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Synthesis and Cytotoxicity Evaluation of Some Isoquinoline Derivatives Related to 1-Arylnaphthalene Lignans

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Abstract: Two series of novel compounds designed as hybrids of 1-arylnaphthalene lignans with dihydroisoquinolines or isoquinolines were synthesized and evaluated for their cytotoxicities on human tumor cell lines, such as A549, Hela, PC-3 and KB. Some of the synthetic compounds exhibited their IC_{50} values on selected cell lines at μmol/L scale.

Keywords: Isoquinoline derivatives, 1-arylnaphthalene lignans, synthesis, cytotoxicity.

1-Arylnaphthalene lignans were reported to possess various biological properties, especially cytotoxicity. The potent antitumor agent, podophyllotoxin **1**, and two of its semi-synthetic derivatives etoposide **2** and teniposide **3** (**Figure 1**) are belong to this family[1,2]. The latter two have been introduced to various protocols for cancer chemotherapy[3]. To search for better alternatives of antitumor agents of this type, podophyllotoxin heterocyclic analogues have been attracting much attention and a number of synthetic and/or biological studies have been reported[4-6]. The findings that some of these analogues, *e.g.*, 2, 4-diaza-4-deoxypodophyllotoxin **4**[6] and azatoxin **5**[7], showed significant antitumor activities as that of **1** or **2**, suggested that the incorporation of nitrogen atoms in the molecular framework would at least not decrease the antitumor activities of the compounds. Most N-heterocyclic analogues available in literatures were based on tetrahydroquinolines and tetrahydroisoquinolines[4-7], while little work based on dihydroisoquinolines and isoquinolines.

As a part of our efforts in searching for potent cytotoxic agents from natural sources or their synthetic derivatives, we designed and synthesized two series of novel compounds as hybrids of 1-arylnaphthalene lignans with dihydroisoquinolines or isoquinolines. Furthermore, all of the synthetic compounds were tested *in vitro* against four cultured human tumor cell lines to evaluate their cytotoxicities.

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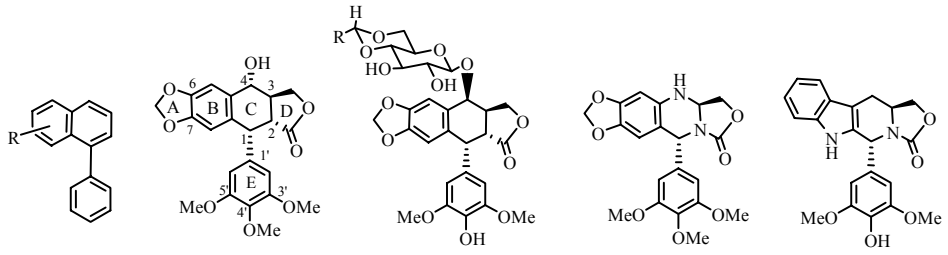
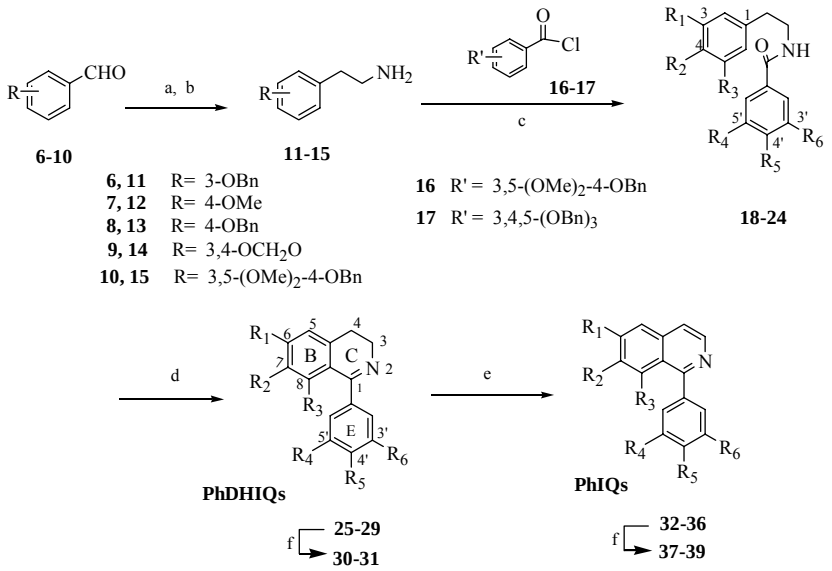
Figure 1 Structural comparison of podophyllotoxin derivatives



Scheme 1 The synthetic route of isoquinoline derivatives



Reagents and conditions: (a) CH_3NO_2, NH_4OAc, reflux, 1 h, 90%; (b) $LiAlH_4$, ether/THF (4:1), reflux 4 h, 85%; (c) Et_3N (2 drops), CH_2Cl_2, rt, 4 h, 78%; (d) $POCl_3$, dry toluene, reflux, 4 h, 64%; (e) 10% Pd/C, decalin, 200 ^oC , 12 h, 40%; (f) 10% Pd/C, H_2, 1 atm, rt, overnight, 95%.

The synthetic strategy adopted to obtain the two series of derivates is described in **cheme 1**, and the substituents of compounds and their properties were shown in **Table 1**. All of the structures were characterized by ^1H NMR and MS[8], and all of these 15 synthetic compounds are novel.

The starting materials, five benzaldehydes **6**–**10**, were commercially available or prepared according to the reported procedures. They were converted to corresponding β-phenylethylamines **11**−**15** *via* Henry reaction followed by reduction of $LiAlH_4$ (80% yield in two steps)[9]. Condensed with two kinds of trisubstituted benzoyl chlorides **16** and **17**，both of them were prepared from methyl gallate, the amines were transformed to

the expected N-phenylethylbenzoylamides **18**−**24** under Schotten−Baumann conditions in 78% yield[9]. The cyclization of the amides to 1-(3, 4, 5-trisubstituted)phenyl-3, 4-dihydroisoquinolines (PhDHIQs) **25**−**29** was accomplished with $POCl_3$ by Bischler−Napieralski reaction[10]. However, we found that not all cyclizations could be achieved to give the expected 3, 4-dihydroisoquinolines. The reaction was found to depend on the substitutes on the phenyl ring of the amines, for 4-methoxy and 4-benzyloxy substituted amides failed to be cyclized. The preparation of the 1-(3, 4, 5- trisubstituted)phenyl-isoquinolines (PhIQs) **32**−**36** was achieved by dehydrogenation in the presence of palladium-carbon from PhDHIQs **25**−**29** in 40% yield[10]. Furthermore, as a part of our synthetic strategy for preparing analogues with phenolic groups, compounds **25**−**26** and **32**−**34** were selected for deprotection affording the corresponding hydroxyl derivatives **30**−**31** and **37**−**39** in good yields.

Table 1 The substitutents of compounds **25**−**39**

Compd.	R_1	R_2	R_3	R_4	R_5	R_6	mp (°C)	Yield (%)
25	OBn	H	H	OCH_3	OBn	OCH_3	129-130	68
26	OCH_2O		H	OCH_3	OBn	OCH_3	gum	82
27	OCH_2O		H	OBn	OBn	OBn	gum	72
28	OCH_3	OBn	OCH_3	OCH_3	OBn	OCH_3	gum	60
29	OCH_3	OBn	OCH_3	OBn	OBn	OBn	gum	65
30	OH	H	H	OCH_3	OH	OCH_3	gum	98
31	OCH_2O		H	OCH_3	OH	OCH_3	108-111	99
32	OBn	H	H	OCH_3	OBn	OCH_3	gum	33
33	OCH_2O		H	OCH_3	OBn	OCH_3	gum	42
34	OCH_3	OBn	OCH_3	OCH_3	OBn	OCH_3	gum	35
35	OCH_2O		H	OBn	OBn	OBn	gum	40
36	OCH_3	OBn	OCH_3	OBn	OBn	OBn	gum	37
37	OH	H	H	OCH_3	OH	OCH_3	258-260	95
38	OCH_2O		H	OCH_3	OH	OCH_3	gum	90
39	OCH_3	OH	OCH_3	OCH_3	OH	OCH_3	gum	92

The *in vitro* cytotoxic activities of the 15 synthetic compounds were measured on four human tumor cell lines, *i.e.*, A549, Hela, PC-3 and KB. Some of these products were found to possess certain cytotoxicity at μmol/L scale. The results were shown in **Table 2**.

Among the tested compounds, the PhDHIQs **25**−**29** exhibited cytotoxicity with wider spectrum than PhIQs **32**−**36**, especially compound **27** which showed cytotoxic against four tumor cell lines and its IC_{50} value against Hela cells was 0.99 μmol/L. Moreover, compound **32** exhibited significant cytotoxicity against A549 cells with IC_{50} value of 0.59 μmol/L. To our surprise, compounds **37**−**39** showed less active than compounds **32**−**34**, which indicated that deprotection of hydroxyl did not remarkably advance the cytotoxicities.

Table 2 *In vitro* cytotoxicity of some synthetic compounds*

Compd.	A549	Hela	PC-3	KB
23	2.67	4.63	4.63	–
24	11.8	4.13	–	11.2
25	2.95	0.99	6.81	1.53
26	5.82	4.68	3.45	–
29	16.2	9.0	–	–
30	0.59	–	–	5.91
31	–	2.37	–	–
38	9.83	–	–	1.94
34	–	–	9.82	–
35	28.1	16.5	22.2	15.2
36	–	15.5	6.83	–
cisplatine	0.14	0.53	1.16	0.34

*The levels of cytotoxicity were denoted by IC_{50} values in μmol/L.
–Denoted those IC_{50} values larger than 100 μg/mL, and compounds with all IC50 values greater than 100 μg/mL on 4 cell lines were viewed as non-cytotoxic and thus were not listed in the table.

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8. Spectral data for compound **27**: ^{1}H NMR (400 MHz, $CDCl_3$ δ ppm): 2.71 (t, 2H, *J*=7.4, 7.2 Hz, C*H*$_2$-4), 3.77 (t, 2H, *J*=8.2, 6.5 Hz, C*H*$_2$-3), 5.10 (s, 2H, OC*H*$_2$Ph), 5.12 (s, 4H, OC*H*$_2$Ph), 5.99 (s, 2H, OC*H*$_2$O), 6.70 (s, 1H, H-5), 6.75 (s, 1H, H-8), 6.92 (s, 2H, H-2′, H-6′), 7.25−7.44 (m, 15H, OCH_2Ph-*H*×3); EIMS *m/z* (%): 569 $[M]^+$ (3), 91 (100). The spectral data of other synthetic compounds were deposited to the editorial office of CCL.
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