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Design, synthesis and antiproliferative activity studies of novel dithiocarbamate–chalcone derivates

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ABSTRACT

A series of novel dithiocarbamate–chalcone derivates were designed, synthesized and evaluated for antiproliferative activity against three selected cancer cell lines (EC-109, SK-N-SH and MGC-803). Majority of the synthesized compounds exhibited moderate to potent activity against all the cancer cell lines assayed. Particularly, compounds **II2** and **II5** exhibited the excellent growth inhibition against SK-N-SH with IC_{50} values of 2.03 μM and 2.46 μM, respectively. Further mechanism studies revealed that compound **II2** could obviously inhibit the proliferation of SK-N-SH cells by inducing apoptosis and arresting the cell cycle at G0/G1 phase.

Cancer, being one of the leading causes of death globally, poses a major socioeconomic hazard to humanity at large. Although there have been progresses in the development of treatment and prevention of cancer, the successful treatment of cancer remains a challenge.[1] Therefore, there is still an urgent need to search for novel antiproliferative agents that have broader spectrum of cytotoxicity to tumor cells.[2]

Chalcones are considered to be the precursors of flavonoids and isoflavonoids[3] that have been screened for their wide range of pharmacological activities as antibacterial,[4,5] anti-tumor,[6,7] antiinflammatory,[8,9] antifungal and antioxidant agents.[10,11] Dithiocarbamate is considered privileged scaffold in drug discovery with a wide array of biological activities. In the literature, dithiocarbamate derivatives have been described as anti-fungal,[12] anti-bacterial,[13] and carbonic anhydrase inhibitors.[14] Besides, the dithiocarbamate has always been used as a linkage to combine different biologically active scaffold to design new chemical entities. Our group have reported two series of dithiocarbamates derivates **1** and **2** as antitumor agents, which can inhibit gastric cancer cell growth, invasion and migration (Fig. 1).[15,16]

Molecular hybridization is a strategy of rational design of new ligands or prototypes based on the recognition of pharmacophoric subunits in the molecular structure of two or more known bioactive derivatives.[17] In the course of our search for new anticancer agents, we recently reported the synthesis and antiproliferative activity of a series of novel *N*-Acyl homoserine lactones (AHLs) analogs **3** with the chalcone and homoserine lactone scaffold linked by the dithiocarbamate group through molecular hybridization approach.[18] The preliminary structure–activity relationship (SAR) studies revealed that the chalcone scaffold and dithiocarbamate group were critical for their inhibitory activity. So in this study, these two biologically important groups are retained and we choose derivative **3** (namely **11a** in Ref. 18) as the lead compound due to its most potent inhibitory activity against MGC-803 cells than other AHLs analogs. In continuation with our efforts toward the discovery of novel anticancer agents, we herein design and optimize chalcone–dithiocarbamate hybrids (Fig. 2).

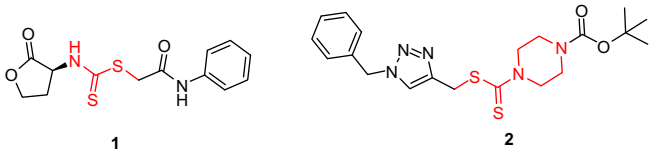

Figure 1. Structures of dithiocarbamates as antitumor agents previously reported.

The synthetic routes towards dithiocarbamate–chalcone analogues (**II1**–**II17**) were shown in Scheme 1. Commercially available substituted benzaldehydes were reacted with substituted acetophenones to form chalcones by Claisen–Schmidt condensation, which was subjected to etherification reaction with 1,3-dibromopropane or 1,2-dibromoethane to afford **5** and **IIb**. The target analogues were easily obtained in high yields with the mature reaction

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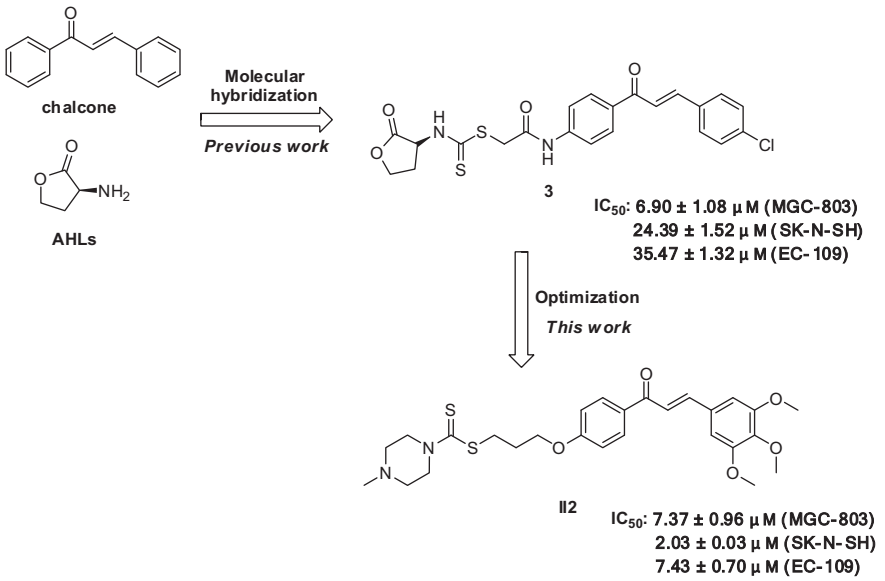
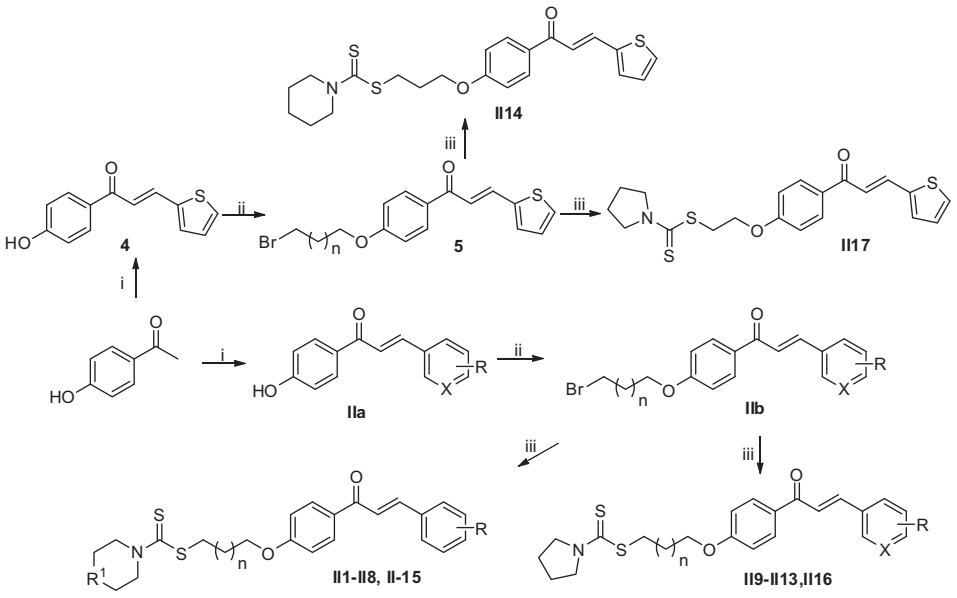


Figure 2. The design and optimization of chalcone–dithiocarbamate derivates.



II1 n = 1, R = 4-Cl, $R^1 = CH_3N$
II2 n = 1, R = 3,4,5-triOMe, $R^1 = CH_3N$
II3 n = 1, R = 3,5-diF, $R^1 = CH_3N$
II4 n = 1, R = 3,5-diCl, $R^1 = CH_3N$
II5 n = 0, R = 3,4,5-triOMe, $R^1 = CH_3N$
II6 n = 1, R = 4-Cl, $R^1 = CH_2$
II7 n = 0, R = 4-Cl, $R^1 = CH_2$
II8 n = 0, R = 3,4,5-triOMe, $R^1 = CH_2$
II15 n = 0, R = 4-Cl, $R^1 = O$
II18 n = 1, R = 4-OCH_3, $R^1 = CH_3N$

II9 n = 1, R = 4-Cl, X = C
II10 n = 1, R = 3,4,5-triOMe, X = C
II11 n = 1, R = 3,5-diF, X = C
II12 n = 0, R = 4-Cl, X = C
II13 n = 1, R = H X = N
II16 n = 0, R = 3,4,5-triOMe X = C

Scheme 1. Synthesis of analogues **II1**–**II17**. Reagents and conditions: (i) substituted aromatic aldehyde, NaOH, EtOH, rt, 60–83% yield; (ii) 1,3-dibromopropane or 1,2-dibromoethane, K_2CO_3, THF, reflux, 72–79% yield; (iii) CS_2, substituted amine, $Na_3PO_4{\cdot}12H_2O$, acetone, rt, 63–76% yield.

conditions developed by our group.[18] Finally, all the chalcone–dithiocarbamate derivatives were fully characterized by ^{1}H NMR, ^{13}C NMR and HRMS.

All synthesized compounds were evaluated for their antiproliferative activity against three human cancer cell lines (MGC-803, EC-109, SK-N-SH) using MTT assay method and compared with the well-known anticancer drug 5-fluorouracil and lead compound AHLs derivative **3** (Table 1). The majority of the synthesized compounds exhibited moderate to potent activity against all the cancer cell lines. Particularly, compounds **II2** and **II5** exhibited excellent