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Environmental fate of sartans after treatment with sodium hypochlorite, the most widespread disinfection process

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A R T I C L E I N F O

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A B S T R A C T

Emerging contaminants (ECs) pose significant environmental and health risks due to their persistence and incomplete removal in conventional wastewater treatment plants (WWTPs). During the disinfection stage – commonly chlorination with sodium hypochlorite – these compounds can transform into disinfection by-products (DBPs), some of which are more toxic than the parent molecules. This review examines the environmental fate of sartans, a class of antihypertensive drugs increasingly detected in aquatic ecosystems. It analyzes the formation, degradation pathways, and ecotoxicological profiles of DBPs from Irbesartan, Olmesartan, and Candesartan. Results show that degradation typically initiates at side chains attached to the biphenyl moiety, producing recurrent DBPs that may serve as indicators of treatment efficiency. Ecotoxicity tests on *Daphnia magna, Aliivibrio fischeri*, and *Raphidocelis subcapitata* revealed that certain DBPs exhibit higher toxicity than their parent drugs, emphasizing the need for improved disinfection strategies to safeguard both environmental and public health.

1. Introduction

Surface waters collect large quantities of pollutants, originating from industrial, agricultural, domestic sources, wastewater treatment plants, surface runoff and atmospheric deposition. Among these substances there are emerging contaminants (ECs), a wide range of chemicals not yet regulated in routine environmental monitoring programs (Directive 2000/60/EC, 2000; Directive 2013/39/EU, 2013), which can be categorized into different classes, such as pharmaceuticals used in human and veterinary medicine (antibiotics, hormones, etc.), personal care products, psychoactive substances used by humans, pesticides, artificial sweeteners, UV filters, etc. (Yang et al., 2021; Scapuzzi et al., 2022; Wang et al., 2024).

These unwanted compounds are released, knowingly or unknowingly, into the aquatic environment, affecting the entire ecosystem (Bolong et al., 2021; Rodrigues et al., 2024; Ealias et al., 2021). Their persistence in the environment and their high biological activity makes these substances harmful at both low and high concentrations (Belgiorno et al., 2021). The environmental sector most affected by pollution by emerging contaminants is the aquatic one, both linked to direct spills and due to their transport from terrestrial sources. The environmental impacts are worrying and still largely to be defined, since these are substances for which there is still insufficient knowledge on their long-term impact and interference with biological processes and ecosystems. The "emerging" nature of these pollutants means that their full consequences on the environment and human health are still being studied and monitored, making complete risk assessment difficult.

Some emerging pollutants can accumulate in living organisms and produce long-term toxic by-products, altering food chains and ecosystem health. Thus, these contaminants can cause an increase in microbial resistance to drugs (Feng et al., 2021; Li et al., 2024); they can be absorbed by plants (Calderón-Preciado et al., 2021) and are associated with the loss of biodiversity (Mills and Chichester, 2021).

The specific effects on human health of emerging pollutants are the subject of intense research, but concerns mainly concern long-term effects, accumulation in organisms and potential interference with biological systems. It is important to note that individual vulnerability and prolonged exposure can influence the severity of the effects. For some of the ECs and their by-products, the potential negative effects on human health and the environment are known, for others there is little information on their capacity for diffusion and transport in the various environmental matrices and on the products of their degradation. In this regard, a further variable is linked to climate change which, with the increase in temperatures, can modify the mechanisms that regulate reactivity, degradation, transport and deposition. However, it is now established that ECs are associated with effects such as carcinogenesis (Hess-Wilson and Knudsen, 2021), mutagenesis (da Costa Araújo et al., 2022), irritation (Das et al., 2025), sensitization (Lei et al., 2015), and

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dysfunctions of reproduction and metabolism as in the case of Endocrine Disruptors (Hess-Wilson and Knudsen, 2021). The occurrence of ECs in our water resources is a constant concern for the health and safety of consumers, considering that existing conventional wastewater treatment plants (WWTPs) were not designed for their removal (Naddeo et al., 2015; Naddeo et al., 2021). So, urban wastewater has become both a research hotspot and a gateway for the spread of ECs into the environment (Zarrelli et al., 2012; Romanucci et al., 2019). There is an increasing demand for additional treatment ("quaternary treatment") to eliminate a wider spectrum of micropollutants, at least in larger WWTPs (Directive (EU) 2020/2184, 2020; Capodaglio, 2020; Kathi and Mahmoud, 2024), with costs that are borne at least in part by those who produce and market them.

In some treatment plants, ozonation (Wang and Chen, 2020; Dhangar and Kumar, 2020), activated carbon adsorption (Wong et al., 2018; Liu et al., 2024; Moreira et al., 2022) and Fenton reaction process (Zhang et al., 2019; Scaria et al., 2021; Medici et al., 2024; Scaria et al., 2021) have been used to remove ECs but they are not yet widely used due to several disadvantages (including high operating costs or the need to acidify the wastewater before the process and neutralize it before disposal). Phytoremediation (Parde et al., 2021; Lavanya et al., 2024; Zhakypbek et al., 2024; Molina et al., 2020) and ultrasound (Naddeo et al., 2015; Gujar et al., 2023) are environmentally friendly methods with lower environmental impacts than other technologies, but the first one has several disadvantages, including the requirement of large surfaces for the construction of the ponds, and the second one does not guarantee the complete removal of ECs (Naddeo et al., 2015; Gujar et al., 2023). Membrane bioreactors allow for the removal of conventional and emerging contaminants producing high-quality effluents but with relatively high operating costs (Hasan et al., 2012; Al-Asheh et al., 2021; Alfonso-Muniozguren et al., 2021). Ultimately, the removal of organic pollutants from wastewater is indeed an aspect of fundamental importance, but to date, it is not at all clear which removal methods could be the most convenient, both from an environmental and economic point of view (Li et al., 2024). To this end, it is necessary to use advanced processes that allow for the obtaining of high-quality effluents that can be discharged into the environment or reused in compliance with the principles of the circular economy, drastically reducing the risks to human health and the quality of ecosystems (Wang et al., 2024; Ding et al., 2024). But, at the same time, the need to use methods that are easy to use, quick to apply and economically accessible is evident.

Currently, chlorination remains by far the most used method in the disinfection of wastewater and will probably remain so for a long time due to its ease of use and low management costs (Warton et al., 2006; Abou-Elela et al., 2012).

Sartans, a class of antihypertensive drugs, are considered emerging pollutants due to their presence in the environment and the potential impact on human health and ecosystems. This class of drugs, which includes just over 20 molecules but the most important ones from a commercial point of view are Irbesartan, Olmesartan and Candesartan, acts by blocking the angiotensin II (AT1) receptor, reducing blood pressure (Ladhari et al., 2021). However, sartans and their metabolites can persist in the environment, contaminating surface and groundwater, soils and living organisms.

The problem related to ECs attracts more interest from the scientific community and the attention of the public opinion. However, most of the studies reported in the literature measure the "disappearance", in the specific case, of the sartan considered, without specifying whether the product has mineralized or transformed into by-products, which could be even more dangerous than the one from which they derive. Thus, this study provides a comprehensive and comparative overview of the transformation of the most commercially relevant sartans, recognized as ECs, following treatment with sodium hypochlorite. It (*i*) systematically compares the effects of chlorination on the degradation of Irbesartan, Olmesartan, and Candesartan; (*ii*) quantifies mineralization and recovery rates and identifies known and new disinfection by-products (DBPs); (*iii*) elucidates, for the first time, specific molecular sites and mechanisms where degradation initiates during chlorination; and (*iv*) correlates the structural features of the resulting DBPs with their ecotoxicological profiles on representative aquatic organisms. Furthermore, the study proposes valsartan acid as a potential probe molecule for monitoring the efficiency of disinfection processes and discusses which sartan, among pharmacologically equivalent compounds, may represent the most environmentally sustainable option based on its degradation behavior.

2. Overview of sartans subjected to chlorination reaction

2.1. Treatment with sodium hypochlorite

In the literature there are three sartans for which data are available regarding their disinfection process in the presence of sodium hypochlorite, namely Irbesartan, Olmesartan and Candesartan – which are among the highest-selling sartans, and which are commonly found in wastewater (Ladhari et al., 2021).

2.1.1. Irbesartan

In the case of Irbesartan (IRB, Fig. 1), 22 DBPs have been isolated and identified (Romanucci et al., 2020; Siciliano et al., 2023), of which DBP4 and DBP20-DBP22 have not been published; in particular, those of the hydrolysis of the N-19/C-23 bond (in the case of DBP6-DBP8 and DBP12), N-22/C-23 bond (in the case of DBP1, DBP10, DBP14 and DBP15) or both (in the case of DBP2, DBP3 and DBP16) have been ascertained, as have those of the oxidation of the *n*-butyl chain linked to carbon C-28 (in the case of DBP9, DBP10, DBP13 and DBP14) and those of the loss of the D and E rings with the formation of DBP4, DBP5, DBP11 and DBP17. Compounds DBP11-DBP17 also indicate the presence of a tetrazolo[1,5-*f*]phenanthridine unit, which is obtained by closing a new six-membered ring through the formation of a bond between the nitrogen N-14 of the tetrazole ring and the carbon C-8 of the phenyl ring B.

Furthermore, the isolation and structural determination of DBP17, in which the oxidation of the aromatic ring B is evident, and of at least two products (DBP18 and DBP19) caused by the partial degradation of the tetrazole ring are currently arousing curiosity. Finally, benzoic acid (DBP20), chlorobenzene (DBP21) and phenol (DBP22) have been identified, which can be the disinfection products of the biphenyl unit.

2.1.2. Olmesartan

In the case of Olmesartan (OLM) (Luongo et al., 2021; Luongo et al., 2021), 22 other disinfection products have been isolated (DBP4, DBP20-DBP41), but none of these have been obtained from the degradation of the tetrazole ring. Most of the isolated products (15 out of 22; DBP23-DBP37) are derived from the oxidative degradation of the side chain linked to the benzyl carbon C-18. Specifically, compared to the starting product, the disinfection by-products are derived from structural variations, generally oxidations, at carbons C-20, C-22, C-23 and C-24 (Fig. 2).

In particular, the loss of aromaticity in the D ring is highlighted, alongside the partial oxidation of carbon C-20, as in the DBP26-DBP28 products. Instead, carbon C-22 can undergo partial oxidation of the side chain, as in DBP24, or complete dealkylation, following the formation of the chloroderivatives DBP25 and DBP28 or the carbonyl derivatives DBP26 and DBP27. Furthermore, decarboxylation always occurs at carbon C-23, with the formation of the corresponding chloroderivatives DBP23-DBP25 or the corresponding oxidized products DBP26-DBP29.

In addition, the n-propyl chain linked to carbon C-20 can either undergo partial oxidation at carbon C-24, with the formation of the products DBP25, DBP27 and DBP28, or its complete oxidation occurs, with the formation of the carbonyl at position C-20, as in DBP29. Furthermore, disinfection products were formed by the opening of the D ring with the formation of DBP30-DBP32 and the corresponding

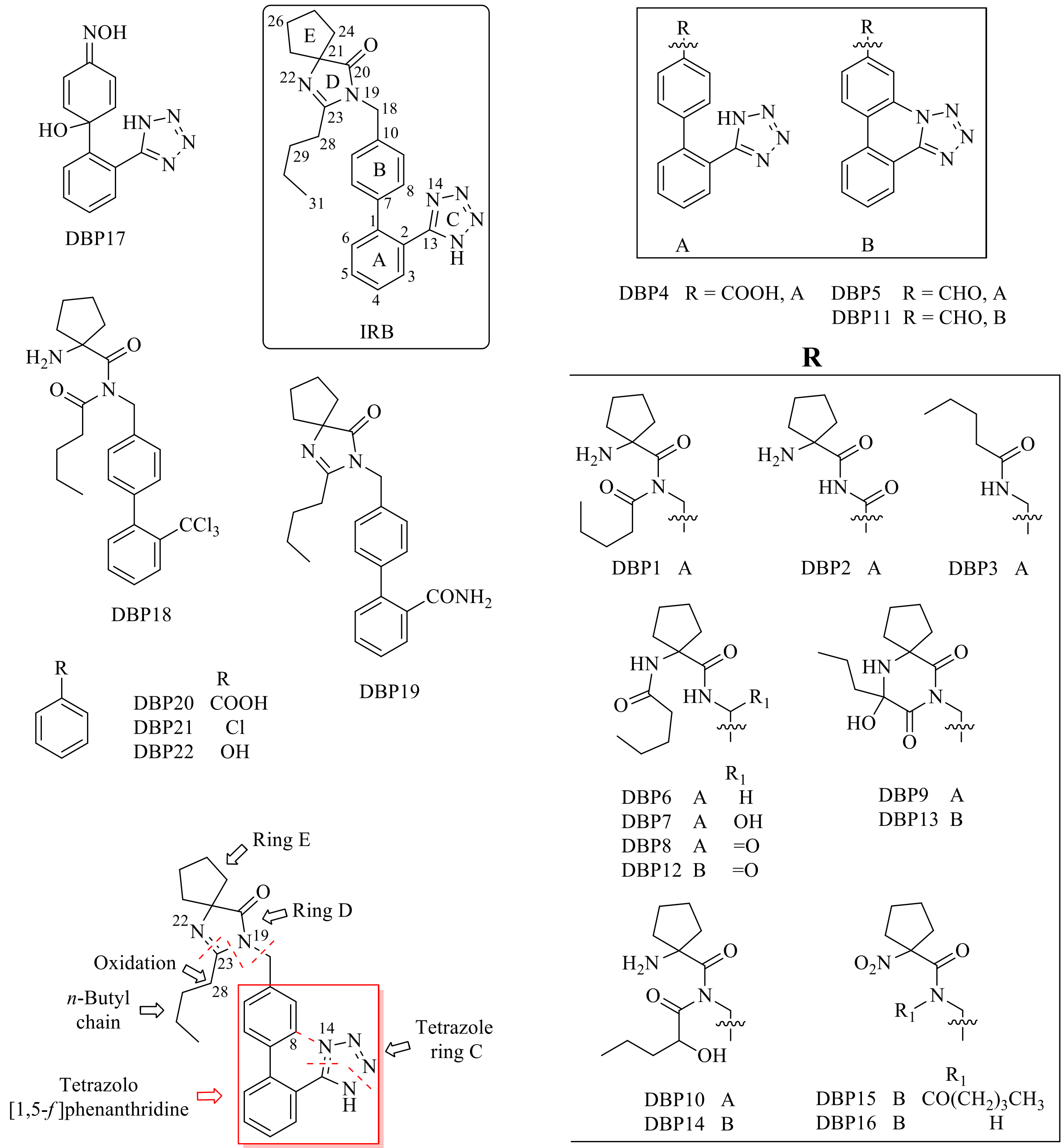

Fig. 1. Chemical structures of Irbesartan (IRB) and its disinfection by-products (DBP1–DBP22), and the sites where structural changes occur.

decarboxylated products DBP33-DBP35 and DBP36-DBP37. Finally, in the case of OLM, valsartan acid (DBP4) and benzoic acid (DBP20) were identified, as well as chlorobenzene (DBP21) and phenol (DBP22).

2.1.3. Candesartan

In the case of Candesartan (CAN) (Luongo et al., 2021), it is evident that the chlorination reaction leads to the formation of 12 DBPs, but none are obtained from the transformation/degradation of the tetrazole ring (Fig. 3). The isolated products are derived from the cleavage of the C-18/N-19 bond (DBP4 and DBP45) and from the cleavage of the N-19/C-23 bond (DBP42-DBP44). Finally, DBP46-DBP49 were obtained from the E ring following the cleavage of the C-18/N-19 bond and the opening of the D ring; additionally, once again, as in the case of CAN, the previously mentioned valsartan (DBP4) and benzoic (DBP20) acids were also identified, as well as chlorobenzene (DBP21) and phenol (DBP22).

2.1.4. Comparison of the effects of the disinfection process of the sartans considered

There are just under twenty sartans on the market, twelve of which have a basic skeleton made up of two aromatic phenyl rings and one of which has a tetrazole ring on the carbon C-2 (Fig. 4) (Ladhari et al., 2021).

The sartans considered were subjected to chlorination reactions lasting 1-2 hours, with 5-10% hypochlorite solutions and ratios of the sartan considered and sodium hypochlorite of 1:6, 1:10 or 1:20 (Table 1). IRB (Abou-Elela et al., 2012; Ladhari et al., 2021) and OLM

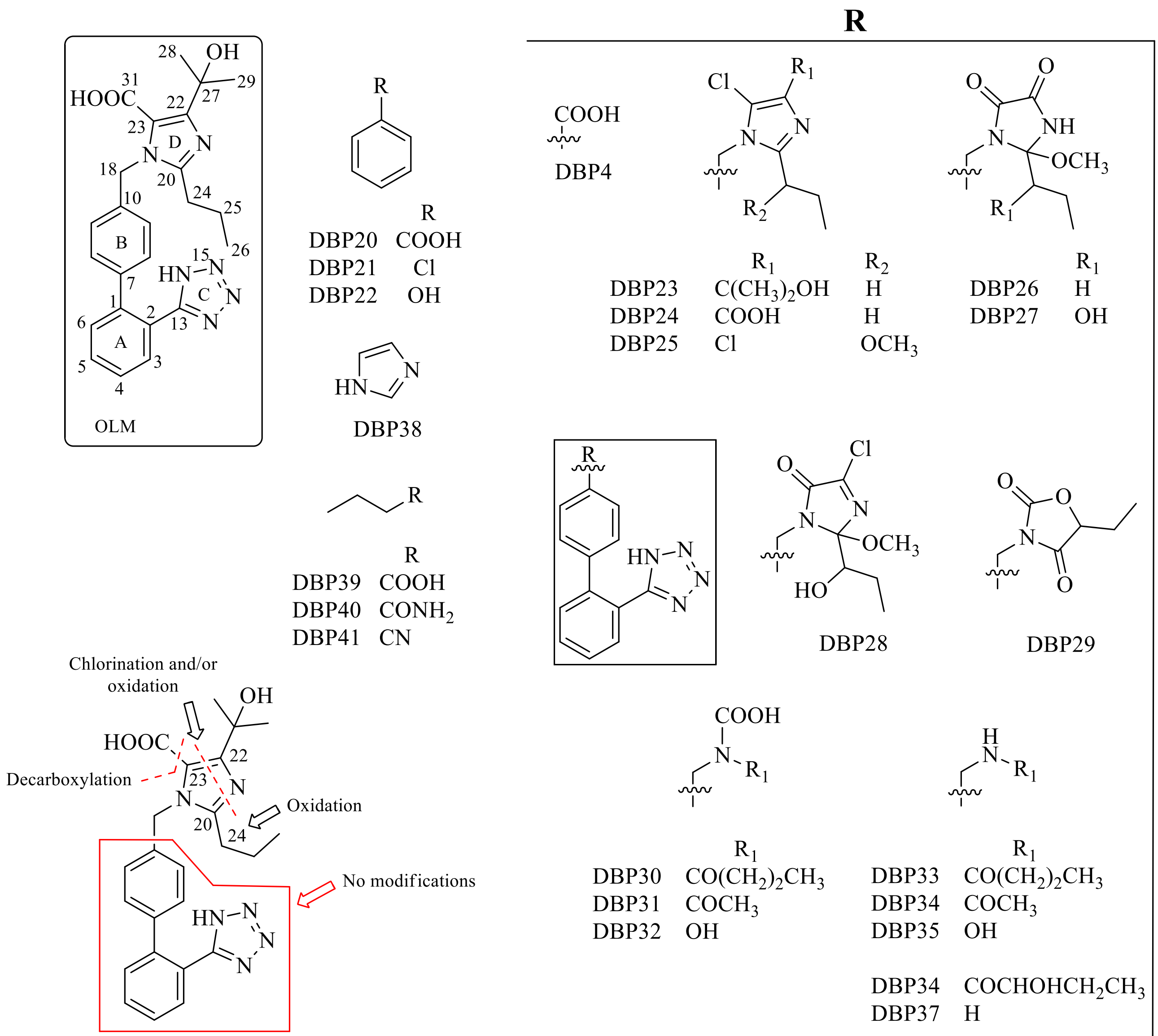

Fig. 2. Chemical structures of Olmesartan (OLM) and its disinfection by-products (DBP4, DBP20-DBP41), and the sites where structural changes occur.

(Romanucci et al., 2020; Siciliano et al., 2023) recovered unchanged at similar percentages (15 and 21%, respectively), while CAN (Luongo et al., 2021) was resistant to any chemical transformation at a percentage almost three times higher (52%). Similarly, IRB and OLM were mineralized at percentages of 65 and 59%, respectively, values almost double compared to the 35% in CAN. However, it is interesting to note that the percentages of transformation are almost comparable, at 16, 20 and 13% for IRB, OLM and CAN, respectively (Fig. 5). Twenty-two DBPs were identified from IRB and OLM, while 12 were identified from CAN, with isolation percentages in the range of 4.30-0.10, 2.01-0.11 and 2.40-0.42, respectively.

A total of 49 different DBPs were identified, of which 32 were identified for the first time (14 from the chlorination of IRB, 14 from OLM and 4 from CAN). Only seven DBPs were chlorinated, namely valsartan acid DBP21 isolated from all three sartans, DBP23-DBP25 and DBP28 isolated from OLM and DBP44-DBP45 isolated from CAN.

Only six DBPs showed a tetrazolo[1,5-*f*]phenanthridine unit (DBP11-DBP16) and only two were obtained from the degradation of pyrrole (DBP18 and DBP19), all of which, however, were obtained exclusively from IRB. Four DBPs were found to be common among the three sartans considered, namely DBP4, DBP20, DBP21 and DBP22.

2.2. Ecotoxicological footprint of parent compounds and related disinfection by-products

Recent studies have shown that alternative disinfection processes, such as combined chloramination-ozonation, can generate complex mixtures of halogenated and/or nitrogenous byproducts (Von Gunten and Hoigne, 1994). In general, variations in temperature, pH, and water composition during real-world wastewater treatment can also significantly influence both the type and amount of DBPs formed from emerging contaminants. Temperature affects the kinetics of oxidation and chlorination reactions, often accelerating transformation rates and favoring the formation of more oxidized DBPs. The pH value controls the speciation of disinfectants ($HOCl/OCl^-$) and of the target pollutants, thereby modulating their reactivity and the resulting DBP profile, in particular lower pH typically enhances the formation of chlorinated DBPs. Additionally, the composition of the water matrix—such as the presence of natural organic matter (NOM), bromide, iodide, or nitrogen compounds—plays a critical role in determining DBP yields. NOM acts as a major precursor for halogenated by-products, while bromide and iodide can generate brominated or iodinated DBPs with higher toxicity. In contrast, ammonia and other nitrogenous species promote the

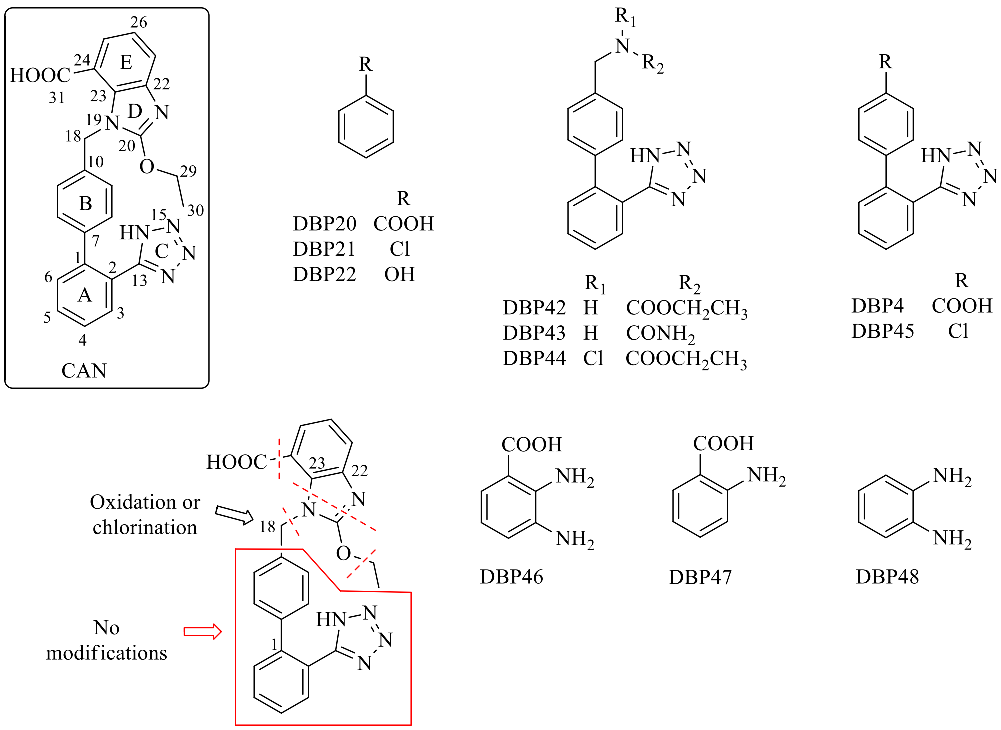

Fig. 3. Chemical structures of Candesartan (CAN) and its disinfection by-products DBPB4, DBP20-DBP22 and DBP42-DBP49, and the sites where structural changes occur.

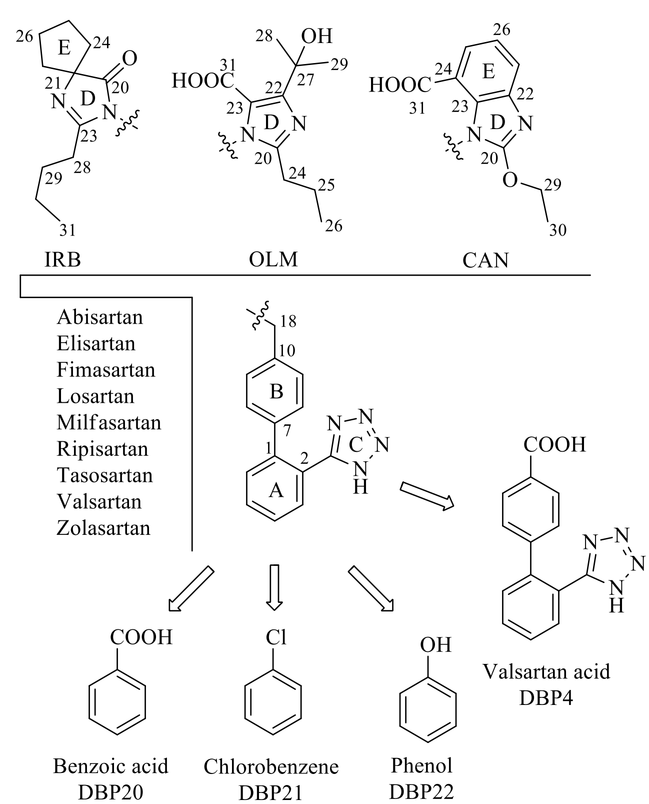

Fig. 4. Chemical structures of sartans with a diphenyl backbone and the common by-products obtained from all analyzed sartans.

formation of nitrogenous DBPs such as haloacetonitriles or nitrosamines. These complex interactions highlight the necessity of controlling operational parameters in wastewater disinfection to minimize the formation of highly toxic DBPs (Du et al., 2025; Lu et al., 2025).

Table 1
Experimental conditions and results of chlorination studies of aqueous solutions of Irbesartan (Abou-Elela et al., 2012; Ladhari et al., 2021), Olmesartan (Romanucci et al., 2020; Siciliano et al., 2023) and Candesartan (Luongo et al., 2021).

	Irbesartan	Olmesartan	Candesartan
Reaction time	2h	1h	2h
NaOCl concentration	10%	10%	5%
Sartan/NaOCl ratio	1:6 1:10	1:6 1:20	1:6
Sartan recovered unchanged	15%	21%	52%
Mineralization	65%	59%	35%
Transformation	16%	20%	13%
DBPs identified	22	18	12
Percentage range of disinfection products	4.30-0.10	2.01-0.11	2.40-0.42
Chlorinated DBPs	2	5	3
Compounds with tetrazolo[1,5-f] phenanthridine units	6	-	-
Compounds degraded to pyrrole	2	-	-
Common compounds of the three Sartans	DBP4, DBP20, DBP21 and DBP22		

2.2.1. Target organisms

To evaluate their ecotoxicological profile, the sartans considered and the related DBPs were tested on three different target organisms, namely *Daphnia magna* (Abou-Elela et al., 2012; Ladhari et al., 2021; Luongo et al., 2021), *Raphidocelis subcapitata* (Romanucci et al., 2020; Siciliano et al., 2023; Luongo et al., 2021), and *Aliivibrio fischeri* (Abou-Elela et al., 2012; Ladhari et al., 2021; Romanucci et al., 2020; Siciliano et al., 2023; Luongo et al., 2021) (Tables 2 and 3).

DBP1-DBP22 (excluding DBP3 and DBP8), obtained from IRB, and DBP42-DBP49, obtained from CAN, were tested on *D. magna*. On *R. subcapitata* and *A. fischeri*, all the obtained DBPs were tested, except

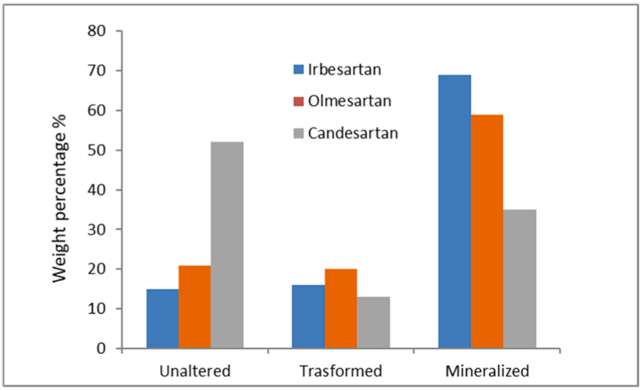

Fig. 5. Weight percentages of unaltered, transformed (sum of all disinfection by-products) and mineralized products.

for DBP3, DBP6, DBP8, DBP12-DBP13 and DBP15-DBP17, which were obtained from IRB, as well as DBP37, which was obtained from OLM (Table 1).

D. magna is a small freshwater crustacean used as a model organism for ecotoxicology (Petrie et al., 2015) and for water quality monitoring (Storey et al., 2011) in laboratory studies. *D. magna* is a useful model species for studying the lethal and sublethal effects of micropollutants and their by-products, being particularly sensitive to a variety of toxicants at different levels of biological organization (Duquesne and Küster, 2010).

R. subcapitata, formerly known as *Selenastrum capricornutum* and *Pseudokirchneriella subcapitata*, is a freshwater microalga with a high sensitivity to several chemical species, which is why it is recommended by several international organizations for ecotoxicity assessments.

A. fischeri is a non-pathogenic, luminescent marine bacterium that is sensitive to a wide range of chemicals and whose toxicity has been assessed by measuring the inhibition of the luminescence emitted by the bacterium. In fact, exposure to a toxic substance disrupts the respiratory process, which affects the metabolic pathway that converts chemical energy into visible light through the electron transfer system.

2.2.2. *Toxicity measured on D. magna*

For both IRB and CAN, only 10% of Daphnia were immobilized at a concentration of 100 mg/L of the drug, which is a huge concentration demonstrating the very low levels or complete absence of toxicity of the products on the cladoceran (Table 3) (Persoone et al., 2003).

Among the DBPs evaluated, the most toxic were DBP10, DBP12 and DBP19, obtained from IRB, and DBP43, DBP48 and DBP49, obtained from CAN. DBP10, DBP12 and DBP19 showed the highest toxicity toward *D. magna*, due to structural modifications that increase molecular reactivity. Oxidation of the *n*-butyl side chain in DBP10 and DBP12 and partial degradation of the tetrazole ring in DBP19 enhance electrophilicity and polarity, respectively, likely leading to stronger interactions with biological membranes and higher toxicity. DBP43 in turn has an oxidized side chain while the two DBP48 and DBP49 are two aromatic derivatives (aniline and its derivative) which are notoriously toxic. The DBPs obtained from OLM were not tested on *D. magna*, which makes any comparison between the DBPs and the possible hypothesis of correlation between the measured activity and the structural profiles difficult. However, *in vivo* evaluations indicated a toxicity of the DBPs that was higher than that of the parental product and much higher than that reported by Carpintero et al. (Carpinteiro et al., 2019) via silico evaluations using ECOSAR software.

2.2.3. *Toxicity measured on R. subcapitata*

It is interesting to note that IRB seems to have even a slight growth-stimulating effect on the alga *R. subcapitata*, while OLM and CAN are simply inactive. The most active compound was DBP10, obtained from IRB and classifiable as very toxic, which was only slightly more active than DBP25 obtained from OLM. In addition to valsartan acid DBP4, DBP23, DBP32, DBP33 and DBP38, isolated from OLM, and DBP43-DBP45 and DBP49, obtained from CAN, were all found to be harmful. The toxicity of these DBPs toward *R. subcapitata* appears to be strongly structure dependent. Derivatives exhibiting oxidized or chlorinated side chains and structural modifications involving the opening or oxidation of the D and E aromatic rings showed markedly higher toxicity compared with unsubstituted or structurally conserved analogues, suggesting that increased oxidation and chlorination enhance both reactivity and ecotoxicological potential in microalgae. All the others appeared non-toxic or, as in the case of many DBPs obtained from IRB,

Table 2
The organisms used to test DBPs of Irbesartan (1-19), Olmesartan (23-41), Candesartan (42-49), and the common ones (4, 20-22) (Romanucci et al., 2020; Siciliano et al., 2023; Luongo et al., 2021; Luongo et al., 2021; Luongo et al., 2021).

No.	*D. magna*	*R. subcapitata*	*A. fischeri*	No.	*D. magna*	*R. subcapitata*	*A. fischeri*
1	x	x	x	30		x	x
2	x	x	x	31		x	x
3	Not tested			32		x	x
5	x	x	x	33		x	x
6	x			34		x	x
7	x	x	x	35		x	x
8	Not tested			36		x	x
9	x	x	x	37	Not tested		
10	x	x	x	38		x	x
11	x	x	x	39		x	x
12	x			40		x	x
13	x			41		x	x
14	x	x	x	42	x	x	x
15	x			43	x	x	x
16	x			44	x	x	x
17	x			45	x	x	x
18	x	x	x	46	x	x	x
19	x	x	x	47	x	x	x
23		x	x	48	x	x	x
24		x	x	49	x	x	x
25		x	x				
26		x	x	4	x	x	x
27		x	x	20	x	x	x
28		x	x	21	x	x	x
29		x	x	22	x	x	x

Table 3
Toxicity classification of DBPs tested on three individual test organisms (Romanucci et al., 2020; Siciliano et al., 2023; Luongo et al., 2021; Luongo et al., 2021; Luongo et al., 2021).

Activity*	D. magna	R. subcapitata	A. fischeri
Biostimulant	8	IRB, 1, 2, 5, 7, 9, 11, 20, 27-29, 34, 41	21, 28, 35, 41
Non toxic	IRB, CAN, 1-2, 5, 7, 9, 11, 14-18, 42, 44, 45	OLM, CAN, 14, 18-19, 21-22, 24, 26, 30, 31, 35, 36, 39-40, 42, 46-48	IRB, OLM, CAN, 2, 5, 7, 9, 14, 20, 22-23, 26-27, 29, 33, 35-36, 38, 39, 44, 46, 47
Harmul	4, 6, 13, 20-22, 47	4, 23, 32, 33, 38, 43-45, 49	1, 11, 18-19, 24-25, 30-32, 40, 42, 45
Toxic	**10, 12, 19, 43, 48, 49**	**25**	**4, 10, 43, 48, 49**
Very toxic		**10**	

*Very toxic to aquatic organisms, percentage of effect (PE) > 80%; toxic to aquatic organisms, PE > 50%; harmful to aquatic organisms, PE 20%–50%; and non-toxic to aquatic organisms, PE < 20%.

slightly stimulated the growth of the algae.

2.2.4. Toxicity measured on *A. fischeri*

Of the three test organisms, *A. fischeri* was the least sensitive. All three starting sartans were non-toxic, which also confirms what has been reported in the literature (Minguez et al., 2016). Two DBPs from IRB and three from CAN were found to be toxic, namely DBP4 and DBP10 and DBP43, DBP48 and DBP49, respectively. These DBPs, which include chlorinated and/or highly oxidized derivatives with modified aromatic or aliphatic regions, exhibited marked toxicity compared to the parent sartans. Probably, the presence of chlorine substituents and oxidative transformations enhances the electrophilic nature of the molecules, increasing their interaction with bacterial cellular components and, consequently, their ecotoxicological potency. For *A. fischeri*, IRB and four of its derivatives (DBP1, DBP11, DBP18 and DBP19) as well as eight derivatives of OLM (DBP24, DBP25, DBP30-DBP32, DBP40, DBP42 and DBP45) were found to be harmful.

2.3. Possible probe molecule to evaluate the effectiveness of disinfection processes

All reactions where sartans were subjected to reactions with sodium hypochlorite led to the formation of valsartan acid (DBP4) as well as benzoic acid (DBP20), chlorobenzene (DBP21) and phenol (DBP22). But if the last three, when found in treated water, can be considered disinfection products of a series of micropollutants of very different natures and uses, valsartan acid, due to its peculiar chemical structure, could certainly be considered a probe molecule to quantify the presence of sartans in wastewater and the efficiency of disinfection methods used in wastewater treatment plants. That is, compared with conventional markers (e.g. carbamazepine or sucralose), DBP4 provides a higher degree of chemical specificity for antihypertensive contaminants, offering a useful complementary indicator of disinfection efficiency and environmental persistence. However, its absolute uniqueness compared to sartans cannot be fully guaranteed, as structurally related biphenyl compounds could, under highly oxidative or chlorinated conditions, produce similar byproducts.

Indeed, the data available so far seems to indicate that the degradation of sartans containing a diphenyl skeleton and a tetrazole ring occurs starting from the periphery of the molecule, with the degradation of the side chain being linked to the nitrogen N-19 and then continues until reaching the basic diphenyl unit.

Imagine a tree was first deprived of its outer branches (what is linked to N-19) and then its trunk was cut (diphenyl skeleton and tetrazole ring). In fact, only the compounds DBP18 and DBP19 obtained from IRB show the degradation of the tetrazole ring, even before the rest of the molecule. Compound DBP17 seems to confirm that the aromatic ring B is degraded through oxidation to the corresponding *p*-quinone after the degradation of the side chain linked to the benzyl carbon.

2.4. Choice of medicines in relation to their impact on the environment

The choice of drugs should consider not only their efficacy and safety for the patient, but also their impact on the environment, especially in terms of fate and disposal. This approach, known as environmental pharmacovigilance, aims to reduce pollution caused by drugs and promote a more sustainable use of resources. This must be done through the design of green drugs (biodegradable and obtained through sustainable synthesis), as well as through education on the rational use of drugs, the improvement of prescription practices, management and disposal of unused drugs.

Specifically, of the three sartans considered, IRB is the one that is recovered unchanged only by 15%, much less than the 21% of OLM and the 52% of CAN. Furthermore, IRB is the one that is mineralized to a greater extent (65%) and with a low percentage by weight of formation of disinfection by-products (16%). Furthermore, among the DBPs obtained it is interesting to underline that only two are chlorinated (one of which is common to all the sartans considered), considering that these are usually among the most toxic and recalcitrant to degradation. Thus, beyond the pharmacological aspect, the data indicate, therefore, that among the three sartans considered, IRB is the one that could have the lowest possible environmental impact, although the variability of real-world conditions in wastewater treatment plants, such as pH, temperature and organic matter content, can substantially influence both the degradation kinetics and the profiles of DBPs.

3. Conclusions

Although present at low concentration levels, emerging contaminants (ECs) can cause toxicological effects in living organisms, promote the phenomenon of antibiotic resistance, show poor biodegradability and, consequently, accumulate in the environment, with the possibility of reaching humans through the food chain. Wastewater treatment plants represent a possible source of EC diffusion into the environment since conventional treatment processes are not specifically aimed at their removal.

Before being released into the environment, wastewater undergoes a disinfection process, which is generally based on the use of sodium hypochlorite. This review considers the environmental fate of a class of drugs, such as sartans, which are among the most widely prescribed antihypertensives and are widely found in aquatic environments. The disinfection by-products (DBPs) of the three most commercially important sartans - Irbesartan, Olmesartan and Candesartan - which are found in wastewater and surface water and are considered ECs, were analyzed and compared. A thorough understanding of the three sartans has been developed that allowed us to compare the percentages of mineralization and the recovery of each of them, as well as to describe the individual DBPs, some of which are common. Furthermore, the structural characteristics of the starting molecules from which their degradation starts have been identified, as well as a probe molecule, the valsartan acid, useful to evaluate the efficiency of wastewater treatment processes. Finally, from the analysis of the ecotoxicological profiles of sartans and their DBPs tested on three test organisms such as *Daphnia magna, Raphidocelis subcapitata* and *Aliivibrio fischeri*, it appears that sartans as such are only slightly toxic, while some of their DBPs have been found to be very toxic, especially on *D. magna* and *A. fischeri*.

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Declaration of competing interest

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

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Data availability

Data will be made available on request.

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