



## Synthesis and in vitro antitumor activity of new butenolide-containing dithiocarbamates

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### ABSTRACT

Three series of butenolide-containing dithiocarbamates were designed and synthesized. Their anti-tumor activity in vitro was evaluated. Among them compound **I-14** exhibited broad spectrum anti-cancer activity against five human cancer cell lines with  $IC_{50} < 30 \mu M$ . Structure–activity relationship analysis showed that the introduction of dithiocarbamate side chains on the C-3 position of butenolide was crucial for anti-tumor activity.

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One of the main objectives of organic and medicinal chemistry is the design, synthesis and production of molecules having value as human therapeutic agents. During the past decade, number of dithiocarbamates were synthesized and evaluated,<sup>1</sup> by which some privileged structures receiving special attention have been found to possess excellent anti-tumor activity.<sup>2,3</sup> For example, structure modification of Brassinin (**1**)<sup>3</sup> (Fig. 1), a dithiocarbamate isolated from cruciferous plants, led to the design and synthesis of a potential cancer chemopreventive agent Sulforamate (**2**)<sup>4</sup> (Fig. 1). Furthermore, the dithiocarbamate portion of the brassinin is a crucial moiety for the anti-tumor activity.<sup>3</sup>

Butenolides (**3**) (Fig. 1) are ubiquitous chemical moieties occurring in a large number of natural products and known to be associated with several biological activities.<sup>5</sup> Many of the butenolide-containing compounds can be considered as potential anti-cancer agent, bactericides, fungicides, etc.<sup>6</sup> There are also a wide variety of pharmacologically active non-natural products bearing the heterocycle as the active site.<sup>7</sup>

In an effort to look for the possible anti-tumor agents, we were interested in the incorporation of dithiocarbamate moiety with butenolide. In addition, it is suspected that there is a close relationship between the position of dithiocarbamates side chain on butenolide and their biological activities. So three series of butenolide containing dithiocarbamates were designed and synthesized in order to investigate the structure–activity relationship and obtain significant insight into the impact of activity on molecular.

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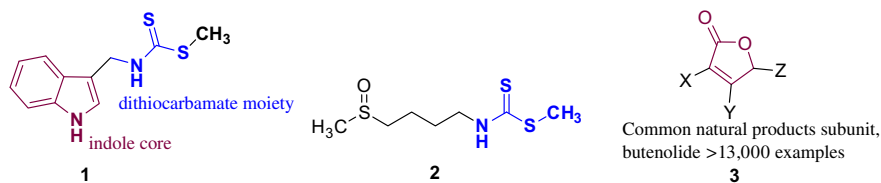
The butenolide derivatives **I** with dithiocarbamates side chain at C-3 position were obtained by the reaction of 3-bromomethyl butenolide (**9**) with  $CS_2$  and various amines in the presence of  $Na_3PO_4 \cdot 11H_2O$  in acetone<sup>8</sup> as shown in Scheme 1. 3-bromomethyl butenolide (**9**) was derived from  $\gamma$ -butyrolactone (**4**) by five-step reaction according to the reported method.<sup>9</sup> The synthesized derivatives were summarized in Table 1.

The butenolide derivatives **II** with dithiocarbamate side chain at C-4 position were obtained by the reaction of 4-bromomethyl butenolide (**12**) with  $CS_2$  and various amines. Compound **12** was prepared by an intramolecular substitution reaction of compound **11** which could be obtained from starting material **10** with 70% yield as shown in Scheme 2.<sup>11</sup>

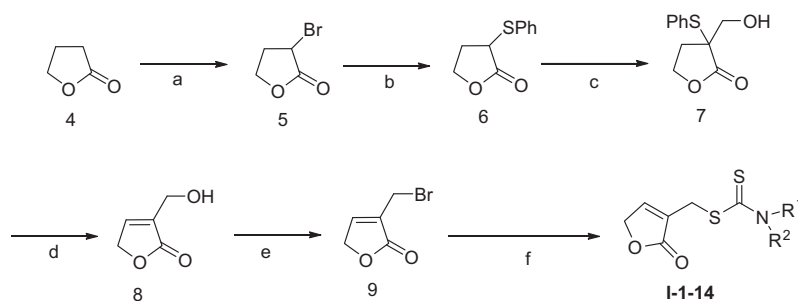
Fortunately, a new scaffold of spirothiazolidine-2-thiones **III** was obtained during the reaction of compound **12** with primary amines. The compounds **II** and the novel spirothiazolidine-2-thiones **III** were shown in Table 2.

All of these compounds were tested for anti-tumor activity against five different human cancer cell lines in vitro by MTT [3-(4,5-dimethylthio-2-yl)-2, 5-diphenyl-tetrazolium bromide] cell proliferation assay.<sup>14</sup> The anti-tumor drug 5-fluorouracil was used as positive control. The results are summarized in Tables 3 and 4.

Analysis of the MTT assay results suggest that the position of dithiocarbamate side chain is crucial for the activity. Butenolides **I** with dithiocarbamate side chain on C-3 position were generally more potent than series **II** with dithiocarbamate side chain on C-4 position, compounds **II** had no or unobvious cytotoxic activity towards all these five cell lines. The bioassay results also suggest that except compound **III-3**, the spirothiazolidine-2-thiones



**Figure 1.** Structures of brassinin (1) sulforamate (2) and butenolides (3).



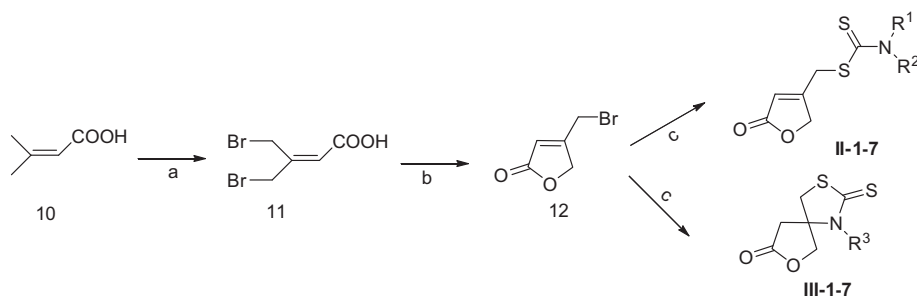
**Scheme 1.** The synthesis of butenolide derivatives I. Reagents and conditions: (a) Br<sub>2</sub>, P, 69%; (b) PhSNa, CH<sub>3</sub>OH, 88%; (c) CH<sub>3</sub>ONa, CH<sub>3</sub>OH, (CH<sub>2</sub>O)<sub>n</sub>, TMEDA, 95%; (d) (1) *m*CPBA, CH<sub>2</sub>Cl<sub>2</sub>, 0 °C; (2) CaCO<sub>3</sub>, CCl<sub>4</sub>, reflux, 82% two steps; (e) PBr<sub>3</sub>, Et<sub>2</sub>O, 0 °C, 83%; (f) CS<sub>2</sub>, NHR<sup>1</sup>R<sup>2</sup>, Na<sub>3</sub>PO<sub>4</sub>·11H<sub>2</sub>O, acetone, 0.5–1 h.

**Table 1**  
The butenolide derivatives I with dithiocarbamate side chain at C-3 position

Products <sup>a</sup>	-NR <sup>1</sup> R <sup>2</sup>	Yield <sup>b</sup> (%)	Products <sup>a</sup>	-NR <sup>1</sup> R <sup>2</sup>	Yield <sup>b</sup> (%)
I-1	CH <sub>3</sub> NH-	83	I-8		90
I-2	C <sub>2</sub> H <sub>5</sub> NH-	85	I-9		93
I-3	(CH <sub>3</sub> ) <sub>2</sub> N-	81	I-10		86
I-4	(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> N-	77	I-11		75
I-5	(CH <sub>3</sub> ) <sub>2</sub> CHNH-	80	I-12		77
I-6		87	I-13		81
I-7		86	I-14 <sup>10</sup>		77

<sup>a</sup> All the products were characterized by IR, NMR and mass spectral data.

<sup>b</sup> Refer to isolated pure products.



**Scheme 2.** Reagents and conditions: (a) 2.2 equiv NBS, Ph(CO)<sub>2</sub>O<sub>2</sub>, CCl<sub>4</sub>, reflux, 95%; (b) 5% aq NaOH, rt 12 h, 73%; (c) CS<sub>2</sub>, amines, Na<sub>3</sub>PO<sub>4</sub>·11H<sub>2</sub>O, acetone, 0.5–1 h.

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