Synthesis and Antitumor Activity of the Thiazoline and Thiazine Multithioether

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ABSTRACT
A series of novel multithioether derivatives were synthesized by the combination of thiazoline and thiazine with dibromides and their structures were characterized by IR, 1H NMR, MS and elemental analysis. The synthesized derivatives were tested for antitumor activity.

Keywords: Thiazoline; Thiazine; Multithioether; Synthesis; Antitumor Activity

1. Introduction
Nitrogen-containing five- or six-membered heterocyclic compounds such as oxazolines, thiazolines and thiazines are of great interest to organic chemists, because they are present in various natural compounds having interesting bioactivities [1-3]. Furthermore, the optically active heterocyclic compounds have been successfully used in asymmetric synthesis as chiral templates [4,5] or ligands [6-9]. Herein, we reported an efficient synthesis of some thiazoline and thiazine multithioethers in a friendly solvent-ethanol and explored the biological activities of the obtained target products against A549 (human lung cancer cell) and Bcap-37 (human breast cancer cell).

2. Results and Discussion
The raw materials thiazolidine-2-thione (1) and 1,3-thiazinane-2-thione (2) were synthesized according to the literature method [10,11]. Then they were treated with different dibromides under different reaction conditions. In the process of experiments, different reaction factors were examined to obtain the optimum reaction conditions such as the reaction temperature, the reaction time, employed bases and solvent and mixing sequence. The results showed that the start materials thiazolidine-2-thione (1) and 1,3-thiazinane-2-thione (2) should be activated by solid KOH and dissolved firstly in order to ensure that the subsequent reaction was fully carried out. The general reaction procedure was as follows (Scheme 1). To an anhydrous ethanol solution (3 mL) of the heterocycle 2-thione (4.4 mmol) (1 or 2), KOH (0.25 g, 4.4 mmol) was added. The suspension was stirred until the solution was clarified. Then, the ethanol solution (2 mL) of different dibromides (3) (2.1 mmol) was slowly added and a white precipitate was obtained gradually. Then the precipitates were filtered, washed with ethanol, and then dried after. The crude products were recrystallized from water and white products were obtained.

The target compounds were characterized by the spectra. Spectroscopic data were in agreement with the desired structures. For example, in terms of the 1H NMR spectra of compound 4, the two protons of the methylene attached to S atom appeared as a singlet at 4.34 and 4.47 ppm in compounds 4e and 4f, respectively; which the two protons of the methylene were splitted as a triplet and a doublet at 3.26 and 3.74 ppm in compounds 4c and 4d respectively. The data of IR, MS and element analysis further confirmed their structures of the target products.

3. Biological Tests
The in vitro antitumor activities of the synthesized target compounds against A-549 (human lung cancer cell) and Bcap-37 (human breast cancer cell) were evaluated by the standard MTT assay (Table 1) [12]. The data revealed that compounds 4g and 5g possessed higher antitumor activities. IC50 values against A-549 and Bcap-37 of compound 4g were 22.58 and 19.41 μg/mL, corresponding the values of compound 5g were 8.26 and 9.30 μg/mL, respectively. As compared with compounds 4a - 4g, compounds 5a - 5g exhibit higher antitumor activities.

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Scheme 1. Synthesis of the thiazoline and thiazine multithioether.

Table 1. IC₅₀ data of A-549 and Bcap-37 of in vitro for the target compounds 4a - 4g and 5a - 5g.

<table>
<thead>
<tr>
<th>Compd.</th>
<th>F.W.</th>
<th>IC₅₀ (µg/mL)</th>
<th>Compd.</th>
<th>F.W.</th>
<th>IC₅₀ (µg/mL)</th>
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<tr>
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<td></td>
<td>A-549</td>
<td>Bcap-37</td>
<td></td>
<td>A-549</td>
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<tr>
<td>4a</td>
<td>264</td>
<td>105.02</td>
<td>105.23</td>
<td>5a</td>
<td>292</td>
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<tr>
<td>4b</td>
<td>278</td>
<td>74.36</td>
<td>80.30</td>
<td>5b</td>
<td>306</td>
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<tr>
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<td>30.46</td>
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<tr>
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<td>41.79</td>
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<tr>
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<td>30.88</td>
<td>5f</td>
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<tr>
<td>4g</td>
<td>340</td>
<td>22.58</td>
<td>19.41</td>
<td>5g</td>
<td>368</td>
</tr>
</tbody>
</table>

4. Experimental

All chemicals and solvents were purchased from Sinopharm, Beijing Chemical Plant. Melting points were recorded on a Digital Melting Point Apparatus. Elemental analysis of carbon, hydrogen and nitrogen were determined on a Flash-1112 series elemental analyser. IR spectra (KBr) were recorded on a Perkin Elmer FTIR. The ¹H NMR and spectra were measured at 25°C on a Bruker Avance-500 NMR spectrometer respectively in DMSO-d₆ solution using TMS as an internal reference. MS spectra were recorded on an Agilent 1100 LC/MS.

Synthesis of thiazoline multithioethers 4a - 4g and 5a - 5g:

Synthesis of 1,2-Bis(2-thiazolin-2-ylsulfanyl) ethane (4a). To an anhydrous ethanol solution (3 mL) of the heterocyclic 2-thione (4.4 mmol), KOH (0.25 g, 4.4 mmol) was added. The suspension was stirred until the solution was clarified. Then, the ethanol solution (2 mL) of different dibromides (3a - 3g) (2.1 mmol) was slowly added and a white precipitate was obtained gradually, continue to react to 72 h. Then the precipitates were filtered, washed with ethanol, and then dried. The crude products were recrystallized from water and white products were obtained (4a). Yield (0.37 g, 69.5%); M.p. 125°C - 127°C.

The other compounds of this series 4b - 4g and 5a - 5g were prepared adopting the above procedure.

The physical and spectral data of the compounds 4a - 4g and 5a - 5g was clarified.

1,2-Bis(2-thiazolin-2-ylsulfanyl) ethane (4a):
IR spectrum, ν, cm⁻¹: 2984, 2952, 2848(CH), 1567 (C=N), 1450 (2CH). ¹H NMR spectrum (500 MHz, DMSO-d₆), δ, ppm (J, Hz): 4.22 (4H, t, CH₂), 3.44 (4H, t, CH₂), 3.41 (4H, t, CH₂), 3.41 (4H, t, CH₂), MS, m/z: 263 (M⁺), 265 (M + 2). Found, %: C 36.64; H 4.45; N 10.66; S 48.70. Calculated,
%: C 36.50; H 4.56; N 10.65; S 48.67.

1,3-Bis(2-thiazolin-2-ylsulfanyl)propane(4b):
Yield, 56.2%; mp 211°C - 212°C; IR spectrum, ν, cm⁻¹: 3025, 2930, 2852(CH), 1572(C≡N), 1423(γ(CH3)). ¹H NMR spectrum (500 MHz, DMSO-d₆), δ, ppm (J, Hz): 7.82 (8H, m, CH₂), 4.67 (2H, CH₂), 3.98 (4H, t, CH₂); MS, m/z: 277 (M⁺), 279 (M + 2). Found, %: C 38.96; H 5.07; N 10.07; S 46.30. Calculated, %: C 38.99; H 5.05; N 10.11; S 46.21.

1,4-Bis(2-thiazolin-2-ylsulfanyl)butane(4c):
Yield, 71.8%; mp 108°C - 110°C; IR spectrum, ν, cm⁻¹: 3026, 2930(CH), 1576(C≡N), 1432(γ(CH3)). ¹H NMR spectrum (500 MHz, DMSO-d₆), δ, ppm (J, Hz): 4.23 (4H, t, CH₂), 3.41 (4H, t, CH₂), 3.26 (4H, t, CH₂), 1.93 (4H, m, CH₂); MS, m/z: 291 (M⁺), 293 (M + 2). Found, %: C 41.31; H 5.60; N 9.58; S 43.97. Calculated, %: C 41.24; H 5.51; N 9.62; S 43.97.

trans-1,4-Bis(2-thiazolin-2-ylsulfanyl)butene(4d):
Yield, 89.9%; mp 48°C - 52°C; IR spectrum, ν, cm⁻¹: 3024, 2944(CH), 1560(C≡N), 1402(γ(CH3)). ¹H NMR spectrum (500 MHz, DMSO-d₆), δ, ppm (J, Hz): 7.88 (4H, m, ArH), 4.34 (4H, s, CH₂), 4.23 (4H, t, CH₂), 3.41 (4H, t, CH₂); MS, m/z: 289 (M⁺), 291 (M + 2). Found, %: C 41.50; H 4.87; N 9.70; S 44.25. Calculated, %: C 41.52; H 4.84; N 9.69; S 44.29.

1,4-Bis(2-thiazolin-2-ylsulfanyl)toluene(4e):
Yield, 61.8%; mp 112°C - 114°C; IR spectrum, ν, cm⁻¹: 3062, 2932, 2844(CH), 1592(C≡N), 1423(γ(CH3)). ¹H NMR spectrum (500 MHz, DMSO-d₆), δ, ppm (J, Hz): 7.28 (4H, m, ArH), 4.34 (4H, s, CH₂), 4.23 (4H, t, CH₂), 3.41 (4H, t, CH₂); MS, m/z: 339 (M⁺), 341 (M + 2). Found, %: C 49.55; H 4.75; N 8.22; S 37.79. Calculated, %: C 49.56; H 4.72; N 8.26; S 37.76.

1,2-Bis(2-thiazolin-2-ylsulfanyl)toluene(4f):
Yield, 58%; mp 112°C - 114°C; IR spectrum, ν, cm⁻¹: 3062, 2982, 2846(CH), 1556(C≡N), 1422(γ(CH3)). ¹H NMR spectrum (500 MHz, DMSO-d₆), δ, ppm (J, Hz): 7.26 (2H, m, ArH), 4.47 (4H, s, CH₂), 4.22 (4H, t, CH₂), 3.99 (4H, t, CH₂); MS, m/z: 340 (M⁺), 342 (M + 2). Found, %: C 49.40; H 4.72; N 8.25; S 37.62. Calculated, %: C 49.41; H 4.71; N 8.23; S 37.65.

1,3-Bis(2-thiazolin-2-ylsulfanyl)toluene(4g):
Yield, 61.7%; mp 62°C - 63°C; IR spectrum, ν, cm⁻¹: 3061, 2982, 2846(CH), 1556(C≡N), 760. ¹H NMR spectrum (500 MHz, DMSO-d₆), δ, ppm (J, Hz): 7.26 (4H, m, ArH), 4.34 (4H, s, CH₂), 4.23 (4H, t, CH₂), 3.41 (4H, t, CH₂); MS, m/z: 339 (M⁺), 341 (M + 2). Found, %: C 49.53; H 4.70; N 8.22; S 37.79. Calculated, %: C 49.55; H 4.72; N 8.27; S 37.78.

1,2-Bis(4,5-Dihydro-1,3-thiazin-2-ylsulfanyl)ethane(5a):
Yield, 71.3%; mp 72°C - 73°C; IR spectrum, ν, cm⁻¹: 2940, 2835(CH), 1602(C≡N), 1452(γ(CH3)). ¹H NMR spectrum (500 MHz, DMSO-d₆), δ, ppm (J, Hz): 3.76 (4H, t, CH₂), 3.19 (4H, t, CH₂), 3.08 (4H, t, CH₂), 1.92 (4H, t, CH₂), 1.89 (4H, m, CH₂); MS, m/z: 291 (M⁺), 293 (M + 2). Found, %: C 41.21; H 5.51; N 9.59; S 43.95. Calculated, %: C 41.23; H 5.50; N 9.64; S 43.96.

1,3-Bis(4,5-Dihydro-1,3-thiazin-2-ylsulfanyl)propane(5b):
Yield, 27.02%; mp 267°C - 268°C; IR spectrum, ν, cm⁻¹: 3025, 2850(CH), 1590(C≡N), 1425(γ(CH3)). ¹H NMR spectrum (500 MHz, DMSO-d₆), δ, ppm (J, Hz): 2.92(8H, m, CH₂), 2.67(2H, m, CH₂), 2.08(4H, t, CH₂); MS, m/z: 305 (M⁺), 307 (M + 2). Found, %: C 43.29; H 5.88; N 9.22; S 42.01. Calculated, %: C 43.28; H 5.90; N 9.18; S 41.97.
CH$_2$), 1.90 (4H, m, CH$_2$). MS, m/z: 367 (M$^+$), 369 (M + 2). Found, %: C 52.34; H 5.42; N 7.68; S 34.86. Calculated, %: C 52.34; H 5.43; N 7.65; S 34.88.

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REFERENCES


