Synthesis and antibacterial activities of pleuromutilin derivatives with thiazole-5-carboxamide and thioether moiety

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Seven novel pleuromutilin derivatives with thiazole-5-carboxamide and thioether moiety in the C_{14} side chain were designed and synthesised. The antibacterial activities of the target compounds were tested via agar-well diffusion method *in vitro*. The results showed that three target compounds still had antibacterial activity against *Staphylococcus aureus* ATCC26112 and *Staphylococcus aureus* SC at a low concentration of 0.05 μg mL^{-1}.

Keywords: pleuromutilins, antibacterial activity, Gram-positive bacteria, agar-well diffusion

Pleuromutilin(Fig. 1, **1**), a naturally occurring antibiotic, was first isolated in 1951 by Kavanagh and co-workers from several species of basidiomycetes including *Pleurotus mutilus*, *Pleurotus passeckerianus*, and *Drosophilia substrata*.[1,2] Early research showed that this kind of antibiotic has modest activity against Gram-positive pathogens and /or mycoplasmas *in vitro* but weak *in vivo* while it is not sensitive to Gram-negative pathogens.[3,4] Pleuromutilin inhibits the formation of bacterial protein through interaction with prokaryotic ribosomes and does not bind to mammalian ribosomes.[5] During the 1970s and early 1980s, a Sandoz group synthesised a series of pleuromutilin derivatives, and indicated that the modification of the C_{14} glycolic acid chain would offer better opportunities to obtain pleuromutilin derivatives with optimum activity, and the combinations of both the thioether group and the matrix moiety (pleuromutilin) gave excellent bioactivity.[6] Based on these structure–activity relationships (SARs), large numbers of pleuromutilin derivatives had been designed and synthesised.[7–15] As a result, tiamulin (Fig. 1, **2**)[7] and valnemulin (Fig. 1, **3**)[8] were developed as therapeutic agents for veterinary medicine to treat diseases in pigs and poultry.[9] Aiming at finding an agent for human use by further chemical modifications of pleuromutilin produced azamulin (Fig. 1, **4**),[10] which had good antibacterial activity but was subject to its poor solubility in water. [11] Later, researchers at GlaxoSmithKline reported the novel pleuromutilin analogue retapamulin (Fig. 1, **5**), which exhibited excellent antibacterial activity *in vitro* and therefore was applied as a topical antimicrobial agent for treatment of human skin infections in 2007.[12,13] Recently, Yoshimi Hirokawa and co-workers designed and synthesised novel thioether pleuromutilin derivatives (Fig. 1, **6**) bearing a purine ring at the C_{14} glycolic side chain. These pleuromutilin analogues showed good solubility in water and excellent antibacterial activity *in vitro* and *in vivo*. [13]

In our previous research, some pleuromutilin derivatives containing substituent pyrazole rings (Fig. 1, **7**)[16] and phenyl rings (Fig. 1, **8**)[17] binding to a carboxamide at the C_{14} side chain were reported and it was found that the pleuromutilin derivatives with a substituent heterocyclic carboxamide exhibited excellent activity while derivatives with the substituent benzamide showed low activity. Here, for the purpose of exploiting new antibacterial agents with high activity, a series of novel pleuromutilin derivatives containing a substituent thiazole ring and a thioether group at the C_{14} position in the side chain have been designed and synthesised, and the antibacterial activities of the target compounds have been tested via the agar-well diffusion method *in vitro*. The results showed that three target compounds had excellent antibacterial activity against *Staphylococcus aureus* ATCC26112 and *Staphylococcus aureus* SC.

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Experimental

Melting points were recorded on XRC-1 melting point apparatus (Sichuan University Instrument Inc., Chengdu, China) without being corrected. ^{1}H NMR spectra were run on a Varian INOVA-400 spectrometer (Varian Inc., Palo Alto, CA, USA) with $CDCl_3$ as the solvent and TMS as the internal standard. Mass spectra were recorded with Agilent 6210 (DOF-MAS) spectrometer (Agilent Inc., Santa Clara, CA, USA) using the electrospray ionisation (ESI) method. IR spectra were recorded with Perkin-Elmer 16PC-FT instrument (Perkin-Elmer Inc., Norwalk Conn, CA, USA). Compounds **3a**, and **3b** were commercially available, compounds **4** and **5** were synthesised according to the literature[18] and compound **7** was synthesised according to the literature.[17]

Synthesis of compounds **2c–g**

$SOCl_2$ (0.2 mol, 23.8 g) was added to a substituted benzoic acid (0.020 mol) and the reaction mixture was refluxed for 2 h. After removal of the excess $SOCl_2$ under reduced pressure, the resulting residue was cooled to room temperature and poured into a mixture of $NH_3{\cdot}H_2O$ (0.8 mol) and ice. The white solid which formed was washed with 2N NaOH to give a crude amide; yields: 62–69%.

Synthesis of compounds **3c–g**

Phosphoric sulfide (2.0 mmol) was added portionwise to a solution of a substituted amide **2** (5.0 mmol) in ethyl ether at 0 °C, the solution was stirred at room temperature overnight and then the solid was filtered off and the solvent was removed under reduced pressure to give a yellow solid; yields: 87–95%.

Synthesis of compounds **5**

Anhydrous magnesium sulfate (10.0 mmol) and ethyl 2-chloro-2-formylacetate **4** (10.0 mmol) were added to a solution of a substituted thioamide **3** (5.0 mmol) in toluene, the reaction mixture was stirred at 100 °C for 2 h, then cooled to room temperature and filtered. The solvent was removed under reduced pressure and the resulting residue was purified by chromatography (petroleum ether/ethyl acetate = 10:1) to provide the desired compound as a brown oil; yields: 41–48%.

Synthesis of compounds **6**[19]

The purified ester **7** (1.5 mmol) was refluxed for 1.5 h with sodium hydroxide (4.0 equiv.), water (10 mL) and ethanol (20 mL), the resulting residue was dissolved in water (30 mL), after removal of the solvent under reduced pressure, extracted with ethyl acetate (10 mL×3), the water layer acidified to pH = 2–3 with 6N HCl, extracted with ethyl acetate again (10 mL×3) and the organic layer was evaporated *in vacuo* to afford a yellow solid; yields: 83–92%.

Synthesis of target molecules **8**

$SOCl_2$ (0.2 mol, 23.8 g) was added to the thiazole acid **6** (2.0 mmol), the solution was heated to reflux whilst the temperature was maintained for 1.5 h, then the solution was cooled to room temperature. After removal of the excess $SOCl_2$ under reduced pressure, CH_2Cl_2 (25 mL) was added to the resulting residue at 0 °C, followed by triethylamine (2.0 mmol). When the solution became clear, a catalytic amount of pyridine (0.20 mmol) and compound **7** (1.80 mmol, 0.84 g) were added at 0 °C respectively. The reaction mixture was allowed to stir at room temperature for 1 h, more CH_2Cl_2 (25 mL) was added to the mixture, which was washed with saturated sodium chloride

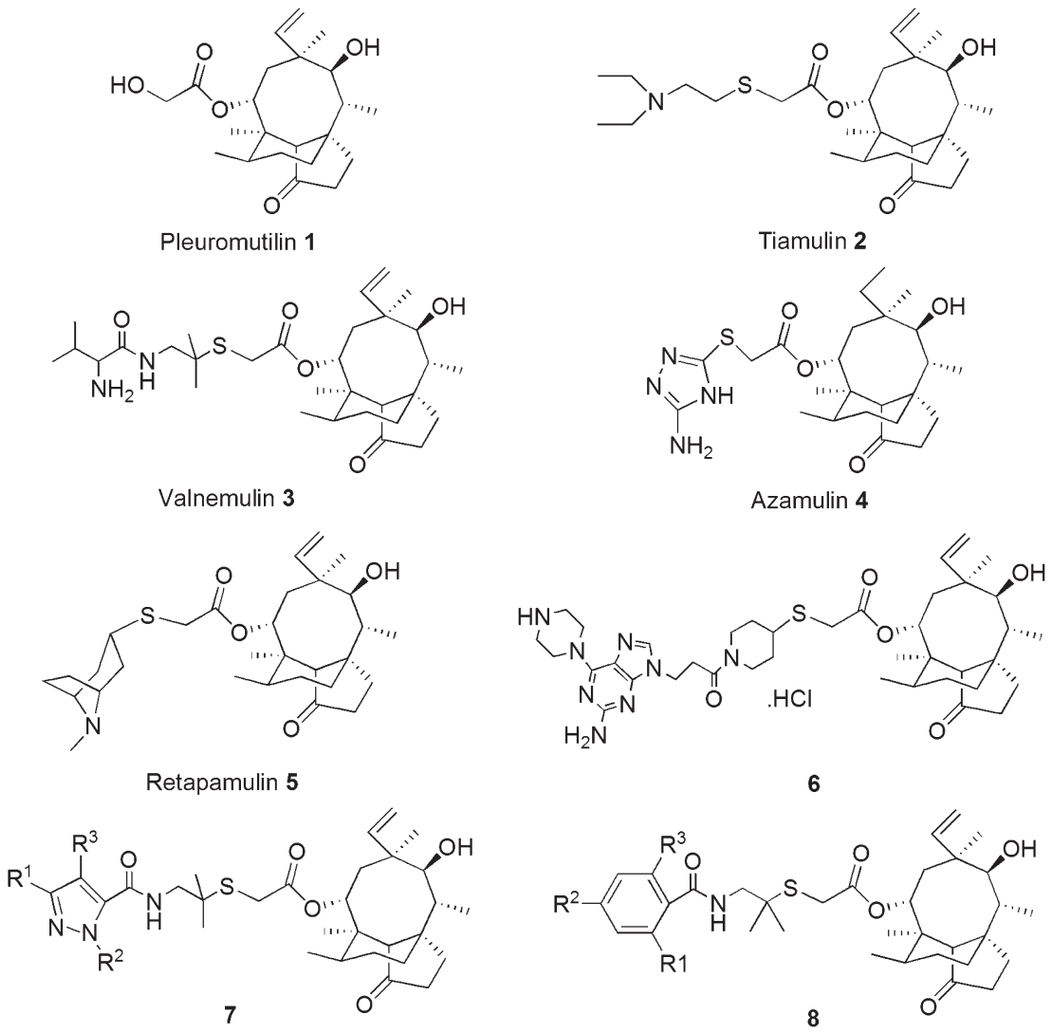


Fig. 1 Structures of pleuromutilin and pleuromutilin derivatives.

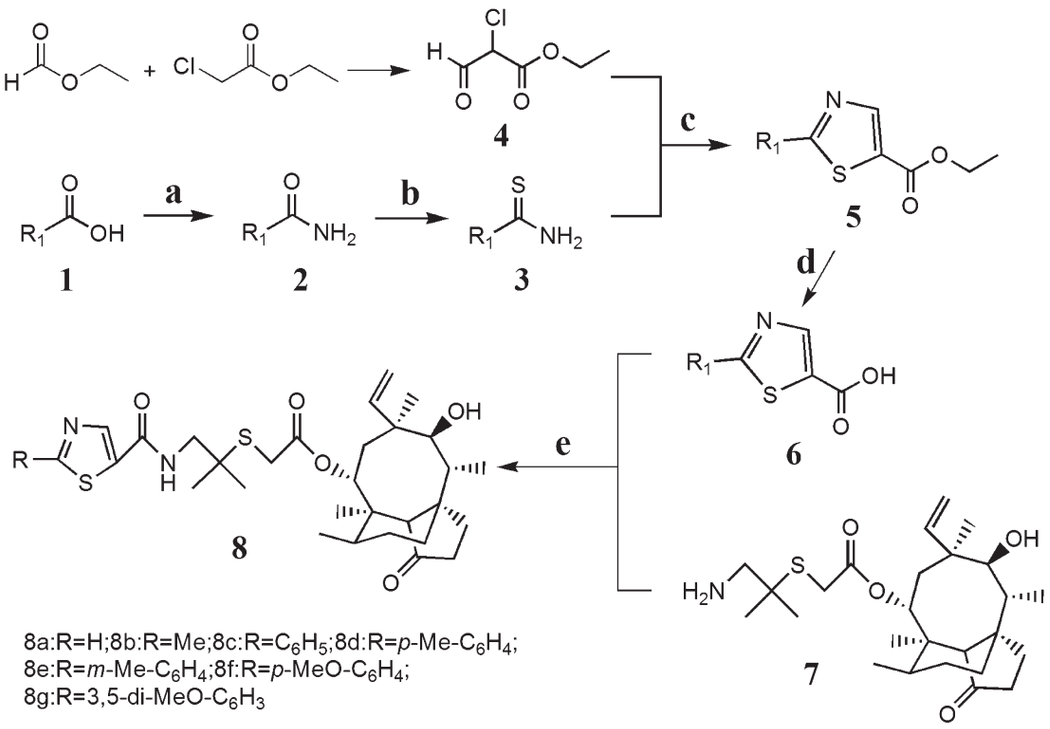
(10 mL×3) and water(10 mL×3), dried with anhydrous Na_2SO_4 overnight and filtered. The CH_2Cl_2 layer was evaporated under reduced pressure and the resulting residue was chromatographed on silica gel (petroleum ester/ethyl acetate = 2:1) to give the target molecule; yields: 71–80%.

Mutilin 14-O-[1-thiazole carboxamide-2-methylpropane-2-yl] thioacetate **(8a):** Yellow solid; yield: 75%; m.p. 82–84 °C; ^{1}H NMR spectrum (400 MHz; d_1-$CDCl_3$; TMS): δ (p.p.m.) = 0.73 (3H, d, *J* = 6.8 Hz), 0.89 (3H, d, *J* = 6.8 Hz), 1.10–1.15 (1H, m), 1.17 (3H, s), 1.31 (3H, s), 1.33 (3H, s), 1.37–1.43 (2H, m), 1.47 (3H, s), 1.53–1.56 (1H, m), 1.62–1.70 (2H, m), 1.77–1.80 (1H, m), 2.05–2.20 (3H, m), 2.22–2.33 (3H, m), 3.16–3.30 (3H, m), 3.36 (1H, d, *J* = 6.4 Hz), 3.42–3.48 (1H, m), 5.17 (1H, d, *J* = 17.6 Hz), 5.22 (1H, d, *J* = 10.8 Hz), 5.75 (1H, d, *J* = 8.8 Hz), 6.46 (1H, dd, J_1 = 17.2 Hz, J_2 = 10.8 Hz), 7.97 (1H, s), 8.45 (1H, s), 8.94 (1H, s). IR (KBr, cm^{-1}) 3442, 3083, 2930, 2860, 1727, 1651, 1545, 1459, 1414, 1379, 1286, 1145, 1118, 1020, 982, 917, 881, 812, 609. HR-MS (ESI): Calcd for $C_{30}H_{44}N_2O_5S_2$ ($M+H^+$): 577.2771. Found: 577.2763.

Mutilin 14-O-[1-(2-methylthiazole carboxamide)-2-methylpropane-2-yl] thioacetate **(8b):** Yellow solid; yield: 73%; m.p. 72–73 °C; ^{1}H NMR spectrum (400 MHz; d_1-$CDCl_3$; TMS): δ (p.p.m.) = 0.73 (3H, d, *J* = 6.8 Hz), 0.89 (3H, d, *J* = 7.2 Hz), 1.10–1.15 (1H, m), 1.17 (3H, s), 1.29 (3H, s), 1.31 (3H, s), 1.37–1.44(2H, m), 1.46(3H,s), 1.53–1.57 (1H, m), 1.62–1.68 (2H, m), 1.76–1.80 (1H, m), 2.05–2.20 (3H, m), 2.22–2.35 (3H, m), 2.76 (3H, s), 3.15–3.29 (3H, m), 3.36 (1H, d, *J* = 6.8 Hz), 3.41–3.46 (1H, m), 5.15–5.24 (2H, m), 5.76 (1H, d, *J* = 8.4 Hz), 6.42–6.49 (1H, m), 7.57 (1H, s), 8.16 (1H, s). IR (KBr, cm^{-1}) 3437, 3079, 2959, 2929, 1728, 1646, 1542, 1455, 1377, 1284, 1117, 1022, 982, 946, 916, 874, 803, 610, 402. HR-MS (ESI): Calcd for $C_{31}H_{46}N_2O_5S_2$ ($M+H^+$): 591.2927. Found: 591.2927.

Mutilin 14-O-[1-(2-phenylthiazole carboxamide)-2-methylpropane-2-yl] thioacetate **(8c):** Yellow solid; yield: 80%; m.p. 91–93 °C; ^{1}H NMR spectrum (400 MHz; d_1-$CDCl_3$; TMS): δ (p.p.m.) = 0.74 (3H, d, *J* = 6.8 Hz), 0.88 (3H, d, *J* = 6.8 Hz), 1.10–1.14 (1H, m), 1.17 (3H, s), 1.31 (3H, s), 1.33 (3H, s), 1.38–1.44 (2H, m), 1.47 (3H, s), 1.52–1.55 (1H, m), 1.61–1.70 (2H, m), 1.76–1.80 (1H, m), 2.05–2.20 (3H, m), 2.22–2.34 (3H, m), 3.17–3.31 (3H, m), 3.35 (1H, d, *J* = 6.4 Hz), 3.46–3.51 (1H, m), 5.18 (1H, dd, J_1 = 17.6 Hz, J_2 = 1.2 Hz), 5.26 (1H, d, *J* = 11.2 Hz), 5.77 (1H, d, *J* = 8.4 Hz), 6.48 (1H, dd, J_1 = 17.6 Hz, J_2 = 10.8 Hz), 7.48–7.50 (3H, m), 7.77 (1H, s), 8.01–8.04 (2H, m), 8.41 (1H, s). IR (KBr, cm^{-1}) 3439, 3082, 2929, 2860, 1728, 1649, 1544, 1455, 1416, 1380, 1286, 1147, 1118, 1021, 979, 916, 766, 691, 640. HR-MS (ESI): Calcd for $C_{36}H_{48}N_2O_5S_2$ ($M+H^+$): 653.3084. Found: 653.3087.

Mutilin 14-O-[1-(2-p-tolylthiazole carboxamide)-2-methylpropane-2-yl] thioacetate **(8d):** Yellow solid, yield: 79%, m.p. 96–98 °C; ^{1}H NMR spectrum (400 MHz; d_1-$CDCl_3$; TMS): δ (p.p.m.) = 0.74 (3H, d, *J* = 6.8 Hz), 0.88 (3H, d, *J* = 6.8 Hz), 1.10–1.14 (1H, m), 1.17 (3H, s), 1.31 (3H, s), 1.33 (3H, s), 1.36–1.43 (2H, m), 1.47 (3H,s), 1.51–1.55 (1H, m), 1.61–1.70 (2H, m), 1.77–1.80 (1H, m), 2.05–2.17 (3H, m), 2.18–2.27 (3H, m), 2.42 (3H, s), 3.17–3.30 (3H, m), 3.35 (1H, d, *J* = 6.4 Hz), 3.45–3.51 (1H, m), 5.18 (1H, d, J_1 = 17.6 Hz), 5.26 (1H, d, *J* = 11.2 Hz), 5.77 (1H, d, *J* = 8.4 Hz), 6.48 (1H, dd, J_1 = 17.2 Hz, J_2 = 10.8 Hz), 7.28 (2H, d, *J* = 10.0 Hz), 7.67 (1H, s), 7.90 (2H, d,



Reaction reagents and conditions: (a) ① $SOCl_2$, reflux, 2 h, ② $NH_3 \cdot H_2O$, 0 °C, 2min; total yields: 62-69%.(b) P_2S_5, Et_2O, 0 °C→rt, overnight, 87-95%. (c) Anhydrous $MgSO_4$, toluene, 100 °C, 2 h, 41-48%. (d) NaOH, H_2O/EtOH, reflux, 1.5 h, 83-92%.
(e) ① $SOCl_2$, reflux, 1.5 h, ② NEt_3, pyridine, CH_2Cl_2, 0 °C→15-20 °C, 1 h; total yield: 71-80%.

Scheme 1 The synthetic route to compound **8a–g**.

J = 8.0 Hz), 8.37 (1H,s). IR (KBr, cm^{-1}) 3431, 3079, 2928, 2866, 1729, 1650, 1540, 1498, 1458, 1426, 1286, 1148, 1118, 1019, 980, 916, 819, 747, 640, 588, 482. HR-MS (ESI): Calcd for $C_{37}H_{50}N_2O_5S_2$ ($M+H^+$): 667.3240. Found: 667.3242.

Mutilin 14-O-[1-(2-m-tolylthiazole carboxamide)-2-methylpropane-2-yl] thioacetate **(8e):** Yellow solid, yield:75%; m.p. 87–88 °C; ^1H NMR spectrum (400 MHz; d_1-$CDCl_3$; TMS): δ (p.p.m.) 0.74 = (3H, d, *J* = 6.8 Hz), 0.88 (3H, d, *J* = 6.8 Hz), 1.10–1.14 (1H, m), 1.17 (3H, s), 1.32 (3H, s), 1.34 (3H, s), 1.37–1.43 (2H, m), 1.47 (3H, s), 1.51–1.55 (1H, m), 1.61–1.70 (2H, m), 1.76–1.80 (1H, m), 2.05–2.17 (3H, m), 2.19–2.34 (3H, m), 2.44 (3H, s), 3.17–3.31 (3H, m), 3.35 (1H, d, *J* = 6.4 Hz), 3.46–3.51 (1H, m), 5.18 (1H, d, *J* = 17.6 Hz), 5.26 (1H, d, *J* = 11.2 Hz), 5.77 (1H, d, *J* = 8.4 Hz), 6.48 (1H, dd, J_1 = 17.2 Hz, J_2 = 10.8 Hz), 7.31 (1H, d, *J* = 7.2 Hz), 7.37 (1H, t, *J* = 7.6 Hz), 7.72 (1H, s), 7.81 (1H, d, *J* = 7.6 Hz), 7.85 (1H, s), 8.40 (1H, s). IR (KBr, cm^{-1}) 3431, 2929, 2867, 1728, 1650, 1541, 1458, 1418, 1388, 1287, 1147, 1118, 1019, 982, 916, 790, 692, 648, 586. HR-MS (ESI): Calcd for $C_{37}H_{50}N_2O_5S_2$ ($M-H^+$): 665.3082. Found: 665.3095.

Mutilin 14-O-[1-(2-(4-methoxyphenyl) thiazole carboxamide)-2-methylpropane-2-yl] thioacetate **(8f):** White solid, yield: 78%; m.p. 93–94 °C; ^1H NMR spectrum (400 MHz; d_1-$CDCl_3$; TMS): δ (p.p.m.) 0.74 = (3H, d, *J* = 6.8 Hz), 0.88 (3H, d, *J* = 6.8 Hz), 1.10–1.14 (1H, m), 1.17 (3H, s), 1.31 (3H, s), 1.33 (3H, s),1.36–1.43 (2H, m), 1.47 (3H, s), 1.51–1.55 (1H, m), 1.61–1.70 (2H, m), 1.76–1.80 (1H, m), 2.05–2.17 (3H, m), 2.18–2.34 (3H, m), 3.17–3.30 (3H, m), 3.35 (1H, d, *J* = 6.4 Hz), 3.45–3.51 (1H, m), 3.88 (3H, s), 5.18 (1H, d, *J* = 17.6 Hz), 5.26 (1H, d, *J* = 11.2 Hz), 5.76 (1H, d, *J* = 8.4 Hz), 6.47 (1H, dd, J_1 = 17.2 Hz, J_2 = 10.8 Hz), 6.99 (2H, d, *J* = 8.8 Hz), 7.67 (1H, s), 7.96 (2H, d, *J* = 8.8 Hz), 8.33(1H, s) IR (KBr, cm^{-1}) 3431, 3079, 2931, 2860, 1728, 1647, 1539, 1459, 1410, 1299, 1256, 1149, 1117, 1028, 980, 917, 836, 801, 605. HR-MS (ESI): Calcd for $C_{37}H_{50}N_2O_6S_2$ ($M+H^+$): 683.3189. Found: 683.3193.

Mutilin 14-O-[1-(2-(3, 5-dimethoxyphenyl) thiazole carboxamide) -2-methylpropane- 2-yl] thioacetate **(8g):**White solid, yield: 71%, m.p. 87–90 °C; ^1H NMR spectrum (400 MHz; d_1-$CDCl_3$; TMS): δ (p.p.m.) 0.73 = (3H, d, *J* = 7.2 Hz), 0.88 (3H, d, *J* = 7.2 Hz), 1.10–1.15 (1H, m), 1.16 (3H, s), 1.32 (3H, s), 1.34 (3H, s), 1.37–1.43 (2H, m), 1.47 (3H, s), 1.51–1.55 (1H, m), 1.61–1.70 (2H, m), 1.76–1.80 (1H, m), 2.05–2.17 (3H, m), 2.22–2.34 (3H, m), 3.17–3.30 (2H, m), 3.35 (1H, d, *J* = 6.4 Hz), 3.45–3.53 (1H,m), 3.92 (6H, d, *J* = 7.2 Hz), 5.17 (1H, d, *J* = 17.6 Hz), 5.22 (1H, d, *J* = 11.2 Hz), 5.77 (1H, d, *J* = 8.4 Hz), 6.47(1H, m), 6.65 (1H, s), 7.50 (1H, s), 7.76 (1H, s), 8.46 (1H, s). IR (KBr, cm^{-1}) 3435, 3084, 2924, 2854, 1729, 1650, 1597, 1539, 1460, 1407, 1288, 1205, 1156, 1118, 1064, 1020. 983, 920, 818, 683, 587, 482, 405. HR-MS (ESI): Calcd for $C_{38}H_{52}N_2O_7S_2$ ($M-H^+$): 711.3137. Found: 711.3145.

Biological assay

Two pathogenic bacterial strains were used in the studies: wild *Staphylcoccus aureus* SC and standard *Staphylcoccus aureus* ATCC26112. The wild *Staphylcoccus aureus SC* were isolated from Sichuan Province in China. The standard *Staphylcoccus aureus* ATCC26112 were obtained from the Basic Medical and Forensic College Sichuan University. McF was used to evaluate the bacteria count and 0.5 McF (amount of bacteria: about 1.5×10^8 colony-forming unit (cfu)/mL) was formulated according to the conditions: 0.048 M $BaCl_2$ 0.5 mL, 0.36 N H_2SO_4 99.5 mL.

The antibacterial activities of the target compounds *in vitro* were tested via an agar-well diffusion method[20,21].

1. Preparation of bacteria solution: The *Staphylococcus aureus* ATCC26112 and *Staphylococcus aureus* SC were inoculated in LB (Luria Bertani) culture medium respectively and then kept at 37 °C for 18 h after they were both recovered. Later, the bacteria solution was corrected to 0.5 McF (amount of bacteria: about 10^8 colony-forming units (cfu)/mL) with saline.

2. Dispensing of drugs: Every sample (1000 μg) was dissolved with ethanol (1 mL) and diluted to 5 μg mL^{-1} with ethanol in a super clean bench; Later, **8a**, **8b** and **8c** were diluted to 2 μg mL^{-1}, 1 μg mL^{-1}, 0.5 μg mL^{-1}, 0.2 μg mL^{-1} and 0.05 μg mL^{-1} for further testing.

3. Antibacterial activity testing: The LB culture medium (with 2.2% agar) was calmed down at about 55 °C after sterilisation by autoclave. 1 mL of bacterial solution (0.5 McF) was added into the LB culture medium (100 mL) [the amount of bacteria: about 10^6 colony-forming units (cfu/mL)], and the resulting mixture was shaken up until it was well-distributed, then the mixture was poured into three plates (20 mL for each). Five wells (6 mm) were made in each plate using a sterile cork borer when the mixture became curdled. A 50 μL solution of each compound (target compounds or reference compounds) were injected into the corresponding well and then the plates were incubated at 37 °C for 24 h.

Results and discussion

Since pleuromutilin has modest activity against Gram-positive bacteria while it lacks activity against Gram-negative bacteria, two Gram-positive bacteria, *S. aureus* ATCC26112 and *S. aureus* SC were chosen to test the antibacterial activities of the target compounds. The results showed that all the target compounds exhibited better antibacterial activity than pleuromutilin at the concentration of 5 μg mL^{-1} and therefore, three target compounds (**8a**, **8b**, **8c**) were chosen to test the antibacterial activity again at another five concentrations (2 μg mL^{-1}, 1 μg mL^{-1}, 0.5 μg mL^{-1}, 0.2 μg mL^{-1} and 0.05 μg mL^{-1}). These three chosen compounds displayed good antibacterial activity even if they were diluted to 0.05 μg mL^{-1}.

It can be seen from the tables that *S. aureus* SC was more sensitive than *S. aureus* ATCC26112 to the target compounds and the target compounds without the substituent phenyl ring binding to the thiazole ring (**8a**, **8b**) exhibited better biological activity than the compounds with a substituent phenyl ring (**8d**, **8e**, **8f**, **8g**).

Conclusion

A series of novel pleuromutilin derivatives with thiazole-5-carboxamide and thioether moiety in the C_{14} side chain were designed and synthesised. The antibacterial activity results indicated that three target compounds displayed excellent activity against *S. aureus* ATCC26112 and *S. aureus* SC at the concentration of 0.05 μg mL^{-1}. This exploration has further proved the SAR of pleuromutilin derivatives we put forward, showing that the heterocyclic carboxamide group was essential to enhance bioactivity with a thioether moiety in the C_{14} side chain of pleuromutilin.[15] It will be helpful for us in designing more potent pleuromutilin derivatives.

Table 1 The antibacterial activity of the target compounds (**8a–g**) at the concentration of 5 μg mL^{-1} toward *S. aureus* ATCC26112 and *S. aureus* SC

Compound	Diameter of inhibition zone/mm	
	S. aureus ATCC26112	*S. aureus* SC
8a	28	30
8b	19	26
8c	18	17
8d	13	16
8e	13	14
8f	14	15
8g	11	12
Pleuromutilin	12	13
Ethanol	6	6

Concentration of pleuromutilin: 5.0 μg mL^{-1}; negative control: ethanol; positive control: pleuromutilin; diameter of the well in each plate: 6 mm.

Table 2 The antibacterial activity of the target compounds (**8a–c**) at different concentrations towards *S. aureus* ATCC26112 and *S. aureus* SC (isolated from Sichuan, China)

	Diameter of inhibition zone (mm)									
	S. aureus ATCC26112					*S. aureus* SC				
Compound	2*	1*	0.5*	0.2*	0.05*	2*	1*	0.5*	0.2*	0.05*
8a	19	18	12	12	10	21	19	16	15	13
8b	18	14	10	8	10	17	15	14	15	12
8c	15	13	10	8	10	17	15	14	15	12
Pleuromutilin	6	6	6	6	6	7	7	7	7	7

Diameter of the wells in each plate: 6 mm.
*Different concentrations of the compounds.
Pictures of the inhibition zone are available in the Electronic Supplementary Information.

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