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Synthesis and antitumor activity of camptothecin-4β-triazolopodophyllotoxin conjugates

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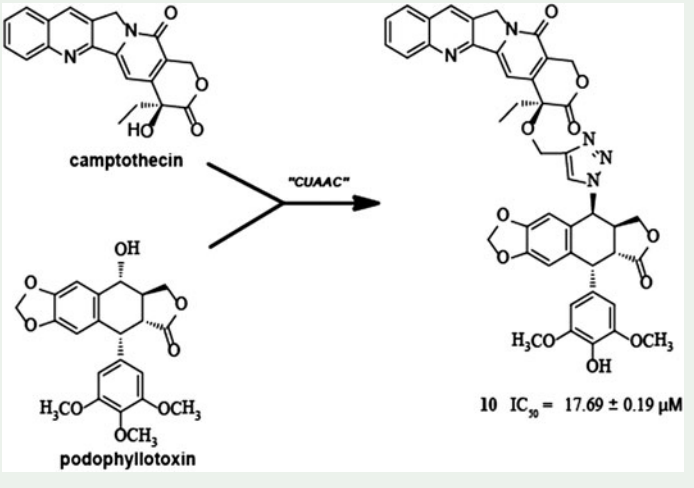
ABSTRACT

Two new compounds (**9** and **10**) having a camptothecin (CPT) analog conjugated to the 4β-azido-4-deoxypodophyllotixin analog by untilizing the copper-catalyzed azide-alkyne cycloadditon (CuAAC) reaction, and were evaluated for their cytotoxicity against a panel of five human cancer cell lines (HL-60, SMMC-7721, A-549, MCF-7 and SW480) using the MTT (3-(4,5-dimethylthiahiazo-2-yl)-2,5-diphenyltetrazolium bromide) assay. Two novel conjugates shown weak cytotoxicity, compound **10** showed highly potent against HL-60 cell line tested, with IC_{50} value 17.69 ± 0.19 μM. This compound suggested its potential as anti-cancer agents for further development.



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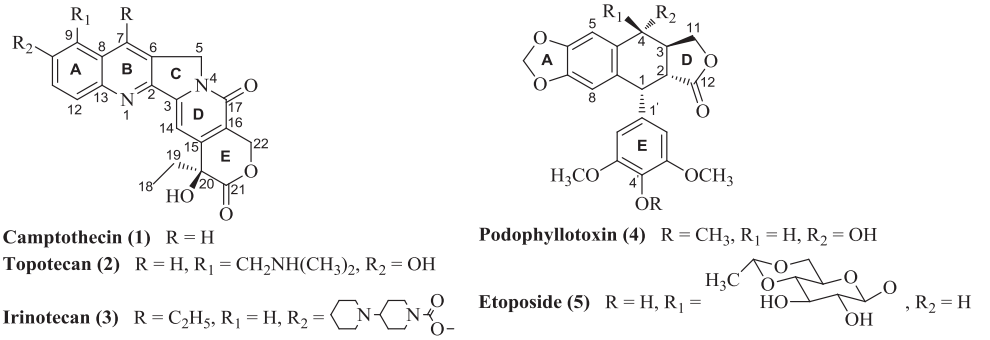


Figure 1. Structures of camptothecin (1) and camptothecin conjugates (2 and 3), podophyllotixin (4) and etoposide (5).

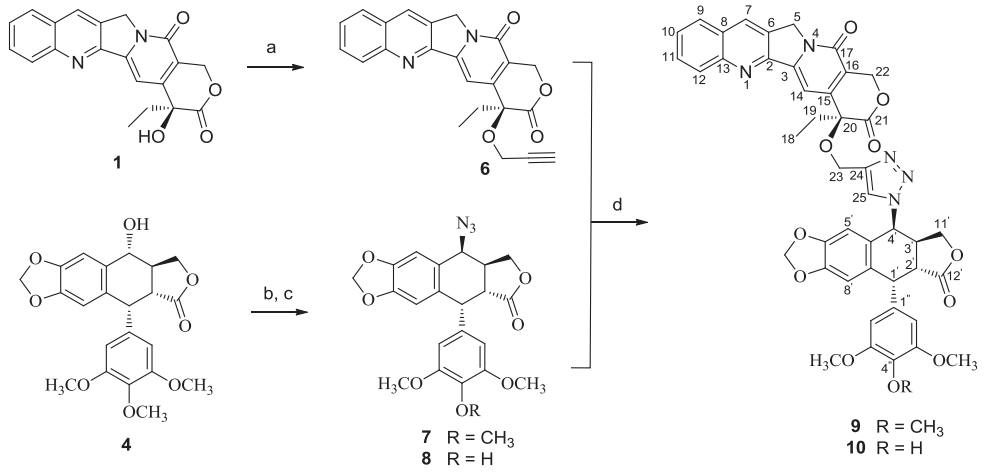
1. Introduction

DNA topoisomerases (Tops) anzymes relax helical supercoiling renerated during transcription, replication, recombination and chromatin remodeling (Wang 2002). Topoisomerases I (Top I) cuts one strand of DNA, relaxes the strands, and then re-annels the strands (Wang 1971), whereas topoisomerases II (Top II) incises double-stranded DNA to facilitate the passae of an intact duples through the gap before rejoining the cut DNA (Gellert et al. 1976). Many evidences suggests that Tops are the targets of important anticancer drugs (Delgado et al. 2018; Reddy et al. 2018; Bielawski et al. 2006).

Camptothecin (CPT, Figure 1), an alkaloid isolated from *Camptotheca acuminate* by Wall and co-workers in 1966, was identified specific inhibitor of Top I (Wall et al. 1966). Historically, several CPT-derivatives, including topotecan and irinotecan (Figure 1) (Johnson et al. 1989; Fukuoka et al. 1992; Sriram et al. 2005), have good water solubility and have been used clinically for the treatment of ovarian, colorecral and small cell lung cancers. Etoposide (VP-16, Figure 1), a semisynthetic derivative of podophyllotoxin, is another widely used anticancer drug by inhibiting Top II isoenzymes (Ye et al. 2012). Previously, numberous podophyllotoxin derivatives were synthesized and used in the chemotherapy for a variety of cancers (Terada et al. 1993; Xiao et al. 2002; Tawa et al. 1997; Chattopadhyay et al. 2004). However, drug resistance is still a critical clinical problem.

It has been demonstrated the inhibitory mechanism of all the above-mentioned Topos inhibitors, inhibitors act by stabilizint the Tops-DNA-drug ternaty comples, ultimately leads to cell death (Tsao et al. 1993; Hsiang et al. 1989; Chen et al. 1984; Ross et al. 1984). The mechanisms of CPT-derivatives resistance characterized to date include (a) reduced drug accumulation, (b) reduced Top I content, (c) altered Top I resulting in decreased formation of protein-linked DNA breaks (PLDBs). The mechanisms of podophyllotoxin-derivatives resistance have been proposed to be involved (a) decreased cellular uptake of drug, (b) quantitative change of Top II, (c) qualitative change of Top II (Chang et al. 2000).

Dual target inhibitors would likely retain cytotoxic activity when resistance was acquired due to alteration of only one drug target, which could possibly overcome



Scheme 1. Synthesis of camptothecin-4?-triazolopodophyllotoxin conjugates 9 and 10. Reagentsand conditions: (a) NaH, DMF, 0 oC, propargyl bromide, then, reflux, overnight, 65%; (b) MeSO3H, NaI, CH2Cl2, then, H2O-Acetone, BaCO3, rt.; (c) NaN3, CHCl3, 40–60%; (d) CuSO4•5H2O, sodium ascorbate, THF, t-BuOH: H2O (1: 1), 4 h, rt, 76–80%.

drug resistance. The aim of this paper was interested in the development of compounds that can act on both Top I and Top II by conjugating derivatives of the prototypical CPT, with an analogue of podophyllotoxin. The (*S*)-α-hrdroxy-δ-lactone moiety contained in CPT-derivatives is a crucial structural feature required for biological activity, and structure activity relationship (SAR) analysis of podophyllotoxin analogues indicated that the conpounds with substitutions in the glycosidic moiety of etoposide can't have significant effect on their anticancer activity.

In recent years, we have been working on the chemical modification of podophyllotoxin and focused on carbohydrate based 1,2,3-triazole derivatives have been generated, some of which exhibited significant anticancer activity (Zi et al. 2013; Zi et al. 2015; Zi et al. 2015; Zi et al. 2017). In this paper, we have synthesized two camptothecin-4β-triazolopodophyllotoxin conjugates and tested for their cytotoxic activity against a panel of five human cancer cell lines HL-60 (leukemia), SMMC-7721 (hepatoma), A-549 (lung cancer), MCF-7 (breast cancer) and SW480 (colon cancer) using MTT (3-(4,5-dimethyl-thiahiazo-2-yl)-2,5-diphenyltetrazolium bromide) assay.

2. Results and discussion

The novel camptothecin-4β-triazolopodophyllotoxin conjugates **9** and **10** were synthesised according to the synthetic route shown in Scheme 1. Camptothecin-20(S)-1-propyne (**6**) was prepared by the treatment of camptothecin (**1**) with sodium hydride (NaH) and propargyl bromide with 65% yield. The preparation of 4β-azido-4-deoxypodophyllotoxin (**7**) and 4β-azido-4-deoxy-4′-demethypodophyllotoxin (**8**) using a similar method have been reported in the literatures (Hansen et al. 1993; Kamal et al. 2000). Then, the azides **7** and **8** were allowed to react with the abole terminal alkyne (**6**) in the presence of copper(II) sulfate pentahydrate ($CuSO_4{\cdot}5H_2O$), sodium ascorbate in t-butyl alcohol (*t*-BuOH) and water (1:1) at room temperature

Table 1. *In vitro* anticancer activity (IC_{50}, μM) of camptothecin-4β-triazolopodophyllotoxin conjugates **9** and **10**.

	IC_{50} (μM)				
Compounds	HL-60	SMMC-7721	A-549	MCF-7	SW480
9	>40	>40	>40	>40	>40
10	17.69 ± 0.19	>40	>40	>40	>40
Camptothecin (1)	<0.064	0.45 ± 0.11	0.09 ± 0.32	0.68 ± 0.47	0.29 ± 0.15
Etoposide (5)	0.31 ± 0.24	8.12 ± 0.72	11.92 ± 0.12	32.82 ± 0.44	17.11 ± 0.67
Cisplatin	1.67 ± 0.44	6.93 ± 0.28	7.42 ± 0.12	10.85 ± 0.51	9.89 ± 0.53

for 4 h to give camptothecin-4β-triazolopodophyllotoxin conjugates **9** and **10** in 76–80% yield (Rostovtsev et al. 2002). All of synthesized compounds were characterized by ^{1}H-NMR, ^{13}C-NMR, electrospray ionization mass spectrometry (ESI-MS) and high-resolution mass spectrometry (HRESI-MS).

Compound **9** was obtained as yellow amorphous powder with a specific rotation of -17.00 (c 0.10, MeOH). Its molecular formula, $C_{45}H_{39}N_5O_{11}$, was established by HRESIMS (m/z 848.2524 $[M + Na]^+$, calcd 848.2538). Its IR spectrum showed the presence of a lcactone carbonyl group (1636 cm^{-1}). The UV absorption bands at 363.00 and 207.50 nm were characteristic of a lignin. The ^{1}H-NMR data showed that the $C^{4'}$-H chemical shifts of 4β-triazole-substituted compounds appears as a doublet at 5.38 ppm, with a coupling constant $J_{3,4} = 4.8$ Hz (<5.0 Hz), indacaating a cis-relationship between $C^{3'}$-H and $C^{4'}$-H. The C-25 chemical shifts of the triazole ring was supported by two characteristic carbon signals at around 146 ppm and 122 ppm in the ^{13}C-NMR spectra.

Compound **10** was obtained as yellow amorphous powder with a specific rotation of −92.86 (c 0.10, MeOH). Its molecular formula, $C_{45}H_{39}N_5O_{11}$, was established by HRESIMS (m/z 834.2384 $[M + Na]^+$, calcd 834.2382). Its IR spectrum showed the presence of a lcactone carbonyl group (1777, 1747 cm^{-1}). The UV absorption bands at 360.00 and 207.00 nm were characteristic of a lignin. The $C^{4'}$-H chemical shifts of 4β-triazole-substituted compounds appears as a doublet at 5.57 ppm, with a coupling constant $J_{3,4} =$ 4.8 Hz (<5.0 Hz), indacaating a cis-relationship between $C^{3'}$-H and $C^{4'}$-H in the ^{1}H-NMR spectra. The C-25 chemical shifts of the triazole ring was supported by two characteristic carbon signals at around 146 ppm and 122 ppm in the ^{13}C-NMR spectra.

Camptothecin, etoposide, and cisplatin were used as positive controls. Their activities were expressed by the IC_{50} value (concentration of drug inhibiting 50% cell growth), which was presented in Table 1. The compounds having IC_{50} value more than 40 μM were considered inactive. As shown in Table 1, compound **9** displayed weak anticancer activity to the five cancer cells ($IC_{50} > 40$ μM). However, compound **10** showed highly potent against HL-60 cell line tested, with IC_{50} value 17.69 ± 0.19 μM.

As compunds **9** and **10** does not show eddicacy, logP and the topological polar surface area (tPSA) may reflect the topoisomerases modulating activity. Here, we have calculated the PSA and ClogP values of compounds **9** and **10** by SyBYL-X 2.0 (data shown in Table 2). For the potent Tops inhibitors, the PSA value fall 100 $Å^2$, while LogP value fall 5 (Onawolea et al. 2017; Pajouhesh and Lenz 2005; van de Waterbeemd and Rose 2008). The two compounds have cLogP values of 1.79 and 2.13, PSA values of 160.7 $Å^2$ and 230.4 $Å^2$, both are expected to have less cell permeability.

Table 2. The CogP values and PBA of camptothecin-4β-triazolopodophyllotoxin conjugates **9** and **10**.

Compounds	Molecular formula	m.p. (°C)	Yield (%)	cLogP	PSA (Å^2)
9	$C_{45}H_{39}N_5O_{11}$	195–197	76	2.13	230.4
10	$C_{44}H_{37}N_5O_{11}$	201–203	80	1.79	160.7
Camptothecin (1)	$C_{20}H_{16}N_2O_4$	–	–	0.90	113.8
Etoposide (5)	$C_{29}H_{32}O_{13}$	–	–	0.03	236.1

3. Experimental

3.1. Genetal information

Melting points were measured by an X-4 melting point apparatus and were uncorrected. MS data were obtained in the ESI mode on API Qstar Pulsar instrument; HRMS data were obtained in the ESI mode on LCMS-IT-TOF (Shimadzu, Kyoto, Japan); NMR spectra were acquired on Bruker AV-400 (Bruker BioSpin GmbH, Rheinstetten, Germany) instruments, using tetramethylsilane (TMS) as an internal standard: chemical shifts (δ) are given in ppm, coupling constants (J) in Hz, the solvent signals were used as references ($CDCl_3$: $\delta_C = 77.2$ ppm; residual $CHCl_3$ in $CDCl_3$: $\delta_H = 7.26$ ppm; CD_3OD: $\delta_C = 49.0$ ppm). Column chromatography (CC): silica gel (200–300 mesh; Qingdao Makall Group CO., LTD; Qingdao; China). All reaction was monitored using thin-layer chromatography (TLC) on silica gel plates.

3.2. Synthesis of camptothecin-20(S)-1-propyne (6)

To a solution of camptothecin (348.4 mg, 1.0 mmol) was added at 0 °C to a suspension of sodium hydride (NaH) (60.0 mg, 1.5 mmol) in dry N,N-Dimethylformamide (DMF) (5 mL) under nitrogen. The mixture was stirred at room temperature for 0.5 h, then the propargyl bromide (0.1 mL, 1.2 mmol) was quickly added and the reaction was refluxed overnight. The solvent was evaporated and the residue was purified on a silica gel chromatography (petroleum ether: acetic ether = 1:1) to afford the product **6** (250.9 mg, 65%). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 8.43 (d, 1H, $J = 6.4$ Hz, C^9-CH), 8.21 (d, 1H, $J = 8.4$ Hz, C^{12}-CH), 7.96 (s, 1H, C^{14}-CH), 7.88 (t, 1H, $J = 7.2$ Hz, C^{10}-CH), 7.77 (t, 1H, $J = 7.2$ Hz, C^{11}-CH), 7.60 (t, 1H, $J = 6.8$ Hz), 5.75–5.73 (m, 1H), 5.63 (d, 1H, $J = 16.4$ Hz), 5.22 (d, 1H, $J = 16.4$ Hz), 3.40 (t, 1H, $J = 9.6$ Hz, C≡CH), 2.82 (s, 2H, CH_2C≡C), 1.89–1.83 (m, 2H, C^{18}-CH_2), 0.98 (t, 3H, $J = 7.6$ Hz, C^{19}-CH_3); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 173.6, 162.5, 157.8, 151.9, 150.4, 149.0, 146.0, 131.8, 131.2, 130.7, 129.6, 128.4, 127.9, 119.6, 98.1, 72.7, 72.4 (C≡CH), 66.2 (C≡CH), 60.3, 36.5 (CH_2-C≡C), 31.4, 21.5, 7.8; MS-ESI *m/z* 409 $[M + Na]^+$.

3.3. General procedure for the synthesis of camptothecin-4β-triazolopodophyllotoxin conjugates (9 and 10)

To a solution of camptothecin-20(S)-1-propyne (**6**) (0.1 mmol) and 4β-azido-4-deoxypodophyllotoxin (**7**)/4β-azido-4-deoxy-4′-demethypodophyllotoxin (8) (0.1 mmol) in tetrahydrofuran (THF) (1.0 mL) and ^{t}BtOH-H_2O (1.0 mL, 1:1) at room temperature were added copper (II) acetate (0.01 mmol) and sodium ascorbate (1.0 M in H_2O, 0.1 M). The

reaction mixture was stirred at room temperature for 4 h until the starting material disappeared as indicated by TLC. The solvent was evaporated and the residue was chromatographed on silica gel (dichloromethane: methyl alcohol = 15:1) to afford the product.

3.3.1. Camptothecin-20(S)-[4β-(1,2,3-trizaol-1-yl-4-deoxypodophyllotoxin)] ether (9)

Yellow amorphous powder; yield 76%; m.p. 195–197 °C (CH_2Cl_2); [α]D 24.6 -17.00 (c 0.10, CH_3OH); UV (CH_3OH) λ_{max} (log ε) 363.00 (0.13), 207 (0.93); IR (KBr) ν_{max} 3444, 2920, 1635, 1399, 1202, 1144, 1053 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.79–7.78 (m, 2H, C^9, C^{10}-H), 7.42–7.40 (m, 1H), 7.28–7.25 (m, 1H), 7.10–7.08 (m, 1H), 7.00 (s, 1H), 6.00 (s, 1H), 5.91–5.90 (m, 2H), 5.79 (s, 1H), 5.60–5.56 (m, 2H), 5.38 (d, 1H, $J = 4.8$ Hz, $C^{4'}$-H), 5.25–5.20 (m, 1H), 4.80–4.76 (m, 1H), 4.00–3.98 (m, 1H), 3.79–3.76 (m, 2H), 3.50–3.42 (m, 1H), 3.35 (s, 3H, $C^{4''}$-OCH_3), 3.30 (s, 6H, $C^{3''}$, $C^{5''}$-OCH_3), 2.50–2.45 (m, 1H), 2.20–2.18 (m 1H), 1.73–1.38 (m, 2H, C^{19}-CH_2), 1.00 (t, 3H, $J = 7.0$ Hz, C^{18}-CH_3); ^{13}C-NMR (CD_3Cl, 100 MHz) δ 173.7 (C-12′), 172.7 (C-21), 157.7 (C-17), 152.7 (C-3″, 5″), 152.7 (C-2), 151.2 (C-15), 150.0 (C-13), 149.3 (C-7′), 148.9 (C-6′), 142.8 (C-3), 141.2 (C-24), 134.0 (C-4″), 133.0 (C-1″), 132.1 (C-9′), 132.0 (C-10′), 131.0 (C-7), 130.9 (C-6), 129.9 (C-11), 128.3 (C-12), 128.1 (C-8), 127.8 (C-9), 124.2 (C-10), 122.4 (C-25), 119.7 (C-16), 110.2 (C-5′), 108.3 (C-8′), 108.0 (C-2″, 6″), 102.0 (OCH_2O), 102.0 (C-14), 97.5 (C-20), 72.6 (C-4′), 68.1 (C-11′), 67.1 (C-22), 66.2 (C-23), 60.7 (C-4″), 56.3 (C-3″, 5″), 53.7 (C-5), 43.4 (C-1′), 41.3 (C-2′), 31.4 (C-19), 29.2 (C-2′), 7.8 (C-18); ESIMS: *m/z* 848 $[M + Na]^+$, HRESIMS: calcd for $C_{45}H_{39}N_5O_{11}Na$ $[M + Na]^+$ 848.2538, found 848.2524.

3.3.2. Camptothecin-20(S)-[4β-(1,2,3-trizaol-1-yl)-4-deoxy-4′-demethylpodophyllotoxin] ether (10)

Yellow amorphous powder; yield 80%; m.p. 201–203 °C (CH_2Cl_2); [α]D 24.3 -92.86° (c 0.14, CH_3OH); UV (CH_3OH) λ_{max} (log ε) 364.00 (1.30), 290.00 (1.07), 245.50 (1.54), 207.00 (1.95); IR (KBr) ν_{max} 3439, 2935, 1747, 1660, 1485, 1236, 1108, 1041, 1002 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 8.28 (s, 1H, C^9-H), 8.13–8.12 (m, 1H, C^{10}-H), 7.87–7.85 (m, 1H), 7.76–7.75 (m, 1H), 7.61–7.52 (m, 2H), 6.51 (s, 1H), 6.39–6.36 (m, 2H), 6.05–5.90 (m, 3H), 5.72–5.60 (m, 2H), 5.57 (d, 1H, $J = 4.8$ Hz, $C^{4'}$-H), 5.29–5.26 (m, 1H), 4.59–4.58 (m, 1H), 4.01–3.83 (m, 3H), 3.84 (s, 6H, $C^{3''}$, $C^{5''}$-OCH_3), 3.10–2.90 (m, 2H), 1.89–1.85 (m, 2H, C^{19}-CH_2), 1.00 (t, 3H, $J = 7.0$ Hz, C^{18}-CH_3); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 173.6 (C-12′), 173.3 (C-21), 157.8 (C-17), 151.6 (C-2), 150.3 (C-15), 149.0 (C-13), 148.4 (C-7′), 148.0 (C-6′), 147.7 (C-3), 146.5 (C-3″, 5″), 146.3 (C-24), 133.9 (C-1″), 132.4 (C-4″), 132.0 (C-9′), 131.9 (C-10′), 131.4 (C-7), 129.9 (C-6), 129.6 (C-11), 128.3 (C-12), 128.1 (C-8), 128.0 (C-9), 126.7 (C-10), 126.5 (C-25), 119.5 (C-16), 110.1 (C-5′), 107.4 (C-8′), 105.8 (C-2″, 6″), 101.8 (OCH_2O), 101.8 (C-14), 97.6 (C-20), 72.6 (C-4′), 69.8 (C-11′), 66.3 (C-22), 62.8 (C-23), 56.3 (C-3″, 5″), 53.7 (C-5), 43.7 (C-1′), 43.6 (C-2′), 31.7 (C-19), 29.2 (C-2′), 7.8 (C-18); ESIMS: *m/z* 834 $[M + Na]^+$, HRESIMS: calcd for $C_{44}H_{37}N_5O_{11}Na$ $[M + Na]^+$ 834.2382, found 834.2384.

3.4. Cell culture and cytotoxicity assay

The following human tumor cell lines were used: HL-60, SMMC-7721, A-549, MCF-7, and SW480. All the cells were cultured in RMPI-1640 or DMEM medium (Hyclone, Logan, UT, USA), supplemented with 10% fetal bovine serum (Hyclone) at 37 °C in a humidified atmosphere with 5% CO_2. Cell viability was assessed by conducting colorimetric measurements of the amount of insoluble formazan formed in living cells based on the reduction of 3-(4,5-dimethyl- thiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) (Sigma, St. Louis, MO, USA). Briefly, adherent cells (100 μL) were seeded into each well of a 96-well cell culture plate and allowed to adhere for 12 h before drug addition, while suspended cells were seeded just before drug addition, both with an initial density of 1×10^5 cells/mL in 100 μL of medium. Each tumor cell line was exposed to the test compound at various concentrations in triplicate for 48 h. After the incubation, MTT (100 μg) was added to each well, and the incubation continued for 4 h at 37 °C. The cells lysed with SDS (200 μL) after removal of 100 μL of medium. The optical density of lysate was measured at 595 nm in a 96-well microtiter plate reader (Bio-Rad 680) to determine the concentration that killed 50% of cells (IC_{50}). Data represent the means of at least three separate experiments. The IC_{50} value was defined as the concentration that caused 50% inhibition of cell proliferation.

3.5. Calculated molecular descriptors

Calculated descriptors such as CLogP and PSA were determined by SyBYL-X 2.0. The structures of compounds 9 and 10 were built and energy minimized under the Tripos force dield with 0.05 kcal/(mol Å). The Gasteiger-Huchel method was used to calculated charges. Energy minimization was performed by the Powell method with 2000 iterations. Then, the distance of linkers was calculated.

4. Conclusions

In summary, the two new camptothecin-4β-triazolopodophyllotoxin conjugates have been synthesized by untilizing the copper-catalyzed azide-alkyne cycloadditon (CuAAC) reaction, and screened for anticancer activity against five human cancer cell lines. Compound **10** showed highly potent against HL-60 cell line tested, with IC_{50} value 17.69 ± 0.19 μM. This compound suggested its potential as anticancer agents for further development.

Disclosure statement

The authors declare no conflict of interest.

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