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# Mimicking $P_{450}$ processes and the use of metalloporphyrins*

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*Abstract*: Metalloporphyrins (MPs) are known to catalyze in vitro a broad range of cytochrome $P_{450}$-mediated reactions occurring in vivo. Most of the biomimetic research using MPs in oxidative catalysis has been directed towards the oxidation of organic compounds presenting significant reactivity features in one functional group. Much less effort has been made to imitate the oxidation of more complex molecules, with a range of functionalities, such as drugs or other xenobiotics. By varying the structure of the porphyrin, the metal ion, the oxidant, and the reaction conditions, it is possible to modulate the regioselectivity of the oxidation reactions. Recently, and along with studies on the synthesis and reactivity of porphyrins, chlorins, and phthalocyanines, our group was able to develop an interesting line of research in the field of biomimetic oxidation of organic compounds using environmentally benign hydrogen peroxide as oxidant and Mn(III) or Fe(III) porphyrin complexes as catalysts. The more up to date results obtained in such work are reviewed here.

*Keywords*: catalysts; metalloporphyrins; pharmaceuticals; porphyrins; oxidation.

## INTRODUCTION

The key route for the elimination of xenobiotics is an enzymatic biotransformation, which, in many cases, is initiated by oxidation reactions catalyzed by enzymes of the cytochrome $P_{450}$ ($CYP_{450}$) group [1–5]. Moreover, $CYP_{450}$ enzymes are responsible for phase I metabolism of about 75 % of known pharmaceuticals. $CYP_{450}$s perform this and other vital biological functions in many cases through the controlled activation of C–H bonds [6]. One of the major challenges of scientific research in recent years has been the understanding of how the enzymatic reactions are performed in vivo. As the isolation of biological entities can be complicated and time-consuming, several synthetic models have been developed to imitate the role of $CYP_{450}$ in living organisms. Although none of these synthetic models can replicate the whole range of $CYP_{450}$-catalyzed reactions, the biomimetic systems show advantages over the usual in vitro methods [4,7–10].

Some of these biomimetic models involve metalloporphyrins (MPs) as catalysts, namely, those based on the *meso*-tetraphenylporphyrin ($TPPH_2$) structure, since MPs are known to catalyze, in vitro, a broad range of $CYP_{450}$-mediated reactions. The pioneer system reported by Groves and collaborators, which was based on the Fe(III) complex of the *meso*-tetraphenylporphyrin [Fe(TPP)Cl] as catalyst and PhIO as the oxygen donor, is considered as the first system able to mimic the cytochrome $P_{450}$ reac-

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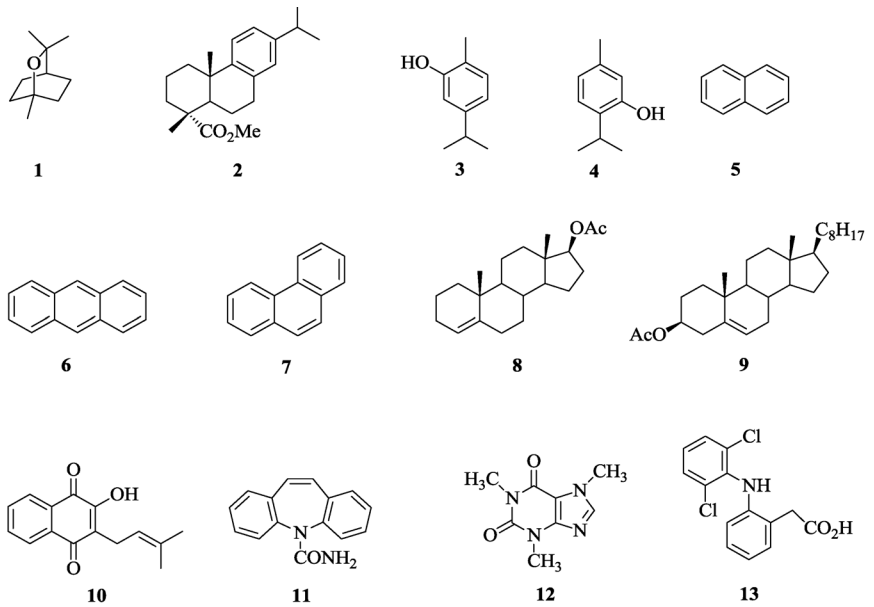
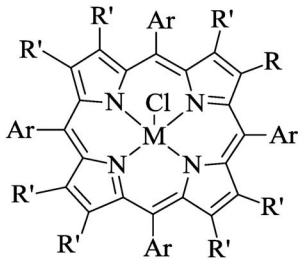
tions, namely, the epoxidation of olefins and the hydroxylation of alkanes [11]. Cr [12] or Mn [13,14] complexes of TPP have also been shown to act as catalysts for the oxygen atom transfer reactions from PhIO to alkene and alkane substrates. In the last few decades, the use of more efficient and robust MPs as catalysts in oxidative systems, particularly Fe(III) and Mn(III) complexes, has been the subject of great interest. The porphyrin Mn complexes proved to be more efficient than the Fe or the Cr ones when PhIO is used as the oxidant, and so they have become the complexes of first choice [15].

Most of the research using MPs in oxidative catalysis has been directed towards the oxidation of organic compounds presenting significant reactivity features in one functional group. Much less effort has been made to imitate the oxidation of more complex molecules, with a range of functionalities, such as pesticides, drugs, or other xenobiotics. By varying the structure of the porphyrin, the metal ion, the oxidant, and the reaction conditions (co-catalyst, solvent, homogeneous or heterogeneous systems), it is possible to modulate the regioselectivity of the oxidation reactions [8,9]. There is always the expectation to create simple and efficient catalytic systems able to compete with selective oxidation processes observed in vivo [16], or even with industrial processes in use. As a consequence of the large interest in MPs as biomimetic catalysts for oxidative transformations, a number of reviews have been published, including books and book chapters [7–10,17–25].

Recently, and along with studies on the synthesis and reactivity of porphyrins, chlorins, and phthalocyanines, our group has been performing studies related to the biomimetic oxidation of organic compounds using mainly the environmentally benign hydrogen peroxide as oxidant and Mn(III) or Fe(III) porphyrin and chorin complexes as catalysts [26–45]. Some of the most significant results obtained in such work are discussed here for compounds **1–13**, (Scheme 1), using the porphyrin complexes shown in Scheme 2.




**Scheme 1**

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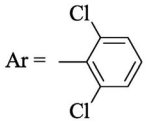
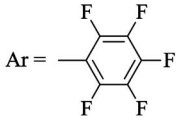
| Ar =  | Mn(TDCPP)Cl | M = Mn | R = R' = H | |
| | Mn(β-$NO_2$TDCPP)Cl | M = Mn | R = $NO_2$ | R' = H |
| | Fe(TDCPP)Cl | M = Fe | R = R' = H | |
| Ar =  | Mn($TF_5$PP)Cl | M = Mn | R = R' = H | |
| | Mn(β-$NO_2TF_5$PP)Cl | M = Mn | R = $NO_2$ | R' = H |
| | Fe($TF_5$PP)Cl | M = Fe | R = R' = H | |

**Scheme 2**

## DISCUSSION

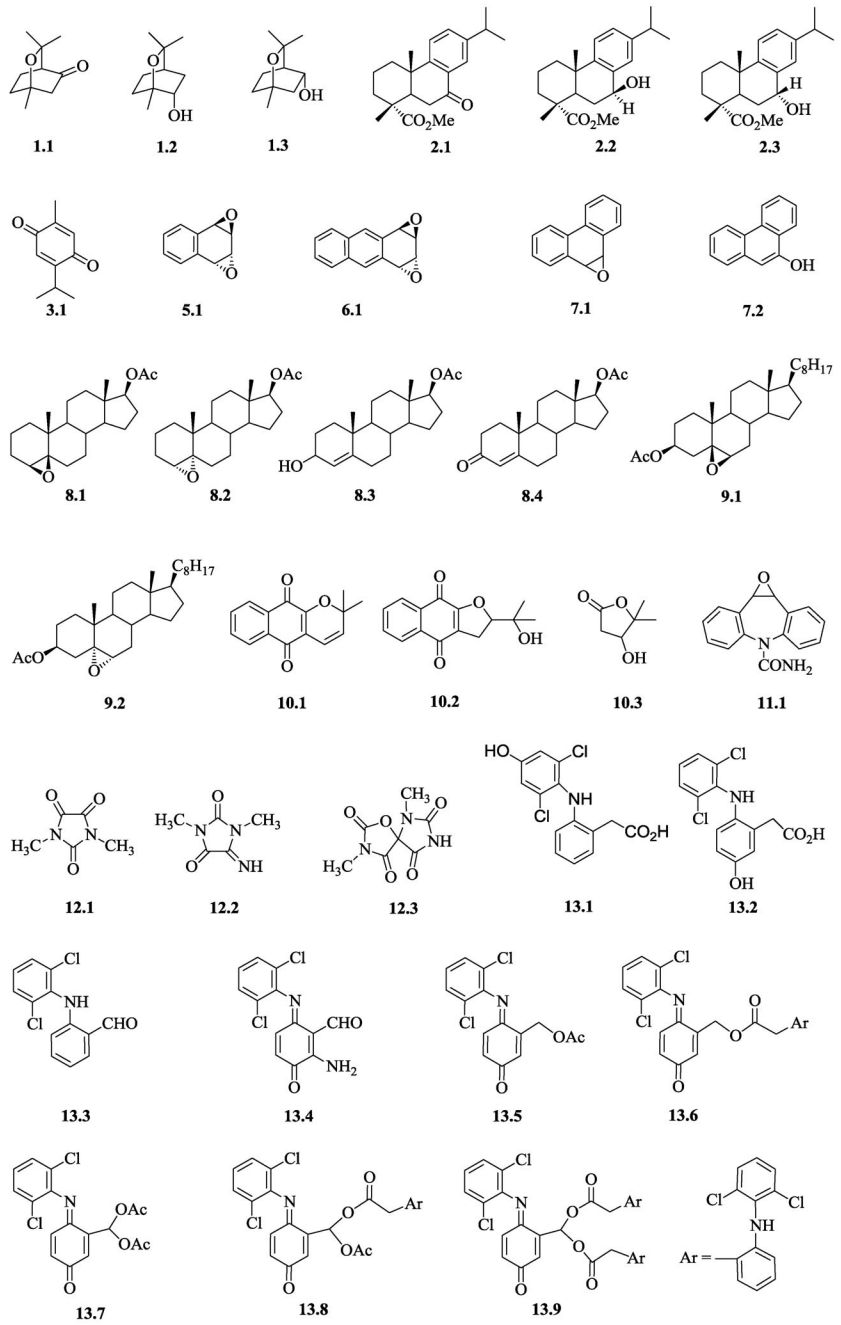
The development of sustainable, environmentally benign, safe, and clean methodologies is one of the most important goals of contemporary research in synthetic organic chemistry [46–49]. Even though the oxidation reactions represent industrial core technologies for converting bulk chemicals into useful products, they are among the most problematic transformations in organic chemistry. Thus, it is not surprising that several publications highlight the need for the development of clean and safe oxidation procedures [48–53].

The transformation of a cheap and accessible substrate into a product of higher commercial value is clearly a transformation of huge importance, being the purpose of many studies. Several natural products, largely of vegetal origin, due to their abundant occurrences, low extraction costs, structural functionalities, and putative applications, are excellent substrates to be considered in catalytic oxidative studies. A vital issue for all kinds of oxidation reactions is the use of environmentally benign oxidants. Among the usually available oxidants, air seems to be the perfect reagent for oxidation reactions [54]. However, the use of air or pure oxygen is tricky to control and dangerous combustions may take place. In addition to molecular oxygen, commercially available aqueous hydrogen peroxide is a relatively cheap and, most of all, a waste-avoiding oxidant. Moreover, hydrogen peroxide is able to oxidize organic compounds with an atom efficiency of 47 %, producing only water as by-product. Due to its properties, hydrogen peroxide is particularly useful for liquid-phase oxidation reactions used in the production of fine chemicals and there is a recent tendency to use this oxidant also for bulk processes [46,47,51,55].

### Oxidation of 1,8-cineole (1), methyl dehydroabietate (2), carvacrol (3), and thymol (4)

Some years ago, Cavaleiro and collaborators [26] reported the catalytic oxidation of 1,8-cineole (**1**), a monoterpenoid that is one of the major components of the essential oils of numerous plant species, and methyl dehydroabietate (**2**), a diterpenic acid, with hydrogen peroxide in the presence of Mn(III) porphyrins as catalysts, using either imidazole or ammonium acetate as co-catalysts. The products obtained in the oxidation of **1** resulted mainly from the oxygenation at positions 2 and 3, giving rise mainly to

compounds **1.1–1.3**, (Scheme 3). The oxidation of **2** gave rise to ketone (**2.1**) and to alcohols (**2.2** and **2.3**), resulting from the oxidation at the benzylic position 7 of the substrate (Scheme 3). The oxidation of terpenes such as carvacrol (**3**) and thymol (**4**) was also performed under similar reaction conditions [27]. Thymoquinone (**3.1**), a diketone of high commercial value, was the only product obtained in the oxidation of carvacrol and thymol (Scheme 3).




**Scheme 3**

### Oxidation of naphthalene (5), anthracene (6), and phenanthrene (7)

An efficient system for the epoxidation of aromatic hydrocarbons with hydrogen peroxide in the presence of **Mn(TDCPP)Cl**, **Mn(β-$NO_2$TDCPP)Cl**, and **Mn($TF_5$PP)Cl** as catalysts was also described [31]. Specifically, if using **Mn(TDCPP)Cl** and **Mn(β-$NO_2$TDCPP)Cl**, naphthalene (**5**) and anthracene (**6**) afforded the *anti*-1,2:3,4-arene diepoxides in very good conversions and selectivities. Actually, **5** and **6** were oxidized in the presence of **Mn(TDCPP)Cl** to the corresponding *anti*-1,2:3,4-arene diepoxides (**5.1**, 81 % and **6.1**, 74 %) at 91 and 100 % conversions, respectively. **Mn(β-$NO_2$TDCPP)Cl** gave rise to similar results on the oxidation of **5** and **6**. The oxidation of phenanthrene (**7**) in the presence of **Mn(TDCPP)Cl** occurred with high selectivity for the epoxidation of the 9,10-bond affording **7.1**. Total conversion of phenanthrene was obtained with both catalysts, namely, **Mn(TDCPP)Cl** and **Mn(β-$NO_2$TDCPP)Cl**. However, **Mn(β-$NO_2$TDCPP)Cl** afforded compound **7.2** as the major product. In the presence of **Mn($TF_5$PP)Cl**, the aromatic hydroxylation of substrates **5–7** and the transformation of the resulting phenols to the related quinones were always the main pathways observed.

### Oxidation of 17β-acetoxy-4-androstene (8) and 3β-acetoxy-5-cholestene (9)

The chemical modification of steroids is known to bring significant biological effects [56]. There are some examples concerning the hydroxylation of steroidal skeletons with *tert*-butyl hydroperoxide (TBHP), *N*-oxides, or iodosylbenzene as oxygen donors in the presence of Ru, Mn, or Os porphyrins [57–65]. An important methodology is the epoxidation of unsaturated $\Delta^4$- and $\Delta^5$-steroids, which has been performed either directly or in a catalytic way, leading to different products' stereoselectivity. In fact, direct epoxidation of both $\Delta^4$- and $\Delta^5$-steroids with organic peroxyacids is known to afford mainly the α-epoxides [66]. On the other hand, the epoxidation of $\Delta^4$- and $\Delta^5$-steroids catalyzed by Ru or Mn porphyrins have led mainly to the β-epoxidation [67–71]. Cavaleiro and collaborators were able to study the oxidation of 17β-acetoxy-4-androstene (**8**) and 3β-acetoxy-5-cholestene (**9**) (Scheme 1), with $H_2O_2$, in the presence of Mn(III) or Fe(III) porphyrins [32,33]. Varying the molecular structure of the porphyrin, as well as the central metal ion, has allowed the preferential formation of the α- or the β-epoxide (Scheme 3). The porphyrins with electron-withdrawing groups in the *o*-positions of the *meso*-phenyls and Mn(III) as the central metal ion, like **Mn(TDCPP)Cl**, gave preferentially the β-epoxide of the $\Delta^4$-and $\Delta^5$-steroids studied. In contrast, **Fe($TF_5$PP)Cl** catalyzed preferentially the α-epoxidation of $\Delta^4$-steroids, also enhancing the stereoselectivity for the α-epoxide in $\Delta^5$-steroids. The results for the oxidation of **8** have shown that the reaction efficiency depends on the catalyst used and on the time of reaction. Maximum conversions of 98, 96, and 100 % have been obtained for catalysts **Mn(TDCPP)Cl**, **Mn(β-$NO_2$TDCPP)Cl**, and **Fe($TF_5$PP)Cl**, respectively. Among Mn porphyrins, the fastest reaction was obtained with **Mn(TDCPP)Cl**, which gave rise to 88 % conversion after 1 h. However, for an equal period, **Fe($TF_5$PP)Cl** led to complete conversion of **8**. The maximum yield for β-epoxide (**8.1**) was achieved with **Mn(TDCPP)Cl** (49 %). Despite the high β-stereoselectivity observed in the reactions catalyzed by **Mn(β-$NO_2$TDCPP)Cl**, lower epoxide yields were registered, since this catalyst favors the allylic oxidation, producing the alcohol (**8.3**) and ketone (**8.4**) in 13 and 18 % yields, respectively. Moderate yields of the epoxides were observed with **Mn($TF_5$PP)Cl**, although nearly equal amounts of α- and β-epoxides were obtained. A change in stereoselectivity was observed in the presence of **Fe($TF_5$PP)Cl**, since this reaction took place with higher selectivity to the α-epoxide (**8.2**). With this catalyst, total conversion and 57 % yield for **8.2** were observed. Moreover, the oxidation of **9** proceeds with 100 % chemoselectivity for the epoxidation reaction (Scheme 3). High conversions were obtained with **Mn(TDCPP)Cl** and **Mn(β-$NO_2$TDCPP)Cl**, and these reactions led to high β-stereoselectivity. **Mn(TDCPP)Cl** was the best catalyst for β-epoxidation, affording **9.1** in 71 % yield and 90 % β-selectivity. The reactions with **Fe($TF_5$PP)Cl** and $H_2O_2$ or the reactions with *m*-CPBA without catalyst gave 100 % conversion, but lower stereoselectivities. In the reaction catalyzed by **Fe($TF_5$PP)Cl**, a β-selectivity of 66 % was achieved [32,33]. In a recent work, **9** was epoxidized to **9.1**

in 99 % yield with complete β-selectivity, using [$Ru^{II}(TF_5PP)(CO)$] covalently attached to poly(ethyleneglycol) and 2,6-dichloropyridine *N*-oxide (2,6-$Cl_2$pyNO) as oxidant [72].

### Oxidation of lapachol (10)

Found in the heartwood of some trees of the *bignoniaceae* family [73–75], lapachol (**10**) (Scheme 1) is the most abundant, naturally occurring naphthoquinone, which has been studied by several authors and proved to be one of the most versatile biologically active compounds [76,77]. Currently these naphthoquinones are considered as privileged structures in medicinal chemistry [75,78], since lapachol and several derivatives are associated to a broad spectrum of biological activities such as anti-tumor, antibiotic, antimalarial, anti-inflammatory, anti-ulcer, antibacterial, fungicidal, and trypanocidal activities. Lapachol (**10**) is thus an excellent candidate for structural modifications with the aim of understanding its structure–activity associations and thus, eventually, develop analogues with improved biological activities. In addition, it is also important to know the metabolites resulting from the in vivo oxidation of these putative drugs, in order to prevent possible secondary effects. Although the oxidation of **10** and some of its analogues have been studied for several decades, almost all of the reported procedures make use of very aggressive oxidizing conditions with little or no environmental concerns at all [79,80].

Very recently, Cavaleiro and collaborators have studied the biomimetic catalytic oxidation of **10** using aqueous hydrogen peroxide and **Mn(TDCPP)Cl**, where *p*-naphthoquinones **10.1** and **10.2** were preferentially formed (Scheme 3). Additionally, the cleavage of lapachol (**10**) molecule took place and a new lactone (**10.3**) was observed and characterized. This means that the presence of **Mn(TDCPP)Cl** not only allows the epoxidation of the side-chain double bond of **10**, but also the epoxidation of the quinone ring double bond took place, giving rise to such structural cleavage. Moreover, a comparison between the catalytic results obtained and those described for the oxidation of **10** using *m*-chloroperbenzoic acid (*m*-CPBA) revealed, besides different reaction products, a completely different selectivity. Unlike the *m*-CPBA approach, where *o*-naphthoquinones were obtained, *p*-naphthoquinones were highly favored with **Mn(TDCPP)Cl** and hydrogen peroxide.

### Oxidation of carbamazepine (11)

Carbamazepine (**11**), one of the most commonly prescribed antiepileptic drugs, and also used in the treatment of trigeminal neuralgia and psychiatric disorders [81,82], is metabolized by the $P_{450}$s, giving rise to the formation of epoxide **11.1** (Scheme 3), which is known as its main in vivo metabolite. Recently, the oxidation of **11** using MPs as biomimetic models has been studied under homogeneous and heterogeneous conditions. Meunier and co-workers [83,84] studied the oxidation of **11** in aqueous media (pH 5) by $KHSO_5$ and $Na_2SO_3/O_2$, using water-soluble Mn and Fe porphyrins. Groves and co-workers [85] studied the oxidation of **11** using the same water-soluble Mn porphyrin as catalyst and *m*-CPBA as the oxidant also in aqueous media (pH 7.4). Yang and Nam [86] also used the same Fe porphyrin complex used by Meunier in a buffer solution, although using hydrogen peroxide and TBHP as the oxygen donors. Assis and co-workers [87] studied also the catalytic activity of **Fe($TF_5$PP)Cl** and **Mn($TF_5$PP)Cl** under heterogeneous and homogeneous conditions in the oxidation of **11** with PhIO and hydrogen peroxide as oxidants. In this case, the **Mn($TF_5$PP)Cl** proved to be the most efficient and selective for the epoxide formation, mainly for PhIO. Assis and co-workers [88] also used, as catalysts, tetraphenylporphyrins bearing crown ether units for the oxidation of **11**; it was found that the catalytic activity of those MPs depends on the number of crown ether units attached to the porphyrin.

Very recently, Cavaleiro and co-workers also performed the in vitro oxidation of **11** using **Mn(TDCPP)Cl** and aqueous hydrogen peroxide, resulting only in the formation of epoxide **11.1**. When a substrate/catalyst molar ratio of 150 was used, the total conversion of **11** was achieved after 2 h of reaction. If a substrate/catalyst molar ratio of 300 was used instead, the total conversion of **11** was

achieved only after 3 h of reaction. For a substrate/catalyst molar ratio of 600, the reaction was even slower and, after 4 h of reaction, there was no evident increase of carbamazepine conversion [43].

### Oxidation of caffeine (12)

Caffeine (**12**) is by far the most universally used legal drug in the world, whether in the form of beverages or combined with analgesics in order to enhance their effects [89–92]. Numerous studies show that 3-*N*-demethylation (the main oxidation pathway) in humans is specifically catalyzed by CYP1A2 [90–93]. It is thus not surprising that caffeine oxidation has been extensively studied in the laboratory. In 1890, Leipen treated an aqueous solution of caffeine with ozone and obtained dimethylparabanic acid (DMPA) (**12.1**) (Scheme 3), as the major product. At the same time, other authors reported that **12.1** was also the final product obtained by the oxidation of caffeine under numerous experimental conditions [94]. In 1979, Kolonko et al. performed studies on the oxidation of **12** with ozone under several conditions and obtained **12.1** as the major product. In 2005, Dalmázio et al. also observed the formation of **12.1** under photolysis conditions [95]. Cavaleiro and co-workers were able to study the oxidation of **12** using hydrogen peroxide as oxidant, and **Mn(TDCPP)Cl** or **Mn($TF_5$PP)Cl** as catalysts (Scheme 2) and ammonium acetate as co-catalyst. The most representative products detected have been **12.1**, **12.2**, and **12.3** (Scheme 3). Depending on the catalyst employed, different selectivity for the products was observed. **Mn(TDCPP)Cl** promotes the formation of the spiro compound (**12.3**) as the major product, whereas when **Mn($TF_5$PP)Cl** is employed, DMPA (**12.1**) is the main product instead [40].

### Oxidation of diclofenac (13)

Diclofenac (**13**), one of the most frequently used anti-inflammatory drugs, is metabolized in humans by cytochrome $P_{450}$ enzymes to hydroxyl derivatives, among which 4'-hydroxydiclofenac (**13.1**), the major metabolite, and 5-hydroxydiclofenac (**13.2**) were isolated and characterized [96–98]. Some metabolites resulting from oxidative decarboxylation of diclofenac mediated by cytochrome $P_{450}$ enzymes have also been reported [99]. Some authors have reported the hydroxylation of **13** catalyzed by MPs with ammonium acetate as co-catalyst and hydrogen peroxide or TBHP as oxidants [100–102]. Moreover, in the presence of oxidants such as periodates, iodosylbenzene, *N*-oxides or hydrogen peroxide, MPs have shown to be good catalysts for the oxidative decarboxylation of carboxylic acids and some anti-inflammatory drugs having a carboxyl moiety [103–109].

Very recently, Cavaleiro and co-workers reported the oxidation of diclofenac (**13**) using Mn(III) porphyrins as catalysts (Scheme 2) with progressive additions of diluted $H_2O_2$, under normal atmosphere, in a mixture of acetonitrile/water at 30 °C. Under the conditions studied, besides the aromatic ring 5-hydroxylation and subsequent quinone-imine formation, the major products result from the oxidative decarboxylation of **13**, which leads to the formation of several derivatives, namely, esters {[6-(2,6-dichlorophenylimino)-3-oxocyclohexa-1,4-dien-1-yl]methyl acetate (**13.5**) and [6-(2,6-dichlorophenylimino)-3-oxocyclohexa-1,4-dien-1-yl]methyl 2-[2-(2,6-dichlorophenylamino)phenyl] acetate (**13.6**)} and geminal diesters {[6-(2,6-dichlorophenylimino)-3-oxocyclohexa-1,4-dien-1-yl]methylene diacetate (**13.7**), {acetoxy[6-(2,6-dichlorophenylimino)-3-oxocyclohexa-1,4-dien-1-yl]}methyl 2-[2-(2,6-dichlorophenylamino)phenyl]acetate (**13.8**), and [6-(2,6-dichlorophenylimino)-3-oxocyclohexa-1,4-dien-1-yl]methylene bis{2-[2-(2,6-dichlorophenylamino)phenyl]acetate} (**13.9**)}. The higher conversions (59–78 %) of **13** were achieved in the presence of **Mn(TDCPP)Cl**, and the reaction products can be related with the co-catalyst used. 2-Amino-6-(2,6-dichlorophenylimino)-3-oxocyclohexa-1,4-dienecarbaldehyde (**13.4**) was only observed in the presence of ammonium acetate as co-catalyst. Replacing ammonium acetate by a sodium acetate/acetic acid mixture, an increase in the amount of 2-(2,6-dichlorophenylamino)benzaldehyde (**13.3**) is registered, accompanied by the absence of compound **13.4**, although products **13.5**, **13.7**, and **13.8** resulting from the esterification with acetic acid present were still obtained. When imidazole was used as the co-catalyst, the formation of aldehyde

(**13.3**) was accompanied by the formation of only the monoester (**13.6**) and of the geminal diester (**13.9**), both resulting from the esterification with diclofenac. Compound **13.3** may result from the decarboxylation of **13** followed by oxidation, as already described in the literature for diclofenac, in vivo [99], and for other carboxylic acids, using a supported Mn(III) porphyrin [109]. The oxidation of **13** in the presence of **Mn(TF$_5$PP)Cl** and ammonium acetate showed to be less efficient, since the conversion never exceeded 22 %.

## CONCLUSIONS

Mn(III) and Fe(III) porphyrins were used for the oxidation of organic compounds, at room temperature, and in the presence of hydrogen peroxide, a safe and environmentally friendly oxidant. These MPs were shown to be excellent catalysts for the in vitro biomimetic oxidative transformation of organic compounds, namely, pharmaceuticals or pharmacologically active compounds, when hydrogen peroxide is used as the oxygen donor. The results show also that MPs are able to imitate the functionalization of complex molecules, with a range of functionalities, such as drugs or other xenobiotics.

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