Med Chem Res (2013) 22:4125–4132
DOI 10.1007/s00044-012-0417-z

MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Synthesis and potential antibacterial activity of new rhodanine-3-acetic acid derivatives

Jing Miao · Chang-Ji Zheng · Liang-Peng Sun · Ming-Xia Song · Li-Li Xu · Hu-Ri Piao

Received: 31 July 2012 / Accepted: 11 December 2012 / Published online: 21 December 2012

Abstract A series of rhodanine-3-acetic acid derivatives were synthesized and investigated for their antibacterial activity against gram-positive bacteria including multi-drug-resistant clinical isolates. Among these compounds, **6k** with a MIC of 2 μg/mL was as active as the standard drug (norfloxacin) but less active than oxacillin against *S. aureus*. The compounds **6b**, **6e**, **6h**, **6k**, **6n**, and **6u** presented better activities against multidrug-resistant *Staphylococcus aureus* than the standard drugs (norfloxacin and oxacillin), especially **6k** with a MIC of 1 μg/mL. However, none of the compounds were active against gram-negative bacteria at 64 μg/mL.

Keywords Rhodanine-3-acetic acid · Antibacterial activity · Minimal inhibitory concentration (MIC)

Introduction

Increasing resistance of microorganisms to currently available antimicrobial drugs is a major cause of morbidity and mortality throughout the world. Therefore, it is imperative to discover new classes of antibiotics. Rhodanine-3-acetic acid was prepared by Körner in 1908 and since that time, it has been prepared and studied as a potential antimycobacterial (Sortino *et al.*, 2007; Liu *et al.*, 2007), antifungal (Terashima *et al.*, 1984; Yoshioka *et al.*, 1989; Momose *et al.*, 1991; Desai *et al.*, 2008; Dolezel *et al.*, 2009), pesticidal (Inamori *et al.*, 1992; Muro *et al.*, 1996), antihypertensive (Frankov *et al.*, 1985), and antineoplastic (Chandrappa *et al.*, 2009; Havrylyuk *et al.*, 2009) agent. In our previous work (Chen *et al.*, 2010), we reported that 2-((5*E*)-5-(4-((*E*)-3-(2,4-dichlorophenyl)-3-oxoprop-1-enyl)benzylidene)-4-oxo-2-thioxothiazolidin-3-yl) acetic acid (lead compound) showed strong activity against gram-positive strains (including multidrug-resistant clinical isolates). Modification of this compound is described in this study (Fig. 1), where the rhodanine-3-acetic acid moiety was reserved, the chalcone moiety was replaced with a 6-benzyloxynaphthalene moiety, and different substituents were tested on the phenyl ring of the benzyl group. Twenty-five rhodanine-3-acetic acid derivatives were synthesized and evaluated for their antimicrobial activity in vitro.

Experimental

Materials

Melting points were determined in open capillary tubes and were uncorrected. Reaction courses were monitored by TLC on silica gel-precoated F254 Merck plates. Developed plates were examined with UV lamps (254 nm). IR spectra were recorded (in KBr) on a FTIR1730. ^{1}H NMR spectra were measured on a Bruker AV-300 spectrometer using TMS as the internal standard. Mass spectra were measured on an HP1100LC (Agilent Technologies, USA). Elemental analyses for C, H, N, and S were within ±0.4 % of the theoretical values and were carried out on a 204Q CHN Rapid Analyzer (Perkin-Elmer, USA). The major chemicals were purchased from Sigma-Aldrich and Fluka.

J. Miao · C.-J. Zheng · L.-P. Sun · M.-X. Song · L.-L. Xu · H.-R. Piao (✉)
Key Laboratory of Natural Resources and Functional Molecules of the Changbai Mountain, Affiliated Ministry of Education, Yanbian University College of Pharmacy, Yanji 133002, Jilin Province, People's Republic of China
e-mail: piaohuri@yahoo.com.cn

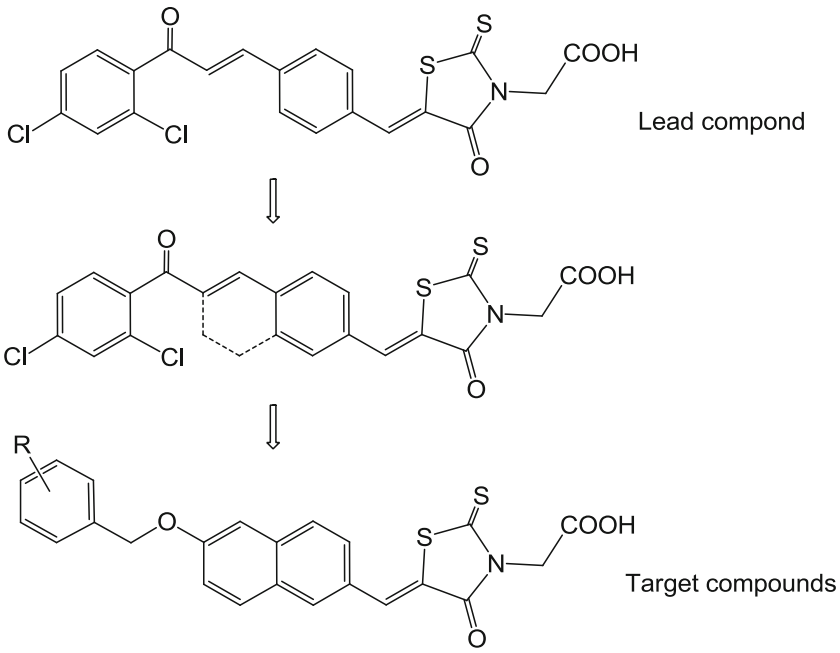


Fig. 1 Lead compound and structure-based design of target compounds

Methods

Synthesis

*General procedure for the synthesis of compound **3***

To a solution of compound **1** (1.0 mmol) and rhodanine-3-acetic acid **2** (1.0 mmol) in absolute ethanol (8.0 mL) was added acetic acid and piperidine. The mixture was stirred for 4–6 h at 40–50 °C. After the solution was cooled, the resulting reaction mixture was filtered off and crude product was purified by 1,4-dioxane to afford pure product **3**.

*(Z)-2-(5-((6-Hydroxynaphthalen-2-yl)methylene)-4-oxo-2-thioxothiazolidin-3-yl)acetic acid (**3**)* Yield 83 %; m.p. 263–264 °C. IR (KBr) cm^{-1}: 3423 (OH), 1705 (C=O). ^1H NMR (DMSO-d_6, 300 MHz, ppm): δ 9.92 (s, 1H, OH), 8.09 (s, 1H), 7.99–7.75 (m, 3H), 7.57 (d, $J = 8.6$ Hz, 1H), 7.18 (d, $J = 6.6$ Hz, 2H), 8.09–7.17 (m, 7H, Ar–H), 4.41 (s, 2H, CH_2). ^{13}C NMR (DMSO-d_6, 75 MHz, ppm): δ 193.15, 167.44, 166.83, 158.22, 135.60, 133.20, 132.23, 130.81, 127.25, 126.49, 120.57, 120.06, 108.95, 47.72, MS *m/z* 346 (M+1). Anal. Calcd. for $C_{16}H_{11}NO_4S_2$: C, 55.64; H, 3.21; N, 4.06; S, 18.57. Found: C, 55.57; H, 3.19; N, 4.02; S, 18.51.

*General procedure for the synthesis of compounds **6a–6x***

To a solution of the respective compounds **5a–5x** (1.0 mmol) in absolute ethanol (8.0 mL) was added rhodanine-3-acetic acid **2** (1.0 mmol), acetic acid, and piperidine. The mixture was stirred for 4–6 h at 40–50 °C. After the solution was cooled, the resulting reaction mixture was filtered off and crude product was purified by 1,4-dioxane to afford pure products **6a–6x**. The yield, melting point, and spectral data of each compound are given below.

*(Z)-2-(5-((6-(Benzyloxy)naphthalen-2-yl)methylene)-4-oxo-2-thioxothiazolidin-3-yl)acetic acid (**6a**)* Yield 87 %; m.p. 291–292 °C. IR (KBr) cm^{-1}: 3419 (OH), 1707 (C=O). ^1H NMR (DMSO-d_6, 300 MHz, ppm): δ 7.80 (s, 1H), 7.64 (d, $J = 8.6$ Hz, 3H), 7.54–7.27 (m, 6H), 7.21 (d, $J = 8.6$ Hz, 2H), 7.80–7.20 (m, 12H, Ar–H), 5.21 (s, 2H, CH_2), 4.51 (s, 2H, CH_2). ^{13}C NMR (DMSO-d_6, 75 MHz, ppm): δ 193.17, 169.19, 166.96, 157.77, 143.58, 136.10, 132.74, 128.75, 128.17, 118.86, 107.46, 66.71, 46.89. MS *m/z* 436 (M+1). Anal. Calcd. for $C_{23}H_{17}NO_4S_2$: C, 63.43; H, 3.93; N, 3.22; S, 14.73. Found: C, 63.39; H, 3.91; N, 3.19; S, 14.75.

*(Z)-2-(5-((6-((4-Methylbenzyl)oxy)naphthalen-2-yl)methylene)-4-oxo-2-thioxothiazolidin-3-yl)acetic acid (**6b**)* Yield 89 %; m.p. 287–288 °C. IR (KBr) cm^{-1}: 3421 (OH), 1701 (C=O). ^1H NMR (DMSO-d_6, 300 MHz, ppm): δ 8.17 (s, 1H), 7.99 (d, $J = 12.0$ Hz, 1H), 7.90–7.95 (m, 2H), 7.22 (d, $J = 6.0$ Hz, 2H), 8.17–7.21 (m, 11H, Ar–H), 5.20 (s, 2H, CH_2), 4.49 (s, 2H, CH_2), 2.32 (s, 3H, CH_3). ^{13}C NMR (DMSO-d_6, 75 MHz, ppm): δ 193.12, 168.43, 167.16, 158.91, 142.78, 138.19, 135.45, 132.84, 131.67, 129.18, 128.53, 127.64, 118.07, 116.05, 108.74, 66.46, 47.03, 20.56. MS *m/z* 450 (M+1). Anal. Calcd. for $C_{24}H_{19}NO_4S_2$: C, 64.12; H, 4.26; N, 3.12; S, 14.27. Found: C, 63.87; H, 4.13; N, 3.09; S, 14.31.

*(Z)-2-(5-((6-((3,4-Dimethylbenzyl)oxy)naphthalen-2-yl)methylene)-4-oxo-2-thioxothiazolidin-3-yl)acetic acid (**6c**)* Yield 84 %; m.p. 293–294 °C. IR (KBr) cm^{-1}: 3407 (OH), 1712 (C=O). ^{1}H NMR (DMSO-d_6, 300 MHz, ppm): δ 8.17 (s, 1H), 8.07–7.83 (m, 3H), 7.68 (d, $J = 8.6$ Hz, 1H), 7.50 (s, 1H), 7.35–7.12 (m, 4H), 8.17–7.15 (m, 10H, Ar–H), 5.17 (s, 2H, CH_2), 4.33 (s, 2H, CH_2), 2.24 (d, $J = 4.9$ Hz, 6H, CH_3). ^{13}C NMR (DMSO-d_6, 75 MHz, ppm): δ 193.12, 169.27, 167.84, 157.01, 143.28, 139.09, 137.37, 133.37, 129.83, 119.09, 117.83, 107.65, 67.71, 46.56, 20.13. MS *m/z* 464 (M+1). Anal. Calcd. for $C_{25}H_{21}NO_4S_2$: C, 64.77; H, 4.57; N, 3.02; S, 13.83. Found: C, 64.73; H, 4.51; N, 3.06; S, 13.80.

*(Z)-2-(5-((6-((3-Methoxybenzyl)oxy)naphthalen-2-yl)methylene)-4-oxo-2-thioxothiazolidin-3-yl)acetic acid (**6d**)* Yield 82 %; m.p. 264–265 °C. IR (KBr) cm^{-1}: 3410 (OH), 1705 (C=O). ^{1}H NMR (DMSO-d_6, 300 MHz, ppm): δ 8.19 (s, 1H), 8.05–7.93 (m, 3H), 7.68 (d, $J = 8.7$ Hz, 1H), 7.51 (d, $J = 2.1$ Hz, 1H), 7.38–7.27 (m, 2H), 7.09 (d, $J = 6.9$ Hz, 2H), 6.96–6.89 (m, 1H), 8.19–6.90 (m, 11H, Ar–H), 5.24 (s, 2H, CH_2), 4.53 (s, 2H, CH_2), 3.78 (s, 3H, OCH_3). ^{13}C NMR (DMSO-d_6, 75 MHz, ppm): δ 193.12, 169.31, 168.04, 160.09, 157.78, 142.15, 138.37, 133.17, 129.54, 126.93, 119.62, 116.13, 107.65, 71.71, 47.79. MS *m/z* 466 (M+1). Anal. Calcd. for $C_{24}H_{19}NO_5S_2$: C, 61.92; H, 4.11; N, 3.01; S, 13.78. Found: C, 61.89; H, 4.07; N, 3.02; S, 13.81.

*(Z)-2-(5-((6-((4-Methoxybenzyl)oxy)naphthalen-2-yl)methylene)-4-oxo-2-thioxothiazolidin-3-yl)acetic acid (**6e**)* Yield 86 %; m.p. 283–284 °C. IR (KBr) cm^{-1}: 3417 (OH), 1701 (C=O). ^{1}H NMR (DMSO-d_6, 300 MHz, ppm): δ 8.18 (s, 1H), 8.04–7.87 (m, 3H), 7.68 (d, $J = 8.6$ Hz, 1H), 7.49 (m, 3H), 7.30 (d, $J = 9.0$ Hz, 1H), 6.97 (d, $J = 8.6$ Hz, 2H), 8.18–6.96 (m, 11H, Ar–H), 5.18 (s, 2H, CH_2), 4.35 (s, 2H, CH_2), 3.77 (s, 3H, OCH_3). ^{13}C NMR (DMSO-d_6, 75 MHz, ppm): δ 193.12, 167.57, 166.71, 159.75, 156.63, 142.91, 137.49, 131.67, 130.54, 129.54, 127.85, 127.14, 120.06, 117.13, 107.65, 70.87, 56.84, 47.74. MS *m/z* 466 (M+1). Anal. Calcd. for $C_{24}H_{19}NO_5S_2$: C, 61.92; H, 4.11; N, 3.01; S, 13.78. Found: C, 61.88; H, 4.09; N, 3.03; S, 13.79.

*(Z)-2-(5-((6-((3,4-Dimethoxybenzyl)oxy)naphthalen-2-yl)methylene)-4-oxo-2-thioxothiazolidin-3-yl)acetic acid (**6f**)* Yield 81 %; m.p. 249–250 °C. IR (KBr) cm^{-1}: 3421 (OH), 1697 (C=O). ^{1}H NMR (DMSO-d_6, 300 MHz, ppm): δ 8.18 (s, 1H), 8.06–7.85 (m, 3H), 7.69 (d, $J = 8.4$ Hz, 1H), 7.52 (s, 1H), 7.32 (d, $J = 9.1$ Hz, 1H), 7.15–6.94 (m, 3H), 8.18–6.96 (m, 10H, Ar–H), 5.17 (s, 2H, CH_2), 4.37 (s, 2H, CH_2), 3.77 (d, $J = 5.4$ Hz, 6H, OCH_3). ^{13}C NMR (DMSO-d_6, 75 MHz, ppm): δ 193.57, 169.84, 166.48, 157.48, 144.72, 138.93, 134.49, 131.17, 127.04, 126.84, 121.14, 121.06, 117.13, 107.65, 71.19, 56.17, 47.89. MS *m/z* 496 (M+1). Anal. Calcd. for $C_{25}H_{21}NO_6S_2$: C, 60.59; H, 4.27; N, 2.83; S, 12.94. Found: C, 60.61; H, 4.22; N, 2.81; S, 12.95.

*(Z)-2-(5-((6-((3-Fluorobenzyl)oxy)naphthalen-2-yl)methylene)-4-oxo-2-thioxothiazolidin-3-yl)acetic acid (**6g**)* Yield 87 %; m.p. 276–277 °C. IR (KBr) cm^{-1}: 3418 (OH), 1703 (C=O). ^{1}H NMR (DMSO-d_6, 300 MHz, ppm): δ 8.19 (s, 1H), 8.05–7.92 (m, 3H), 7.68 (d, $J = 8.7$ Hz, 1H), 7.55–7.30 (m, 5H), 7.19 (t, $J = 8.5$ Hz, 1H), 8.19–7.16 (m, 11H, Ar–H), 5.29 (s, 2H, CH_2), 4.54 (s, 2H, CH_2). ^{13}C NMR (DMSO-d_6, 75 MHz, ppm): δ 193.12, 168.93, 166.67, 165.09, 157.86, 143.91, 139.42, 130.54, 128.04, 122.79, 119.13, 114.13, 107.65, 70.52, 46.83. MS *m/z* 454 (M+1). Anal. Calcd. for $C_{23}H_{16}FNO_4S_2$: C, 60.91; H, 3.56; N, 3.09; S, 14.14. Found: C, 60.87; H, 3.52; N, 3.06; S, 14.18.

*(Z)-2-(5-((6-((4-Fluorobenzyl)oxy)naphthalen-2-yl)methylene)-4-oxo-2-thioxothiazolidin-3-yl)acetic acid (**6h**)* Yield 84 %; m.p. 286–287 °C. IR (KBr) cm^{-1}: 3419 (OH), 1696 (C=O). ^{1}H NMR (DMSO-d_6, 300 MHz, ppm): δ 8.18 (s, 1H), 8.07–7.86 (m, 3H), 7.70–7.52 (m, 4H), 7.36–7.17 (m, 3H), 8.18–7.22 (m, 11H, Ar–H), 5.25 (s, 2H, CH_2), 4.37 (s, 2H, CH_2). ^{13}C NMR (DMSO-d_6, 75 MHz, ppm): δ 193.16, 169.08, 166.41, 161.09, 157.86, 143.91, 139.58, 138.76, 130.27, 128.44, 127.59, 126.34, 119.71, 105.65, 70.84, 46.96. MS *m/z* 454 (M+1). Anal. Calcd. for $C_{23}H_{16}FNO_4S_2$: C, 60.91; H, 3.56; N, 3.09; S, 14.14. Found: C, 60.89; H, 3.55; N, 3.07; S, 14.16.

*(Z)-2-(5-((6-((2-Bromobenzyl)oxy)naphthalen-2-yl)methylene)-4-oxo-2-thioxothiazolidin-3-yl)acetic acid (**6i**)* Yield 84 %; m.p. 296–297 °C. IR (KBr) cm^{-1}: 3417 (OH), 1708 (C=O). ^{1}H NMR (DMSO-d_6, 300 MHz, ppm): δ 8.20 (s, 1H), 8.09–7.89 (m, 3H), 7.73–7.66 (m, 3H), 7.58–7.41 (m, 2H), 7.39–7.29 (m, 2H), 8.20–7.32 (m, 11H, Ar–H), 5.28 (s, 2H, CH_2), 4.52 (s, 2H, CH_2). ^{13}C NMR (DMSO-d_6, 75 MHz, ppm): δ 193.12, 169.08, 166.57, 157.42, 143.18, 139.08, 131.56, 129.07, 128.34, 127.63, 125.17, 118.53, 116.03, 105.65, 69.12, 47.85. MS *m/z* 513 (M+1). Anal. Calcd. for $C_{23}H_{16}BrNO_4S_2$: C, 53.70; H, 3.14; N, 2.72; S, 12.47. Found: C, 53.66; H, 3.13; N, 2.65; S, 12.49.

*(Z)-2-(5-((6-((3-Bromobenzyl)oxy)naphthalen-2-yl)methylene)-4-oxo-2-thioxothiazolidin-3-yl)acetic acid (**6j**)* Yield 81 %; m.p. 293–294 °C. IR (KBr) cm^{-1}: 3419 (OH), 1696 (C=O). ^{1}H NMR (DMSO-d_6, 300 MHz, ppm): δ 8.19 (s, 1H), 8.07–7.86 (m, 3H), 7.74–7.67 (m, 2H), 7.57–7.51 (m, 3H), 7.42–7.32 (m, 2H), 8.19–7.32 (m, 11H, Ar–H), 5.27 (s, 2H, CH_2), 4.44 (s, 2H, CH_2). ^{13}C NMR (DMSO-d_6, 75 MHz, ppm): δ 193.16, 169.12, 166.41, 161.87, 157.52, 143.08,

139.46, 132.82, 129.43, 128.58, 127.44, 125.78, 119.54, 117.61, 105.82, 70.18, 47.71. MS *m/z* 513 (M+1). Anal. Calcd. for $C_{23}H_{16}BrNO_4S_2$: C, 53.70; H, 3.14; N, 2.72; S, 12.47. Found: C, 53.69; H, 3.11; N, 2.68; S, 12.46.

*(Z)-2-(5-((6-((4-Bromobenzyl)oxy)naphthalen-2-yl)methylene)-4-oxo-2-thioxothiazolidin-3-yl)acetic acid (**6k**)* Yield 85 %; m.p. 302–303 °C. IR (KBr) cm^{-1}: 3422 (OH), 1712 (C=O). ^1H NMR (DMSO-d_6, 300 MHz, ppm): δ 8.18 (s, 1H), 8.07–7.85 (m, 3H), 7.73–7.45 (m, 6H), 7.35–7.31 (m, 1H), 8.18–7.11 (m, 11H, Ar–H), 5.25 (s, 2H, CH_2), 4.36 (s, 2H, CH_2). ^{13}C NMR (DMSO-d_6, 75 MHz, ppm): δ 193.12, 169.07, 166.39, 157.91, 142.68, 138.72, 135.86, 131.83, 129.83, 128.64, 126.75, 124.43, 122.04, 119.61, 105.82, 70.87, 47.64. MS *m/z* 513 (M+1). Anal. Calcd. for $C_{23}H_{16}BrNO_4S_2$: C, 53.70; H, 3.14; N, 2.72; S, 12.47. Found: C, 53.68; H, 3.13; N, 2.71; S, 12.49.

*(Z)-2-(5-((6-((2-Chlorobenzyl)oxy)naphthalen-2-yl)methylene)-4-oxo-2-thioxothiazolidin-3-yl)acetic acid (**6l**)* Yield 81 %; m.p. 291–292 °C. IR (KBr) cm^{-1}: 3415 (OH), 1703 (C=O). ^1H NMR (DMSO-d_6, 300 MHz, ppm): δ 8.19 (s, 1H), 8.08–7.87 (m, 3H), 7.74–7.64 (m, 2H), 7.59–7.51 (m, 2H), 7.48–7.30 (m, 3H), 8.19–7.32 (m, 11H, Ar–H), 5.32 (s, 2H, CH_2), 4.44 (s, 2H, CH_2). ^{13}C NMR (DMSO-d_6, 75 MHz, ppm): δ 193.17, 169.08, 166.40, 157.47, 145.52, 139.08, 137.56, 132.07, 130.34, 129.63, 127.10, 126.68, 119.85, 107.65, 67.08, 47.79. MS *m/z* 470 (M+1). Anal. Calcd. for $C_{23}H_{16}ClNO_4S_2$: C, 58.78; H, 3.43; N, 2.98; S, 13.65. Found: C, 58.79; H, 3.41; N, 2.96; S, 13.68.

*(Z)-2-(5-((6-((3-Chlorobenzyl)oxy)naphthalen-2-yl)methylene)-4-oxo-2-thioxothiazolidin-3-yl)acetic acid (**6m**)* Yield 83 %; m.p. 285–286 °C. IR (KBr) cm^{-1}: 3409 (OH), 1704 (C=O). ^1H NMR (DMSO-d_6, 300 MHz, ppm): δ 8.18 (s, 1H), 8.07–7.87 (m, 3H), 7.72–7.55 (m, 2H), 7.53–7.29 (m, 5H), 8.18–7.32 (m, 11H, Ar–H), 5.27 (s, 2H, CH_2), 4.50 (s, 2H, CH_2). ^{13}C NMR (DMSO-d_6, 75 MHz, ppm): δ 193.16, 169.21, 166.33, 158.47, 144.52, 143.17, 139.28, 131.73, 129.07, 128.34, 127.63, 127.19, 125.16, 124.57, 119.43, 107.60, 69.18, 46.93. MS *m/z* 470 (M+1). Anal. Calcd. for $C_{23}H_{16}ClNO_4S_2$: C, 58.78; H, 3.43; N, 2.98; S, 13.65. Found: C, 58.76; H, 3.41; N, 2.96; S, 13.67.

*(Z)-2-(5-((6-((4-Chlorobenzyl)oxy)naphthalen-2-yl)methylene)-4-oxo-2-thioxothiazolidin-3-yl)acetic acid (**6n**)* Yield 86 %; m.p. 313–314 °C. IR (KBr) cm^{-1}: 3424 (OH), 1693 (C=O). ^1H NMR (DMSO-d_6, 300 MHz, ppm): δ 8.18 (s, 1H), 8.07–7.85 (m, 3H), 7.70–7.66 (m, 1H), 7.57–7.43 (m, 5H), 7.35–7.31 (m, 1H), 8.18–7.22 (m, 11H, Ar–H), 5.27 (s, 2H, CH_2), 4.36 (s, 2H, CH_2). ^{13}C NMR (DMSO-d_6, 75 MHz, ppm): δ 193.12, 169.34, 166.57, 159.08, 142.82, 136.73, 133.48, 132.73, 131.73, 128.34, 127.63, 127.01, 119.72, 107.82, 69.79, 46.67. MS *m/z* 470 (M+1). Anal. Calcd. for $C_{23}H_{16}ClNO_4S_2$: C, 58.78; H, 3.43; N, 2.98; S, 13.65. Found: C, 58.75; H, 3.42; N, 2.95; S, 13.70.

*(Z)-2-(5-((6-((2-Cyanobenzyl)oxy)naphthalen-2-yl)methylene)-4-oxo-2-thioxothiazolidin-3-yl)acetic acid (**6o**)* Yield 83 %; m.p. 325–326 °C. IR (KBr) cm^{-1}: 3422 (OH), 1697 (C=O). ^1H NMR (DMSO-d_6, 300 MHz, ppm): δ 8.21 (s, 1H), 8.08–7.92 (m, 4H), 7.84–7.60 (m, 5H), 7.35 (d, $J = 9.0$ Hz, 1H), 8.21–7.34 (m, 11H, Ar–H), 5.42 (s, 2H, CH_2), 4.46 (s, 2H, CH_2). ^{13}C NMR (DMSO-d_6, 75 MHz, ppm): δ 193.12, 169.08, 166.47, 158.83, 144.39, 143.16, 139.08, 137.56, 134.07, 131.34, 127.64, 127.14, 119.54, 113.82, 106.73, 67.57, 46.67. MS *m/z* 461 (M+1). Anal. Calcd. for $C_{24}H_{16}N_2O_4S_2$: C, 62.59; H, 3.50; N, 6.08; S, 13.93. Found: C, 62.57; H, 3.51; N, 6.05; S, 13.91.

*(Z)-2-(5-((6-((4-Cyanobenzyl)oxy)naphthalen-2-yl)methylene)-4-oxo-2-thioxothiazolidin-3-yl)acetic acid (**6p**)* Yield 87 %; m.p. 327–328 °C. IR (KBr) cm^{-1}: 3419 (OH), 1707 (C=O). ^1H NMR (DMSO-d_6, 300 MHz, ppm): δ 8.19 (s, 1H), 8.05 (d, $J = 9.1$ Hz, 1H), 7.95–7.88 (m, 4H), 7.73–7.67 (m, 3H), 7.50 (s, 1H), 7.36 (dd, $J = 9.0$, 2.4 Hz, 1H), 8.19–7.34 (m, 11H, Ar–H), 5.38 (s, 2H, CH_2), 4.54 (s, 2H, CH_2). ^{13}C NMR (DMSO-d_6, 75 MHz, ppm): δ 193.12, 167.11, 166.66, 157.87, 142.39, 135.10, 133.26, 132.44, 131.90, 130.86, 128.40, 128.17, 127.99, 127.03, 119.86, 107.56, 66.51, 46.68. MS *m/z* 461 (M+1). Anal. Calcd. for $C_{24}H_{16}N_2O_4S_2$: C, 62.59; H, 3.50; N, 6.08; S, 13.93. Found: C, 62.56; H, 3.48; N, 6.05; S, 13.95.

*(Z)-2-(5-((6-((2,4-Dichlorobenzyl)oxy)naphthalen-2-yl)methylene)-4-oxo-2-thioxothiazolidin-3-yl)acetic acid (**6q**)* Yield 83 %; m.p. 308–309 °C. IR (KBr) cm^{-1}: 3427 (OH), 1691 (C=O). ^1H NMR (DMSO-d_6, 300 MHz, ppm): δ 8.19 (s, 1H), 8.07–7.91 (m, 3H), 7.72–7.68 (m, 3H), 7.58–7.48 (m, 2H), 7.34 (dd, $J = 8.9$, 2.2 Hz, 1H), 8.19–7.16 (m, 10H, Ar–H), 5.30 (s, 2H, CH_2), 4.54 (s, 2H, CH_2). ^{13}C NMR (DMSO-d_6, 75 MHz, ppm): δ 193.15, 169.38, 167.34, 158.51, 140.57, 138.24, 135.65, 133.23, 132.72, 130.83, 129.13, 119.86, 107.56, 66.14, 46.71. MS *m/z* 505 (M+1). Anal. Calcd. for $C_{23}H_{15}Cl_2NO_4S_2$: C, 54.77; H, 3.00; N, 2.78; S, 12.71. Found: C, 54.75; H, 2.97; N, 2.76; S, 12.72.

*(Z)-2-(5-((6-((3,4-Dichlorobenzyl)oxy)naphthalen-2-yl)methylene)-4-oxo-2-thioxothiazolidin-3-yl)acetic acid (**6r**)* Yield 84 %; m.p. 251–252 °C. IR (KBr) cm^{-1}: 3422 (OH), 1699 (C=O). ^1H NMR (DMSO-d_6, 300 MHz, ppm): δ 8.19 (s, 1H), 8.04 (d, $J = 9.0$ Hz, 1H), 7.95 (d, $J = 8.7$ Hz, 1H), 7.89 (s, 1H), 7.81 (s, 1H), 7.69 (d, $J = 8.2$ Hz, 2H), 7.52 (d, $J = 9.0$ Hz, 2H), 7.36 (d, $J = 8.9$ Hz, 1H),

8.19–7.34 (m, 10H, Ar–H), 5.29 (s, 2H, CH_2), 4.36 (s, 2H, CH_2). ^{13}C NMR (DMSO-d_6, 75 MHz, ppm): δ 193.21, 169.82, 167.42, 157.49, 143.42, 139.18, 138.27, 136.91, 135.72, 134.19, 132.57, 128.59, 128.07, 127.35, 118.57, 116.16, 109.73, 69.17, 46.69. MS *m/z* 505 (M+1). Anal. Calcd. for $C_{23}H_{15}Cl_2NO_4S_2$: C, 54.77; H, 3.00; N, 2.78; S, 12.71. Found: C, 54.73; H, 2.96; N, 2.77; S, 12.70.

(Z)-2-(5-((6-((2,6-Dichlorobenzyl)oxy)naphthalen-2-yl)methylene)-4-oxo-2-thioxothiazolidin-3-yl)acetic acid ***(6s)*** Yield 82 %; m.p. 284–285 °C. IR (KBr) cm^{-1}: 3412 (OH), 1709 (C=O). ^{1}H NMR (DMSO-d_6, 300 MHz, ppm): δ 8.21 (s, 1H), 8.05–8.01 (m, 2H), 7.91 (s, 1H), 7.75–7.46 (m, 5H), 7.30 (dd, J = 9.0, 2.2 Hz, 1H), 8.21–7.28 (m, 10H, Ar–H), 5.41 (s, 2H, CH_2), 4.38 (s, 2H, CH_2). ^{13}C NMR (DMSO-d_6, 75 MHz, ppm): δ 193.13, 169.82, 167.42, 157.15, 142.19, 138.16, 134.38, 133.94, 132.46, 131.75, 128.74, 119.78, 117.64, 107.73, 67.86, 46.83. MS *m/z* 505 (M+1). Anal. Calcd. for $C_{23}H_{15}Cl_2NO_4S_2$: C, 54.77; H, 3.00; N, 2.78; S, 12.71. Found: C, 54.72; H, 2.98; N, 2.79; S, 12.68.

(Z)-2-(4-Oxo-2-thioxo-5-((6-((3-(trifluoromethyl)benzyl)oxy)naphthalen-2-yl)methylene)thiazolidin-3-yl)acetic acid ***(6t)*** Yield 87 %; m.p. 261–262 °C. IR (KBr) cm^{-1}: 3502 (OH), 1701 (C=O). ^{1}H NMR (DMSO-d_6, 300 MHz, ppm): δ 8.19 (s, 1H), 8.04 (d, J = 9.0 Hz, 1H), 7.99–7.80 (m, 4H), 7.75–7.65 (m, 3H), 7.54 (s, 1H), 7.37 (d, J = 9.0 Hz, 1H), 8.19–7.35 (m, 11H, Ar–H), 5.38 (s, 2H, CH_2), 4.45 (s, 2H, CH_2). ^{13}C NMR (DMSO-d_6, 75 MHz, ppm): δ 193.21, 169.75, 167.37, 157.78, 143.38, 141.46, 139.82, 132.67, 131.81, 130.94, 129.46, 128.27, 112.49, 73.46, 47.61. MS *m/z* 504 (M+1). Anal. Calcd. for $C_{24}H_{16}F_3NO_4S_2$: C, 57.25; H, 3.20; N, 2.78; S, 12.74. Found: C, 57.24; H, 3.18; N, 2.79; S, 12.71.

(Z)-2-(4-Oxo-2-thioxo-5-((6-((4-(trifluoromethyl)benzyl)oxy)naphthalen-2-yl)methylene)thiazolidin-3-yl)acetic acid ***(6u)*** Yield 85 %; m.p. 293–294 °C. IR (KBr) cm^{-1}: 3502 (OH), 1702 (C=O). ^{1}H NMR (DMSO-d_6, 300 MHz, ppm): δ 8.19 (s, 1H), 8.05 (d, J = 9.1 Hz, 1H), 7.98–7.86 (m, 2H), 7.81–7.67 (m, 5H), 7.52 (d, J = 1.9 Hz, 1H), 7.36 (dd, J = 9.0, 2.3 Hz, 1H), 8.19–7.34 (m, 11H, Ar–H), 5.39 (s, 2H, CH_2), 4.41 (s, 2H, CH_2). ^{13}C NMR (DMSO-d_6, 75 MHz, ppm): δ 193.12, 166.90, 166.82, 157.92, 141.51, 132.79, 131.77, 130.82, 128.40, 128.13, 127.96, 127.02, 125.38, 119.38, 107.57, 66.58, 47.53. MS *m/z* 504 (M+1). Anal. Calcd. for $C_{24}H_{16}F_3NO_4S_2$: C, 57.25; H, 3.20; N, 2.78; S, 12.74. Found: C, 57.23; H, 3.19; N, 2.80; S, 12.75.

(Z)-2-(5-((6-((4-Iodobenzyl)oxy)naphthalen-2-yl)methylene)-4-oxo-2-thioxothiazolidin-3-yl)acetic acid ***(6v)*** Yield 81 %; m.p. 314–315 °C. IR (KBr) cm^{-1}: 3435 (OH), 1695 (C=O). ^{1}H NMR (DMSO-d_6, 300 MHz, ppm): δ 8.18 (s, 1H), 8.03 (d, J = 9.0 Hz, 1H), 7.97–7.85 (m, 2H), 7.78 (d, J = 8.1 Hz, 2H), 7.68 (d, J = 8.6 Hz, 1H), 7.49 (s, 1H), 7.33 (d, J = 6.9 Hz, 3H), 8.18–7.32 (m, 11H, Ar–H), 5.23 (s, 2H, CH_2), 4.39 (s, 2H, CH_2). ^{13}C NMR (DMSO-d_6, 75 MHz, ppm): δ 193.12, 169.13, 166.83, 157.72, 143.18, 138.27, 136.81, 131.43, 129.67, 128.95, 128.32, 119.38, 117.29, 105.77, 69.86, 47.64. MS *m/z* 561 (M+1). Anal. Calcd. for $C_{23}H_{16}INO_4S_2$: C, 49.21; H, 2.87; N, 2.49; S, 11.42. Found: C, 49.19; H, 2.84; N, 2.46; S, 11.45.

(Z)-2-(5-((6-((4-Nitrobenzyl)oxy)naphthalen-2-yl)methylene)-4-oxo-2-thioxothiazolidin-3-yl)acetic acid ***(6w)*** Yield 82 %; m.p. 327–328 °C. IR (KBr) cm^{-1}: 3426 (OH), 1707 (C=O). ^{1}H NMR (DMSO-d_6, 300 MHz, ppm): δ 8.29 (d, J = 8.5 Hz, 2H), 8.19 (s, 1H), 8.05 (d, J = 9.0 Hz, 1H), 7.93 (d, J = 10.2 Hz, 2H), 7.79 (d, J = 8.2 Hz, 2H), 7.68 (d, J = 8.7 Hz, 1H), 7.51 (s, 1H), 7.37 (d, J = 8.8 Hz, 1H), 8.30–7.36 (m, 11H, Ar–H), 5.44 (s, 2H, CH_2), 4.53 (s, 2H, CH_2). ^{13}C NMR (DMSO-d_6, 75 MHz, ppm): δ 193.12, 167.13, 165.43, 157.46, 147.18, 145.34, 144.94, 138.61, 132.28, 129.91, 128.27, 127.29, 117.37, 105.51, 69.44, 47.64. MS *m/z* 481 (M+1). Anal. Calcd. for $C_{23}H_{16}N_2O_6S_2$: C, 57.49; H, 3.36; N, 5.83; S, 13.35. Found: C, 57.46; H, 3.35; N, 5.81; S, 13.36.

(Z)-2-(5-((6-((4-(Dimethylamino)benzyl)oxy)naphthalen-2-yl)methylene)-4-oxo-2-thioxothiazolidin-3-yl)acetic acid ***(6x)*** Yield 82 %; m.p. 319–320 °C. IR (KBr) cm^{-1}: 3421 (OH), 1705 (C=O). ^{1}H NMR (DMSO-d_6, 300 MHz, ppm): δ 8.25 (s, 1H), 8.13–8.05 (m, 2H), 7.92 (s, 1H), 7.85–7.65 (m, 4H), 7.47 (d, J = 8.1 Hz, 2H), 7.22 (d, J = 8.5 Hz, 1H), 8.25–7.21 (m, 11H, Ar–H), 5.21 (s, 2H, CH_2), 4.41 (s, 2H, CH_2), 3.13 (s, 6H, CH_3). ^{13}C NMR (DMSO-d_6, 75 MHz, ppm): δ 193.12, 169.13, 167.43, 158.46, 149.18, 138.34, 132.94, 129.61, 128.28, 127.91, 119.27, 118.29, 116.37, 105.76, 70.18, 47.63. MS *m/z* 479 (M+1). Anal. Calcd. for $C_{25}H_{22}N_2O_4S_2$: C, 62.74; H, 4.63; N, 5.85; S, 13.40. Found: C, 62.73; H, 4.62; N, 5.81; S, 13.43.

Evaluation of antibacterial activity in vitro

In vitro antibacterial activity assay method was referred in Ref. (Chen *et al.*, 2010).

Results and discussion

Chemistry

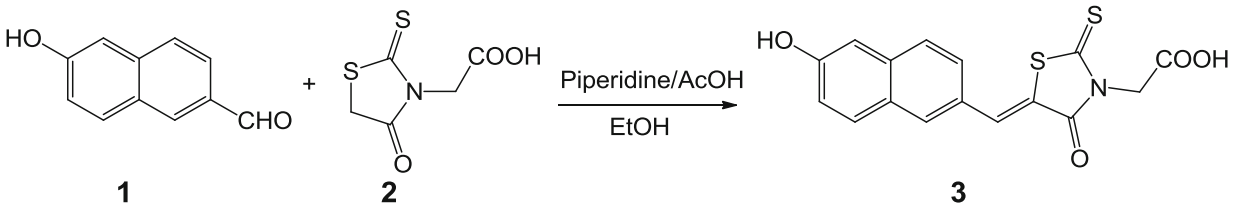
(*Z*)-2-(5-((6-Hydroxynaphthalen-2-yl)methylene)-4-oxo-2-thioxothiazolidin-3-yl)acetic acid (**3**) was synthesized for the first time by a Knoevenagel condensation (Albuquerque *et al.*, 1997) between 6-hydroxy-2-naphthaldehyde (**1**) and rhodanine-3-acetic acid (**2**) in good yields (Scheme 1). Compound **2** was prepared by a previously described method (Brown *et al.*, 1956). Compounds **6a–6x** were synthesized in two steps as shown in Scheme 2. The intermediates **5a–5x** were obtained by reacting **4a–4x** with **1** in the presence of K_2CO_3 in DMF at 90 °C (Patil *et al.*, 2010) and these intermediates were further subjected to rhodanine-3-acetic acid (**2**) with catalytic amount of acetic acid and piperidine in ethanol at 50 °C to afford compounds **6a–6x**. All the synthesized compounds were investigated by FTIR, ^{1}H NMR, ^{13}C NMR, mass spectral, and elemental analyses.

Antimicrobial activity

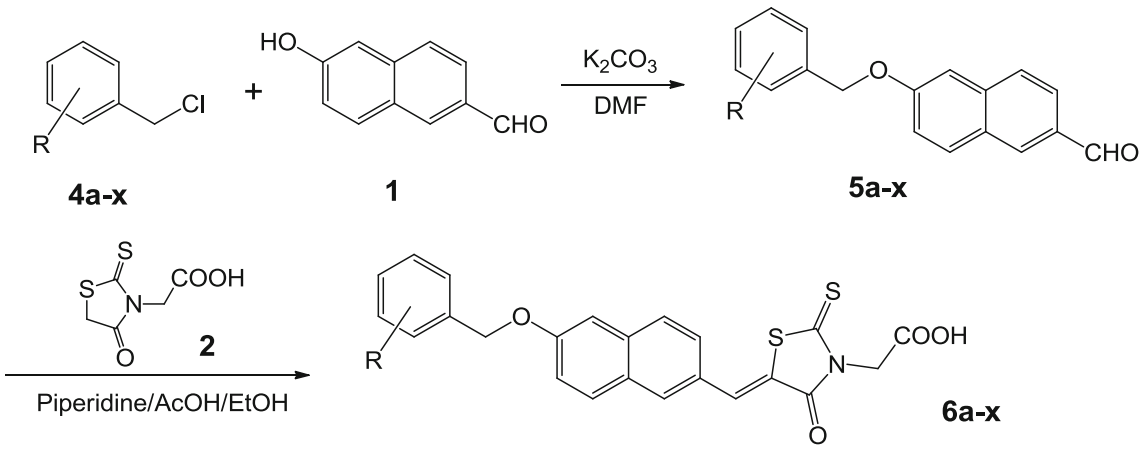
In vitro antimicrobial activity was evaluated by determining the minimum inhibitory concentration (MIC) for different strains (including multidrug-resistant clinical isolates). Oxacillin and norfloxacin were used as positive controls.

Synthesized compound **3** showed no antibacterial activity in vitro against gram-positive and gram-negative strains at 64 μg/mL. We then introduced hydrophobic groups at the hydroxy group of compound **3** and formed the ether derivatives (**6a–6x**). The results showed that, as expected, some derivatives exhibited potent antibacterial activities against gram-positive strains, but still showed no activity against gram-negative strains (Table 1).

Compounds **6b**, **6e**, **6f**, **6h**, **6k**, **6n**, and **6u** were highly active against *Staphylococcus aureus* (*S. aureus* RN4220 and *S. aureus* KCTC 503) with MICs of 2–8 μg/mL, in which the 4-bromine substituted **6k** with a MIC of 2 μg/mL was as active as the standard drug (norfloxacin) but less active than oxacillin. After analyzing the activities of



Scheme 1 Synthetic scheme for the synthesis of compound **3**



6a:R=H	6g:R=3-F	6m:R=3-Cl	6s :R=2,6-$(Cl)_2$
6b:R=4-CH_3	6h:R=4-F	6n :R=4-Cl	6t :R=3-CF_3
6c:R=3,4-$(CH_3)_2$	6i :R=2-Br	6o :R=2-CN	6u :R=4-CF_3
6d:R=3-OCH_3	6j :R=3-Br	6p :R=4-CN	6v :R=4-I
6e:R=4-OCH_3	6k:R=4-Br	6q :R=2,4-$(Cl)_2$	6w:R=4-NO_2
6f: R=3,4-$(OCH_3)_2$	6l :R=2-Cl	6r :R=3,4-$(Cl)_2$	6x :R=4-$N(CH_3)_2$

Scheme 2 Synthetic scheme for the synthesis of compounds **6a–6x**

Table 1 Inhibitory activity of compounds **2**, **3**, and **6a–6x** expressed as MIC (μg/mL)

Compounds	*S. aureus*		*E. coli*	
	4220	503	1924	1356
2	>64	>64	>64	>64
3	>64	>64	>64	>64
6a	64	64	>64	>64
6b	2	4	>64	>64
6c	>64	>64	>64	>64
6d	>64	>64	>64	>64
6e	4	8	>64	>64
6f	4	8	>64	>64
6g	>64	>64	>64	>64
6h	4	4	>64	>64
6i	>64	>64	>64	>64
6j	32	64	>64	>64
6k	2	2	>64	>64
6l	>64	>64	>64	>64
6m	>64	>64	>64	>64
6n	2	4	>64	>64
6o	>64	>64	>64	>64
6p	>64	>64	>64	>64
6q	>64	>64	>64	>64
6r	>64	>64	>64	>64
6s	>64	>64	>64	>64
6t	>64	>64	>64	>64
6u	4	4	>64	>64
6v	>64	>64	>64	>64
6w	64	32	>64	>64
6x	64	64	>64	>64
Oxacillin	1	1	>64	>64
Norfloxacin	2	2	16	16

S. aureus RN4220, *Staphylococcus aureus* RN4220; *S. aureus* 503, *Staphylococcus aureus* 503; *E. coli* 1924, *Escherichia coli* CCARM 1924; *E. coli* 1356, *Escherichia coli* CCARM 1356

synthesized compounds **3** and **6a–6x**, the following structure–activity relationships (SARs) were obtained. Introducing a class of hydrophobic groups onto the phenolic hydroxyl group of compound **3** resulted in enhancing the antibacterial activity of some derivatives, compound **6k** (MIC = 2 μg/mL) was 32-fold more potent than compound **3** (MIC > 64 μg/mL). Furthermore, the antibacterial activity was significantly influenced by the position of the substituent on the phenyl ring. Most derivatives substituted at the 4-position (except **6v**, **6w**, and **6x**) had good antibacterial activity, and no clear correlation was determined for the relationship between the electronic property of the substituent and antibacterial activity.

For those compounds exhibiting potency against *S. aureus*, we also evaluated their antibacterial activity against several clinical isolates of multidrug-resistant gram-positive bacteria (Table 2). Compounds **6b**, **6e**, **6f**, **6h**, **6k**, **6n**, and **6u** were active with MICs of 1–8 μg/mL. Compound **6k** exhibited more potent activity than norfloxacin against all of the microorganisms tested with a MIC of 1 μg/mL; hence, the derivative substituted at the 4-position still exhibited more potent activity than the other derivatives. Regardless, these compounds still had low potency for quinolone-resistant *S. aureus* (QRSA) compared to oxacillin. In contrast to the previously reported rhodanine-3-acetic acid derivatives bearing a chalcone moiety, the derivatives bearing a 6-benzyloxynaphthalene moiety presented more potent activity in general. This suggests that the chalcone moiety can be replaced by a naphthalene moiety and that changing the flexible chalcone moiety to a more rigid structure may be beneficial to increase the antibacterial activity. Further modification of the compound **6k** is in progress.

Table 2 MIC values (in μg/mL) against clinical isolates of multidrug-resistant gram-positive bacterial strains

Compounds	MRSA		QRSA	
	3167	3506	3505	3519
6a	64	64	64	64
6b	2	4	4	8
6e	2	2		8
6f	8	8	8	8
6h	4	2	4	4
6j	64	64	>64	>64
6k	1	1	4	4
6n	2	2	4	4
6u	2	2	64	64
6w	4	8	8	4
6x	>64	>64	>64	>64
Oxacillin	>64	>64	1	1
Norfloxacin	8	4	>64	>64

MRSA 3167, methicillin-resistant *S. aureus* CCARM 3167; MRSA 3506, methicillin-resistant *S. aureus* CCARM 3506; QRSA 3505, quinolone-resistant *S. aureus* CCARM 3505; QRSA 3519, quinolone-resistant *S. aureus* CCARM 3519

Conclusion

Based on our previous work, we have described a simple and efficient protocol for the synthesis of novel rhodanine-3-acetic acid derivatives (**3**, **6a–6x**) in good yields. All the synthesized compounds have been investigated for their in vitro antimicrobial activities. Most of the compounds showed reasonably potent antibacterial activities against gram-positive bacteria (particularly against multidrug-resistant strains of clinical isolates). Compound **6k** with a

MIC of 1 μg/mL was found to be the most potent against the multidrug-resistant strains than norfloxacin. Future SAR studies are ongoing in the continuing search for novel antibacterial agents.

Acknowledgments This study was supported by the National Science Foundation of China (20962021 and 81260468).

References

Albuquerque JF, Galdino SL, Chantegrel J, Thomasson F, Pitta IR, Luu-Duc C (1997) Substituted thio-arylidene thiazolidinones: synthesis and structural study. Ann Pharm Fr 55:201–205

Brown FC, Bradsher CK, Morgan EC, Tetenbaum M, Wilder P (1956) Some 3-substituted rhodanines. J Am Chem Soc 78:384–388. doi:10.1021/ja01583a037

Chandrappa S, Kavitha CV, Shahabuddin MS, Vinaya K, Ananda Kumar CS, Ranganatha SR, Raghavan SC, Rangappa KS (2009) Synthesis of 2-(5-((5-(4-chlorophenyl)furan-2-yl)methylene)-4-oxo-2-thioxothiazolidin-3-yl) acetic acid derivatives and evaluation of their cytotoxicity and induction of apoptosis in human leukemia cells. Bioorg Med Chem 17:2576–2584. doi:10.1016/j.bmc.2009.01.016

Chen ZH, Zheng CJ, Sun LP, Piao HR (2010) Synthesis of new chalcone derivatives containing a rhodanine-3-acetic acid moiety with potential antibacterial activity. Eur J Med Chem 45:5739–5743. doi:10.1016/j.ejmech.2010.09.031

Desai NC, Shah MD, Bhavsar AM, Saxena AK (2008) Synthesis and QSAR studies of 4-oxo-thiazolidines and 2-oxo-azetidines as potential antibacterial agents. Indian J Chem 47B:1135–1144

Dolezel J, Hirsova P, Opletalova V, Dohnal J, Marcela V, Kunes J, Jampilek J (2009) Rhodanineacetic acid derivatives as potential drugs: preparation, hydrophobic properties and antifungal activity of (5-arylalkylidene-4-oxo-2-thioxo-1,3-thiazolidin-3-yl)acetic acids. Molecules 14:4197–4212. doi:10.3390/molecules14104197

Frankov IA, Kirillov MV, Sokolova TN, Skupskaya R, Kharitonovich AN, Chizhevskaya II (1985) Synthesis and pharmacological properties of alkyl derivatives of 3-carboxyalkylrhodanine. Khimiko-Farmakotsevticheskii Zhurnal 19:943–946

Havrylyuk D, Zimenkovsky B, Vasylenko O, Zaprutko L, Gzella A, Lesyk R (2009) Synthesis of novel thiazolone-based compounds containing pyrazoline moiety and evaluation of their anticancer activity. Eur J Med Chem 44:1396–1404. doi:10.1016/j.ejmech.2008.09.032

Inamori Y, Muro C, Tanaka R, Adachi A, Miyamoto K, Tsujibo H (1992) Phytogrowth-inhibitory activity of sulfur-containing compounds. I. Inhibitory activities of thiazolidine derivatives on plant growth. Chem Pharm Bull 40:2854–2856

Liu Q, Zhang YY, Lu HL, Li QY, Zhou CH, Wang MW (2007) Rhodanine derivatives as novel peroxisome proliferator-activated receptor γ agonists. Act Pharm Sin 28:2033–2039. doi:10.1111/j.1745-7254.2007.00657.x

Momose Y, Meguro K, Ikeda H, Hatanaka C, Oi S, Shodha T (1991) Studies on antidiabetic agents. X. Synthesis and biological activities of pioglitazone and related compounds. Chem Pharm Bull 39:1440–1445. doi:10.1248/cpb.39.1440

Muro C, Yasuda M, Sakagami Y, Yamada T, Tsujibo H, Numata A, Inamori Y (1996) Inhibitory activities of rhodanine derivatives on plant growth. Biosci Biotech Biochem 60:1368–1371. doi:10.1271/bbb.60.1368

Patil V, Tilekar K, Mehendale-Munj S, Mohan R, Ramaa CS (2010) Synthesis and primary cytotoxicity evaluation of new 5-benzylidene-2, 4-thiazolidinedione derivatives. Eur J Med Chem 45:4539–4544. doi:10.1016/j.ejmech.2010.07.014

Sortino M, Delgado P, Juarez S, Quiroga J, Abonia R, Insuasty B, Nogueras M, Rodero L, Garibotoo FM, Enriz RD, Zacchino SA (2007) Synthesis and antifungal activity of (*Z*)-5-arylidenerhodanines. Bioorg Med Chem 15:484–494. doi:10.1016/j.bmc.2006.09.038

Terashima H, Hama K, Yamamoto R, Tsuboshima M, Kikkawa R, Hatanaka I, Shigeta Y (1984) Effects of a new aldose reductase inhibitor on various tissues in vitro. J Pharmacol Exp Ther 229:226–230

Yoshioka T, Fujita T, Kanai T, Aizawa Y, Kurumada T, Hasegawa K, Horikoshi H (1989) Studies on hindered phenols and analogues. 1. Hypolipidemic and hypoglycemic agents with ability to inhibit lipid peroxidation. J Med Chem 32:421–428. doi:10.1021/jm00122a022