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Synthesis of novel 1,3-diaryl pyrazole derivatives bearing rhodanine-3-fatty acid moieties as potential antibacterial agents

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ABSTRACT

In the present study, a series of 1,3-diaryl pyrazole derivatives bearing rhodanine-3-fatty acid moieties were synthesized and their antimicrobial activities were tested against various Gram-positive and Gram-negative bacteria. 1,3-diaryl-4-formylpyrazoles were synthesized as key intermediates following a Vilsmeier–Haack strategy. Several compounds with an MIC of 2 μg/mL, exhibited stronger antibacterial activity against the methicillin-resistant *Staphylococcus aureus* (MRSA) than the controls. None of the compounds showed any activity against Gram-negative bacteria.

1. Introduction

Development of novel antimicrobial drugs is still in demand because of the increasing incidence of infection caused by the rapid development of microbial resistance to most of the known antibiotics [1]. Pyrazoles are a novel class of heterocyclic compounds possessing a wide variety of applications in the agrochemical and pharmaceutical industries [2,3]. Many pyrazole derivatives have been reported to possess diverse pharmacological activities such as antimicrobial [4–8], anti-inflammatory [9–12], and anti-viral among others [13]. In our previous work [14], we found that several rhodanine-3-acetic acid derivatives bearing a chalcone moiety showed strong activities against Gram-positive strains (Fig. 1). Herein, we report our ongoing study of modifications to rhodanine-3-acetic acid derivatives with an aim to develop more efficient antimicrobial agents. We focused on reserving the rhodanine moiety, replacing the chalcone moiety by 1,3-diaryl pyrazole, substituting the acetic acid moiety with different fatty acids, and simultaneously introducing different substituents into the phenyl ring. Thus, twenty-four rhodanine-3-fatty acid derivatives bearing 1,3-diaryl pyrazole were synthesized and evaluated for their antimicrobial activity *in vitro*.

2. Chemistry

A group of 1,3-diaryl pyrazole derivatives containing rhodanine-3-fatty acid moieties (**6**–**29**) were designed and synthesized according to Scheme 1. The starting benzyl hydrazones (**3**) were prepared by substituted acetophenones with phenylhydrazine and sodium acetate in ethanol. Subsequent reactions of **3** under Vilsmeier–Haack [15] conditions afforded 1,3-diaryl-4-formylpyrazoles (**4**). The resulting **4** series were subjected to Knoevenagel condensation with various rhodanine-3-fatty acids (**5**) to form the target compounds **6**–**29**. All the synthesized compounds were confirmed by FTIR, ^{1}H NMR, ^{13}C NMR, mass spectral and elemental analyses.

3. Results and discussion

In vitro antimicrobial activity was evaluated with different strains (including multidrug-resistant clinical isolates) using the minimum inhibitory concentration (MIC) which is defined as the lowest concentration at which no visible growth is observed. Oxacillin and norfloxacin were used as positive controls.

As shown in Table 1, most synthesized compounds showed good antibacterial activity *in vitro* against Gram-positive strains, particularly the chlorine and bromine substituted compounds (e.g. **9**, **11**, **14**, **20**, **22**, **23**, **24**, **25**, and **27**). None of the compounds showed any activity against Gram-negative bacteria.

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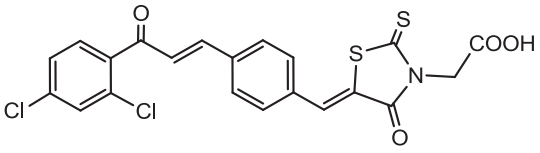
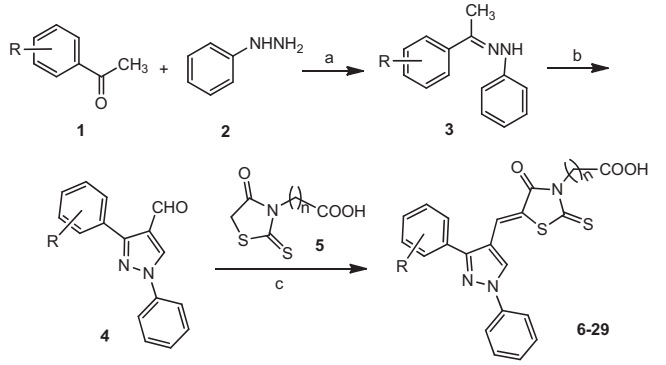


Fig. 1. Structure of the previously reported compound.

The results for the rhodanine-3-acetic acid derivatives (**6**–**21**) showed that the antibacterial activity was significantly influenced by the position of the substituent on the phenyl ring. Five electron donating groups derivatives were designed and prepared, containing *p*-CH_3, 2,4-$(CH_3)_2$, *m*-OCH_3, *p*-OCH_3, *o*-OCH_3. The pharmacology test revealed that their activities were poorer than electron withdrawing groups derivatives, for this reason we are not clear and need further work. The compound **17** with 4-NO_2 has poorer solubility than 4-Cl substituent, for the reason may lead to reduce the activity. 2,4-Chlorine substituted **11** and 4-chlorine substituted **20** exhibited the best antibacterial activity against *Staphylococcus aureus* (*S. aureus* RN4220 and *S. aureus* KCTC 503) with MICs of 8 μg/mL. To investigate the effects of the substituents on the nitrogen atom of the rhodanine to the antibacterial activity, the acetic acid moiety was changed to various fatty acids with different carbon chain lengths, and relatively fixed the substituents on the phenyl ring such as 2,4-chlorine or 4-chlorine simultaneously. The result showed, as expected, some derivatives (e.g. **23**, **24**, **25**, and **27**) exhibited better antibacterial activities against Gram-positive strains, particularly, compound **27** with a MIC of 4 μg/mL was comparable to the standard drug (norfloxacin) against *S. aureus* (*S. aureus* RN4220 and *S. aureus* KCTC 503). However, no activities against any Gram-negative strains were noted.

For those compounds exhibiting potency against *S. aureus* (*S. aureus* RN4220 and *S. aureus* KCTC 503), we also evaluated their antibacterial activity against several clinical isolates of multidrug-resistant Gram-positive bacteria (Table 2). The results showed that almost all of the tested compounds showed potent antibacterial activities against clinical isolates of multidrug-resistant Gram-positive bacteria. Actually, the activities of the compounds **22**, **23**, **24**, **25**, and **27,** which possessed the longer ($n = 2$–4) carbon chain fatty acids substituted at position-3 of the rhodanine, were superior to the Norfloxacin and Oxacillin in respect to MRSA, and were comparable to the Norfloxacin in respect to QRSA. Compound



6:R=4-CH_3 n=1
7:R=3-Cl n=1
8:R=4-OCH_3 n=1
9:R=3-Br n=1
10:R=H n=1
11:R=2,4-$(Cl)_2$ n=1
12:R=4-F n=1
13:R=2-F n=1
14:R=4-Br n=1
15:R=3-OCH_3 n=1
16:R=2-Cl n=1
17:R=4-NO_2 n=1
18:R=2,4-$(CH_3)_2$ n=1
19:R=Phenyl(3,4-fused) n=1
20:R=4-Cl n=1
21:R=2-OCH_3 n=1
22:R=4-Cl n=2
23:R=2,4-$(Cl)_2$ n=2
24:R=4-Cl n=3
25:R=2,4-$(Cl)_2$ n=3
26:R=4-Cl n=4
27:R=2,4-$(Cl)_2$ n=4
28:R=4-Cl n=5
29:R=2,4-$(Cl)_2$ n=5

Scheme 1. Synthesis of compounds **6**–**29**. Reagents and conditions: (a) AcOH, NaOH, EtOH, reflux, 1 h (b) (i) DMF, $POCl_3$, 0–5 °C, 0.5 h (ii) **3**, DMF, 50 °C, 3 h (c) Piperidine, AcOH, EtOH, 40–50 °C, 4 h.

Table 1
Inhibitory activity of compounds **6**–**29** (expressed as MIC (μg/mL)) against representative strains of Gram-positive (*Staphylococcus aureus*) and Gram-negative (*Escherichia coli*) bacteria.

Compound	R	*n*	*S. aureus*		*E. coli*	
			4220	503	1924	1356
6	4-CH_3	1	16	>64	>64	>64
7	3-Cl	1	16	>64	>64	>64
8	4-OCH_3	1	>64	>64	>64	>64
9	3-Br	1	8	32	>64	>64
10	H	1	64	64	>64	>64
11	2,4-$(Cl)_2$	1	8	8	>64	>64
12	4-F	1	>64	>64	>64	>64
13	2-F	1	64	64	>64	>64
14	4-Br	1	8	8	>64	>64
15	3-OCH_3	1	64	64	>64	>64
16	2-Cl	1	32	32	>64	>64
17	4-NO_2	1	>64	>64	>64	>64
18	2,4-$(CH_3)_2$	1	16	16	>64	>64
19	Phenyl(3,4-fused)	1	>64	>64	>64	>64
20	4-Cl	1	8	8	>64	>64
21	2-OCH_3	1	>64	>64	>64	>64
22	4-Cl	2	8	16	>64	>64
23	2,4-$(Cl)_2$	2	8	4	>64	>64
24	4-Cl	3	8	4	>64	>64
25	2,4-$(Cl)_2$	3	8	4	>64	>64
26	4-Cl	4	>64	>64	>64	>64
27	2,4-$(Cl)_2$	4	4	4	>64	>64
28	4-Cl	5	>64	>64	>64	>64
29	2,4-$(Cl)_2$	5	32	8	>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.

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

Compound	R	*n*	MRSA		QRSA	
			3167	3506	3505	3519
6	4-CH_3	1	16	16	16	64
7	3-Cl	1	16	32	16	64
9	3-Br	1	8	16	16	64
10	H	1	32	32	32	32
11	2,4-$(Cl)_2$	1	4	4	8	8
13	2-F	1	64	64	64	64
14	4-Br	1	8	8	8	8
15	3-OCH_3	1	32	64	64	64
16	2-Cl	1	16	32	32	32
18	2,4-$(CH_3)_2$	1	16	16	16	16
20	4-Cl	1	8	8	8	16
22	4-Cl	2	4	4	4	8
23	2,4-$(Cl)_2$	2	4	4	4	4
24	4-Cl	3	4	4	4	4
25	2,4-$(Cl)_2$	3	4	4	4	4
27	2,4-$(Cl)_2$	4	2	2	2	2
29	2,4-$(Cl)_2$	5	4	32	32	4
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.

27 ($n = 4$) exhibited the most potent activity against both MRSA and QRSA with a MIC of 2 μg/mL. Furthermore, it was also clearly observed from the results for the 2,4-dichloro substituted derivatives (**11**, **23**, **25**, **27**, and **29**) that the activity was significantly influenced by the length of carbon chain of the fatty acid moiety. In this regard, more derivatives possessing different rhodanine-3-fatty acids need to be designed and synthesized to elucidate the structure–activity relationship and this work is currently in progress in our laboratories.

4. Conclusion

In summary, in connection with our previous work, a series of 1,3-diaryl pyrazoles containing rhodanine-3-fatty acid moieties were designed and synthesized. All the synthesized compounds have been investigated for their *in vitro* antimicrobial activities. Most of the compounds exhibited potential antibacterial activities against Gram-positive bacteria, particularly against multidrug-resistant strains of clinical isolates. Compound **27** bearing a rhodanine-3-pentanoic acid displayed the most potent activity with a MIC of 2 μg/mL which was more potent than the standard drugs (norfloxacin and oxacillin) against MRSA. The results suggest that the new skeleton possessing 1,3-diaryl pyrazole and rhodanine-3-fatty acids may provide valuable leads for designing and development of novel antibacterial agents.

5. Experimental protocols

5.1. Chemistry

Melting points were determined in open glass capillaries in an electrical melting point apparatus and are 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 and ^{13}C NMR spectra were recorded in pure DMSO-d_6 on Bruker NMR spectrometers at 300 MHz and 75 MHz respectively using tetramethylsilane (TMS) as internal standard. Chemical shifts were expressed in δ, ppm. 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.

5.2. General synthetic procedure for the key intermediates

Intermediates **3** and **4** were synthesized according to the literature [1]. Intermediate **5** was synthesized using the reported procedure [16].

5.3. General synthetic procedure for the target compounds ***6*–*29***

To a solution of 1,3-diaryl-4-formylpyrazoles **4** (1.0 mmol) and rhodanine analogs **5** (1.0 mmol) in absolute ethanol (8.0 mL) was added drops of acetic acid and piperidine. The reaction mixture was stirred at 40–50 °C, until the completion of the reaction as evidenced by TLC. After the solution was cooled, the resulting reaction mixture was filtered off and crude product was purified by 95% ethanol to afford pure products **6**–**29**. The yield, melting point and spectral data of each compound are given below.

5.3.1. (Z)-2-(4-oxo-5-((1-phenyl-3-(p-tolyl)-1H-pyrazol-4-yl) methylene)-2-thioxothiazolidin-3-yl)acetic acid (*6*)

Yield 89%; m.p. 302–304 °C. IR (KBr) cm^{-1}: 3419 (OH), 1707 (C=O). ^{1}H NMR (DMSO-d_6, 300 MHz, ppm): δ 13.45 (s, 1H), 8.84 (s, 1H), 8.07–7.88 (m, 2H), 7.59–7.37 (m, 8H), 4.71 (s, 2H), 2.40 (s, 3H). MS m/z 436 (M+1). Anal. Calcd. for $C_{22}H_{17}N_3O_3S_2$: C, 60.67; H, 3.93; N, 9.65; S, 14.72. Found: C, 60.55; H, 3.91; N, 9.66; S, 14.71.

5.3.2. (Z)-2-(5-((3-(3-chlorophenyl)-1-phenyl-1H-pyrazol-4-yl) methylene)-4-oxo-2-thioxothiazolidin-3-yl)acetic acid (*7*)

Yield 91%; m.p. 313–315 °C. IR (KBr) cm^{-1}: 3419 (OH), 1707 (C=O). ^{1}H NMR (DMSO-d_6, 300 MHz, ppm): δ 8.84 (s, 1H), 8.06 (d, J = 8.1 Hz, 2H), 7.74 (s, 1H), 7.61–7.53 (m, 6H), 7.43 (t, J = 7.35 Hz, 1H), 4.49 (s, 2H). ^{13}C NMR (DMSO-d_6, 75 MHz, ppm): δ 245.30, 192.60, 167.12, 166.25, 152.27, 138.53, 133.68, 133.15, 130.98, 129.80, 122.63, 119.47, 115.74, 109.53, 40.20, 38.95. MS m/z 456 (M+1). Calcd. for $C_{21}H_{14}ClN_3O_3S_2$: C, 55.32; H, 3.09; N, 9.22; S, 14.07. Found: C, 55.31; H, 3.07; N, 9.20; S, 14.08.

5.3.3. (Z)-2-(5-((3-(4-methoxyphenyl)-1-phenyl-1H-pyrazol-4-yl) methylene)-4-oxo-2-thioxothiazolidin-3-yl)acetic acid (*8*)

Yield 87%; m.p. 308–310 °C. IR (KBr) cm^{-1}: 3419 (OH), 1707 (C=O). ^{1}H NMR (DMSO-d_6, 300 MHz, ppm): δ 8.78 (s, 1H), 8.05 (d, J = 8.1 Hz, 2H), 7.63–7.51 (m, 5H), 7.41 (t, J = 7.4 Hz, 1H), 7.14 (d, J = 8.7 Hz, 2H), 4.46 (s, 2H), 3.85 (s, 3H). MS m/z 452 (M+1). Calcd. for $C_{22}H_{17}N_3O_4S_2$: C, 58.52; H, 3.79; N, 9.31; S, 14.20. Found: C, 58.50; H, 3.77; N, 9.30; S, 14.21.

5.3.4. (Z)-2-(5-((3-(3-bromophenyl)-1-phenyl-1H-pyrazol-4-yl) methylene)-4-oxo-2-thioxothiazolidin-3-yl)acetic acid (*9*)

Yield 88%; m.p. 315–317 °C. IR (KBr) cm^{-1}: 3419 (OH), 1707 (C=O). ^{1}H NMR (DMSO-d_6, 300 MHz, ppm): δ 8.83 (s, 1H), 8.07 (d, J = 7.6 Hz, 2H), 7.87 (d, J = 1.6 Hz, 1H), 7.74 (m, 1H), 7.66 (d, J = 7.9 Hz, 1H), 7.54 (m, 4H), 7.43 (t, J = 7.4 Hz, 1H), 4.35 (s, 2H). MS m/z 501 (M+1). Calcd. for $C_{21}H_{14}BrN_3O_3S_2$: C, 50.41; H, 2.82; N, 8.40; S, 12.82. Found: C, 50.39; H, 2.80; N, 8.38; S, 12.81.

5.3.5. (Z)-2-(5-((1,3-diphenyl-1H-pyrazol-4-yl)methylene)-4-oxo-2-thioxothiazolidin-3-yl)acetic acid (*10*)

Yield 83%; m.p. 322–324 °C. IR (KBr) cm^{-1}: 3419 (OH), 1707 (C=O). ^{1}H NMR (DMSO-d_6, 300 MHz, ppm): δ 8.83 (s, 1H), 8.06 (d, J = 7.6 Hz, 2H), 7.71–7.48 (m, 8H), 7.43 (t, J = 7.4 Hz, 1H), 4.54 (s, 2H). MS m/z 422 (M+1). Calcd. for $C_{21}H_{15}N_3O_3S_2$: C, 59.84; H, 3.59; N, 9.97; S, 15.21. Found: C, 59.81; H, 3.57; N, 9.96; S, 15.22.

5.3.6. (Z)-2-(5-((3-(2,4-dichlorophenyl)-1-phenyl-1H-pyrazol-4-yl) methylene)-4-oxo-2-thioxothiazolidin-3-yl)acetic acid (*11*)

Yield 89%; m.p. 299–301 °C. IR (KBr) cm^{-1}: 3419 (OH), 1707 (C=O). ^{1}H NMR (DMSO-d_6, 300 MHz, ppm): δ 8.90 (s, 1H), 8.05 (d, J = 8.1 Hz, 2H), 7.90 (s, 1H), 7.66–7.52 (m, 4H), 7.44 (t, J = 7.3 Hz, 1H), 7.19 (s, 1H), 4.49 (s, 2H). MS m/z 491 (M+1). Calcd. for $C_{21}H_{13}Cl_2N_3O_3S_2$: C, 51.43; H, 2.67; N, 8.57; S, 13.08. Found: C, 51.41; H, 2.65; N, 8.56; S, 13.09.

5.3.7. (Z)-2-(5-((3-(4-fluorophenyl)-1-phenyl-1H-pyrazol-4-yl) methylene)-4-oxo-2-thioxothiazolidin-3-yl)acetic acid (*12*)

Yield 90%; m.p. 310–312 °C. IR (KBr) cm^{-1}: 3419 (OH), 1707 (C=O). ^{1}H NMR (DMSO-d_6, 300 MHz, ppm): δ 8.81 (s, 1H), 8.06 (d, J = 8.4 Hz, 2H), 7.74–7.69 (m, 2H), 7.57 (t, J = 7.8 Hz, 2H), 7.49–7.40 (m, 4H), 4.30 (s, 2H). MS m/z 440 (M+1). Calcd. for $C_{21}H_{14}FN_3O_3S_2$: C, 57.39; H, 3.21; N, 9.56; S, 14.59. Found: C, 57.37; H, 3.20; N, 9.55; S, 14.57.

5.3.8. (Z)-2-(5-((3-(2-fluorophenyl)-1-phenyl-1H-pyrazol-4-yl) methylene)-4-oxo-2-thioxothiazolidin-3-yl)acetic acid (*13*)

Yield 90%; m.p. 306–308 °C. IR (KBr) cm^{-1}: 3419 (OH), 1707 (C=O). ^{1}H NMR (DMSO-d_6, 300 MHz, ppm): δ 8.85 (d, J = 4.9 Hz, 1H),

8.09–7.99 (m, 2H), 7.69–7.52 (m, 4H), 7.50–7.36 (m, 3H), 7.34–7.29 (m, 1H), 4.49 (s, 2H). MS *m/z* 440 (M+1). Calcd. for $C_{21}H_{14}FN_3O_3S_2$: C, 57.39; H, 3.21; N, 9.56; S, 14.59. Found: C, 57.35; H, 3.19; N, 9.58; S, 14.56.

*5.3.9. (Z)-2-(5-((3-(4-bromophenyl)-1-phenyl-1H-pyrazol-4-yl) methylene)-4-oxo-2-thioxothiazolidin-3-yl)acetic acid (**14**)*

Yield 89%; m.p. 303–305 °C. IR (KBr) cm^{-1}: 3419 (OH), 1707 (C=O). ^1H NMR (DMSO-d_6, 300 MHz, ppm): δ 8.85 (s, 1H), 8.06 (d, J = 7.8 Hz, 2H), 7.79 (d, J = 8.4 Hz, 2H), 7.69–7.51 (m, 5H), 7.43 (t, J = 7.2 Hz, 1H), 4.58 (s, 2H). MS *m/z* 501 (M+1). Calcd. for $C_{21}H_{14}BrN_3O_3S_2$: C, 50.41; H, 2.82; N, 8.40; S, 12.82. Found: C, 50.40; H, 2.83; N, 8.39; S, 12.83.

*5.3.10. (Z)-2-(5-((3-(3-methoxyphenyl)-1-phenyl-1H-pyrazol-4-yl) methylene)-4-oxo-2-thioxothiazolidin-3-yl)acetic acid (**15**)*

Yield 87%; m.p. 300–302 °C. IR (KBr) cm^{-1}: 3419 (OH), 1707 (C=O). ^1H NMR (DMSO-d_6, 300 MHz, ppm): δ 8.84 (s, 1H), 8.07 (d, J = 8.1 Hz, 2H), 7.59 (t, J = 3.8 Hz, 2H), 7.56–7.42 (m, 3H), 7.21 (d, J = 6.8 Hz, 2H), 7.14–7.09 (m, 1H), 4.54 (s, 2H), 3.84 (s, 3H). MS *m/z* 452 (M+1). Calcd. for $C_{22}H_{17}N_3O_4S_2$: C, 58.52; H, 3.79; N, 9.31; S, 14.20. Found: C, 58.49; H, 3.76; N, 9.33; S, 14.19.

*5.3.11. (Z)-2-(5-((3-(2-chlorophenyl)-1-phenyl-1H-pyrazol-4-yl) methylene)-4-oxo-2-thioxothiazolidin-3-yl)acetic acid (**16**)*

Yield 85%; m.p. 309–311 °C. IR (KBr) cm^{-1}: 3419 (OH), 1707 (C=O). ^1H NMR (DMSO-d_6, 300 MHz, ppm): δ 8.89 (s, 1H), 8.06 (d, J = 7.9 Hz, 2H), 7.71 (d, J = 7.7 Hz, 1H), 7.68–7.49 (m, 5H), 7.44 (t, J = 7.3 Hz, 1H), 7.18 (s, 1H), 4.46 (s, 2H). MS *m/z* 456 (M+1). Calcd. for $C_{21}H_{14}ClN_3O_3S_2$: C, 55.32; H, 3.09; N, 9.22; S, 14.07. Found: C, 55.30; H, 3.07; N, 9.23; S, 14.06.

*5.3.12. (Z)-2-(5-((3-(4-nitrophenyl)-1-phenyl-1H-pyrazol-4-yl) methylene)-4-oxo-2-thioxothiazolidin-3-yl)acetic acid (**17**)*

Yield 81%; m.p. 321–323 °C. IR (KBr) cm^{-1}: 3419 (OH), 1707 (C=O). ^1H NMR (DMSO-d6, 300 MHz, ppm): δ 8.88 (d, J = 1.1 Hz, 1H), 8.42–8.40 (m, 2H), 8.12–7.89 (m, 4H), 7.67–7.51 (m, 3H), 7.44 (t, J = 7.3 Hz, 1H), 4.52 (s, 2H). MS *m/z* 467 (M+1). Calcd. for $C_{21}H_{14}N_4O_5S_2$: C, 54.07; H, 3.02; N, 12.01; S, 13.75. Found: C, 54.05; H, 3.01; N, 11.99; S, 13.76.

*5.3.13. (Z)-2-(5-((3-(2,4-dimethylphenyl)-1-phenyl-1H-pyrazol-4-yl)methylene)-4-oxo-2-thioxothiazolidin-3-yl)acetic acid (**18**)*

Yield 88%; m.p. 297–299 °C. IR (KBr) cm^{-1}: 3419 (OH), 1707 (C=O). ^1H NMR (DMSO-d6, 300 MHz, ppm): δ 8.82 (s, 1H), 8.05 (d, J = 7.9 Hz, 2H), 7.57 (t, J = 7.8 Hz, 2H), 7.41 (t, J = 7.4 Hz, 1H), 7.27–7.10 (m, 4H), 4.26 (s, 2H), 2.38 (s, 3H), 2.23 (s, 3H). MS *m/z* 450 (M+1). Calcd. for $C_{23}H_{19}N_3O_3S_2$: C, 61.45; H, 4.26; N, 9.35; S, 14.27. Found: C, 61.43; H, 4.25; N, 9.32; S, 14.28.

*5.3.14. (Z)-2-(5-((3-(naphthalen-2-yl)-1-phenyl-1H-pyrazol-4-yl) methylene)-4-oxo-2-thioxothiazolidin-3-yl)acetic acid (**19**)*

Yield 87%; m.p. 324–326 °C. IR (KBr) cm^{-1}: 3419 (OH), 1707 (C=O). ^1H NMR (DMSO-d6, 300 MHz, ppm): δ 8.88 (s, 1H), 8.22 (s, 1H), 8.16–7.98 (m, 5H), 7.82 (d, J = 8.4 Hz, 1H), 7.70–7.57 (m, 5H), 7.44 (t, J = 7.3 Hz, 1H), 4.51 (s, 2H). MS *m/z* 472 (M+1). Calcd. for $C_{25}H_{17}N_3O_3S_2$: C, 63.68; H, 3.63; N, 8.91; S, 13.60. Found: C, 63.65; H, 3.61; N, 8.90; S, 13.62.

*5.3.15. (Z)-2-(5-((3-(4-chlorophenyl)-1-phenyl-1H-pyrazol-4-yl) methylene)-4-oxo-2-thioxothiazolidin-3-yl)acetic acid (**20**)*

Yield 92%; m.p. 312–314 °C. IR (KBr) cm^{-1}: 3419 (OH), 1707 (C=O). ^1H NMR (DMSO-d6, 300 MHz, ppm): δ 8.84 (d, J = 2.1 Hz, 1H), 8.06 (d, J = 8.2 Hz, 2H), 7.75–7.50 (m, 7H), 7.43 (t, J = 7.3 Hz, 1H), 4.48 (s, 2H). MS *m/z* 456 (M+1). Calcd. for $C_{21}H_{14}ClN_3O_3S_2$: C, 55.32; H, 3.09; N, 9.22; S, 14.07. Found: C, 55.31; H, 3.06; N, 9.23; S, 14.08.

*5.3.16. (Z)-2-(5-((3-(2-methoxyphenyl)-1-phenyl-1H-pyrazol-4-yl) methylene)-4-oxo-2-thioxothiazolidin-3-yl)acetic acid (**21**)*

Yield 84%; m.p. 307–309 °C. IR (KBr) cm^{-1}: 3419 (OH), 1707 (C=O). ^1H NMR (DMSO-d6, 300 MHz, ppm): δ 8.83 (d, J = 1.6 Hz, 1H), 8.05 (d, J = 8.0 Hz, 2H), 7.56 (dd, J = 14.0, 7.3 Hz, 3H), 7.49–7.39 (m, 2H), 7.34 (d, J = 1.7 Hz, 1H), 7.25 (d, J = 8.3 Hz, 1H), 7.13 (t, J = 7.4 Hz, 1H), 4.68 (s, 2H), 3.77 (s, 3H). MS *m/z* 452 (M+1). Calcd. for $C_{22}H_{17}N_3O_4S_2$: C, 58.52; H, 3.79; N, 9.31; S, 14.20. Found: C, 58.50; H, 3.77; N, 9.30; S, 14.21.

*5.3.17. (Z)-3-(5-((3-(4-chlorophenyl)-1-phenyl-1H-pyrazol-4-yl) methylene)-4-oxo-2-thioxothiazolidin-3-yl)propanoic acid (**22**)*

Yield 87%; m.p. 286–288 °C. IR (KBr) cm^{-1}: 3419 (OH), 1707 (C=O). ^1H NMR (DMSO-d6, 300 MHz, ppm): δ 8.79 (s, 1H), 8.04 (d, J = 8.0 Hz, 2H), 7.60 (m, 7H), 7.42 (t, J = 7.4 Hz, 1H), 4.22–4.14 (t, J = 6.0 Hz, 2H), 2.98–2.87 (t, J = 6.0 Hz, 2H). MS *m/z* 470 (M+1). Calcd. for $C_{22}H_{16}ClN_3O_3S_2$: C, 56.22; H, 3.43; N, 8.94; S, 13.65. Found: C, 56.20; H, 3.41; N, 8.92; S, 13.66.

*5.3.18. (Z)-3-(5-((3-(2,4-dichlorophenyl)-1-phenyl-1H-pyrazol-4-yl)methylene)-4-oxo-2-thioxothiazolidin-3-yl)propanoic acid (**23**)*

Yield 89%; m.p. 279–281 °C. IR (KBr) cm^{-1}: 3419 (OH), 1707 (C=O). ^1H NMR (DMSO-d6, 300 MHz, ppm): δ 8.85 (d, J = 3.9 Hz, 1H), 8.04 (d, J = 8.2 Hz, 2H), 7.89 (s, 1H), 7.68–7.52 (m, 4H), 7.43 (t, J = 7.3 Hz, 1H), 7.16 (d, J = 3.1 Hz, 1H), 4.19–4.08 (t, J = 7.5 Hz, 2H), 2.40–2.29 (t, J = 7.5 Hz, 2H). ^{13}C NMR (DMSO-d6, 75 MHz, ppm): δ 248.32, 192.50, 172.89, 166.43, 150.96, 138.53, 133.95, 129.61, 122.09, 119.44, 116.95, 101.71, 43.53, 39.54. MS *m/z* 503 (M+1). Calcd. for $C_{22}H_{15}Cl_2N_3O_3S_2$: C, 52.39; H, 3.00; N, 8.33; S, 12.71. Found: C, 52.37; H, 2.97; N, 8.32; S, 12.72.

*5.3.19. (Z)-4-(5-((3-(4-chlorophenyl)-1-phenyl-1H-pyrazol-4-yl) methylene)-4-oxo-2-thioxothiazolidin-3-yl)butanoic acid (**24**)*

Yield 86%; m.p. 258–260 °C. IR (KBr) cm^{-1}: 3419 (OH), 1707 (C=O). ^1H NMR (DMSO-d6, 300 MHz, ppm): δ 8.82 (s, 1H), 8.06 (d, J = 7.8 Hz, 2H), 7.75–7.63 (m, 4H), 7.56 (dd, J = 16.1, 8.2 Hz, 3H), 7.43 (t, J = 7.4 Hz, 1H), 4.06 (t, J = 6.8 Hz, 2H), 2.29 (t, J = 7.2 Hz, 2H), 1.96–1.81 (m, 2H). ^{13}C NMR (DMSO-d6, 75 MHz, ppm): δ 228.84, 192.96, 173.66, 166.68, 152.56, 138.53, 134.05, 129.96, 122.53, 119.41, 115.67, 43.73, 39.54. MS *m/z* 484 (M+1). Calcd. for $C_{23}H_{18}ClN_3O_3S_2$: C, 57.08; H, 3.75; N, 8.68; S, 13.25. Found: C, 57.06; H, 3.74; N, 8.67; S, 13.26.

*5.3.20. (Z)-4-(5-((3-(2,4-dichlorophenyl)-1-phenyl-1H-pyrazol-4-yl)methylene)-4-oxo-2-thioxothiazolidin-3-yl)butanoic acid (**25**)*

Yield 87%; m.p. 269–271 °C. IR (KBr) cm^{-1}: 3419 (OH), 1707 (C=O). ^1H NMR (DMSO-d6, 300 MHz, ppm): δ 8.87 (s, 1H), 8.04 (d, J = 8.2 Hz, 2H), 7.90 (d, J = 0.7 Hz, 1H), 7.68–7.51 (m, 4H), 7.43 (t, J = 7.3 Hz, 1H), 7.16 (s, 1H), 4.02 (t, J = 7.0 Hz, 2H), 2.16 (t, J = 7.3 Hz, 2H), 1.90–1.75 (m, 2H). MS *m/z* 503 (M+1). Calcd. for $C_{23}H_{17}Cl_2N_3O_3S_2$: C, 53.28; H, 3.31; N, 8.11; S, 12.37. Found: C, 53.26; H, 3.30; N, 8.10; S, 12.35.

*5.3.21. (Z)-5-(5-((3-(4-chlorophenyl)-1-phenyl-1H-pyrazol-4-yl) methylene)-4-oxo-2-thioxothiazolidin-3-yl)pentanoic acid (**26**)*

Yield 88%; m.p. 291–292 °C. IR (KBr) cm^{-1}: 3419 (OH), 1707 (C=O). ^1H NMR (DMSO-d6, 300 MHz, ppm): δ 8.82 (s, 1H), 8.05 (d, J = 8.1 Hz, 2H), 7.76–7.61 (m, 4H), 7.61–7.48 (m, 3H), 7.44 (d, J = 6.5 Hz, 1H), 4.01 (t, J = 6.0 Hz, 2H), 2.19 (t, J = 6.6 Hz, 2H), 1.51 (m, 4H). MS *m/z* 499 (M+1). Calcd. for $C_{24}H_{20}ClN_3O_3S_2$: C, 57.88; H, 4.05; N, 8.44; S, 12.88. Found: C, 57.86; H, 4.04; N, 8.42; S, 12.89.

*5.3.22. (Z)-5-(5-((3-(2,4-dichlorophenyl)-1-phenyl-1H-pyrazol-4-yl)methylene)-4-oxo-2-thioxothiazolidin-3-yl)pentanoic acid (**27**)*

Yield 89%; m.p. 283–285 °C. IR (KBr) cm^{-1}: 3419 (OH), 1707 (C=O). ^1H NMR (DMSO-d6, 300 MHz, ppm): δ 8.87 (d, J = 1.3 Hz, 1H), 8.04 (d, J = 8.1 Hz, 2H), 7.90 (s, 1H), 7.63–7.55 (m, 4H), 7.45 (d, J = 6.3 Hz, 1H), 7.17 (d, J = 1.3 Hz, 1H), 3.99 (t, J = 6.0 Hz, 2H), 2.16 (t, J = 6.5 Hz, 2H), 1.61 (m, 2H), 1.49 (m, 2H). ^{13}C NMR (DMSO-d6, 75 MHz, ppm): δ 192.72, 174.57, 166.62, 150.99, 138.51, 133.77, 129.60, 127.74, 122.32, 119.43, 116.93, 56.01, 40.37, 39.26. MS m/z 533 (M+1). Calcd. for $C_{24}H_{19}Cl_2N_3O_3S_2$: C, 54.14; H, 3.60; N, 7.89; S, 12.04. Found: C, 54.12; H, 3.59; N, 7.87; S, 12.06.

*5.3.23. (Z)-6-(5-((3-(4-chlorophenyl)-1-phenyl-1H-pyrazol-4-yl) methylene)-4-oxo-2-thioxothiazolidin-3-yl)hexanoic acid (**28**)*

Yield 91%; m.p. 278–280 °C. IR (KBr) cm^{-1}: 3419 (OH), 1707 (C=O). ^1H NMR (DMSO-d6, 300 MHz, ppm): δ 8.80 (d, J = 3.1 Hz, 1H), 8.04 (d, J = 8.2 Hz, 2H), 7.67 (m, 4H), 7.60–7.49 (m, 3H), 7.42 (t, J = 7.4 Hz, 1H), 3.97 (t, J = 6.8 Hz, 2H), 2.16 (t, J = 7.2 Hz, 2H), 1.62 (m, 2H), 1.51 (m, 2H), 1.30 (m, 2H). MS m/z 513 (M+1). Calcd. for $C_{25}H_{22}ClN_3O_3S_2$: C, 58.64; H, 4.33; N, 8.21; S, 12.52. Found: C, 58.61; H, 4.32; N, 8.23; S, 12.53.

*5.3.24. (Z)-6-(5-((3-(2,4-dichlorophenyl)-1-phenyl-1H-pyrazol-4-yl)methylene)-4-oxo-2-thioxothiazolidin-3-yl)hexanoic acid (**29**)*

Yield 90%; m.p. 270–272 °C. IR (KBr) cm^{-1}: 3419 (OH), 1707 (C=O). ^1H NMR (DMSO-d6, 300 MHz, ppm): δ 11.97 (s, 1H), 8.88 (s, 1H), 8.05 (d, J = 7.6 Hz, 2H), 7.91 (d, J = 0.8 Hz, 1H), 7.69–7.51 (m, 4H), 7.44 (t, J = 7.4 Hz, 1H), 7.17 (s, 1H), 3.97 (t, J = 7.2 Hz, 2H), 2.19 (t, J = 7.3 Hz, 2H), 1.60 (m, 2H), 1.49 (m, 2H), 1.29 (m, 2H). ^{13}C NMR (DMSO-d6, 75 MHz, ppm): δ 247.63, 192.73, 174.26, 166.60, 151.01, 138.52, 133.77, 129.61, 127.83, 122.35, 119.44, 116.93, 44.12, 39.82, 33.37. MS m/z 547 (M+1). Calcd. for $C_{25}H_{21}Cl_2N_3O_3S_2$: C, 54.94; H, 3.87; N, 7.69; S, 11.73. Found: C, 54.93; H, 3.85; N, 7.66; S, 11.75.

5.4. Evaluation of antibacterial activity in vitro

In vitro antibacterial activity assay method was referred in Ref. [14].

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