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

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Arylnaphthalene 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 aryl-naphthalene lactone analogs.

## Introduction

Certain structural features of natural products are responsible for their biological activities. Identifying such special scaffolds is of great interest to researchers.<sup>1,2</sup> Laboratory synthesis of molecules containing similar scaffolds has served as an effective strategy for new drug synthesis.<sup>3</sup> Naturally occurring aryl-naphthalene lactones are a subclass of lignans present in many dietary or medicinal plants.<sup>4</sup> As a representative example, 1-arylnaphthalene lactone lignans (Fig. 1, 1–9)<sup>5</sup> are reported to exhibit a lot of biological activities<sup>6</sup> such as antibacterial,<sup>7</sup> antiviral,<sup>8–11</sup> antitumor,<sup>12–14</sup> antiplatelet,<sup>15,16</sup> phosphodiesterase inhibition,<sup>17,18</sup> 5-lipoxygenase inhibition,<sup>19–21</sup> HIV reverse transcriptase inhibition<sup>22–24</sup> and cytotoxic activities.<sup>25</sup>

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.<sup>26,27</sup> The aryl-naphthalene lactones in Fig. 2 (10–17) are structurally classified into two types, denoted type I and type II. Daurinol is a type II aryl-naphthalene 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.<sup>28,29</sup> Some cytotoxic lignan derivatives have already reached phase I and II clinical trials as antitumor agents including GP-11,<sup>30</sup> NK-611,<sup>31,32</sup> TOP-53,<sup>33</sup> NPF,<sup>34</sup> and GL-331.<sup>35–39</sup> Moreover, recently lignan F11782 has been reported as a novel catalytic inhibitor of topoisomerases I and II (key promoters of DNA replication).<sup>40</sup>

Many routes are available for the synthesis of aryl-naphthalene lactones. 1-Phenyl naphthalene anhydride can be obtained through dimerization followed by reduction (in Zn/AcOH) of phenylpropionic acid. Alternatively, 1-phenyl-dihydronaphthofuran can be oxidized using Jones reagent into type 1 and type 2 lactones. The synthesis of aryl-naphthalene 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.<sup>41–43</sup> The Mori group<sup>44</sup> and Anastas group<sup>45,46</sup> have reported the synthesis of aryl-naphthalene lactone analogs using Pd and Ag-catalyzed [2 + 2 + 2] cyclization, respectively. The Tanabe group also synthesized aryl-naphthalene lactone analogs using the regiocontrolled benzannulation of diaryl(*gem*-dichlorocyclopropyl)methanols,<sup>47</sup> see Table 1.

The present review will summarize recent advances in the synthesis of aryl-naphthalene 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 aryl-naphthalene lactone containing analogs, particularly for drug discovery and development.

## Synthesis of aryl-naphthalene lactones

Park *et al.*,<sup>48</sup> 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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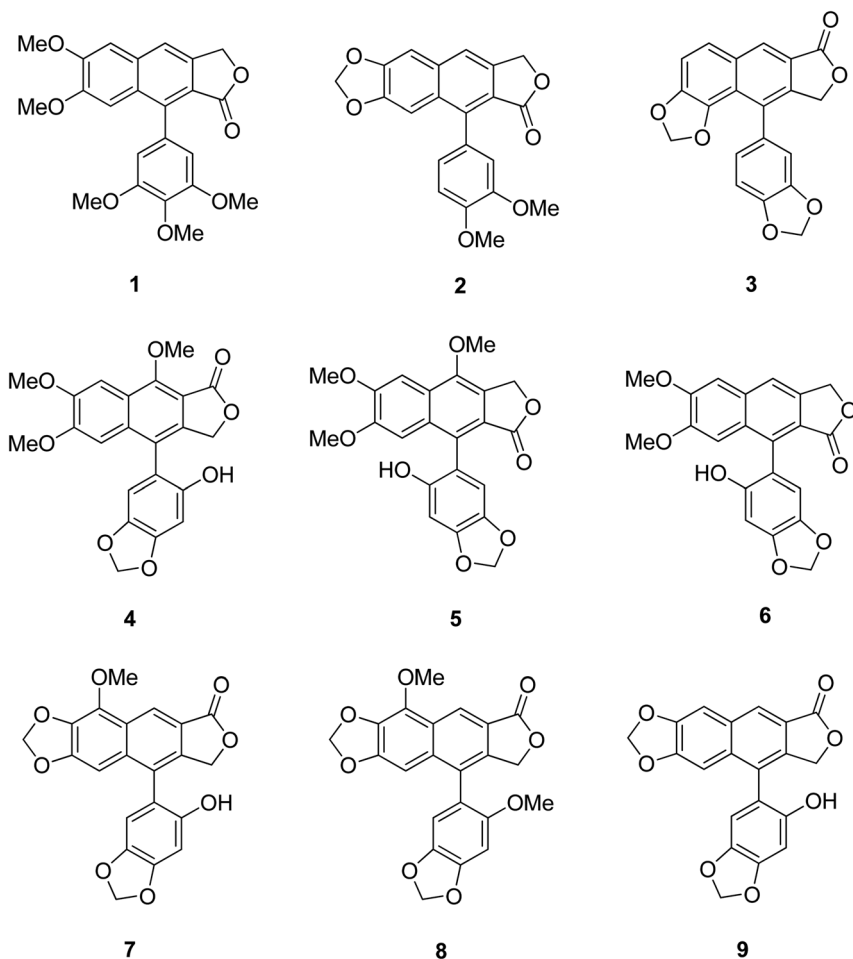


Fig. 1 Some representative bioactive arynaphthalene lactone lignans.

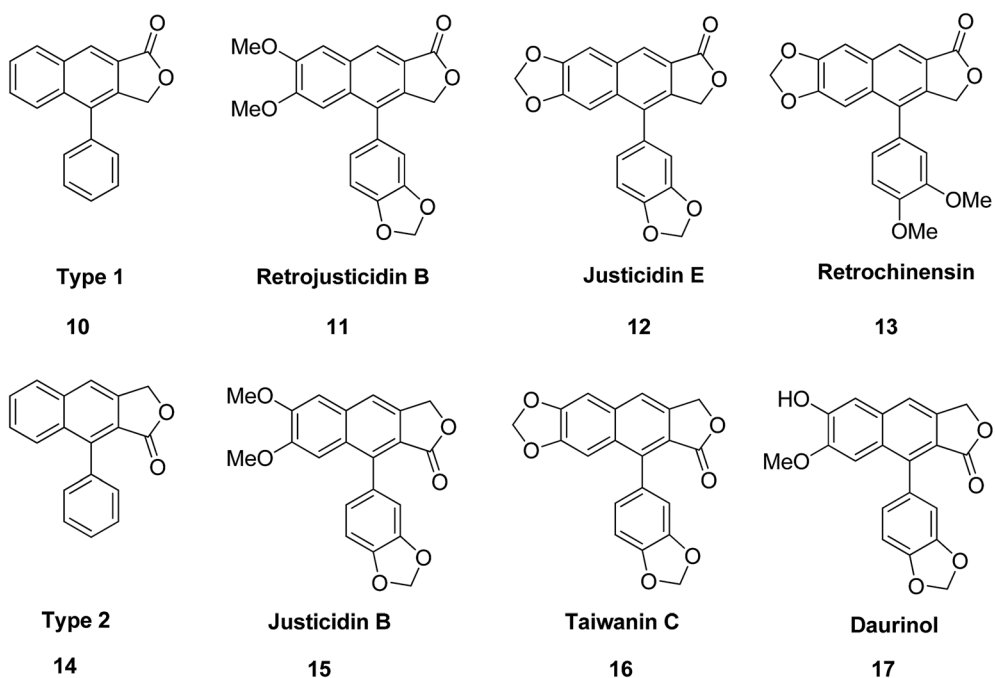


Fig. 2 The representative bioactive type 1 and type 2 arynaphthalene lactones.



Table 1 Some of the starting materials and reagents used for the synthesis of aryl-naphthalene lactone analogues

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	Diyne and arynes	Pd catalyzed	CH <sub>3</sub> 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 <sub>3</sub> COOH	50–65

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 K<sub>2</sub>CO<sub>3</sub>, 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 CH<sub>2</sub>Cl<sub>2</sub> 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).

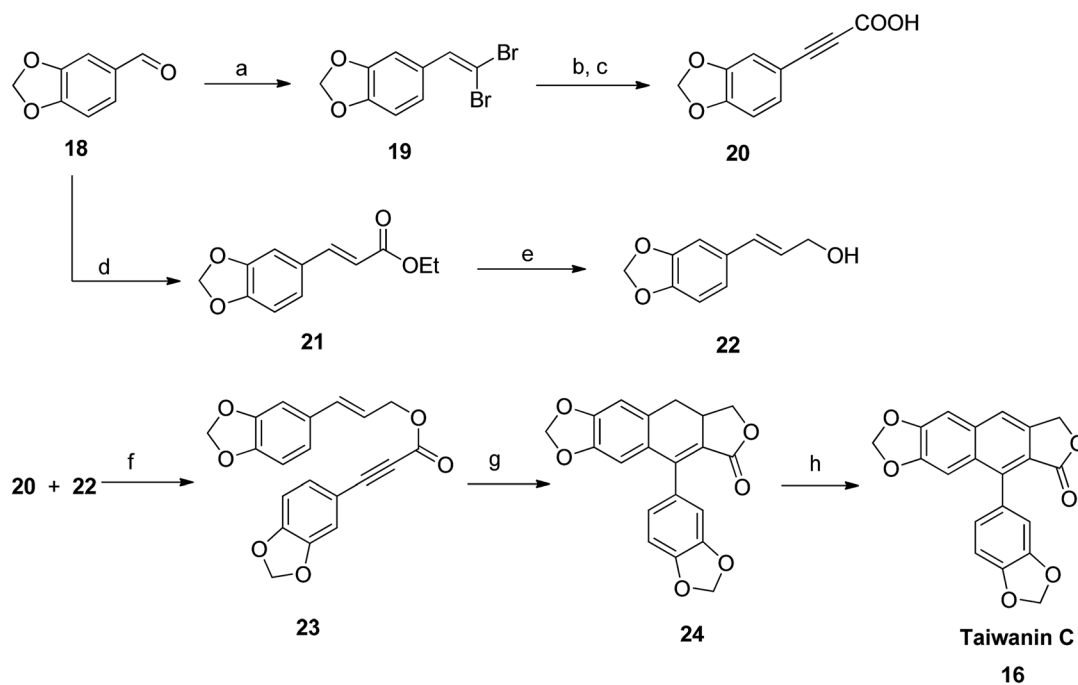
Justicidin E (**12**) was also prepared following the same strategy. The ester group in compound **21** was hydrolyzed using alkaline solution to get the respective acid **25**. The *gem*-dibromoalkene **19** was converted to arylpropargyl alcohol **26**. Both **25** and **26** were coupled using coupling 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 aryl-naphthalene lactone daurinol (**17**)

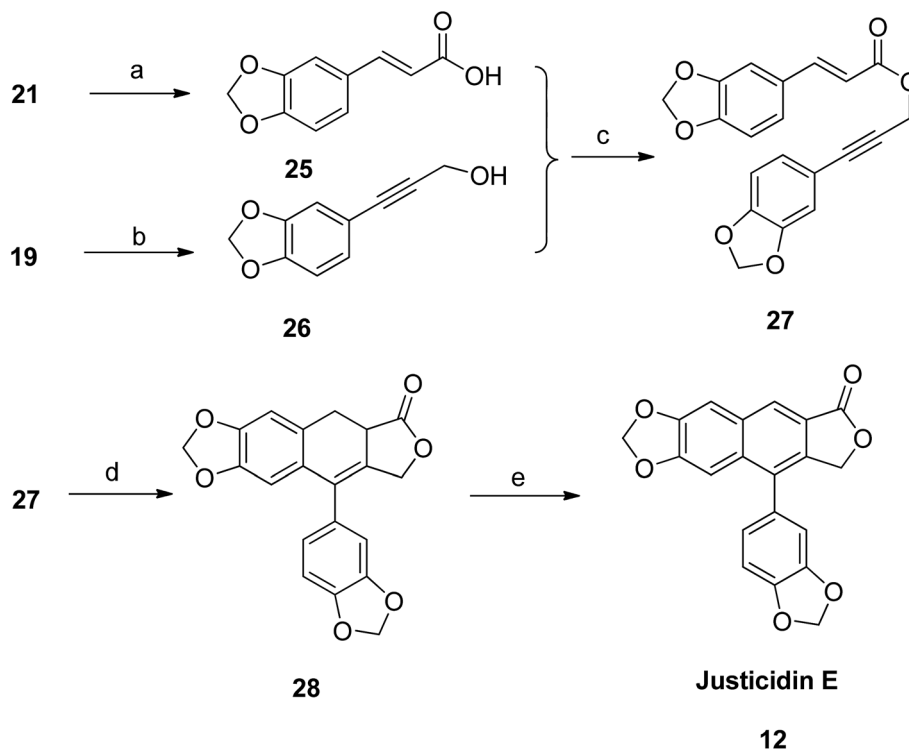
Initially, benzylation of isovanillin was performed to obtain compound **29**. Afterwards, coupling of compound **21** with **29** was carried out using DCC and DMAP in CH<sub>2</sub>Cl<sub>2</sub> to form compound **30**. Dihydronaphthalene **31** was thus obtained from an intramolecular Diels–Alder 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.*<sup>49</sup> reported the synthesis of aryl-naphthalene 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) PPh<sub>3</sub>, CBr<sub>4</sub> and CH<sub>2</sub>Cl<sub>2</sub>, rt; (b) *n*-BuLi and THF, –78 °C, then ClCO<sub>2</sub>Me, –78 °C to rt; (c) K<sub>2</sub>CO<sub>3</sub> and EtOH, rt; (d) triethyl phosphonoacetate, NaH and THF, 0 °C; (e) DIBAL-H and CH<sub>2</sub>Cl<sub>2</sub>, –78 °C; (f) DCC, DMAP and CH<sub>2</sub>Cl<sub>2</sub>, rt; (g) Ac<sub>2</sub>O, mw, 140 °C; (h) DDQ and benzene, 80 °C.

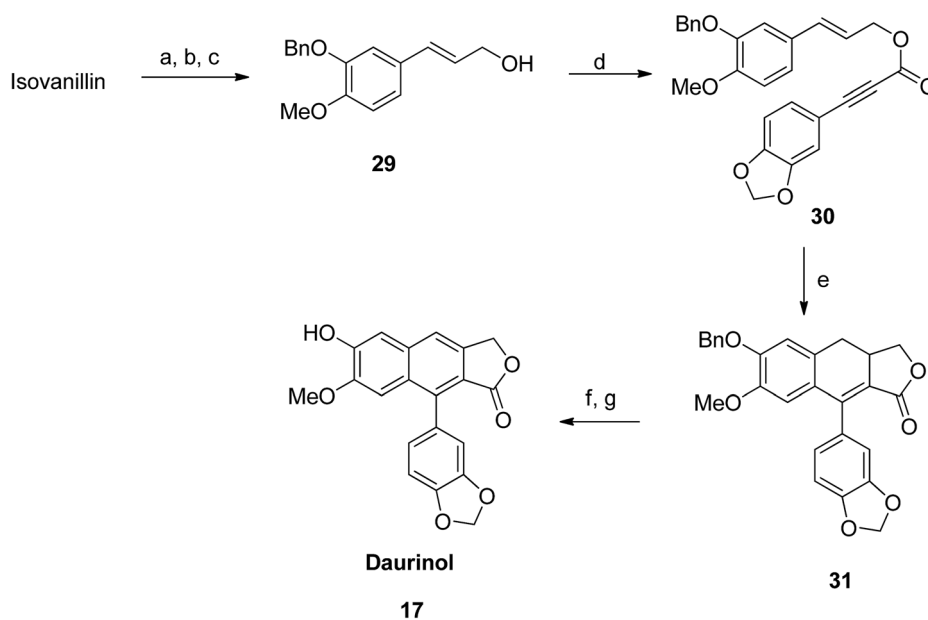




Scheme 2 Synthesis of justicidin E (12). Reagents and conditions: (a) KOH and H<sub>2</sub>O/THF, rt; (b) *n*-BuLi and THF, -78 °C, then (CH<sub>2</sub>O)<sub>*n*</sub>; (c) DCC, DMAP and CH<sub>2</sub>Cl<sub>2</sub>, rt; (d) Ac<sub>2</sub>O, mw, 140 °C; (e) DDQ and benzene, 80 °C.

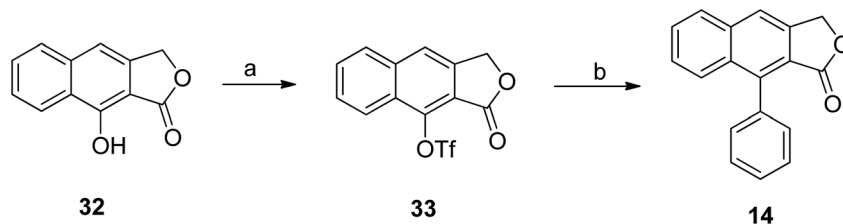
NaH.<sup>50</sup> A Suzuki reaction was further performed to introduce an aryl group to compound 33 using palladium, phenyl boronic acids and additives (depending on the substrates) to get compound 14 (Scheme 4).<sup>51,52</sup>

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.<sup>49</sup> Compound 34 reacted with



Scheme 3 Synthesis of daurinol (17). Reagents and conditions: (a) BnBr, K<sub>2</sub>CO<sub>3</sub> and EtOH, 50 °C; (b) triethyl phosphonoacetate, NaH and THF, 0 °C; (c) *n*-BuLi and THF, -78 °C, then (CH<sub>2</sub>O)<sub>*n*</sub>, -78 °C to rt; (d) compound number 20, DCC, DMAP and THF, rt; (e) Ac<sub>2</sub>O, 140 °C; (f) DDQ and benzene, 80 °C; (g) H<sub>2</sub>, Pd/C and MeOH, rt.





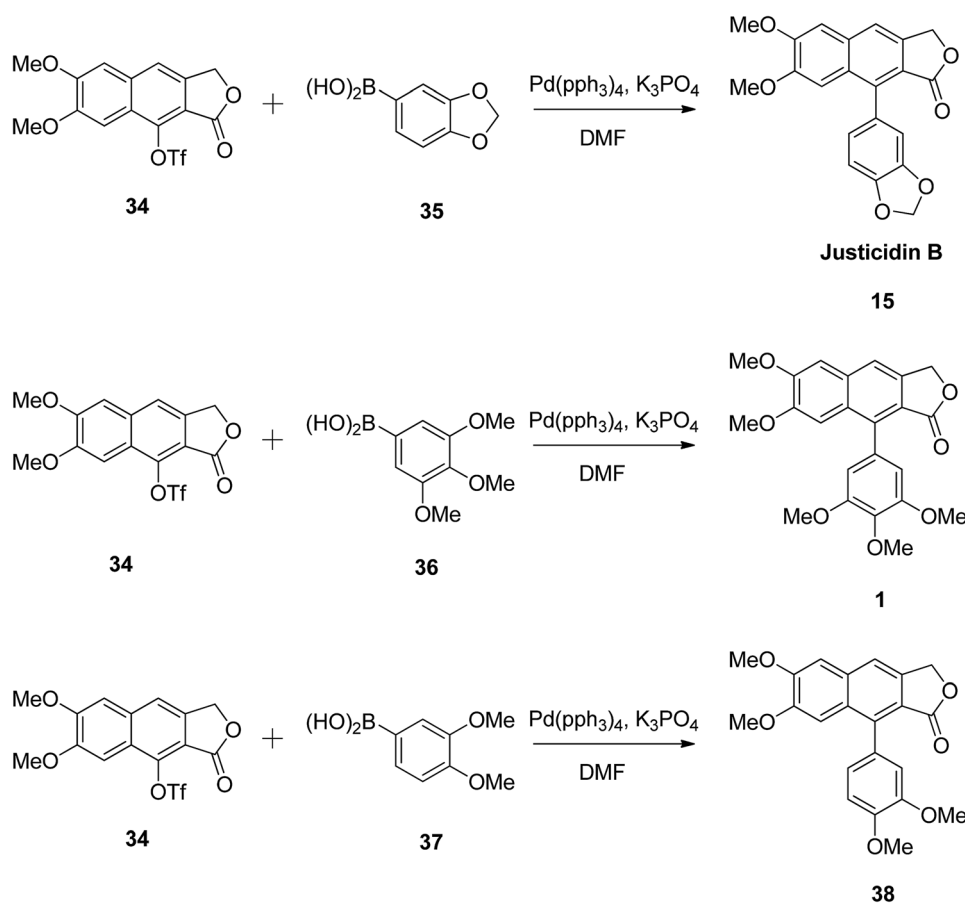
**Scheme 4** Synthesis of aryl-naphthalene lactone. Reagents and conditions: (a)  $\text{PhN}(\text{Tf})_2$ ,  $\text{Et}_3\text{N}$ , DMAP, THF; (b)  $\text{Pd}(\text{PPh}_3)_4$ ,  $\text{PhB}(\text{OH})_2$ ,  $\text{K}_3\text{PO}_4$ , DMF.

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 aryl-naphthalene lactone derivatives to elucidate the structure–activity relationships of these compounds for biological studies.

He *et al.*<sup>53</sup> reported a simple protocol for the total synthesis of aryl-naphthalene lactones. Briefly, compound **39** reacted with a zinc analog to yield 9-amino-6,7-methylenedioxy-naphtho[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-methylenedioxy-naphtho[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).

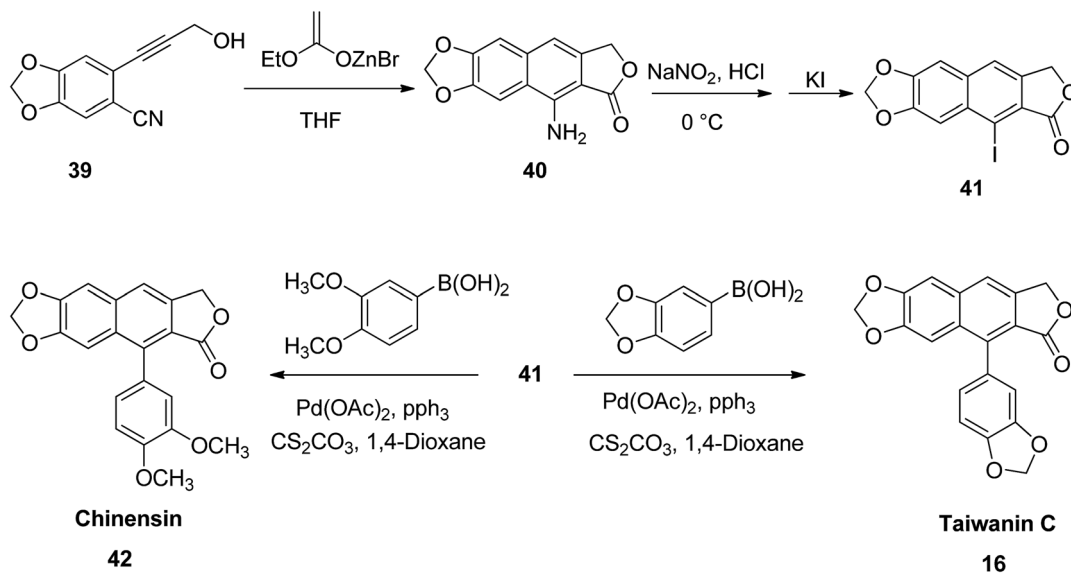
Similarly, the coupling of compound **41** with 3,4-dimethoxyphenyl boronic acid leads to the formation of chinensin (**42**). The broad scope of compounds **16** and **42** established the versatility of the new strategy. Thus, a number of aryl-naphthalene lactone lignans with diverse substitution patterns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

Hui *et al.*<sup>54</sup> synthesized a large number of aryl-naphthalene 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

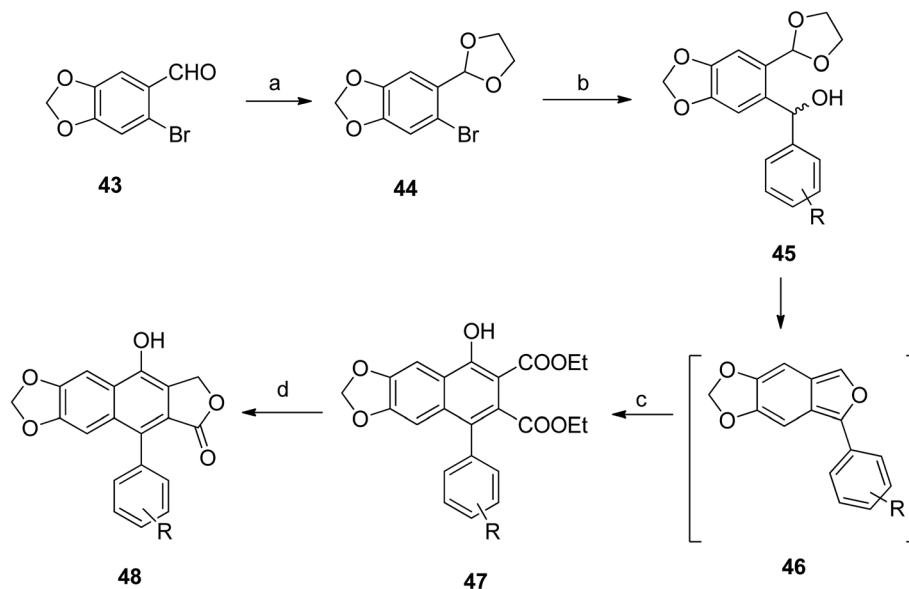
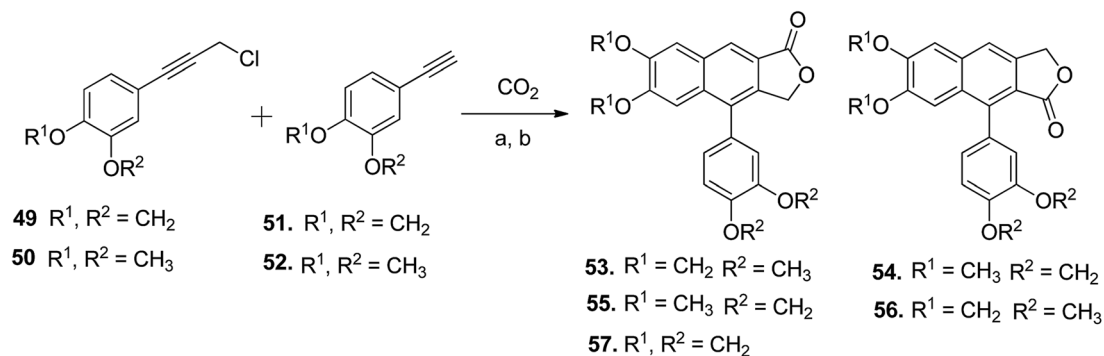


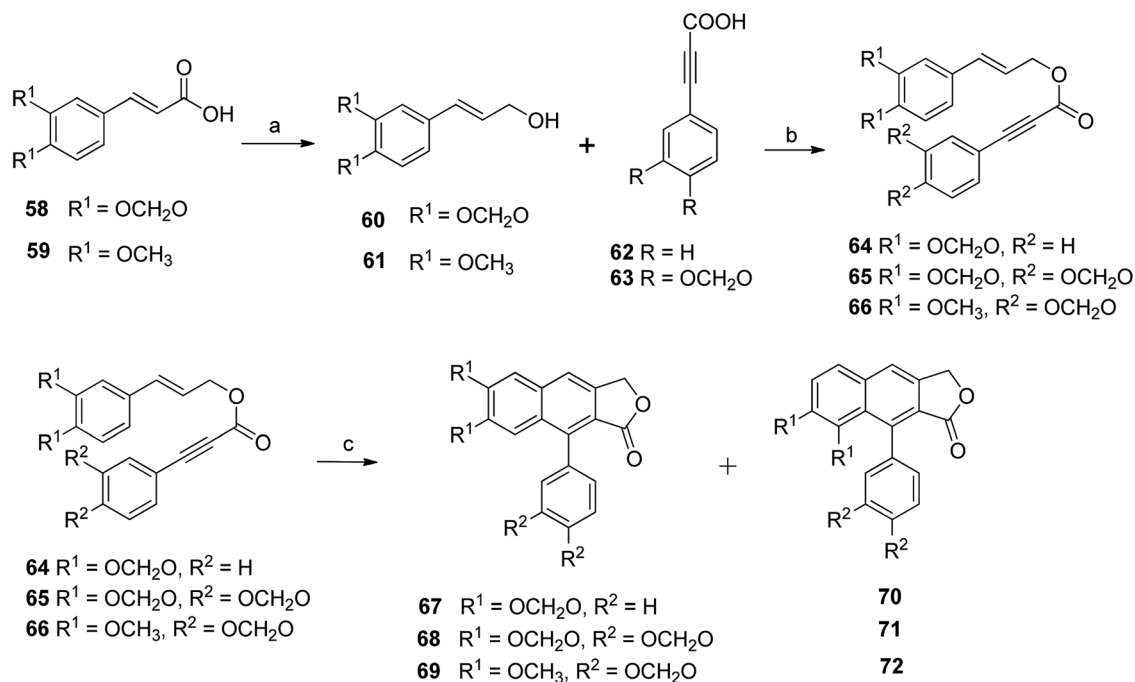
**Scheme 5** Synthesis of aryl-naphthalene lactones.





Scheme 6 Synthesis of chinensin and taiwanin C.

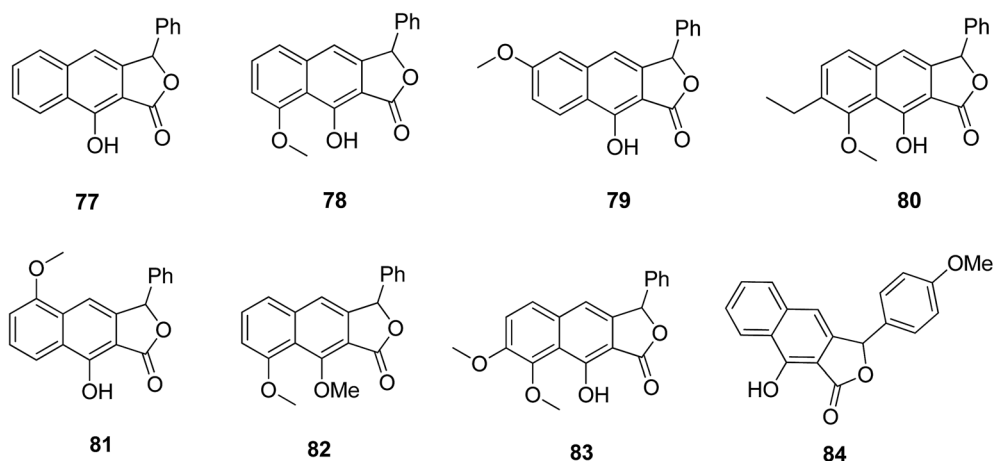
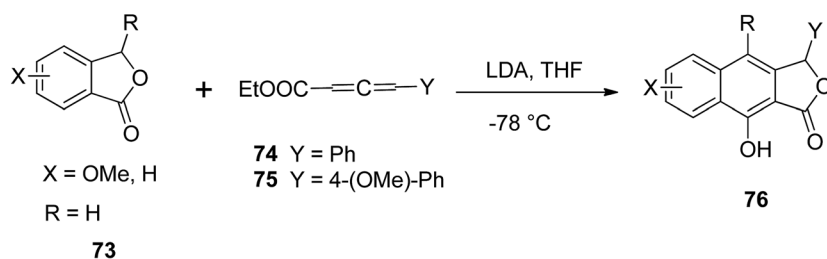
Scheme 7 Synthesis of novel aryl naphthalene lactone lignans. Reagents and conditions: (a) glycol, benzene and *p*-TsOH.H<sub>2</sub>O; (b) Ar-CHO, *n*-BuLi and THF, -78 °C; (c) DEADC, CH<sub>2</sub>Cl<sub>2</sub> and AcOH; (d) NaBH<sub>4</sub>, MeOH, then 10% HCl.Scheme 8 Synthesis of novel aryl naphthalene lactone lignans. Reagents and conditions: (a) SOCl<sub>2</sub> and DMA; (b) K<sub>2</sub>CO<sub>3</sub>, 18-crown-6, 4 Å molecular sieves and DMA, 100 °C.



**Scheme 9** Synthesis of aryl-naphthalene lactone lignan natural products. Reagents and conditions: (a)  $\text{H}_2\text{SO}_4$ , MeOH, DIBALH and DCM; (b) DCC, DMAP and DCM; (c)  $\text{PhNO}_2$  and MWI,  $180^\circ\text{C}$ , 5 min.

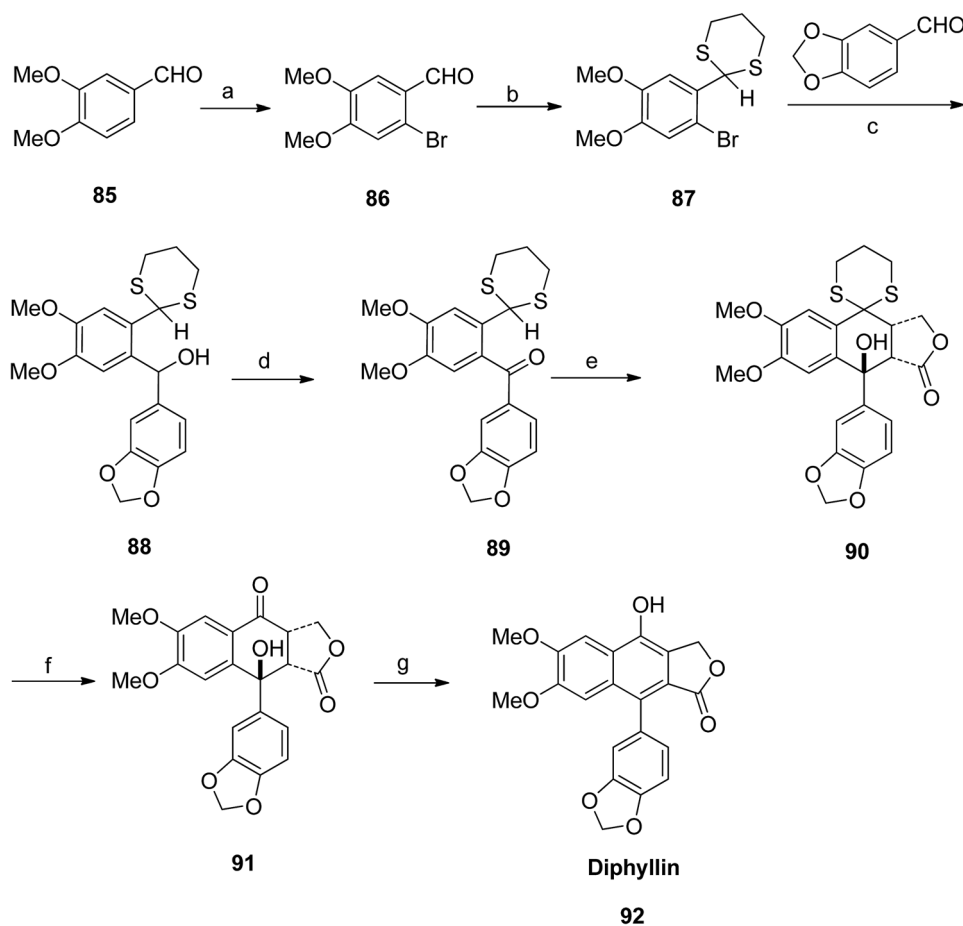
acid formed compound **47**. The final product (**48**) was obtained from the reaction of **47** with sodium borohydride and methanol (Scheme 7).

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

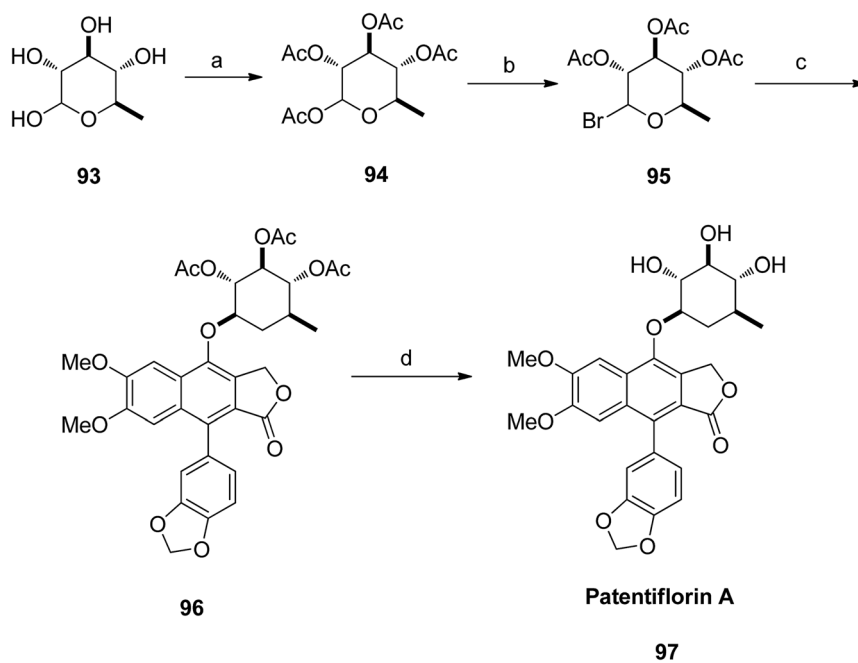


**Scheme 10** Synthesis of aryl-naphthalene lactone derivatives. Reagents and conditions: (a) LDA (3 equiv.) and THF,  $-78^\circ\text{C}$  to rt, 6–7 h, quenched with 3 M HCl; (b) MeI,  $\text{K}_2\text{CO}_3$  and acetone, room temperature, 4–8 h; (c) crude product,  $\text{K}_2\text{CO}_3$  and acetone, room temperature, 3 days.



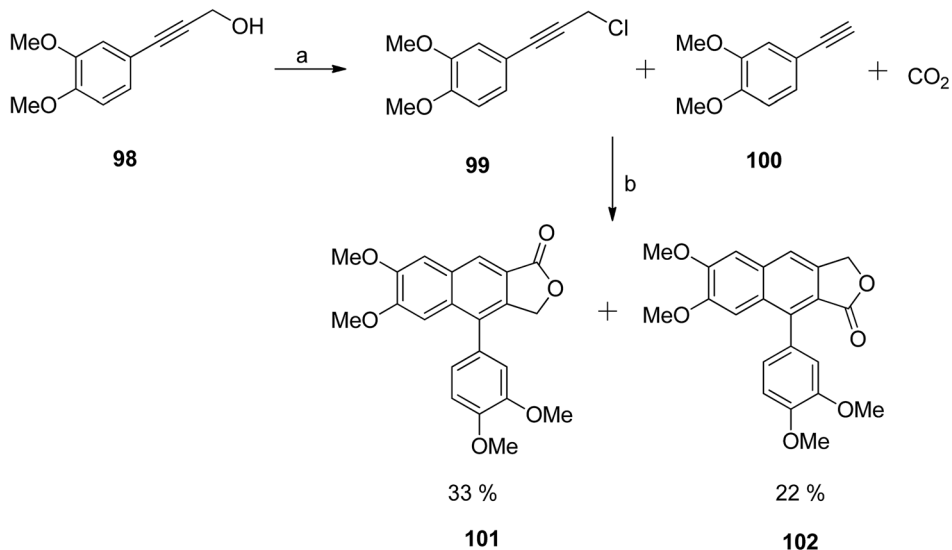


**Scheme 11** Total synthesis of diphyllin. Reagents and conditions: (a) Br and MeOH, rt, 6 h; (b) HS(CH<sub>2</sub>)<sub>2</sub>SH (*p*-TsOH) and benzene, reflux, 10 h; (c) *n*-BuLi and THF, -78 °C to rt, 2 h; (d) MnO<sub>2</sub> and CH<sub>2</sub>Cl<sub>2</sub>, rt, 16 h; (e) Compound number 89 (14.3 mmol), LDA and THF, -78 °C to rt, 1 h; (f) HgO, HgCl<sub>2</sub> and MeCN, reflux, 3 h; (g) *p*-TsOH and benzene, reflux, 16 h.

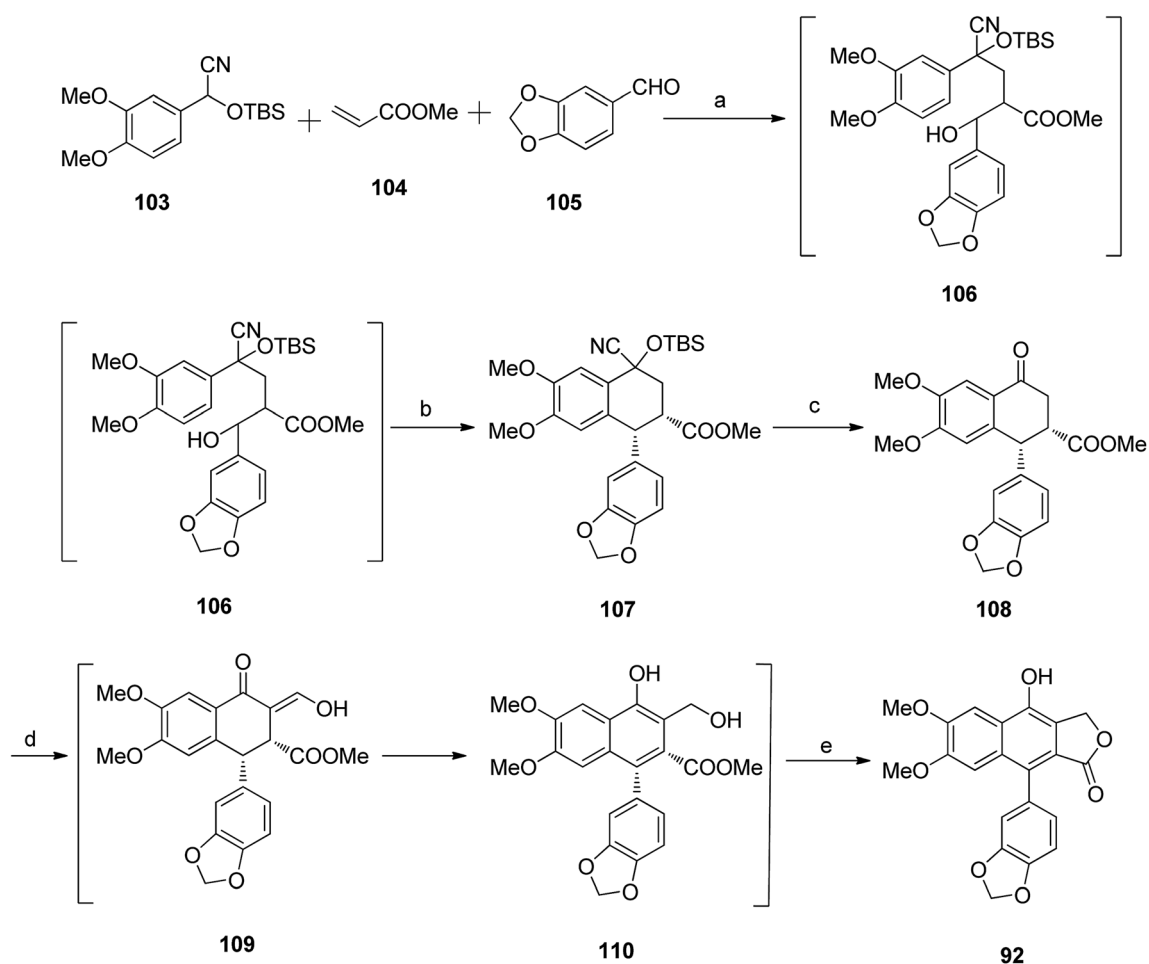


**Scheme 12** Total synthesis of patentiflorin A. Reagents and conditions: (a) DMAP, Ac<sub>2</sub>O and pyridine, rt, overnight; (b) HBr/HOAc and CH<sub>2</sub>Cl<sub>2</sub>, rt, 15 min, 99%; (c) TBAB, NaOH and CHCl<sub>3</sub>, 40 °C, 6 h; (d) K<sub>2</sub>CO<sub>3</sub> and MeOH, rt, 1 h.



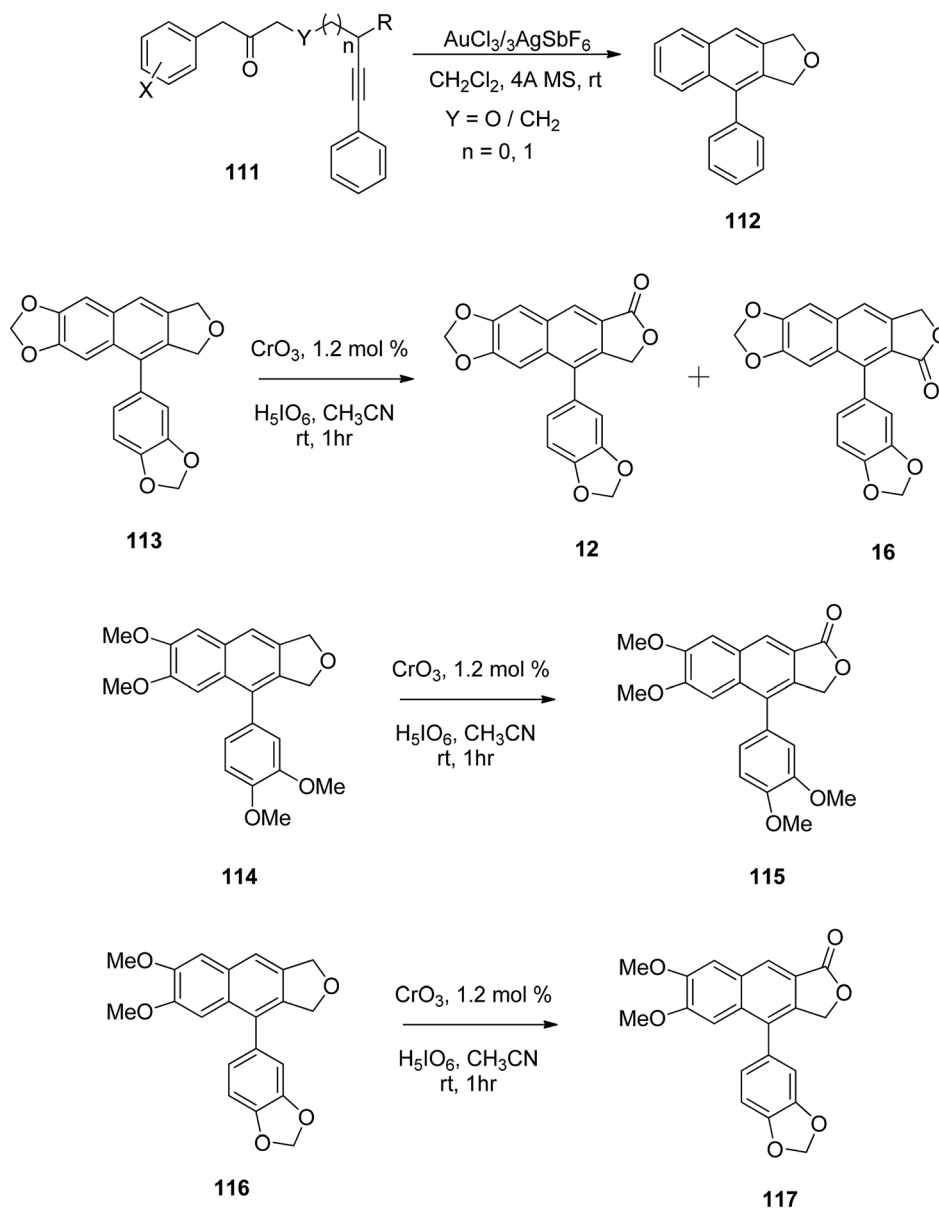


**Scheme 13** Synthesis of arynaphthalene lactones. Reagents and conditions: (a)  $\text{SOCl}_2$  and DMA; (b) AgI,  $\text{K}_2\text{CO}_3$ , 18-crown-6, DMAc and molecular sieves.



**Scheme 14** Synthesis of arynaphthalene lactone diphyllin **92**. Reagents and conditions: (a) THF at  $-78^\circ\text{C}$ ; (b) TFA/DCM,  $0^\circ\text{C}$ , 2 h; (c)  $^t\text{Bu}_4\text{NF}/\text{CH}_2\text{Cl}_2$ , rt, 1 h; (d) NaOMe, HCOOMe and benzene; (e) 6N HCl/chloroform, rt, 1 h.





Scheme 15 Synthesis of aryl-naphthalene lactones.

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.*<sup>56</sup> devised a new route for the synthesis of a series of novel aryl-naphthalene 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  $\text{PhNO}_2$  to yield a 2 : 1 mixture of aryl-naphthalene lactone **67** and its regioisomer (**70**). Likewise, compound **65** under the same reaction conditions furnished a 2 : 1 mixture of aryl-naphthalene lignan **68** and its regioisomer (**71**). The reaction of compound **66** gave a 3 : 1 mixture of aryl-naphthalene lignans **69** and **72** (Scheme 9).

Mal and Jana<sup>57</sup> 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 aryl-naphthalene lactone **76**. Various functional groups (**77**–**84**) were tolerated well under the reaction conditions (Scheme 10).

Patrick Foley *et al.*<sup>58</sup> 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  $\text{MnO}_2$  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



HgCl<sub>2</sub>. 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 protocol<sup>55</sup> was first optimised for the synthesis of unsubstituted aryl-naphthalene lactones. Afterwards, the methodology was extended towards the synthesis of a tetramethoxy-substituted aryl-naphthalene lactone natural product analog<sup>58</sup> (Scheme 13). The chloride precursor **99** was obtained from the 3,4-dimethoxyphenylpropargyl alcohol **98**. Reaction of **99** and **100** with CO<sub>2</sub> in the presence of a Ag catalyst formed two major isomers (**101** and **102**) in a 2 : 1 ratio.

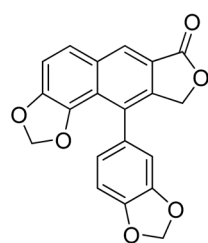
Ogiku *et al.*<sup>59</sup> reported the synthesis of diphyllin **92** following the synthesis route in Scheme 14. The conjugate addition of the anion generated from compound **103** with LDA to methyl acrylate, followed by trapping of the resultant enolate with piperonal *in situ*, furnished a mixture 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 Balamurugan<sup>60</sup> used oxidation methods for the synthesis of different aryl-naphthalene lactones.

Arylnaphthalenes fused with furan served as precursors in the preparation of aryl-naphthalene lactone lignan and its analogs. The benzylic oxidation of compound **112** has already been reported using Jones reagent, which resulted in both possible aryl-naphthalene lactones.<sup>61</sup> However, the CrO<sub>3</sub>/H<sub>3</sub>IO<sub>6</sub>/CH<sub>3</sub>CN system offers smooth benzylic oxidation at room temperature.<sup>62</sup> Under these conditions benzylic oxidation was carried out for compounds **113**, **114** and **116** to yield aryl-naphthalene 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**).

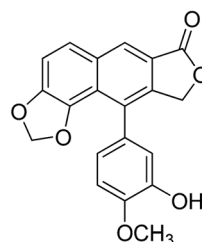
## Biological studies

Janmanchi *et al.*<sup>63</sup> 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 EC<sub>50</sub> values for each were 0.06 and 0.14 μM, 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.

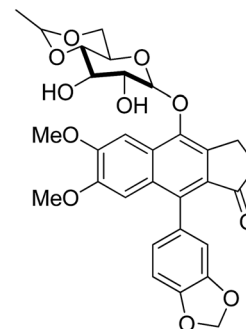


Helioxanthin

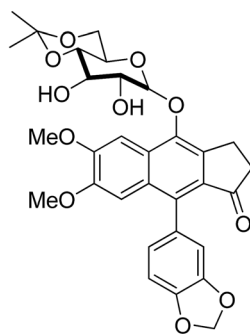
**118**



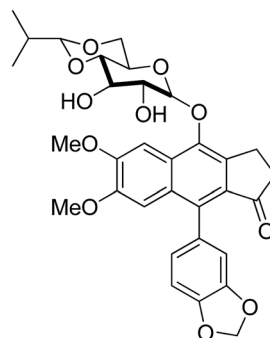
**119**



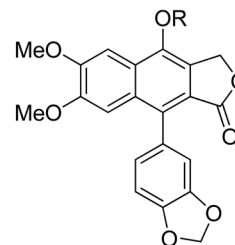
**120**



**121**



**122**

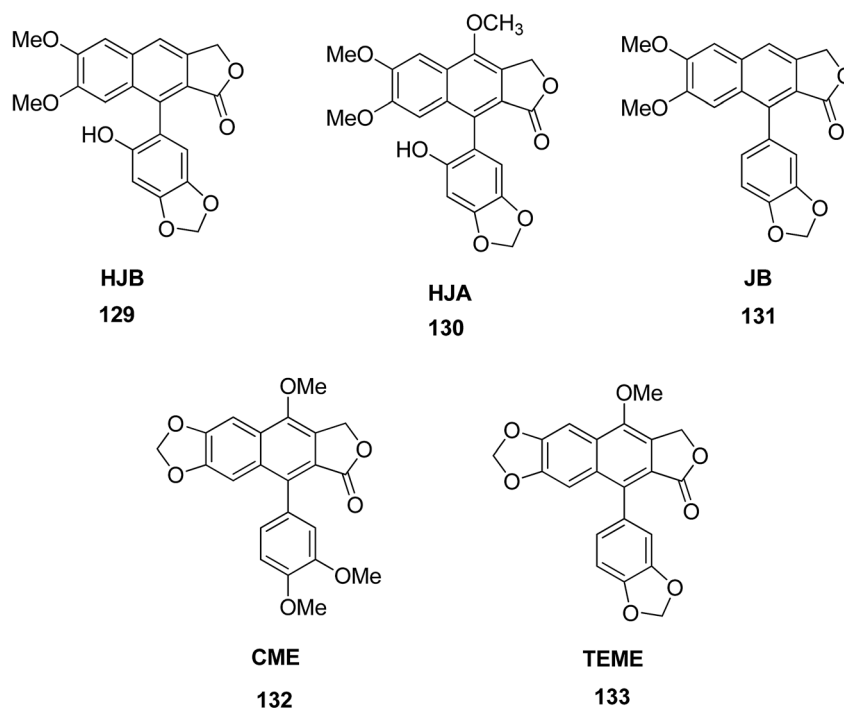


**123** R = OH  
**124** R = methyl  
**125** R = ethyl  
**126** R = n-propyl  
**127** R = n-butyl  
**128** R = n-pentyl



Da-Kuo Shi *et al.*<sup>64</sup> 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  $\mu\text{M}$ – $\text{nM}$  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 aryl-naphthalenes 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 aryl-naphthalene 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.

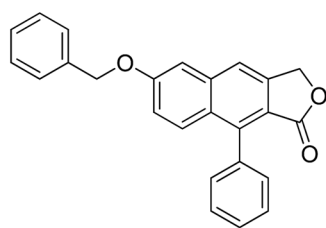
Yu *et al.*<sup>65</sup> isolated nine natural lignan justicidin A analogs and tested their cytotoxic activities against hepatocellular carcinoma (HepG2) cell lines. Compounds **123**–**128** showed potent antitumor activity, better than that of the standard drug etoposide. These compounds showed good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

Luo *et al.*<sup>66</sup> isolated five aryl-naphthalene 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

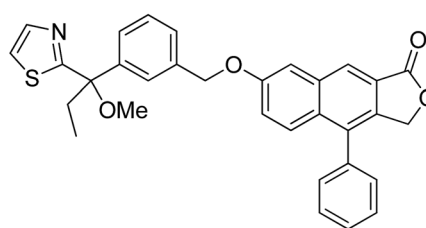
The naphthalenic lignan lactones with an oxymethylene or methyleneoxy linker are non-redox 5-lipoxygenase inhibitors. 5-Lipoxygenase is involved in the biosynthesis of leukotrienes from arachidonic acid. Compound **134** showed potent non-redox inhibition activity against the enzyme. The design of a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

Hui *et al.*<sup>69</sup> reported a series of novel aryl-naphthalene 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 anti-tumor activity, having an  $IC_{50}$  value of 18.9  $\mu\text{M}$  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.

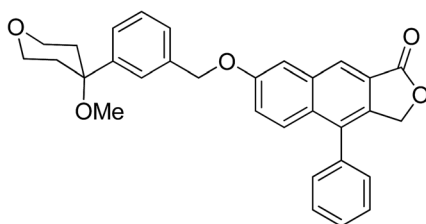




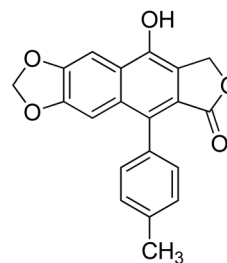
134



135



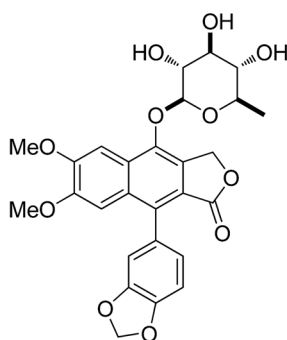
136



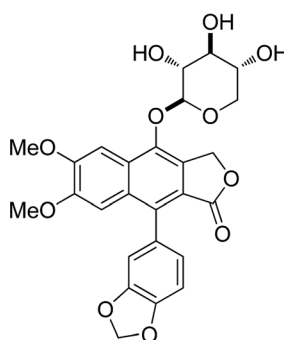
137

Zhang *et al.*<sup>70</sup> 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 T-tropic HIV-1 isolates and showed significantly higher activity than the standard anti-HIV drug, zidovudine (AZT).

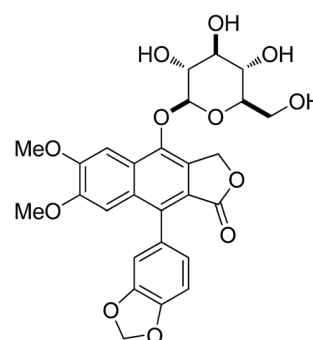
effective than AZT in inhibiting four different HIV-1 isolates, either M- or T-tropic, in human PBMCs with IC<sub>50</sub> values in the range 14–32 nM. Hence, ANL glycosides have the potential to be developed as novel anti-HIV drugs in the future.



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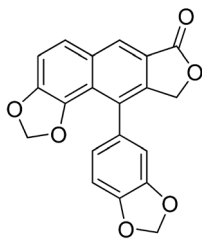


140

Patentiflorin A (**138**) and two congeners (**139–140**) were synthesized *via* structural modifications and tested as anti-HIV aryl-naphthalene 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

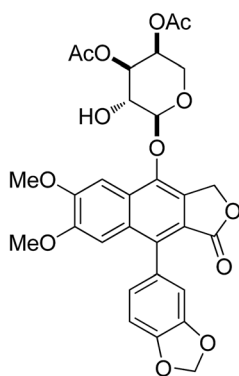
Hajdu *et al.*<sup>71</sup> isolated helioxanthin (**141**) from fresh roots of *Heliopsis helianthoides var. scabra* and evaluated its *in vitro* brain tumor activity. Compound **141** inhibited the migration of melanoma and brain endothelial cells, and also reduced the adhesion of melanoma cells to 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.



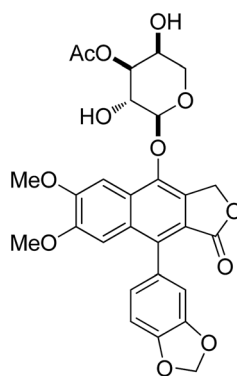


141

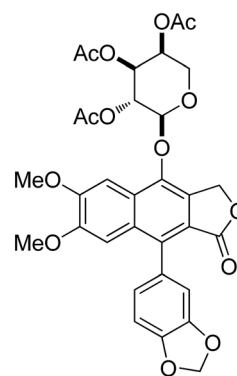
Ren *et al.*<sup>72</sup> isolated two new (**142** and **143**) and four known (**3–6**) aryl-naphthalene lignan lactones from *Phyllanthus poilanei* collected in Vietnam, with one further known analog (**144**) being prepared from phyllanthusmin C (**4**). Some of these aryl-naphthalene lignan lactones were cytotoxic toward HT-29 human colon cancer cells. Compounds **142** and **144** were found to be the more potent inhibitors, with IC<sub>50</sub> 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.



142



143



144

## Abbreviations

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

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## Conclusion

Aryl-naphthalene lactone lignan analogs display multiple biological and pharmacological activities. In recent years, large numbers of aryl-naphthalene 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 aryl-naphthalene 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.

## References

- 1 D. J. Newmann and G. M. Cragg, *J. Nat. Prod.*, 2007, **70**, 461–477.
- 2 K. Kumar and H. Waldmann, *Angew. Chem., Int. Ed.*, 2009, **48**, 3224–3242.
- 3 J. P. Nandy, M. Prakesch, S. Khadem, T. Reddy, U. Sharma and P. Arya, *Chem. Rev.*, 2009, **109**, 1999–2060.
- 4 J. E. Park, J. Lee, S. Y. Seo and D. Shin, *Tetrahedron Lett.*, 2014, **55**, 818–820.
- 5 R. S. Ward, *Nat. Prod. Rep.*, 1999, **16**, 75–96.
- 6 S. Apers, A. Vlietinck and L. Pieters, *Phytochem. Rev.*, 2003, **2**, 201–217.
- 7 K. Kawazoe, A. Yutani, K. Tamemoto, S. Yuasa, H. Shibata, T. Higuti and Y. Takaishi, *J. Nat. Prod.*, 2001, **64**, 588–591.
- 8 K. S. Sagar, C. C. Chang, W. K. Wang, J. Y. Lin and S. S. Lee, *Bioorg. Med. Chem.*, 2004, **12**, 4045–4054.



- 9 H. Yeo, Y. Li, L. Fu, J. L. Zhu, E. A. Gullen, G. E. Dutschman, Y. Lee, R. Chung, E. S. Huang, D. J. Austin and Y. C. Cheng, *J. Med. Chem.*, 2005, **48**, 534–546.
- 10 Y. Li, L. Fu, H. Yeo, J. L. Zhu, C. K. Chou, Y. H. Kou, S. F. Yeh, E. Gullen, D. Austin and Y. C. Cheng, *Antiviral Chem. Chemother.*, 2005, **16**, 193–201.
- 11 D. Janmanchi, Y. P. Tseng, K. C. Wang, R. L. Huang, C. H. Lin and S. F. Yeh, *Bioorg. Med. Chem.*, 2010, **18**, 1213–1226.
- 12 P. B. McDoniel and J. R. Cole, *J. Pharm. Sci.*, 1972, **61**, 1992–1994.
- 13 A. Pelter, R. S. Ward, P. Satyanarayana and P. Collins, *J. Chem. Soc., Perkin Trans. 1*, 1983, 643–647.
- 14 A. S. Capilla, I. Sánchez, D. H. Caignard, P. Renard and M. D. Pujola, *Eur. J. Med. Chem.*, 2001, **36**, 389–393.
- 15 C. C. Chen, W. C. Hsin, F. N. Ko, Y. L. Huang, J. C. Ou and C. M. Teng, *J. Nat. Prod.*, 1996, **59**, 1149–1150.
- 16 J. R. Weng, H. H. Ko, T. L. Yeh, H. C. Lin and C. N. Lin, *Arch. Pharm.*, 2004, **337**, 207–212.
- 17 T. Ukita, Y. Nakamura, A. Kubo, Y. Yamamoto, M. Takahashi, J. Kotera and T. Ieko, *J. Med. Chem.*, 1999, **42**, 1293.
- 18 T. Iwasaki, K. Kondo, T. Kuroda, Y. Moritani, S. Yamagata, M. Sugiura, H. Kikkawa, O. Kaminuma and K. Ikezawa, *J. Med. Chem.*, 1996, **39**, 2696–2704.
- 19 M. Thérien, B. J. Fitzsimmons, J. Scheigets, D. Macdonald, L. Y. Choo, J. Guay, J. P. Falguyret and D. Riendeau, *Bioorg. Med. Chem.*, 1993, **3**, 2063–2066.
- 20 D. Delorme, Y. Ducharme, C. Brideau, C. C. Chan, N. Charet, S. Desmarais, D. Dubé, J. P. Falguyret, R. Fortin, J. Guay, *et al.*, *J. Med. Chem.*, 1996, **39**, 3951–3970.
- 21 Y. Ducharme, C. Brideau, D. Dubé, C. C. Chan, J. P. Falguyret, J. W. Gillard, J. Guay, *et al.*, *J. Med. Chem.*, 1994, **37**, 512–518.
- 22 C. W. Chang, M. T. Lin, S. S. Lee, C. S. Karin, K. C. S. Chen Liu, F. L. Hsu and J. Y. Lin, *Antiviral Res.*, 1995, **27**, 367–374.
- 23 S. S. Lee, M. T. Lin, C. L. Liu, Y. Y. Lin and K. C. S. Chen Liu, *J. Nat. Prod.*, 1996, **59**, 1061–1065.
- 24 C. Cow, C. Leung and J. L. Charlton, *Can. J. Chem.*, 2000, **78**, 553–561.
- 25 S. J. Wu and T. S. Wu, *Chem. Pharm. Bull.*, 2006, **54**, 1223–1225.
- 26 S. Hemmatia, T. J. Schmidt and E. Fuss, *FEBS Lett.*, 2007, **581**, 603–610.
- 27 T. J. Schmidt, S. Hemmati, M. Klaes, B. Konuklugil, A. Mohagheghzadeh, I. Ionkova, E. Fuss and A. W. Alfermann, *Phytochemistry*, 2010, **71**, 1714–1728.
- 28 C. Ramesh, N. Ravindranath, T. S. Ram and B. Das, *Chem. Pharm. Bull.*, 2003, **51**, 1299–1300.
- 29 S. J. Wu and T. S. Wu, *Chem. Pharm. Bull.*, 2006, **54**, 1223–1225.
- 30 J. Z. Wang, X. Tian, H. Tsumura, K. Shimura and H. Ito, *Anticancer. Drug. Des.*, 1993, **8**, 193–202.
- 31 L. Daley, Y. Guminski, P. Demerseman, A. Kruczynski, C. Etievant, *et al.*, *J. Med. Chem.*, 1998, **41**, 4475–4485.
- 32 I. Rassmann, R. Thodtmann, M. Mross, A. Huttmann, W. E. Berdel, *et al.*, *Invest. New Drugs*, 1998, **16**, 319–324.
- 33 T. Utsugi, J. Shibata, Y. Sugimoto, K. Aoyagi, K. Wierzba, *et al.*, *Cancer Res.*, 1996, **56**, 2809–2814.
- 34 L. Daley, P. Meresse, E. Bertounesque and C. Monneret, *Tetrahedron Lett.*, 1997, **38**, 2673–2676.
- 35 D. S. Van Vliet and K. H. Lee, *Tetrahedron Lett.*, 1990, **40**, 2259–2262.
- 36 T. S. Huang, C. C. Lee, Y. Chao, C. H. Shu, L. T. Chen, *et al.*, *Pharm. Res.*, 1999, **16**, 997–1002.
- 37 T. S. Huang, C. H. Shu, C. C. Lee, L. T. Chen and J. Whang-Peng, *Apoptosis*, 2000, **5**, 79–85.
- 38 C. C. Lee and T. S. Huang, *Pharm. Res.*, 2001, **18**, 846–851.
- 39 S. K. Lin, H. C. Huang, L. L. Chen, C. C. Lee and T. S. Huang, *Mol. Pharmacol.*, 2001, **60**, 768–775.
- 40 J. M. Barret, C. Etievant, C. Baudouin, K. Skov, M. Charveron, *et al.*, *Anticancer Res.*, 2002, **22**, 187–192.
- 41 R. Stevenson and J. V. Weber, *J. Nat. Prod.*, 1989, **52**, 367–375.
- 42 R. Stevenson and J. V. Weber, *J. Nat. Prod.*, 1991, **54**, 310–314.
- 43 P. T. Anastas and R. Stevenson, *J. Nat. Prod.*, 1991, **54**, 1687–1691.
- 44 Y. Sato, T. Tamura and M. Mori, *Angew. Chem., Int. Ed. Engl.*, 2004, **43**, 2436–2440.
- 45 N. Eghbali, J. Eddy and P. T. Anastas, *J. Org. Chem.*, 2008, **73**, 6932–6935.
- 46 P. Foley, N. Eghbali and P. T. Anastas, *J. Nat. Prod.*, 2010, **73**, 811–813.
- 47 Y. Nishii, T. Yoshida, H. Asano, K. Wakasugi, J. Morita, Y. Aso, E. Yoshida, J. Motoyoshiya, H. Aoyama and Y. Tanabe, *J. Org. Chem.*, 2005, **70**, 2667–2678.
- 48 J. E. Park, J. Lee, S. Y. Seo and D. Shin, *Tetrahedron Lett.*, 2014, **55**, 818–820.
- 49 F. Hayat, L. Kang, C. Y. Lee and D. Shin, *Tetrahedron*, 2015, **71**, 2945–2950.
- 50 Y. Xia, P. Qu, Z. Liu, R. Ge, Q. Xiao, Y. Zhang and J. Wang, *Angew. Chem., Int. Ed.*, 2013, **52**, 2543–2546.
- 51 F. Alonso, I. P. Beletskaya and M. Yus, *Tetrahedron*, 2008, **64**, 3047–3101.
- 52 M. M. Heravi and E. Hashemi, *Tetrahedron*, 2012, **68**, 9145–9178.
- 53 Y. He, X. Zhang and X. Fan, *Chem. Commun.*, 2014, **50**, 5641–5643.
- 54 J. Hui, Y. Zhao and L. Zhu, *Med. Chem. Res.*, 2012, **21**, 3994–4001.
- 55 P. Foley, N. Eghbali and P. T. Anastas, *J. Nat. Prod.*, 2010, **73**, 811–813.
- 56 I. S. Kocsis and K. M. Brummond, *Org. Lett.*, 2014, **16**, 4158–4161.
- 57 M. Dipakranjan and S. Jana, *J. Org. Chem.*, 2016, **81**, 11857–11865.
- 58 P. Foley, N. Eghbali and P. T. Anastas, *Green Chem.*, 2010, **12**, 888–892.
- 59 T. Ogiku, S. Yochida, T. Kuroda, H. Ohmizu and T. Iwasaki, *Synlett*, 1992, 651–652.
- 60 V. Gudla and R. Balamurugan, *J. Org. Chem.*, 2011, **76**, 9919–9933.
- 61 R. Ahmed, T. L. Holmes and R. J. Stevenson, *Heterocycl. Chem.*, 1974, **11**, 687–690.
- 62 S. Yamazaki, *Org. Lett.*, 1999, **1**, 2129–2132.



- 63 D. Janmanchi, Y. P. Tseng, K. C. Wang, R. L. Huang, C. H. Lin and S. F. Yeh, *Bioorg. Med. Chem.*, 2010, **18**, 1213–1226.
- 64 D. K. Shi, W. Zhang, N. Ding, M. Li and Y. X. Li, *Eur. J. Med. Chem.*, 2012, **47**, 424–431.
- 65 Y. Zhao, W. Dan, H. Jie and Z. Li, *Med. Chem. Res.*, 2010, **19**, 71–76.
- 66 J. Luo, Y. Hu, W. Kong and M. Yang, *Plos One.*, 2014, **3**, e93516.
- 67 Y. Ducharme, C. Brideau, D. Dubé, C. C. Chan, J. P. Falguyret, J. W. Gillard, J. Guay, J. H. Hutchinson, C. S. McFarlane, D. Riendeau, J. Scheigetz and Y. Girard, *J. Med. Chem.*, 1994, **37**, 512–518.
- 68 S. Apers, A. Vlietinck and L. Pieters, *Phytochem. Rev.*, 2003, **2**, 201–217.
- 69 J. Hui, Y. Zhao and L. Zhu, *Med. Chem. Res.*, 2012, **21**, 3994–4001.
- 70 A. J. Zhang, E. R. Booms, Y. F. Guan, D. Y. Wang, K. L. Liu, W. F. Li, V. H. Nguyen, N. M. Cuong, D. D. Soejarto, H. H. S. Fong and L. Rong, *J. Nat. Prod.*, 2017, **80**, 1798–1807.
- 71 Z. Hajdu, J. Hasko, I. A. Krizbai, I. Wilhelm, N. Jedlinszki, C. Fazakas, J. Molna, P. Forgo and J. Hohmann, *J. Nat. Prod.*, 2014, **77**, 2641–2650.
- 72 Y. Ren, D. D. Lantvit, Y. Deng, R. Kanagasabai, J. C. Gallucci, T. N. Ninh, H. Chai, D. D. Soejarto, J. R. Fuchs, *et al.*, *J. Nat. Prod.*, 2014, **77**, 1494–1504.

