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Research paper

Synthesis and biological activities of dithiocarbamates containing 2(5H)-furanone-piperazine

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ABSTRACT

A series of new dithiocarbamates containing a 2(5H)-furanone-piperazine group was synthesized. These compounds show good *in vitro* cytoxic activity. Among them, compound **6c** exhibits the best inhibitory activity against HeLa cell lines with an IC_{50} of 0.06 ± 0.01 μM for 72 h, and it has good inhibitory activity against SMMC-7721 cell lines with an IC_{50} of 0.006 ± 0.04 μM for 72 h, but the toxicity was lower against LO2 cell lines with an IC_{50} of 45.76 ± 0.01 μM. The result showed that compound **6c** is far more cytoxic towards cancer cell lines than towards benign cell lines compared with cytosine arabinoside (ARA) *in vitro*.

1. Introduction

Cancer is a disease during which malignant tumors might occur, and it seriously endangers human life and health. According to the survey, about 60 million individuals are diagnosed with cancer every year [1]. The number of new cancer cases has reached 368.2 million in China, with 2229 deaths in 2013. Lung cancer, liver cancer, stomach cancer, esophageal cancer, and colorectal cancer are the five leading causes of cancer death, accounting for about 60% of all cancer deaths [2]. Each year, more than 300,000 women die of cervical cancer, which is the third most common cancer in women worldwide [3]. Therefore, there is an urgent need for developing new anticancer agents [4–9].

Dithiocarbamic acid ester is an easily accessible moiety in organic synthesis [10,11]. It has been widely used in the synthesis and development of new drugs. Dithiocarbamics exhibit a wide range of biological activities [12–15], such as anticancer [16], antitumor [17], antibacterial [18]. On the other hand, 2(5H)-furanone derivatives are widely found in natural products and have been used in cancer treatment due to the notable bioactivity [19–23]. In our previous studies, we designed and synthesized a range of 2(5H)-furanone derivatives containing piperazine-sulfonamide [24,25]. These compounds exhibit remarkable anti-HeLa activity, leading to an IC_{50} of 0.02 μM for 24 h under the standard MTT assay [14].

In this continuing study, we report a convenient one-pot method to synthesize dithiocarbamic acid ester derivatives containing a 2(5H)-furanone-piperazine group. The subsequent biological studies show that these compounds showed higher cytoxic activity against some cancer cell lines than against benign cell lines.

2. Results and discussion

2.1. Chemistry

The enantiomerically pure 5-(S)-5-alkoxy-4-piperazineyl-3-bromo-2(5H)-furanones (**5a, 5b**) were prepared by the procedure shown in Scheme 1 [25]. Reaction of furfural **1** with Br_2/H_2O afforded mucobromic acid **2** by sequential dibromination and oxidation. Acetalation of **2** with chiral alcohols gave rise to γ-substituted butenolides **3**. Multiple recrystallization processes was used for **3** to provide the enantiomerically pure 5-(S)-alkoxy-3, 4-dibromo-2(5H)-furanone compounds **4** [26,27]. Following the protocol we previously reported, **4** was transformed into

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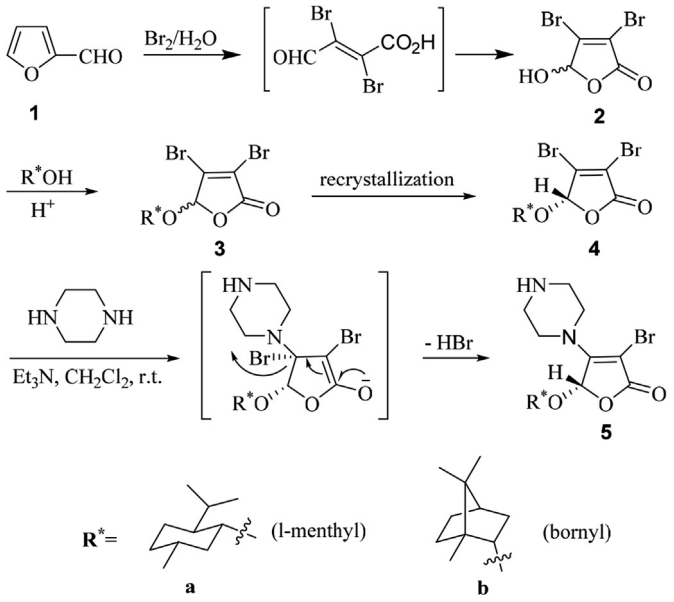


Scheme 1. Synthesis of compounds **5**.

compound **5** [25] by treatment with piperazine and triethylamine through a Michael addition-elimination process.

Synthesis of dithiocarbamate-contained 2(5H)-furanone-piperazines **6** is shown in Scheme 2. This three-component reaction was simply performed by mixing compounds **5** and carbon disulfide followed by addition of electrophiles such as allyl bromide, benzyl bromide or methyl chloroacetate. The reactions were completed within 1.5–3.5 h, affording 50–75% yields of compounds **6**. We also tested other halogenated electrophiles such as 1-bromopropane, *n*-butyl bromide, iso-butyl bromide and epichlorohydrin under the otherwise identical reaction conditions, however no expected products were observed. The weaker electrophilicity of these reagents and the poor stability of the desired products were proposed to account for the observed coupling efficiency.

2.2. Biological evaluation

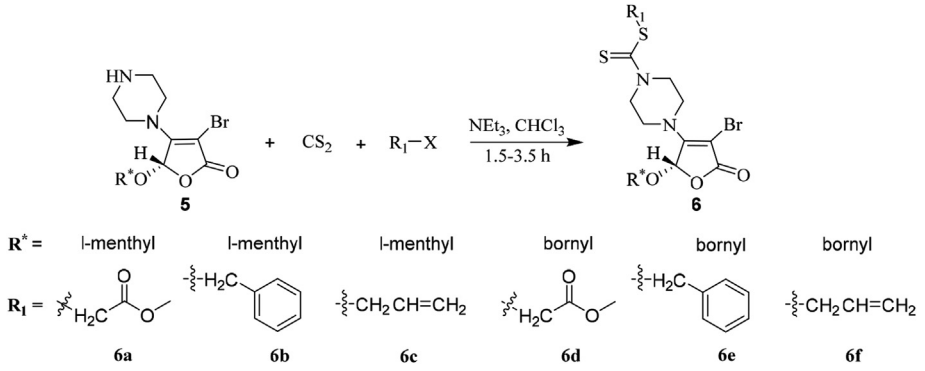
The newly synthesized compounds **6a-c,** vincristine (VCR) and cytosine arabinoside (ARA) were screened for *in vitro* cytoxic activity against two cancer cell lines, including human cervical carcinoma cell lines (HeLa), human liver cancer cell lines (SMMC-7721) and were assessed for toxicities against human normal liver cell lines (LO2) by the standard MTT assay *in vitro*. The cytotoxicity *in vitro* of the tested compounds were shown in Table 1 in the form of the IC_{50}, which were carried out using SPSS 22.0 software and descriptive data were expressed as mean ± standard deviation. To our delight, compounds **6a-c** displayed good inhibition activities on these two cancer cell lines (Table 1). Among the tested compounds, compound **6c** possessed stronger inhibitory activity against HeLa cell lines with the IC_{50} value of 0.06 ± 0.01 μM at 72 h, making it more potent than the clinical chemotherapy drugs cytarabine [28] (IC_{50} = 0.95 μM) and etoposide (IC_{50} = 7.20–7.23 μM) [29], while compound **6b** was the most potent to SMMC-7721 cell lines, with an IC_{50} of 0.004 ± 0.05 μM, showing potent higher inhibitory activity *in vitro* than cytosine arabinoside (ARA) (0.013 ± 0.09), although lower than vincristine (VCR). As for LO2 cell lines, except for compound **6a**, the newly synthesized compound **6b** and **6c** showed lower toxicities than vincristine (VCR) and cytosine arabinoside (ARA). As a whole, compounds **6b** and **6c** showed higher cytoxic activity against some cancer cell lines than against benign cell lines compared with cytosine arabinoside (ARA) *in vitro*.

As shown in Fig. 1, it is clear that the inhibitory rate increased with the increased concentration as for HeLa cell lines. In SMMC-7721 cell lines, the compounds **6a-c**, VCR and ARA displayed similar anti-proliferative activities at different concentrations for 72 h. However since the tested compounds showed lower toxicity *in vitro* to LO2 cell lines at 0.01 μg/mL for 72 h, and the cell inhibition rate data were negative, so the data were not involved in drawing Fig. 1. Furthermore, in order to investigate whether compound **6b** could induce cell apoptosis, human liver cancer cell lines (SMMC-7721) treated with different concentrations of compound **6b** were subjected to Annexin V-FITC/PI. From Fig. 2, the percentage of early and late apoptotic cells increased (lower right quadrant and upper right

Table 1
Cytoxic activities against HeLa, SMMC-7721 and LO2 cell lines with compounds **6a-c**, VCR or ARA for 72 h.

Compounds	IC_{50}[a] (μM) on cell lines		
	HeLa	SMMC-7721	LO2
6a	0.32 ± 0.07	0.006 ± 0.04	0.11 ± 0.02
6b	0.26 ± 0.01	0.004 ± 0.05	0.37 ± 0.02
6c	0.06 ± 0.01	0.006 ± 0.04	45.76 ± 0.01
VCR	–	0.003 ± 0.03	0.20 ± 0.01
ARA	–	0.013 ± 0.09	0.17 ± 0.04

HeLa = human cervical carcinoma cell lines. SMMC-7721 = human liver cancer cell lines. LO2 = human normal liver cell lines.
VCR = vincristine. ARA = cytosine arabinoside.
[a] IC_{50} values represent the compound concentration (μM) required to inhibit tumor cell proliferation by 50%, and were calculated using concentrations in triplicate and experiment was repeated, only values with a standard deviation < 10% mean were considered.



Scheme 2. Synthesis of compounds **6a-f**.