Med Chem Res
DOI 10.1007/s00044-013-0648-7

MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Synthesis and antibacterial evaluation of furan derivatives bearing a rhodanine moiety

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Received: 30 December 2012 / Accepted: 22 May 2013

Abstract Two series of furan derivatives bearing a rhodanine moiety (**4a–l** and **5a–l**) have been synthesized, characterized, and evaluated for their antibacterial activity. The majority of these compounds showed potent levels of inhibitory activity against a variety of different Gram-positive bacteria, including multidrug-resistant clinical isolates, with minimum inhibitory concentration (MIC) values in the range of 2–16 μg/mL. In particular, compound **4l** was found to be the most potent of the synthesized compounds against the multidrug-resistant strains, with a MIC value of 2 or 4 μg/mL. None of the compounds exhibited any activity against the Gram-negative bacteria *Escherichia coli* 1356 at 64 μg/mL. An examination of the cytotoxicities of these agents revealed that they displayed low levels of toxicity toward HeLa cells. All of the compounds synthesized in the current paper were characterized by ^{1}H and ^{13}C NMR, infrared, and mass spectroscopy.

Keywords Rhodanine · Furan · Antibacterial activity

Introduction

The increasing levels of resistance exhibited by bacterial pathogens toward antibiotic agents have been well documented in recent years, with particular emphasis on Gram-positive and Gram-negative bacteria from ambulatory and hospitalized patients (Witte, 1999; Heinemann *et al.*, 2000; Levy, 1998; Komine *et al.*, 2008; Service, 1995). Compounds beating oxo or azo heterocycles are well known to be biologically important (Gil and Bräse, 2009; Butler, 2004). Furan-containing compounds show a diverse array of favorable biological and pharmacological properties and have consequently been used as medicines in a variety of different disease areas (Ivie, 1987). Furan derivatives obtained from synthetic and natural sources have recently been the subject of considerable levels of interest because of their wide range of pharmaceutical applications (Kupchan *et al.*, 1971; Shevchenko, 1999; Qu *et al.*, 2012; Ding *et al.*, 2012). A large number of the naturally occurring furans have shown interesting biological activities, such as antimicrobial (Khan *et al.*, 2005; Hofnung *et al.*, 2002), cytotoxic, and antitumor properties (Bandurraga *et al.*, 1982), as well as several other potentially useful activities (Jin *et al.*, 2012; Mamta *et al.*, 2012).

Rhodanine compounds are known to be effective antibacterial compounds. We previously reported the synthesis and antimicrobial evaluation of a series of rhodanine-3-acetic acid derivatives (Chen *et al.*, 2010) bearing a chalcone moiety (Fig. 1) that showed potent inhibitory activity toward a variety of different Gram-positive bacterial strains, including multidrug-resistant clinical isolates. Herein, as part of our ongoing research toward the development of novel antibacterial agents, we have designed and synthesized two series of furan derivatives containing a rhodanine moiety (**4a–l** and **5a–l**). These compounds were subsequently characterized and evaluated for their antibacterial activity.

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Published online: 05 June 2013

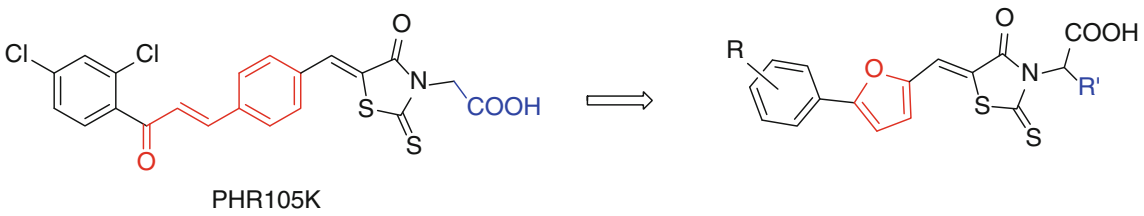


Fig. 1 Previously reported compound PHR105K and the structure-based design of the target compounds

Experimental

Materials

Melting points were determined in open capillary tubes and are reported uncorrected. The reactions were monitored by thin-layer chromatography (TLC) on silica gel precoated F254 Merck plates. The developed TLC plates were examined with a UV lamp (254 nm). Infrared (IR) spectra were recorded as KBr disks on a FT-IR1730. ^{1}H NMR spectra were measured on Bruker AV-300 spectrometer, using tetramethylsilane as internal standard. Mass spectra were measured on an HP1100LC (Agilent Technologies, USA).

Methods

Synthesis

General procedure for the preparation of compounds ***3***

A mixture of aniline (30 mmol) and sodium nitrite (30.30 mmol) in hydrochloric acid (8 mL) and water (6 mL) was stirred for 1 h at 0 °C. After the completion of the reaction, the mixture was filtered and acetone (30 mL), furfural (30 mmol), and cupric chloride (3 mmol) were added slowly to the filtrate, and then the mixture was stirred for 12 h at 20 °C. The excess solvent was removed under reduced pressure and the residue was dissolved in ethyl acetate and extracted with water, dried over $MgSO_4$, and the solvent was evaporated under reduced pressure. The resulting residue was purified by silica gel column chromatography (dichloromethane/methanol = 200:1).

General procedure for the preparation of compounds ***4***

A mixture of compounds **3** (2 mmol), (2*S*)-3-methyl-2-(4-oxo-2-thioxothiazolidin-3-yl)pentanoic acid (2 mmol), 10 drops piperidine, and 10 drops glacial acetic acid in ethanol (15 mL) was refluxed for 4 h. After cooling, the solvent was evaporated under reduced pressure. The resulting residue was purified by silica gel column chromatography (dichloromethane/methanol = 100:1) to obtain a yellow solid.

2-((5E)-5-(4-((E)-3-(2,4-Dichlorophenyl)-3-oxoprop-1-enyl) benzylidene)-4-oxo-2-thioxothiazolidin-3-yl)acetic acid (previously reported compound PHR105K) Yield: 53 %; m.p. 235–236 °C. IR (KBr) cm^{-1}: 3449 (OH), 1687 (C=O). ^{1}H NMR (DMSO-*d*6, 300 MHz, ppm): δ 4.75 (s, 2H, CH_2), 7.43 (d, J = 15.3 Hz, 1H, CH=CH), 7.96 (s, 1H, CH), 7.80 (d, J = 15.3 Hz, 1H, CH=CH), 7.38–7.99 (m, 7H, Ar–H), 13.50 (s, 1H, COOH). ^{13}C NMR (DMSO-*d*6, 300 MHz, ppm): δ 193.37 (C=S), 192.62 (C=O), 167.71 (COOH), 166.78 (C=O), 145.44 (C=C), 137.59 (C=C), 136.88 (Ar–C), 136.33 (Ar–C), 135.40 (Ar–C), 133.24 (Ar–C), 131.82 (Ar–C), 131.67 (Ar–C), 130.28 (Ar–C), 128.16 (Ar–C), 123.57 (C=C), 45.52 (C–N). MS *m*/*z* 479 (M+1).

*(Z)-3-Methyl-2-(4-oxo-2-thioxo-5-((5-(p-tolyl)furan-2-yl) methylene)thiazolidin-3-yl)pentanoic acid (**4a**)* Yield: 87 %. m.p. 115–117 °C. IR (KBr) cm^{-1}: 2966 (OH), 1713 (C=O). ^{1}H NMR (DMSO-*d*6, 300 MHz, ppm): δ 0.75 (t, J = 7.5 Hz, 3H, CH_3), 0.89 (m, 1H, CH), 1.11 (d, J = 6 Hz, 3H, CH_3), 1.21 (m, 2H, CH_2), 2.33 (s, 3H, CH_3), 5.18 (d, J = 9 Hz, 1H, CH), 7.27 (d, J = 3 Hz, 1H, CH), 7.33 (s, 1H, CH), 7.68 (s, 1H, CH), 7.36–7.74 (m, 4H, Ar–H), 13.15 (s, 1H, COOH). ^{13}C NMR (DMSO-*d*6, 75 MHz, ppm): δ 194.45 (C=S), 169.23 (COOH), 166.77 (C=O), 153.64 (C–O), 149.28 (C–O), 139.85 (C=C), 130.36 (Ar–C), 128.62 (Ar–C), 126.28 (Ar–C), 125.78 (Ar–C), 124.98 (C–S), 119.82 (Ar–C), 116.60 (Ar–C), 110.22 (C=C), 109.55 (C=C), 61.95 (C–N), 33.50 (CH), 25.30 (CH_2), 21.51 (Ar–CH_3), 18.08 (CH_3), 11.34 (CH_3). MS *m*/*z* 417 (M+1).

*(Z)-3-Methyl-2-(4-oxo-2-thioxo-5-((5-(4-(trifluoromethoxy) phenyl)furan-2-yl)methylene)thiazolidin-3-yl)pentanoic acid (**4b**)* Yield: 88 %. m.p. 112–114 °C. IR (KBr) cm^{-1}: 3028 (OH), 1713 (C=O). ^{1}H NMR (DMSO-*d*6, 300 MHz, ppm): δ 0.80 (t, J = 7.5 Hz, 3H, CH_3), 0.97 (m, 1H, CH), 1.13 (d, J = 6 Hz, 3H, CH_3), 1.20 (m, 2H, CH_2), 5.23 (d, J = 9 Hz, 1H, CH), 7.40 (s, 1H, CH), 7.44 (s, 1H, CH), 7.54–8.01 (m, 4H, Ar–H), 7.76 (s, 1H, CH), 13.22 (s, 1H,

COOH). ^{13}C NMR (DMSO-*d*6, 75 MHz, ppm): δ 193.97 (C=S), 173.56 (COOH), 168.73 (C=O), 166.30 (Ar–C), 156.90 (C–O), 152.68 (C–O), 149.55 (C=C), 148.59 (Ar–C), 127.70 (Ar–C), 126.43 (Ar–C), 123.73 (C–S), 121.94 (OCF_3), 119.24 (Ar–C), 117.18 (Ar–C), 115.19 (C=C), 111.15 (C=C), 61.49 (C–N), 33.02 (CH), 24.81 (CH_2), 17.56 (CH_3), 10.84 (CH_3). MS *m*/*z* 486 (M+1).

*(Z)-2-(5-((5-(3-Chloro-4-fluorophenyl)furan-2-yl)methylene)-4-oxo-2-thioxothiazolidin-3-yl)-3-methylpentanoic acid (**4c**)* Yield: 89 %. m.p. 113–115 °C. IR (KBr) cm^{-1}: 2966 (OH), 1713 (C=O). ^{1}H NMR (DMSO-d_6, 300 MHz, ppm): δ 0.80 (t, $J = 7.5$ Hz, 3H, CH_3), 0.97 (m, 1H, CH), 1.16 (d, $J = 6$ Hz, 3H, CH_3), 1.22 (m, 2H, CH_2), 5.22 (d, $J = 9$ Hz, 1H, CH), 7.45 (d, $J = 6$ Hz, 1H, CH), 7.66 (t, $J = 9$ Hz, 1H, CH), 7.73 (s, 1H, CH), 7.40–8.10 (m, 3H, Ar–H), 13.22 (s, 1H, COOH). ^{13}C NMR (DMSO-d_6, 75 MHz, ppm): δ 193.84 (C=S), 168.71 (COOH), 166.26 (C=O), 162.00 (Ar–C), 155.85 (C–O), 149.51 (C–O), 142.55 (C=C), 128.47 (Ar–C), 126.55 (Ar–C), 124.88 (Ar–C), 123.56 (C–S), 119.08 (Ar–C), 117.87 (Ar–C), 111.23 (C=C), 109.50 (C=C), 61.48 (C–N), 33.02 (CH), 24.82 (CH_2), 17.57 (CH_3), 10.87 (CH_3). MS *m*/*z* 454 (M+1).

*(Z)-3-Methyl-2-(4-oxo-5-((5-phenylfuran-2-yl)methylene)-2-thioxothiazolidin-3-yl)pentanoic acid (**4d**)* Yield: 88 %. m.p. 103–105 °C. IR (KBr) cm^{-1}: 2966 (OH), 1713 (C=O). ^{1}H NMR (DMSO-d_6, 300 MHz, ppm): δ 0.80 (t, $J = 7.5$ Hz, 3H, CH_3), 0.97 (m, 1H, CH), 1.16 (d, $J = 6$ Hz, 3H, CH_3), 1.23 (m, 2H, CH_2), 5.23 (d, $J = 9$ Hz, 1H, CH), 7.39 (d, $J = 3$ Hz, 1H, CH), 7.47 (d, $J = 6$ Hz, 1H, CH), 7.75 (s, 1H, CH), 7.44–7.90 (m, 5H, Ar–H), 13.21 (s, 1H, COOH). ^{13}C NMR (DMSO-d_6, 75 MHz, ppm): δ 193.88 (C=S), 172.68 (COOH), 167.38 (C=O), 156.23 (C–O), 149.68 (C–O), 143.10 (C=C), 128.32 (Ar–C), 127.98 (Ar–C), 126.78 (Ar–C), 124.96 (Ar–C), 122.88 (C–S), 118.67 (Ar–C), 117.68 (Ar–C), 111.20 (C=C), 108.99 (C=C), 61.47 (C–N), 33.11 (CH), 25.09 (CH_2), 17.91 (CH_3), 10.96 (CH_3). MS *m*/*z* 403 (M+1).

*(Z)-3-Methyl-2-(5-((5-(naphthalen-2-yl)furan-2-yl)methylene)-4-oxo-2-thioxothiazolidin-3-yl)pentanoic acid (**4e**)* Yield: 87 %. m.p. 116–118 °C. IR (KBr) cm^{-1}: 2966 (OH), 1713 (C=O). ^{1}H NMR (DMSO-d_6, 300 MHz, ppm): δ 0.81 (d, $J = 6$ Hz, 3H, CH_3), 0.95 (m, 1H, CH), 1.16 (d, $J = 6$ Hz, 3H, CH_3), 1.24 (m, 2H, CH_2), 5.21 (d, $J = 9$ Hz, 1H, CH), 7.36 (d, $J = 3$ Hz, 1H, CH), 7.53 (t, $J = 9$ Hz, 1H, CH), 7.69 (m, 1H, CH), 7.66–8.40 (m, 7H, Ar–H), 13.21 (s, 1H, COOH). ^{13}C NMR (DMSO-d_6, 75 MHz, ppm): δ 194.44 (C=S), 169.23 (COOH), 166.82 (C=O), 158.73 (C–O), 149.94 (C–O), 134.08 (C=C), 130.76 (Ar–C), 129.49 (Ar–C), 129.37 (Ar–C), 127.90 (Ar–C), 127.45 (Ar–C), 127.03 (Ar–C), 126.47 (Ar–C), 126.12 (Ar–C), 125.30 (Ar–C), 124.01 (Ar–C), 119.93 (C–S), 117.45 (C=C), 114.50 (C=C), 61.98 (C–N), 33.52 (CH), 25.32 (CH_2), 18.05 (CH_3), 11.34 (CH_3). MS *m*/*z* 453 (M+1).

*(Z)-2-(5-((5-(4-Bromophenyl)furan-2-yl)methylene)-4-oxo-2-thioxothiazolidin-3-yl)-3-methylpentanoic acid (**4f**)* Yield: 88 %. m.p. 111–113 °C. IR (KBr) cm^{-1}: 3028 (OH), 1713 (C=O). ^{1}H NMR (DMSO-d_6, 300 MHz, ppm): δ 0.80 (t, $J = 7.5$ Hz, 3H, CH_3), 0.97 (m, 1H, CH), 1.16 (d, $J = 6$ Hz, 3H, CH_3), 1.22 (m, 2H, CH_2), 5.22 (d, $J = 9$ Hz, 1H, CH), 7.39 (m, 1H, CH), 7.43 (m, 1H, CH), 7.73 (s, 1H, CH), 7.77–7.84 (m, 4H, Ar–H), 13.21 (s, 1H, COOH). ^{13}C NMR (DMSO-d_6, 75 MHz, ppm): δ 194.65 (C=S), 168.95 (COOH), 167.03 (C=O), 153.62 (C–O), 148.95 (C–O), 140.10 (C=C), 131.56 (Ar–C), 129.91 (Ar–C), 128.28 (Ar–C), 126.78 (Ar–C), 125.62 (C–S), 119.26 (Ar–C), 117.59 (Ar–C), 111.01 (C=C), 109.14 (C=C), 61.48 (C–N), 34.26 (CH), 24.98 (CH_2), 17.90 (CH_3), 11.32 (CH_3). MS *m*/*z* 481 (M+1).

*(Z)-2-(5-((5-(4-Chlorophenyl)furan-2-yl)methylene)-4-oxo-2-thioxothiazolidin-3-yl)-3-methylpentanoic acid (**4g**)* Yield: 90 %. m.p. 112–114 °C. IR (KBr) cm^{-1}: 2966 (OH), 1713 (C=O). ^{1}H NMR (DMSO-d_6, 300 MHz, ppm): δ 0.80 (t, $J = 7.5$ Hz, 3H, CH_3), 0.97 (m, 1H, CH), 1.16 (d, $J = 6$ Hz, 3H, CH_3), 1.22 (m, 2H, CH_2), 5.23 (d, $J = 9$ Hz, 1H, CH), 7.40 (m, 1H, CH), 7.43 (m, 1H, CH), 7.74 (s, 1H, CH), 7.60–7.90 (m, 4H, Ar–H), 13.21 (s, 1H, COOH). ^{13}C NMR (DMSO-d_6, 75 MHz, ppm): δ 195.24 (C=S), 169.20 (COOH), 166.76 (C=O), 157.67 (C–O), 149.85 (C–O), 142.35 (C=C), 134.35 (Ar–C), 132.56 (Ar–C), 129.89 (Ar–C), 127.76 (Ar–C), 126.57 (Ar–C), 124.24 (Ar–C), 119.67 (C–S), 117.49 (C=C), 111.45 (C=C), 61.98 (C–N), 33.52 (CH), 25.32 (CH_2), 18.06 (CH_3), 11.35 (CH_3). MS *m*/*z* 437 (M+1).

*(Z)-2-(5-((5-(3-Chlorophenyl)furan-2-yl)methylene)-4-oxo-2-thioxothiazolidin-3-yl)-3-methylpentanoic acid (**4h**)* Yield: 87 %. m.p. 110–112 °C. IR (KBr) cm^{-1}: 2966 (OH), 1713 (C=O). ^{1}H NMR (DMSO-d_6, 300 MHz, ppm): δ 0.80 (t, $J = 7.5$ Hz, 3H, CH_3), 0.96 (m, 1H, CH), 1.16 (d, $J = 6$ Hz, 3H, CH_3), 1.26 (m, 2H, CH_2), 5.24 (d, $J = 9$ Hz, 1H, CH), 7.43 (d, $J = 3$ Hz, 1H, CH), 7.62 (m, 1H, CH), 7.75 (s, 1H, CH), 7.49–7.94 (m, 4H, Ar–H), 13.22 (s, 1H, COOH). ^{13}C NMR (DMSO-d_6, 75 MHz, ppm): δ 194.34 (C=S), 169.18 (COOH), 166.74 (C=O), 157.04 (C–O), 150.03 (C–O), 134.56 (C=C), 131.68 (Ar–C), 130.86 (Ar–C), 129.41 (Ar–C), 124.53 (Ar–C), 123.98 (Ar–C), 123.29 (Ar–C), 119.61 (C–S), 117.87 (C=C), 112.02 (C=C), 61.98 (C–N), 33.52 (CH), 25.32 (CH_2), 18.06 (CH_3), 11.36 (CH_3). MS *m*/*z* 437 (M+1).

*(Z)-2-(5-((5-(2-Chlorophenyl)furan-2-yl)methylene)-4-oxo-2-thioxothiazolidin-3-yl)-3-methylpentanoic acid (**4i**)* Yield: 89 %. m.p. 114–116 °C. IR (KBr) cm^{-1}: 2966 (OH), 1713 (C=O). ^{1}H NMR (DMSO-d_6, 300 MHz, ppm): δ 0.80 (t, $J = 7.5$ Hz, 3H, CH_3), 0.98 (m, 1H, CH), 1.16 (d, $J = 6$ Hz, 3H, CH_3), 1.24 (m, 2H, CH_2), 5.23 (d, $J = 9$ Hz, 1H, CH), 7.45 (m, 1H, CH), 7.60 (m, 1H, CH), 7.80 (s, 1H, CH), 7.46–7.98 (m, 4H, Ar–H), 13.22 (s, 1H, COOH). ^{13}C NMR (DMSO-d_6, 75 MHz, ppm): δ 194.42 (C=S), 169.13 (COOH), 166.79 (C=O), 154.99 (C–O), 149.62 (C–O), 131.60 (C=C), 131.02 (Ar–C), 130.47 (Ar–C), 128.81 (Ar–C), 127.41 (Ar–C), 123.56 (Ar–C), 123.29 (Ar–C), 119.61 (C–S), 118.33 (C=C), 115.40 (C=C), 62.03 (C–N), 33.52 (CH), 25.35 (CH_2), 18.05 (CH_3), 11.34 (CH_3). MS *m/z* 437 (M+1).

*(Z)-3-Methyl-2-(4-oxo-2-thioxo-5-((5-(o-tolyl)furan-2-yl)methylene)thiazolidin-3-yl)pentanoic acid (**4j**)* Yield: 88 %. m.p. 96–98 °C. IR (KBr) cm^{-1}: 3028 (OH), 1713 (C=O). ^{1}H NMR (DMSO-d_6, 300 MHz, ppm): δ 0.81 (t, $J = 7.5$ Hz, 3H, CH_3), 0.96 (m, 1H, CH), 1.16 (d, $J = 6$ Hz, 3H, CH_3), 1.26 (m, 2H, CH_2), 3.18 (s, 3H, CH_3), 5.25 (d, $J = 9$ Hz, 1H, CH), 7.21 (s, 1H, CH), 7.46 (m, 1H, CH), 7.78 (s, 1H, CH), 7.46–7.93 (m, 4H, Ar–H), 13.21 (s, 1H, COOH). ^{13}C NMR (DMSO-d_6, 75 MHz, ppm): δ 194.31 (C=S), 169.21 (COOH), 166.77 (C=O), 158.64 (C–O), 149.16 (C–O), 135.74 (C=C), 132.11 (Ar–C), 129.75 (Ar–C), 128.42 (Ar–C), 127.46 (Ar–C), 127.07 (C–S), 124.21 (Ar–C), 119.92 (Ar–C), 117.03 (C=C), 114.05 (C=C), 61.97 (C–N), 33.50 (CH), 25.31 (CH_2), 22.18 (Ar–CH_3), 18.07 (CH_3), 11.35 (CH_3). MS *m/z* 416 (M+1).

*(Z)-2-(5-((5-(4-Bromophenyl)furan-2-yl)methylene)-4-oxo-2-thioxothiazolidin-3-yl)-3-methylpentanoic acid (**4k**)* Yield: 90 %. m.p. 97–99 °C. IR (KBr) cm^{-1}: 2966 (OH), 1713 (C=O). ^{1}H NMR (DMSO-d_6, 300 MHz, ppm): δ 0.80 (t, $J = 7.5$ Hz, 3H, CH_3), 0.95 (m, 1H, CH), 1.15 (d, $J = 6$ Hz, 3H, CH_3), 1.25 (m, 2H, CH_2), 5.22 (d, $J = 9$ Hz, 1H, CH), 7.13 (m, 1H, CH), 7.39 (m, 1H, CH), 7.76 (s, 1H, CH), 7.39–7.82 (m, 4H, Ar–H), 13.18 (s, 1H, COOH). ^{13}C NMR (DMSO-d_6, 75 MHz, ppm): δ 194.48 (C=S), 169.18 (COOH), 166.77 (C=O), 152.95 (C–O), 149.55 (C–O), 131.53 (C=C), 126.81 (Ar–C), 125.89 (Ar–C), 123.91 (Ar–C), 119.56 (Ar–C), 118.09 (C–S), 117.18 (Ar–C), 116.91 (Ar–C), 114.60 (C=C), 114.45 (C=C), 61.98 (C–N), 33.52 (CH), 25.32 (CH_2), 18.04 (CH_3), 11.34 (CH_3). MS *m/z* 421 (M+1).

*(Z)-2-(5-((5-(2,5-Dichlorophenyl)furan-2-yl)methylene)-4-oxo-2-thioxothiazolidin-3-yl)-3-methylpentanoic acid (**4l**)* Yield: 88 %. m.p. 114–116 °C. IR (KBr) cm^{-1}: 2966 (OH), 1713 (C=O). ^{1}H NMR (DMSO-d_6, 300 MHz, ppm): δ 0.80 (t, $J = 7.5$ Hz, 3H, CH_3), 0.96 (m, 1H, CH), 1.16 (d, $J = 6$ Hz, 3H, CH_3), 1.26 (m, 2H, CH_2), 5.22 (d, $J = 9$ Hz, 1H, CH), 7.44 (d, $J = 3$ Hz, 1H, CH), 7.52 (m, 1H, CH), 7.79 (s, 1H, CH), 7.58–7.94 (m, 4H, Ar–H), 13.23 (s, 1H, COOH). ^{13}C NMR (DMSO-d_6, 75 MHz, ppm): δ 194.50 (C=S), 169.10 (COOH), 166.74 (C=O), 153.35 (C–O), 149.99 (C–O), 133.25 (C=C), 132.98 (Ar–C), 130.39 (Ar–C), 129.00 (Ar–C), 128.83 (Ar–C), 127.94 (C–S), 123.20 (Ar–C), 119.36 (Ar–C), 119.06 (C=C), 116.16 (C=C), 62.06 (C–N), 33.54 (CH), 25.37 (CH_2), 18.03 (CH_3), 11.35 (CH_3). MS *m/z* 471 (M+1).

*General procedure for the preparation of compounds **5***

A mixture of compounds **3** (2 mmol), (*S*)-2-(4-oxo-2-thioxothiazolidin-3-yl)-3-phenylpropanoic acid (2 mmol), 10 drops piperidine, and 10 drops glacial acetic acid in ethanol (15 mL) was refluxed for 4 h. After cooling, the solvent was evaporated under reduced pressure. The resulting residue was purified by silica gel column chromatography (dichloromethane/methanol = 100:1) to obtain a yellow solid.

*(Z)-2-(5-((5-(3-Chloro-4-fluorophenyl)furan-2-yl)methylene)-4-oxo-2-thioxothiazolidin-3-yl)-3-phenylpropanoic acid (**5a**)* Yield: 88 %. m.p. 118–120 °C. IR (KBr) cm^{-1}: 3028 (OH), 1713 (C=O). ^{1}H NMR (DMSO-d_6, 300 MHz, ppm): δ 3.52 (d, $J = 9$ Hz, 2H, CH_2), 5.90 (m, 1H, CH), 7.15 (m, 1H, CH), 7.40 (m, 1H, CH), 7.68 (s, 1H, CH), 7.15–8.09 (m, 8H, Ar–H), 13.46 (s, 1H, COOH). ^{13}C NMR (DMSO-d_6, 75 MHz, ppm): δ 193.74 (C=S), 170.28 (COOH), 169.25 (C=O), 166.53 (C–O), 165.55 (C–O), 156.27 (Ar–C), 155.04 (C=C), 149.95 (Ar–C), 148.77 (Ar–C), 136.99 (Ar–C), 129.48 (Ar–C), 128.72 (Ar–C), 127.04 (Ar–C), 125.43 (Ar–C), 123.91 (Ar–C), 121.30 (Ar–C), 121.13 (Ar–C), 119.21 (Ar–C), 117.85 (C–S), 111.69 (C=C), 108.94 (C=C), 58.54 (C–N), 33.56 (CH_2). MS *m/z* 489 (M+1).

*(Z)-2-(4-Oxo-2-thioxo-5-((5-(4-(trifluoromethoxy)phenyl)furan-2-yl)methylene)thiazolidin-3-yl)-3-phenylpropanoic acid (**5b**)* Yield: 88 %. m.p. 116–118 °C. IR (KBr) cm^{-1}: 2966 (OH), 1713 (C=O). ^{1}H NMR (DMSO-d_6, 300 MHz, ppm): δ 3.50 (d, $J = 9$ Hz, 2H, CH_2), 5.90 (m, 1H, CH), 7.14 (m, 1H, CH), 7.42 (m, 1H, CH), 7.69 (s, 1H, CH), 7.13–8.08 (m, 9H, Ar–H), 13.44 (s, 1H, COOH). ^{13}C NMR (DMSO-d_6, 75 MHz, ppm): δ 193.37 (C=S), 173.90 (COOH), 167.82 (C=O), 166.08 (C–O), 158.16 (C–O), 156.81 (Ar–C), 150.87 (C=C), 149.45 (Ar–C), 148.58 (Ar–C), 139.68 (Ar–C), 136.49 (Ar–C), 135.30 (Ar–C), 128.99 (Ar–C), 128.23 (Ar–C), 127.65 (Ar–C), 126.69 (Ar–C), 126.43 (Ar–C), 123.62 (Ar–C), 121.92 (OCF_3), 118.86 (C–S), 111.84 (C=C), 111.11 (C=C), 58.04 (C–N), 33.06 (CH_2). MS *m/z* 520 (M+1).

*(Z)-2-(5-((5-(4-Bromophenyl)furan-2-yl)methylene)-4-oxo-2-thioxothiazolidin-3-yl)-3-phenylpropanoic acid (**5c**)* Yield: 88 %. m.p. 115–117 °C. IR (KBr) cm^{-1}: 3028 (OH), 1713 (C=O). ^{1}H NMR (DMSO-d_6, 300 MHz, ppm): δ 3.52 (d, $J = 9$ Hz, 2H, CH_2), 5.89 (m, 1H, CH), 7.14 (m, 1H, CH), 7.41 (m, 1H, CH), 7.68 (s, 1H, CH), 7.14–7.85 (m, 9H, Ar–H), 13.45 (s, 1H, COOH). ^{13}C NMR (DMSO-d_6, 75 MHz, ppm): δ 193.80 (C=S), 169.26 (COOH), 166.57 (C=O), 157.67 (C–O), 149.82 (C–O), 139.48 (C=C), 137.00 (Ar–C), 135.46 (Ar–C), 133.25 (Ar–C), 132.98 (Ar–C), 132.79 (Ar–C), 129.48 (Ar–C), 128.73 (Ar–C), 128.08 (Ar–C), 127.17 (Ar–C), 126.77 (Ar–C), 124.13 (Ar–C), 123.06 (Ar–C), 119.30 (C–S), 117.66 (C=C), 111.46 (C=C), 58.55 (C–N), 33.61 (CH_2). MS *m/z* 515 (M+1).

*(Z)-2-(5-((5-(2-Chlorophenyl)furan-2-yl)methylene)-4-oxo-2-thioxothiazolidin-3-yl)-3-phenylpropanoic acid (**5d**)* Yield: 86 %. m.p. 117–119 °C. IR (KBr) cm^{-1}: 2966 (OH), 1713 (C=O). ^{1}H NMR (DMSO-d_6, 300 MHz, ppm): δ 3.51 (d, $J = 9$ Hz, 2H, CH_2), 5.88 (m, 1H, CH), 7.15 (m, 1H, CH), 7.45 (m, 1H, CH), 7.72 (s, 1H, CH), 7.14–7.92 (m, 9H, Ar–H), 13.47 (s, 1H, COOH). ^{13}C NMR (DMSO-d_6, 75 MHz, ppm): δ 193.86 (C=S), 169.24 (COOH), 166.58 (C=O), 154.88 (C–O), 149.52 (C–O), 138.47 (C=C), 136.99 (Ar–C), 131.59 (Ar–C), 130.98 (Ar–C), 130.43 (Ar–C), 129.47 (Ar–C), 128.73 (Ar–C), 128.50 (Ar–C), 127.35 (Ar–C), 127.18 (Ar–C), 123.51 (Ar–C), 121.09 (Ar–C), 119.25 (Ar–C), 118.37 (C–S), 115.39 (C=C), 114.33 (C=C), 58.57 (C–N), 33.56 (CH_2). MS *m/z* 471 (M+1).

*(Z)-2-(5-((5-(3-Chlorophenyl)furan-2-yl)methylene)-4-oxo-2-thioxothiazolidin-3-yl)-3-phenylpropanoic acid (**5e**)* Yield: 88 %. m.p. 112–114 °C. IR (KBr) cm^{-1}: 2966 (OH), 1713 (C=O). ^{1}H NMR (DMSO-d_6, 300 MHz, ppm): δ 3.52 (d, $J = 9$ Hz, 2H, CH_2), 5.89 (m, 1H, CH), 7.15 (m, 1H, CH), 7.40 (d, $J = 3$ Hz, 1H, CH), 7.69 (s, 1H, CH), 7.15–7.91 (m, 9H, Ar–H), 13.46 (s, 1H, COOH). ^{13}C NMR (DMSO-d_6, 75 MHz, ppm): δ 193.78 (C=S), 169.19 (COOH), 166.54 (C=O), 156.99 (C–O), 149.96 (C–O), 136.99 (C=C), 134.55 (Ar–C), 132.23 (Ar–C), 131.67 (Ar–C), 131.24 (Ar–C), 130.85 (Ar–C), 129.43 (Ar–C), 128.73 (Ar–C), 127.36 (Ar–C), 127.15 (Ar–C), 124.53 (Ar–C), 123.87 (Ar–C), 119.26 (Ar–C), 117.94 (C–S), 111.99 (C=C), 107.43 (C=C), 58.57 (C–N), 33.56 (CH_2). MS *m/z* 471 (M+1).

*(Z)-2-(5-((5-(4-Chlorophenyl)furan-2-yl)methylene)-4-oxo-2-thioxothiazolidin-3-yl)-3-phenylpropanoic acid (**5f**)* Yield: 87 %. m.p. 115–117 °C. IR (KBr) cm^{-1}: 3028 (OH), 1713 (C=O). ^{1}H NMR (DMSO-d_6, 300 MHz, ppm): δ 3.52 (d, $J = 9$ Hz, 2H, CH_2), 5.89 (m, 1H, CH), 7.15 (m, 1H, CH), 7.40 (m, 1H, CH), 7.68 (s, 1H, CH), 7.14–7.86 (m, 9H, Ar–H), 13.45 (s, 1H, COOH). ^{13}C NMR (DMSO-d_6, 75 MHz, ppm): δ 193.38 (C=S), 168.79 (COOH), 166.08 (C=O), 156.79 (C–O), 149.00 (C–O), 136.50 (C=C), 134.26 (Ar–C), 133.02 (Ar–C), 131.05 (Ar–C), 129.00 (Ar–C), 128.24 (Ar–C), 127.20 (Ar–C), 126.70 (Ar–C), 126.34 (Ar–C), 125.44 (Ar–C), 124.23 (Ar–C), 123.40 (Ar–C), 118.76 (Ar–C), 116.68 (C–S), 113.98 (C=C), 109.52 (C=C), 58.06 (C–N), 33.09 (CH_2). MS *m/z* 471 (M+1).

*(Z)-2-(5-((5-(2-Fluorophenyl)furan-2-yl)methylene)-4-oxo-2-thioxothiazolidin-3-yl)-3-phenylpropanoic acid (**5g**)* Yield: 88 %. m.p. 114–116 °C. IR (KBr) cm^{-1}: 2966 (OH), 1713 (C=O). ^{1}H NMR (DMSO-d_6, 300 MHz, ppm): δ 3.52 (d, $J = 9$ Hz, 2H, CH_2), 5.88 (m, 1H, CH), 7.15 (m, 1H, CH), 7.43 (m, 1H, CH), 7.72 (s, 1H, CH), 7.14–7.90 (m, 9H, Ar–H), 13.47 (s, 1H, COOH). ^{13}C NMR (DMSO-d_6, 75 MHz, ppm): δ 193.38 (C=S), 169.23 (COOH), 166.57 (C=O), 160.62 (Ar–C), 152.89 (C–O), 149.49 (C–O), 137.00 (C=C), 131.62 (Ar–C), 131.02 (Ar–C), 129.47 (Ar–C), 128.72 (Ar–C), 127.17 (Ar–C), 126.85 (Ar–C), 125.90 (Ar–C), 123.83 (Ar–C), 119.21 (Ar–C), 118.18 (Ar–C), 117.16 (C–S), 116.89 (Ar–C), 115.26 (C=C), 114.43 (C=C), 58.56 (C–N), 33.58 (CH_2). MS *m/z* 455 (M+1).

*(Z)-2-(4-Oxo-5-((5-phenylfuran-2-yl)methylene)-2-thioxothiazolidin-3-yl)-3-phenylpropanoic acid (**5h**)* Yield: 88 %. m.p. 117–119 °C. IR (KBr) cm^{-1}: 3028 (OH), 1713 (C=O). ^{1}H NMR (DMSO-d_6, 300 MHz, ppm): δ 3.52 (d, $J = 9$ Hz, 2H, CH_2), 5.89 (m, 1H, CH), 7.15 (m, 1H, CH), 7.36 (d, $J = 3$ Hz, 1H, CH), 7.68 (s, 1H, CH), 7.14–7.86 (m, 10H, Ar–H), 13.45 (s, 1H, COOH). ^{13}C NMR (DMSO-d_6, 75 MHz, ppm): δ 193.87 (C=S), 168.11 (COOH), 166.59 (C=O), 158.83 (C–O), 151.39 (C–O), 142.58 (C=C), 137.02 (Ar–C), 129.80 (Ar–C), 129.49 (Ar–C), 128.92 (Ar–C), 128.73 (Ar–C), 127.18 (Ar–C), 126.31 (Ar–C), 125.79 (Ar–C), 124.96 (Ar–C), 124.22 (Ar–C), 122.58 (Ar–C), 119.44 (Ar–C), 117.22 (C–S), 114.68 (C=C), 110.82 (C=C), 58.54 (C–N), 33.61 (CH_2). MS *m/z* 437 (M+1).

*(Z)-2-(5-((5-(Naphthalene-2-yl)furan-2-yl)methylene)-4-oxo-2-thioxothiazolidin-3-yl)-3-phenylpropanoic acid (**5i**)* Yield: 88 %. m.p. 122–124 °C. IR (KBr) cm^{-1}: 2966 (OH), 1713 (C=O). ^{1}H NMR (DMSO-d_6, 300 MHz, ppm): δ 3.52 (d, $J = 9$ Hz, 2H, CH_2), 5.89 (m, 1H, CH), 7.15 (m, 1H, CH), 7.36 (d, $J = 3$ Hz, 1H, CH), 7.76 (s, 1H, CH), 7.15–8.51 (m, 12H, Ar–H), 13.46 (s, 1H, COOH). ^{13}C NMR (DMSO-d_6, 75 MHz, ppm): δ 193.88 (C=S), 169.28 (COOH), 166.62 (C=O), 158.53 (C–O), 154.89 (C–O), 149.84 (C=C), 138.08 (Ar–C), 137.04 (Ar–C), 134.07 (Ar–C), 132.56 (Ar–C), 130.72 (Ar–C), 129.46 (Ar–C), 129.36

(Ar–C), 128.71 (Ar–C), 127.87 (Ar–C), 127.36 (Ar–C), 127.16 (Ar–C), 127.01 (Ar–C), 126.44 (Ar–C), 126.11 (Ar–C), 125.23 (Ar–C), 123.86 (Ar–C), 119.55 (C–S), 117.59 (C=C), 114.48 (C=C), 58.55 (C–N), 33.59 (CH_2). MS *m*/*z* 487 (M+1).

*(Z)-2-(4-Oxo-2-thioxo-5-((5-(p-tolyl)furan-2-yl)methylene) thiazolidin-3-yl)-3-phenylpropanoic acid (**5j**)* Yield: 87 %. m.p. 118–120 °C. IR (KBr) cm^{-1}: 2966 (OH), 1713 (C=O). ^{1}H NMR (DMSO-d_6, 300 MHz, ppm): δ 3.35 (s, 3H, CH_3), 3.50 (d, $J = 9$ Hz, 2H, CH_2), 5.89 (m, 1H, CH), 7.17 (m, 1H, CH), 7.29 (d, $J = 3$ Hz, 1H, CH), 7.66 (s, 1H, CH), 7.17–7.75 (m, 9H, Ar–H), 13.44 (s, 1H, COOH). ^{13}C NMR (DMSO-d_6, 75 MHz, ppm): δ 193.86 (C=S), 167.90 (COOH), 166.58 (C=O), 157.63 (C–O), 153.45 (C–O), 143.64 (C=C), 137.05 (Ar–C), 129.80 (Ar–C), 129.02 (Ar–C), 128.87 (Ar–C), 128.03 (Ar–C), 127.15 (Ar–C), 126.88 (Ar–C), 125.61 (Ar–C), 124.82 (Ar–C), 124.34 (Ar–C), 122.32 (Ar–C), 119.85 (Ar–C), 118.96 (C–S), 114.99 (C=C), 110.85 (C=C), 58.53 (C–N), 33.65 (CH_2), 22.20 (Ar–CH_3). MS *m*/*z* 451 (M+1).

*(Z)-2-(4-Oxo-2-thioxo-5-((5-(o-tolyl)furan-2-yl)methylene) thiazolidin-3-yl)-3-phenylpropanoic acid (**5k**)* Yield: 87 %. m.p. 112–114 °C. IR (KBr) cm^{-1}: 2966 (OH), 1713 (C=O). ^{1}H NMR (DMSO-d_6, 300 MHz, ppm): δ 3.17 (s, 3H, CH_3), 3.52 (d, $J = 9$ Hz, 2H, CH_2), 5.81 (m, 1H, CH), 7.11 (m, 1H, CH), 7.18 (m, 1H, CH), 7.67 (s, 1H, CH), 7.10–7.78 (m, 9H, Ar–H), 13.45 (s, 1H, COOH). ^{13}C NMR (DMSO-d_6, 75 MHz, ppm): δ 193.88 (C=S), 167.91 (COOH), 166.58 (C=O), 157.63 (C–O), 153.43 (C–O), 143.66 (C=C), 137.10 (Ar–C), 129.81 (Ar–C), 129.52 (Ar–C), 128.86 (Ar–C), 128.03 (Ar–C), 127.13 (Ar–C), 126.87 (Ar–C), 125.55 (Ar–C), 124.86 (Ar–C), 124.34 (Ar–C), 122.28 (Ar–C), 119.96 (Ar–C), 118.55 (C–S), 114.99 (C=C), 110.32 (C=C), 58.52 (C–N), 33.67 (CH_2), 22.28 (Ar–CH_3). MS *m*/*z* 451 (M+1).

*(Z)-2-(5-((5-(2,5-Dichlorophenyl)furan-2-yl)methylene)-4-oxo-2-thioxothiazolidin-3-yl)-3-phenylpropanoic acid (**5l**)* Yield: 88 %. m.p. 115–117 °C. IR (KBr) cm^{-1}: 3028 (OH), 1713 (C=O). ^{1}H NMR (DMSO-d_6, 300 MHz, ppm): δ 3.52 (d, $J = 9$ Hz, 2H, CH_2), 5.88 (m, 1H, CH), 7.15 (m, 1H, CH), 7.42 (d, $J = 3$ Hz, 1H, CH), 7.79 (s, 1H, CH), 7.15–8.04 (m, 8H, Ar–H), 13.48 (s, 1H, COOH). ^{13}C NMR (DMSO-d_6, 75 MHz, ppm): δ 193.58 (C=S), 169.19 (COOH), 166.54 (C=O), 153.27 (C–O), 149.90 (C–O), 145.71 (C=C), 136.98 (Ar–C), 136.26 (Ar–C), 133.24 (Ar–C), 132.94 (Ar–C), 130.35 (Ar–C), 129.46 (Ar–C), 128.96 (Ar–C), 128.74 (Ar–C), 127.90 (Ar–C), 127.20 (Ar–C), 123.16 (Ar–C), 119.98 (Ar–C), 118.84 (C–S), 116.14 (C=C), 115.32 (C=C), 58.59 (C–N), 33.56 (CH_2). MS *m*/*z* 505 (M+1).

In vitro evaluation of the antibacterial activity of the compounds

The antibacterial activities of the compounds were evaluated in vitro in 96-well microtiter plates. A serial dilution method was used to obtain the minimum inhibitory concentration (MIC) values of the synthesized compounds against several different bacterial strains, including multi-drug-resistant clinical isolates. Oxacillin and norfloxacin were used as positive controls. The test bacteria were grown to the mid-log phase in Mueller–Hinton broth (MHB) and subsequently diluted 1000-fold in the same medium. The bacteria of 105 CFU/mL were inoculated into MHB and dispensed at 0.2 mL/well in a 96-well microtiter plate. Oxacillin and norfloxacin were used as positive controls. The test compounds were prepared in dimethyl sulfoxide (DMSO), with the final concentrations of the compounds not exceeding 0.05 %. A two-fold serial dilution technique was used to obtain final concentrations of 64–0.5 μg/mL. The MIC value was defined as the concentration of test compound required to completely inhibit the growth of the bacteria during a 24-h incubation period at 37 °C. The growth of the bacteria was determined by measuring the absorption at 650 nm using a microtiter enzyme-linked immunosorbent assay (ELISA) reader. All of the experiments were conducted in triplicate.

Evaluation of cytotoxicity

Human cervical (HeLa) cell monolayers were used as an in vitro model of the cervico-vaginal epithelium for testing the cytotoxicities of the new compounds. HeLa cells were grown in Dulbecco's modified Eagle medium (DMEM) supplemented with fetal bovine serum (10 %), and antibiotics (penicillin–streptomycin mixture [100 U/mL]). Cells at 80–90 % confluence were split by trypsin (0.25 % in phosphate-buffered saline (PBS); pH 7.4), and the medium was changed at 24-h intervals. The cells were cultured at 37 °C in a 5 % CO_2 incubator. The cells were grown for 3 passages and $\sim 1 \times 10^4$ cells were seeded into each well of a 96-well plate and incubated overnight to allow the cells to become attached to the substrate. After 24 h, the medium was replaced with DMEM supplemented with 10 % FBS containing a variety of different concentrations of the test compounds and incubated for 48 h. A 10 μL portion of an MTT solution (5 mg/mL in PBS) was then added to each well. Following a 4-h period of incubation, the medium was removed and the resulting formazan crystals were dissolved in DMSO (100 μL). Following a period of shaking for 10 min, the optical density was measured at 570 nm using a microtiter ELISA reader. The assay was conducted four times. The IC_{50} values were defined as the concentrations inhibiting the cell growth by 50 %.

Results and discussion

Chemistry

The furan derivatives were synthesized according to the route presented in Scheme 1. According to the previously described method (Cui *et al.*, 2010), anilines were used as the starting materials and reacted with furfural to afford the corresponding monosubstituted 5-phenylfuran-2-carbaldehydes (**3**). The *N*-substituted rhodanines were prepared according to a method previously described in the literature (Wang *et al.*, 2008). The 24 target compounds (**4a–l** and **5a–l**) were obtained via the Knoevenagel condensation reactions of the 5-phenylfuran-2-carbaldehydes (**3**) with the *N*-substituted rhodanines in good yields. The structures of the desired compounds were determined by IR, ^{1}H and ^{13}C NMR, and mass spectral and elemental analyses.

Biological evaluation

The antimicrobial activities of the synthesized compounds were evaluated in vitro using the broth microdilution method to obtain their MIC values against a variety of different bacterial strains, including multidrug-resistant clinical isolates. Oxacillin and norfloxacin were used as positive controls.

The synthesized compounds (**4a–l** and **5a–l**) were screened for their antibacterial activities against a number of different Gram-positive organisms, including *Staphylococcus aureus* RN4220, *S. aureus* KCTC 503, and *S. aureus* KCTC 209; and the Gram-negative organism *Escherichia coli* 1356. The results indicated that most of the synthesized compounds exhibited potent levels of inhibitory activity against the three Gram-positive bacterial strains (*S. aureus* RN 4220, *S. aureus* KCTC 209, and *S. aureus* KCTC 503) with MIC values in the range of 2–16 μg/mL. Compounds **5a–l** exhibited good levels of inhibitory activity against the Gram-positive bacteria *S. aureus* RN4220 with MIC values in the range of 2–4 μg/mL. Compounds **4a–l** and **5a–l** exhibited moderate to good levels of inhibition against *S. aureus* KCTC 209 and *S. aureus* KCTC 503, with MIC values in the range of 8–16 μg/mL. None of the compounds showed any inhibitory activity against the Gram-negative strain *E. coli* 1356 (MICs > 64 μg/mL), as shown in Table 1.

The compounds were also evaluated for their inhibitory activities against several clinical isolates of multidrug-resistant Gram-positive bacterial strains, including the methicillin-resistant *S. aureus* strains MRSA CCARM 3167 and MRSA CCARM 3506, and the quinolone-resistant *S. aureus* strains QRSA CCARM 3505 and QRSA CCARM 3519. The results are shown in Table 2. All of the compounds exhibited moderate activities against the strains tested with MIC values in the range of 4–16 μg/mL against the MRSA CCARM (3167 and 3506) and QRSA CCARM (3505 and 3519) strains.

From the results shown in Table 2, it is clear that compounds **4l** and **5a** displayed the most potent levels of inhibitory activities against MRSA CCARM 3506 (MIC = 2 μg/mL), whereas compounds **4g**, **4i**, **4k**, **5c**, **5e**, **5f**, and **5i** showed good levels of inhibitory activity against the four multidrug-resistant Gram-positive bacterial strains

Scheme 1 Synthetic scheme for the synthesis of the target compounds **4a–l** and **5a–l**

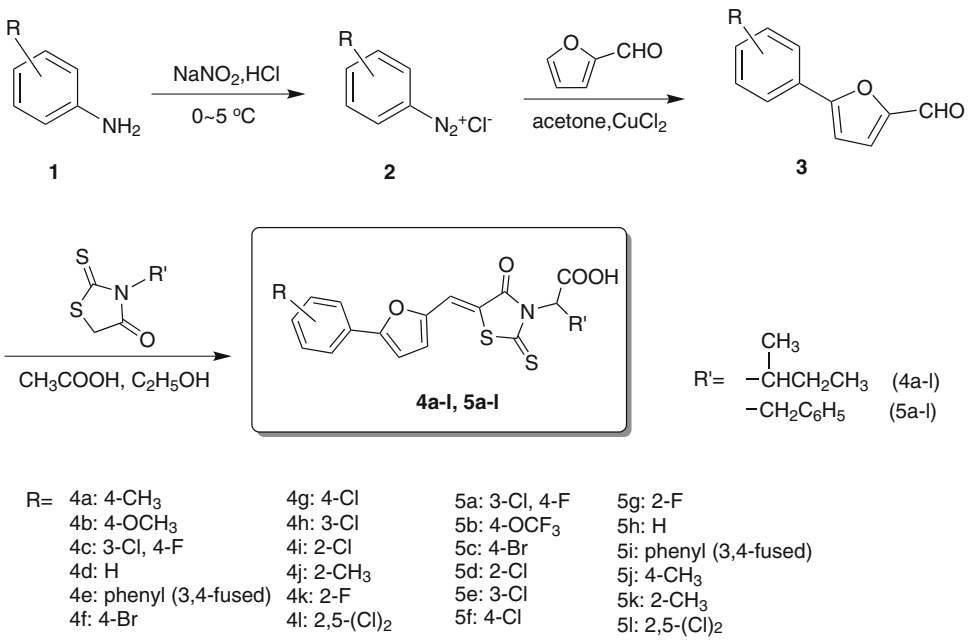
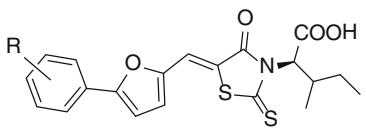
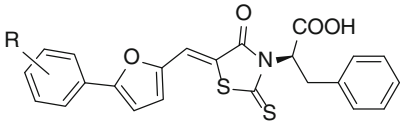


Table 1 Inhibitory activity (MIC, μg/mL) of compounds **4a–l** and **5a–l** against bacteria



4a-4l



5a-5l

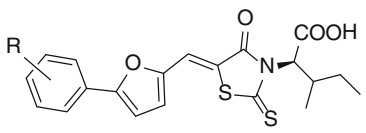
Compound	R	Gram-positive strains			Gram-negative strain
		S. aureus			*E. coli*
		4220	209	503	1356
4a	4-CH_3	4	8	16	>64
4b	4-OCF_3	4	16	16	>64
4c	3-Cl,4-F	4	16	16	>64
4d	H	8	8	16	>64
4e	Phenyl(3,4-fused)	8	8	8	>64
4f	4-Br	2	8	16	>64
4g	4-Cl	2	8	8	>64
4h	3-Cl	4	16	16	>64
4i	2-Cl	2	8	16	>64
4j	2-CH_3	4	16	16	>64
4k	2-F	2	8	16	>64
4l	2,5-$(Cl)_2$	2	16	16	>64
5a	3-Cl, 4-F	2	8	8	>64
5b	4-OCF_3	4	16	8	>64
5c	4-Br	2	8	8	>64
5d	2-Cl	4	8	16	>64
5e	3-Cl	4	16	16	>64
5f	4-Cl	2	16	16	>64
5g	2-F	4	8	16	>64
5h	H	4	8	8	>64
5i	Phenyl(3,4-fused)	4	8	8	>64
5j	4-CH_3	2	8	16	>64
5k	2-CH_3	4	16	16	>64
5l	2,5-$(Cl)_2$	2	16	16	>64
Norfloxacin	–	2	2	2	16
Oxacillin	–	1	1	1	>64

S. aureus RN 4220, *Staphylococcus aureus RN* 4220; *S. aureus* 503, *Staphylococcus aureus* 503; *S. aureus* 209, *Staphylococcus aureus* 209; *E. coli* 1356, *Escherichia coli CCARM* 1356

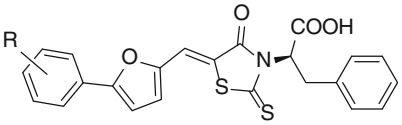
(MIC = 4 μg/mL). No clear structure–activity relationship pattern was found between the antibacterial activities and the positions and physicochemical properties of the different substituents on the phenyl ring.

To investigate whether the antibacterial activities of compounds **4b** and **5f** related specifically to their selective toxicity toward the bacteria, we evaluated their cytotoxicities (Table 3). Compounds **4b** and **5f** did not affect the cell viability of HeLa cells at their MIC values (4 or 2 μg/mL, respectively), but were cytotoxic at much higher concentrations. The disparity between their cytotoxicities and antibacterial activities of compounds **4b** and **5f** suggested that these compounds exhibited their in vitro antibacterial activities at non-cytotoxic concentrations.

Table 2 Inhibitory activity (MIC, μg/mL) of compounds **4a–l** and **5a–l** against clinical isolates of multidrug-resistant Gram-positive strains



4a-4l



5a-5l

Compound	R	Multidrug-resistant Gram-positive strains			
		MRSA		*QRSA*	
		3167	3506	3505	3519
4a	4-CH_3	8	8	8	8
4b	4-OCF_3	16	8	8	8
4c	3-Cl,4-F	8	8	8	8
4d	H	8	8	16	8
4e	Phenyl(3,4-fused)	8	8	8	8
4f	4-Br	8	8	8	8
4g	4-Cl	8	4	4	8
4h	3-Cl	8	8	8	8
4i	2-Cl	8	4	8	8
4j	2-CH_3	8	8	16	8
4k	2-F	8	4	8	8
4l	2,5-$(Cl)_2$	4	2	4	4
5a	3-Cl, 4-F	8	2	8	8
5b	4-OCF_3	16	8	16	16
5c	4-Br	8	4	8	8
5d	2-Cl	8	8	8	8
5e	3-Cl	8	4	8	8
5f	4-Cl	8	4	8	8
5g	2-F	8	8	8	8
5h	H	8	8	8	8
5i	Phenyl(3,4-fused)	4	8	8	4
5j	4-CH_3	8	8	8	8
5k	2-CH_3	8	8	16	8
5l	2,5-$(Cl)_2$	8	8	8	8
Norfloxacin	–	8	4	>64	>64
Oxacillin	–	>64	>64	1	1

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

Table 3 Cytotoxic activity of compounds **4b** and **5f** against HeLa cell

Compound	IC_{50} (μg/mL)
4b	16.23
5f	8.69

Conclusion

In summary, based on our previous work, we have synthesized two series of rhodanine derivatives. The antimicrobial activities of these compounds were evaluated and compared with standard drugs. The results revealed that most of the compounds exhibited good levels of antibacterial activity against Gram-positive bacteria as well as multidrug-resistant strains of clinical isolates. In particular, compounds **4f**, **4g**, **4i**, **4k**, **4l**, **5a**, **5c**, **5f**, **5j**, and **5l** showed excellent levels of antimicrobial activity, with MIC values of 2 μg/mL against the Gram-positive bacterial strains *S. aureus* RN 4220. The mechanism of action of the compounds tested in this study currently remains unknown. Most of the synthesized

compounds produced a bactericidal action on selected Gram-positive bacterial strains, including multidrug-resistant clinical isolates. Compound **4l** was found to be the most potent of the synthesized compounds against the multidrug-resistant strains, with a MIC value of 2 or 4 μg/mL. Furthermore, this material was more potent than the control drug norfloxacin. Compounds **4b** and **5f** exhibited in vitro antibacterial activity at non-cytotoxic concentrations. Thus, further studies of related compounds in the context of their structure–activity relationship, toxicity, and other biological effects might be helpful in designing new antimicrobials for therapeutic use.

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

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