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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Antiproliferative activity of ursolic acid/glycyrrhetinic acid-uracil/thymine hybrids

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Abstract

As pharmacophore hybridization has been used frequently in the discovery of new drugs, ursolic acid/glycyrrhetinic acid-uracil/thymine hybrids have been synthesized and evaluated their antiproliferative activity by the MTT assay. The results displayed that, the hybrids of glycyrrhetinic acid (**7a**–**7b** to **10a**–**10b**) exhibited slightly better antiproliferative activity than that of ursolic acid hybrids (**3a**–**3b** to **6a**–**6b**). Two single glycyrrhetinic acid-thymine hybrids (**8a** and **10a**) possessed good antiproliferative activity against tested A549 cell line ($IC_{50} = 10.7$ and 18.3 μM, respectively). And three hybrids (**3a**, **5a**, and **10b**) exhibited about 80% inhibitory ratio against tested Hela cell line.

Keywords Ursolic acid · Glycyrrhetinic acid · Uracil · Thymine · Antiproliferative activity

Introduction

As cancer is a serious threat to people's lives and health, some research looking for more effective anticancer candidates are needed (Xiao et al. 2016). In the last few decades, nearly half of commercial drugs were natural products or their derivatives (Hansen and Andersen 2016; Patridge et al. 2016). Pentacyclic triterpenes (Paduch and Kandefer-Szerszen 2014), which are ubiquitous in the plant kingdom, have very important ecological and agronomic functions, and contribute more to pest and disease resistance. Ursolic acid (**UA**, **1**) and Glycyrrhetinic acid (**GA**, **2**), which belong to pentacyclic triterpenes, are the active ingredients of herbal medicine (Babalola and Shode 2013; Hussain et al. 2018). They possess diversity biological activities, such as hepatoprotection, antioxidant, anti-inflammatory antitumor, hypoglycemic, lipid lowering, anti-HIV, antivirus activities (Dar et al. 2016, Xu et al. 2017). They are also reported that they are multidrug resistance modulators and potential chemosensitizers (Yadav et al. 2014; Chen et al. 2016; Yang et al. 2016).

On the other hand, pyrimidine, a heteroatomic aromatic compound, has been widely used as a pharmacophore in the research of anticancer drugs (Labib and Lamie 2016; Addepalli et al. 2018). Uracil and thymine, as a part of nucleosides, nucleic acids, and nucleotides, not only promotes self-assembly, but also have the capability for DNA delivery (Slavíček et al. 2009; Sharma et al. 2016). They have been paid much more attention because of a wide array of biological activities and synthetic accessibility (Mallavadhani et al. 2014; Pałasz and Cież 2015). For example, cytarabine is clinically used to treat chronic granulocytes, lymphocytic leukemia, and malignant lymphoma. Therefore, the pyrimidinyl groups have been constructed in many new structures in various antitumor researches.

Nowadays, in order to optimize and enhance original certain biological properties, fusing two bioactive moieties by covalent bonds which named pharmacophore hybridization has been used frequently in the discovery of new drugs (Cheng et al. 2016). In our group, we have prepared several oleanolic acid-uracil/thymine conjugates, and discovered these hybrids displayed much more potent inhibitory activities compared with oleanolic acid and commercial

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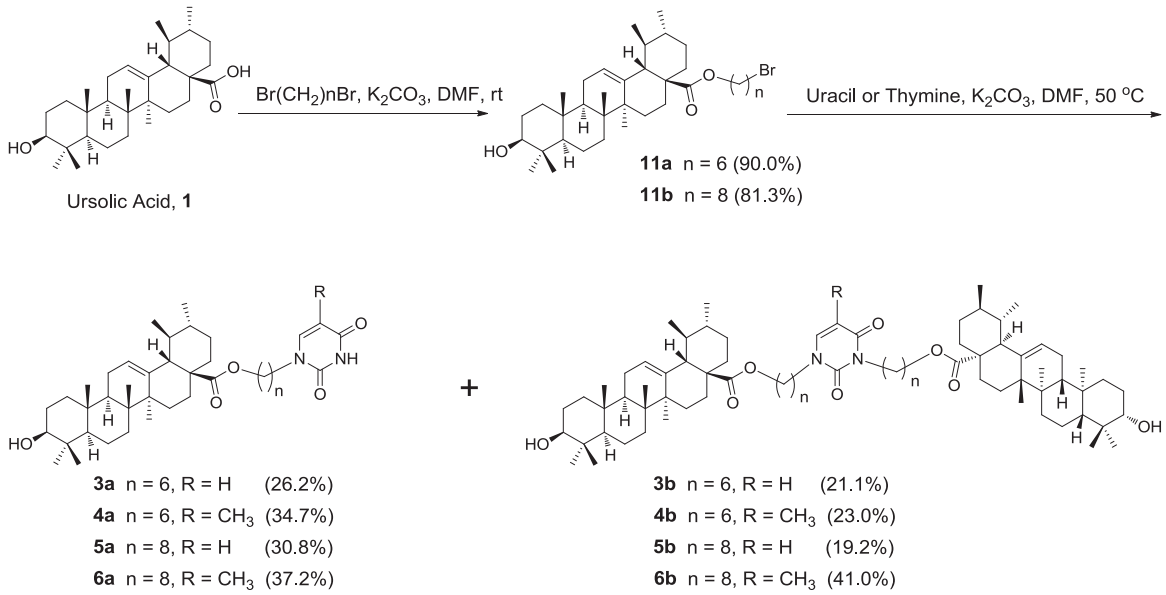
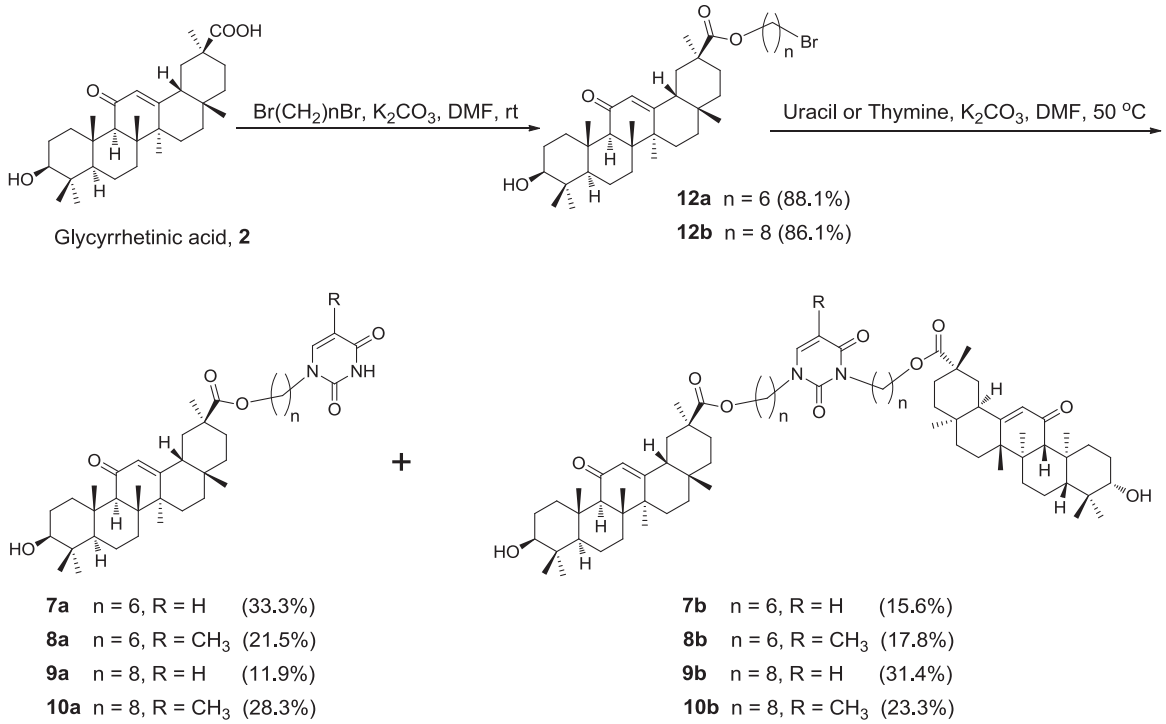


Scheme 1 Synthesis of ursolic aicd-uracil/thymine hybrids, where *n* is the number of methylene groups



Scheme 2 Synthesis of glycyrrhetinic acid-uracil/thymine hybrids, where *n* is the number of methylene groups

anticancer drug 5-fluorouracil (5-FU) (Cheng et al. 2016). Inspired from these information, in the present study, sixteen ursolic acid/glycyrrhetinic acid-uracil/thymine hybrids have been synthesized and evaluated their antiproliferative activity by the MTT assay (Kuzio et al. 2004) (Schemes 1, 2; and Table 1). The results displayed that, hybrids of glycyrrhetinic acid (**7a**–**7b** to **10a**–**10b**) exhibited slightly better antiproliferative activity than that of ursolic acid hybrids (**3a**–**3b** to **6a**–**6b**). Only one hybrid (**8a**) possessed IC_{50} at about 10 µM against tested A549 cell line. And three hybrids (**3a**, **5a**, and **10b**) exhibited about 80% inhibitory ratio against tested Hela cell line.

Table 1 In vitro antitumor activities of **3a–3b** to **10a–10b** against different cell lines

Compound		IC_{50} (μM)[a]			Inhibitory ratio (20 μM, $\bar{x} \pm SD$, %)			
	Structure	Hep-G2	A549	HL-7702	HeLa	BGC-823	NCI-H460	BEL-7404
3a	$n = 6$, R=H	No[b]	No	53.9 ± 2.7	87.11 ± 4.69	28.39 ± 3.25	20.68 ± 2.76	No
3b	$n = 6$, R=H	No	No	No	9.99 ± 1.35	2.30 ± 0.63	23.95 ± 2.54	6.62 ± 1.13
4a	$n = 6$, R=CH_3	No	No	62.6 ± 3.4	50.91 ± 6.42	10.45 ± 2.77	23.48 ± 3.82	No
4b	$n = 6$, R=CH_3	No	No	No	35.35 ± 4.18	No	21.31 ± 2.75	10.79 ± 1.90
5a	$n = 8$, R=H	No	266.9 ± 20.3	50.2 ± 3.6	76.19 ± 5.77	26.09 ± 2.83	16.89 ± 1.49	No
5b	$n = 8$, R=H	No	No	No	No	No	25.41 ± 4.92	5.01 ± 0.78
6a	$n = 8$, R=CH_3	No	83.9 ± 6.7	42.1 ± 2.1	3.98 ± 0.45	No	24.71 ± 3.93	4.43 ± 1.12
6b	$n = 8$, R=CH_3	93.5 ± 10.2	No	No	No	17.72 ± 3.33	18.42 ± 2.71	7.90 ± 1.56
7a	$n = 6$, R=H	68.8 ± 7.1	No	72.2 ± 2.4	25.93 ± 3.23	40.05 ± 3.09	10.19 ± 1.82	21.52 ± 2.79
7b	$n = 6$, R=H	No	No	No	No	38.01 ± 2.05	24.69 ± 3.76	26.58 ± 3.56
8a	$n = 6$, R=CH_3	164.9 ± 11.7	10.7 ± 0.9	304.9 ± 4.6	36.39 ± 2.08	46.16 ± 1.46	20.86 ± 1.35	25.77 ± 2.75
8b	$n = 6$, R=CH_3	No	81.5 ± 7.4	261.5 ± 4.28	7.98 ± 1.02	30.24 ± 2.79	23.52 ± 2.04	29.32 ± 3.82
9a	$n = 8$, R=H	138.9 ± 10.9	74.9 ± 5.6	145.6 ± 2.8	26.27 ± 2.99	10.28 ± 1.37	10.27 ± 2.71	19.85 ± 3.84
9b	$n = 8$, R=H	154.3 ± 15.3	No	No	No	26.72 ± 2.15	17.49 ± 4.21	10.16 ± 0.79
10a	$n = 8$, R=CH_3	53.8 ± 6.4	18.3 ± 1.5	77.7 ± 1.9	9.82 ± 2.19	57.42 ± 2.33	5.45 ± 0.88	No
10b	$n = 8$, R=CH_3	No	69.1 ± 5.9	62.43 ± 2.57	83.36 ± 5.74	25.89 ± 3.84	17.02 ± 2.19	15.51 ± 2.01
5-FU		No	31.9 ± 2.5	66.6 ± 3.2	26.47 ± 1.87	69.23 ± 1.62	32.52 ± 0.88	28.44 ± 1.03

[a]The IC_{50} value was the concentration of the compound which inhibited tumor cell growth by 50%, and was presented as the mean ± SD (standard deviation) from three separate experiments

[b]No inhibition detected

Materials and methods

General: All the chemical reagents and solvents were used of analytical grade and used without further purification unless specially indicated. All commercial reagents were purchased from Aladdin (Shanghai) Industrial Corporation. Melting points were measured on a RY-1 melting point apparatus. ^1H and ^{13}C nuclear magnetic resonance (NMR) spectra were recorded on a Bruker AV-500 or AV-300 spectrometer. Chemical shifts are reported as values from an internal tetramethylsilane standard. HR-MS were recorded on a Thermo Scientific Accela—Exactive High Resolution Accurate Mass spectrometer.

Synthesis

General procedure I for esterification of UA and GA to prepare compounds 11a/b or 12a/b

To a solution of **UA** or **GA** (1.09 mmol) in DMF (5 mL), K_2CO_3 (0.15 g, 1.09 mmol) and α,ω-dibromoalkane (5.47 mmol) were added and stirred for 12 h at room temperature. Then, the mixture was diluted with EtOAc (50 mL). The organic layer was washed successively with 1 N HCl, saturated aqueous $NaHCO_3$ and brine, dried over anhydrous Na_2SO_4, filtered and concentrated to obtain the residue. Purification was carried out by flash column chromatography.

Compound **11a** (Mallavadhani et al. 2013; Huang et al. 2018). Prepared from **UA** (0.50 g, 1.09 mmol) and 1,6-dibromohexane (0.83 mL, 5.47 mmol) according to general procedure I. The residue wad purified by flash column chromatography (petroleum ether: EtOAc = 3: 1). Yield: 0.61 g, 90.0%, white solid.

Compound **11b** (Mallavadhani et al. 2013; Huang et al. 2018). Prepared from **UA** (2.00 g, 4.38 mmol) and 1,8-dibromooctane (3.32 mL, 21.90 mmol) according to general procedure I. The residue wad purified by flash column chromatography (petroleum ether: EtOAc = 4: 1). Yield: 2.30 g, 81.3%, white solid.

Compound **12a** (Schwarz et al. 2014; Huang et al. 2018). Prepared from **GA** (2.00 g, 4.25 mmol) and 1,6-dibromohexane (3.22 mL, 21.25 mmol) according to general procedure I. The residue wad purified by flash column chromatography (petroleum ether: EtOAc = 5: 2). Yield: 2.37 g, 88.1%, white solid.

Compound **12b** (Schwarz et al. 2014; Huang et al. 2018). Prepared from **GA** (2.00 g, 4.25 mmol) and 1,8-dibromooctane (3.95 mL, 21.25 mmol) according to general procedure I. The residue wad purified by flash column chromatography (petroleum ether: EtOAc = 5:2). Yield: 2.42 g, 86.1%, white solid.

General procedure II for *N*-alkylation reaction of uracil/thymine to afford 3a–3b to 10a–10b

To a solution of ω-bromoalkyl glycyrrhetinate or ursolate (0.64 mmol) in DMF (6.00 mL), K_2CO_3 (0.27 g, 1.92 mmol) and uracil or thymine (1.92 mmol) were added. After stirring at 50 °C for 12 h, the mixture was diluted with H_2O (50 mL) and extracted with EtOAc (3 × 30 mL). The combined organic layers were washed successively with 1 N HCl, saturated aqueous $NaHCO_3$ and brine, dried over anhydrous Na_2SO_4, filtered and concentrated to obtain the residue. Purification was carried out by flash column chromatography.

Compounds **3a** and **3b**. Prepared from compound **11a** (0.40 g, 0.64 mmol) and uracil (0.22 g, 1.92 mmol) according to general procedure II. Compounds **3a** (0.11 g, 26.2%) and **3b** (0.08 g, 21.1%) were obtained by flash column chromatography (petroleum ether: EtOAc = 2: 3).

Compound **3a**. White solid, mp 111–113 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.73, 0.77, 0.90, 0.98, 1.07, (5s, each 3H, 5 × CH_3), 0.84 (d, 3H, J = 6.5 Hz, CH_3), 0.93 (d, 3H, J = 6.2 Hz, CH_3), 0.70–2.01 (m, 30H), 2.21 (d, 1H, J = 11.7 Hz, H-18), 3.21 (dd, 1H, J = 4.7, and 11.1 Hz, H-3), 3.67–3.74 (m, 2H, NCH_2), 3.90–4.03 (m, 2H, CO_2CH_2), 5.22 (t, 1H, J = 3.6 Hz, H-12), 5.68 (d, 1H, J = 7.8 Hz, H-5^{Ura}), 7.13 (d, 1H, J = 7.8 Hz, H-6^{Ura}), 8.96 (s, 1H, NH). ^{13}C NMR (125 MHz, $CDCl_3$) δ 15.4 15.6, 17.0, 17.1, 18.3, 21.2, 23.3, 23.5, 24.2, 25.7, 26.1, 27.2, 27.9, 28.1, 28.4, 29.0, 30.6, 33.0, 36.7, 36.9, 38.6, 38.7, 38.8, 39.0, 39.5, 42.0, 47.5, 48.0, 48.8, 52.8, 55.1, 63.9, 79.0, 102.1, 125.5, 138.2, 144.3, 150.7, 163.6, 177.6. HRMS (ESI) *m/z*: $[M-H]^+$ calculated for $C_{40}H_{61}N_2O_5$: 649.4586, found: 649.4593.

Compound **3b**. White solid, mp 110–112 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.75, 0.78, 0.91, 0.94, 0.99, 1.07 (6s, each 6H, 12 × CH_3), 0.86 (d, 6H, J = 6.3 Hz, 2 × CH_3), 0.74–2.02 (m, 60H), 2.22 (d, 2H, J = 11.2 Hz, H-18, and H-18′), 3.21 (dd, 2H, J = 4.6 and 10.1 Hz, H-3, and H-3′), 3.69–3.74 (m, 2H, NCH_2), 3.90–3.94 (m, 2H, NCH_2), 3.94–4.02 (m, 4H, 2 × CO_2CH_2), 5.23 (t, 2H, J = 3.1 Hz, H-12 and H-12′), 5.71 (d, 1H, J = 7.8 Hz, H-5^{Ura}), 7.08 (d, 1H, J = 7.8 Hz, H-6^{Ura}). ^{13}C NMR (125 MHz, $CDCl_3$) δ 15.8, 16.0, 17.3, 17.4, 17.5, 18.6, 21.50, 21.51, 23.6, 23.9, 24.5, 26.0, 26.1, 26.5, 27.0, 27.5, 27. 8, 28.3, 28.5, 28.8, 28.9, 29.3, 31.0, 33.4, 37.0, 37.1, 37.3, 38.9, 39.1, 39.17, 39.19, 39.38, 39.39, 39.9, 41.5, 42.35, 42.37, 47.8, 47.9, 48.3, 48.4, 50.1, 53.17, 53.19, 55.51, 55.53, 64.2, 64.5, 79.29, 79.34, 102.0, 125.8, 125.9, 138.49, 138.52, 142.3, 151.7, 163.4, 177.89, 177.91. HRMS (ESI) *m/z*: $[M+Na]^+$ calculated for $C_{76}H_{120}N_2NaO_8$: 1211.8937, found: 1211.8921.

Compounds **4a** and **4b**. Prepared from compound **11a** (0.40 g, 0.64 mmol) and thymine (0.24 g, 1.92 mmol) according to general procedure II. Compounds **4a** (0.15 g, 34.7%) and **4b** (0.09 g, 23.0%) were obtained by flash column chromatography (petroleum ether:EtOAc = 2:3).

Compound **4a**. White solid, mp 104–106 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.75, 0.78, 0.95, 0.99, 1.08 (5s, each 3H, 5 × CH_3), 0.86 (d, 3H, J = 6.4 Hz, CH_3), 0.92 (d, 3H, J = 5.2 Hz, CH_3), 1.93 (s, 3H, CH_3^{Thy}), 0.70–2.00 (m, 30H), 2.22 (d, 1H, J = 11.1 Hz, H-18), 3.22 (d, 1H, J = 7.1 Hz, H-3), 3.65–3.72 (m, 2H, NCH_2), 3.68 (m, 2H, CO_2CH_2), 5.23 (t, 1H, J = 3.3 Hz, H-12), 6.97 (s, 1H, H-6^{Thy}), 8.44 (s, 1H, NH). ^{13}C NMR (125 MHz, $CDCl_3$) δ 12.7, 15.8, 16.0, 17.4, 17.5, 18.6, 21.5, 23.6, 23.9, 24.5, 26.1, 26.5, 27.5, 28.3, 28.5, 28.8, 29.4, 31.0, 33.4, 37.1, 37.3, 38.9, 39.1, 39.2, 39.4, 39.9, 42.4, 47.8, 48.4, 48.8, 53.2, 55.5, 64.3, 79.3, 110.9, 125.8, 138.5, 140.7, 151.1, 164.6, 177.9. HRMS (ESI) *m/z*: $[M+Na]^+$ calculated for $C_{41}H_{64}N_2NaO_5$: 687.4707, found: 687.4729.

Compound **4b**. White solid, mp 118–120 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.75, 0.78, 0.91, 0.99 (4s, each 6H, 8 × CH_3), 0.85 (dd, 6H, J = 1.2 and 6.5 Hz, 2 × CH_3), 0.94 (dd, 6H, J = 2.2 and 6.3 Hz, 2 × CH_3), 1.08 (d, 6H, J = 2.9 Hz, 2 × CH_3), 1.93 (s, 3H, CH_3^{Thy}), 0.72–2.04 (m, 60H), 2.22 (d, 2H, J = 11.7 Hz, H-18 and H-18′), 3.2 (dd, 2H, J = 4.7 and 11.1 Hz, H-3 and H-3′), 3.66–3.72 (m, 2H, NCH_2), 3.90–4.04 (m, 6H, 2 × CO_2CH_2, NCH_2), 5.23 (t, 2H, J = 3.5 Hz, H-12 and H-12′), 6.94 (s, 1H, H-6^{Thy}). ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.1, 15.4, 15.6, 16.98, 17.04, 17.1, 18.3, 21.2, 23.2, 23.5, 24.2, 25.7, 25.8, 26.2, 26.7, 27.1, 27.5, 27.9, 28.1, 28.4, 28.5, 29.0, 30.6, 33.0, 36.7, 36.9, 38.6, 38.7, 38.79, 38.82, 39.0, 39.5, 41.4, 41.97, 41.99, 47.45, 47.50, 47.95, 47.99, 49.4, 52.78, 52.81, 55.1, 55.2, 63.9, 64.1, 78.9, 79.0, 109.7, 125.4, 125.5, 138.1, 138.2, 151.3, 163.7, 177.5. HRMS (ESI) *m/z*: $[M+Na]^+$ calculated for $C_{77}H_{122}N_2NaO_8$: 1225.9093, found: 1225.9112.

Compounds **5a** and **5b**. Prepared from compound **11b** (0.43 g, 0.67 mmol) and uracil (0.23 g, 2.00 mmol) according to general procedure II. Compounds **5a** (0.14 g, 30.8%) and **5b** (0.08 g, 19.2%) were obtained by flash column chromatography (petroleum ether: EtOAc = 2: 3).

Compound **5a**. White solid, mp 93–95 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.75, 0.78, 0.95, 0.99, 1.08 (5s, each 3H, 5 × CH_3), 0.86 (d, 3H, J = 6.4 Hz, CH_3), 0.92 (d, 3H, J = 4.5 Hz, CH_3), 0.71–2.03 (m, 34H), 2.22 (d, 1H, J = 11.3 Hz, H-18), 3.22 (d, 1H, J = 9.0 Hz, H-3), 3.62–3.79 (m, 2H, NCH_2), 3.91–4.04 (m, 2H, CO_2CH_2), 5.23 (t, 1H, J = 3.4 Hz, H-12), 5.69 (d, 1H, J = 7.9 Hz, H-5^{Ura}), 7.15 (d, 1H, J = 7.9 Hz, H-6^{Ura}), 8.91(s, 1H, NH). ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.4, 15.5, 16.9, 17.0, 18.2, 21.1, 23.2, 23.4, 24.1, 25.8, 26.3, 27.1, 27.9, 28.0, 28.4, 28.9, 29.0, 30.6, 33.0, 36.7, 36.9, 38.5, 38.6, 38.8, 39.0, 39.5, 42.0, 47.5, 48.0, 48.8, 52.8, 55.1, 64.1, 78.9, 102.0, 114.5, 125.4, 138.1, 144.3, 150.6, 163.4, 177.5. HRMS (ESI) *m/z*: $[M+Na]^+$ calculated for $C_{42}H_{66}N_2NaO_5$: 701.4864, found: 701.4885.

Compound **5b**. White solid, mp 96–98 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.75, 0.78, 0.92, 0.95, 0.99 (5s, each 6H, 10 × CH_3), 0.86 (d, 6H, J = 6.4 Hz, 2 × CH_3), 0.94 (d, 6H, J = 4.8 Hz, 2 × CH_3), 0.71–2.06 (m, 68H), 2.23 (d, 2H, J = 11.4 Hz, H-18, and H-18′), 3.22 (dd, 2 H, J = 4.4 and 9.8 Hz, H-3 and H-3′), 3.66-3.78 (m, 2H, NCH_2), 3.90–3.98 (m, 6H, 2 × CO_2CH_2, NCH_2), 5.23 (t, 2H, J = 3.0 Hz, H-12 and H-12′), 5.71 (d, 1 H, J = 7.8 Hz, H-5^{Ura}), 7.08 (d, 1H, J = 7.8 Hz, H-6^{Ura}). ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.4, 15.5, 16.9, 17.0, 18.2, 21.1, 23.2, 23.4, 24.1, 25.85, 25.94, 26.4, 26.8, 27.1, 27.4, 27.9, 28.0, 28.4, 28.5, 29.0, 29.1, 30.6, 33.0, 33.9, 36.6, 36.9, 38.5, 38.7, 38.8, 39.0, 39.5, 41.2, 42.0, 42.3, 47.5, 48.0, 49.7, 52.8, 55.1, 57.0, 64.0, 64.2, 78.9, 82.1, 101.5, 107.2, 125.4, 130.0, 138.1, 139.6, 141.9, 177.5. HRMS (ESI) *m/z*: $[M+Na]^+$ calculated for $C_{80}H_{128}N_2NaO_8$: 1267.9563, found: 1267.9567.

Compounds **6a** and **6b**. Prepared from compound **11b** (0.40 g, 0.62 mmol) and thymine (0.24 g, 1.90 mmol) according to general procedure II. Compounds **6a** (0.16 g, 37.2%) and **6b** (0.16 g, 41.0%) were obtained by flash column chromatography (petroleum ether:EtOAc = 2:3).

Compound **6a**. White solid, mp 104-106 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.75, 0.78, 0.91, 0.95, 0.99, 1.08 (6s, each 3H, 6 × CH_3), 0.86 (d, 3H, J = 5.8 Hz, CH_3), 1.90 (s, 3 H, CH_3^{Thy}), 0.73–2.10 (m, 34H), 2.23 (d, 1H, J = 11.3 Hz, H-18), 3.21 (d, 1H, J = 5.5 Hz, H-3), 3.58–3.74 (m, 2H, NCH_2), 3.98 (m, 2H, CO_2CH_2), 5.23 (t, 1H, J = 3.1 Hz, H-12), 6.97(s, 1H, H-6^{Thy}), 8.45 (s,1H, NH). ^{13}C NMR (125 MHz, $CDCl_3$) δ 12.7, 15.8, 16.0, 17.4, 17.5, 18.6, 21.5, 23.6, 23.9, 24.5, 26.3, 26.7, 27.5, 28.3, 28.5, 28.8, 29.38, 29.41, 29.5, 31.0, 33.4, 37.1, 37.3, 38.9, 39.1, 39.2, 39.4, 39.9, 42.4, 47.9, 48.4, 48.9, 53.2, 55.5, 64.5, 79.3, 110.9, 125.8, 138.5, 140.7, 151.2, 164.6, 177.9. HRMS (ESI) *m/z*: $[M+Na]^+$ calculated for $C_{43}H_{68}N_2NaO_5$: 715.5020, found: 715.5029.

Compound **6b**. White solid, mp 91–94 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.75, 0.78, 0.92, 0.95, 0.99, 1.08 (6s, each 6H, 12 × CH_3), 0.86 (d, 6H, J = 6.4 Hz, 2 × CH_3), 1.91 (s, 3 H, CH_3^{Thy}), 0.69–2.06 (m, 68H), 2.23 (d, 2H, J = 11.1 Hz, H-18 and H-18′), 3.22 (dd, 2H, J = 4.8 and 10.4 Hz, H-3 and H-3′), 3.66–3.71 (m, 2H, NCH_2), 3.90–3.98 (m, 6H, 2 × CO_2CH_2, NCH_2), 5.23 (t, 2H, J = 3.5 Hz, H-12 and H-12′), 6.94 (s, 1H, H-6^{Thy}). ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.4, 15.8, 15.97, 15.98, 17.36, 17.45, 17.46, 18.7, 21.5, 23.6, 23.9, 24.5, 26.3, 26.4, 26.8, 27.3, 27.5, 27.6, 27.9, 28.3, 28.5, 28.85, 28.90, 29.41, 29.44, 29.46, 29.52, 29.6, 31.0, 33.4, 37.05, 37.07, 37.3, 39.0, 39.1, 39.19, 39.21, 39.40, 39.41, 39.9, 41.8, 42.37, 42.38, 47.86, 47.89, 48.36, 48.37, 49.8, 53.17, 53.19, 55.5, 55.6, 64.5, 64.6, 79.3, 79.4, 110.0, 125.8, 125.9, 138.50, 138.52, 138.6, 151.7, 164.1, 177.93, 177.94. HRMS (ESI) *m/z*: $[M+Cl]^+$ calculated for $C_{81}H_{130}ClN_2O_8$: 1293.9521, found: 1293.9560.

Compounds **7a** and **7b**. Prepared from compound **12a** (0.40 g, 0.63 mmol) and uracil (0.21 g, 1.90 mmol) according to general procedure II. Compounds **7a** (0.14 g, 33.3%) and **7b** (0.06 g, 15.6%) were obtained by flash column chromatography (petroleum ether:EtOAc = 2:3).

Compound **7a**. White solid, mp 112–114 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.81 (s, 6H, 2 × CH_3), 1.01, 1.12, 1.13, 1.4, 1.37 (5s, each 3H, 5 × CH_3), 0.70–2.08 (m, 27H), 2.34 (s, 1H, H-9), 2.77 (d, 1H, J = 11.3 Hz, H-18), 3.23 (dd, 1H, J = 6.0 and 10.0 Hz, H-3), 3.60–3.84 (m, 2H, NCH_2), 3.96–4.24 (m, 2H, CO_2CH_2), 5.63 (s, 1H, H-12), 5.68 (d, 1H, J = 7.9 Hz, H-5^{Ura}), 7.30 (d, 1H, J = 7.9 Hz, H-6^{Ura}), 8.39 (s, 1H, NH). ^{13}C NMR (125 MHz, $CDCl_3$) δ 15.9, 16.7, 17.8, 19.0, 23.7, 26.3, 26.5, 26.7, 26.8, 27.6, 28.4, 28.8, 28.9, 29.0, 29.4, 31.4, 32.2, 33.1, 37.4, 38.0, 39.4, 39.5, 41.4, 43.6, 44.4, 45.8, 48.9, 49.0, 55.2, 62.2, 64.5, 79.0, 102.3, 128.6, 145.1, 151.2, 164.1, 169.9, 176.8, 200.6. HRMS (ESI) *m/z*: $[M-H]^+$ calculated for $C_{40}H_{59}N_2O_6$: 663.4379, found: 663.4367.

Compound **7b**. White solid, mp 139–141 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.81 (s, 12H, 4 × CH_3), 1.00, 1.12, 1.13, 1.4, 1.37 (5s, each 6H, 10 × CH_3), 0.72–2.06 (m, 54H), 2.34 (s, 2H, H-9 and H-9′), 2.77 (d, 2H, J = 12.7 Hz, H-18 and H-18′), 3.22 (dd, 2H, J = 5.9 and 10.1 Hz, H-3 and H-3′), 3.60–3.78 (m, 2H, NCH_2), 3.85–3.97 (m, 2H, NCH_2), 4.07 (m, 4H, 2 × CO_2CH_2), 5.61 (s, 1H, H-12), 5.63 (s, 1H, H-12′), 5.69 (d, 1H, J = 7.8 Hz, H-5^{Ura}), 7.22 (d, 1H, J = 7.8 Hz, H-6^{Ura}). ^{13}C NMR (125 MHz, $CDCl_3$) δ 15.9, 16.7, 17.8, 19.0, 23.7, 26.0, 26.2, 26.6, 26.69, 26.72, 26.8, 26.9, 27.6, 27.7, 28.4, 28.8, 28.86, 28.91, 29.00, 29.4, 31.4, 32.2, 33.1, 37.4, 38.0, 38.1, 39.4, 41.4, 43.5, 43.6, 44.27, 44.33, 45.67, 45.72, 48.6, 48.9, 50.0, 55.2, 62.1, 62.2, 64.5, 64.7, 78.97, 79.03, 101.8, 128.7, 128.8, 142.7, 151.7, 163.4, 169.5, 169.8, 176.7, 200.4, 200.6. HRMS (ESI) *m/z*: $[M+H]^+$ calculated for $C_{76}H_{117}N_2O_{10}$: 1217.8703, found: 1217.8709.

Compounds **8a** and **8b**. Prepared from compound **12a** (0.52 g, 0.82 mmol) and thymine (0.31 g, 2.47 mmol) according to general procedure II. Compounds **8a** (0.12 g, 21.5%) and **8b** (0.09 g, 17.8%) were obtained by flash column chromatography (petroleum ether:EtOAc = 2:3).

Compound **8a**. White solid, mp 103–105 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.82 (s, 6H, 2 × CH_3), 1.02, 1.14, 1.15, 1.16, 1.39 (5s, each 3H, 5 × CH_3), 1.94 (s, 3H, CH_3^{Thy}), 0.72–2.06 (m, 27H), 2.34 (s, 1H, H-9), 2.79 (d, 1H, J = 13.5 Hz, H-18), 3.25 (dd, 1H, J = 5.1 and 11.1 Hz, H-3) 3.70–3.75 (m, 2H, NCH_2), 4.10–4.19 (m, 2H, CO_2CH_2), 5.63 (s, 1H, H-12), 8.79 (s, 1H, H-6^{Thy}), 7.14 (s, 1H, NH). ^{13}C NMR (125 MHz, $CDCl_3$) δ 12.6, 15.9, 16.7, 17.8, 19.0, 23.7, 26.2, 26.5, 26.7, 26.8, 27.6, 28.4, 28.8, 28.9, 29.0, 29.4, 31.4, 32.2, 33.1, 37.4, 38.0, 39.45, 39.47, 41.4, 43.6, 44.3, 45.7, 48.7, 48.9, 55.2, 62.2, 64.6, 79.0, 110.8, 128.7, 141.0, 151.2, 164.6, 169.8, 176.8, 200.6. HRMS (ESI) *m/z*:

$[M+H]^+$ calculated for $C_{41}H_{63}N_2O_6$: 679.4681, found: 679.4689.

Compound **8b**. White solid, mp 110–112 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.83 (s, 12 H, $4\times CH_3$), 1.00, 1.15, 1.16, 1.7, 1.39 (5s, each 6H, $10\times CH_3$), 1.95 (s, 3H, CH_3^{Thy}), 0.72–2.06 (m, 54H), 2.34 (s, 2H, H-9 and H-9′), 2.80 (dd, 2H, $J = 3.1$ and 13.5 Hz, H-18 and H-18′), 3.25 (dd, 2H, $J = 5.1$ and 11. 2 Hz, H-3 and H-3′), 3.66–3.75 (m, 4H, $2\times NCH_2$), 3.93–4.20 (m, 4H, $2\times CO_2CH_2$), 5.63 (s, 1 H, H-12), 5.66 (s, 1 H, H-12′), 7.10 (s, 1 H, H-6^{Thy}). ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.3, 15.9, 16.67, 16.69, 17.8, 19.0, 23.69, 23.71, 26.0, 26.2, 26.6, 26.68, 26.71, 26.8, 26.9, 27.55, 27.59, 27.8, 28.4, 28.72, 28.75, 28.86, 28.89, 29.01, 29.4, 31.4, 32.1, 32.2, 33.1, 37.36, 37.39, 38.0, 38.1, 39.40, 39.43, 41.3, 41.4, 41.6, 43.49, 43.54, 44.26, 44.31, 45.67, 45.71, 48.6, 48.9, 49.7, 55.2, 62.08, 62.14, 64.6, 64.8, 79.0, 79.1, 109.9, 128.7, 128.8, 138.9, 151.7, 164.1, 169.5, 169.8, 176.8, 200.4, 200.5. HRMS (ESI) *m/z*: $[M+H]^+$ calculated for $C_{77}H_{119}N_2O_{10}$: 1231.8859, found: 1231.8887.

Compounds **9a** and **9b**. Prepared from compound **12b** (0.40 g, 0.60 mmol) and uracil (0.21 g, 1.90 mmol) according to general procedure II. Compounds **9a** (0.05 g, 11.9%) and **9b** (0.12 g, 31.4%) were obtained by flash column chromatography (petroleum ether: EtOAc = 2: 3).

Compound **9a**. White solid, mp 105–107 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.81, 1.13 (2s, each 6H, $4\times CH_3$), 1.01, 1.15, 1.37 (3s, each 3H, $3\times CH_3$), 0.80–2.07 (m, 31H), 2.34 (s, 1H, H-9), 2.77 (d, 1H, $J = 13.4$ Hz, H-18), 3.23 (dd, 1H, $J = 6.0$ and 10.0 Hz, H-3), 3.65–3.84 (m, 2H, NCH_2), 3.91–4.25 (m, 2H, CO_2CH_2), 5.61 (s, 1H, H-12), 5.67 (d, 1H, $J = 7.6$ Hz, H-5^{Ura}), 7.24 (d, 1H, $J = 7.9$ Hz, H-6^{Ura}), 8.73 (s, 1H, NH). ^{13}C NMR (125 MHz, $CDCl_3$) δ 15.9, 16.7, 17.8, 19.0, 23.8, 26.3, 26.6, 26.7, 26.8, 27.6, 28.4, 28.8, 28.9, 29.0, 29.31, 29.33, 29.4, 31.5, 32.2, 33.1, 37.4, 38.1, 39.5, 41.4, 43.6, 44.4, 45.8, 48.8, 49.1, 55.3, 62.2, 64.8, 79.1, 102.3, 128.8, 145.0, 151.0, 163.8, 169.8, 176.9, 200.6. HRMS (ESI) *m/z*: $[M+Na]^+$ calculated for $C_{42}H_{64}N_2NaO_6$: 715.4657, found: 715.4682.

Compound **9b**. White solid, mp 125–127 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.81, 1.12 (2s, each 12H, $8\times CH_3$), 1.01, 1.20, 1.36 (3s, each 6H, $6\times CH_3$), 0.68–2.10 (m, 62H), 2.34 (s, 2H, H-9, and H-9′), 2.78 (dd, 2H, $J = 7.4$ and 13.4 Hz, H-18 and H-18′), 3.23 (dd, 2H, $J = 5.9$ and 10.1 Hz, H-3 and H-3′), 3.69–3.80 (m, 2H, NCH_2), 3.88–3.97 (m, 2H, NCH_2), 4.09 (m, 4H, $2\times CO_2CH_2$), 5.62 (s, 1H, H-12), 5.64 (s, 1H, H-12′), 5.69 (d, 1H, $J = 7.8$ Hz, H-5^{Ura}), 7.17 (d, 1H, $J = 7.8$ Hz, H-6^{Ura}). ^{13}C NMR (125 MHz, $CDCl_3$) δ 15.9, 16.7, 17.8, 19.0, 23.7, 26.2, 26.3, 26.7, 26.8, 27.2, 27.61, 27.63, 27.8, 28.4, 28.75, 28.77, 28.9, 28.98, 29.00, 29.32, 29.35, 29.40, 29.42, 29.5, 31.4, 32.1, 32.2, 33.1, 37.4, 38.0, 38.1, 39.5, 41.4, 41.6, 43.5, 43.6, 44.30, 44.32, 45.69, 45.72, 48.6, 48.8, 50.1, 55.3, 62.12, 62.14, 64.76, 64.84, 79.0, 79.1, 101.8, 128.76, 128.84, 142.5, 151.7, 163.5, 176.79, 176.81, 200.45, 200.54. HRMS (ESI) *m/z*: $[M+Na]^+$ calculated for $C_{80}H_{124}N_2NaO_{10}$: 1295.9201, found 1295.9200.

Compounds **10a** and **10b**. Prepared from compound **12b** (0.40 g, 0.60 mmol) and thymine (0.24 g, 1.90 mmol) according to general procedure II. Compounds **10a** (0.12 g, 28.3%) and **10b** (0.09 g, 23.3%) were obtained by flash column chromatography (petroleum ether:EtOAc = 2:3).

Compound **10a**. White solid, mp 99–101 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.81 (s, 6H, $2\times CH_3$), 1.00, 1.13, 1.14, 1.15, 1.37 (5s, each 3 H, $5\times CH_3$), 1.19 (s, 3 H, CH_3^{Thy}), 0.70–2.10 (m, 31H), 2.34 (s, 1H, H-9), 2.77 (d, 1H, $J =$ 13.5 Hz, H-18), 3.24 (dd, 1H, $J = 6.6$ and 8.7 Hz, H-3), 3.56–3.58 (m, 2H, NCH_2), 3.96–4.27 (m, 2H, CO_2CH_2), 5.63 (s, 1H, H-12), 7.01 (s, 1H, H-6^{Thy}), 8.38 (s, 1H, NH). ^{13}C NMR (125 MHz, $CDCl_3$) δ 12.6, 15.9, 16.7, 17.8, 19.0, 23.7, 26.3, 26.66, 26.71, 26.8, 27.6, 28.4, 28.8, 28.9, 29.0, 29.3, 31.4, 32.2, 33.1, 37.4, 38.0, 39.4, 41.4, 43.5, 44.3, 45.7, 48.75, 48.81, 55.2, 62.1, 64.8, 79.0, 110.8, 128.8, 140.9, 151.1, 164.6, 169.7, 176.8, 200.6. HRMS (ESI) *m/z*: $[M+Na]^+$ calculated for $C_{43}H_{66}N_2NaO_6$: 729.4813, found: 729.4819.

Compound **10b**. White solid, mp 74–76 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.82 (s, 12H, $4\times CH_3$), 1.01, 1.13, 1.14, 1.15, 1.37 (5s, each 6H, $10\times CH_3$), 1.93 (s, 3H, CH_3^{Thy}), 0.71–2.11 (m, 62H), 2.34 (s, 2H, H-9 and H-9′), 2.80 (dd, 2H, $J = 4.5$ and 9.2 Hz, H-18 and H-18′), 3.24 (dd, 2H, $J = 5.2$ and 10.9 Hz, H-3 and H-3′), 3.64–4.02 (m, 4H, $2\times NCH_2$), 4.10 (m, 4H, $2\times CO_2CH_2$), 5.64 (s, 1H, H-12), 5.66 (s, 1H, H-12′), 6.99 (s, 1H, H-6^{Thy}). ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.4, 15.9, 16.7, 17.8, 19.0, 23.72, 23.73, 26.2, 26.3, 26.74, 26.77, 26.79, 27.2, 27.59, 27.61, 27.9, 28.4, 28.7, 28.8, 28.9, 28.97, 28.99, 29.38, 29.41, 29.5, 31.4, 32.1, 32.2, 33.1, 37.4, 38.05, 38.09, 39.5, 41.4, 41.8, 43.5, 43.6, 44.29, 44.31, 45.69, 45.71, 48.6, 48.7, 49.8, 55.2, 62.11, 62.14, 64.76, 64.84, 79.0, 79.1, 109.9, 128.77, 128.83, 138.7, 151.7, 164.1, 169.6, 169.7, 176.80, 176.82, 200.47, 200.54. HRMS (ESI) *m/z*: $[M+Na]^+$ calculated for $C_{81}H_{126}N_2NaO_{10}$: 1309.9305, found: 1309.9345.

In vitro cytotoxicity

MTT assay (Kuzio et al. 2004): cells were seeded in 96-well plates and incubated in the CO_2 incubator at 37 °C. When the cells adhered, compounds at different concentrations were added to each well. After incubation for another 72 h, 20 µL of MTT (5%) was added to each well and incubated for an additional 4 h. The viable cells were stained with MTT and scanned with an electrophotometer at 570 nm. Each concentration treatment was done in triplicate wells. The IC_{50} values were estimated by fitting the inhibition data

to a dose-dependent curve using a logistic derivative equation.

Results and discussion

Synthesis

Targeted ursolic acid/glycyrrhetinic acid-uracil/thymine hybrids (**3a–3b** to **10a–10b**) were synthesized as description in Schemes 1 and 2. To begin with, **UA** or **GA** (1 equiv.) was esterified with corresponding α,ω-dibromoalkane (5 equiv.) in the presence of potassium carbonate (1 equiv.) to prepare compounds **11a/b** or **12a/b** in high yield (79.9–90.0%). Following, compounds **11a/b** (Mallavadhani et al. 2013; Huang et al. 2018) or **12a/b** (Schwarz et al. 2014; Huang et al. 2018) (1 equiv.) were treated with uracil or thymine (3 equiv.) under potassium carbonate (3 equiv.) at 50 °C to generate targeted single products **3a–10a** (11.9–37.2%) and dual products **3b–10b** (15.6–41.0%). Targeted compounds **3a–3b** to **10a–10b** have been characterized by ^{1}H-NMR and ^{13}C-NMR spectrum and mass spectrometry.

Antitumor activity evaluation

The targeted compounds **3a–3b** to **10a–10b** was evaluated by MTT asaay (Kuzio et al. 2004) against Hep-G2, A549, HL-7702, Hela, BGC-823, NCI-H460 and BEL-7404 cell lines in vitro with 5-FU as positive control (Table 1). The results revealed that, though oleanolic acid-uracil/thymine conjugates possessing high antiproliferative activity (Cheng et al. 2016), but in this study, only two single glycyrrhetinic acid-thymine hybrids (**8a** and **10a**) exhibited good antiproliferative activity against tested A549 cell line (IC_{50} = 10.7 and 18.3 μM respectively), while four hybrids (**3a**, **4a**, **5a**, and **10b**) exhibited moderate antiproliferative activity against tested Hela cell line (Inhibitory ration at 20 μM were 87.11, 50.91, 76.19, and 83.36% respectively), and only one hybrid (**10a**) possessed moderate antiproliferative activity against tested BGC-823 cell line (Inhibitory ration at 20 μM was 57.42%). Overall, the derivatives of glycyrrhetinic acid (**7a–7b** to **10a–10b**) exhibited slightly better antiproliferative activity than that of ursolic acid derivatives (**3a–3b** to **6a–6b**).

Conclusion

As pharmacophore hybridization has been used frequently in the discovery of new drugs, ursolic acid/glycyrrhetinic acid-uracil/thymine hybrids have been synthesized and evaluated their antiproliferative activity by the MTT assay. Oleanolic acid, ursolic acid and glycyrrhetinic acid all belong to pentacyclic triterpenes, which have similar structural skeletons. Though the oleanolic acid-uracil/thymine conjugates displayed much more potent inhibitory activities compared with oleanolic acid and commercial anticancer drug 5-fluorouracil (5-FU) against tested tumor cell lins (Cheng et al. 2016), the ursolic acid/glycyrrhetinic acid-uracil/thymine hybrids in this study, haven't exhibited expected antitumor activities. However, the hybrids of glycyrrhetinic acid (**7a–7b** to **10a–10b**) exhibited slightly better antiproliferative activity than that of ursolic acid hybrids (**3a–3b** to **6a–6b**).

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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