experimental system (Fig. 2a and b). After 50 mg/L the improvement in reaction kinetics is marginal (data for 100 mg/L not shown). In addition, in [23,26], the photolysis rate was considerably lower than the corresponding rate for oxidation due to the hydroxyl radicals, and was considered negligible. Here, the oxidation kinetics are estimated as follows:

$$k_i = k_{phot} + k_{HO-i} \tag{6}$$

where, i: the H$_2$O$_2$ addition (mg/L)

As an example, the k_{HO}/k_{phot} ratio was calculated 5.5 for 10 mg/L (more details are given in Table 3). Hence, although these measurements reveal the high contribution of the photolysis in the process, they can be partially attributed to the specific reactor
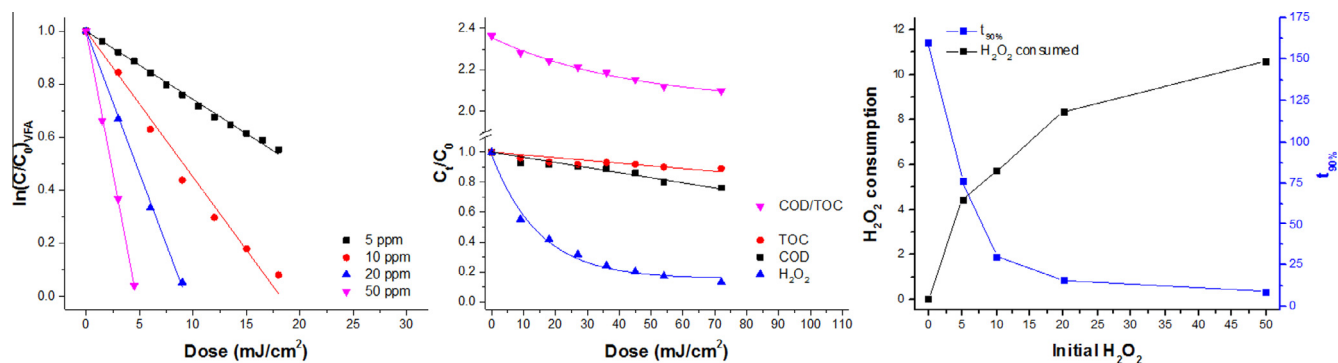
Fig. 2. UV/H_2O_2 Advanced Oxidation of Venlafaxine: degradation and process optimization. (a) Degradation of VFA by UV/H_2O_2 with addition of 5–50 mg/L H_2O_2. (b) Evolution of COD/TOC ratio (for 50 mg/L initial H_2O_2 addition). (c) Consumption of H_2O_2 (black axis and traces) and changes in the $t_{90\%}$ (blue axis and traces) as a function of initial H_2O_2 amounts. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

geometry that has relatively short optical path, and light attenuation is small. Therefore, this design influences the economical parameters of the degradation process.

Nevertheless, the consumption of H_2O_2 increases with increasing addition. We further notice that the overall oxidation of the system proceeds towards mineralization of the existing carbon content for each case. A 4-h exposure to UV/H_2O_2 system with 50 mg/L H_2O_2 (i.e. for as long as there was H_2O_2 present) the COD and TOC removal is improved compared to the plain UV system, and an additional 20% was removed for both parameters. However, according to the absorbance spectra recorded, after the removal of VFA, the remaining intermediates and by-products are not removed equally fast, and a lower second order k_{HO} must be in effect (detailed graphs can be found in the Supplementary Fig. S2).

3.2. Fenton-related AOPs degradation of Venlafaxine

In order to fully attribute the effects of the synthetic photo-Fenton process against the degradation of VFA, a stepwise construction of the process took place. Hence, solar exposure, Fenton treatment in the dark and the combined process took place and the results are presented in the respective groups. To our knowledge, this is the first instance where VFA is systematically treated

by the photo-Fenton process and therefore, the different parts will be analyzed separately.

3.2.1. Solar photolysis of Venlafaxine

The experiments of simulated solar exposure of VFA were performed in order to establish solar photolysis rates and check the potential photo-transformation of the drug. Santoke et al. [29] proved that Venlafaxine is undergoing limited photolysis. Here, after 24 h of irradiation at relatively high solar irradiance (900 W/cm^2) a mere 12% of the initial VFA amount has been removed. As such, a $k_{sol} = 0.0002$ min^{-1} was measured (Table 3). As far as the COD and TOC of the solution are concerned, limited removal was observed. COD was removed at 13% and 4% TOC was eliminated during the course of 24 h (for more details, see Supplementary Fig. S2). However, the direct action of solar light includes (1) the excitation of the organic compound at singlet-excited state [30], (2) its intersystem crossing to triplet state and (3) its reaction with oxygen to form singlet oxygen [31]. Afterwards, the micropollutant returns to ground state, but the singlet oxygen created by the reaction with water participates in (i) the superoxide radical anion formation from oxygen and consequently (ii) to the formation of H_2O_2 from water [31] or (iii) the direct attack to double bonds present in the molecule. Although of lesser importance, these results will play the role of reference when the photo-Fenton process will be described from its parts.

3.2.2. Fenton-driven degradation of Venlafaxine in the dark

The degradation of VFA in the dark due to the Fenton reaction was assessed in a range of parameters, such as the initial pH and the starting Fenton reagents concentration. Literature suggests that the reactivity of Venlafaxine with hydroxyl radicals is ranging among 8×10^9 to 10^{10} M^{-1} s^{-1} (see Table 1) and that the Fenton reaction contribution is important, when the reagents concentration is increased [32]. Fig. 3 presents 4 of the Fe|H_2O_2 ratios tested (indicatively chosen), in the 3 different pH levels of operation, i.e. 3, 5 and 7. The results of the optimization are summarized in Fig. 3a (analytical data in Supplementary Figs. S3a–S3c), for 24 h of treatment for each batch process.

As expected, Fig. 3 shows that at pH = 3 the results were optimal (see also Table 3), as the Fenton process greatly benefits of the soluble iron at that pH [33]. Although limited by the regeneration of Fe^{3+} back to Fe^{2+}, 3 out of the 4 processes were able to degrade more than 50% of the initial content. These processes contained H_2O_2 in the highest amount, which played the role of the reductant of ferric iron, as indicated in the following reactions:
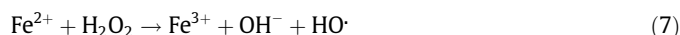
$$Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + OH^- + HO^\cdot \qquad (7)$$

Table 3
Measured pseudo-first order degradation kinetics of Venlafaxine per AOP and matrix.

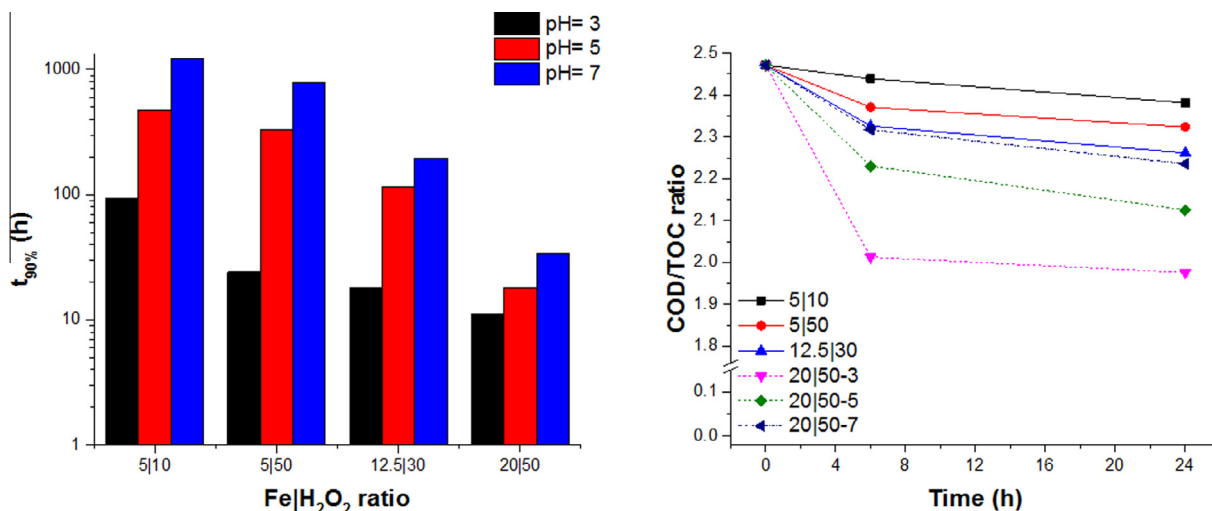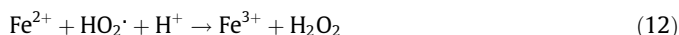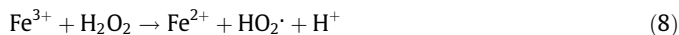| Pseudo first order reaction kinetics k (min^{-1})		
UV alone	**MQ**	
k_{phot}^{11W}	0.0141	
UV/H_2O_2	**MQ**	k_{HO}/k_{phot}
k_5^{11W}	0.0392	1.78
k_{10}^{11W}	0.0757	4.37
k_{20}^{11W}	0.1412	9.01
k_{50}^{11W}	0.2948	19.91
k_{100}^{11W}	0.3726	25.43
Solar light	**MQ**	Synergy$_{12.5|58.3} = \frac{k_{pF}}{k_F + k_{sol}}$
k_{sol}^{900}	0.0002	89.46
Fenton (pH = 3)	**MQ**	
$k_F^{12.5|58.3}$	0.0026	
photo-Fenton (pH = 3)	**MQ**	
$k_{pF}^{5|10}$	0.0161	
$k_{pF}^{5|50}$	0.1443	
$k_{pF}^{12.5|30}$	0.1814	
$k_{pF}^{12.5|58.3}$	0.2505	
$k_{pF}^{20|50}$	0.2363	

Fig. 3. Fenton-driven Advanced Oxidation of Venlafaxine: degradation and process optimization. (a) Degradation of VFA by the Fenton process, by addition of various $Fe|H_2O_2$ ratios. (b) Evolution of COD/TOC ratio (for the same $Fe|H_2O_2$ ratios).

$$Fe^{3+} + H_2O_2 \rightarrow Fe^{2+} + HO_2\cdot + H^+ \tag{8}$$

$$HO_2\cdot \leftrightharpoons H^+ + O_2\cdot^- \tag{9}$$

$$HO\cdot + H_2O_2 \rightarrow HO_2\cdot + H_2O \tag{10}$$

$$HO\cdot + Fe^{2+} \rightarrow Fe^{3+}OH^- \tag{11}$$

$$Fe^{2+} + HO_2\cdot + H^+ \rightarrow Fe^{3+} + H_2O_2 \tag{12}$$

$$Fe^{3+} + HO_2\cdot \rightarrow Fe^{2+} + O_2H^+ \tag{13}$$

$$HO_2\cdot + HO_2\cdot \rightarrow H_2O_2 + O_2 \tag{14}$$

The generation of the Reactive Oxygen Species (ROS) by the Fenton process is dependent on the catalyst regeneration, i.e. the Fe^{3+} turnover back to Fe^{2+}. However, the reaction kinetics of Eq. (7) compared with the others is orders of magnitude higher, and for this reason, the regeneration of the catalyst, especially by Eq. (8), is considered a limiting step. In water, Fe^{3+} forms different aqua-complexes, according to its pH, with precipitation tendencies as the pH increases. The iron speciation in water changes according to the Pourbaix diagram and Salgado et al. [34] have updated the original contribution, with the most recent knowledge. At acidic pH, the most abundant form of iron is [Fe^{2+}] which is the strongest reductive form. The optimal value to perform the Fenton reaction is near 3; from pH 0–4, the rate increases with the pH [35]. After this pH, the majority of the iron species are insoluble (Fe_2O_3, or other colloidal forms) and therefore, the reactivity drops.

However, moving up to pH = 5 the degradation potential is diminished and only the 20|50 addition $Fe|H_2O_2$ ratio was sufficient to inflict a 70% degradation after 24 h. At pH = 7 this ratio was limited to a 35% degradation of VFA. Nevertheless, as a sufficient amount of H_2O_2 was still measured after 24 h, the process could continue, albeit in lower rates. At pH $\geqslant$5, solid $Fe(OH)_2$ species dominate, since they are more readily oxidized (compared to Fe^{2+} and $FeOH^+$) [36]. Nevertheless, until pH 5.8 the contribution of the homogeneous photo-Fenton is still considerable [37]. Finally among pH 5 and 7 (up to 8), solid iron species dominate and no further increase in its concentration appear [36]. However, at this pH HO_2 is formed in higher quantities and indirectly helps Fe^{2+} formation through the Eq. (13) [38]. The soluble iron species have very different rate constants reported, which practically means that their participation in redox reactions depends on the distribution of these species (Fe^{2+}, $FeOH^+$, and solid $Fe(OH)_2$) [36].

As pseudo-first order kinetics were established for the degradation process, the $t_{90\%}$ was established for each ratio and pH level. It can be observed that the theoretical $t_{90\%}$ can reach 1000 h in the near-neutral pH and low $Fe|H_2O_2$ ratios, although increasing the amounts can reduce it to merely a day, which is great improvement. The acidic pH on the other hand ensures proper removal and never exceeds 100 h of treatment, while 11 h are necessary with high reactants concentration.

Finally, during the 24-h treatment by the Fenton process the mineralization rate of the organic matter remains low for high pH and low concentrations of Fe and H_2O_2. The biggest removal noted was at pH = 3 and 20|50 ratio. Nevertheless, the COD/TOC ratio indicates a fast initial degradation step and a decelerated process afterwards. As no process was H_2O_2-limited for any pH or ratio, this indicates that the VFA structure contains some easily removed groups, which readily react with the $HO\cdot$ radicals (see Supplementary Fig. S4 and Table S1, for analytical COD & TOC measurements, and H_2O_2, respectively). In Fig. 4, axis x shows the wavelength (nm), y the absorbance (a.u.) and z either the $Fe|H_2O_2$ ratio (left group) or the pH level (right group). The corresponding absorbance spectra indicate the formation of different intermediates and complexes with iron, depending on the pH and the $Fe|H_2O_2$ ratio. Nevertheless, the VFA removal is confirmed to be low for most cases, and the participation of the iron is demonstrated by the absorbance in higher wavelength UV and visible light; Fe can bind to acidic groups or side-chains and create stable organo-complexes. Also, the stability of the solution after 6 h, indicates the low levels of reaction with the organics present. However, these absorbance spectra suggests that these complexes are photo-active, as they absorb UV and visible light in higher rates than the original solution with iron (t = 0) and therefore we anticipate their possible involvement in the photo-Fenton process.

3.2.3. The photo-Fenton driven degradation of Venlafaxine

The final step in this section considers the combined photo-Fenton process mode of action. In Fig. 5, we summarize the experiments performed, in a similar manner to the Fenton process. As pseudo-first order kinetics were established, Fig. 5a shows the evolution of $t_{90\%}$ as the Fenton reactants and the pH levels increase (detailed data on the photo-Fenton action can be found in the Supplementary Fig. S5 and the H_2O_2 consumption at Table S1). A very
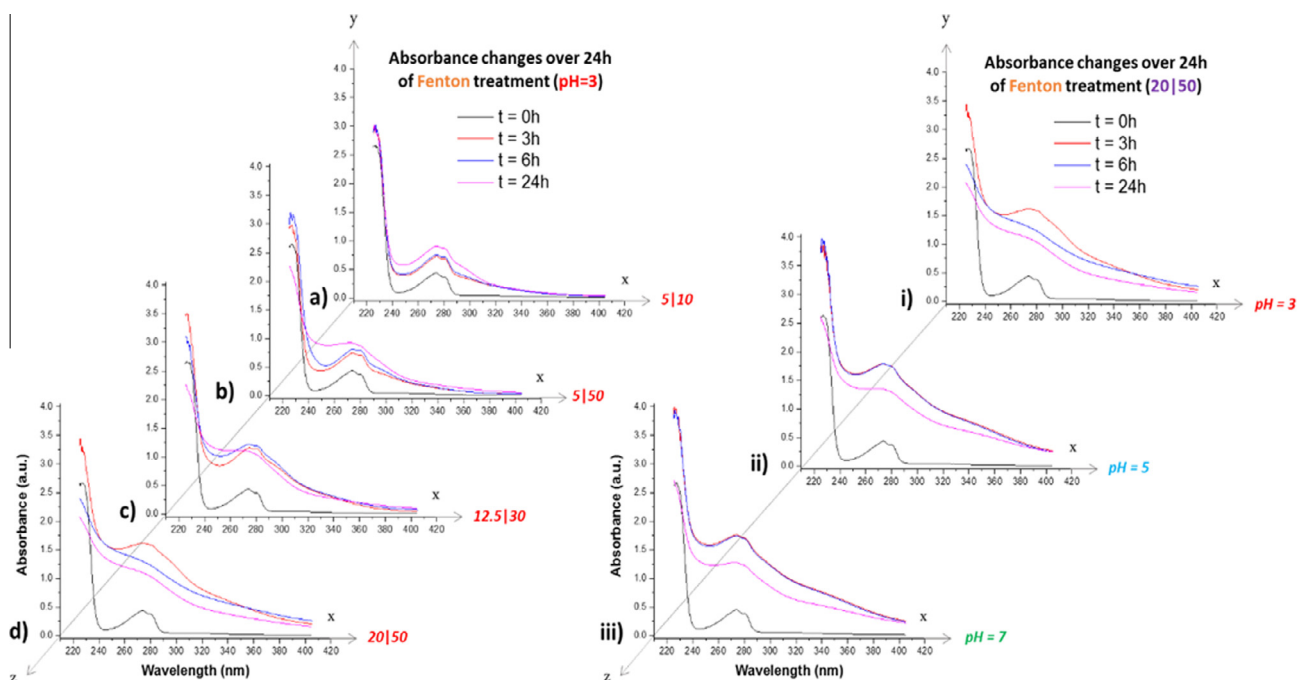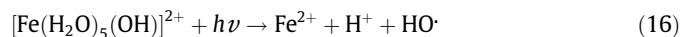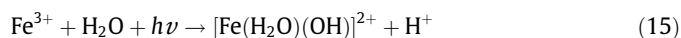
Fig. 4. Absorbance spectra during the 24-h Fenton treatment of Venlafaxine, for various Fe|H$_2$O$_2$ ratios (panels a–d) and pH levels (panels i–iii). Fe|H$_2$O$_2$ ratios: (a) 5|10, pH = 3. (b) 5|50, pH = 3. (c) 12.5|30, pH = 3. (d) 20|50, pH = 3. pH levels: (i) 20|50, pH = 3. (ii) 20|50, pH = 5. (iii) 20|50, pH = 7.

similar trend with the Fenton process is observed, but the t$_{90\%}$, even the theoretical one is now measured in minutes rather than hours. The synergy of the Fenton with light is very high, yielding t$_{90\%}$ as low as 10 min for 20|50 at pH = 3.

As the mode of action of the Fenton process has been previously explained, here we will assess only the changes and improvements inflicted by light. The most notable difference among these results and the Fenton process in the dark, is the change in the time scale, from hour to minute range. Here, all experiments were completed within 3 h. Although some processes (5|10 ratio) did not conclude, the great number of completed experiments within the experimental time demonstrates the efficiency of the photo-Fenton process. In presence of light, the iron recycling is facilitated by the absorption of light by the photosensitive aqua-hydroxy- and organo-complexes. At pH = 3, the prevalent form is [Fe(H$_2$O)$_5$(OH)]$^{2+}$; in general, the photo-reduction can be

summarized with the following two reactions 15 and 16, also leading to an extra hydroxyl radical production:

$$Fe^{3+} + H_2O + h\nu \rightarrow [Fe(H_2O)(OH)]^{2+} + H^+ \qquad (15)$$

$$[Fe(H_2O)_5(OH)]^{2+} + h\nu \rightarrow Fe^{2+} + H^+ + HO^\cdot \qquad (16)$$

At higher pH, the contribution in radicals' formation is reduced, along with the photo-active compounds concentration. The production of the hydroxyl radical, as described before, induces hydroxylation of two possible sites simultaneously or independently, or even reaction with the nitrogen group [29], resulting to efficient degradation [39,40].

As the mineralization rate indicates (Fig. 5b), the overall removal of organic matter in the solution stays limited, within the duration of the experiment. According to the H$_2$O$_2$ consump-
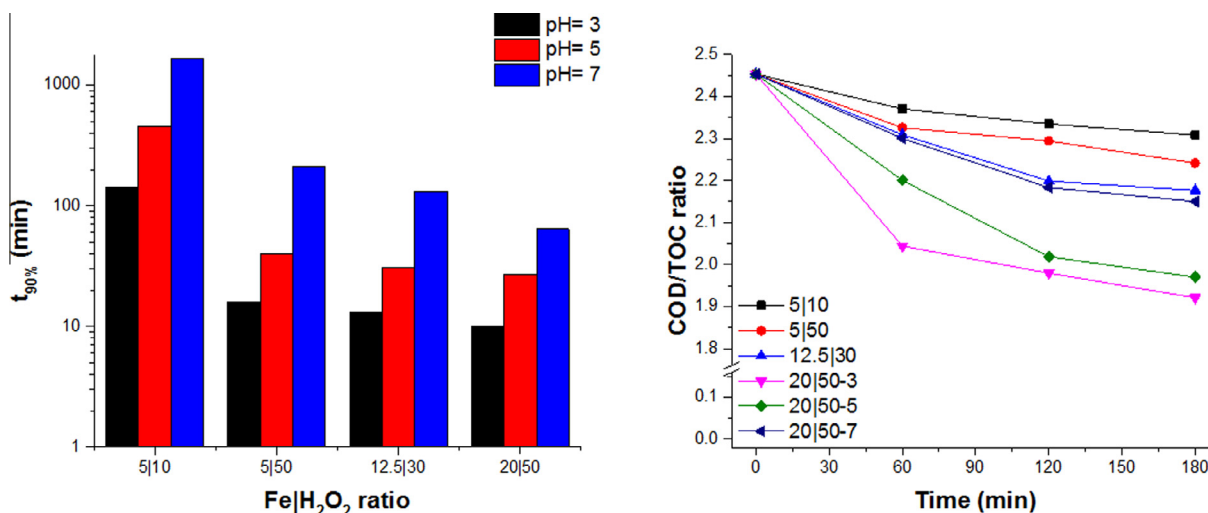

Fig. 5. Treatment of Venlafaxine by the photo-Fenton process (irradiance: 900 W/m^2). (a) Evolution of the t$_{90\%}$ with increasing Fe|H$_2$O$_2$ ratio and pH. (b) COD/TOC ratio evolution by the solar photo-Fenton process at various Fe|H$_2$O$_2$ ratios (pH = 3) and increasing pH for a 20|50 ratio.

tion rates, and the residual H_2O_2 at the end of 3 h, which is lower than the respective after 24 in its Fenton counterpart, the process is, or will be, H_2O_2-limited for some combinations. Hence, the COD and TOC removal is halting and re-dosing would be necessary to continue the degradation (detailed COD and TOC measurements can be found in the Supplementary Fig. S6).

Finally, the combined photo-Fenton process effects are also demonstrated in the changes in absorbance spectra, in Fig. 6. The photoactivity of the complexes remains high, which means an active ligand-to-metal charge transfer could be facilitated:

$$[\text{Fe}^{3+} - \text{L}]^{3+} + 2H_2O \overset{h\nu(\text{LMCT})}{\rightarrow} [\text{Fe}(H_2O)_2]^{2+} + \text{L}^{\cdot+} \qquad (17)$$
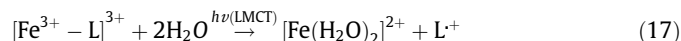
The sacrificial ligand is offered from either VFA or some degradation intermediate and the regenerated Fe^{2+} will re-participate in the Fenton reaction. The changes found can be grouped under either (i) the higher complex formation (higher absorbance) compared to the Fenton system, (ii) the significantly faster plateau achievement or (iii) the bigger differences in the neutral and near-neutral process (differences between pH = 3 and 7).

3.3. Venlafaxine degradation experiments in wastewater and urine

3.3.1. Experiments in real secondary wastewater effluents and human urine

The occurrence of VFA and its metabolites in surface waters [11] indicates the improper elimination in WWTPs and their extreme adverse effects underlines the need for their degradation prior to their discharge, with AOPs able to play the last, polishing step [41]. Table 4 summarizes literature values and own measurements of VFA in WWTPs, at various stages, from influents to effluents.

In our work, we assessed the degradation of VFA with the same AOPs analyzed in the previous parts, found in three different secondary effluents, namely activated sludge (AS), moving bed bioreactors (MBBR), and coagulation-flocculation effluent. For more information on the nature and the composition of the effluents, as well as COD and TOC removal, interested readers should refer

to [19,42,43,44] and our supplementary material (Table S2). Fig. 7 depicts the degradation measurements in the two families of AOPs per process and per effluent. As expected, the UV-based AOPs presented the fastest degradation kinetics, as summarized also in Table 4.

Recent works have demonstrated their efficiency in VFA degradation by the Fenton and Fenton-like processes ([22,40]), confirming the feasibility of its application in real WW samples. Venlafaxine degradation is a function of contradicting factors in real effluents. On the antagonists of the process, we can mention the (i) suspended solids, blocking UV and solar light transmission, (ii) the Effluent Organic Matter (EfOM), consisting in still particulate organic matter (POM), biodegradable organic matter, refractory organic matter and other MPs, which all compete for the oxidants generated by AOPs [19] and screen the light [30], (iii) the ROS scavengers, such as (bi)carbonates, nitrate and nitrite [31], and (iv) the microorganisms. On the other hand, the very presence of some substances has been proven to enhance the self-purification capabilities of the effluents, such as (a) the presence of photo-sensitizable organic matter (PhOM), which further produces ROS, and (b) the nitrates and the carbonates, which contribute in producing nitrate radicals, carbonate radicals and ROS, all with mild oxidative potential [19]. In the end, what we perceive as "degradation" is the net force of all these factors, which leans on the negative side overall, compared to simulated WW or water.

As far as the initial content is concerned, the similar values in AS and MBBR have been recently verified [45] and the close values in CF effluents are a result of the low solubility and the hydrophobicity, as expressed by the $\log k_{ow}$; VFA tends to adsorb to the generated flocs and is "removed" by settling. More specifically, the degradation kinetics follow a similar trend to the content of suspended matter and organic content in the effluents, as well as the alkalinity of the matrix, an indicator of (bi)carbonates content and therefore a precursor of HO scavenging. As shown in [43–45], the physicochemical characteristics of the effluents measured, verify a trend, as the MBBR effluents have the best characteristics for applying AOPs, followed by AS and then CF.
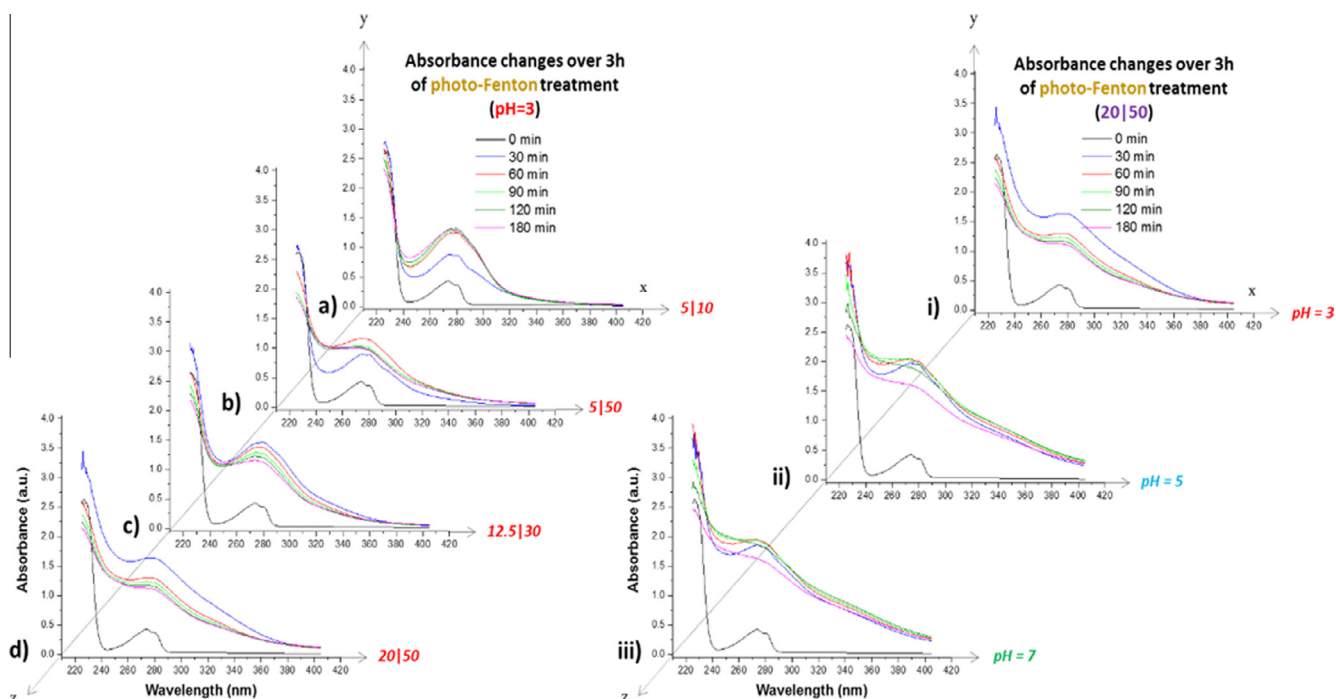

Fig. 6. Absorbance spectra during the 3-h photo-Fenton treatment of Venlafaxine, for various Fe|H_2O_2 ratios (panels a–d) and pH levels (panels i–iii). Fe|H_2O_2 ratios: (a) 5|10, pH = 3. (b) 5|50, pH = 3. (c) 12.5|30, pH = 3. (d) 20|50, pH = 3. pH levels: (i) 20|50, pH = 3. (ii) 20|50, pH = 5. (iii) 20|50, pH = 7.

Table 4
Occurrence and fate of Venlafaxine in urban WW effluents.

|	Venlafaxine occurrence in WWTPs							
	Treatment stage	Quantity (ng/L)	Source					
Pre-treatment	Influent	500–1100	[10]					
		800	[11]					
		623 ± 18	Own measurements					
		235 ± 21	[39]					
	Primary treatment	374 ± 111	Own measurements					
Secondary Treatment	Biological treatment (high/low HRT)	900–1000	[10]	Degradation of Venlafaxine (this work)				
		140–150	[40]	Measured pseudo-first order kinetics k (min⁻¹)				
		95–188	[39]	UV-C	UV/H₂O₂	Solar	Fenton	photo-Fenton
	AS	281 ± 83	Own measurements	0.073	nc	0.0001	0.006	0.033
	MBBR	224 + 67	Own measurements	0.08	nc	0.0001	0.007	0.035
	CF	299 + 9	Own measurements	0.042	nc	0.0001	0.001	0.032
	Effluents	95–188	[39]					
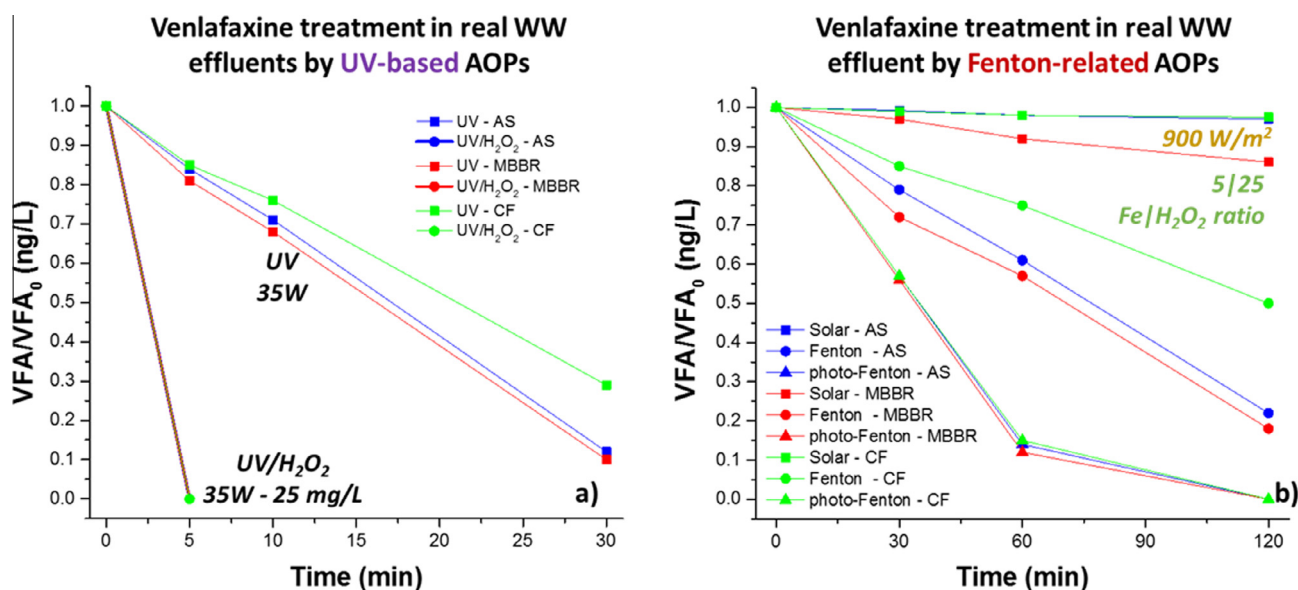
Fig. 7. Treatment of Venlafaxine by AOPs in urban WW effluents. The experimental conditions are marked in the corresponding graphs. (a) VFA degradation by UV-based AOPs in AS, MBBR and CF effluents. (b) VFA degradation by the Fenton-related processes in AS, MBBR and CF effluents.

Concerning the experiments in human urine, based on manufacturer, medical and pharmaco-kinetical data, we have found that the normal dose of Venlafaxine (as Effexor) for patients is 75 mg/day and can reach up to 150 mg/day in severe cases. Out of the administered amount, 92% is recovered in urine, as the renal excretion pathway is prevailing. However, VFA in urine appears in only 5% (1–10% [10]), unconjugated O-desmethyl Venlafaxine (29%), conjugated O-desmethyl Venlafaxine (26%), 1% N-desmethyl Venlafaxine, and the rest as the other intermediates. Hence, a normal person excretes ∼2 L urine per day, it is normal to expect µg/L concentrations in patients. As such, 10 µg/L spiking was performed in urine collected by healthy individuals. The COD of the solution varied significantly from 2.5 to 8.5 g/L. Therefore, collection and homogenization over the course of 6 h was performed to mitigate the differences in chemical and optical properties. The average urine characteristics can be found in the supplementary material (Table S2). Besides, 10% diluted urine experiments took place, to assess the possibility of yielding higher UV transmittance in exchange of higher treatment volumes. The results of the study are summarized in Fig. 8.

During the experiments in undiluted urine, the efficacy of UV alone in degrading VFA was low. As urine contains light absorbing compounds (organic matter, nitro-, phosphoro- and other groups), light attenuation was a limiting step in the degradation process [44]. The step-wise addition of H₂O₂ (50 and 100 mg/L) was beneficial, reaching up to ∼30% degradation of VFA. Other researchers have also demonstrated the increase in PhACs' degradation by the addition of H₂O₂ in the bulk [46]. The positive aspects of H₂O₂ addition are found also in the COD removal, where up to 15% of COD and 13% of DOC were removed. In real urine, this amount corresponds to 750 mg/L, from a 5000-average COD. Diluting the urine ×10 times has modified the matrix significantly, allowing up to 80% degradation of VFA (spiking was done after dilution) and the H₂O₂ addition further improved degradation, up to 100%.

Furthermore, the dilution of urine has been studied in another contaminant (Iohexol) by our group [47], and the optimization experiments revealed that a near-optimal performance could be obtained by 10% dilution of the matrix. The effect of dilution improves the transmittance of urine, thus improving light absorption by the organic matter in solution, but also improve the homolytic disruption of H₂O₂, the subsequent increase in HO· production and the decrease in scavenging by the organic matter. On the other hand, the ×10 times increase of the treated volume holds technical and engineering implications, as well as questions on the water used for dilution. Here, as a proof of concept we have shown that the effects are multiple and since the human urine production is small, even this dilution is not a limiting agent to a potential application.

Finally, no photo-Fenton experiments were performed as the k in synthetic urine was too low and the treatment of urine in open
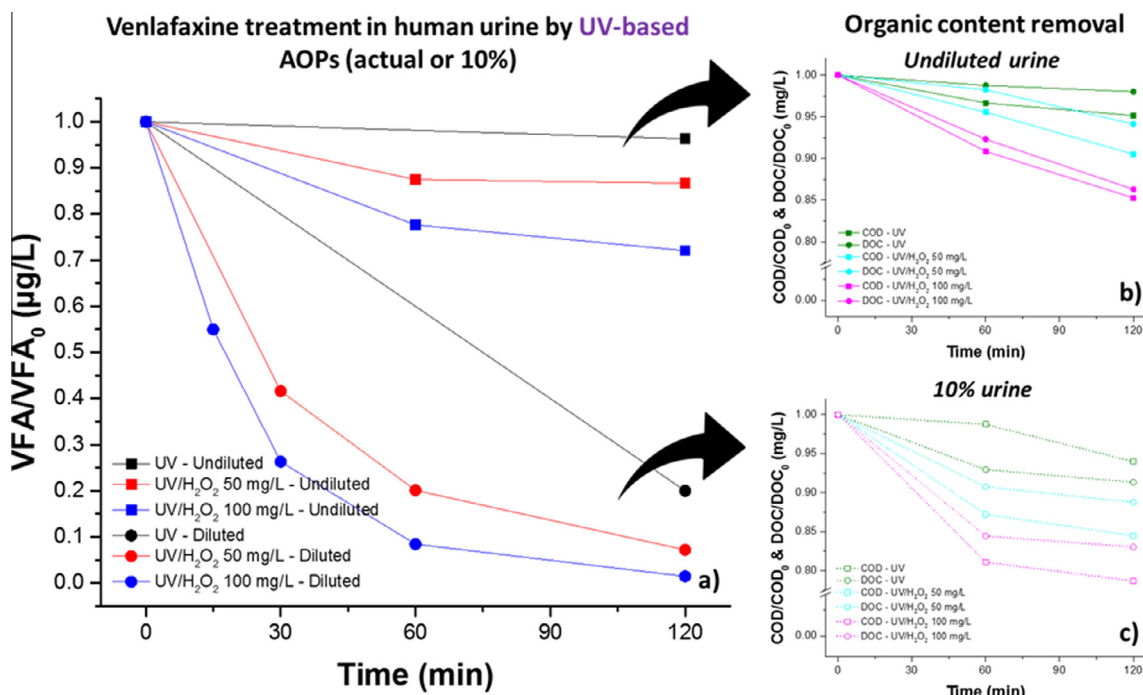
Fig. 8. Treatment of Venlafaxine by UV-based methods in human urine. (a) VFA degradation by UV-based AOPs (0, 50 or 100 mg/L H_2O_2 and 0/100% or 10–90% urine/water ratio. (b) COD reduction and DOC (0.45 μm filtration) removal in the same conditions.

vessels seems impractical. Nevertheless, medium (MP) UV lamps could be suggested as a potential substitute for monochromatic UV or solar light, as they emit an array of peaks and photo-Fenton reaction could be sustained.

3.4. Elucidation of the AOP-driven degradation pathway and inherent biodegradability properties of Venlafaxine

3.4.1. Degradation pathway of Venlafaxine by AOPs through TOF-MS

The identification of degradation products is essential for providing the risk assessment information of drug residues in the environment, as well as for the improvement of water treat-

ment technologies. In our study, Venlafaxine degradation products were identified after each degradation procedure (UV, UV/H_2O_2, solar treatment, Fenton and solar photo-Fenton). All identified products were shown in supplementary Table S4, including their molecular formula, theoretical and experimental m/z value, double bond equivalent (DBE) and mass accuracy in ppm (accepted structures with error less than 5 ppm). Ten degradation products were identified in overall: one for solar treatment, six for UV treatment, five for UV/H_2O_2 treatment, seven for Fenton degradation and seven for photo-Fenton treatment. Based on the identified structures, a simple mechanistic scheme was proposed (Fig. 9).
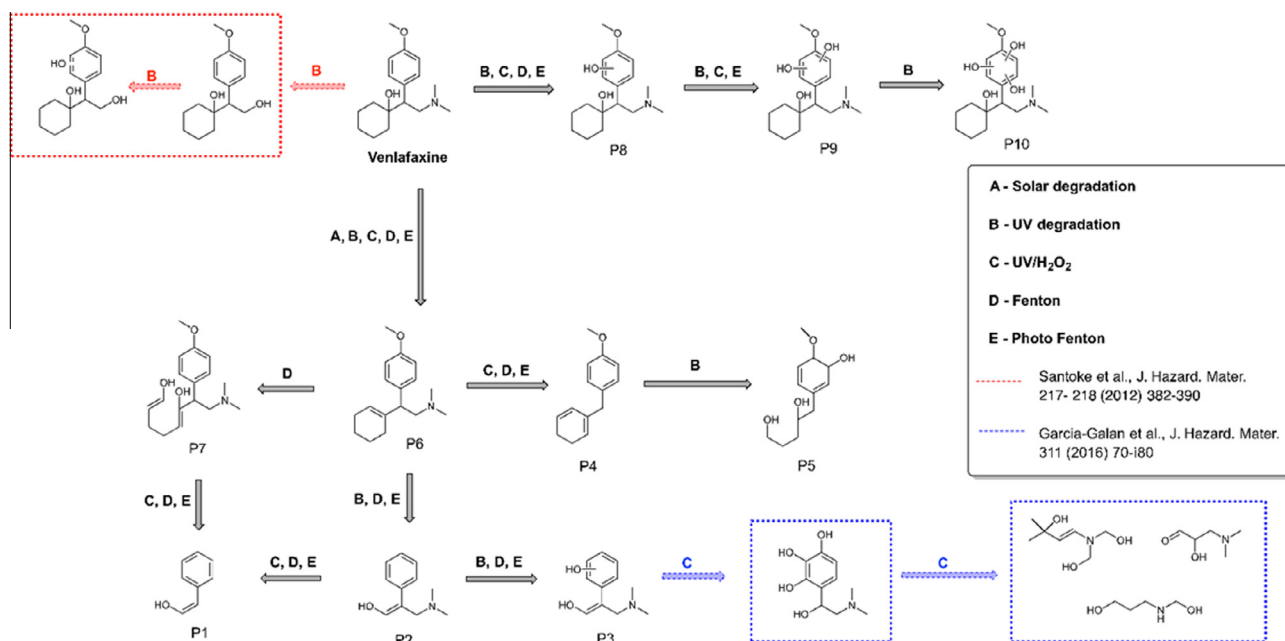

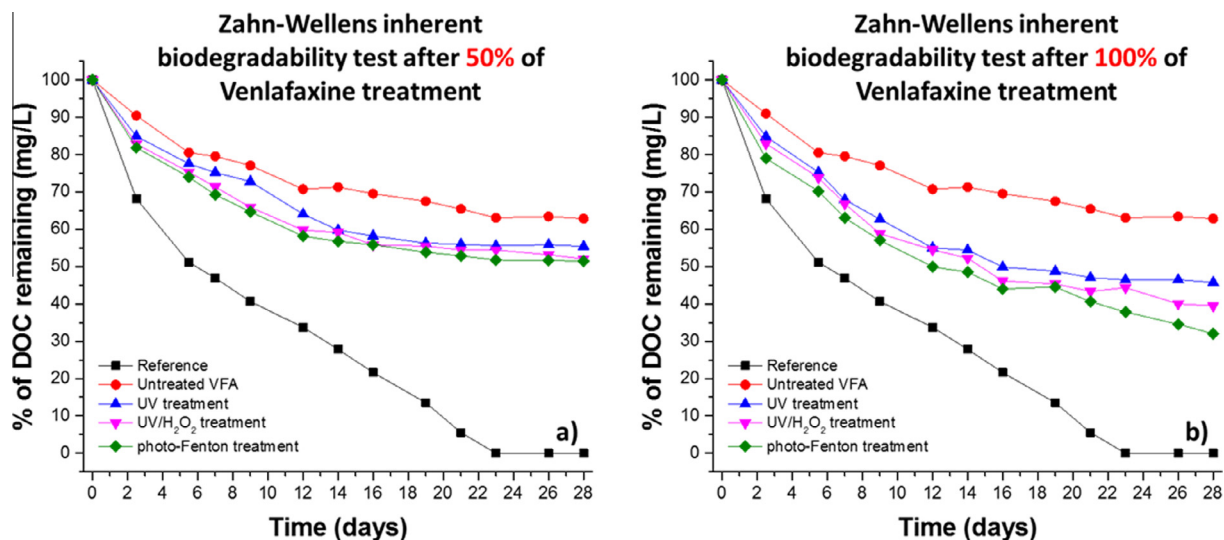**Fig. 9.** Combined Venlafaxine degradation pathway.

Fig. 10. Zahn-Wellens inherent biodegradability test of Venlafaxine and treated solutions. (a) ZW test after treatment of 50% of the initial VFA solution. (b) ZW test after treatment of 100% of the initial VFA solution. Note that results are normalized towards the initial DOC to enable comparison.

Transformation of Venlafaxine can occur via four dominant reactions: (1) sequential hydroxylation of the aromatic ring, (2) transformation of the methoxy- group, (3) hydroxylation and shortening of the cyclohexanol ring and (4) attack on the nitrogen group. Firstly, the degradation pathway of VFA was sequential hydroxylation: once hydroxylated VFA yielding m/z 294.2072 (P8) was identified in all treatments except solar treatment; followed by di-hydroxylated product with m/z 310.202 (P9) identified in UV, UV/H_2O_2 and photo-Fenton treatment; and tri-hydroxylated product with m/z 326.1956 (P10) identified only in the UV treatment (Treatment B). The sequence of the identified hydroxylated degradation products implies that UV light was the main driving force in the multiple hydroxylation of the aromatic ring. Here, the identified products were also reported in the literature [23,24,29,48]. Santoke et al. identified two products formed by the attack of HO· radical on the aromatic ring and the N-chain, but they were not identified in this study (marked with red dashed arrow in the degradation pathway) [29].

A second degradation pathway started with dehydrated Venlafaxine's product m/z 260.2012 (P6), identified in all degradation procedures. Combinations of dehydration and hydroxylation reactions present a transformation pathway also dominant for VFA UV/TiO_2 treatments [24]. HO· attack on the tertiary C-atom and cyclohexanol structure led to the formation of products with m/z 215.1431, m/z 229.1429 and m/z 292.1914; P4, P5 and P7, respectively.

Demethylation presents a well-known VFA transformation route in biological and chemical reactions [29,49,50]. Transformation of the methoxy group was identified within the products m/z 121.0654 (P1), m/z 178.1231 (P2) and m/z 194.1182 (P3), which were at the same time the final degradation products. Aliphatic nitrogen products identified by Garcia-Galan et al. [23], were not identified in this study, however they were also included in the degradation scheme (marked with blue dashed arrow in the degradation pathway) to complement the overall VFA degradation routes. It should be noted that the structures of identified products for different UV/H_2O_2 treatments depend not only on the reaction time, but also on the H_2O_2 concentration used in the experiments. Finally, the appearance of apparent biodegradable compounds calls for assessment of the biodegradability assessment of VFA and the AOP-treated effluents containing it.

3.4.2. Zahn-Wellens (ZW) biodegradability test of AOP-treated Venlafaxine solutions

As literature suggests low removal of VFA in WWTPs, we assessed the biodegradability of VFA, by subjecting it first through an AOP. This strategy has been successfully used in various effluents [51,52]. Therefore, treatment of VFA solutions until 50% and 100% initial concentration degradation, along with a reference compound (diethylene glycol) and untreated VFA were subjected to a 28-day Zahn-Wellens inherent biodegradability tests [53,54]. In parallel, DOC was followed at the corresponding blanks (test suspension and inoculum blank). In order to avoid self-inhibition problems, the initial VFA amount was reduced to 10 mg/L. The results of the study are summarized in Fig. 10.

First of all, the test is considered valid as 70% of the initial DOC of the reference compound has been degraded (>72%) within 14 days. This indicates the suitability of the activated sludge inoculum. Secondly, VFA alone was removed at 35%, which corresponds to similar degradation rates of VFA in biological treatment facilities (see Table 4). As far as the applied AOPs are concerned, 50% pre-treatment of VFA resulted in 20–25% biodegradability improvement. The most efficient process was the photo-Fenton reaction, only by marginal difference. According to TOF-MS analysis for VFA in this work, and Orbitrap-MS for Iohexol [44], using AOPs where iron is involved always leads to enhanced modifications on the target contaminant. If VFA was eliminated 100% a further 10–15% was achieved, depending on the process. This indicates that over the course of 28 days, almost 70% of the initial DOC was eliminated, reaching the threshold for considering the solution biodegradable. Of course, further treatment of the parent solutions would achieve the threshold with greater ease, and correlation with the initial DOC removal should be made instead. Hence, by extrapolation, it could be possible to propose a pre-treatment step in industries or hospitals, where mass flows of similar contaminants are released, if the said facilities do not employ their own WWTPs, as it would seriously ease the burden off the municipal WWTPs.

4. Conclusions

The ubiquitous presence of drugs in surface waters demands strict control frameworks and efficient removal methods at the

level of WWTPs. Under this scope, the degradation of the antidepressant Venlafaxine was systematically investigated, through the application of 5 AOPs. UV-based technologies (UV-C light alone and UV/H_2O_2) and Fenton-related techniques (solar photolysis, Fenton and photo-Fenton oxidation) were assessed as control measures and their efficiency was estimated.

The investigation on the degradation kinetics has shown that Venlafaxine demonstrates moderate photolysis under UV, and the addition of H_2O_2 with the simultaneous HO· generation enhances the degradation potential of the chosen treatment. On the other hand, solar photolysis was found limited, but in combination with the action of the Fenton process (in the dark), the photo-Fenton process was efficient in degrading the contaminant, with decreasing, but not diminishing performance tendencies as we approached the neutral pH.

The tests in wastewater and urine revealed a drop in efficiency, due to the presence of antagonists in the matrix. Urban wastewater and human urine tests indicated that the actual conditions expected in the field demand intensive treatment; in wastewater the degradation of Venlafaxine is subjected to similar problems as most ng L^{-1} contaminants present, but the efficient removal is possible, and the human urine experiments indicate an innovative treatment proposal, by the use of UV to collect and treat on-site the emerging contaminants, and addition of H_2O_2, if high simultaneous DOC removal is desired, before dispersion in the wastewater matrices.

The mechanistic interpretation (degradation pathway) based on our own TOF-MS experiments and recent advances in the field revealed the opportunity of converting Venlafaxine to its biodegradable intermediates. The Zahn-Wellens tests performed showed that pre-treatment of Venlafaxine solutions increases biodegradability, and under certain conditions, conversion of the mixture of intermediates into biodegradable is possible.

In the light of the above findings, we conclude that the non-selective and highly oxidative character of the Advanced Oxidation Processes is capable in controlling substances before their discharge in natural aquifers and their upcoming environmental consequences. Environmental protection has a well-established ally in traditional contaminant categories (priority pollutants, organic matter) and the application of AOPs can play a role of outmost importance towards this direction in the near future.

Acknowledgments

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.cej.2016.09.084.

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