Strategies for the synthesis of bioactive pyran naphthoquinones

Vitor Francisco Ferreira,* Sabrina Baptista Ferreira and Fernando de Carvalho da Silva

Received 17th June 2010, Accepted 6th August 2010
DOI: 10.1039/c0ob00277a

Taking into account the numerous reports in the literature related to pyran naphthoquinones in searching for new pharmacologically promising molecules against different therapeutic targets, this review intends to explore the synthetic methodologies for preparing these bioactive compounds.

Introduction

Pyran derivatives occur in nature fused to several heterocycles and carbocycles. Many of these naturally occurring pyrans, and their synthetic analogues, are important precursors for the synthesis of natural products. Pyran naphthoquinone derivatives as represented by β-lapachone, especially, have shown a diversity of biological activities that are of importance for drug development, including anticancer, antibacterial and anti-inflammatory activity. As a result, the syntheses of pyran naphthoquinones with different substitution patterns have drawn much research interest. Several synthetic methods have been reported in the literature, clearly demonstrating that the naphthoquinone framework has significance for the development of new substances with promising biological activities. This review intends to discuss strategies for modifying the carbonyls and the pyran rings of pyran naphthoquinones in order to obtain new bioactive analogues of these compounds.

Universidade Federal Fluminense, Instituto de Química, Departamento de Química Orgânica, CEG, Campus do Valonguinho, 24020-141 Niterói, Rio de Janeiro, Brazil. E-mail: cegvito@vm.uff.br; Fax: +55 2126292136; Tel: +55 2126292345

The quinones

Quinones naturally occur in various families of plants, fungi bacteria and insects linking the electron transport chains in the metabolic pathway with the oxidative processes. Because of these properties, these substances have been studied in many aspects; some have become pharmaceuticals and others are prototypes to develop new drugs. Indeed, this fact can be evidenced by the large number of publications in the literature exploring the actions of these substances in various biological functions.[1,2,3] Briefly, quinones have been studied

Professor Vitor Francisco Ferreira

Professor Vitor Francisco Ferreira was born in Rio de Janeiro/Brazil in 1953. He obtained his BS in chemistry in 1976 and MSc in the chemistry of natural products in 1980 under the guidance of Professor Antonio Ventura Pinto at Universidade Federal do Rio de Janeiro. He then moved to the USA as a doctoral student in the research group of Professor Ernest Wenkert at the University of California San Diego. There he received the Hart Memorial Award for best foreign student in 1982 (UCSD). In 1984 he returned to Brazil and was appointed as fellow researcher at the National Institute of Technology. In 1990, He moved to Universidade Federal Fluminense as Associate Professor and started his own research group. In 1992 He became a full professor at same university. In 2007 he became member of Brazilian Academy of Science and in 2008 was admitted at the "Ordem Nacional do Meríto Científico do Brasil". His research interests include synthesis using readily available carbohydrate, synthetic methods using diazocompounds and, synthesis of bioactive compounds for neglected diseases.

Sabrina Baptista Ferreira

Sabrina Baptista Ferreira was born in Rio de Janeiro/RJ, Brazil in 1979. She received her Industrial Pharmacy degree from Universidade Federal Fluminense, in 2001 and her M.Sc. in chemistry from Universidade Federal do Rio de Janeiro in 2004 under the supervision of the Professors Warner B. Kover (Universidade Federal do Rio de Janeiro) and Núbia Boechat (Fiocruz–Farmanguinhos). She undertook a Ph.D. at the same institution under the supervision of Professors Vitor F. Ferreira (Universidade Federal Fluminense) and Carlos Roland Kaiser (Universidade Federal do Rio de Janeiro), completing in 2008. She is the winner of various scholarships, including scholarship "Bolsa Nota 10" provided by FAPERJ as an award for best students. She is currently a postdoctoral fellow in the Universidade Federal Fluminense, working with Professor Vitor F. Ferreira. Her research interests focus on the discovery and development of new synthetic strategy of quinones, fluoro compounds, triazoles and carbohydrates and medicinal chemistry.

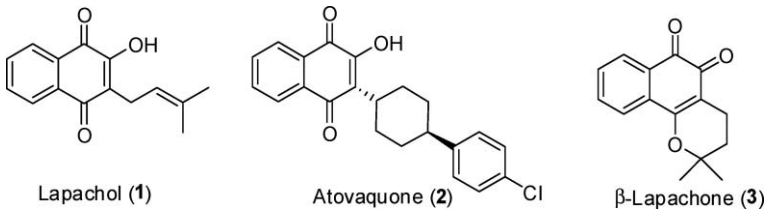


Fig. 1 Natural and synthetic bioactive naphthoquinones.

for their antitumor,[4,5] molluscicidal,[6,7] leischmanicidal,[8] anti-inflammatory,[9] antifungal[10] and trypanocidal[11,12] activities.

Reports point out that the biological profiles of these substances are centered on their *ortho* or *para*-quinonoid moiety, a group that generally accepts one and/or two electrons (redox cycling) to form the corresponding radical anion or dianion species *in situ*, thus creating intracellular hypoxic conditions due to an excess of superoxide anion radical.[13] This anion radical is readily converted into hydrogen peroxide by superoxide dismutase enzyme (SOD) or by transformation into hydroxyl radical by the iron-catalyzed Fenton reaction.[14,15,16,17] Another important feature of this class of compounds is their cytotoxicity to mammalian and cancer cells, possibly due to affecting topoisomerases, a group of enzymes that are very important for DNA replication in cells.[18]

The lapachol family: a historical view

Among the quinone class, there are two important isomeric natural products, lapachol (**1**) and β-lapachone (**3**) (Fig. 1), which have attracted substantial interest from the scientific community.

Lapachol (**1**) is a natural naphthoquinone that occurs naturally in the grain of several wooden trees of the Bignoniaceae family and is widely used in American folk medicine for the treatment of several diseases. It was first isolated from *Tabebuia avellanedae*, but it occurs in several other species of the genus *Tabebuia* (Tecoma). These trees are commonly known in South America as *ipês*, and as *Lapacho*, *Pau d'Arco* (bow tree), *Red Lapacho*, *ipê roxo* (red thick bark) and *Taheebo*.[19,20] It also occurs in many other families such as Verbenaceae, Proteaceae, Leguminosae, Sapotaceae, Scrophulariaceae and Malvaceae.[21] Lapachol is the most abundant quinone in the family Bignoniaceae, particularly in the genus *Tabebuia* (Tecoma), and is isolated with other, no less important, heterocyclic quinones.[22] Lapachol is easily extracted from the sawdust of the wood of ipê.[23] It is currently exported as a crude extract by the PVP Company (Brazil) at a cost of US $1,200/kg. At one time, lapachol was marketed for use as an adjunct in the treatment of certain cancers by the Pharmaceutical Laboratory of Pernambuco State (LAFEPE), but it is no longer available in Brazil.

The history of lapachol in Brazil starts in 1956, when it was isolated by Gonçalves Lima and coworkers from the core of the purple ipê (bouquet tree). Along with this work, the authors found strong antimicrobial activity against the strains *Bacillus subtilis*, *B. anthracis*, *B. cereus*, *Staphylococcus aureus*, *Micrococcus flavus*, and *Escherichia coli*.[24,25] More recently, a screen of 1,266 compounds with known pharmaceutical activities identified three compounds, among them lapachol, that prolonged survival of *Candida albicans*-infected nematodes and inhibited *in vivo* filamentation of *C. albicans*.[26] In 1968, Gonçalves Lima and coworkers also found that the extract of the purple *ipê* had anticancer activity in experimental tumors, making this compound and its derivatives of interest to several research groups.[27] In the same year, Rao and coworkers demonstrated its activity on the Yoshida sarcoma with permanent regression in about 30% of tumors, and identified important analgesic properties.[28,29] Indeed, lapachol (**1**) reduces cancer metastasis[30,31] and has activity on DNA topoisomerase enzymes that are essential for the integrity of the DNA molecule.[32] The 5-hydroxy analog of lapachol (**1**) is also a natural product that is isolated from *Tectona grandis* and showed some cytotoxicity in the brine shrimp test (*Artemia salina*).[33]

In view of the importance and the variety of biological activities of **1** against several enzymes and microorganisms, it has been considered an excellent model compound for the development of more selective and more active compounds. Indeed, Lapachol (**1**)[34] and derivatives thereof[35,6] showed promising activity against *Biomphalaria glabrata*, the snail that is an intermediate host of *Schistosomiasis mansoni*. Additionally, several derivatives of lapachol (**1**) was found to have anticancer,[36] anti-inflammatory,[37,38] antileishmanicidal,[39,40] antimicrobial,[41,42,43] antipsoriatic,[34] antifungal,[42] antileishmanial,[44] viruscidal,[45] larvicidal (*Aedes aegypti*),[46] and tripanocidal[47,48,49] activities. Studies have shown that the biological activity of lapachol is related to its ability to induce oxidative stress at the level of the enzyme P450 reductase.[50]

Fernando de Carvalho da Silva

Fernando de Carvalho da Silva was born in Rio de Janeiro/RJ, Brazil in 1979. He received his Industrial Chemistry degree from Universidade Federal Fluminense (UFF), Niterói/RJ, Brazil in 2002 and obtained his PhD from UFF under the supervision of the Professors Vitor F. Ferreira and Maria Cecília B. V. de Souza where he received a scholarship named "Bolsa Nota 10" provide by FAPERJ as an award for best students. After post-doctoral trainings at Universidade de Aveiro (Portugal) in the group's professor J. A. S. Cavaleiro (2007–2008) and other under supervisor of the professor Angelo C. Pinto (2008–2009) at Universidade Federal do Rio de Janeiro. Now he is professor in the Universidade Federal Fluminense. His research interests focus on the organic synthesis of diazocompounds, β-enaminones, 1,2,3-triazoles, quinones, metathesis, porphyrins and carbohydrates.

In this process, the reactive species generated, anion radicals and superoxides, promote the cleavage of DNA.[51] This mechanism of action is important because several microorganisms are much more sensitive to oxidative stress than the human host.[52,53]

These studies have shown that lapachol has a promising structure and therefore may be a prototype for other substances with improved potency and selectivity against microorganisms and tumor cells. In this regards, a search for potential antimalarial agents identified lapachol as a lead compound and a large collection of synthetic analogues was prepared. This search resulted in Atovaquone® (**2**),[54] a highly lipophilic drug that closely resembles the structure of an ubiquinone. It acts selectively in sensitive parasites by affecting their mitochondrial electron transport and parallel processes, such as ATP and dihydroorotate dehydrogenase, which both catalyzes the synthesis of uridine monophosphate.[55] Currently, a combination of **2** and proguanil (Malarone) is being used to treat malaria[56] and also is useful for the treatment of patients with mild to moderate infection caused by *Pneumocystis carinii*.[57]

β-Lapachone (**3**) is a natural *ortho*-pyran-naphthoquinone obtained as a minor component of heartwood from the Lapacho trees and is readily obtained in high yield from lapachol (**1**) by cyclization in concentrated sulfuric acid.[21] This important naphthoquinone has many different pharmacological activities. It aroused the attention of the scientific community when Stoppani, Cruz and Docampo demonstrated that its strong activity against the hemoflagellate protozoan *Trypanosoma cruzi*[58,59,60,61] occurs *via* a mechanism involving the generation of superoxide anion radicals and H_2O_2, which subsequently cause damages to several cell components and inhibit nucleic acids and protein syntheses.[62] *T. cruzi* is the etiological agent of Chagas disease, in both acute and chronic infections.[63] This disease is endemic in Latin America, and it is a serious public health problem in many countries, with 16 to 18 million people infected with the parasite and more than 100 million people at risk of infection through contact with the insect vector or *via* blood transfusion. The only therapeutic agent available in Brazil for the treatment of Chagas disease is benznidazole (Rochagan®), a drug developed in the 1970 s that is not always effective and presents serious side effects.[64]

Despite showing high activity against this parasite, compound **3** never became a drug for the treatment of Chagas disease due to its high cytotoxicity. Since then, new analogs and derivatives of this substance have been synthesized in the search for compounds with better trypanocidal profile and less cytotoxicity.[65,66,67,68,69,49]

As β-lapachone did not become a drug for the treatment of Chagas disease, the attention of further investigations turned to its cytotoxic activity against tumor cells. The first such study reporting the activity of lapachone with neoplasic cells was published in 1978 by Schuerch and Wehrli, wherein it was found that this compound inhibited oncornavirus reverse transcriptase and eukaryotic DNA polymerase-alpha enzymes.[70] In 1984, Boorstein and Pardee reported that β-lapachone enhances the lethality of human fibroblasts.[71] Pursuing this line of research, Pardee and coworkers found that β-lapachone suppressed HIV-1 replication in both acute and chronic infection[72] and also inhibited the activity of topoisomerase by blocking the formation of cleavable complex topoisomerase I-DNA.[73] Indeed, after these works, hundreds of reports on the activity of β-lapachone against various tumor cells were reported in just over fifteen years.[18] For instance, anticancer activities were reported[74] against human cancer cell lines from leukemia[75] and prostate,[76] malignant glioma,[77] hepatoma,[78] colon,[79] breast,[80] lung[81] and pancreatic cancers.[82] β-lapachone (**3**) has been reported to enhance the lethality of human cancer cells in association with other drugs such as taxol,[83] mitomycin C (ovarian)[71] and paclitaxel.[84] Boothman and coworkers discovered another remarkable property of β-lapachone (**3**), that is, its ability to act as a co-adjuvant in killing human cancer cells during radiotherapy treatment. It seems that it inhibits sub-lethal radiation damage repair.[85,86] Since then, this capability has been exploited by several researchers and is currently a medical procedure under patent.[87,88] Very recently, a new modality of radiotherapy using gold nanoparticles containing β-lapachone for radiosensitization enhanced radiotherapeutic efficacy.[89] Currently, a modified cyclodextrin host–guest complex of β-lapachone associated with gemcitabine, named ARQ501, is undergoing multiple Phase II clinical trials for use against pancreatic cancer and adenocarcinoma.[90]

Several possible mechanisms to explain the cytotoxic effect of **3** against cancer cells have been proposed. The most recent proposal suggests that a redox cycle between NAD(P)H and quinone oxidoreductase 1 (NQO1) enzyme causes the depletion of NAD(P)H and NADH in the cells.[91,92,93] This consequently decreases ATP and increases cytochrome C and cytosolic Ca^{2+}, which then affect other pathways in the cell cycle checkpoint, resulting in the selective apoptotic cell death of cancer cells.[94] It has also been suggested that the generation ROS affects the kinases that are involved in cell cycle progression, leading to cell death.

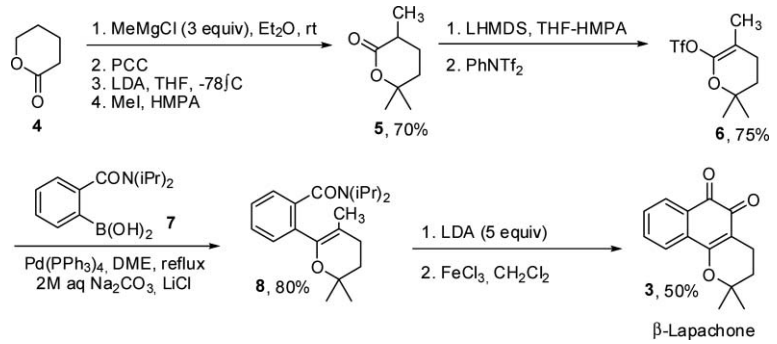
Due to the trypanocidal and anticancer activities of β-lapachone and easy availability from natural sources, it has become a privileged structure in medicinal chemistry. In this respect, many synthetic routes for obtaining **3** have been developed, as well as many derivatives that have been prepared and biologically evaluated.

The structure of β-lapachone (**3**) has inspired a search for new derivatives with better trypanocidal activity and better activity as anticancer agents. In this regard, several heterocyclic derivatives have been constructed to replace the carbonyl or have been attached to the naphthoquinone nucleus, and other minor changes were introduced at the carbonyl. However, the greatest number of derivatives produced involved changes to the pyran ring. Many of these derivatives were much more active and less cytotoxic than **3**, but none has reached a more advanced clinical stage.

β-Lapachone (**3**) was prepared for the first time in 1892 by Hooker from lapachol (**1**) by an acid-catalyzed cyclization. Since then, this protocol has become commonly used for the synthesis of **3** from **1**. Therefore, many methods have been developed for the preparation of lapachol considering that it is easily transformed into **3**. However, other synthetic routes were also developed without the use of lapachol as a starting material. Snieckus and coworker developed a synthesis of **3** based on the combination of a directed *ortho* metalation and the Suzuki cross coupling reaction. The disadvantage of this synthesis is the number of steps and the moderate yields of some steps (Scheme 1).[95]

Modification of the carbonyls of naphthoquinones

In the search for new analogs of β-lapachone (**3**), many modifications were made to its structure and other pyran naphthoquinones. Two kinds of modifications have been explored: changes to the



Scheme 1 Synthesis of β-Lapachone (**3**) by *ortho* metalation and the Suzuki cross coupling reaction.

redox center and changes to the pyran ring. The redox center can be modified selectively at C-6 (monosubstituted derivatives) or at both carbonyls, forming another carbocyclic or heterocyclic ring as depicted in Fig. 2. It should be noted that this position is more reactive to nucleophiles due to its more electrophilic character.[96]

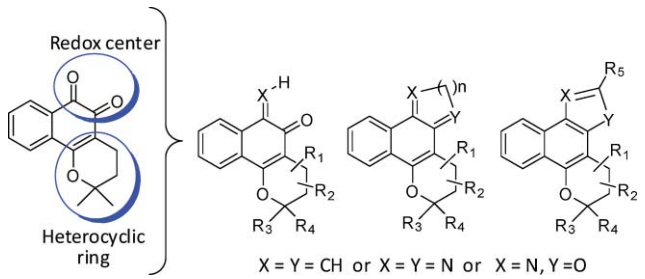
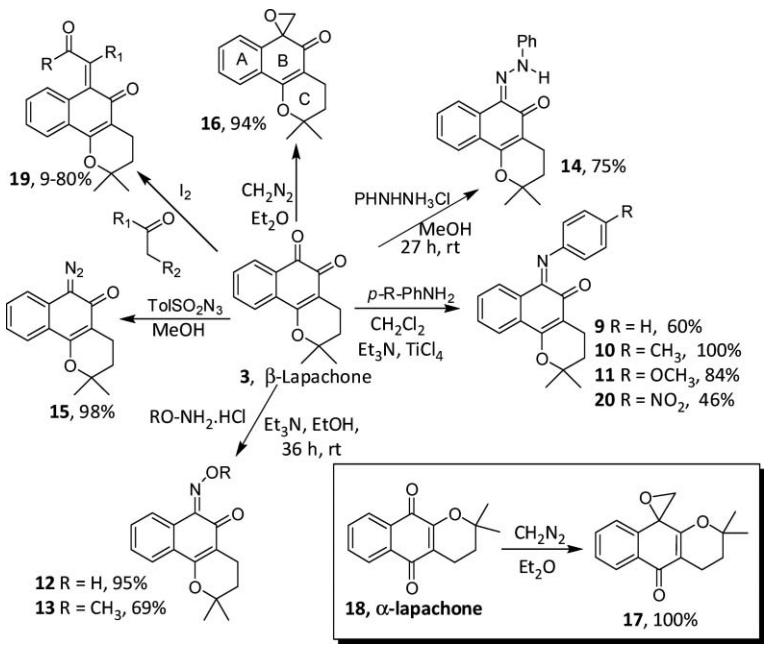


Fig. 2 Pyran naphthoquinone analogs of β-lapachone (**3**).

Di Chenna and coworkers, in a search for more cytotoxic derivatives of **3**, reported the synthesis of monoarylimines by the reaction of **3** with the appropriately substituted aniline catalyzed by $TiCl_4$.[97] The imines were formed exclusively at the 6-position to form the *Z* diastereoisomer, whose structure was determined by X-ray diffraction. A cytotoxicity test with a panel of 12 cultures of human cancer cells showed **9** (GI_{50} 0.20 μM), **10** (GI_{50} 0.19 μM) and **11** (GI_{50} 0.096 μM) were highly active and selective for tumor cells in breast MDA-MB-435 (Scheme 2). However, Boothman and coworkers proved that these Schiff bases are converted to **3** through spontaneous hydrolysis, and that the rates of hydrolysis vary depending on the power of the electron-withdrawing substituents in position on the aromatic ring. In fact, these derivatives of **3** are potentially useful products for therapy against human tumors with high levels of NQO1.[81] The oxime (**12**) and methyloxime (**13**) were also obtained with the same regioselectivity. The derived methyloxime (**13**) was used for the synthesis of oxazinones with potential anti-inflammatory and antioxidant activities.[98] The reaction of **3** with phenylhydrazine hydrochloride formed mainly Z isomer of 6-phenylhydrazone (**14**).[99] More recently, Renou and coworkers prepared the monoarylhydrazones of α-lapachone and found relevant anticancer activity against malignant cell lines.[100]



Scheme 2 Analogs of β-lapachone (**3**) selectively modified in C-6.

Diazo derivatives of naphthoquinones are easily obtained by diazotization in methanol and *p*-toluenesulfonylhydrazine. β-Lapachone (**3**) formed selectively the diazo-naphthalenone (**15**) with a yield of 98%.[101] In particular, this substance was tested against *T. cruzi* and many bacteria; although it was not shown to have any kind of activity, it is a valuable intermediate for the synthesis of other derivatives of **3**.

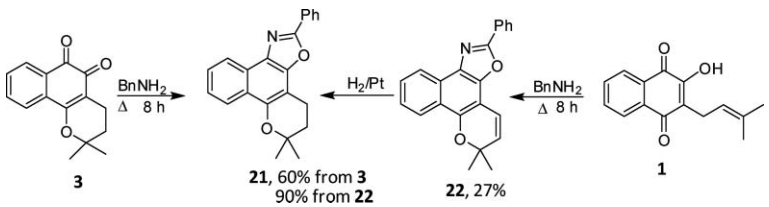
The oxirane derivative **16** (Scheme 2) showed lower cytotoxicity and trypanocidal activities (IC_{50} 12 μM) than β-lapachone (**3**) (IC_{50} 0.9 μM).[102,103] As the core quinone moiety was modified with the introduction of the oxirane ring on the carbonyl C-6, it affected the formation of free radicals and reactive oxygen species. However, the oxirane derivative of α-lapachone (**17**) showed higher trypanocidal activity (IC_{50} 1.3 μM) than α-lapachone (**18**, IC_{50} > 50 μM) without cytotoxicity to mammalian cells. Since the presence of the redox center in the quinones is described as the most important feature responsible for the antiproliferative activity against *T. cruzi*, it seems that another mechanism of action is operating in this case. Indeed, this compound showed lethality of 97% and 84% against trypomastigotes of *T. cruzi* to Y and Colombian strains, respectively.[104] This substance is a potential candidate for chemotherapy of Chagas disease, as it exerts trypanocidal activity with a low cytotoxicity profile to human cells.

Ortho-quinone methides (*o*-QMs) are highly reactive intermediates containing an exocyclic methylidene vicinal to a carbonyl.[105] These intermediaries have wide applicability in organic synthesis, and several synthetic methods were developed to obtain and use them. The *o*-QMs are involved in various biological processes by inhibiting enzymes such as phosphodiesterases and making cross-links with DNA. Their electrophilicity towards amines, thiols, water, DNA, amino acids and peptides has been used as a strategy for the development of anticancer drugs such as mitomycin C. Ferreira and coworkers recently described the synthesis of the stable *o*-QM (**19**) derived from β-lapachone (Scheme 2) by iodine-catalyzed aldol condensations between β-lapachone (**3**) and various ketones.[106] These *o*-QMs can be important synthetic intermediates for the access of other bioactive compounds.

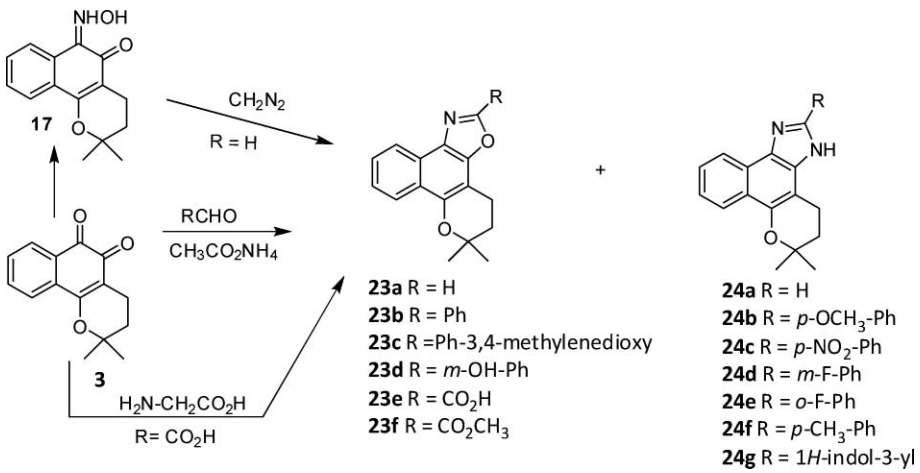
Ventura Pinto and coworkers prepared the first oxazole derivative **21** from lapachol or from β-lapachone (**3**) by their reactions with benzylamines (Scheme 3). For the route from lapachol, a mechanism involving the participation of the tautomeric 1,2-quinone was postulated.[107]

Aiming to develop a new lead compound against *T. cruzi*, the same group developed new methodologies to obtain aryl-naphtho[1,2-d]oxazole (**23a–f**) and aryl-naphtho[1,2-d]imidazoles (**24a–g**) derivatives from β-lapachone (**3**), and several other 1,2-naphthoquinones (Scheme 4).[108,109] The naphtho[1,2-d]oxazole **23a** was a more active compound than **3** against *T. cruzi*. The introduction of an aromatic group to the oxazole nucleus showed a strong influence on the trypanocidal activity. Compound **23b**, with a phenyl group, and compound **23c**, with a 3,4-methylenedioxy-phenyl group attached to the aromatic ring, demonstrated increased activity. The compounds 23d-f showed no significant activity values. Also, several naphtho[1,2-d]imidazoles **24a–g** were synthesized from **3** and were generally more active than the naphtho[1,2-d]oxazole against trypomastigotes, epimastigotes and amastigotes forms of *T. cruzi* Among them, the derivatives **24a**, **24f** and **24g** showed the highest trypanocidal activity, **24a** being 10.6 times more active than β-lapachone (**3**).[110]

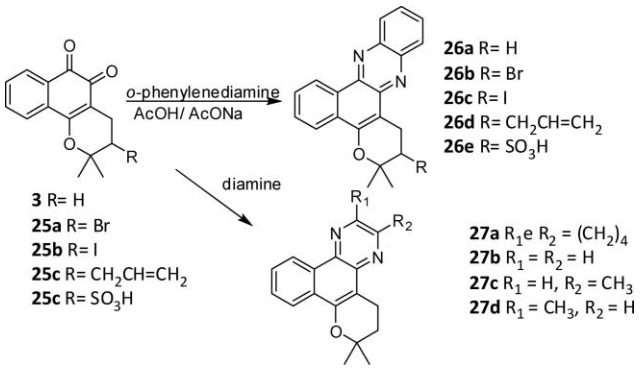
β-Lapachone (**3**) was also transformed into several phenazines by condensation with 1,2-diamines under acid catalysis (Scheme 5). In this regard, Pinto and coworkers reported the synthesis of phenazine from nor-β-lapachone and β-lapachone,[111]



Scheme 3 Naphtho[1,2-d]oxazole derivative from lapachol (**1**) or β-lapachone (**3**).



Scheme 4 Naphtho[1,2-d]oxazole and naphtho[1,2-d]imidazole derivatives from β-lapachone (**3**).



Scheme 5 Phenazines obtained from β-lapachone (**3**) and analogues.

which were then tested against four different strains of *Plasmodium falciparum* and compared to chloroquine *in vitro* and *in vivo*. The parasite BHZ 26/86 (originating Candeias, Rondônia) and W2 (chloroquine and mefloquinone resistant clone) were more susceptible to chloroquine than phenazine; in particular, those containing polar groups [**26c**, IC_{50} (BHZ 26/86) 1.90 ± 0.05 μM, IC_{50} (W2) 3.04 ± 0.1 μM and 59E, IC_{50} (BHZ 26/86) 1.75 ± 0.02 μM, IC_{50} (W2) 1.67 ± 0.05 μM].[112] Other heterocycles, such as pyrazine,[113] were synthesized and evaluated for their ability to inhibit growth of human promyelocytic leukemia cells HL-60 by Campillo and coworkers, who then observed that pyrazine **27a** has low activity (IC_{50} > 100 μM) in comparison with β-lapachone (IC_{50} 0.27 ± 0.04 μM).[114,115]

2*H*-Chromene derivatives of naphthoquinones can be prepared by a general methodology that involves the reaction of *ortho*-naphthoquinones with allyltriphenylphosphonium salts in the presence of an aqueous solution of NaOH and chloroform.[116] The reaction proceeded with the *in situ* formation of an ylide, and subsequent reaction with an *ortho*-naphthoquinone to produce an *o*-QM intermediate, which cyclizes to a 2*H*-chromene **29a–f** (Scheme 6). It is noteworthy that the attack of the phosphorus ylide occurred exclusively at the more reactive carbonyl carbon of the *ortho*-naphthoquinone.

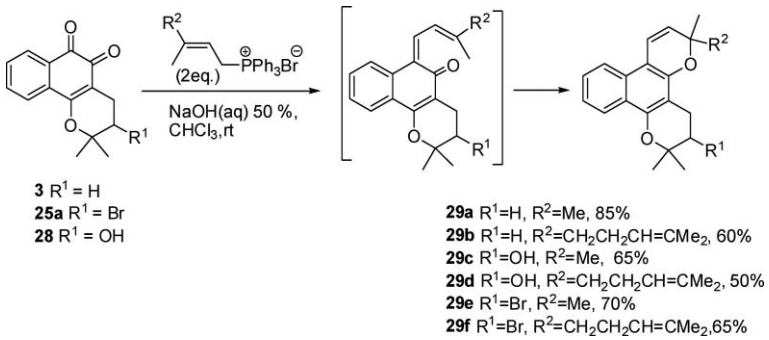
Methods for the synthesis of pyran ring

Most of the naphthoquinones substituted in the pyran rings shown in the earlier examples for the preparation of mono- and disubstituted derivatives were mainly obtained from lapachol (**1**). However, there are other procedures to construct the pyran ring on the naphthoquinone moiety. In this regard, two types of methodologies have been based on *o*-QM intermediates that are prepared *in situ* through a Knoevenagel reaction of either lawsone (2-hydroxy-1,4-naphthoquinone, **30**) or phenols with aldehydes.

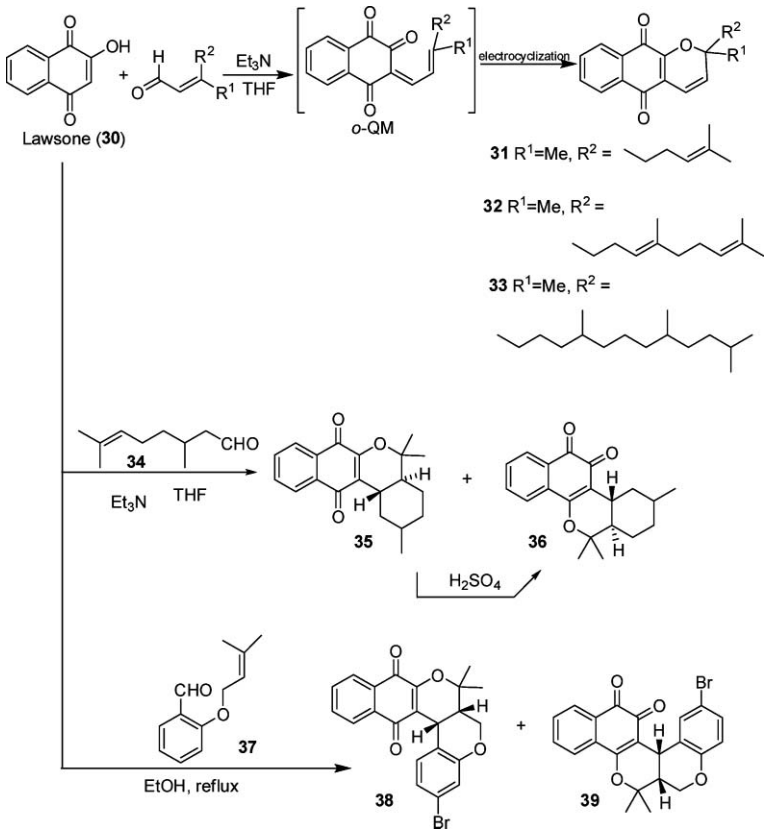
One of the most distinctive features of the *o*-QM chemistry is its remarkable ability either to act as a hetero diene in hetero Diels–Alder reactions or to participate in electrocyclization reactions. Ferreira and coworkers used both methodologies for preparing analogues of α-lapachone (**31–33**)[117] and tetracyclic naphthoquinones (**35** and **36**)[118] by reacting lawsone (**30**) with α,β-unsaturated monoterpene aldehydes and citronellal (**34**), respectively. These reactions have been extended to the synthesis of other α-dehydrolapachones.[119,120] Snieckus and coworkers reported a facile procedure for preparing β-lapachone (**3**) by using tandem Knoevenagel-electrocyclization reactions from naphthols and α,β-unsaturated aldehydes under the influence of phenylboronic acid,[121] and more recently, its asymmetric version with (*S*)-(–)-citronellal produced compounds.[122] A similar reaction was carried out by the same group using the aldehydes **37**, which produced the naphthoquinones **38** and **39** in a 1 : 1 ratio with 94% overall yield and both had strong catalytic inhibition on human topoisomerase II (Scheme 7).

The scope of using *o*-QMs as hetero dienes in hetero Diels–Alder reactions was expanded to a general three-component reaction that was very useful for preparing a wide variety of α- and β-lapachones and other heterocyclic compounds.[123] The reaction between 2-hydroxy-1,4-naphthoquinone (**30**) and *p*-formaldehyde forms the *o*-QM intermediate *in situ*, which then reacts with olefins to generate α- (**40**, **42–43**) and β- (**41**, **44**) pyran naphthoquinones in moderate to good yields. It should be noted, that these reaction formed mainly the α isomers. This protocol was used for the synthesis of β-lapachone (**3**) in one single step in good yield (Scheme 8).[124]

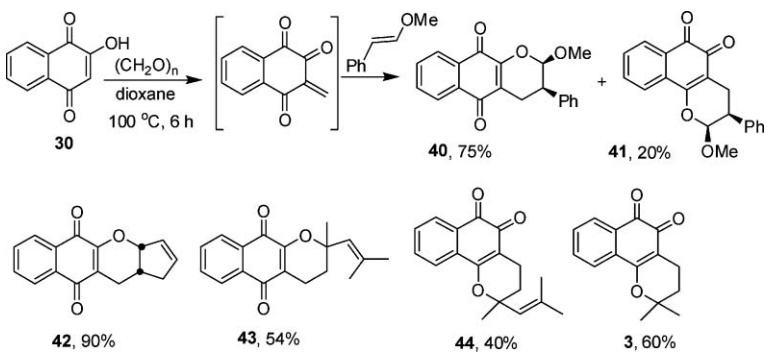
This three-component reaction has a drawback that limits its scope in synthesis. Under the reported conditions, the reaction only works with formaldehyde. However, by using a dienophile that is more reactive toward the inverse demand Diels–Alder reaction, such as the silyl enol ethers (**51**), it is possible to perform the reaction and obtain the pyran naphthoquinones (**46**) and (**47**) in moderate yields. From these results, it is observed that the reaction occurs regioselectively to provide α-lapachone derivatives, indicating that interaction of the *o*-QM intermediate with the silyl enol ether (**51**) is the more energetically favorable



Scheme 6 Synthesis of 2*H*-chromenes from β-lapachone derivatives.



Scheme 7 Synthesis of dehydrolapachones and tetracyclic naphthoquinones *via o*-QMs.

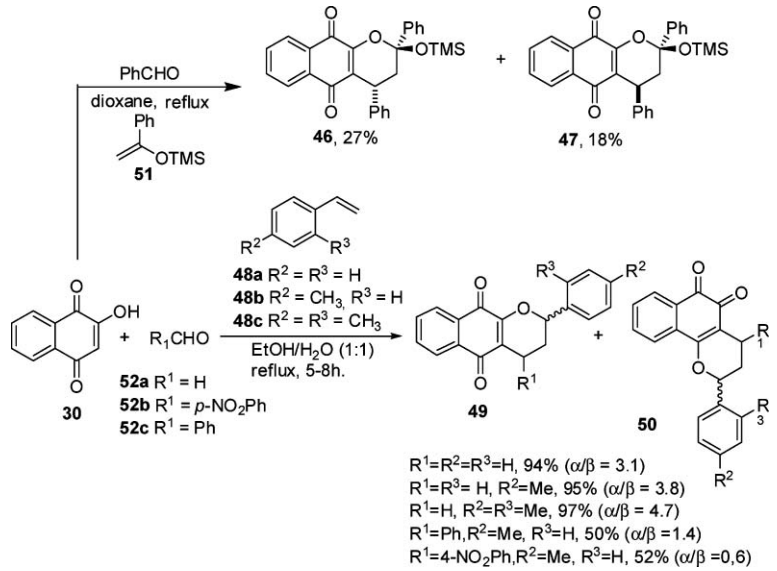


Scheme 8 Pyran naphthoquinones obtained tandem Knoevenagel and hetero Diels–Alder reactions.

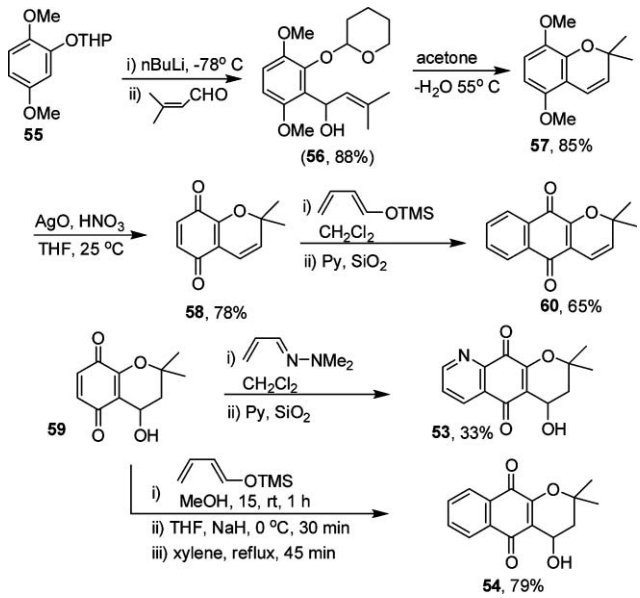
pathway (Scheme 9). Although the problem of poor reactivity with aldehydes other than formaldehyde has been solved, this method is still dependent upon using silyl enol ethers, which need more elaborate procedures to be prepared. Recently, this problem was completely solved by adjusting the reaction conditions. If these reactions are performed in refluxing ethanol–water (1 : 1), several aldehydes (**52**) and styrenes (**48**) can be used, forming α- (**49**) and β-pyran naphthoquinones (**50**) in better yields and with short reaction times. In most of these cases, the reactions are more selective for the β-pyran naphthoquinones (Scheme 9).

Tapia and coworkers use the tandem Knoevenagel-electrocyclization protocol to synthesize the benzopyranquinones (**53**) and (**54**), which were used as building block in Diels–Alder reactions for the construction of the aromatic[125,126,127] and heteroaromatic rings. For the synthesis of benzopyranquinone, the tetrahydropyranyl derivative **55** was transformed to *o*-hydroxy-γ,γ-dimethyl allyl alcohol **56** by the reaction of **55** with 3-methyl-2-butenal under basic conditions. The mild hydrolysis of **56** removed the protecting group and was followed by dehydration and intramolecular electrocyclization, which led to **57**.[128] Reactions of benzopyranquinones **58** and **59** with several dienophiles[129] produced the pyran naphthoquinones **60**, **53** and **54** (Scheme 10).

Another protocol for preparing α- and β-pyranonaphthoquinones is the reaction of lawsone with Michael acceptors. The β-substituted ketone adducts can be reduced and cyclized to form the two pyran naphthoquinone isomers. The drawback of this



Scheme 9 Synthesis of α- and β-pyran naphthoquinones by tandem Knoevenagel and hetero Diels–Alder reactions.



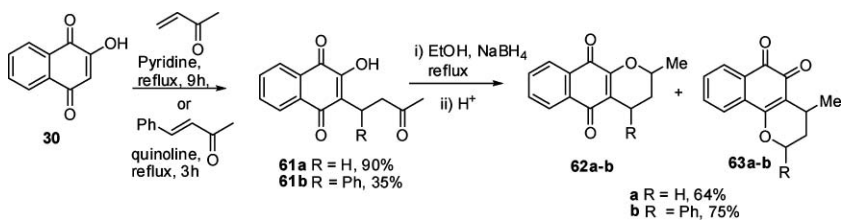
Scheme 10 Synthesis of pyran naphthoquinones by tandem Knoevenagel-electrocyclization.

protocol is that the Michael addition itself is very sensitive to steric hindrance at the β-carbon. For instance, the reaction of lawsone (**30**) with MVK works very well and adduct **61a** is obtained in 90%; however, the same reaction with benzalacetone forms adduct **61b** in only 35% yield (Scheme 11).

Final Remarks

Quinones constitute an important class of naturally occurring compounds found in many plants, fungi and bacteria. They possess reactivity as oxidants and electrophiles, reactivity that contributes to their activity in biological systems. Lapachol (**1**) and β-lapachone (**3**) are two quinones that, more than a century after their discovery, still attract the attention of the scientific community. There is still potential for additional synthetic and pharmacological studies involving the naphthoquinone β-lapachone (**3**) and its analogues and derivatives, as reviewed herein. The discovery of more active and selective novel derivatives remains an important issue to be studied. In this context, several research groups are interested in the development of potentially useful new compounds containing the naphthoquinone system. Today, the greatest interest in naphthoquinones involves their effects on inducing apoptosis related to tumor cells and their action against *T. cruzi*.

Actually, the most promising methodology with broader potential for obtaining structural diversity in pyran naphthoquinones is based on the reactive intermediate *o*-QM and its reaction with alkenes, along with other yet to be discovered reactions. However, to advances in this methodology it is essential to



Scheme 11 Synthesis of pyran naphthoquinones by reaction of lawsone with Michael acceptors.

develop asymmetric synthetic protocols for preparing chiral pyran naphthoquinones.

References

1 G. Bringmann, Y. Reichert and V. V. Kane, *Tetrahedron*, 2004, **60**, 3539–3574; M. Hassani, W. Cai, D. C. Holley, J. P. Lineswala, B. R. Maharjan, G. R. Ebrahimian, H. Seradj, M. G. Stocksdale, F. Mohammadi, C. C. Marvin, J. Gerdes, H. D. Beall and M. Behforouz, *J. Med. Chem.*, 2005, **48**, 7733–7749; J. H. Lee, J. H. Cheong, Y. M. Park and Y. H. Choi, *Pharmacol. Res.*, 2005, **51**, 553–560; E. B. Skibo and C. Xing, *J. Med. Chem.*, 2001, **44**, 3545–3562.
2 H. Hussain, K. Krohn, V. U. Ahmad, G. A. Miana and I. R. Greend, *Arkivoc*, 2007, **Part II**, 145–171.
3 M. Fedoryshyn, M. Nur-E-Alam, L. Zhu, A. Luzhetskyy, J. Rohr and A. Bechthold, *J. Biotechnol.*, 2007, **130**, 32–38.
4 K. C. Liu, J. Li and S. Sakya,, *Mini Rev. Med. Chem.*, 2004, **4**, 1105–1125.
5 C. Asche, *Mini-Rev. Med. Chem.*, 2005, **5**, 449–467.
6 A. F. Santos, P. A. L. Ferraz, A. V. Pinto, M. C. F. R. Pinto, M. O. F. Goulart and A. E. G. Sant'Ana, *Int. J. Parasitol.*, 2000, **30**, 1199–1202.
7 T. P. Barbosa, C. A. Camara, T. M. S. Silva, R. M. Martins, A. C. Pinto and M. D. Vargas, *Bioorg. Med. Chem.*, 2005, **13**, 6464–6469.
8 M. J. Teixeira, Y. M. Almeida, J. R. Viana, J. G. Holanda Filha, T. P. Rodrigues, J. R. C. Jr. Prata, I. C. B. Coelho, V. S. Rao and M. M. L. Pompeu, *Phytother. Res.*, 2001, **15**, 44–48.
9 E. R. Almeida, *J. Ethnopharmacol.*, 1990, **29**, 239–241.
10 S. Gafner, J. L. Wolfender, M. Nianga, H. Stoeckli-Evans and K. Hostettmann, *Phytochemistry*, 1996, **42**, 1315–1320.
11 C. N. Pinto, A. P. Dantas, K. C. G. de Moura, F. S. Emery, P. F. Polequevitch, M. C. F. R. Pinto, S. L. de Castro and A. V. Pinto, *Arzneim Forsc.(Drug Res.*, 2000, **50**, 1120–1128.
12 K C. G. F. de Moura, S. Emery, C. Neves-Pinto, M. C. F. R. Pinto, A. P. Dantas, K. Salomão, S. L. de Castro and A. P. Pinto, *J. Braz. Chem. Soc.*, 2001, **12**.
13 T. J. Monks and D. C. Jones, *Curr. Drug Metab.*, 2002, **3**, 425–438.
14 E. V. M. Santos, J. W. M. Carneiro and V. F. Ferreira, *Bioorg. Med. Chem.*, 2004, **12**, 87–93.
15 A. Brunmark and E. Cadenas, *Free Radical Biol. Med.*, 1989, **7**, 435–477.
16 T. J. Monks, R. P. Hanslik, G. M. Cohen, D. Ross and D. G. Graham, *Toxicol. Appl. Pharmacol.*, 1992, **112**, 2–16.
17 J. L. Bolton, M. A. Trush, T. M. Penning, G. Dryhurst and T. J. Monks, *Chem. Res. Toxicol.*, 2000, **13**, 135–160.
18 A. B. Pardee, Y. Z. Li and C. J. Li, *Curr. Cancer Drug Targets*, 2002, **2**, 227–242.
19 S. G. C. Fonseca, R. M. C. Braga and D. P. Santana, *Rev. Bras. Farm.*, 2003, **84**, 9–16.
20 J. R. G. Castellanos, J. M. Prieto and M. Heinrich, *J. Ethnopharmacol.*, 2009, **121**, 1–13.
21 M. N. da Silva, V. F. Ferreira and M. C. B. V. de Souza, *Quim. Nova*, 2003, **26**, 407–416.
22 R. D. Gibbs, *Chemotaxonomy of Flowering Plants*, University Press: Montreal 1974.
23 V. F. Ferreira, *Quim. Nova na Escola*, 1996, 35–37.
24 O. G. Lima, I. L. D'Albuquerque, M. P. Machado, E. Silva and G. P. Pinto, *Separata dos Anais da Sociedade de Biologia de Pernambuco*, 1956, **14**, 129–135.
25 O. G. de Lima and E. Weigert, *Rev. Ints. Antibiot.*, 1972, **12**, 3–12.
26 J. Breger, B. B. Fuchs, G. Aperis, T. I. Moy, F. M. Ausube and E. Mylonakis, *PLoS Pathog.*, 2007, **3**, e18–178.
27 C. F. Santana, O. G. Lima, I. L. D'Albuquerque, A. L. Lacerda and D. G. Martins, *Rev. Inst. Antibiot.*, 1968, **8**, 89–94.
28 K. V. Rao, T. J. Mcbride and J. J. Oleson, *Cancer Res.*, 1968, **28**, 19521954.
29 M. C. F. Linardi, M. M. de Oliveira and R. P. Sampaio, *J. Med. Chem.*, 1975, **18**, 1159–1161.
30 I. T. Balassiano and S. A. Paulo, *Oncol. Rep.*, 2005, **13**, 329–233.
31 M. Maeda, M. Murakami, T. Takegami and T. Ota, *Toxicol. Appl. Pharmacol.*, 2008, **229**, 232–238.
32 A. Esteves-Souza, D. V. Figueiredo, A. Esteves, C. A. Câmara, M. D. Vargas, A. C. Pinto and A. Echevarria, *Braz. J. Med. Biol. Res.*, 2007, **40**.
33 R. M. Khan and S. M. Mlungwana, *Phytochemistry*, 1999, **50**, 439–442.
34 K. Muller, A. Sellmer and W. Wiegrebe, *J. Nat. Prod.*, 1999, **62**, 1134–1136.
35 A. F. Santos, P. A. L. Ferraz, F. C. de Abreu, E. Chiari, M. O. F. Goulart and A. E. Sant'Ana, *Planta Med.*, 2001, **67**, 92–93.
36 K. O. Eyong, P. S. Kumar, V. Kuete, G. N. Folefoc, E. A. Nkengfack and S. Baskaran, *Bioorg. Med. Chem. Lett.*, 2008, **18**, 5387–5390.
37 E. R. Almeida, A. A. Silva-Filho, E. R. Santos and C. A. C. Lopes, *J. Ethnopharmacol.*, 1990, **29**, 239–241.
38 A. A. M. Lira, E. A. Sester, A. L. M. Carvalho, R. R. Strattmann, M. M. Albuquerque, A. G. Wanderley and D. P. Santana, *AAPS PharmSciTech*, 2008, **9**, 163–168.
39 M. J. Teixeira, Y. M. de Almeida, J. R. Viana, J. G. Holanda-Filha, T. P. Rodrigues, J. R. Prata-Jr., I. C. Coêlho, V. S. Rao and M. M. Pompeu, *Phytother. Res.*, 2001, **15**, 44–48.
40 F. G. Austin, *Am. J. Trop. Med. Hyg.*, 1974, **23**, 412–419.
41 M. Cortes, J. Katalinic and J. Valderrama, *An. Quim.*, 1983, **79**, 202–205.
42 M. A. A. de Souza, A. R. da Silva, M. A. Ferreira, M. J. de Lemos, R. G. Ramos, A. B. B. Ferreira and S. R. de Souza, *Quim. Nova*, 2008, **31**, 1670–1671.
43 G. Corrêa, R. Vilela, R. F. S. Menna-Barreto, V. Midle and M. Benchimol, *Parasitol. Int.*, 2009, **58**, 424–437.
44 N. M. F. Lima, C. S. Correia, L. L. Leon, G. M. C. Machado, M. F. Madeira, A. E. G. Santana and M. O. F. Goulart, *Int. Oswaldo Cruz.*, 2004, **99**, 757–761.
45 E. P. Sacau, A. Estévez-Braun, A. G. Ravelo, E. A. F. Ferro, T. Harunkuni and N. Hoyoku, *Bioorg. Med. Chem.*, 2003, **11**, 483–488.
46 M. F. Oliveira, L. T. L. G. Mattos and C. Marcos, *An. Acad. Bras. Ciênc.*, 2002, **74**, 211–221.
47 M. O. F. Goulart, C. L. Zani, J. Tonholo, L. R. Freitas, F. C. Abreu, A. B. Oliveira, D. S. Raslan, S. Starling and E. Chiari, *Bioorg. Med. Chem. Lett.*, 1997, **7**, 2043–2048.
48 C. Salas, R. A. Tapia, K. Ciudad, V. Armstrong, M. Orellana, U. Kemmerling, J. Ferreira, J. D. Maya and A. Morello, *Bioorg. Med. Chem.*, 2008, **16**, 668–674.
49 A. V. Pinto and S. L. Castro, *Molecules*, 2009, **14**, 4570–4590.
50 R. J. Weaver, M. Dickins and M. D. Burke, *Biochem. Pharmacol.*, 1993, **46**, 1183–1197.
51 Y. Kumagai, Y. Tsurutani, M. Shinyashiki, S. H. Takeda, Y. Nakai, T. Yoskikawa and N. Shimojo, *Environ. Toxicol. Pharmacol.*, 1997, **3**, 245–250.
52 M. M. P. Portela, S. H. F. Villamil, L. J. Perissinotti and A. O. Stoppani, *Biochem. Pharmacol.*, 1996, **52**, 1875–1882.
53 P. A. L. Ferraz, F. C. de Abreu, A. V. Pinto, V. Glezer, J. Tonholo and M. O. F. Goulart, *J. Electroanal. Chem.*, 2001, **507**, 275–286.
54 C. J. Canfield, M. Pudney and W. E. Gutteridge, *Exp. Parasitol.*, 1995, **80**, 373–381.
55 M. Fry and M. Pudney, *Biochem. Pharmacol.*, 1992, **43**, 1545–1553.
56 I. K. Srivastava and A. B. Vaidya, *Antimicrob. Agents Chemother.*, 1999, **43**, 1334–1339.
57 W. T. Hughes, V. L. Gray, W. E. Gutteridge, V. S. Latter and M. Pudney, *Antimicrob. Agents Chemother.*, 1990, **34**, 225–228.
58 R. Docampo, F. S. Cruz, A. Boveris, R. P. Muniz and D. M. Esquivel, *Arch. Biochem. Biophys.*, 1978, **186**, 292–297.
59 F. S. Cruz, R. Docampo and A. Boveris, *Antimicrob. Agents Chemoter.*, 1978, **14**, 630–633.
60 A. Boveris, R. Docampo, J. F. Turrens and A. O. Stoppani, *Biochem. J.*, 1978, **75**, 431–439.
61 S. G. Goijman and A. O. Stoppani, *Arch. Biochem. Biophys.*, 1985, **240**, 273–280.
62 M. Dubin, S. H. F. Villamil and A. O. Stoppani, *Medicina (B Aires)*, 2001, **61**, 343–350.
63 K. C. G. de Moura, K. Salomão, R. F. S. Menna-Barreto, F. S. Emery, M. C. F. R. Pinto, A. V. Pinto and S. L. Castro, *Eur. J. Med. Chem.*, 2004, **39**, 639–645.
64 J. A. Castro, M. M. de Mecca and L. C. Bartel, *Hum. Exp. Toxicol.*, 2006, **25**, 471–479.
65 J. N. Lopes, F. S. Cruz, R. Docampo, M. E. Vasconcellos, M. C. R. Sampaio, A. V. Pinto and B. Gilbert, *Ann. Trop. Med. Parasitol.*, 1978, **72**, 523–531.
66 A. V. Pinto, V. F. Ferreira, R. S. Capella, B. Gilbert, M. C. F. R. Pinto and J. S. Silva, *Trans. R. Soc. Trop. Med. Hyg.*, 1987, **81**, 609–610.

67 A. M. Gonçalves, M. E. Vasconcellos, R. Docampo, F. S. Cruz, W. De Souza and W. Leon, *Mol. Biochem. Parasitol.*, 1980, **1**, 167–176.
68 M. Dubin, S. H. F. Villamil and A. O. Stoppani, *Biochem. Pharmacol.*, 1990, **39**, 1151–1160.
69 N. V. de Witte, A. O. Stoppani and M. Dubin, *Arch. Biochem. Biophys.*, 2004, **432**, 129–135.
70 A. R. Schuerch and W. Wehrli, *Eur. J. Biochem.*, 1978, **84**, 197–205.
71 R. J. Boorstein and A. Pardee, *Biochem. Biophys. Res. Commun.*, 1984, **118**, 828–834.
72 C. J. Li, L. J. Zhang, B. J. Dezuhe, C. S. Crumpacker and A. B. Pardee, *Proc. Natl. Acad. Sci. U. S. A.*, 1993, **90**, 1839–1842.
73 C. J. Li, A. L. Zhang and A. B. Pardee, *J. Biol. Chem.*, 1993, **268**, 22463–22468.
74 E. N. da Silva-Jr, M. C. B. V. de Souza, A. V. Pinto, M. C. F. R. Pinto, M. O. F. Goulart, C. Pessoa, L. Costa-Lotufo, R. C. Montenegro, M. O. Moraes and V. F. Ferreira, *Bioorg. Med. Chem.*, 2007, **15**, 7035–7041.
75 S. M. Planchon, S. Wuerzberger, B. Frydman, D. T. Witiak, P. Hutson, D. R. Church, G. Wilding and D. A. Boothman, *Cancer Res.*, 1996, **55**, 3706–3711.
76 C. L. Li, C. Wang and A. B. Pardee, *Cancer Res.*, 1995, **55**, 3712–3715.
77 M. Weller, S. Winter, C. Schmidt, P. Esser, A. Fontana, J. Dichgans and P. Groscurth, *Int. J. Cancer*, 1997, **73**, 707–714.
78 C. C. Lai, T. J. Liu, L. K. Ho, M. J. Don and Y. P. Chau, *Histol. Histopathol.*, 1998, **13**, 89–97.
79 H. J. Woo, K. Y. Park, C. H. Rhu, W. H. Lee, B. T. Choi, G. Y. Kim, Y. M. Park and Y. H. Choi, *J. Med. Food*, 2006, **9**, 161–168.
80 S. M. Wuerzberger, J. J. Pink, S. M. Planchon, K. L. Byers, W. G. Bornmann and D. A. Boothman, *Cancer Res*, 1998, **58**, 1876–1885.
81 E. A. Bey, M. S. Bentle, K. E. Reinicke, Y. Dong, C. R. Yang, L. Girard, J. D. Minna, W. G. Bornmann, J. Gao and D. A. Boothman, *Proc. Natl. Acad. Sci. U. S. A.*, 2007, **104**, 11832–11837.
82 Y. Li, C. J. Li, D. Yu and A. B. Pardee, *Mol. Med.*, 2000, **6**, 1008–1015.
83 C. J. Li, Y. Z. Li, A. V. Pinto and A. B. Pardee, *Proc. Natl. Acad. Sci. U. S. A.*, 1999, **96**, 13369–13374.
84 G. Augello, A. Santulli, M. Giuliano, R. Di Fiore, C. Messina, G. Tesoriere and R. Vento, *J. Cell. Physiol.*, 2010, **222**, 433–443.
85 D. A. Boothman, S. Greer and A. B. Pardee, *Cancer Res.*, 1987, **47**, 5361–5366.
86 D. A. Boothman, D. K. Trask and A. B. Pardee, *Cancer Res.*, 1989, **49**, 605–612.
87 H. J. Park, K. J. Ahn, S. D. Ahn, E. Choi, S. W. Lee, B. Williams, E. J. Kim, R. Griffin, E. A. Bey, W. G. Bornmann, J. Gao, D. A. Boothman and C. W. Song, *Int. J. Radiat. Oncol. Biol. Phys.*, 2005, **61**, 212–219.
88 E. K. Choi, K. Terai, I. M. Ji, Y. H. Kook, K. H. Park, E. T. Oh, R. J. Griffin, B. U. Lim, J. S. Kim, D. S. Lee, D. A. Boothman, M. Loren, C. W. Song and H. J. Park, *Neoplasia*, 2007, **9**, 634–642.
89 S. Y. Jeong, S. J. Park, S. M. Yoon, J. Jung, H. N. Woo, S. L. Yi, S. Y. Song, H. J. Park, C. Kim, J. S. Lee, J. S. Lee and E. K. Choi, *J. Controlled Release*, 2009, **139**, 239–245.
90 Q. Zhang, Y. Peng, X. I. Wang, S. M. Keenan, S. Arora and W. J. Welsh, *J. Med. Chem.*, 2007, **50**, 749–754.
91 J. J. Pink, S. M. Planchon, C. Tagliarino, M. E. Varnes, D. Siegel and D. A. Boothman, *J. Biol. Chem.*, 2000, **275**, 5416–5424.
92 J. J. Pink, S. Wuerzberger-Davis, C. Tagliarino, S. M. Planchon, X. H. Yang, C. J. Froelich and D. A. Boothman, *Exp. Cell Res.*, 2000, **255**, 144–155.
93 S. M. Planchon, J. J. Pink, C. Tagliarino, W. G. Bornmann, M. E. Varnes and D. A. Boothman, *Exp. Cell Res.*, 2001, **267**, 95–106.
94 Y. Li, X. Sun, J. T. LaMont, A. B. Pardee and C. J. Li, *Proc. Natl. Acad. Sci. U. S. A.*, 2003, **100**, 2674–2678.
95 M. A. F. Brandão, A. B. Oliveira and V. Snieckus, *Tetrahedron Lett.*, 1993, **34**, 2437–2440.
96 M. N. Silva, M. C. B. V. de Souza, V. F. Ferreira, A. V. Pinto, M. C. R. F. Goulart, S. M. V. Wardell and J. L. Wardell, *Arkivoc*, 2003, **Part X**, 156–168.
97 P. H. di Chenna, V. B. Doctorovich, R. F. Baggio, M. T. Garland and G. Burton, *J. Med. Chem.*, 2001, **44**, 2486–2489.
98 D. N. Nicolaides, D. R. Gautam, K. E. Litinas, D. J. Hadjipavlou-Litina and C. A. Kontogiorgis, *J. Heterocycl. Chem.*, 2004, **41**, 605–611.
99 C. E. M. Carvalho, V. F. Ferreira, A. V. Pinto, M. C. F. R. Pinto and W. Harrison, *Dyes Pigm.*, 2002, **52**, 209–214.
100 S. G. Renou, S. E. Asis, M. I. Abasolo, D. G. Bekerman and A. M. Bruno, *Pharmazie*, 2003, **58**, 690–695.
101 V. F. Ferreira, A. Jorqueira, K. Z. Leal, H. R. X. Pimentel, P. R. Seidl, M. N. da Silva, M. C. B. V. de Souza, A. V. Pinto, J. L. Wardell and S. M. S. V. Wardell, *Magn. Reson. Chem.*, 2006, **44**, 481–490.
102 A. Jorqueira, R. M. Gouvêa, V. F. Ferreira, M. N. da Silva, M. C. de Souza, A. A. Zuma, D. F. Cavalcanti, H. P. Araujo, D. O. Santos and S. C. Bourguignon, *Parasitol. Res.*, 2006, **99**, 429–433.
103 V. F. Ferreira, A. Jorqueira, A. M. T. Souza, M. N. da Silva, M. C. B. V. de Souza, R. M. Gouvêa, C. R. Rodrigues, A. V. Pinto, H. C. Castro, D. O. Santos, H. P. Araújo and S. C. Bourguignon, *Bioorg. Med. Chem.*, 2006, **14**, 5459–5466.
104 S. C. Bourguignon, H. C. Castro, D. O. Santos, C. R. Alves, V. F. Ferreira, I. L. Gama, F. C. da Silva, W. S. Seguis and R. T. Pinho, *Exp. Parasitol.*, 2009, **122**, 91–96.
105 S. B. Ferreira, F. C. da Silva, A. C. Pinto, D. T. G. Gonzaga and V. F. Ferreira, *J. Heterocycl. Chem.*, 2009, **46**, 1080–1097.
106 M. N. da Silva, S. B. Ferreira, A. Jorqueira, M. C. B. V. de Souza, A. V. Pinto, C. R. Kaiser and V. F. Ferreira, *Tetrahedron Lett.*, 2007, **48**, 6171–6173.
107 J. P. Chaves, M. C. F. R. Pinto and A. V. Pinto, *J. Braz. Chem. Soc.*, 1980, **1**, 22–30.
108 A. V. Pinto, C. N. Pinto, C. F. R. Pinto, R. S. Rita, C. A. C. Pezzella and S. L. Castro, *Arzneim Forsch(Drug Res*, 1997, **47**, 74–79.
109 F. S. Emery, R. S. F. Silva, K. C. G. de Moura, M. C. F. R. Pinto, M. B. Amorim, V. R. S. Malta, R. H. A. K. Santos, M. Honório, A. B. F. da Silva and A. V. Pinto, *An. Acad. Bras. Cienc.*, 2007, **79**, 29–33.
110 R. F. S. Menna-Barreto, A. Henriques-Pons, A. V. Pinto, J. A. Morgado-Diaz, M. J. Soares and S. L. J. de Castro, *J. Antimicrob. Chemother.*, 2005, **56**, 1034–1041.
111 R. S. F. Silva, M. B. de Amorim, M. C. F. R. Pinto, F. S. Emery, M. O. F. Goulart and A. V. Pinto, *J. Braz. Chem. Soc.*, 2007, **18**, 759–764.
112 V. F. de Andrade-Neto, M. O. F. Goulart, J. F. da Silva Filho, M. J. da Silva, M. C. F. R. Pinto, A. V. Pinto, M. G. Zalis, L. H. Carvalho and A. U. Krettli, *Bioorg. Med. Chem. Lett.*, 2004, **14**, 1145–1149.
113 P. Singh, A. Dandia, K. Natani, V. Sharma, R. Ratnani, A. L. Bingham, M. B. Hursthouse and M. E. Light, *Synth. Commun.*, 2007, **37**, 113–118.
114 E. Pérez-Sacau, A. Estévez-Braum, A. G. Ravelo, D. G. Yapu and A. G. Turba, *Chem. Biodiversity*, 2005, **2**, 264–274.
115 E. Pérez-Sacau, R. G. Díaz-Peñate, A. Estévez-Braun, A. G. Ravelo, J. M. García-Castellano, L. Pardo and M. Campillo, *J. Med. Chem.*, 2007, **50**, 696–706.
116 F. C. da Silva, A. Jorqueira, R. M. Gouvêa, M. C. B. V. de Souza, R. A. Howie, J. L. Wardell, S. M. S. V. Wardell and V. F. Ferreira, *Synlett*, 2007, 3123–3126.
117 V. F. Ferreira, A. V. Pinto and L. C. M. Coutada, *An. Acad. Bras. Cienc.*, 1980, **52**, 477–479.
118 V. F. Ferreira, A. V. Pinto and L. C. M. Coutada, *Synth. Commun.*, 1982, **12**, 195–199.
119 A. B. de Oliveira, D. T. Ferreira and D. S. Raslan, *Tetrahedron Lett.*, 1988, **29**, 155–158.
120 Y. R. Lee and W. K. Lee, *Synth. Commun.*, 2004, **34**, 4537–4543.
121 G. B. C. Alves, R. S. C. Lopes, C. C. Lopes and V. Snieckus, *Synthesis*, 1999, 1875–1877.
122 S. Jiménez-Alonso, H. C. Orellana, A. Estévez-Braun, A. G. Ravelo, E. Pérez-Sacau and F. Machín, *J. Med. Chem.*, 2008, **51**, 6761–6772.
123 V. Nair and P. M. Treesa, *Tetrahedron Lett.*, 2001, **42**, 4549–4551.
124 S. B. Ferreira, C. R. Kaiser and V. F. Ferreira, *Org. Prep. Proced. Int.*, 2009, **41**, 211–215.
125 F. Zuloaga, R. Tapia and C. Quintanar, *J. Chem. Soc., Perkin Trans. 2*, 1995, 939–943.
126 R. A. Tapia, J. A. Valderrama and C. Quintanar, *Heterocycles*, 1994, **38**, 1797–1804.
127 R. A. Tapia, L. Alegria, J. A. Valderrama, M. Cortés, F. Pautet and H. Fillion, *Tetrahedron Lett.*, 2001, **42**, 887–889.
128 R. A. Tapia, C. Lizama, C. López and J. A. Valderrama, *Synth. Commun.*, 2001, **31**, 601–606.
129 R. A. Tapia, C. Salas, A. Morello, J. D. Maya and A. Toro-Labbeé, *Bioorg. Med. Chem.*, 2004, **12**, 2451–2458.

