We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

6,300

Open access books available

172,000

International authors and editors

190M

Downloads

Our authors are among the

154

Countries delivered to

TOP 1%

most cited scientists

12.2%

Contributors from top 500 universities

WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com

Green Oxidation Reactions of Drugs Catalyzed by Bio-inspired Complexes as an Efficient Methodology to Obtain New Active Molecules

Emerson Henrique de Faria¹, Gustavo Pimenta Ricci¹, Frederico Matias Lemos¹, Marcio Luis Andrade e Silva¹, Ademair Alves da Silva Filho², Paulo Sérgio Calefi¹, Eduardo José Nassar¹ and Katia Jorge Ciuffi¹

¹*Universidade de Franca - Av. Dr. Armando Salles Oliveira, 201. Parque Universitário, Franca- SP Brasil – CEP - 14.404-600*

²*Universidade Federal de Juiz de Fora - Faculdade de Farmácia e Bioquímica, Departamento Farmacêutico, Campus Universitário, Martelos, Juiz de Fora-MG. Brasil*

1. Introduction

The cytochromes P450 (P450s) are an important class of heme-containing enzymes that act as monooxygenases. P450s have a variety of critical roles in biology and are considered the most versatile enzymes in nature because of their key part in the metabolism of biomolecules and xenobiotics.

The P 450 reacts with one oxygen atom from distinct oxidants such as dioxygen (O₂), forming the active oxidant species, the so-called metal-oxo complex (high-valent iron(IV)-oxo intermediate), which is able to transfer the oxygen atom to several substrates like alkanes, alkenes, aromatic compounds and amines, among others. This active species is also responsible for the cleavage of C-C bonds in organic substrates. The key feature of P450 enzymes is their ability to perform this reaction selectively, under mild conditions.

Synthetic metalloporphyrins have been extensively used as biomimetic catalysts due to their ability to act as P450 models. Ironporphyrins, in particular, have been employed as models because they are capable of catalyzing organic oxidations. Besides their biological and catalytic properties, ironporphyrins can also be immobilized onto organic polymers as well as amorphous and crystalline inorganic materials, such as silica, alumina, and clays.

The immobilization of metalloporphyrins onto inorganic supports has been found to yield efficient, selective catalysts for the oxidation of oxidizable groups, promoting a special environment for the approach of the substrate to the catalytically active species, thus mimicking the “site-isolation principle” of biological enzymes. The sol-gel process is considered an ideal methodology to prepare the ironporphyrin heterogeneous catalysts.

Synthetic metalloporphyrins also have potential application in the design of green processes for the accomplishment of many kinds of oxidations mimicking the P450 reactions.

Over the last decade the search for efficient and environmentally friendly oxidation procedures that could be used to develop green processes for many kinds of oxidation

reactions has been intensified. Also, since the oxidation of organic compounds with high selectivity is of extreme importance in synthetic chemistry, many attempts have been made in order to oxidize compounds and produce target components that cannot be easily obtained by conventional routes. A very interesting and promising field for the application of metalloporphyrin catalysts lies in the area of natural product oxidation, with potential use as drugs for clinical practice. This can be achieved by employing clean oxidants like hydrogen peroxide or molecular oxygen.

Lignans have attracted much interest over the years on account of their broad range of biological activities, including antitumoral, trypanocidal, antimicrobial, and anti-inflammatory activities, so alternatives that promote and improve their production are necessary.

(-)-Hinokinin, a dibenzylbutyrolactone lignan, possesses antileishmanial, anti-inflammatory, antigenotoxicity [5-9], and significant *in vitro* and *in vivo* trypanocidal activities against *Trypanosoma cruzi*, the etiologic agent of Chagas' disease.

Licarín-A, a neolignan obtained from the oxidative coupling of isoeugenol, displays significant antiparasitic activity against the adult forms of *Schistosoma mansoni*.

Taking into account the antiparasitic potential and the possible production of derivatives from Licarín-A and (-)-Hinokinin, there is great interest in the search for new approaches that will enable the oxidation of these lignans to be carried out, since the oxidized products are probably biologically active.

Enzymatic biological models have been widely employed throughout all the phases of drug design and development. *In vivo* oxidations carried out by enzymes like P450s can be easily mimicked under mild conditions by using synthetic metalloporphyrin systems. More specifically, ironporphyrins have been utilized as P450 models due to their ability to catalyze countless organic reactions.

In this chapter, the catalytic activity of ironporphyrins supported on an alumina or silica matrix, prepared by the sol-gel methodology, in the oxidation of lignans such as licarín-A and (-)-cubebin is investigated, in the search for novel systems for the accomplishment of green oxidation reactions by bio-inspired catalysts. Special attention is given to the reaction products and their potential biological activities.

2. Cytochromes P450 (P450s)

The cytochromes P450 (P450s) are an important class of heme-containing enzymes that contain a protoporphyrin IX as the active center and act as monooxygenases. As observed in Figure 1, the protoporphyrin presents one S of a cysteine as the fifth ligand and a free sixth coordination site available for the binding of molecular oxygen (McMurry & Groves, 1986; Lewis, 2001; Lohmann & Karst, 2008). The P450s have a relatively hydrophobic active site cavity.

Cytochrome P450 enzymes are present in all five biological kingdoms. In mammalian species, P450s are present in most tissues and are largely found in the liver (McMurry & Groves, 1986; Lewis, 2001; Siroká & Drastichová, 2004; Mansuy, 2007; Munro et al., 2007; Lohmann & Karst, 2008).

P450s have a variety of critical roles in biology and are considered the most versatile enzymes in nature because of their key part in the metabolism and degradation of biomolecules and xenobiotics. Their role in the endogenous metabolism of steroids is considered the primary function of the organism (McMurry & Groves, 1986; Lewis, 2001;

Fig. 1. Representative structure of cytochrome P450.

Siroká & Drastichová, 2004; Mansuy, 2007; Munro et al., 2007; Lohmann & Karst, 2008), a crucial step in the adaptation of living organisms to their always changing chemical environment (Mansuy, 2007). It is accepted that in the prehistoric organisms one function of the P450 enzymes was the hydroxylation of organic substrates, so that the oxidized products could be employed as energy source (McMurry & Groves, 1986; Lewis, 2001; Siroká & Drastichová, 2004; Mansuy, 2007; Munro et al., 2007; Lohmann & Karst, 2008).

Usually, the exposure of an organism to xenobiotics implies biological responses, generally in the form of biotransformation of the pharmacological or toxic substance, which generally depends on the conversion of the absorbed compound into an active metabolite or not, with a view to its elimination. During the biotransformation, a lipid-soluble xenobiotic or endobiotic compound is enzymatically transformed into polar, water-soluble, and excretable metabolites. The metabolic products are often less active than the parent drug or even inactive. However, some biotransformation products (metabolites) may have enhanced activity or toxic effects compared with the initial compound. A key enzymatic system that determines the body's ability to deal with drugs and chemicals is represented by P450 (Meyer, 1996).

Briefly, drugs and other xenobiotics are transformed via multiple reactions in two distinct stages, namely phase I and phase II reactions. Phase I reactions are regarded as being responsible for preparing the drug for phase II reactions. Phase II reactions are usually the true "detoxification" pathways, leading to compounds that account for most of the inactive, excreted drug products (Tanaka, 2001).

In plant organisms, the production of some significant secondary metabolites, such as lignin, terpenoids, steroids, essential oils, and opioid precursors (Lohmann & Karst, 2008), which

are essential for the production of some drugs for use in humans, is also based on cytochrome functions (Lewis, 2001).

The P450s react with one oxygen atom from distinct oxidants such as dioxygen (O_2), forming the active oxidant species, the so-called metal-oxo complex (high-valent iron(IV)-oxo intermediate, $Fe^{IV}(O)P^+$), which is able to transfer the oxygen atom to several substrates like alkanes, alkenes, aromatic compounds and amines, among others. This active species is also responsible for the cleavage of C-C bonds in organic substrates. In the mechanism called “rebound mechanism”, the hydrogen abstraction from substrates such as alkanes (R-H) by the $Fe^{IV}(O)P^+$ species takes place, producing an alkyl radical R· and an iron(III)hydroxo complex as intermediates. This is followed by the caged alkyl radical rebound to the hydroxyl group, generating the alcohol (Lewis, 2001; Mansuy, 2007). (Figure 2).

Fig. 2. Rebound mechanism of metalloporphyrin-catalyzed hydroxylations

The key feature of P450 enzymes is their ability to perform this reaction selectively, under mild conditions, by monooxygenation of the substrate (McMurry & Groves, 1986; Lewis, 2001; Siroká & Drastichová, 2004; Mansuy, 2007; Munro et al., 2007; Lohmann & Karst, 2008).

2. Cytochromes P450 models

The development of research on P450s has largely paralleled that on drug metabolism, and there are strong connections between these two areas (Gibson & Skett, 1994).

Indeed, it is very important to know and follow the mechanisms organisms undergo after exposure to a xenobiotic. Deeper understanding of the catalytic reactions carried out by enzymes, especially with respect to the nature of the active oxidizing species, has recently been achieved thanks to studies on enzyme models (Bernardou & Meunier, 2004; Nam, 2007; Lohmann & Karst, 2008), particularly synthetic enzymes.

By means of synthetic models, it is possible to quickly predict information about the biotransformation of a drug during the search for and development of new therapeutic agents, which in turn enables prediction of their toxic effect (Lewis, 2001; Mansuy, 2007). Furthermore, the use of enzyme models diminishes animal testing, not to mention the fact that problems related to the isolation of natural enzymes and cells are also eliminated (Bernardou & Meunier, 2004).

Enzymatic biological models have been widely employed throughout all the phases of drug design and development. *In vivo* oxidations carried out by enzymes like P450s can be easily mimicked under mild conditions by using synthetic metalloporphyrin systems. More specifically, ironporphyrins and manganeseporphyrins have been utilized as P450 models due to their ability to catalyze countless organic reactions (Bernardou et al., 1991).

Several porphyrin systems have been reported in the literature, and over the years three main generations of these catalysts have been prepared (Mansuy, 2007). Figure 3 shows some structures, representing the three generations of porphyrins. Ironporphyrins, in particular, have been more employed as models because they are capable of catalyzing organic oxidations pretty similarly to the biological enzyme.

Fig. 3. Structural formula of several metalloporphyrins: (a) meso-tetrakisphenylporphinato iron III (FeTPP), meso tetrakisphenylporphinato manganese III (MnTPP), (b) meso tetrakis(pentafluorophenyl)porphinato iron III (FeTFPP), tetrakis(pentafluorophenyl)porphinato manganese III (MnTFPP), (c) meso-Tetrakis(2,6-dichlorophenyl)porphinato iron III, (d) β -octa-fluoro-meso-tetrakis(pentafluorophenyl)porphinato iron III.

Besides their biological and catalytic properties, synthetic metalloporphyrins can also be immobilized onto organic polymers as well as amorphous and crystalline inorganic materials, such as silica, alumina, and clays (Figure 4).

Fig. 4. Kaolinite functionalized with a second-generation of metalloporphyrin, Fe(TFPFP) [adapted from (Bizaia et al.,2009)]

The immobilization of metalloporphyrins onto inorganic supports has been found to yield efficient, selective catalysts for the oxidation of oxidizable groups, promoting a special environment for the approach of the substrate to the catalytically active species, thus mimicking the “site-isolation principle” of biological enzymes (Lewis, 2001; Mansuy, 2007). The sol-gel process is considered a practical methodology for the preparation of heterogeneous ironporphyrin catalysts. We (de Lima et al., 2001; de Oliveira, et al., 2001; Sacco et al., 2001; Bizaia et al., 2009; de Faria et al., 2004 ; Mac Leod et al., 2006 ; Machado et al., 2009) have presented interesting results regarding the efficiency of ironporphyrin catalysts supported on silica or alumina (Figure 5).

Fig. 5. Porphyrins entrapped in an alumina matrix by non-hydrolitic sol-gel process [adapted from (Lima et al., 2001).

Synthetic metalloporphyrins also have potential application in the design of green processes for the accomplishment of many kinds of oxidations that mimic the P450 reactions.

Since the pioneering work of Groves (Groves et al., 1979), synthetic metalloporphyrins have been used as biomimetic catalysts of a multitude of reactions, mainly of oxidations of saturated and unsaturated hydrocarbons (Mansuy, 2007). Over the last years, the great versatility of these biomimetic metalloporphyrins has been extended to the oxidation of countless substrates, thus generating important molecules for application in fine chemistry and in the pharmaceutical industry. Important examples of such reactions are selective DNA cleavage, oxidation of pesticides and lignins, and oxidation of chlorinated aromatic compounds (Mansuy, 2007).

During the last decade, the development of synthetic systems mimicking the activity of cytochrome P450 by using metalloporphyrin catalysts and various oxygen atom donors has been reported. Some catalytic oxidation reactions described in the literature are summarized in Table 1, but this is not an overview from the literature data. A major review can be found in references (Lewis, 2001; Bernardou & Meunier, 2004; Mansuy, 2007; Lohmann & Karst, 2008).

Table 1 gives some examples of the use of these model systems in the the metabolism of xenobiotics. It is noteworthy that first- and second-generation ironporphyrins are more often employed as catalysts, using Iodosylbenzene (PhIO), NaOCl, meta-chloroperoxybenzoic acid (m-CPBA), or O₂/Pt-colloid as oxygen donor.

It is also worthy of note that synthetic metalloporphyrin catalysts are also very interesting for application in sophisticated organic synthesis and high-value products, such as fine chemicals. Apart from studies on xenobiotics, these catalysts can also be employed to promote chemical transformations that can potentially replace expensive industrial processes and which normally would not lead to the same product selectivity achieved by means of synthetic metalloporphyrins or biological systems.

It is always preferable to use oxidants containing only one oxygen atom when the study of the reaction model is concerned. Iodosylbenzene, for instance, is a widely employed oxidant in the academic field. This polymeric solid does not contain a weak O-H bond, thus eliminating the occurrence of free radical chain reactions normally initiated by oxidants like alkyl hydroperoxides R-O-O-H (Groves, 2006). However, this oxidant is expensive and hazardous. In fact, while iodosylbenzene is the preferred oxidant in studies related to oxidative metabolism, because it is very good for predicting drug metabolism, it is no longer indicated for research on bio or chemotransformation.

Over the last decade the search for efficient and environmentally friendly oxidation procedures that could be used to develop green processes for many kinds of oxidation reactions has been intensified. Also, because the highly selective oxidation of organic compounds is of extreme importance in synthetic chemistry, many attempts have been made in order to oxidize compounds and produce target components that cannot be easily obtained by conventional routes.

A very interesting and promising field for the application of metalloporphyrin catalysts lies in the area of natural product oxidation, with potential use in the discovery of new drugs for utilization in clinical practice. This could be achieved by employing clean oxidants like hydrogen peroxide or molecular oxygen. Nevertheless, although dioxygen is considered an ideal oxidant, it is difficult to use this very reactive compound because it is hard to control reaction selectivity, not to mention the security issues related to this gas.

Porphyrin	Matrix	Substrate	Reaction	Oxidant	References
[Fe(TPFPP)] [Fe(TDFSP)] [Fe(TCFSP)]	Homogeneous Kaolinite Si-APTS Chrys	Cyclohexane Heptane	Oxidation	PhIO	Nakagaki & Wypych, 2007
Mn(TDCPP)Cl	Homogeneous	Cyclooctene Non-1-ene <i>cis</i> -stilbene Cyclohexane		H ₂ O ₂	Thellend et al., 1994
[Fe(TPP)]Cl [Mn(TPP)]Cl [Fe(TFPP)]Cl [Mn(TFPP)]Cl		Piperine Piplartine		PhIO	Schaab et al., 2010
Mn-TMPyP Fe-TMPyP		DNA		O ₂ K ₂ O	Pitié et al., 2006
Fe(TCPP)Cl Mn(TCPP)Cl Mn(TFPP)Cl		Primidone		<i>t</i> -BOOH	Mac Leod et al., 2008
Horseradish-peroxidase		Chlorophyll	Degradation	H ₂ O ₂	Hynninen et al., 2010
[Fe(TPPF ₂₀)] [Fe(TPPCl ₈)] [Fe (TPPCL ₈ β-Br ₈)]		Fenitrothion Cyanophos Tolclofos-methyl butamifos Fenthion			Fujisawa & Katagi, 2005
β- and <i>meso</i> -substituted iron-porphyrins		Permethrin Fenvalerate			Fujisawa & Katagi, 2009
Gold(III)porphyrin		Carcinomas	Anticancer activity	---	van Rijt & Sadler, 2009

Table 1. Examples of model systems based on P450 in the metabolism of xenobiotics.

It is widely accepted that hydrogen peroxide is another ideal oxidant because of its high active oxygen content, availability, and non-toxicity. Moreover, it is considered to be non-polluting, since it produces only water as product (Goti & Cardona, 2008). Oxidations with hydrogen peroxide are highly atom-economic. Furthermore, hydrogen peroxide is a safe, readily available, cheap reagent.

Although the oxidation of natural products by synthetic ironorphyrins is a new area, it is a very promising field because it is well established that the chemical transformation of abundant and cheap natural products can make other more valuable compounds with interesting biological activities available.

3. Synthetic metalloporphyrins in the oxidation of plants

Natural products, especially medicinal plants, have great importance for the development of new drugs used in human and animal medicines. According to Rates (Rates, 2001) about 25% of the drugs prescribed worldwide are sourced from natural plants, and of the 252 drugs considered as basic and essential by the World Health Organization (WHO), 11% are exclusively originated from plants. In addition, many synthetic drugs have been and are being obtained from natural precursors, since they represent a valuable alternative for the development of new medicines (Elisabetsky et al., 1995; Balunas & Kinghorn, 20005). Examples of important drugs obtained from plants are digoxin (obtained from *Digitalis* sp. and used in heart failure) and taxol (obtained from *Taxus brevifolia* and used as antitumor). Thus, medicinal plants are an important source of new chemical substances with potential therapeutic applicability.

Concerning the production of active compounds, the diversity of the plant kingdom represents an extraordinary reserve of new molecules, but only a small percentage of plant species in the world have been investigated from a chemical viewpoint, and the biological and pharmacological screenings of their constituents are even scarcer (Cordell, 2000).

Pharmacological research on the active principles of medicinal plants has provided important advances in the therapeutics of many diseases, and various substances found in plants have been used as useful tools in pharmacological, physiological, and biochemical studies (Souza Brito, 1996; Rates, 2001).

The transformation of abundant natural products can transform them into economically valuable compounds, boosting their application in several areas of human health. One interesting review can be found in the reference (Simões et al., 2009). In this subject area some interesting research has been carried out on essential oils from plants. Terpenoids, which are widely distributed in nature, play an important role as fragrance, flavoring, and medicaments for the treatment of various diseases. Their chemical transformation by means of oxidation with several oxidants using synthetic metalloporphyrin as biomimetic catalysts of P450s has been reported in the literature (Toshiro et al., 1999). Konoike et al. (Konoike et al., 1999) have described the use of the ironporphyrin (FeTFPP, Figure 3)/metachloroperbenzoic acid system in the allylic hydroxylation of position 11 of triterpenes bearing a sterically hindered olefin. This oxidation position was obtained with the oleanolic acid, ursolic acid, and dihydrolanosterol, and their derivatives were efficiently (67%) converted to the corresponding allylic alcohols. Despite the high conversion rate achieved with the homogeneous catalytic system, the reaction presented some drawbacks, such as the employed temperature -78°C , and no possibility of catalyst reuse, since in fact no reuse of the homogeneous catalyst was mentioned.

The paper by Rosália et al. (Rosália et al., 1999) has described oxidation of the monoterpenes: carvacrol, thymol, and *p*-cymene, Figure 6, using manganeporphyrins (MnTDCPP and MnTFPP), Figure 3, /hydrogen peroxide as catalyst/oxidant. The oxidation of carvacrol and thymol selectively produced the thymoquinone, a high-value product compared with the starting reagents, because it has anticancer, anti-inflammatory, and hepatoprotective effects (Ravindran et al., 2010). The homogeneous manganese catalyst /hydrogen peroxide systems were very efficient for the production of thymoquinone, but no catalyst reuse was mentioned.

Milos (Milos, 2001) has reported that good thymoquinone production, Figure 6, (~ 60.0 %) was achieved by oxidizing the essential oil of oregano with the oxidant potassium

Fig. 6. Schematic representation of carvacrol and thymol oxidation to production of thymoquinone and possible byproducts.

monopersulfate, using an ironporphyrin (FeTPP, Figure 2) as biomimetic catalyst. The great differential in this work (Milos, 2001) is that, contrary to Rosália et al. (Rosália et al., 1999), Millo et al. worked directly with the oregano essential oil isolated from dried plant material, whereas Rosália worked with commercially available reagents.

Another major accomplishment of Milos's work (Milos, 2001) is the fact that a first-generation ironporphyrin, which is usually cheaper and easier to synthesize, was employed. However, this ironporphyrin can be easily destroyed under drastic reaction conditions, which would impair catalyst reuse.

Cavaleiro et al. (Cavaleiro, et al., 1996) have been one of the first to report the processing of 1,8-cyneole, Figure 7, one of the major components of the essential oils of *Eucalyptus globules*, using the clean oxidant, hydrogen peroxide. Although this oil is abundant, it is inert and had little economic significance. The oxidation of cyneole by a manganseporphyrin (MnTDCPP or MnTFPP, Figure 3)/hydrogen peroxide system generated oxygenated products with high added value. The homogeneous catalysts were very efficient, and the use of a cocatalyst improved hydrogen peroxide efficiency, consequently allowing for higher substrate conversion using shorter reaction times and smaller amounts of H_2O_2 , without loss of selectivity. No catalyst reuse was reported.

Fig. 7. Structure of 1,8-cyneole.

Another greatly important and largely available terpenoid is limonene, Figure 8, which is a source of a great variety of oxyfunctionalized derivatives. Some literature works have reported the chemical transformation of this substrate by mangesoporphyrins/ H_2O_2 systems (Skrobot et al., 2003). Metalloporphyrin systems have also been employed as efficient catalysts in the epoxidation of pinene to pinene oxide, Figure 8, which is a useful

intermediate in the synthesis of several sandalwood fragrances (Maraval et al., 2002; Skrobot et al., 2003) have reported on excellent studies about this substrate using these systems.

Fig. 8. Schematic representation of limonene oxyfunctionalization and possible derivatives: limoneneoxide, carveol and carvone

Skrobot et al. (Skrobot et al., 2003) have described the use of manganeseporphyrins (manganese(III) tetra(4-*N*-benzylpyridyl)porphyrin, in particular) as catalysts for the epoxidation of pinene and for the hydroxylation of carvacrol, Figure 6, using hydrogen peroxide as oxidant. The catalysts were used in either homogeneous solution or supported on Y zeolite. The results reported by the authors were very interesting, since the heterogeneous system gave similar results to those achieved with the homogeneous system. This was considered promising because it is normally expected that heterogeneous catalysts will lead to reduced conversion rates, due to the difficult access of the substrate to the active site and diffusion of the products back into solution. However, despite the use of a clean oxidant, re-use of the heterogeneous catalyst prepared by Skrobot et al. (Skrobot et al., 2003) revealed loss of catalytic activity, attributed to leaching of the manganeseporphyrin from the zeolite.

Even though literature works have described several tests using metalloporphyrin models, we have verified that only a few works have tested the substrate directly extracted from plants. Recently Schaab et al. (Schaab et al., 2010) employed the system ironporphyrin/iodosylbenzene in the oxidation of the substrate pipartine, a potential anticancer plant (isolated from *Piper tuberculatum*). They showed that ironporphyrin is a good catalyst for prediction of drug metabolism by P450. Nevertheless, most studies were accomplished using standardized, commercially available compounds. Moreover, the oxidant of choice in the majority of the studies is iodosylbenzene, which is very good for predicting drug metabolism, but is no longer indicated for studies on bio or chemical transformation of substances for medicinal uses. Also, many works have employed homogeneous catalysts and there is no mention of catalyst reuse, probably because of the relative difficulty in isolating it from the reaction medium.

Still, among the works reported above involving the chemical transformation of plants, it can be noted that most papers focus on studies of terpenoids and their derivatives. Thus, increasing the research on the oxidation of active ingredients from other medicinal plants and establishing larger association between chemistry and pharmacology are still necessary, in view of the possibility of discovering new pharmacologically active chemicals. Lignans are among the chemicals produced by plants that deserve special interest and therefore must be chemically and pharmacologically exploited.

4. Oxidation of lignans by ironporphyrins

Lignoid term is a generic name, which features a group of secondary metabolites whose skeleton is formed exclusively by the group phenylpropanoid (C3-C6) n , where n is restricted to a few units (Ward, 1999). Because of the wide diversity of occurrence, the broad spectrum of biological activities, and the important role they play in plant development, the lignoids have been the target of several studies (MacRae & Towers, 1984; Saleem et al., 2005). Among them, there are lignans and neolignans. Lignans are dimers derived from condensation by oxidative coupling of cinnamyl alcohols with each other or with cinnamic acids, whose carbon γ (C3) of side chain is oxidized (Ward, 1999; Gottlieb & Yoshida, 1989). Thus, lignans are biosynthesized by dimerization, via oxidative coupling of phenylpropanoids units (C6C3), forming a variety of structurally distinct subclasses. An example of these substances is cubebin (Figure 9a), a dibenzylbutyrolactone lignan obtained from the seeds of *Piper cubeba* (Piperaceae), which has anti-inflammatory (Souza et al., 2004; Silva et al., 2005); and trypanocidal (Bastos et al., 2001) activities.

Fig. 9. Structure of cubebin (a) and veraguensin (b).

Neolignans are dimers derived from condensation by oxidative coupling of allyl and /or propenyl phenols and, unlike lignans, are free of oxidation in the γ carbon atom. An example of this class is veraguensin (Figure 9b), a tetrahydrofuran neolignan found in *Nectandra megapotamica* (Lauraceae), which has anti-inflammatory (Da Silva Filho et al., 2004) trypanocidal (Lopes, et al. 1998; Da Silva Filho et al., 2004), properties.

In general, the biological and commercial importance of these compounds can be represented by derivatives of podophyllotoxin (Figure 10), a lignan obtained from *Podophyllum peltatum* (Berberidaceae) and used in the treatment of cancer (Bastos et al., 1996).

Fig. 10. Chemical structures of podophyllotoxin (a), etoposide (b), etopophos (c) and teniposide (d).

Actually, lignans have interesting biological properties, and useful drugs have been developed from the well-known lignans podophyllotoxin and steganacin (of the phenyltetraline and dibenzocyclooctane classes, respectively) for the treatment of cancer as well as other ailments. Crude plant materials containing lignans have long been used in folk medicine (Rehnberg & Magnusson, 1990).

Another major focus of the search for active natural products has been the antiparasitic activities of compounds, especially the schistosomicidal, trypanocidal (De Souza et al., 2005), and leishmanicidal (Barata et al., 2000) activities of these substances. Such activities are respectively represented by methylcubebin (Figure 11a), veraguensin (Figure 9b), and surinamensin (Figure 11b), showing that lignans and neolignans prototypes are promising for the development of new antiparasitic drugs.

Fig. 11. Structure of methylcubebin (a) and surinamensin (b).

On account of the biological activities of lignans, including their anticancer, antitumoral, trypanocidal, antimicrobial, and anti-inflammatory activities, some alternatives that will promote and improve their production are necessary.

(-)-Hinokinin, Figure 12, a dibenzylbutyrolactone lignan, possesses antileishmanial, anti-inflammatory, antigenotoxic (Souza et al., 2004; Da Silva et al., 2005; Medola et al., 2007), and significant *in vitro* and *in vivo* trypanocidal activities against *Trypanosoma cruzi*, the etiologic agent of Chagas' disease (Saraiva et al., 2007). Considering its promising biological activities, as well as its potential use as trypanocidal drug, large quantities of (-)-hinokinin are needed. (-)-Hinokinin and (-)-cubebin co-occur in *P. cubeba*, where they are among the major components of the biomass (Souza et al., 2004; Silva et al., 2007). In a traditional process, the oxidation of (-)-cubebin, catalyzed by pyridinium chlorochromate, PCC, (De Souza et al., 2005) can produce additional quantities of (-)-hinokinin. However, PCC is toxic and contains chromium (VI), a potential carcinogen. Besides its direct toxicity, the use of heavy metals (chromium) is a potential environmental problem to both water and soil qualities, and consequently to plant, animal, and human life (Barros et al., 2007).

Fig. 12. Chemical structure of (-)-Hinokinin

As part of our work on oxidative catalytic systems involving ironporphyrins (Papacdero et al., 2006), as well as of our studies on the synthesis and biological activities of lignans (Bastos, et al., 1996; Da Silva Filho et al., 2004; Souza et al., 2005) our group has developed a synthetic method for production of (-)-hinokinin consisting of the oxidation of (-)-cubebin catalyzed by biomimetic heterogeneous metalloporphyrin catalytic systems. Cubebin was isolated by us directly from *Piper cubeba*. (Powdered seeds of *Piper cubeba* L., bought from the market, were exhaustively extracted by maceration with 96% ethanol. The concentrated crude extract was partitioned between the hexane and methanol/water (9:1) phases and purified by liquid chromatography and crystallization).

The genus *Piper* has over 700 species distributed in both hemispheres. *Piper cubeba*, belonging to the Piperaceae family, is one of the folkloric plants used as a spice in many countries, including Indonesia, India, Europe in the middle ages, and Morocco. It has also been used for the treatment of dysentery, syphilis, abdominal, pain, diarrhea, enteritis, and asthma (Usia et al., 2005). *P. cubeba* has been investigated by our research group, too, aiming to evaluate the biological activities of extracts, isolated compounds, and dibenzylbutyrolactone semi-synthetic derivatives.

Similarly to what was reported previously by our group in the case of the epoxidation of alkenes (De Lima et al., 2001), the immobilization of ironporphyrin on alumina prepared by the non-hydrolytic sol-gel route (NHG) is a very interesting and efficient method for the construction of selective catalysts for cubebin oxidation. The ironporphyrin was efficiently supported on the matrix and it did not leach from the support in the employed reaction conditions.

The oxidation of (-)-cubebin (a), catalyzed by the heterogeneous FeTFPP-NHG system, was performed with two oxidants, namely iodosylbenzene or H_2O_2 , at atmospheric pressure and room temperature (Figure 13).

Fig. 13. Schematic representation of cubebin oxidation to (-)-hinokinin catalyzed by ironporphyrin.

The oxidation of (-)-cubebin was efficiently catalyzed in the case of both oxidants, leading to the sole production of (-)-hinokinin (b). Higher yields of this product and 100% selectivity were obtained when PhIO was used as the oxygen donor, compared with H_2O_2 (70%) (Figure 13). It is noteworthy that the catalytic activity of the FeTFPP-

NHG/acetonitrile/PhIO system was similar to the oxidizing activity of PCC (98 % hinokinin yield). Considering that the formation of (-)-hinokinin catalyzed by ironporphyrins was performed under mild and environmentally-friendly conditions, the results obtained here are better than those achieved using PCC. These results are quite interesting and, to our knowledge, there are no similar works reported in the literature.

The great advantage of the heterogeneous catalyst is its reuse, and the high efficiency and stability of a catalytic system can be confirmed via catalyst reuse. To this end, the solid catalysts were separated from the reaction mixture after each experiment by simple filtration and dried before being used in a subsequent run. In the case of our system, the catalyst was reused in five consecutive runs, without loss in terms of selectivity. So it can be claimed that the non-hydrolytic sol-gel method allowed for construction of an economically viable catalyst that can be successfully reused. SEM techniques revealed that catalyst structure was preserved after the five reuse experiments, a clear indication of the stability and robustness of the catalytic system prepared by the non-hydrolytic sol gel process.

The results obtained here give strong evidence that the active catalytic species responsible for the oxidation of cubebin is the metal-oxo complex (high-valent iron(IV)-oxo intermediate, $\text{Fe}^{\text{IV}}(\text{O})\text{P}^+$), so it can be said that an efficient catalyst bioinspired on P450s was built.

Licarin-A, a neolignan obtained from the oxidative coupling of isoeugenol, displays significant antiparasitic activity against the adult forms of *Schistosoma mansoni*.

Taking into account the antiparasitic potential and the possible production of derivatives from licarin-A, such as (-)-hinokinin, a dibenzylbutyrolactone lignan, there is great interest in the search for new approaches that will enable the oxidation of these lignans to be carried out, since the oxidized products are probably biologically active.

Our group has also examined the oxidation of licarina-A, Figure 14, by a system bioinspired on the P450s, more specifically the second-generation ironporphyrin FeTFPP^+ immobilized on silica and the oxidants iodosylbenzene, or hydrogen peroxide.

The licarin-A was obtained by oxidative coupling, using (*E*)-isoeugenol (10.5 mmol), dissolved in methanol (50 mL), citrate-phosphate buffer (450 mL, 20 mM, pH 3) and horseradish peroxidase (HRP, 20 mL, 2500U) (Nascimento et al., 2001). The mixture was stirred while H_2O_2 30% (0.57 mL) was added dropwise over 10 min. Licarin-A (a white solid) was purified by column chromatography (silica gel 60 0.040-0.063 mm) with hexane-ethyl acetate (8:2 v/v).

Initially, FeTFPP^+ was covalently bound to the silica support by means of the sol-gel method, which consisted in reacting the metalloporphyrin with 3-aminopropyltriethoxysilane (APTES), as previously described by Ciuffi et al (Ciuffi, et al., 2000). The oxidation of licarin-A catalyzed by silica- FeTFPP occurred in mild conditions, and the products were isolated by high performance liquid chromatography.

The ironporphyrin was efficiently supported on the matrix and did not leach from the support under the employed reaction conditions.

As in the case of cubebin, the oxidation of licarin A catalyzed by the heterogeneous FeTFPP -silica was performed by using one of the following oxidants: PhIO or H_2O_2 , at atmospheric pressure and room temperature (Figure 5). Although the studies using the oxidant H_2O_2 are only preliminary, the oxidation was efficiently catalyzed in the case of both oxidants, but high selectivity was obtained only with iodosylbenzene (100 %), compared with 30% selectivity achieved with H_2O_2 , since in the latter case other products (alcohols) were also detected.

The loss of selectivity in the reactions carried out with hydrogen peroxide as oxidant could be a strong indication of the involvement of free radical mechanisms, a consequence of the

homolytic cleavage of the peroxide. Therefore, as already done in an earlier work by our group, tests in the presence of radical trap were accomplished, since these traps would eliminate the occurrence of any free radical mechanisms in this type of reaction.

As in the case of cubebin oxidation, the results obtained for licarin A oxidation strongly suggest that the active catalytic species responsible for the oxidation is the metal-oxo complex (high-valent iron(IV)-oxo intermediate, $\text{Fe}^{\text{IV}}(\text{O})\text{P}^+$).

Because our studied on licarin A oxidation are in the initial stage, recyclability of the catalyst has not yet been investigated.

It is noteworthy that metalloporphyrin catalysts are able to oxidize the products directly extracted from plants or previously purified.

It is also worth mentioning that the experiments were repeated at least three times in the case of both substrates, and total reproducibility was achieved.

Fig. 14. Schematic representation of cubebin and licarin oxidation by iroporphyrin heterogeneous catalysts and possible products.

5. Conclusions

Natural products, especially those found in medicinal plants, have great importance for the development of new drugs for use in human and animal medicines.

On account of the biological activities of natural products, including anticancer, antitumoral, trypanocidal, antimicrobial, and anti-inflammatory activities, some alternatives that promote and improve their production are necessary and many attempts have been made in order to oxidize natural plant compounds and produce target components that are not easily obtained by conventional routes.

The use of metalloporphyrin catalysts, biomimics of P450s, is very promising. However, a lot of work remains to be done regarding the use of the clean oxidant hydrogen peroxide and catalyst reuse. One approach to overcoming the latter difficulty is immobilization of the synthetic metalloporphyrins on solid supports.

6. References

- Balunas, M. J. & Kinghorn, A. D. (2005). Drug discovery from medicinal plants. *Life Sciences*, 78, 5, (2005) 431-441, 0024-3205.
- Barata, L.E.S.; Santos, L.S.; Ferri, P.H.; Phillipson, J.D.; Paine, A. & Croft, S.L. (2000). Anti-leishmanial activity of neolignans from *Virola* species and synthetic analogues. *Phytochemistry* 55,6,(2000) 589-595, 0031-9422 .
- Barros, A.J.M., Prasad, S., Leite, V.D. & Souza, A.G. (2007). Biosorption of heavy metals in upflow sludge columns. *Bioresource Technology*, 98, 7, (2007)1418-1425, 0960-8524.
- Bastos, J. K.; Burandt, C. L.; Nanayakkara, N.P.D.; Bryant, L. & McChesney, J.D. (1996). Quantitation of aryltetralin lignans in plant parts and among different populations of *Podophyllum peltatum* by reversed-phase high-performance liquid chromatography. *Journal of Natural Products*, 59, 4, (1996) 406-408, 0163-3864.
- Bastos, J.K., Gottlieb, O.R., Sarti, S.J. & Filho, D.S. (1996). Isolation of lignans and sesquiterpenoids from leaves of *Zanthoxylum naranjillo*, *Natural Product Letters* 9, 1, (1996) 65-70, 1478-6419.
- Bastos, J.K.; Carvalho, J.C.T.; De Souza, G.H.B.; Pedrazzi, A.H.P. & Sarti, S.J (2001). Anti-inflammatory activity of cubebin, a lignan from the leaves of *Zanthoxylum naranjillo* Griseb. *Journal of Ethnopharmacology*, 75, 2-3, 279-282, 0378-8741.
- Bernadou J.; Bonnafous M.; Labat, G.; Loiseau, P. & Meunier, B. (1991). Model systems for metabolism studies. Biomimetic oxidation of acetaminophen and ellipticine derivatives with water-soluble metalloporphyrins associated to potassium monopersulfate. *Drug Metabolism and Disposition*. 19,2, (1991) 360-365, 0090-9556.
- Bernadou, J. & Meunier, J. (2004). Biomimetic Chemical Catalysts in the Oxidative Activation of Drugs *Advanced.Synthesis & Catalysis*, 346, (2004) 171-184. 1615-4150.
- Bizaia, N.; de Faria, E. H.; Ricci, G. P.; Calefi, P. S.; Nassar, E. J.; Castro K. A. D. F.; Nakagaki, S.; Ciuffi, K. J.; Trujillano, R.; Vicente, M. A.; Gil. A. & Korili, S. A. (2009). Porphyrin-Kaolinite as Efficient Catalyst for Oxidation Reactions, *ACS Applied Materials & Interfaces*, 1, 11, (2009) 2667-2678. 1944-8244.
- Cavaleiro, J. A. S.; Nascimento, G. M. S. F. C.; Neves, M. G. P. M. S.; Pinto, M. T.; Silvestre, A. J. D. & Vicente, M. G. H. (1996). Oxidation of natural compounds catalyzed by Mn(III) porphyrin complexes. *Tetrahedron Letters*, 37, 11, (1996) 1893-1896, 0040-4020.
- Ciuffi, K.J., Sacco, H.C., Biazotto, J.C., Vidoto, E.A., Nascimento, O.R., Leite, C.A.P., Serra, O.A. & Iamamoto, Y. (2000) Synthesis of fluorinated metalloporphyrinosilica imprinted with templates through sol-gel process. *Journal of Non-Crystalline Solids*, 273, 1-3, (2000) 100-108, 0022-3093.
- Cordell, G. A. (2000). Biodiversity and drug discovery. Asymbiotic relationship. *Phytochemistry*, 55, (2000) 463-480, 0031-9422.
- Da Silva Filho, A.A., Albuquerque, S., Silva, M.L.A.E., Eberlin, M.N., Tomazela, D.M. & Bastos, J.K. (2004). Tetrahydrofuran Lignans from *Nectandra megapotamica* with Trypanocidal Activity. *Journal of Natural Products*, 67, 1, 42-45, 0163-3864.
- Da Silva, R.; De Souza; G.H.B.; Da Silva, A.A.; De Souza, V.A.; Pereira, A.C.; Royo, V.D.A.; Silva, M.L.A.; P.M. Donate, P.M.; A.L.M. Araújo, A.L.M. ; J.C.T. Carvalho, J.C.T. & Bastos, J.K. (2005). Synthesis and biological activity evaluation of lignan lactones

- derived from (-)-cubebin. *Bioorganic and Medicinal Chemistry Letters*, 15, 4,(2005) 1033-1037, 0960-894X.
- de Faria, A. L.; Airoidi, C.; Doro, F. G.; Fonseca, M. G. & das Dores Assis, M. (2004). Anchored ironporphyrins—the role of talc-aminofunctionalized phyllosilicates in the catalysis of oxidation of alkanes and alkenes. *Applied Catalysis A: General*, 268, 1-2, (2004) 217-226, 0926-860X.
- de Lima, O. J. ; De Aguirre, D. P. ; De Oliveira, D. C. ; Da Silva, M. A. ; Mello C. ; Leite, C. A. P. ; Sacco, H. C. & Ciuffi, K. J. (2001). Porphyrins entrapped in an alumina matrix. *Journal of Materials. Chemistry*, 11, (2001) 2476–2481, 0959-9428.
- de Oliveira, D. C.; Sacco, H. C.; Nascimento, O. R.; Iamamoto, Y. & Ciuffi, K. J. (2001). Amino ironporphyrinosilica hybrid materials. *Journal of Non-Crystalline Solids*, 284, 1-3 (2001), 27-33, 0022-3093.
- De Souza, V.A.; Da Silva, R.; Pereira, A.C.; Royo, V.D.A.; Saraiva, J.; Montanheiro, M.; De Souza, G.H.B.; Da Silva Filho, A.A.; Grando, M.D.; Donate, P.M.; Bastos, J.K.; Albuquerque, S.; Silva & M.L.A. (2005). Trypanocidal activity of (-)-cubebin derivatives against free amastigote forms of *Trypanosoma cruzi*. *Bioorganic and Medicinal Chemistry Letters*, 15, 2, (2005) 303-307, 0960-894X.
- De Souza, V.A.; Da Silva, R.; Pereira, A.C.; Royo, V.D.A.; Saraiva, J.; Montanheiro, M., De Souza, G.H.B., da Silva Filho, A.A.; Donate, P.M. & Bastos, J.K.; Albuquerque S., Silva, M.L.A. (2005) Synthesis and biological activity evaluation of lignan lactones derived from (-)-cubebin. *Bioorganic and Medicinal Chemistry Letters*, 15, 2, (2005) 303-307, 0968-0896.
- Elisabetsky, E.; Amador, T. A.; Albuquerque, R. R.; Nunes, D. S. & Carvalho, A. C. T. (1995). Analgesic activity of *Psychotri colorata* (Wild ex R and S) Muell Arg. *Alkaloids. J. Ethnopharmacology*, 148, (1995)77–83, 0378-8741.
- Gibson, G. G. & Skett, P. (1994). *Introduction to Drug Metabolism*, Chapman and Hall, 0412399105, London.
- Goti, A. & Cardona, F. (2008). *Chemistry and Materials Science, Green Chemical Reactions, NATO Science for Peace and Security Series*, 9781-1-4020-8458-4, Leece.
- Gottlieb, O.R. & Yoshida, M. (1989). *Natural products of woods plants. Chemicals extraneous to the lignocellulosic cell wall*. Springer -Verlag, 0302-9743, Berlin.
- Groves, J. T. (2006). High-valent iron in chemical and biological oxidations. *Journal of . Inorganic Biochemistry*, 100, 2006,434 – 447, 0162-0134.
- Groves, J. T.; Nemo, T. E. & Myers, R. S. (1979). Hydroxylation and epoxidation catalyzed by iron-porphine complexes. Oxygen transfer from iodosylbenzene. *Journal of. American Chemical Society*, 101, 4 (1979), 1032-1033 , 0002-7863.
- Lewis, D. F. V. (2001). *Guide to Cytochrome P450 Structure and Function*, Taylor & Francis, 0 748 40897 5, London.
- Lohmann, W. & Karst, U. (2008). Biomimetic modeling of oxidative drug metabolism - strategies, advantages and limitations. *Analytical and. Bioanalytical Chemistry*, 391, (2008), 79-96, 1618-2642
- MacLeod, T. C. O.; Guedes, D. F.C.; Lelo, M. R.; Rocha, R. A.; Caetano, B. L.; Ciuffi, K. J. & Assis, M. D. (2006). Catalytic activity of Jacobsen catalyst encapsulated in an alumina matrix by the sol-gel process. *Journal of Molecular Catalysis A: Chemical*, 259, 1-2, (2006), 319-327., 1381-1169.
- Machado, G. S.; de Freitas Castro, K. A. D.; de Lima, O. J.; Nassar, E. J.; Ciuffi, K. J. & Nakagaki, S. (2009). Aluminosilicate obtained by sol-gel process as support for an anionic iron porphyrin: Development of a selective and reusable catalyst for

- oxidation reactions. *Colloids and Surfaces A: Physicochemical and Engineering Aspects*, 349, 1-3, (2009) 162-169, 0927-7757.
- Macrae, W.D. & TOWERS, G.H.N. (1984). Biological activities of lignans. *Phytochemistry*, 23, 6,(1984) 1207-1220, 0031-9422.
- Mansuy, D. (2007). A brief history of the contribution of metalloporphyrin models to cytochrome P450 chemistry and oxidation catalysis. *Comptes Rendus Chimie*, 10, (2007) 392-413. 1631-0748.
- Maraval, V.; Ancel, J. E. & Meunier, B. (2002). Manganese(III) Porphyrin Catalysts for the Oxidation of Terpene Derivatives: A Comparative Study. *Journal of Catalysis*, 206,(2002) 349-357, (2002), 0021-9517.
- McMurry, T.J & Groves, J.T. (1986). *Cytochrome P-450, Structure, Mechanism and Biochemistry*, Plenum Press, 0-306-48324-6, New York. pp. 1-28.
- Medola, J.F.; Cintra, V.P.; Pesqueira e Silva, E.P.; de Andrade Royo, V.; da Silva, R.; Saraiva, J.; Albuquerque, S.; Bastos, J.K.; Silva, M.L.A. & Tavares, D.C. (2007). (-)-Hinokinin causes antigenotoxicity but not genotoxicity in peripheral blood of Wistar rats. *Food and Chemical Toxicology*, 45, 4, (2007) 638-642, 0278-6915.
- Meyer, Urs A. (1996). Overview of enzymes of drug metabolism, *Journal of Pharmacokinetics and Pharmacodynamics*, 24, 5, (1996) 449-459, 1567-567X.
- Milllos, M. (2001). A comparative study of biomimetic oxidation of oregano essential oil by H₂O₂ or KHSO₅ catalyzed by Fe (III) meso-tetraphenylporphyrin or Fe (III) phthalocyanine. *Applied Catalysis A: General*, 216, (2001) 157-161, 0926-860X.
- Munro, A. W.; Girvan, H. M. & McLean, K. J. (2007). Variations on a (t)heme—novel mechanisms, redox partners and catalytic functions in the cytochrome P450 superfamily. *Natural Product Reports*, 24, (2007) 585-609, 0265-0568.
- Nam, W. (2007). High-Valent Iron (IV)-Oxo Complexes of Heme and Non-Heme Ligands in Oxygenation Reactions, *Accounts of Chemical Research*, 40, (2007) 522-531, 0001-4842.
- Nascimento, I.R.; Lopes, L. M.X. , Davin, L. B. & Lewis, N.G. (2001). Stereoselective synthesis of 8,9-licarinediols. *Tetrahedron*, 2001, 56, (2001) 9181-9193, 0040-4020
- Papacidero, A. T.; Rocha, L. A.; Caetano, B. L.; Molina, E.; Sacco, H. C.; Nassar, E. J.; Martinelli, Y.; Mello, C.; Nakagaki, S. & Ciuffi, K. J. (2006). Preparation and characterization of spherical silica-porphyrin catalysts obtained by the sol-gel methodology. *Colloids and Surfaces A: Physicochemical and Engineering Aspects*, 275, 1-3, (2006), 27-35, 0927-7757.
- Rates, S. M. K. (2001). Plants as source of drugs. *Toxicon*, 39, 5,(2001) 603-61, 0041-0101.
- Ravindran, J.; Nair, H. B.; Prasad, B. S. S.; Tekmal, R. R. & Aggarwal, B. B. (2010). Bisdemethylcurcumin and structurally related hispolon analogues of curcumin exhibit enhanced prooxidant, anti-proliferative and anti-inflammatory activities *in vitro*. *Biochemical Pharmacology*. 79, 11, (2010), 1658-1666, 0006-2952.
- Rehnberg, N. & Magnusson, G.(1990). Total synthesis of the lignans (-)- and (+)-burseran, (-)-cubebin, and (-)-hinokinin by diastereoselective conjugate addition of benzyl anions to 2-(R) and (s)-benzyloxy-2,5-dihydro-4-(3,4-methylenedioxybenzoyl)furan. *Tetrahedron Letters*, 29, 29, (1988) 3599-3602, 0040-4020.
- Rosália, R. L.; Martins, M. G. P. M. S.; Neves, A.; Silvestre, J. D.; Silva; A. M. S. & Cavaleiro, J. A. S. (1999). Oxidation of aromatic monoterpenes with hydrogen peroxide catalysed by Mn(III) porphyrin complexes. *Journal of Molecular Catalysis A: Chemical*,137, 1-3, (1999) 41-47. 1381-1169.
- Sacco, H. C.; Ciuffi, K. J.; Biazotto, J. C.; Mello, C.; de Oliveira, D. C.; Vidoto, E. A.; Nascimento, O. R.; Serra, O. A. & Iamamoto, Y. (2001). Ironporphyrins trapped sol-

- gel glasses: a chemometric approach. *Journal of Non-Crystalline Solids*, 284, (2001) 174-182, 0022-3093.
- Saleem, M.; Kim, H.J.; Ali, M. S. & Lee, Y. S. (2005). An update on bioactive plant lignans. *Natural Product Reports*, 22, 6, (2005) 696-716, 0265-0568.
- Saraiva, J.; Vega, C.; Rolon, M.; Da Silva, R.; E Silva, M.L.A.; Donate, P.M.; Bastos, J.K.; Gomez-Barrio A. & De Albuquerque, S. (2007). In vitro and in vivo activity of lignan lactones derivatives against *Trypanosoma cruzi*. *Parasitology Research*, 100, 4, (2007) 791-795, 0932-0113.
- Schaab, E. H.; Crotti, A. E. M.; Iamamoto, Y.; Kato, M. J.; Lotufo, L. V. C. & Lopes, N. P. (2010). Biomimetic oxidation of Piperine and Piplartine catalyzed by Iron(III) and Manganese(III) Porphyrins. *Biological & Pharmaceutical Bulletin*, 33, 5, (2010) 912-916, 0918-6158.
- Silva, M.L.A.; Coimbra, H.S.; Pereira, A.C.; Almeida, V.A.; Lima, T.C.; Costa, E.S.; Vinhólis, A.H.C.; Royo, V. A.; Silva, R.; da Silva Filho, A.A.; Cunha, W.R.; Furtado, N.A.J.C.; Martins, C.H.G.; Carvalho, T.C. & Bastos, J.K. (2007). Evaluation of Piper cubeba extract, (-)-cubebin and its semi-synthetic derivatives against oral pathogens. *Phytotherapy Research*, 21, 5, 2007, 420-422, 0951-418X.
- Silva, R.; Souza, G.H.B.; Da Silva, A.A.; De Souza, V.A.; Pereira, A.C.; Royo, V.de A.; E Silva, M.L.A.; Donate, P.M.; De Matos Araújo, A.L.S.; Carvalho, J.C.T. & Bastos, J.K. (2005). Synthesis and biological activity evaluation of lignan lactones derived from (-)-cubebin. *Bioorganic & Medicinal Chemistry Letters*, 15, (2005) 1033-1037, 0960-894X.
- Simões, M. M. Q.; De Paula, R.; Neves, M. G. P. M. S. & Cavaleiro, J. A. S. (2009). Metalloporphyrins in the biomimetic oxidative valorization of natural and other organic substrates. *Journal of Porphyrins and Phthalocyanines*, 13, (2009) 589-596, 1088-4246.
- Siroká, Z. & Drastischová, J. (2004). Biochemical Markers of Aquatic Environment Contamination – Cytochrome P450 in Fish. A Review. *Acta Veterinaria Brno*, 73, (2004) 123-132, 0001-7213
- Skrobot, F. C.; Valente, A. A.; Neves, G.; Rosa, I.; Rocha, J. & Cavaleiro, J. A. S. (2003). Monoterpenes oxidation in the presence of Y zeolite-entrapped manganese(III) tetra(4-N-benzylpyridyl) porphyrin. *Journal of Molecular Catalysis A: Chemical*, 201, 1-2, (2003) 211-222, 1381-1169.
- Souza Brito, A. R. M. (1996). How to study the pharmacology of medicinal plants in underdeveloped countries. *The Journal of Ethnopharmacology*, 54, 2-3, (1996) 131-138, 0378-8741.
- Souza, G.H.B.; Da Silva Filho, A.A.; De Souza, V.A.; Pereira, A.C.; Royo, V.de A.; E Silva, M.L.A.; Da Silva, R.; Donate, P.M.; Carvalho, J.C.T. & Bastos, J.K. (2004). Analgesic and anti-inflammatory activities evaluation of (-)-O-acetyl, O-methyl, (-)-O-dimethylethylamine cubebin and their preparation from (-)-cubebin. *II Farmaco*, 59, (2004) 55-61, 0014-827X.
- Tanaka, E. (2001). Polymorphism of Drug Metabolizing Enzymes in Humans. *Sepsis*, 4, (2001) 247-254. 1385-0229.
- Toshiro, K.; Yoshitaka, A. & Yasuhiko, K. (1999). A novel allylic hydroxylation of sterically hindered olefins by Fe-porphyrin-catalyzed mCPBA oxidation. *Tetrahedron Letters*, 40 (1999) 6971-6974. 0040-4020.
- Usia T.; Watabe, T.; Kadota, S. & Tezuka, Y. (2005). Potent CYP3A4 inhibitory constituents of Piper cubeba. *Journal of Natural Products*, 68 1, (2005) 64-68, 0163-3864.
- Ward, R. S. (1999). Lignans, neolignans and related compounds. *Natural Product Reports*, 16, 1, (1999) 75-96, 0265-0568.

Biomimetic Based Applications

Edited by Prof. Marko Cavrak

ISBN 978-953-307-195-4

Hard cover, 572 pages

Publisher InTech

Published online 26, April, 2011

Published in print edition April, 2011

The interaction between cells, tissues and biomaterial surfaces are the highlights of the book "Biomimetic Based Applications". In this regard the effect of nanostructures and nanotopographies and their effect on the development of a new generation of biomaterials including advanced multifunctional scaffolds for tissue engineering are discussed. The 2 volumes contain articles that cover a wide spectrum of subject matter such as different aspects of the development of scaffolds and coatings with enhanced performance and bioactivity, including investigations of material surface-cell interactions.

How to reference

In order to correctly reference this scholarly work, feel free to copy and paste the following:

Emerson Henrique de Faria, Gustavo Pimenta Ricci, Frederico Matias Lemos, Marcio Luis Andrade e Silva, Ademair Alves da Silva Filho, Paulo Sérgio Calefi, Eduardo José Nassar and Katia Jorge Ciuffi (2011). Green Oxidation Reactions of Drugs Catalyzed by Bio-inspired Complexes as an Efficient Methodology to Obtain New Active Molecules, Biomimetic Based Applications, Prof. Marko Cavrak (Ed.), ISBN: 978-953-307-195-4, InTech, Available from: <http://www.intechopen.com/books/biomimetic-based-applications/green-oxidation-reactions-of-drugs-catalyzed-by-bio-inspired-complexes-as-an-efficient-methodology-t>

INTECH
open science | open minds

InTech Europe

University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
Fax: +385 (51) 686 166
www.intechopen.com

InTech China

Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821

© 2011 The Author(s). Licensee IntechOpen. This chapter is distributed under the terms of the [Creative Commons Attribution-NonCommercial-ShareAlike-3.0 License](https://creativecommons.org/licenses/by-nc-sa/3.0/), which permits use, distribution and reproduction for non-commercial purposes, provided the original is properly cited and derivative works building on this content are distributed under the same license.

IntechOpen

IntechOpen