

High throughput screening of photocatalytic conversion of pharmaceutical contaminants in water

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High throughput screening of photocatalytic conversion of pharmaceutical contaminants in water[☆]



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ABSTRACT

The susceptibility for photon-induced degradation of over 800 pharmaceutical compounds present in the LOPAC¹²⁸⁰ library, was analyzed by UV/Vis spectroscopy in the absence or presence of TiO₂ P25 in water. In general, few compounds were effectively degraded in the absence of the TiO₂ photocatalyst (3% of all compounds tested), while in the presence of TiO₂, the majority of compounds was converted, often to a large degree. Differences in degree of degradation are evaluated on the basis of molecular weight, as well as the chemical nature of the drug compounds (functional groups and pharmacological classes). In general, if the molecular weight increases, the degradation efficacy decreases. Relatively high degrees of conversion can be achieved for (relatively small) molecules with functional groups such as aldehydes, alcohols, ketones and nitriles. A low degree of conversion was observed for compounds composed of conjugated aromatic systems. Trends in degradation efficacy on the basis of pharmacological class, e.g. comparing hormones and opioids, are not obvious.

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1. Introduction

The increase in concentration of emerging contaminants in waste water (pharmaceuticals, metabolites, endocrine-disrupting drugs) raises health concerns, and might disturb the general balance of the ecosystem (Halling-Sorensen et al., 1998; Hernando et al., 2006). Caffeine, codeine, naproxen, acetaminophen, diclofenac, ofloxacin and ibuprofen, have been reported to be present in surface and ground water in the range of a few ng L⁻¹ to a few mg L⁻¹ (Bueno et al., 2012; Fatta-Kassinos et al., 2011). Standard wastewater treatment, either chemical or biological, is unable to completely degrade these emerging contaminants (Joss et al., 2006; Radjenovic et al., 2008). Advanced oxidative processing (AOP)

eliminates some of these compounds from water, making use of the *in situ* generation and subsequent reaction of (unselective) hydroxyl radicals (HO[•]) (Hoffmann et al., 1995; Lee and Park, 2013). The disadvantage of this technology is that sacrificial agents, such as iron salts and/or hydrogen peroxide, are needed (Lee and Park, 2013). Heterogeneous photocatalysis can also induce complete mineralization of organic contaminants to CO₂ and H₂O (Spasiano et al., 2015). Decomposition in such process is achieved through the generation of intermediary oxidative species (HO[•], O₂^{•-}), created by reduction of oxygen and oxidation of water by electron-hole pairs, formed when a semiconductor (ZnO, WO₃, or TiO₂) is exposed to light (Hoffmann et al., 1995). Photocatalysis is considered highly sustainable, and the fact that the technology does not require sacrificial agents or high pressure or temperature, but only an environmentally benign, cheap semiconductor (TiO₂), makes it very attractive. Titanium dioxide (TiO₂) is the most effective photocatalyst for water treatment applications so far described, particularly due to its high stability in water (Chong et al., 2010).

Photocatalysis approaches have previously been evaluated for removal of organic compounds from water, such as dyes, phenols

[☆] This paper has been recommended for acceptance by Charles Wong.

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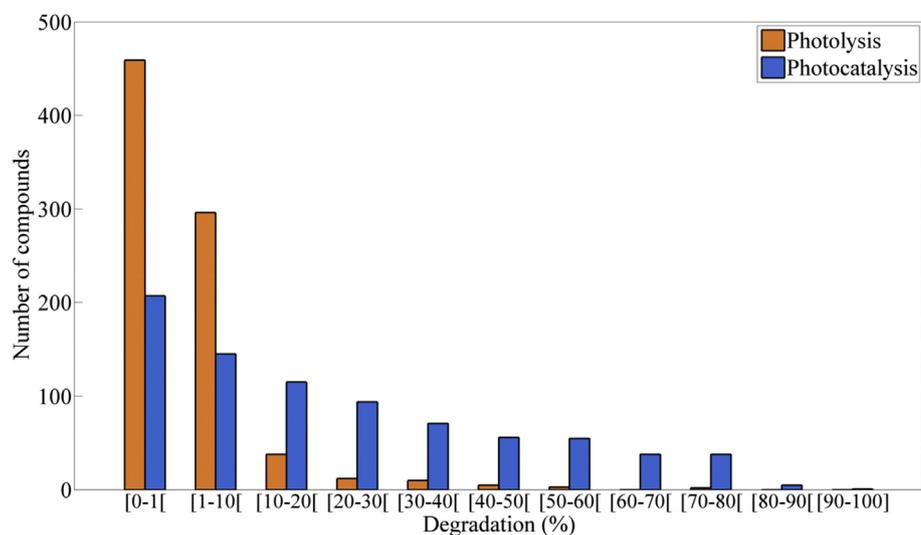


Fig. 1. Ranking of the compounds in a LOPAC¹²⁸⁰ library, based on the degradation percentages achieved after 5 min illumination either by photolysis (375 nm exposure) or photocatalysis (375 nm exposure, TiO₂ P25).

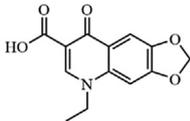
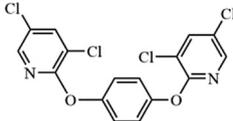
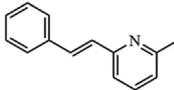
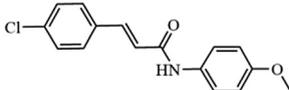
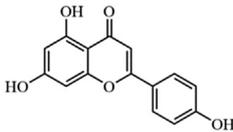
and pharmaceuticals (diclofenac, naproxen) (Ahmed et al., 2011; Dalrymple et al., 2007; Malato et al., 2007). However, to the best of our knowledge, little is known about the degradation mechanism of these compounds and which specific molecular functionality enhances the susceptibility to photocatalytic degradation.

High throughput screening (HTS) is a powerful tool to evaluate the degradation probability of a wide variety of drug-related

compounds, and to help identify whether this probability is a function of specific functionality in the molecular structure. Two analytical methods were previously used for combinatorial screening of photocatalytic degradation: the first is High Performance Liquid Chromatography (HPLC) (Lettmann et al., 2001), used in evaluation of the decomposition of 4-chlorophenol, and the second fluorescence imaging, used for study of the decomposition

Table 1

Comparison of selected compounds in photolytic or photocatalytic degradation percentages.

Compounds	Photolysis degradation (%)	Photocatalytic degradation (%)
 Oxolinic acid	76	80
 TCPOBOP	44	57
 SIB 1893	42	40
 SB-366791	57	83
 Apigenin	6	63

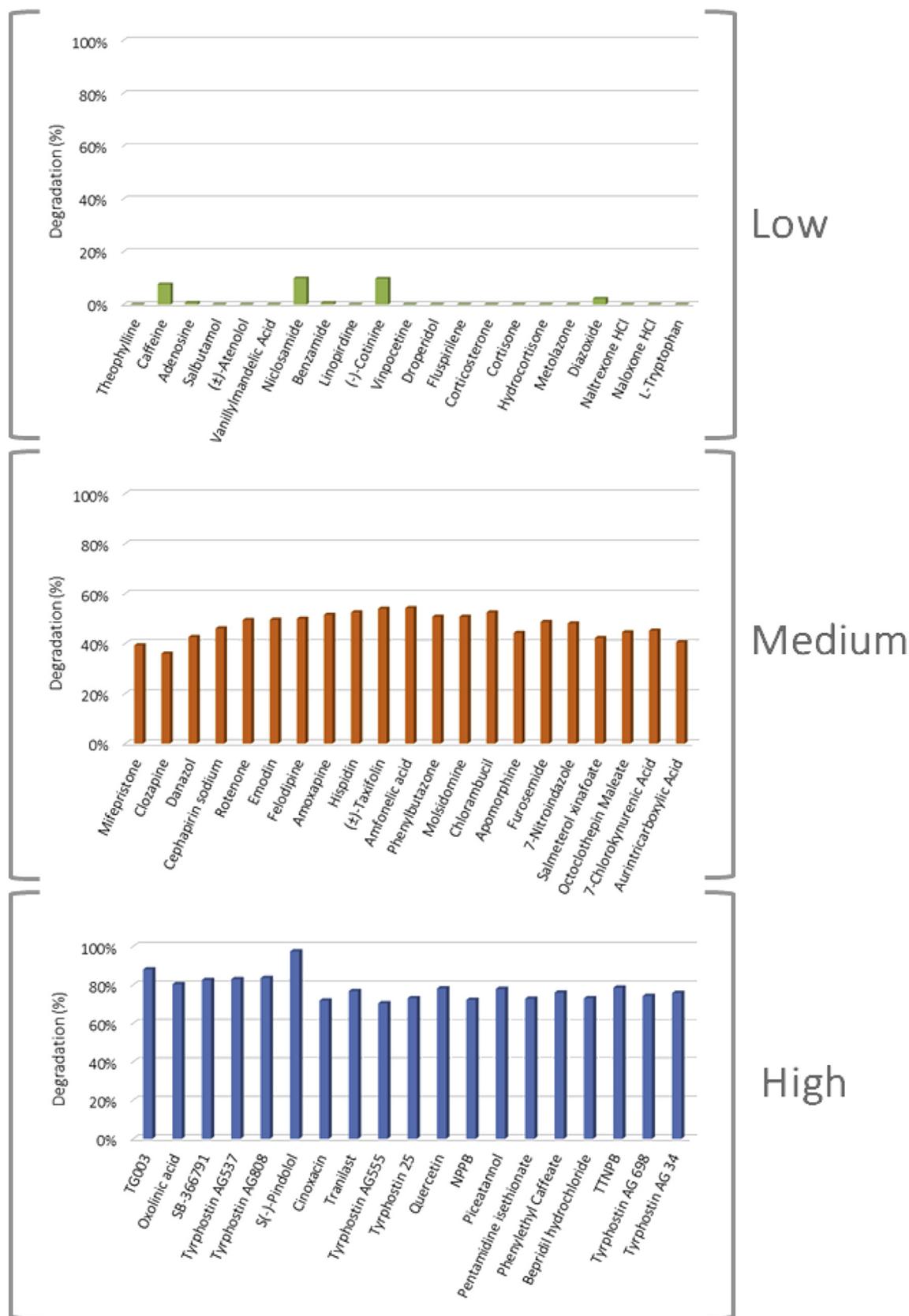


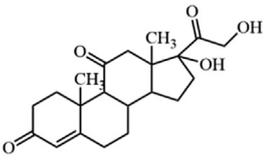
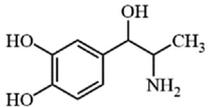
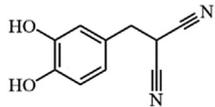
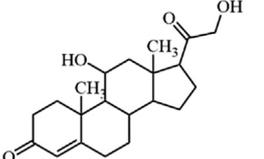
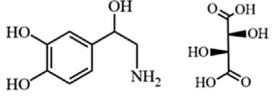
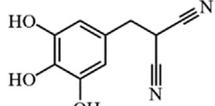
Fig. 2. Photocatalytic degradation percentages achieved for some of the most representative compounds in LOPAC¹²⁸⁰.

of 1,6-hexamethylenediamine (Xiao et al., 2006). One of the most elaborate studies reported to date describes the substrate-specific activity of eight commercial TiO₂ samples to decompose 19

different substrates (Ryu and Choi, 2007).

In this work we describe, for the first time, a HTS assay to study oxidative photodegradation efficacy of compounds present in a

Table 2
Compounds with similar chemical functionality and the respective degradation percentages. The similarity results suggests consistency of the 96-well plate method.

Compounds	Degradation (%)	Compounds	Degradation (%)	Compounds	Degradation (%)
	0		17		75
Cortisone		(-)-alpha-Methylnorepinephrine		Tyrphostin 23	
	0		18		73
Corticosterone		(±)-Norepinephrine (+)bitartrate		Tyrphostin 25	

LOPAC¹²⁸⁰ library, which is a library of 1280 pharmacologically active compounds divided in drug target classes, such as hormones and neurotransmitters. A miniaturized microplate photo-reactor, in combination with a UV–Vis microplate spectrometer were used for analysis, as described previously by Romão and coworkers (Romão et al., 2015). Although visible light sensitive catalysts exist, such as BiVO₄ or WO₃, the efficacy is typically significantly smaller than of TiO₂-P25 upon UV excitation. TiO₂-P25 was therefore chosen as photocatalyst, which also allows for a better comparison with existing literature.

2. Materials and methods

2.1. Materials

To evaluate the ability of photocatalysis to oxidize pharmaceutical compounds, a LOPAC¹²⁸⁰ library was used, obtained from Sigma Aldrich. LOPAC¹²⁸⁰ is a library of pharmacologically active compounds dissolved in dimethyl sulfoxide (DMSO), comprising FDA-approved molecules and other drugs used in industrial processes, thus making it a very suitable for the purpose of this study. Evonik TiO₂ P25 was used as the photocatalyst, and used without modification.

2.2. Microplate photo-reactor setup for LOPAC¹²⁸⁰ screening

The experimental setup used for determination of photocatalytic efficacy was described and validated previously (Romão et al., 2014). To initiate a photon-induced degradation experiment, the LOPAC¹²⁸⁰ library was distributed over sixteen 96-well plates (concentration of 2000 μM). In the absence of catalyst, 25 μL of the library solutions were diluted in demineralized water to reach the final working volume of 200 μL (final concentration 25 μM) in UV transparent 96-well microplates (Corning). To evaluate photocatalytic efficacy, an aqueous slurry of TiO₂ P25 at 0.25 g L⁻¹ was prepared and transferred in equal volumes (192.4 μL/well) to the 96-well plates, followed by the addition of 27.6 μL from the LOPAC¹²⁸⁰ stock solution, resulting in a final working volume of 220 μL (final concentration of 25 μM). The concentration of the compounds in the library was thus typically in the range of 1.1–37.6 mg/L. We like to stress that in urban wastewater effluents, antibiotics such as ibuprofen, metronidazole and atenolol were found at the respective concentrations of 0.15, 0.09 and 0.12 mg/L

(Fatta-Kassinos et al., 2011), significantly lower than applied here. The (equimolar 25 μM) concentration range of 1.1–37.6 mg/L was chosen on the basis of the detection limit of the UV spectrometric method.

In both experimental conditions (photolysis and photocatalysis), the 96-well plates were illuminated from the top with a multi-tubular light source at a distance of 5 cm (3.21 mW cm⁻², 360–380 nm) for 5 min. In the case of the photocatalytic experiment, the aqueous suspension was transferred into a 96-well filter microplate (Corning, hydrophilic 0.2 μm PVDF membrane) and the solution filtered into a new 96-well microplate by centrifugation at 300 rpm for 3 min in order to separate-off the photocatalyst. Afterwards, just 200 μL was transferred into a new UV transparent 96-well microplate (Corning). This guarantees an equal volume *per well* and the same path length, *l*, required for proper application of the Lambert-Beer law ($A = \epsilon \cdot l \cdot c$) when using the microplate spectrophotometer (Multiskan™ GO, Thermo Scientific). Measurements were processed and used to assess the degradation profile of each compound, in each well, through the intensity decrease in absorbance spectra (at peak value). Previous to any reaction, the maximum in the absorbance spectrum for each compound was determined in the spectral range of 200–800 nm, and used for concentration determination (the spectrum of DMSO in water was used as background).

2.3. Data analysis

The spectral data obtained (photolysis and photocatalytic degradation) for each compound of the LOPAC¹²⁸⁰ library were saved into a spreadsheet forming a dataset. Afterwards, information about the molecular weight, pharmacological class and functional groups was gathered and stored for all compounds. For data handling and further processing, the dataset was imported into MATLAB, used for clustering and extraction of relevant information. Series of scripts were therefore created to cover data mining steps involving data pre-processing, management and visualization (bar graphs, scatter and box plots).

3. Results and discussion

3.1. Photolysis vs photocatalysis

Prior to the determination of the photo (catalytic) conversion

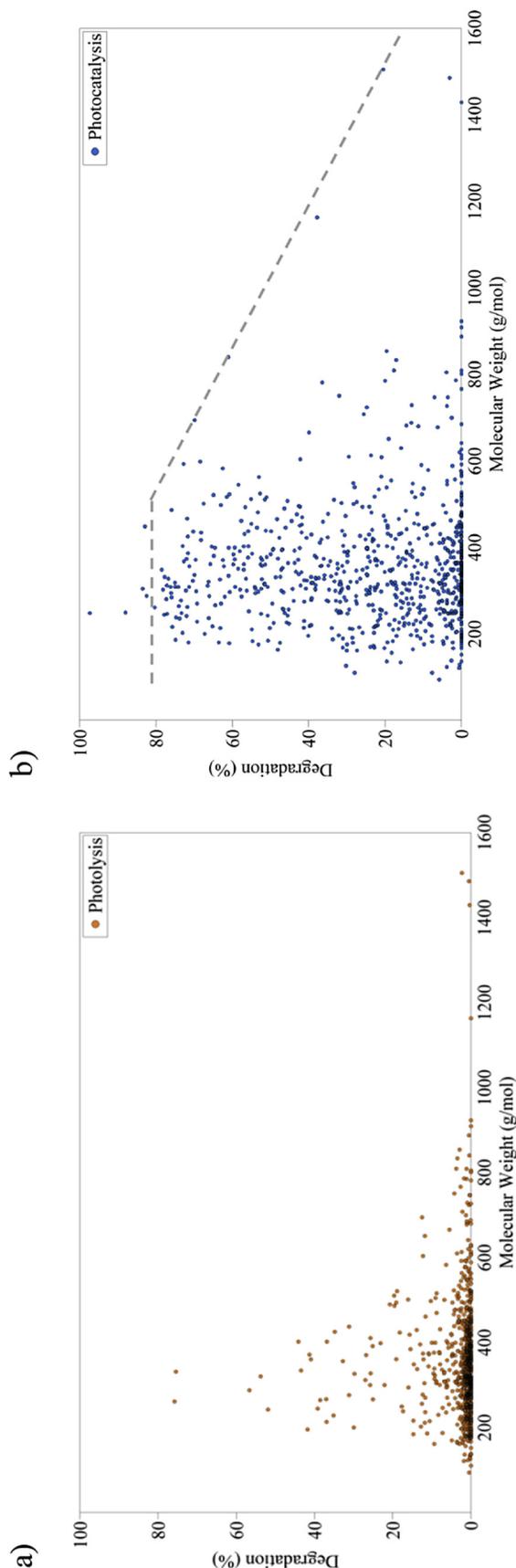


Fig. 3. MW distribution correlated with degradation percentage. a) Photolysis. b) Photocatalysis. The dashed grey line is only indicative. When the MW increases, the maximum degradation percentage generally decreases.

efficiency, UV–Vis spectra of the 1280 compounds were measured. Several compounds had to be excluded from the study, since they did not show any UV/Vis absorption peak. From the initial 1280 compounds, 825 compounds were found suitable for further analysis. Other methods, such as LC–MS, should be used to study the degradation rate of the other 455 compounds, but such analysis is hard to conduct in a combinatorial fashion. An overview of the results for the 825 compounds from LOPAC¹²⁸⁰ is shown in Fig. 1. TiO₂ P25 induced photocatalysis is clearly superior over photolysis, showing a significantly higher number of compounds with high degradation percentages. Photolysis could only decompose few compounds up to degradation efficiencies of 40% (5), 50% (3) and 70% (2).

In Table 1, some of the few compounds showing high degradation percentages solely by photolysis are highlighted. Notably, the degradation of these compounds (oxolinic acid, TCPOBOP, Molsidomine, SIB 1893 and SB-366791) was not significantly higher in the presence of the photocatalyst. A common feature of the compounds decomposed merely by photolysis, is the presence of benzene and pyridine rings, apparently yielding compounds susceptible to oxidation upon photo-activation. Certainly the efficacy in photochemical degradation will be higher for most compounds when lower excitation wavelengths than 360–380 nm would have been used. Oxolinic Acid has an absorption maximum at 366 nm, which explains the high photochemical degradation percentage.

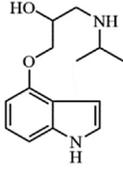
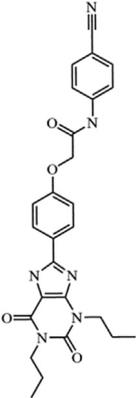
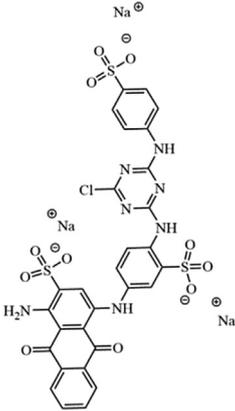
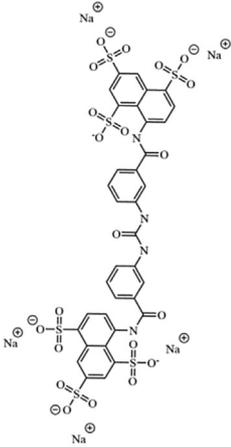
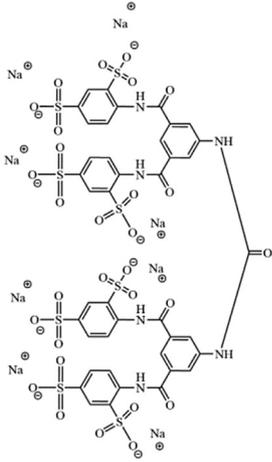
For the large majority the presence of TiO₂ P25 significantly increases the percentage of degradation, such as of Apigenin (Table 1).

Fig. 2 shows the respective photocatalytic degradation percentages of a large set of selected compounds from the LOPAC¹²⁸⁰ library. The results are categorized by High, Medium and Low levels of degradation (after 5 min of illumination). In the group of a low degree of degradation are compounds such as caffeine, adenosine and cortisone, while in the group of a high degree of degradation are (S)-pindolol and several compounds from the tyrothostin family (drugs that inhibit enzymes responsible for the activation of certain proteins). The high reproducibility of the screening method is confirmed by the results shown in Table 2: compounds with similar chemical backbone tend to have similar degradation values in photocatalysis.

3.2. Molecular weight (MW)-dependent degree of conversion

Fig. 3 shows an attempt to correlate the MW of the substrate and the percentage of degradation, both in photolysis and photocatalysis configuration. As previously observed, in photolysis a lower degree of degradation is predominant. In Fig. 3.b, a decreasing trend in maximum degradation rates seems to be present as a function of increasing MW. Nevertheless a relation between MW and degradability of the organic molecules is not obvious. Only above 500 g mol⁻¹ the maximum achievable percentage is significantly lower. For compounds with a MW around 250 g mol⁻¹ up to 97% degradation was frequently achieved, whereas molecules with a MW higher than 500 g mol⁻¹ show lower (maximum) values. This is in agreement with the perception that more time is needed to break and oxidize all the chemical bonds. Table 3 highlights a few organic compounds with different MW and their corresponding decomposition percentage. On the basis of these data, the dashed gray line in Fig. 3.b was drawn, reporting the local maxima. Table 3 clearly shows that when the MW increases, the complexity in the chemical backbone also increases, which likely contributes to the fact that degradation becomes more difficult. Another important factor is derived from the interaction between the compounds with the catalyst surface that

Table 3
Compounds with different MWs and their degradation percentages.

Molecular Weight (g/mol)	248	487	840	1163	1500
Compounds					
	S(-)-Pindolol	MRS 1754	Reactive Blue 2	NF 023	NF449 octasodium salt
Degradation (%)	97,37	75,99	61,07	37,82	20,47

can be affected by the molecular structure flexibility/rigidity which increases with increasing MW.

3.3. Pharmacological classes

The LOPAC library can be divided in drug target classes, e.g., GPCRs (G protein-coupled receptors), ligands, hormones and neurotransmitters. Neurotransmitters can again be subdivided in other classes, such as adenosine, adrenoceptors, histamine, imidazoline, and opioids, among others (Sigma-Aldrich). Fig. 4 shows degradation percentages organized by pharmacologically active classes. In this Figure, central values (vertical black line which indicates the

mean) never exceed degradation percentages above 10% for photolysis. Leukotriene and melatonin stand out for their relatively high degradation values, when compared to other compounds. The leukotriene class does not have a characteristic chemical group, but includes benzene, ester, amine and carboxylic acid functionality.

On the other hand, the compounds within the melatonin class usually have indole (benzene and pyrrole rings) and amide groups, suggesting that these are susceptible to oxidation upon light activation.

Histamine, imidazoline, GABA and opioids are the least susceptible to photocatalytic degradation. The histamine class covers derivatives from imidazole with a side-chain amine, similar to

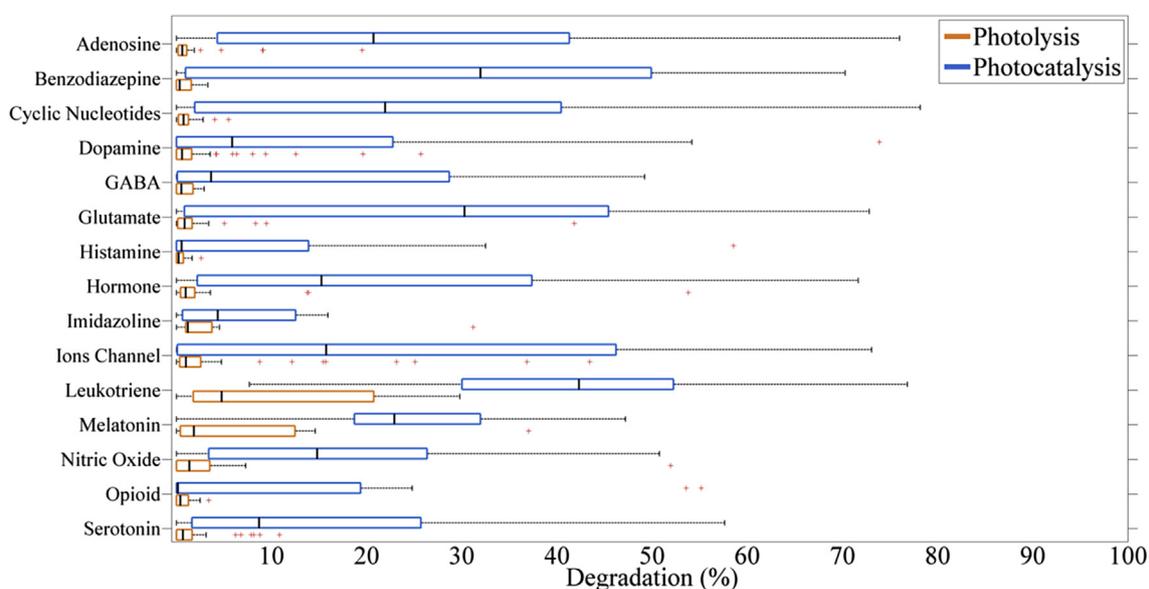


Fig. 4. Pharmacological classes selected from the LOPAC1280 library, and the corresponding degradation distribution for photolysis and photocatalysis. The blue (photocatalysis) or orange (photolysis) bars indicate the percentage range to which most of the compounds were degraded, while the grey lines (photocatalysis) or single dots (photolysis) represent significantly lower probability. The mean is indicated by the vertical black line in both cases. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

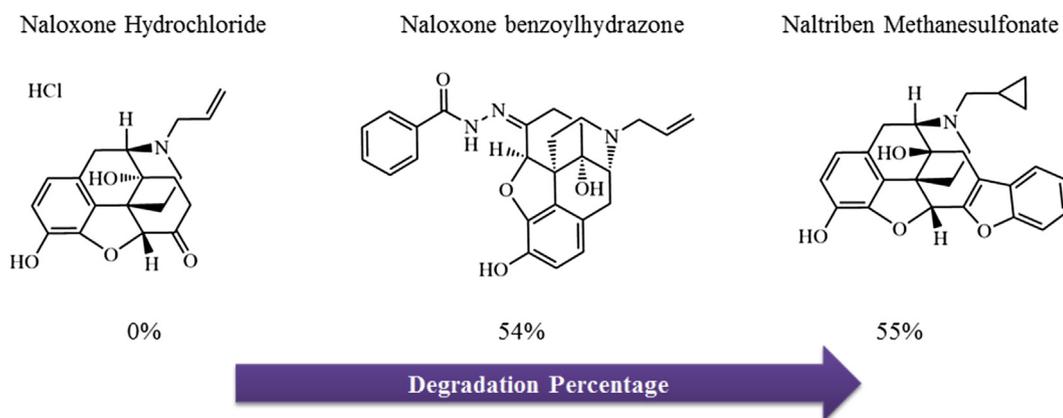


Fig. 5. Compounds from the opioid class and the corresponding degradation percentages achieved by photocatalysis.

many derivatives from this family present in the library. A salt of histamine (histamine dihydrochloride) was not degraded, and a similar compound, 4-Imidazoleacrylic acid, undergoes only 2% of degradation. Imidazolines, the name given to the derivatives of imidazole, also showed very low degradation percentages (Fig. 4). The Imidazole molecule is difficult to be oxidized or, at least, demands more reaction time for dis-colorization. The compounds included in the opioid class resemble morphine, containing aromatic rings and a quaternary carbon atom bound to a tertiary amine group linked to two carbon atoms. This class also shows a very low degradation percentage, as show in Fig. 4. Naloxone hydrochloride, naltrexone hydrochloride, levallorphan tartrate which have a very similar chemical structure to morphine, showed hardly degradation. Higher degradation percentages were obtained for naloxone benzoylhydrazone and naltriben methanesulfonate, which might be ascribed to the presence of an additional phenyl group or an azo bond (N=N). The oxidation reaction might be initiated by the activation of these groups (Fig. 5).

It has been described that morphine can be completely mineralized by photocatalysis (Lin et al., 2013), however the concentration used was 3.5 μM . In the present screening study, the concentration was significantly higher, at 25 μM . The fact that other opioids, such as naltriben methanesulfonate could be mineralized by 50%, confirms that this class is suitable for degradation by photocatalysis.

The adenosine class includes, as the name implies, adenosine, adenine, or caffeine molecules, and derivatives thereof. From this class, 82% of the compounds showed a degradation percentage

below 50%. Theobromine is an exception, and 71% conversion was reached. Caffeine is a compound present at high concentrations in sewage and it has been reported that its complete mineralization is difficult to achieve (Carotenuto et al., 2014; Matsuo et al., 2004), which is confirmed by the results obtained in our study.

The Adrenoceptor class comprises compounds such as epinephrine (adrenaline) and norepinephrine (noradrenaline), which consists of a 1,2-dihydroxybenzene molecule with a side-chain amine and derivatives. In the case of adrenaline and noradrenaline, the degradation percentages achieved were respectively 3 and 18%, showing potential for degradation by photocatalysis. In the literature the photocatalytic degradation reported for a compound from the same class, atenolol, is 10% (Ji et al., 2013), in agreement with the percentage range obtained in the present study.

Hormones comprise another class of compounds represented in LOPAC¹²⁸⁰, including molecules from the corticosteroids family (compounds with three to six-carbon rings combined with a five-carbon ring). Examples of this are corticosterone, cortisone, and hydrocortisone, among others. However, while these were not degraded, other steroid hormones such as progesterone and 4-Androsten-4-ol-3,17-dione yielded degradation percentages of 32% and 58%, respectively. Fig. 6 shows that this class of compounds can be degraded by photocatalysis and that small differences in the functional groups can affect the degradation percentages observed. A derivative of cortisone, cortisone-acetate, can be degraded by this method, however to fully mineralize this compound with a concentration of 25 μM , 90 min of illumination were necessary (Romão

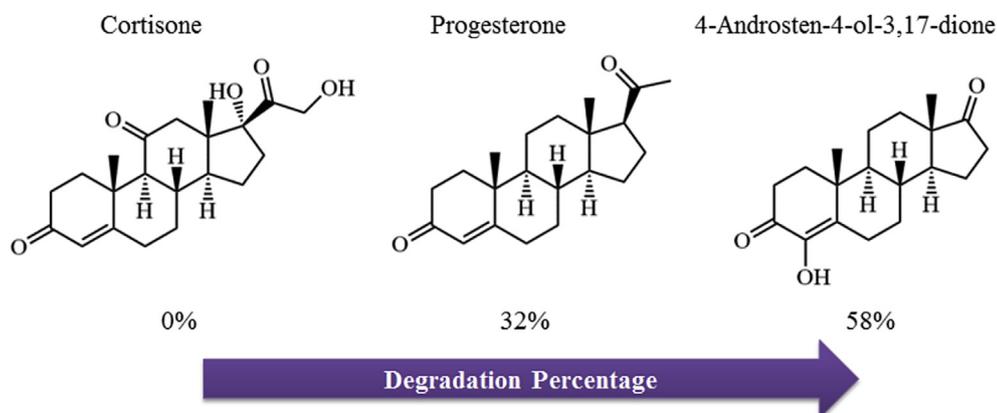


Fig. 6. Compounds belonging to the corticosteroids family and their corresponding degradation percentages achieved by photocatalysis.

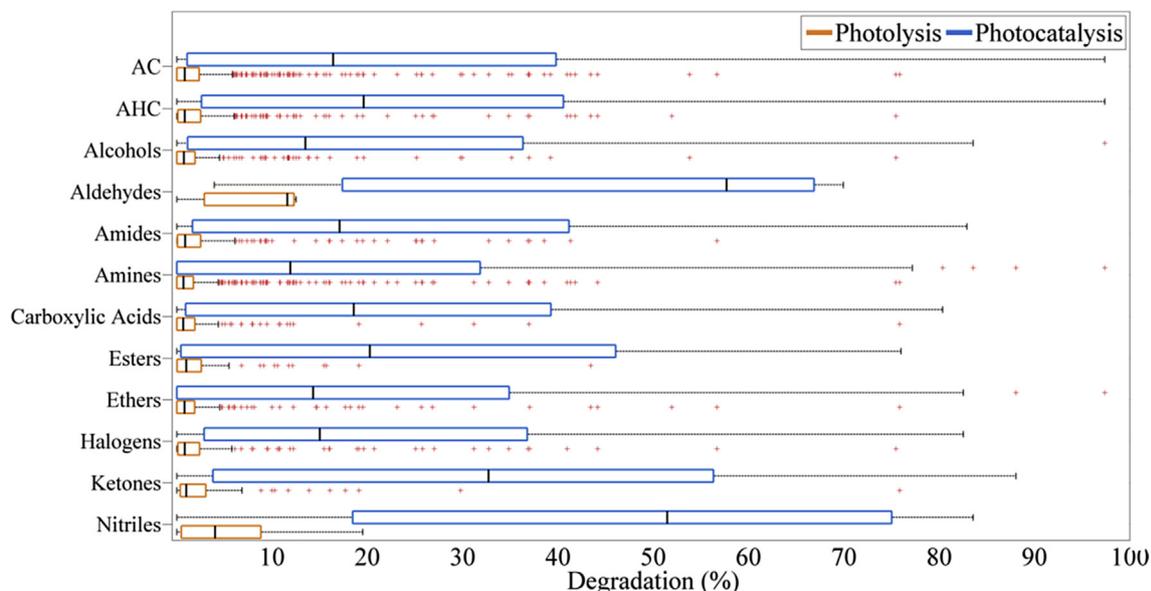


Fig. 7. Degradation percentages for different functional groups. The blue (photocatalysis) or orange (photolysis) bars indicate the percentage range to which most of the compounds were degraded, while the grey lines (photocatalysis) or single dots (photolysis) represent significantly lower probability. The mean is indicated by the vertical black line in both cases. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

et al., 2015).

Melatonin and derivatives thereof, were relatively easy to degrade. This class of compounds has a specific chemical group, being an indole molecule with a side-chain amide. Likely, these groups contribute to relatively easy oxidation (Merabet et al., 2009).

It should be noticed that not all the classes present in the LOPAC¹²⁸⁰ library are necessarily associated with (a) specific chemical group(s) or backbone unit, but rather categorized by its biological functionality. Therefore, further analysis is done targeting the effect of the chemical nature of the compounds used in this study.

3.4. Further focus on functional groups

Each compound from the LOPAC¹²⁸⁰ library was characterized by its intrinsic chemical nature, considering its structural composition and chemical bonds. The functional groups considered were: aromatic cyclic (AC) compounds, aromatic heterocyclic (AHC) compounds, alcohols, aldehydes, amides, amines, carboxylic acid, esters, ether, halogens, ketones and nitriles. Fig. 7 shows an elaborated view of the degradation percentages on the basis of these functional groups.

For various functional groups, the range in degradation percentage is broad, but we still find the difference in mean (average) degradation percentage for various functional groups significant, providing interesting leads in particular for substrate susceptibility towards TiO₂ induced photocatalytic conversion. There are some functional groups that show relatively high susceptibility for degradation: aldehydes, ketones and nitriles. Looking at the compounds included in the aromatic heterocyclic (AHC) group, indole molecules stand out, which is in agreement with the results found for the melatonin class.

Finally, in order to understand why 207 compounds (Fig. 1) were not degraded, their chemical structure was evaluated in more detail. Overall, these molecules contain cyclic aromatic compounds and are derivatives of purine, caffeine, pyrimidine, pyridine and imidazoline.

To explain differences in susceptibility of compounds for photocatalytic degradation, some aspects of the mechanism of photocatalytic degradation should be considered. When the oxidation mechanism involves reaction of the substrates with dissolved hydroxyl radicals, (generated upon light activation on the surface of TiO₂, followed by desorption), little effect of the functional groups can be expected. However, an alternative mechanism involves adsorption of molecules on the surface of TiO₂, followed by direct transfer of photo-generated holes to the adsorbed molecules. It is well known that susceptibility for adsorption on oxide surfaces is very much dependent on functional groups of molecules, and the difference in observed reactivity might be associated with such adsorption-based mechanism.

The results presented here should be considered preliminary. Obviously, the kinetics and formation of intermediates in the degradation process are relevant and need to be studied in more detail, especially as a function of process conditions. Comparing degradation kinetics of molecules with large molecular mass at longer degradation times, should also be performed, to identify intermediate products and degradation pathways. To this end, the use of analytical techniques, such as HPLC in combination with MS, is viable. We also recommend future study of the eco-toxicity of the compounds of the library, to determine urgency of mitigation. Finally the eco-toxicity of partially oxidized intermediates (if any) should be considered, which might be even more toxic than the undegraded pharmaceutical compounds.

4. Conclusions

This study evaluates the applicability of TiO₂ P25, by far the most used photocatalyst, to eliminate new emerging contaminants from wastewater, included in the LOPAC¹²⁸⁰ library.

High degradation efficiencies were obtained for molecules with functional groups such as aldehydes, alcohols, ketones, nitriles, and amides. Indole derived molecules were particularly susceptible towards photocatalytic degradation. Compounds with conjugated aromatic systems, and derivatives from compounds such as adenosine, caffeine and imidazole, were relatively difficult to convert by

TiO₂-based photocatalysis and showed low degradation values.

UV–Vis spectrometry provides an easy, fast and reliable quantification method. However, it does not allow to follow intermediates or confirm if the molecules were completely converted into CO₂ and H₂O (and Nitrate). This requires more elaborate study and analysis by e.g. HPLC-MS.

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