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Synthesis of 14-deoxy-11,12-didehydroandrographolide analogues as potential cytotoxic agents for cholangiocarcinoma

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ABSTRACT

A series of 14-deoxy-11,12-didehydroandrographolide analogues were synthesized from naturally occurring andrographolide and their cytotoxicity evaluated against nine cancer cell lines including cholangiocarcinoma. Analogues **5a** and **5b** exhibited the most potent cytotoxicity with ED_{50}s of 3.37 and 3.08 μM on KKU-M213 cell lines and 2.93 and 3.27 μM on KKU-100 cell lines, respectively. Selective cytotoxicity on cholangiocarcinoma cell lines identified in this study highlight the importance of structural modification in the development of drugs for this cancer.

Cholangiocarcinoma is a primary cancer of the bile duct epithelial cells that lacks a specific treatment. Over the past decade the incidence of cholangiocarcinoma has increased worldwide as well as in northeastern Thailand.[1] Despite advances in surgical techniques, chemotherapy, and radiotherapy, 5-year patient survival after diagnosis remains at about 10%.[2] Tumors of the bile duct generally respond poorly to combination chemotherapy with gemcitabine/oxaliplatin (or cisplatin) or gemcitabine/capecitabine with average survival generally under 15 months.[3] With such low patient survivals, novel and effective therapeutic agents are urgently needed. Natural products are foremost in research efforts to combat cholangiocarcinoma. Semi-synthesis based on a natural scaffold or core structure of a natural molecule can be used to create new compounds with greater biological activity than the parent.[4] Natural products have long been the great source in drug discovery process. More than 100 new compounds derived from natural products which promising therapeutic properties including anticancer activity are in clinical development.[5]

Andrographis paniculata Nees (Acanthaceae) is a medicinal plant widely cultivated in tropical regions in Asia. Traditionally, it is used for the treatment of cold, fever, laryngitis and infections in many Asian countries. The plant extract provides a rich source of diterpene lactones including andrographolide **1**, 14-deoxy-11,12-didehydroandrographolide **2**, neoandrographolide and 14-deoxyandrographolide (Fig. 1),[6] which have been reported to exhibit a wide spectrum of biological activities including antibacterial,[7] anti-inflammatory,[8] anti-cancer[9] and immunostimulatory activities.[10]

14-Deoxy-11,12-didehydroandrographolide (**2**), contains two hydroxyl groups at C-3 and C-19, α,β-unsaturated-γ-lactone and *exo*-methylene groups, respectively.[6a] Compound (**2**) shows some degree of anti-influenza A,[11] anti-inflamatory,[12] anti-cardiovascular disease,[13] anti-diabetic[14] and anti-cancer activities.[15] The high natural abundance and impressive biological activities of andrographolide, have made it an interesting precursor for chemical modifications and the generation of new analogues. Synthetic analogues with andrographolide as the core structure have attracted much attention,[16] however, 14-deoxy-11,12-didehydroandrographolide **2** has attracted less attention for chemical modification. This is probably due to previous studies on SAR of the andrographolide structure that reported the α,β-unsaturated-γ-lactone at C-12 and C-13 to function as Michael acceptor is crucial for its biological activity. Analogues lacking this exocyclic double bond including 14-deoxy-11,12-didehydroandrographolide **2** lose their efficacy on some activites.[17]

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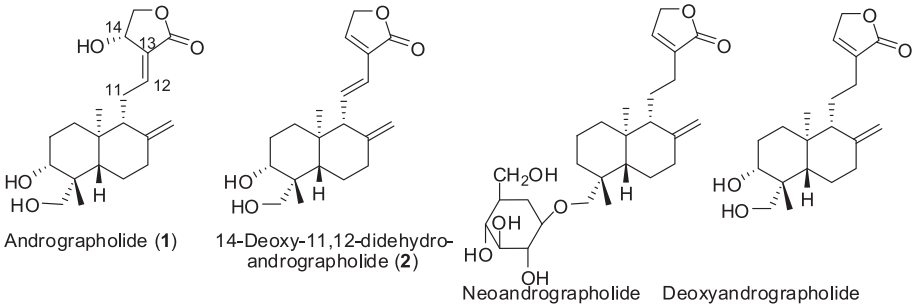


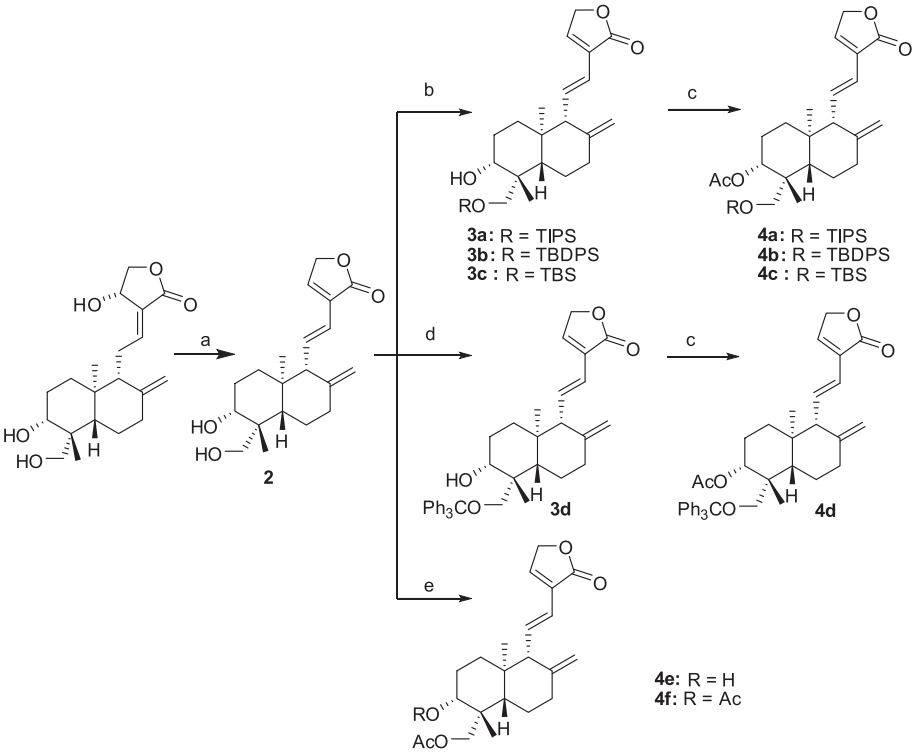
Fig. 1. Structures of active constituents of *A. paniculata*.

Some reports on synthetic 14-deoxy-11,12-didehydroandrographolide-based compounds have shown anti-HBV activity,[18] cytotoxic activity[19] and α- and β-glucosidase inhibitory activity.[20]

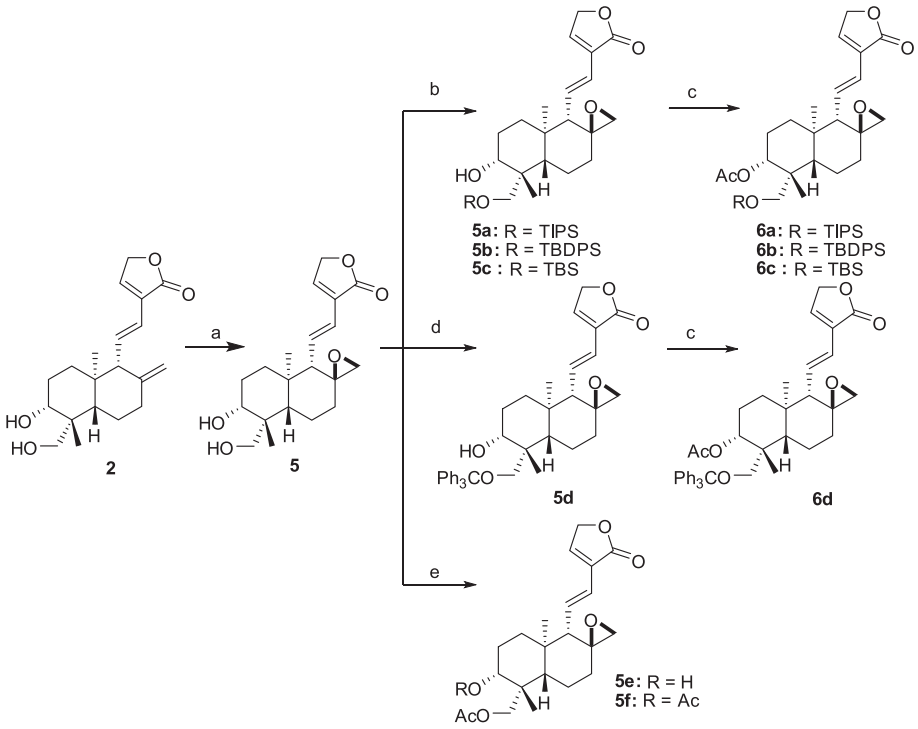
We have shown that synthetic analogues of andrographolide possessing silylether and trityl groups exhibit greater cytotoxic activity than the natural compound.[21] Some analogues show good cytotoxic activity *in vitro* against cholangiocarcinoma cell lines.[22] In this present work, we report the synthesis of new analogues of 14-deoxy-11,12-didehydroandrographolide (**2**) to study the structure-activity relationship (SAR) by modifying the two hydroxyl groups at C-3 and C-19 to silyl ether, alkyl ethers and acetyl, and the *exo*-methylene group to epoxide group as shown in Schemes 1 and 2. All synthetic analogues were screened for cytotoxic activity *in vitro* against nine selected cancer cell lines including three cholangiocarcinoma cell lines, KKU-M213, HuCC-A1 and KKU-100.

14-Deoxy-11,12-didehydroandrographolide **2** can be isolated from *A. paniculata* or, by synthesis from andrographolide. In the present study, we prepared compound **2** by refluxing andrographolide in the presence of pyridine and Al_2O_3.[23]

A synthetic series was started by chemical modification of **2** by silylation at C-19 with TIPSCl and pyridine to obtain 19-*O*-TIPS-14-deoxy-11,12-didehydroandrographolide **3a** in moderate yield (63%) in the presence of pyridine (Scheme 1). Analogues **3b** and **3c** were produced in good yields from the reaction of **2** and TBDPS-Cl or TBS-Cl. 19-*O*-Trityl derivative was prepared by reaction of **2** with triphenylmethylchloride at 70 °C, with excellent product yields (99%). Acetylation of **2** provided a mixture of **4e** and **4f** with 93% total yield which was easily separated by column chromatography. Acetylation of the remaining hydroxyl group at C-3 position of **3a**-**3d** was carried out in acetic anhydride producing products in moderate to high yield (64–95%) as shown in Scheme 1.



Scheme 1. Reagents and conditions: (a) pyridine, Al_2O_3, reflux (b) TIPSCl, pyridine, rt, 4 h, for **3a**, 63%; TBDPSCl; pyridine, rt, 1 h, for **3b**, 70%; TBSCl, pyridine, rt, 1 h, for **3c**, 79%; (c) Ac_2O, 140 °C, 1–1.5 h, (**4a**) 64%; (**4b**) 95%; (**4c**) 76%; (**4d**) 75%; (d) Triphenylmethyl chloride, pyridine, 70 °C, 1 h, 99%; (e) Ac_2O, 70 °C, 4.5 h, (**4e**) 59%; (**4f**) 34%; total 93%.



Scheme 2. Reagents and conditions: (a) mCPBA, CH_2Cl_2, rt, 1 h, 99%; (b) TIPSCl, pyridine, rt, 4 h, (**5a**) 59%; TBDPSCl; pyridine, rt, 1 h, (**5b**) 74%; TBSCl, pyridine, rt, 1 h, (**5c**) 70%; (c) Ac_2O, 140 °C, 1–1.5 h, (**6a**) 69%; (**6b**) 70%; (**6c**) 70%; (**6d**) 75%; (d) Triphenylmethyl chloride, pyridine, 70 °C, 1 h, (**5d**) 63%; (e) Ac_2O, 70 °C, 4.5 h, (**5e**) 60%; (**5f**) 30%; total 90%.

In the previous studies, the andrographolide containing epoxide at C-8 position and diacetyl at C-3 and C-19 showed significant improving of cytotoxicity against cancer cells.[24] Therefore, the second series of epoxy analogues of **2** was synthesized as shown in Scheme 2 to study the cytotoxic activity of this scaffold.

Epoxidation of 14-deoxy-11,12-didehydroandrographolide **2** with *meta*-perchlorobenzoic acid in DCM afforded an isomeric mixture of 8,17-epoxy-14-deoxy-11,12-didehydroandrographolide product **5** in 99% yield. Then, the hydroxyl of compound **5** at C-19 position was modified to silylether, trityl or acetyl to afford pure isomer **5a**–**5f** after chromatography separation as shown in Scheme 2. Silylation of **5** gave triisopropylsilyl (TIPS), *tert*-butyldiphenylsilyl (TBDPS) and *tert*-butyldimethylsilyl (TBS) ether analogues **5a**–**5c** in good yields. Tritylation of compound **5** under basic condition with trityl chloride at 70 °C for 1.0 h afforded trityl ether **5d** in 63% yield. Acetylation at C-19 and/or C-3 hydroxyl groups afforded **5e** and **5f** in total 90% yields.

Acetylation of the remaining C-3 hydroxyl groups of compounds **5a**–**5d** were performed by heating in acetic anhydride at 140 °C and resulted in products **6a**–**6d** in good yields as shown in Scheme 2.

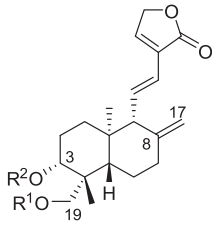
Cytotoxic activity of the parent compound **2** and a new series of synthetic analogues **3**–**6** were treated for 72 h *in vitro* against the selected nine cancer cell lines including P-388 (murine lymphatic leukaemia cell), KB (human oral nasopharyngeal carcinoma), HT-29 (human Colorectal Adenocarcinoma Cell), MCF-7 (human breast cancer), A-549 (human lung carcinoma), ASK (rat glioma), three cholangiocarcinoma cell lines; KKU-M213, HuCC-A1, KKU-100 and one normal cell HEK-293 (normal embryonic kidney cells) using a sulforhodamine B (SRB) assay.[25] All tested analogues were dissolved in DMSO (0.1%). Ellipticine, a potent anti-cancer agent was used as a positive control. Results are expressed as ED_{50} values (drug concentration causing 50% growth inhibition) in μM (Table 1 and 2).

Synthetic analogues **3a**–**3d**, **4c**, **5a**–**5b** and **5d** displayed greater cytotoxic activity than that of the parent compound **2** in most cancer cell lines. Comparison the cytotoxic activities of C-19 silyl, trityl-ether and acetyl analogues, **3a**–**3d** and **4e** indicated the importance of the substituted group at C-19 on the 14-deoxy-11,12-didehydroandrographolide core on potency to cancer cell lines. In the silyl series, C19-*O*-TBDPS analogue **3b** showed higher activity than silylether analogues **3a** and **3c** in several cell lines. However, C19-*O*-TBS analogue **3c** showed selective and stronger cytotoxic activity to cholangiocarcinoma cell KKU-100 than positive control ellipticine. C19-trityl analogue **3d** exhibited highest cytotoxic activity to P-388 cell with an ED_{50} of 3.87 μM while C19-*O*-TIPS-analogue **3a** exhibited its highest activity on ASK cancer cell with an ED_{50} 7.35 μM. Cytotoxicity of C-19 acetyl analogues **4e** and **4f** decreased in all cell lines compared with that of silyl and trityl compounds (Table 1).

Anti-cancer activity from 19-*O*-substituted analogues decreased in 3,19-*O*-disubstituted compounds **4a**–**4d** and **4f**, in association with the substitution of acetate groups at C-3. Interestingly, analogue **4a** exhibited potent selective cytotoxic activity on KKU-100 cancer cell lines with an ED_{50} of 4.10 μM, greater than that of ellipticine.

The modification of *exo*-alkene C-8 of 14-deoxy-11,12-didehydroandrographolide to compound epoxide **5** led to a dramatic decrease of cytotoxicity in all cell lines compared with parent compound 2 (Table 2). However, modification of **5** by conversion of C-19 hydroxyl to silyl-, tritry-ether and acetyl led to an increase in cytotoxic activity. Epoxide analogues **5a**, **5b** and **5d** exhibited higher cytotoxic activities than those from similar substituted compounds **3a**, **3b** and **3d** on several cancer cells while **5c** showed lower activity than **3c** on five cancer cells. Among the epoxide analogues, compounds **5a** and **5b** exhibited greater inhibition to cancer cells, especially three cholangiocarcinoma (KKU-M213 and KKU-100) than that by the positive control ellipticine. Compound

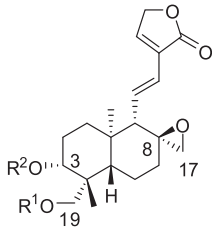
Table 1
Cytotoxic activity of 14-deoxy-11,12-didehydroandrographolide derivative against nine human cancer cells and one normal cell.



Compound	R^1	R^2	ED_{50} ± SE (μM)[a] (SRB assay)									
			P-388	KB	HT-29	MCF-7	A-549	ASK	KKU-M213	HuCC-A1	K-100	HEK-293
2	H	H	35.01 ± 0.28	5.07 ± 0.03	28.55 ± 0.43	18.67 ± 0.89	28.15 ± 1.45	>50	>50	35.83 ± 0.73	36.86 ± 3.37	7.53 ± 0.20
3a	TIPS	H	5.96 ± 0.02	4.70 ± 0.02	7.14 ± 0.09	5.46 ± 0.08	7.95 ± 0.20	7.35 ± 0.23	7.06 ± 0.65	6.72 ± 0.27	18.24 ± 0.69	5.28 ± 0.25
3b	TBDPS	H	5.51 ± 0.20	4.45 ± 0.03	6.48 ± 0.07	4.44 ± 0.25	6.49 ± 0.11	7.72 ± 0.58	5.07 ± 0.04	5.53 ± 0.20	14.74 ± 0.59	4.40 ± 0.03
3c	TBS	H	8.24 ± 0.29	5.12 ± 0.05	8.48 ± 0.20	7.61 ± 0.25	17.16 ± 0.12	9.61 ± 0.10	27.37 ± 2.78	18.17 ± 2.39	3.09 ± 0.70	6.61 ± 0.21
3d	Tr	H	3.87 ± 0.16	4.94 ± 0.03	8.38 ± 0.09	4.86 ± 0.10	6.79 ± 0.10	7.45 ± 0.16	5.42 ± 0.17	7.78 ± 0.27	36.24 ± 1.16	4.68 ± 0.07
4a	TIPS	Ac	12.14 ± 0.41	7.17 ± 0.42	17.91 ± 0.25	7.07 ± 0.21	22.02 ± 0.54	29.42 ± 0.06	12.62 ± 0.78	10.23 ± 0.15	4.10 ± 0.21	8.28 ± 0.32
4b	TBDPS	Ac	14.53 ± 0.75	5.15 ± 0.04	32.51 ± 0.63	7.77 ± 0.06	9.47 ± 0.13	>50	16.03 ± 0.16	24.29 ± 1.44	>50	5.57 ± 0.16
4c	TBS	Ac	6.56 ± 0.05	4.94 ± 0.02	12.82 ± 1.24	6.37 ± 0.10	9.18 ± 0.01	16.23 ± 1.30	12.08 ± 0.82	15.96 ± 0.82	14.02 ± 1.57	6.36 ± 0.20
4d	Tr	Ac	12.87 ± 0.98	6.36 ± 0.02	21.89 ± 0.91	9.12 ± 0.04	12.00 ± 0.95	39.86 ± 0.75	9.98 ± 0.10	38.55 ± 1.20	>50	7.02 ± 0.20
4e	Ac	H	27.65 ± 1.25	25.66 ± 0.54	45.04 ± 0.10	31.07 ± 1.39	32.75 ± 1.26	>50	>50	>50	40.25 ± 2.70	27.77 ± 0.71
4f	Ac	Ac	27.68 ± 1.39	25.72 ± 0.74	41.87 ± 0.78	28.78 ± 0.24	33.96 ± 0.30	42.45 ± 1.46	37.30 ± 0.97	40.93 ± 1.08	>50	24.96 ± 0.50
Ellipticine			2.12 ± 0.17	2.34 ± 0.03	2.68 ± 0.17	1.66 ± 0.09	2.37 ± 0.21	2.17 ± 0.23	4.75 ± 0.43	3.46 ± 0.83	4.16 ± 0.23	2.27 ± 0.10

[a] Each value represents mean ± SE from three different experiments performed in triplicate. Cell lines used are P-388 (murine lymphatic leukaemia cell), KB (human oral nasopharyngeal carcinoma), HT-29 (human Colorectal Adenocarcinoma), MCF-7 (human breast carcinoma), A-549 (human lung carcinoma), ASK (rat glioma), Hek-293 (normal human embryonic kidney cell) and three cholangiocarcinoma cell lines; KKU-M213 (adenosquamous cell carcinoma), KKU-100 (poorly differentiate adnocarcinoma), HuCC-A1 (human cholangiocarcinoma cell) and one normal cell HEK-293 (normal embryonic kidney cells). Ellipticine was used as a positive control. The results are expressed as ED_{50} values (drug concentration causing 50% growth inhibition) in μM. ED_{50} more than 50 μM was considered inactive.

Table 2
Cytotoxic activity of 8,17-epoxy-14deoxy-11,12-didehydroandrographolide derivative against nine human cancer cells and one normal cell.



Compound	R^1	R^2	ED_{50} ± SE (μM)[a] (SRB assay)									
			P-388	KB	HT-29	MCF-7	A-549	ASK	KKU-M213	HuCC-A1	K-100	HEK-293
5	H	H	>50	>50	>50	>50	>50	>50	>50	>50	>50	>50
5a	TIPS	H	3.86 ± 0.08	4.59 ± 0.03	2.28 ± 0.42	4.98 ± 0.12	6.58 ± 0.01	6.60 ± 0.09	3.37 ± 0.31	7.35 ± 0.13	2.93 ± 0.36	4.04 ± 0.23
5b	TBDPS	H	4.13 ± 0.08	4.02 ± 0.04	4.43 ± 0.04	4.23 ± 0.04	6.22 ± 0.15	6.81 ± 0.15	3.08 ± 0.17	6.41 ± 0.13	3.27 ± 0.18	4.97 ± 0.16
5c	TBS	H	15.07 ± 2.47	19.24 ± 1.01	7.24 ± 0.09	8.18 ± 0.11	9.36 ± 0.18	18.97 ± 4.58	8.57 ± 0.21	>50	9.25 ± 0.10	6.15 ± 0.00
5d	Tr	H	3.33 ± 0.12	4.92 ± 0.05	6.21 ± 0.05	5.38 ± 0.09	5.88 ± 0.10	6.47 ± 0.18	4.68 ± 0.18	7.81 ± 0.07	28.75 ± 2.68	5.39 ± 0.14
6a	TIPS	Ac	7.84 ± 0.14	8.48 ± 0.11	7.40 ± 0.08	7.84 ± 0.08	8.65 ± 0.18	15.72 ± 1.28	7.22 ± 0.30	8.92 ± 0.16	17.51 ± 0.31	7.39 ± 0.07
6b	TBDPS	Ac	5.25 ± 0.11	5.19 ± 0.10	5.22 ± 0.05	6.38 ± 0.12	8.31 ± 0.10	8.96 ± 0.33	5.13 ± 0.11	8.08 ± 0.02	4.50 ± 0.18	6.01 ± 0.05
6c	TBS	Ac	7.45 ± 0.07	25.81 ± 0.15	18.59 ± 0.74	16.55 ± 0.27	24.10 ± 0.41	22.41 ± 0.76	19.13 ± 1.69	23.35 ± 0.14	16.44 ± 059	18.08 ± 0.56
6d	Tr	Ac	5.28 ± 0.08	5.12 ± 0.01	6.74 ± 0.11	6.84 ± 0.05	8.16 ± 0.29	8.29 ± 0.40	10.16 ± 2.35	9.74 ± 0.09	14.09 ± 0.20	5.99 ± 0.05
5e	Ac	H	19.97 ± 0.44	>50	48.93 ± 0.16	43.50 ± 1.30	46.26 ± 1.89	>50	48.93 ± 2.56	>50	>50	38.13 ± 0.74
5f	Ac	Ac	>50	>50	>50	>50	>50	>50	>50	>50	>50	>50
Ellipticine		2.12 ± 0.17		2.34 ± 0.03	2.68 ± 0.17	1.66 ± 0.09	2.37 ± 0.21	2.17 ± 0.23	4.75 ± 0.43	3.46 ± 0.83	4.16 ± 0.23	2.27 ± 0.10

[a] Each value represents mean ± SE from three different experiments performed in triplicate. Cell lines used are P-388 (murine lymphatic leukaemia cell), KB (human oral nasopharyngeal carcinoma), HT-29 (human Colorectal Adenocarcinoma), MCF-7 (human breast carcinoma), A-549 (human lung carcinoma), ASK (rat glioma), Hek-293 (normal human embryonic kidney cell) and three cholangiocarcinoma cell lines; KKU-M213 (adenosquamous cell carcinoma), KKU-100 (poorly differentiate adnocarcinoma), HuCC-A1 (human cholangiocarcinoma cell) and one normal cell HEK-293 (normal embryonic kidney cells). Ellipticine was used as a positive control. The results are expressed as ED_{50} values (drug concentration causing 50% growth inhibition) in μM. ED_{50} more than 50 μM was considered inactive.

5a also showed highest inhibitory activity against HT-29 cancer cell with ED_{50s} of 2.28 μM, than that by ellipticine. Introduction of acetyl at C-3 to analogues **6a**–**6d** and **5f** led to a dramatic decrease in cytotoxicity relative to that from compounds **5a**–**5e** indicating the crucial role of the acetate group in reducing cytotoxicity.

In conclusion, we have successfully modified the hydroxyl groups at C-3, C-19 and *exo*-methylene at C-8 of **2** to generate 21 new analogues with different cytotoxicities relative to specific cancer cells. All analogues were simply prepared in moderate to excellent yields using 14-deoxy-11,12-didehydroandrographolide **2**, that was synthesized from natural andrographolide. Eight

analogues (**3a**–**3d**, **4c**, **5a**–**5b** and **5d**) of the 14-deoxy-11,12-didehydro-andrographolide (**2**) showed much higher cytotoxic activity than that of the parent **2** on all cancer cells including P-388, KB, HT-29, MCF-7, LU-1, ASK, KKU-M213, HuCC-A1 and KKU-100. Structure activity relationship studies of the synthetic analogues indicated the introduction of silyl ether or triphenylmethyl ether group in C-19 of the parent compound led to increased cytotoxicity against the cancer cells. C-19 TBS-analogue **3c** and **4a** demonstrated selective potent cytotoxic activity over the anti-cancer drug, ellipticine on cholangiocarcinoma cell KKU-100. Moreover, epoxy analogues **5a** and **5b** were most potent with ED_{50}s of 3.37 and 3.08 μM on KKU-M213 cell lines and 2.93 and 3.27 μM on KKU-100 cell lines, respectively. They also exhibited greater cytotoxicity than ellipticine. To the best of our knowledge, this is the first report of selective cytotoxic activity among synthetic analogues of 14-deoxy-11,12-didehydroandrographolide **2** against cholangiocarcinoma cancer cells. These analogues may facilitate the development of more efficient drugs against cholangiocarcinoma cancer.

Note

In remembrance of His Majesty King Bhumibol Adulyadej (1927–2016), for his life-time dedication to Thailand and people.

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Conflicts of interest

We declare that we have no conflict of interest.

A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.bmcl.2017.10.063.

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