

# Supporting Information

## Synthesis and Bioactivity of Thiazolethioacetamides as Potential Metallo- $\beta$ -Lactamase Inhibitors

YiLin Zhang<sup>1,\*</sup>, Yong Yan<sup>1</sup>, Xuejun Wang<sup>1</sup>, Kewu Yang<sup>2</sup>

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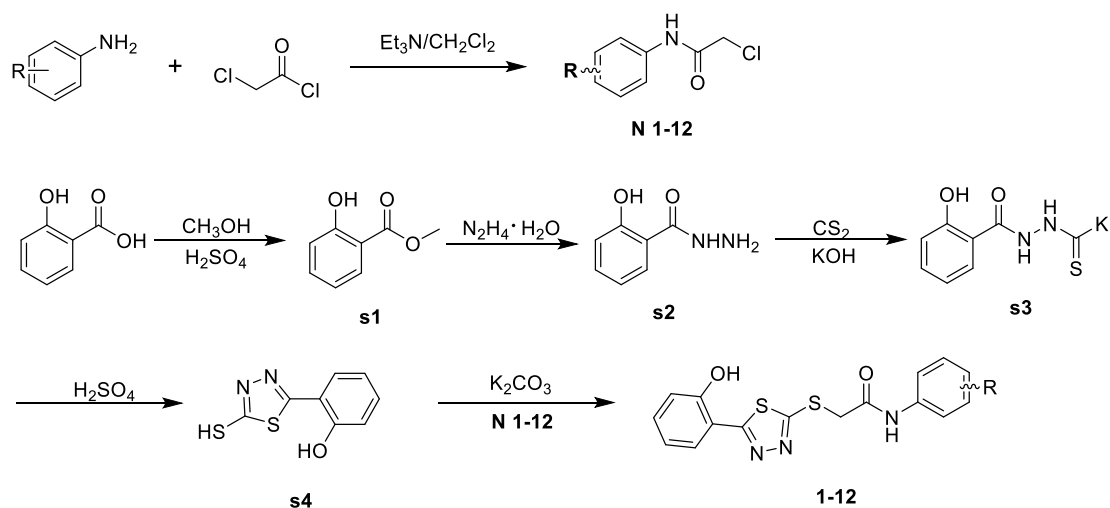
## Synthetic Experimental Procedures

### General

General chemicals were purchased from TCI and were used without further purification. All antibiotics used were purchased from Sigma-Aldrich.  $^1\text{H}$  NMR and  $^{13}\text{C}$  NMR spectra were recorded with a Bruker DRX 600 MHz spectrometer. The peaks patterns are indicated as follows: s, singlet; d, doublet; t, triplet; q, quartet; dd, doublet doublet; m, multiplet. The spectra were recorded with TMS as internal standard. Coupling constants (J) were reported in hertz (Hz). Chemical shifts were given in part per million (ppm) on the delta scale. Analytical Thin Layer Chromatography (TLC) was carried out on silica gel F<sub>254</sub> plates with visualization by ultraviolet radiation. HRMS spectra were recorded on a Bruker MicroTOF-Q II mass spectrometer. Inhibition studies were performed on an Agilent-8453 UV-visible spectrometer.

### Synthesis and characterization

The synthetic route of the twelve thiazolethioacetamides was shown in Scheme 1. N-substituted-2-chloroacetamides (**N 1-12**) were first prepared by acylation between substituted anilines and chloroacetyl chloride. The methyl-2-hydroxybenzoate (**s1**) were prepared by esterifying of salicylic acid and converted into hydrazides **s2** by condensing with hydrazine. The hydrazides reacted with CS<sub>2</sub> under basic condition to give **s3**, and then stirred with H<sub>2</sub>SO<sub>4</sub> in ice-water bath to afford 2-(5-mercapto-1,3,4-thiadiazol-2-yl)phenol (**s4**).



**Scheme 1. Synthetic route of halogen-substituted thiazolethioacetamides**

A solution of 2-(5-mercapto-1,3,4-thiadiazol-2-yl)phenol (**s4**) (3 mmol) and K<sub>2</sub>CO<sub>3</sub> (3.6 mmol) dissolved in H<sub>2</sub>O (15 mL) were added in a 50 mL three-neck round bottomed flask, kept stirring for 30 min. After N-substituted-2-chloroacetamides (**N1-12**) (3 mmol) dissolved in hot ethanol (5 mL) was added drop wise, the reaction mixture was heated to reflux for 6 h. Reaction mixture was cooled to RT and neutralized

with 5 M HCl to a pH approximately 7.0. The resulting white solid was collected by filtration, washed with H<sub>2</sub>O repeatedly (3×80 mL) and dried in vacuo to obtain **1-12**.

## **<sup>1</sup>H and <sup>13</sup>C NMR data of halogen-substituted triazolethioacetamides:**

### **1. N-(4-chlorophenyl)-5-(5-phenyl-4H-1,2,4-thiazolyl)thioacetamide (1)**

White powder, yield 72.5 %, <sup>1</sup>H NMR (600 MHz, DMSO-d<sub>6</sub>): δ 10.90 (s, 1H), 7.84 (d, J = 8.2 Hz, 1H), 7.61 (d, J = 8.6 Hz, 2H), 7.44 (d, J = 8.6 Hz, 2H), 7.42-7.36 (m, 2H), 6.97 (d, J = 8.3 Hz, 1H), 4.23 (s, 2H). <sup>13</sup>C NMR (151 MHz, DMSO-d<sub>6</sub>): δ 171.11, 168.63, 163.32, 157.74, 133.73, 133.41, 130.29, 129.46, 129.28, 122.69, 119.42, 117.14, 114.91, 33.30. HRMS [M+Na]<sup>+</sup> (m/z) for C<sub>17</sub>H<sub>13</sub>ClN<sub>2</sub>O<sub>2</sub>S<sub>2</sub>: calcd. 399.9957, obsd. 399.9861.

### **2. N-(3-chlorophenyl)-5-(5-phenyl-4H-1,2,4-thiazolyl)thioacetamide (2)**

White powder, yield 68.1 %, <sup>1</sup>H NMR (600 MHz, DMSO-d<sub>6</sub>): δ 11.32 (s, 1H), 7.86 (s, 1H), 7.56 (s, 3H), 7.41 (s, 2H), 7.00 (s, 1H), 6.94 (s, 1H), 4.23 (s, 2H). <sup>13</sup>C NMR (151 MHz, DMSO-d<sub>6</sub>): δ 171.10, 163.31, 163.03, 157.98, 136.21, 133.49, 133.20, 130.83, 129.34, 128.93, 128.50, 127.40, 119.27, 117.21, 116.49, 33.34. HRMS [M+Na]<sup>+</sup> (m/z) for C<sub>17</sub>H<sub>13</sub>ClN<sub>2</sub>O<sub>2</sub>S: calcd. 399.9957, obsd. 399.9870.

### **3. N-(3,4-dichlorophenyl)-5-(5-phenyl-4H-1,2,4-thiazolyl)thioacetamide (3)**

Yellow powder, yield 63.8 %, <sup>1</sup>H NMR (600 MHz, DMSO-d<sub>6</sub>): δ 10.92 (s, 1H), 7.83 (dd, J = 13.1, 8.3 Hz, 2H), 7.78 (d, J = 1.6 Hz, 1H), 7.45 (dd, J = 8.6, 2.3 Hz, 1H), 7.39 (t, J = 7.7 Hz, 1H), 7.00 (d, J = 8.1 Hz, 1H), 6.92 (t, J = 7.6 Hz, 1H), 4.22 (s, 2H). <sup>13</sup>C NMR (151 MHz, DMSO-d<sub>6</sub>): δ 171.38, 163.50, 158.80, 157.96, 135.09, 133.96, 132.16, 131.84, 131.58, 131.00, 129.89, 129.47, 119.91, 117.56, 116.90, 33.86. HRMS [M+H<sub>2</sub>O] (m/z) for C<sub>16</sub>H<sub>11</sub>Cl<sub>2</sub>N<sub>3</sub>O<sub>2</sub>S<sub>2</sub>: calcd. 428.9713, obsd. 428.9940.

### **4. N-(2,4-dichlorophenyl)-5-(5-phenyl-4H-1,2,4-thiazolyl)thioacetamide (4)**

Yellow powder, yield 67.6 %, <sup>1</sup>H NMR (600 MHz, DMSO-d<sub>6</sub>): δ 11.87 (s, 1H), 10.89 (s, 1H), 7.90-7.77 (m, 2H), 7.63-7.53 (m, 2H), 7.36 (t, J = 7.7 Hz, 1H), 6.91 (d, J = 34.7 Hz, 1H), 4.36 (d, J = 15.7 Hz, 1H), 4.25 (d, J = 17.2 Hz, 1H). <sup>13</sup>C NMR (151 MHz, DMSO-d<sub>6</sub>): δ 170.84, 163.73, 158.21, 157.65, 135.58, 133.59, 133.00, 132.04, 130.27, 129.20, 119.92, 119.86, 117.59, 117.53, 116.70, 29.47. HRMS [M+Na]<sup>+</sup> (m/z) for C<sub>16</sub>H<sub>11</sub>Cl<sub>2</sub>N<sub>3</sub>O<sub>2</sub>S: calcd. 433.9505, obsd. 433.9440.

### **5. N-(4-chloro-2-nitrophenyl)-5-(5-phenyl-4H-1,2,4-thiazolyl)thioacetamide (5)**

White powder, yield 57.5 %, <sup>1</sup>H NMR (600 MHz, DMSO-d<sub>6</sub>): δ 9.83 (s, 1H), 7.74 (s, 1H), 7.73 (s, 1H), 7.67 (s, 1H), 7.66 (s, 1H), 7.43 (s, 1H), 7.09 (d, J = 8.3 Hz, 2H), 4.08 (s, 2H). <sup>13</sup>C NMR (151 MHz, DMSO-d<sub>6</sub>): δ 170.58, 157.72, 156.24, 146.02, 136.50, 134.94, 134.10, 133.31, 126.71, 125.79, 125.51,

119.77, 119.43, 117.13, 33.51. HRMS  $[M+Na]^+$  (m/z) for  $C_{16}H_{11}ClN_4O_4S_2$ : calcd. 444.9808, obsd. 444.0481.

#### 6. N-(5-chloro-2-nitrophenyl)-5-(5-phenyl-4H-1,2,4-thiazolyl)thioacetamide (6)

Brown powder, yield 81.4 %,  $^1H$  NMR (600 MHz, DMSO- $d_6$ ):  $\delta$  10.93 (s, 1H), 8.30 (d, J = 8.8 Hz, 1H), 7.91 (d, J = 8.6 Hz, 1H), 7.83 (d, J = 7.7 Hz, 1H), 7.40 (t, J = 7.0 Hz, 1H), 7.02-6.98 (m, 1H), 6.97 (d, J = 8.1 Hz, 1H), 6.92 (t, J = 7.5 Hz, 1H), 4.42 (d, J = 17.5 Hz, 1H), 4.31 (d, J = 17.3 Hz, 1H).  $^{13}C$  NMR (151 MHz, DMSO- $d_6$ ):  $\delta$  170.50, 163.31, 157.72, 156.19, 144.28, 141.51, 139.66, 139.05, 131.62, 131.00, 129.23, 127.56, 119.44, 117.14, 116.22, 33.52. HRMS  $[M+Na]^+$  (m/z) for  $C_{16}H_{11}ClN_4O_4S_2$ : calcd. 444.9808, obsd. 444.9692.

#### 7. N-(2-chloro-4-nitrophenyl)-5-(5-phenyl-4H-1,2,4-thiazolyl)thioacetamide (7)

Yellow powder, yield 75.8 %,  $^1H$  NMR (600 MHz, DMSO- $d_6$ ):  $^1H$  NMR (600 MHz, DMSO- $d_6$ ):  $\delta$  10.95 (s, 1H), 8.63 (s, 1H), 8.39 (d, J = 8.9 Hz, 1H), 8.03 (d, J = 8.8 Hz, 1H), 7.83 (s, 1H), 7.40 (t, J = 7.2 Hz, 1H), 6.97 (d, J = 8.1 Hz, 1H), 6.92 (t, J = 7.5 Hz, 1H), 4.43 (d, J = 17.1 Hz, 1H), 4.27 (d, J = 17.3 Hz, 1H).  $^{13}C$  NMR (151 MHz, DMSO- $d_6$ ):  $\delta$  170.44, 157.73, 157.06, 156.28, 146.90, 139.55, 133.58, 131.53, 129.32, 126.58, 126.10, 119.59, 119.44, 117.14, 117.00, 33.55. HRMS  $[M+Na]^+$  (m/z) for  $C_{16}H_{11}ClN_4O_4S_2$ : calcd. 444.9808, obsd. 444.9676.

#### 8. N-(4-(trifluoromethoxy)phenyl)-5-(5-phenyl-4H-1,2,4-triazolyl)thioacetamide (8)

White powder, yield 87.4%,  $^1H$  NMR (600 MHz, DMSO- $d_6$ ):  $\delta$  7.86 (d, J = 8.0 Hz, 1H), 7.59-7.53 (m, 1H), 7.39 (t, J = 7.7 Hz, 1H), 7.00 (d, J = 8.2 Hz, 1H), 6.92 (t, J = 7.5 Hz, 1H), 4.25 (s, 2H).  $^{13}C$  NMR (151 MHz, DMSO- $d_6$ ):  $\delta$  171.19, 163.31, 157.85, 148.15, 133.83, 133.51, 130.56, 129.32, 121.84, 121.01, 119.34, 117.19, 116.41, 33.32. HRMS  $[M+Na]^+$  (m/z) for  $C_{17}H_{12}F_3N_3O_3S_2$ : calcd. 450.0170, obsd. 450.0049.

#### 9. N-(4-fluorophenyl)-5-(5-phenyl-4H-1,2,4-thiazolyl)thioacetamide (9)

White powder, yield 56.9%,  $^1H$  NMR (600 MHz, DMSO- $d_6$ ):  $\delta$  11.91 (s, 1H), 10.90 (s, 1H), 7.84 (d, J = 7.9 Hz, 1H), 7.45 (dd, J = 8.9, 5.0 Hz, 2H), 7.38 (dt, J = 13.1, 5.5 Hz, 3H), 6.97 (d, J = 8.2 Hz, 1H), 6.93 (t, J = 7.5 Hz, 1H), 4.23 (s, 2H).  $^{13}C$  NMR (151 MHz, DMSO- $d_6$ ):  $\delta$  171.28, 163.35, 162.66, 161.03, 159.57, 157.78, 133.58, 131.10, 130.64, 129.28, 119.43, 117.16, 116.17, 33.22. HRMS  $[M+Na]^+$  (m/z) for  $C_{16}H_{12}FN_3O_2S_2$ : calcd. 384.0253, obsd. 384.0151.

#### 10. N-(3-fluorophenyl)-5-(5-phenyl-4H-1,2,4-thiazolyl)thioacetamide (10)

White powder, yield 69.7 %,  $^1H$  NMR (600 MHz, DMSO- $d_6$ ):  $\delta$  7.83 (dd, J = 7.9, 1.6 Hz, 1H), 7.58 (dd, J = 15.1, 8.4 Hz, 1H), 7.40-7.36 (m, 1H), 7.36-7.32 (m, 2H), 7.27 (d, J = 8.3 Hz, 1H), 6.98 (d, J = 7.6 Hz,

1H), 6.90 (t, J = 7.2 Hz, 1H), 4.23 (s, 2H). <sup>13</sup>C NMR (151 MHz, DMSO-d<sub>6</sub>): δ 171.04, 163.30, 162.82, 161.20, 158.07, 136.31, 133.39, 130.75, 129.35, 124.81, 119.11, 117.20, 116.62, 115.94, 115.80, 33.26. HRMS [M+Na]<sup>+</sup> (m/z) for C<sub>16</sub>H<sub>12</sub>FN<sub>3</sub>O<sub>2</sub>S<sub>2</sub>: calcd. 384.0253, obsd. 384.0161.

#### **11. N-(2-fluorophenyl)-5-(5-phenyl-4H-1,2,4-thiazolyl)thioacetamide (11)**

White powder, yield 56.9 %, <sup>1</sup>H NMR (600 MHz, DMSO-d<sub>6</sub>): δ 11.90 (s, 1H), 10.93 (s, 1H), 7.83 (d, J = 8.0 Hz, 1H), 7.57 (dd, J = 12.5, 7.0 Hz, 1H), 7.53 (t, J = 7.5 Hz, 1H), 7.45 (t, J = 9.2 Hz, 1H), 7.39 (d, J = 8.2 Hz, 2H), 6.97 (d, J = 7.9 Hz, 1H), 6.92 (t, J = 7.5 Hz, 1H), 4.39 (d, J = 17.2 Hz, 1H), 4.29 (d, J = 17.2 Hz, 1H). <sup>13</sup>C NMR (151 MHz, DMSO-d<sub>6</sub>): δ 170.69, 163.43, 158.25, 157.90, 156.54, 133.61, 131.60, 130.94, 129.16, 125.26, 122.23, 119.39, 117.17, 116.62, 116.19, 33.14. HRMS [M+Na]<sup>+</sup> (m/z) for C<sub>16</sub>H<sub>12</sub>FN<sub>3</sub>O<sub>2</sub>S<sub>2</sub>: calcd. 384.0253, obsd. 384.0145.

#### **12. N-(2,6-difluorophenyl)-5-(5-phenyl-4H-1,2,4-triazolyl)thioacetamide (12)**

White powder, yield 72.2%, <sup>1</sup>H NMR (600 MHz, DMSO-d<sub>6</sub>): δ 11.89 (s, 1H), 11.01 (s, 1H), 7.84 (s, 1H), 7.66 (s, 1H), 7.39 (d, J = 9.1 Hz, 3H), 6.97 (s, 1H), 6.92 (t, J = 7.4 Hz, 1H), 4.49 (s, 2H). <sup>13</sup>C NMR (151 MHz, DMSO-d<sub>6</sub>): δ 170.21, 163.62, 158.96, 158.04, 157.28, 156.93, 133.72, 132.54, 129.16, 119.42, 117.24, 116.12, 112.79, 33.10. HRMS [M+Na]<sup>+</sup> (m/z) for C<sub>16</sub>H<sub>11</sub>F<sub>2</sub>N<sub>3</sub>O<sub>2</sub>S<sub>2</sub>: calcd. 402.0159, obsd. 402.0032.