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Lignans: Chemical and Biological Properties

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1. Introduction

The plant kingdom has formed the basis of folk medicine for thousands of years and nowadays continues to provide an important source to discover new biologically active compounds (Fabricant & Farnsworth, 2001; Gurib-Fakim, 2006; Newman, 2008). The research, development and use of natural products as therapeutic agents, especially those derived from higher plants, have been increasing in recent years (Gurib-Fakim, 2006). Several lead metabolites such as vincristine, vinblastine, taxol and morphine have been isolated from plants, and many of them have been modified to yield better analogues for activity, low toxicity or better solubility. However, despite the success of this drug discovery strategy, only a small percentage of plants have been phytochemically investigated and studied for their medicinal potential (Ambrosio et al., 2006; Hostettmann et al., 1997; Soejarto, 1996).

The first step in the search of new plant-based drugs or lead compounds is the isolation of the secondary metabolites. In the past, the natural products researchers were more concerned with establishing the structures and stereochemistry of such compounds but, in recent years, a great number of studies have concentrated efforts on their biological activities (Ambrosio et al., 2006). This multidisciplinary approach was reinforced by the substantial progress observed in the development of novel bioassay methods. As a consequence, a great number of compounds isolated from plants in the past have been “rediscovered” (Ambrosio et al., 2008; Ambrosio et al., 2006; Houghton, 2000; Porto et al., 2009a; Porto et al., 2009b; Tirapelli et al., 2008).

Several classes of secondary metabolites are synthesized by plants and, among those, lignans are recognized as a class of natural products with a wide spectrum of important biological activities. **Table 1** summarizes the main biological properties described in the literature for lignans.

The term “Lignan” was first introduced by Haworth (1948) to describe a group of dimeric phenylpropanoids where two C₆-C₃ are attached by its central carbon (C8), as shown in **Figure 1**. More recently, Gotlieb (1978) proposed that micromolecules with two phenylpropanoid units coupled in other manners, like C5-C5' for example should be named “neolignans” (Umezawa, 2003). According to Gordaliza et al (2004), lignans can be found in more than 60 families of vascular plants and have been isolated from different plant parts, exudates and resins.

Biological activity	Reference
Antiviral	(Charlton, 1998; Cos et al., 2008; McRae & Towers, 1984; Yousefzadi et al., 2010)
Anticancer	(McRae & Towers, 1984; Pan et al., 2009; Saleem et al., 2005; Yousefzadi et al., 2010)
Cancer prevention	(Huang et al., 2010; Webb & McCullough, 2005)
Anti-inflammatory	(Saleem et al., 2005)
antimicrobial	(Saleem et al., 2005)
antioxidant	(Fauré et al., 1990; Pan et al., 2009; Saleem et al., 2005)
immunosuppressive	(Saleem et al., 2005)
Hepatoprotective	(Negi et al., 2008)
Osteoporosis prevention	(Habauzit & Horcajada, 2008)

Table 1. Main biological activities of lignans

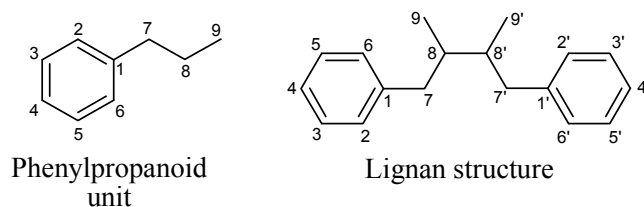


Fig. 1. Phenylpropanoid unit and lignan structure

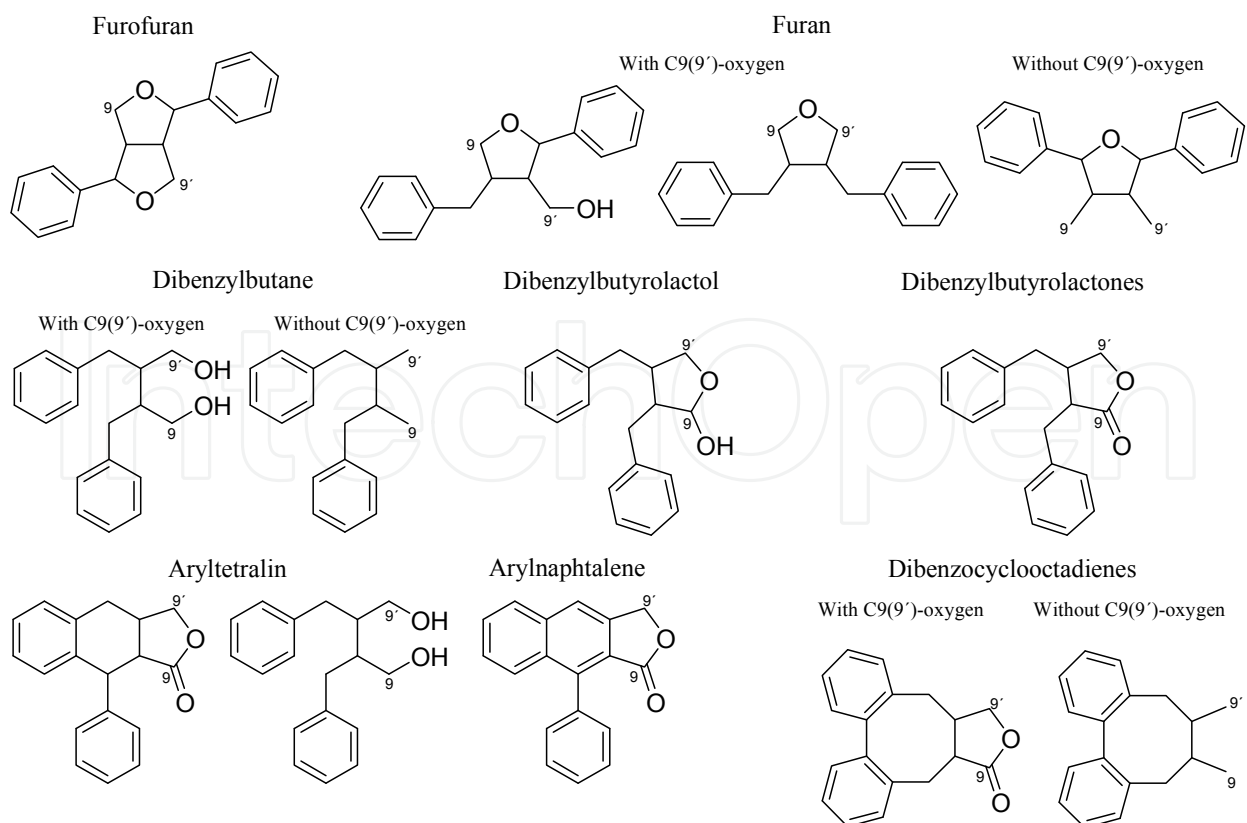


Fig. 2. Main subclasses of lignans. Adapted from Suzuki & Umezawa (2007).

Most of the known natural lignans are oxidized at C9 and C9' and, based upon the way in which oxygen is incorporated into the skeleton and on the cyclization patterns, a wide range of lignans of very different structural types can be formed. Due to this fact, lignans are classified in eight subgroups and (Chang et al., 2005; Suzuki & Umezawa, 2007), among these subgroups, the furan, dibenzylbutane and dibenzocyclooctadiene lignans can be further classified in "lignans with C9 (9')-oxygen" and "lignans without C9 (9')-oxygen". **Figure 2** displays the main classes of lignans, as well as their subgroups. It is noteworthy that, despite its structural variation, lignans also display a substantial variation on its enantiomeric composition (Umezawa et al., 1997). In this sense, these metabolites can be found as pure enantiomers and as enantiomeric compositions, including racemates (Macias et al., 2004).

2. Chemical aspects of lignans

As mentioned before, lignins and lignans are both originated from C₆-C₃ units, thus indicating that these metabolites are biosynthesized through the same pathway in the earlier steps. As seen in **Figure 3**, aromatic aminoacids *L*-phenylalanine and *L*-tyrosine are produced from shikimic acid pathway, and then converted in a series of cinnamic acid

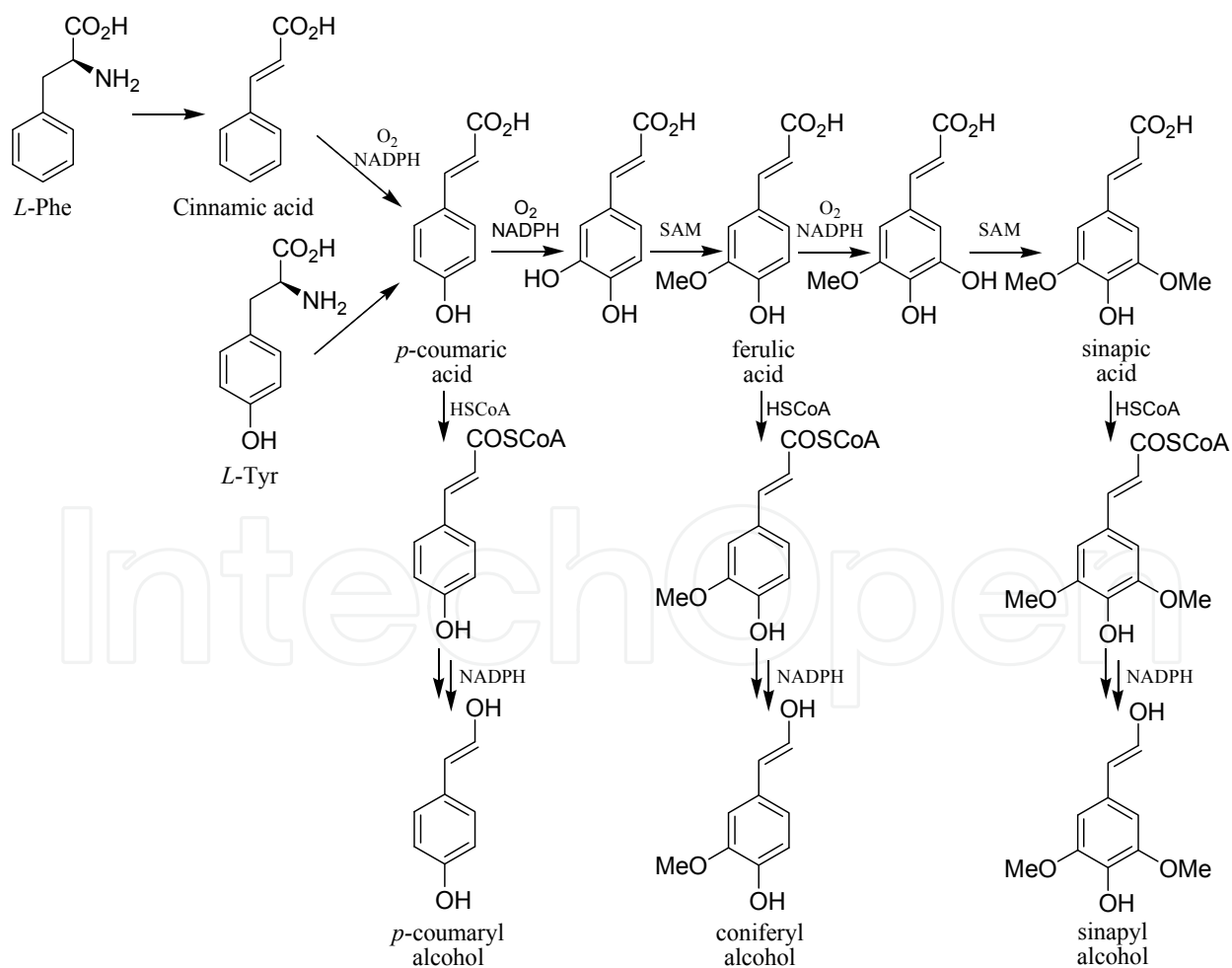


Fig. 3. Biosynthesis of hydroxycinnamyl alcohol monomers, the precursors of lignans according to Dewick (2002).

derivatives. The reduction of these acids via coenzyme A of related esters and aldehydes forms three alcohols (*p*-coumaryl alcohol, coniferyl alcohol and sinapyl alcohol) that are the main precursors of all lignins and lignans.

The peroxidase induces one-electron oxidation of the phenol group allowing the delocalization of the unpaired electron through resonance forms. In these hydroxycinnamyl alcohols, conjugation allows the unpaired electron to be delocalized also into the side chain. After this point, radical pairing of these resonance structures originates reactive dimeric systems susceptible to nucleophilic attack from hydroxyl groups, leading to a wide range of lignans, as shown in **Figure 2**.

Among these subgroups, the biosynthesis of C₉ (9′)-oxygen lignans is the most well known. This type of lignan is formed through the enantioselective dimerization of two coniferyl alcohol monomeric units (D resonance form of coniferyl alcohol radical, **Figure 4**) into pinosresinol via intermolecular 8,8′ oxidative coupling with the aid of dirigent protein (Dewick, 2002; Suzuki & Umezawa, 2007).

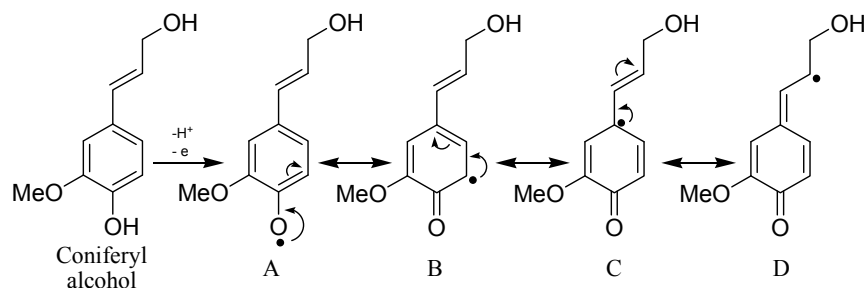


Fig. 4. Resonance forms of coniferyl alcohol radical

The following steps involve sequential stereoselective enzymatic reduction of pinosresinol by pinosresinol/lariciresinol reductase to generate lariciresinol and then secoisolariciresinol by secoisolariciresinol dehydrogenase. The main steps of this biosynthetic proposal are depicted in **Figure 5**. Secoisolariciresinol gives the presumably common precursor of all dibenzylbutyrolactol lignans and, through the formation of matairesinol and yatein, also forms the aryltetralin lignans. These subclasses of lignans includes some important bioactive compounds such as cubebin (**1**) and podophyllotoxin (Canel et al., 2000; de Souza et al., 2005; Gordaliza et al., 2004; Saraiva et al., 2007; Silva et al., 2007; Silva et al., 2009; Srivastava et al., 2005; You, 2005; Yousefzadi et al., 2010).

3. Podophyllotoxin: chemical and biological approaches

Podophyllotoxin (**Figure 6**), a naturally occurring aryltetralin lignin, is one of the most important compound due to its high toxicity and current use as a local antiviral agent (Yousefzadi et al., 2010). Moreover, this metabolite has been used to obtain structural analogues which are employed as anticancer drugs (Ayres & Loike, 1990; Yousefzadi et al., 2010) and several semi-synthetic podophyllotoxin-related derivatives showed to be topoisomerase II inhibitor, acting as an antimetabolic compound (You, 2005; Yousefzadi et al., 2010). **Figure 6** also shows the clinically valuable anticancer agents, etoposide, teniposide and etoposide phosphate, obtained from podophyllotoxin.

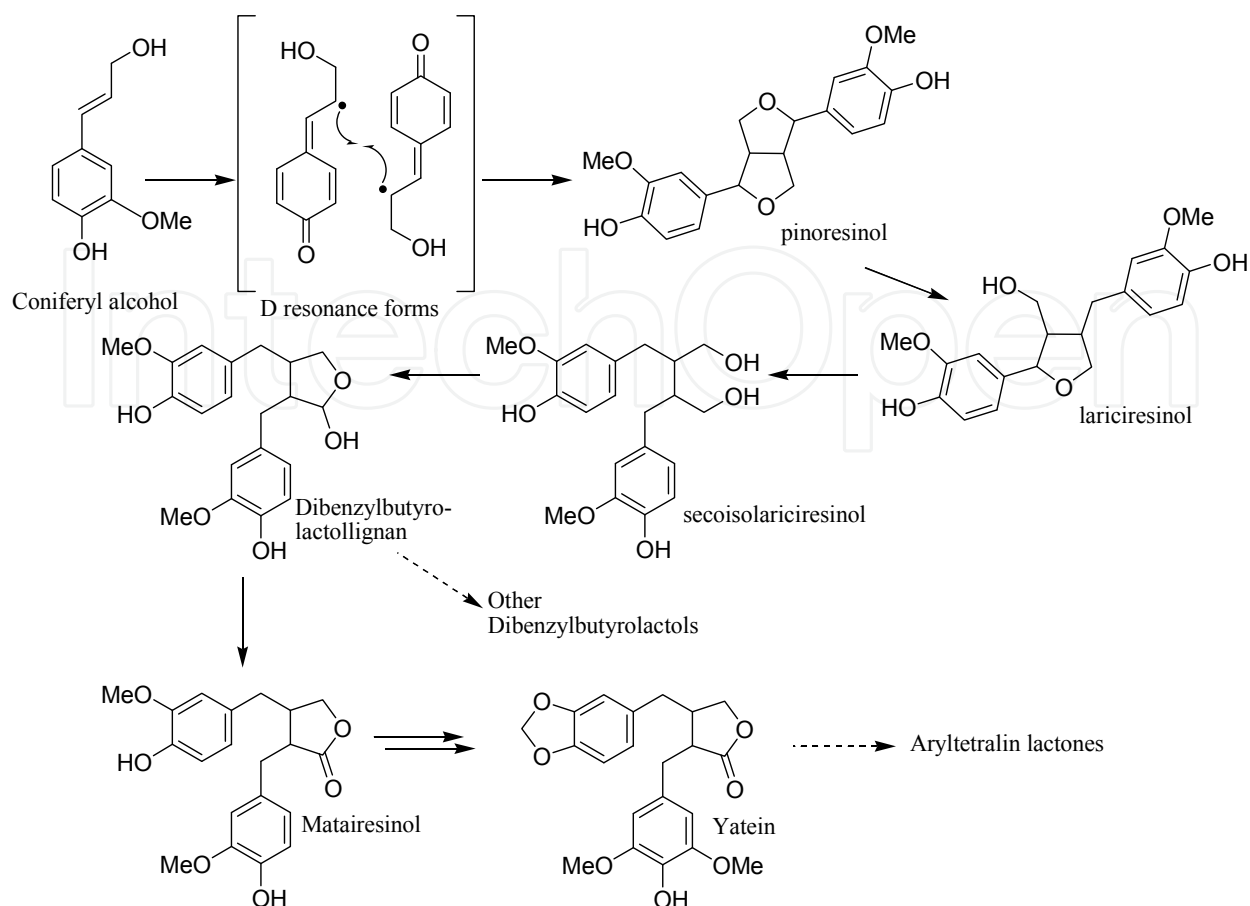


Fig. 5. Biosynthesis of dibenzylbutyrolactols and aryltetralin lactones (Canel et al., 2000).

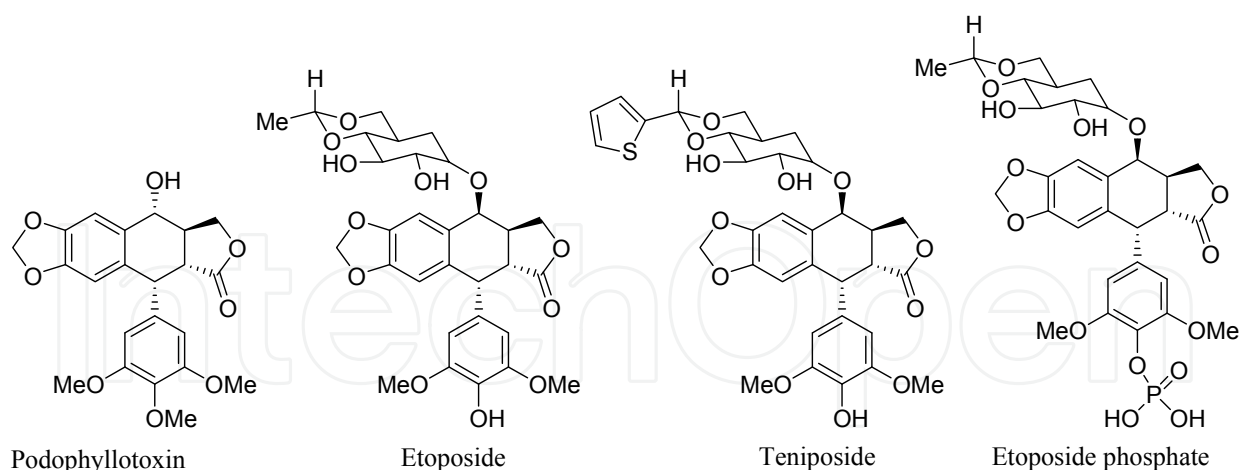


Fig. 6. Chemical structures of clinically available podophyllotoxin derivatives.

According to You (2005), podophyllotoxin still can be considered a hot prototype for discovery and development of novel anticancer agents, even in the 21st century. This leading compound has been isolated from the roots of *Podophyllum* species and more recently from other genus, such as *Linum* (Yousefzadi et al., 2010). Due to its importance in anticancer therapy, several biotechnological approaches including the use of cell cultures, biotransformation processes and metabolic engineering techniques to manipulate the

biosynthetic pathway (**Figure 7**), have been currently developed and are alternatives for the production of podophyllotoxin.

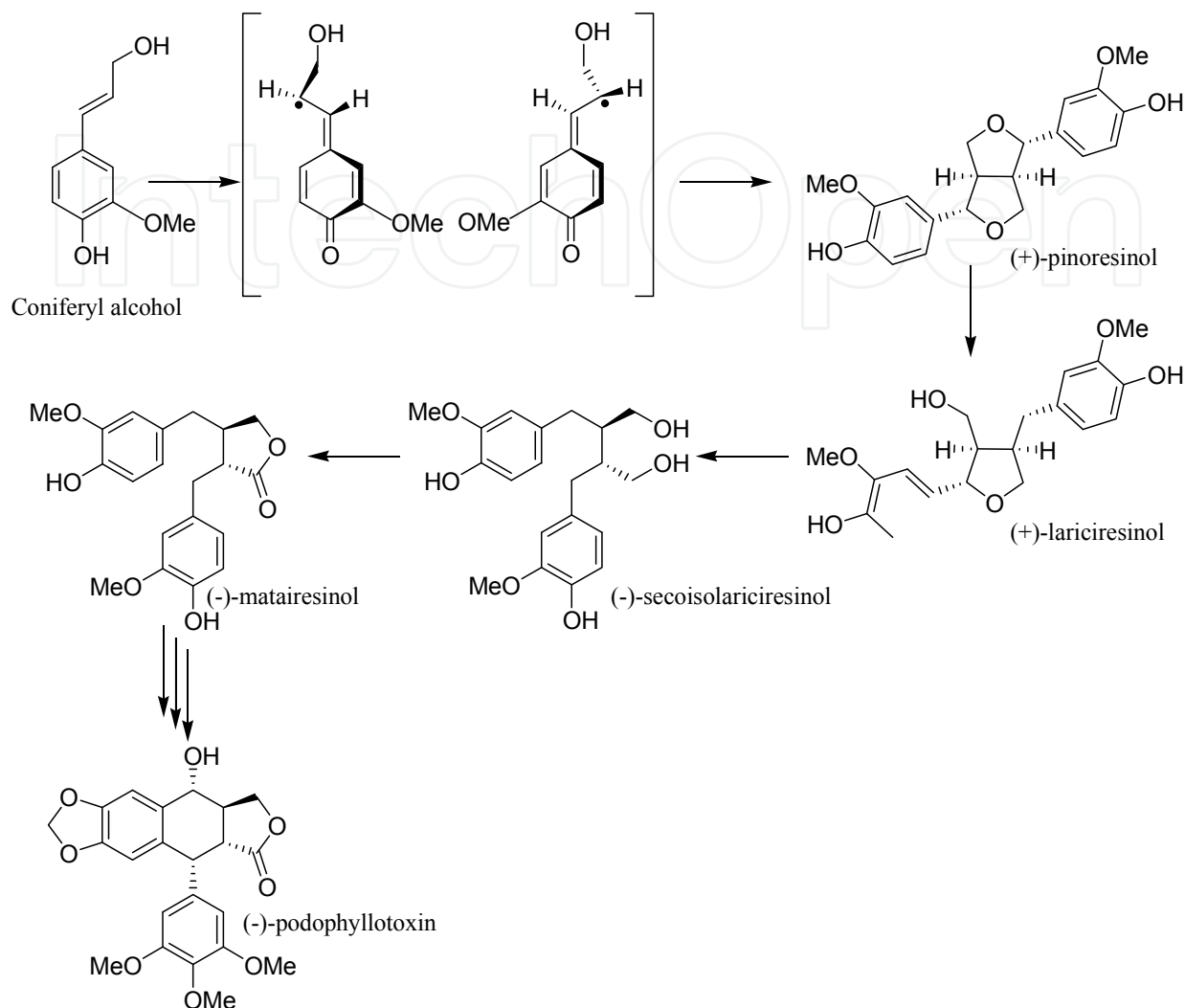


Fig. 7. Biosynthesis proposal of podophyllotoxin according to Canel et al., 2000.

Despite the fact that etoposide, teniposide and etoposide phosphate are clinically valuable anticancer agents, several adverse effects and drug resistance have been associated with the use of these drugs (You, 2005). In this sense, several studies focusing to prepare novel derivatives and to understand the structure-activity relationship (SAR) of podophyllotoxins have been published (You, 2005). Based on these data a great number of potential drug candidates were synthesized (You, 2005; Yousefzadi et al., 2010). **Figure 8** shows the structures of new antineoplastic candidates developed from podophyllotoxin chemical skeleton.

In order to better explore the biological potential of this class of metabolites, our research group has concentrated efforts to investigate the biological activity of some dibenzylbutyrolactone lignans, mainly cubebin (**Figure 9, 1**) and its semi-synthetic derivatives. In this sense, the most significant achievements in our investigations are described in the following sections.

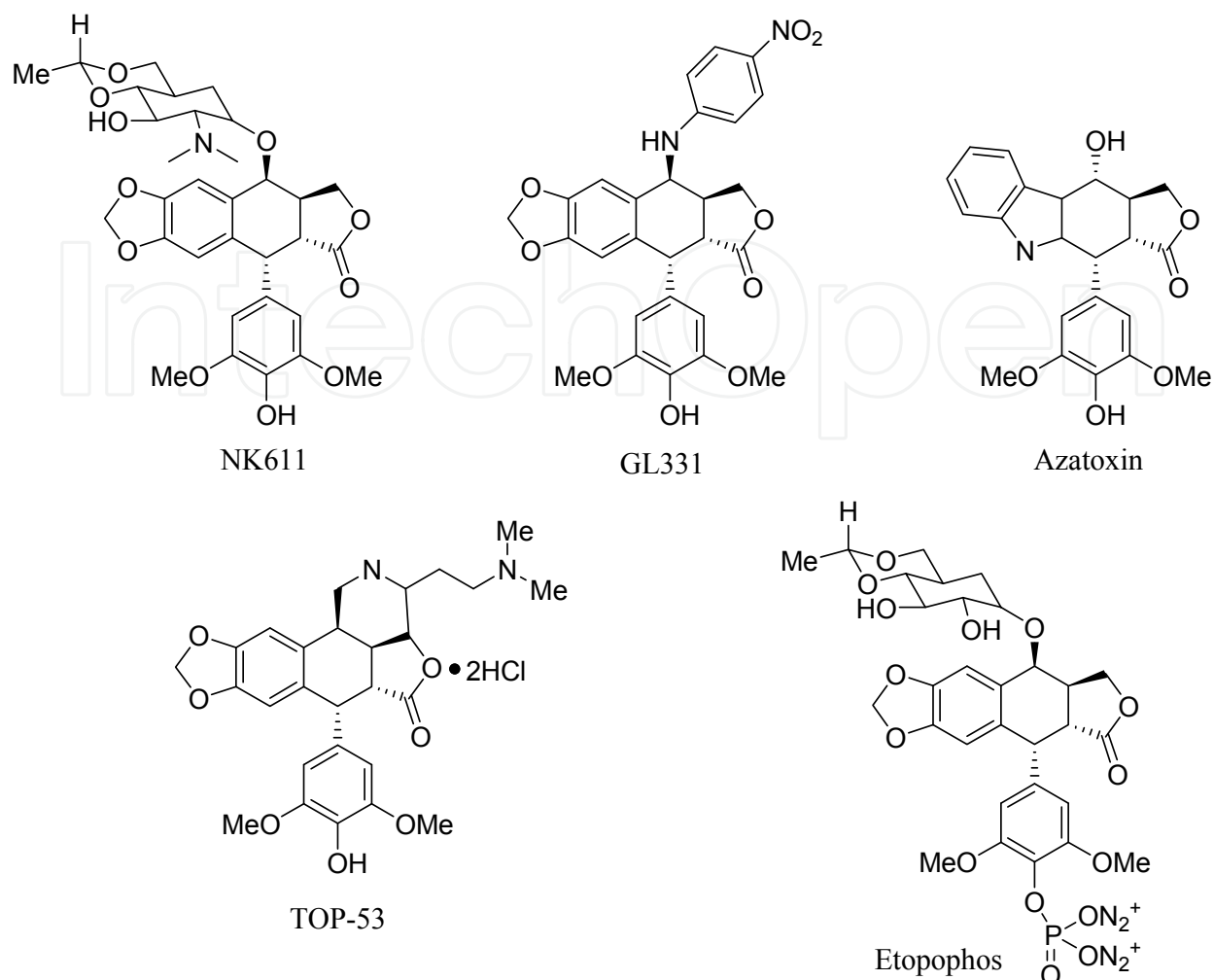


Fig. 8. Examples of antineoplastic candidates developed from podophyllotoxin chemical skeleton.

4. Trypanocidal activity of cubebin and its derivatives

The Chagas' disease, or American trypanosomiasis, is endemic in Central and South America and it is estimated that 16–18 million people are currently infected with the protozoan flagellate *Trypanosoma cruzi* (Molfetta et al., 2005) and more than 100 million are exposed to the risk of infection (Takeara et al., 2003).

Since its discovery in 1909, Chagas' disease infection has been difficult to control due to its multiple characteristics (de Souza et al., 2005). One of the main causes of these difficulties are to find an efficient compound to combat the aetiologic agent (*T. cruzi*) is directly linked to the morphologic characteristics of its strains, mainly due to the occurrence of various sub-populations of the parasite, leading to a different host tissue's tropism (de Souza et al., 2005).

Clinical treatment of infected patients is relied on two nitroheterocyclic drugs, the nifofuran nifurtimox, Lampit[®], which production has now been discontinued, and the 2-nitroimidazole benzimidazole, Rochagan[®] (Paulino et al., 2005). Both drugs, if administered during the acute phase of the disease, could cure 50-70% of the patients. However, these

drugs display limited efficacy in the treatment of the chronic phase of the disease and are quite toxic for the patients (de Souza et al., 2005). Therefore, there is an urgent demand for the discovery and development of novel therapeutic compounds to treat Chagas' disease

De Souza et al. (2005) (de Souza et al., 2005) have reported the trypanocidal activity of cubebin (**1**) and its semi-synthetic derivatives against free amastigote forms of *T. cruzi*. **Figure 9** also shows the compounds obtained by partial synthesis from cubebin (**1**), as well as the reagents and conditions used in these reactions.

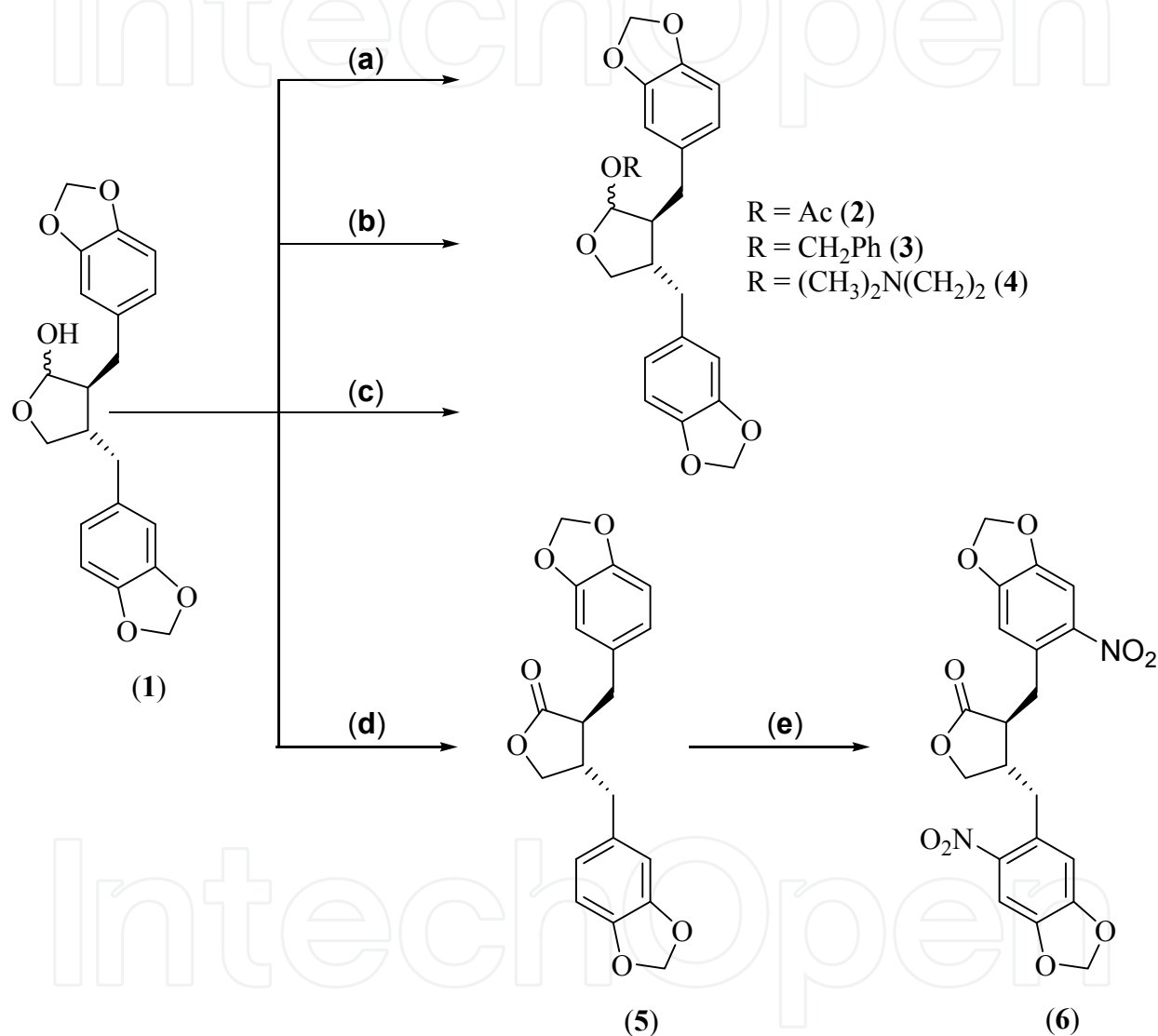


Fig. 9. Reagents and conditions: (a) Ac_2O , Py, room temperature, 24 h; (b) NaH, BnBr, THF, room temperature, 24h; (c) EtONa, $(\text{CH}_3)_2\text{CH}_2\text{Cl}$, EtOH, reflux, 6h; (d) PCC, CH_2Cl_2 , room temperature, 12h; (e) HNO_3 , 2h, -10°C .

The natural cubebin (**1**), used as the starting compound to obtain the evaluated dibenzylbutyrolactone derivatives, did not display activity against trypomastigote forms of *T. cruzi* (Bastos et al., 1999). Hence, the biological evaluation against amastigote forms was undertaken only for lignans **2**, **3**, **4**, **5** and **6**. Cubebin was selected as starting compound because of its availability, being easily isolated in large amounts from the seeds of *Piper*

cubeba (de Souza et al., 2005). **Table 2** shows the results of the trypanocidal activity evaluation of compounds **2**, **3**, **4**, **5**, **6** and benznidazole, against amastigote forms of Y strain of *T. cruzi*.

Compounds	Concentration (μM) X % of lyse (\pm SD)				IC ₅₀ (μM)
	0.5	2.0	8.0	32.0	
2	14.5 \pm 1.9	26.0 \pm 2.5	29.0 \pm 5.2	26.4 \pm 1.2	1.5 X 10 ⁴
3	37.0 \pm 1.4	38.0 \pm 7.0	46.8 \pm 6.4	68.8 \pm 2.9	5.7
4	32.6 \pm 2.6	55.4 \pm 4.3	50.8 \pm 1.0	57.8 \pm 8.0	4.7
5	47.6 \pm 9.5	57.0 \pm 1.1	57.6 \pm 8.9	63.6 \pm 5.2	0.7
6	34.6 \pm 7.9	48.7 \pm 1.4	38.9 \pm 2.0	48.5 \pm 6.1	95.3
Benznidazole	38.4 \pm 3.0	67.0 \pm 7.2	69.0 \pm 4.0	68.6 \pm 1.7	0.8

Table 2. Results of the trypanocidal activity evaluation of compounds **2**, **3**, **4**, **5**, **6** and benznidazole, against amastigote forms of Y strain of *T. cruzi* (de Souza et al., 2005).

The production of compound **2** by substitution of the lactol hydrogen of cubebin by an acetyl group led to a strong reduction of its trypanocidal activity, in comparison with all other evaluated compounds belonging to the same group (IC₅₀ = 1.5 X 10⁴ μM ; **Table 2**). Furthermore, the comparison of compounds **2** and **3** indicate that the biological activity against the amastigote forms of *T. cruzi* was significantly affected by the nature of the substituting group at position C-9, which played an important role in the reduction of the calculated IC₅₀ value for compound **3** (IC₅₀ = 5.7 μM ; **Table 2**). Likewise, cubebin derivative **4**, bearing an amino group at the lactol ring, displayed an activity quite similar to compound **3**.

Analysis of the obtained results, displayed in **Table 2**, indicate that compound **5** was the most active, with an IC₅₀ value of 0.7 μM similar to that displayed by benznidazole (IC₅₀ = 0.8 μM), a standard drug used as the positive control. On the other hand, most of the other evaluated compounds displayed much lower activity, with the exception of compounds **3** (IC₅₀ = 5.7 μM) and **4** (IC₅₀ = 4.7 μM), which showed significant activity.

In this study, De Souza et al. (2005) also pointed out that hinokinin (**HK**, **5**) is a promising compound to continue examining, since at 0.5 μM it displayed higher activity than benznidazole and at the other assayed concentrations (2.0, 8.0 and 32.0 μM) it showed similar activity.

In view of higher trypanocidal activity displayed by **HK** (**5**) against free amastigote forms of *T. cruzi* (**Table 2**; (de Souza et al., 2005), this lignan was selected to be assayed against epimastigote and intracellular amastigote forms of *T. cruzi*, both in vitro and in vivo assays (Saraiva et al., 2007). The results of the trypanocidal activity against epimastigote and intracellular amastigote forms of *T. cruzi* are shown in **Tables 3 and 4**, respectively.

Compounds	Concentration (μM) X % of lyse (\pm SD)					IC ₅₀ (μM)
	0.5	2.0	8.0	32.0	128.0	
HK	21.79 \pm 1.82	99.03 \pm 0.15	100.0 \pm 0.35	100.0 \pm 0.35	100.0 \pm 0.64	0.67
Nifurtimox	11.78 \pm 13.92	49.38 \pm 6.71	65.46 \pm 5.36	81.54 \pm 2.71	97.54 \pm 1.80	3.08
benznidazole	0	1.23 \pm 5.87	26.18 \pm 10.71	51.13 \pm 5.23	76.09 \pm 2.74	30.89

Table 3. Results of the trypanocidal activity evaluation of **HK**, benznidazole and nifurtimox against epimastigote forms of CL strain of *T. cruzi* (Saraiva et al., 2007).

Compounds	Concentration (μM) X % of lyse (\pm SD)				IC ₅₀ (μM)
	2.0	8.0	32.0	128.0	
HK	25.84 \pm 1.09	31.92 \pm 9.29	61.72 \pm 9.17	100.0 \pm 0.40	18.36
Nifurtimox	44.6 \pm 0.99	63.78 \pm 1.25	83.31 \pm 0.79	90.63 \pm 1.13	3.54
benznidazole	14.33 \pm 2.65	35.81 \pm 0.65	57.28 \pm 1.99	78.75 \pm 0.67	20.00

Table 4. Results of the trypanocidal activity evaluation of HK, benznidazole and nifurtimox against intracellular amastigote forms of CL strain of *T. cruzi* (Saraiva et al., 2007).

As it can be observed in **Table 3**, **HK** showed a very significant activity against epimastigote forms of *T. cruzi*, displaying IC₅₀ value (0.67 μM) much lower than benznidazole and nifurtimox, used as positive controls (Saraiva et al., 2007). **HK**, also showed to be very active against intracellular amastigote forms, displaying IC₅₀ value of 18.36 μM , which was similar to benznidazole (IC₅₀ = 20.0 μM , **Table 4**).

The *in vivo* assays (Saraiva et al., 2007) were performed using five groups of five BALB/c males, weighing approximately 20 g each. The groups were as follows: group 1, animals without infection; group 2, control infected animals; group 3, animals treated with solvent; group 4, animals treated with benznidazole 40 mg kg⁻¹ day⁻¹; group 5, animals treated with **HK** 40 mg kg⁻¹ day⁻¹. The animals were inoculated with 2 X 10⁴ trypomastigote forms of *T. cruzi* (Y strain). The treatment was initiated 48 h after infection and maintained for 20 days. The animals were treated twice a day with 20 mg kg⁻¹ benznidazole and **HK** orally. The results obtained showed that the treatment with **HK** promoted 70.8% of parasitaemia reduction in the parasitaemic peak, while benznidazole displayed approximately 29.0% of parasite reduction (Saraiva et al., 2007). In addition, **HK** was able to reduce the number of parasites more than benznidazole not only in the parasitaemic peak, but also in all course of infection (Saraiva et al., 2007).

Moreover, it was observed that the groups treated with **HK** displayed better survival rates than the group treated with benznidazole, with survival until the 22nd and 16th day after the beginning of the infection, respectively (Saraiva et al., 2007). Despite the obtained significant results for the *in vivo* assays, the treatment with **HK** or benznidazole did not cause parasitological cure. Overall, considering the promising results displayed by **HK** against both the epimastigote and amastigote forms of the parasite in the *in vitro* assay, as well as the good result displayed in the *in vivo* assay, this lignan has been considered as a lead compound for the development of new drugs for the treatment of Chagas' disease (Saraiva et al., 2007).

In order to obtain better efficacy of **HK** towards the intracellular forms of the parasite, our research group prepared and investigated the effect of **HK** load poly(D,L-lactide-co-glycolide) microparticules.

5. Hinokinin-load poly(D,L-lactide-co-glycolide) microparticules for Chagas' disease

The drug delivery system were developed for the purposes of bringing, uptaking, retaining, releasing, activating, localizing, and targeting the drugs at the right timing, period, dose, and place (Ueda & Tabata, 2003). The use of biodegradable polymers, as poly(D,L-lactic-co-glycolic acid; PLGA), for the controlled release of therapeutic agents is now well established.

These systems have been extensively utilized for oral and parenteral administration (Saraiva et al., 2010). The physical properties and the Food and Drug Administration approval of poly(lactide-co-glycosides) make them the most extensively studied commercially available biodegradable polymers (Birnbaum et al., 2000).

The microparticles can be able to sustain the release of the drug for a considerable period of time, to reduce the required frequency of administration increasing patient compliance, to avoid plasmatic fluctuations, to decrease side effects, and to facilitate dosage administration (Hans & Lowman, 2002). In this sense, our research group prepared **HK**-loaded PLGA microparticles to protect HK of biological interactions and promote its sustained release for treatment of Chagas' disease. Moreover, the trypanocidal effect of microparticles containing **HK** was evaluated *in vivo*.

The **HK**-loaded PLGA microparticles were prepared with success (Saraiva et al., 2010) and presented narrow distribution size and a mean diameter of 0.862 μm , with PDI of 0.072 mm. Scanning electron micrographs of PLGA microparticles obtained showed that **HK** loaded microparticles presented, smooth and spherical surface. Due to their small diameter, the **HK** microparticles obtained are better suited for parenteral delivery (Cegnar et al., 2005).

The trypanocidal *in vivo* experiments were performed using Female Swiss mice (weigh, 20-22 g) which were infected intraperitoneally with 2×10^4 trypomastigotes forms of *T. cruzi*. The treatment (20 days) was performed through subcutaneous route and initiated 48 h after infection, according to Saraiva et al. (2010).

The treatment of infected mice with 40 mg kg^{-1} of **HK**-loaded microparticles each 2 days was able to provoke significant decrease in parasitemia levels compared with those recorded in untreated controls ($P < 0.05$ at days 12, 14, 16, 19 and 21 post-infection with *T. cruzi*). The treatment with an equivalent amount of empty microparticles (without **HK**) had no effect on the parasitemia compared to untreated controls (Saraiva et al., 2010). Moreover, administration of **HK**-loaded microparticles was able to reduce the number of parasites more than the treatment with 20 mg kg^{-1} day $^{-1}$ of **HK** not only in the parasitemic peak, but also in the course of infection ($P < 0.05$ at days 14, 16, 19 and 21 post-infection with *T. cruzi*) (Saraiva et al., 2010). The use of PLGA microparticles as vehicle for HK delivery can improve HK trypanocidal activity. It may be attributed to the fact that it can protect HK of biological interactions and promote its sustained release, with maintenance of its plasmatic concentration in therapeutic levels (Saraiva et al., 2010).

The **HK**-loaded microparticles developed by our research group can be considerable a promising system for sustained release of **HK** for therapeutic use and could be used in future clinical studies (Saraiva et al., 2010). Also, it is very important to point out that other *in vivo* assays have been developed by our research group in order to evaluate the parasitological cure of infection and the activity of this delivery system coating **HK** against other strains of *T. cruzi*.

6. Influences of stereochemistry on trypanocidal activity of dibenzylbutyrolactone lignans

We have been reporting the significant trypanocidal activity of dibenzylbutyrolactone lignans, mainly the semi-synthetic **HK**. Such results aroused the interest within our group

to study the effect of stereochemistry in this biological property. For this purpose, methylpluviatolide, one of the most powerful compounds regarding trypanocidal activity (Bastos et al., 1999) was synthesized in its *trans* and *cis* racemic forms. Thus, allowing us to evaluate the trypanocidal activity not only of a mixture of these two stereoisomers, but also of the pure enantiomers, which were separated by chiral HPLC (da Silva et al., 2008).

Trans (tM) and *cis* (cM) racemic forms of methylpluviatolide were prepared by a procedure described by Landais et al. (1991) and Charlton and Chee (1997) (Figure 10).

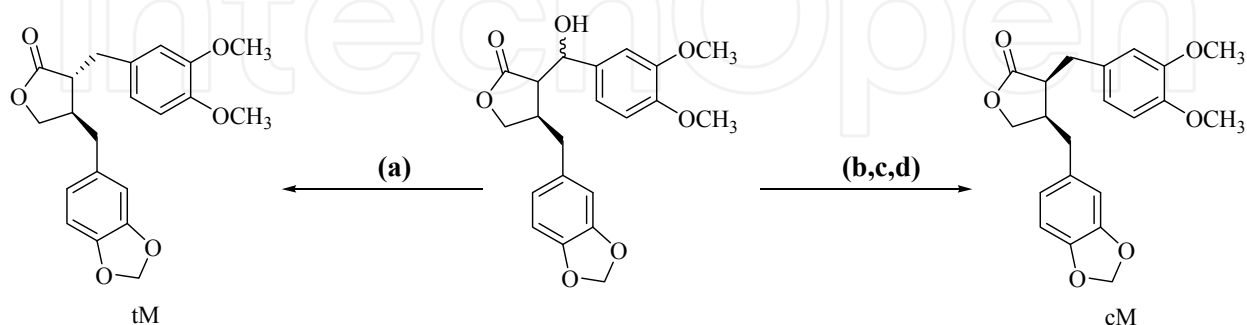


Fig. 10. Reagents and conditions: (a) H₂, 4 atm, Pd/C, ETOH, HClO₄, 60h, room temperature; (b) THF, AC₂O, Et₃N, DMAP, 2h, room temperature; (c) DBU, CH₂Cl₂, 5h, room temperature; (d) H₂, 4 atm, Pd/C, ETOH, 60h, room temperature.

The results obtained for the racemic mixture of *trans* and *cis* methylpluviatolide against *T. cruzi* showed that racemic *cis*-stereoisomer (2) is inactive, while the racemic *trans*-stereoisomer (1) display significant trypanocidal activity, with an IC₅₀ of 89.3 μM (da Silva et al., 2008).

On the basis of these results, a separation of the *trans*-stereoisomer from the racemic mixture was undertaken by chiral HPLC using an analytical Chiracel OJ (4.6 x 250 mm) column, aiming to evaluate the trypanocidal activity of each enantiomer separately. The chromatogram gave a well resolved peak separation, allowing the isolation of both enantiomers (da Silva et al., 2008), which were evaluated against trypomastigote forms of the Y strain of *T. cruzi*. Table 5 shows the results of the trypanocidal activity evaluation of (+)-*trans*- methylpluviatolide (+tM) and (-)-*trans*- methylpluviatolide (-tM) against trypomastigote forms of the Y strain of *T. cruzi*.

Compounds	Concentration (μM) X % of lyse (± SD)			IC ₅₀ (μM)
	8.0	32.0	128.0	
+tM	5.3±2.5	7.6±3.4	9.9±2.5	1.3 X 10 ⁶
-tM	40.6±3.6	52.3±4.4	79.7±0.0	18.7

Table 5. Results of the trypanocidal activity evaluation of +tM or -tM against trypomastigotes forms of the Y strain of *T. cruzi*. (da Silva et al., 2008).

The results show that +tM is completely inactive, whereas the -tM displayed good activity, with an IC₅₀ of 18.7 μM (da Silva et al., 2008). These results indicate that despite being completely inactive, the +tM blocks the action of the -tM when they are present in a racemic mixture. It should be taken into consideration that the +tM might bind to the active sites as a

competitive antagonist, which may be confirmed by comparison of the IC_{50} value of the racemic mixture with that of the **-tM** itself (da Silva et al., 2008).

In conclusion, this study pointed the importance of the stereochemistry on trypanocidal activity of dibenzylbutyrolactone lignans and brings new perspective in the importance to understand the trypanocidal structure-activity relationship for this class of natural compounds.

7. Antimicrobial potential of some natural and semi-synthetic lignans against *Mycobacteria* and oral pathogens

The lignans possess a wide spectrum of biological activities, including antimicrobial (Saleem et al., 2005). Considering this fact, our research group also decided to investigate the potential of some natural and semi-synthetic lignans against mycobacteria and oral pathogens (Silva et al., 2007; Silva et al., 2009).

Tuberculosis is a severe infectious disease caused by mycobacteria belonging to the *Mycobacterium tuberculosis* complex. According to WHO, tuberculosis affects nearly 30% of the world's population and is responsible for 3 million deaths worldwide each year, mainly in developing countries (Raviglione, 2003). The current chemotherapy of this pathology has been based on the use of combined drug therapy with rifampicin, isoniazid, and pyrazinamide. However, the incorrect use and long drug administration, as well as the high cost and countless side-effects have led people to abandon the treatment before being completely cured, leading to resistant bacilli (Timmins & Deretic, 2006). In addition, the existence of drug-resistant tuberculosis reinforces the need to develop new safe and effective antimycobacterial drugs. In this sense, our research group evaluated the antimycobacterial activity of several lignans obtained from cubebin (Silva et al., 2009).

As shown in **Figure 11**, (-)-cubebin (**1**) was isolated from powdered seeds of *Piper cubeba* and then submitted to various semi-synthetic procedures to obtain hinokinin (**HK**, **5**), (-)-O-acetyl-cubebin (**2**), (-)-O-methyl-cubebin (**7**), (-)-O-(N,N-dimethylamine-ethyl)-cubebin (**4**) and (-)-6,6'-dinitrohinokinin (**6**). All these compounds were assayed *in vitro* by the microdilution technique on a Resazurin microtiter assay (REMA) plate, using a procedure adapted from (Palomino et al., 2002).

Cubebin (**1**) did not display any activity against the investigated strains (**Table 6**). **HK** (**5**) was moderately active against *Mycobacterium tuberculosis*, with a MIC value equal to $62.5 \mu\text{g mL}^{-1}$. Compound (**2**), whose lactol group is acetylated, displayed activity against *M. tuberculosis* (MIC = $125 \mu\text{g mL}^{-1}$) and *M. avium* (MIC = $62.5 \mu\text{g mL}^{-1}$). The best result was achieved with compound **7**, whose lactol group is methylated, leading to a MIC value equal to $31.25 \mu\text{g mL}^{-1}$ against *M. avium*. The other compounds were not active against any of the studied mycobacteria. In the case of the lactol-containing compounds evaluated here, it seems to be essential that the lactol group is absent, and the substituent of this group should be small, as in the case of **2** and **7**. *M. kansasii* (ATCC 12478) was the most resistant mycobacterium concerning the evaluated compounds, with MIC values varying between 1000 and $2000 \mu\text{g mL}^{-1}$.

To sum up, cubebin and hinokinin semi-synthetic derivatives were prepared and evaluated for their antimycobacterial activity. Some derivatives were active against *M. tuberculosis* and *M. avium*, suggesting that this class of compounds may lead to a new generation of antituberculosis agents (Silva et al., 2009).

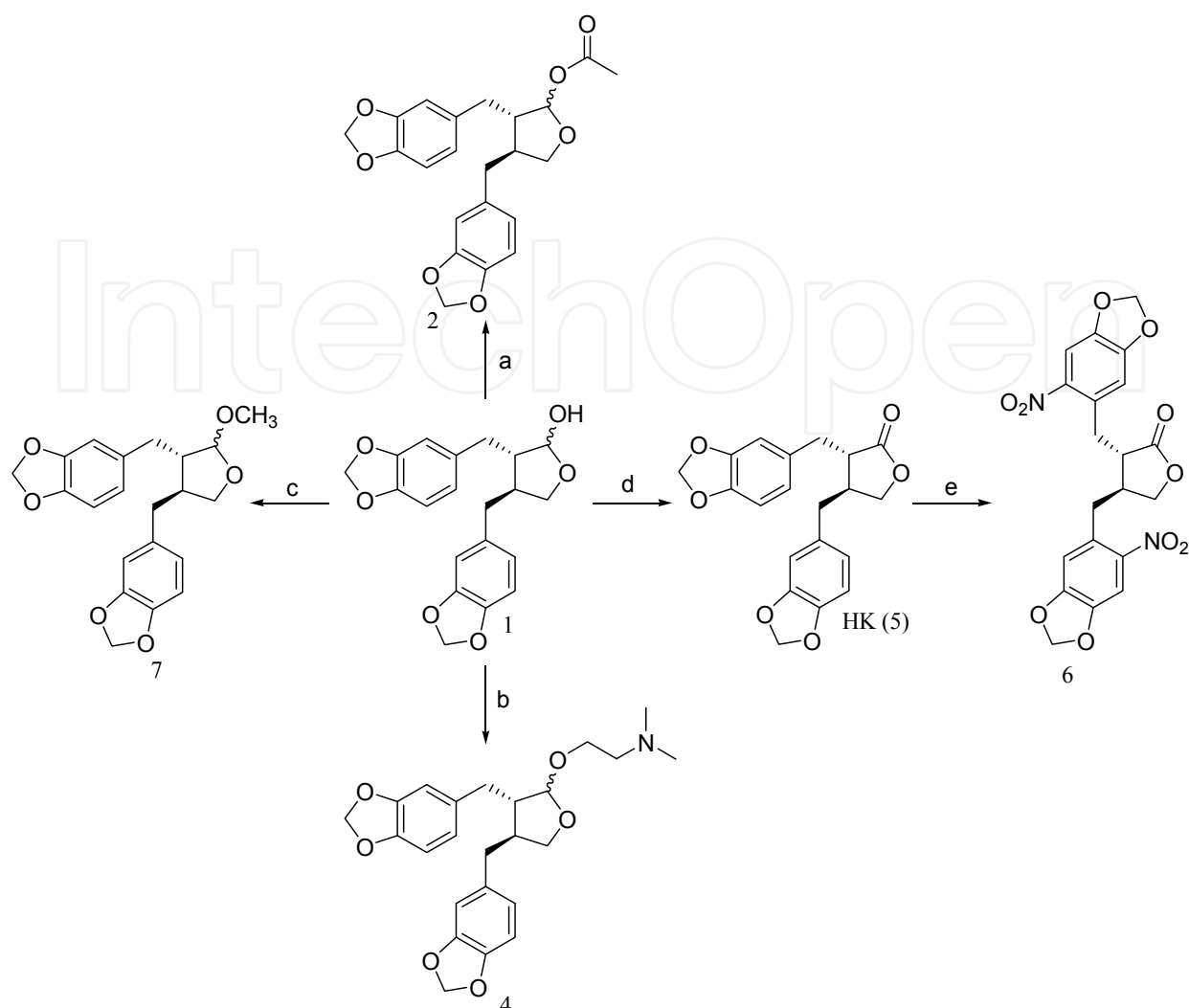


Fig. 11. Chemical structures and conditions of the reactions (a) Acetic anhydride, room temperature, 24h. (b) Dimethylethylammonium chloride, EtONa, dry THF, room temperature, N₂ atmosphere, 6h. (c) Methyl iodide, NaH, dry THF, room temperature, 6h. (d) PCC (pyridinium chlorochromate) in dry methylene chloride, 24h, in an ice bath with continuous stirring. (e) HNO₃, chloroform, -6°C, 2h.

Compound	MIC [$\mu\text{g mL}^{-1}$]		
	<i>M. tuberculosis</i>	<i>M. kansasii</i>	<i>M. avium</i>
1	500	2000	1000
2	125	1000	62.5
4	250	2000	250
5	62.5	2000	500
6	1000	2000	1000
7	250	2000	31.25
Rifampicin ^a	0.031	0.015	0.062

^a Standard antibiotic

Table 6. Minimal inhibitory concentration (MIC) of cubebin (1) and its derivatives against *M. tuberculosis*, *M. kansasii*, and *M. avium*.

Recently, our research group also investigated the antimicrobial activity of cubebin and related derivatives against oral pathogens, mainly those responsible for caries disease, which are intimately related with the dental plaque formation.

Dental plaque is defined as a biofilm consisting of cariogenic bacteria adhered on the tooth surface and plays an important role in the development of dental caries (Chung et al., 2006; Xie et al., 2008), one of the main oral diseases that affect humankind (More et al., 2008; Souza et al., 2010). This destructive infection of the dental hard tissues can progress and if untreated, lead to the death of vital pulp tissue and tooth loss (Allaker & Douglas, 2009). Bacteria from the genus *Streptococci* are commonly isolated from the oral cavity (Hirasawa & Takada, 2002) and have been responsible for this infectious disease. Among them, *Streptococcus mutans* is considered one of the main cariogenic microorganisms, due to its ability to synthesize extracellular polysaccharides from sucrose, mainly water-insoluble glucan, and initiate plaque formation (Koo et al., 2000). Other aerobic bacteria such as *Enterococcus faecalis*, *Lactobacillus casei*, *Streptococcus mitis*, *S. sanguinis*, *S. sobrinus* and *S. salivarius* are also important in the latter formation of the dental biofilm (Chung et al., 2006).

The mechanical removal of the dental plaque is the most efficient procedure to prevent caries, but the majority of the population does not perform this removal efficiently (Ambrosio et al., 2008). Moreover, dental treatment is often very expensive and not readily accessible, especially in developing countries (More et al., 2008). In this sense, the use of chemicals as a complementary measure is necessary and has demonstrated to be of great value in the prevention of the formation and in the decreasing of the tooth surface biofilm (Furiga et al., 2008).

Extensive efforts have been made toward the search for anticariogenic compounds that can be incorporated into dental products, aiming at complementing the mechanical removal. Several antibiotics, such as ampicillin, chlorhexidine, sanguinarine, metronidazole, phenolic-antiseptics and quaternary ammonium-antiseptics have been used to prevent dental caries. Among these compounds, chlorhexidine is considered a gold standard anticariogenic and has received the approval of the American Dental Association Council on Dental Therapeutics (Ambrosio et al., 2008). However, the regular use of oral care products containing this chemical are often associated with tooth and restoration staining, changes in the taste of food, and a burning sensation at the tip of the tongue (Greenberg et al., 2008; More et al., 2008; Porto et al., 2009b). In addition, chlorhexidine is much less effective in reducing the levels of *Lactobacillus* species, which are strongly related to caries evolution (Ambrosio et al., 2008). All these problems, therefore, denote that finding new, safe and effective anticariogenic compounds is still needed.

Thus, our research group tested compounds **1**, **4**, **5**, and **6** (**Figure 11**) and another semi-synthetic derivative (O-benzyl cubebin, **8**, **Figure 12**) using the broth microdilution method (Andrews, 2001) against the following microorganisms: *Enterococcus faecalis* (ATCC 4082), *Streptococcus salivarius* (ATCC 25975), *Streptococcus mitis* (ATCC 49456), *Streptococcus mutans* (ATCC 25275), *Streptococcus sobrinus* (ATCC 33478), *Streptococcus sanguinis* (ATCC 10556) and *Candida albicans* (ATCC 28366) (Silva et al. 2007). **Table 7** displays the minimum inhibitory concentration values obtained for these compounds

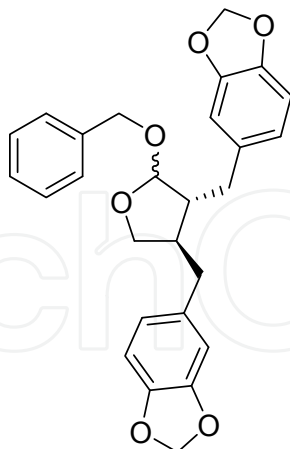


Fig. 12. Structure of O-benzyl cubebin (compound 8)

Compound	Microorganism						
	<i>E. faecalis</i>	<i>S. salivarius</i>	<i>S. sanguinis</i>	<i>S. mitis</i>	<i>S. mutans</i>	<i>S. sobrinus</i>	<i>C. albicans</i>
1	0.35	0.25	0.22	0.20	0.32	0.27	0.28
4	0.31	0.21	0.21	0.19	0.28	0.23	0.23
5	0.38	0.25	0.25	0.25	0.32	0.28	0.28
6	0.30	0.20	0.21	0.18	0.27	0.23	0.23
8	0.31	0.20	0.23	0.18	0.29	0.23	0.28
CHD^a	5.9x10 ⁻³	1.7 x10 ⁻³	3.9x10 ⁻³	5.9x10 ⁻³	5.9x10 ⁻³	1.5x10 ⁻³	7.9x10 ⁻³

^a Chlorhexidine

Table 7. Values of minimum inhibitory concentrations (in milimolar) of cubebin and its semi-synthetic derivatives against oral pathogens

The semi-synthetic derivative **6** was the most active one against all the evaluated microorganisms (Table 7). Compounds **5** and **6** are lignan-lactones and differ from cubebin by the presence of a carbonyl group at C9 (Figure 11). Analysis of the obtained results suggested that the presence of the carbonyl group at C9 with introduction of polar groups in the aromatic rings is beneficial for the antimicrobial activity.

The obtained results for antimicrobial activity are in accordance to those obtained for anti-inflammatory and analgesic activities. Compounds possessing a lactone ring bearing two methylenedioxyaryl groups display significant anti-inflammatory and analgesic activities, and the introduction of polar groups in the aromatic rings is advantageous for these activities. However, with regard to trypanocidal activity, the introduction of nitro groups at the aromatic rings is harmful for this activity. Besides, the lignan-lactone **HK** (**5**) was the most active compound against *T. cruzi* (de Souza et al., 2005).

8. Future perspectives

Despite of the wide spectrum of biological activities related to lignans, the literature used to emphasize the antioxidant properties and the role of these metabolites in cancer treatment and prevention. (Fauré et al., 1990; McRae & Towers, 1984; Pan et al., 2009; Saleem et al., 2005; Yousefzadi et al., 2010). However, in recent years our research group pointed out the importance of such metabolites, specially cubebin and their semi-synthetic derivatives, as potential antichagasic agents (da Silva et al., 2008; de Souza et al., 2005; Saraiva et al., 2010; Saraiva et al., 2007). The very promising results obtained against *T. cruzi* suggested that further investigations of these lignans against other parasitic diseases should be performed. In this sense, our group is now focusing the evaluation of such compounds against, for example, *Schistosoma mansoni* and *Fasciola hepatica*, as well as the obtainment of new cubebin-related semi-synthetic derivatives.

In addition, our results on the antimicrobial activities of these metabolites also highlighted their potential as new antimicrobial agents (Silva et al., 2007; Silva et al., 2009). In this context, the literature also reports additional experiments with the objective of investigating other features of the antimicrobial activity, such as the time-kill curve experiments based on D'Arrigo et al (2010) and investigations about a possible synergistic effect between the most effective tested lignans and the current used antimicrobial agents (White et al., 1996).

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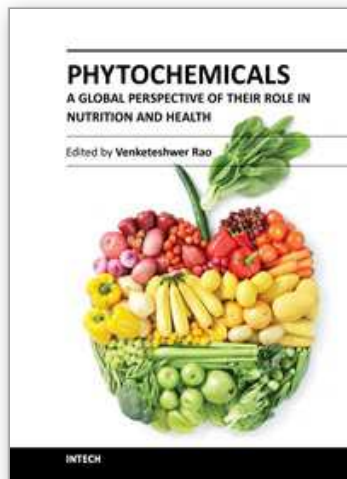
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Phytochemicals are biologically active compounds present in plants used for food and medicine. A great deal of interest has been generated recently in the isolation, characterization and biological activity of these phytochemicals. This book is in response to the need for more current and global scope of phytochemicals. It contains chapters written by internationally recognized authors. The topics covered in the book range from their occurrence, chemical and physical characteristics, analytical procedures, biological activity, safety and industrial applications. The book has been planned to meet the needs of the researchers, health professionals, government regulatory agencies and industries. This book will serve as a standard reference book in this important and fast growing area of phytochemicals, human nutrition and health.

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