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Fate of citalopram during water treatment with O_3, ClO_2, UV and fenton oxidation

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HIGHLIGHTS

- Citalopram was degraded by O_3, ClO_2, UV-irradiation and fenton oxidation.
- Five transformation products of citalopram were identified.
- Three transformation products are new to the science.

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ABSTRACT

In the present study we investigate the fate of citalopram (CIT) at neutral pH using advanced water treatment technologies that include O_3, ClO_2 oxidation, UV irradiation and Fenton oxidation. The ozonation resulted in 80% reduction after 30 min treatment. Oxidation with ClO_2 removed >90% CIT at a dosage of 0.1 mg L^{-1}. During UV irradiation 85% reduction was achieved after 5 min, while Fenton with addition of 14 mg L^{-1} (Fe^{2+}) resulted in 90% reduction of CIT. During these treatment experiments transformation products (TPs) were formed from CIT, where five compounds were identified by using high resolution and tandem mass spectrometry. Among these desmethyl-citalopram and citalopram N-oxide have been previously identified as human metabolites, while three are novel and published here for the first time. The three TPs are a hydroxylated dimethylamino-side chain derivative, a butyrolactone derivative and a defluorinated derivative of CIT.

1. Introduction

Pharmaceuticals are chemical substances designed to produce a pharmacological effect in humans and animals, and are being used in ever increasing amounts in both human and veterinary medicine. The discharge of these agents from the hospital, municipal or industrial wastewater treatment plants (WWTPs) or the improper disposal of unwanted drugs results in the contamination of environmental waters, where the WWTPs are a major point source (Kosjek et al., 2008). The persistence of the parent pharmaceuticals together with their continuous intake and release are leading to detectable concentrations in surface waters (Wiegel et al., 2004) and may represent a direct threat to the aquatic wildlife and a potential health risk to humans (Hao et al., 2006).

Selective serotonin reuptake inhibitors (SSRIs) are effective antidepressant drugs and representative of these is citalopram (CIT) 1-(3-dimethyaminopropyl)-1-(4-fluoro-phenyl(-5-phthalancarbonitrile), which is highly prescribed in Northern Europe, e.g. in Norway, Denmark and Finland with the consumption of 120–160 g per 1000 inhabitants (Christensen et al., 2007) and included in lists over the top sold prescribed pharmaceuticals (Nuijs et al., 2010; Official Statistics of Sweden, 2010), as well as elsewhere in the world (Kosjek and Heath, 2010). CIT is marketed under the trade names, Cipramil® or Celexa®. In humans it is metabolized into the active metabolites desmethylcitalopram (DCIT), di-desmethylcitalopram (DDCIT), citalopram-N-oxide (CIT-NO) and into an inactive deaminated propionic acid derivative; between 12% and 23% of CIT is excreted unaltered in the urine (Arrow–Citalopram, 2011). After excretion it is released into wastewaters and has been determined in both WWTP influents and effluents and in receiving waters (Lamas et al., 2004; Himmelbach et al., 2006; Lajeunesse et al., 2008; Schultz and Furlong, 2008; Vasskog et al., 2008; Metcalfe et al., 2010). The concentration of CIT varied between 63 and 304 ng L^{-1} in influent (Vasskog et al., 2008) and 11–322 ng L^{-1} in effluent (Himmelbach et al., 2006; Lajeunesse et al., 2008; Vasskog et al., 2008; Metcalfe et al., 2010) and downstream WWTPs 40–90 ng L^{-1} (Schultz and Furlong, 2008; Metcalfe

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et al., 2010). In addition the two metabolites, DCIT and DDCIT, were determined in both influents in concentrations ranging between 118–426 and 6–20 ng L^{-1}, respectively and effluents 46–300 and 1–10 ng L^{-1}, respectively (Vasskog et al., 2008). The sorption of CIT onto sewage sludge was approximately 10% (Hörsing et al., 2011), whereas photolysis and hydrolysis had been found to have little effect on removal (Kwon and Armbrust, 2005; Styrishave et al., 2011). During the photolytic breakdown of CIT at pH 9.0, the parent compound degraded into two transformation products (TPs) identified as DCIT and CIT-NO, which are identical to human metabolites (Kwon and Armbrust, 2005). Resent investigation of biodegradation under both aerobic and anoxic conditions demonstrated that CIT was moderately removed (60–44%, respectively; Suarez et al., 2010). Clearly, CIT is not sufficiently removed by conventional water treatment and advanced treatment technologies need to be developed in order to identify appropriate methods to be applied in upgrading existing treatment strategies (Kim and Tanaka, 2009). This paper focuses on identification of TPs formed during treatment using O_3, ClO_2, Fenton oxidation and UV irradiation all of which are proven alternatives for dealing with recalcitrant compounds. O_3 has frequently been studied and is considered to be the most promising oxidation method for the removal of micropollutants (Ternes et al., 2003; Joss et al., 2008; Sharma, 2008; Hollender et al., 2009; Hansen et al., 2010; Lee and Von Gunten, 2010), including sulphonamides and macrolide antibiotics, and estrogens (Huber et al., 2005; Andersen et al., 2007). ClO_2 is a powerful disinfectant, which selectively oxidises specific functional groups for example phenolic moieties and tertiary amines, and compared to O_3 produces less toxic by-products such as trihalomethanes (Rav-Acha, 1984; Huber et al., 2005). It has been used to oxidise flouroquinolones (Wang et al., 2010), carbamazepine (Kosjek et al., 2009), non-steroidal anti-inflammatory drugs (Hey et al., 2012b) and estrogens (Andersen et al., 2007). Kinetic studies including O_3, ClO_2 and other oxidants performed by Lee and Von Gunten (2010) showed that O_3 was completely consumed after 1 h whereas more than 10% remained of ClO_2. Further kinetic comparison concluded that ClO_2 reactivity was slower than O_3 (Sharma, 2008). Fenton oxidation which uses iron and H_2O_2 is an attractive oxidative system for water treatment since iron is both abundant and non-toxic and because H_2O_2 is relatively safe to use and is considered environmentally benign (Andreozzi et al., 1999). It has been applied to improve the biodegradability of a pharmaceutical wastewater (Tekin et al., 2006), and in combination with UV irradiation for studying the breakdown of the nonsteroidal anti-inflammatory drug diclofenac (Pérez-Estrada et al., 2005). Photo-electro-Fenton oxidation was found efficiently degraded clofibric acid (Sirés et al., 2007). UV treatment has been applied either alone or in combination with a radical source (H_2O_2) to study the breakdown of pharmaceutical agents for example carbamazepine (Kosjek et al., 2009), diazepam (Kosjek et al., 2011b) and ketoprofen (Kosjek et al., 2011a).

Despite its widespread prescription CIT and SSRI compounds in general have received little attention in terms of their removal and transformation during advanced water treatments. To address this fact we studied the behaviour of CIT under neutral pH conditions when subjected to advanced treatment processes, O_3, ClO_2 and Fenton oxidation, UV irradiation, and did attempt to identify TPs formed during these breakdown processes.

2. Material and methods

2.1. Chemicals and stock solutions

CIT hydrobromide salt, DCIT and CIT-NO hydrochloride salts and DDCIT tartrate were kindly donated by Lundbeck A/S, Copenhagen, Denmark. Fluoxetine hydrochloride (FLU) was purchased from Sigma–Aldrich (St. Louis, MO, USA). All reagent chemicals ($FeSO_4{\cdot}7H_2O$, H_2O_2, HCl, $NaClO_2$, Na_2SO_3, NaOH, H_2SO_4) and solvents were of analytical grade purity.

Stock solutions of CIT (1 g L^{-1}) and FLU (0.5 g L^{-1}) were prepared in methanol and stored at −18 °C. For the Fenton experiments 1 M Fe^{2+} stock solution was prepared by dilution of $FeSO_4{\cdot}7H_2O$ in MilliQ water (Millipore, Billerica, MA, USA), and 10 M H_2O_2 was prepared from 30% H_2O_2. The Fenton reaction was interrupted with 4 M NaOH.

A ClO_2 stock solution with an approximate concentration of 1 g L^{-1} was prepared by adding 25 mL HCl (9% w/v) and 25 mL $NaClO_2$ (7.5% w/v) to 400 mL MilliQ water, and made up to 1 L with MilliQ after 12 h (Hey et al., 2011). The stock solution was normalised using the "DPD-method" and an Allcon spectrophotometer (Alldos GmbH, Germany). A Na_2SO_3 solution, which was used to quench the ClO_2 oxidation, was prepared by diluting this solution to a concentration of 50 mg L^{-1}.

2.2. Treatment experiments

The starting concentration of CIT was 100 μg L^{-1} for all experiments. The treatment experiments were carried out in a phosphate buffered mineral medium (pH 7; 3.2 mM) prepared according to Andersen et al. (2005), with the exception of the Fenton treatment which was carried out at a pH 3. Table SM-1 in Supplementary Materials (SM) describes the treatment conditions. Different treatment intensities were applied in order to enable the formation of TPs in concentrations that would allow their identification.

O_3 treatment was performed using an O_3 generator rated at 400 mg h^{-1} from O_3-Technology AB (Vellinge, Sweden) which was supplied by an atmospheric air provided by an aquarium pump. O_3 formed in the generator was delivered through a teflon tube and a diffuser stone into a 1 L borosilicate bottle containing a solution of CIT. New O_3 treated samples were made at time intervals up to 90 min.

The ClO_2 treatment was conducted in 1 L borosilicate bottles, where CIT was exposed to ClO_2 in concentrations up to10.26 mg L^{-1}. The test solutions were left to react in darkness for 2 h before the reaction was quenched with Na_2SO_3 according to Kosjek et al., 2009.

The UV treatment was performed in an annular reactor with a circulating flow system setup. The equipment consisted of a steel reactor (8 L), a water pump (85 L h^{-1}) and a medium pressure metal-halogen UV lamp (690 W). The UV lamp (Bau 47, Scan Research A/S, Denmark) emitted a polychromatic light at 400–185 nm, with an enhanced emission between 250 and 190 nm. The lamp spectrum output has been presented previously (Kosjek et al., 2009). Samples were withdrawn during treatment at various time intervals between 0 and 4 h.

Based on the study published by Goi and Trapido (2002), Fenton treatment was performed at a molar ratio Fe^{2+}/H_2O_2 1/10, where the concentrations of Fe^{2+} varied from 0.0003 to 12.5 mM. The pH of 500 mL samples containing 100 μg L^{-1} CIT in MilliQ water was before the addition of Fe^{2+} and H_2O_2 adjusted to 3 with 1 M H_2SO_4, in order to increase the efficiency of the Fenton reaction. After 30 min the reaction was quenched by adding 4 M NaOH until a pH 9 was reached (Goi and Trapido, 2002). The samples were centrifuged to remove the Fe_2O_3 that formed the reaction.

2.3. Sample preparation and chemical analysis

A 200 g samples were withdrawn from the reaction mixtures described under Section 2.2 and adjusted to pH 12 by addition of NaOH. The internal standard FLU was added at a final concentration of 10 μg L^{-1} prior to solid phase extraction (SPE) using Oasis®

HLB 60 mg/3 mL cartridges (Waters, Milford, MA, USA). The SPE cartridges were conditioned by 5 mL MeOH followed by 5 mL Milli-Q water adjusted to pH 12 with NaOH. After the enrichment phase the cartridges were then dried by applying a vacuum, and subsequently the analytes were eluted with 3 mL MeOH. The extracts were evaporated to a volume of 1 mL prior to GC–MS analysis, which was performed without the derivatisation. When using LC–MS/MS MeOH was replaced by acetonitrile/water (75/25, v/v).

2.4. Instrumental analysis

GC–MS was used for quantification of CIT in treated samples. Details on the instrumental equipment and operational parameters are gathered in Section SM-1. LC–MS/MS was employed for qualitative analysis, i.e. identification of TPs formed during above described treatment processes. For more information regarding LC–MS/MS see Section SM-1.

3. Results and discussion

The purpose of the present study was to investigate the removal of CIT during treatment with O_3, ClO_2, UV-irradiation, Fenton oxidation in order to identify any TPs formed during treatment.

3.1. Removal of citalopram during O_3, ClO_2, UV and Fenton treatment

O_3 treatment removed 80% of CIT within 30 min (Fig. 1a), albeit the complete removal of CIT was not observed during the 90 min of ozonation. Together with the decay of the parent compound we observed the formation of a TP (Fig. 1a) later identified as DCIT (see Section 3.2). Additionally four TPs were identified (see Section 3.2). An explanation for the decrease in the removal rate of CIT after the initial fast reactions in the first 30 min of treatment can be that the reaction between O_3 and TPs was favoured over the reaction between O_3 and CIT (Fig. 1a). ClO_2 removed CIT at low doses. The dozes of ClO_2 applied to determine the fate of CIT ranged from the molar ratio 1:1 up to 1:500. The molar ratio of 1:1, which corresponded to 21 $\mu g\,L^{-1}$ of ClO_2, removed 40% of CIT, whereas by addition of 0.11 $mg\,L^{-1}$ ClO_2 approximately 5% of CIT remained in the treated sample (Fig. 1b). We determined five TPs being formed during the ClO_2 treatment. Their identity matching those formed during the ozonation, though they had different abundances (see Section 3.2). An explanation to that the increased molar ratio did not remove CIT completely can be that the reaction between TPs and ClO_2 was favoured over the reaction between CIT and ClO_2.

Fig. 1c shows how 92% of CIT was removed within the first 7 min of UV irradiation, while after 30 min CIT was not detected in the treated sample. No TPs were detected in the UV-treated samples, which may be justified by its rapid removal (and possibly also its TPs) during irradiation. Compared to carbamazepine, which was treated using the same experimental setup (Kosjek et al., 2009) including the UV-lamp (400–185 nm), it can be concluded that CIT is more prone to UV breakdown. Unlike this study, Kwon and Armbrust (2005) employed wavelengths >290 nm to investigate the breakdown of CIT, and obtained a half-life of 65 d at pH 9. CIT has its absorbance maximum at 238 nm, which is outside the range of Kwon and Armbrust (2005) experiment, and this could explain the difference in reaction times.

Fenton oxidation removed approximately 90% of CIT (Fig. 1d) and as in the case of UV irradiation, no TPs were observed. As both Fenton and UV-irradiation are non-selective oxidants, we assume that together with CIT the TPs were rapidly degraded.

A recent study where ClO_2 was used to treat biological treated wastewater revealed the reduction efficiency for among other pharmaceuticals CIT, which was reduced to 90% by addition of 5–8 $mg\,L^{-1}$ depending of type of effluent (Hey et al., 2012a,b). Even though an efficient removal of the parent compound CIT was revealed, its disappearance in the reaction mixture provides only a partial indication of treatment efficiency, since TPs more resilient to degradation may be formed. In addition, the overall toxicity of

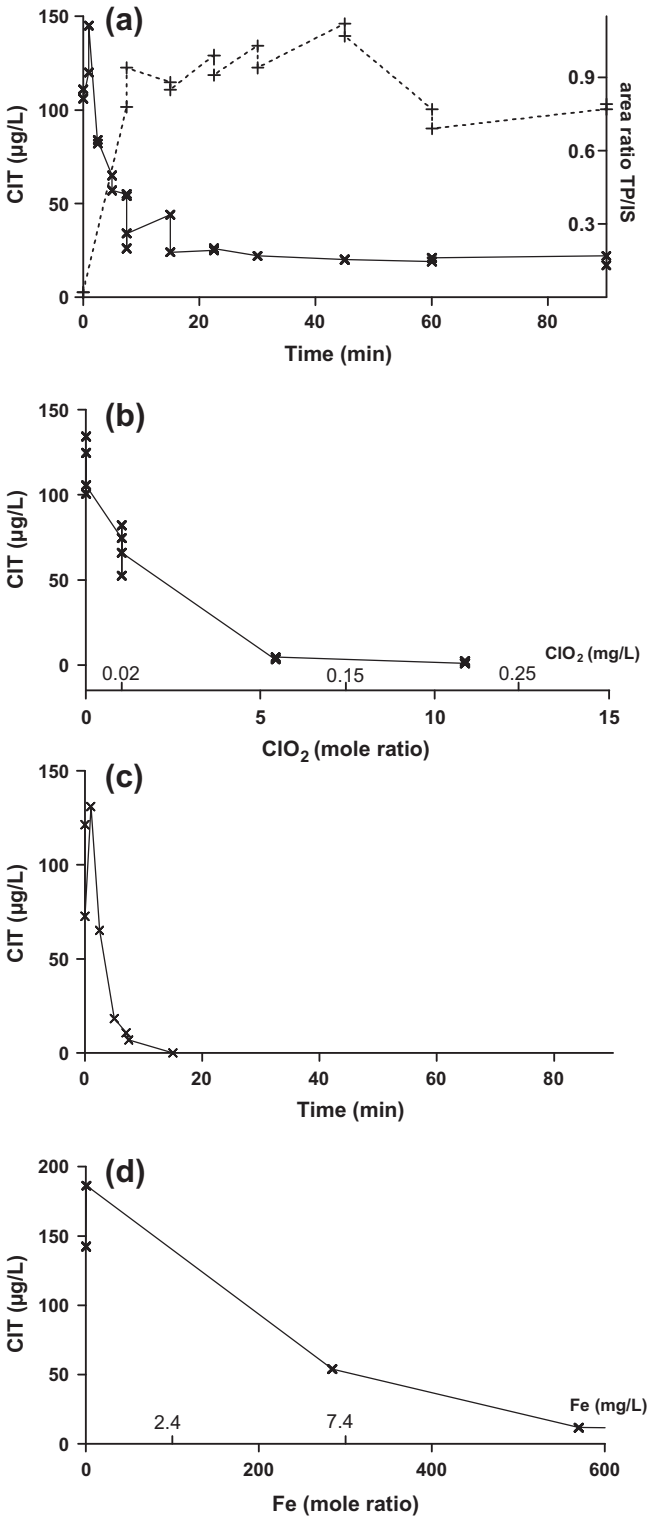

Fig. 1. (a) Removal of CIT as a function of time with treatment with O_3 ((×) CIT (+) TP), (b) removal of CIT by treatment with ClO_2, (c) removal of CIT as a function of time with treatment with UV irradiation, and (d) removal of CIT by treatment with Fenton reaction.

treated water arising from a mixture of stable TPs may pose their own environmental and health risks. Thus, it is important not to overlook TPs when comparing the efficiency of various water treatment technologies.

3.2. Identification of TPs

Under the given LC conditions CIT eluted at 2.4 min, and its MS spectrum obtained using positive electrospray ionisation acquired in time-of-flight mode reveals a protonated molecule at $[M + H]^+$ 325.1711 corresponding to the elemental composition $C_{20}H_{22}N_2OF$ (Table 1) at a mass error of −1.5 ppm. The MS/MS spectrum of protonated CIT is illustrated in Fig. 2a and typically shows cleavages of water and a dimethyl amino group (in both sequences) to produce the fragment ion at *m/z* 262 with the elemental composition $C_{18}H_{13}NF$. Further, *m/z* 262 is subjected to losses of either a methyl or ethyl group at *m/z* 247 and 234, respectively. The most characteristic fragment ion in the MS/MS spectrum of CIT is, however, *m/z* 109 that corresponds to a fluorotropylium cation (C_7H_6F; Fig. 2a).

Using MetaboLynx™ processing of the LC–MS data, a new compound emerged at the retention time (t_R) of 3.9 min, which was absent in the control samples. The compound has a protonated molecule at $[M + H]^+$ 311.1555, to which the elemental composition $C_{19}H_{20}N_2OF$ with a −1.6 ppm mass error (Table 1). Fig. SM-1b, shows how this compound lacks one carbon atom and two hydrogens in comparison to the parent compound CIT, suggesting the loss of a methyl group. Correspondingly, its MS/MS spectrum shows the cleavage of H_2O at *m/z* 293 and subsequent cleavage of $–NH_2CH_3$ group at *m/z* 262. The ions from *m/z* 262 and below correspond to those found in the MS/MS spectrum of the parent compound (Fig. SM-1a and b). Accordingly, this TP is identified as DCIT. The compound was confirmed with the authentic standard taking into account its t_R, MS/MS fragmentation and HRMS data. DCIT is not only the TP formed during ClO_2 and O_3 treatment, but it is also the product of human metabolism. DCIT is in the liver further metabolised into DDCIT (Kwon and Armbrust, 2005). The latter was, however, not detected as a TP in the investigated treatment processes, indicating either that DDCIT is unstable under given treatment conditions, or that DCIT is subjected to a further transformation pathway that differs from human metabolism. Fig. SM-1c shows the MS/MS spectrum of the protonated ($[M + H]^+$ 297.2) DDCIT molecule, which was obtained from DDCIT authentic standard to study its MS/MS behaviour. It can be noted that the fragmentation of DDCIT left forming the fragment ion *m/z* 262 is analogous to that of CIT and DCIT.

Two more TPs detected by post-acquisition data processing eluted at t_R 2.9 and 6.4 min (see Fig. SM-2), and showed their protonated molecules at $[M + H]^+$ 341.1662 and 341.1667, respectively. The same elemental composition, $C_{20}H_{22}N_2O_2F$, was assigned to both TPs at a mass error lower than 0.9 ppm. In comparison to the parent compound these two TPs involve one additional oxygen atom. Despite the unique elemental composition, their t_R and their MS/MS spectra prove their different identity. The TP-341, which eluted first (at t_R 2.9 min), shows a MS/MS fragmentation pattern that is analogous to that of CIT, but differing in that two H_2O molecules are cleaved (Fig. 2b). The first cleavage of H_2O forms a fragment ion at *m/z* 323 ($C_{20}H_{20}N_2OF$), and the second at *m/z* 305 ($C_{20}H_{18}N_2F$). Further loss of $(CH_3)_2NH–$ group forms the *m/z* 260 ion with the elemental composition of $C_{18}H_{11}NF$. Alternatively, an entire N-methyl(N-hydroxymethyl)amino group is cleaved from *m/z* 323 and forms *m/z* 262 with the elemental composition of $C_{18}H_{13}NF$. This cleavage is crucial to identifying the position of the additional oxygen, which is attached to one of the methyl groups and forms the N-methyl-(N-hydroxymethyl)amino-N-ethyl side chain. The MS/MS spectrum of TP-341 is illustrated in Fig. 2b.

The MS/MS 341 of the second-eluted TP (t_R 6.4 min) results in the cleavage of $–NH(CH_3)_2O$ group thus forming the fragment ion at *m/z* 280, which corresponds to the elemental composition $C_{18}H_{15}NOF$ (see Fig. SM-3). This is subjected to a further loss of H_2O at *m/z* 262, characteristic for CIT and the above discussed analogues. Based on its fragmentation pattern the proposed structure of the TP is citalopram-N-oxide. This compound is not only the abundant TP formed particularly in the O_3 treatment, but is also formed during human metabolism. Due to the commercial availability of its authentic standard we were able to undoubtedly confirm its identity.

At t_R 1.6 min another TP emerged with $[M + H]^+$ 339.1502, which at −2.1 ppm mass error corresponds to the elemental composition $C_{20}H_{20}N_2O_2F$. That is, in comparison to TP-341 and CIT-NO, two protons lower. The MS/MS spectrum of protonated TP-339 is illustrated in Fig. 2c. The fragmentation pattern of this TP is at higher masses analogous to CIT, showing the cleavage of dimethylamino group and water (or *vice versa*) producing a fragment ion at *m/z* 276 ($C_{18}H_{11}NOF$). Further on, the loss of H_2O is shown at *m/z* 258 ($C_{18}H_9NF$), or alternatively, the CO group is cleaved at *m/z* 248 ($C_{17}H_{11}NF$). Based on this we propose that the TP is a butyrolactone derivative.

Finally, a TP with the protonated mass $[M + H]^+$ 323.1765 was detected at 3.1 min. The calculation of its elemental composition resulted in the elemental formulae $C_{20}H_{23}N_2O_2$ (+1.5 ppm mass error, Table 1) indicating that the TP lacks the fluorine atom, but involves an additional oxygen and hydrogen instead. The identification process of the TP-323 is illustrated in Fig. 2d. It can be noted that the fragmentation corresponds to that of CIT with all the ion fragments being 2 Da lower. The crucial fragment ion is *m/z* 107, which represents the hydroxyl-tropylium cation instead of the fluorinated analogue present in CIT and all remaining TPs. This indicates that the structure of TP-323 has the fluorine replaced by the hydroxyl group.

Tandem and high resolution MS was used to identify five stable TPs. The chemical structures of two TPs were confirmed by their authentic standards: DCIT and CIT-NO. DDCIT was despite the targeted screening for this compound not detected in the treated samples, though its authentic standard facilitated the identification of other TPs based on a comparison of their MS/MS spectra. The structures of the remaining three TPs were proposed as a side chain

Table 1
LC–MS data on CIT, TPs and metabolites.

Compound	t_R (min)	Theoretical $[M + H]^+$	Elemental formula $[M+H]^+$	Mass error (ppm)	Authentic standard	Formed by
CIT	2.4	325.1716	$C_{20}H_{22}N_2OF$	−1.5	+	Parent compound
TP: DMCIT	3.9	311.1560	$C_{19}H_{20}N_2OF$	−1.6	+	Human metabolism, O_3, ClO_2
DDMCIT	3.6	297.1403	$C_{18}H_{18}N_2OF$	+4.7	+	Human metabolism
TP-341	2.9	341.1665	$C_{20}H_{22}N_2O_2F$	−0.9		O_3, ClO_2
TP: CIT-NO	6.4	341.1665	$C_{20}H_{22}N_2O_2F$	+0.6	+	Human metabolism, O_3, ClO_2
TP-339	1.6	339.1509	$C_{20}H_{20}N_2O_2F$	−2.1		O_3, ClO_2
TP-323	3.1	323.1760	$C_{20}H_{23}N_2O_2$	+1.5		O_3, ClO_2

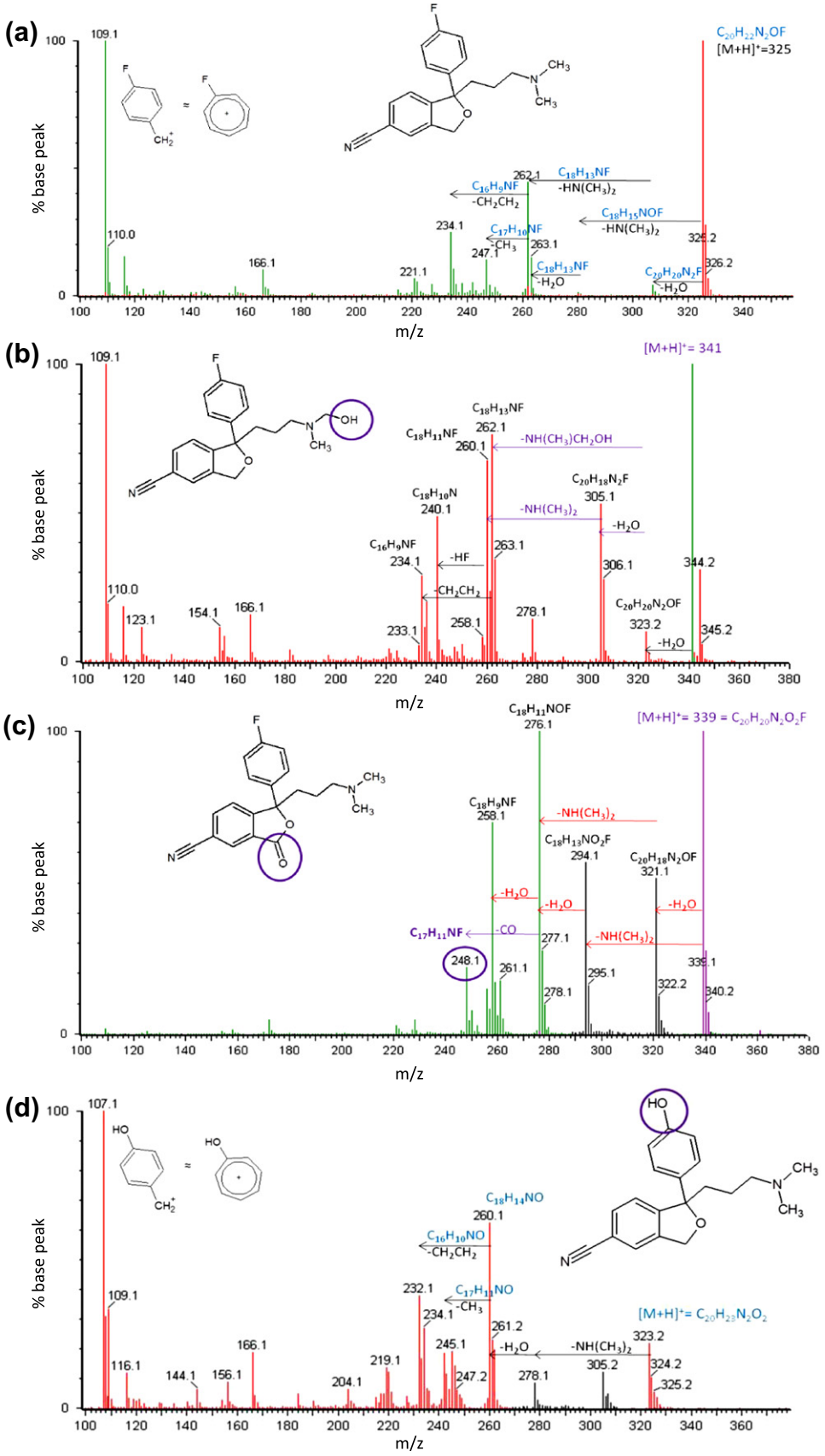

Fig. 2. MS/MS spectra of: (a) CIT and three novel degradation products, (b) TP-341, (c) TP-339, and (d) TP-323, formed during oxidation treatments. Their mass fragments and chemical structures are proposed.

hydroxylated CIT (TP-341: 1-(4-fluorophenyl)-1-{3-[(hydroxymethyl)(methyl)amino]propyl}-1,3-dihydro-2-benzofuran-5-carbonitrile, Fig. 2b), butyrolactone of CIT (TP-339: 1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-3-oxo-1,3-dihydro-2-benzofuran-5-carbonitrile, Fig. 2c) and defluorinated/hydroxylated CIT (TP-323: 1-[3-(dimethylamino)propyl]-1-(4-hydroxyphenyl)-1,3-dihydro-2-benzofuran-5-carbonitrile, Fig. 2d). Based on the TPs identified within this study the following breakdown pathways are proposed: Similarly as in the metabolic breakdown, CIT is demethylated into DCIT, and further probably into DDCIT, though the latter was not detected in our study, either due to the resistance of DCIT, or due to the instability of DDCIT. The second breakdown pathway also mimics the human metabolism and gives rise to formation of CIT-NO. The remaining three breakdown pathways we propose are unique for the abiotic, not metabolic breakdown of CIT and comprise oxidation of dihydrofuran ring C-atom with formation of butyrolactone, oxidative defluorination and hydroxylation of the dimethylamino-side chain. No traces of further breakdown products were detected, which may be either due to their presence in concentrations insufficient for detection, or resistance of the identified TPs.

4. Conclusions

This study highlights the removal and transformation of the widely used antidepressant pharmaceutical CIT under exposure to O_3, ClO_2, UV irradiation and Fenton oxidation. Under the prevailing test conditions for UV-irradiation and Fenton oxidation no TPs were found. However, when O_3 and ClO_2 were used CIT breakdown did not lead to complete mineralisation, and TPs were formed in the reaction mixtures. Two of the TPs, DCIT and CIT-NO, had been identified before, and are also formed during human metabolism of CIT. We propose three new TPs, not previously reported in scientific literature, of CIT, which were formed by the following transformation reactions: hydroxylation of the dimethylamino-side chain, oxidation of dihydrofuran ring C-atom with formation of butyrolactone, and oxidative defluorination. Even though no toxicity studies were included in the present study, the interpretation of the identified products environmental and health impact should account for that the products may be more harmful compared to the parent compound. Hopefully, this study will increase attention into the transformation of pharmaceuticals and possible risks related to their presence in the environment, which should encourage further research into more efficient treatment technologies to limit the entrance of such compounds into environmental waters.

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Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.chemosphere.2012.05.024.

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