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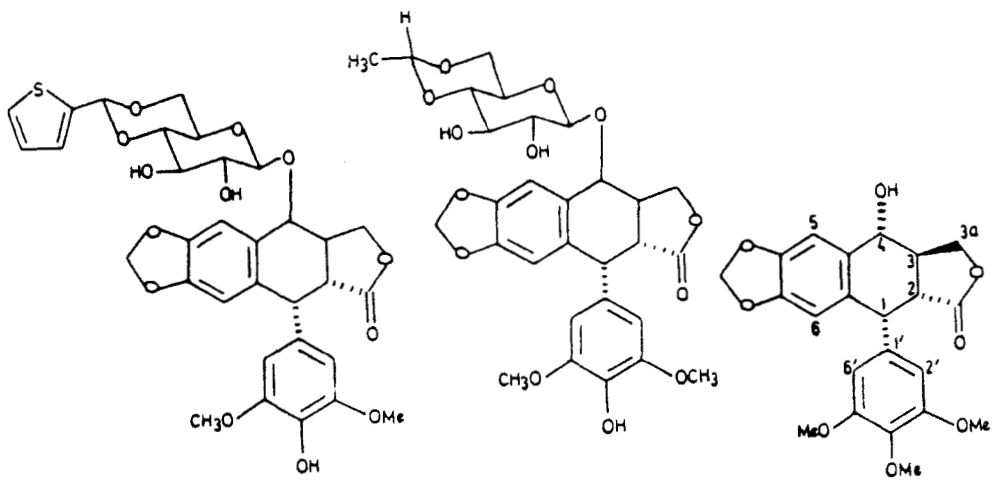
Cytotoxic lignans from *Haplophyllum* species

A. Ulubelen[1,2], R.R. Gil[3], G.A. Cordell[3], A.H. Meriçli[1] and F. Meriçli[1]

[1]Faculty of Pharmacy, University of Istanbul, 34452, Istanbul, Turkey
[2]TUBITAK, Marmara Research Center, Department of Chemistry, P.O.Box 21, 41470, Gebze-Kocaeli, Turkey
[3]Program for Collaborative Research in the Pharmaceutical Sciences, Department of Medicinal Chemistry and Pharmacognosy, College of Pharmacy, University of Illinois at Chicago, Chicago, IL 60602, USA.

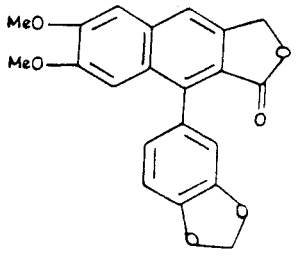
Abstract: Four new lignans were isolated from *Haplophyllum ptilostylum*, their structures were establihed by spectral data, using COSY, HETCOR, COLOC, selective INEPT experiments. Pharmacological tests were performed on human cell lines and HIV-1 reverse transcriptase.

The success of semisynthetic anticancer drugs etoposide (**1**) and teniposide (**2**) focused the attention on the availability of podophyllotoxin (**3**) which was first isolated from *Podophyllum peltatum* L. later in higher quantity from *P.hexandrum* [1]. Since the total synthesis of podophyllotoxin is uneconomic, either systematic cultivation of the plant or tissue culture methods could be used to produce compound **3**, a third way is to screen seed bearing plants for aryltetraline lignans [2]. During the

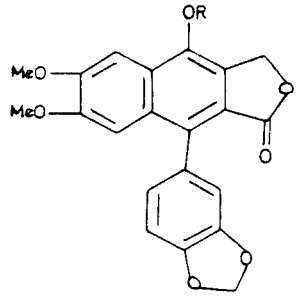


1 Teniposide 2 Etoposide 3 Podophyllotoxin

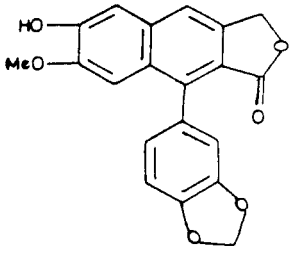
screening of this type plants, arylnaphtalene lignans were also found to possess antitumor activity. Since antitumor active arylnaphtalene lignans were isolated from *Haplophyllum* species together with diarylbutyrolactone lignans, this group of plants were also investigated. Among these plants *H.tuberculatum* yielded justicin A, B, diphyllin and tuberculatin [3], as well as antibacterial and antimitotic compounds polygamain and kusunokinin [4]. From *H.myrtifolium* two new lignans, an arylnaphtalene type, haplomyrtin and a diarylbutyrolactone type, (-)-haplomyrfolin were isolated [5]. *H.cappadocicum* revealed the presence of justicin A, B, diphyllin, 4-deoxyisodiphyllin, daurinol and isodaurinol [6]. Daurinol derivatives, daurinol glucoside and mono-O-acetyldaurinol glucoside were found in *H.buxbaumii* [7]. Our studies with *Haplophyllum* species showed the presence of antitumor active lignans, justicin B (**4**) from *H.buxbaumii* [8], diphyllin (**5**) and a new compound 4-acetyl-diphyllin (**6**) from *H.telephioides* [9]. From *H.ptilostylum* we have obtained compound **4** together with isodaurinol (**7**) [10], as well as arylbutyrolactone lignans, matairesinol (**8**) and arctigenin (**9**) [11].



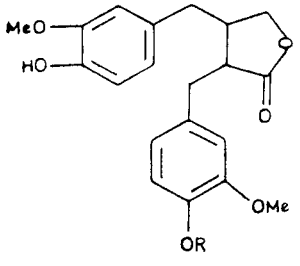
4 Justicin B



5 R=H Diphyllin
6 R=Ac 4-Acetyldiphyllin



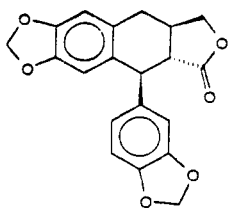
7 Isodaurinol



8 R=H Matairesinol
9 R=Me Arctigenin

In recent studies with the same extracts of *H.ptilostylum* four new compounds were isolated. One of them was a new isomer of polygamain (1β-polygamain) (**10**), the other three were arylbutyrolactone

type lignans (**11-13**). The structures were established by using ^{1}H NMR, ^{13}C NMR and various techniques such as COSY, HETCOR, COLOC, DEPT and selective INEPT experiments. Compound **11** was established as 4-[6",7"-dihydroxygeranoyl]-matairesinol. Compound **12** was found as a mixture of two isomers and could only be differentiated from the ^{13}C NMR spectrum and selective INEPT experiments and they were found as two isomers of 4-isopentylhaplomyrfolin type A and type B. In compound **13** the lactone ring of matairesinol moiety was reduced to alcohol and it carries a geraniol side chain. Compound **13** was also a mixture of two isomers corresponding to type A and type B. The structure of **13** was established as 4-geranoyl-9-hydroxymateiresinol. The bioassay showed that neither of the compounds was cytotoxic against a lung carcinoma (LU-1), a hormon dependant human prostate and hormon dependant breast cancer cell lines, but some moderate activity (IC_{50}=111.7 μg/ml) was observed for compound **10** in the HIV-1 reverse transcriptase (p66/p51) assay. Additional cytotoxicity tests is under investigation.



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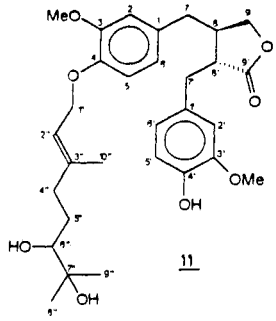

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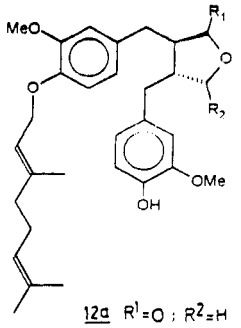
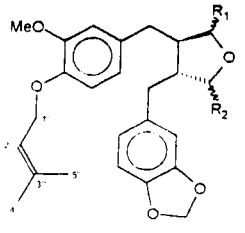


12a R^1=O ; R^2=H
12b R^1=H ; R^2=O



13a R^1=H ; R^2=OH
13b R^1=OH ; R^2=H

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