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Research Article

# Lignans: Insight to Chemistry and Pharmacological Applications-An Overview

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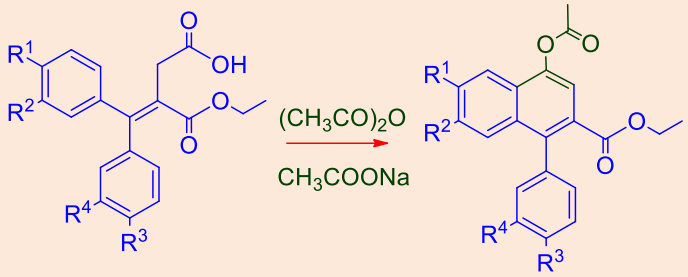
**Abstract**

Lignans are widely distributed in the plant kingdom and have been found in species belonging to more than seventy families. These are found in several foods, mostly in seeds, beans and berries. Sesame seed lignans are perhaps best known for their positive health effects as antioxidants. In recent times, lignans attracted much interest in the researchers due to their wide range of biological applications and their utility as useful synthons. This review describes up to date developments in the lignan chemistry, with a more emphasis on their natural sources, methods developed for synthetic analogues and critical discussion on biological activities.

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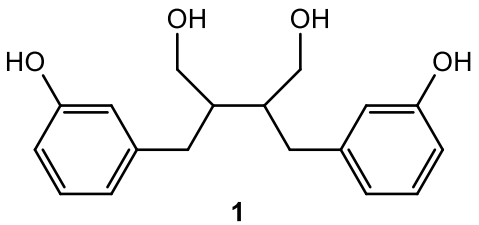
## Introduction

The lignans are a group of secondary metabolites found in plants, which are produced by oxidative dimerization of two phenylpropanoid units and show bioactive diversity as their chemical assembly. The range of their structures and biological activities is broad. Various lignans are known to have anti-tumour, antimitotic and antiviral activity and to specifically inhibit certain enzymes [1]. Novel lignans continue to be described by natural products chemists at a steady rate and knowledge of their variety, as well as their range of occurrence in the plant kingdom, is continually expanding [2]. Many natural products, known as phenylpropanoids, are built up of a propylbenzene skeleton derived from cinnamyl units. When a part of the human diet, some plant lignans are metabolized by intestinal bacteria to mammalian lignans such as enterodiol (**1**) and enterolactone (**2**).

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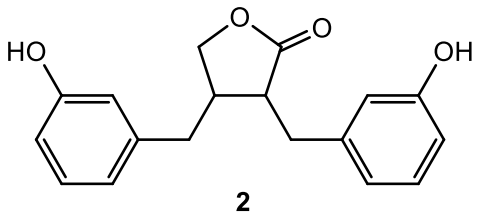
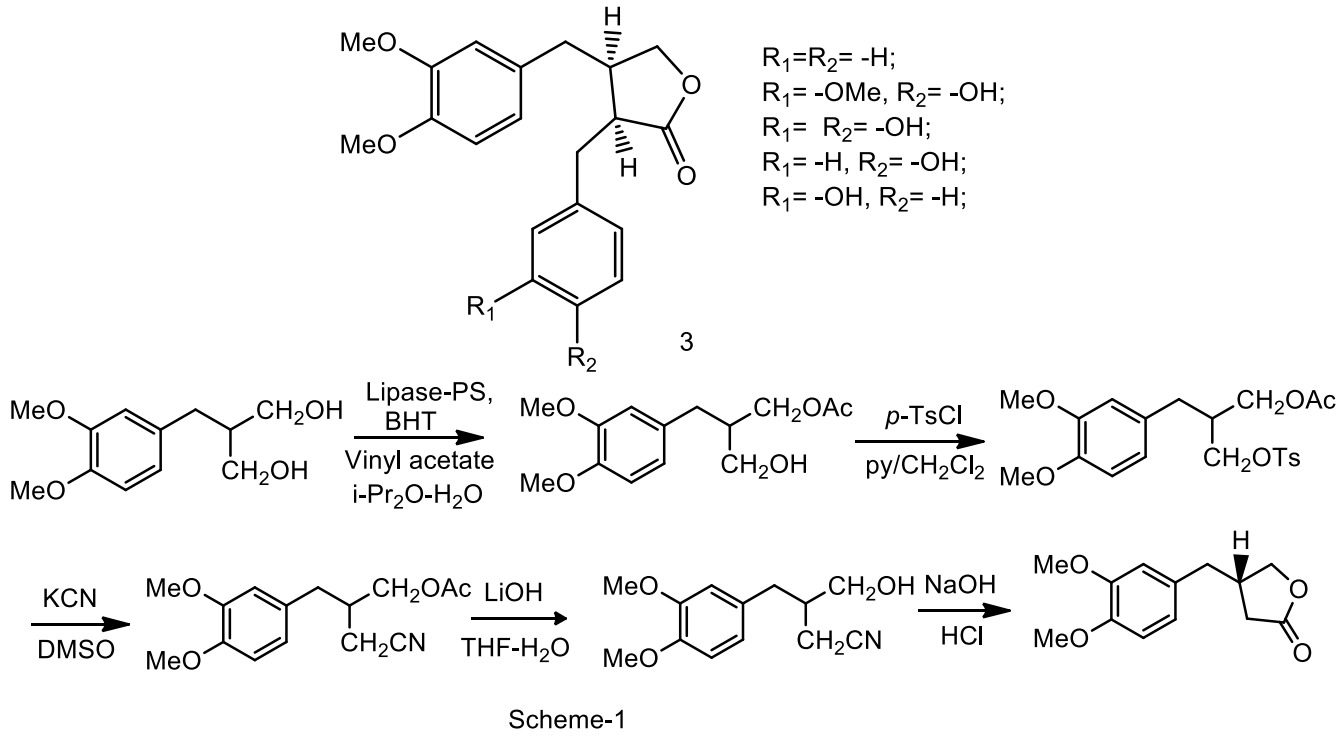



**2**

Lignans probably participate in plant development, and also play an important role in plant defense against various biological pathogens and pests. In addition, lignans also possess significant pharmacological activities, including antitumor, anti-inflammatory, immunosuppressive, cardiovascular, antioxidant and antiviral actions. From a chemical point of view, lignans show an enormous structural diversity, although their molecular backbone consists only of two phenylpropane units. Different families of lignans include the aryltetrahydronaphthalenes, podophyllotoxin, the diverse family of dibenzocyclooctadienes, the dibenzylbutanediol lignans [3-5].

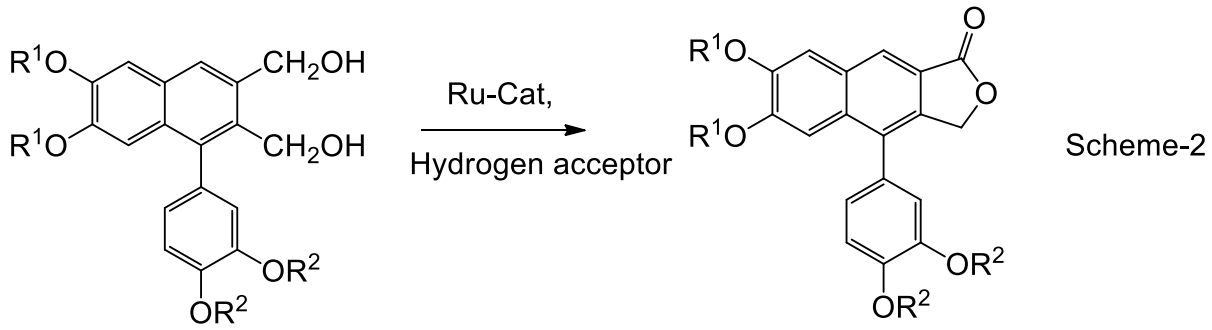
## Synthetic strategies of lignans

Lignans of the podophyllotoxin and dibenzylbutyrolactone series have received considerable interest because of their wide range of biological activities, including activity as antitumor and antiviral agents function as platelet-aetivating-factor (PAF) antagonists and use in folk medicine. Five optically active dibenzylbutyrolactone lignans (**3**) were synthesized through a lipase-catalyzed transesterification of the prochiral diol (**Scheme 1**) [6]. This route leads to high yields of the dibenzylbutyrolactone lignan analogues in absolute enantiomeric optical purity. The synthesized compounds were evaluated for their inhibitory activity against HIV- 1 replication in acutely infected H9 cells. The known natural dibenzylbutyrolactone lignan (-)-arctigenin was used as a template for the structural modifications on the benzyl moiety at position C-8.



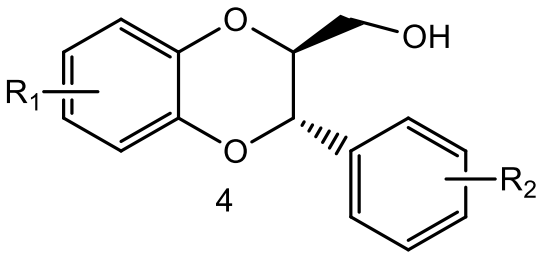

Scheme-1

An efficient route to the synthesis of dibenzylbutanediol lignans was reported, which involves a Stobbe condensation and alkylation reaction followed by the resolution of (±)-diacid with quinine, then the transformation of functional groups to dibenzylbutanediol lignans. The dibenzylbutanediol lignans synthesized were evaluated on HIV Tat *trans* activation in human epithelial cells, HSV-1 gene and human leukemic, liver, prostate, stomach, and breast cancer cell *in vitro* [7]. Ruthenium catalyzed hydrogenation of cyclic anhydrides and dehydrogenation of diols have been successfully applied to the highly regioselective synthesis of arylnaphthalene lignans (**Scheme 2**) [8]. Ruthenium catalyzed hydrogenation of a cyclic anhydride and dehydrogenation of a diol are among promising synthetic methods of lactones.



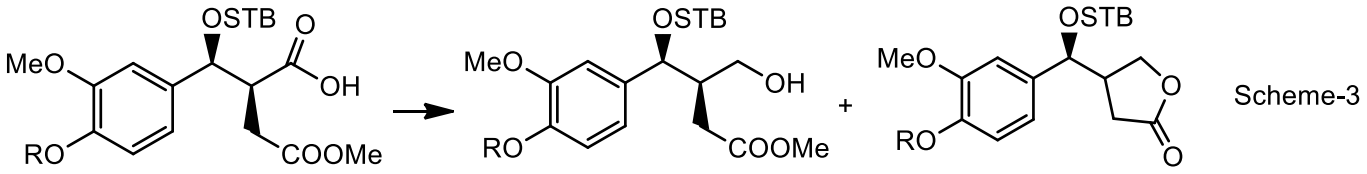

Scheme-2

An asymmetric and regioselective total synthesis approach to 1,4-benzodioxane lignans (**4**) was reported. The report says that (2R, 3R)- and (2S, 3S)-3-(4-hydroxy-3-methoxyphenyl)-2-hydroxymethyl-1,4-benzodioxan-6-carbaldehyde lignans and a natural 1,4-benzodioxane neolignan was synthesized firstly by the synthesis approach [9].



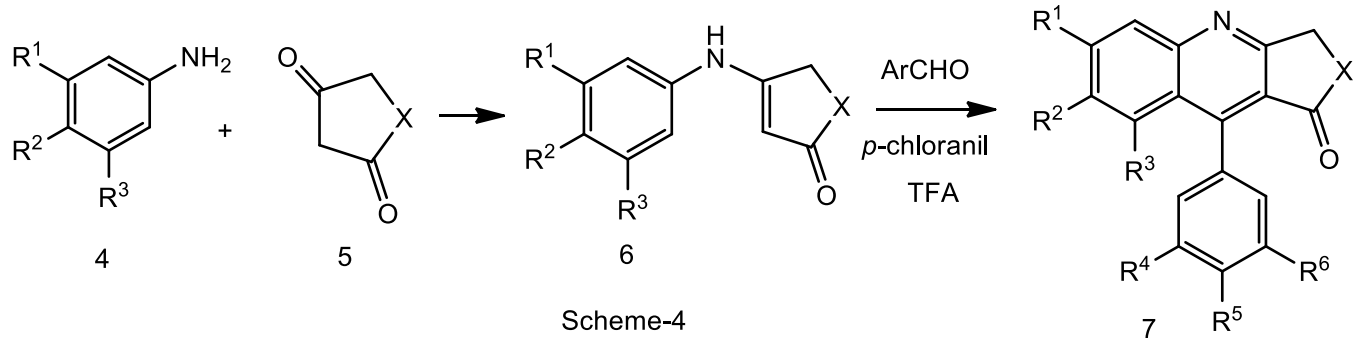

4

A competent and general asymmetric synthesis of 7'-hydroxydibenzylbutyrolactone lignans such as (7'S)-hydroxymatairesinol and (7'S)-hydroxyarctigenin has achieved from N-succinyl-2-oxazolidinone in six steps (**Scheme 3**), where diastereoselective aldol reaction and stereoselective alkylation serve as the key steps [10].




Scheme-3

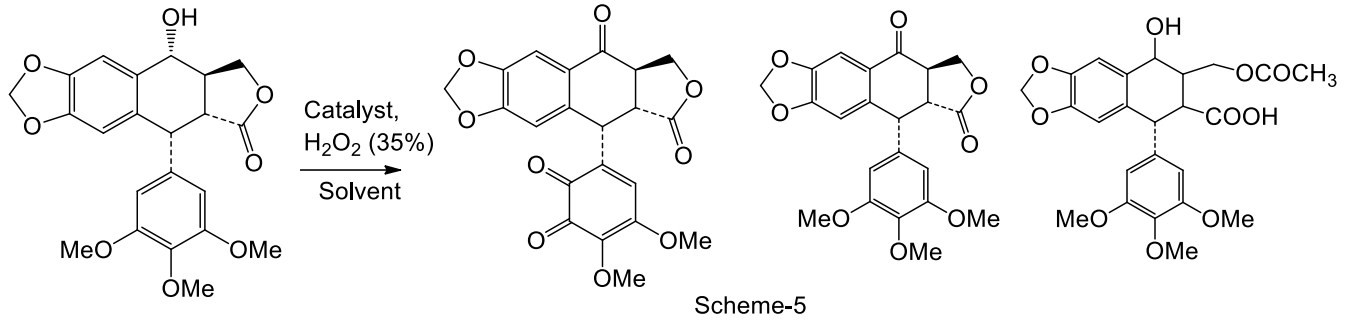
Methyl α-piperonylhemisuccinate was resolved into both its (R)-(+) and (S)-(-)-antipodes by (-) and (+)-ephedrine, respectively. Calcium borohydride reduction of the (R)-( +) and (S)-(-)-hemiesters afforded the crystalline, optically pure, (R)-(+) and (S)- (-)-β-piperonyl-γ-butyrolactones, respectively, and in high yields. The latter were converted into (-) and (t)-isodeoxypodophyllotoxin respectively [11]. Reaction of anilines (**4**) with tetronic acid (**5,** X=O) or 1,3-cyclopentanedione (**5,** X=$CH_2$) (3) produced anilinolactones (**6,** X=O) and anilinocyclopentenone (**6,** X=$CH_2$), respectively, which were then condensed with benzaldehydes to yield 4-aza-l-arylnaphthalene lignan analogs (**7**) (**Scheme 4**) [12].




4 5 6 7

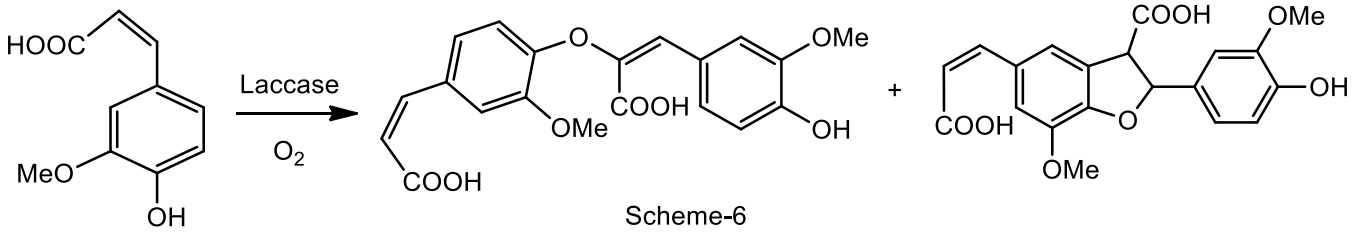
Scheme-4

A recent review describes the different strategies for the racemic or enantiospecific total syntheses of plant and mammalian 3,4-dibenzyltetrahydrofuran lignans. The multi-step approaches have various key step strategies: Diels–Alder reactions, Stobbe condensations, Michael additions, alkylations, nitrile oxide cycloadditions, radical cyclisations, dianion and oxidative couplings [13]. Raffaele *et al* [14] reported the novel and efficient procedure for the preparation of highly oxidised aryltetralin lignans, such as isopodophyllotoxone and (-)-aristologone derivatives, by oxidation of podophyllotoxin and galbulin with methylrhenium trioxide (MTO) and novel MTO heterogeneous catalysts (**Scheme 5**). It is noteworthy that in the case of isopodophyllotoxone derivatives the functionalisation of the C-4 position of the C-ring and the ring-opening of the D-lactone moiety increased the activity against topoisomerase II while causing the undesired inhibition of tubulin polymerisation to disappear. The novel (-)-aristologone derivatives showed apoptogenic activity against resistant human lymphoma cell lines.




Scheme-5

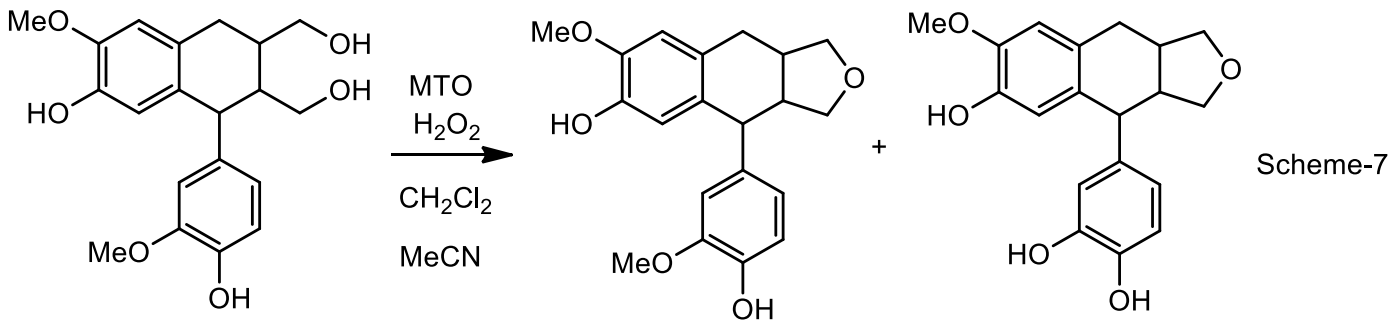
Sylvain and coworkers [15] reported the use of a biphasic reaction solvent during the laccase catalysed transformation of sinapinic and ferulic acids. Their reaction carried out in ethyl acetate as added non-miscible co-solvent was observed to be advantageous compared to buffer alone that resulted in higher product selectivity, higher yields and higher product stability. Reactions run in biphasic medium are marginally longer but offer an easy separation protocol allow getting the highest yield reported so far for the synthesis of the two bis-lactone lignans originating from sinapinic and ferulic acids (**Scheme 6**).




Scheme-6

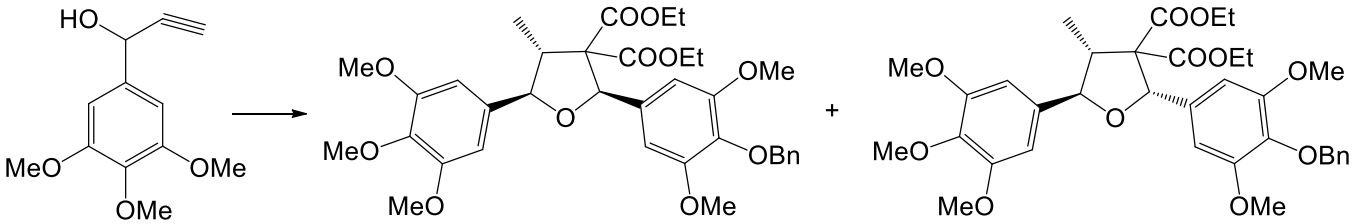
A series of 6-methoxy-2-methoxymethyl-3-(3,4-methylenedioxyphenyl)-l,4-benzodioxan-7-yl group of haedoxans analogs synthesized were evaluated for their insecticidal activity. The study revealed that 2-(2,6-Dimethoxyphenoxy)-l-hydroxy-6-(2-methoxy-5-methoxyethoxyphenyl)-3,7-dioxabicyclo-[3.3.0]octane, which lacked the 3-(3,4-methylenedioxybenzyloxy) moiety of the benzodioxanyl group, was not insecticidal, but caused prolonged paralysis of the housefly. It is evident that the 1,4-benzodioxane framework charging the 3-(3,4-methylene-dioxy)phenyl group is important for the insecticidal activity of haedoxans [16].

1-Arylnaphthalene lignans were synthesized in good yields from O-t-butyldimethylsilylcyanohydrins in two steps based on a new approach involving a tandem conjugate addition-aldol reaction, followed by an acid-catalyzed construction of the naphthalene ring [17]. Lignans are a large group of naturally occurring phenols widely spread within the plant kingdom that are derived from the shikimic acid biosynthetic pathway. Highly oxidized lignans produced during the cytochrome P-450 metabolism in the cells show biological activities significantly different from those of their parent natural compounds. Lignan precursors of mammalian enterolignans were treated with a methyltrioxorhenium/hydrogen peroxide catalytic system to afford new compounds oxidized at benzylic as well as in arylic positions (**Scheme 7**) [18]. The evaluation of the antioxidant and apoptogenic activity by in vivo protocols of these compounds showed some interesting structure–activity relationships related to the oxidation degree of the molecules.




Scheme-7

Ken-ichi *et al* [19] have synthesized a series of tetra-substituted 2,5-dihydrofuran lignans using a sequential Michael addition-carbocyclization with palladium as the catalyst (**Scheme 8**). The synthetic compounds were evaluated against trypomastigote forms of *Trypanossoma cruzi* and the higher activity for diastereoisomeric compounds could be correlated to the *trans* configuration of the aromatic rings.

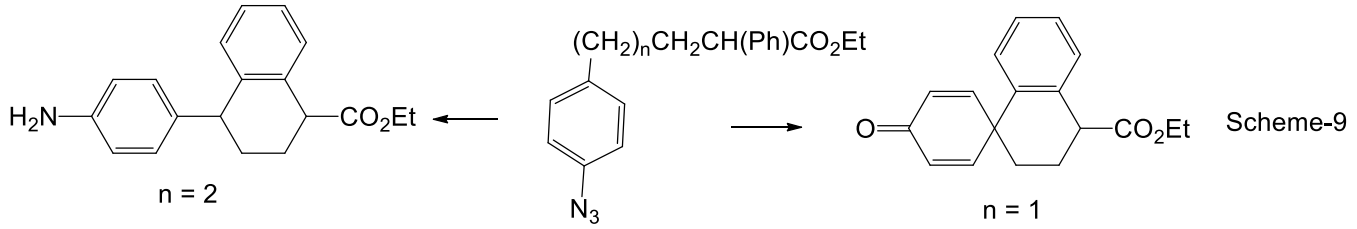



Scheme-8

Literature reveals that synthetic analogues of lignans containing sulphur bridges exhibit the anti-parasitic activity. Mônica *et al* [20] synthesized thiophene-based lignan analogues by using a selective and high performance synthetic strategy based on the Negishi cross-coupling reaction. Their report reveals that the synthesized compounds were quickly obtained and showed great purity, low toxicity toward a mammalian cell line, and leishmanicidal activity with different potencies.

An efficient synthesis of enantiomerically pure α-hydroxylated lactone lignans starting from commercially available diisopropyl malate was reported by Michael and coworkers [21]. The method involves the stereoselective alkylation with various benzyl bromides and saponification to produce the corresponding succinic acids. Acetalization afforded the dioxolanones, which were stereoselectively alkylated. The synthesized compounds were investigated for their inhibition of the proliferation of HT29 colon cancer cells.

Intramolecular cyclization via nitrenium ion of 2-phenylpentanoic/2-phenylbutanoic acid esters with a terminal *p*-azidophenyl group gives direct access to tetrahydronaphthalene lignan esters. The *p*-azidophenyl-substituted butanoate led to an ethyl spirodienone carboxylate, while its homologue pentanoate gave ethyl 4-(4-aminophenyl)-1,2,3,4-tetrahydronaphthalene-1-carboxylate in good yield (**Scheme 9**) [22]. In contrast, the *m*-azidophenyl-substituted esters suffered aromatic nucleophilic addition of trifluoromethanesulfonate. The synthesized compounds were evaluated for their capacity to inhibit *in vitro* growth of the cell lines MCF-7 (breast cancer), NCI-H460 (lung cancer), SF-268 (CNS cancer), and UACC-62 (melanoma).

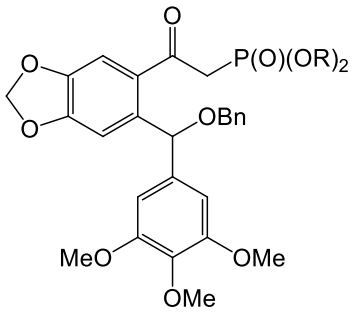



Scheme-9

Piero Frediani and coworkers [23] developed a general synthetic procedure for isotopomeric dihydro-2(3H)furanones (γ-butyrolactones) containing two, four, or six deuterium atoms. The labeled dihydro-2(3H)furanones were synthesized in quantitative yield from the succinic acid or fumaric, maleic, or acetylendicarboxylic acids in the presence of $Ru_4H_4(CO)_8(PBu_3)_4$ using a deuterium pressure of 180 bar at 180 ºC. The methodology was applied to the total synthesis of a hexadeuterated matairesinol lignan. The strategies concerned with developing general routes for the synthesis of lignans by two routes involving tandem conjugate addition reactions and Diels Alder reactions for the synthesis of podophyllotoxin derivatives, the asymmetric synthesis of lignans and involves the application of these reactions, with the introduction of a menthyloxy group as a chiral auxiliary, to achieve the asymmetric synthesis of podophyllotoxin derivatives was reviewed [24].

Cyclopropyl esters are found to be useful intermediates in the synthesis of several synthetic analogs of lignans. Ethyl cyanoacetate was proved to be an excellent reagent for transforming alkenes to esters of three membered cyclic systems; it was used effectively in the synthesis of cyclopropane derivatives [25-26], piperidone analogues [27-29] and pyrrolines [30] as useful intermediates for lignan synthesis. Koprowski and coworkers [31] investigated the

oxidation reaction of electron rich alkoxy substituted β-aryl β-hydroxyphosphonates to corresponding β-ketophosphonates (**8**, **9**, **10**), used in syntheses of lignans with various oxidizing agents such as PCC, PDC, CAN, $KMnO_4/SiO_2$, $KMnO_4/CuSO_4$, $MnO_2$, $CrO_3/SiO_2$, etc. was investigated. They have also studied the effect of oxidants and reaction conditions on the reaction efficiency and yield of the products.

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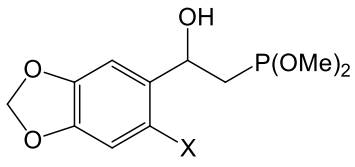


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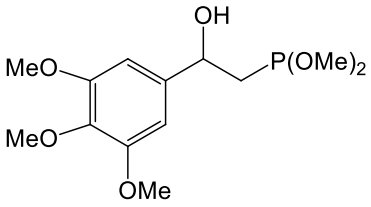
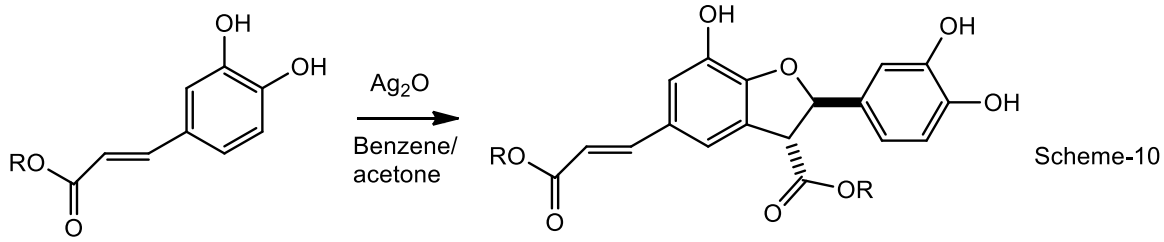


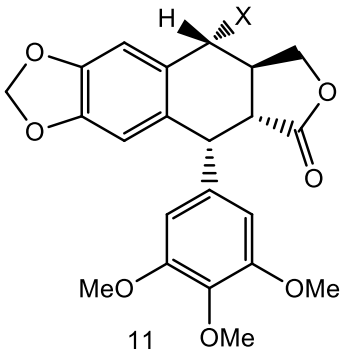

10

A series of synthetic dihydrobenzofuran lignans and related benzofurans synthesized by silver oxide mediated oxidation cinnamic acid esters (**Scheme 10**). The synthesized compounds were evaluated for their cytotoxicity in a screening panel consisting of various human tumour cell lines, and for their antiprotozoal activity against *L. donovani* (axenic amastigotes), chloroquine resistant *Plasmodium falciparum* (strain K1), *Trypanosoma brucei rhodesiense* and *T. cruzi*, and for cytotoxicity on L6 cells. No promising cytotoxicities against human tumour cell lines were observed for newly synthesized compounds [32].




Scheme-10

Diphenylamine was condensed with maleic anhydride in the presence of sodium hydride and dry benzene to produce 4-N,N-diphenyl amine-4-oxo-2-butenoic acid. Intramolecular cyclization of 4-N,N-diphenyl amine-4-oxo-2-butenoic acid with PPE afforded 1-phenyl-1H-benzo[*b*]azepine-2,5-dione. The compound 1-phenyl-1H-benzo[b]azepine-2,5-dione has shown considerable activity against *F. Solani* and *A. Flavus* fungal strains [33]. The l-aryl-2-methyl-tetrahydronaphthoic acid anhydride (**11**) reacts with stabilized phosphorus ylide exclusively at the carbonyl remote from the 1-aryl substituent [34]. These transformed products have been converted into a variety of compounds related in structure to deoxyisopicrophyllotoxin. Pelter and coworkers [35] reported the regiospecifc synthesis of 2,6-diaryl-3,7-dioxabicyclo-[3.3.0]octane lignans (**12**) for the first time. Their method involves the utilization of new four carbon synthon suitable for regiospecific and stepwise anion production resulting in unsymmetrically substituted (**12**).

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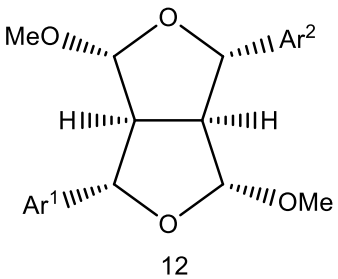
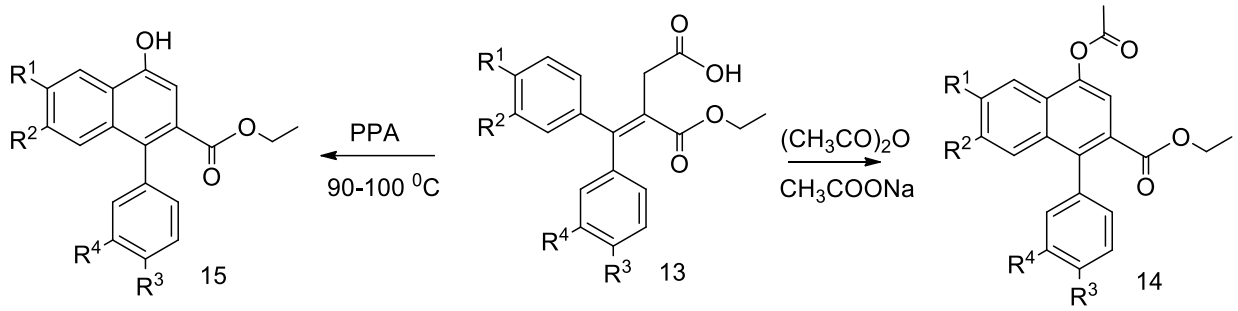



12

Methyl α-veratrylhemisuccinate was resolved into its (R)-(+) and (S)- (-)antipodes by (S)-(-) and (R)-(+)- α-methylbenzylamine respectively. Calcium borohydride reduction of the (R)-(+)-hemiester afforded (R)-(+)-β-veratryl-γ-butyrolactone. The latter was used for the synthesis of various naturally occuring lignans such as (+)-dimethylisolariciresinol, (-)-kusunokinin and (-)-dimethylmatairesinol [36]. Francesco *et al* [37] describe the synthesis of new heterodimers, having a phenylcoumaran skeleton, by horseradish peroxidase catalyzed cross-coupling reactions of methyl esters of substituted hydroxycinnamic acids. They studied the cross-coupling reactions and their implications for the understanding of the lignification process in vascular plants. They observed that the reactions seem to be governed by a combination of factors such as oxidation potential and radical reactivity.

A series of new lignan analogues were synthesized by simple and accessible procedure was reported. The cyclocondensation reaction of 3-(ethoxycarbonyl)-4,4-(diaryl)but-3-enoic acids (**13**) with acetic anhydride in glacial acetic acid produced ethyl 4-acetoxy-6-ethoxy-1-(4-aryl)-2-naphthoates (**14**) and with polyphosphosphoric acid yielded ethyl 1-aryl-6-ethoxy-4-hydroxy-2-naphthoates (**15**) in good yields (**Scheme 11**). The synthesized new compounds were tested for their antimicrobial inhibitory effect against different bacterium and fungi species [38]. On the other hand, a series of new lignans were synthesized by the cyclocondensation reaction of (Z)-3-(ethoxycarbonyl)-4,4-(diaryl)but-3-enoic acids with acetic anhydride in glacial acetic acid produced ethyl 4-acetoxy-1-aryl-2-naphthoates and with polyphosphosphoric acid yielded ethyl 1-aryl-4-hydroxy-2-naphthoates. The synthesized new compounds showed promising antimicrobial susceptibility [39].




Scheme-11

## Biological importance of lignans

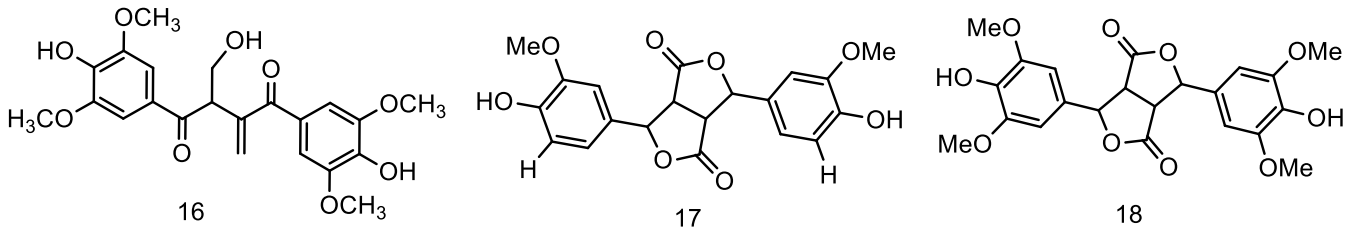
The range of the structures and biological activities associated with lignans is broad. The lignans are known to have anti-tumour, antimitotic and antiviral activity and to specifically inhibit certain enzymes. Toxicity to fungi, insects and vertebrates is observed for some lignans and a variety of physiological activities have been reported. The depth of the blological activities of lignans has appreciated relatively recent times. Much interest has been focussed on their effectiveness as antineoplastlc agents [40].

Two new lignans, a naphthalene derivative named junaphtoic acid and (-)-3-demethylyatein were isolated from the acidic fraction of n-hexane extract from the leaves of Juniperus *sabina*. Their structures were established by spectroscopic and chemical means. *Juniperus subinu* is a mountain shrub whose essential oil is an abortive and whose extracts have shown cytotoxic and cytostatic activities [41]. (+)- and (-)-Liriodenol (**16**), a pair of unprecedented enantiomeric lignans bearing a 1,1-disubstituted olefinic group, were isolated from the barks of Liriodendron hybrid. The structure and relative configurations were determined by comprehensive analysis of MS and NMR spectroscopy. The cytotoxicity of these three lignans (±)-, (+)-, and (-)-liriodenol was evaluated *in vitro* against four selected human tumor cell lines, where (+)-liriodenol showed more significant cytotoxic effects than the (±)- and (-)-liriodenol enantiomers [42].

Coran and coworkers [43] reported the synthesis of series of butanolide and tetrahydrofuran lignans. They have comparatively tested the synthesized compounds as platelet activating factor (PAF) antagonists. In particular, the influence of the tetrahydrofurans ether oxygen as compared with the γ-lactone system of butanolides was studied. The results of their study showed that the two classes of compounds were practically acting as bioisosters.

Parasitic diseases continue to be a major worldwide health problem, and there is an urgent need for development of therapeutic drugs. Márcio Luis Andrade *et al* [44] describe synthesis of dehydrodiferulic acid dilactone (**17**) and dehydrodisinapic acid dilactone (**18**) furofuran lignans by oxidative coupling of ferulic and sinapic acids, respectively. Their schistosomicidal, trypanocidal, and leishmanicidal activities were evaluated in vitro against Schistosoma mansoni adult worms, trypomastigote and amastigotes forms of Trypanosoma cruzi, and promastigote forms of

Leishmania amazonensis. Compound (**17**) did not display significant schistosomicidal activity, but it presented potent trypanocidal activity, since it induced death of trypomastigotes and amastigotes respectively. Compound (**18**) had slight trypanocidal and schistosomicidal activities.




Gomisin J and gomisin N, dibenzocyclooctadiene type lignans isolated from Schisandra chinensis, inhibit Wnt/β-catenin signaling in HCT116 cells. Gomisins J and N appear to inhibit Wnt/β-catenin signaling by disrupting the interaction between β-catenin and its specific target DNA sequences rather than by altering the expression of the β-catenin protein. Therefore, gomisins J and N, the novel Wnt/β-catenin inhibitors discovered may serve as potential agents for the prevention and treatment of human colorectal cancers. The Wnt/β-catenin signaling pathway is a crucial pathway regulating cell proliferation, differentiation, migration, survival, and death. The inhibitors of the Wnt/β-catenin signaling pathway may be valuable candidates for use as cancer chemopreventive or chemotherapeutic agents. Lignans are another major class of natural products that are well-known for their cancer chemopreventive potential [45].

## Conclusions

Lignans represent a well-known group of natural products with anti-protozoal activity. This review summarizes chemistry and biological activities associated with the lignans. Novel lignans continue to be isolated from the natural sources by chemists at a steady rate is expanding. The natural sources of lignans, isolation methodology, various synthetic strategies developed for the preparation of lignans and biological applications and their mode of action were critically discussed. Still there is a need to pursue an understanding of their possible roles in human physiology.

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