Full Paper

Design, Synthesis, and Biological Testing of 4β-[(4-Substituted)-1,2,3-triazol-1-yl]podophyllotoxin Analogues as Antitumor Agents

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A series of 4β-[(4-substituted)-1,2,3-triazol-1-yl]podophyllotoxin analogues have been synthesized with high regio-selectivity by employing copper(I)-catalyzed 1,3-dipolar cycloaddition of 1-*O*-propargyl monosaccharides with C4β-azido podophyllotoxin and C4β-azido-4′-*O*-demethyl podophyllotoxin. All the compounds were evaluated for their anticancer activity against a panel of six human cancer cell lines. Among these, 4′-*O*-demethyl podophyllotoxin congeners are showing promising anticancer activity mainly against HCT-15 (colon) and DU-145 (prostate) cells.

Keywords: Copper(I) / Cycloaddition / Podophyllotoxin / Regio-selectivity

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Introduction

Podophyllotoxin **1** (Fig. 1) is a lignan isolated from the roots of the North American *Podophyllum peltatum* Linnaeus, the Tibetan *P. emodi* Wall, or the Taiwanese species *Podophyllum pleinthum* [1]. It has been known to inhibit the assembly of tubulin into microtubules through tubulin binding, but the high toxicity of podophyllotoxin has limited its application as a drug in cancer chemotherapy [2]. The biological activity of **1** has led to extensive structural modification resulting in several clinically useful compounds. Many derivatives of podophyllotoxin that are potent inhibitors of mitosis have been synthesized and examined as antitumor agents. Among these, etoposide VP-16 [3], compound **2**, and teniposide VM-26 [4], compound **3,** are two semisynthetic glucosidic cyclic acetals of podophyllotoxin (Fig. 1). The clinical efficacy and intriguing mechanism of the podophyllotoxin-derived

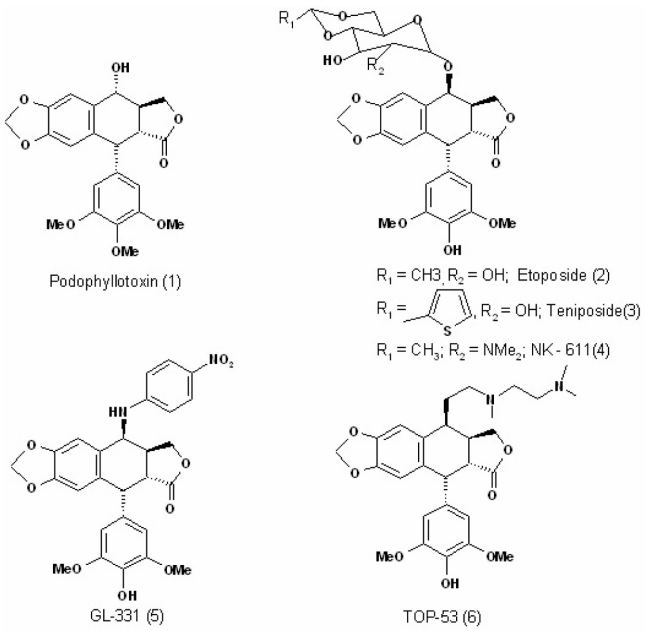

Figure 1. Structure of compounds **1 – 6**: Podophyllotoxin, etoposide, teniposide, NK-611, GL-331, and TOP-53.

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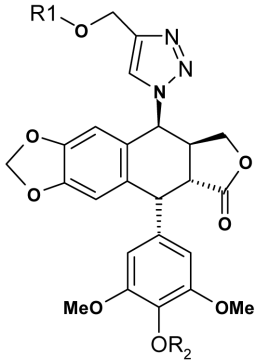
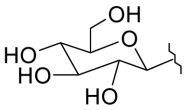
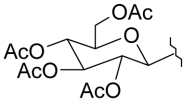
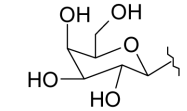
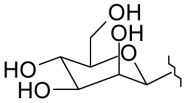
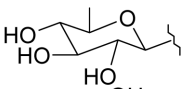
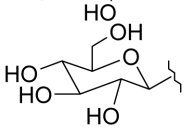
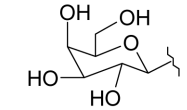
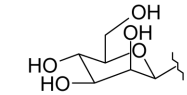
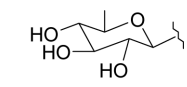
Abbreviations: comparative molecular field analysis (CoMFA); Quantitative Structure-Activity Relationship (QSAR)

glucosides has greatly stimulated interest in further studies on the modification of the C-4 substituted of **2** for better antitumor activity. Their clinical efficacy is due to their ability to inhibit the enzyme DNA-topoisomerase II by stabilizing a cleavable complex in which the DNA is cleaved and covalently linked to enzyme. They are currently used in chemotherapy for various types of cancer, including small cell lung cancer, testicular carcinoma, lymphoma, and Kaposi's sarcoma [2, 5]. To improve topoisomerase-II inhibition and to overcome the problems of drug resistance, myelosuppression, and poor oral availability, extensive efforts have been made world over. Molecular area-oriented chemical modification of podophyllotoxin has revealed structural features critical for the topoisomerase-II inhibition includes 4′-demethylation, 4-epimerization, trans-lactone D ring with 2α, 3β configuration, and free rotation of ring E. Such structure – activity relationships (SAR) [6] unambiguously demonstrate that C-4 is the only molecular area tolerable to significant structural diversification. In NK-611, compound **4,** (Fig. 1) the 2″-hydroxyl group in the glucose ring of **2** has been replaced with an *N,N*-dimethylamino moiety. The main advantage of this compound is its superior water solubility compared to that of **2**. It is currently undergoing phase-I clinical evaluation. Two 4β-analogs GL-331, compound **5,** and TOP-53, compound **6,** of podophyllotoxin (Fig. 1), reported recently, have exhibited potential anticancer activity. Compound GL-331 is a 4β-arylamino derivative, which is currently under phase-II clinical trials against several forms of cancer, especially resistant malignancies [7]. GL-331, a 4β-arylamino derivative, was more active than etoposide both *in vitro* and *in vivo*, and retained cytotoxicity against resistant cells. 4β-alkylated derivatives TOP-53 [8], currently under phase-I clinical trials, was a more potent topoisomerase-II inhibitor than etoposide. It exhibited high activity to non-small cell line cancer in both tumor cells and animal tumor models [9] and showed nearly wild-type potency against a mutant yeast type-II enzyme highly resistant to etoposide [10].

Etopophos, an etoposide prodrug in which a disodium-phosphate salt was prepared at the 4′-phenolic oxygen, is also in phase-II clinical trials. Topoisomerase-II inhibitory activity, antitumor spectra, and significantly different drug-resistance profiles demonstrated by NK-611, etopophos, GL-331, and TOP-53 suggested the important role of various C-4 substitutions to the activity profiles of etoposide analogs and the feasibility of optimizing these compounds through rational C-4 modification. This postulate, further reinforced by composite pharmacophore model proposed by Mac Donald *et al*. [11] and the comparative molecular field analysis (CoMFA) models generated by Zhiyan Xiao *et al*. [12] indicated that the C-4 molecular area could accommodate considerable structural diversity. The CoMFA model further demonstrated that bulky substituents at C-4 might be favorable for topoisomerase-

Table 1. A series of nine compounds of 4β-[(4-substituted)-1,2,3-triazol-1-yl]podophyllotoxin derivatives.



Compound	R_1	R_2	Yield (%)
10a		CH_3	89
10b		CH_3	95
10c		CH_3	90
10d		CH_3	88
10e		CH_3	90
10f		H	86
10g		H	88
10h		H	85
10i		H	87

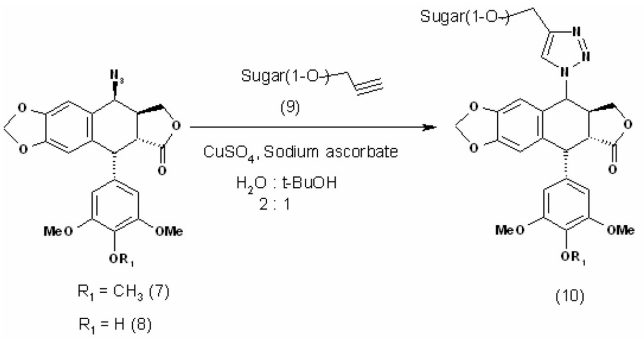
II inhibition and enhanced cytotoxicity [13]. Accordingly, a lot of derivatization has been done at the C-4 position of epipodophyllotoxin, in order to generate the lead molecules. Accordingly, numerous derivatives have been generated at C-4 position of epipodophyllotoxin and their cytotoxicity has been evaluated. Copper-mediated click chemistry has gained immense importance in recent years, offering distinct advantages over the conventional azide-terminal acetylene cycloaddition to generate triazolyl moieties with very high regio-selectivity. Thus, the copper (I)-catalyzed reaction yields exclusively the single 1,4-disubstituted isomer in about 90% yield at room temperature [14], whereas the reaction under conventional heating conditions leads to the formation of 1,4- and 1,5-disubstituted triazole isomers [14].

As a part of our drug-discovery program, we initiated a research program directed towards the rational design and synthesis of lead compounds for potentially interesting drugs from 4β-podophyllotoxin azides. Accordingly, a series of novel regio-selective epipodophyllotoxin derivatives (Table 1) bearing bulky 4-substituted triazoles at the C-4 side chain have been synthesized. All these compounds were evaluated for their *in-vitro* anticancer activity against a panel of human cancer cell lines DU-145 (prostate), PC-3 (prostate), A-549 (lung), HOP-62 (lung), HCT-15 (colon), SF-295 (CNS).

Results and discussion

Chemistry

As illustrated in Scheme 1, 4β-[(4-substituted)-1,2,3-triazol-1-yl]podophyllotoxin derivatives were synthesized by the cycloaddition reaction of C4β-azido-4′-*O*-demethyl podophyllotoxin and C-4β-azido-podophyllotoxin with prop-2-ynyl-β-D-sugar pyranosides (prop-2-ynyl-β-D-glucopyranoside, prop-2-ynyl-β-D-mannopyranoside, prop-2-nyl-β-D-galactopyranoside, and prop-2-ynyl-β-D-rhamnopyranoside). These terminal alkynes were synthesized according to the literature procedure in which commercially available β-D-glucopyranose penta-acetate, β-D-galactopyranose penta-acetate, β-D-mannopyranose penta-acetate and β-D-rhamnoyranose tetracetate were reacted with propargyl alcohol in the presence of BF_3-Et_2O catalyst to obtain in high yield and selectivity, the corresponding propargyl derivatives [15] followed by deacetylation with NaOMe in MeOH [15]. C4β-Azido-4′-*O*-demethyl podophyllotoxin was synthesized according to the literature procedure in which the podophyllotoxin was first converted to 4′-*O*-demethyl-epipodophyllotoxin by the inversion of 4-hydroxyl and simultaneous demethylation of 4′-OCH_3 using CH_3SO_3H and NaI in dichloromethane for 5 h to the corresponding iodo-derivative followed by hydrolysis with H_2O/Me_2CO/barium carbonate to 4′-*O*-demethyl-epipodophyllotoxin [16]. The key intermediate, 4β-azido-4′-*O*-demethyl-podophyllotoxin was obtained in excellent yield by treating the latter with TFA and NaN_3 [16]. On the other hand, epipodophyllotoxin was obtained by the reaction of podophyllotoxin with CH_3SO_3H and NaI in acetonitrile for 15 min followed by hydrolysis with H_2O/Me_2CO/barium carbonate.



Scheme 1. Click-chemistry strategy for the synthesis of novel triazolyl-podophyllotoxins.

4β-Azido-podophyllotoxin was obtained in excellent yield (>85%) by treating epipodophyllotoxin with TFA and NaN_3. The azides **7** and **8** obtained were allowed to react with the above terminal-alkynes **9** in presence of $CuSO_4 \times 5\ H_2O$, sodium ascorbate in *t*-butyl alcohol and water (1 : 2) at room temperature to selectively get 4β-[(4-substituted)-1,2,3-triazol-1-yl] derivatives in excellent yield. Using this click chemistry protocol, a series of nine compounds of 4β-[(4-substituted)-1,2,3-triazol-1-yl]podophyllotoxin derivatives have been synthesized (Table 1). Our subsequent literature survey revealed a report by Chen *et al*. [17] who presented α- and β-isomers of only three 5-substituted triazoles, the synthesis of which has been achieved in moderate yields through the alkylidine phosphorane dipolar cycloaddition with podophyllotoxin azide under benzene reflux conditions and further, the resulting triazoles were screened against a single cell line *i. e.,* L1210, and the magnitude of cytotoxicity was found to be in parity with etoposide. Carbohydrate-based triazolyl analogues cannot be obtained by the alkylidine phosphorane cycloaddition method. The 1,3-dipolar cycloaddition of 4β-azidopodophyllotoxin with alkynes under solvent-free microwave irradiation to the corresponding 4β-1,2,3-triazol-1-yl-podophyllotoxins was reported by Shi *et al.* [17], but the method involving microwave irradiation leads to the formation of 1,4- and 1,5-disubstituted triazole isomers with the exception of symmetrical alkynes. However, no biological data has been presented for these compounds,. whereas the click

Table 2. IC_{50} values (μM) of *in-vitro* cytotoxicity of 4β-[(4-substituted)-1,2,3-triazol-1-yl]podophyllotoxin against a panel of human cancer cell lines.

	Cell lines[a)]					
Compound	**DU-145**	**PC-3**	**A-549**	**HCT-15**	**HOP-62**	**SF-295**
10a	25.8	127	125	15	ND[b)]	26.8
10b	42	221	556	ND[b)]	142	35.1
10c	237	316	59.9	16	178	14.5
10d	18.6	94.9	51.8	237	121	53.4
10e	26.5	268	114	ND[b)]	ND[b)]	88
10f	**3.11**	34.6	**3**	**0.93**	8.55	**2.01**
10g	**4.95**	24.3	**6.88**	**1**	**5.27**	**16.1**
10h	**2.73**	8.62	**7.33**	**3.57**	**5.96**	**2.51**
10i	**5.04**	20.8	**7.04**	**2.14**	**16.2**	**8.29**
Etoposide	**2.97**	100	**7.63**	**1**	**4.8**	**5.69**

[a)] Cell lines: DU-145 (prostate), PC-3 (prostate), A-549 (lung), HOP-62 (lung), HCT-15 (colon), SF-295 (CNS).
[b)] ND = not determined.

approach presented by us being environmentally benign and high yielding, provides a library of structurally distinct 4-substituted podophyllotoxin triazolyls and the cytotoxicity evaluation has been performed against a panel of six human cancer cell lines, but few are found to exhibit an impressive cytotoxicity.

All the products were characterized by ^{1}H-NMR, ^{13}C-NMR, IR, ESI-MS, and elemental analysis. In ^{1}H-NMR, cyclization of azides to triazoles was confirmed by the shift of the 4-α H to around δ 6 and the resonance of H-5 in the triazole ring in the aromatic region. The structure was further supported by the ^{13}C-NMR, which showed all the carbon signals corresponding to triazole derivatives. ESI-.MS of all compounds showed the [M + Na] adduct as the molecular ion.

Biology

Media and cell lines

The six human cancer cell lines used for the test were DU-145 (prostate), PC-3 (prostate), A-549 (lung), HOP-62 (lung), HCT-15 (colon), and SF-295 (CNS). Cells were maintained in RPMI-1640 medium with 2 mM glutamine, supplemented with 10% fetal bovine serum and containing 100 μg/mL streptomycin and 100 units/mL penicillin at 37°C in an atmosphere of 5% CO_2 and 90% relative humidity in a carbon dioxide incubator.

By comparing the cytotoxic potential of these compounds (Table 2) with regard to the methoxy moieties as well as the different sugar substitutions, the following conclusions can be drawn:

(a) The presence of a hydroxy moiety on the ring E is essential; compounds containing the dimethoxy moiety (**10f – 10i**) are more active than those containing a trimethoxy moiety (**10a – 10e**). (b) Introducing the 4″-substituted, sugar-based compounds led to enhanced cytotoxic activity and it is in par with etoposide. (c) Compounds in which the sugar moiety is per-acylated (**10b**) are having less activity than compounds where there are free sugars. (d) From the IC_{50} values of entire ring E-containing dimethoxy-substituted compounds, it was found that the activity was at par with different sugar-substituted derivatives *viz*., glucose-, galactose-, rhamnose-, and mannose-bearing analogues. (e) It was found that these compounds generally exhibited promising activity against the two cell lines, DU-145 and HCT-15. (f) Among all the com-

Table 3. The *log*-p values of compound **10a – 10i** and etoposide.

Entry	Log **p**	**n OHNH**[a)]	**n ON**[b)]	**Mass (amu)**	**n Violations**[c)]	**n Rotb**[d)]	**MPSA (A^{02})**[e)]	**Volume (A^{03})**
10a	−0.504	4	16	657.63	2	9	202.57	551.82
10b	+1.877	0	20	825.78	2	17	193.34	697.86
10c	−0.504	4	16	657.63	2	9	202.57	551.82
10d	−0.504	4	16	657.63	2	9	202.57	551.82
10e	+0.504	3	15	641.63	2	8	182.34	543.56
10f	−0.78	5	16	643.60	2	8	213.56	534.29
10g	−0.78	5	16	643.60	2	8	213.56	534.29
10h	−0.78	5	16	643.60	2	8	213.56	534.29
10i	+0.228	4	15	627.60	2	7	182.345	526.03
Etoposide	+0.698	3	13	588.56	2	5	160.86	493.50

[a)] n OHNH = number of OH and NH groups.
[b)] n ON = number of O and N atoms.
[c)] n Violations = number of violations of Lipinski rule.
[d)] n Rotb = number of rotatable bonds.
[e)] MPSA = molecular polar surface area.
All parameters of the Table were calculated using molinspiration software.

pounds synthesized, compound **10f**, which contained a dimethoxy moiety on ring E and a glucose moiety on the triazolyl ring, was found to be the most promising in this study.

In Table 3, a list of QSAR parameters for the derivatives is presented comparing them with the standard etoposide, a drug derived from podophyllotoxin itself. Similar to etoposide, the molecular weight of each analogue generated by us exceeded the Lipinski limit (etoposide M.W. 588.56). The *log* P values of the derivatives ranged between −0.78 to +1.87.

In conclusion, a series of novel 4β-[(4-substituted)-1,2,3-triazol-1-yl]podophyllotoxin derivatives were synthesized and screened for anticancer activity against a panel of six human cancer cell lines. From the derived cytotoxicity data it was found that all the compounds with a dimethoxy moiety on ring-E are having activity comparable with that of the standard drug etoposide. It was observed that compound **10f** is most active among all the screened compounds, and even more potent than etoposide against the above studied cell lines.

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The authors have declared no conflict of interest.

Experimental

Melting points were recorded on Büchi Melting point apparatus D-545 (Büchi Labortechnik, Flawil, Switzerland); IR spectra (KBr discs) were recorded on Bruker Vector 22 instrument (Bruker Bioscience, Billerica, MA, USA). NMR spectra were recorded on Bruker DPX instrument (Bruker) in $CDCl_3$ with TMS as internal standard for protons and solvent signals as internal standard for carbon spectra. Chemical shift values are given in δ (ppm) and coupling constants are given in Hz. Mass spectra were recorded on ESI-esquire 3000 Bruker Daltonics instrument (Bruker). The progress of all reactions was monitored by TLC on 2 × 5 cm precoated silica gel 60 F_{254} plates of thickness of 0.25 mm (Merck, Darmstadt, Germany). The chromatograms were visualized under UV 254–366 nm and iodine.

General procedure

*Synthesis of compounds **10a, 10c–10i***

To a solution of **9** (3 mmol) in *t*-butyl alcohol and water (1 : 2, 10 mL) was added $CuSO_4 \times 5\ H_2O$ (3.0 mmol), sodium ascorbate (15.0 mmol) followed by epipodophyllotoxin azide (3 mmol). The reaction mixture was stirred at room temperature for 8 h. After completion, the reaction mixture was diluted with 30 mL of water and extracted with ethylacetate (3 × 20 mL). The combined extracts were washed with brine, dried over Na_2SO_4, and evaporated on rotary evaporator. The crude product obtained was crystallized in diethyl ether to yield the pure product.

*Synthesis of compound **10b***

To a solution of **10a** (2 mmol) in acetic anhydride (6 mL), pyridine (1.5 mL) was added and stirred at room temperature for 6 h. After completion, water was added (40 mL) and extracted with ethylacetate (2 × 20 mL). The combined extracts were dried over Na_2SO_4 and evaporated on rotary evaporator to give white solid (95%).

Spectral data (**10f**): mp. 208–210°C; $[\alpha]_D^{25}$ −36.86 (c = 0.8, MeOH); IR (KBr): 1058, 1126, 1239, 1458, 1591, 1774, 2923, 3440 cm^{-1}; ^{1}H-NMR (200 MHz, CD_3OD): 3.19–3.36 (m, 8H, C^{11}-CH_2β, C^2-CH, C^3-CH, $C^{3'''}$-CH, $C^{4'''}$-CH, $C^{5'''}$-CH, $C^{6'''}$-CH_2), 3.65–3.79 (m, 8H, C^{11}-CH_2a, $C^{2'''}$-CH, $C^{3'}$-OCH_3, $C^{5'}$-OCH_3), 4.38 (d, *J* = 7.6 Hz, 2H, $C^{6''}$-CH_2O), 4.75–4.79 (m, 2H, $C^{1'''}$-CH, C^1-CH), 5.98 (d, *J* = 4.3 Hz, 2H, OCH_2O), 6.26 (d, *J* = 3.8 Hz, 1H, C^4-CH), 6.38 (s, 2H, $C^{2'}$-CH, $C^{6'}$-CH), 6.65 (s, 1H, C^8-CH), 6.68 (s, 1H, C^5-CH), 7.83 (s, 1H, $C^{5''}$-C=CH-N); ^{13}C-NMR (50 MHz, CD_3OD): 38.58 (C-3), 44.80 (C-1), 45.21 (C-4), 56.82 (2 × OCH_3), 59.93 (C-2), 63.07 (C-6‴), 68.86 (C-6″), 69.00 (C-11), 71.63 (C-4‴), 75.00 (C-3‴), 76.55 (C-5‴), 78.10 (C-2‴), 103.27 (-OCH_2O-), 103.91 (C-1‴), 109.35 (C-2′, C-6′), 111.25 (C-5, C-8), 124.36 (C-4′), 126.12 (C-5″), 133.41 (C-10), 135.63 (C-9), 136.57 (C-1′), 144.57 (C-6), 147.65 (C-4″), 150.81 (C-7), 152.23 (C-3′, C-5'), 173.26 (C-12); ESI MS $[M + Na]^+$: 666.2; Anal. calcd. ($C_{30}H_{33}N_3O_{13}$): C: 55.99, H: 5.17, N: 6.53; found C: 55.92, H: 5.11, N: 6.51; Anal. calcd. ($C_{30}H_{33}N_3O_{13}$): C: 55.99, H: 5.17, N: 6.53; found C: 55.92, H: 5.11, N: 6.51.

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