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Design and synthesis of C-12 dithiocarbamate andrographolide analogues as an anticancer agent

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ABSTRACT

A series of 21 new analogues of C-12 dithiocarbamate andrographolide was designed and synthesized from natural andrographolide isolated from a common Thai plant, *Andrographis paniculata*. The reaction used to manipulate the andrographolide scaffold was conducted in one pot under mild reaction conditions. This avoided toxic catalysts and gave nearly quantitative yields of new analogues, generally without by-products and can be easily scaled -up for industrial processing. All new analogues were evaluated against nine cancer cell lines, some analogues exhibited greater selective cytotoxic activity to MCF-7 cancer cell than that of the parent andrographolide and cancer drugs.

Breast cancer is by far the most common cancer in women worldwide that continue to display alarming annual increases in incidence and mortality rates.[1–3] Chemotherapy is an effective but non-specific treatment that can have toxic effects including infection.[4–6] Various active compounds from plants and their semi-synthetic derivatives have been assessed for their efficacy in breast cancer treatment.[7] Plants can provide inexpensive and effective sources for the prevention and treatment of cancer. With diversity in their structure, those natural compounds with promising intrinsic therapeutic property have served as a template for the design and synthesis of candidate compounds with improved therapeutic properties.[8–10] Andrographolide, a naturally occurring bioactive compound with multidimensional therapeutic effects is an important compound in cancer drug development.[11] These properties have led to extensive structural modifications and analogues with improved potential as anticancer drugs including breast cancer. Interestingly it does not induce cytotoxicity in normal human breast epithelial cells.[12–14]

Andrographolide is a diterpenoid lactone and is the major active component of *Andrographis paniculata* that is used in traditional herbal medicine in South East Asia. Andrographolide is of interest because of its potential as a bioactive pharmacophore, capable of energizing a wide range of biological activities including antioxidant, anti-inflammatory, antibacterial, antiretroviral, antidiabetic, antimalarial, antihypertension in addition to its anti-cancer properties.[15–18] This impressive biological profile was our stimulus to improve its potency and selectivity, through structure modification, to a range of cytotoxic analogues.[19–21] Structure modification of andrographolide into a library of new analogues with the appropriate structural diversity has shown improved potency in biological activities.[21] *A. paniculata* is a common Thai plant from which andrographolide is easily isolated and purified by simple chromatographic techniques with 2% over all yields.[22,23] Our previous studies demonstrated that functionalization of andrographolide scaffold led to several compounds which exhibit potent cytotoxic activity toward several cancer cell lines.[24–28]

Our objective in the present study was to modify the structure of andrographolide extracted from *A. paniculata* to improve potency in the cytoxicity of several cancer cells including breast cancer. We designed andrographolide to combine with dithiocarbamate moieties to obtain a series of new dithiocarbamate andrographolide analogues. Dithiocarbamates, are a common class of carbamate organic molecules in which both oxygen atoms are replaced by sulfur atoms. They exhibit a broad spectrum of biological activities including antifungal, antibacterial, antioxidant and anticancer.[29–34] In addition, dithiocarbamates structures are found in natural products such as brassinin isolated from cabbage, with derivatives displaying potential cancer chemopreventive activity.[34] Therefore, introduction of this moiety to

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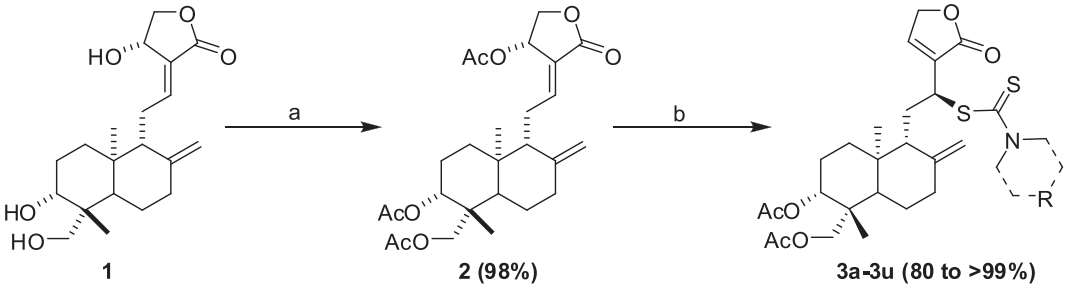


Scheme 1. Reagents and Conditions; a) Ac_2O, 145 °C; b) *sec*.amine, CS_2, CH_3CN, 3 °C - rt.

andrographolide scaffold is expected to improve the efficacy in cytotoxic activity over natural andrographolide and drug.

In the present study, we explored the modification of andrographolide *via* tandem three steps reactions by *in-situ* generation of dithiocarbamate and addition at C-12 of andrographolide followed by elimination reactions in one pot under mild conditions leading to a series of 12-dithiocarbamate-14-deoxyandrographolide analogues.

Initially, 3,14,19-Ac-Andrographolide **2** was synthesized by refluxing at 145 °C. This produced 98%yields from the acetylation reaction of the three hydroxyl groups of andrographolide (Scheme 1). Compound **2** is expected to increase the potency due to increase in lipophilicity[35] and was used as the precursor for synthesis of a series of 12-dithiocarbamate-14-deoxyandrographolide analogues. The synthesis was designed by generation of a substituted dithiocarbamate, prepared from amine and carbondisulfide in acetonitrile[29] as nucleophile and introducing by tandem Michael addition to C-12 position of **2** and elimination of acetyl group at C-14 that led to the final product in one pot reaction. This straightforward one pot strategy was employed directly to synthesize dithiocarbamate andrographolide and avoid isolation of an intermediate dithiocarbamate. The reaction was performed without any base or catalyst. The first morpholine-dithiocarbamate andrographolide analog **3a** was obtained in nearly quantitative yields in 3 h. as shown in Table 1.

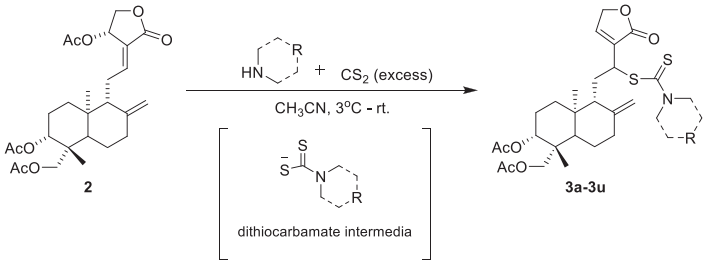
Piperazine containing compounds have been reported to possess anticancer activity.[29,30,32] Therefore, we introduced piperazine in combination with dithiocarbamate to the andrographolide scaffold to investigate its cytotoxic activity. When 2-substituted-piperazine was employed to react with CS_2 to produce dithiocarbamate nucleophiles, reaction time was longer than with morpholine in the first example, but with excellent yields to 99% of final products **3b-3m** (Table 1). Various alkyl-benzyl amines were also examined for study their structure relationship with substituted dithiocarbonate on andrographolide. Designed products **3n-3u** were obtained in almost quantitative yields. The preparation of new dithiocarbamate-andrographolide analogues by one pot reaction proceeded smoothly and efficiently at 0 °C to room temperature to produce twenty-one analogues in excellent yields proving the versatility of this one pot method. To the best of our knowledge, this is the first report of the synthesis of dithiocarbamate andrographolide analogues by one pot tandem in-situ generation of substituted dithiocarbamate nucleophile/conjugate addition and elimination reaction.

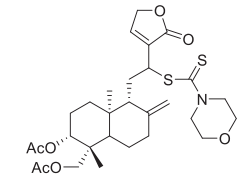
Cytotoxic activities of andrographolide and all synthetic analogues were evaluated against selected cancer cell lines by *in vitro* screening: P-388 (murine leukaemia cell line), KB (human epidermoid carcinoma of the mouth), HT-29 (human Colorectal Adenocarcinoma), MCF-7 (human breast cancer), A-549 (human lung carcinoma), ASK (rat glioma), KKU-M213 (human Intrahepatic Cholangiocarcinoma), HuCCA-1 (human cell line derived from cholangiocarcinoma) and KKU-055 (human poorly differentiated cholangiocarcinoma cell line established from biliary tract) (Table 2). Sulforhodamine B (SRB) assay was carried out to evaluate the cytotoxic activities of synthesized compounds. All tested analogues were dissolved in DMSO (less than 0.05%). Ellipticine, a potent anti-cancer agent was used as a positive control. Cells at 10^4 cells/well were seeded in 96-well plates with varying concentrations of compounds (0.1–50 μM). All cell lines, except for suspension P-388 cells, are adherent cells which were received treatment for 72 h. P-388 cells were treated for 48 h. At the end of a treatment period, cells were washed, fixed with trichloroacetic acid (TCA) and stained with 0.4% SRB dissolved in 1% acetic acid. A cellular protein-bound dye was extracted for the determination (optical density 515 nm) in a 96 well microliter plate reader. Amount of bound dye was extrapolated to measure cell viability. Cytotoxic potency was expressed as IC_{50}, the concentration that inhibit 50% of cell viability.

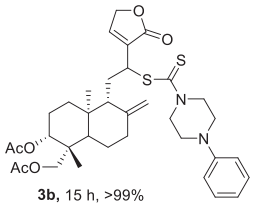
Cytotoxic activities of modified analogues (Table 2) indicated the importance of introduced substituted dithiocarbamate group at C-12 on andrographolide. Acetylation of three hydroxyl groups of andrographolide to compound **2** did not alter activity relative to the parent andrographolide. However, with the introduction of morpholine dithiocarbamate on the C-12 of andrographolide (compound **3a**), cytotoxic activity increased significantly in most cancer cell lines especially HuCCA-1 cancer cells (5 folds comparing with **1**). Andrographolide containing dithiocarbamate might provide lipophilicity to the compound, allowing it to pass the cell membrane by passive diffusion and function through different mechanisms of action. Moreover, a variety of metal complexes of dithiocarbamates have received considerable attention as potential anticancer agents with various degree of DNA binding affinity and cytotoxicity which can be electronically adjusted by the choice of different substituents.[36] Introduction of the bioactive moiety, substituted-piperazine dithiocarbamate on andrographolide led to analogues **3b-3m** and a dramatic increase in potency of all cancer cells except analogues **3k-3m**. In this series, analog **3f** displayed stronger activity than the parent andrographolide especially on MCF-7 (3 folds) and ASK cancer cells (7 folds) with IC_{50} of 2.56 and 4.74 μM, respectively. Pyrimidylpiperazine analog **3g** exhibited selective cytotoxic activity against MCF-7 cancer cells and stronger activity than positive control ellipticine with an IC_{50} of 0.84 μM. Despite increasing cytotoxicity of piperazine analogues, three diaryl dithiocarbamate analogues **3k-3n**, showed less cytotoxicity than other compounds indicating the crucial role of two bulky aryl groups in reducing cytotoxicity. Introducing alkyl-benzylamine dithiocarbamate at C-12 of andrographolide increased cytotoxic activity in analogues **3n-3u**. Among analogues **3n-3u**, methyl-benzylamine analog **3n** exhibited highest activities relative to other analogues on six cancer cell lines, especially MCF-7 cancer cells with an IC_{50} of 0.59 μM and KKU-055 cancer cells with an IC_{50} of 1.36 μM, higher activities than that of drug ellipticin. In this series, methyl-fluorobenzylamine analog **3o** also showed selective inhibitory activity against MCF-7 cancer cell with an IC_{50} value 0.68 μM.

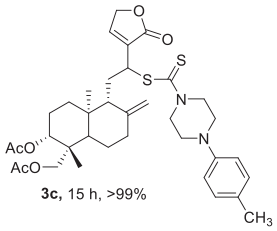
In conclusion, a series of new 12-dithiocarbamate-14-deoxyandrographolide analogues was designed and synthesized under mild reaction conditions in one pot. This avoids hazardous solvents and toxic catalysts and produces nearly quantitative yields, in most cases without by-products. All synthetic analogues were evaluated for their cytotoxic activity against nine cancer cell lines. Most of the synthesized andrographolide exhibited significant cytotoxic activity in these cancer cell

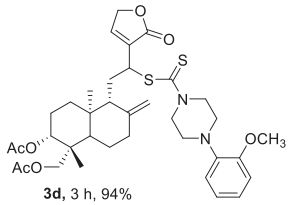
Table 1
. 12-dithiocarbamate-14-deoxyandrographolide analogues **3a-u.**

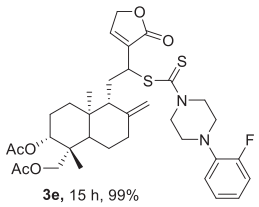


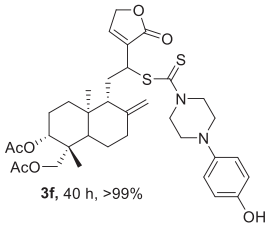

3a, 3 h, 98%

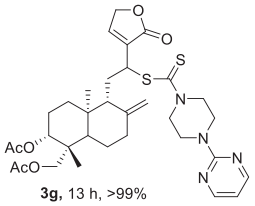

3b, 15 h, >99%

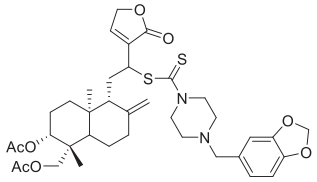

3c, 15 h, >99%

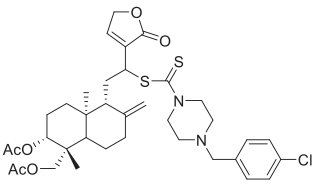

3d, 3 h, 94%

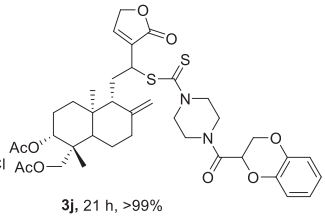

3e, 15 h, 99%

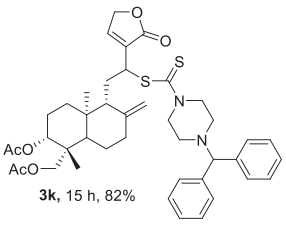

3f, 40 h, >99%

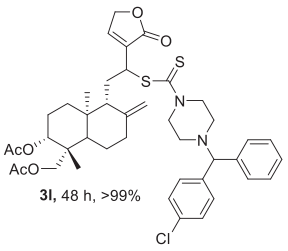

3g, 13 h, >99%

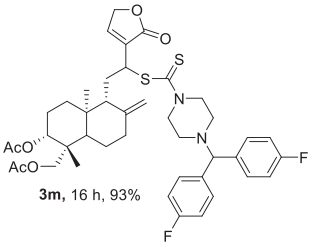

3h, 48 h, 84%

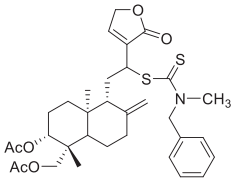

3i, 10 h, >99%

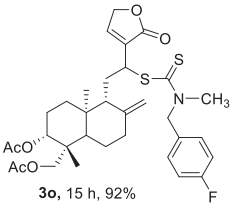

3j, 21 h, >99%

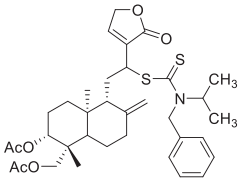

3k, 15 h, 82%

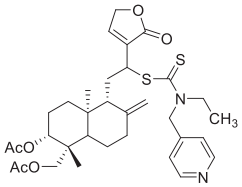

3l, 48 h, >99%

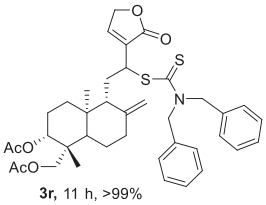

3m, 16 h, 93%

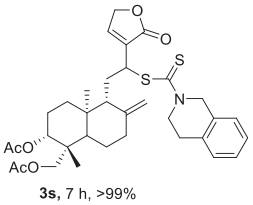

3n, 8 h, 99%

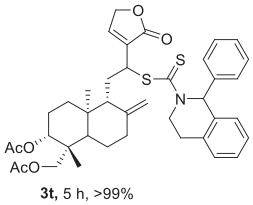

3o, 15 h, 92%

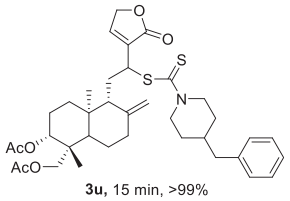

3p, 37 h, 99%


3q, 2.5 h, >99%


3r, 11 h, >99%


3s, 7 h, >99%


3t, 5 h, >99%


3u, 15 min, >99%

lines. SAR analysis indicated the introduction of substituted dithiocarbamate moeities at C12 position of andrographolide effectively improves its cytotoxic efficacy and selectivity on breast cancer cell MCF-7. Among the synthetic dithiocarbamate-andrographolide, **3n** exhibited the strongest activities relative to other analogues especially on MCF-7 and KKU-055 cancer cells with an IC_{50} value 0.59 and 1.36 μM respectively, while **3g** and **3o** showed selective cytotoxic activity to MCF-7 cancer cells. Therefore, compound **3n** could serve as a promising candidate for further studies as an anticancer agent against breast cancer.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Table 2
Cytotoxic activities of 12-dithiocarbamate-14-deoxyandrographolide analogues against cancer cell lines.

Compd.	IC_{50} (μM)[a] (SRB assay)								
	P-388	KB	HT-29	MCF-7	A-549	ASK	KKU-M213	HuCCA-1	KKU055
1	6.52	31.73	8.91	8.48	32.02	34.81	9.36	23.61	17.73
2	6.64	28.09	21.63	7.95	> 50	22.50	14.80	20.07	5.02
3a	5.74	5.96	4.14	2.93	14.75	9.25	5.16	4.79	5.24
3b	4.30	23.54	8.08	6.53	28.86	15.64	6.47	9.59	9.27
3c	5.50	19.45	8.29	6.06	27.79	27.97	6.49	17.53	14.84
3d	5.76	17.84	6.58	4.72	28.46	14.34	5.59	8.08	7.62
3e	5.74	18.92	7.06	6.05	27.87	9.53	5.22	8.63	9.39
3f	5.75	6.00	4.93	2.56	22.12	4.74	4.91	4.88	5.29
3g	4.31	6.92	4.53	0.84	17.98	7.20	5.30	5.73	5.30
3h	4.58	21.44	7.91	5.68	29.54	14.91	7.51	11.61	9.75
3i	4.80	> 50	13.74	5.56	32.82	26.18	6.76	21.56	6.22
3j	3.40	22.70	9.18	3.92	23.40	25.50	6.16	17.28	5.59
3k	36.50	> 50	> 50	42.30	> 50	> 50	> 50	> 50	> 50
3l	22.60	> 50	> 50	21.66	> 50	> 50	> 50	> 50	27.74
3m	14.26	42.45	> 50	24.19	> 50	> 50	29.16	> 50	28.31
Ellipticine	1.79	1.92	2.16	1.79	2.25	2.19	1.81	2.43	2.43

Compound.	IC_{50} (μM)[a] (SRB assay)								
	P-388	KB	HT-29	MCF-7	A-549	ASK	KKU-M213	HuCCA-1	KKU055
1	6.52	31.73	8.91	8.48	32.02	34.81	9.36	23.61	17.73
2	6.64	28.09	21.63	7.95	> 50	22.50	14.80	20.07	5.02
3n	2.17	25.32	6.22	0.59	6.94	6.92	4.83	8.63	1.36
3o	3.59	25.67	6.14	0.68	11.63	16.85	5.15	7.78	3.04
3p	4.06	24.78	6.73	3.75	22.48	20.34	5.52	8.64	5.29
3q	5.85	17.08	4.29	2.48	9.42	18.00	5.66	7.07	4.05
3r	4.94	8.66	6.54	4.76	22.88	7.22	5.67	7.64	6.02
3s	4.38	25.02	7.08	3.95	25.14	20.07	5.59	7.19	5.55
3t	5.33	18.05	9.63	5.60	29.79	23.42	6.81	9.39	6.44
3u	4.85	33.60	15.31	5.46	29.12	28.54	6.76	19.69	6.42
Ellipticine	1.79	1.92	2.16	1.79	2.25	2.19	1.81	2.43	2.43

[a] IC_{50} values (the concentration that inhibit 50% of cell viability) in μM. 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) and three cholangiocarcinoma cell lines; KKU-M213 (adenosquamous cell carcinoma), HuCC-A1 (human cholangiocarcinoma cell), KKU-055 (poorly differentiated cholangiocarcinoma). Ellipticine was used as a positive control. IC_{50} more than 50 μM was considered inactive.

Acknowledgements

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bmcl.2020.127263.

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