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Arylnaphthalene lactone analogues: synthesis and development as excellent biological candidates for future drug discovery

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AryInaphthalene lactones are natural products extracted from a wide range of different parts of plants. The

progressing interest in the synthesis of these compounds is due to their significant biological activities,

which have made them potential candidates in drug discovery and development. This review mainly

covers recent developments in the synthesis and biological applications of arylnaphthalene lactone analogs.

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Introduction

Certain structural features of natural products are responsible for their biological activities. Identifying such special scaffolds is of great interest to researchers.^{1,2} Laboratory synthesis of molecules containing similar scaffolds has served as an effective strategy for new drug synthesis.³ Naturally occurring arylnaphthalene lactones are a subclass of lignans present in many dietary or medicinal plants.⁴ As a representative example, 1arylnaphthalene lactone lignans (Fig. 1, **1–9**)⁵ are reported to exhibit a lot of biological activities⁶ such as antibacterial,⁷ antiviral,^{8–11} antitumor,^{12–14} antiplatelet,^{15,16} phosphodiesterase inhibition,^{17,18} 5-lipoxygenase inhibition,^{19–21} HIV reverse transcriptase inhibition^{22–24} and cytotoxic activities.²⁵

Arylnaphthalene lactone lignans contain two arylpropanoid units, in which the aromatic rings are polyoxygenated (*i.e.*, coniferyl alcohol). In biosynthetic pathways the two units are assembled using enzymes.^{26,27} The arylnaphthalene lactones in Fig. 2 (**10–17**) are structurally classified into two types, denoted type I and type II. Daurinol is a type II arylnaphthalene lactone. It is a potent anticancer agent isolated from *Haplophyllum dauricum* and traditionally it has been used for the treatment of cancer in Mongolia, Russia, and China.

Lignans are distributed widely in higher classes of plants and as secondary metabolites are also known to protect plants from herbivores. This forms a basis for the growing interest in exploiting lignans and their synthetic analogs as potential anticancer agents.^{28,29} Some cytotoxic lignan derivatives have already reached phase I and II clinical trials as antitumor agents including GP-11,³⁰ NK-611,^{31,32} TOP-53,³³ NPF,³⁴ and GL-331.³⁵⁻³⁹ Moreover, recently lignan F11782 has been reported as a novel catalytic inhibitor of topoisomerases I and II (key promoters of DNA replication).⁴⁰

Many routes are available for the synthesis of arylnaphthalene lactones. 1-Phenyl naphthalene anhydride can be obtained through dimerization followed by reduction (in Zn/ AcOH) of phenylpropionic acid. Alternatively, 1-phenyldihydronaphthofuran can be oxidized using Jones reagent into type 1 and type 2 lactones. The synthesis of arylnaphthalene lactones bearing aryl ethers or phenolic OHs on a benzene ring was carried out by the Stevenson group using an intramolecular Diels-Alder reaction of 3-arylprop-2-yn-1-yl-3-arylpropiolate or 3-arylprop-2-en-1-yl-3-arylpropiolate.⁴¹⁻⁴³ The Mori group⁴⁴ and Anastas group45,46 have reported the synthesis of arylnaphthalene lactone analogs using Pd and Ag-catalyzed [2 + 2 + 2]cyclization, respectively. The Tanabe group also synthesized arylnaphthalene lactone analogs using the regiocontrolled benzannulation of diaryl(gem-dichlorocyclopropyl)methanols,47 see Table 1.

The present review will summarize recent advances in the synthesis of arylnaphthalene lactone lignan containing analogs, and their diverse biological activities and structure–activity relationships (SARs). In particular, the review will focus on the synthesis and biological activities (*in vitro* and *in vivo*) of arylnaphthalene lactone containing analogs, particularly for drug discovery and development.

Synthesis of arylnaphthalene lactones

Park *et al.*,⁴⁸ synthesized taiwanin C using an intramolecular Diels–Alder method. The starting material piperonal **18** was converted to *gem*-dibromoalkene **19** (route a: *via* reaction with

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Fig. 1 Some representative bioactive arylnaphthalene lactone lignans.

Туре 1



Retrojusticidin B

Justicidin E



Retrochinensin

13







16



Daurinol

17

Fig. 2 The representative bioactive type 1 and type 2 arylnaphthalene lactones.

Ref.	Starting material(s)	Reagent(s)	Solvent	Type 1 and type II ANL yields (%)
41	Arylpropargyl, arylpropiolate esters	4-Vinylpyridin, (P4-VP)	Xylene	50-60
42	Phenylpropiolic acid, phenylpropargyl alcohol	P4-VP, acid catalyst	Xylene	45-50
43	Isovanillin	Benzyl chloride	Xylene	70-75
44	Diynes and arynes	Pd catalyzed	CH ₃ CN	40-70
45	1-Phenyldihydronaphthofuran	Jones reagent	DMAc	20-30
46	Phenylpropargyl chloride, phenylacetylene	Ag catalyzed	DMA	16-30
47	AACMs	Lewis acid	CF ₃ COOH	50-65

Table 1 Some of the starting materials and reagents used for the synthesis of arylnaphthalene lactone analogues

triphenylphosphine and carbontetrabromide at room temperature) and to piperonal ester **21** (route d: *via* reaction with sodium hydride and triethyl phosphonoacetate at 0 °C). The dibromocompound **19** reacted with *n*-BuLi in THF (at -78 °C) to generate an alkyne anion, which, upon addition of methyl chloroformate and subsequent hydrolysis with K₂CO₃, resulted in formation of acid intermediate **20**. 3-Arylallyl alcohol **22** was then prepared *via* reduction of piperonal ester **21** with DIBAL-H. Compounds **20** and **22** were coupled with coupling reagents DCC and DMAP in CH₂Cl₂ to yield compound **23**. Finally, an intramolecular Diels–Alder precursor dihydronaphthalene **24** was readily converted to taiwanin C **16** in the presence of a catalyst, DDQ (Scheme 1).

Justicidin E (12) was also prepared following the same strategy. The ester group in compound 21 was hydrolyzed using alkaline solution to get the respective acid 25. The *gem*-dibromoalkene 19 was converted to arylpropargyl alcohol 26. Both 25 and 26 were coupled using coupling reagents DCC and DMAP to

get the precursor compound 27. Under intramolecular Diels-Alder conditions, the compound 27 was cyclised to dihydronaphthalene (28). Subsequently, compound 28 was aromatized to give the desired analog justicidin E(12) using DDQ as a catalyst (Scheme 2).

Synthesis of type I arylnaphthalene lactone daurinol (17)

Initially, benzylation of isovanillin was performed to obtain compound **29**. Afterwards, coupling of compound **21** with **29** was carried out using DCC and DMAP in CH_2Cl_2 to form compound **30**. Dihydronaphthalene **31** was thus obtained from an intramolecular Diels–Alder reaction of **30**. Further aromatization (using an oxidant) followed by hydrogenolysis (of benzyl ether) converted **30** to the desired daurinol **17** (Scheme 3).

Hayet *et al.*⁴⁹ reported the synthesis of arylnaphthalene lactone from naphthol (32). Compound 32 was converted to triflate 33 using *N*-phenylbis(trifluoromethanesulfonimide) and



Scheme 1 Synthesis of taiwanin C. Reagents and conditions: (a) PPh₃, CBr₄ and CH₂Cl₂, rt; (b) *n*-BuLi and THF, -78 °C, then ClCO₂Me, -78 °C to rt; (c) K₂CO₃ and EtOH, rt; (d) triethyl phosphonoacetate, NaH and THF, 0 °C; (e) DIBAL-H and CH₂Cl₂, -78 °C; (f) DCC, DMAP and CH₂Cl₂, rt; (g) Ac₂O, mw, 140 °C; (h) DDQ and benzene, 80 °C.

Review



Scheme 2 Synthesis of justicidin E (12). Reagents and conditions: (a) KOH and H_2O/THF , rt; (b) *n*-BuLi and THF, $-78 \degree C$, then $(CH_2O)_n$; (c) DCC, DMAP and CH_2Cl_2 , rt; (d) Ac₂O, mw, 140 °C; (e) DDQ and benzene, 80 °C.

NaH.⁵⁰ A Suzuki reaction was further performed to introduce an aryl group to compound **33** using palladium, phenyl boronic acids and additives (depending on the substrates) to get compound **14** (Scheme 4).^{51,52}

The versatility of the reaction was established by synthesising justicidin B (15), 3,4,5-trimethoxyphenylnaphthalene lactone (1), and 3,4-dimethoxyphenylnaphthalene lactone (38) using the same methodology.⁴⁹ Compound 34 reacted with



Scheme 3 Synthesis of daurinol (17). Reagents and conditions: (a) BnBr, K_2CO_3 and EtOH, 50 °C; (b) triethyl phosphonoacetate, NaH and THF, 0 °C; (c) *n*-BuLi and THF, -78 °C, then (CH₂O)_{*n*}, -78 °C to rt; (d) compound number 20, DCC, DMAP and THF, rt; (e) Ac₂O, 140 °C; (f) DDQ and benzene, 80 °C; (g) H₂, Pd/C and MeOH, rt.



Scheme 4 Synthesis of aryInaphthalene lactone. Reagents and conditions: (a) PhN(Tf)₂, Et₃N, DMAP, THF; (b) Pd(PPh₃)₄, PhB(OH)₂, K₃PO₄, DMF.

different boronic acids (**35**, **36** and **37**) in the presence of Pd and a base (Scheme 5). The authors believe that this approach can be widely utilised in the synthesis of arylnaphthalene lactone derivatives to elucidate the structure–activity relationships of these compounds for biological studies.

He *et al.*⁵³ reported a simple protocol for the total synthesis of arylnaphthalene lactones. Briefly, compound **39** reacted with a zinc analog to yield 9-amino-6,7-methylenedioxynaphtho[2,3-c]furan-1(3*H*)-one (**40**). This, upon reaction with sodium nitrite in an aqueous hydrochloric acid, followed by addition of potassium iodide, furnished 9-iodo-6,7-methylenedioxynaphtho[2,3-c]furan-1(3*H*)-one (**41**). The Suzuki coupling of compound **41** with benzo[*d*][1,3]dioxol-5-yl boronic acid leads to the principle compound taiwanin C (**16**) (Scheme 6).

Similarly, the coupling of compound **41** with 3,4-dimethoxyphenyl boronic acid leads to the formation of chinensin (**42**). The broad scope of compounds **16** and **42** established the versatility of the new strategy. Thus, a number of arylnaphthalene lactone lignans with diverse substitution patterns or functional moieties can be obtained. This can significantly enhance their biological properties for future drug discovery programs.

Hui *et al.*⁵⁴ synthesized a large number of arylnaphthalene lactone derivatives from **43** in multi-step reactions. Compound **43** reacted with *p*-TsOH in glycol and benzene to form compound **44**, which reacted with different aldehydes to give compound **45**. Intramolecular cyclization of **45** formed compound **46**. Reaction of **46** with DEADC in DCM and acetic



Scheme 5 Synthesis of arylnaphthalene lactones.



Scheme 6 Synthesis of chinensin and taiwanin C.



Scheme 7 Synthesis of novel arylnaphthalene lactone lignans. Reagents and conditions: (a) glycol, benzene and *p*-TsOH.H₂O; (b) Ar–CHO, *n*-BuLi and THF, –78 °C; (c) DEADC, CH₂Cl₂ and AcOH; (d) NaBH₄, MeOH, then 10% HCl.



Scheme 8 Synthesis of novel arylnaphthalene lactone lignans. Reagents and conditions: (a) SOCl₂ and DMA; (b) K₂CO₃, 18-crown-6, 4 Å molecular sieves and DMA, 100 °C.



Scheme 9 Synthesis of aryInaphthalene lactone lignan natural products. Reagents and conditions: (a) H₂SO₄, MeOH, DIBALH and DCM; (b) DCC, DMAP and DCM; (c) PhNO₂ and MWI, 180 °C, 5 min.

acid formed compound **47**. The final product (**48**) was obtained from the reaction of **47** with sodium borohydride and methanol (Scheme 7).

Patrick Foley *et al.*⁵⁵ demonstrated the silver-catalyzed one-pot synthesis of arylnaphthalene lactone cores (**53–57**) using carbon dioxide, arylphenylpropargyl chloride (**49** and **50**), and



Scheme 10 Synthesis of arylnaphthalene lactone derivatives. Reagents and conditions: (a) LDA (3 equiv.) and THF, -78 °C to rt, 6-7 h, quenched with 3 M HCl; (b) MeI, K₂CO₃ and acetone, room temperature, 4-8 h; (c) crude product, K₂CO₃ and acetone, room temperature, 3 days.



Scheme 11 Total synthesis of diphyllin. Reagents and conditions: (a) Br and MeOH, rt, 6 h; (b) $HS(CH_2)_2SH$ (*p*-TsOH) and benzene, reflux, 10 h; (c) *n*-BuLi and THF, -78 °C to rt, 2 h; (d) MnO₂ and CH₂Cl₂, rt, 16 h; (e) Compound number **89** (14.3 mmol), LDA and THF, -78 °C to rt, 1 h; (f) HgO, HgCl₂ and MeCN, reflux, 3 h; (g) *p*-TsOH and benzene, reflux, 16 h.



Scheme 12 Total synthesis of patentiflorin A. Reagents and conditions: (a) DMAP, Ac₂O and pyridine, rt, overnight; (b) HBr/HOAc and CH₂Cl₂, rt, 15 min, 99%; (c) TBAB, NaOH and CHCl₃, 40 °C, 6 h; (d) K₂CO₃ and MeOH, rt, 1 h.



Scheme 13 Synthesis of arylnaphthalene lactones. Reagents and conditions: (a) SOCl₂ and DMA; (b) AgI, K₂CO₃, 18-crown-6, DMAc and molecular sieves.



Scheme 14 Synthesis of arylnaphthalene lactone diphyllin 92. Reagents and conditions: (a) THF at -78 °C; (b) TFA/DCM, 0 °C, 2 h; (c) ^{*n*}Bu₄NF/CH₂Cl₂, rt, 1 h; (d) NaOMe, HCOOMe and benzene; (e) 6N HCl/chloroform, rt, 1 h.



arylphenylacetylenes (51 and 52). This new approach was employed in the synthesis of retrochinensin, justicidin B, retrojusticidin B, chinensin, justicidin E and taiwanin C (Scheme 8).

Kocsis *et al.*⁵⁶ devised a new route for the synthesis of a series of novel arylnaphthalene lactone lignans along with their regioisomers. Compounds **59** and **60** reacted with sulphuric acid, methanol and DIBALH to give compounds **60** and **61**, which, upon reaction with compounds **62** and **63** under optimized DDA, formed styrenyl precursors (**64–66**). Compound **64** reacted with PhNO₂ to yield a 2 : 1 mixture of arylnaphthalene lactone **67** and its regioisomer (**70**). Likewise, compound **65** under the same reaction conditions furnished a 2 : 1 mixture of arylnaphthalene lignan **68** and its regioisomer (**71**). The reaction of compound **66** gave a 3 : 1 mixture of arylnaphthalene lignans **69** and **72** (Scheme 9). Mal and Jana⁵⁷ described a single step synthesis of naphthalene lactone analogs. Various phthalides 73 reacted with allene carboxylates 74 and LDA in THF to yield the respective arylnaphthalene lactone 76. Various functional groups (77–84) were tolerated well under the reaction conditions (Scheme 10).

Patrick Foley *et al.*⁵⁸ isolated derivatives of diphyllin (92) and patentiflorin A (97) from the medicinal plant *Justicia gendarussa*. The synthetic pathway adopted by the group included bromination of **85** to give compound **86**, which further reacted with *p*-TsOH to form compound **87**. Reaction of **87** with benzo[d][1,3]dioxole-5-carbaldehyde and *n*-BuLi furnished compound **88**. Compound **88** was treated with MnO₂ to form compound **89**. Compound **90** was obtained upon reaction of **89** with LDA. Compound **90** was converted to **91** when reacted with HgO and HgCl₂. Finally, compound **91** was treated with *p*-TsOH to give diphyllin (**92**) (Scheme 11).

The aglycone diphyllin (92) served as a key intermediate for the synthesis of patentiflorin A (97), which was obtained *via* glycosylation of diphyllin 92 at C-7 with D-quinovose 93 (Scheme 12).

The previously described silver-catalysed one-pot synthetic protocol⁵⁵ was first optimised for the synthesis of unsubstituted arylnaphthalene lactones. Afterwards, the methodology was extended towards the synthesis of a tetramethoxy-substituted arylnaphthalene lactone natural product analog⁵⁸ (Scheme 13). The chloride precursor **99** was obtained from the 3,4 dimethoxyphenylpropargyl alcohol **98**. Reaction of **99** and **100** with CO_2 in the presence of a Ag catalyst formed two major isomers (**101** and **102**) in a 2 : 1 ratio.

Ogiku *et al.*⁵⁹ reported the synthesis of diphyllin **92** following the synthesis route in Scheme 14. The conjugate addition of the anion generated from compound **103** with LDA to methyl acrylate, followed by trapping of the resultant enolate with piperonal *in situ*, furnished a mixture of diastereomers **106**. The crude product was further treated with TFA to give compound **107**, which reacted with tetra-*n*-butyl ammonium fluoride to yield stereoisomers of compound **108**. Compound **108** reacted with HCOOMe and NaOMe to form a mixture of intermediate **109** and compound **110**. The reaction mixture was treated with conc. HCl to afford diphyllin **92**.

Gudla and Balamurugan⁶⁰ used oxidation methods for the synthesis of different arylnaphthalene lactones.

Arylnaphthalenes fused with furan served as precursors in the preparation of arylnaphthalene lactone lignan and its analogs. The benzylic oxidation of compound **112** has already been reported using Jones reagent, which resulted in both possible arylnaphthalene lactones.⁶¹ However, the CrO₃/H₅IO₆/CH₃CN system offers smooth benzylic oxidation at room temperature.⁶² Under these conditions benzylic oxidation was carried out for compounds **113**, **114** and **116** to yield arylnaphthalene lactones **12**, **16**, **115** and **117** (Scheme 15). Substrate **113**, which contains fused dioxlane in the naphthalene ring resulted in a mixture of lactones, justicidin E (**12**) and taiwani C (**16**).

Biological studies

Janmanchi *et al.*⁶³ reported helioxanthin **118** analogs as potential anti-hepatitis B virus agents. Modification of the lactone ring and methylenedioxy unit of helioxanthin resulted in different antiviral activities. Compound **119** was found to be the most effective anti-HBV agent, inhibiting secretion of viral surface antigens and e antigens in HepA2 cells. The EC₅₀ values for each were 0.06 and 0.14 μ M, respectively. Compound **119** not only inhibited wild-type HBV and lamivudine-resistant strains but also suppressed the HBV mRNA, core proteins, and viral promoters successfully. This type of analog exhibits unique actions that are different to those of existing therapeutic drugs currently in use as novel anti-HBV agents.



Da-Kuo Shi *et al.*⁶⁴ reported a series of novel compounds containing glycosylated diphyllin with different sugar derivatives. They tested them against many human tumor cell lines. Some of the synthesized compounds showed promising cytotoxicity with IC_{50} values in the μ M–nM range. Compounds **120**, **121** and **122** are potent against HCT-116, MCF-7, and KD tumor cell lines. Sugar moieties with cyclic lipophilic groups at C4' and C6' showed a further increase in bioactivity. All the synthesized compounds were tested using a Topo II-induced kDNA decatenation assay and the results were consistent with their *in vitro* investigated along with their structure–activity relationships. The results showed that HJB, HJA and JB significantly repressed the growth of K562 cells by reducing proliferation and SOD activity led by apoptosis. The decreasing order of anti-proliferative activity of the five tested arylnaphthalenes was HJB > HJA > JB > CME, TEME. SAR studies suggested that hydroxyl substitution at C-1' and C-6' significantly increases the anti-proliferative activity of arylnaphthalene lignans, while a methoxyl at C-1' significantly decreases this effect consistently.



cytotoxicity. This signifies that Topo II is one of the targets for such compounds, and also showed G0/G1 arrest and DNA fragmentation, which leads to the death of the cell by apoptosis in human leukemia HL-60 cell lines. These results suggest that the sugar moiety on C4 of diphyllin is key for its antitumor activity. The SAR analysis revealed that (i) the sugar moiety on the diphyllin is essential, (ii) equatorial C'4-OH on the sugar is superior to an axial one, and (iii) a proper cyclic lipophilic group at the C'4 and C'6 of sugar might enhance the anticancer activity.

Yu *et al.*⁶⁵ isolated nine natural lignan justicidin A analogs and tested their cytotoxic activities against hepatocellular carcinoma (HepG2) cell lines. Compounds **123–128** showed potent antitumor activity, better than that of the standard drug etoposide. These compounds showed good antitumor activity. In their reported investigations modifications of justicidin A analogs further increased the antitumor activity.

Luo *et al.*⁶⁶ isolated five arylnaphthalene lignans including 6'-hydroxy justicidin A (HJA) **129**, 6'-hydroxy justicidin B (HJB) **130**, justicidin B (JB) **131**, chinensinaphthol methyl ether (CME) **132**, and taiwanin E methyl ether (TEME) **133** from *Justicia procumbens*. The effects of these lignans on the proliferation and apoptosis of human leukemia K562 cell lines were

The naphthalenic lignan lactones with an oxymethylene or methyleneoxy linker are non-redox 5-lipoxygenase inhibitors. 5-Lipoxygenase is involved in the biosynthesis of leukotrienes from arachidonic acid. Compound **134** showed potent nonredox inhibition activity against the enzyme. The design of a 5-lipoxygenase inhibitor helped alleviate asthmatic, inflammatory, and rheumatoid arthritis diseases. Further modification of **134** led to the synthesis of **135** and **136**.⁶⁷ Compound **136** is more active than **135**, and is involved in the production of leukotriene B4 in human polymorphonuclear leukocytes (IC₅₀ **1.5** nM) and in human blood (IC₅₀ 50 nM); no significant inhibition was observed in the case of **135**.⁶⁸

Hui *et al.*⁶⁹ reported a series of novel arylnaphthalene lignan analogs as anticancer candidates against A549, SW480 and KB cell lines, and one normal cell line, HEK293. Compound **137** contains a *para*-methyl on the D-ring and showed potent antitumor activity, having an IC₅₀ value of 18.9 μ M against KB cells and cytotoxicity to HEK293. Fluorescent staining has confirmed that compound **137** induced apoptosis of KB cells. Western blot analysis has shown that compound **137** increased the expression of cleaved-caspase-3 and bax while reducing the expression of bcl-2.



Zhang *et al.*⁷⁰ isolated compound **138** from *Justicia gendarussa* plants in Vietnam and reported it as a potent anti-HIV-1 agent. Compound **138** was tested against M- and Ttropic HIV-1 isolates and showed significantly higher activity than the standard anti-HIV drug, zidovudine (AZT). effective than AZT in inhibiting four different HIV-1 isolates, either M- or T-tropic, in human PBMCs with IC_{50} values in the range 14–32 nM. Hence, ANL glycosides have the potential to be developed as novel anti-HIV drugs in the future.



Patentiflorin A (138) and two congeners (139–140) were synthesized *via* structural modifications and tested as anti-HIV arylnaphthalene lignin (ANL) glycosides in the search for new drugs. The quinovopyranosyloxy group in the structure (138) was found to be essential for the high level of anti-HIV activity. Patentiflorin A (138) was further tested for HIV-1 gene expression of the R/U5 and U5/gag transcripts. The results confirmed that the compound potentially inhibited HIV-1 reverse transcription. In the SAR study, patentiflorin A (138) showed potential as an anti-HIV-1 drug, and showed a broad activity spectrum against M- and T-tropic HIV-1 isolates. The compound (138) was found to be more Hajdu *et al.*⁷¹ isolated helioxanthin (141) from fresh roots of *Heliopsis helianthoides var. scabra* and evaluated its *in vitro* brain tumor activity. Compound 141 inhibited the migration of melanoma and brain endothelial cells, and also reduced the adhesion of melanoma cells to the brain endothelium. Furthermore, compound 141 enhanced the blood-brain barrier function and the expression of the tight junction protein ZO-1 at the junctions of the endothelial cells. These findings confirmed that 141 potentially interferes with different steps of brain metastasis formation and enhances the barrier function of cerebral endothelial cells.



Ren *et al.*⁷² isolated two new (**142** and **143**) and four known (**3–6**) arylnaphthalene lignan lactones from *Phyllanthus poilanei* collected in Vietnam, with one further known analog (**144**) being prepared from phyllanthusmin C (**4**). Some of these arylnaphthalene lignin lactones were cytotoxic toward HT-29 human colon cancer cells. Compounds **142** and **144** were found to be the more potent inhibitors, with IC₅₀ values of 170 and 110 nM, respectively. Compound **142** showed better activity in *in vivo* hollow fiber assays using HT-29 cells implanted in immunodeficient NCr nu/nu mice. The mechanistic studies also showed that the compound mediates its cytotoxic effects by inducing tumor cell apoptosis.

Abbreviations

AACMs	Aryl(aryl')-2,2-dichlorocyclopropylmethanols
DIBAL-H	Diisobutylaluminium hydride
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DCC	N,N'-Dicyclohexylcarbodiimide
DMAP	4-Dimethylaminopyridine
DEADC	Diethyl azodicarboxylate
DMAc	Dimethylacetamide
LDA	Lithium diisopropylamide
p-TsOH	<i>p</i> -Toluenesulfonic acid
TFA	Trifluoroacetic acid

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Conclusion

Arylnaphthalene lactone lignan analogs display multiple biological and pharmacological activities. In recent years, large numbers of arylnaphthalene lactone compounds have been extracted from different families of plants. They have been synthesized and evaluated for their anticancer, antibacterial, antiviral, antitumor, antiplatelet, phosphodiesterase inhibition, 5-lipoxygenase inhibition, HIV reverse transcriptase inhibition and cytotoxic activities. In the present review, we have mainly focused on the synthesis and *in vitro* and *in vivo* biological activities of arylnaphthalene lactone lignan containing analogs, and the possible interest in them for future drug discovery research programs.

Conflicts of interest

The authors declare no conflict of interest.

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