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Synthesis and antitumor activity of new tetrahydrocurcumin derivatives *via* click reaction

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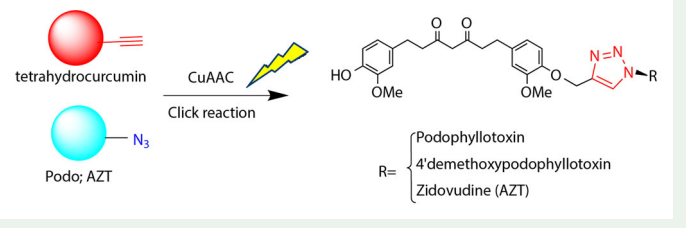
ABSTRACT

Three new derivatives of tetrahydrocurcumin **6**, **7** and **9** have been prepared as potent antitumor agents using copper(II)-catalyzed 'click chemistry'. Their structures were identified using ^{1}H-NMR, ^{13}C-NMR and HRMS techniques. MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) assay has been carried out to investigate the *in vitro* cytotoxicity against human cervical carcinoma (HeLa), human lung adenocarcinoma (A549), human hepatoma carcinoma (HepG2) and human colon carcinoma (HCT-116). Compound **6** has showed significant inhibitory activity against HCT-116 cell line with an IC_{50} value of 17.86 μM compared to tetrahydrocurcumin (50.96 μM) and positive control etoposide (19.48 μM) while showed no inhibitory activity against NCM460 cell line. Compounds **7** showed moderate inhibitory activity compared to tetrahydrocurcumin and etoposide while compound **9** showed no obvious inhibitory activity. The results suggested further structure modifications of tetrahydrocurcumin to improve its anticancer activity.



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1. Introduction

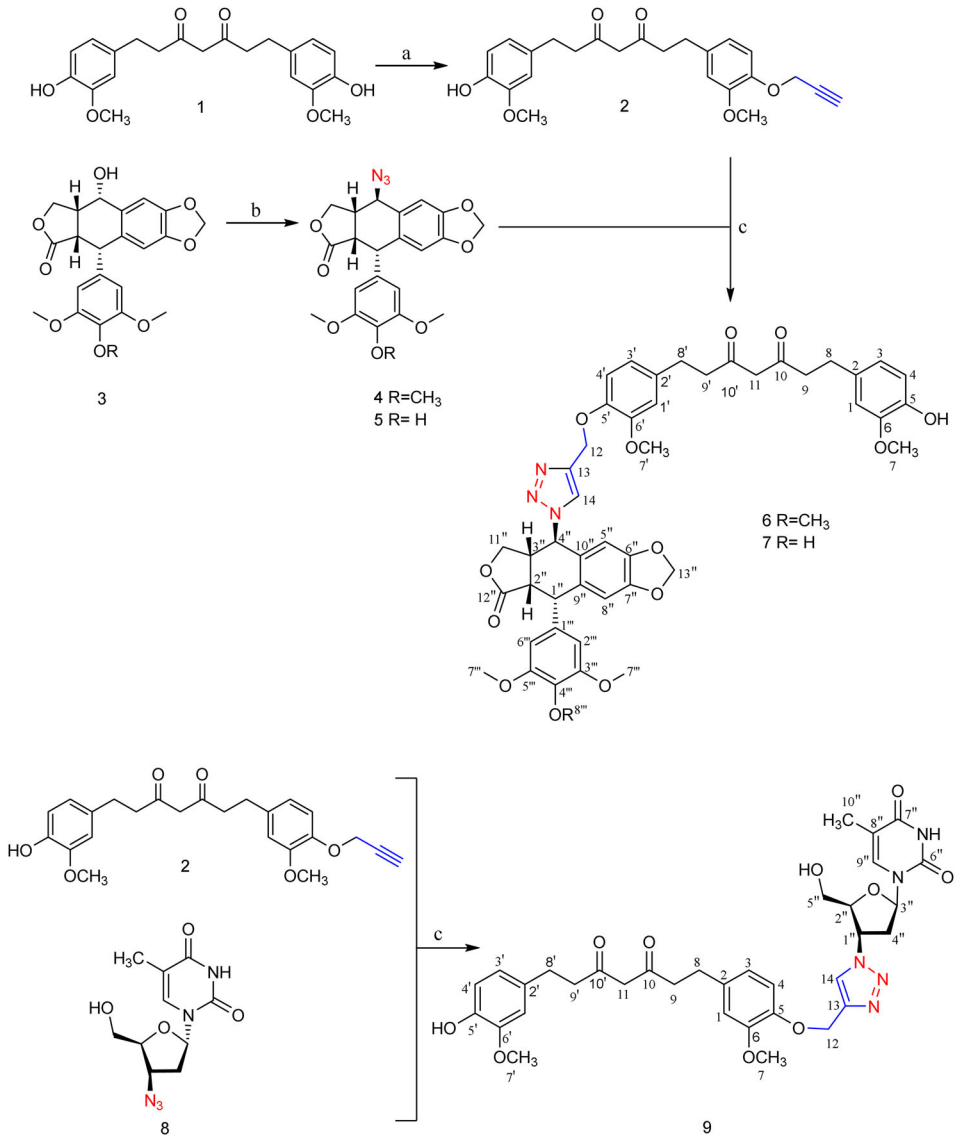
Cancer is a disease in which the cells are getting to be unusual by spreading out of control and it is the second leading cause of death worldwide. In 2018 and according to the WHO (World Health Organization 2018), there were 9.6 million deaths due to cancer diseases. New potential anticancer agents have been prepared utilising molecular hybridisation method by association of pharmacophoric moieties of different bioactive molecules (Kamal et al. 2019). This strategy was beneficial to improve the bioactivity and properties of promising synthesised compounds. The hybrid derivatives may interact with dual targets to overcome resistance, reduce toxicity and lower adverse effects (Raghavendra et al. 2018; Hodon et al. 2019).

Natural products play a vital role in drug discovery particularly in the treatment of cancer diseases. The major isolated phytochemical from the rhizome of turmeric *Curcuma longa* which is a member of the family *Zingiberaceae* (Lakhan et al. 2015; Roso et al. 2016) shows potent inhibitory activity against cancer cells (Singh and Khar 2006; Melguizo et al. 2018). Tetrahydrocurcumin, an active metabolite of curcumin in which has been demonstrated the cytotoxicity as anticancer agent. *In vitro* studies have investigated the inhibitory activity of tetrahydrocurcumin against human breast cancer (Han et al. 2016); cervical cancer (Yoysungnoen et al. 2016); colon cancer (Lakowski et al. 2017); Leukemia (Tseng et al. 2019); lung cancer (Song et al. 2018). Tetrahydrocurcumin was found to have anticancer effects through various mechanisms including decrease of VEGFR levels and termination of DNA strand elongation (Pan et al. 2020). Tetrahydrocurcumin is a lead compound compared to curcumin due to its high reactivity, instability and low bioavailability (Baker 2017) and can be more stable under physiological conditions due to lacks the α,β-double bond conjugated to the carbonyl group (Esatbeyoglu et al. 2012a, 2012b).

Podophyllotoxin (PPT) is a natural product isolated from rhizomes roots of the *podophyllum species* (Suzuki et al. 2019). *In vitro* and *in vivo* studies were proved that podophyllotoxin can bind to tubulin and inhibit microtubule polymerisation, block tumor cell division and thus podophyllotoxin (PPT) possesses antitumor activity (Wang et al. 2018; Zhang et al. 2018; Atanasova et al. 2019). PPT is also a scaffold of antineoplastic drugs such as etoposide, teniposide and etopophos (Zi et al. 2020); Nerella et al. 2019; Wei et al. 2019).

Zidovudine (**8**) is indicated as HIV agent and other virus infected diseases. Meanwhile, it also could bind preferentially to telomeres by inhibiting telomerase and terminating telomerase DNA strand elongation leading to tumor cell senescence and apoptosis (Gomez et al. 2012; Berrino et al. 2020). Zidovudine (AZT) has been utilised in stage I and II clinical trials alone or in combination with other drugs for pancreatic cancer, gastrointestinal cancers and other progressed malignancies (Gomez et al. 2012).

Due to the importance of nitrogen containing heterocycles in medicinal chemistry (Mahal et al 2020 keep it; Salman et al, 2020; Zinad et al. 2020, 2021) and further chemical modifications of tetrahydrocurcumin have been developed by our group, new pyrazole and Schiff base derivatives of tetrahydrocurcumin were synthesised. Most of these derivatives were displayed potent anticancer activity than the parent tetrahydrocurcumin (Mahal et al. 2017, 2019). Herein, we report the synthesis of two



Scheme 1. Synthesis, structure and numbering (as used in NMR signal assignment) of THC-4β-triazolo-podophyllotoxin conjugates **6, 7** and THC-4β-triazolo-zidovudine conjugate **9**. Reagents and conditions: (a) K_2CO_3, propargyl bromide, DMF, N_2, r.t. 24 h. (b) sodium azide, trichloromethane, trifluoroacetic acid, r.t. overnight. (c) copper (II) sulfate pentahydrate, sodium ascorbate, THF, *t*-BuOH-H_2O, r.t. 12 h.

tetrahydrocurcumin-PPT and tetrahydrocurcumin-AZT conjugates and test their anticancer activity against four human cancer cell lines (HeLa, A549, HepG2, HCT-116).

2 Results and discussion

2.1. Chemistry

Compounds **6**, **7** and **9** were synthesised according to the steps shown in scheme 1. Mono-tetrahydrocurcumin-alkyne **2** was obtained by the reaction of tetrahydrocurcumin **1** with propargyl bromide using a base of potassium carbonate (K_2CO_3) and a solvent of dimethylformamide (DMF) at room temperature for 24 hours. 4β-azido-4-deoxypodophyllotoxin (**4)** and 4β-azido-4-deoxy-4′-demethypodophyllotoxin (**5**) were prepared using the previous published procedures (Hansen et al.1993; Kamal et al. 2000). The reaction of compound (**2**) with the azides (**4**, **5)** was carried out utlising copper sulfate (II) pentahydrate ($CuSO_4 \bullet 5H_2O$), monosodium ascorbate in THF (2 mL) and a mixture of *t*-BuOH:H_2O (2 mL, *v:v* = 1:1) at room temperature for 12 h. The obtained yields of tetrahydrocurcumin-4β-triazole-podophyllotoxin conjugates **6**, **7** were 41%, 45%, respectively, and the yield of tetrahydrocurcumin-4β-triazole-zidovudine conjugates were 41%. The synthesised compounds were structurally identified using ^{1}H-NMR, ^{13}C-NMR and HRESI-MS techniques.

Compound **6, 7** and **9** was obtained as yellow oil and purity tested by UPLC was 96.13%, 92.55%, 100%, respectively. Scheme 1. shows the structures of newly prepared compounds with atom numbering for elucidation of the structures using ^{1}H-NMR, ^{13}C-NMR and mass techniques. The ^{1}H-NMR spectrum revealed existing of doublet signal at 4.7 ppm corresponding to C4□-H indicating a cis-relationship between C3□-H and C4□-H. The ^{1}H-NMR spectrum of compound **6** indicated five singlets signals ranging from 3.85 to 3.76 ppm corresponding to five OCH_3 groups while compound **7** investigated three singlet signals ranging from 3.85 to 3.80 ppm due to three OCH_3 groups. The ^{1}H-NMR spectrum of compounds **6** and **7** revealed the presence of two signals of at 5.98 ppm corresponding to C13□-H_2 and at 5.50 ppm due to C12-H_2 groups. Three signals for both compounds **6** and **7** between 204 to 173 due to the three CO groups appeared in ^{13}C-NMR spectrum. ^{13}C-NMR spectrum indicated two signals at 144.1 and 124.8 ppm of C-13 and C-14 groups in triazole ring and revealed the presence of signals ranging from 60.92 to 56.06 ppm corresponding to three OCH_3 groups. ESI-HRMS revealed the molecular formulas of compound **6** ($C_{46}H_{48}N_3O_{13}$) and compound **7** ($C_{45}H_{46}N_3O_{13}$). The ^{1}H-NMR spectrum of compound **9** indicated the presence of one singlet signal at 8.45 ppm due to NH_2. One singlet signal at 3.86 ppm due to the six protons of OCH_3 groups. The ^{1}H-NMR spectrum revealed the presence of singlet signal at 5.64 ppm due to C12-H_2 group. ^{13}C-NMR spectrum showed five singlet signals from 59.22 to 56.09 ppm due to five OCH_3 groups. ^{13}C-NMR spectrum indicated two signals at 144.09 ppm and 122.10 ppm corresponding to C-12 and C13 of triazole ring, respectively. Four signals corresponding to four C = O groups appeared from 204 ppm to 150 ppm in the ^{13}C-NMR spectrum. ESI-HRMS proved the molecular formula of the compound **9** ($C_{34}H_{40}N_5O_{10}$).

2.2. Cytotoxic activity

MTT assay was used to evaluate cytotoxic properties of the compounds against four cancer cell lines (HeLa, A549, HepG2, HCT-116). Tetrahydrocurcumin and etoposide

were used as positive controls. The activity of the compounds **6**, **7** and **9** were carried out based on drug concentration of 50% for cell growth inhibition (IC_{50}) as shown in Table S1. The bioactivity of intermediates **2, 4** and **5** showed no significant difference compared to the corresponding scaffold and compound **8**, zidovudine exhibited slight activity only against Hela cell lines. Compound **6** and **7** showed promising anticancer activity against HCT-116 (IC_{50}=17.86) and HeLa (83.19 μM) cell lines. Compound **6** showed potent inhibitory activity against HCT-116 compared to positive controls of tetrahydrocurcumin (50.96 μM) and etoposide (19.48 μM). Using one-way ANOVA, compound **6** showed significant difference IC_{50} value compared to tetrahydrocurcumin ($P<0.05$) while showed no significant difference in comparison to the etoposide ($P>0.05$). Compound **7** showed potent inhibitory activity against HeLa (156.67 μM) and HCT-116 (114.86 μM) cell lines. However, compound **9** showed no obvious activity against four cancer cell lines ($IC_{50}>200\mu M$). The selectivity index values (SI: $IC_{50\ normal\ cell}/IC_{50\ tumor\ cell}$) was used to evaluate the safety and effectiveness of compounds. Although podophyllotoxin and 4′-demethoxypodoohylltoxin displayed significant anticancer bioactivity ($IC_{50}<1.56\ \mu M$) but it was also showed strong toxicity to human normal intestinal epithelial cell ($IC_{50}<1.56\ \mu M$, SI<1). The SI of compound **6** (SI = 3.96) was 4.2 times higher than tetrahydrocurcumin (SI = 0.95) and 4.6 times higher than etoposide (SI = 0.86).

3 Experimental

3.1. General experimental procedures

All reagents and solvents were obtained from commercial sources (Guangzhou Chemical Reagent; Shanghai Bide Pharmaceutical Technology Co., Ltd; Shanghai Macklin Biochemical Co., Ltd. Tianjin Damao Chemical Reagent Factory). Tetrahyrdocurcumin was obtained from Shanghai D&B Biological Science and Technology Co., Ltd. Podophyllotoxin and 4′-demethoxypodoohylltoxin was purchased from Shanghai Aladdin Co., Ltd. Zidovudine was purchased from Shanghai Yuanye Co., Ltd. Silica gel (200 ∼ 300 mesh) was purchased from Yantai Jiangyou Silica Gel Development Co., Ltd.

HRMS data were acquired in ESI mode on Orbitrap Eclipse device. UPLC data were performed using Agilent 1290 Infinity II HDR-DAD instrument. NMR data were acquired on AVANCE IIITM HD 600 MHz instrument. Chemical shifts (δ) are given in ppm, coupling constants (*J*) in Hz. The splitting pattern abbreviations are as follows: s = singlet, d = doublet, dd = doublet of doublets, ddd = doublet of doublet of doublets, t = triplet, m = multiplet, brs = broad singlet.

3.2. General procedures for synthesis of tetrahydrocurcumin-4β-triazolopodophyllotoxin conjugates 6 and 7

Copper (II) sulfate pentahydrate (10 mg) and monosodium ascorbate (2 g in 10 mL H_2O, 0.3 mL) were added to mixture of compound **2** (200 mg, 0.487 mmol) and 4β-azido-4-deoxy-podophyllotoxin (**4**) (217 mg, 0.496 mmol)/or 4β-azido-4-deoxy-4′-demethypodophyllotoxin (**5**) (210 mg, 0.496 mol) in THF (2 mL) and t-BuOH-H_2O (2 mL, *v:v* = 1:1) and stirring at room temperature until the reaction is complete (observation

by TLC). The residue after evaporation of the solvent was loaded onto silica gel column using DCM:EtOAC (*v:v* = 10:1) to afford the target.

3.2.1. 1,7-Bis(4-hydroxy-3-methoxyphenyl) heptane-3,5-dione-[4ß-(1,2,3-trizaol-1-yl-4-deoxypodophyllotoxin)] ether (6)

Yellow oil, (184.53 mg, 0.217 mmol, 45%). ^{1}H-NMR (600 MHz, $CDCl_3$): δ 6.92 (s, 1H, ArH), 6.79 (dd, *J* = 7.8, 1.2 Hz, 2H, ArH), 6.64 (s, 1H, ArH), 6.62 (t, *J* = 1.8 Hz, 2H, ArH), 6.59 (ddd, *J* = 7.8, 3.6, 2.4 Hz, 2H, ArH), 6.51 (s, 1H, ArH), 6.30 (s, 1H, ArH), 5.98 (dd, *J* = 28.8, 2.4 Hz, 2H), 5.51 (s, 2H, CH_2), 4.74 (d, *J* = 5.4 Hz, 1H), 4.33 (dd, *J* = 9.0, 7.2 Hz, 1H), 4.16 (t, *J* = 6.6 Hz, 1H), 3.85 ~ 3.76 (m, 15H, OMe), 3.12 (d, *J* = 7.2 Hz, 1H), 2.97 (s, 1H), 2.881 ~ 2.880 (m, 1H), 2.74 ~ 2.67 (m, 6H), 1.61 (s, 3H). ^{13}C-NMR (150 MHz, $CDCl_3$) δ 204.54 (C-10), 204.49 (C-10′), 173.25 (C-12′′), 152.97 (C-3′′′, 5′′′), 149.53 (C-6′), 148.22 (C-6, 5′), 146.57 (C-6′′, 7′′), 144.51 (C-5), 144.13 (C-13), 137.76 (C-1′′′, 4′′′), 134.37 (C-2), 133.30 (C-2′), 132.44 (C-9′′, 10′′), 124.81 (C-14), 122.65 (C-3), 120.94 (C-3′), 114.46 (C-4), 111.23 (C-1, 5′′), 110.67 (C-1′, 4′), 108.78 (C-8′′), 108.39 (C-2′′′, 6′′′), 102.12 (C-13′′), 77.37 (C-11, 12), 67.41 (C-4′′), 66.16 (C-11′′), 60.92 (C-8′′′), 58.68 (C-7′), 56.51 (C-7), 56.06 (C-7′′′), 44.70 (C-1′′), 43.77 (C-2′′), 41.75 (C-9, 9′), 37.26 (C-3′′), 29.18 (C-8′), 23.89 (C-8). ESI-HRMS Calcd for $C_{46}H_{48}N_3O_{13}$ $[M+H]^+$:850.3182, found 850.3193.

3.2.2. 1,7-Bis(4-hydroxy-3-methoxyphenyl) heptane-3,5-dione-[4ß-(1,2,3-trizaol-1-yl-4-deoxy-4-demethoxypodophyllotoxin)] ether (7)

Yellow oil, (162.95 mg, 0.217 mmol, 45%). ^{1}H-NMR (600 MHz, $CDCl_3$) δ 6.92 (s, 1H, ArH), 6.79 (dd, 2H, *J* = 7.98, 1.44 Hz, ArH), 6.63 (s, 1H, ArH), 6.62 ~ 6.61 (m, 2H, ArH), 6.59 (ddd, *J* = 8.16, 3.18, 2.04, 2H, ArH), 6.51 (s, 1H, ArH), 6.32 (d, 1H, ArH), 5.98 (dd, 2H), 5.48 (d, *J* = 16.98 Hz, 3H), 4.73 (d, *J* = 4.98, 1H, CH), 4.32 ~ 4.31 (m, 1H), 4.16 (t, 1H), 3.83 (s, 12H, OMe), 3.13 ~ 1.60 (12H, CH_2). ^{13}C-NMR (150 MHz, $CDCl_3$) δ 204.54 (C-10, 10′), 173.32 (C-12′′), 149.52 (C-6′), 148.17 (C-3′′′, 5′′′), 146.75 (C-6, 5′), 146.55 (C-6′′, 7′′), 144.49 (C-5), 144.11 (C-13), 134.56 (C-1′′′, 4′′′), 133.46 (C-2), 132.44 (C-2′), 129.86 (C-9′′, 10′′), 124.79 (C-14), 122.64 (C-3), 120.93 (C-3′), 114.44 (C-4), 111.21 (C-1, 5′′), 110.67 (C-1′, 4′), 108.74 (C-8′′), 107.97 (C-2′′′, 6′′′), 102.10 (C-13′′), 67.42 (C-11, 12), 66.16 (C-4′′, 11′′), 58.69 (C-7′), 56.69 (C-7), 56.05 (C-7′′′), 44.71 (C-1′′), 43.60 (C-2′′), 41.84 (C-9, 9′), 37.18 (C-3′′), 29.17 (C-8′), 23.89 (C-8). ESI-HRMS Calcd for $C_{45}H_{46}N_3O_{13}$ $[M+H]^+$:836.3025, found 836.3025.

3.3. General procedures for synthesis of tetrahydrocurcumin-4β-triazolopodozidovudine conjugate (9)

Copper (II) sulfate pentahydrate (10 mg) and monosodium ascorbate (2 g in 10 mL H_2O, 0.3 mL) were added to mixture of compound **2** (200 mg, 0.487 mmol) and zidovudine (**8**) (108 mg, 0.406 mmol) in THF (2 mL) and t-BuOH-H_2O (2 mL, *v:v* = 1:1) and stirring at room temperature until the reaction is complete (observation by TLC). The residue after evaporation of the solvent was loaded onto silica gel column using DCM:EtOAC (*v:v* = 10:1) to afford the target.

3.3.1. 1,7-Bis(4-hydroxy-3-methoxyphenyl) heptane-3,5-dione-3′-(1,2,3-trizaol-1-yl)-3′-deoxythymidine (9)

Yellow oil, (135.12 mg, 0.200 mmol, 41% yield). ^{1}H-NMR (600 MHz, $CDCl_3$): δ 8.45 (s, 1H), 6.79 (dd, $J = 8.4$, 2.4 Hz, 2H, ArH), 6.64 (dd, $J = 5.4$, 2.4 Hz, 2H, ArH), 6.59 (ddd, $J = 8.4$, 3.6, 1.8 Hz, 2H, ArH), 6.16 (t, $J = 6.6$ Hz, 1H, ArH), 5.64 (d, $J = 21.0$ Hz, 2H), 5.23 ∼ 5.20(m, 1H), 4.31 ∼ 4.30 (m, 1H), 4.13(t, $J = 7.2$ Hz, 1H), 3.98 (dd, $J = 12$, 2.4 Hz, 1H), 3.86 (s, 6H, OMe), 3.72 (dd, $J = 12.6$, 2.4 Hz, 1H), 3.15 (dd, $J = 7.2$, 2.4 Hz, 1H), 2.77 ∼ 2.72(m, 6H), 1.94 (d, $J = 1.2$ Hz, 3H), 1.60 (s, 8H), 1.25 (s, 1H). ^{13}C-NMR (150 MHz, $CDCl_3$) δ 204.57 (C-10, 10′), 163.39 (C-7′′), 150.38 (C-6′′, 6′), 146.59 (C-6, 5′), 144.64 (C-5), 144.09 (C-13), 137.94 (C-9′′), 132.62 (C-2), 132.54 (C-2′), 122.10 (C-14), 121.06 (C-3, 3′), 114.53 (C-4), 111.57 (C-1), 111.46 (C-1′, 4′), 111.35 (C-8′′), 89.18 (C-3′′), 85.21 (C-11, 2′′), 66.53 (C-12, 1′′), 61.89 (C-5′′), 59.22 (C-7′), 56.09 (C-7), 44.45 (C-9), 44.33 (C-9′), 37.40 (C-4′′), 29.16 (C-8), 29.10 (C-8′), 12.60 (C-10′′). ESI-HRMS Calcd for $C_{34}H_{40}N_5O_{10}$ $[M + H]^+$:678.2770, found 678.2784.

4. Conclusions

We have synthesised three new tetrahydrocurcumin-4β-triazolo conjugates using copper catalyzed azide-alkyne cycloaddition (CuAAC) reaction and tested their inhibitory activity against four human cancer cell lines. Compound **6** showed potent antiproliferative bioactivity with satisfactory selectivity against HCT-116 cell line (IC_{50}=17.86 μM, SI = 4.09) superior to parent tetrahydrocurcumin and positive control of etoposide. We conclude that the modification of tetrahydrocurcumin leading to compound **6** using click reaction can enhance cytotoxic activity against anti-colon cancer cell lines and meanwhile reduced toxicity of podophyllotoxin and **4**′-demethoxypodophyllotoxin as well. Further modifications of tetrahydrocurcumin leading to improve its anticancer activity are recommended.

Disclosure statement

No potential conflict of interest was reported by authors.

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