



# Structure-activity relationships of novel dithiocarbamates containing $\alpha,\beta$ -unsaturated ketone fragment as potent anticancer agents

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## Abstract

Based on the structure of novel lead compound **8** discovered by our group, systematic structural modification was carried out. A series of compound **8**'s derivatives were synthesized and evaluated for their activities against human non-small cell lung cancer cell line H460. Among them, twelve compounds showed significant proliferation inhibition activities with IC<sub>50</sub> values <1  $\mu$ M and compound **12r** was the most potent one. Further study on compound **12r** revealed that it has significant inhibitory effect on the growth of eight kinds of cancer cell lines with IC<sub>50</sub> values <1  $\mu$ M. Especially for cell lines A375 and HCT116, the IC<sub>50</sub> values of **12r** achieved 63 nM and 66 nM, respectively. Meanwhile, our research results also revealed the following structure-activity relationships: (a) different substitutions on the benzene ring or heteroaromatic rings greatly effect on the activity; (b) the presence of  $\alpha,\beta$ -unsaturated ketone fragment is favorable for the activity; (c) the receptor cavity binding with amine moiety might be a relatively small hydrophobic cavity. These results will be valuable for the further development of this novel kind of dithiocarbamates.

**Keywords** Dithiocarbamates ·  $\alpha,\beta$ -unsaturated ketone · Anticancer · H460

## Introduction

Discovery of lead compounds is one of the key steps in the new drug development. Though the target-based drug discovery (TDD) has been the dominant approach to drug discovery in the past three decades, phenotypic drug discovery (PDD) approach is still a way not to be ignored due to their promise of delivering first in-class drugs (Swinney and Anthony 2011).

Dithiocarbamate represents a privileged scaffold in medicinal chemistry and this kind of compounds showed a broad spectrum of biological activities (Buac et al. 2012;

Ronconi et al. 2013; Bala et al. 2014; Li et al. 2015a), especially anti-tumor activity (Gaspari et al. 2006; Huang et al. 2009; Duan et al. 2013a; Duan et al. 2013b; Akinboye et al. 2015; Ding et al. 2016; Fu et al. 2016; Fu et al. 2017; Laskar et al. 2018; Liu et al. 2017; Skrott et al. 2017; Wei et al. 2018; Xie et al. 2018; Yang et al. 2018). Some representative dithiocarbamates with anticancer activities reported in recent were listed in Fig. 1. Disulfiram (**1**), an alcohol-abuse drug, was found to be effective against diverse cancer types and targets cancer via p97 segregase adaptor NPL4 and this result was published in Nature (Skrott et al. 2017). Compound **2**, a novel 2-aminobenzamide containing dithiocarbamate moiety as histone deacetylase inhibitors, displayed potent antiproliferative activity against diverse human tumor cell lines (Xie et al. 2018). Thieno[2,3-d]pyrimidine derivative **3** exhibited cytotoxicity in cancer cells by targeting tubulin to activate the spindle assembly checkpoint (Yang et al. 2018). (1S, 4S)-2,5-diazabicyclo[2.2.1]heptane-dithiocarbamate-nitrostyrene hybrid (**4**) was identified as potent antiproliferative and apoptotic inducing agent against cervical cancer cell lines (Laskar et al. 2018). Formononetin-dithiocarbamate hybrid (**5**) could inhibit

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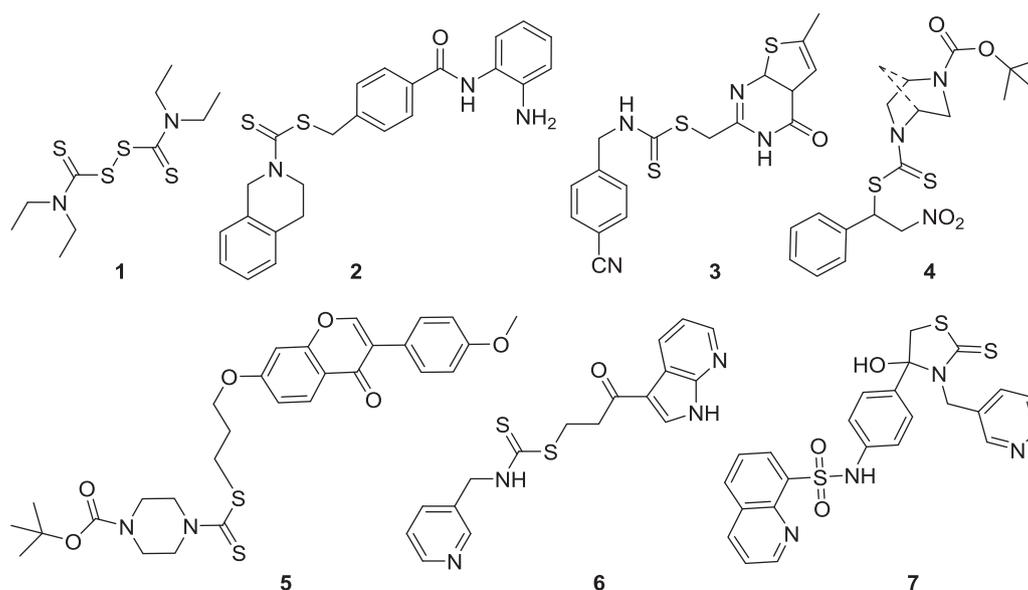
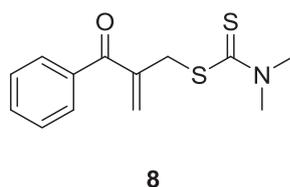


Fig. 1 Structures of some dithiocarbamates with anticancer activities

Fig. 2 The structure and the activities of lead compound **8**



Cell line	inhibition rate at 10 $\mu$ M (%)
H460	92.0 (IC <sub>50</sub> = 1.59 $\mu$ M)
BGC823	87.4
Hela	87.6
HCT116	88.6
MDA-MB-231	94.0

growth and migration of PC-3 cells via MAPK/Wnt signaling pathways (Fu et al. 2017). Our group have also been interested in dithiocarbamates, and several novel kinds of them were found to show excellent antitumor activities (Hou et al. 2006; Li et al. 2011; Li et al. 2013; Li et al. 2015b; Zhang et al. 2015; Li et al. 2018), such as compounds **6** (Zhang et al. 2015) and **7** (Li et al. 2018) as potent PKM2 inhibitor.

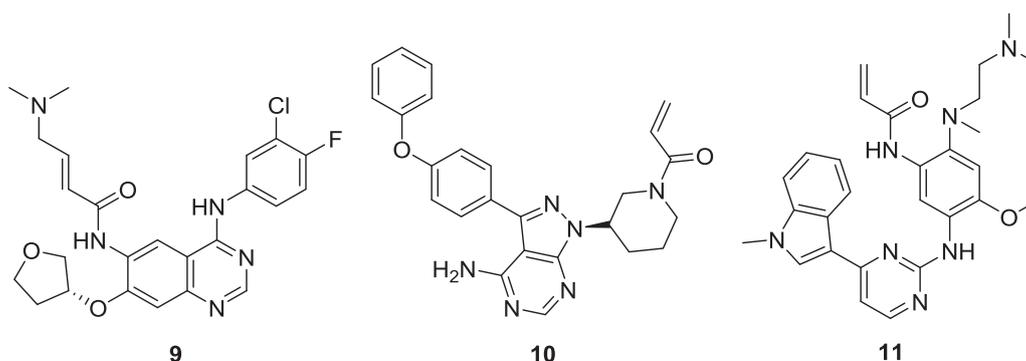
Recently, we identified compound **8** with significant antitumor activities (Fig. 2) from a random screening of an in-house compound library (about 1000 in total). As far as we know, this is a new kind of dithiocarbamates which contains  $\alpha,\beta$ -unsaturated ketone fragment. Meanwhile,  $\alpha,\beta$ -unsaturated ketone fragment is an important pharmacophores (Adams et al. 2004; Chen et al. 2009; Wu et al. 2010; Butturini et al. 2013), and it appears in the structure of many drugs, such as Afatinib (**9**) (Dungo and Keating 2013), Ibrutinib (**10**) (Byrd et al. 2013), and Osimertinib (**11**) (Greig 2016) (Fig. 3). Thus, compound **8** is a valuable lead compound for further study. In this paper, the structure activity relationships of compound **8** were investigated and more potent compound **12r** was identified.

## Materials and methods

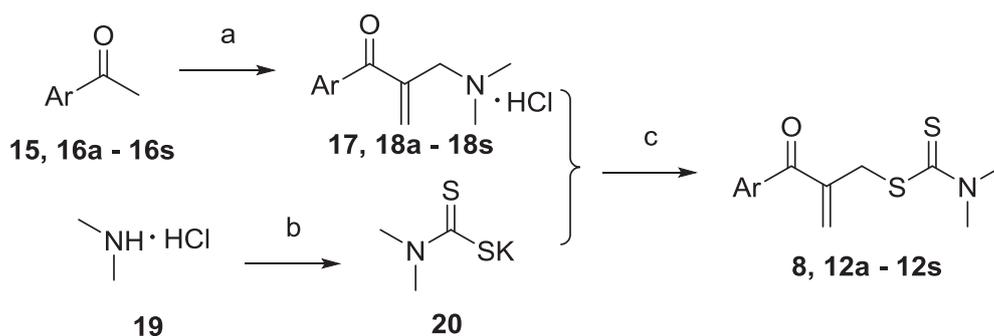
All commercial reagents and solvents were used without further purification unless otherwise specified. Column chromatography was conducted using silica gel. Thin-layer chromatography (TLC) was performed on silica gel GF-254 aluminium plates. Visualization was carried out using UV (254 nm/366 nm). <sup>1</sup>H NMR and <sup>13</sup>C NMR spectra were recorded on Bruker AVANCE<sup>III</sup> 400 MHz and 101 MHz spectrometer respectively, and NMR spectra were referenced to the residual solvent shifts for <sup>1</sup>H and <sup>13</sup>C as internal standards, and  $\delta$ -values are given in ppm. Mass spectrometry was performed with a Bruker Apex IV FTMS by using the electro spray ionization (ESI) mode. Melting points were determined on X5 microscope and were uncorrected.

## Chemistry

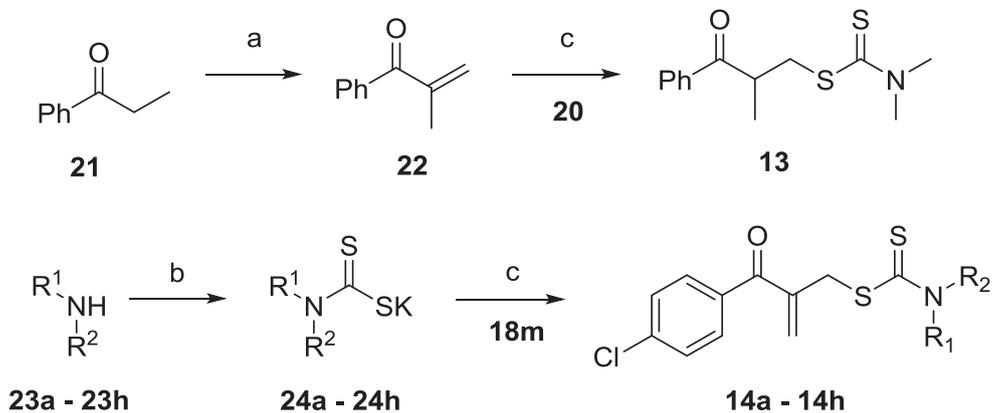
The synthetic routes of target compounds **8**, **12a–12s**, **13** and **14a–14h** are depicted in Scheme 1. Various aryl or hetero aryl ketones, **15** and **16a–16s** which were commercially available, reacted respectively with



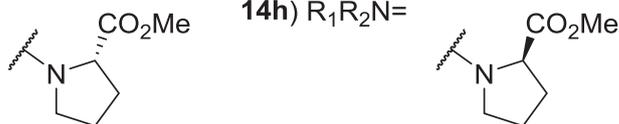
**Fig. 3** Chemical structures of representative drugs with  $\alpha,\beta$ -unsaturated ketone



**8)** Ar=Ph; **12a)** Ar=4-MeO-Ph; **12b)** Ar=2-MeO-Ph; **12c)** Ar=4-HO-Ph;  
**12d)** Ar=4-Me-Ph; **12e)** Ar=3-Me-Ph; **12f)** Ar=benzo[d][1,3]dioxol-5-yl;  
**12g)** Ar=4-NO<sub>2</sub>-Ph; **12h)** Ar=3-NO<sub>2</sub>-Ph; **12i)** Ar=2-NO<sub>2</sub>-Ph; **12j)** Ar=4-CN-Ph;  
**12k)** Ar=4-F-Ph; **12l)** Ar=4-Cl-Ph; **12m)** Ar=2-Cl-Ph; **12n)** Ar=2-Cl--Ph;  
**12o)** Ar=3,4-dichlorophenyl; **12p)** Ar=furan-2-yl; **12q)** Ar=thiophene-2-yl;  
**12r)** Ar=pyrrole-2-yl; **12s)** Ar=pyridine-3-yl



**14a)** R<sub>1</sub>R<sub>2</sub>N=diethylamino; **14b)** R<sub>1</sub>R<sub>2</sub>N=dipropylamino; **14c)** R<sub>1</sub>R<sub>2</sub>N=dibutylamino;  
**14d)** R<sub>1</sub>R<sub>2</sub>N=pyrrolidin-1-yl; **14e)** R<sub>1</sub>R<sub>2</sub>N=piperidin-1-yl; **14f)** R<sub>1</sub>R<sub>2</sub>N=1-morpholino;  
**14g)** R<sub>1</sub>R<sub>2</sub>N=



**Scheme 1** Synthesis of target compounds. Reaction conditions: (a) AcOH, dimethylamine hydrochloride, (HCHO)<sub>n</sub>, reflux; (b) H<sub>2</sub>O, CS<sub>2</sub>, K<sub>2</sub>CO<sub>3</sub>; (c) H<sub>2</sub>O, K<sub>2</sub>CO<sub>3</sub>

paraformaldehyde and dimethylamine hydrochloride in refluxing acetic acid to form the corresponding key intermediates **17** and **18a–18s** (Butturini et al. 2013) which were used directly without further purification. Then, dimethylamine hydrochloride (**19**) was reacted with carbon disulfide in water using potassium carbonate as base to afford the intermediate **20**. Finally, intermediates **17** and **18a–18s** were dissolved in the aqueous potassium carbonate solution, and intermediate **20** was added dropwise to the above solution. The resulted mixture was stirred for 1 h to provide the corresponding targets **8** and **12a–12s**. The synthetic route of compound **13** was similar to that of compounds **8** and **12a–12s**, and the only difference is the use of propiophenone (**21**) as starting material. Compounds **14a–14h** were gained by replacing the dimethylamine moiety of compound **12m** with different secondary amines.

### General method for synthesis of final compounds

Aryl or heteroaryl ketone (**15**, **16a–16s** or **21**, 10 mmol) was added into the mixture of paraformaldehyde (0.60 g, 20 mmol) and dimethylamine hydrochloride (1.63 g, 20 mmol) in acetic acid (25 mL). The reaction mixture was heated under reflux for 12 h, followed by the removal of the solvent to give the crude intermediate (**17**, **18a–18s** or **22**). A mixture of amine (**19** or **23a–23h**, 6 mmol), potassium carbonate (1.38 g, 10 mmol) and H<sub>2</sub>O (15 mL) was stirred for 15 min, and CS<sub>2</sub> (0.38 g, 5 mmol) was added dropwise. After stirring 1 h, **20** or **24a–24h** was obtained. The intermediate (**17**, **18a–18s** or **22**) was dissolved in the aqueous potassium carbonate solution (2.76 g, 20 mmol K<sub>2</sub>CO<sub>3</sub> in 15 mL H<sub>2</sub>O), and **20** or **24a–24h** was added dropwise to the above solution. The reaction mixture was stirred at room temperature for 1 h and then extracted with ethyl acetate (10 mL × 3). The combined organic phase washed with water (15 mL × 2), dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated under vacuum to afford the crude product. The crude product was purified by column chromatography to give target compound **8**, **12a–12s**, **13** or **14a–14h**.

### 2-Benzoylallyl dimethylcarbamodithioate (**8**)

Yield 25%; Yellow oil; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 7.73–7.75 (m, 2 H, Ar-H), 7.51–7.55 (m, 1 H, Ar-H), 7.41–7.44 (m, 2 H, Ar-H), 6.31 (s, 1 H, C = CHH), 5.78 (s, 1 H, C = CHH), 4.40 (s, 2 H, C-CH<sub>2</sub>-C = S), 3.55 (s, 3 H, N-CH<sub>3</sub>), 3.35 (s, 3 H, N-CH<sub>3</sub>); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>): δ 196.8 (C = S), 196.3 (C = O), 142.8 (C-C = CH<sub>2</sub>), 137.3 (Ar-C), 132.2 (Ar-C), 129.4 (Ar-C), 129.0 (C = CH<sub>2</sub>), 128.1 (Ar-C), 45.4 (N-CH<sub>3</sub>), 41.3 (N-CH<sub>3</sub>), 37.8 (C-CH<sub>2</sub>-S); HRMS *m/z* (pos): 266.0672 C<sub>13</sub>H<sub>16</sub>NO<sub>2</sub>S<sub>2</sub> (calcd. 266.0668).

### 2-(4-Methoxybenzoyl)allyl dimethylcarbamodithioate (**12a**)

Yield 17%; Yellow oil; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.80 (d, *J* = 8.8 Hz, 2 H, Ar-H), 6.92 (d, *J* = 8.8 Hz, 2 H, Ar-H), 6.20 (s, 1 H, C = CHH), 5.71 (s, 1 H, C = CHH), 4.39 (s, 2 H, C-CH<sub>2</sub>-S), 3.86 (s, 3 H, O-CH<sub>3</sub>), 3.54 (s, 3 H, N-CH<sub>3</sub>), 3.35 (s, 3 H, N-CH<sub>3</sub>); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>): δ 196.4 (C = S), 195.6 (C = O), 163.3 (Ar-C), 143.0 (C-C = CH<sub>2</sub>), 132.1 (Ar-C), 129.9 (Ar-C), 127.1 (C = CH<sub>2</sub>), 113.5 (Ar-C), 55.5 (O-CH<sub>3</sub>), 45.5 (N-CH<sub>3</sub>), 41.5 (N-CH<sub>3</sub>), 39.90 (C-CH<sub>2</sub>-S); HRMS *m/z* (pos): 296.0781 C<sub>14</sub>H<sub>18</sub>NO<sub>2</sub>S<sub>2</sub> (calcd. 296.0774).

### 2-(2-Methoxybenzoyl)allyl dimethylcarbamodithioate (**12b**)

Yield 21%; Yellow oil; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.39 (t, *J* = 7.9 Hz, 1 H, Ar-H), 7.25 (d, *J* = 7.4 Hz, 1 H, Ar-H), 6.95 (dd, *J* = 15.0, 7.8 Hz, 2 H, Ar-H), 6.32 (s, 1 H, C = CHH), 5.76 (s, 1 H, C = CHH), 4.40 (s, 2 H, C-CH<sub>2</sub>-S), 3.77 (s, 3 H, O-CH<sub>3</sub>), 3.54 (s, 3 H, N-CH<sub>3</sub>), 3.37 (s, 3 H, N-CH<sub>3</sub>); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 197.0 (S-C = S), 196.9 (C = O), 157.2 (Ar-C), 144.4 (C-C = CH<sub>2</sub>), 131.7 (Ar-C), 130.9 (Ar-C), 129.2 (Ar-C), 128.4 (Ar-C), 120.2 (C = CH<sub>2</sub>), 110.5 (Ar-C), 55.7 (O-CH<sub>3</sub>), 45.5 (N-CH<sub>3</sub>), 41.5 (N-CH<sub>3</sub>), 36.9 (C-CH<sub>2</sub>-S); HRMS *m/z* (pos): 296.0782 C<sub>14</sub>H<sub>18</sub>NO<sub>2</sub>S<sub>2</sub> (calcd. 296.0774).

### 2-(4-Hydroxybenzoyl)allyl dimethylcarbamodithioate (**12c**)

Yield: 41%; mp 57.9–59.7 °C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.74 (d, *J* = 8.7 Hz, 2 H, Ar-H), 6.91 (d, *J* = 8.6 Hz, 2 H, Ar-H), 6.22 (s, 1 H, C = CHH), 5.74 (s, 1 H, C = CHH), 4.40 (d, *J* = 8.9 Hz, 2 H, C-CH<sub>2</sub>-S), 3.55 (d, *J* = 11.5 Hz, 3 H, N-CH<sub>3</sub>), 3.34 (s, 3 H, N-CH<sub>3</sub>); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 196.9 (S-C = S), 196.4 (C = O), 161.1 (Ar-C), 142.8 (C-C = CH<sub>2</sub>), 132.6 (Ar-C), 129.2 (Ar-C), 128.0 (C = CH<sub>2</sub>), 115.4 (Ar-C), 45.6 (N-CH<sub>3</sub>), 41.6 (N-CH<sub>3</sub>), 38.9 (C-CH<sub>2</sub>-S); HRMS *m/z* (pos): 282.0623 C<sub>13</sub>H<sub>16</sub>NO<sub>2</sub>S<sub>2</sub> (calcd. 282.0617).

### 2-(4-Methylbenzoyl)allyl dimethylcarbamodithioate (**12d**)

Yield: 23%; mp 51.3–52.7 °C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.65 (d, *J* = 8.1 Hz, 2 H, Ar-H), 7.21 (d, *J* = 8.0 Hz, 2 H, Ar-H), 6.25 (s, 1 H, C = CHH), 5.74 (s, 1 H, C = CHH), 4.37 (s, 2 H, C-CH<sub>2</sub>-S), 3.52 (s, 3 H, N-CH<sub>3</sub>), 3.32 (s, 3 H, N-CH<sub>3</sub>), 2.38 (s, 3 H, Ar-CH<sub>3</sub>); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 196.6 (S-C = S), 196.4 (C = O), 143.2 (Ar-C),

142.9 (C-C=CH<sub>2</sub>), 134.6 (Ar-C), 129.8 (Ar-C), 129.0 (Ar-C), 128.4 (C=CH<sub>2</sub>), 45.4 (N-CH<sub>3</sub>), 41.5 (N-CH<sub>3</sub>), 38.2 (C-CH<sub>2</sub>-S), 21.7 (Ar-CH<sub>3</sub>); HRMS *m/z* (pos): 280.0831 C<sub>14</sub>H<sub>18</sub>NOS<sub>2</sub> (calcd. 280.0824).

### 2-(3-Methylbenzoyl)allyl dimethylcarbamodithioate (12e)

Yield: 29%; mp 33.5–37.0 °C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.60–7.46 (m, 2 H, Ar-H), 7.32 (dt, *J* = 14.9, 7.6 Hz, 2 H, Ar-H), 6.31 (s, 1 H, C=CHH), 5.79 (s, 1 H, C=CHH), 4.41 (s, 2 H, C-CH<sub>2</sub>-S), 3.55 (s, 3 H, N-CH<sub>3</sub>), 3.36 (s, 3 H, N-CH<sub>3</sub>), 2.39 (s, 3 H, Ar-CH<sub>3</sub>); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 197.1 (S-C=S), 196.5 (C=O), 143.0 (C-C=CH<sub>2</sub>), 138.1 (Ar-C), 137.4 (Ar-C), 133.2 (Ar-C), 129.9 (Ar-C), 129.2 (C=CH<sub>2</sub>), 128.1 (Ar-C), 126.9 (Ar-C), 45.6 (N-CH<sub>3</sub>), 41.5 (N-CH<sub>3</sub>), 38.0 (C-CH<sub>2</sub>-S), 21.4 (Ar-CH<sub>3</sub>); HRMS *m/z* (pos): 280.0832 C<sub>14</sub>H<sub>18</sub>NOS<sub>2</sub> (calcd. Found: 280.0824).

### 2-(Benzo[d][1,3]dioxole-5-carbonyl)allyl dimethylcarbamodithioate (12f)

Yield: 34%; mp 57.7–58.5 °C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.38 (dd, *J* = 8.1, 1.7 Hz, 1 H, Ar-H), 7.29 (d, *J* = 1.6 Hz, 1 H, Ar-H), 6.82 (d, *J* = 8.1 Hz, 1 H, Ar-H), 6.18 (s, 1 H, C=CHH), 6.03 (s, 2 H, O-CH<sub>2</sub>-O), 5.70 (s, 1 H, C=CHH), 4.36 (s, 2 H, C-CH<sub>2</sub>-S), 3.54 (s, 3 H, N-CH<sub>3</sub>), 3.34 (s, 3 H, N-CH<sub>3</sub>); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 196.4 (S-C=S), 195.2 (C=O), 151.6 (Ar-C), 147.9 (Ar-C), 142.9 (C-C=CH<sub>2</sub>), 131.6 (Ar-C), 127.2 (Ar-C), 126.3 (C=CH<sub>2</sub>), 109.5 (O-CH<sub>2</sub>-O), 107.7 (Ar-C), 101.8 (Ar-C), 45.5 (N-CH<sub>3</sub>), 41.5 (N-CH<sub>3</sub>), 38.5 (C-CH<sub>2</sub>-S); HRMS *m/z* (pos): 310.0565 C<sub>14</sub>H<sub>16</sub>NO<sub>3</sub>S<sub>2</sub> (calcd. 310.0566).

### 2-(4-Nitrobenzoyl)allyl dimethylcarbamodithioate (12g)

Yield: 17%; mp 65.1–67.3 °C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.29 (d, *J* = 8.5 Hz, 2 H, Ar-H), 7.88 (d, *J* = 8.5 Hz, 2 H, Ar-H), 6.44 (s, 1 H, C=CHH), 5.79 (s, 1 H, C=CHH), 4.38 (s, 2 H, C-CH<sub>2</sub>-S), 3.57 (s, 3 H, N-CH<sub>3</sub>), 3.39 (s, 3 H, N-CH<sub>3</sub>); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 196.0 (S-C=S), 195.3 (C=O), 149.8 (Ar-C), 143.2 (C-C=CH<sub>2</sub>), 142.7 (Ar-C), 130.6 (C=CH<sub>2</sub>), 130.4 (Ar-C), 123.5 (Ar-C), 45.6 (N-CH<sub>3</sub>), 41.5 (N-CH<sub>3</sub>), 37.1 (C-CH<sub>2</sub>-S); HRMS *m/z* (pos): 311.0514 C<sub>13</sub>H<sub>15</sub>N<sub>2</sub>O<sub>3</sub>S<sub>2</sub> (calcd. 311.0519).

### 2-(3-Nitrobenzoyl)allyl dimethylcarbamodithioate (12h)

Yield: 14%; mp 81.4–82.7 °C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.57 (dd, *J* = 12.4, 1.6 Hz, 1 H, Ar-H), 8.49–8.34 (m, 1 H,

Ar-H), 8.09 (dd, *J* = 11.2, 4.5 Hz, 1 H, Ar-H), 7.67 (td, *J* = 8.0, 4.0 Hz, 1 H, Ar-H), 6.49–6.32 (m, 1 H, C=CHH), 5.80 (d, *J* = 6.3 Hz, 1 H, C=CHH), 4.40 (d, *J* = 14.8 Hz, 2 H, C-CH<sub>2</sub>-S), 3.57 (d, *J* = 10.5 Hz, 3 H, N-CH<sub>3</sub>), 3.39 (d, *J* = 6.0 Hz, 3 H, N-CH<sub>3</sub>); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 195.9 (S-C=S), 194.6 (C=O), 148.1 (Ar-C), 143.0 (C-C=CH<sub>2</sub>), 135.2 (Ar-C), 130.0 (Ar-C), 129.6 (Ar-C), 129.6 (C=CH<sub>2</sub>), 126.7 (Ar-C), 124.3 (Ar-C), 45.6 (N-CH<sub>3</sub>), 41.5 (N-CH<sub>3</sub>), 37.3 (C-CH<sub>2</sub>-S); HRMS *m/z* (pos): 311.0520 C<sub>13</sub>H<sub>15</sub>N<sub>2</sub>O<sub>3</sub>S<sub>2</sub> (calcd. For 311.0519).

### 2-(2-Nitrobenzoyl)allyl dimethylcarbamodithioate (12i)

Yield: 11%; mp 83.5–84.1 °C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.15 (d, *J* = 8.2 Hz, 1H, Ar-H), 7.73 (t, *J* = 7.4 Hz, 1 H, Ar-H), 7.63 (t, *J* = 7.7 Hz, 1 H, Ar-H), 7.42 (d, *J* = 7.4 Hz, 1 H, Ar-H), 6.35 (s, 1 H, C=CHH), 5.55 (s, 1 H, C=CHH), 4.43 (s, 2 H, C-CH<sub>2</sub>-S), 3.54 (s, 3 H, N-CH<sub>3</sub>), 3.40 (s, 3 H, N-CH<sub>3</sub>); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 196.4 (S-C=S), 193.9 (C=O), 146.5 (Ar-C), 143.9 (C-C=CH<sub>2</sub>), 135.4 (Ar-C), 134.1 (Ar-C), 130.7 (Ar-C), 129.0 (C=CH<sub>2</sub>), 124.5 (Ar-C), 45.7 (N-CH<sub>3</sub>), 41.6 (N-CH<sub>3</sub>), 36.2 (C-CH<sub>2</sub>-S); HRMS *m/z* (pos): 311.0514 C<sub>13</sub>H<sub>15</sub>N<sub>2</sub>O<sub>3</sub>S<sub>2</sub> (calcd. 311.0519).

### 2-(4-Cyanobenzoyl)allyl dimethylcarbamodithioate (12j)

Yield: 38%; mp 64.5–66.4 °C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.84 (d, *J* = 8.3 Hz, 2 H, Ar-H), 7.75 (d, *J* = 8.4 Hz, 2 H, Ar-H), 6.42 (s, 1 H, C=CHH), 5.77 (s, 1 H, C=CHH), 4.39 (s, 2 H, C-CH<sub>2</sub>-S), 3.57 (s, 3 H, N-CH<sub>3</sub>), 3.39 (s, 3 H, N-CH<sub>3</sub>); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 196.1 (S-C=S), 195.5 (C=O), 143.0 (Ar-C), 141.1 (C-C=CH<sub>2</sub>), 132.1 (Ar-C), 130.3 (Ar-C), 121.9 (Ar-C), 118.0 (C=CH<sub>2</sub>), 115.6 (Ar-C), 45.6 (N-CH<sub>3</sub>), 41.5 (N-CH<sub>3</sub>), 37.3 (C-CH<sub>2</sub>-S); HRMS *m/z* (pos): 291.0617 C<sub>14</sub>H<sub>15</sub>N<sub>2</sub>OS<sub>2</sub> (calcd. 291.06203).

### 2-(4-Fluorobenzoyl)allyl dimethylcarbamodithioate (12k)

Yield: 25%; Yellow oil; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.79 (dd, *J* = 8.7, 5.5 Hz, 2 H, Ar-H), 7.10 (t, *J* = 8.6 Hz, 2 H, Ar-H), 6.27 (s, 1 H, C=CHH), 5.73 (s, 1 H, C=CHH), 4.37 (s, 2 H, C-CH<sub>2</sub>-S), 3.54 (s, 3 H, N-CH<sub>3</sub>), 3.35 (s, 3 H, N-CH<sub>3</sub>); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 196.2 (S-C=S), 195.5 (C=O), 166.3 (Ar-C, *J* = 253.9 Hz), 143.0 (C-C=CH<sub>2</sub>), 133.6 (Ar-C, *J* = 3.0 Hz), 132.2 (Ar-C, *J* = 9.1 Hz), 128.5 (C=CH<sub>2</sub>), 115.4 (Ar-C, *J* = 21.8 Hz), 45.5 (N-CH<sub>3</sub>), 41.5 (N-CH<sub>3</sub>), 37.9 (C-CH<sub>2</sub>-S); HRMS *m/z* (pos): 284.0569 C<sub>13</sub>H<sub>15</sub>FNOS<sub>2</sub> (calcd. 284.0574).

**2-(3-Fluorobenzoyl)allyl dimethylcarbamodithioate (12l)**

Yield: 21%; Yellow oil;  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.49 (d,  $J = 7.7$  Hz, 1 H, Ar-H), 7.45–7.35 (m, 2 H, Ar-H), 7.19 (td,  $J = 8.0, 2.2$  Hz, 1 H, Ar-H), 6.29 (s, 1 H, C = CHH), 5.75 (s, 1 H, C = CHH), 4.33 (s, 2 H, C-CH<sub>2</sub>-S), 3.50 (s, 3 H, N-CH<sub>3</sub>), 3.32 (s, 3 H, N-CH<sub>3</sub>);  $^{13}\text{C NMR}$  (101 MHz,  $\text{CDCl}_3$ )  $\delta$  196.0 (S-C = S), 195.5 (C = O), 162.4 (Ar-C,  $J = 248.1$  Hz), 142.8 (C-C = CH<sub>2</sub>), 139.5 (Ar-C,  $J = 6.4$  Hz), 130.0 (Ar-C,  $J = 7.7$  Hz), 129.5 (C = CH<sub>2</sub>), 125.4 (Ar-C,  $J = 3.0$  Hz), 119.3 (Ar-C,  $J = 21.4$  Hz), 116.2 (Ar-C,  $J = 22.5$  Hz), 45.5 (N-CH<sub>3</sub>), 41.46 (N-CH<sub>3</sub>), 37.7 (C-CH<sub>2</sub>-S); HRMS  $m/z$  (pos): 284.0571  $\text{C}_{13}\text{H}_{15}\text{FNOS}_2$  (calcd. 284.0574).

**2-(4-Chlorobenzoyl)allyl dimethylcarbamodithioate (12m)**

Yield: 37%; mp 55.8–57.1 °C;  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.64 (d,  $J = 8.4$  Hz, 2 H, Ar-H), 7.34 (d,  $J = 8.3$  Hz, 2 H, Ar-H), 6.24 (s, 1 H, C = CHH), 5.69 (s, 1 H, C = CHH), 4.30 (s, 2 H, C-CH<sub>2</sub>-S), 3.47 (s, 3 H, N-CH<sub>3</sub>), 3.29 (s, 3 H, N-CH<sub>3</sub>);  $^{13}\text{C NMR}$  (101 MHz,  $\text{CDCl}_3$ )  $\delta$  195.6 (S-C = S), 195.6 (C = O), 142.9 (C-C = CH<sub>2</sub>), 138.7 (Ar-C), 135.6 (Ar-C), 131.0 (Ar-C), 129.0 (C = CH<sub>2</sub>), 128.6 (Ar-C), 45.5 (N-CH<sub>3</sub>), 41.5 (N-CH<sub>3</sub>), 37.8 (C-CH<sub>2</sub>-S); HRMS  $m/z$  (pos): 300.0278  $\text{C}_{13}\text{H}_{15}\text{ClNOS}_2$  (calcd. 300.0278).

**2-(2-Chlorobenzoyl)allyl dimethylcarbamodithioate (12n)**

Yield: 29%; Yellow oil;  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.33 (dt,  $J = 8.1, 4.8$  Hz, 2 H, Ar-H), 7.29–7.20 (m, 2 H, Ar-H), 6.41 (s, 1 H, C = CHH), 5.70 (s, 1 H, C = CHH), 4.37 (s, 2 H, C-CH<sub>2</sub>-S), 3.49 (s, 3 H, N-CH<sub>3</sub>), 3.33 (s, 3 H, N-CH<sub>3</sub>);  $^{13}\text{C NMR}$  (101 MHz,  $\text{CDCl}_3$ )  $\delta$  196.3 (S-C = S), 195.7 (C = O), 143.4 (C-C = CH<sub>2</sub>), 137.9 (Ar-C), 133.0 (Ar-C), 131.1 (Ar-C), 131.0 (Ar-C), 130.0 (Ar-C), 129.9 (C = CH<sub>2</sub>), 126.5 (Ar-C), 45.6 (N-CH<sub>3</sub>), 41.59 (N-CH<sub>3</sub>), 36.3 (C-CH<sub>2</sub>-S); HRMS  $m/z$  (pos): 300.0273  $\text{C}_{13}\text{H}_{15}\text{ClNOS}_2$  (calcd. 300.0278).

**2-(3,4-Dichlorobenzoyl)allyl dimethylcarbamodithioate (12o)**

Yield: 35%; mp 60.3–62.5 °C;  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.79 (s, 1 H, Ar-H), 7.55 (d,  $J = 8.2$  Hz, 1 H, Ar-H), 7.48 (d,  $J = 8.1$  Hz, 1 H, Ar-H), 6.30 (s, 1 H, C = CHH), 5.73 (s, 1 H, C = CHH), 4.31 (s, 2 H, C-CH<sub>2</sub>-S), 3.51 (s, 3 H, N-CH<sub>3</sub>), 3.33 (s, 3 H, N-CH<sub>3</sub>);  $^{13}\text{C NMR}$  (101 MHz,  $\text{CDCl}_3$ )  $\delta$  195.9 (S-C = S), 194.4 (C = O), 142.8 (C-C = CH<sub>2</sub>), 137.0 (Ar-C), 136.8 (Ar-C), 133.0 (Ar-C), 131.3 (Ar-C), 130.4 (Ar-C), 129.4 (C = CH<sub>2</sub>), 128.9 (Ar-C), 45.6 (N-CH<sub>3</sub>), 41.5

(N-CH<sub>3</sub>), 37.5 (C-CH<sub>2</sub>-S); HRMS  $m/z$  (pos): 333.9884  $\text{C}_{13}\text{H}_{14}\text{NCl}_2\text{OS}_2$  (calcd. 333.9888).

**2-(Furan-2-carbonyl)allyl dimethylcarbamodithioate (12p)**

Yield: 15%; Yellow oil;  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.65 (s, 1 H, Ar-H), 7.20 (d,  $J = 3.4$  Hz, 1 H, Ar-H), 6.54 (dd,  $J = 3.3, 1.5$  Hz, 1 H, Ar-H), 6.26 (s, 1 H, C = CHH), 6.22 (s, 1 H, C = CHH), 4.39 (s, 2 H, C-CH<sub>2</sub>-S), 3.54 (s, 3 H, N-CH<sub>3</sub>), 3.35 (s, 3 H, N-CH<sub>3</sub>);  $^{13}\text{C NMR}$  (101 MHz,  $\text{CDCl}_3$ )  $\delta$  196.4 (S-C = S), 182.4 (C = O), 151.8 (Ar-C), 147.1 (Ar-C), 142.6 (C-C = CH<sub>2</sub>), 121.7 (Ar-C), 120.3 (C = CH<sub>2</sub>), 112.1 (Ar-C), 45.5 (N-CH<sub>3</sub>), 42.5 (N-CH<sub>3</sub>), 38.1 (C-CH<sub>2</sub>-S); HRMS  $m/z$  (pos): 256.0459  $\text{C}_{11}\text{H}_{14}\text{NO}_2\text{S}_2$  (calcd. 256.0461).

**2-(Thiophene-2-carbonyl)allyl dimethylcarbamodithioate (12q)**

Yield: 23%; Yellow oil;  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.64 (t,  $J = 4.3$  Hz, 2 H, Ar-H), 7.09 (dd,  $J = 4.8, 3.9$  Hz, 1 H, Ar-H), 6.16 (s, 1 H, C = CHH), 5.95 (s, 1 H, C = CHH), 4.34 (s, 2 H, C-CH<sub>2</sub>-S), 3.50 (s, 3 H, N-CH<sub>3</sub>), 3.31 (s, 3 H, N-CH<sub>3</sub>);  $^{13}\text{C NMR}$  (101 MHz,  $\text{CDCl}_3$ )  $\delta$  196.1 (S-C = S), 188.2 (C = O), 143.1 (Ar-C), 143.0 (C-C = CH<sub>2</sub>), 134.3 (Ar-C), 128.0 (C = CH<sub>2</sub>), 126.7 (Ar-C), 45.5 (N-CH<sub>3</sub>), 41.5 (N-CH<sub>3</sub>), 38.3 (C-CH<sub>2</sub>-S); HRMS  $m/z$  (pos): 272.0232  $\text{C}_{11}\text{H}_{14}\text{NOS}_3$  (Calcd. 272.0232).

**2-(1H-pyrrole-2-carbonyl)allyl dimethylcarbamodithioate (12r)**

Yield: 5%; mp 133.1–135.7 °C;  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  9.85 (s, 1 H, Ar-H), 7.05–7.06 (m, 1 H, Ar-H), 6.83–6.84 (m, 1 H, Ar-H), 6.21 (s, 1 H, Ar-H), 6.01 (s, 1 H, C = CHH), 5.96 (s, 1 H, C = CHH), 4.33 (s, 2 H, C-CH<sub>2</sub>-S), 3.47 (s, 3 H, N-CH<sub>3</sub>), 3.26 (s, 3 H, N-CH<sub>3</sub>);  $^{13}\text{C NMR}$  (101 MHz,  $\text{CDCl}_3$ )  $\delta$  196.6 (S-C = S), 184.8 (C = O), 142.7 (Ar-C), 130.8 (C-C = CH<sub>2</sub>), 125.7 (Ar-C), 125.6 (Ar-C), 118.9 (C = CH<sub>2</sub>), 110.8 (Ar-C), 45.5 (N-CH<sub>3</sub>), 41.4 (N-CH<sub>3</sub>), 38.7 (C-CH<sub>2</sub>-S); HRMS  $m/z$  (pos): 255.0622  $\text{C}_{11}\text{H}_{15}\text{N}_2\text{OS}_2$  (calcd. 255.0620).

**2-Nicotinoylallyl dimethylcarbamodithioate (12s)**

Yield: 10%; Yellow oil;  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.94 (d,  $J = 1.6$  Hz, 1 H, Ar-H), 8.77 (dd,  $J = 4.8, 1.6$  Hz, 1 H, Ar-H), 8.05 (dt,  $J = 7.9, 1.9$  Hz, 1 H, Ar-H), 7.40 (dd,  $J = 7.8, 4.9$  Hz, 1 H, Ar-H), 6.42 (s, 1 H, C = CHH), 5.82 (s, 1 H, C = CHH), 4.41 (s, 2 H, C-CH<sub>2</sub>-S), 3.56 (s, 3 H, N-CH<sub>3</sub>), 3.38 (s, 3 H, N-CH<sub>3</sub>);  $^{13}\text{C NMR}$  (101 MHz,

$\text{CDCl}_3$ )  $\delta$  196.1 (S-C = S), 195.3 (C = O), 152.8 (Ar-C), 150.5 (Ar-C), 143.2 (C-C = CH<sub>2</sub>), 136.9 (Ar-C), 133.0 (Ar-C), 130.1 (Ar-C), 123.3 (C = CH<sub>2</sub>), 45.6 (N-CH<sub>3</sub>), 41.5 (N-CH<sub>3</sub>), 37.4 (C-CH<sub>2</sub>-S); HRMS  $m/z$  (pos): 267.0625 C<sub>12</sub>H<sub>15</sub>N<sub>2</sub>OS<sub>2</sub> (calcd. 267.0620).

### 2-Benzoylallyl dimethylcarbamodithioate (13)

Yield 18%; Yellow oil; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  8.00 (dd,  $J$  = 5.2, 3.3 Hz, 2 H, Ar-H), 7.60–7.54 (m, 1 H, Ar-H), 7.52–7.41 (m, 2 H, Ar-H), 4.13–3.98 (m, 1 H, C-CH-CH<sub>3</sub>), 3.67 (dd,  $J$  = 13.7, 8.2 Hz, 1 H, CH-CHH-S), 3.56 (dd,  $J$  = 13.7, 8.2 Hz, 1 H, CH-CHH-S), 3.55 (s, 3 H, N-CH<sub>3</sub>), 3.31 (s, 3 H, N-CH<sub>3</sub>), 1.33 (d,  $J$  = 7.1 Hz, 3 H, CH-CH<sub>3</sub>); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$  202.9 (S-C = S), 197.3 (C = O), 136.1 (Ar-C), 133.2 (Ar-C), 128.7 (Ar-C), 128.6 (Ar-C), 45.4 (N-CH<sub>3</sub>), 41.5 (N-CH<sub>3</sub>), 40.5 (C-CH-CH<sub>3</sub>), 39.4 (C-CH<sub>2</sub>-S), 18.1 (C-CH<sub>3</sub>); HRMS  $m/z$  (pos): 268.0828 C<sub>13</sub>H<sub>18</sub>NOS<sub>2</sub> (Calcd. 268.0824).

### 2-(4-Chlorobenzoyl)allyl diethylcarbamodithioate (14a)

Yield: 24%; Yellow oil; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.72 (d,  $J$  = 8.5 Hz, 2 H, Ar-H), 7.41 (d,  $J$  = 8.5 Hz, 2 H, Ar-H), 6.30 (s, 1 H, C = CHH), 5.74 (s, 1 H, C = CHH), 4.40 (s, 2 H, C-CH<sub>2</sub>-S), 4.04 (q,  $J$  = 6.9 Hz, 2 H, N-CH<sub>2</sub>-CH<sub>3</sub>), 3.74 (dd,  $J$  = 13.7, 6.6 Hz, 2 H, N-CH<sub>2</sub>-CH<sub>3</sub>), 1.27 (dd,  $J$  = 11.3, 6.7 Hz, 6 H, N-(CH<sub>2</sub>-CH<sub>3</sub>)<sub>2</sub>); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$  195.9 (S-C = S), 194.5 (C = O), 143.0 (C-C = CH<sub>2</sub>), 138.8 (Ar-C), 135.7 (Ar-C), 131.1 (Ar-C), 128.8 (C = CH<sub>2</sub>), 128.6 (Ar-C), 49.7 (CH<sub>2</sub>-CH<sub>3</sub>), 46.8 (CH<sub>2</sub>-CH<sub>3</sub>), 37.4 (C-CH<sub>2</sub>-S), 12.6 (CH<sub>2</sub>-CH<sub>3</sub>), 11.6 (CH<sub>2</sub>-CH<sub>3</sub>); HRMS  $m/z$  (pos): 328.0590 C<sub>15</sub>H<sub>19</sub>CINOS<sub>2</sub> (Calcd. 328.0591).

### 2-(4-Chlorobenzoyl)allyl dipropylcarbamodithioate (14b)

Yield: 24%; Yellow oil; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.73 (d,  $J$  = 8.5 Hz, 2 H, Ar-H), 7.43 (d,  $J$  = 8.5 Hz, 2 H, Ar-H), 6.30 (s, 1 H, C = CHH), 5.75 (s, 1 H, C = CHH), 4.40 (s, 2 H, C-CH<sub>2</sub>-S), 3.97–3.87 (m, 2 H, N-CH<sub>2</sub>-CH<sub>2</sub>), 3.66–3.58 (m, 2 H, N-CH<sub>2</sub>-CH<sub>2</sub>), 1.84–1.66 (m, 4 H, N-(CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>3</sub>)<sub>2</sub>), 0.95 (q,  $J$  = 7.1 Hz, 6 H, N-(CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>3</sub>)<sub>2</sub>); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$  193.0 (S-C = S), 195.1 (C = O), 143.0 (C-C = CH<sub>2</sub>), 138.9 (Ar-C), 135.8 (Ar-C), 131.1 (Ar-C), 128.8 (C = CH<sub>2</sub>), 128.6 (Ar-C), 57.0 (N-CH<sub>2</sub>-CH<sub>2</sub>), 54.4 (N-CH<sub>2</sub>-CH<sub>2</sub>), 37.4 (C-CH<sub>2</sub>-S), 20.7 (CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>3</sub>), 19.6 (CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>3</sub>), 11.2 (CH<sub>2</sub>-CH<sub>3</sub>); HRMS  $m/z$  (pos): 356.0901 C<sub>17</sub>H<sub>23</sub>CINOS<sub>2</sub> (calcd. 356.0904).

### 2-(4-Chlorobenzoyl)allyl dibutylcarbamodithioate (14c)

Yield: 22%; Yellow oil; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.73 (d,  $J$  = 8.4 Hz, 2 H, Ar-H), 7.42 (d,  $J$  = 8.4 Hz, 2 H, Ar-H), 6.29 (s, 1 H, C = CHH), 5.74 (s, 1 H, C = CHH), 4.40 (s, 2 H, C-CH<sub>2</sub>-S), 3.99–3.94 (m, 2 H, N-CH<sub>2</sub>-CH<sub>2</sub>), 3.67–3.61 (m, 2 H, N-CH<sub>2</sub>-CH<sub>2</sub>), 1.74–1.64 (m, 4 H, N-(CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>3</sub>)<sub>2</sub>), 1.39–1.32 (m, 4 H, N-(CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>3</sub>)<sub>2</sub>), 0.95 (dt,  $J$  = 20.6, 7.4 Hz, 6 H, N-(CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>3</sub>)<sub>2</sub>); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$  195.9 (S-C = S), 194.9 (C = O), 143.0 (C-C = CH<sub>2</sub>), 138.9 (Ar-C), 135.8 (Ar-C), 131.1 (Ar-C), 128.6 (C = CH<sub>2</sub>), 128.6 (Ar-C), 55.2 (N-CH<sub>2</sub>-CH<sub>2</sub>), 55.5 (N-CH<sub>2</sub>-CH<sub>2</sub>), 37.4 (C-CH<sub>2</sub>-S), 29.4 (N-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>), 28.4 (N-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>), 20.1 (CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>3</sub>), 20.1 (CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>3</sub>), 13.9 (CH<sub>2</sub>-CH<sub>3</sub>), 13.7 (CH<sub>2</sub>-CH<sub>3</sub>); HRMS  $m/z$  (pos): 384.1227 C<sub>19</sub>H<sub>27</sub>CINOS<sub>2</sub> (calcd. 384.1217).

### 2-(4-Chlorobenzoyl)allyl pyrrolidine-1-carbodithioate (14d)

Yield 36%; mp 59.8–61.5 °C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.73 (d,  $J$  = 8.5 Hz, 2 H, Ar-H), 7.43 (d,  $J$  = 8.5 Hz, 2 H, Ar-H), 6.36 (s, 1 H, C = CHH), 5.77 (s, 1 H, C = CHH), 4.42 (s, 2 H, C-CH<sub>2</sub>-S), 3.96 (t,  $J$  = 6.9 Hz, 2 H, N-CH<sub>2</sub>-CH<sub>2</sub>), 3.66 (t,  $J$  = 6.8 Hz, 2 H, N-CH<sub>2</sub>-CH<sub>2</sub>), 2.14–2.05 (m, 2 H, N-CH<sub>2</sub>-CH<sub>2</sub>), 2.04–1.95 (m, 2 H, N-CH<sub>2</sub>-CH<sub>2</sub>); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$  195.8 (S-C = S), 191.9 (C = O), 143.2 (C-C = CH<sub>2</sub>), 138.8 (Ar-C), 135.7 (Ar-C), 131.1 (Ar-C), 129.0 (C = CH<sub>2</sub>), 128.6 (Ar-C), 55.2 (N-CH<sub>2</sub>-CH<sub>2</sub>), 50.6 (N-CH<sub>2</sub>-CH<sub>2</sub>), 36.7 (C-CH<sub>2</sub>-S), 26.1 (N-CH<sub>2</sub>-CH<sub>2</sub>), 24.3 (N-CH<sub>2</sub>-CH<sub>2</sub>); HRMS  $m/z$  (pos): 326.0435 C<sub>15</sub>H<sub>17</sub>CINOS<sub>2</sub> (calcd. 326.0435).

### 2-(4-Chlorobenzoyl)allyl piperidine-1-carbodithioate (14e)

Yield: 15%; mp 59.6–61.2 °C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.73 (d,  $J$  = 8.6 Hz, 2 H, Ar-H), 7.44–7.39 (m, 2 H, Ar-H), 6.31 (s, 1 H, C = CHH), 5.75 (s, 1 H, C = CHH), 4.42 (s, 2 H, C-CH<sub>2</sub>-S), 4.30 (br, 2 H, N-CH<sub>2</sub>-CH<sub>2</sub>), 3.89 (br, 2 H, N-CH<sub>2</sub>-CH<sub>2</sub>), 1.71–1.64 (m, 6 H, CH<sub>2</sub>-(CH<sub>2</sub>)<sub>3</sub>-CH<sub>2</sub>); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$  195.9 (S-C = S), 194.6 (C = O), 143.1 (C-C = CH<sub>2</sub>), 138.8 (Ar-C), 135.7 (Ar-C), 131.1 (Ar-C), 128.8 (C = CH<sub>2</sub>), 128.6 (Ar-C), 37.4 (C-CH<sub>2</sub>-S), 24.3 (CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>); HRMS  $m/z$  (pos): 340.0594 C<sub>16</sub>H<sub>19</sub>CINOS<sub>2</sub> (calcd. 340.0591).

### 2-(4-Chlorobenzoyl)allyl morpholine-4-carbodithioate (14f)

Yield: 23%; mp 75.1–76.3 °C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.72 (d,  $J$  = 8.5 Hz, 2 H, Ar-H), 7.43 (d,  $J$  = 8.5 Hz, 2 H,

Ar-H)), 6.33 (s, 1 H, C = CHH), 5.79 (s, 1 H, C = CHH), 4.44 (s, 2 H, C-CH<sub>2</sub>-S), 4.15 (m, 4 H, N-(CH<sub>2</sub>-CH<sub>2</sub>)<sub>2</sub>), 3.77 (br, 4 H, O-(CH<sub>2</sub>-CH<sub>2</sub>)<sub>2</sub>); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 196.7 (S-C = S), 195.7 (C = O), 142.7 (C-C = CH<sub>2</sub>), 139.0 (Ar-C), 135.6 (Ar-C), 131.1 (Ar-C), 129.3 (C = CH<sub>2</sub>), 128.6 (Ar-C), 66.3 (O-(CH<sub>2</sub>-CH<sub>2</sub>)<sub>2</sub>), 52.1-50.2 (N-(CH<sub>2</sub>-CH<sub>2</sub>)<sub>2</sub>), 37.2 (C-CH<sub>2</sub>-S); HRMS *m/z* (pos): 342.0380 C<sub>15</sub>H<sub>17</sub>ClNO<sub>2</sub>S<sub>2</sub> (calcd. 342.0383).

#### (S)-Methyl 1-(((2-(4-chlorobenzoyl)allyl)thio)carbonothioyl) pyrrolidine-2-carboxylate (14g)

Yield: 17%; Yellow oil; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.71-7.69 (m, 2 H, Ar-H), 7.42 (d, *J* = 8.4 Hz, 2 H, Ar-H), 6.29 (d, *J* = 9.6 Hz, 1 H, C = CHH), 5.74 (d, *J* = 9.5 Hz, 1 H, C = CHH), 4.92 (ddd, *J* = 10.3, 8.7, 2.2 Hz, 1 H, N-CH-CO<sub>2</sub>CH<sub>3</sub>), 4.41-4.32 (m, 2 H, C-CH<sub>2</sub>-S), 4.20-3.68 (m, 2 H, N-CH<sub>2</sub>-CH<sub>2</sub>), 3.71 (d, *J* = 35.3 Hz, 3 H), 2.40-2.01 (m, 4 H, CH<sub>2</sub>-(CH<sub>2</sub>)<sub>2</sub>-CH); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 195.8 (C = S), 195.7 (C = S), 194.3 (C = O), 193.4 (C = O), 171.0 (C = O), 170.6 (C = O), 142.6 (C-C = CH<sub>2</sub>), 138.8 (Ar-C), 135.7 (Ar-C), 131.1 (Ar-C), 129.2 (C = CH<sub>2</sub>), 128.9 (C = CH<sub>2</sub>), 128.6 (Ar-C), 128.6 (Ar-C), 66.4 (N-CH-CO<sub>2</sub>CH<sub>3</sub>), 62.6 (N-CH-CO<sub>2</sub>CH<sub>3</sub>), 55.5 (O-CH<sub>3</sub>), 52.4 (O-CH<sub>3</sub>), 52.7 (N-CH<sub>2</sub>-CH<sub>2</sub>), 50.9 (N-CH<sub>2</sub>-CH<sub>2</sub>), 37.0 (C-CH<sub>2</sub>-S), 36.9 (C-CH<sub>2</sub>-S), 31.5 (CH-CH<sub>2</sub>-CH<sub>2</sub>), 29.2 (CH-CH<sub>2</sub>-CH<sub>2</sub>), 24.6 (CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>), 22.3 (CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>); HRMS *m/z* (pos): 384.0499 C<sub>17</sub>H<sub>19</sub>ClNOS<sub>2</sub> (calcd. 384.0489).

#### (R)-Methyl 1-(((2-(4-chlorobenzoyl)allyl)thio)carbonothioyl) pyrrolidine-2-carboxylate (14h)

Yield: 20%; Yellow oil; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.71-7.69 (m, 2 H, Ar-H), 7.42 (d, *J* = 8.4 Hz, 2 H, Ar-H), 6.29 (d, *J* = 9.7 Hz, 1 H, C = CHH), 5.74 (d, *J* = 9.5 Hz, 1 H, C = CHH), 4.92 (ddd, *J* = 10.3, 8.7, 2.1 Hz, 1 H, N-CH-CO<sub>2</sub>CH<sub>3</sub>), 4.41-4.32 (m, 2 H, C-CH<sub>2</sub>-S), 4.20-3.69 (m, 2 H, N-CH<sub>2</sub>-CH<sub>2</sub>), 3.71 (d, *J* = 35.5 Hz, 3 H), 2.43-2.01 (m, 4 H, CH<sub>2</sub>-(CH<sub>2</sub>)<sub>2</sub>-CH); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 195.8 (C = S), 195.7 (C = S), 194.3 (C = O), 193.5 (C = O), 171.0 (C = O), 170.6 (C = O), 142.6 (C = CH<sub>2</sub>), 138.8 (Ar-C), 135.7 (Ar-C), 131.1 (Ar-C), 129.2 (C = CH<sub>2</sub>), 128.9 (C = CH<sub>2</sub>), 128.6 (Ar-C), 66.4 (N-CH-CO<sub>2</sub>CH<sub>3</sub>), 62.8 (N-CH-CO<sub>2</sub>CH<sub>3</sub>), 55.5 (O-CH<sub>3</sub>), 52.4 (O-CH<sub>3</sub>), 52.7 (N-CH<sub>2</sub>-CH<sub>2</sub>), 50.9 (N-CH<sub>2</sub>-CH<sub>2</sub>), 37.0 (C-CH<sub>2</sub>-S), 36.9 (C-CH<sub>2</sub>-S), 31.5 (CH-CH<sub>2</sub>-CH<sub>2</sub>), 29.2 (CH-CH<sub>2</sub>-CH<sub>2</sub>), 24.6 (CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>), 22.4 (CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>); HRMS *m/z* (pos): 384.0491 C<sub>17</sub>H<sub>19</sub>ClNOS<sub>2</sub> (calcd. 384.0489).

#### Antiproliferative activity assays

The inhibition rate of compound **8** was determined by MTT assay on cell line H460, BGC823, Hela, HCT116

and MDA-MB-231, and the antiproliferative activity of the target compounds was determined by MTT assay on cell line H460. The antiproliferative activity of compound **12r** was determined by MTT assay on the following cell lines: H460, A549, MDA-MB-231, MCF-7, A375, HCT116, PC3 and HepG2. All cells used in the research were prepared at 3.5 × 10<sup>3</sup> cells/mL concentration and each 100 μL cell suspension was seeded onto 96-well microtiter plates for 24 h (37 °C, 5% CO<sub>2</sub>). Then various appropriate dilutions of tested compounds were added and incubated for 72 h. For the control group, equivalent concentration of DMSO (final concentration 0.5%) was added. MTT (3-[4,5-dimethylthiazol-2-yl]-diphenyl tetrazolium bromide) method was used to measure the number of surviving cells and recorded the OD value at 492/620 nm. The inhibition rate of the compounds was calculated, and the IC<sub>50</sub> values were calculated using Prism Graphpad software of the triplicate experiment.

## Results and Discussion

### Modification of lead compound **8**

#### Optimization of aromatic rings

Our optimization effort started with the modification of the aromatic rings of lead compound **8** (Table 1). A variety of substituted aromatic rings and heteroaromatic rings were selected to replace the benzene ring in lead compound **8**. All target compounds were synthesized and evaluated for their anti-proliferative activities against H460 cell based on our previous results (Li et al. 2015b).

The results showed in Table 1 indicated that most of the compounds exhibited better activity than lead compound **8**. The position of substituents on the benzene ring had a remarkable impact on the activity. Electron donating group on the para position (**12c**, 4-OH, IC<sub>50</sub> = 0.61 μM; **12d**, 4-Me, IC<sub>50</sub> = 1.09 μM) was beneficial for the activity. On the contrary, ortho substituted electron donating group, such as **12b** (2-OMe-, IC<sub>50</sub> = 6.51 μM), led to a 6-fold decrease in potency. Electron withdrawing group was suitable in all positions (**12g-12j**). However, halogen atoms had different influence on the activity. For example, the activity of 4-chlorine substituted compound **12m** (IC<sub>50</sub> = 0.57 μM) was six times more potent than that of 2-chlorine substituted compound **12n** (IC<sub>50</sub> = 3.61 μM). It was noteworthy that disubstituted derivatives (**12f** and **12o**) also showed excellent activity. Moreover, the modification with five-membered heteroaromatic rings (**12p**, furan-2-yl-, IC<sub>50</sub> = 0.52 μM; **12q**, thiophene-2-yl-, IC<sub>50</sub> = 1.23 μM; **12r**, pyrrole-2-yl-, IC<sub>50</sub> = 0.46 μM) also gave a satisfied results. In

**Table 1** Structures and activities of compounds **12a–12s** against H460 cell line<sup>a</sup>

Compd.	Ar	IC <sub>50</sub> <sup>b</sup> (μM)
<b>8</b>	Ph	1.59
<b>12a</b>	4-MeO-Ph	0.70
<b>12b</b>	2-MeO-Ph	6.51
<b>12c</b>	4-OH-Ph	0.61
<b>12d</b>	4-Me-Ph	1.09
<b>12e</b>	3-Me-Ph	0.80
<b>12f</b>		0.63
<b>12g</b>	4-NO <sub>2</sub> -Ph	0.54
<b>12h</b>	3-NO <sub>2</sub> -Ph	0.54
<b>12i</b>	2-NO <sub>2</sub> -Ph	0.63
<b>12j</b>	4-CN-Ph	0.73
<b>12k</b>	4-F-Ph	3.60
<b>12l</b>	3-F-Ph	1.10
<b>12m</b>	4-Cl-Ph	0.57
<b>12n</b>	2-Cl-Ph	3.61
<b>12o</b>	3,4-dichlorophenyl	0.74
<b>12p</b>	Furan-2-yl	0.52
<b>12q</b>	Thiophene-2-yl	1.23
<b>12r</b>	Pyrrole-2-yl	0.46
<b>12s</b>	Pyridine-3-yl	2.10
<b>13</b>	---	4.88

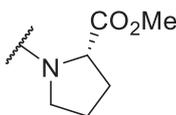
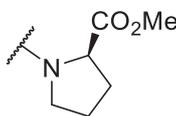
<sup>a</sup>H460 cell line: human non-small cell lung cancer<sup>b</sup>Dose-response curves were determined at five concentrationsThe IC<sub>50</sub> values are the concentrations needed to inhibit cell growth by 50% as determined from these curves

comparison, the activity was slightly decreased by modification with six-membered heteroaromatic rings (**12 s**, pyridin-3-yl-,  $IC_{50} = 2.10 \mu M$ ).

In order to confirm the function of the  $\alpha,\beta$ -unsaturated ketone fragment, compound **13**, a double bond reduced

derivatives of compound **8**, was also designed and synthesized. As expected, compound **13** ( $IC_{50} = 4.88 \mu M$ ) was less potent 3 times than compound **8** ( $IC_{50} = 1.59 \mu M$ ). Thus,  $\alpha,\beta$ -unsaturated ketone fragment plays a critical role in the anti-cancer activity.

**Table 2** The anti-proliferative activity of compound **14a–14h** against H460<sup>a</sup>

Compd.	R <sub>1</sub> R <sub>2</sub> N-	IC <sub>50</sub> <sup>b</sup> ( $\mu M$ )
<b>12m</b>	dimethylamino	0.57
<b>14a</b>	diethylamino	3.04
<b>14b</b>	dipropylamino	>50
<b>14c</b>	dibutylamino	>50
<b>14d</b>	pyrrolidin-1-yl	2.87
<b>14e</b>	piperidin-1-yl	2.26
<b>14f</b>	1-morpholino	4.31
<b>14g</b>		6.39
<b>14h</b>		6.31

<sup>a</sup>H460 cell line: human non-small cell lung cancer.

<sup>b</sup>Dose-response curves were determined at five concentrations. The  $IC_{50}$  values are the concentrations needed to inhibit cell growth by 50% as determined from these curves.

## Optimization of amine moiety

Based on the optimization results of the aromatic ring moiety, we chose compound **12m** to further optimize the amine moiety. Replacing dimethylamine with various secondary amines, including common cyclic and acyclic amines frequently occurring in drug structure, led to the compounds **14a–14h**. As shown in Table 2, it was clear that the activity decreased dramatically with the increase of amine size. The  $IC_{50}$  values of compounds **12m** ( $Me_2N-$ ), **14a** ( $Et_2N-$ ), **14b** ( $n-Pr_2N-$ ) and **14c** ( $n-Bu_2N-$ ) were 0.57, 3.04, >50 and >50  $\mu M$ , respectively. The activities of derivatives (**14d** and **14e**) with pyrrolidine and piperidine as amine moiety were similar to that of **14a**. These results suggested that the receptor cavity binding with amine moiety might be relatively small. Changing the piperidyl group in compound **14e** to morpholinyl group resulted in compound **14f**, which was less potent about two times than **14e**. Thus, the receptor cavity binding with amine moiety should be a hydrophobic cavity. Meanwhile, we also prepared **14g** and **14h** by using methyl L-prolinate and methyl D-prolinate as amine moiety, respectively. Both compound **14g** and **14h** had similar activities, which proved that antitumor activity was not affected by the chiral amine moiety. Therefore, small size hydrophobic amino groups were more beneficial for the activity.

## The antitumor spectrum of 12r

Based on the above optimized results, **12r** was identified as the most potent antitumor agent. We next assessed the antiproliferative effect of **12r** against eight kinds of tumor cell lines, including H460, A549, MDA-MB-231, MCF-7, A375, HCT116, PC3 and HepG2. As shown in Table 3, **12r** could inhibit the growth of eight cell lines with  $IC_{50}$  values <1  $\mu M$ . Especially for cell lines A375 and HCT116, the  $IC_{50}$  values achieved 63 nM and 66 nM, respectively.

**Table 3** Antiproliferative activities of compounds **12r** against various tumor cell lines<sup>a</sup>

Cell line	$IC_{50}^b$ ( $\mu M$ )	Cell line	$IC_{50}^b$ ( $\mu M$ )
H460	0.46	A375	0.063
A549	0.27	HCT116	0.066
MDA-MB-231	0.31	PC3	0.34
MCF-7	0.27	HepG2	0.21

<sup>a</sup>H460, A549: human non-small cell lung cancer; MDA-MB-231, MCF-7: breast adenocarcinoma; A375: melanoma; HCT116: colon cancer; PC3: prostate cancer; HepG2: hepatocellular carcinoma

<sup>b</sup>Dose-response curves were determined at five concentrations. The  $IC_{50}$  values are the concentrations needed to inhibit cell growth by 50% as determined from these curves

## Conclusion

A systematic structural modification was carried out based on the structure of novel lead compound **8**. A series of compound **8**'s derivatives were synthesized and evaluated for their in vitro antitumor activities. The compound **12r** was identified as the most potent one which had significant inhibitory effect on the growth of eight kinds of cancer cell lines with  $IC_{50}$  values <1  $\mu M$ . Especially for cell lines A375 and HCT116, the  $IC_{50}$  values achieved 63 nM and 66 nM, respectively. Meanwhile, some valuable structure-activity relationships were revealed as follows: (a) different substitution on the benzene ring or heteroaromatic rings greatly affected on the activity; (b) the presence of  $\alpha,\beta$ -unsaturated ketone fragment was favorable for the activity; (c) the receptor cavity binding with amine moiety might be a relatively small hydrophobic cavity. The further studies of **12r** are currently in progress.

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## Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflict of interest.

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## References

- Swinney DC, Anthony J (2011) How were new medicines discovered? *Nat Rev Drug Discov* 10:507–519
- Buac D, Schmitt S, Ventro G, Kona FR, Dou QP (2012) Dithiocarbamate-based coordination compounds as potent proteasome inhibitors in human cancer cells. *Mini-Rev Med Chem* 12:1193–1201
- Ronconi L, Nardon C, Boscutti G, Fregona D (2013) Perspective gold (III)-dithiocarbamate anticancer therapeutics: learning from the past, moving to the future. In Prudhomme M (ed) *Advances in anticancer agents in medicinal chemistry*, Bentham Science Publishers, Amsterdam, pp 130–172
- Bala V, Gupta G, Sharma VL (2014) Chemical and medicinal versatility of dithiocarbamates: an overview. *Mini-Rev Med Chem* 14:1021–1032
- Li R, Wang Y, Ge Z, Li R (2015a) Progress in studies on synthesis and biological properties of dithiocarbamates. *Youji Huaxue* 35:1805–1819
- Gaspari P, Banerjee T, Malachowski WP, Muller AJ, Prendergast GC, DuHadaway J, Bennett S, Donovan AM (2006) Structure-activity study of brassinin derivatives as indoleamine 2,3-dioxygenase inhibitors. *J Med Chem* 49:684–692
- Huang W, Ding Y, Miao Y, Liu M, Li Y, Yang G (2009) Synthesis and antitumor activity of novel dithiocarbamate substituted chromones. *Eur J Med Chem* 44:3687–3696
- Duan Y, Zheng Y, Li X, Wang M, Ye X, Guan Y, Liu G, Zheng J, Liu H (2013a) Design, synthesis and antiproliferative activity studies

- of novel 1,2,3-triazole-dithiocarbamate-urea hybrids. *Eur J Med Chem* 64:99–110
- Duan Y, Ma Y, Zhang E, Shi X, Wang M, Ye X, Liu H (2013b) Design and synthesis of novel 1,2,3-triazole-dithiocarbamate hybrids as potential anticancer agents. *Eur J Med Chem* 62:11–19
- Akinboye ES, Bamji ZD, Kwabi-Addo B, Ejeh D, Copeland RL, Denmeade SR, Bakare O (2015) Design, synthesis and cytotoxicity studies of dithiocarbamate ester derivatives of emetine in prostate cancer cell lines. *Bioorgan Med Chem* 23:5839–5845
- Ding P, Gao M, Mao B, Cao S, Liu C, Yang C, Li Z, Liao J, Zhao H, Li Z, Li J, Wang H, Xu X (2016) Synthesis and biological evaluation of quinazolin-4(3H)-one derivatives bearing dithiocarbamate side chain at C2-position as potential antitumor agents. *Eur J Med Chem* 108:364–373
- Fu D, Zhang S, Liu Y, Zhang L, Liu J, Song J, Zhao R, Li F, Sun H, Liu H, Zhang Y (2016) Design, synthesis and antiproliferative activity studies of novel dithiocarbamate-chalcone derivatives. *Bioorg Med Chem Lett* 26:3918–3922
- Fu D, Zhang L, Song J, Mao R, Zhao R, Liu Y, Hou Y, Li J, Yang J, Jin C, Li P, Zi X, Liu H, Zhang S, Zhang Y (2017) Design and synthesis of formononetin-dithiocarbamate hybrids that inhibit growth and migration of PC-3 cells via MAPK/Wnt signaling pathways. *Eur J Med Chem* 127:87–99
- Laskar S, Sánchez-Sánchez L, Flores SM, López-Muñoz H, Escobar-Sánchez ML, López-Ortiz M, Hernández-Rodríguez M, Regla I (2018) Identification of (1S,4S)-2,5-diazabicyclo[2.2.1]heptane-dithiocarbamate-nitrostyrene hybrid as potent antiproliferative and apoptotic inducing agent against cervical cancer cell lines. *Eur J Med Chem* 146:621–635
- Liu Y, Xie Z, Zhao D, Zhu J, Mao F, Tang S, Xu H, Luo C, Geng M, Huang M, Li J (2017) Development of the first generation of disulfide-based subtype-selective and potent covalent pyruvate dehydrogenase kinase 1 (PDK1) inhibitors. *J Med Chem* 60:2227–2244
- Skrott Z, Mistrik M, Andersen KK, Friis S, Majera D, Gursky J, Ozdian T, Bartkova J, Turi Z, Moudry P, Kraus M, Michalova M, Vaclavkova J, Dzubak P, Vrobel I, Pouckova P, Sedlacek J, Miklovcova A, Kutt A, Li J, Mattova J, Driessen C, Dou QP, Olsen J, Hajduch M, Cvek B, Deshaies RJ, Bartek J (2017) Alcohol-abuse drug disulfiram targets cancer via p97 segregase adaptor NPL4. *Nature* 552:194–199
- Wei M, Zhang J, Ma F, Li M, Yu J, Luo W, Li X (2018) Synthesis and biological activities of dithiocarbamates containing 2(5H)-furanone-piperazine. *Eur J Med Chem* 155:165–170
- Xie R, Li Y, Tang P, Yuan Q (2018) Design, synthesis and biological evaluation of novel 2-aminobenzamides containing dithiocarbamate moiety as histone deacetylase inhibitors and potent anti-tumor agents. *Eur J Med Chem* 143:320–333
- Yang C, Peng B, Cao S, Ren T, Jiang W, Wang F, Li Y, Wang G, Li Z, Xu S, Liao J, Wang H, Li J, Xu X (2018) Synthesis, cytotoxic evaluation and target identification of thieno[2,3-d]pyrimidine derivatives with a dithiocarbamate side chain at C2 position. *Eur J Med Chem* 154:324–340
- Hou X, Ge Z, Wang T, Guo W, Cui J, Cheng T, Lai C, Li R (2006) Dithiocarbamic acid esters as anticancer agent. Part 1: 4-Substituted-piperazine-1-carbodithioic acid 3-cyano-3,3-diphenylpropyl esters. *Bioorg Med Chem Lett* 16:4214–4219
- Li R, Zhang X, Li Q, Ge Z, Li R (2011) Novel EGFR inhibitors prepared by combination of dithiocarbamic acid esters and 4-anilinoquinazolines. *Bioorg Med Chem Lett* 21:3637–3640
- Li Y, Wang Z, Yan X, Chen M, Bao J, Wu G, Ge Z, Zhou D, Wang Y, Li R (2013) IC-4, a new irreversible EGFR inhibitor, exhibits prominent anti-tumor and anti-angiogenesis activities. *Cancer Lett* 340:88–96
- Li R, Wang H, Li Y-B, Wang Z, Wang X, Wang Y, Ge Z, Li R (2015b) Discovery and optimization of novel dual dithiocarbamates as potent anticancer agents. *Eur J Med Chem* 93:381–391
- Zhang Y, Liu B, Wu X, Li R, Ning X, Liu Y, Liu Z, Ge Z, Li R, Yin Y (2015) New pyridin-3-ylmethyl carbamodithioic esters activate pyruvate kinase M2 and potential anticancer lead compounds. *Bioorgan Med Chem* 23:4815–4823
- Li R, Ning X, Zhou S, Lin Z, Wu X, Chen H, Bai X, Wang X, Ge Z, Li R, Yin Y (2018) Discovery and structure-activity relationship of novel 4-hydroxy-thiazolidine-2-thione derivatives as tumor cell specific pyruvate kinase M2 activators. *Eur J Med Chem* 143:48–65
- Adams BK, Ferstl EM, Davis MC, Herold M, Kurtkaya S, Camalier RF, Hollingshead MG, Kaur G, Sausville EA, Rickles FR, Snyder JP, Liotta DC, Shoji M (2004) Synthesis and biological evaluation of novel curcumin analogs as anti-cancer and anti-angiogenesis agents. *Bioorgan Med Chem* 12:3871–3883
- Chen J, Sun Z, Zhang Y, Zeng X, Qing C, Liu J, Li L, Zhang H (2009) Synthesis of gibberellin derivatives with anti-tumor bioactivities. *Bioorg Med Chem Lett* 19:5496–5499
- Wu C, Coumar MS, Chu C, Lin WH, Chen Y, Chen CT, Shiao H, Rafi S, Wang S, Hsu H, Chen CH, Chang C, Chang T, Lien T, Fang M, Yeh KC, Chen C, Yeh TK, Hsieh SH, Hsu JTA, Liao C, Chao YS, Hsieh HP (2010) Design and synthesis of tetrahydropyridothieno[2,3-d]pyrimidine scaffold based epidermal growth factor receptor (EGFR) kinase inhibitors: the role of side chain chirality and Michael acceptor group for maximal potency. *J Med Chem* 53:7316–7326
- Butturini E, Carcereri DPA, Chiavegato G, Rigo A, Cavalieri E, Darra E, Mariotto S (2013) Mild oxidative stress induces S-glutathionylation of STAT3 and enhances chemosensitivity of tumoural cells to chemotherapeutic drugs. *Free Radical Bio Med* 65:1322–1330
- Dungo RT, Keating GM (2013) Afatinib: first global approval. *Drugs* 73:1503–1515
- Byrd JC, Furman RR, Coutre SE, Flinn IW, Burger JA, Blum KA, Grant B, Sharman JP, Coleman M, Wierda WG (2013) Targeting BTK with ibrutinib in relapsed chronic lymphocytic leukemia. *New Engl J Med* 369:32–42
- Greig SL (2016) Osimertinib: first global approval. *Drugs* 76:263–273