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Synthesis and Antitumor Activity of 4β-(1,2,3-Triazol-1-yl) podophyllotoxins

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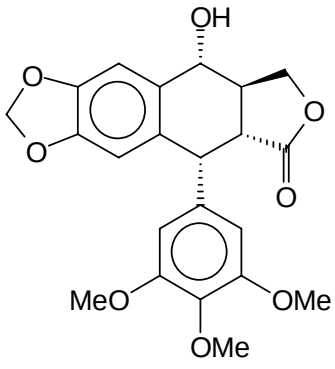
Abstract: Three 4β-(1,2,3-triazol-1-yl) podophyllotoxins **2~4** have been synthesized and tested for their antitumor activity *in vitro*. The compound **3** was found to be much more cytotoxic than the clinically used etoposide (VP-16) against L1210 cells.

Keywords: Podophyllotoxin, antitumor, synthesis.

Semisynthetic analogues of the naturally occurring podophyllotoxin **1** have renewed interest in recent years as a result of the development of etoposide (VP-16) as anticancer drug[1-6]. In previous studies[7-13], we found that a number of 4β-amino- or amido-podophyllotoxins were as active or more active than VP-16. Here, we report the synthesis and *in vitro* antitumor activity of three 4β-(1,2,3-triazol-1-yl) podophyllotoxins with structural features shown in formulae**2~4**.



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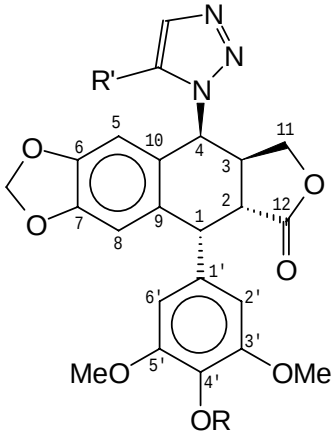
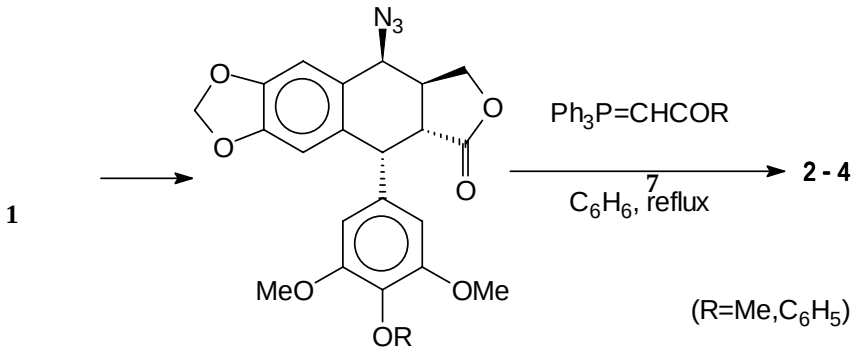


2 R= R′= Me
3 R=Me, R′= -C_6H_5
4 R=H, R′= Me

Scheme 1. Synthesis of 4β-(1,2,3-triazol-1-yl)podophyllotoxins



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5 R=Me; **6** R=H

Table 1. Physical Properties and Analytic Data of Compounds **2~4**

Compound*	Yield (%)	m.p. (°C)	IR(KBr) (cm^{-1})	MS(EI,70eV) m/z
2	63	141-143	1778 (lactone), 1585, 1505 and 1482 (aromatic C=C)	479 (M^+,54), 397 (24) 196 (65), 381 (10)
3	52	232-235	1780 (lactone), 1585, 1505 and 1485 (aromatic C=C)	541 (M^+,39), 495 (5) 397 (32), 396 (100)
4	42	160-162	1762(lactone), 1580, 1510 and 1480 (aromatic C=C)	465 (M^+,23), 383 (34) 382(100), 369(4)

* The microanalyses were in satisfactory agreement with the calculated values (C, H and N) within ± 0.27%.

The 4β-(1,2,3-triazol-1-yl)podophyllotoxins **2~4** were synthesized as shown in **Scheme 1**. A mixture of podophyllotoxin 1 and HN3 in CH2Cl2 was treated with a solution of BF3·OEt2 in CH2Cl2 to give 4β-azidopodophyllotoxin 5. The bulky C-1α pendant aromatic ring dictates the reaction to be stereoselective in yielding the 4β-azido isomer as the major products. The ratio between 4β-azidopodophyllotoxin 5 and its 4α-isomer was about 15:1 according to TLC analysis. The assignment of the configuration at C-4 for compound 5 was based on the difference of $J_{3,4}$ coupling constants. The 4β-substituted podophyllotoxins have a $J_{3,4} \approx 4.5$Hz, due to a *cis* relationship between H-3 and H-4[14,15]. The 4α-substituted isomers, however, have a $J_{3,4}$

≥ 10.0Hz as H-3 is *trans* to H-4[14,15].

The 4β-azido-4′-O-demethylpodophyllotoxin 6 was obtained from 1 in three steps by our previous method7-13. The 1,3-dipolar cycloaddition of azides 5 and 6 with the corresponding alkylidenephosphoranes 716 in anhydrous benzene under reflux resulted in 1,2,3-triazoles 2, 3 and 4, respectively.

All new compounds were characterized by m.p., IR, 1HNMR and MS spectra as well as elemental analysis as shown in T**able 1** and **2**.

Table 3. ^{1}H NMR Data of Compounds **2-4**

Compound	δ(ppm)
2	7.517 (s,1H), 6.611 (s,1H), 6.411 (s,1H), 6.352 (s,2H), 5.943 (dd,2H), 5.683 (d, J = 5.4Hz, 1H), 4.788 (d, J = 5.1Hz, 1H), 4.208 (t,1H),3.942 (dd,1H), 3.797 (s, 3H), 3.752 (s, 6H), 3.208 (m, 1H), 3.013 (dd,1H), 2.365 (s, 3H).
3	7.771 (s, 1H), 7.590 and 7.375 (m, 5H), 6.603 (s, 1H), 6.417 (s, 1H), 6.311 (s, 2H), 5.942 (dd, J = 1.2,15.0 Hz, 2H), 5.723 (d, J = 5.4 Hz, 1H), 4.788 (d, J = 5.1 Hz, 1H), 4.184-4.095 (m, 2H), 3.772 (s, 3H), 3.723 (s, 6H), 3.194-3.051 (m, 2H).
4	7.52(s, 1H), 6.62 (s, 1H), 6.42 (s, 1H), 6.37 (s, 2H), 5.94 (brs, 2H), 5.68 (d, J= 5.4 Hz, 1H), 5.46(s, 1H), 4.79 (d, J = 5.1Hz, 1H), 4.22(t, 1H), 3.92 (d, 1H), 3.78 (s, 6H), 3.37 (s, 3H), 3.21-3.01 (m, 2H).

The *in vitro* cytotoxicity test was carried out in L1210 cells. **2** (ID_{50} = 0.13μM) and **4** (ID_{50} = 0.17μM) exhibited almost equivalent activity to VP-16 (ID_{50} = 0.15μM), whereas **3** (ID_{50} = 0.0030μM) was 50-fold more cytotoxic than VP-16 against L1210 cells. Further biological evaluation of synthesized compounds is in progress, and the results will be reported elsewhere.

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